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Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation

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Background
Evidence from recent clinical trials suggests that transcranial direct current stimulation (tDCS) may have potential in treating neuropsychiatric disorders. However, the optimal frequency at which tDCS sessions should be administered is unknown.

Objective/Hypothesis
This study investigated the effects of daily or second daily tDCS sessions on motor cortical excitability, over a 5-day period.

Methods
Twelve healthy volunteers received daily or second daily sessions of tDCS to the left primary motor cortex over the study period, in a randomized, intraindividual crossover design. Motor cortical excitability was assessed before and after tDCS at each session through responses to transcranial magnetic stimulation.

Results
Over a fixed 5-day period, tDCS induced greater increases in MEP amplitude when given daily rather than second daily. Analyses showed that this difference reflected greater cumulative effects between sessions rather than a greater response to each individual tDCS session.

Conclusions
These results demonstrate that in the motor cortex of healthy volunteers, tDCS alters cortical excitability more effectively when given daily rather than second daily over a 5-day period.

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Transcranial direct current stimulation (tDCS) is a non-invasive technique for stimulating the brain, whereby a weak direct current is passed through electrodes placed on the scalp to modulate neuronal excitability in targeted brain regions. tDCS has been shown to cause polarity-specific changes in the cortex[1-4] with stimulation under an anodal electrode leading to increases in cortical excitability, whereas a cathodal electrode produces the opposite effect. Moreover, studies have shown that a single session of tDCS produces changes in cortical excitability that can last up to 90 minutes poststimulation.[5,6] Accordingly, tDCS holds promise as a tool for noninvasively and painlessly treating a number of neurologic and psychiatric conditions, including Parkinson's disease,[7,8] neuropathic pain,[9] and depression.[10-13]

However, optimal parameters for administering tDCS have yet to be defined. For example, the depression studies varied in using 1-2 mA, and gave tDCS twice per day,[12] every weekday[11] or every second day (three sessions per week).[10,13] As the studies varied in a number of aspects, information on optimal stimulus parameters cannot be derived from comparisons between studies.

Studies of tDCS as a treatment for chronic pain have also varied in the treatment parameters. Although Fenton et al.[14] applied 1 mA once a day for 2 days, others have applied 2 mA for 30 minutes as a single treatment[15] or for 20 minutes once a day for 5 days[9,16] with all reporting symptom alleviation after tDCS.

At this point, it is thus unclear whether alteration of treatment parameters such as session frequency, number of sessions or current intensity enhances the efficacy of tDCS. This study aimed to specifically clarify whether in a fixed treatment period, daily or second daily stimulation sessions would constitute the more effective as well as efficient schedule for administering tDCS. In this study of healthy participants, anodal tDCS was given to the motor cortex as cortical excitability outcomes can be readily examined through electromyography measurements of peripheral muscle activation. The study used an experimental paradigm pioneered by Nitsche and colleagues,[3,5,17] which uses single pulse transcranial magnetic stimulation (TMS) to measure differences in cortical excitability before and after tDCS.

This study examined (1) whether daily or second daily tDCS led to greater cumulative between-session ("offline") changes in cortical excitability across 5 days; and (2) whether the frequency of stimulation sessions would affect the net effect of each successive individual tDCS sessions (i.e., whether the increase in cortical excitability from a single tDCS session would decline more over the 5 days with daily compared with second daily tDCS).

Methods

Participants

Twelve healthy, right-handed males (mean age 21.4 years; range 20-27) participated in the experiment, which was approved by the human research ethics committee of the University of New South Wales. For expedience, females were excluded from the study due to effects of menstrual variation on cortical excitability being a potential confound in women of reproductive age.[18,19] Subjects were not on any medications and had no history of acute or chronic medical, neurologic, or psychiatric disease. All gave informed written consent and were paid for participation. The experiment used a crossover design with the two conditions being daily (A) and second daily (B) tDCS over 5 days. Participants were randomly allocated to commence with condition A or B, followed by the other condition after a minimum 2 week washout period (average 5.2 weeks, range 2-15 weeks). On a separate day before commencing experimental procedures, all participants underwent a 1 hour screening, in which they were familiarized with the laboratory and the physical sensations of undergoing tDCS and TMS.

Direct current stimulation

For each tDCS session, a 2 mA current was delivered for 20 minutes by an Eldith DC-stimulator (NeuroConn GmbH, Germany) through conductive rubber electrodes ($7 \times 5 = 35$ cm^2) that were covered by saline-soaked sponges and held in place by two bands.[20] Anodal tDCS was applied to the left primary motor cortex, with the electrode centred over the representational field of the right first dorsal interosseus (FDI) as identified using TMS. The cathode was placed over the contralateral orbit.

Measurements of motor cortical excitability

Following the same paradigm used in several experiments in this field,[21-23] motor evoked potentials (MEPs) elicited in the right FDI by single pulse TMS were recorded via surface electromyography (EMG) with disposable disc electrodes (Ag-AgCl) placed on a tendon-belly arrangement. For reproducibility of electrode position, the positive electrode (2 cm diameter) was placed one third of the distance from the proximal end of the muscle. TMS was given to the left primary motor cortex through a 70-mm figure-of-eight coil (Magstim 200, Magstim Co., Dyfed, UK) placed tangentially to the skull with the handle oriented posterolaterally. Optimal coil position

was identified as the site consistently producing the largest MEPs. EMG signals were filtered (16-1000 Hz), amplified, digitized (2000 Hz), and recorded (CED 1902 amplifiers, CED 1401 and Signal 4 software, Cambridge Electronic Design, Cambridge, UK).

Procedure

In each experimental session, participants were seated in a chair with their arms resting on an armrest and pillow. They were instructed to keep their arms still but relaxed throughout the experiment. The motor cortical representational field of the right FDI was then identified using single TMS pulses. The position of this optimal site was measured relative to the vertex, recorded, and marked with a waterproof pen. The coil orientation for eliciting optimal MEPs in the FDI was also marked by drawing a line on the scalp that outlined the contour of the coil. At the beginning of each experimental session, this position was confirmed as the optimal site for evoking MEPs and was remarked. Resting motor threshold for the FDI was established, defined as the lowest TMS intensity at which a MEP of at least 0.05 mV was produced in three of six responses. This was measured before the test session on Monday and Friday of each testing week.

On the Monday of each experimental week, the TMS intensity required to elicit an average MEP response of 1 mV was established. This intensity was then used for all MEP measurements in that week. On each day, 20 MEPs were elicited at 0.2 Hz to establish a baseline measure of cortical excitability. tDCS was then administered. Immediately after tDCS, another set of 20 MEPs was recorded. Further sets of 20 MEPs were recorded at every fifth minute for the first 30 minutes and then at 60, 90, and 120 minutes post-tDCS (Figure 1).

Statistical analyses

For each subject, the 20 MEP amplitudes measured at each time point were averaged and normalized as a ratio of the initial baseline measure for each test week. As the aim was to measure net changes in excitability as a result of tDCS, rather than the time course of changes after each session, and because MEP measurements are typically highly variable, post-tDCS MEP means for each day were collapsed to provide a single measure of cortical excitability after stimulation and compared to pre-tDCS values.

To test whether frequency of tDCS affected (1) cumulative changes in excitability across the week, and (2) within-session changes in excitability across successive sessions, mean MEP amplitudes were compared using a $2 \times 2 \times 3$ fully repeated measures analysis of covariance (ANCOVA) with the factors being tDCS frequency (daily and second daily), time (pre-tDCS and post-tDCS), and day (Monday, Wednesday, and Friday). Planned contrasts tested for pairwise differences across the factor of day (i.e., Monday versus Wednesday, Monday versus Friday). Randomization (i.e., whether participants received daily or second daily tDCS in their first week) was entered as a covariate to control for any possible carryover effects from the first to the second week of testing.

In addition, separate 2×2 fully repeated measures ANCOVAs (also controlling for randomization) were conducted for the pre-tDCS MEP amplitudes and the motor threshold measures with tDCS frequency (daily and second daily) and day (Monday and Friday) being the two factors.

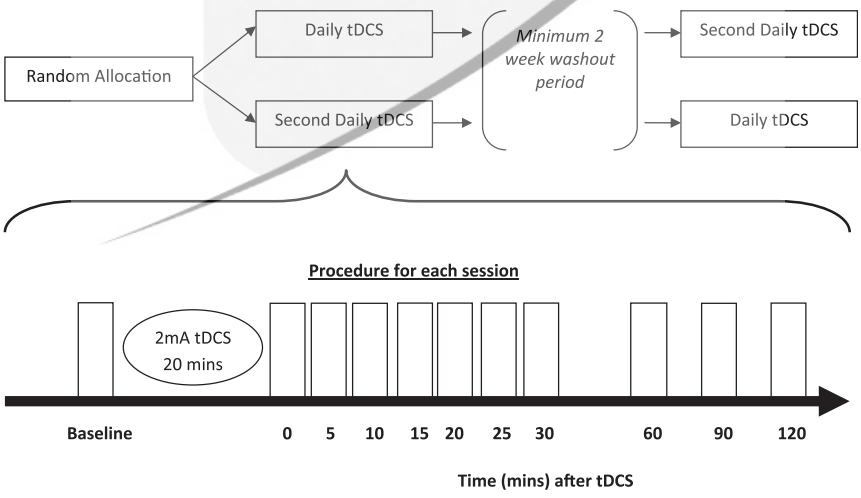

Figure 1 Experimental design. Top half illustrates the crossover design of the study. Bottom half illustrates procedure for each testing session; each block of testing consists of 20 motor evoked potentials.

These analyses further tested for the hypothesized difference in offline cumulative excitability across the week between the daily and second daily tDCS conditions.

Results

The TMS intensity required to elicit 1 mV responses was 52.9 ± 9.9% (expressed as percentage of maximum machine power) in the daily condition and 51.8 ± 8.8% in the second daily condition; there was no significant difference ($t = 1.13$, $P = 0.28$). Resting motor thresholds at the start of each week, 43.5 ± 7.7 for the daily condition and 43.6 ± 7.1 for second daily were also not significantly different ($t = -0.09$, $P = 0.93$).

The three-factor ANCOVA found a significant main effect of tDCS frequency ($F_{1,10} = 9.27$, $P = 0.01$) and time ($F_{1,10} = 9.59$, $P = 0.01$). MEP values are illustrated in Figure 2.

Cumulative excitability across the week

There was a significant interaction between tDCS frequency and day when comparing Monday and Friday results (three-factor ANCOVA, $F_{1,10} = 4.89$, $P = 0.05$) with simple effects revealing that when tDCS was administered daily, the mean MEP amplitudes were higher on Friday compared with Monday ($F_{1,10} = 4.55$, $P < 0.05$), whereas there was no difference between Monday and Friday MEP values in the second daily condition ($F_{1,10} = 2.06$, $P > 0.1$). In addition, the analysis of pre-tDCS baseline measures found a significant interaction between tDCS frequency and day (two-factor ANCOVA, $F_{1,10} = 5.58$, $P < 0.05$) with simple effects showing that the Friday baseline was significantly higher when tDCS was given daily compared to second daily ($F_{1,10} = 12.04$, $P < 0.05$), whereas normalized Monday baselines–by definition–did not differ. The analysis of motor thresholds (two-factor ANCOVA), however, did not find any significant main effect of day or tDCS frequency, nor was there a significant interaction.

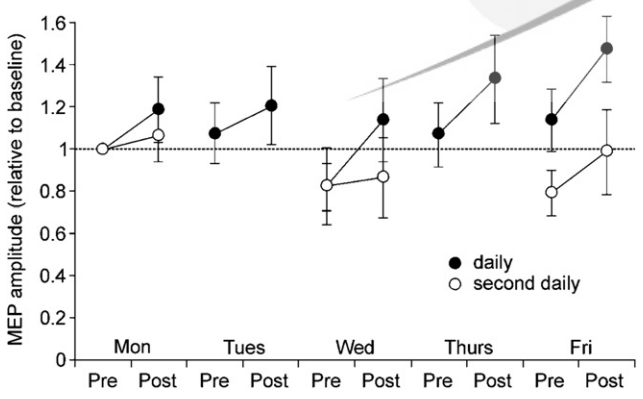

Figure 2 Mean MEP amplitudes (± SEM) before and after tDCS for each testing session.

Intrasession changes in excitability across the week

There were no significant interactions between time and day, nor between tDCS frequency, time and day (three-factor ANCOVA), indicating that across the week, the degree to which cortical excitability increased immediately after tDCS did not change (Supplementary Figure).

Discussion

Extending findings from previous studies,[2,3,17] which showed that single sessions of anodal tDCS given at 1 mA for 5 to 13 minutes induced increases in motor cortical excitability that lasted for minutes to hours post-stimulation, the current study found that tDCS given continuously at 2 mA for 20 minutes also induced changes in excitability that lasted for at least 2 hours, with further cumulative increases in excitability when sessions were repeated on a daily basis over a 5-day period.

However, we found that cumulative, offline increases in excitability did not occur when stimulation was given second daily (three sessions) over a 5-day period. This result was unchanged after controlling for any possible carryover effects of condition allocation in the first week of testing. Others have also found that the time interval between stimulation sessions was a critical factor in determining the outcomes of the second period of stimulation. For example, Monte-Silva et al.[24] found that for cathodal tDCS, lasting inhibitory effects (measured 1-2 hours after the second stimulation period) were enhanced if the two periods of stimulation were separated by 24 hours, but not when the interval was 3 hours. For anodal tDCS, Fricke et al.[25] showed that excitatory effects could be enhanced, negated or unaffected as the interstimulation period was varied between 0 and 30 minutes.

The only other study to examine the effects of multiple sessions of tDCS to the motor cortex also administered five stimulation periods on consecutive weekdays.[26] Outcomes were measured in terms of performance on a challenging motor skill task. This study showed that improvements in motor skill learning were preserved between sessions in the active but not sham stimulation group, suggesting that consecutive sessions of tDCS can consolidate motor learning and mitigate previously reported[27,28] decreases in performance after a rest period.

The current study extends these prior findings by investigating direct neurophysiologic outcomes (MEPs), comparing the effects of daily or second daily stimulation sessions across a 5-day period and testing tDCS at a higher stimulus intensity. Our results suggest that a time interval of

1 day was within the window for consolidative and cumulative excitatory effects, whereas a 2-day interval was outside the critical period for these effects.

As indicated, though, by the absence of an interaction between the factors of tDCS frequency, time and day, the greater excitability with daily tDCS cannot be explained in terms of the immediate response to each individual tDCS session being increasingly greater across the week. This suggests that the increase in excitability was the result of an "offline" effect, whereby cumulative increases in motor cortex excitability were sustained between stimulation sessions rather than resulting from an increased responsiveness to each successive tDCS session. This is supported by the analysis of baseline MEPs (i.e., pre-tDCS), which found a significantly higher Friday baseline with daily tDCS compared with second daily. In contrast, motor thresholds did not change across the week, which suggests that the altered MEPs did not result from long-term changes in membrane excitability.[29,30]

There are, however, several limitations to the present study. One is that participants were not blinded to stimulation condition (daily or second daily), although it was considered unlikely that lack of blinding to this factor would have affected the results as neither the participants nor the experimenters had preconceptions about the relative efficacy of daily and second daily tDCS. Participant blinding was not attempted also for practical reasons, for though we have found effective methods for blinding to sham tDCS for parallel designed studies,[13] it is less likely that this method would have resulted in effective blinding in a crossover trial, with participants receiving active and sham tDCS on consecutive weekdays.

It is also possible that the difference found between daily and second daily tDCS was due to the number of tDCS sessions received rather than the frequency of the sessions. Therefore, adding two further second daily sessions may have produced the same increase in cortical excitability over 9 days as that seen with five consecutive daily sessions. Indeed, a follow-up analysis comparing the first three sessions for the daily (i.e., Monday, Tuesday, Wednesday) and second daily conditions (i.e., Monday, Wednesday, Friday) did not find any difference in the increase in cortical excitability over these 3 days. This possibility thus cannot be discounted. Nonetheless, in terms of informing clinical applications, where the speed of response and total duration of the treatment period are often critical considerations, the current results suggest that within a fixed treatment period, daily tDCS would be a more effective approach than sessions spaced second daily.

Two important caveats should be noted in terms of the applicability of present results to the therapeutic stimulation field. First, these results were found in the motor cortex of healthy, young men, whereas tDCS is more commonly applied to other cortical areas in clinical populations ranging in age, gender, and medications taken. It could therefore be argued that current findings may not pertain to other cortical regions or clinical populations. However, it should be noted that neurophysiologic studies, which typically use the present motor cortex paradigm with healthy samples,[2,21] have long informed clinicians about the safety parameters and application of tDCS, and a growing literature[10,11,31,32] supports the external validity of such studies when applying tDCS to other brain regions for treating a range of conditions. Nevertheless, a daily versus second daily treatment regimen should be tested within a randomized clinical trial in the relevant patient population before conclusions are drawn about the optimal tDCS protocol for treating that condition. Second, effects were only studied over 1 week, whereas it is likely that repeated sessions of tDCS need to be given over several weeks to maximize therapeutic effects, for example as found for a related stimulation therapy, repetitive TMS, in depression.[33] For ethical reasons, we did not extend the study beyond 1 week because of the increased possibility of inducing prolonged effects in healthy volunteers with no potential therapeutic benefit.

In summary, this study found that over a 5-day period, daily tDCS led to greater increases in neuronal excitability than second daily tDCS. The effectiveness of this strategy should be tested empirically in trials for each condition for which tDCS treatment is proposed.

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Supplementary data

Supplementary data related to this article can be found online at doi: 10.1016/j.brs.2011.04.006.

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