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Timing-dependent priming effects of tDCS on ankle motor skill learning

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Abstract

Transcranial direct current stimulation (tDCS) has gained increasing interest in neurorehabilitation with its ability to modulate cortical excitability, and thereby influence neural plasticity and functional recovery. While the beneficial effects of tDCS on motor learning and function have been recognized, there is no clear consensus regarding the timing of the tDCS priming protocol in relation to the intervention especially with respect to lower limb motor learning. Depending on the time of priming in relation to the training task, the neural mechanisms of priming (gating vs. homeostatic plasticity) are different and thereby subsequently affect motor learning. Hence, the aim of this study was to examine the interaction of tDCS with subsequent vs. concurrent motor learning using an ankle visuomotor skill learning paradigm. Twelve healthy participants were tested under three stimulation conditions: 1) anodal tDCS prior to the motor task (tDCS-before), 2) anodal tDCS during the motor task (tDCS-during) and 3) sham tDCS during the motor task (tDCS-sham). Results revealed that tDCS application *during* practice of a skilled motor task increased motor performance compared to tDCS applied *prior* to motor practice. Both tDCS groups demonstrated enhanced motor learning when tested 24 hours after practice. We conclude that the priming effects of tDCS are timing dependent, and maybe a critical regulatory feature in determining outcomes of priming with tDCS.

Keywords

tDCS; motor skill; ankle; neuroplasticity

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1. Introduction

Neuroplasticity is the ability of the nervous system to reshape its anatomical and functional connectivity and properties in response to external or internal stimuli. Although the exact mechanisms associated with functional recovery after lesions of the nervous system are still unclear, neuroplasticity is considered a leading candidate mechanism associated with motor learning after neurological injury. As motor training alone is sometimes insufficient to meet functional demands of recovery after neurological injury, there is increasing research examining priming modalities such as transcranial direct current stimulation (tDCS) to increase the effectiveness of physical rehabilitation (Gomez Palacio Schjetnan et al., 2013; Madhavan and Shah, 2012; Schlaug et al., 2008). tDCS involves delivering continuous low intensity direct currents (0.5 – 2.0 mA) via surface electrodes attached to the scalp, to modulate activity of the cortical neurons in a polarity specific manner. Anodal tDCS can up regulate corticospinal excitability, indicated by an increase in mean motor evoked potential (MEP) amplitude (Nitsche and Paulus, 2000; Nitsche and Paulus, 2001) and when applied to the motor cortex (M1) during motor training results in improved motor performance and learning (Boggio et al., 2006; Nitsche et al., 2003; Reis et al., 2009; Zimerman et al., 2012) with retention of acquired skills as long as 3 months post stimulation (Reis et al., 2009). The physiological effects of tDCS are attributed to immediate changes to shifts in membrane potential, with after effects being induced by NMDA receptor modulations (Stagg and Nitsche, 2011).

Typically tDCS up-regulating protocols are paired with motor training to induce enhancements in motor learning (Geroian et al., 2011; Saucedo Marquez et al., 2013). Currently, there is no clear consensus regarding the timing of the tDCS priming protocol in relation to the intervention, as studies have applied tDCS both *before* motor training (Antal et al., 2011; Kuo et al., 2008; Stagg et al., 2009) and *during* motor training (Cuyppers et al., 2013; Madhavan et al., 2011; Reis et al., 2009) resulting in large variations of the expected outcomes ranging from limited to large improvements. An increased understanding of state-dependent or metaplastic neuromodulation has led to the postulation that the likelihood of inducing synaptic modulation is contingent on the history of neuronal activity (Bienenstock et al., 1982; Jung and Ziemann, 2009; Turrigiano and Nelson, 2004). According to the Bienenstock–Cooper–Munro rule for homeostatic plasticity, a high level of prior synaptic activity will reduce the facilitatory effects of a concurrent facilitatory neuromodulatory protocol (and vice versa) and is related to changes in sensitivity of postsynaptic glutamate receptors. Another proposed mechanism for priming includes ‘gating’. Gating occurs by disinhibition of intracortical inhibitory circuits as a result of increase in calcium in the targeted cortical neurons. Gating occurs instantaneously and is achieved *concurrently* with motor training (Ziemann and Siebner, 2008).

Hence the timing of stimulation relative to motor practice could be an important regulatory component of priming. Stagg et al., (2011) demonstrated that anodal tDCS applied *during* an upper limb sequence learning task enhanced the rate of learning compared to tDCS applied *before* practice. Thirugnanasambandam et al., (2011) demonstrated that short lasting voluntary hand contractions performed immediately *after* tDCS to the hand motor area reversed tDCS-induced motor cortical excitability. As studies examining state-dependent

neuroplasticity of tDCS are limited, and relatively untested with respect to lower limb motor skill learning, we tested the interaction of tDCS with subsequent vs. concurrent motor learning. In accordance with the theory of homeostatic plasticity, we hypothesized that anodal tDCS *during* practice will result in enhanced motor performance and learning while tDCS applied *before* practice will inhibit motor learning.

Briefly, twelve participants were recruited and tested under three stimulation conditions: anodal tDCS prior to a motor task (tDCS-before), anodal tDCS during a motor task (tDCS-during) and sham tDCS during a motor task (tDCS-sham). We used a visuomotor tracking task to examine the time dependence of tDCS with respect to ankle motor skill learning (Madhavan et al., 2010; Madhavan et al., 2011). The accuracy of tracking the target sequence was calculated on a scale between 0–100, and was recorded as the accuracy index (AI) of motor performance. AI was tested before stimulation (PRE), 10 minutes post stimulation (POST10), 25 minutes after the end of stimulation (POST25) and 24 hours post practice (POST24h). Corticomotor excitability of the lower limb M1 was evaluated using single pulse transcranial magnetic stimulation (TMS) by recording motor evoked potentials (MEP) from the tibialis anterior (TA) muscle prior to stimulation (PRE), immediately post stimulation (POST0), and 25 minutes after the end of stimulation (POST25). AI and MEP amplitudes were normalized to the respective baseline value by dividing the average practice and post values by the average baseline value for each participant.

Results

All participants tolerated the experiment well. No adverse effects due to tDCS, TMS or the training task were reported.

1.1 Accuracy Index

The two-way ANOVA for changes in normalized AI revealed a significant effect of interaction of CONDITION and TIME ($F_{2, 14} = 1.80$, $p = 0.043$) and a main effect of Time ($F_{2, 7} = 12.39$, $p = 0.001$) (Figure 2). To examine simple effects, we performed a one-way ANOVA to compare the three CONDITIONS across each time point. We found that the tDCS-during condition was significantly different from tDCS-before at PRAC3 (10% greater, $p = 0.045$), PRAC4 (11% greater, $p = 0.035$), POST10 (8% greater, $p = 0.046$) and POST25 (10% greater, $p = 0.007$) time points. We also noted that the tDCS-during condition was significantly different from tDCS-sham at PRAC3 (10% greater, $p = 0.034$), PRAC4 (13% greater, $p = 0.029$), POST10 (11% greater, $p = 0.040$), POST25 (9% greater, $p = 0.025$) and POST24h (12% greater, $p = 0.027$) time points. tDCS-before was significantly different from tDCS-sham only at POST24h (10% greater, $p = 0.047$). We also performed a one-way ANOVA across TIME for each stimulation condition. This analysis revealed a significant effect of TIME for the tDCS-during ($p = 0.001$) and tDCS-before ($p = 0.002$) but not for tDCS-sham ($p = 0.122$). In the tDCS-during condition, all PRAC and POST time points were significantly higher than PRE AI. For the tDCS-before stimulation condition, PRAC1, PRAC2 and POST24h were significantly higher than PRE AI. In the tDCS-sham condition, none of the practice and post time point AI was higher than PRE AI.

1.2 MEP Amplitude

The two-way repeated measures ANOVA performed on normalized MEP amplitude revealed no significant main effects or interactions of CONDITION and/or TIME (Figure 3). A trend towards greater change in MEP amplitude was seen in tDCS-during at POST0 and for tDCS-before at POST25.

2. Discussion

In the present study, we explored the timing-dependent priming effects of tDCS application to the healthy lower limb M1 on ankle visuomotor skill learning. The behavioral effect of tDCS was examined by calculating an accuracy measure of ankle motor skill performance. Changes in lower limb corticomotor excitability influenced by tDCS and/or skill learning were examined using TMS. Our results showed that tDCS application *during* practice of a skilled motor task increased motor performance greater than tDCS applied *prior* to motor practice. However the timing of application did not affect retention of performance (POST24h) as both tDCS groups demonstrated enhanced motor learning when tested 24 hours after practice.

Our result of increased motor performance during concurrent application of tDCS is consistent with previous reports using similar paradigms in the upper limb (Boggio et al., 2006; Reis et al., 2009; Stagg et al., 2011). Motor learning is typically accompanied by activity dependent modifications of synapses inducing Hebbian plasticity in the form of LTP-like or LTD-like changes within the cortical neurons (Abbott and Nelson, 2000; Muellbacher et al., 2002; Ziemann et al., 2004). Neuronal circuits involved with ankle tracking were likely active or at a heightened state during performance of the motor task, and hence, it is possible that these were more accessible to the membrane shifting properties of tDCS during concurrent application thereby shaping synaptic plasticity and resulting in improved motor performance and learning. Because the excitability inducing tDCS was delivered *during* motor training, the boost in motor performance and learning is an example of priming by “gating” (Ziemann and Siebner, 2008). One of the potential mechanisms for enhancement of LTP during gating is removal of voltage sensitive magnesium ions due to depolarization resulting in stronger NMDA receptor-mediated postsynaptic responses due to increased intracellular calcium entry.

tDCS applied *prior* to the task (tDCS-before) did not improve motor performance in the same manner as concurrent application. In this respect, our results *partly* support the BCM rule of homeostatic plasticity in the lower limb motor cortex. Homeostatic plasticity is the ability of neurons to decrease activity after a period of high synaptic activity (and vice versa) (Leslie et al., 2001; Turrigiano et al., 1998) and is related to changes in postsynaptic activity (Misonou et al., 2006; Watt et al., 2000; Wierenga et al., 2005). When a non-invasive brain stimulation protocol and a motor learning task are applied sequentially, the direction of modulation of the intervention can be switched depending on whether a similar direction modulatory priming protocol was applied first. For example, if an LTP inducing priming protocol is followed by a motor learning task, the homeostatic principle predicts an inhibition of motor learning. This has been supported by other studies that have examined the BCM rule using a tDCS-rTMS paradigm (Lang et al., 2004; Siebner et al., 2004) or

tDCS-task paradigm (Antal et al., 2008; Kuo et al., 2007; Thirugnanasambandam et al., 2011). Hence, in the present study we expected that up-regulating activity of cortical neurons prior to performing the motor task will result in decreased learning. This was only partially supported as there was a significant increase in motor performance during the early stages of learning with a resultant decrease at the end of practice. Retention of learning was also increased at the POST24-hour time point. These results may be explained by the fact that dosage of tDCS may not have been of sufficient strength to cause the shift in cortical excitability that is required to trigger the homeostatic mechanisms. This result is similar to other studies, which have noted only a minor role of homeostatic modulation of tDCS on behavioral consequences (Antal et al., 2008; Kuo et al., 2007). This explanation of low dosage of current is supported by the lack of significant change in the normalized MEP amplitudes accompanying the behavioral data. A larger dosage of current may have induced the necessary up regulation needed to cause homeostatic plasticity, however this may be beyond the safety limits of current application. The lack of a significant up-regulation could also be possibly explained by substantial variations in inter-individual response, or other factors such as BDNF levels, which have also been noted with other brain stimulation protocols such as rTMS (Cassidy et al., 2014; Fritsch et al., 2010; Lopez-Alonso et al., 2014; Madhavan and Stinear, 2010b). It is also possible that tDCS applied to the resting M1 could be activating different neuronal circuits than tDCS applied consecutively with the task.

Another possibility for our results only partially supporting the BCM rule could be because of the timing of the training intervention that followed tDCS application. The time interval that separates the priming protocol and intervention has been suggested to be crucial for induction of homeostatic effects. Although the timing issue has not been fully explored, a few studies have suggested that at least 90 minutes of delay is needed to induce the reversibility inducing homeostatic effects (Jung and Ziemann, 2009; Murakami et al., 2012). It is possible that a longer delay between tDCS and the motor task could impact homeostatic plasticity.

The present study is also limited by the fact that we did not use cathodal tDCS to test homeostatic plasticity but instead we preferred to compare subsequent vs. concurrent stimulations. In our previous experience and in other studies, it has been found that cathodal tDCS application to the lower limb M1 is not strong enough to elicit the necessary down regulation (Jeffery et al., 2007). Hence we are limited by the technical aspects of tDCS to understand the behavioral consequence of homeostatic plasticity to the lower limb M1.

An intriguing finding was similar motor accuracy during POST24 hours testing session in the tDCS-during and tDCS-before conditions. We expected a decrease in learning for the tDCS-before condition. This suggests that tDCS-learning interactions were partly non-homeostatic and other synaptic mechanisms may have been in place to compensate for the reduced motor performance. The brain is a complex organ and it maintains other regulatory mechanisms such as synaptic scaling and synaptic redistribution to regulate overall neuronal activity, which may explain the enhanced retention of performance.

In contrast to our behavioral findings, we did not see any significant changes in corticomotor excitability measures. Studies using TMS and neuroimaging have demonstrated that

visuomotor skill training is associated with plastic changes in the motor cortex in terms of expansion of cortical representation and increased corticomotor excitability in healthy humans (Jensen et al., 2005; Pascual-Leone et al., 1994; Perez et al., 2004). We also expected an increase in corticomotor excitability for all conditions including sham stimulation. Numerous studies have shown that anodal tDCS up regulates cortical excitability and this upregulation lasts beyond the tDCS application itself. Hence we expected the tDCS-during condition to be significantly more modulated than the other two conditions. However, although there was a trend towards greater increase in corticospinal excitability in the post stimulation time points for the tDCS-during condition, there were no significant changes across the three conditions. This observation is in agreement with other studies which demonstrated homeostatic metaplasticity even in the absence of altered synaptic excitability by the conditioning stimulation (Hamada et al., 2008; Jung and Ziemann, 2009). We would also like to note that there was a trend towards increased corticomotor excitability in the tDCS-before condition at the Post25 time point. This increase may help explain why the extent of skill acquisition was indistinguishable for the two tDCS conditions at POST24h time points.

In conclusion, the results of the present study suggest that the timing of tDCS stimulation with respect to motor training maybe a critical regulatory factor of motor performance as the boost in motor learning is mediated by the mechanisms of gating vs. homeostatic plasticity. In the present study, applying tDCS concurrently with motor practice resulted in better motor performance than tDCS prior to motor practice. Further temporal and longitudinal studies are needed to fully understand the physiological effects of tDCS based priming. Enhancing motor learning in neurorehabilitation using priming protocols needs to be based on a clear understanding of the mechanisms of priming (gating vs. homeostatic plasticity) in order to optimize the interaction of priming and motor training.

4. Experimental Procedure

4.1 Participants

Twelve healthy participants (4 males, 8 females, age range 22–32 years) with no neurological disorders were recruited to participate in this study. A description of the study was provided, and informed consent approved by the local Institutional Review Board was obtained from all participants. Before inclusion in the study, the subjects were screened for contraindications to TMS procedures which included presence of metal implants, cardiac pacemakers, unexplained headaches, history of seizures or epilepsy, and medications likely to alter cortical excitability. All participants were right leg dominant (preferred leg to kick a ball).

4.2 Study Design

Each participant received testing under three stimulation conditions separated by at least seven days. The participants were also assessed the following day approximately 24-hours after each testing session. The three conditions included: 1) anodal tDCS prior to the motor task (tDCS-before), 2) anodal tDCS during the motor task (tDCS-during) and 3) sham tDCS

during the motor task (tDCS-sham). The three conditions were block randomized to avoid order effects (Figure 1).

4.3 Experimental Protocol

During each session, the participant was seated comfortably in a chair with his/her non-dominant (left) leg strapped to a custom-built ankle device. Muscle activity was recorded from the left tibialis anterior (TA) muscle belly using surface electromyography. For the ankle tracking task, the participant was instructed to track a computer generated sinusoidal wave pattern as closely as possible with ankle dorsiflexion and plantarflexion. In the tDCS-before condition, tDCS was applied over a course of 15 minutes prior to ankle tracking practice. In the tDCS-during condition, tDCS was applied for 15 minutes while the subject practiced the ankle tracking task. During the tDCS-sham condition, subjects did not receive any real stimulation but performed the tracking task during sham stimulation. Sham stimulation involved ramping up and down of the tDCS current for 30 seconds at the beginning and end of the session (Gandiga et al., 2006; Hummel and Cohen, 2005; Zimerman et al., 2012).

4.4 Electromyography

Surface Ag/AgCl electrodes were placed over the muscle belly of the TA. The reference electrode was placed over the spinous process of the seventh cervical vertebrae. Before placing the EMG electrodes, the skin was shaved if needed, and rubbed with alcohol to reduce impedance. All EMG data were sampled at 2000Hz, amplified *1000 and band pass filtered (10–500Hz) with a Delsys EMG system (Bagnoli-8, Boston, MA, USA). The EMG data collection was performed using Spike2 software (Cambridge Electronic Design, Cambridge, UK).

4.5 Transcranial direct current stimulation

A simple form of constant current stimulator (Chatanooga Ionto, Hixson, TN, USA) was used to deliver 1mA of direct current for 15 minutes. A 4 cm × 2 cm oblong saline soaked sponge electrode (2 cc) was placed over the leg area of M1, identified by hot spotting for the left TA muscle during single pulse TMS for each testing session. For 10 out of 12 participants, this position was 1cm lateral and 1 cm posterior to the vertex. For the other 2 subjects the hotspot was 2–3 cm lateral and 3 cm posterior to the vertex. A 7 cm × 5 cm carbonized electrode was placed over the contralateral supraorbital region. Before placing the electrodes, the skin was cleaned with alcohol. All participants tolerated the tDCS well and no adverse effects related to the application of tDCS were observed or reported.

4.6 Transcranial Magnetic Stimulation (TMS)

TMS was applied using a single-pulse stimulator (Magstim, Dyfed, Wales, UK) via a 110 cm double cone coil. The coil was oriented to induce a posterior–anterior current flow in cortex.. Spike2 software was used to trigger the stimulator and also record the trigger pulses. A tight fitting cap was placed on the participant's head (above the tDCS electrodes). During TMS, the participants were provided with visual feedback of their muscle activity and instructed to maintain a tonic contraction of the TA that represented 10% maximum

voluntary contraction (MVC). MVC trials were done at the beginning of each session. Corticomotor excitability of the left TA muscle representation was assessed using single pulse TMS at 120% active motor threshold for each subject. Active motor threshold (AMT) was defined as the stimulus intensity resulting in identifiable MEPs of at least 0.4 mV peak to peak in 50% of successive trials from the contralateral TA (Madhavan and Stinear, 2010a). Stimulation intensities for 120% AMT ranged from 35–67% of maximum stimulator output (MSO). Ten MEPs were recorded prior to tDCS stimulation (PRE), immediately post stimulation (POST0), and 25 minutes after the end of stimulation (POST25).

4.7 Ankle Motor task

We used a custom built manipulandum for ankle motor testing and practice (Madhavan et al., 2010; Madhavan et al., 2011). This device consisted of two adjustable plates and straps to secure the foot and shank in place. Participants performed ankle dorsiflexion and plantarflexion to match a sinusoidal wave on the computer screen as accurately as possible. A computer generated a waveform at a random frequency (0.2–0.4 Hz) and amplitude (60–80% of the individual's maximum comfortable range of motion). The same target waveform was used for all the testing trials. Participants performed two 'test' tracking trials before stimulation (PRE), 10 minutes post stimulation (POST10) and 25 minutes post practice (POST25). Participants returned 24 hours after the tDCS/training session to measure retention (POST24h). During practice, the participants performed the motor task with a random waveform sequence for 15 minutes with a one-minute rest interval after every four minutes.

4.8 Data Analyses

MATLAB (The Mathworks Inc, Natick, USA) was used to analyze all the data imported from Spike2 software. Peak to peak single pulse MEP amplitude at 120% AMT was used to evaluate changes in corticomotor excitability induced by the tDCS/training and the average of 10 stimuli was calculated for each participant. Accuracy Index (AI) for the ankle motor task was calculated according to the formula: $AI = 100(P - E)/P$, where E is the root mean square (rms) between the target line and the response line, and P is the rms value between sine wave and the midline separating the upper and lower phases of the sine wave (Madhavan et al., 2010; Madhavan et al., 2011). The maximum score possible is 100%. To examine changes in the AI during practice, the average of every four minutes of tracking was calculated resulting in three practice bins (PRAC1, PRAC2, and PRAC3). Average AI was also calculated for PRE, POST0, POST25 and POST24h time points. Average MEP amplitude was calculated for PRE, POST 0, and POST 25 time points. AI and MEP amplitudes were normalized to the respective baseline value by dividing the average practice and post values by the average baseline value for each participant.

4.9 Statistical Analyses

Statistical analyses were performed on the normalized AI and MEP amplitudes using IBM SPSS software version 19. We performed a two-way repeated measures ANOVA with CONDITION (tDCS-before, tDCS-during and tDCS-sham) and TIME (PRE, PRAC1, PRAC2, PRAC3, PRAC4, POST0, POST25 and POST24h) as the within-subject factors to examine changes in normalized AI. We performed a two-way repeated measures ANOVA

with CONDITION (tDCS-before, tDCS-during and tDCS-sham) and TIME (PRE, POST25 and POST24h) as the within-subject factors to examine changes in normalized MEP amplitudes. Fisher's LSD test was used for *post hoc* analyses. A significance level of 0.05 was adopted.

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Highlights

- Timing of tDCS application with respect to motor training is important
- tDCS application during motor practice enhances motor performance than tDCS before practice
- The timing of tDCS application does not influence retention of skill acquisition
- The mechanisms of priming differ depending on the timing of the priming protocol

Figure 1.
Schematic of study design. The waveform represents ankle tracking and boxes represent TMS testing.

Figure 2.

Changes in tracking accuracy for the three stimulation conditions. Figure 2 depicts normalized AI score for the various time points (PRE, PRAC1, PRAC2, PRAC3, PRAC4, POST0, POST25 and POST24h). * denotes a significant difference between tDCS-during and tDCS-before, + denotes a significant difference between tDCS-during and tDCS-sham and ^ denotes a significant difference between tDCS-before and tDCS-sham at each time point ($p < 0.05$). Data are averages of 12 participants and error bars denote standard errors.

Figure 3.

Changes in corticospinal excitability for the three stimulation conditions. Figure 3 compares the average changes in normalized motor evoked potential for tDCS-before (grey bars), tDCS-during (black bars), and tDCS-sham (white bars) at the Post0 and Post25 time points. No significant main effects or interaction was noted. Data are averages of 12 participants and error bars denote standard errors