Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: An investigation for induction of counter-regulatory mechanisms

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Abstract

Background: Transcranial direct current stimulation (tDCS) is used to induce neuroplasticity in the human brain. Within certain limits of stimulation duration, anodal tDCS (a-tDCS) over the primary motor cortex induces long term potentiation- (LTP) like plasticity. A reversal of the direction of plasticity has however been described with prolonged a-tDCS protocols.

Objective: We aimed to systematically investigate the intervention duration threshold for reversal of a-tDCS-induced effects on corticospinal excitability (CSE) and to determine the probable mechanisms involved in these changes.

Methods: Fifteen healthy participants received a-tDCS of 1 mA for five different durations in pseudo-random session order. Transcranial magnetic stimulation (TMS) was delivered over the left M1, and motor evoked potentials (MEPs) of a contralateral hand muscle were recorded before, immediately and 30 min following intervention to measure CSE changes. Short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long interval facilitation (LIF) were assessed via paired-pulse TMS protocols.

Results: A-tDCS significantly increased CSE as expected at stimulation durations of 22 and 24 min. However, this effect of a-tDCS on CSE decreased and even reversed when stimulation duration increased to 26, 28, and 30 min. Respective alterations of ICF, LIF, and SICI indicate the involvement of glutamatergic, and GABAergic systems in these effects.

Conclusions: These results confirm a duration threshold for reversal of the excitability-enhancing effect of a-tDCS with stimulation durations \( \leq 26 \) min. Counter-regulatory mechanisms are discussed as a mechanistic foundation for these effects, which might prevent excessive brain activation.

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Introduction

Modulation of corticospinal excitability (CSE) by transcranial direct current stimulation (tDCS) is directly influenced by the duration, intensity, and polarity of the applied currents. Anodal tDCS (a-tDCS) of the primary motor cortex (M1) increases, while cathodal tDCS (c-tDCS) decreases CSE. Early studies by Refs. [1,2] have shown a linear relation between CSE enhancement and a-tDCS intensity (up to 1 mA, electrode size 35 cm²), and duration for up to 13 min [1,2]. This observation has been supported by a large number of studies [3–7], and led to the assumption of polarity-dependent excitatory effects of a-tDCS on CSE, independent from stimulation duration, and intensity.

This assumption was however challenged by several other studies [8–11] which indicated no change or even a reduction of CSE following application of a-tDCS. The results of these studies led to the conclusion that a more complex interaction does exist between the applied a-tDCS parameters, direction, and size of CSE changes. Indeed, it has been suggested that stimulation parameters...
such as polarity, duration, and intensity of the applied current, but also other factors such as the history of synaptic activity, training, consumption of certain foods such as caffeine or energy drinks, and poor sleep may affect the response to neuromodulatory intervention effects of non-invasive brain stimulation, including those of tDCS [12]. Out of these factors, the focus of the present study was the history of synaptic activity of the target area of the respective intervention, which is closely related to the dynamic online effects of stimulation duration on synaptic activity, and neuronal excitability. Synaptic plasticity is an activity-dependent form of plasticity [13,14]. Indeed, changes in the level of synaptic activity can affect the induction and direction of synaptic plasticity [15], which could destabilize neuronal networks [16]. Therefore, counter-regulatory, homeostatic mechanisms have been described by the Bienenstock-Cooper-Munro (BCM) rule (1982). According to this rule, the bidirectional modification threshold of synaptic plasticity is not static, but dynamically slides based on the history of synaptic activity between long-term potentiation (LTP) or depression (LTD). This sliding threshold is important to keep neuronal activity of the brain within an optimal physiological range to prevent excessive excitation or inhibition [17,18]; [16]. Therefore, depending on the inhibitory or excitatory nature of previous brain activity, the respective modification threshold will slide towards LTP or LTD, and change the effects of a given stimulation protocol on CSE [13,14,19]. Likewise, several studies using different intervention protocols have shown that this rule is applicable to non-invasive brain stimulation of the human motor cortex [20–22]; [55]; [8]. For tDCS [8], revealed that when the duration of 1 mA a-tDCS was doubled from 13 to 26 min (13 ÷ 13), the excitatory effect on CSE reversed into excitability diminution [8]. In accordance with the BCM rule, it can be speculated that for the prolonged application, the initial part of the stimulation changed the history of the synaptic activity of the target area towards facilitation (LTP-like effects as obtained for 13 min a-tDCS). This initial increase of excitability, and spontaneous activity would then reduce the modification threshold in favour of LTD induction for the remaining duration of the intervention. These homeostatic mechanisms would change the directionality of later tDCS effects on CSE. Although several studies shed light on probable mechanisms underlying such a counter-regulation of plasticity [23,24]; [55]; [8], the duration threshold for this effect has not been determined yet.

The main aim of the current study was thus to systematically determine the intervention duration threshold for reversal of M1 a-tDCS (1 mA) effects on CSE. Moreover, we aimed to explore the respective mechanisms underlying this reversal effect. Based on the foregoing studies, we hypothesized that application of a-tDCS (1 mA) over M1 for ≥ 26 min might reverse the excitatory effects of stimulation on CSE due to a calcium-dependent mechanism [25]. A-tDCS after-effects depend on voltage-dependent calcium channels [25], and glutamatergic receptor activation, specifically, N-methyl-D-aspartate receptor (NMDAR) efficiency, which also have calcium channel properties [56]. Reduction of GABA activity seems to have a gating effect on the respective glutamatergic plasticity [26]. For the excitability-reducing effects of 26 min a-tDCS, it was shown that calcium channel block prevented this effect, and it was suggested that this might be caused by calcium overflow-induced counterregulatory mechanisms, which might include the activation of hyperpolarizing potassium channels [5,24]. Therefore, we expected that this neuronal counter-regulation would be associated with an increase of inhibitory and a decrease of facilitatory brain activity, whereas stimulation duration below 26 min should reduce intracortical inhibition, but enhance facilitation [27].

### Material and methods

#### Participants

A total of 15 healthy non-smoking volunteers (8 female) aged between 19 and 39 years (mean age ± SD: 24.66 ± 7.5) were recruited. The sample size was calculated (power of 0.8 and α = 0.05) based on the critical effect size generated from a pilot study on eight participants. All participants were right-handed according to the Edinburgh Handedness Inventory [28] and screened for contraindications to transcranial magnetic stimulation (TMS) [29] and tDCS [30]. None of the participants reported any neurological or psychiatric disease. Participants were asked not to consume any caffeine or alcohol from the day before the experimental sessions, and sleep about 6–7 h at night before the session. Ethical approval was obtained from the Human Ethics Committee at Monash University, Melbourne, Australia, and the study protocol was conducted in accordance with the Declaration of Helsinki. Before the experiments, all participants provided informed consent.

#### Study design

A randomised double-blinded crossover design was applied in this study. Each volunteer participated in five experimental sessions, which were pseudo-randomly ordered. Order of sessions was counterbalanced, and the respective sessions were separated by at least seven days [31]. All experimental sessions started at the same time of the day for each individual to reduce the risk of circadian influences [32,33]. Due to the nature of this study, no sham condition was included. Participants were blinded to a-tDCS conditions and the purpose of the study. The selection of stimulation parameters was based on the study of Monte-silva et al. (2013); where a-tDCS with 1 mA and 35 cm² electrodes for 26 min and showed a reversal of CSE alterations [8]. In the present study, these parameters (1 mA, 35 cm²) were applied to explore the effects of a-tDCS on CSE for 22, 24, 26, 28, and 30 min stimulation duration.

Two researchers were involved in the current study, one as an assessor and the other as a-tDCS administrator. The assessor, responsible for data collection and analysis, was blinded to all experimental conditions. The administrator, who was responsible for delivering a-tDCS interventions, was not involved in any data collection or analysis.

#### Experimental procedures

**Electromyography (EMG)**

Surface EMG was recorded from the right first dorsal interosseus (FDI) with pre-gelled self-adhesive Ag/AgCl electrodes (inter-electrode distance 2 cm) in a belly-tendon montage. The reference electrode was placed on the styloid prominence of the ipsilateral ulna. The skin over the FDI was gently abraded and then cleaned to reduce electrode-skin impedance and improve the recorded EMG responses [34]. EMG signals were filtered (bandwidth 10–500 Hz), amplified (∗ 1000), and digitized at a sampling rate of 1 kHz, using a Powerlab 4/35 system (ADInstruments, Australia). MEPs were recorded using LabChart 8 software (ADInstruments, Australia), and stored in a PC for offline analysis.

**Transcranial magnetic stimulation (TMS)**

TMS was applied via an angulated figure-of-eight coil connected to a MagPro R30 stimulator (MagVenture, Denmark). The coil was positioned over the left M1 with an angle of 45° from the midline and the handle pointing backwards (posterior-anterior current orientation). The “motor hotspot” was defined as the coil position...
from which TMS-induced MEPs of maximum amplitude could be recorded in the target muscle with a given medium TMS intensity. The spot was marked on the scalp for exact repositioning of the coil throughout each session. Resting motor threshold (RMT) at the M1 hot-spot was obtained using the parameter estimation by sequential testing (PEST) method [35]. MEP amplitudes were recorded to monitor intervention-generated CSE changes. The TMS intensity (as a percentage of maximum stimulator output, %MSO) was adjusted to elicit a mean MEP amplitude of about 1 mV peak-to-peak (SI$_{1$mV}) in the resting FDI [1,2,36]. Baseline MEP means within the range of 1 mV ± 20% were accepted [7]. All TMS procedures were done by the same experimenter (MHZ), who was well-trained in TMS.

**Assessment of CSE: single-pulse TMS induced MEPs (1 mV)**

Twenty-five single-pulse TMS induced MEPs were recorded using the SI$_{1$mV} before (T$_{pre}$), immediately (T$_0$) and 30min (T$_30$) after the application of a-tDCS. The same intensity was used for all time bins to monitor tDCS-induced changes of CSE.

**Assessment of intracortical excitability: paired-pulse TMS induced MEPs**

Intracortical excitability changes were assessed by a TMS paired-pulse protocol, including 75 stimuli, and interstimulus intervals (ISIs) of 3, 10, and 150 ms. In this protocol, short intracortical inhibition (SICI, 3 ms), intracortical facilitation (ICF, 10 ms), and long interval facilitation (LIF, 150 ms [37]; were assessed by combining a subthreshold conditioning stimulus (CS: 80% of RMT) with a suprathreshold test stimulus (TS: SI$_{1$mV}) [59]). TS intensity was adjusted to achieve a baseline MEP of about 1 mV (SI$_{1$mV}) and readjusted after the application of a-tDCS in order to compensate for effects of the intervention on the MEP amplitude if required [27].

**Anodal-transcranial direct current stimulation**

A-tDCS was delivered through a battery-driven stimulator (NeuroConn, Germany). The current was applied through a pair of saline-soaked surface sponge electrodes (5 × 7 cm, 35 cm$^2$). The active electrode (anode) was centred over the FDI hotspot of the left M1 as identified by TMS. The return electrode (cathode) was positioned over the right supraorbital area. Current intensity of 1 mA was applied for five durations (22, 24, 26, 28, and 30 min) in randomised order on different days. There was a 15s ramp-up/down at the beginning and end of the stimulation to minimize any potential discomfort. During stimulation, participants were instructed to keep their hands in a relaxed position.

Fig. 1 summarizes the experimental design of the current study.

**Monitoring of side effects**

All participants were asked to complete a questionnaire during all experimental conditions to record side or adverse effects of a-tDCS. The questionnaire contained rating scales for the presence and severity of some common side effects such as itching, tingling or burning sensation under the electrodes [38,39], and other adverse effects, including headache and pain during and after stimulation [30]. All participants rated the unpleasantness of any scalp sensation by a numeric analogue scale (NAS; e.g. 0 = no sensation to 10 = worst sensation imaginable) during and after stimulation. Finally, at the end of each experiment, participants were asked to indicate if they distinguished any difference between received stimulation compared to the previous session(s). They replied, choosing ‘Yes’, ‘No’, or ‘cannot say’ as the answer.

**Statistical analyses**

To exclude baseline differences between the five tDCS-sessions, a one-way repeated measure ANOVA (rmANOVA) was used for all dependent variables (RMT, SI$_{1$mV}, MEP amplitude). Peak-to-peak amplitudes of 25 single-pulse MEPs were calculated and averaged online for each time point of measurement, using a custom-designed macro. The size of the conditioned MEP was expressed as a percentage of the unconditioned test MEPs for SICI, ICF, and LIF. The Shapiro-Wilk test was applied to explore the normality of each dataset. The post-intervention values were normalized, and are given as ratios of the respective baselines. A rmANOVA was conducted to assess the effects of two repeated measure factors, ‘Experimental conditions’ (a-tDCS durations of 22, 24, 26, 28 and 30 min) and ‘Time’ (T$_{pre}$, T$_0$, and T$_{30}$) on CSE, SICI, ICF, and LIF. Mauchly’s test was used to assess the validity of the sphericity assumption for the rmANOVA; it requires that the variances of each set of difference scores are equal. Greenhouse-Geisser-corrected significance values were used when the sphericity assumption did not apply [40]. In case of significant results of the ANOVA, Bonferroni-corrected post hoc paired-sample t-tests were conducted to test whether the baseline value of each experimental condition differed significantly from post-intervention time points (T$_0$ and T$_{30}$).

An analysis of covariance (ANCOVA) with session order as co-variate was performed, to exclude that this factor had an impact on the results, which would hint for instability of the results due to this methodological aspect.

For side effect analysis, mean intensity values were calculated based on the numerical analogue scale ratings. A one-way ANOVA was carried out on the rating scale data recorded to assess any significant differences between sessions. To determine whether participants were successfully blinded to the experimental conditions, after completion of each experiment, participants were asked whether they could differentiate between stimulation they received at each session. Data were analysed using Pearson’s chi-square. Means are reported ± standard error of the mean (SEM). Statistical analyses were computed using SPSS 25 (IBM, NY, USA), and the critical level of significance was set to $p = 0.05$.

**Results**

All fifteen participants completed all experimental sessions. The Shapiro-Wilk test confirmed normality of all data sets. The results of the respective one-way rmANOVAS revealed no significant difference of baseline RMT, SI$_{1$mV} (CSE), and MEPs (SICI, ICF, LIF) between all experimental sessions, Table 1.

Moreover, the results of the respective ANCOVAs show no significant impact of this co-variate on the outcome ($F = 0.05$, df = 4, Sig = 0.94 for CSE, please see Table 2 for the remaining results).

**Effects of different A-tDCS durations on CSE**

The two-way rmANOVA conducted for single pulse amplitudes showed a significant main effect of ‘Experimental condition’ ($F(4, 50) = 19.19$, $P < 0.001$, $\eta^2 = 0.60$, $1-\beta = 0.98$) and a significant ‘experimental conditions × time’ interaction ($F(8, 112) = 11.39$, $P < 0.001$, $\eta^2 = 0.46$, $1-\beta = 0.96$). However, the results showed no significant main effect of ‘time’ ($F(2, 28) = 3.88$, $P = 0.03$, $\eta^2 = 0.21$, $1-\beta = 0.65$). Fig. 2 (A1–E1) shows the respective CSE changes of all participants for the five a-tDCS durations. Bonferroni-corrected post-hoc t-tests revealed that peak-to-peak MEP amplitudes significantly increased (T$_0$, T$_{30}$) following tDCS durations of 22 and 24 min, as compared to baseline ($p < 0.01$). On the other hand, MEP amplitudes were significantly reduced following stimulation
durations of 26 (T₀), 28, and 30 min (T₀, T₃₀), as compared to baseline (p < 0.01).

Effects of different A-tDCS durations on SICI

The rmANOVA revealed a significant main effect of 'Experimental conditions' (F(4, 56) = 8.55, P < 0.001, η² = 0.37, 1-β = 0.94), and a significant 'Experimental conditions x time' interaction on SICI (F(8, 112) = 10.01, P < 0.001, η² = 0.41, 1-β = 0.97). However, there was no significant main effect of 'time' (F(2, 28) = 0.25, P = 0.77, η² = 0.01, 1-β = 0.08). Pairwise comparisons revealed significant differences for tDCS durations of 22, 28, and 30 min. Specifically, SICI decreased significantly in the 22 min a-tDCS condition (T₀, T₃₀), while it increased significantly after 28 min (T₃₀), and 30 min (T₀, T₃₀) a-tDCS, as compared to the respective baseline values (Fig. 2; A2-E2). Table 1 summarizes the means ± SEM for reported side effects under the anode and cathode for each of the experimental conditions. No reports of burning sensations, headaches, or pain were recorded during or after stimulation.

Safety and side effects of A-tDCS

No adverse effects were reported after a-tDCS, except tingling sensations and light itching under the electrodes during stimulation reported by some of the participants in all experimental conditions. Side effects were recorded at the beginning, middle and end of stimulation. Table 3 summarizes the means ± SEM for reported side effects under the anode and cathode for each of the experimental sessions. No reports of burning sensations, headaches, or pain were recorded during or after stimulation.

Moreover, the Chi-square test conducted to control for successful blinding showed no significant differences between the experimental conditions [χ²(4, n = 15) = 7.52, P = 0.12], demonstrating that participants were not able to identify the respective stimulation protocol. The percentage of participants who could not guess the a-tDCS condition they had been received correctly, and replied ‘No’ was 96% (excluding ‘cannot say’ responders) and 92% (including ‘cannot say’ responders). Blinding of the participants of the present study was therefore successful.

Discussion

The results of the current study confirm the existence of a duration threshold for the reversal of excitability-enhancing effects of a-tDCS (1 mA) on CSE at 26 min. This finding is in line with the experimental conditions and LIF-based stimulation protocol. The percentage of participants who could not guess the a-tDCS condition they had been received correctly, and replied ‘No’ was 96% (excluding ‘cannot say’ responders) and 92% (including ‘cannot say’ responders). Blinding of the participants of the present study was therefore successful.
study of [8]; in which the excitability-enhancing effects of a-tDCS reversed after doubling stimulation duration from 13 to 26 min [8]. Accordingly, unlike shorter (<26 min) applications, longer (>26 min) applications of a-tDCS (1 mA) reversed the excitatory effects of stimulation on CSE. Moreover, the results of the present study confirm that the CSE reversal at longer intervention durations (>26 min) is associated with an increase of inhibitory and decrease of excitatory intracortical mechanisms. tDCS was well tolerated in all experimental sessions, and the blinding procedure was successful.

Effects of A-tDCS durations on CSE and intracortical excitability

A-tDCS durations <26 min

We hypothesized that application of a-tDCS < 26 min would increase CSE and assumed that this enhancement would be accompanied by reduced SICI, and increased ICF, and LIF. Our findings support these hypotheses. In detail, our results show that CSE was significantly increased following a-tDCS, in line with the results of previous studies [27]: [43]; [3–7,41]. Furthermore, the results are in line with the hypothesized SICI reduction, which also aligns with respective results of the previous findings [27,42]. As expected, the results also show an increase of ICF and LIF after a-tDCS. In addition, these results confirm those of previous findings [27,43] which are indicative for an involvement of facilitatory mechanisms in the respective results.

TDCS affects the stimulated area by different mechanisms and can induce changes in different brain areas ([57]). The primary mechanisms are assumed to be calcium-dependent and mainly related to glutamatergic activity [25,44] with a gating effect on GABA_A receptors [25–27,42], which is supported by the current results of the paired-pulse protocols. Indeed, glutamate receptors and specifically the NMDAR are involved in ICF ([54]); [58] [45]. Therefore, it can be concluded that the activity of NMDARs in M1 and therefore, glutamatergic activity was intensified following a-tDCS < 26 min. This would result in an increase of intracellular Ca^{2+} in the postsynaptic neuron that enhances ICF and increases CSE ([23]).

SICI is considered to be primarily dependent on GABAergic interneuronal activity [26,44]; [42]. A reduction of GABAergic activity by a-tDCS has been already shown in previous studies [26,46,47]. This reduction of GABA activity would indirectly enhance NMDAR responses and intracellular Ca^{2+} concentration [48], and therefore contribute to the observed CSE enhancement. Finally, the LIF enhancement observed for a-tDCS < 26 min, as an index of late cortical disinhibition, fits well with the resulting increase of CSE caused by the respective tDCS protocols.

A-tDCS durations ≥26 min

We hypothesized that application of a-tDCS ≥ 26 min would reduce and may even reverse the facilitatory effect of the intervention on CSE. The current findings support this hypothesis. These findings are in principle agreement with other studies showing the non-linear effect of a-tDCS [8,10,11]. They furthermore support the assumption of a duration and intensity window for anodal tDCS that results in linear effects, and that exceeding stimulation parameters beyond respective limits results in non-linearities. We also assumed that the hypothesized CSE reduction would involve respective intracortical excitability alterations. The current findings, showing a gradual decrease of ICF and LIF following a-tDCS ≥ 26 min, support the respective hypothesis with respect to a reduction of intracortical facilitatory mechanisms in case of increased stimulation duration. Moreover, the gradual increase of SICI following a-tDCS ≥ 26 min in the current study suggests an enhancement of inhibitory mechanisms involved in the non-linear effects induced by prolonged a-tDCS. Although SICI was not enhanced at 26 and 28 min significantly, we observed a respective trend-wise effect. Moreover, the significant enhancement of SICI for the a-tDCS duration of 30 min supports this hypothesis and confirms increasing inhibitory activities.

It seems that neuronal counter-regulatory mechanisms are activated by prolonged stimulation duration, which reverses CSE. The already above-mentioned Ca^{2+} overflow induced by prolonged stimulation [8], might activate counteracting potassium channels [24] which would limit Ca^{2+} influx [49], and might convert effects. ICF reduction and SICI enhancement, revealed by current results, is in accordance with proposed mechanisms of synaptic scaling, which opposite scaling directions of inhibitory and excitatory synapses of respective neuronal circuits [50,51]. This suggests that a high level of synaptic activity induced by prolonged a-tDCS enhances activation of intracortical inhibitory interneurons on excitatory interneurons and decrease NMDA currents. This mechanism would then scale down synaptic strengths. These hypothesized mechanisms are however speculative at present and should be confirmed by future studies.

Safety and side effects of a-tDCS

All participants tolerated the applied currents in the different experimental conditions well. There were no dropouts due to adverse or side effects of a-tDCS. Itching sensations were reported by all participants in all sessions. No reports of burning sensations, headache, or pain were mentioned during or after stimulation.

Limitations of the study

Our findings should be interpreted in the context of some limitations. First, the data was obtained from a healthy population; therefore, the results may not necessarily be extrapolated to the patients with neurological, or psychiatric disorders. Second, the effects were evaluated in young participants (under 40 years); older individuals may respond differently to the applied a-tDCS conditions. Finally, in the current study, the effect of a-tDCS was assessed only for up to 30 min post-stimulation, which limits our understanding with respect to possible further lasting effects or delayed developing changes.

Suggestions for future studies

Future experiments should conduct additional excitability measures during stimulation to receive more profound knowledge about the temporal dynamics of the development of plasticity by tDCS, and add mechanistic information via exploration of the contribution of ion channels and neurotransmitters to the effects of stimulation. Moreover, investigations exploring the duration threshold of M1 a-tDCS in older adults and patients with neurological disorders would be valuable to enhance the transferability of the findings. Studies applying different stimulation intensities, electrode sizes, and stimulation montages in both healthy
participants and patients in a systematic manner would provide valuable information about the parameter range of a-tDCS. In addition, behavioural outcome measures would be worthwhile to investigate if reversal of the CSE effects also affects the relevant motor or cognitive behaviours. Finally, we observed a higher variability of responses to a-tDCS with shorter durations in the present study. Future systematic studies should disentangle possible causes for the differences of variability, which might be methodological, because higher MEP amplitudes allow for larger variability, or physiological, because of instability of effects in transition zones between excitability-enhancing, and -reducing effects.

Fig. 2. The effects of different durations of a-tDCS on corticospinal excitability (CSE; A1-E1), short intracortical inhibition (SICI; A2-E2), intracortical facilitation (ICF; A3-E3), and long interval facilitation (LIF; A4-E4). A1-4: 22 min, B1-4: 24 min, C1-4: 26 min, D1-4: 28 min, E1-4: 30 min (* shows significant differences, p < 0.05). Each dot represents one participant. Lines show the means. Error bars show SEM.
Conclusions

The results of this study show that increasing the duration of a-tDCS does not necessarily enhance its efficacy to induce LTP-like plasticity, but might even convert the direction of effects. Moreover, the results show that respective corticospinal effects are mirrored at the level of intracortical circuits. These findings stress an essential role of metaplastic mechanisms for the effects of a-tDCS. The a-tDCS duration threshold for the reversal of the effects identified in this study confirms the assumption of a ‘ceiling effect’ of stimulation protocols in healthy participants, which might not be easily overcome with the application of prolonged interventions, but might require sophisticated adaptation.

Declaration of competing interest

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CRediT authorship contribution statement

Maryam Hassanzahrae: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration. Michael A. Nitsche: Data curation, Writing - review & editing. Maryam Zoghi: Conceptualization. Shapour Jaberzadeh: Conceptualization, Methodology, Data curation, Writing - review & editing, Supervision.

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