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Post-stimulation time interval-dependent effects of motor cortex anodal tDCS on reaction time task performance

Andrés Molero-Chamizo[a1]*, José Ramón Alameda Bailén[a]*, Tamara Garrido Béjar[a], Macarena García López[a], Inmaculada Jaén Rodríguez[a], Carolina Gutiérrez Lérida[a], Silvia Pérez Panal[a], Gloria González Ángel[a], Laura Lemus Corchero[a], María J. Ruiz Vega[a], Michael A. Nitsche[b,c], Guadalupe N. Rivera-Urbina[d]*

[a]University of Huelva. Department of Psychology. Huelva, Spain

[b]Leibniz Research Centre for Working Environment and Human Resources, Dortmund, Germany

[c]Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

[d]Autonomous University of Baja California, México

*These authors contributed equally to this work

Correspondence address:

[1]Andrés Molero-Chamizo

University of Huelva. Department of Psychology, Psychobiology Area.

Campus El Carmen. 21071 Huelva, Spain

Telephone number (34)959218478

E-mail: andres.molero@dpsi.uhu.es

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Abstract

Anodal transcranial direct current stimulation (tDCS) induces long term potentiation-like plasticity, which is associated with long-lasting effects on different cognitive, emotional and motor performances. Specifically, tDCS applied over the motor cortex is considered to improve reaction time in simple and complex tasks. The timing of tDCS relative to task performance could determinate the efficacy of tDCS to modulate performance. The aim of this study was to compare the effects of a single session of anodal tDCS applied over the left motor cortex on performance of a go/no-go simple reaction time task carried out at three different time points after tDCS, namely 0, 30 or 60 min after stimulation. Sixty subjects were randomly assigned to one of six groups: M1 anodal tDCS-task performance at 0 min (n = 10); M1 sham tDCS-task performance at 0 min (n = 10); M1 anodal tDCS-task performance at 30 min (n = 10); M1 sham tDCS-task performance at 30 min (n = 10); M1 anodal tDCS-task performance at 60 min (n = 10); M1 sham tDCS-task performance at 60 min (n = 10). Anodal tDCS improved task performance during the whole course of the task only when stimulation was applied immediately before performance. In contrast, performance observed one hour after stimulation was not different compared to sham stimulation. Performance 30 min after stimulation was only improved in the last block of the reaction time task. These findings suggest that the motor cortex excitability changes induced by tDCS can improve motor responses, and these effects critically depend on the time interval between stimulation and task performance.

Keywords: Anodal direct current; Primary motor cortex; Reaction time; Transcranial direct current stimulation

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1. Introduction

The primary motor cortex is the effector link of a brain network responsible for voluntary motor activities (Shadmehr and Krakauer, 2008; Shenoy et al., 2013). Experimental motor tasks are used to evaluate different aspects of human movement with regard to motor cortex contribution. Simple reaction time tasks are useful tools to evaluate relatively elementary motor processes by go/no-go response procedures (Miller and Low, 2001; Niemi and Näätänen, 1981). Given that motor activities are accompanied by enhanced motor cortex activity, state-dependent alterations of excitability should have a specific effect on reaction time task performance.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which induces respective alterations of cortical excitability (Nitsche and Paulus, 2000, 2001, 2011; Nitsche et al., 2002, 2003a, 2005; Priori et al., 2009; Stagg and Nitsche, 2011). The primary effect of tDCS is an alteration of neuronal resting membrane potentials. Long-term potentiation and depression-like excitability alterations are accomplished by prolonged stimulation (Nitsche and Paulus, 2001, 2011; Nitsche et al., 2003a,b; Nitsche et al., 2005; Stagg et al., 2009). Respective excitability alterations have been shown to modify motor performance ranging from simple reaction time tasks to motor skill learning (Antal et al., 2004; Nitsche et al., 2003c; Reis et al., 2009; Wade and Hammond, 2015).

Since the neurophysiological effects of motor cortex tDCS can remain for a considerable period after stimulation (Nitsche and Paulus, 2000, 2001), also the impact on motor performance might outlast the stimulation itself. For motor learning processes,

in which long term potentiation (LTP) plays a critical role, some studies have shown tDCS effects on implicit motor learning when stimulation was applied during task performance (Nitsche et al., 2003c; Savic and Meier, 2016). When the effect of anodal and cathodal tDCS on motor performance was tested by applying stimulation either during or before task performance, faster learning was found by anodal tDCS only when stimulation was applied during task performance (Stagg et al., 2011). Interestingly, slower performance in a simple cognitive task (the Flanker task) was reported when prefrontal cortex cathodal tDCS (compared with sham) was applied during, but not before, task performance (Nozari et al., 2014). However, in simple reaction time tasks, where LTP should play no significant role and simple alterations of excitability might suffice to alter performance, the effect of stimulation on reaction time might be less affected by online/offline timing of stimulation in relation to task performance. In accordance, cathodal tDCS applied before motor performance increased reaction time, whereas anodal tDCS reduced it (Leite et al., 2011). Therefore, for relatively simple reaction time tasks, also tDCS applied before performance may induce functional alterations. However, the critical time interval until which tDCS is able to elicit such functional changes if applied before task performance has not been systematically explored.

The aim of this study was to compare the effect of left motor cortex anodal tDCS on performance of a simple reaction time task conducted 0, 30 or 60 min after tDCS in dexterous subjects to evaluate the post-stimulation time-interval dependent effects of neuromodulation on motor performance.

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2. Materials and methods

2.1. Participants

Sixty right-handed volunteers, 31 women and 29 men (mean age = 25.9 ± 3.03 years), participated in the study. All subjects were healthy and without evidence for neurological or psychiatric disorders and none of them was under central nervous system-active medication. Each participant was instructed to avoid alcohol and caffeine during the day of the experiment. Subjects provided written informed consent prior to participation. The Ethics Committee of the University of Huelva approved the experimental procedures. The study complies with the principles of the World Medical Association Declaration of Helsinki.

2.2. Procedure

2.2.1. tDCS

Anodal stimulation over the primary motor cortex (M1) was delivered by a battery driven constant-current stimulator (TCT Research tDCS Stimulator, TST Kowloon, Hong Kong) with conductive rubber electrodes, which were placed between two saline soaked sponges. The anode electrode was placed over C3 (representing M1) according to the 10-20 EEG international system for electrode placement (Herwig et al., 2003; Klem et al., 1999), and stimulation was applied for 15 min by a 5 × 5 saline soaked sponge electrode (25 cm^2) at 1.5 mA. Stimulation was gradually ramped up and down for 10 sec at the beginning and the end of stimulation, respectively. The cathode return

electrode (5 × 7 cm; 35 cm²) was placed over the right supraorbital ridge (Fp2 according to the 10-20 EEG international system). The electrodes were fixed onto the head by a tDCS headstrap (CMUS1209, Caputron Universal Strap, USA). For sham tDCS, current was increased and then decreased over 10 sec at the beginning and end of the session, respectively, to ensure some tingling sensation typical for real tDCS, but avoid after-effects of stimulation. Subjects were blinded for tDCS conditions. Long lasting excitability alterations of the motor cortex of about 1 hour duration have been observed with similar tDCS protocols applied over the primary motor cortex (Jamil et al., 2017; Nitsche and Paulus, 2001).

2.2.2. Simple reaction time task

In the present study, subjects performed a simple reaction time task in front of a computer screen (19') located at about 50 cm eye distance. A go/no-go response task was performed. Four different geometric shapes of approximately 15 cm² size (a blue circle, a yellow square, a green triangle and a red diamond) were randomly displayed at the center of the computer screen for 3000 ms. The task included 100 presentations in five blocks of 20. The inter-stimulus interval was set to 2000 ms. The green triangle and the red diamond were displayed in the first 20 presentations (first block) to accustom the participants with the experimental procedure. Feedback on performance was available only in this block. In the remaining four blocks (test blocks), the blue circle and yellow square were displayed. Subjects were instructed to respond as fast as possible only to the target stimulus (the specific shape/color) indicated on the screen at

the start of each block by pressing the space bar on the computer keyboard and ignore the other stimulus. The target stimulus was randomized between blocks. The duration of the whole task did not exceed 9 min. The time interval between the onset of the target and the response (reaction time) was recorded. Omission (no response) and commission (wrong response) errors were also recorded. Outlier values of reaction time for the correct responses and reaction time for errors were not analyzed. Figure 1 depicts the experimental characteristics of the simple reaction time task used.

FIGURE 1 APPROXIMATELY HERE, PLEASE

2.3. Design

A sham-controlled double-blinded randomized design was used. Participants were randomly assigned to one of six groups: A0, anodal tDCS-task performance interval 0 min (n = 10); S0, sham tDCS-task performance interval 0 min (n = 10); A30, anodal tDCS-task performance interval 30 min (n = 10); S30, sham tDCS-task performance interval 30 min (n = 10); A60, anodal tDCS-task performance interval 60 min (n = 10); S60, sham tDCS-task performance interval 60 min (n = 10). All subjects received anodal or sham stimulation for 15 min as described above, and 0, 30 or 60 min after the end of the tDCS session they completed the first 20 trials (practice block with the green triangle or red diamond shapes and feedback on performance) and then the following four blocks of the simple reaction time task (test blocks with two different shapes to those of the first block and without feedback). Subjects of the A/S30 and A/S60 groups

remained at rest for 30 or 60 min post-stimulation respectively in an adjacent waiting room, and performed the simple reaction time task after the respective time interval. Neither the subjects nor the researchers were aware of the tDCS condition. A third person was programming the stimulation condition (anodal vs. sham) for each subject in randomized and counterbalanced order according to the study groups. An offline analysis of the reaction time data for each block of the task was performed. Figure 2 represents the experimental procedure.

FIGURE 2 APPROXIMATELY HERE, PLEASE

2.4. Statistics

A 2 × 3 × 4 repeated-measures ANOVA, with two between-subjects factors, the first being the stimulation condition (anodal vs. sham) and the second factor being the time interval between the completion of tDCS and task performance (performance at 0, 30 or 60 min post-stimulation), was conducted to analyze the mean reaction time of each group for the four test blocks of the task (within-subjects factor). The time interval between the onset of the target and the response, that is, the reaction time, served as the dependent variable. When the respective interactions were significant, LSD post-hoc t-tests were applied to analyze the differences. A one-way ANOVA was conducted to analyze the average reaction time of each of the six groups in the set of the four test blocks of the task. The critical level of significance for reaction time differences in all tests was set to $p < 0.05$. Percentages of errors were calculated. Outlier values of

reaction time for the correct responses (i.e. less than 200 ms and more than 2000 ms) and reaction time for errors were excluded from analysis. The analyses were carried out using SPSS software.

3. Results

None of the participants reported serious adverse effects during or after the application of tDCS. Tingling sensations were reported more frequently in the group with anodal stimulation. Participants under sham stimulation reported tingling sensations only at the beginning and/or the end of the tDCS session. In this group, the correct estimate of the stimulation condition was not higher than a random estimate. In the anodal group, the estimate of anodal stimulation was moderately higher than that of sham stimulation (57.19%). A univariate analysis by the chi-square test revealed no significant differences between observed and expected percentages of correct identification of the stimulation condition ($p = 0.15$). An ANOVA of the reaction times in the initial block of stimuli (practice block preceding the four test blocks) conducted to evaluate baseline performance revealed no significant differences between groups ($F[5,59] = 0.73$; $p = 0.31$). The percentages of omission and commission errors were not significantly different between groups ($p = 0.071$ and $p = 0.051$, respectively).

Table 1 shows the results of the ANOVAs conducted to analyze differences between groups in each of the four test blocks of the task and in the set of the test blocks.

TABLE 1 APPROXIMATELY HERE, PLEASE

FIGURE 3 APPROXIMATELY HERE, PLEASE

The repeated-measures ANOVA for reaction time of the four test blocks reveals a significant effect of the factor block (F[3,54] = 7.615; $p < 0.001$), which indicates that the overall mean reaction time was different between blocks. This is a typical effect found in simple reaction time tasks when stimuli are displayed in different blocks of presentation. There also was a significant effect of the factor stimulation (F[1,54] = 22.446; $p < 0.001$) and the interaction between stimulation and time interval (F[2,54] = 4.836; $p = 0.012$). Post-hoc tests revealed that the mean reaction time of the A0 group was significantly lower than that of the S0 group in the first ($p < 0.001$), second ($p < 0.001$), third ($p < 0.001$) and fourth ($p = 0.001$) block of the task. The mean reaction time of the A30 and A60 groups was significantly lower than that of the S0 group in the first ($p = 0.006$ and $p = 0.002$, respectively), second ($p = 0.002$ and $p < 0.001$, respectively), third ($p = 0.001$ and $p < 0.001$, respectively) and fourth ($p = 0.017$ and $p = 0.007$, respectively) block of the task. The mean reaction time of the A30 group was significantly lower than that of the S30 group only in the fourth block of the task ($p = 0.046$), and was higher than that of the A0 group in the first ($p = 0.001$), second ($p = 0.001$), third ($p = 0.002$) and fourth block ($p = 0.005$).

The mean reaction time of the S0 group was significantly higher than that of the S60 group in the first ($p = 0.006$), second ($p = 0.006$) and third ($p = 0.023$) block. The mean reaction time of the S30 group was significantly higher than that of the A60 group

in the second ($p = 0.022$) and third ($p = 0.037$) block. Finally, the mean reaction time of the A0 group was significantly lower than that of the S60 group in the third ($p = 0.006$) and fourth ($p = 0.030$) block of the task. No other significant differences were found.

The one-way ANOVA of the reaction times for the compound set of the four test blocks indicate a significant effect of the factor group ($F[5,59] = 6.732$; $p < 0.001$). Post hoc comparisons revealed that the average reaction time of the A0 group was lower than that of the S0 ($p < 0.001$), S30 ($p = 0.001$) and S60 ($p = 0.013$) groups. The average reaction time of the S0 group was higher than that of the A30 ($p = 0.002$), A60 ($p < 0.001$) and S60 ($p = 0.01$) groups.

Taken together, these findings reveal that anodal tDCS reduced the mean reaction time in each of the four test blocks and the average reaction time in the compound set of the four test blocks, compared to sham stimulation, only when the task was performed immediately after stimulation. Anodal stimulation also reduced mean reaction time when the task was performed 30 min after stimulation, but this effect was only significant in the last test block. No significant differences between anodal and sham groups were found when the task was performed one hour after stimulation.

4. Discussion

The results show that the tDCS protocol applied in the present study reduces mean reaction time in the test blocks of a simple reaction time task performed immediately after stimulation, when compared to sham stimulation. In contrast, anodal tDCS applied 60 min before the task had no effect on mean reaction times. For the intermediate time

interval of 30 min post-stimulation, the effect of anodal tDCS on reaction times was relatively minor. A reduction of reaction time was only observed in one test block of the task. Thus, the effects of anodal tDCS seem to critically depend on the specific time interval between stimulation and task performance.

It has been shown that the excitability-altering effects of motor cortex tDCS can remain for several minutes after the end of stimulation, depending on stimulation duration (Nitsche and Paulus, 2000, 2001). However, the functional effects of tDCS on motor performance and coordination so far have been tested primarily during stimulation (Cuypers et al., 2013; Foerster et al., 2013; Leenus et al., 2015; Nitsche et al., 2003c; Pavlova et al., 2014) or immediately thereafter (Drummond et al., 2017; Leite et al., 2011). Systematic knowledge about the interval between stimulation and task performance which still results in behavioral consequences was however missing so far. Therefore, in the present study we explored the behavioral effect of motor cortex anodal tDCS applied immediately vs. 30 and 60 min before performance of a simple reaction time task.

The results are principally compatible with the modulatory after-effects of tDCS on motor cortex excitability (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a; Nitsche et al., 2005; Stagg et al., 2011; Ziemann et al., 2008), and in accordance with previous reaction time experiments (Leite et al., 2011). Because tDCS-induced alterations of cortical excitability with similar stimulation durations can last for more than one hour (Nitsche] Paulus 2001), functional effects might have also been expected after an interval of one hour post-stimulation. Considering that anodal stimulation had a minor effect, when performance was evaluated after an interval of 30 min, it seems that

the functional effects of tDCS on the task are weakened with the passage of time, probably according to the time course of cortical excitability alterations. Thus, the time of clearest performance improvement is consistent with the maximum excitability enhancement immediately after tDCS, which then gradually declines. To substantiate this hypothesis, it would be important to combine reaction time recordings directly with physiological measures in the same participanta to explore the relation between task performance and cortical excitability in larger detail.

Some limitations of this study should be considered. No cathodal stimulation was applied in this study, which limits the scope of the conclusions. Cathodal tDCS can interfere with different cognitive processes (Javadi and Walsh, 2012; Nozari et al., 2014), motor performance (Convento et al., 2014) and reaction time task performance (Carlsen et al., 2015). Moreover, inclusion of this stimulation condition in this study would have reduced the at least theoretical possibility of unspecific effects, which are however improbable, given that subjects could not reliably discern between real and sham stimulation, and stimulation was not performed simultaneously with task performance. Moreover, inclusion of a larger sample size could have further strengthened the conclusions. Given the variability of stimulation effects, it is unclear of the exact time course of tDCS effects on reaction time transfers exactly to other groups of participants. It could also be of interest to compare stimulation before and during performance directly in order to elucidate the most effective tDCS procedure to improve reaction time in future studies.

4.1. Conclusions

The impact of anodal tDCS applied before performance of a simple reaction time task critically depends on the interval between stimulation and task performance. tDCS applied immediately before a reaction time task improved motor performance. When the same task was performed 30 or 60 min after stimulation, minor or no effects emerged.

Since tDCS is currently being used as a therapeutic tool for the treatment of mental (Sabella, 2014; Shin et al., 2015; Tortella et al., 2015) and neurological (Fregni et al., 2015; Giordano et al., 2017) pathologies with different degrees of effectiveness, knowledge of the duration of the functional after-effects and the potential effect of cortical stabilization after multiple sessions of tDCS are relevant targets in the field of non-invasive neuromodulation for clinical purposes.

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FIGURE LEGENDS

Figure 1. Simple reaction time task description. The direction of the arrows represents that the specific target in each block (green triangle or red diamond for the first block, and blue circle or yellow square for the remaining four blocks) was displayed in randomized order. Task duration was about 9 min.

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Figure 2. Experimental procedure and time course of the experiment for each group. The reaction time task (RT task) was conducted immediately, 30 min or 60 min after tDCS. A0, primary motor cortex (M1) anodal tDCS-task performance interval 0 min; S0, M1 sham tDCS-task performance interval 0 min; A30, M1 anodal tDCS-task performance interval 30 min; S30, M1 sham tDCS-task performance interval 30 min; A60, M1 anodal tDCS-task performance interval 60 min; S60, M1 sham tDCS-task performance interval 60 min.

Figure 3. Mean scores of the reaction time of each group (+/- standard deviation) for each block of the task. A, B and C show the mean reaction time of the anodal vs. sham groups for each of the three different post-stimulation time intervals (0, 30 and 60 min), respectively. B1-B4, blocks 1-4. *$p < 0.05$. The mean reaction time of the sham group in the task performed immediately after stimulation was significantly higher than that of the anodal group in each of the blocks. However, the mean reaction time of the sham group was significantly higher compared to the anodal group only in the fourth block when the task was performed 30 min after stimulation, and was not different from that of the anodal group in any of the blocks when the task was performed one hour after stimulation. D represents the average reaction time of each of the six groups in the compound set of the four blocks of the task. The average reaction time of the anodal group at 0 min was lower than that of all sham groups (*$p < 0.05$). The average reaction time of the anodal groups at 30 and 60 min was lower than that of the sham group at 0 min (**$p < 0.05$), which was in turn higher than that of the sham group at 60 min (***$p < 0.05$).