Transcranial direct current stimulation treatment protocols: should stimulus intensity be constant or incremental over multiple sessions?

Verònica Gálvez1,2,3, Angelo Alonzo1,2, Donel Martin1,2 and Colleen K. Loo1,2,4

1 School of Psychiatry, University of New South Wales, Sydney, Australia
2 Black Dog Institute, Sydney, Australia
3 Neuroscience Group, Bellvitge Biomedical Research Institute (IDIBELL), & Mood Disorders Clinical and Research Unit, Psychiatry Department, Bellvitge University Hospital, University of Barcelona (UB), Barcelona, Spain
4 St. George Hospital, Sydney, Australia

Abstract

Interest in transcranial direct current stimulation (tDCS) as a new tool in neuropsychiatry has led to the need to establish optimal treatment protocols. In an intra-individual randomized cross-over design, 11 healthy volunteers received five tDCS sessions to the left primary motor cortex on consecutive weekdays at a constant or gradually increasing current intensity, in two separate weeks of testing. Cortical excitability was assessed before and after tDCS at each session through peripheral electromyographic recordings of motor-evoked potentials. Both conditions led to significant cumulative increases in cortical excitability across the week but there were no significant differences between the two groups. Motor thresholds decreased significantly from Monday to Friday in both conditions. This study demonstrated that, in the motor cortex, administration of tDCS five times per week whether at a constant intensity or at a gradually increasing intensity was equally effective in increasing cortical excitability.

Introduction

Interest in transcranial direct current stimulation (tDCS) as a therapeutic tool in neuropsychiatry has re-emerged recently due to its potential as a neuro-modulation technique (Nitsche et al. 2008). tDCS has been used, experimentally, to treat painlessly a wide range of neurological and psychiatric disorders, such as Parkinson’s disease (Benninger et al. 2010), migraine (Antal et al. 2011), stroke (Schlaug et al. 2008) or depression (Boggio et al. 2008; Loo et al. 2010a). Therapeutic studies using tDCS have not reached, however, a consensus regarding stimulation parameters in terms of optimizing therapeutic outcomes. Hence, the protocol approach for maximum therapeutic efficacy remains uncertain.

During tDCS, a weak electrical current is administered transcranially through rubber electrodes placed on the scalp. Studies have demonstrated that several minutes of stimulation can induce lasting changes in neuronal excitability (Nitsche & Paulus, 2001). Clinical trials of tDCS typically administered multiple sessions of tDCS on the assumption that repeated stimulation will result in cumulative and sustained changes in cerebral function (Baker et al. 2010; Benninger et al. 2010; Loo et al. 2010a; Martin et al. 2011; Mori et al. 2010). In fact, recent evidence supports the theory that the excitatory effects derived from tDCS might be cumulative both at a cortical (Alonzo et al. 2011) and a behavioural level in both healthy and clinical populations (Boggio et al. 2007, 2008; Fregni et al. 2006a, b; Loo et al. 2012; Reis et al. 2009).
Studies on tDCS safety indicate a favourable profile (Iyer et al. 2005; Nitsche & Paulus, 2000; Nitsche et al. 2004). Current experimental protocols using electrode sizes between 25 and 35 cm² and applying currents of 1–2 mA for durations of up to 20 min (resulting in charge densities of approximately 0.03–0.09 C/cm²) are considered safe in humans (Iyer et al. 2005; Nitsche & Paulus, 2000, 2001; Nitsche et al. 2003).

In the depression trials cited above, tDCS was given at 1 or 2 mA (electrode size between 25 and 35 cm²), on a daily or second daily basis with the stimulation intensity kept constant across sessions and with no major side-effects reported (Boggio et al. 2008; Loo et al. 2010a, 2012; Martin et al. 2011). It is notable, however, that with electroconvulsive therapy (ECT), which also involves multiple sessions of electrical stimulation given transcranially, increases in seizure threshold (Fricke et al. 2008) and decreases in seizure strength (McCall et al. 1997) have been found across successive treatment sessions, leading to recommendations that the stimulus dose be increased over the course of treatment (APA, 2001). Further, a recent trial found that the first ECT treatment session, although given at a substantially lower dose than subsequent sessions, nevertheless accounted for approximately 50% of overall improvement (Kellner et al. 2010). This suggests that treatment sessions early in the course do not need to be given at the maximal doses used in later sessions to attain therapeutic effectiveness. Excessive dosing, particularly early in the ECT course, may provoke strong homeostatic responses in the form of rapid rises in seizure threshold that are counter-therapeutic as rapid escalations in dose are required to maintain therapeutic efficacy in later sessions, creating a problem when dose limits are reached (Loo et al. 2010b).

While tDCS differs in several respects from ECT, being a non-convulsive treatment that uses a unidirectional current of much lower magnitude, it is nevertheless possible that homeostatic processes akin to the rising seizure threshold seen with ECT play a role. Indeed, there is some evidence that homeostatic mechanisms induced by prior tDCS stimulation can modulate the effects of subsequent stimulation sessions at inter-session intervals of minutes to hours (Fricke et al. 2011; Monte-Silva et al. 2010). As in ECT, with tDCS, dose commencement at a submaximal level with gradual increase may be a more effective treatment strategy than delivery at the maximum dose in all sessions. Thus, in this study, we investigated whether progressive increases in stimulus intensity would increase the effects of tDCS stimulation given daily over five consecutive days compared to keeping the current intensity constant.

**Method**

**Participants**

This study included 11 male, right-handed, healthy participants aged 18–40 yr (mean 24.36 yr ± 4.91) and was approved by the Human Research Ethics Committee of the University of New South Wales. All participants gave written informed consent, were screened by a medical practitioner (V. G.) in a clinical interview and were excluded if presented any of the following: any psychiatric, general medical or neurological illness; current smoking; alcohol use above Australian National Health and Medical Research Council guidelines; excessive caffeine intake; illicit drug use; herbal medication use; electronic implants (e.g. cochlear implants, pacemakers); musculoskeletal problems; skin diseases; medications that could affect brain excitability (e.g. benzodiazepines, pseudoephedrine, dextromethorphan). All participants met safety criteria for transcranial stimulation after being screened according to the Transcranial Magnetic Stimulation (TMS) Adult Safety Screen (Keel et al. 2001). Handedness was assessed according to the 10-item version of the Edinburgh Handedness Inventory (Oldfield, 1971). Females were excluded due to the effects of menstrual cycle variation on cortical excitability in women of reproductive age. There is a large body of evidence suggesting that ovarian steroids alter neuronal function in women and have important effects on cortical excitability (Smith et al. 2002).

**Experimental design**

The study utilized a randomized intra-individual cross-over design (see Fig. 1), with the two conditions being five daily sessions of anodal tDCS with either a constant current intensity across daily sessions (‘constant condition’) or a gradual increase in current strength across sessions (‘increasing condition’). The two conditions were separated by a minimum 4-wk washout period. Randomization was performed via a computer-generated random number sequence.

**TMS procedure**

TMS of the left motor cortex was performed with a figure-of-eight coil (70 mm) and a Magstim 200 machine (Magstim Company, UK). The coil was placed at the optimal position for eliciting motor-evoked potentials (MEPs) from the right first dorsal interosseus (FDI) and held tangentially to the skull with the handle oriented postero–laterally.
Measurements of motor cortical excitability

Surface electromyography (EMG) was recorded from the right FDI with disposable disc electrodes (Ag–AgCl) placed on a tendon-belly arrangement on the muscle. To guarantee identical electrode position over the muscle belly in every experimental session over the week of testing, the point at which the electrode was centred was marked on the skin with a waterproof pen on the first day, covered at the end of each session with adhesive tape and re-marked at the beginning of all subsequent experimental sessions. 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, UK).

Anodal tDCS was administered through a pair of conductive rubber electrodes covered by saline-soaked sponges (7 x 5, 35 cm²) using methods previously described (Loo et al. 2011). The current was delivered continuously at 2 mA for 20 min through a battery-driven constant-current stimulator (Eldith-DC; NeuroConn GmbH, Germany). The anode was positioned over the left primary motor cortex area representing the right FDI as identified beforehand with TMS and the cathode over the right supraorbital area. This electrode arrangement is known to produce significant excitability changes in human motor cortical activity (Nitsche & Paulus, 2001). Participants were blinded to the experimental conditions.

Experimental procedure

Participants were seated in a chair with their arms placed on a pillow. They were trained on keeping the right arm still during the procedure. To guarantee a constant attentional level and optimal level of arousal over the experiment (Conte et al. 2007), participants were told to stay relaxed, awake, keep the attention at the same level and not think about things of major personal importance (Fricke et al. 2011). To ensure relaxation, visual EMG feedback was given. EMG recording electrodes were placed on the right FDI muscle. The motor cortical representational field of the right FDI was then identified through single TMS pulses and the coil position was marked on the scalp with a waterproof pen. To guarantee optimal and consistent coil positioning over the motor cortex for every session, the spot was re-marked on the scalp and covered by a plastic self-adhesive tape at the end of every session. In addition, this position was confirmed at the beginning of the experimental session of each day as the optimal site for evoking MEP in the FDI, using single TMS test pulses.

Resting motor threshold (MT), defined as the lowest TMS intensity at which a MEP of at least 0.05 mV was produced in three out of six responses, was measured prior to the test session on the Monday and Friday of each week. In addition, on the Monday of each week, the TMS intensity required to elicit an average MEP response of 1 mV was established. This testing intensity was then used for all MEP measurements for that week. Twenty TMS pulses were given at this intensity.
Statistical analyses

For each participant, the 20 MEP amplitudes measured at each time-point were averaged and normalized to the initial baseline MEP measure for that experimental week. As the main study aim was to measure net changes in excitability as a result of tDCS, rather than the time-course of changes per se, and because MEP measurements are typically highly variable, post-tDCS MEP values for each session were collapsed into a single post-tDCS mean value for further analysis.

To test the effect of each condition on cumulative cortical excitability, a $2 \times 2 \times 5$ fully repeated measures analysis of variance (ANOVA) was conducted with the factors being tDCS condition (constant and increasing), time (pre-tDCS and post-tDCS) and day (Monday–Friday). A $2 \times 5$ fully repeated measures ANOVA was also conducted for baseline (pre-tDCS) MEP with the factors of tDCS condition (constant and increasing) and day (Monday–Friday) to test for lasting, ‘off-line’ excitatory effects. In both analyses, a priori contrasts with Bonferroni’s correction for multiple comparisons tested for pairwise differences on the factor of day, comparing results between Monday and each subsequent day.

In addition, to test whether any observed changes in MEP amplitude over the week were the result of changes in resting MT, a $2 \times 2$ fully repeated measures ANOVA was conducted for the MT measures with tDCS condition (constant and increasing) and day (Monday and Friday) being the two factors.

Results

The TMS intensity required to elicit an average of 1 mV MEP (expressed as percentage of maximum machine power) on the Monday of each testing week was $50.0 \pm 12.48$ in the constant condition and $49.64 \pm 11.79$ in the increasing condition; there was no significant difference ($t_{10} = 0.25, p = 0.81$). Resting MTs at the start of each week, $41.1 \pm 9.9$ for the constant condition and $41.4 \pm 8.4$ for the increasing condition, were also not significantly different ($t_{9} = 0.28, p = 0.78$).

All participants tolerated tDCS with no major side-effects reported. For the three factor ANOVA, there was no significant main effect of tDCS condition ($F_{1,10} = 0.27, p = 0.61$), although there was a significant main effect of time ($F_{1,10} = 5.27, p < 0.05$) and significant differences in the planned comparisons between Monday and Thursday ($F_{1,10} = 7.71, p < 0.05$) and Monday and Friday ($F_{1,10} = 11.79, p < 0.05$). The pairwise comparisons between Monday and Tuesday and Monday and Wednesday were not significant. There were also no significant interactions.

In the $2 \times 5$ ANOVA, baseline (pre-tDCS) values did not differ between conditions. Although similar to the main analysis, there was a significant difference in baseline values between Monday and Thursday ($F_{1,10} = 7.32, p < 0.05$) and Monday and Friday ($F_{1,10} = 12.44, p < 0.05$), but no interaction effects.

The analysis of MT showed a significant difference ($F_{1,10} = 26.60, p < 0.01$) between Monday (mean = $41.1 \pm 9.9$ for the constant condition, mean = $41.4 \pm 8.4$ for the increasing condition) and Friday (mean = $39.3 \pm 10.0$ for the constant condition, mean = $38.7 \pm 8.8$ for the increasing condition), with no significant main effect of condition, nor a significant interaction between condition and day.

Discussion

Congruent with previous studies (Nitsche & Paulus, 2001), the present study found that anodal tDCS produced an increase in motor cortex excitability post-stimulation. Furthermore, this study found that successive sessions of anodal tDCS, given either at a constant strength over five consecutive days or gradually increasing the dosage over the same duration, produced increases in excitability that were cumulative and could last for at least 2 h post-stimulation (see Fig. 2). However, there was no difference between the two strategies in the degree of excitability produced, with Friday pre-stimulation values being significantly higher than Monday pre-stimulation values. In addition, for both conditions, the resting MT on Friday was significantly lower than the threshold on Monday, suggesting a number of potential mechanisms in action: an increase in membrane excitability (Ardolino et al. 2005), an increase in
Fig. 2. Baseline (BL) [pre-transcranial direct current stimulation (tDCS)] and post-tDCS motor-evoked potential (MEP) values (±S.E.M.) across the week in both testing conditions (constant vs. increasing). For both conditions, MEPs were significantly higher by Thursday and Friday compared to the Monday MEPs. In addition, Friday BL MEPs were significantly higher than Monday BL MEPs. There were no significant differences between the two conditions.
the excitability of the axons of the stimulated neurons or an increase of the excitability of synaptic connections, at both the cortical and spinal level (di Lazzaro et al. 2008; Paulus et al. 2008). Although mechanisms underlying long-lasting effects of tDCS have yet to be elucidated, especially those regarding repetitive, spaced tDCS sessions, it is highly possible that these long-lasting functional changes in the motor cortex occur via synaptic plasticity mechanisms, modulating the strength of the underlying synaptic connections (Stagg & Nitsche, 2011) and therefore suggesting a long term potentiation phenomenon. This may also account for the apparent ‘offline’ effect in both experimental conditions, whereby cortical excitability resulted from cumulative increases in excitability sustained between stimulation sessions rather than from an increased responsiveness to each successive tDCS session.

Previous studies have analysed the effect of consecutive tDCS sessions on motor cortex excitability through different testing protocols. Interestingly, Monte-Silva et al. (2010) found that the effects of anodal tDCS were increased if a second period of stimulation was given during the after-effects of the first one, but was reduced if the second stimulation was given when the after-effects of the first stimulation had disappeared. However, results from Fricke et al. (2011) indicate that the effect of repeated short periods of anodal and cathodal tDCS follow a time-dependent rule compatible with homeostatic mechanisms. The most likely explanation for this non-uniformity of results may lie in the longer durations of tDCS used by Monte-Silva et al. (2010), which could allow time for other processes to develop (e.g. brain-derived neurotrophic factor secretion) that replace the shorter-lasting effects on voltage gated calcium channels suggested by Fricke et al. (2011) to underlie the homeostatic plasticity mechanisms indicated by their results. Further, the differing results observed between Fricke et al. (2011) and the present study may also be due to differences in the mechanisms or the neurons affected, the timing of the stimulation or the duration of the induced shifts in excitability (Fricke et al. 2011).

In particular, differences between Fricke et al. (2011) and the present study may be due to the timing of the inter-tDCS intervals. While in Fricke et al. (2011), successive shorter tDCS sessions (5–7 min) were separated by a maximum of 30 min, in the present study, successive 20-min tDCS sessions were administered with a break of 24 h over five successive days. Within this longer period between stimulation sessions, homeostatic mechanisms may no longer exert an effect such that successive tDCS sessions may have added to previous increases in cortical excitation. In addition, our stimulation protocol could also have developed other plasticity processes, such as those depending on protein synthesis, which, in turn, could have contributed to the long-lasting excitatory effects observed in our sample.

Present results, however, do not preclude the possibility that higher current intensities or greater differences in current intensity across sessions could lead to differences in excitation. For safety reasons, a maximum current amplitude of 2 mA was used (Iyer et al. 2005). As our aim was to investigate the optimal approach to therapeutic stimulation, we chose to compare two stimulus protocols that would putatively yield the greatest effects, i.e. (1) applying tDCS at the maximum protocol intensity in all stimulation sessions or (2) starting at a lower intensity and gradually increasing this to the maximum over the stimulation sessions. Thus, the two protocols did not use an equivalent total charge across the five sessions and it is possible that this negated an actual advantage conferred by the strategy of gradually increasing the stimulus intensity. Although a study design comparing two protocols that delivered the same total charge would answer this question, we considered it more important to investigate the two most therapeutically relevant approaches. Unlike ECT, in which higher electrical doses lead to greater risks of cognitive side-effects (Sackeim et al. 1993), with tDCS, no significant side-effects have been described with repeated sessions given at the maximum dose level currently used in clinical trials (Boggio et al. 2008; Loo et al. 2012). Congruent with previous results, no significant side-effects were found. Thus, there was no reason for tDCS not to be given at the maximum level for all sessions in the constant condition.

A limitation of this study is that it only tested tDCS over five sessions given on consecutive weekdays, whereas it is likely that therapeutic applications, for example, in depression, would require repeated sessions over several weeks for optimal effects (Loo & Mitchell, 2005). Therefore, it is possible that significant differences between the two stimulation protocols would be evident if tested over 10–20 sessions. For ethical reasons, given the involvement of healthy volunteers for whom there was no potential benefit from repeated tDCS sessions, we did not extend the stimulation periods beyond 5 d.

Two important caveats should be noted in terms of interpretation and applicability of these results to the clinical field. One is the fact that our design did not include a control group. Without this group, it may be contended that the increase in excitation towards the
end of the week by both experimental groups may not have been the result of successive tDCS sessions. However, to our knowledge there is no evidence to suggest that there should be a natural, systematic increase in cortical excitation across the week in the absence of any interventions. Even though cortical excitability may be a highly variable measure between individuals, our study methodology minimized this type of variability by using a within-subjects design. Furthermore, a recent study by Alonzo et al. (2011), using the same methodology, found that consecutive tDCS sessions on a daily basis over a 5-d period caused a significant increase in cortical excitability across the week, whereas second daily tDCS over the same period did not. This suggests that changing tDCS parameters can differentially alter cortical excitability and that any changes across the week would not simply be a consequence of natural excitability changes from Monday to Friday. Second, these results have been found in the motor cortex of healthy male volunteers, while tDCS is more likely to be applied to other cortical areas in clinical populations. It could therefore be argued that the present findings could not be extrapolated into clinical populations. Nevertheless, a large body of literature supports the external validity of motor cortex studies when applying tDCS to other cerebral areas for treating experimentally a wide range of neuropsychiatric conditions, ranging from depression (Loo et al. 2010a, 2012; Martin et al. 2011) to neuropathic pain (Fregni et al. 2006b; Soler et al. 2010) or tinnitus (Vanneste et al. 2010). Moreover, our results in the motor cortex support results obtained in therapeutic tDCS trials, in which the effect of repeated tDCS sessions has been shown to have cumulative behavioural effects (Boggio et al. 2007, 2008; Fregni et al. 2006a,b; Loo et al. 2012). Cortical excitability changes are, ultimately, the predecessors of behavioural changes (Stagg & Nitsche, 2011). However, the present protocol 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 clinical conditions. Among neurophysiological studies performed on the motor cortex, the present study is one of only two studies to show that successive sessions of tDCS lead to cumulative increases in cortical excitation (Alonzo et al. 2011).

Although preliminary, this study has important implications for the therapeutic use of tDCS. From a practical perspective, a gradual increase in stimulus intensity over the first few sessions may not compromise therapeutic efficacy and may be useful, for example, in patients prone to stimulation-induced headaches as we have noticed in clinical trials of tDCS that headaches tend to occur in stimulation sessions earlier in the treatment course (unpublished observations). On the other hand, there is currently no compelling evidence for commencing tDCS at submaximal stimulation levels and gradually increasing this over the treatment period.

Additional research is needed to establish optimal tDCS neuromodulation protocols for therapeutic purposes, including further investigation of different current intensities.

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Statement of Interest

None.

References


Soler MD, Kumru H, Pelayo R, Vidal J, et al. (2010). Effectiveness of transcranial direct current stimulation...
