Authors:

Jung Mi Jo, MD
Yun-Hee Kim, MD, PhD
Myoung-Hwan Ko, MD, PhD
Suk Hun Ohn, MD
Bohyun Joen, MD
Kwang Ho Lee, MD, PhD

Affiliations:

From the Department of Physical Medicine and Rehabilitation (JMJ, Y-HK, BJ), Stroke and Cerebrovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; Department of Physical Medicine and Rehabilitation (M-HK), Research Institute of Clinical Medicine, Chonbuk National University Medical School, Jeonju, Republic of Korea; Department of Physical and Rehabilitation Medicine (SHO), Hallym University Sacred Heart Hospital; and Department of Neurology (KHL), Stroke and Cerebrovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Correspondence:

All correspondence and requests for reprints should be addressed to Yun-Hee Kim, MD, PhD, Division for Neurorehabilitation, Department of Physical Medicine and Rehabilitation, Stroke and Cerebrovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Republic of Korea.

Disclosures:

Supported by the Korea Research Foundation Grant funded by the Korean Government (KRF-2008-1093-000) and by a KOSEF grant funded by the Korean government (M10644000022-06N4400-02210).

0894-9115/09/8805-0404/0
American Journal of Physical Medicine & Rehabilitation

DOI: 10.1097/PHM.0b013e3181a0e4cb

ORIGINAL RESEARCH ARTICLE

Enhancing the Working Memory of Stroke Patients Using tDCS

ABSTRACT

Jo JM, Kim Y-H, Ko M-H, Ohn SH, Joen B, Lee KH: Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil 2009;88: 404–409.

Objectives: We investigated whether anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex affected the working memory performance of patients after a stroke.

Design: Ten patients (mean age 47.7 yrs) with cognitive deficits after a first-ever stroke participated in this single-blind, crossover, and sham-controlled experiment. Each patient was randomly assigned to undergo two transcranial direct current stimulation sessions: anodal dorsolateral prefrontal cortex and sham stimulation within 48 hrs of a washout period. All participants performed a two-back working memory task before and after the administration of the transcranial direct current stimulation. Accuracy (correction rate), recognition accuracy (correction rate-commission error rate), and response time were measured during each experiment.

Results: Repeated-measures analysis of variance indicated a significant interaction effect of transcranial direct current stimulation type and time on the recognition accuracy. Post hoc analyses revealed a significant difference between prestimulation and poststimulation in the anodal stimulation group but not in the sham stimulation group. Regarding the accuracy, the paired *t* test indicated significant improvement only after anodal transcranial direct current stimulation without a significant interaction effect between the two transcranial direct current stimulation types. The response time was not significantly different in the anodal and sham stimulation groups.

Conclusion: Our results demonstrated that anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex was associated with enhanced working memory performance as indexed by the recognition accuracy in patients after a stroke.

Key Words: Stroke, Transcranial Direct Current Stimulation (tDCS), Working Memory

Acquired brain damage after a stroke often results in chronic cognitive deficits. Such cognitive deficits can critically affect the activities of daily living and, when present, are poor predictors for long-term functional independence.[1] Specifically, strokes are often associated with impairment of the working memory (WM), which is used for temporary storage and manipulation of information and plays a central role in long-term memory, language, and executive function.[2] The cortical structures related to verbal WM include the prefrontal cortex, frontal eye field, supplementary motor area, and parietal cortex, as demonstrated in many neuroimaging studies.[3,4] Among these regions, the dorsolateral prefrontal cortex (DLPFC, Brodman areas 9 and 46) plays a crucial role in WM such that verbal WM is handled mainly by the left hemisphere and spatial WM is a function of the right hemisphere.[5–7] Understandably, memory enhancement is a major interest to those involved in cognitive neuroscience and rehabilitation. In addition to pharmacotherapeutic and psychotherapeutic approaches for enhancing memory,[8] brain stimulation using magnetic or electrical stimulation techniques has recently been investigated.[9,10]

Recent studies have highlighted the importance of noninvasive brain stimulation as a means of modulating cortical excitability. Transcranial direct current stimulation (tDCS) has been reported as an effective method for manipulating human brain excitability through continuous application of a weak direct current on the scalp.[11] The effect of tDCS varies depending on the polarity of the electrode; anodal polarization increases cortical excitability, whereas cathodal polarization decreases it.[11] Recent human studies have demonstrated that anodal polarization increases the excitability of the motor, visual, and prefrontal cortices and improves motor skill, WM, and verbal fluency in both healthy subjects and patients with brain disorders.[10,12–14] Our previous study demonstrated that anodal tDCS applied to the left DLPFC had a time-dependent positive impact on the WM of healthy participants.[14] In patients with Parkinson's disease, anodal tDCS over the left DLPFC improved the WM as demonstrated by the accuracy in the three-back cognitive task.[12]

However, there has been no report of using tDCS to enhance the WM of stroke patients. In this study, we investigated whether anodal tDCS over the left DLPFC was associated with enhanced verbal WM performance in patients with cognitive impairment after a stroke. We hypothesized that DLPFC stimulation would enhance the WM regardless of the individual brain lesion in patients after a stroke.

METHODS

Subjects

Ten patients with a first-ever stroke participated in this study (seven males and three females). The mean age of the patients was 47.9 ± 8.9 yrs. The inclusion criteria were as follows: unilateral right hemisphere stroke, age younger than 70 yrs, and noticeable cognitive disorder after stroke. All participants were evaluated with the Korean version of Mini-Mental Status Examination, digit and visual span tests to screen the cognitive function. A formal neurocognitive test battery was also applied as needed. Patients were excluded from the study for the following reasons: seizure disorder, intracranial metal insertion or cardiac pacemaker, or history of other neuropsychiatric diseases. Written informed consent was obtained from all participants before inclusion in the study, and the study protocol was approved by our local Ethics Committee. The demographic and clinical characteristics of the participants are shown in Table 1.

Experimental Design

The experimental design was based on two previous studies in which the effects of anodal tDCS on WM in healthy volunteers and patients with Parkinson's disease were investigated.[12,14] This study was designed as a single-blind, crossover, sham-controlled experiment. Each subject participated in two stimulation conditions (anodal DLPFC and sham stimulation) similar to that described elsewhere.[12,15] The order of stimulation was randomly assigned for all participants. To avoid carryover effects, each stimulation session was separated by at least 48 hrs to wash out the effects of the previous run. To avoid a possible learning effect, two different WM tasks were designed and randomly distributed. Before starting the experiment, all patients participated in a familiarization session using different WM task set until response accuracy reached a plateau. In each experimental session, patients performed the two-back verbal WM task before the tDCS to establish a baseline measurement and at 25 mins after starting the stimulation (Fig. 1*A*).

Cognitive Paradigm and Experimental Procedure

A two-back verbal WM task, similar to those described elsewhere, was used as the cognitive paradigm.[10,12,14,16] The exposure time and size of the stimuli were modified for patients with cognitive dysfunction. Stimuli were generated using SuperlabPro v.2.0 software (Cedrus Corporation, San Pedro, CA). A pseudorandom set of 10 Korean letters was displayed on a monitor, and the subjects were instructed to press a keyboard if the letter

TABLE 1 Demographic and clinical characteristics of participants

n	Age, yrs	Sex	Duration of Stroke, mos	Brain Lesion	Stroke Risk Factors		Digit Span Test		Visual Span Test	
					HTN	DM	FW	BW	FW	BW
1	44	M	4	Rt. BG hemorrhage	−	−	5	3	4	1
2	54	M	2	Rt. MCA infarction	+	−	6	4	2	1
3	58	M	4	Rt. Cerebellar hemorrhage	−	−	4	2	2	2
4	28	M	2	Rt. Frontal hemorrhage	−	−	4	2	3	1
5	47	M	2	Rt. PICA infarction	+	−	5	3	2	2
6	56	F	2	Rt. Parietal hemorrhage	+	+	3	1	2	1
7	47	F	2	Rt. CR infarction	+	−	5	4	4	4
8	54	M	2	Rt. Frontal hemorrhage	+	−	5	2	3	1
9	43	F	1	Rt. BG hemorrhage	+	−	4	3	5	4
10	48	M	3	Rt. MCA infarction	−	−	5	3	2	2
Mean ± SD	47.9 ± 8.7	M = 7, F = 3	2.4 ± 1.0	Hemorrhage = 6 Infarction = 4			4.8 ± 0.8	2.9 ± 1.0	2.9 ± 1.1	1.9 ± 1.2

M, male; F, female; HTN, hypertension; DM, diabetes mellitus; FW, forward; BW, backward; Rt., right; BG, basal ganglia; MCA, middle cerebral artery; PICA, posterior inferior cerebellar artery; CR, corona radiata.

presented was the same as the letter presented two stimuli previously (Fig. 1*B*). Each letter was displayed for 900 msecs, followed by a blank screen for 600 msecs between stimuli. The total number of targets was 30, and the total number of foil stimuli was 60. The accuracy (correction rate; number of correct responses/total targets) and the response time were measured. Also, recognition accuracy (correction rate-commission error rate) was considered an outcome that reflected the overall performance of the task. The patients reported a subjective feeling of fatigue and concentration after finishing each experiment, as assessed by the visual analog scale in which one represented "no concentration or no fatigue" and ten represented the "highest levels of concentration or fatigue."

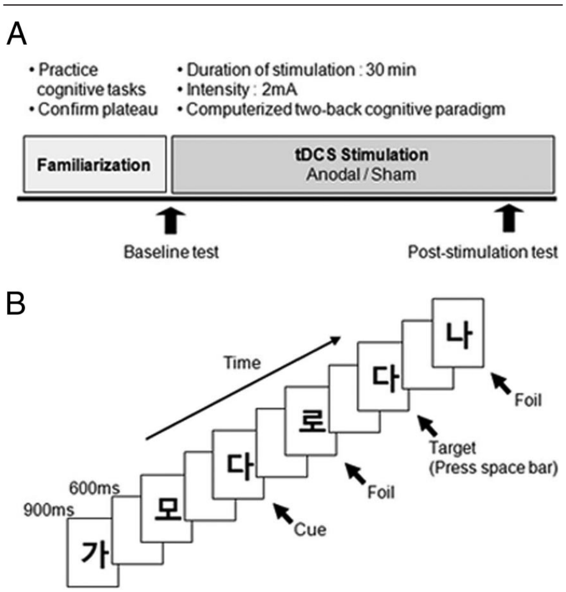

FIGURE 1 A, *Experimental design. For familiarization, patients practiced cognitive tasks until the response accuracy reached a plateau. Patients performed the two-back verbal WM task before tDCS to establish a baseline measurement and at 25 mins after starting stimulation.* B, *Two-back verbal WM paradigm. Subjects were instructed to press the keyboard if the letter presented was the same as the letter presented two stimuli before.*

tDCS Application

Stimulation was applied using a constant-current regulator Phoresor II PM850 (Iomed Inc., Salt Lake City, UT). Saline-soaked electrodes (5 × 5 cm) were placed on the scalp in the following manner. For the anodal DLPFC stimulation, the anode was placed over the left DLPFC as determined by the International 10/20 Electroencephalogram System corresponding to F3, and the cathode was placed in the right supraorbital area. A constant current of 2 mA was administered for 30 mins. The electrode placement was identical for the sham DLPFC stimulation; however, the stimulator was turned on for only 10 secs during which the current intensity was gradually increased and then decreased to diminish the perception of the sham.

Data Analysis

All analyses were performed using the software package SPSS 15.0 (Chicago, IL). A repeated-measures analysis of variance was used to test whether there was an overall effect of the intervention (tDCS type) on each outcome measure across time (prestimulation *vs.* poststimulation). The results were further analyzed with two-tailed paired-samples t tests for within-subjects comparisons using the Bonferroni correction for multiple comparisons. All results are expressed as mean ± SD. Statistical significance refers to $P < 0.05$.

RESULTS

Ten patients completed the entire set of experiments. There were some adverse effects during tDCS that disappeared after a few seconds. Transient aching or burning sensations were reported in six cases, and transient skin redness at the electrode contact site was reported in three cases.

Repeated-measures analysis of variance indicated a significant interaction effect of tDCS type and time on the recognition accuracy ($F(1,18) = 5.433$, $P = 0.032$). Post hoc analyses with two-tailed paired-samples t tests using the Bonferroni multiple-comparison correction revealed a significant difference between prestimulation and poststimulation in the anodal stimulation group ($t(9) = 3.863$, $P = 0.004$) but not in the sham stimulation group ($t(9) = 0.878$, $P = 0.403$). The significant effects on recognition accuracy were not the result of a difference at baseline across tDCS type; a two-tailed two-sample t test comparing recognition accuracy at baseline did not show any significant difference ($t(18) = 0.751$, $P = 0.462$) (Table 2 and Fig. 2*A*).

As to other outcome measures, the interaction effects of tDCS type and time were not significant. Nevertheless, the paired t test showed that the accuracy was improved only after anodal tDCS ($P = 0.021$, Table 2 and Fig. 2*B*), without any significant difference at baseline between the two tDCS types. There were no significant differences in the response time between the prestimulation and poststimulation data for either condition ($P > 0.05$) (Table 2 and Fig. 2*C*). No significant changes were reported for fatigue and concentration after the experiments for either condition.

TABLE 2 Working memory performances at baseline and after intervention

	Anodal DLPFC Stimulation	Sham DLPFC Stimulation
Accuracy		
Baseline	0.520 ± 0.164	0.570 ± 0.197
Poststimulation	0.633 ± 0.136[a]	0.600 ± 0.215
Recognition accuracy		
Baseline	0.435 ± 0.182	0.495 ± 0.174
Poststimulation	0.587 ± 0.118[a]	0.525 ± 0.194
Response time		
Baseline	694.9 ± 80.3	673.4 ± 68.7
Poststimulation	672.7 ± 73.7	676.0 ± 87.3

Values are described as the mean ± SD.
[a] Significant at $P < 0.05$ *vs*. baseline.
DLPFC, dorsolateral prefrontal cortex.

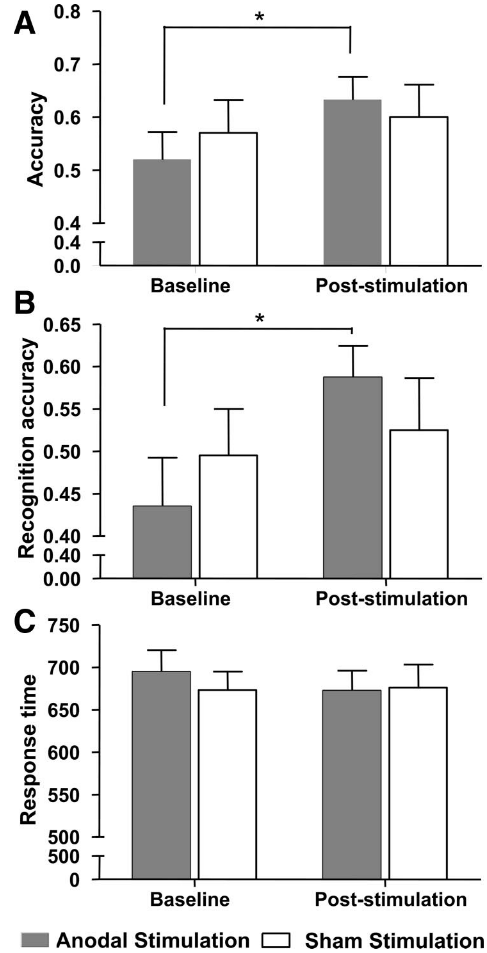

FIGURE 2 *Changes in accuracy (*A*), recognition accuracy (*B*), and reaction times (*C*) induced by tDCS.* A *and* B*, The accuracy and recognition accuracy were improved by anodal tDCS but not by sham stimulation. There was a significant interaction effect of tDCS type and time on the recognition accuracy.* C*, The reaction time was not changed by anodal or sham stimulation conditions. *Significant at P < 0.05* vs. *baseline.*

DISCUSSION

Anodal tDCS applied over the left DLPFC for 30 mins at an intensity of 2 mA was associated with enhanced verbal WM performance in patients after a stroke. Among the outcome measures, recognition accuracy was improved after anodal stimulation of the left DLPFC, with a significant interaction effect compared with the sham stimulation. Accuracy, which is a common measure of WM and has been used in a number of studies,[12,13,17] was significantly improved after anodal tDCS stimulation, but without an interaction effect in analysis of variance, probably because of the small number of subjects in our study. These results suggest that anodal tDCS on the left DLPFC produced a positive effect on WM performance by improving both correct response and error detection rates.

A cognitive process such as WM consists of subcomponents, the corresponding states of which are temporally distinguishable by using a proper cognitive task. However, the effects of anodal tDCS on these individual processes in WM have not been investigated in detail. In a two-back WM task, the subject must perform multiple cognitive operations, including encoding of new stimuli, update and maintenance of past stimuli, and recognition and response of whether each new stimulus matches the two-back stimulus. In neuroimaging studies, different prefrontal activation was shown in different phases[18,19] or in response to the positive or negative probe[18,20,21] of a WM task. The prefrontal cortex is considered to be involved in WM, particularly in processes that distinguish target and nontarget stimuli during recognition, so that stimulation on the prefrontal cortex can enhance the recognition component of WM. Even though the participants' brain lesions were in the right hemisphere, the verbal WM among all participants enrolled in this study was improved after left DLPFC stimulation. The tDCS has been investigated as a potential tool for modulating motor, sensory, and cognitive function.[13,22,23] Conceivably, anodal tDCS induces neuronal depolarization and enhances neuronal excitability, whereas cathodal tDCS has the opposite effects.[11,24] The increased recognition accuracy of WM tasks after anodal stimulation in this study was thought to reflect enhanced local cortical excitability of the left DLPFC. No change in reaction time suggests that slowed responses cannot account for the enhanced recognition accuracy after anodal DLPFC stimulation.

A number of recent studies have reported on the beneficial effects of various types of anodal tDCS on WM in healthy participants and in patients with brain injuries.[12,13,17] Fregni et al.[10] reported that left prefrontal anodal stimulation for 10 mins at 1 mA in healthy participants enhanced WM performance; the effects depended on the stimulation site and polarity. Iyer et al.[13] demonstrated that verbal fluency improved during anodal stimulation for 20 mins at 2 mA, and this improvement did not occur during sham or cathodal polarization. In contrast, Boggio et al.[12] reported a change in prefrontal excitability and WM performance in patients with Parkinson's disease with tDCS for 20 mins at 2 mA but not after stimulation at 1 mA. In our previous study with healthy participants, anodal tDCS applied over the left DLPFC at 1 mA enhanced the verbal WM in a time-dependent manner.[14] The accuracy of WM tasks increased after 10 mins of tDCS, and this effect was further enhanced by 30 mins of stimulation. Referring to the two aforementioned studies, we applied tDCS for 30 mins at 2 mA to obtain the maximal effect from the stimulation. However, because of safety concerns, we did not extend the duration of the stimulation beyond 30 mins.

The limitations of this study include the following. First, the effect of different intensities and durations of the anodal DLPFC tDCS on WM performance was not investigated and needs further study to develop an optimal stimulation protocol in the clinical setting. Second, the possible confounding effect of the cathodal electrode on the performance of cognitive task was not taken into consideration in our analysis. Blindness of real *vs.* sham stimulation was also an issue not totally resolved. In addition, an attentional effect of tDCS on the performance of WM was not clearly separated by using control-task design. In future studies, specific WM components affected by tDCS need to be investigated by combined use of various neuroimaging methods. Examination of functional networks and local activations engaged in WM processing will improve our understanding of the effects of tDCS by analysis of patterns of brain activation accompanying the changes in cognitive performance.

In conclusion, the results of this study showed that anodal tDCS over the left DLPFC positively impacted WM in terms of the recognition accuracy in patients with cognitive deficits after a stroke. Anodal tDCS might therefore be a potential therapeutic modality for the treatment of cognitive deficits in stroke patients.

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