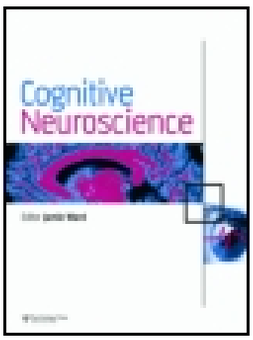

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ARTICLE

Prefrontal transcranial direct current stimulation (tDCS) enhances behavioral and EEG markers of proactive control

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ABSTRACT

This study examined the effects of stimulation targeting dorsolateral prefrontal cortex (DLPFC) on behavioral and neural oscillatory markers of proactive cognitive control in healthy adults. We hypothesized that active stimulation targeting the DLPFC would enhance proactive control compared to sham, leading to changes in the pattern of error rates and gamma-band power on the Dot Pattern Expectancy (DPX) task. We recorded EEG while participants completed the DPX, after receiving either 20 minutes of active DLPFC stimulation at 2 mA or sham stimulation in a counterbalanced within-participants design. The results showed significant tDCS-induced changes in the pattern of error rates on the DPX task indicative of enhanced proactive control, as well as predicted increases in gamma power associated with the engagement of proactive control. These results provide support for the role of DLPFC-mediated gamma activity in proactive cognitive control, and further, indicate that proactive control can be enhanced with non-invasive neurostimulation.

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tDCS; gamma; proactive control; EEG

Introduction

Cognitive control is an umbrella term for a set of functions that support goal-directed cognition and behavior. Two important elements of cognitive control are *proactive control* and *reactive control*. *Proactive control* refers to goal and context maintenance in order to anticipate upcoming cognitive demands, whereas reactive control refers to the on-demand engagement of executive processes in response to increased cognitive demands (e.g. Braver, Paxton, Locke, & Barch, 2009).

An example of proactive control is when participants use the rules of a task to prepare for an upcoming response. This type of goal or context maintenance is defined as 'processes involved in activating task-related goals or rules, actively representing them.maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection' (Barch & Smith, 2008, p. 13). Proactive control has been consistently associated with the dorsolateral prefrontal cortex (DLPFC) in neuroimaging studies, as a key component of a more extensive frontal-parietal cognitive control network (D'Esposito et al., 1995; Esposito, 2007; Lesh, Niendam, Minzenberg, & Carter, 2011; MacDonald, 2000; MacDonald & Carter, 2003; Niendam et al., 2014). EEG studies have found increased proactive control demands to be associated with increased high-frequency gamma-band (~30–80 Hz) activity measured at frontal electrode sites (e.g. Cho, Konecky, & Carter, 2006; Minzenberg et al., 2010). This is consistent with a large literature connecting intracranially-recorded gamma range activity to higher-order cognitive functions, including a recent study that found sustained DLPFC gamma-band activity in response to increased cognitive control demands (Bartoli et al., 2017).

In contrast, an example of reactive control is that participants tend to slow down after making an error on a task. This type of post-error adjustment, also called adaptive control, has been consistently associated with low-frequency neural oscillations in the theta band (~4–7 Hz) measurable over frontal cortex in scalp-recorded EEG (Cavanagh & Frank, 2014). Recent studies using non-invasive neurostimulation techniques such as transcranial direct current stimulation (tDCS) have further shown that anodal stimulation of frontal cortex leads to enhanced behavioral performance on adaptive control tasks, as well as increases in associated theta-band oscillatory measures (e.g. Reinhart, Zhu, Park, & Woodman, 2015).

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The potential impact of tDCS on proactive control performance and its associated neural correlates has not yet been tested. Our goal in the current study was to use anodal tDCS to stimulate the DLPFC in healthy adults, and evaluate tDCS-induced changes in behavior and neural oscillatory activity in the gamma range related to the engagement of proactive control. As noted above, the DLPFC plays a central role in theoretical accounts of cognitive control (e.g. Lesh et al., 2011), and has been consistently implicated in neuroimaging studies of proactive control in particular (e.g. MacDonald, 2000; MacDonald & Carter, 2003). Thus, we hypothesized that stimulation targeting the DLPFC would improve proactive control performance.

To assess proactive control, we recorded EEG while participants completed the dot-pattern expectancy (DPX) task (Jones, Sponheim, & MacDonald, 2010; MacDonald, Carter, Flory, Ferrell, & Manuck, 2007; MacDonald et al., 2005). On this task, participants are asked to classify cues and probes as targets or non-targets. Targets consist of a particular dot pattern probe ('X') that is preceded by a particular dot pattern cue ('A'), known as an 'AX' trial. All other stimuli are non-targets. AX trials comprise the majority of all stimuli, leading participants to develop an expectation to make a 'match' response to probes following 'A' cues, and to 'X' probes generally.

This design has two important features that make it useful for studying proactive control. First, strong anticipation of an 'X' probe after encountering an 'A' cue (i.e. the engagement of proactive control) leads to an increased error rate on AY trials (Jones et al., 2010; MacDonald et al., 2007, 2005). Second, weaker proactive control is reflected by the error rate on BX trials, on which the 'B' cue context must be maintained in order to correctly inhibit the pre-potent target response and instead identify the 'X' probe as a non-target in this condition (Jones et al., 2010; MacDonald et al., 2007, 2005). In other words, failure to use proactive control to support goal maintenance would be an advantage on AY trials, but a disadvantage on BX trials.

In the current study, participants completed the DPX task after 20 minutes of active DLPFC stimulation (2 mA) and sham stimulation, with sessions completed on separate days and testing order randomized. We predicted that, compared to sham stimulation, active stimulation would enhance DLPFC-mediated proactive control processes, leading to changes in both behavioral performance on the task and activity in the gamma frequency band. Specifically, as successful goal maintenance is associated with an AY>BX error pattern (see: Barch, Carter, MacDonald, Braver, & Cohen, 2003; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Henderson et al., 2012; Lopez-Garcia et al., 2016; MacDonald et al., 2005), we predicted that active stimulation would increase AY errors and decrease BX errors, compared to sham.

Our EEG analysis focused on the delay period between cue and probe, during which time the cue context must be maintained in order to guide responding to the upcoming probe. We predicted that gamma power would be increased in the delay after B cues compared to A cues, reflecting the increased proactive control demands in this condition. We hypothesized that active stimulation would significantly enhance this B > A difference in delay period gamma power, compared to sham stimulation. This pattern of results would provide causal evidence for the hypothesized roles of the DLPFC and gamma-band activity in supporting proactive control (e.g. Gratton, Cooper, Fabiani, Carter, & Karayanidis, 2018), and would further suggest that proactive control in healthy adults can be enhanced via non-invasive neurostimulation.

Methods

Participants

21 healthy undergraduate participants (17 female) gave informed consent and took part in this study, which was approved by the Institutional Review Board at the University of California, Davis. Participants were compensated with course credit. The average participant age was 21 (range: 18–30). One participant did not complete the second session, and so all analyses reported in this paper reflect the final sample of N = 20.

Protocol overview

Participants received active and sham tDCS on different days, with order of sessions randomized across participants (average interval between sessions: 5.5 days, range: 2–13 days) and participants blinded

to protocol condition. During tDCS administration, participants completed the N-back task, which is thought to promote engagement of the prefrontal circuits targeted by our active stimulation protocol. Specifically, some previous work suggests that combining tDCS with a task that engages relevant circuits yields greater cognitive enhancement than stimulation alone (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011). The N-back is a working memory task that engages bilateral DLPFC (Owen, McMillan, Laird, & Bullmore, 2005; Perlstein, Dixit, Carter, Noll, & Cohen, 2003). Details on the N-back task are provided below. Immediately following stimulation, electrodes were prepared for recording (~10 minutes) and EEG was recorded as participants completed the DPX task, as well as an unrelated memory task (RISE) that will be analyzed separately. Details on the DPX task are provided below.

N-back task

During the N-back task, participants monitor a sequence of letters and respond when a letter matches one presented *n* trials previously. During stimulation, participants first completed a practice overview that consisted of 100 trials of 0-back, 2-back and 3-back conditions. This was followed by a 100-trial block in the 2-back condition, and a 100-trial block in the 3-back condition. Response (yes or no as to whether the current letter was a match) was made via keyboard button press.

DPX task

As noted above, the DPX task is a modification of the AX expectancy task in which dot-patterns are used as cue-probe pairs rather than letters. The version used here was developed by the CNTRACS initiative and is freely available online (http://cntracs.ucdavis.edu/dpx). Participants were presented with 144 trials across 4 blocks of 36 trials each, in four conditions: AX (72%), AY (11%), BX (11%) and BY (6%). AX trials (dot-pattern 'X' when preceded by dot pattern 'A') represent targets; all

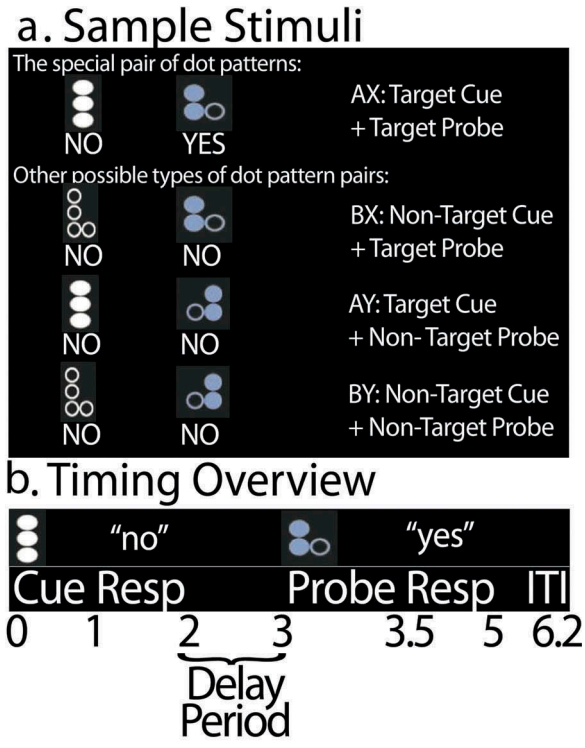

Figure 1. Panel A: Sample stimuli and instructions for the DPX task. Panel B: DPX trial timing information.

cues and other cue-probe combinations represent non-targets. See Figure 1 for stimuli examples and timing information. The 1000 ms delay period in between cue response and probe onset was the focus of our EEG analyses.

tDCS

Both stimulation conditions (active and sham) were administered using a neuroConn battery-driven stimulator. Direct current was administered with a pair of electrodes wrapped in 5 × 7 cm saline-soaked sponges, using an electrode montage commonly used to target DLPFC (Laakso et al., 2016).[1] The anodal electrode was placed over left DLPFC (site: F3), and the cathodal electrode was placed at the right supraorbital site (FP2). During active stimulation, current was administered for 20 minutes at an intensity of 2 mA, with a 30 second ramp-up and ramp-down. Sham stimulation followed the same

[1]While this electrode montage is commonly used to enhance activity in DLPFC, it is important to keep in mind that the bipolar nature of tDCS means that changes in electric fields will not be restricted to those induced by the anode. For this reason, it is not recommended to place anodal and cathodal electrodes in the same location on either side of the brain, as this can make it difficult to interpret whether stimulation effects in the targeted region are anodal, cathodal or a combination of the two (Reinhart, Cosman, Fukuda, & Woodman, 2017). While we have avoided this configuration in the current study, the placement of the cathode on FP2 does still impact electric fields in some cortical regions, although current flow modeling of this configuration shows consistent electric fields in the superior frontal and middle frontal gyri (BA9 and BA46) (see Laakso et al., 2016).

procedure, but only included the 30 second ramp-up and ramp-down at the beginning and end of the 20 minute period.

EEG

EEG was acquired with a BioSemi ActiveTwo system (http://www.biosemi.com) and 32-channel electrode cap. An electrode located near Cz (common mode sense: CMS) was used as the recording reference, (except for four electrodes used to measure eye movements: one electrode above and one below the left eye were referenced to each other, and two placed on the outer canthi were referenced to each other). EEG was amplified with bandpass cutoffs at 0.05 and 100 Hz and digitized at a sampling rate of 1024 Hz, later downsampled to 250 Hz. Data processing and analysis were performed using MATLAB, using the EEGLAB toolbox with ERPlab plugin, and custom scripts. Data processing was performed using MATLAB (Mathworks) with the EEGLAB toolbox (Delorme & Makeig, 2004). Independent component analysis (ICA) was used to correct for eye-blink artifacts. Single-trial waveforms were screened for amplifier blocking, horizontal eye movements, and any remaining blinks or movement-related artifacts over epochs of 4000 ms, starting −500 ms before cue onset.

EEG spectral power was calculated using the EEGlab toolbox, by convolving single-trial epochs with seven-cycle complex Morlet wavelets. Power for 78 log-spaced frequencies from 3–80 Hz was averaged across trials within a condition and log-transformed. Power estimates were binned into low gamma (30–50 Hz) and high gamma (50–80 Hz) frequency bands.

Results

Behavioral: DPX task

Behavioral data are summarized in Figure 2. As noted above, our analyses were focused on AY and BX trials, so as to measure error rates related to the engagement of lack of engagement of proactive control. A repeated measures ANOVA with the within-participants factors of Stimulation (Active, Sham) and Condition (AY, BX) revealed a significant interaction of Stimulation and Condition ($F(1,19) = 6.402$; $p = 0.02$; $\eta p^2 = 0.25$), with the predicted pattern that error rates were higher for BX trials than AY trials following sham stimulation, with the opposite pattern being found after active stimulation indicating that cognitive control was more highly engaged. Follow-up paired t-tests showed a significant effect of Stimulation for the AY condition (Stim>Sham; $p = 0.046$; $\eta p^2 = 0.19$).

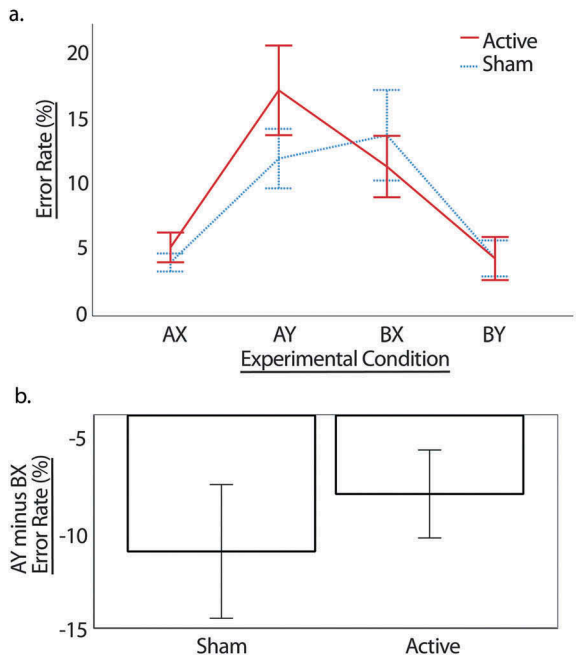

Figure 2. Panel A: Error rates for all trial types on the DPX task. Solid red line: error rates following active stimulation. Dotted blue line: error rates following sham stimulation. Panel B: AY minus BX error rates on the DPX task following active stimulation and sham stimulation. All error bars represent standard error.

EEG (DPX task)

Our central hypotheses focused on activity during the delay period between cue and probe. Specifically, we hypothesized that active stimulation would enhance proactive control compared to sham stimulation, leading to an increase in gamma power during the delay period following B cues compared to A cues. We conducted separate repeated measures ANOVA (rANOVA) of delay period power for the frequency bands below, with within-participants factors of Stimulation (Active, Sham), Condition (B Cues, A Cues), and the topographic factors Cluster (Frontal, Central, Posterior) and Electrode (Left, Middle, Right). We expected that delay-period

effects in the gamma band would be maximal at the Frontal electrode cluster, as has been shown in previous work (Cho et al., 2006; Minzenberg et al., 2010). Central and Posterior clusters were included in order to characterize the distribution of the effect, i.e. whether effects observed at the Frontal cluster were focal or were present across the scalp. Electrode clusters were therefore defined as follows: Frontal (Left: FC1; Middle: Fz; Right: FC2), Central (Left: CP1; Middle: Cz; Right: CP2) and Posterior (Left: PO3; Middle: Pz; Right: PO4). Significant interactions were followed up with rANOVA of the B Cue minus A Cue difference in delay period power, with the within-participants factors of Stimulation (Active, Sham), Cluster (Frontal, Central, Posterior) and electrode (Left, Middle, Right). The Greenhouse-Geisser correction was applied to all analyses with more than one degree of freedom in the numerator. Results are summarized below and in Figures 3 and 4.

Low gamma (30–50 Hz)

The omnibus rANOVA showed a significant interaction of Stimulation by Condition by Electrode ($F(2,38) = 3.674$; $p = 0.049$; $\eta p^2 = 0.16$), and of Stimulation by Condition by Cluster by Electrode ($F(4,76) = 4.093$; $p = 0.015$; $\eta p^2 = 0.18$), such that delay period B cue power was greater than A cue power with a frontal maximum. Follow-up analyses confirmed that the effect of stimulation protocol was driven by increased frontal gamma power for B cues, relative to A cues (Stimulation by Electrode interaction: ($F(2,38) = 4.67$; $p = 0.033$; $\eta p^2 = 0.2$).

High gamma (50–80 Hz)

There was a marginal main effect of Condition ($F(1,19) = 3.552$; $p = 0.075$ $\eta p^2 = 0.15$), such that delay period high gamma power tended to be increased following B cues compared to A cues, but there were no significant effects of Stimulation in this frequency range.

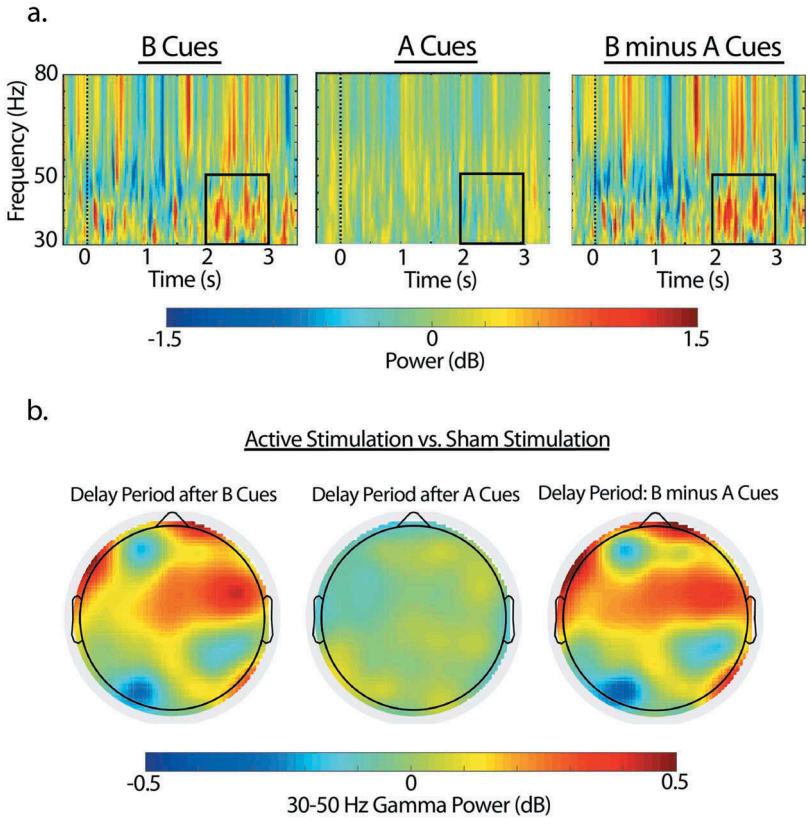

Figure 3. Panel A: Time-frequency results at the Frontal electrode cluster for the Active stimulation minus Sham stimulation contrast, time-locked to the cues and extending through the delay period (2000–3000 ms) to the onset of the probes at 3000 ms. The black boxes indicate delay period low gamma band activity (30–50 Hz from 2000 to 3000 ms post-cue onset). Panel B: Topographic distribution of the effects of stimulation (Active minus Sham) on delay period low gamma power.

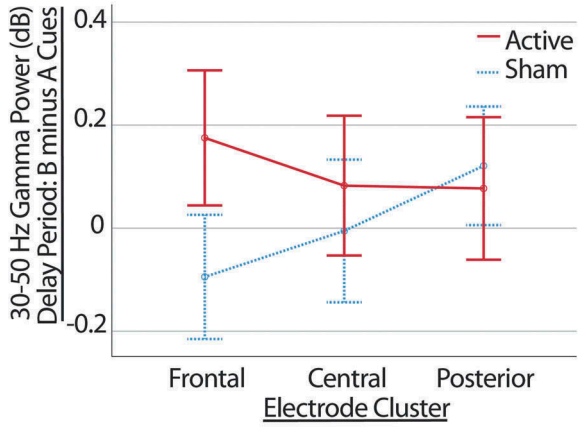

Figure 4. Delay period low gamma power for the B Cues minus A Cues contrast, by Stimulation (Active, Sham) and Cluster (Frontal, Central, Posterior). Error bars represent standard error.

N-back task

While the primary focus of this experiment was on the DPX task that followed tDCS administration, we also analyzed the data for the 3-back completed during tDCS. We observed no statistically significant differences in performance between Active and Sham stimulation using paired samples t-tests in accuracy (Active mean: 89.6; Sham Mean: 90.4), hit rate (Active mean: 79.4; Sham: 81.3) or false alarm rate (Active mean: 6.5; Sham mean: 5.9). However, higher N-back hit rate (correct responses to targets) was associated with lower BX error rate on the DPX task after Active stimulation but not Sham. This correlation was significant using either the N-back hit rate from the same Active session ($r = -0.63$; $r^2 = 0.397$; $p = 0.003$) or from the Sham session ($r = -0.551$; $r^2 = 0.303$; $p = 0.012$), and survived corrections for multiple comparisons (alpha level of 0.0167). No other correlations were significant.

Discussion

Our goal in this study was to examine the effects of DLPFC stimulation on behavioral and neural oscillatory markers of proactive control in healthy adults. We found significant tDCS-induced changes in the pattern of error rates on the DPX task, as well as in delay-period gamma power associated with the engagement of proactive control. We discuss the behavioral effects of stimulation before turning to the EEG effects and possible mechanisms of action below.

In order to respond correctly on a BX trial, participants must use the context provided by the B cue to avoid making their typical response to an X probe. That is, BX trials represent an exception to the rule in which participants respond 'yes' to an X (except after a 'B' cue, which happens infrequently). The engagement of proactive control to maintain the 'B' cue context during the delay between cue and probe would therefore promote correct responding on these trials. In contrast, as there is only ever one correct response to a 'Y' probe ('no'), irrespective of the cue type that preceded it, failure to maintain the context provided by the cue on an AY trial could actually help performance (because 'A' cues most often precede 'X' probes). Following sham stimulation, error rates were higher for BX trials than AY trials following sham stimulation. This pattern reversed after active stimulation. This reversal of the error rate pattern following active stimulation is the predicted pattern associated with increased engagement of proactive control, as it indicates stronger use of the context provided by the cues to prepare to respond to the upcoming probes (see Lopez-Garcia et al., 2016).

As noted above, participants completed the N-back during stimulation in order to promote engagement of the prefrontal circuits targeted by our stimulation protocol, specifically the DLPFC, which is both engaged by the N-back (Owen et al., 2005; Perlstein et al., 2003) and central to proactive control processes (e.g. MacDonald, 2000; MacDonald & Carter, 2003). Lower BX error rates following Active stimulation were significantly correlated with higher hit rates on the N-back task that was completed concurrently with tDCS. Interestingly, this correlation was significant for the N-back hit rate measured during either Active or Sham stimulation (both were correlated with BX error rate after Active stimulation; neither was correlated with BX error rate after Sham stimulation). Thus it was not the case that individuals who performed better on the N-back necessarily performed better on the DPX, as the correlation did not hold for DPX performance after Sham. This pattern suggests that individuals who perform better on the N-back generally (measured during either Sham or Active stimulation) show the largest effects of stimulation on behavior. This also suggests that variability in tDCS effects on proactive control could be related to individual differences in cognitive control (i.e. 'the rich get richer').

For trials on which participants responded correctly, our EEG results showed that gamma-band power was increased in the delay period between cue and probe for the B cue condition relative to the A cue condition. B cues are relatively demanding of proactive control as they signal an upcoming probe to which participants must overcome their prepotent response tendency in order to respond appropriately. The B > A delay period gamma power difference was maximal at frontal electrode sites, consistent with previous work that has associated increased proactive control demands with increased frontal gamma-band activity (Cho et al., 2006; Minzenberg et al., 2010). In line with our hypotheses linking DLPFC-mediated gamma activity to the engagement of proactive control, we found that this B > A gamma power effect in the delay period between cue and probe was significantly larger after active stimulation compared to sham stimulation. Further, the tDCS-induced increase in delay period gamma power was driven by the B cue condition, as can be seen on the topographic maps of this effect in Figure 3. This indicates that stimulation of the DLPFC did not lead to general increases in gamma-band power, but rather that stimulation increased gamma power specifically associated with a high demand for proactive control.

High-frequency activity in the gamma band (~30–-80 Hz) can be observed throughout cortex via intracranial recordings (see Bartoli et al., 2017 for an example of DLPFC gamma activity) and in scalp-recorded EEG (see Minzenberg et al., 2010 for an example of proactive-control linked gamma activity). Gamma activity has also been shown to be strongly associated with BOLD response measured by fMRI (e.g. Magri, Schridde, Murayama, Panzeri, & Logothetis, 2012; Mukamel et al., 2005). This has led gamma oscillations to be considered to be a signature of 'local' cortical activity, in contrast to lower frequency oscillations such as in the theta band (~4–7 Hz), which have been proposed to be a mechanism of long distance communication across cortical regions (e.g. Cavanagh & Frank, 2014). Gamma oscillations have been most extensively studied in relation to perceptual processes, and are thought to be a core element of neuronal computation (Fries, 2009). In addition to gamma associated with perception, changes in gamma activity have been observed in response to increased demands in a range of cognitive domains, including working memory and cognitive control. For example, gamma band power has been shown to increase along with set size on working memory tasks, leading to the suggestion that gamma oscillations play a role in the maintenance of information over time (Howard, 2003; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012; van Vugt, Sederberg, & Kahana, 2007). Maintenance of task-relevant context, also known as goal maintenance or proactive control, has also been associated with increased gamma activity in previous work (Cho et al., 2006; Minzenberg et al., 2010). Although the focus of both of these studies was on a clinical population (individuals with schizophrenia), both also report results in healthy adults that have particular relevance to the current study. Specifically, both (Cho et al., 2006; Minzenberg et al., 2010) found increased gamma power during the delay period of a proactive control task in which the context of a cue must be maintained in order to prepare to respond to an upcoming probe. Frontal gamma activity related to proactive control has been suggested to be linked to GABAergic activity in the DLPFC (Minzenberg et al., 2010). While the current dataset cannot speak to the underlying cellular/molecular mechanisms driving the oscillatory effects observed at the scalp, our results do demonstrate that such effects are sensitive to DLPFC stimulation, providing evidence to support a role for DLPFC-mediated gamma-band activity in proactive control.

The mechanisms of action that underlie tDCS-induced changes in behavior and EEG are not yet fully understood. Stimulation is thought to increase neural excitability, which has largely been explored using motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) (Nitsche & Paulus, 2000). Typically, in these studies active or sham tDCS is administered to primary motor cortex, and motor responses are then evoked using TMS. The magnitude of the MEPs can then be recorded. There is evidence using this approach that motor excitability is increased during the administration of anodal tDCS, as well as after stimulation has concluded (Jamil et al., 2017; Nitsche & Paulus, 2000, 2001). Additional evidence that anodal tDCS can induce sustained changes in excitability comes from studies that used a similar approach in combination with pharmacological manipulations aimed at blocking NMDA-mediated synaptic plasticity (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003, 2004). These studies

suggest that tDCS can induce both transient increases in excitability as well as more sustained changes (it should be noted that most of the available data defines sustained in terms of several minutes), at least in the motor cortex. In the current study, we found behavioral and EEG evidence of enhanced proactive control on a task completed within about 30 minutes after DLPFC-targeted stimulation (compared to sham), which started about 10 minutes after tDCS administration. This result is consistent with the idea that anodal tDCS can induce neuroplastic changes in brain activity.

Conclusions

Consistent with our hypotheses, we observed significant enhancement of both behavioral and neural oscillatory markers of proactive control in healthy adults following tDCS stimulation targeting the DLPFC, compared to sham stimulation. This data provides a unique test of the hypothesis that proactive control, and specifically goal/context maintenance, is at least partially supported by DLPFC-mediated gamma-band activity. In addition to supporting this theoretical model, these results indicate that proactive control engagement can be enhanced in healthy adults via non-invasive neurostimulation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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