Contralateral and ipsilateral motor effects after transcranial direct current stimulation

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Transcranial direct current stimulation over the left motor area influenced both contralateral and ipsilateral finger sequence movements in seven healthy adults. Effects for the two hands were reversed: anodal stimulation improved right-hand performance significantly more than cathodal stimulation, whereas cathodal stimulation improved left-hand performance significantly more than anodal stimulation. The results show that stimulating a motor region directly, or indirectly by modulating activity in the homologous region on the opposite hemisphere, can affect motor skill acquisition, presumably by facilitating effective synaptic connectivity. This outcome provides evidence for the role of interhemispheric inhibition in corticomotor functioning, and also has implications for treatment methods aimed at facilitating motor recovery after stroke. *NeuroReport* 17:671–674 © 2006 Lippincott Williams & Wilkins.

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Introduction

Transcranial direct current stimulation (tDCS) noninvasively modulates the excitability of a targeted brain region by altering neuronal membrane potentials [1,2]. Anodal tDCS has been found to increase cortical excitability and the potentiation of *N*-methyl-D-aspartate (NMDA) receptor efficacy, and cathodal tDCS has been found to decrease excitability, with effects lasting beyond the period of stimulation [1,3,4]. Several studies have shown that tDCS can enhance cognitive and behavioral skills associated with the targeted brain area. For example, anodal tDCS to the left prefrontal cortex was found to increase working memory [5] and to improve verbal fluency [6], and anodal tDCS to the motor cortex contralateral to stroke patients' paretic arm facilitated temporary motor recovery [7].

A change in excitability in one hemisphere can produce indirect excitability effects in the other hemisphere by means of interhemispheric projections [8,9]. Thus, tDCS could potentially directly alter the excitability in a stimulated region, and indirectly alter excitability in the homologous region of the opposite hemisphere. If the predominant mode of interhemispheric interaction between primary motor cortices is inhibitory, as previous research suggests [10–13], then altering excitability in one motor cortex might produce opposite effects for contralateral and ipsilateral hands. To test this hypothesis, we modulated excitability in the left motor region using tDCS, and examined both direct and indirect effects on patterned sequential finger movements.

Methods

Participants

Seven healthy, right-handed adults gave their informed, written consent to participate in the experiment, which followed a protocol approved by the local Institutional Review Board.

Procedure

Participants underwent one session each for three conditions (anodal, cathodal, and nonstimulation) while sitting in a comfortable office chair. For the anodal and cathodal sessions, 20-min of 1 mA tDCS were applied to participants' left motor region, centered on C3 of the 10–20 electroencephalogram system; a number of tDCS studies have successfully employed this system to identify brain locations for stimulation [5,6,14,15]. The anodal and cathodal stimulation sessions were separated by at least 30 min, with counterbalanced ordering across participants. Although excitability changes due to tDCS have been found to last up to 60 min or longer [3,16], there have been no reports of performance effects lasting longer than 30 min after a single session of tDCS [5–7,14]. A battery-driven, constant current stimulator (Phoresor, Iomed Inc., Salt Lake City, Utah, USA) delivered the 1 mA electrical current to the scalp by means of a saline-dampened active electrode (area=15 cm^2) secured over the left motor region, and a reference electrode (area=30 cm^2) positioned over the right supraorbital region. The reference electrode was functionally ineffective within this experimental design [17]. For both anodal and cathodal stimulation, the tDCS current ramped up over the first few seconds, and then remained on for the remainder of the 20-min. The nonstimulation control session was conducted without attaching electrodes, but was otherwise identical to the anodal and cathodal sessions. Pilot testing (*N*=3) revealed no significant differences between our nonstimulation condition and a sham stimulation condition, as applied in some previous studies [5–7,14].

Task

The task instructions for a single trial were to use the numbered keys on a standard computer keyboard to repeat a unimanual pattern of five sequential keystrokes (e.g. 42534) as accurately and as many times as possible within 30 s. Before the first experimental trial, there were two warm-up trials for each hand. Participants performed three trials of the unimanual finger sequence task with their right and left hands (counterbalanced ordering) before and immediately after tDCS. A different keystroke pattern was used for each session (anodal, cathodal, and nonstimulation). Patterns of equal difficulty were identified through pilot testing. The keystroke patterns for the two hands always formed a mirror image (e.g. 42534 for the left hand and 35243 for the right hand).

Data analyses

We calculated the percentage of change in the total number of correct sequential keystrokes over three trials, comparing performance before and after tDCS. To compute the dependent variable, and to isolate the effects due to tDCS, we subtracted the percentage of change for the nonstimulation condition from the percentage of change for the anodal and cathodal conditions, for each participant; this controlled for basic learning effects that were present in all three conditions. We applied a two-way repeated measures analysis of variance to the data, with factors 'hand' (left and right) and 'tDCS condition' (cathodal and anodal).

Results

All participants completed the experimental procedures. The analysis of variance yielded no main effects, but the interaction between the factors 'hand' and 'tDCS condition' was significant, $F(1,6)=24.325$, $P=0.003$; tDCS elicited opposite effects for the two hands. An LSD post-hoc analysis revealed significant differences between cathodal and anodal tDCS for the right hand, $P=0.047$ (see Fig. 1, top panel), and for the left hand, $P=0.034$ (see Fig. 1, bottom panel).

To ensure that the calculated effects were not due to differences in the pre-tDCS scores, we used two-tailed, paired-samples *t*-tests to compare the pre-tDCS scores for all three conditions, within each hand. None of these six tests yielded a significant result. The six *P* values ranged from 0.252 to 0.666.

We found that applying tDCS to one motor region elicited direct and indirect effects on finger sequence movements. Anodal stimulation over C3 enhanced performance of sequential finger movements for the contralateral hand more than cathodal stimulation. Cathodal stimulation over the same motor region enhanced ipsilateral performance of sequential finger movements more than anodal stimulation,

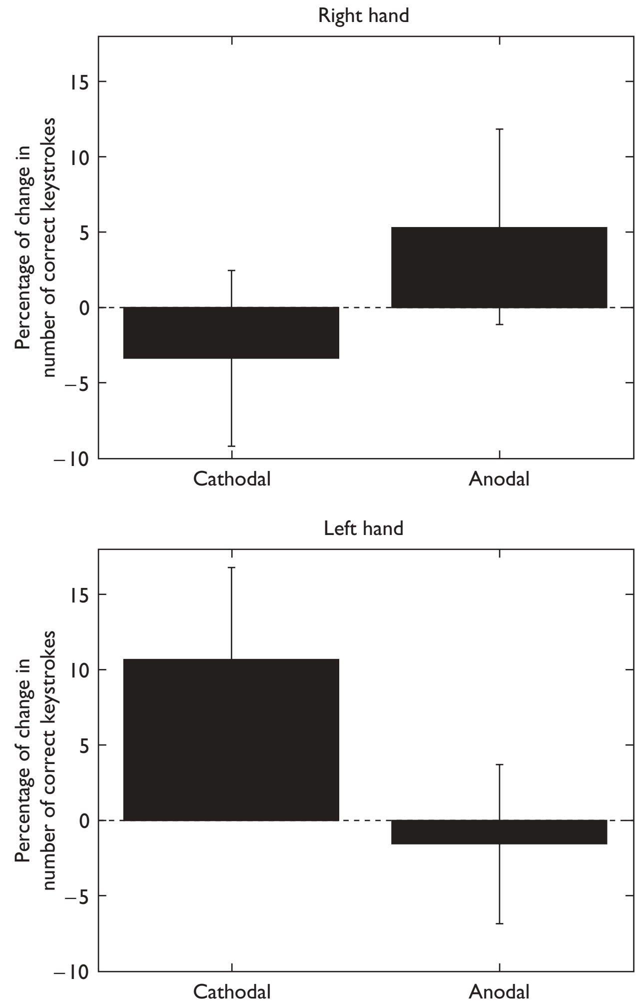

Fig. 1 The mean percentage of change in the total number of correct sequential keystrokes for cathodal and anodal transcranial direct current stimulations (tDCSs), relative to the nonstimulation control condition. The tDCS over left MI had opposite effects for the right hand (anodal significantly greater than cathodal) compared with the left hand (cathodal significantly greater than anodal).

presumably by modulating excitability in the homologous region of the opposite hemisphere.

The improvement in the left hand for cathodal relative to anodal stimulation was associated with an increased rate of keystrokes; a two-tailed, paired-samples *t*-test yielded a significant difference ($P=0.019$) in the percentage of change for the total number of keystrokes for cathodal relative to anodal stimulation. The detrimental effects in the right hand for cathodal relative to anodal stimulation were associated with a nonsignificant trend towards an increased number of errors.

Discussion

The indirect effects on performance for the ipsilateral hand might provide evidence that tDCS modulated inhibitory interhemispheric projections. We posit that cathodal tDCS induced a decrease in left motor cortical excitability, which dampened the inhibitory influence of the left motor area on the homologous right motor area, and that this disinhibition of the right motor cortex (and the subsequent increase in excitability there) caused the enhanced performance in the left-hand sequential finger movements. This hypothesis is also supported by previous research [10], including studies with stroke patients in which a decrease in neural excitability of the primary motor area ipsilateral to the paretic arm (induced by transcranial magnetic stimulation) improved time to completion on motor coordination tasks [11] and pinch acceleration [12] for that arm.

The findings for the contralateral hand partially mirror those found in a previous investigation into tDCS effects on motor learning [17]. Nitsche and colleagues [17] applied anodal and cathodal tDCS over the left primary motor, premotor and prefrontal cortices, and studied implicit motor learning for the contralateral hand using a serial reaction time task. Their results, similar to those of the present study, included a significant improvement in performance associated with anodal tDCS applied over primary motor cortex, but not over the premotor and prefrontal cortices. Taken together, these two studies point to the involvement of primary motor cortex in both implicit and explicit motor learning, and to the facilitative effects of anodal stimulation on such learning. Contrary to our findings here, the study by Nitsche and colleagues [17] also yielded a notable trend, which fell short of significance, towards improved performance in the contralateral hand owing to cathodal stimulation over the primary motor cortex. This contrast in outcomes for these two studies is probably attributable to differences in the task demands: whereas the present study involved an explicit motor task with continuous motor movements, Nitsche and colleagues [17] used an implicit motor task with delays greater than 500 ms between each motor movement. For continuous motor learning in an explicit context, a reduction in excitability might be detrimental to performance, owing to a subsequent decrease in the formation of functional neural connections (see the following paragraph for further detail). In the context of relatively sparse motor movements in an implicit context, a reduction in excitability might benefit performance by reducing noise in the system, thus enabling appropriate commands to register more efficiently [17].

It is likely that increasing excitability in a motor region by means of tDCS, whether directly or indirectly, raises the probability of forming stronger and more effective synaptic connections between activated neurons [1]. The development of such connectivity because of NMDA receptor-dependent long-term potentiation has been shown to correlate with motor skill learning [18]. Liebetanz and colleagues provided evidence for the role of NMDA receptors in tDCS-modulated corticomotor excitability, by showing that NMDA receptor antagonists such as dextromethorphan suppressed the poststimulation effects of both anodal and cathodal tDCS, whereas NMDA agonists such as D-cycloserine selectively potentiated the effects of anodal tDCS [1,16]. Furthermore, research has shown that practicing a motor behavior increases neural excitability in motor cortical areas associated with the muscles involved in that behavior [19]. Thus, and in accordance with the results presented here, a tDCS-induced increase in motor cortical excitability might enhance performance. Conversely, a tDCS-induced decrease in motor cortex excitability (due to direct cathodal or indirect anodal stimulation) might impede the improvement following repeated performances of the motor sequencing task.

In the present study, the anodal and cathodal tDCS sessions were separated by at least 30 min. As there are no previous reports of behavioral changes due to tDCS persisting more than 30 min, we considered this interval between stimulation sessions to be long enough to avoid having one tDCS session interfere with the behavioral effects for the following tDCS session. The influence of tDCS on motor cortical excitability however, as mentioned above, has been reported to last 60 min or longer. Even if the behavioral effects of stimulation did last beyond 30 min in the present experiment, the corresponding effect on the results could only have been to introduce additional noise, because the order of stimulation conditions was counterbalanced across participants. Few studies have investigated the time course of tDCS effects on performance; Rogalewski and colleagues [14] did find that 7 min of 1 mA cathodal stimulation over C4 significantly decreased tactile discrimination for up to 7 min beyond stimulation, and Antal and colleagues [20] found that 7 min of 1 mA cathodal stimulation over V5 significantly improved motion perception for 10 min beyond stimulation, but not for 20 min. Considering the lack of information on how long tDCS effects last, we believe that further studies must be pursued in order to systematically evaluate the duration of behavioral changes following tDCS. A better understanding of the relationship between excitability and behavioral change is crucial to the development of tDCS as an important rehabilitative tool.

Conclusion

We found measurable effects on motor skill after applying tDCS over the left motor cortex for both the contralateral and ipsilateral hands. The effects were reversed for the left hand compared with the right hand: anodal tDCS led to a relative improvement in contralateral performance, and to a relative decrease in ipsilateral performance. In contrast, cathodal tDCS improved ipsilateral performance, but led to a relative decrease in contralateral performance. These findings point to the functional role of interhemispheric inhibition in motor performance. The study also provides evidence for an effective relation between cortical excitability levels in the primary motor cortex and improvement in motor performance, whereby an increase in excitability augments improvement, and a decrease in excitability reduces improvement in explicit motor skill acquisition. Our results are highly relevant for experiments seeking to influence regional brain functions through direct or indirect noninvasive stimulation.

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