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

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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 determine the efficacy of tDCS to modulate performance. The aim of this study was to compare the effects of a single session of anodal tDCS (1.5 mA, for 15 min) applied over the left primary motor cortex (M1) versus sham stimulation 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. Performance zero min after anodal tDCS was improved during the whole course of the task. Performance 30 min after anodal tDCS was improved only in the last block of the reaction-time task. Performance 60 min after anodal tDCS was not significantly different throughout the entire 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

The primary motor cortex is the effector link of a brain network responsible for voluntary motor activities (Shadmehr & Krakauer, 2008; Shenoy, Sahani, & Churchland, 2013). Experimental motor tasks are used to evaluate different aspects of human movement with regard to motor cortex contribution. Simple reaction-time (RT) tasks are useful tools to evaluate relatively elementary motor processes by go/no-go response procedures (Miller & Low, 2001; Niemi &

Näätänen, 1981). Given that motor activities are accompanied by enhanced motor cortex activity, state-dependent alterations of excitability should have a specific effect on RT task performance.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that induces respective alterations of cortical excitability (Nitsche et al., 2003a; Nitsche, Liebetanz, Tergau, & Paulus, 2002; Nitsche & Paulus, 2000, 2001, 2011; Nitsche et al., 2005; Priori, Hallett, & Rothwell, 2009; Stagg & 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 et al., 2003a, b; Nitsche & Paulus, 2001, 2011; Nitsche et al., 2005; Stagg et al., 2009). Respective excitability alterations have been shown to modify motor performance ranging from simple RT tasks to motor skill learning (Antal et al., 2004; Nitsche, Schauenburg, et al., 2003; Reis et al., 2009; Wade & Hammond, 2015).

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,

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Cuypers, Vanvlijmen, & Meesen, 2015; Nitsche, Schauenburg, et al., 2003; Pavlova, Kuo, Nitsche, & Borg, 2014) or immediately thereafter (Drummond, Hayduk-Costa, Leguerrier, & Carlsen, 2017; Leite, Carvalho, Fregni, & Gonçalves, 2011). Since the neurophysiological effects of motor cortex tDCS can remain for a considerable period after stimulation (Nitsche & Paulus, 2000, 2001), also the impact on motor performance might outlast the stimulation itself. TDCS influences both motor learning (Nitsche, Schauenburg, et al., 2003; Savic & Meier, 2016) and performance of simple motor and cognitive tasks (Nozari, Woodard, & Thompson-Schill, 2014) when stimulation is applied during task execution. However, for relatively simple RT tasks, tDCS applied before performance may also induce functional alterations (Devanathan & Madhavan, 2016; Müller, Orosz, Treszl, Schmid, Sperner, 2008). In accordance, in a motor set-shifting task, in which one of two motor responses was correct in each trial, cathodal tDCS conducted before performance slowed motor RTs (Leite et al., 2011).

TDCS-generated neuroplasticity is thought to enhance learning-related plasticity (LTP) when task performance and stimulation are conducted simultaneously. Indeed, LTP-like plasticity-inducing tDCS improved motor learning when stimulation was applied during task performance (Nitsche, Schauenburg, et al., 2003; Savic & 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). Thus, task-related LTP-like plasticity in combination with tDCS may play a critical role during motor learning for performance improvement. The mechanism might be conjoint activation of task-relevant neurons via task performance and tDCS, if applied simultaneously, which will make it easier for the respective neuronal connections to cross the threshold for plasticity induction. Application of tDCS before motor learning will, however, result in already stimulation-induced plasticity before performance, which might lead to mixed effects on different synapses, including homeostatic processes. Consequently, tDCS might, in this case, induce plasticity of non-task-related synapses, which might reduce or abolish learning-related performance improvements. In simple RT tasks, however, plasticity is suggested not to play a major role, because no new sequences, movements, or other specific task aspects have to be learned to a relevant degree. Here, independent from its plasticity-strengthening effects, intervention-dependent alterations of cortical activity and excitability, during and after tDCS, might suffice to modify performance (Antal, Ambrus, & Chaieb, 2014). As a consequence, the effect of stimulation on RT might be less affected by online/off-line timing of stimulation, in relation to task performance—that is, if the stimulation is applied during task execution (online) or before (off-line). In these simple tasks,

the time interval between stimulation and task execution should then primarily determine the results (Carlsen, Eagles, & MacKinnon, 2015; Filmer, Mattingley, & Dux, 2013). However, the critical time interval until which tDCS is able to elicit motor 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 go/no-go simple RT task conducted 0, 30 or 60 min after tDCS in dexterous subjects to evaluate the poststimulation time-interval-dependent effects of neuromodulation on motor performance. If performance in simple RT tasks is improved by previous application of tDCS, in accordance with the duration of the aftereffects of tDCS on cortical excitability (Nitsche & Paulus, 2000, 2001), a reduction of the mean RT would be expected after anodal tDCS, at least in the first poststimulation time intervals.

Since tDCS is currently being used as a therapeutic tool for the treatment of mental (Kuo, Paulus, & Nitsche, 2014; Lefaucheur, 2016; Lefaucheur et al., 2017; Sabella, 2014; Shin, Foerster, & Nitsche, 2015; Tortella et al., 2015) and neurological (Flöel, 2014; Fregni et al., 2015; Giordano et al., 2017; Lefaucheur, 2016; Lefaucheur et al., 2017) pathologies with different degrees of effectiveness, knowledge of the duration of the functional aftereffects and the potential effect of cortical stabilization after multiple sessions of tDCS may also be relevant for clinical purposes.

Method

Participants

Sixty right-handed volunteers, 31 women and 29 men (mean age = 25.9 ± 3.03 years), participated in the study. Sample size was determined based on previous studies about the effect of tDCS on RT tasks (Drummond et al., 2017; Verissimo, Barradas, Santos, Miranda, & Ferreira, 2016). All subjects were healthy and without evidence of 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 code of Ethics of the World Medical Association Declaration of Helsinki.

Procedure

tDCS

Anodal stimulation over the primary motor cortex (M1) was delivered by a battery-driven constant-current

stimulator (TCT Research Ltd tDCS Stimulator, TST Kowloon, Hong Kong) (Brennan et al., 2017; Wexler, 2015) with conductive rubber electrodes that 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, Satrapi, & Schonfeldt-Lecuona, 2003; Klem, Lüders, Jasper, & Elger, 1999). The cathode return electrode 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 head strap (CMUS1209, Caputron Universal Strap, USA). The size of the anode and cathode electrodes was 5 × 5 cm (25 cm^2) and 5 × 7 cm (35 cm^2), respectively. Stimulation was applied for 15 min at an intensity of 1.5 mA. Stimulation was gradually ramped up and down for 10 s at the beginning and the end of stimulation, respectively. For sham tDCS at 1.5 mA, current was increased and then decreased over 10 s at the beginning and end of the session, respectively, to ensure some tingling sensation, typical for real tDCS, but avoiding after-effects of stimulation. 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 & Paulus, 2001). Subjects were blinded for tDCS conditions, and after task conduction they were asked about the stimulation condition to probe successful blinding.

Simple RT task

In the present study, subjects performed a simple RT task in front of a computer screen (19-in.) located at about 50 cm from eye distance. A go/no-go response task was performed. Two different geometric shapes of approximately 15 cm^2 size (a blue circle and a yellow square or a green triangle and a red diamond) were randomly displayed at the center of the computer screen for 3,000 ms. 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 to ignore the other stimulus. The task included a total of 100 trials distributed in five blocks of 20 trials each. The interstimulus interval was set at 2,000 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 about performance was available only in this block. In the remaining four blocks (test blocks), the blue circle and yellow square were displayed. 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, that is, the RT, was recorded. Omission (i.e., no response in a trial that required a response) and commission (i.e., response in a trial that required no response) errors were also recorded. Figure 1 depicts the experimental characteristics of the simple RT task used.

Experimental 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 zero min ($n = 10$); S0, sham tDCS-task performance interval zero 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 ($n = 10$). Zero, 30, or 60 min after the end of the tDCS session, subjects completed the first 20 trials and then the following four blocks of the simple RT task. Subjects of the A/S30 and A/S60 groups remained at rest for 30 or 60 min poststimulation, respectively, in an adjacent waiting room, and performed the simple RT task after the respective time interval. Figure 2 represents the experimental procedure.
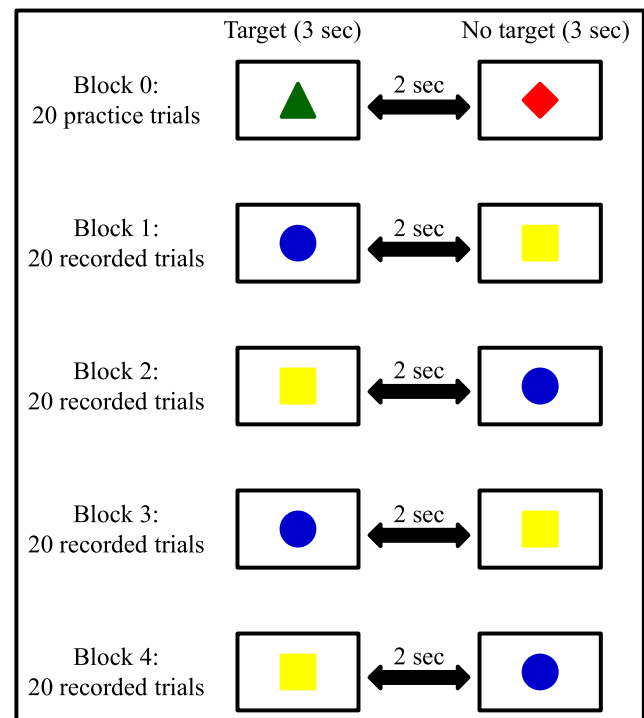

Fig. 1 Simple RT task description. The direction of the arrows represents that the specific target in each block (green triangle or red diamond for the practice block, and blue circle or yellow square for the remaining four blocks) was displayed in randomized order for 2 seconds. Task duration was about 9 min. (Color figure online)
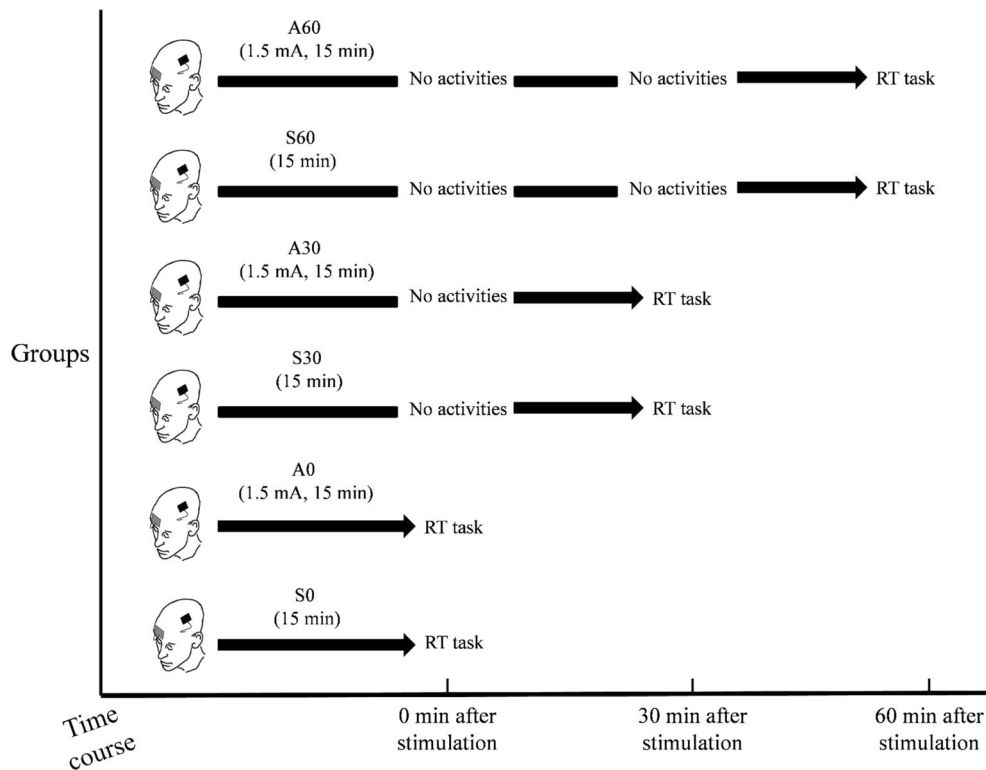
Fig. 2 Experimental procedure and time course of the experiment for each group. The reaction time task (RT task) was conducted immediately, 30 min or 60 min after tDCS. A0 = primary motor cortex (M1) anodal tDCS-task performance interval zero min; S0 = M1 sham

tDCS-task performance interval zero 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

Data analysis

A mixed-model $2 \times 3 \times 4$ 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 poststimulation), was conducted to analyze the mean RT 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 RT, served as the dependent variable. When the respective interactions were significant, LSD post hoc tests were applied to analyze the differences. Only RTs for correct responses were included in the main analysis. For incorrect responses, percentages of errors were calculated for the set of the task and differences were analyzed by Student's t tests. An univariate analysis by the chi-square test was conducted to analyze possible differences in percentages of correct identification of the tDCS condition (anodal vs. sham). A 2×3 ANOVA was conducted to analyze the mean RT of each group in the practice block of the task. The critical level of significance for RT differences in all tests was set to $p < .05$. The analyses were carried out using SPSS software. TDCS responders in each poststimulation time interval were identified in relation to the mean RT of the respective sham groups (assuming that these measures are a

reference of performance without an effect of intervention). Percentage of performance improvement under real tDCS refers also to the mean RT of the sham tDCS control group.

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, $\chi^2(1, N = 60)$, revealed no significant differences between observed and expected percentages of correct identification of the stimulation condition ($p = .15$). An ANOVA of the RTs in the initial block of stimuli (practice block preceding the four test blocks) conducted to evaluate baseline performance revealed no significant differences between groups, $F(5, 59) = 0.73$, $p = .31$, $\eta_p^2 = .03$. Results of the respective Student's t tests indicate that the percentages of omission and commission errors in the set of the task were not

Table 1 Results of the main ANOVA

	df	F value	p value	η_p^2	Statistical power $(1 - \beta)$
2 × 3 × 4 ANOVA					
Stimulation	1	22.446	<.001*	.294	.996
Time interval	2	0.771	.468	.028	.174
Block	3	7.615	<.001*	.124	.986
Stimulation × Time Interval	2	4.836	.012*	.152	.778
Time Interval × Block	6	0.415	.868	.015	.169
Stimulation × Block	3	0.444	.722	.008	.1389
Stimulation × Time Interval × Block	6	1.716	.120	.060	.639

Note. A mixed three-way ANOVA (stimulation condition vs. time interval vs. block) was calculated to analyze the mean reaction time of each group for the four blocks of the task. *$p < .05$. df = degrees of freedom

significantly different between groups ($p = .071$ and $p = .051$, 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. Table 2 shows the mean RTs for each block and stimulation condition and the demographic characteristics of participants in each group. Figure 3 shows the mean scores of the RT of each group for each block of the task and each post-tDCS time interval.

The mixed repeated-measures ANOVA for RT of the four test blocks reveals a significant effect of the factor block, $F(3, 54) = 7.615$, $p < .001$, $\eta_p^2 = .124$, which indicates that the overall mean RT was different between blocks. This is a typical effect found in simple RT tasks when stimuli are displayed in different blocks of presentation. There also was a significant effect of the factor stimulation, $F(1, 54) = 22.446$, $p < .001$, $\eta_p^2 = .294$, and the interaction between stimulation and time

Table 2 Mean RT in milliseconds for each block and group

	B1	B2	B3	B4
zero min (ma = 25.00 ± 2.92)				
Sham (4w, 6m)	498.40	465.01	481.30	458.54
Anodal (5w, 5m)	379.01	334.97	341.43	331.72
45%w, 55%m				
30 min (ma = 27.90 ± 3.26)				
Sham (5w, 5m)	474.45	433.06	429.70	446.16
Anodal (6w, 4m)	412.61	383.38	388.68	373.83
55%w, 45%m				
60 min (ma = 24.80 ± 2.90)				
Sham (5w, 5m)	459.58	399.57	427.33	408.48
Anodal (6w, 4m)	398.76	360.66	398.68	366.03
55%w, 45%m				

Note. Percentages of women/men and mean age ± standard deviation are shown in each group (gender percentages and mean age were not different between the groups, $p > .05$). B1–4 = Blocks 1 to 4; w = women; m = men; ma = mean age ± standard deviation

interval, $F(2, 54) = 4.836$, $p = .012$, $\eta_p^2 = .152$. Post hoc tests revealed that the mean RT of the A0 group was significantly lower than that of the S0 group in the first ($p < .001$), second ($p < .001$), third ($p < .001$), and fourth ($p = .001$) block of the task. The mean RT of the A30 group was significantly lower than that of S30 group only in the fourth block of the task ($p = .046$). The mean RT of the A60 group was not significantly different from that of the S60 group in any of the four blocks ($p = .740$, $p = .248$, $p = .098$, and $p = .177$, respectively).

Considering previous studies on motor cortex excitability in which responders to anodal tDCS were estimated via analysis of motor evoked potentials variability (Tremblay et al., 2016), an estimation of responders to anodal tDCS was here calculated with respect to the mean RT of the respective sham control group. In the zero-min poststimulation time interval, the estimate of responders to anodal tDCS showed that the RT of two participants (20%) was 35% faster as compared to the mean RT of the sham group (475.81 ms), and the RT of seven participants (70%) was 30% faster as compared to the mean RT of the sham group. The participant of the anodal group who did not reach the 30% of reduction of RT had a RT that was 28% faster than the mean RT of the sham group. In the 30-min poststimulation time interval, the estimate of responders revealed that the RT of two participants (20%) was 20% faster as compared to the mean RT of the sham group (445.85 ms), and the RT of five participants (50%) was 10% faster. In the 60-min poststimulation time interval, the RT of three participants (30%) was 20% faster as compared to the mean RT of the sham group (423.74 ms), and the RT of three participants (30%) was 10% faster.

Discussion

The results show that the tDCS protocol applied in the present study reduces mean RT in the test blocks of a simple RT task performed immediately after stimulation, when compared to sham stimulation. In contrast, anodal tDCS applied 60 min
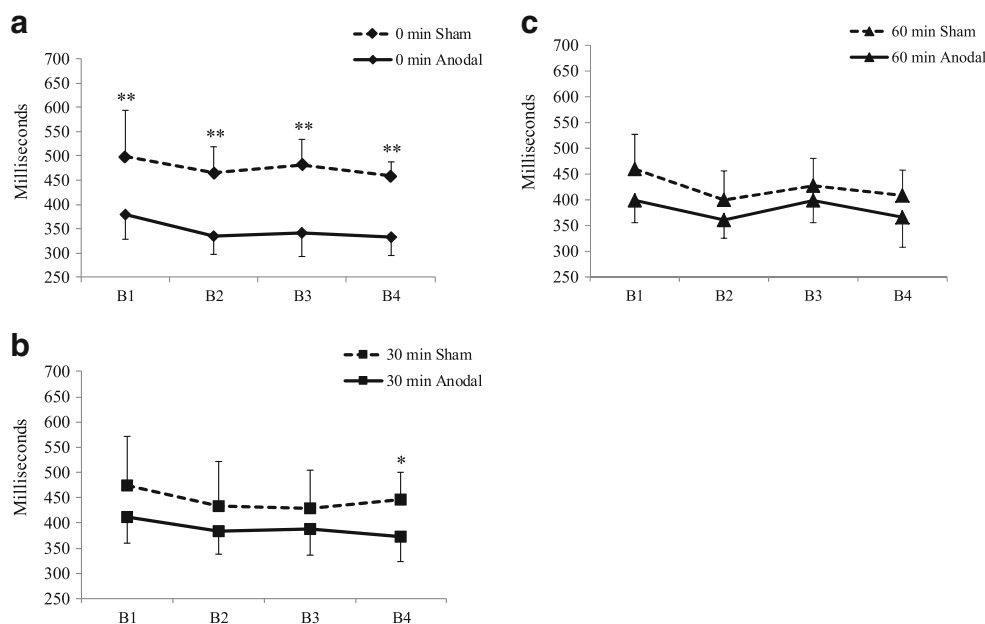
Fig. 3 Mean scores of the RT of each group (± standard deviation) for each block of the task. **a**, **b**, and **c** show the mean RT of the anodal versus sham groups for each of the three different poststimulation time intervals (0, 30, and 60 min), respectively. B1–B4 = Blocks 1–4. (******) and (*****) = significant differences between tDCS conditions at zero min ($p < .01$) and 30 min ($p < .05$) poststimulation, respectively

before the task had no effect on mean RTs. For the intermediate time interval of 30 min poststimulation, the effect of anodal tDCS on RTs was relatively minor. A reduction of RT 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. All effect sizes were above 0.12, and statistical power was above or near to 0.8, which indicates large-to-medium effect size and high-to-moderate power of the results.

The results are principally compatible with the modulatory after-effects of tDCS on motor cortex excitability (Nitsche et al., 2003a; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2005; Stagg et al., 2011; Ziemann et al., 2008), and in accordance with previous RT experiments (Leite et al., 2011). Because tDCS-induced alterations of cortical excitability with similar stimulation durations can last for more than 1 hour (Nitsche & Paulus, 2001), functional effects might have also been expected after an interval of 1 hour poststimulation. 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 RT recordings directly with physiological measures in the same participants to explore the relation between task performance and cortical excitability in larger detail. Also, given the interindividual variability of

stimulation effects, it remains unclear if the exact time course of tDCS effects on RT transfers exactly to other groups of participants. It could be of further interest to compare stimulation before and during performance directly in order to identify the most effective tDCS procedure to improve RT in future studies.

Significant physiological interindividual differences have been reported in relation to the application of tDCS but also to other neuromodulatory noninvasive brain stimulation tools. Such differences may have a relevant influence on the results when tDCS effects on motor RT are evaluated. Interindividual differences in the cortical physiological responsivity to the application of tDCS have been shown after anodal stimulation over the motor cortex (Jamil et al., 2017; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014; Strube, Bunse, Malchow, & Hasan, 2015; Wiethoff, Hamada, & Rothwell, 2014). These might at least partially be based on interindividual differences of the electric fields generated in the hand motor area by motor cortex tDCS (Laakso, Tanaka, Koyama, De Santis, & Hirata, 2015). In the present study, tDCS was applied over the motor cortex, and therefore the results may have been influenced by such physiological interindividual differences. The standard deviation of mean RT was however in no case larger than 100 ms, which is a common standard deviation in RT tasks. In addition, in the zero-min poststimulation time interval, the estimate of responders to anodal tDCS revealed that 20%, 70%, and 10% of participants had a 35%, 30%, and 28% reduction in RT, respectively, with respect to the mean reaction time of the sham group. Thus, while the size of the effects showed

some interindividual heterogeneity, directionality was quite uniform.

The results of the present study are in principle accordance with those of others, which showed an impact of tDCS on RT tasks. For example, when RT was evaluated before and after 10 min of tDCS application, faster RTs were found after stimulation (Drummond et al., 2017). Other studies showed a similar impact of tDCS on motor performance in RT tasks (Müller et al., 2008; Nitsche, Schauenburg, et al., 2003). A recently published study reported however that neither anodal nor cathodal tDCS applied over the motor cortex affected performance in a simple visual motor RT task (Horvath, Carter, & Forte, 2016). Two specific aspects of that study might have prevented respective effects. First, baseline performance was relatively fast before intervention due to training effects, which might have led to ceiling effects. Second, timing of stimulation differed relevantly between that and the present study, which might have also an impact on intervention results (Woods et al., 2016).

Some limitations of this study should be considered. No cathodal stimulation over M1 was applied in this study, which limits the scope of the conclusions. Cathodal tDCS can interfere with different cognitive processes (Javadi & Walsh, 2012; Nozari et al., 2014), motor performance (Convento, Bolognini, Fusaro, Lollo, & Vallar, 2014) and RT 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. Another limitation is that the effect of the cathodal electrode positioned over the right supraorbital ridge potentially could have influenced the results. However, the right frontopolar cortex is not known to be involved in simple motor RT task performance. In accordance, in a previous study (Nitsche, Schauenburg, et al., 2003), left premotor cortex anodal stimulation, with the cathode over the right frontopolar cortex, as well as left prefrontal cortex anodal stimulation, also with the cathode over the right frontopolar cortex, did not affect performance with the right hand in a serial reaction-time task for sequences, but also random stimulus orders. This does not, however, absolutely preclude a possible influence of cathodal stimulation over the right supraorbital ridge on task performance. This limitation could be addressed in the future with the inclusion of more tDCS conditions, for example, with extracephalic positions of the cathodal electrode. Finally, modeling studies exploring the electric fields associated with the application of tDCS suggest activation of areas beyond the targeted cortical regions, not only for motor cortex (Laakso et al., 2015; Laakso et al., 2016), but also prefrontal tDCS (Laakso et al., 2016). Therefore, in the present study, it cannot be ruled out completely that a stimulation effect on nontargeted areas influenced the results. Future studies should limit this possible effect of tDCS on adjacent areas to the primary motor cortex (mainly the premotor cortex) with more focal stimulation protocols.

Conclusions

Based on the findings of this study, it can be concluded that the impact of anodal tDCS applied before performance of a go/no-go simple RT task critically depends on the interval between stimulation and task performance. TDCS applied immediately before a RT task improved motor performance. When the same task was performed 30 or 60 min after stimulation, minor or no effects emerged.

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