Enhancing Working Memory Training with Transcranial Direct Current Stimulation

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Abstract

■ Working memory (WM) is a fundamental cognitive ability that supports complex thought but is limited in capacity. Thus, WM training interventions have become very popular as a means of potentially improving WM-related skills. Another promising intervention that has gained increasing traction in recent years is transcranial direct current stimulation (tDCS), a noninvasive form of brain stimulation that can modulate cortical excitability and temporarily increase brain plasticity. As such, it has the potential to boost learning and enhance performance on cognitive tasks. This study assessed the efficacy of tDCS to supplement WM training. Sixty-two participants were randomized to receive either right prefrontal, left prefrontal, or sham stimulation with concurrent visuospatial WM training over the course of seven training sessions. Results showed that tDCS enhanced training performance, which was strikingly preserved several months after training completion. Furthermore, we observed stronger effects when tDCS was spaced over a weekend break relative to consecutive daily training, and we also demonstrated selective transfer in the right prefrontal group to nontrained tasks of visual and spatial WM. These findings shed light on how tDCS may be leveraged as a tool to enhance performance on WM-intensive learning tasks. ■

INTRODUCTION

Working memory (WM) is a fundamental cognitive ability that is limited in capacity and supports complex thought. It is highly predictive of academic and professional success (Alloway & Alloway, 2010; Gathercole, Pickering, Knight, & Stegmann, 2004), and thus, interventions to improve WM are highly sought. Training of WM typically leads to substantial improvements on the trained task and has also been shown by many studies to enhance various aspects of cognitive functioning, from improving performance on nontrained WM and executive function tasks (Schwaighofer, Fischer, & Buhner, 2015; Melby-Lervåg & Hulme, 2013) to broader tests such as those indexing fluid intelligence (see Weicker, Villringer, & Thone-Otto, 2016; Au et al., 2016; Karbach & Verhaeghen, 2014, for recent meta-analyses). However, obtaining reliable results often requires extensive training on the order of weeks or even months, thereby rendering participant compliance difficult and research costs high. These practical constraints have often led to underpowered studies (Bogg & Lasecki, 2014) and inconsistent results in the literature. Therefore, the field would benefit from a catalyst to intensify or expedite the effects of WM training. Herein, we evaluated the efficacy of transcranial direct current stimulation (tDCS) to boost the effects of training on both trained and untrained measures of WM and executive function over a short period of 7 days. In contrast with previous investigations, the design of the current study included both a long-term follow-up as well as a training schedule that permitted us to explore the impact of spacing on training performance. Thus, the present research not only adds to the growing literature in support of the effects of tDCS on WM, but it also offers novel insights with regard to the cumulative efficacy of multisession stimulation, the effects of intersession spacing, and the long-term durability of stimulation-enhanced training.

The use of tDCS for cognitive enhancement has sparked great interest over the past decade. tDCS is commonly thought to modify cortical excitability by altering the relative ionic distribution across neural membranes. If so, this can lead to polarity-specific increases or decreases in the resting membrane potential of neurons lying underneath the anodal or cathodal electrodes, respectively (Stagg & Nitsche, 2011). Moreover, this can directly affect brain plasticity by making relevant networks more or less likely to fire in concert (Keeser et al., 2011), and it seems to modulate long-term potentiation (LTP)-like plasticity at the synapse via alterations of GABAergic and glutamatergic neurotransmission (Stagg & Nitsche, 2011; Wagner, Valero-Cabre, & Pascual-Leone, 2007; Ardolino, Bossi, Barbieri, & Priori, 2005; Nitsche et al., 2004).

Many studies that evaluate the use of tDCS to augment WM performance have now been conducted, the majority

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of which specifically use the *n*-back task as we do in the present report (cf. Brunoni & Vanderhasselt, 2014). Despite mixed initial results (Horvath, Forte, & Carter, 2015; Brunoni & Vanderhasselt, 2014; Tremblay et al., 2014), recent meta-analyses confirm reliable net effects of tDCS on WM performance (Hill, Fitzgerald, & Hoy, 2016; Summers, Kang, & Cauraugh, 2015). Importantly, it is worth noting that the precise parameters under which tDCS may most optimally exert its benefits are not well understood, and consequently, there is much methodological heterogeneity among studies (cf. Horvath, Carter, & Forte, 2014). In other words, it is likely that a more thorough mechanistic understanding of optimal stimulation conditions might lead to even larger effects in future studies.

For example, most extant studies employed single-session designs. However, converging evidence from the motor cortex indicates that the effects of tDCS can accumulate over consecutive daily sessions, such that gains are greater in later versus earlier sessions (Hashemirad, Zoghi, Fitzgerald, & Jaberzadeh, 2016). This has been demonstrated both by enhanced excitability (Ho et al., 2016; Alonzo, Brassil, Taylor, Martin, & Loo, 2012) as well as enhanced motor learning (Reis et al., 2009; Boggio et al., 2007). It has been documented that offline effects, which refer to enhancements present immediately after stimulation, are related to LTP-like consolidation (Stagg & Nitsche, 2011), which presents a viable mechanism to explain how tDCS effects may accumulate over consecutive sessions. Although direct evaluations of single relative to multiple sessions of stimulation have not been evaluated with cognitive tasks, proof of concept has been demonstrated whereby anodal stimulation over left dorsolateral pFC (DLPFC) during a WM task led to enhanced performance the next day (Martin, Liu, Alonzo, Green, & Loo, 2014). It is plausible, therefore, that the single-session designs prevalent in the extant literature mask the potential of tDCS to enhance learning and consolidation between sessions.

Additionally, the effects of tDCS seem to be site specific (Bikson, Name, & Rahman, 2013), a particularly important consideration in cognitive studies, which target behaviors involving a functional network of multiple brain regions. This renders the choice of stimulation site an important matter. For WM, the DLPFC has proven itself to be a prime target (Tremblay et al., 2014). However, the DLPFC itself is functionally lateralized such that the left hemisphere tends to mediate verbal WM performance whereas the right mediates visuospatial WM performance (Wager & Smith, 2003; Smith, Jonides, & Koeppe, 1996). The existing literature does a good job of addressing half the equation, with the majority of studies targeting left DLPFC using a verbal WM task, as modeled after the seminal work by Fregni et al. (2005). To lend credence to the specificity of this montage, Kim et al. (2014) showed that greater behavioral improvements in verbal WM correlated with greater current density over the left DLPFC, using a tDCS setup similar to the one used in the present report. However, there is a relative dearth of studies using visuospatial WM tasks or right DLPFC stimulation, and direct evaluations of interactions between WM domain and hemisphere are even more rare.

The motivation for this study was to evaluate the efficacy and durability of multisession tDCS on visuospatial WM-training performance, with an emphasis on possible interactions between the spatial nature of the training and the laterality of DLPFC stimulation. This was of particular interest to us in light of previous training research demonstrating enhanced transfer effects to visuospatial relative to verbal tasks (Jaeggi, Buschkuehl, Shah, & Jonides, 2014; Schneiders, Opitz, Krick, & Mecklinger, 2011; Buschkuehl et al., 2008). We hypothesized a generalized effect of tDCS on improving spatial WM performance, with cumulative gains resulting in a steeper rate of improvement in the stimulated group. Because of the functional lateralization of the DLPFC, we expected the strongest advantage to be in the right DLPFC group. Additionally, our 7-day training schedule, which excluded training on weekends, afforded us a natural opportunity to explore spacing effects in our design, which have been reported to positively impact outcomes both in terms of motor excitability with tDCS as well as cognitive training without tDCS (Wang, Zhou, & Shah, 2014). We predicted that greater training gains would be observed when stimulation was spaced apart by a weekend break compared with consecutive daily sessions. Furthermore, although our principal aims in this study centered on the effects of tDCS on WM training, an auxiliary goal was to assess transfer effects onto untrained visual and verbal WM tasks. Given the brevity of our 7-day training schedule and the fact that our Sham tDCS group also received WM training, we did not expect very pronounced transfer differences between groups. However, to the extent that we found transfer at all, we predicted a selective advantage of right DLPFC stimulation in augmenting performance on visual WM measures. Finally, but no less significantly, we evaluated the durability of training gains at a follow-up session several months after conclusion of training. If tDCS is to have a substantial impact on cognitive training, it is important to demonstrate that the effects of the stimulation are not ephemeral but are long-lasting. In this regard, to anticipate our results, we find a striking preservation of the effect of stimulation months after the stimulation and training have ceased.

METHODS

Participants

Right-handed individuals between the ages of 18 and 35 years were recruited from the campuses of the University of California, Irvine, and the University of Michigan, Ann Arbor. Participants were excluded if they had any history of psychological or neurological disorders (including seizures and strokes), previous cognitive training or neurostimulation, past or present drug/alcohol abuse, or if they were taking any medications that would affect attention or memory. Eighty-one individuals were deemed eligible and were recruited to participate. Eleven voluntarily withdrew after consent because of scheduling difficulties, two were excluded for falling asleep during the experiment, four were excluded because of computer errors during data collection, and two were excluded as outliers based on their training data (see Results section). Ultimately 62 healthy, college-aged participants, split evenly between universities, were included in the final sample. All research procedures were approved by the institutional review boards at both universities, and each participant provided informed consent.

General Procedure

We used a between-subject pretest–posttest intervention design and randomized participants into one of three intervention groups (Figure 1). Twenty received active tDCS over the right DLPFC (Active Right), 20 received active tDCS over the left DLPFC (Active Left), and 22 received sham stimulation over either the right or left DLPFC (Sham). All groups received 7 days of visuospatial n-back training concurrently with either Active or Sham stimulation. To preserve the integrity of blinding, participants were not a priori informed about the existence of a sham group. All participants were simply told that the aim of the study was to investigate the effects of electrical stimulation over the pFC to enhance WM training.

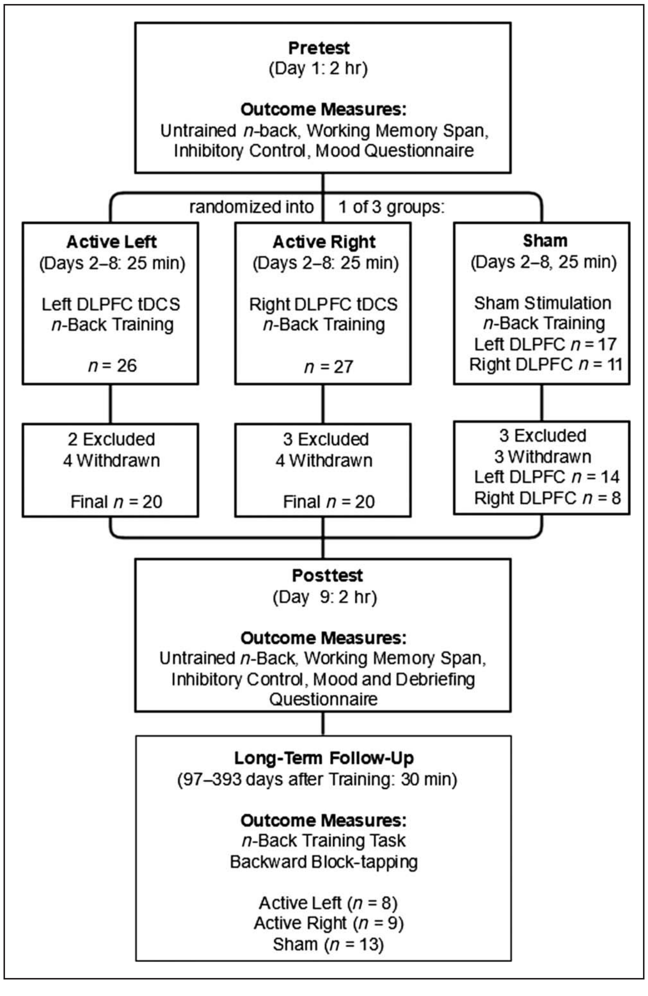

Figure 1. Overall flow chart of study design and attrition rate.

During the intervention period, participants attended seven daily training plus stimulation (or training plus sham) sessions, excluding weekends. Each session lasted approximately 45 min, including setup and cleanup. Duration of stimulation, including sham stimulation, was fixed at 25 min. If participants finished the training task early, they were asked to sit quietly until stimulation discontinued. Immediately before stimulation, participants were asked to rate their level of motivation for the study on a 1–10 scale, with 10 being very highly motivated. Upon the conclusion of stimulation, participants were asked to indicate any possible symptoms or side effects they experienced. Immediately before and after stimulation, participants rated their level of alertness on a 1–10 scale, with 10 being most alert. The average alertness rating during each session was used as the dependent variable. All study procedures from pre- to posttest were concluded within 2 business weeks for all participants, with no more than one intervening weekend. Upon conclusion of the study, participants were debriefed about the existence of a sham group and were asked to guess their condition.

All participants were invited back for a follow-up session to examine the stability of training and transfer effects following a long break from the intervention. Forty-one participants returned for the follow-up (14 Active Right, 13 Active Left, and 14 Sham). The mean delay between the final training session and the follow-up was 221 days (range = 97–393; *SD* = 82). During this follow-up session, participants completed a single session of the trained n-back task (without tDCS) as well as the Backward Block-tapping task.

WM Training

The training task used was a computerized adaptive version of the visuospatial n-back task used previously (Buschkuehl, Hernandez-Garcia, Jaeggi, Bernard, & Jonides, 2014; Jaeggi et al., 2010, 2014; see Figure 2). A series of blue squares was displayed, each in one of eight possible spatial locations. Participants were asked to indicate whether the current square was in the same position as the square presented n trials ago by responding with the letter “a” to targets and “l” to nontargets, using a standard computer keyboard. The difficulty of the task adapted continuously based on the trainee’s performance. Each stimulus was presented for 500 msec followed by a blank screen for 2500 msec. A training session consisted of 15 blocks, each with $20 + n$ trials where 6 were targets and $14 + n$ were nontargets. Training duration for one session typically lasted between 20 and 25 min. Accuracy rates of 70% and 90% (inclusive) were used as cutoffs to

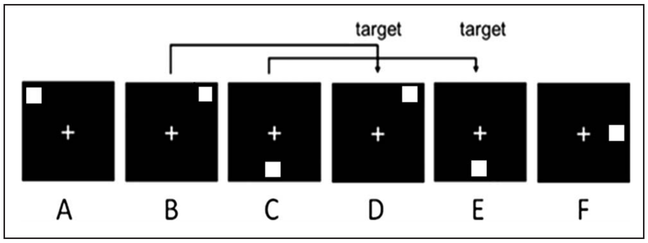

Figure 2. Visualization of the training task. A 2-back condition is demonstrated. Trials D and E each match the stimulus presented 2-back ago. All other trials are nontarget trials. During training, *n*-level adapted continuously to participants' fluctuating performance.

decrease and increase the level of *n* in the next block, respectively. For the first three training sessions, participants started at a 1-back level, and for the last four and the follow-up session, they started at 2-back. Training performance per session (i.e., the dependent variable) was operationalized as the average *n*-back level of the last 12 of 15 blocks. The first three blocks of each session were treated as warm-up blocks and not considered in the analyses.

Transcranial Direct Current Stimulation

Stimulation was administered via a Soterix Medical 1 × 1 Low-Intensity tDCS device (Model 1300A; New York, NY) using 5 × 7 cm sponge electrodes placed horizontally on the head. The anode was placed over either right or left DLPFC (sites F4 and F3 in the international 10–20 EEG system), and the cathode was placed over the contralateral supraorbital area (sites Fp1 or Fp2). Sponges were securely fastened to the head using 5-in. wide Velcro straps that covered the sponges entirely to prevent flaring out of sponge edges that can occur with narrower straps, leading to nonuniform skin contact (cf. Horvath et al., 2014). Additionally, the anodal sponge was laterally shifted away from the cathode by approximately three centimeters such that the edge (and not the center) of the sponge lay directly over the target, a setup that has been suggested to maximize the peak current density underneath the target site (Faria, Hallett, & Miranda, 2011). Stimulation lasted 25 min, with a current intensity of 2 mA, which ramped up and down for the first and last 15 sec of stimulation. Sham tDCS was set up in the same way, except the current was shut off in-between the 15-sec ramping periods at the beginning and end of each session.

Transfer Measures

Pre- and posttesting consisted of outcomes that assessed the generalization of training gains onto untrained variants of the *n*-back, WM span, and inhibitory control tasks. Each cognitive measure consisted of a short practice round before the actual test; these measures were divided into verbal and visual variants to assess interactions of these measures with stimulation site. Additionally, affect was assessed via questionnaire. Pre- and posttest sessions lasted approximately 2 hr each and were administered 1 day immediately before and after the intervention period.

Affect Rating

We used the 60-item Positive and Negative Affect Schedule (Watson, 1988) to assess mood and emotional experience along two dominant dimensions that consistently emerge across studies of affective structure, General Positive Affect and General Negative Affect. Each dimension is measured from the responses to 10 items, and each item is rated on a 1–5 scale in order of increasing valence. Participants were asked to base all responses on emotional experiences within the past week. DLPFC stimulation has been reported to modulate affective symptoms and emotional regulation (Feeser, Prehn, Kazzer, Mungee, & Bajbouj, 2014; Shiozawa et al., 2014), which in turn can interact with WM function. Therefore, it is plausible that our training design, whether via overlapping or distinct pathways, could modulate both WM performance as well as affective experience.

*Untrained n-*Back

To evaluate near-transfer training gains, we evaluated performance on untrained variants of the trained visuospatial *n*-back task, consisting of both an auditory–verbal and a nonspatial visual *n*-back task. Our previous research with the same training task has demonstrated positive transfer effects both within and across modalities to untrained *n*-back variants (Buschkuehl et al., 2014; Jaeggi et al., 2010).

In the auditory *n*-back task, participants were required to process a continuous stream of spoken letters presented through headphones. Difficulty varied sequentially from 2- through 4-back, with three blocks at each level. The visual *n*-back task consisted of colored and textured circles presented in the center of the screen. Difficulty increased from 2- to 3-back, with nine blocks at each level. In both *n*-back variants, stimuli were presented for 3-sec intervals, with 500 msec of presentation and a 2500-msec intertrial interval, and each block contained 20 + *n* trials. The primary dependent variable of interest was hit rate minus false alarm rate (P_R; Snodgrass & Corwin, 1988).

WM Span

Meta-analyses demonstrate robust immediate effects of WM training on a variety of simple and complex span measures (Schwaighofer et al., 2015; Weicker et al., 2016; Melby-Lervåg & Hulme, 2013). Similarly, tDCS has been reported to improve performance in Digit Span (Park, Seo, Kim, & Ko, 2014; Martin et al., 2013) as well as Operation and Symmetry Spans (Richmond, Wolk, Chein, & Olson, 2014). We therefore tested whether our short training regimen could also elicit similar transfer effects.

To measure auditory/verbal span, we administered the Digit Span task, as per the standardized administration rules used in the WAIS-IV (Wechsler, 2008). Trained examiners read aloud a series of digits at a rate of 1 per second, and participants were asked to repeat them back verbally in either forward or backward order. Span length increased from three to nine digits in the Forward condition and three to eight digits in the Backward condition, with two trials at each span. Testing was discontinued if a participant missed both trials of a particular span, and the primary dependent variable was the total number of trials correctly repeated.

The Block-tapping task (Schellig, 1993) is a visual analogue of the Digit Span. In our computerized version, nine white squares were displayed, and participants were required to reproduce a sequence of positions presented at a rate of 1 per second by clicking in either the given or the backward order. In both the Forward and Backward conditions, span lengths increased from three to nine or until a participant made three consecutive errors. The primary dependent variable was the total number of trials correctly reproduced.

We used parallel test versions at pre- and posttest for both WM span tasks.

Inhibitory Control

WM and inhibitory control are closely related, sharing neural substrates in the pFC (Nee et al., 2013). Therefore, training the former may improve the latter, supported by our previous research (Zhang, Buschkuehl, Bernat, & Jaeggi, 2014; Hsu, Buschkuehl, Jonides, & Jaeggi, 2013; Jaeggi, Buschkuehl, Jonides, & Shah, 2011). To assess possible enhancing effects of tDCS, we assessed inhibitory control in two ways. First, we embedded lure trials into our visual n-back task; these were identical to target stimuli except that they were presented in the wrong position (corresponding to trials $n \pm 1$ back). These lures comprised 33% of total trials and indexed the participant's ability to inhibit inappropriate, but salient, distracters. Performance was measured as the percentage correct among lure trials.

Additionally, we employed the AX-CPT task (Cohen, Barch, Carter, & Servan-Schreiber, 1999) to directly measure inhibitory control. The task consisted of a continuous stream of letters presented visually on a computer screen for 300 msec each with an ISI of 1000 msec. Participants responded to each letter via a button press but had to make a target response for 70% of trials in which the letter "X" followed the letter "A." Although this happened on the majority of "A" trials, creating prepotent response tendencies, participants had to make a "nontarget" response for a small percentage (10%) of trials when "A" was followed by another letter ("AY" trials). The remaining 20% of trials were filler trials. The primary dependent variable was the percentage accuracy during "AY" trials and participants completed 13 blocks of 60 trials each.

Analytical Approach

Statistical analyses were conducted using STATA version 13 (StataCorp, 2013). Baseline characteristics between conditions were compared using ANOVAs for continuous variables and χ^2 tests for categorical variables. To evaluate training effects between groups, as well as potential confounds such as level of alertness and motivation, we ran 3 × 7 mixed-design ANOVAs with the between-subject factor, Condition (Active Right, Active Left, Sham) and the within-subject factor, Session (1–7). Significant interactions were followed with planned Helmert contrasts to evaluate pairwise differences in gain scores (Session 7 minus Session 1, or Follow-up Session minus Session 1) for the following groups: Combined Active (Active Right and Active Left) versus Sham to evaluate global effects of tDCS, and Active Right versus Active Left to assess potential laterality-dependent effects of stimulation. An additional analysis was run on gains between Sessions 3 and 4, where by the nature of our 9-day design, approximately half our participants experienced an intervening weekend and approximately half trained on consecutive weekdays (Thursday and Friday). This allowed us to evaluate potential effects of spacing on training (cf. Wang et al., 2014).

To evaluate transfer effects, we used ANCOVAs to test each posttest or follow-up measure against the factor, Condition, using pretest performance as a covariate. Significant effects were followed up with planned Helmert contrasts to assess pairwise differences in the adjusted posttest means among the Combined Active versus Sham and Active Right versus Active Left contrasts.

Planned contrasts were evaluated with one-tailed tests when hypotheses were directional (i.e., Combined Active > Sham and Active Right > Active Left in the context of a visual measure). Two-tailed tests were used for Active Right versus Active Left contrasts in the context of an auditory or verbal outcome measure due to the lack of a directed hypothesis.

RESULTS

Outlier Analysis

Outliers were removed from the data set based on average training performance over all seven sessions, using a criterion of 2 *SD* for the combined Active group and the Sham group, separately. This resulted in the identification of two low-performing outliers (1 Active Right and 1 Active Left), both of whom averaged below a 2-back level across all seven training sessions and whose data were excluded from all subsequent analyses. Additionally, one participant's data (from the Sham group) were lost on the Auditory n-back and AX-CPT tasks because of computer

Table 1. Demographic and Baseline Information of the Three Groups

	Active Right	*Active Left*	*Sham*	*p*
Years of education	15.05 (1.88)	15.25 (2.15)	14.32 (1.09)	.27
Age (years)	20.91 (2.34)	21.55 (2.86)	20.52 (1.93)	.57
% Women	65	55	64	.78
Pretest *n*-back composite (P_R^a)	0.60 (0.12)	0.65 (0.16)	0.59 (0.16)	.40

Values in parentheses are standard deviations. *p* Values are calculated from one-way ANOVAs for continuous variables and χ^2 test for categorical variables (% Women).

[a] P_R is calculated as percentage hits minus percentage false alarms.

errors. All other data from this participant were included in analyses.

Baseline Characteristics

Demographic and baseline characteristics are presented in Table 1. One-way ANOVAs with the factor Condition were calculated separately for each dependent variable: years of education, age, and baseline *n*-back composite (a composite representing the average performance on the untrained Auditory and Visual *n*-back measures to index baseline WM abilities related to *n*-back performance). No differences were found between groups on any baseline measure (ps > .27). Additionally, a χ^2 test was run on sex (% women), revealing no significant differences (p = .78).

Training Gains

We next sought to test the effects of tDCS on training using a 3 × 7 mixed ANOVA with the factors Condition and Session.[1] We found a main effect of Session, $F(6, 354) = 28.65$, $p < .001$, $\eta_p^2 = .33$, a marginal effect of Condition, $F(2, 59) = 2.57$, $p = .08$, $\eta_p^2 = .09$, and importantly, a significant Session × Condition interaction, $F(12, 354) = 2.04$, $p = .02$, $\eta_p^2 = .06$.

Planned comparisons (Helmert contrasts) revealed that this interaction was driven by larger gains (Session 7 minus Session 1) in the Combined Active group relative to Sham, $t(60) = 2.86$, $p = .002$ (one-tailed), $d = .77$, indicating that tDCS was effective in augmenting WM training (see Figure 3). Notably, the contrast between Active Right and Active Left was not significant, $t(38) = -.61$, $p = .27$, one-tailed, $d = .20$, suggesting that both stimulation groups benefited equally.

Additionally, we verified the homogeneity of participants in the Sham group by comparing the training performance of those who received a left DLPFC montage versus a right DLPFC montage. Because no current was run through these participants (except for the brief ramp up and down), we expected no differences. This was confirmed with a 2 × 7 ANOVA with the between-subject factor Condition (Sham Left, Sham Right) and the within-subject factor Session (1–7), There was a main effect of Session, $F(6, 120) = 3.50$, $p = .003$, $\eta_p^2 = .15$, indicating that WM training was equally successful for both groups. However, there was no main effect of Condition, $F(1, 20) = .62$, $p = .44$, $\eta_p^2 = .03$), and no Session × Condition interaction, $F(6, 120) = 1.24$, $p = .29$, $\eta_p^2 = .06$, confirming the homogeneity of the Sham group.

We also carried out a post hoc analysis to examine the effect of spacing between training sessions. By design, study visits were constrained to fit into two consecutive weeks, with one intervening weekend. Therefore, most participants had to start the study on either a Monday or Tuesday to finish the 9-day study by the following Thursday or Friday. This naturally created a Monday and Tuesday cohort of participants, whose third and fourth sessions respectively fell either on Thursday and Friday (Consecutive group) or on Friday and Monday (Spaced group; see Figure 4A). We therefore compared gain scores over these sessions for both the Consecutive and Spaced groups, separately for Active and Sham participants, to evaluate the effect of a 2-day break on training performance. Some participants voluntarily were tested on weekends and were excluded from these analyses because their schedules did not fit the definition of the Consecutive or Spaced group. Because our previous analysis showed that both Active Right and Active Left benefited similarly from the training, we combined the two groups for this analysis to increase power.[2] Among

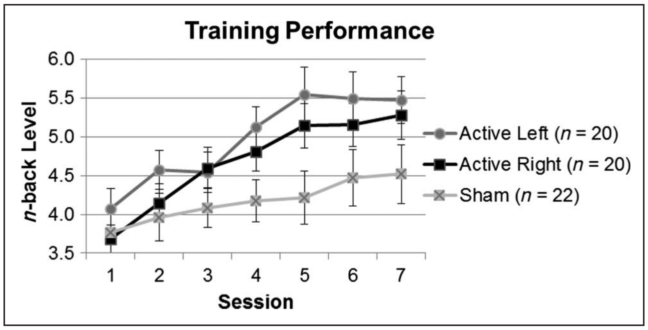

Figure 3. Training data across seven sessions. Both the Active Left and Active Right groups show significantly greater gains than the Sham group, but comparable gains relative to each other. The *y* axis represents average *n*-back level achieved per session. Error bars represent standard errors.

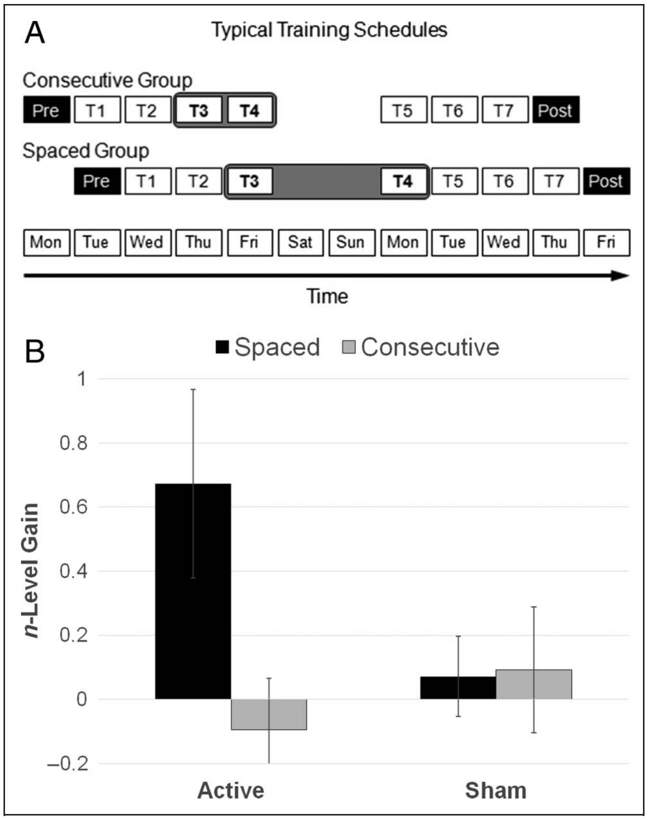

Figure 4. Gain score analyses between Sessions 3 and 4. (A) Typical training schedules show that Sessions 3 and 4 are separated by a weekend in the Spaced group, but occur on consecutive weekdays in the Consecutive group. (B) Active participants in the Spaced group (mean ± *SD*: 0.67 ± 1.18) have higher gain scores between these sessions than those in the Consecutive (mean ± *SD*: −0.09 ± 0.62) group. No differences emerge in the Sham group (Spaced mean ± *SD*: 0.07 ± 0.33; Consecutive mean ± *SD*: 0.09 ± 0.76). Error bars represent standard errors.

Active participants, we found larger gains in the Spaced group ($n = 16$) compared with the Consecutive group ($n = 15$; see Figure 4), $t(29) = 2.25$, $p = .01$, one-tailed, $d = .82$. This pattern was not observed among Sham participants ($n = 15$ and $n = 7$ for Spaced and Consecutive, respectively), $t(20) = .07$, $p = .95$, $d = .03$ (Figure 4B).

Alertness and Motivation

To rule out certain confounding influences on training, we conducted separate 3 × 7 ANOVAs for both motivation and alertness, which were assessed by self-report during each training session. For motivation, there was no main effect of Condition, $F(2, 349) = .05$, $p = .95$, $\eta_p^2 = .00$, nor of Session, $F(6, 349) = 1.780$, $p = .10$, $\eta_p^2 = .03$, and no Session × Condition interaction, $F(12, 349) = 1.39$, $p = .17$, $\eta_p^2 = .05$. For alertness, there was no main effect of Condition, $F(2, 349) = .53$, $p = .59$, $\eta_p^2 = .02$, nor of Session, $F(6, 349) = 1.20$, $p = .30$, $\eta_p^2 = .02$, and no Session × Condition interaction, $F(12, 349) = 1.34$, $p = .19$, $\eta_p^2 = .05$.

Side Effects and Blinding

Pairwise *t* tests showed no significant differences between the Combined Active and Sham groups on any self-reported side effects (i.e., headache, neck pain, scalp pain, tingling, itchiness, hotness, skin redness, sleepiness, trouble concentrating, acute mood changes, nervousness, or changes in visual perception; all *p*s > .12). Furthermore, after debriefing participants about the existence of a sham condition, participants were unable to reliably guess their condition, with the majority of participants believing they were in the Active condition (83% of Active Right, 65% of Active Left, and 68% of Sham participants; $\chi^2 = 1.72$, $p = .42$). Confidence ratings about condition made on a −10 to +10 scale also were not significantly different. Negative and positive values represented sham and active guesses, respectively, and higher magnitudes indicated higher confidence (mean ± *SD*: Active Right, 5.00 ± 5.96; Active Left, 2.88 ± 7.41; Sham, 2.95 ± 7.00; $F(2, 59) = 0.56$; $p = .57$).

Transfer Measures

Despite the short timeframe of our 7-day intervention, a duration usually too short to manifest convincing transfer onto untrained outcomes (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008), we carried out a provisional analysis to evaluate the potential for tDCS to enhance transfer effects over and above sham WM training. Means, standard deviations, *p* values, retest reliabilities, and effect sizes are presented in Table 2. ANCOVA statistics are presented in Table 3. Significance thresholds were not corrected for multiple comparisons in this provisional analysis, and therefore, results should be interpreted as preliminary.

Significant differences were observed for the Visual *n*-back, Backward Block-tapping, and Forward Digit Span tasks (see Figure 5 and Table 3). Planned contrasts showed that the adjusted posttest means of the Combined Active group were significantly greater than those of the Sham group in Visual *n*-back, $t(60) = 2.59$, $p < .01$ (one-tailed), $d = .70$, but the effect was only marginal in Backward Block-tapping, $t(60) = 1.61$, $p = .06$ (one-tailed), $d = .43$, and absent in the Forward Digit Span, $t(60) = .86$, $p = .23$ (one-tailed).

However, the Active Right vs Active Left contrasts revealed significant differences in all three tests: Visual *n*-back: $t(38) = 2.38$, $p = .01$ (one-tailed), $d = .77$; Backward Block-tapping: $t(38) = 2.26$, $p = .01$ (one-tailed), $d = .73$; Forward Digit Span: $t(38) = -2.46$, $p = .02$, $d = -.80$. The first two tasks favored Active Right, whereas the Forward Digit Span favored Active Left. In all three tasks, the nonfavored stimulation group performed comparably to the Sham group (Figure 5 and Table 2), thus obscuring effects in the Combined Active versus Sham analysis. Of note, Active Right also outperformed Sham, $t(40) = 2.53$, $p = .01$ (one-tailed), $d = .80$, in the Backward Block-tapping

Table 2. Descriptive Data of Training and Transfer Measures

	Active Right (n = 20)				*Active Left (n = 20)*				*Sham (n = 22)*[a]			
	Pre	*Post*	*r*	*d*	*Pre*	*Post*	*r*	*d*	*Pre*	*Post*	*r*	*d*
Trained n-Back												
n-Level	3.68 (.80)	5.28 (1.39)	.56	1.30	4.07 (1.17)	5.48 (1.35)	.66	1.10	3.77 (1.21)	4.52 (1.77)	.75	0.45
Untrained n-Back (P_R)												
Auditory *n*-back	0.57 (0.12)	0.69 (0.13)	.18	1.01	0.61 (0.17)	0.72 (0.16)	.69	0.64	0.58 (0.15)	0.66 (0.16)	.59	0.53
Visual *n*-back	0.64 (0.16)	0.81 (0.14)	.44	1.14	0.69 (0.17)	0.73 (0.19)	.79	0.23	0.60 (0.20)	0.62 (0.22)	.60	0.13
Forward digit span	8.90 (1.97)	8.60 (2.33)	.34	−0.14	9.15 (2.56)	10.30 (2.47)	.80	0.46	8.41 (2.38)	8.60 (2.63)	.64	0.07
Backward digit span	5.90 (2.02)	6.20 (2.42)	.76	0.13	7.35 (2.64)	7.35 (2.98)	.62	0.00	5.36 (2.11)	5.41 (1.74)	.66	0.02
Forward block-tapping	12.70 (2.40)	12.80 (2.09)	.27	0.04	12.25 (2.02)	12.90 (2.83)	.38	0.26	12.45 (3.10)	12.91 (2.56)	.55	0.16
Backward block-tapping	10.55 (2.26)	12.35 (1.95)	.45	0.85	10.65 (3.03)	10.55 (2.91)	.23	−0.03	10.64 (3.13)	10.82 (2.13)	.53	0.07
Inhibitory Control (% Accuracy)												
Visual lures	0.78 (0.12)	0.91 (0.14)	.43	0.98	0.84 (0.11)	0.92 (0.05)	.24	0.95	0.72 (0.17)	0.83 (0.16)	.81	0.62
AX-CPT	0.68 (0.20)	0.66 (0.14)	.45	−0.09	0.64 (0.19)	0.61 (0.18)	.70	−0.17	0.60 (0.17)	0.61 (0.22)	.70	0.07
Positive and Negative Affect Schedule Scales												
Positive affect	31.61 (5.90)	29.83 (6.42)	.68	−0.29	31.47 (10.45)	30.39 (9.87)	.85	−0.11	32.41 (6.40)	28.14 (5.55)	.43	−0.71
Negative affect	15.78 (4.73)	14.78 (2.96)	.52	−0.24	17.26 (6.93)	17.32 (6.11)	.81	0.01	18.59 (6.42)	17.23 (5.94)	.52	−0.22

Values in parentheses are standard deviations. r = correlation between pre- and posttest. For the trained *n*-back, pre and post refer to Session 1 and Session 7, respectively.

Cohen's d effect sizes for correlated samples were calculated as $(\text{Mean}_{\text{Post}} - \text{Mean}_{\text{Pre}}) / \frac{\sqrt{SD^2_{\text{Pre}} + SD^2_{\text{Post}} - 2r * SD_{\text{Pre}} * SD_{\text{Post}})}}{\sqrt{2(1-r)}}$.

[a] All *n*s for Sham = 22, except for Auditory *n*-back and AX-CPT where n = 21.

Table 3. ANCOVA Results of Transfer Measures

	Condition			*Active vs. Sham*			*Right vs. Left*		
Outcome Measure	*F(2, 58)*	*p*	η_p^2	*t(60)*	*p*	*d*	*t(38)*	*p*	*d*
Auditory *n*-back	0.57[a]	.57	.02	1.07	.15	.29	0.01	.99[b]	.00
Visual *n*-back	**6.33**	**<.01**	**.18**	**2.59**	**<.01**	.70	**2.38**	**.01**	.77
Forward digit span	**3.38**	**.04**	**.10**	0.86	.20	.23	**−2.46**	**.03**[b]	−.80
Backward digit span	0.47	.63	.02	0.95	.17	.26	−0.22	.83[b]	−.07
Forward Block-tapping	0.61	.54	.02	0.51	.31	.14	−0.98	.17	−.32
Backward Block-tapping	**8.74**	**<.01**	**.12**	1.61	.06	.43	**2.26**	**.01**	.73
Visual lures	1.26	.15	.04	1.44	.08	.39	0.60	.28	.19
AX-CPT[a]	0.28	.75	.01	0.35	.36	.09	0.66	.51[b]	.21
Positive affect[b]	1.74	.19	.06	**1.82**	**.04**	.49	0.38	.71[b]	.12
Negative affect[b]	0.81	.45	.03	0.04	.48	.01	1.27	.21[b]	.41

Significant effects are **bolded**. Planned contrasts are reported for all outcomes in this table, but interpretations in the text are only based on outcomes where the Condition factor is significant. Cohen's *d* effect sizes, which represent adjusted posttest means between groups, differ from the within-group effect sizes reported in Table 2.

[a] Within-subject *df* = 52.

[b] Two-tailed test, otherwise one-tailed.

task, but Active Left did not improve significantly relative to Sham in the Forward Digit Span, $t(40) = 1.49$, $p = .07$ (one-tailed), $d = .48$.

Follow-up Effects

Because of the promising effects we demonstrated on the trained *n*-back task and Backward Block-tapping, we decided to conduct a follow-up analysis to assess the long-term stability of training and transfer effects. Approximately 3 months after the last participant completed the study, we invited all participants to return to the laboratory to complete an abbreviated battery consisting of just those tasks for which we observed the strongest effects immediately after training completion. Fourteen Active Right, 13 Active Left, and 14 Sham participants returned.

Although the time lag between the end of training and the follow-up assessment was variable among participants, ranging from 97 to 393 days, there was no significant difference between groups: Combined Active (mean ± *SD*: 207.48 ± 79.11), Sham (mean ± *SD*: 246.43 ± 82.78), $t = 1.47$, $p = .15$. An ANCOVA revealed a significant effect in favor of the Combined Active group on the trained *n*-back task by comparing gain scores from the first to the eighth (follow-up) session, controlling for time lag (see Figure 6), $F(2, 37) = 4.03$, $p = .03$, $\eta_p^2 = .18$, $d = 1.04$. No effect was observed on the time lag covariate, $F(1, 37) = 0.001$, $p = .99$, $\eta_p^2 < .001$, and similarly to the original seven training sessions, no effect was observed between Active Left and Active Right groups, $F(1, 24) = .04$,

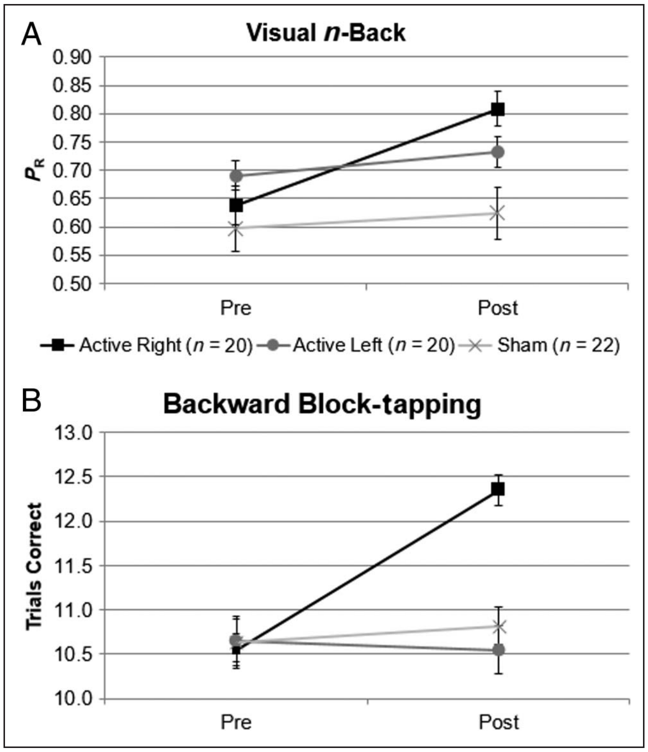

Figure 5. Transfer to visual WM. (A) The *y* axis is measured as P_R, the hit rate minus false alarm rate. (B) The *y* axis refers to the total number of correct trials. Maximum possible score is 21. Both transfer measures show significant improvement in the Active Right condition, compared with both the Sham and Active Left conditions.

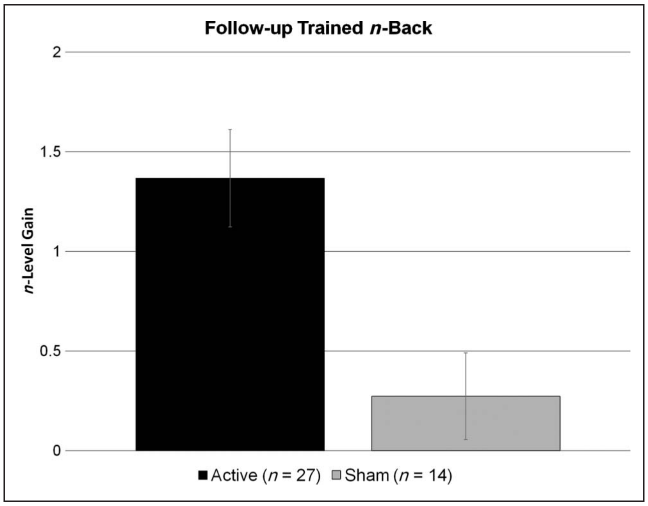

Figure 6. Follow-up results. Plot of gain from baseline in Active versus Sham group at follow-up. The Active group maintained significantly greater performance relative to the Sham group at follow-up. Error bars represent standard error.

$p = .84$, $\eta_p^2 = .002$, $d = .16$; time lag covariate, $F(1, 24) = .27$, $p = .61$, $\eta_p^2 = .01$.

No effects were observed for follow-up scores on the Backward Block-tapping task controlling for pretest performance and time lag, $F(1, 37) = .08$, $p = .78$, $\eta_p^2 = .002$; pretest covariate, $F(1, 37) = 17.19$, $p < .001$, $\eta_p^2 = .32$; time lag covariate, $F(1, 37) = 0.001$, $p = .99$, $\eta_p^2 < .001$.

DISCUSSION

The primary finding of this study is that tDCS was successful in enhancing the WM training performance of healthy, young adults and is potentially a useful tool to supplement *n*-back training interventions. These enhancements were more pronounced when training sessions were spaced apart by a weekend, and the enhanced effect due to stimulation was maintained for several months after training completion. Furthermore, our results cannot be explained by circumstantial factors such as baseline demographics, level of alertness, motivation, or mood, which were well matched between groups, and all participants were led to believe they received active stimulation (i.e., they were blind to the existence of a sham group). Even after being debriefed upon conclusion of the study, participants could not reliably distinguish their condition, with no significant differences in their guesses or reported levels of confidence about stimulation condition. Moreover, there was also no significant difference between the Combined Active and Sham groups on self-reported side effects.

Although WM enhancement with tDCS has been extensively explored before (Jantz, Katz, & Reuter-Lorenz, 2016), yielding inconsistent results across studies that nevertheless aggregate into a small to moderate positive net effect (Hill et al., 2015; Summers et al., 2015), this study contributes to a nascent literature exploring the use of tDCS in multisession training paradigms. These studies are an important departure from previous single-session experiments in that they allow for the potential of tDCS effects on between-session learning to manifest. In contrast to previous WM training studies (Richmond et al., 2014; Martin et al., 2013), we provide the first evidence that tDCS can enhance the rate of learning between training sessions. Our ANOVA showed a significant Condition × Session interaction supporting a steeper rate of improvement in the combined Active group relative to Sham. This is in contrast to Martin et al. (2013), who failed to find significant differences between groups when baseline performance was controlled. And although Richmond et al. (2014) were more successful in demonstrating group differences in verbal WM training after left DLPFC stimulation, they found only a main effect but no interaction, thereby demonstrating an enhanced (upwards-shifted) learning curve with no difference in learning rate.

Several key differences may explain these discrepant results. First, Martin et al. (2013) used a more difficult dual *n*-back task that typically shows shallower improvement curves relative to single *n*-back (Jaeggi et al., 2010). This may have restricted their ability to discriminate a differential learning rate relative to sham controls. Richmond et al. (2014), on the other hand, chose to stimulate mostly offline, with only 5 min of overlap between stimulation and commencement of training, arguing that the effects of tDCS typically last well beyond the stimulation period itself. Although this argument is supported by some previous research, we note that online and offline effects likely operate via different mechanisms (Stagg & Nitsche, 2011) and that the nature of cognitive activity during stimulation may influence the later effects of tDCS (Gill, Shah-Basak, & Hamilton, 2015; Bikson et al., 2013). For example, it is thought that online effects operate mainly via membrane depolarization whereas offline effects are thought to rely on a combination of membrane depolarization and LTP-like plasticity (Stagg & Nitsche, 2011). Therefore, online stimulation, which promotes targeted activation of task-relevant regions, may also selectively facilitate later LTP-like plasticity in neuronal populations of interest. In fact, reports confirm that online stimulation is superior to offline both in increasing cortical perfusion during stimulation (Stagg et al., 2013) as well as enhancing between-session consolidation of learning (Martin et al., 2014). Therefore, online stimulation may have played an important role in manifesting between-session learning effects in our study that Richmond et al. (2014) failed to detect. These effects are not unusual in light of evidence from motor cortex demonstrating cumulative effects from daily stimulation (Alonzo et al., 2012; Reis et al., 2009; Boggio et al., 2007). Accordingly, we point out that there are no differences between our Active and Sham groups on Training

Day 1 but differences gradually became more pronounced each day until reaching significance midweek (see Figure 3). Additionally, our results suggest that these differences are durable and manifest at follow-up even several months posttraining; the average follow-up time was 7–8 months after the initial intervention. Coupled with our finding of spacing effects after a weekend break from training, our study implicates an important role for tDCS in learning and consolidation.

Furthermore, an interesting finding in our data is that although tDCS provided a general benefit on the training task, irrespective of stimulated hemisphere, our transfer results suggested selective improvement by right DLPFC stimulation on tasks with a visual and/or spatial component. This latter finding is in line with our hypothesis and fits with evidence of a left/right hemispheric dissociation for verbal and visual WM function, respectively. Moreover, we also found modest evidence for a left DLPFC advantage on the Forward Digit Span task (pre to post gains: $d = .46$), although this result should be interpreted with caution: Although the contrast against Active Right was significant, the contrast against Sham was not. However, this does provide a nice complement to the finding by Richmond et al. (2014) that left DLPFC stimulation enhanced verbal WM training, but not spatial. Although these results in combination are suggestive of a role for tDCS in strategically targeting the functional neuroanatomy of the brain (cf. Bikson et al., 2013), this argument is severely hampered by the lack of functional specificity in our training data, where both Active tDCS groups improved comparably despite the visuospatial nature of the training. Future studies therefore should seek to further elucidate a potential dissociation between left and right prefrontal stimulation in terms of verbal and visual WM tasks, using well-designed visual and verbal test batteries that can verify this effect at the level of latent constructs. Until then, our transfer results should be interpreted as preliminary.

Limitations

Although our study lends great support to the efficacy of tDCS in enhancing learning during WM training, the lack of functional specificity in the training data cannot rule out the alternative hypothesis that stimulation effects are general and not related to the DLPFC. For example, there is a large literature on tDCS-induced motor effects (Hashemirad et al., 2016; Summers et al., 2015), and it is known that tDCS induces wide-spread perfusion changes across the brain (Stagg et al., 2013), which may inadvertently excite motor areas that can confound improved cognitive performance with increased motoric priming/readiness. Although we cannot definitively exclude this possibility, previous research has shown that stimulation of the DLPFC but not motor cortex improves WM performance (Boggio et al., 2006; Fregni et al., 2005), and also that multisession stimulation to the DLPFC over 2 weeks can improve cognitive, but not motor, skills in Parkinsonian patients (Doruk, Gray, Bravo, Pascual-Leone, & Fregni, 2014). Together, this suggests that the effects of stimulation to prefrontal and motor cortices operate fairly independently of one another.[3]

Additionally, we point out that our finding of sustained effects is limited by potential self-selection biases with regard to the individuals who were willing to come back again for a follow-up months after completing the initial study. Furthermore, because of the post hoc nature of the follow-up, the sham participants had already been unblinded. However, because neither group received tDCS at follow-up and expectations of sustained effects after such a long interval (in most cases, over half a year) were likely muted, we argue that placebo effects at follow-up may not have played a very substantial role. Nevertheless, future studies should test the permanence of tDCS learning effects more rigorously by implementing a more standardized follow-up protocol for all participants.

Another limitation of our study concerns our provisional transfer results. Only three of the eight comparisons among our cognitive transfer measures revealed significant effects between groups (Visual n-back, Backwards Block-tapping, and Forwards Digit Span). Although all of our measures were theoretically grounded in previous literature, our results are not immune to issues of multiple comparisons. Nevertheless, the percentage of significant results (3/8 = 38%) exceeds the false discovery rate, which assumes that 5% of our transfer measures would suffer from Type I errors based on our threshold for significance testing ($p < .05$). Moreover, our findings of improvement selectively on the visual n-back and Block-tapping tasks in the Active Right group are theoretically justified in that they align with both our hypothesis of selective visual benefits as well as previous WM training results, which have unanimously demonstrated transfer to either an n-back or WM span task as a result of tDCS (Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Park et al., 2014; Richmond et al., 2014; Martin et al., 2013).

An important caveat to our visual WM transfer findings is that we did not detect any effects in the Forward version of Block-tapping, despite our findings with the Backward version. This is not necessarily surprising in that the Forward and Backward versions do not share identical properties. The latter tends to be more difficult and participants perform worse, as evidenced both in our study (Table 2) as well as others (Monaco, Costa, Caltagirone, & Carlesimo, 2013). Backward Block-tapping may therefore involve more central executive resources in addition to short-term retention of visuospatial information (Vandierendonck, Kemps, Fastame, & Szmalec, 2004). Consequently, it may share more overlapping properties with the trained n-back task than the forward version. Moreover, selective tDCS effects on only the backward version of Block-tapping have been reported before (Wu et al., 2014).

Conclusion

This study successfully demonstrated that tDCS can durably enhance the performance curve of *n*-back training studies and therefore is a promising adjunctive tool to use in WM training interventions. Moreover, this enhancement was even more pronounced when stimulation sessions were separated by a weekend break, and we also exhibited some preliminary success in demonstrating selective transfer with right DLPFC stimulation on measures of visual or spatial WM. These results are meaningful amidst the controversy surrounding the efficacy of WM training, particularly with respect to far transfer, which is often found in meta-analyses (Au et al., 2015; Schwaighofer et al., 2015; Weicker et al., 2016; Karbach & Verhaeghen, 2014) but not consistently among primary studies. However, given the small meta-analytic effects on domains such as attention, reasoning, and executive functioning, individual studies are often underpowered with respect to far transfer (Bogg & Lasecki, 2014). Because recruiting and maintaining large samples over an extended period of time can be logistically challenging for many training studies, the prospect that tDCS might strengthen these effects would go a long way toward overcoming these issues and allow more reliable investigations into the true benefits and limitations of cognitive training interventions. Finally, because most *n*-back training studies employ considerably more than seven sessions, a time period too short to allow most participants to reach their individual ceilings, an enticing open question is whether tDCS merely facilitates reaching ceiling more quickly, or whether it can actually raise this ceiling relative to sham with more training sessions.

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Notes

1. A separate analysis was run using Site as an additional factor. There was a main effect ($p = .04$) indicating University of Michigan students outperformed University of California students. This may be associated with demographic differences (e.g., SAT and ACT average) between the two universities (U.S. Department of Education, Institute of Education Sciences [IES], 2014). Critically, however, there was no Session × Site × Condition interaction, indicating similar patterns of improvement across both universities. Because of the lack of this triple interaction and to prevent loss of power by further reducing our sample size, site analyses were not probed further and are not reported.

2. Both Active Right and Active Left groups individually show the same trends as the Combined Active group, but contrasts are not significant, likely because of power issues.

3. We also reanalyzed our training data with RT as the dependent variable instead of *n*-level. There was a main effect of session ($p < .001$), indicative of decreasing RTs over the course of training, but no Session × Condition interaction ($p = .83$), meaning all groups improved comparably. Therefore, the increased *n*-back accuracy we see in the Active groups, in the absence of improved RT latencies versus sham, argues against a motoric priming effect of tDCS. This analysis was only carried out on *n*-levels of 2, 3, and 4 because these were the only levels that 100% of participants were able to achieve.

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