Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants

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Abstract

Computer-administered cognitive training (CT) tasks are a common component of cognitive remediation treatments. There is growing evidence that transcranial direct current stimulation (tDCS), when given during cognitive tasks, improves performance. This randomized, controlled trial explored the potential synergistic effects of CT combined with tDCS in healthy participants. Altogether, 60 healthy participants were randomized to receive either active or sham tDCS administered during training on an adaptive CT task (dual n-back task), or tDCS alone, over 10 daily sessions. Cognitive testing (working memory, processing speed, executive function, reaction time) was conducted at baseline, end of the 10 sessions, and at 4-wk follow-up to examine potential transfer effects to non-trained tasks. Altogether, 54 participants completed the study. Over the 10 ‘online’ sessions, participants in the active tDCS+CT condition performed more accurately on the CT task than participants who received sham tDCS+CT. The performance enhancing effect, however, was present only during tDCS and did not result in greater learning (i.e. improvement over sessions) on the CT task. These results confirm prior reports of enhancement of cognitive function during tDCS stimulation. At follow-up, the active tDCS+CT group, but not the sham tDCS+CT group, showed greater gains on a non-trained test of attention and working memory than the tDCS-only group (p<0.01). Although this gain can mainly be attributable to training, this result suggests that active tDCS may have a role in further enhancing outcomes.

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Introduction

Cognitive remediation is defined as: ‘a behavioral training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization.’ (Cognitive Remediation Experts Workshop, Florence, Italy, April 2010). A commonly used form of intervention is computer-facilitated cognitive training (CT). This form of cognitive remediation has been found to be effective, with results of a meta-analysis showing a moderate sized transfer effect on general cognition of $d=0.38$ (Grynszpan et al., 2011). Many of these CT interventions target working memory (WM) in particular, due to increasing evidence that training WM is effective in generating transfer effects, causing broader cognitive improvement (Klingsberg et al., 2002, 2005; Jaeggi et al., 2008, 2010). While effective, CT interventions are limited by the fact that many are time-consuming, with treatments generally
requiring multiple sessions weekly with interventions spanning at least 5 wk (Grynszpan et al., 2011). This is particularly problematic for clinical populations where motivation and treatment adherence are pertinent issues. As such, there is scope for new methods to enhance outcomes and increase the clinical utility of such treatments.

Recently there has been considerable interest in the use of transcranial direct current stimulation (tDCS) to improve cognition (Fox, 2011). tDCS is a non-invasive technique that involves passing a direct electrical current through the cerebral cortex via electrodes placed upon the scalp. The current is of low amplitude and below the threshold for action potential induction, but leads to changes in neuronal excitability through membrane polarization and changes in synaptic strength (Arul-Anandam and Loo, 2009). The technique can be used to change the excitability of neurons in a polarity-dependent manner, such that spontaneous neural activity within a specific region can be either increased or decreased depending under which electrode it is placed (i.e. the anode or positive electrode or the cathode or negative electrode). After only a few minutes of stimulation, changes in cortical excitability that lasted well over 1 h have been demonstrated (Nitsche and Paulus, 2000, 2001).

In healthy adults, a single session of tDCS using small currents (1–2 mA) has been shown to transiently improve ‘online’ (i.e. during the period of stimulation) cognitive performance on executive tasks (e.g. verbal fluency; Iyer et al., 2005), WM tasks (Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011) and measures of learning and memory (Flöel et al., 2012; Javadi and Walsh, 2012). These findings have exciting potential therapeutic implications, particularly for rehabilitation. Preliminary evidence indicates that, when multiple repeated tDCS sessions are combined with either standard training or standard rehabilitation protocols for motor or language recovery following stroke, greater gains are made than with training or standard rehabilitation treatments alone (Reis et al., 2009; Lindenberg et al., 2010; Fridriksson et al., 2011; Ditye et al., 2012). While the current findings using repeated tDCS sessions in combination with training have so far been limited to using tDCS primarily to enhance motor learning and recovery, there is potential for tDCS also to be used to enhance higher level cognitive skills, for example, those targeted in cognitive remediation, such as WM.

In the current study we investigated a novel approach for enhancing the clinical utility of cognitive remediation, by directly investigating whether tDCS enhanced performance on an adaptive CT task and improved cognitive outcomes from CT. Specifically, we hypothesized that tDCS combined with CT would elicit better performance on the CT task than sham tDCS combined with CT and that the combination of active tDCS with CT would generate greater transfer effects on non-trained tasks than either sham tDCS with CT or tDCS alone.

Method
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. Participants were each paid $200 upon completion of the study.

Participants
Participants were 60, healthy, right-handed adults (university students) recruited through an advertisement on the university careers website. Exclusion criteria were: concurrent medication likely to affect cognitive performance; pregnancy or possible pregnancy; history of drug or alcohol abuse or dependence in the last 3 months; any current psychiatric or neurological disorder; recent head injury (in the last 3 months); history of seizure or stroke. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). Scores >40 were considered indication of right-handedness. The progression of participants through the trial is shown in Fig. 1.

Procedure
Prior to the baseline assessment, participants were randomly assigned to one of three experimental groups in a ratio of 2:2:1: active tDCS with CT (active tDCS+CT); sham tDCS with CT (sham tDCS+CT); active tDCS- only (tDCS-only). The participants allocated to receive CT were not informed as to their treatment condition, but were told that there was a possibility that they were receiving active or sham tDCS stimulation.

Participants attended 13 sessions: baseline testing, 10 experimental sessions, post-testing and 4-wk follow-up. The CT task was completed at baseline, post-testing and follow-up and at all the experimental sessions for the active and sham tDCS+CT groups. In all experimental sessions, the CT task commenced after 5 min of active or sham tDCS and continued for approximately
25 min. To examine potential transfer effects, cognitive testing was completed at baseline, post-testing and follow-up. Sessions 1–12 were conducted on consecutive weekdays at a similar time of day. The follow-up session was conducted at least 4 wk (mean = 32.6, S.D. = 6.64 d) after post-testing. Following the 10th experimental session, participants in the tDCS+CT training conditions were asked to guess whether they had received active or sham tDCS. Participants were unblinded to their condition (i.e. active or sham tDCS+CT) after the follow-up session.

**Cognitive training task**

An adaptive dual n-back WM training task (BrainFitnessPro; Mindsparke Software, USA) was chosen due to demonstrated transfer effects in healthy participants (Jaeggi et al., 2008, 2010). Prior to baseline testing, participants were first given a verbal explanation of the task before practising 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. Stimuli consisted of nine squares arranged in a 3 × 3 grid for the visual modality and nine letters for the auditory modality, which were presented simultaneously at a rate of 3 s sequentially. Participants were required to press the ‘A’ letter key whenever the currently presented square was at the same position as the one n stimulus preceding it and the ‘L’ letter key whenever the auditory stimulus (letters) matched the same as n positions.
back in the sequence. The value of ‘n’ was the same for both modalities of stimuli. 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. Each training session consisted of 20 blocks of trials. 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 average d prime (d’) and average overall level of difficulty ‘n’ for each session (13 sessions total). d’ was calculated from measurement of the hit rate and false alarm rate (i.e. $d’ = Z(\text{hit rate}) - Z(\text{false alarm rate})$) for each trial block comprising each session (i.e. 20 per session). A higher d’ indicates a greater ability to identify hits (and therefore minimize misses) and to correctly reject false alarms.

Assessment of transfer effects

Potential transfer effects were examined using the following cognitive tests: Digit Span Forwards and Backwards (Wechsler, 1981); Letter Number Sequencing (Wechsler, 1997); Trial Making Tests (TMT) A and B (Reitan and Wolfson, 1985); Serial Sevens (Spreen and Strauss, 1998); Controlled Oral Word Association Test (COWAT; Benton and Hamsher, 1989); simple and choice reaction time tests. The reaction time tests comprised 10 practice and 50 test trials. Parallel forms of the TMT, COWAT and Serial Sevens were used to minimize practice effects. The order of parallel forms of tasks was randomized and counterbalanced between conditions. Cognitive testing was conducted by investigators who were not blinded to treatment condition.

tDCS

tDCS was applied daily on 10 consecutive weekdays during all experimental sessions using an Eldith DC-simulator (NeuroConn GmbH, Germany). Active tDCS was given continuously for 30 min at 2 mA, with 30 s ramping up and down of current. For all conditions, the anode (7 × 5 cm, 35 cm²) was placed over the left F3 site. Ofine performance effects on the CT task were examined at post-test and follow-up using one-way analyses of variance (ANO Vas) for continuous variables and $\chi^2$ tests for categorical variables. Repeated measures ANOVAs, with the with-subject factor being the 10 experimental sessions and condition (active DCS+CT vs. sham DCS+CT) as the between-subject factor, examined ‘online’ performance on the CT task across the experimental sessions. These analyses were then repeated, with baseline performance as a covariate. Student t tests were used to examine group differences between the active and sham tDCS+CT conditions on the CT task at baseline and at each following time-point.

‘Offline’ performance effects on the CT task were then examined at post-test and follow-up using one-way analyses of covariance (ANOCVs) with condition (tDCS-only, sham tDCS+CT and active tDCS+CT) as the fixed factor and baseline performance as a covariate.
To assess transfer effects on non-trained tasks, differences in change on cognitive outcomes between treatment conditions at post-test and follow-up were examined using one-way ANCOVAs with condition (tDCS-only, sham tDCS+CT and active tDCS+CT) as the fixed factor and baseline performance as a covariate. Where the effect of condition was statistically significant, planned contrasts examined differences between the treatment conditions at the respective time-point. Integrity of blinding (i.e., participants’ guess of ‘active’ or ‘sham’) was assessed for the tDCS+CT conditions using a $\chi^2$ test. Statistical significance was set at $p < 0.05$.

Results

Participants

Altogether, 54 participants completed the study (see Fig. 1). Two participants’ data were excluded from analysis. One participant informed research staff on the seventh experimental session day that he had failed to properly understand the CT task instructions and after clarification his performance dramatically improved. Another had highly variable CT task outcomes due to suboptimal effort. Demographic details and baseline measurements on the CT task for 52 participants’ analyses are shown in Table 1. There were no significant baseline differences between the active tDCS+CT and sham tDCS+CT conditions on any of the CT task outcomes. For the non-trained cognitive tasks, there was a significant difference between the active tDCS+CT and tDCS-only groups on choice reaction time and TMT-B (see Table 2).

Performance on the CT task

‘Online’ effects

For $d'$ there was a significant main effect of time ($F_{2.74,110} = 5.58, p < 0.01$) and condition ($F_{1,40} = 4.68, p = 0.04$), although the time × condition interaction effect was not statistically significant ($F_{2.74,110} = 1.28, p = 0.29$). The participants in the active tDCS+CT condition performed at a higher level of accuracy relative to the sham tDCS+CT on the CT task across the 10 experimental sessions. When this analysis was repeated with baseline performance as a covariate, there was still a main effect of time ($F_{3.91,153} = 18.6, p < 0.01$) although the difference between conditions was no longer statistically significant ($F_{3.91,153} = 2.48, p = 0.12$), interaction effect ($F_{3.91,153} = 0.90, p = 0.47$). The average $d'$ for both active and sham tDCS+CT conditions across all sessions in the study and between-group differences at individual time-points are shown in Fig. 2.

For difficulty ‘n’ across the 10 experimental sessions, there was a significant main effect of time ($F_{2.12,85} = 41.2, p < 0.001$). The main effect of condition ($F_{1,40} = 2.06, p = 0.16$) and time × condition interaction effect ($F_{2.12,85} = 1.33, p = 0.27$), however, failed to reach statistical significance. When this analysis

Table 1. Demographic data and baseline performance on the cognitive training task

<table>
<thead>
<tr>
<th>Group, mean (s.d.)</th>
<th>Active tDCS+CT (N = 21)</th>
<th>Sham tDCS+CT (N = 21)</th>
<th>tDCS-only (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>5/5*</td>
<td>13/8*</td>
<td>12/9*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>21.7 (2.54)</td>
<td>23.2 (6.80)</td>
<td>23.1 (2.78)</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>14.4 (1.78)</td>
<td>14.7 (2.63)</td>
<td>15.9 (2.83)</td>
</tr>
<tr>
<td>Cognitive training task</td>
<td>1.70 (0.44)</td>
<td>1.86 (0.37)</td>
<td>2.01 (0.31)</td>
</tr>
<tr>
<td>d'</td>
<td>2.12 (0.17)</td>
<td>2.21 (0.20)</td>
<td>2.31 (0.26)</td>
</tr>
<tr>
<td>‘n’</td>
<td>167 (30.0)</td>
<td>162 (22.8)</td>
<td>170 (19.1)</td>
</tr>
<tr>
<td>Total hits</td>
<td>106 (65.1)</td>
<td>75.3 (53.4)</td>
<td>66.0 (27.3)</td>
</tr>
<tr>
<td>Total false alarms</td>
<td>0.80</td>
<td>0.71</td>
<td>0.48</td>
</tr>
</tbody>
</table>

tDCS, Transcranial direct current stimulation; CT, cognitive training.

* Actual tally recorded.
Table 2. Raw scores for non-trained cognitive outcomes for each treatment condition across the three testing time-points (mean, S.D.)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Post-test</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tDCS-only</td>
<td>Sham tDCS+CT</td>
<td>Active tDCS+CT</td>
</tr>
<tr>
<td>Reaction time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT (ms)</td>
<td>277 (23.2) N = 9</td>
<td>288 (63.5) N = 20</td>
<td>270 (39.2) N = 20</td>
</tr>
<tr>
<td>CRT (ms)</td>
<td>586 (84.4)* N = 9</td>
<td>538 (73.2) N = 19</td>
<td>517 (42.4)* N = 20</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A (s)</td>
<td>38.3 (8.47) N = 10</td>
<td>37.9 (11.8) N = 21</td>
<td>31.6 (6.25) N = 21</td>
</tr>
<tr>
<td>Serial 7s (s)</td>
<td>55.5 (15.4) N = 10</td>
<td>48.1 (17.1) N = 21</td>
<td>46.6 (25.3) N = 21</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT</td>
<td>35.7 (10.1) N = 10</td>
<td>36.0 (8.91) N = 21</td>
<td>40.4 (11.5) N = 21</td>
</tr>
<tr>
<td>TMT B (s)</td>
<td>70.7 (17.2)** N = 9</td>
<td>59.9 (16.2) N = 21</td>
<td>52.1 (14.1)** N = 21</td>
</tr>
</tbody>
</table>

tDCS, Transcranial direct current stimulation; CT, cognitive training; SRT, simple reaction time; CRT, choice reaction time; TMT, Trial Making Test; COWAT, Controlled Oral Word Association Test.

* Analyses of group differences controlled for baseline performance.
Difference between conditions: * p < 0.05; ** p < 0.01.
was repeated, controlling for baseline performance, the effect of time was no longer significant ($F_{2.09,81.7} = 1.10$, $p = 0.36$); the effect of condition ($F_{1,39} = 0.32$, $p = 0.58$) and interaction effect ($F_{2.09,81.7} = 0.88$, $p = 0.42$) also remained not statistically significant. The levels of difficulty ‘n’ for both the active tDCS+CT and sham tDCS+CT conditions across all sessions are shown in Supplementary Fig S1.

**‘Offline’ effects**

Analyses of $d’$ at post-test showed a significant main effect of condition ($F_{2.48} = 4.82$, $p = 0.01$). Planned contrasts showed no difference between the active and sham tDCS+CT groups ($p = 0.79$). Both the active tDCS+CT ($p = 0.01$) and sham tDCS+CT ($p < 0.01$) outperformed the tDCS-only group at this time-point. At follow-up, there was also a main effect of condition ($F_{2.48} = 8.79$, $p < 0.01$); similarly at this time-point there was no difference between the active and sham tDCS+CT groups ($p = 0.71$). Both these conditions outperformed the tDCS-only group ($p’s < 0.01$).

For difficulty ‘n’ at post-test, there was a significant main effect of condition ($F_{2.48} = 5.09$, $p = 0.01$). Planned contrasts showed no difference between the active and sham tDCS+CT groups ($p = 0.45$), although both these groups outperformed the tDCS-only group ($p’s < 0.05$). At follow-up, there was again a significant main effect of condition ($F_{2.48} = 4.94$, $p = 0.01$). While there was no difference between the active and sham tDCS groups ($p = 0.33$), both these groups outperformed the tDCS-only group ($p’s < 0.05$).

**Transfer effects on non-trained tasks**

The cognitive outcomes on non-trained tasks across the three testing time-points are shown in Table 2. At post-test, there were no differences between conditions. At follow-up, there was a main effect of condition on the Digit Span Test ($F_{2.19} = 3.69$, $p = 0.03$).
Planned contrasts showed that the active tDCS+CT showed greater improvement from baseline compared to the tDCS-only condition ($p<0.01$). There was no difference, however, between the active tDCS+CT and sham tDCS+CT conditions ($p=0.18$) or between the sham tDCS+CT and tDCS-only conditions ($p=0.10$).

**Safety**

The most common side-effects observed with active tDCS were feelings of tingling/itching or burning during stimulation and transient skin redness at the electrode sites after stimulation. Other less commonly reported side-effects (e.g. light-headedness/dizziness, headache and fatigue) were mild, did not result in distress and did not require any medical intervention.

**Integrity of blinding**

Integrity of blinding was assessed in 27 participants in the active and sham tDCS+CT conditions. The difference between the active and sham guesses between the two groups was not statistically significant ($\chi^2=1.19$, $p=0.28$).

**Discussion**

This is the first study to examine the use of tDCS to enhance the efficacy of CT, administered over multiple sessions. Results show preliminary evidence for an enhanced ‘online’ effect of tDCS during CT, with participants who received active tDCS performing more accurately on the CT task compared to those who received sham tDCS across repeated training sessions. This performance-enhancing effect, however, was only present during tDCS and did not cause greater learning on the CT task (i.e. improvement in task difficulty ‘n’ across the 10 experimental sessions).

In previous studies, a single session of anodal tDCS to the LDLPFC has been shown to increase accuracy of task performance on 2-back and 3-back WM tasks (Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011). For example, it has been previously shown that 1 mA anodal tDCS significantly improved ‘online’ accuracy during a 3-back WM task commenced after 20 min of tDCS and that this effect was maintained ‘offline’ for 30 min after cessation of tDCS (Ohn et al., 2008). The current results extend these findings to show that tDCS given during a difficult adaptive dual n-back WM training task enhanced ‘online’ accuracy but not learning. This effect, however, was not maintained at two ‘offline’ sessions conducted at post-test and follow-up.

The use of multiple sessions of tDCS to enhance training has been minimally studied. Previously, the combination of tDCS with training tasks in healthy participants has shown enhanced motor skill learning together with maintained skill acquisition over five daily sessions (Reis et al., 2009) and performance improvements over four daily sessions on a response inhibition CT task (Ditye et al., 2012). However, in the latter study, the performance benefit was not maintained on day 5 without tDCS. Similarly, we failed to find any difference in accuracy on the CT task between the active and sham tDCS conditions at either post-test or follow-up, suggesting that cognitive performance enhancement of tDCS may be limited to the period during and immediately after stimulation.

Studies that have investigated the potential transfer effects from training on the dual n-back CT task have yielded inconsistent results. Jaeggi et al. (2008) found improvements on digit span and a test of non-verbal reasoning following training. More recently, these findings failed to be replicated in a large, well-controlled, randomized study (Redick et al., 2012). Consistent with this later study, we similarly failed to find any transfer effects immediately following training across multiple non-trained cognitive measures assessing WM, executive functioning, processing speed and reaction time. It is possible that the lack of any immediate training-related transfer effects may have been due to the relatively short duration of the current intervention (i.e. approximately 2 wk).

Cognitive improvement, in the form of better attention and WM as measured by the Digit Span Test, instead was only observed in the combined active tDCS+CT condition at follow-up when compared to the tDCS-only condition. This suggests that training was responsible for the observed delayed transfer effects, a result that supports other work showing the utility of CT using adaptive WM training tasks to cause improvement in WM (Klingsberg et al., 2002; Olesen et al., 2004; Jaeggi et al., 2008). Although sham tDCS+CT did not produce superior transfer effects to tDCS alone, the lack of significant difference between the active and sham tDCS groups meant that this study was unable to demonstrate that active tDCS enhanced the transfer effects from CT. Nevertheless, results were in the predicted direction, with the difference between active and sham tDCS groups on this task at follow-up equating to an effect size of $d=0.43$. A sample size of 86 participants per group would be required to detect this sized effect with two-tailed $\alpha=0.05$ and 80% power. Of note, a similar delayed training effect was recently observed following combined tDCS and WM training in a rat model, although...
different stimulus and treatment parameters were used (Dockery et al., 2011).

An important consideration in our failure to show clear differences between the effects of active and sham tDCS may be the montage used in this study. The cathodal electrode was placed in an extracephalic position to avoid confounding effects from inhibitory stimulation of other cortical areas. However, an unavoidable consequence of this wider spacing of electrodes is that the intensity of stimulation under the anode is reduced (Bikson et al., 2008). As a result, both physiological (Moliadze et al., 2010) and behavioural effects, including skill learning (Schambra et al., 2011), have been shown to be reduced when the inter-electrode distance is increased. Notwithstanding, we used this montage as meaningful clinical effects have previously been demonstrated (Martin et al., 2011).

Our study had several limitations. First, there were chance non-significant baseline differences in CT performance between the active tDCS+CT and sham tDCS+CT groups. Due to the relatively small sample size and overall small-sized online effect of tDCS, when this baseline difference was controlled for in a secondary analysis, this effect was no longer statistically significant. Future studies investigating the additive effect of tDCS during CT should match participants on baseline performance prior to commencing CT. Further, the non-equivalent allocation of participants into treatment conditions limited the interpretation of differences in changes in cognitive outcomes between the three conditions. Cognitive testing was conducted by investigators who were not blinded to treatment condition and it is possible that this may have inadvertently influenced cognitive outcomes. As mood was not assessed, it cannot be ruled out that potential mood effects of anodal LDLPFC tDCS may have affected outcomes in both active tDCS conditions. Finally, the relatively short duration of CT (5 h in total), together with the non-trained cognitive measures chosen, also potentially limited the ability for us to demonstrate transfer effects from tDCS combined with CT. Future studies should consider utilizing greater total duration of training, higher stimulation intensity if the reference electrode is placed extracephalically and more sensitive non-trained cognitive outcomes (e.g. computerized measures of WM and executive function) to examine transfer effects from CT. Increased transfer effects using this approach may possibly also be found in clinical populations where greater cognitive gains might be expected.

In summary, the findings from the current study support earlier reports of enhanced cognitive function during the period of tDCS stimulation, but failed to demonstrate enhancement of outcomes from CT with tDCS. It is possible that several methodological issues may account for this negative finding, an observation that should inform the design of future studies.

Acknowledgements

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Statement of Interest

In the last 3 yr, Professor Colleen Loo has received honoraria from Astra-Zeneca and Pfizer as an invited speaker at psychiatry conferences. The talks were unrelated to the topic of this manuscript.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145713000539

References


