Transcranial direct current stimulation: before, during, or after motor training?

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Noninvasive brain stimulation has recently been used to augment motor training-induced plasticity. However, the exact time during which noninvasive brain stimulation can be combined with motor therapy to maximize neuroplasticity and behavioral changes is unknown. We conducted a randomized sham-controlled crossover trial to examine when (before, during, or after training) transcranial direct current stimulation (tDCS) should be applied to best reinforce motor training-induced plasticity in 12 healthy right-handed participants (mean age: 21.8 ± 1.6) who underwent active or sham tDCS combined with motor training. Transcranial magnetic stimulation-elicited motor-evoked potentials from the right first dorsal interosseous muscle were recorded before (baseline) and immediately after each session. The training task comprised four practice trials – 3 min each (30 s pause between trials) – of repetitive finger movements (thumb abduction/adduction) with the right hand. Anodal tDCS (1 mA, 13 min, on the motor primary cortex) was applied before, during, and after the training. Compared with baseline motor-evoked potentials and the sham condition, tDCS that was applied before, but not during or after, the motor task enhanced corticospinal excitability. These data suggest that tDCS performed before – not during or after – promotes optimization of motor training-induced plasticity.

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Introduction

Since the discovery that the brain is plastic, cortical neuroplasticity has been associated with motor learning and functional recovery in patients after injury [1]. Facilitating neuroplastic changes by further activating areas of the brain augments the response by the motor system to traditional therapies and thus promotes maximum functional recuperation in musculoskeletal and neurological conditions [2,3]. Noninvasive brain stimulation (NIBS) appears to be a valuable tool for such conditions because it induces cortical neuroplasticity by altering synaptic strength in the human brain painlessly and reversibly [4].

NIBS has been used as a supplement to traditional therapeutic interventions, such as motor training, to maximize the effects of individual interventions [2,5]. Because enhancements in cortical excitability are believed to mediate motor functional recovery [6], this result supports the concept of combining brain stimulation with physical therapy to promote recovery after brain injury.

These findings indicate that the integration of transcranial neuromodulatory techniques into physiotherapy practice will form the basis for future therapeutic regimens [3]. However, in addition to the patent need for clinical trials to confirm the validity of this approach, other important aspects in determining the optimal method of combining NIBS with motor training should not be overlooked. One such aspect is the identification of the exact window during which NIBS should be applied to modulate brain plasticity and optimize the effects of motor training.

Neural plasticity is controlled by homeostatic regulatory mechanisms to maintain neuronal excitability at stabilized levels within a physiological dynamic range [7,8]. The combination of repeated finger movements with NIBS interferes with neural plasticity, likely by modulating mechanisms of homeostatic plasticity [9,10]. Further, basal cortical activity levels influence the effects of NIBS [11,12].

In this study, using transcranial direct current stimulation (tDCS), we aimed to determine when (before, during, or after motor training) NIBS should be applied to increase exercise-induced plasticity without activating regulatory homeostatic mechanisms. tDCS is a NIBS technique that is increasingly being used to examine homeostatic plasticity in the intact human cortex [13,14]. By applying weak direct currents through the scalp, tDCS enables us to increase or reduce corticospinal excitability [15,16]. In healthy individuals, anodal tDCS on the primary motor

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cortex improves cortical excitability, as evidenced by enhanced motor-evoked potential (MEP) amplitudes of hand muscles, whereas cathodal tDCS decreases it, on the basis of the decrease in MEP [15,16].

Materials and methods

Participants

Twelve healthy volunteers (two men, mean age 21.8 ± 1.6 years) were recruited from the local university community and participated in the experiments. The volunteers were all assessed by the Edinburgh Handedness Inventory [17]. All participants provided their informed consent for the experiment, which was approved by the local research ethics committee and was conducted in accordance with the Declaration of Helsinki. None of the participants was involved in regular physical activity at the time of the study, had a history of neurological, or psychiatric diseases, pregnancy, cardiac pacemaker and history of epilepsy, and surgery involving metallic implants.

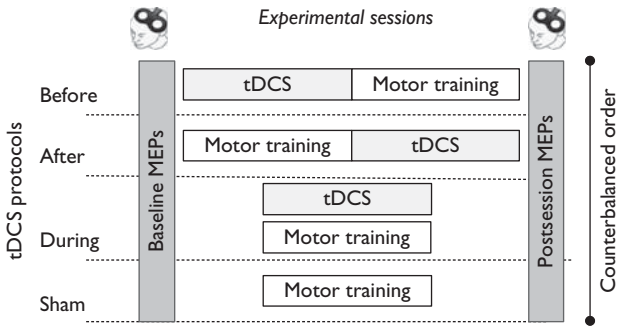
Experimental design

The experiment was conducted on the basis of a double-blinded sham-controlled complete crossover design. Each volunteer visited the laboratory four times, with at least 48 h between each visit. This has been suggested to be a good interval to minimize carry-over effects [18]. Under the experimental conditions, the participants performed motor cortical excitability assessments before and immediately after the end of the session, and received active/sham tDCS (i) before, (ii) immediately after, or (iii) during motor training. A schematic representation of the experimental design can be found in Fig. 1. Participants were blinded to experimental tDCS (active or sham). Participants and researchers who performed outcome measure and analyzed the data were blinded with respect to the tDCS protocols.

Motor cortical excitability assessment

For cortical excitability assessment (primary outcome), the participants were seated in a comfortable chair with head and arm rests. MEPs elicited by single-pulse transcranial magnetic stimulation (TMS) were recorded to monitor excitability changes of the representational motor cortical area of the right first dorsal interosseous (FDI). Single-pulse TMS was performed by a magnetic stimulator (Neurosoft Company, Ivanovo, Russia) with a figure-of-eight magnetic coil (diameter of one winding = 70 mm, peak magnetic field = 2.2 T). The coil was held tangentially to the skull, with the handle pointing backwards and laterally at an angle of 45° from the midline. The optimal position was defined as the site where stimulation resulted consistently in the largest MEPs. Surface electromyogram was recorded from the right FDI with Ag–AgCl electrodes in a belly-tendon montage. The signals were amplified and filtered with a time constant of 80 ms and a low-pass filter of 5.0 Hz,

Fig. 1



Experimental design. In each experimental session, the participants performed two cortical excitability assessments by transcranial magnetic stimulation (TMS) before (baseline) and after (postsession) the tDCS protocol application. TMS was applied over the left motor cortical representational area of the right first dorsal interosseous muscle to elicit motor-evoked potentials (MEPs). Four different tDCS protocols were tested to find the best time of combining tDCS (1 mA, 13 min, on the primary motor cortex) with motor training to maximize neuroplastic changes: (i) before – tDCS before motor training; (ii) after – tDCS immediately after motor training, (iii) during – tDCS during motor training, and (iv) sham – sham tDCS with motor training. The order of the different stimulation protocols was counterbalanced among participants. tDCS, transcranial direct current stimulation.

then digitized at an analogue-to-digital rate of 20 kHz and further relayed into a laboratory computer using the Neuro-MEP-Micro software (Neurosoft Company). The intensity was adjusted to elicit, on average, baseline MEPs of 1 mV peak-to-peak amplitude and was maintained constant for the postsession assessment. Each day, motor cortical excitability was assessed before and immediately after the experimental session (Fig. 1).

Transcranial direct current stimulation

Continuous direct current (1 mA, current density 0.029 mA/cm^2) was applied for 13 min through two saline-soaked surface sponge electrodes (surface 35 cm^2) and delivered by a clinical constant-current stimulator with a maximum output of 10 mA. The anode electrode was positioned over the motor cortex representational area of the right FDI muscle as identified by TMS and the other electrode was placed above the right supraorbital region. This electrode arrangement is known to induce corticospinal excitability enhancement for about 1 h after the end of stimulation in the human motor cortex [15]. Three different moments of anodal tDCS application (before, during, or after training) were tested to identify the exact temporal window during which the DC stimulation should be delivered to increase motor training-induced neuroplastic effects. In the sham session, tDCS was applied over M1 for 30 s, a method shown to achieve a good level of blinding [19]. The order of stimulation protocols was counterbalanced across the groups. The tDCS were administered by a separate researcher who did not participate in outcome measurements or data analysis.

Motor training

Here, participants were asked to perform repetitive abduction–adduction movements of the right thumb. The motor training consisted of four blocks of 3 min each with 30 s breaks in between. The motor training protocol was elaborated considering the time of the electrical stimulation, 13 min.

Data analysis

Individual MEP amplitude means were calculated for each time, including baseline and postsession. The postsession MEPs were normalized intraindividually and were calculated as baseline ratios. Statistical analyses were carried out by a repeated-measures analysis of variance with tDCS protocols (before, after, during, and sham) and time (before and after stimulation) as the within factor. In addition, to test whether the baseline absolute value differed significantly from the post-intervention values, a paired-samples Student's *t*-test was applied. A *P*-value of less than 0.05 was considered significant for all statistical analyses. The Mauchly test of sphericity was checked and as it was not violated, the Greenhouse–Geisser correction was not performed.

Results

As shown in Table 1, the results of the analysis of variance showed a significant main effect for tDCS protocols and a significant interaction between tDCS protocols and time. The main effect of time was not significant. Thirteen minutes of repetitive finger movements (sham tDCS protocol) did not alter the cortical excitability. However, if the motor task was performed immediately after the anodal stimulation, the cortical excitability was increased significantly compared with the baseline values ($P < 0.001$) and the sham condition ($P < 0.001$). Interestingly, when excitatory tDCS was applied during or immediately after motor practice, the anodal tDCS-induced excitatory effects on corticospinal excitability in the primary motor cortex were abolished (Fig. 2).

Discussion

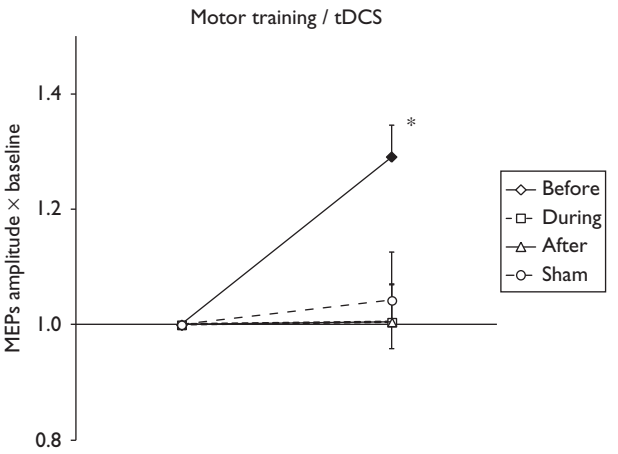
This study was carried out to examine the time-dependent interactions between tDCS and motor training. We found that excitatory tDCS that was applied before motor training increased MEP amplitudes. However, MEPs remained unchanged when tDCS was administered during or immediately after the motor task.

Table 1 Result of the repeated-measures ANOVA

	d.f.	*F*	*P*	Observed power
tDCS protocols	3	6.502	0.002*	0.949
Time	1	2.443	0.149	0.293
tDCS protocols × time	3	6.502	0.002*	0.949

ANOVA, analysis of variance; *F*, *F*-value; *P*, probability; tDCS, transcranial direct current stimulation.
*Significance (critical *P*-value 0.05).

Fig. 2



Timing-dependent interactions between tDCS and motor training. The baseline-standardized mean of motor-evoked potential (MEP) amplitudes elicited by single-pulse TMS after four different tDCS protocols is shown: (i) before – tDCS before motor training; (ii) after – tDCS immediately after motor training, (iii) during – tDCS during motor training, and (iv) sham – sham tDCS with motor training. Vertical bars show the SEM. Filled symbol indicates significant deviation of the cortical excitability from the baseline value. *Significant deviation of active tDCS (before tDCS protocol) versus the sham tDCS condition. tDCS, transcranial direct current stimulation.

The motor task alone had no influence on motor corticospinal excitability, as measured by MEP amplitudes.

Our findings on the effect of the motor task alone (tDCS sham protocol) contrast those of previous studies, which have shown that motor practice is associated with increased MEPs in the muscle that is involved in training [20,21]. It is possible that the execution time of the motor task in our study (13 min) is not sufficient to enhance corticospinal excitability significantly. The changes in brain activity that are induced by practicing a thumb movement appear to depend on the duration of training. Studies have reported significant increases in cortical electrical activity in M1 after repeated movements of the thumb-administered motor training for at least 30 min [22]. Supporting this hypothesis, similar to our results, Iezzi *et al.* [23] failed to observe any changes in corticospinal excitability, as measured by MEP size, after 4 min of thumb movements.

Consistent with earlier findings [11], in our study, MEP amplitudes were enhanced when excitatory tDCS was applied to the primary motor cortex before the motor task. Because the increase in cortical excitability correlates with clinical recovery [22,24], our findings indirectly corroborate earlier studies that have suggested that priming the brain with NIBS before exercise improves clinical outcomes [3,25].

Motor training and tDCS appear to share mechanisms of action in inducing neuroplastic changes in the human

cortex. Both modalities are accompanied by alterations in synaptic efficacy [6,18]. It is possible that shifts in corticospinal excitability that are induced by motor activity interact with the priming motor neural network by tDCS, which could reinforce the neuroplastic changes [2].

Notably, this potentiated plastic effect was not observed when transcranial stimulation was applied during or after the motor training. When the tDCS-induced cortical activation was performed concurrently with or subsequent to motor activity, the excitatory effects that should have been elicited by motor training were abolished. Certain mechanisms – although they are hypothetical, because they were not examined directly – explain these findings. Understanding these mechanisms is essential to examine the phenomenon of homeostatic plasticity or metaplasticity [8]. Metaplasticity is a type of regulation of plasticity in which a change in the physiological and biochemical state of neurons and synapses alters their ability to effect synaptic plasticity. The crucial assumption in homeostatic plasticity is that the threshold for the induction of synaptic plasticity varies as a function of previous neural activity [26]. Several groups have studied metaplasticity through the interaction between NIBS and motor training – finding, for example, that repetitive TMS after effects are reversed by previous tDCS-induced modulation [23,27].

Thus, it is likely that the absence of tDCS-induced effects in our study when tDCS was applied during or after motor training is because of the induction of metaplasticity. On the basis of the intracellular calcium concentration-dependent synaptic plasticity theory [28], we believe that tDCS administered during motor training can be enhanced by the intracellular calcium concentration in the zone in which the regulatory mechanisms of metaplasticity are activated, mitigating the enhancement in cortical excitability. Similar results have been observed by Huang *et al.* [9], who found that theta burst stimulation during muscle contraction in healthy individuals does not alter cortical excitability, as measured by MEP. Differences in the method of inducing synaptic plasticity between motor training and tDCS might have led to disparities in previous neural activity (calcium entry), varying the effects between the before-tDCS and after-tDCS protocols.

Another mechanism that was not studied directly here but can explain our findings is the interindividual variability in tDCS effects. A recent study showed that under the same experimental conditions, tDCS has varying effects [29]. Diurnal and other variations affect cortical excitability [12,30], which differ between individuals and might impact the effects of tDCS. Further studies are needed to examine these possible mechanisms.

One limitation of our study is that MEPs that were elicited by single-pulse TMS were recorded to monitor changes in excitability of the representational motor cortical area of the right FDI – this muscle was not directly involved in the activities that we measured. However, neuromodulation was not as focal; thus, the TMS results might represent changes in cortical excitability that occur as a result of the motor task.

Conclusion

Our data suggest that NIBS should be applied before, but not after or during, a motor training task to avoid the activation of regulatory homeostatic mechanisms – that is, brain stimulation should prime cortical excitability for subsequent motor training sessions to optimize motor learning processes.

This evidence should guide the implementation of the combination of NIBS and motor therapy in clinical practice. Previous studies have used NIBS to increase the effectiveness of motor rehabilitation [31,32]. However, a better understanding of homeostatic mechanisms remains essential for optimizing the use of NIBS in rehabilitation programs. In this context, more systematic studies are needed to examine the dynamic interaction of the induction of plasticity to establish adequate combinations of brain stimulation and motor learning tasks.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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