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Post-training Stimulation of the Right Dorsolateral Prefrontal Cortex Impairs Working Memory Training Performance

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Abstract

Research investigating transcranial direct current stimulation (tDCS) to enhance cognitive training augments both our understanding of its long-term effects on cognitive plasticity as well as potential applications to strengthen cognitive interventions. Previous work has demonstrated enhancement of working memory training while applying concurrent tDCS to the dorsolateral prefrontal cortex (DLPFC). However, the optimal stimulation parameters are still unknown. For example, the timing of tDCS delivery has been shown to be an influential variable that can interact with task learning. In the present study, we used tDCS to target the right DLPFC while participants trained on a visuospatial working memory task. We sought to compare the relative efficacy of online stimulation delivered during training to offline stimulation delivered either immediately before or afterwards. We were unable to replicate previously demonstrated benefits of online stimulation; however, we did find evidence that offline stimulation delivered after training can actually be detrimental to training performance relative to sham. We interpret our results in light of evidence suggesting a role of the right DLPFC in promoting memory interference, and conclude that while tDCS may be a promising tool to influence the results of cognitive training, more research and an abundance of caution are needed before fully endorsing its use for cognitive enhancement. This work suggests that effects can vary substantially in magnitude and direction between studies, and may be heavily dependent on a variety of intervention protocol parameters such as the timing and location of stimulation delivery, about which our understanding is still nascent.

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Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization,* J.A., B.K., J.J., S.M.J.; *Methodology*, J.A., B.K., T.R.A., S.M.J.; *Software,* S.M.J.; *Investigation,* J.A., A.M., S.T.; *Formal Analysis*, J.A.; *Resources*, J.J., S.M.J.; *Writing – Original Draft*, J.A.; *Writing – Review & Editing*, all authors; *Supervision*, J.J., S.M.J.; *Project Administration*, A.M., S.T.; *Funding Acquisition*, J.J., S.M.J.

Conflicts of Interest

S.M.J has an indirect financial interest in the MIND Research Institute, Irvine, CA, whose interests are related to this work. No other authors declare any conflicts of interests or sources of funding.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon request.

Keywords

transcranial direct current stimulation; online tDCS; offline tDCS; stimulation timing; consolidation; memory interference; cognitive training

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive means of electrical brain stimulation that has garnered considerable interest among cognitive training researchers due to its potential to influence learning and improve cognitive functioning. TDCS applied via sponge electrodes on the scalp has been shown to modulate cortical excitability (Nitsche & Paulus, 2000) as well as regional cerebral blood flow (Lang et al., 2005) across a broad swath of cortex between and around the stimulating electrodes. In our previous work (Au et al., 2016; Katz et al., 2017), we used tDCS to target the dorsolateral prefrontal cortex (DLPFC), a region known to be important for working memory (WM) and other executive functions (Barbey et al., 2013; Curtis & D'Esposito, 2003; Fregni et al., 2005). We found not only a considerable performance advantage over the course of a week-long WM training intervention using a visuospatial n-back task, but also long-lasting benefits that persisted up to a year later.

These long-lasting effects have been replicated in a similar study by an independent team (Ruf et al., 2017), and moreover are generally in line with the positive results seen in most other longitudinal tDCS-WM training studies (Berryhill, 2017; Jones et al., 2015; Martin et al., 2013; Richmond et al., 2014). This pattern of results suggests that the benefits of tDCS go beyond merely temporary increases in regional activity. One compelling mechanism for these improvements is that tDCS may act to facilitate long-term potentiation (LTP) and LTP-like plasticity in WM training studies that may in turn improve learning consolidation during training (reviewed in Au et al., 2017). Polarity-dependent cellular changes in LTP and BDNF, an important protein for synaptic plasticity, have already been demonstrated in a number of animal studies both *in vitro* (Fritsch et al., 2010; Ranieri et al., 2012) and *in vivo* (Podda et al., 2016; Rohan et al., 2015), with behavioral correlates in improved spatial memory on the Morris Water Maze task (Podda et al., 2016). Related behavioral benefits in humans have also been demonstrated, with evidence of both declarative (Javadi & Cheng, 2013; Sandrini et al., 2014, 2019) and procedural (Cabral et al., 2015; Janine Reis et al., 2009; Rumpf et al., 2017; Tecchio et al., 2010) memory consolidation lasting hours to months.

Despite these positive findings in other memory domains, it is not immediately clear why such long-lasting effects would exist when it comes to WM, where information is stored for seconds rather than days or months. However, it is important to consider the bidirectional relationship between WM and long-term memory (LTM) — any information that enters WM must first be retrieved from LTM, and may also, with enough repetitions or salience, be re-encoded back into LTM. This can be clearly described with respect to declarative memory, where any explicit memories that are eventually formed, such as memorizing the multiplication table, must at some point first pass through the attentional

filters of WM, such as when practicing the multiplication problems. However, procedural information shared between WM and LTM is also thought to act in an analogous fashion (Oberauer, 2009; Reiman, 2015); in fact, recent studies suggest that the procedural processes of WM and other executive functions can also be consolidated in much the same way as declarative information (P.-C. Chen et al., 2020; Ferrarelli et al., 2019; Pugin et al., 2015; Sattari et al., 2019). Specifically, several studies have documented that training-related improvements using the n-back task (the intervention used in our previous study; Au et al., 2016) were observed only if the interval between sessions included sleep or a nap, but not wake (Kuriyama et al., 2008; Lau et al., 2015; Zinke et al., 2018), suggesting that sleep-dependent consolidation augments WM performance, thus, mirroring what is observed in other memory systems. In further support of this, WM improvements after training seem to be correlated with slow-wave sleep activity (Ferrarelli et al., 2019; Pugin et al., 2015), a critical factor for the consolidation of perceptual and motor procedural skills (Crupi et al., 2009; Huber et al., 2004; Määttä et al., 2010).

Given the body of evidence in support of a role of consolidation in WM training, and specifically when augmented by tDCS, we sought to determine whether we could interact directly with this consolidation process by applying stimulation immediately *after* training during a period of quiet rest. This rest period after a learning event has previously been shown effective in improving later behavioral performance, both in the presence of tDCS (Javadi & Cheng, 2013; Rumpf et al., 2017; Sandrini et al., 2014; Tecchio et al., 2010) and absence of tDCS (Brokaw et al., 2016; Humiston et al., 2019; Wamsley, 2019). Nevertheless, we note that results with post-learning tDCS have been mixed, with two studies demonstrating null results (J. Chen et al., 2020; J. Reis et al., 2015) and two even demonstrating *disruptive* effects on consolidation (King et al., 2020; Marián et al., 2018).

Although most studies to date apply either offline stimulation *before* a task to prime the targeted cortical area or online stimulation *during* task performance to potentiate task-relevant networks, the purpose of the current study was to test the relative efficacy of offline stimulation *after* training in order to interact directly with the consolidation process. Only a few studies to date have compared these stimulation timing conditions to each other. Furthermore, from a meta-analytic perspective, there is no clear consensus as to which timing parameter is ideal, as both online and offline stimulation have been documented to be more advantageous depending on various moderators such as the task, population, or montage (Dedoncker et al., 2016; Hill et al., 2016; Hsu et al., 2015; Summers et al., 2016). Similarly, the few empirical studies that have directly compared these timing conditions to each other have sometimes demonstrated an advantage of online stimulation (Fertonani et al., 2014; Martin et al., 2014; Oldrati et al., 2018; Sriraman et al., 2014; Stagg et al., 2011) and sometimes an advantage of offline stimulation *before* task performance (Buchwald et al., 2019; Cabral et al., 2015; Giacobbe et al., 2013; Pirulli et al., 2013; Workman et al., 2019), and only a handful of studies have even investigated stimulation *after* task performance, (Cabral et al., 2015; J. Chen et al., 2020; Javadi & Cheng, 2013; King et al., 2020; Marián et al., 2018; Rumpf et al., 2017; Sandrini et al., 2014, 2019; Tecchio et al., 2010). To our knowledge, only one study has ever directly compared all three timing conditions, and identified an advantage of stimulating beforehand for eliciting motor-evoked potentials (Cabral et al., 2015). In this study, we sought to compare the relative efficacy

of these three timing conditions during WM training by applying stimulation to the right DLPFC[1] using the same montage that we and others have previously used to induce positive training effects (Au et al., 2016; Mancuso et al., 2016). Although we expected to replicate our previous effects with online stimulation, we were most interested in whether offline stimulation administered post-training would produce even greater effects due to its ability to interact directly with the consolidation process. To this end, we also included a weekend spacing manipulation in our paradigm (described in Methods), since we previously observed that participants showed the greatest training gains after a weekend break compared to gains between consecutive weekdays (Au et al., 2016), in line with well-established work on the positive effects of spaced learning for consolidating learned information (Cepeda et al., 2006; Ebbinghaus, 1885). Given the mixed and limited nature of earlier research, we did not have an a priori hypothesis regarding the relative efficacy of offline stimulation delivered pre-training.

Methods:

Participants

Eighty-two neurologically and psychiatrically healthy right-handed participants (mean age: 20.40, SD: 1.68, 63% female) were recruited at the University of California, Irvine and University of Michigan campuses. One participant regularly failed to advance beyond 1-back, even after one week of training. Given our population of healthy college undergraduates, this level of performance was considered non-compliant; no other participant in our sample failed to advance beyond 1-back even once during their training. Therefore, this participant was excluded, leaving 81 total participants in our final sample. All research procedures were approved by the Institutional Review Boards at both universities and each participant provided informed consent.

General Procedure

On Day 1, all participants began training on the same version of an adaptive visuospatial n-back WM task before being assigned to one of four stimulation conditions (offline pre-training, online, offline post-training, and sham) for the remainder of training, which lasted a total of 6 days plus a 1-month follow-up. This allowed us to obtain a metric of unstimulated baseline performance that is comparable across all groups, an important consideration given the robust evidence that baseline ability moderates the efficacy of tDCS (Benwell et al., 2015; Jones & Berryhill, 2012; Katz et al., 2017; Looi et al., 2016; Tseng et al., 2012). Another important consideration in our study design was that all participants were constrained to begin their sessions on either a Tuesday or a Wednesday, so that the weekend break consistently fell either after the third or fourth training session for all participants. This allowed us to control for and assess potential weekend-related effects since we previously found that the greatest training improvement occurred after the weekend (Au et al., 2016).

On Day 2, each participant was pseudorandomly triaged into his or her respective condition using an Excel algorithm designed to balance participants' baseline scores and starting-days across conditions. This algorithm served to ensure on a rolling basis that average baseline scores among all conditions were comparable and that there was an even representation

from the Tuesday and Wednesday cohorts in each stimulation condition. We note that when carefully conducted, pseudorandomization can sometimes be as or more effective than true randomization (Green et al., 2019), and in our case was used to control for potential baseline and weekend interactions with tDCS.

Each training session lasted approximately one hour, including set-up and clean-up. Duration of stimulation, including sham stimulation, was fixed at 25 minutes, while the n-back training typically lasted between 18 and 22 minutes. Participants in the offline stimulation conditions (pre- and post-training) were asked to sit quietly and remain alert (i.e., asked not to fall asleep) during stimulation, and to simply allow their minds to wander without fixating on any one thing in particular. Otherwise, they were given no task or any further instructions during stimulation. Participants in the online and sham conditions were asked to sit quietly for 10 minutes beforehand to control for total time spent in the lab. This 10-minute period was chosen (instead of the full 25 minutes as in the offline conditions) as a compromise between controlling for quiet time prior to training while minimizing participants' restlessness and suspicions[2]. All participants, including sham participants, were told they were receiving active tDCS, and that the purpose of the study was to compare differences in stimulation timing. This was done in accordance with our previous study (Au et al., 2016), and because past research has shown that 2mA of tDCS, as used in our first study, can be distinguishable from sham by some participants (O'Connell et al., 2012). Participants were debriefed at the end of their 1-month follow-up session and asked to judge whether they received active or sham stimulation. See Figure 1 for a visual representation of the study protocol.

Working Memory Training

We used the same training task that we previously demonstrated to be responsive to tDCS (Au et al., 2016). 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 non-targets, using a standard computer keyboard. The difficulty of the task adapted continuously based on the trainee's performance. Each stimulus was presented for 500ms followed by a blank screen for 2,500ms. A training session consisted of 15 blocks, each with 20+n trials where six trials were targets and 14+n trials were non-targets. Training duration for one session typically lasted between 18–22 minutes. Accuracy rates of 70% and 90% (inclusive) were used as cut-offs to 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 out 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) using 5×7cm sponge electrodes placed horizontally on the head. The anode was placed over the right DLPFC (slightly lateral to site F4 by about 1 cm in the international

10–20 EEG system) and the cathode was placed over the contralateral supraorbital area (site Fp1). The anode was positioned slightly lateral to F4 because previous modeling work has found the peak current intensity to lie between electrodes, rather than directly underneath (Faria et al., 2011). Our decision to stimulate the right DLPFC represents a slight departure from our previous study in which half of the participants receiving tDCS were stimulated on the right DLPFC and the other half on the left. Since we previously found general effects of tDCS with no significant laterality differences, we chose to target only the right DLPFC in all our stimulation groups this time in order to reduce the total number of group comparisons. The right DLPFC was chosen over the left due to its established role in visuospatial WM (Giglia et al., 2014; Smith et al., 1996; S. Wang & Ku, 2018).

Electrode positions (F4 and Fp1) were identified according to the system devised by Beam et al. (2009), which has been successfully used to target the DLPFC and modulate WM performance in previous neurostimulation studies (Bagherzadeh et al., 2016; Fried et al., 2014; Trumbo et al., 2016). This system is based on the international 10–20 system, but requires fewer head measurements, thus reducing both the time involved as well as the potential for human error. Stimulation lasted 25 minutes with a current intensity of 2mA, which ramped up and down for the first and last 15 seconds of stimulation. Sham tDCS was set up in exactly the same way, except the current was shut off unbeknownst to participants between the 15-second ramping periods.

Analytical Approach

Statistical analyses were conducted using STATA version 13 (StataCorp, 2013) and JASP 0.9.1.0 (JASP Team, 2018). Training data were analyzed with a linear mixed effects model that accounted for the hierarchical nature of the data (i.e., sessions nested within subjects), with the following equation:

$$\mathrm{NBack}_{ij} = \beta_0 + \beta_1 \mathrm{Session}_{ij} + \beta_2 \mathrm{Online}_{ij} + \beta_3 \mathrm{Before}_{ij} + \beta_4 \mathrm{After}_{ij} + \mu_{0i} + \mu_{1j} Session_{ij} + \varepsilon_{ij}$$

where NBack_{ij} represents the dependent measure (average n-back level for a particular session) for the i^{th} participant for the j^{th} session, β_0 represents the overall regression intercept, $\beta_{1–4}$ represents vectors of fixed effect beta weight coefficients for the Session and Condition (dummy variables for Online and both Offline conditions, referenced to Sham condition) predictors, μ_{0i} represents the participant-level random effect intercept that shifts the regression line up or down according to each participant's starting ability, $\mu_{1j}\mathrm{Session}_{ij}$ represents the participant-level random effects slope that accounts for between-participant variability in learning rate across sessions, and ε_{ij} represents a vector of error terms using the *cov(unstructured)* command in Stata which does not assume that the random effects estimates (slopes and intercepts) are independent and allows for correlation between the two. This model with both a random slope and random intercept was selected on both theoretical and statistical grounds. It allows us to capture both the random variation in baseline ability (intercept) between participants as well as the random variation in learning rate (slope). Moreover, this model (AIC/BIC=1309/1359) demonstrated the best fit to our data, compared to a model with just a random intercept (AIC/BIC = 1340/1382), or no random effects (AIC/

BIC=1709/1747). The command line used in Stata was as follows: *mixed nback session i.condition c.session#condition || subj:session, cov(unstructured)*.

Follow-up effects were evaluated with a one-way ANCOVA comparing the mean n-back level achieved among each of the four groups during the 1-month follow-up session, controlling for starting performance on session one. The assumption of equality of variances was tested with Levene's test, and if violated, would be corrected with Welch's ANOVA (Liu, 2015). Weekend effects were evaluated with a 2×4 repeated measures ANOVA, with the within-subjects factor Time and the between-subjects factor Condition. The Time factor consisted of two levels: Weekend Gains and Weekday Gains. Weekend gains were calculated by taking the difference between sessions 3 and 4 (Wednesday cohort) or between 4 and 5 (Tuesday cohort). Average weekday gains were calculated based on the average gain between all pairs of consecutive weekdays, with the exception of the first two days because stimulation was not applied on the first session (i.e., average of gain between sessions 2–3, 4–5, and 5–6 in the Wednesday cohort or sessions 2–3, 3–4, and 5–6 in the Tuesday cohort). No sphericity test was conducted because the assumption of sphericity is always met when the repeated measure only has two levels (JASP Team, 2018).

Results:

Demographics, Sample Size, and Baseline Ability

Our sample size was determined by a power analysis based on training effects from our previous study (Au et al., 2016). Since the current study was focused on evaluating and optimizing the consolidation effect of tDCS on WM training, we based our power analysis on the effect size from our previously reported long-term follow up ($d = 1.04$). With α set to 0.05 and β set to 0.80, we determined that 21 individuals per group would be an appropriate sample size to capture this effect. In the end, after attrition and exclusions, our final analytic sample comprised 19 individuals in the offline pre-training condition (12 female, age ± SD = 20.71 ± 2.13), 21 in the online condition (14 female, age ± SD = 20.48 ± 1.72), 22 in the offline post-training condition (15 female, age ± SD = 20.35 ± 1.45), and 20 in the sham condition (12 female, age ± SD = 20.08 ± 1.26). True to our pseudorandomization algorithm, baseline n-back levels were comparable across groups (mean ± SD: pre-training – 3.62 ± 1.13, online – 3.17 ± 1.07, post-training – 3.38 ± 0.79, sham – 3.31 ± 0.81), with a one-way ANOVA showing no main effect of condition ($F_{3,77} = 0.789$, $p = 0.504$).

Current Modeling

We modeled the electric field intensity generated from our montage using Comets2 (Lee et al., 2017). Results showed that our montage effectively targeted the prefrontal cortex, with an electric field intensity ranging between .2 – .35 V/m around the right DLPFC (Figure 2B). However, the peak intensity is actually centered around the frontal pole (~.4 V/m). The electric potential model (Figure 2C) shows the highest potential around and posterior to the right DLPFC, with increasingly negative potential around the frontal pole.

Sham Debriefing

Of the 81 participants in our sample, 73 came back for the 1-month follow-up and upon the conclusion of the study were debriefed about the existence of a sham group and asked to guess their condition. Of those participants receiving active tDCS, 83.93% correctly guessed their condition and 64.71% of sham participants also guessed that they had in fact received active tDCS. The difference was not significant ($\chi 2 = 2.95$, $p = .086$). Moreover, regardless of their retrospective guesses, it is important to reiterate that all participants were led to believe they were receiving active tDCS during training.

Training Effects

Our linear mixed effects regression model found a main effect of session ($b = .357$, $z = 6.92$, $p < 0.001$) indicating that all groups improved over time, but importantly, found an interaction between session and the post-training offline condition ($b = -0.152$, $z = -2.13$, $p = 0.033$) such that the post-training offline condition underperformed relative to sham. No other main effects or interactions were significant (p's > .251; see Table 1). However, at the 1-month follow-up, our ANCOVA showed no main effect of condition ($F_{3,68} = 1.940$, p=0.131, η_p^2 =0.079), suggesting no group differences in performance remained at follow-up. There was no violation of equal variances according to Levene's test ($F_{3,69} = 1.273$, $p = 0.291$). See Figure 3 for all training curves. Furthermore, our analysis of spacing effects showed no main effect of time ($F_{1,77}$= 0.857, p=0.358, η_p^2 =0.011) or time × condition interaction ($F_{3,77} = 1.855$, p=0.144, η_p^2 =0.067), suggesting that training performance across a weekend was no different than performance across consecutive weekdays and that this null effect was consistent between conditions (Figure 4).

Post-hoc Analyses

Since the detrimental effects of post-training stimulation relative to sham are a novel finding in the WM-tDCS literature, we conducted an exploratory *post-hoc* analysis to probe for idiosyncratic effects specific to the post-training condition. First, we re-ran our previous mixed effects linear regression, but referenced to the post-training condition rather than sham. Results once again revealed the significant interaction with the sham condition ($b = 0.152$, $z = 2.13$, $p = 0.033$), but this time also an interaction with the online condition ($b = .187$, $z = 2.62$, $p = 0.009$), but not the pre-training offline condition ($b = 0.067$, $z = 0.93$, $p = 0.352$). See Table 1 for full results.

We also reanalyzed the 1-month follow-up data to specifically explore differences related to the post-training condition. To do so, we re-ran our previous one-way ANCOVA model, but regrouped the condition factor to have two levels: post-training and the average of the other three conditions. We found a significant main effect of condition ($F_{1,70} = -5.653$, $p = 0.020$, η_p^2 =0.075), indicating worse performance in the post-training group ($d = -0.60$). Moreover, individual contrasts against each of the other three conditions also found marginal or significant underperformance: (vs. pre-training: $t_{69} = 1.682$, $p = 0.097$, $d = -0.599$; vs. online: $t_{69} = 2.242$, $p = 0.028$, $d = -0.466$; vs. sham: $t_{69} = 1.809$, $p = 0.075$, $d = -0.534$). Similarly, we reanalyzed the weekend effects with the same re-grouping of the condition factor. There was no main effect of condition ($F_{1,79}$= 0.108, p=0.743, η_p^2 =0.001), a marginal main effect of time in favor of weekend spacing ($F_{1,79} = 3.711$, $p = 0.058$, η_p^2

=0.045), and importantly, a significant time by condition interaction ($F_{1,79}$ = 4.896, p = 0.030, η_p^2 =0.058) indicating stronger gains after a weekend relative to the average weekday gain in the post-training condition only. Individual contrasts against each of the other three conditions separately suggested this interaction was primarily driven by differences against the sham condition (t_{77} = 2.272, p = 0.026, d=0.734), but not online (t_{77} = 1.612, p = 0.111, d=0.473) nor pre-training (t_{77} = 1.403, p = 0.165, d=0.443). See Figure 4.

Discussion:

Our goal in the current study was to determine the optimal timing to deliver tDCS in order to more effectively enhance consolidation of WM training gains. We targeted the right DLPFC for stimulation with the expectation that this would facilitate visuospatial WM. According to our computational current model, stimulation did indeed target the right DLPFC. However, we note that the peak intensity was actually centered closer to the frontal pole (~0.35 – 0.4 V/m) than the right DLPFC (~0.25–0.3 V/m), so there is likely room for further optimization in the montage. Still, there are several reasons to assume that the right DLPFC was sufficiently targeted here. First, it is not known whether this small difference in electric field intensity between the right DLPFC and frontal pole is functionally meaningful. Moreover, the electric potential (Figure 2C) is highest over and around the right DLPFC, suggesting strong anodal influence, with presumably more excitation of the underlying tissue, and increasingly negative towards the frontal pole on the way to the left supraorbital area, suggesting increasing cathodal influence, with presumably more inhibition despite the higher electric field intensity. Finally, we point out that the effects of tDCS are not just anatomically specific, but also functionally specific (Bikson & Rahman, 2013). In other words, task-dependent neural activity is selectively potentiated. So, to the extent that the n-back training task preferentially recruits the right DLPFC over the frontal pole, tDCS will also preferentially target the right DLPFC over the frontal pole.

With reasonable confidence that our montage effectively stimulated the right DLPFC, it is somewhat surprising that we were unable to replicate our previously reported advantage of online tDCS (Au et al., 2016). We discuss potential reasons for this further below in the Limitations section, but more pertinently, the main result of this paper is that we found a *disadvantage* of receiving tDCS post-training, compared to training with sham stimulation. Although this ran counter to the goal of our study to optimize skill consolidation from WM training, such disruptive effects are not without precedent. In fact, two recent studies corroborate our results. King et al. (2020) found that post-training tDCS to the right motor cortex disrupted later motor skill consolidation, despite benefits observed with left hemisphere stimulation in a previous study by the same group (Rumpf et al., 2017). Similarly, Marián et al. (2018) showed that right DLPFC stimulation after verbal memory encoding impaired consolidation and behavioral performance one week later. Notably, other studies that have reported facilitation effects of post-encoding tDCS on declarative memory all targeted the left DLPFC (Javadi & Cheng, 2013; Sandrini et al., 2014, 2019). As a corollary to these results, Asthana et al. (2013) showed that inhibition of the left DLPFC with cathodal stimulation could block consolidation of fear memories. Taken together, there is a growing body of evidence that the left DLPFC plays a role in facilitating memory consolidation, which raises the question of whether the disruptive effects described above

(King et al., 2020; Marián et al., 2018) and in our study could be attributed to targeting of the right hemisphere (see also Robertson, 2012).

Despite evidence that the DLPFC may facilitate memory consolidation, its executive role in the selection and inhibition of competing memories also permits a mechanism for memory suppression (Anderson, 2004; Anderson & Green, 2001). For example, the right DLPFC specifically has been implicated in promoting adaptive memory interference (Cohen & Robertson, 2011; Robertson, 2012), and excessive activity in this region is one of the functional brain abnormalities that has been linked to memory deficits in individuals with mild cognitive impairment or Alzheimer's disease (Bai et al., 2009; Sperling et al., 2010; L. Wang et al., 2006). Experimentally, greater right DLPFC activity has been recorded in healthy individuals during interference paradigms designed to disrupt memory (Diekelmann et al., 2011). In contrast, less activity in the right DLPFC was associated with better memory performance and less interference from competing memories (Kuhl et al., 2007). Moreover, even though initial retrieval of a memory is associated with relatively greater DLPFC activity, multiple studies have found that each subsequent retrieval is associated with increasingly less activity, and further that this pattern of incremental prefrontal disengagement was predictive of later memory retention and increased forgetting of competing memories (Eriksson et al., 2011; Karlsson Wirebring et al., 2015; Keresztes et al., 2014; Kuhl et al., 2007).

Thus, extant neuroimaging evidence points to an inverse correlation between activity in the right DLPFC and memory performance. However, a series of experiments using transcranial magnetic stimulation (TMS) also suggest a causal role of the right DLPFC in diminishing memory performance. For example, Turriziani et al. (2012) found that excitatory TMS over the right DLPFC impaired subsequent retrieval of declarative memory, while inhibitory TMS facilitated retrieval. Similarly, Sandrini et al. (2013) used TMS to disrupt the right DLPFC 24 hours after encoding during a memory reactivation protocol and also found improvement during subsequent retrieval. This provides evidence that the role of the right DLPFC in forgetting persists beyond the initial learning period, and presumably can occur when a memory becomes labile again such as during memory reactivation or reconsolidation (see also Maren, 2011). The reasons for the influence of the right DLPFC over memory performance are made more clear by Cohen and Robertson (2011), who presented two different memory tasks sequentially to participants. Under normal circumstances, the second task should interfere with the first, thus impairing later recall. However, using TMS to disrupt right DLPFC activity after the two memory tasks actually eliminates this interference effect and restores memory for the first task. This provides evidence that resources within the right DLPFC may be necessary for memory interference to occur, which is in line with a more recent study that showed even voluntary forgetting is compromised in a directed forgetting paradigm when the right DLPFC is disrupted by TMS (Xie et al., 2020).

In light of the evidence for the role of the right DLPFC in promoting interference and forgetting, the shallower learning curve of our offline post-training group is not surprising. Under normal circumstances, a period of quiet rest after a learning event would be expected to encourage consolidation (Brokaw et al., 2016; Craig & Dewar, 2018; Dewar et al., 2014; Humiston et al., 2019). This is thought to at least in part be attributed to activation of the

default mode network during rest, which much as in sleep, fosters a neural environment conducive to consolidation (Kaplan et al., 2016; Miall & Robertson, 2006). This is important because DLPFC stimulation, specifically with the same montage used in our study, has been shown to deactivate this network (Peña-Gómez et al., 2012). Thus, in this post-training resting environment, where memories and engrams related to recently learned materials are reactivated and rendered labile (Nader, 2003; Nader et al., 2005), stimulation of the right DLPFC may disrupt consolidation processes via two different, but possibly overlapping, mechanisms. Not only might it promote interference of newly labile memories, but it may also disengage the brain from its default resting state, prepping it for external sensory input and cognitive activity rather than internally guided consolidation of recently acquired memories or skills.

Finally, we draw attention to our exploratory *post-hoc* analyses. There were two important findings here that were not apparent in our main results. First, the underperformance of the offline post-training group seems to persist even 1 month after the end of training, suggesting the learning deficit engendered by tDCS is pronounced and long-lasting. Second, despite these deficits, having a weekend break from stimulation seemed to have somewhat of a restorative effect on performance. Importantly, virtually all the training gains in this group, such as they were, occurred either after the weekend or after the unstimulated baseline training session. In contrast, the average gain score between consecutive stimulated weekdays hovered near zero (Figure 3). Spacing apart learning sessions, such as over a weekend, is typically associated with greater memory or skill increases due to a longer consolidation period (Cepeda et al., 2006; Ebbinghaus, 1885), and we previously demonstrated that this spacing effect also applies to n-back training in the presence of online tDCS, but not sham (Au et al., 2016). However, this time the effect did not appear in our online tDCS group but did appear in a group where consolidation and reconsolidation processes were presumably inhibited. Since this group still underperforms relative to all other groups, even after the weekend, we hesitate to interpret this as a facilitation effect of spacing on memory consolidation. Rather, it may also simply be a washout of the disruptive effects of post-training stimulation. Due to the exploratory, *post-hoc* nature of these analyses, as well as the presence of a couple of pronounced outliers (Figure 3), we refrain from speculating much further on the underpinnings of this weekend effect other than to say that future studies evaluating post-training stimulation should carefully consider the potential for washout effects when planning follow-up testing. Our preliminary, exploratory results suggest that disruptive effects may be captured 24 hours later, but not 72.

Limitations

The biggest limitation to the current study is that we were unable to replicate our previous online tDCS effects (Au et al., 2016), despite using the same training task and a very similar procedure. We observed neither an overall benefit of online tDCS relative to sham nor a weekend spacing effect. One crucial difference between the two studies lies in the stimulation site. Whereas the present study stimulated the right DLPFC, we previously investigated both hemispheres using two separate groups. We previously saw an overall effect of tDCS with no interactions suggesting differences between stimulation sites. However, the left DLPFC group did numerically outperform the right DLPFC group, and

moreover, a meta-analysis by Mancuso et al. (2016) shows not only that the majority of tDCS studies investigating WM function stimulate the left DLPFC, but also that the few which stimulate the right hemisphere do not aggregate into a net meta-analytic effect. Although, in the current study, we chose to stimulate the right DLPFC due to its role in visuospatial WM (Smith et al., 1996), it might still be a less optimal stimulation target than the left DLPFC, which has more robust empirical support behind it in terms of enhancing WM performance (Mancuso et al., 2016). Thus, there remains an impetus for further research exploring specific tDCS/cognitive training parameters such as electrode placement and potential interactions with the modality of stimulus material.

Conclusions:

We were unable to replicate our previously demonstrated online tDCS enhancement effects. Despite this, the intriguing findings identified here in regards to offline stimulation delivered after training may offer important insight to two underexplored areas that have significant relevance for researchers designing future tDCS/training paradigms. First, only a minority of studies have delivered stimulation *after* the behavioral task of interest, and while some previous research has suggested this to be a potent way to boost early consolidation processes (Javadi & Cheng, 2013; Rumpf et al., 2017; Sandrini et al., 2014, 2019; Tecchio et al., 2010), we add to accumulating research that shows how certain manipulations can block or impair these processes instead (Asthana et al., 2013; King et al., 2020; Marián et al., 2018). Second, our results also lend support to a functional role of the right DLPFC in promoting memory interference during a period of memory reactivation or reconsolidation (Bekinschtein et al., 2018; Cohen & Robertson, 2011; Diekelmann et al., 2011; Eriksson et al., 2011; Kuhl et al., 2007; Robertson, 2012; Turriziani et al., 2012). Altogether, we conclude that tDCS can have significant and meaningful impacts on cognitive training, but the strength and direction of these effects can vary dramatically depending on stimulation timing, location, and a variety of other factors. Researchers should keep in mind that these effects may, in some circumstances, be deleterious to training performance. Despite this, continued, careful work in this space may help to better elucidate the underlying neural mechanisms supporting task-based tDCS. Given the excitement this technology has generated for use cases in both the clinical and the public spheres, we caution that a more comprehensive understanding of both the technology and functional brain anatomy is warranted before fully embracing its use.

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Significance

Transcranial direct current stimulation (tDCS) is a noninvasive means of electrical brain stimulation that can influence synaptic plasticity and enhance learning. However, the optimal stimulation parameters are still an active area of research. This study tested the relative efficacy of delivering tDCS to the right dorsolateral-prefrontal cortex (DLPFC) before, during, or after working memory training. Although none of the conditions demonstrated any learning benefits, we did observe learning *impairment* when stimulation was delivered after training. This study strengthens our understanding of the functional role of the right DLPFC, as well as the uses and misuses of tDCS to augment learning.

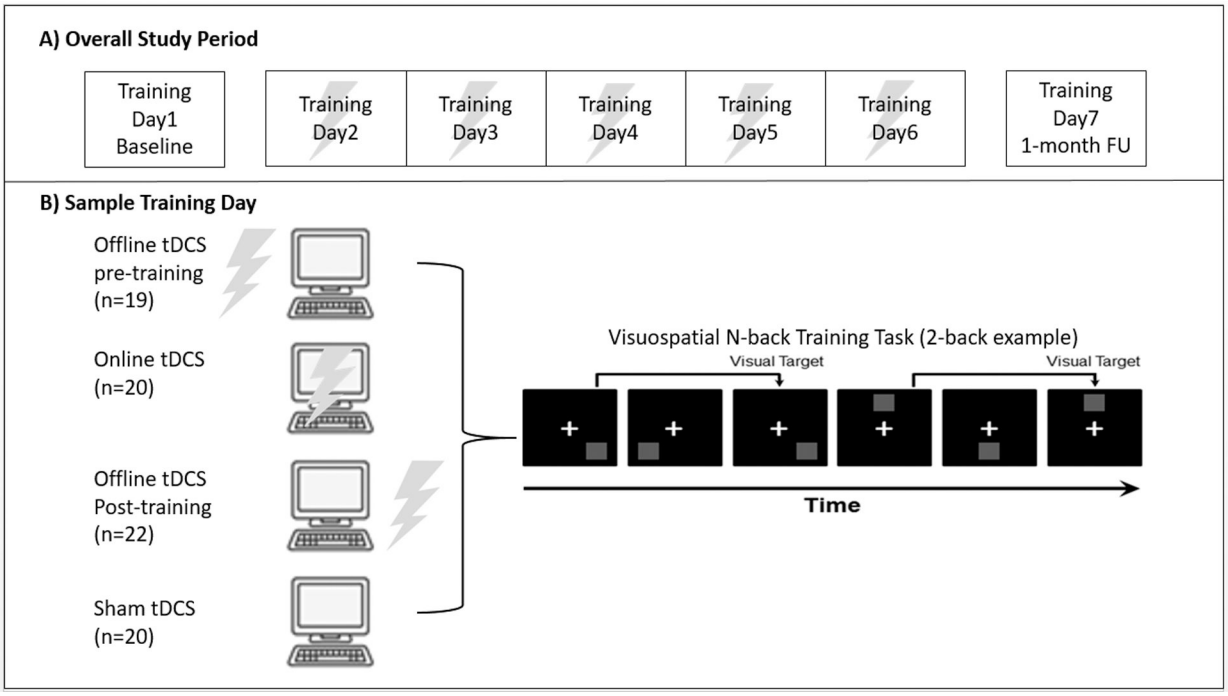

Figure 1: Study Design.

(A) Participants came in for a total of seven sessions, the first and last of which did not involve any stimulation. (B) Sample training day consisted of stimulation according to the participant's group assignment (indicated by lightning bolts before, during, or after the computer icon) as well as training on the visuospatial n-back task (indicated by the computer icon). A sample 2-back block is depicted.

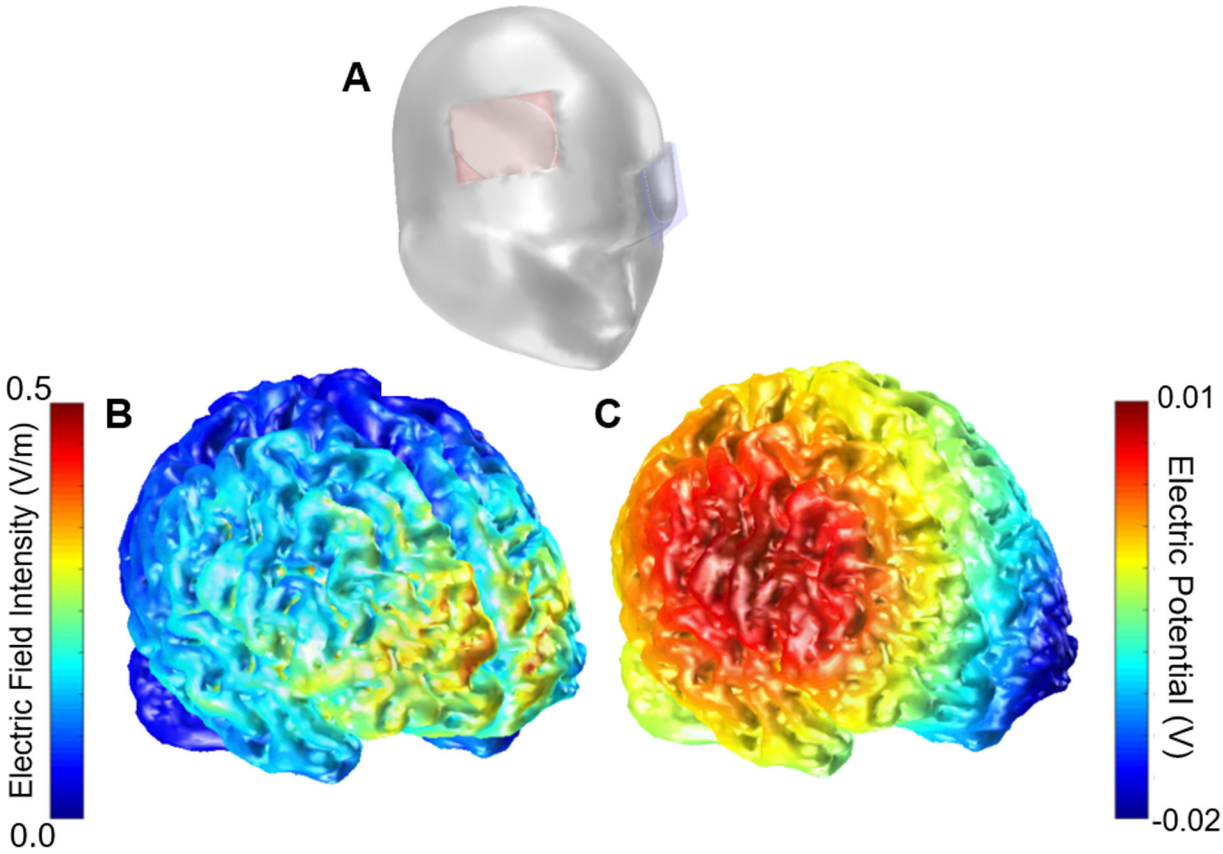

Figure 2. Computational model.

(A) tDCS montage is shown with anode (red) centered just 1cm lateral to position F4 and cathode (blue) centered over Fp1. (B) Electric field modeling of the anterior aspect of the brain shows peak electric field intensity between the anode over the right DLPFC and the cathode over the left supraorbital ridge, with current reaching the entire frontal cortex, and extending into the right motor cortex. (C) The electric potential model demonstrates the flow of current from the positive anode to the negative cathode. Note that the strongest positive potential is over and around the right DLPFC.

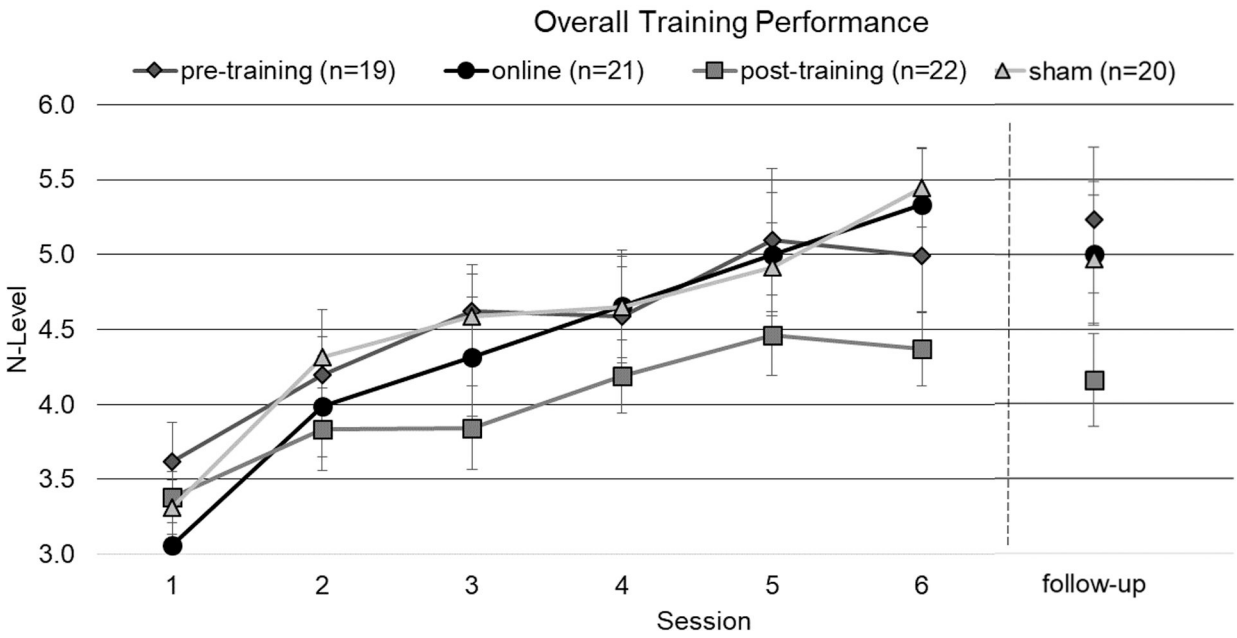

Figure 3: Training performance.

Training curves for all groups are shown. The post-training condition significantly underperformed relative to the other groups, who all performed similarly to each other. Post-hoc analyses show that this underperformance persisted at the 1-month follow-up. All error bars represent SEM.

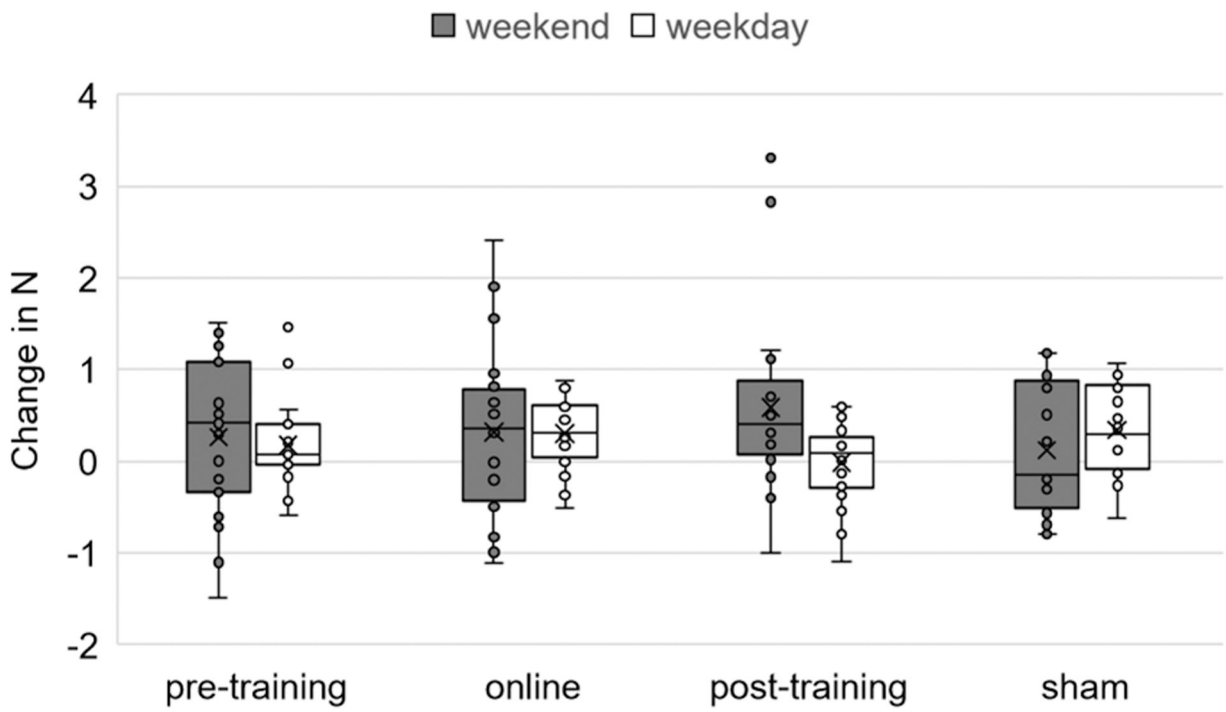

Figure 4: Weekend Effect.

No significant effects were found in our omnibus ANOVA, indicating no overall effect of weekend spacing on training performance. However, our exploratory *post-hoc* analyses suggested greater gains specifically in the post-training condition after a weekend compared to consecutive weekdays. See Discussion for appropriate interpretation. The lower and upper boundaries of the boxes represent the first and third quartiles, respectively, and the end of the whiskers represent +/− 1.5 times the interquartile range. The median is indicated by a horizontal line and mean is indicated by an "X". Dots represent individual participants. * $p < .05$

Table 1.

Linear Mixed Model

Reference Group	Predictor	B	SE B	p
Sham	Offline pre-training	0.279	0.357	0.435
	Online	−0.221	0.352	0.530
	Offline post-training	0.010	0.344	0.978
	Offline pre-training X Session	−0.085	0.074	0.251
	Online X Session	0.035	0.073	0.634
	Offline post-training X Session	−0.152	0.071	0.033*
Offline post-training	Offline pre-training	0.269	0.349	0.440
	Online	−0.231	0.344	0.502
	Sham	−0.010	0.344	0.978
	Offline pre-training X Session	0.067	0.072	0.352
	Online X Session	0.187	0.071	0.009*
	Sham X Session	0.152	0.071	0.033*
	Random Effects	**Estimate**	**Standard Error**	
Both	Intercept Variance	0.835	0.009	
	Slope Variance	0.027	0.198	
	Intercept-Slope Covariance	0.028	0.030	

Two separate linear mixed models were run, referenced to either the sham or offline post-training groups. The dependent variable is the average n-back level. Significant interactions were found between the offline post-training group and the sham/online groups, with beta coefficients suggesting a disadvantage of .152 and .187 n-back levels per day, respectively.