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RESEARCH ARTICLE

Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation

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Abstract The capacity for transcranial direct current stimulation (tDCS) to increase learning and cognition shows promise for the development of enhanced therapeutic interventions. One potential application is the combination of tDCS with cognitive training (CT), a psychological intervention which aims to improve targeted cognitive abilities. We have previously shown that tDCS enhanced performance accuracy, but not skill acquisition, on a dual *n*-back working memory (WM) CT task over repeated sessions. In the current study, we investigated the optimal timing for combining tDCS with the same CT task to enhance within and between session performance outcomes across two daily CT sessions. Twenty healthy participants received in a randomised order 30 min of anodal tDCS to the left dorsolateral prefrontal cortex immediately before ('offline' tDCS) and during performance ('online' tDCS) on a dual *n*-back WM CT task, in an intra-individual cross-over design. Analyses examined within and between session consolidation effects of tDCS on CT performance outcomes. Results showed that 'online' tDCS was associated with better within session skill acquisition on the CT task, with a significant difference found between conditions the following day. These results suggest that 'online' tDCS is superior to 'offline' tDCS for enhancing skill acquisition when combining anodal tDCS with CT. This finding may assist with the development of enhanced protocols involving the combination of tDCS with CT and other rehabilitation protocols.

Keywords Cognitive training · Timing · Transcranial direct current stimulation · Working memory

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Introduction

Modulation of cortical excitability through the use of non-invasive brain stimulation shows promise for the development of novel therapeutic applications involving new learning and cortical reorganisation, for example, in rehabilitation following illness or injury. Transcranial direct current stimulation (tDCS) has emerged as an effective tool for this purpose, with studies in the motor cortex showing that when anodal tDCS is given at low current intensities for short durations, there are associated and sustained increases in cortical excitability (Nitsche and Paulus 2000, 2001; Batsikadze et al. 2013). These effects have further been shown to be cumulative, with daily repeated sessions associated with incremental increases in excitability over a 1-week period (Alonzo et al. 2012; Galvez et al. 2013). The cumulative effects demonstrated in these studies may underlie the early success of tDCS for the treatment of neuropsychiatric conditions, such as depression and schizophrenia (e.g. Loo et al. 2012; Kalu et al. 2012; Brunelin et al. 2012; Brunoni et al. 2013). In addition, they have led to increased interest into the use of tDCS as a method to

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enhance or 'boost' behavioural interventions, for example, motor learning and rehabilitation following stroke (Reis et al. 2009; Lindenberg et al. 2010; Fridriksson et al. 2011; Halko et al. 2011; Bolognini et al. 2011; Schambra et al. 2011), and more recently, cognitive rehabilitation (Ditye et al. 2012; Martin et al. 2013b; Leśniak et al. 2013; Park et al. 2013).

In a recent randomised sham-controlled trial, we investigated whether tDCS could enhance outcomes from cognitive training (CT), a common method of cognitive rehabilitation which aims to improve targeted cognitive abilities (Martin et al. 2013b). In this study, active or sham anodal tDCS was given to the left dorsolateral prefrontal cortex (LDLPFC) together with concurrent ('online') CT on a dual *n*-back working memory (WM) task, over ten daily sessions conducted across consecutive weekdays. Results showed that participants who received active tDCS improved in terms of enhanced performance accuracy (*d* prime), but not overall skill acquisition (difficulty '*n*'), on the CT task across the combined sessions. This study aimed to further investigate these effects by examining the optimal timing for combining tDCS with CT.

The timing of administration of tDCS in relation to task execution has been identified as important for behavioural outcomes with tDCS. Both 'online' effects (that is, during the administration of tDCS) and 'offline' effects (where administration of tDCS is immediately before task performance) have been studied. For example, anodal tDCS when applied to the motor cortex 'online' increased motor learning, although 'offline' tDCS decreased learning (Stagg et al. 2011). Interestingly, opposing effects have been found in the primary visual cortex, with only 'offline' (but not 'online') anodal tDCS found to increase visual perceptual learning (Pirulli et al. 2013). For enhancing executive functioning, anodal tDCS to the LDLPFC has been shown to improve performance on multiple abilities, including WM (Brunoni and Vanderhasselt 2014), verbal generativity (Iyer et al. 2005) and implicit decision-making (Kincses et al. 2004). When applied to the LDLPFC, behavioural facilitation has been found with both 'online' (Kincses et al. 2004; Iyer et al. 2005; Fregni et al. 2005; Ohn et al. 2008; Andrews et al. 2011; Teo et al. 2011; Javadi and Walsh 2012; Martin et al. 2013b) and 'offline' (Cerruti and Schlaug 2008; Zaehle et al. 2011; Loo et al. 2012) tDCS. However, for LDLPFC tDCS, the issue of the timing of tDCS in relation to performance outcomes has not been systematically investigated. Determining the optimal timing for applying tDCS to the LDLPFC to enhance behavioural outcomes is of particular interest as deficits in executive functions are key features of neuropsychiatric illnesses such as schizophrenia, and the development of novel therapeutic interventions to address these deficits is therefore of clinical importance.

The present study was thus designed to directly test the effects of the timing of application of tDCS (i.e. 'online' vs 'offline') on performance on the same dual *n*-back WM CT task used in our prior study (Martin et al. 2013b), so as to optimise the method for combining tDCS with CT. We hypothesised that 'online' LDLPFC tDCS would be optimal for modulating performance on the CT task in line with previous research in the motor cortex (Stagg et al. 2011).

Method

Participants

Twenty healthy right-handed participants completed the study. Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield 1971). Exclusion criteria were concurrent medication likely to affect mental performance, current history of drug or alcohol abuse or dependence in the last 3 months, any psychiatric or neurological disorder, recent head injury (in the last 3 months) or history of seizure or stroke. This study was approved by the human research ethics committee of the University of New South Wales, Sydney and performed in accordance with the principles outlined in the Australian National Statement of Ethical Conduct in Human Research. Written informed consent was obtained from all participants prior to study commencement.

Procedure

The study used an intra-individual crossover experimental design. All participants received both active LDLPFC tDCS immediately before (i.e. 'offline' tDCS) and during performance (i.e. 'online' tDCS) on the CT task. Participants were randomised to commence with online or offline tDCS in a counterbalanced order (1:1 ratio). The online and offline test conditions were separated by at least 1 month. For each condition, participants attended on two consecutive days. This was done to assess within session effects of tDCS on CT task performance and also between session consolidation of performance on the following day. On day 1, half of the participants (group A) received 'offline' tDCS before CT and then returned the next day (day 2) to complete the CT task without tDCS. The other half of the participants (group B) received 'online' tDCS during CT, before returning on day 2 to complete the CT without tDCS. In the 'offline' condition, CT was commenced immediately following tDCS, and in the 'online' condition, CT was commenced 5 min after tDCS onset. CT was approximately 25 min in duration to coincide with the 30 min of 'online' tDCS, consistent with our previous study (Martin et al. 2013b). Participants in both groups then

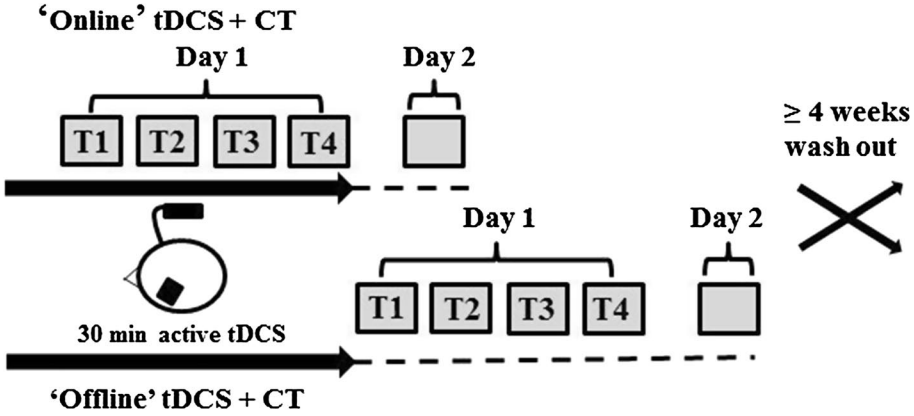

Fig. 1 Study design. *Notes Solid line* represents active tDCS. *tDCS* transcranial direct current stimulation, *CT* cognitive training, '*T*' five blocks of trials on the CT task

returned to complete the second condition following a wash out period of at least 1 month. The experimental design for the study is shown in Fig. 1.

tDCS

For both conditions, tDCS was given continuously for 30 min at 2 mA using an Eldith DC-simulator (NeuroConn GmbH, Germany). The anode (7 × 5 cm, 35 cm^2) was placed over the left F3 electrode site (identified on the scalp using an EEG cap based on the 10/20 system), and the cathode (10 × 10 cm, 100 cm^2) was placed extracephalically on the right upper arm (Martin et al. 2011). The use of an extracephalic cathode was used to prevent cathode-related inhibitory effects at a cortical site. Conductive rubber electrodes covered by sponges soaked in saline were used and held in place by rubber bands. For both conditions, the current was gradually increased over 30 s. At the end of each session, participants were asked to report any side effects using a structured checklist as previously described (Martin et al. 2013a).

Cognitive training task

An adaptive dual *n*-back WM task (BrainFitnessPro, Mindsparke Software) was administered via computer on each day for both conditions. This is the task used in our prior study (Martin et al. 2013b). Prior to commencing the first session, participants firstly were given a verbal explanation of the task before having an opportunity to practice the task at level $n = 2$ for a minimum of three blocks of 20 trials until total hits were ≥50 %. During the task, participants were required to respond to two independent streams of stimuli, auditory and visual. The visual stimuli were presented in a 3 × 3 square grid, and the auditory stimuli (nine letters) were simultaneously presented at a rate of 3 s. Participants were required to press the 'A' key whenever the currently presented visual stimulus (square) was at the same position as the one *n* stimuli preceding it, and the 'L' key whenever the auditorily presented letters matched the same as *n* positions back in the sequence. The difficulty '*n*' was the same for both modalities of stimuli. Each session consisted of 20 blocks of trials. For every block of trials (each block = 20 + *n* trials), there were always six visual and six auditory hits with one of each being coincident. The level of task difficulty '*n*' was adjusted after each block of trials, and the level of difficulty of the task adapted according to participants' performance, such that difficulty '*n*' was increased by one if two or fewer mistakes were made in each modality (e.g. $n = 2$ becomes $n = 3$), or decreased by one if more than four mistakes were made per modality. Outcome measures for this task were the level of difficulty '*n*', and the average *d* prime (d') averaged for each five blocks of trials (i.e. T1–T4). d' was calculated from measurement of the hit rate and false alarm rate [i.e. $d' = Z$ (hit rate) – Z (false alarm rate)] for each block of trials in each session.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 20.0 (IBM corp., Armonk, NY). Repeated-measures ANOVAs examined performance outcomes (difficulty '*n*' and d') on the CT task. Within session effects were analysed with the within subject factors being condition ('online' or 'offline' tDCS with CT) and time (i.e. 4 time points for day 1, with each time point being the average of five trial blocks). Between session consolidation of performance was similarly analysed though with the within subject factor time being the last time point for day 1 (i.e. T4) and the first time point for day 2. For all analyses, the factor of session order (i.e. group A or B) was included as a covariate. Analyses of simple effects were conducted to interpret significant interaction effects. Post hoc tests examined differences between the conditions at each time point. Statistical significance was set at $p < .05$.

Results

Participants

tDCS was well tolerated with only minimal side effects reported, including skin redness, and an itching or slight burning sensation felt underneath the electrodes during stimulation. One participant's data were excluded from analysis because their results (d') significantly deviated from the remainder of the sample (i.e. >3 SDs). The mean age of the participants was 22.8 years (SD = 3.2), 63 % were male ($N = 12$), and the average years of education was 14.8 (SD = 2.1).

Within and between session effects of timing of tDCS on skill acquisition

Results from the repeated-measures ANOVAs examining within and between session effects are shown in Table 1. For difficulty '*n*', the main effect of condition and time × condition interaction was highly significant ($p < 0.001$ and $p < 0.01$, respectively), with better overall performance found in the 'online' tDCS condition. Analysis of simple effects revealed no effect of time for the 'online' condition [$F(3,15) = .54$, $p = 0.67$], although a significant effect of time for the 'offline' condition [$F(3,15) = 3.91$, $p = 0.03$]. For between session effects, there were main effects of condition and time, though the time × condition interaction failed to reach significance ($p = 0.09$). A significant difference in performance between conditions was found on day 2 (see Fig. 2).

Table 1 Results of the repeated-measures ANOVAs for within and between session performance effects on the CT task

Outcomes	Factor	*df*	*F*	*p*	η^2
Difficulty '*n*'					
Within session	Condition	1	19.0	<.001**	.528
	Time	3	1.95	.134	
	Time × condition	3	4.37	.008**	.204
Between session	Condition	1	12.6	.002**	.426
	Time	1	5.16	.036*	.233
	Time × condition	1	3.26	.089	
d'					
Within session	Condition	1	3.65	.073	
	Time	3	2.49	.128	
	Time × condition	3	.05	.983	
Between session	Condition	1	5.69	.029*	.251
	Time	1	.04	.848	
	Time × condition	1	.03	.862	

For all models, the effect of order was included as a covariate

** $p < 0.01$; * $p < 0.05$

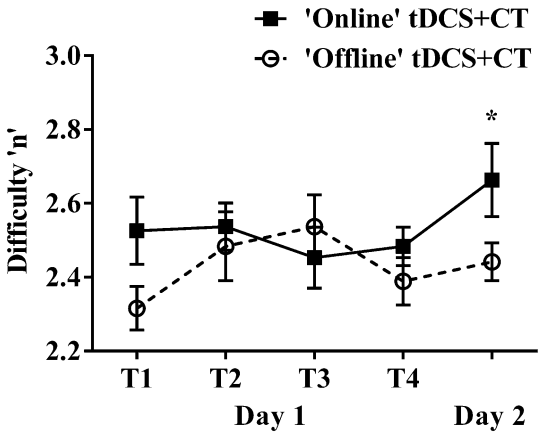

Fig. 2 Within and between session effects of 'online' and 'offline' tDCS on skill acquisition on the cognitive training task. *Notes tDCS* transcranial direct current stimulation, *CT* cognitive training. *Error bars* represent standard errors. *p <0.05

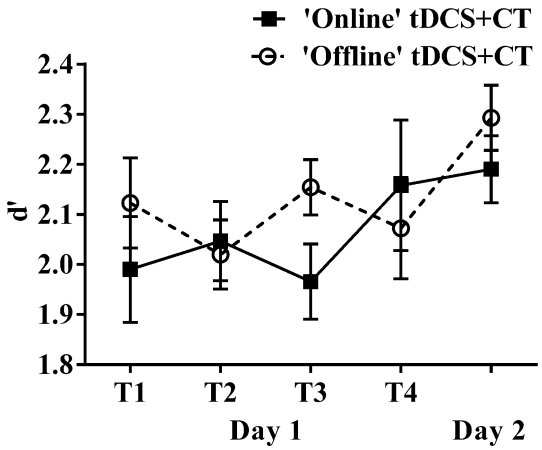

Fig. 3 Within and between session effects of 'online' and 'offline' tDCS on performance accuracy on the cognitive training task. *Notes tDCS* transcranial direct current stimulation, *CT* cognitive training. *Error bars* represent standard errors. *p <0.05

Within and between session effects of timing of tDCS on performance accuracy

For discriminability (d'), the main effect of condition differed at a trend level (better performance in the 'offline' condition). For between session performance, the main effect of condition was significant indicating better overall performance accuracy with the 'offline' condition (see Fig. 3).

Discussion

In the present study, we explored the effect of timing of the application of tDCS on performance outcomes for tDCS

combined with CT. Results showed better within session skill acquisition occurred with 'online' tDCS relative to 'offline' tDCS, with significantly better performance found the following day. In contrast, performance accuracy (d') tended to be better with 'offline' tDCS.

The cognitive effects of anodal tDCS when given to the LDLPFC have been extensively studied, particularly in relation to WM (Fregni et al. 2005; Ohn et al. 2008; Andrews et al. 2011; Teo et al. 2011; Zaehle et al. 2011; Martin et al. 2013b; Brunoni and Vanderhasselt 2014). The efficacy of tDCS to enhance WM performance, however, has varied between studies, likely due to methodological differences, including the timing of the application of tDCS in relation to task execution, differences in WM tasks and tDCS stimulus parameters (e.g. current strength, duration of stimulation and electrode size and placements), as well as possibly inter-individual differences, which affect participants' response to tDCS. Using a 3-back WM task, 'online' anodal tDCS to the LDLPFC has been associated with increased performance accuracy (Fregni et al. 2005; Ohn et al. 2008), with improvements in one study found to be maintained for 30 min following tDCS cessation (Ohn et al. 2008). Similarly, we found enhanced performance accuracy (i.e. d') with 'online' tDCS given to the LDLPFC on a dual *n*-back WM CT task relative to sham tDCS over repeated sessions (Martin et al. 2013b).

The current results extend this previous work by demonstrating that during within session performance of WM CT combined with tDCS, participants showed better skill acquisition with 'online' (concurrent) tDCS relative to with 'offline' tDCS, with a significant difference found between conditions the following day. During performance on the CT task, the difficulty level was automatically adjusted after every trial block (20 per session). With repeated practice of the task, the average level of difficulty gradually increases over repeated CT sessions, reflecting learning and skill acquisition (Jaeggi et al. 2008; Martin et al. 2013b; Redick et al. 2013). In the current study, participants obtained an overall higher level of difficulty on the CT task when tDCS was given simultaneously during CT task performance (i.e. 'online' tDCS), suggesting better overall skill acquisition with 'online' relative to 'offline' tDCS.

These results are consistent with previous research showing increased learning with 'online', but not 'offline', anodal tDCS given to the motor cortex (Stagg et al. 2011), suggesting that the principle of enhancing activation of neuronal pathways *during* practice tasks to increase training results may also apply to brain regions other than the motor cortex. Recent neuroimaging work examining the time course of frontal tDCS stimulation effects suggest brain activation is greater during than after stimulation (Stagg et al. 2013; Rae et al. 2013). Due to the functional importance of the LDLPFC to WM performance (Mottaghy et al. 2000; Mull and Seyal 2001), the current results could therefore be interpreted to suggest that the degree of LDLPFC activation from tDCS during WM task performance is important for performance effects.

Enhanced skill acquisition with 'online' tDCS combined with motor training over repeated sessions has been shown in a number of previous studies (Reis et al. 2009, 2013; Schambra et al. 2011). Interestingly, in these studies, differential effects of tDCS on within and between session consolidation effects were found, with results showing that the majority of the learning effects occurred through tDCS enhancement of between session consolidation of skill acquisition and that simultaneous 'online' tDCS during training was necessary to obtain these gains. Although in the current study the consolidation of skill acquisition between the tDCS timing conditions failed to reach statistical significance, the advantage of 'online' tDCS was evident the next day, as shown by a significant difference between conditions on day 2. Enhanced consolidation with 'online' tDCS has been shown to occur in the first few hours following training (Reis et al. 2013). Due to the limited within session advantage of tDCS (Reis et al. 2009, 2013; Bullard et al. 2011), better consolidation may in turn be the primary mechanism by which anodal tDCS facilitates learning in combined protocols over repeated sessions.

In contrast, results suggested performance accuracy (i.e. discriminability performance, d') was better in the 'offline' condition on the CT task. The poorer performance accuracy with 'online' relative to 'offline' tDCS between sessions may have been due to a trade-off for the greater task difficulty between sessions with 'online' tDCS.

A limitation to this study was that there was no control (i.e. sham) condition included so we were unable to compare different tDCS timing effects to performance outcomes without tDCS. Stagg et al. (2011) showed that 'offline' tDCS decreased motor learning, so a possible alternative explanation for the current findings may be that 'offline' tDCS had an inhibitory effect on learning, consistent with proposed homeostatic metaplastic mechanisms (Siebner et al. 2004). In line with this interpretation are the results from a recent study in the motor cortex showing 2 mA anodal tDCS given for 26 min decreased cortical excitability for up to 60 min immediately following stimulation (Monte-Silva et al. 2013). Notwithstanding the possibility of inhibitory effects with 'offline' tDCS, the current results nevertheless are consistent with Stagg et al. (2011) in providing further support to the use of 'online' rather than 'offline' tDCS in combined protocols.

This is the first study to explore the issue of the timing of tDCS applied to the LDLPFC combined with CT. The study showed differential effects on within and between session performance outcomes with tDCS combined with

CT due to the timing of the application of tDCS. Our results suggest that 'online' tDCS was better than 'offline' tDCS for enhancing skill acquisition when combining tDCS with CT. These results together have the potential to inform the development of tDCS-enhanced protocols in training and rehabilitation. As the training-enhancing effects of tDCS are further explored and perhaps extended to other applications, care, however, should be taken to tailor the tDCS stimulation approach for each neuropsychiatric application and brain region, rather than simply transposing motor or prefrontal stimulation protocols, with attention to considerations of electrode montage and current direction relative to target regions (Bai et al. 2014).

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