Does the Longer Application of Anodal-transcranial Direct Current Stimulation Increase Corticomotor Excitability Further? A Pilot Study

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ABSTRACT

Introduction: Anodal transcranial direct current stimulation (a-tDCS) of the primary motor cortex (M1) has been shown to be effective in increasing corticomotor excitability.

Methods: We investigated whether longer applications of a-tDCS coincide with greater increases in corticomotor excitability compared to shorter application of a-tDCS. Ten right-handed healthy participants received one session of a-tDCS (1mA current) with shorter (10 min) and longer (10+10 min) stimulation durations applied to the left M1 of extensor carpi radialis muscle (ECR). Corticomotor excitability following application of a-tDCS was assessed at rest with transcranial magnetic stimulation (TMS) elicited motor evoked potentials (MEP) and compared with baseline data for each participant.

Results: MEP amplitudes were increased following 10 min of a-tDCS by 67% (p = 0.001) with a further increase (32%) after the second 10 min of a-tDCS (p = 0.005). MEP amplitudes remained elevated at 15 min post stimulation compared to baseline values by 65% (p = 0.02).

Discussion: The results demonstrate that longer application of a-tDCS within the recommended safety limits, increases corticomotor excitability with after effects of up to 15 minutes post stimulation.
results in cortical depolarization and increases the size of MEPs in the target muscles of the specific area being stimulated, indicating increased corticomotor excitability (Nitsche & Paulus, 2000, 2001). On the other hand, application of the negative charged electrode (cathode) over M1 (cathodal tDCS, c-tDCS) leads to hyperpolarization and reduces the size of the transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEPs), indicating decreased corticomotor excitability.

The extent of modulatory effects induced by a-tDCS, depends on the current density and duration of its application (Purpura & McMurtry, 1965a; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2008). For example, a series of studies have examined the effects of different durations of a-tDCS on corticomotor excitability indicating a linear relationship between the duration of application and the increase in corticomotor excitability (Nitsche & Paulus, 2000, 2001; Furubayashi et al., 2008). Nitsche and Paulus (2000) reported that when comparing shorter and longer application of a-tDCS (1, 2, 3, 4 and 5 min) there was a linear relationship between the duration of a-tDCS and the increase in corticomotor excitability (Nitsche & Paulus, 2000). In addition, a large number of studies have shown that a-tDCS increases corticomotor excitability that lasts beyond the stimulation period (Purpura & McMurtry, 1965; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2005; Boros et al., 2008; Furubayashi et al., 2008; Nitsche et al., 2008; Utz et al., 2010; Fricke et al., 2011).

The safety of tDCS as a neuromodulatory technique is determined by both the current density which is established by the amplitude (A) per surface area of the stimulating electrode (cm²), and the duration of stimulation (Nitsche et al., 2003b). Experimental data has shown that current densities below 25 mA/cm² are safe and have no detrimental effects on the underlying cerebral tissue (McCreery et al., 1990). In addition, the current density is independent of stimulation duration; therefore identifying the optimal duration of stimulation is important for the safe application of tDCS (Nitsche et al., 2003a).

There are several cross-sectional studies that have used a-tDCS to induce corticomotor excitability; however, no studies to date have used an application duration of more than 13 min in healthy individuals (Nitsche et al., 2005; Boros et al., 2008). Therefore the primary aim of the current study was to compare the effects of shorter (10 min) and longer (10+10 min) durations of a-tDCS on the excitability of M1 for the right extensor carpi radialis muscle (ECR) and to investigate if longer (10+10 min) durations of a-tDCS could be tolerated or not. We hypothesized that longer application (10+10 min) of a-tDCS would induce larger increases in corticomotor excitability compared to shorter application (10 min) and that the application would be well tolerated by participants.

2. Methods

2.1. Participants

Ten healthy volunteers (four males, six females), aged between 20-51 years, (mean age 35.8 ± 8.9 years) participated in this study (Table 1). Participants were recruited from Monash University students or staff. All participants were consistent right-handers according to the 10-item version of the Edinburgh Handedness Inventory (mean laterality index =100) (Oldfield, 1971). Prior to the experiment, all participants completed the Adult Safety Screening Questionnaire to determine their suitability for TMS and tDCS application (Keel et al., 2001). Volunteers with a family history of epilepsy or any other neurological/psychiatric disorders and

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<th>Subject characteristics</th>
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those with metallic implants/implanted electrical devices or pacemakers were excluded. Participants were informed about the experimental procedures and gave their written informed consent according to the declaration of Helsinki. All experimental procedures were approved by the Human Research Ethics Committee of the University.

2.2. Experimental Design

Figure 1 illustrates the one-way within-subjects experimental design used in this study. All recruited individuals participated in one experimental session. Corticomotor excitability of their ECR M1 was measured (using TMS) before the application of a-tDCS (baseline value) and at three time points following a-tDCS, including: immediately post 10 min (post-test 1), immediately post 10+10 min (post-test 2) and 15 min post a-tDCS (follow up).

2.3. Electromyographic (EMG) Recording

Participants were seated in a chair with their forearm pronated and resting on the armrest of a purpose-built chair (Figure 2). MEPs were recorded from the right ECR muscle using Ag/AgCl disposable surface electrodes with an inter-electrode distance of 2 cm. The ground electrode was placed over the styloid process of ipsilateral ulnar bone (Oh, 2003). In order to ensure good surface contact and reduce skin resistance, a standard skin preparation procedure of cleaning and abrad-

Figure 2. Participants were seated in a podiatry chair with their forearm pronated and resting on the armrest of the chair. A) TMS application with a figure of eight magnetic coil placed at 45° angle to the midline and tangential to the scalp for eliciting MEPs over the left M1. EMG was recorded from ECR muscle. Recording and ground electrodes were secured with tape. B) a-tDCS application with the anode electrode placed over the M1 for ECR and the cathode electrode was placed over the contralateral supra orbital area. The electrodes were fixed in place by two custom-designed straps.
ing was performed for each site of electrode placement (Gilmore & Meyers, 1983; Schwartz, 2003). All EMG signals (MEPs) were sampled at 2048 Hz and collected on a PC running commercially-available software PowerLab (ADinstruments, Australia) via a laboratory analogue-digital interface (PowerLab 8/30, ADInstrument, Australia) for later off-line analysis. EMG signals were filtered and amplified (1000×) with bandpass filtering between 20 Hz and 500 Hz and digitized at 1 kHz for 200 ms.

2.4. Measurement of Corticomotor Excitability by TMS

MEPs were evoked by TMS of the contralateral motor area controlling the right ECR using a Magstim 200² (Magstim company limited, UK), with a 70 mm wide figure of 8 magnetic coil. The size of evoked MEPs was considered as a dependent variable to assess changes in corticomotor excitability of M1 in the dominant side prior and following the application of a-tDCS. The optimal stimulation site (hotspot) for evoking MEPs from ECR was determined and marked to ensure accurate positioning of the coil between trials. The orientation of the coil was set at a 45° angle to the midline and tangential to the scalp, so that the induced current flowed in a posterior-anterior direction. Resting motor threshold (RMT) was determined by applying TMS at the optimal M1 site for evoking responses in ECR muscle at rest. RMT was defined as the minimal stimulus intensity that evoked 5 MEPs in a series of 10 with an amplitude of at least 50 µV (Rothwell et al., 1999). Following this, the test intensity was set at 120% of RMT. Twelve stimuli were given to elicit MEPs for the assessment of corticomotor excitability at each time point (see Figure 1).

2.5. Anodal-tDCS of the Primary Motor Cortex

A-tDCS was delivered by an Intelect® Advanced Therapy System (Chattanooga, USA) through a pair of saline-soaked sponge electrodes (42 cm²). The active electrode (anode) was fixed with two straps over the left M1 for the right ECR as identified by TMS, and the indifferent electrode was placed over the right contralateral supra orbital area. The stimulation intensity was set to 1 mA and a-tDCS was applied continuously for 10 min which was repeated following TMS assessment of corticomotor excitability. Therefore, overall, each participant received 20 min (10+10 min) of a-tDCS with a time interval of 3 min between two stimulation periods.

2.6. Data Management and Statistical Analyses

In determining the optimal site, all MEPs collected (n = 12) with 200-millisecond recordings for each condition were displayed and averaged online for visual inspection, and then stored off-line for further analysis.

Figure 3 displays the resting state of muscle prior to stimulation, the stimulus artifact and a typical MEP response. MEP latency was calculated from the stimulus artifact to the first deflection of MEP and the size of MEP amplitude was measured from the maximum peak to the minimum peak of the recorded MEP. Mean and SE of MEP peak-to-peak amplitude (µV) from TMS.
measurements at rest were calculated for the time points of baseline, immediately post-test 1, immediately post-test 2 and follow up.

A one-way within-subjects ANOVA was conducted to compare the effects of short and long durations of a-tDCS on corticomotor excitability at four different time points. Significance was set at $p \leq 0.05$, all results are displayed as means $\pm$ SE and statistical analysis was performed using SPSS software version 19.

3. Results

All participants tolerated the intervention used in this study and all finished the experiments. No side effects other than a mild tingling or itchiness were reported.

The ANOVA indicated that corticomotor excitability increased significantly over time ($F_{3,27} = 20.32, p = 0.000, \eta^2 = 0.69$). Furthermore, a series of pairwise comparisons revealed that the average MEP amplitude confidence level immediately following 10 min of a-tDCS ($M = 220.58 \, \mu V, \, SE = 22.77, \, 95\% \, CI \, [169.09, 272.06], \, p = 0.001$), 10+10 min a-tDCS ($M = 292.63 \, \mu V, \, SE = 31.99, \, 95\% \, CI \, [220.31, 364.95], \, p = 0.005$)
and 15 min following 10+10 min a-tDCS (M = 218.04 μV, SE = 37.59, 95% CI [133.05, 303.02], p = 0.02) was significantly higher than the average MEP amplitude confidence level obtained at baseline (M = 131.93 μV, SE = 16.35, 95% CI [94.96, 168.90] (Figure 4 & 5). Also, the MEP amplitude of ECR showed significant differences between post test 1 and following post test 2 (p = 0.03). Figure 5 indicates that there were no significant differences between 15 min follow up and both of the previous measurements (p > 0.05).

4. Discussion

The purpose of this study was to explore the effects of short duration and long duration of a-tDCS on modulating corticomotor excitability. Both short duration (10 min) and long duration (10+10 min) increased corticomotor excitability by 67% and 122% respectively. Further, there were significant after-effects of a-tDCS application, with corticomotor excitability still elevated 15 min after tDCS stimulation. This suggests several important findings. Foremost, corticomotor excitability was facilitated following a-tDCS with both short and long stimulation periods. Second, long duration a-tDCS elicited further facilitation in corticomotor excitability compared to short duration, showing that duration of stimulation is important for the therapeutic use of a-tDCS. In addition, the application of 10+10 min of a-tDCS using 6×7 cm (42 cm²) electrodes was safe and well tolerated by all participants.

It was hypothesized that short duration (10 min) a-tDCS would facilitate corticomotor excitability and that an additional 10 min would elicit further increases compared to just 10 min of a-tDCS. In the present study we demonstrated a significant increase (67%) in the TMS-evoked MEPs following 10 min a-tDCS when compared to baseline. This finding is in agreement with several other studies that have used stimulation periods of between 5, 7 and 9 min (Nitsche & Paulus, 2000, 2001; Uy & Ridding, 2003; Lang et al., 2004; Nitsche et al., 2005; Fricke et al., 2011). Furthermore, the present finding following short duration of a-tDCS is also in agreement with Lang et al. (2004), Antal et al. (2007) and Furubayashi et al. (2008) who also demonstrated a single session of a-tDCS for 10 min increased corticomotor excitability.

The novel aspect of the current study was the application of an additional 10 min a-tDCS. We hypothesized that longer application (10+10 min) of a-tDCS would induce a larger increase in corticomotor excitability compared to a single 10 min stimulation period. The results are consistent with previous studies that have shown facilitated corticomotor excitability following 13 min of a-tDCS when compared to shorter applications (Nitsche et al., 2005; Boros et al., 2008), showing that longer applications of a-tDCS modulates corticomotor excitability to a greater extent compared to shorter applications.

Although the mechanism of a-tDCS remains largely unknown, the increases in MEP amplitudes observed in the current study are likely to be related to the effects of the direct currents inducing membrane polarization. These effects have been demonstrated in M1 by plasticity-inducing protocols (Nitsche & Paulus, 2000). As such it’s conceivable that the increases in corticomotor excitability shown in the current study may have occurred due to mechanism associated with long-term potentiation. For example, anodal stimulation has been shown to result in neuronal membrane depolarization at the cellular level with increases in intracellular Ca²⁺ levels that increase in corticomotor excitability (Nitsche et al., 2004). The induction of longer stimulation may have resulted in greater shifts in the resting membrane potential, thus modulating enhanced synaptic efficacy (Nitsche & Paulus, 2000).

Longer a-tDCS stimulation has been shown to trigger a membrane potential change that leads to N-methyl-D-aspartate (NMDA) receptor activation and/or more Ca²⁺ influx into neurons (Liebetanz et al., 2002). It is well understood that long-lasting NMDA-receptor dependent cortical excitability and subsequent action potential activity shifts, are involved in neuroplastic modification, such as activity-dependent synaptic plasticity. The larger increase in corticomotor excitability following the longer application of a-tDCS in the present study is most likely due to increased neuronal membrane excitability and/or NMDA receptor efficacy (Liebetanz et al., 2002). Either membrane potential or synaptic mechanisms (increased presynaptic release of excitatory transmitters or an increased postsynaptic Ca²⁺ influx) (Bennett et al., 2000) or both; may explain the larger increase in corticomotor excitability following longer application of a-tDCS. Therefore, we suggest that this longer application of a-tDCS allows time for other processes to develop, involving physiological factors associated with synaptic plasticity; that replaces the smaller size in corticomotor excitability following shorter stimulations.

The present study has also shown significant after-effects of increased corticomotor excitability following a-tDCS. This finding is consistent with a number of studies that have demonstrated enhanced corticomotor
excitability following the application of 1 mA a-tDCS (Nitsche & Paulus, 2001; Hummel & Cohen, 2006; Antal et al., 2007; Boros et al., 2008; Furubayashi et al., 2008). The after effects lasted at least 15 min post stimulation and the amplitude of the TMS evoked MEPs began to decrease nearly 15 min after the offset of a-tDCS, even though it remained higher than the baseline value. Experimental data has previously shown that shorter duration of stimulation of 5 and 7 min, results in after effects that are maintained for no longer than 5 min, and the application of a-tDCS for 9, 11 and 13 min results in elevated MEP amplitudes up to 30, 45 and 90 min, respectively (Nitsche & Paulus, 2001).

It is unlikely that membrane potential change is the only mechanism responsible for modulating the after-effects on increased corticomotor excitability produced by a-tDCS. Lasting effects beyond the stimulation must be explained by other mechanisms, such as adrenergic mechanisms which have been found to be involved in the stabilization of after effects (Nitsche et al., 2004; Nitsche et al., 2005) and must conform to the above speculated mechanism involved in longer a-tDCS application. Although this is a potential mechanism of action, the exact mechanism of action of a-tDCS still remains unclear and these concepts are purely hypothetical at present.

5. Conclusion

In conclusion, we have shown that it is possible to induce greater levels of corticomotor excitability following longer periods of a-tDCS application compared to shorter periods (i.e. 10 min), with these effects remaining elevated at least 15 min after the end of stimulation. Further experiments should explore the presumed physiological mechanisms more directly. In addition, further research is needed using a larger sample size and long-term follow-ups. The results of this study can be useful for increasing corticomotor excitability by repeating a-tDCS application within a session compared to longer applications of a-tDCS which may produce opposite effects (Monte Silva et al., 2011).

Glossary

a-tDCS: Anodal transcranial direct current stimulation
c-tDCS: Cathodal transcranial direct current stimulation
TMS: Transcranial magnetic stimulation
ECR: Extensor carpi radialis
EMG: Electromyography
MEP: Motor evoked potential
M1: Primary motor cortex
NMDA: N-methyl-D-aspartate
RMT: Resting motor threshold

References


