Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation

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Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive powerful method to modulate brain activity. It can enhance motor learning and working memory in healthy subjects. To investigate the effects of anodal tDCS (1 mA, 20 min) of the dominant and non-dominant primary motor cortex (M1) on hand motor performance in healthy right-handed volunteers, healthy subjects underwent one session of both sham and active anodal stimulation of the non-dominant or dominant primary motor cortex. A blinded rater assessed motor function using the Jebsen Taylor Hand Function Test. For the non-dominant hand, active tDCS was able to improve motor function significantly—there was a significant interaction between time and condition of stimulation ($p=0.003$). Post hoc tests showed a significant enhancement of JTT performance after 1 mA anodal tDCS of M1 (mean improvement of 9.41%, $p=0.0004$), but not after sham tDCS (mean improvement of 1.3%, $p=0.84$). For the dominant hand, however, neither active nor sham tDCS resulted in a significant change in motor performance. Our findings show that anodal tDCS of the non-dominant primary motor cortex results in motor function enhancement and thus confirm and extend the notion that tDCS can change behavior. We speculate that the under-use of the non-dominant hand with its associated consequences in cortical plasticity might be one of the reasons to explain motor performance enhancement in the non-dominant hand only.

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The development of non-invasive techniques of brain stimulation, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), has opened new windows of opportunities to modulate brain function in a painless and non-invasive way, and thus behavioral changes are possible depending on the parameters of stimulation, such as intensity, duration and site of stimulation. For instance, it has been demonstrated that rTMS can improve motor function in healthy subjects [13] and stroke patients [16] as well as working memory [11] in healthy subjects and in patients with major depression [17]. Similarly, tDCS has been associated with an improvement in motor learning and working memory in normal subjects [6,12] and motor performance in stroke patients [5,7]. In tDCS, a weak electric current is applied continuously between two electrodes positioned on the scalp with the effects depending on the position and polarity of the electrodes, i.e., whereas anodal stimulation increases cortical excitability, cathodal stimulation decreases it [18]. Recently Hummel et al. [7] and our group [5] demonstrated that anodal tDCS of the lesioned primary motor cortex in patients with chronic stroke results in an improvement in the distal motor skill as measured by the Jebsen Taylor Hand Function Test. We set out to investigate whether similar motor improvement could be achieved in healthy right-handed subjects. We delivered stimulation to both the dominant and non-dominant hemispheres. The rationale of testing both hemispheres is that differences in the use of the dominant hand and non-dominant hand could...
mimic at some extent the differences between the parietic and non-parietic hands in stroke patients. The asymmetric use of the non-dominant compared to the dominant hand results in a relatively decreased dexterity of the non-dominant hand, extensively demonstrated in the literature [2,24]. This asymmetric motor skill can be explained not only by decreased use and training of the hand muscles, but also by the relatively decreased cortical excitability in the non-dominant motor cortex. Indeed TMS studies showed that the dominant, compared to the non-dominant, motor cortex is characterized by having a lower motor threshold, higher motor evoked potential [4] and shorter silent period [25]. Therefore, tDCS could represent an effective means to increase the excitability in the non-dominant motor cortex and thus enhance the motor performance. An additional importance of this study lies in the fact that tDCS may represent in the future an important alternative therapy for motor recovery in stroke patients and therefore this study provides additional evidence regarding the behavioral motor effects of this technique.

Eight healthy subjects (all females) participated in this study. The age range was 22–26 years (mean of 22.8 years). Left-handed subjects were excluded as the laterality in the motor hand function detected by neuropsychological tests might not be present in these subjects [24]. The Edinburgh Handedness Inventory was used to determine handedness. All subjects were college students, thus all shared the same level of education. Subjects gave informed consent and the local Human Subjects Review Committee (Institute of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil) approved the study, which was conducted in strict adherence to the Declaration of Helsinki.

Eight subjects participated in experiment 1. In this experiment, each participant underwent two different treatments: sham and active anodal tDCS of primary motor cortex of the non-dominant hand (right hemisphere). The order of these conditions was counterbalanced and randomized across subjects. There was an interval of at least 48 h between each session of tDCS to minimize carryover effects and contamination of the sham stimulation session by a preceding real tDCS session.

Initially, in order to familiarize subjects with the Jebsen Taylor Hand Function Test, they performed this test 10 times. This number of practice sessions was sufficient to reach a stable performance as suggested by a previous study [7]. Subjects were then randomized to receive sham or active tDCS treatment. For each condition of stimulation, subjects performed the task three times for the baseline (pre-tDCS) evaluation and three times after the stimulation.

Five of the subjects who participated in experiment 1 also participated in experiment 2. This experiment was similar to experiment 1, however the left, dominant primary motor cortex was targeted in this experiment. Importantly, there was an interval period of 6 months between the two experiments, and therefore subjects performed the same training session of the Jebsen Taylor Hand Function Test.

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm²) and delivered by a specially developed, battery-driven, constant current stimulator (Schneider Electronic, Gleichen, Germany). To stimulate the primary motor cortex (M1), the anodal electrode was placed over C3 or C4 (international 10/20 EEG system). The other electrode was placed over the contralateral supraorbital area. A constant current of 1 mA intensity was applied for 20 min—this parameter of stimulation is safe according to past human studies [8,19,20]. Subjects felt the current as an itching sensation at both electrodes at the beginning of the stimulation. For the sham stimulation, the electrodes were placed in the same position; however, the stimulator was turned off after 30 s [7]. In addition, for both conditions (active and sham stimulation), current intensity was gradually increased and decreased (ramp up and down) during the period of 10 s. This procedure blinded subjects to the respective stimulation conditions [18].

The Jebsen Taylor (JTT) Hand Function Test [10] was designed as a broad measure of hand function and is widely used by physical and occupational therapists in clinical practice and clinical trials. The details of this test are described elsewhere [5,7]. As we were assessing the after-effects of tDCS, subjects performed JTT immediately before and after tDCS. Both at baseline and immediately after, subjects performed this test three times (there was no interval between each test). Because the total performance time for these three tasks was not superior to 5 min, this was adequate to evaluate the after-effects of tDCS as a previous study showed that the effects of 13 min of tDCS on cortical excitability can last up to 90 minutes [21]. A rater blinded to the experimental and treatment conditions evaluated subjects’ performance.

The primary outcome for analysis was change in the total time of JTT performance. Analyses were done with Statistica for Windows (version 6.1, USA). The distribution of these data was assessed using the Shapiro–Wilk test; homogeneity of variance was assessed by Levene’s test. Because these tests showed that these data were normally and homogeneously distributed, tests with the assumptions of normal distribution were used. A repeated measures analysis of variance (ANOVA) was performed to study the main effect of time (pre- and post-tDCS) and condition (active iDCS and sham iDCS) and the interaction term time × condition on total JTT time. We performed different models for experiments 1 and 2 as the number of subjects was not the same in these two experiments. Finally, we performed additional models in which the dependent variable was the time to perform the JTT subtests (cards, small objects, feeding, checkers, light and heavy cans). For the pre-stimulation performance, we averaged the three baseline tests, and for the post-stimulation performance, we averaged the three tests performed post-treatment. We also performed an ANOVA to investigate a possible treatment order effect by comparing subjects’ performance between sham iDCS first and active iDCS first. When appropriate, post-hoc comparisons were carried out using Tukey’s HSD test. Furthermore, comparison between baseline (mean of the three baseline tests) and the last three trials of the training phase (mean of the last three tests of training period) was performed using Student’s t-test. This analysis was performed for both experiments. Data are reported as mean and standard deviation if not stated otherwise. Statistical significance refers to a two-tailed p-value <0.05.

All subjects tolerated iDCS well and there were no adverse effects related to the application of this therapy. All subjects...
underwent training and reached a performance plateau as shown in Fig. 1. Furthermore, there was no significant difference in motor performance between the last three sessions of training and baseline.

A two-way ANOVA with repeated measures on time showed that the main effect of group was not significant ($F_{1,14} = 0.9$, $p = 0.36$), but there was a significant effect of time ($F_{1,14} = 22.3$, $p = 0.0003$) and significant interaction effect ($F_{1,14} = 12.6$, $p = 0.003$). Post hoc comparisons demonstrated that motor performance after anodal tDCS was significantly improved ($p = 0.0004$, mean improvement of 9.41%) when compared to baseline. There was no significant motor performance change after sham stimulation ($p = 0.84$, mean performance change of 1.3%). Fig. 1 shows the results of motor performance during the training phase and at baseline and post-treatment after sham and active anodal tDCS (Fig. 2 shows details of the motor performance at baseline and post-treatment for the active tDCS group).

Interestingly the results were consistent for four of the subtests of the JTT test, i.e., individual ANOVAs for each subtest found a significant interaction effect between time (pre- and post-stimulation) and condition of stimulation for the following subtests: turning over cards ($F = 7.7$, $p = 0.015$), picking up small objects ($F = 10.4$, $p = 0.0062$), moving large empty cans ($F = 8.4$, $p = 0.012$) and moving large weighted cans ($F = 8.7$, $p = 0.010$).

Table 1 shows the performance of each group (anodal and sham tDCS) in each JTT subtest.

Finally, we tested for an order effect. The motor performance was evaluated considering the order of stimulation (active and sham tDCS). The result of the repeated measures ANOVA showed that there was no significant effect of order of stimulation ($F < 1$ for the main term of order).

We repeated the same analysis for experiment 2 (dominant hand). Initially we performed a two-way repeated measures ANOVA in order to test whether the motor performance was correlated with stimulation condition and time (pre- and post-treatment). This analysis disclosed that there was no significant group effect ($F_{1,8} = 0.27$, $p = 0.61$), time effect ($F_{1,8} = 0.81$, $p = 0.39$) or interaction (time × group) effect ($F_{1,8} = 0.37$, $p = 0.56$). Indeed the absolute values showed the lack of effects after active stimulation in this experiment: in the active group there was a mean improvement in the motor function of 0.81% only (compared to 9.4% of the non-dominant hand performance).

Table 1

<table>
<thead>
<tr>
<th>JTT Subtest</th>
<th>Anodal</th>
<th>Sham</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Cards</td>
<td>314 ± 59</td>
<td>277 ± 66</td>
<td>315 ± 65</td>
</tr>
<tr>
<td>Small objects</td>
<td>535 ± 41</td>
<td>500 ± 59</td>
<td>517 ± 39</td>
</tr>
<tr>
<td>Feeding</td>
<td>744 ± 215</td>
<td>689 ± 164</td>
<td>821 ± 237</td>
</tr>
<tr>
<td>Checkers</td>
<td>318 ± 50</td>
<td>294 ± 49</td>
<td>324 ± 26</td>
</tr>
<tr>
<td>Light cans</td>
<td>383 ± 36</td>
<td>329 ± 48</td>
<td>378 ± 45</td>
</tr>
<tr>
<td>Heavy cans</td>
<td>424 ± 54</td>
<td>373 ± 49</td>
<td>423 ± 57</td>
</tr>
</tbody>
</table>

* Significant at $p < 0.05$. Values are mean ± S.D. for non-dominant hand performance.
under the same experimental conditions). Because the results of experiment 2 showed no significant effect of active tDCS on motor function, we did not proceed with the post hoc tests and additional analyses (see Fig. 2 for details).

The main finding of our study was a significant enhancement of motor performance of the non-dominant hand as indexed by the Jebsen Taylor Hand Function Test after active, but not sham, tDCS of the contralateral primary motor cortex. In addition, active and sham tDCS of the dominant primary motor cortex did not result in a significant hand motor function improvement. The motor function enhancement after anodal tDCS of M1 is in line with other studies that showed an improvement in motor function and other aspects of cognition induced by tDCS. Nitsche et al. [22] showed that anodal tDCS improves a serial reaction time task performance when the primary motor, but not the premotor or the prefrontal cortex is stimulated [22]. In two other studies from the same group, Antal et al. [1] showed that the performance in a visuo-motor task is increased significantly in the early learning phase during anodal stimulation of M1 and V5 (middle temporal cortex) and Kincses et al. [12] showed that anodal prefrontal stimulation improves implicit learning (as measured by a probabilistic classification learning task). Finally, Fregni et al. [6] showed that working memory enhancement occurs after anodal tDCS of the dorsolateral prefrontal cortex. This evidence suggests that anodal tDCS might improve cognitive function focally, which might be explained by its effects on the neuronal membrane, i.e., anodal tDCS is associated with a depolarization of the neural tissue [26] that might facilitate the overall neural activity of the stimulated area. Indeed, animals studies have shown that anodal tDCS increases the neural firing rate in the stimulated area [3].

The results of this investigation should be compared to similar studies in stroke patients. Two studies, using the same methodology, showed that anodal stimulation of the affected M1 improves motor function of the paretic hand [5,7]. The magnitude of motor improvement as indexed by the JTT was 6.7% in Fregni’s study and 8.9% in Hummel’s study, similar to the motor improvement of 9.4% shown in this study. This finding raises an interesting hypothesis: perhaps the motor improvement observed in stroke patients after anodal tDCS is due to the reversal of the deleterious effects of the decreased use of the affected hand, as this is similar to the improvement in the non-dominant hand in healthy subjects. This hypothesis is also in line with the therapeutic effects of constraint-induced therapy, which improves motor function by forcing the use of the paretic hand, and in which successful treatment is associated with an increase in the local cortical excitability [15] (mimicking the effects of anodal tDCS).

The fact that the improvement of the motor function was obtained in the non-dominant hand, rather than the dominant hand, needs to be further discussed. Such results suggest that under-use of one of the hands leads to functional changes in the non-dominant motor cortex that can contribute to the decreased dexterity of this hand and that can be reversed partially by facilitation of this area by anodal tDCS. In this case, the lack of effects in the dominant hemisphere might be due to a ceiling effect: given that this area is already optimally activated, an additional increase in the excitability by anodal tDCS would not result in additional behavioral benefits for these subjects. On the other hand, the relative lack of use of the non-dominant hand might result in an asymmetric cortical excitability between the dominant and non-dominant hemisphere (i.e., the non-dominant M1 showing a decreased excitability compared to the dominant M1) and therefore a focal increase in the motor cortex excitability of the non-dominant hemisphere might equal the excitability between both hemispheres, accounting for the motor enhancement. Interestingly, when the dominant hemisphere is inhibited using 1-Hz rTMS, its performance decreases to the level of the non-dominant hemisphere [9]; therefore, indicating that the increased excitability in the dominant primary motor cortex is indeed partially responsible for the superior motor performance of the dominant hand. Analogously, a stroke leads to a decrease of the activity in the lesioned hemisphere and therefore this decreased activity might represent the functional component of the motor deficits that can be reversed partially by anodal tDCS as shown by behavioral [5,7] and neurophysiological [7] data.

In our study, we aimed to explore the impact of the after-effects of tDCS on motor function. It has been demonstrated that the weak current delivered by tDCS causes a subthreshold hyper- or depolarization that results in a prolonged change in the cortical excitability that outlasts the period of stimulation [21]. In two elegant studies from the same group, Liebetanz et al. [14] and Nitsche et al. [23] showed that the after-effects of tDCS might be associated with a change in the synaptic strengthening due to a modulation of NMDA receptors. Liebetanz et al. [14] showed that a NMDA-receptor antagonist, dextromethorphan, suppresses the after-effects of both anodal and cathodal DC stimulation on motor cortical excitability, therefore, suggesting an association between NMDA receptors and DC-induced neuroplasticity [14]. Another evidence suggesting that the motor performance change in our study might have been associated with changes in the synaptic strengthening comes from a recent study showing that memantine, a NMDA-antagonist, can block training-induced (as obtained by repetitive synchronized movement of two limbs) cortex plasticity as indexed by motor output map changes [27]. Therefore, in light of these previous studies, further studies should explore whether the behavioral improvement observed in our study can be blocked by NMDA antagonists, and thus shed light on the mechanisms of action of tDCS on motor function modulation.

One can argue, based on our findings, that the differences in the motor performance change after tDCS between the dominant and non-dominant hand is due to the parameters of stimulation. In other words, the current intensity and duration might not have been strong enough to induce behavioral effects in the dominant hand; however, we believe that this alternative explanation is unlikely due to the reasons aforementioned.

Our findings show that anodal tDCS of the primary motor cortex can enhance motor performance of the non-dominant hand in healthy subjects. Future studies evaluating the effects of tDCS coupled with motor training could indeed reveal an approach of motor function enhancement that might be used in stroke patients.
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