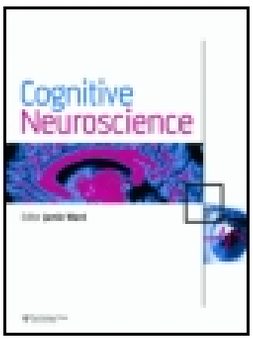

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ARTICLE

Impact of oscillatory tDCS targeting left prefrontal cortex on source memory retrieval

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ABSTRACT

Research on transcranial direct current stimulation (tDCS) has grown rapidly, but there is controversy regarding whether and how tDCS could impact memory performance. We report a study that addressed this question by examining the effects of oscillatory tDCS (otDCS) on subsequent episodic memory performance and concomitant recordings of neural oscillations. Neural oscillations in the theta band (4–7 Hz) have been shown to be important for episodic memory and especially for source memory retrieval. Here, we tested the effects of anodal otDCS at theta (5.5 Hz) over the left DLPFC on theta oscillations and memory performance. In two sessions, participants completed an item and source recognition paradigm with word stimuli. Between study and test, participants received otDCS in one session and sham stimulation in the other. Surprisingly, behavioral results showed that, relative to the sham stimulation, otDCS impaired source memory performance. Analyses of EEG data during memory retrieval revealed that otDCS changed pre-stimulus theta power and in particular reduced the specificity of theta activity during source memory retrieval. Our results suggest that non-invasive brain stimulation can impact memory and oscillatory activity in counterintuitive ways, and that direct neural activity measures can facilitate meaningful interpretation of behavioral effects of stimulation.

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Introduction

Recollection of past events, or episodic memory retrieval, recruits a set of brain structures including the hippocampus, parahippocampal cortex, medial and dorsolateral prefrontal cortex, and medial and ventrolateral parietal cortex (i.e., cortico-hippocampal network; Nyberg et al., 2000; Ranaganth & Ritchey, 2012; Rugg & Vilberg, 2013; Wagner, Shannon, Kahn, & Buckner, 2005). Although it is unclear how activity is coordinated across the elements of this distributed network, some evidence indicates that neural oscillations might play a role. Several electroencephalography (EEG) and magnetoencephalography (MEG) studies have shown that regions in the cortico-hippocampal network described above exhibit prominent theta band (4–7 Hz) oscillations associated with episodic memory retrieval (Anderson, Rajagovindan, Ghacibeh, Meador, & Ding, 2009; Backus, Schoffelen, Szebényi, Hanslmayr, & Doeller, 2016; Burke et al., 2013, 2014; Foster, Kaveh, Dastjerdi, Miller, & Parvizi, 2013; Lega, Jacobs, & Kahana, 2012; Lega, Burke, Jacobs, & Kahana, 2016; Rutishauser, Ross, Mamelak, & Schuman, 2010; Watrous, Tandon, Conner, Pieters, & Ekstrom, 2013; see Hsieh & Ranganath, 2014, for review). Importantly, theta oscillations in the frontal regions have also been associated with successful retrieval of contextual details from an event (Addante, Watrous, Yonelinas, Ekstrom, & Ranganath, 2011; Kaplan et al., 2014; Watrous et al., 2013; White et al., 2013; see Hsieh & Ranganath, 2014 for review), also known as 'source memory retrieval' (Mitchell & Johnson, 2009).

Although there is compelling evidence linking theta oscillations to episodic memory retrieval, it is unclear whether manipulations of theta activity can affect memory performance. Electrical brain stimulation may be a promising approach to manipulate brain oscillations. Some findings indicate that increasing prefrontal cortical excitability using anodal transcranial direct current stimulation (tDCS) over prefrontal cortex can improve memory performance (Gaynor & Chua, 2017; Javadi, Cheng, & Walsh, 2012; Javadi & Walsh, 2012; Kirov, Weiss, Siebner, Born, & Marshall, 2009). For example,

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anodal tDCS to dorsolateral prefrontal cortex (DLPFC) immediately after encoding but prior to retrieval increased recollection accuracy while neither sham stimulation to this region nor active stimulation to a control (parietal) region affected recollection accuracy (Gray, Brookshire, Casasanto, & Gallo, 2015). This evidence is controversial, however—some have argued that behavioral effects of tDCS are not robust and are largely mixed across studies (Horvath et al., 2015b; Hoy et al., 2013; Jantz, Katz, & Reuter-Lorenz, 2016; Hill, Fitzgerald, & Hoy, 2016; Kim, Ekstrom, & Tandon, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016, for reviews on the tDCS effects on episodic and working memory), and others have even argued that common tDCS protocols might not even influence brain activity (Horvath et al., 2015a; Vöröslakos et al., 2018).

To determine whether or how tDCS can affect memory, and to determine the role of theta activity in memory retrieval, we conducted a combined tDCS and EEG study of episodic retrieval. Previous studies have suggested that oscillatory tDCS (otDCS; Kirov et al., 2009; Marshall, Helgadóttir, Mölle, & Born, 2006; Marshall, Kirov, Brade, Mölle, & Born, 2011)—that is, direct current (DC) that is amplitude-modulated at a target frequency—can be used to modulate neural oscillations. otDCS is presumed to modulate oscillatory activity in two ways—both directly, via frequency-specific amplitude modulation (i.e., AC effect), and indirectly via DC effects on cortical excitability (Santarnecchi et al., 2015 for review). Importantly, both effects are associated with increased theta activity (e.g., DC: Miller, Berger, & Sauseng, 2015; AC: Helfrich et al., 2014; Hermann et al., 2013). Note, the present study is not designed to disentangle from one effect from the other, but instead to capitalize on their potential combined effects on rhythmic neuronal activity and investigate the role of theta activity in source memory retrieval. We used an anodal otDCS stimulation protocol with electrode placement aimed at modulating activity in left dorsolateral prefrontal cortex (DLPFC; Javadi & Walsh, 2012; Javadi et al., 2012; Nikolin, Loo, Bai, Dokos, & Martin, 2015; Sandrini et al., 2014; Zwissler et al., 2014; see Nitsche et al., 2008, for DLPFC targeting) and stimulation set to 5.5 Hz in order to manipulate theta oscillations (otDCS; Kirov et al., 2009; Marshall et al., 2006, 2011). We tested effects of DLPFC stimulation on a source memory retrieval task, because left DLPFC activation in healthy adults (Cansino, Maquet, Dolan, & Rugg, 2002; Dobbins, Foley, Schacter, & Wagner, 2002; Rugg, Fletcher, Chua, & Dolan, 1999; Slotnick, Moo, Segal, & Hart, 2003; also see Fletcher & Henson, 2001; Nolde, Johnson, & Raye, 1998 for review and Spaniol et al., 2009 for a meta-analysis) is enhanced during correct source discrimination, and patients with left DLPFC lesions exhibit impaired source memory retrieval (Duarte, Ranganath, & Knight, 2005; Janowsky, Shimamura, & Squire, 1989; also see Szczepanski & Knight, 2014).

We hypothesized that by inducing frontal theta oscillations prior to retrieval, theta otDCS to the frontal region would have beneficial effects on source memory retrieval. To test this hypothesis, we used a source memory task from a prior study in which we showed that theta activity was enhanced during successful item and source retrieval, as compared to successful item recognition in the absence of source retrieval (Addante et al., 2011). In this paradigm, participants encode words in the context of animacy or pleasantness judgments, and they subsequently perform item and source recognition. Addante et al. (2011) showed that theta oscillatory power was enhanced immediately before presentation of test items that elicited successful source retrieval.

One of the most important aspects of the present study is that we sought to test the effects of otDCS on behavior and on task-evoked brain activity, as measured by EEG. Because tDCS can produce electrical artifacts in concurrent EEG recordings, we decided to administer otDCS for an extended duration (i.e., 20 minutes; Nitsche & Paulus, 2000, 2001; but see Nitsche et al., 2008, for review) between the encoding and retrieval phases. Based on research showing that neural activity can be modulated by transcranial electrical stimulation up to 60 minutes after stimulation, we expected that stimulation would influence behavioral performance and concurrent measures of neural activity during the memory retrieval phase. EEG was recorded during the retrieval phase in order to allow for analyses of persistent effects of stimulation on brain activity, free of stimulation artifacts (see Methods for details).

Methods

Participants

Twenty-one healthy young adults without any neurological or psychiatric disorders were recruited from the University of California–Davis Psychology Department subject pool.[1] None of the participants were taking any medication affecting the central nervous system at the time of participation. One participant was excluded from the analysis due to technical problems during an EEG recording session. The study was approved by the University of California–Davis Institutional Review Board protocol for research on human subjects. All subjects gave written informed consent and received $60 as compensation for their participation in the two sessions.

General procedure

The within subjects experimental procedure is presented in (Figure 1(a)). Participants completed one active and one sham tDCS session on different days, with an interval of 2–7 days between sessions. The order of active and sham sessions was counterbalanced across subjects to control for any potential order effects. In each session, participants first performed the memory encoding task, followed by either theta or sham stimulation for 20 minutes. During stimulation, participants performed a cognitive control task (e.g., dot pattern expectancy task (DPX), Jones, Sponheim, & MacDonald, 2010; MacDonald et al., 2005, 2007) intended to drive prefrontal activity. After completion of the stimulation phase, they were prepared for EEG recording (duration about 10–15 minutes). Following electrode placement, EEG was recorded as the participant performed the source memory retrieval task (about 30–35 minutes after the beginning of the stimulation). After completion of the memory experiment, participants performed a separate cognitive control task as part of a separate experiment that is not reported here.

Source memory paradigm

Participants first completed a 10-minute encoding task in which they studied 200 words over 4 blocks (50 words in each block). In each trial, they were presented with one word and asked to make a binary judgment (e.g., yes or no) on either pleasantness (indicate whether each item is pleasant or not) or animacy (indicate whether each item is alive in real life or not) for each word (see Figure 1(b)). The two encoding tasks were presented in a blocked ABBA design that was counterbalanced between subjects to control for potential order effects. Each encoding block started with task instructions for the upcoming block, followed by 10 practice trials. Stimuli presented in practice trials were not used in the retrieval phase.

During retrieval, participants were tested with the 200 words they had studied during encoding along with 100 new words that they had not seen during encoding phase (lures). There were 6 retrieval blocks, each with 50 trials (a total of 300 trials). Each retrieval trial started with a fixation cross which stayed in the middle of the screen for 1000 ms followed by presentation of a test item for 1500 ms. Participants were instructed to engage in covert retrieval at the onset of test items, but wait and withhold responses until presented with a response prompt (See Figure 1 (b)). The first response screen prompted participants to make an item-recognition confidence judgment, and the second one prompted a source-recognition judgment. For item recognition judgments, participants rated their confidence as to whether or not the item had been studied during encoding using a 5-point scale ranging from 1 (sure new) to 5 (sure old). For source recognition judgments, participants rated their confidence as to whether they studied the word in the context of a pleasantness or animacy judgment. Each source decision was made on a 5-point confidence scale from 1 (sure pleasantness) to 5 (sure animacy). Responses were self-paced and therefore intertrial intervals were jittered with subject-paced responses. Word stimuli were always presented in white font, lowercase letters centered on a black screen (Figure 1(b)).

otDCS

Immediately following the encoding phase, active or sham stimulation was applied using a battery-driven stimulator (neuroConn, GmbH, Germany). Direct current

[1]The sample size was based on the previous tDCS and EEG studies that were conducted in our lab using the same task and similar tasks (Addante et al., 2011; Clarke, Roberts, & Ranganath, 2018; Hsieh, Ekstrom, & Ranganath, 2011; Roberts, Hsieh, & Ranganath, 2012).

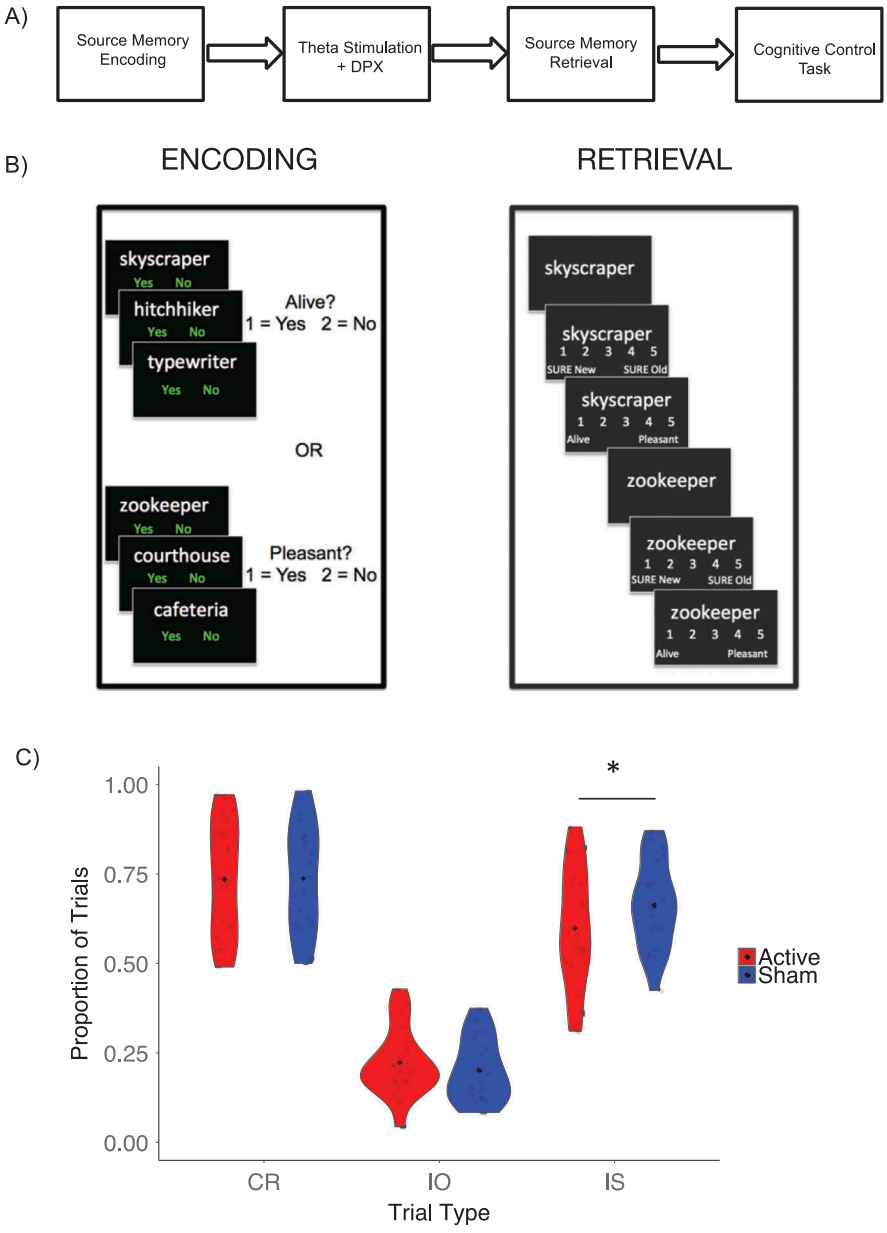

Figure 1. The experimental design and behavioral results. (a) Depiction of the experimental procedure. (b) Encoding and retrieval trials from the source memory task. Prior to stimulation, participants performed a semantic decision task for words presented on the screen. In each encoding block, they either made a pleasantness judgment indicating whether the presented word was pleasant or not or an animacy judgment indicating whether the presented word was alive or not. Immediately after stimulation, participants performed a retrieval task in which they were asked to make an item recognition and a source memory judgment to previously learned items during the encoding phase and to new items that were not presented before. (c) Behavioral memory performance. otDCS decreased the proportion of item+source (IS) responses and did not affect item-only (IO) responses and correct rejections (CR). The black dot in the middle represents the mean with individual data points plotted in the background. The colored area provides an overview of the shape of the distribution via vertically mirrored density plots.

was delivered via a pair of electrodes wrapped in 5 × 7 cm saline-soaked sponges. The anode electrode was placed over left DLPFC (site F3 of the International 10–20 system; Jasper, 1958), and the cathode was placed over the contralateral supraorbital area. This stimulation montage is suitable for targeting DLPFC because it allows the stimulation current to effectively modulate neuronal excitability in cortical regions under F3 (Nitsche et al., 2008). For the active stimulation condition, a rhythmically fluctuating current (ramping up and down between 0.5 mA and 1.0 mA, cycling approximately every 182 ms (5.5 Hz)) was applied for 20 minutes.

We adopted a strategy of applying tDCS 'offline (i.e., not during our task of interest)' while participants performed an unrelated task (DPX) in order to maximize the efficacy of stimulation while preventing EEG contamination by stimulation artifact. Specifically, evidence suggests that tDCS is more effective when it is applied during a task-activated state (i.e., 'online' stimulation) than during a relatively idle state (i.e., 'offline' stimulation; Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Stagg et al., 2011; but also see Filmer, Varghese, Hawkins, Mattingley, & Dux, 2017; Martin, Liu, Alonzo, Green, & Loo, 2014; and see Au et al., 2016, for review), however, for the present study, it was critical that EEG recordings were free of electrical artifacts that can be produced by concurrent tDCS. Therefore, in order to take advantage of the effectiveness of task-activated target stimulation without having the EEG recording contaminated by stimulation artifacts, we applied tDCS offline while participants performed a task that drives prefrontal activity. This experimental design assured that EEG data reflected stimulation-induced changes of internal oscillations rather than extrinsically-generated oscillations elicited directly by stimulation.

In addition, to ensure that tDCS effects carried over during source memory task with concurrent EEG recording, we capitalized on the fact that stimulation applied for a prolonged duration has lasting modulation effects (Nitsche et al., 2008; Nitsche & Paulus, 2001) and administered tDCS for an extended duration (20 minutes). To note, effect endurance after tDCS depends on current-intensity and stimulation duration, and we chose the prolonged stimulation duration because increasing intensity can result in unwanted effects such as affecting deep neuronal populations in addition to the targeted DLPFC and/or causing pain sensation (Nitsche et al., 2008). In the sham condition, current was applied for the initial ramp-up and then ramped down. This procedure ensured that subjects experienced mild discomfort triggered during the initial current ramp-up phase in both active and sham stimulation conditions.

EEG acquisition

EEG was recorded using a BioSemi (http://www.biosemi.com) Active Two Recording System with a 32-channel electrode cap conforming to the standard International 10–20 System of electrode location. Vertical and horizontal electrooculogram (EOG) was recorded from additional active electrodes placed lateral to each eye and above and below the right eye and was used to detect artifacts due to blink, eye movement or other muscle movements. EEG and EOG signals were sampled at 1,024 Hz. The Common Mode Sense (CMS) active electrode located on the scalp near Cz was used as a reference during the EEG data recording. Participants were instructed to minimize eye movements, blinking, and jaw and face muscle tension.

EEG data processing and analyses

EEG data from both sessions were processed and analyzed using custom scripts in MATLAB and functions from EEGLAB (Delorme & Makeig, 2004). Continuous EEG data were down-sampled to 512 Hz, re-referenced to the average of left and right mastoids, and high-pass filtered at 0.5 Hz. Data were epoched from 1250 ms before the onset of the test item to 2450 ms following the test item and baseline subtracted in the time domain using −200 to 0 ms as the baseline time window. This baseline subtraction was conducted to adjust for direct current (DC) offsets to allow for easy detection of artifacts. This subtraction in the time domain, however, should not affect the spectral decomposition analysis. A relatively long epoch length was used in order to extract time-frequency information from both pre-stimulus and post-stimulus periods. Raw EEG data were inspected for artifacts and trials with excessive activity were rejected. Following this, independent component analysis (ICA) was performed to identify and remove the artifacts resulting from eye blinks from the remaining trials. A second visual inspection was made after the ICA to remove remaining artifacts.

After artifact rejection and correction, time-frequency information was extracted from the data. Spectral decomposition was performed on pre-processed EEG data from each participant data using 5.7 cycle Morlet wavelet decomposition (Roach & Mathalon, 2008) ranging from 4–100 Hz.

For each participant, time-frequency data from each session were extracted and separated into three types of trials 1) 'item-only' = correct item recognition, incorrect source recognition of studied items 2) 'item+source' = correct item and correct source recognition of studied items 3) 'correct rejections' = correctly rejected new items.

Statistical analyses

Behavioral data

To facilitate data analyses for EEG, 1–5 scale recognition confidence ratings were binned into binary response categories. For item recognition judgments, 4 and 5 responses (i.e., probably old and sure old) were binned as 'old' responses, 1 and 2 responses (i.e., probably new and sure new) were binned as 'new' responses, and '3' responses were binned separately as 'don't know' responses. Thus, a 4 or 5 response to an old item would be considered a 'hit' and a 1 or 2 response to a new item would be considered a 'correct rejection'. For source recognition judgments, we binned 4 and 5 responses as 'pleasantness judgment' responses and 1–2 responses as 'animacy judgments' responses, and 3 responses were assigned to the 'don't know' bin.

In order to separate the influence of otDCS on item recognition and source memory retrieval, we further separated correct item recognition trials (hits) into trials associated with correct source decisions—'item + source' trials (IS)—and trials associated with incorrect source decisions—'item-only' trials (IO). We also examined the impact of otDCS on correct rejection ('CR') trials. For each of these trial types, the mean proportion of trials were calculated (IO = number of item-only trials/total number of old item trials, IS = number of item+source trials/total number of old item trials, CR = number of correct rejections/total number of new item trials) and used as the dependent variable in one-way analysis of variance (ANOVA) conducted separately for each trial type.

EEG data

The tDCS manipulation in this study targeted specifically neural oscillations at theta frequency (5.5 Hz). Therefore, all the following statistical analyses were performed on the data averaged over the theta frequency range (4–6 Hz). In a previous study with the same paradigm, we found that theta activity during the pre-stimulus baseline period was increased prior to presentation of items that elicited correct source retrieval (Addante et al., 2011). Accordingly, we ran one set of analyses on pre-stimulus activity and one set of analyses on post-stimulus activity and did not baseline correct both data for these analyses in order to keep them parallel to analyses conducted in Addante et al. (2011). Statistical analyses of EEG data focused on left frontal [LF: F3, F7], left central [LC: C3, T7], and left parietal [LP: P3, P7] regions of interest (ROI) that were previously shown to be sensitive to successful source memory retrieval in this paradigm (Addante et al., 2011). The left frontal ROI included the electrode site F3 that was also the site of the stimulating electrode.

EEG signals from different trial type bins were compared within and across stimulation sessions with ANOVAs conducted with stimulation type [Active, Sham], trial type [IS, IO, CR], and regions [LF, LC, LP] as independent variables. Separate analyses were performed for pre-stimulus and post-stimulus time periods.

Results

Behavioral performance: otDCS reduces source memory accuracy

Our first analysis tested whether otDCS altered participants' memory performance, and if so, whether the effect of otDCS would be specific to item or source memory. We hypothesized that otDCS would increase the likelihood of frontal theta activity during memory retrieval, thereby resulting in improved source memory performance relative to the sham session. Proportions of IO [$F(1, 19) = 3.97$, $p_{adj} = .14$] and correct rejection [$F(1, 19) = 0.3$, $p_{adj} = .87$] trials were comparable between active otDCS and sham stimulation sessions. However, importantly, the proportion of IS trials were significantly smaller in the otDCS session compared to the sham session [$F(1, 19) = 12.65$, $p_{adj} = .006$]. These findings collectively suggest that otDCS decreased the likelihood that participants correctly remembered the source details while leaving item recognition intact.

otDCS-related theta activity during retrieval

Our behavioral results suggest that otDCS reduced the likelihood of successful memory retrieval. We considered at least two potential explanations for this effect—one possibility is that otDCS between study and test led to a reduction of theta at test, perhaps due to a fatigue-like effect. Alternatively, otDCS might have stimulated excessive theta activity that resulted in noisy oscillatory activity that

drowned out intrinsic oscillations that contribute to recollection. In the following sections, we statistically tested the impact of stimulation on the theta oscillations during pre- and post-stimulus periods for different trial types separately.

otDCS influenced pre-stimulus theta associated with source memory retrieval

As noted in the Introduction, Addante et al. (2011) demonstrated that, in this paradigm, pre-stimulus theta activity was higher during IS trials than during IO trials. We therefore assessed the differences in pre-stimulus theta power between trial types from the left lateral ROI where effects were most prominent in the Addante et al. study. We conducted a 3-way ANOVA with stimulation type [sham vs. otDCS], trial type [item-only, item +source, correct rejections], and regions [LF: F3, F7, LC: C3, T7 and LP: P3, P7] as independent variables, and theta power from the −400 to −150 time window as the dependent variable.[2] This analysis revealed a significant Stimulation x Trial Type interaction [$F(1.79, 34.04) = 4.35$; $p = 0.02$]. Pairwise comparisons revealed theta power was significantly greater in the IS than IO trials for the sham session [$t(75.98) = 2.145$, $p = 0.034$], replicating the previous finding (Addante et al., 2011), whereas this difference was not observed for the otDCS session [$t(75.98) = 1.017$, $p = 0.32$] (See Figures 2(a,b), 3(a)). In addition, theta power was significantly greater in CR than IS trials for the active otDCS session [$t(75.98) = -2.81$, $p = 0.007$], whereas this difference was not observed for the sham session [$t(75.98) = 1.32$, $p = 0.2$].

There was also a main effect of region showing that LF had higher theta power compared to LP and LC regions, however, this effect did not interact with stimulation type [region: $F(1.23, 23.35) = 7.6$; $p = 0.008$, region x stimulation: $F(1.43, 27.14) = 1.97$; $p = 0.5$]. There was no other significant effect.

otDCS did not affect post-stimulus theta

We conducted a 3-way ANOVA to test the effects of stimulation type [sham vs. otDCS], trial type [item-only, item+source, correct rejections], and regions [LF, LC, LP] on the post-stimulus onset theta power (150ms to 600ms).[3] This analysis showed that stimulus-evoked theta power did not differ across stimulation sessions [$F(1,19) < 0.50$]. There was also no significant interaction effect involving stimulation condition (all p's >0.30). ANOVA revealed significant interaction between trial type and region ($F(2.31,43.96) = 6.55$; $p = 0.002$), and post hoc tests revealed that theta power was significantly greater in IS than IO trials in the LC ROI for both sham (consistent with results of Addante et al., 2011) and active stimulation sessions. Additionally, CR trials had significantly higher post-stimulus theta than IS and IO trials at LP ROI. This is a novel observation and is discussed below. (Figure 3(b)) depicts the post-stimulus power for different trial types for sham and active sessions.

Discussion

The goal of the present study was to test the hypothesis that augmenting theta oscillations via oscillatory tDCS should improve source memory retrieval. We used the same source memory retrieval task used by Addante et al. (2011), and results from the sham stimulation condition replicated their primary findings: frontal and parietal theta oscillations were enhanced preceding the onset of items that were associated with successful item and source recognition, relative to items that were recognized in the absence of correct source memory retrieval (Addante et al., 2011). We expected that otDCS administration between study and test would have effects on brain activity that persist into the test phase. More specifically, we predicted that stimulation would increase source memory accuracy and enhance the relationship between theta activity and source memory retrieval reported by Addante et al. (2011). To our surprise, active otDCS impaired source memory accuracy. Moreover, EEG analyses revealed that otDCS induced changes in pre-stimulus theta power, such that the selective enhancement of theta power preceding correct source memory retrieval was eliminated. Collectively, these results suggest that non-specific changes of background

[2]Note that the −150 to 0 ms interval was not included due to possible influences of post-stimulus activity on wavelet power estimates.

[3]We did not include the 0–150 ms interval due to possible influences of pre-stimulus activity on wavelet power estimates. Having a larger post-stimulus time window (150 ms–1500 ms) did not change the results.

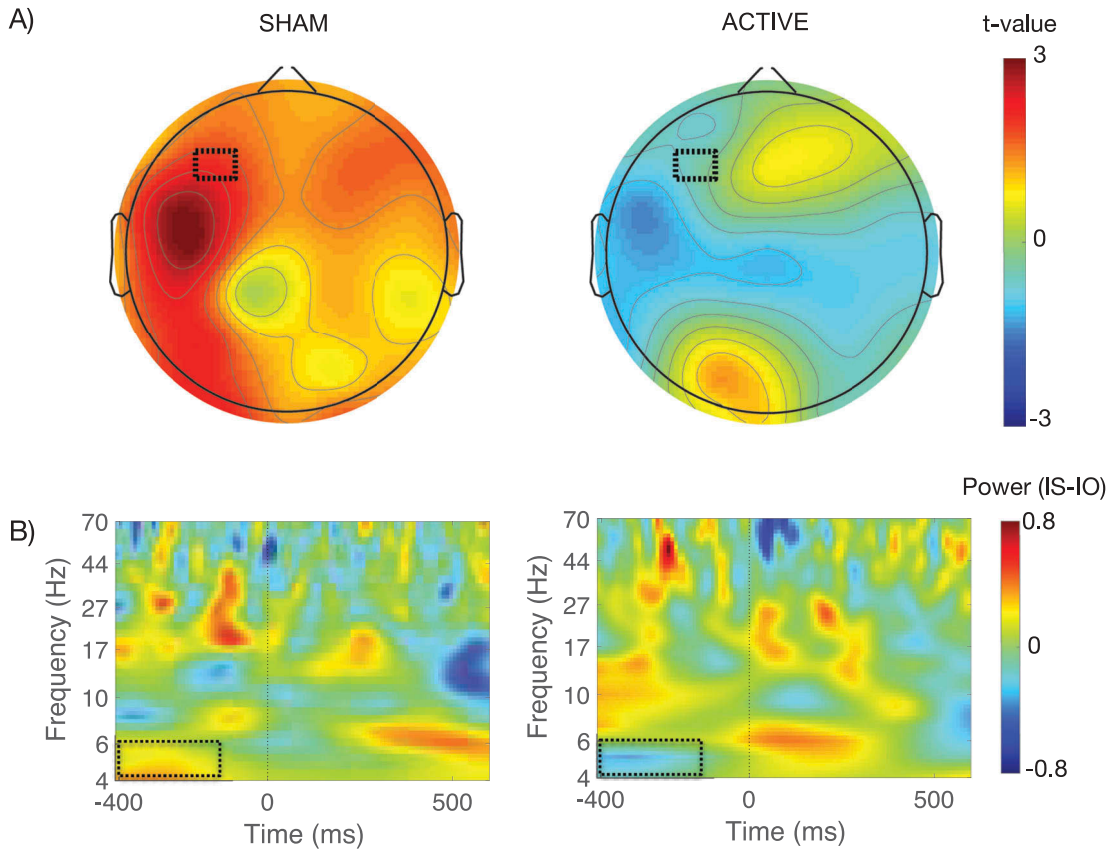

Figure 2. otDCS altered pre-stimulus power differences between item+source (IS) and item-only (IO) responses at the left lateral regions. a) Topographic t-value map of pre-stimulus theta-band activity differences between item+source item-only trials during the −400 to −150 ms time window for the sham (left) and active (right) sessions. Dashed box marks the the stimulation target site (F3). b) Spectrograms showing the difference in power between item+source and item-only trials for the sham (left) and active (right) conditions. Results are shown for the left hemisphere ROIs (LF, LC, and LP) that were used in the statistical analyses. Dashed box shows theta oscillations during the pre-stimulus period (−400 to −150ms).

theta might have detrimental effects on the source retrieval process.

The finding of reduced source memory retrieval following frontal otDCS is surprising and the pattern of results is particularly interesting for two reasons. First, frontal otDCS impaired source memory retrieval, but it did not significantly affect item-only and correct rejection responses. These behaviorally-specific effects of otDCS suggest that it is unlikely that stimulation influenced global variables that can result in general cognitive impairment. Second, it is notable that, in our paradigm, otDCS was administered between the encoding and retrieval phases of the task. Moreover, there was an approximately 20-minute-long interval between the otDCS application and the retrieval phase of the experiment (due to EEG preparation time). Together, these considerations suggest that the selective source retrieval impairment reflected effects of otDCS on memory consolidation or on memory retrieval. Neuromodulation during otDCS could be expected to influence memory consolidation, whereas persistent aftereffects of stimulation could influence memory retrieval processes. With behavioral data alone, we could not know whether otDCS actually affected theta activity, as intended, nor could we know whether the effects extended to the retrieval phase of the experiment. Fortunately, the EEG data provided important insights into the neural effects of otDCS.

EEG data in the present study were recorded during the memory retrieval task, at least 20 minutes after the end of the stimulation period. Based on previous findings from Addante et al. (2011), we contrasted theta power between conditions without correcting for baseline theta power. The results showed that otDCS eliminated baseline theta increases selectively associated with correct source

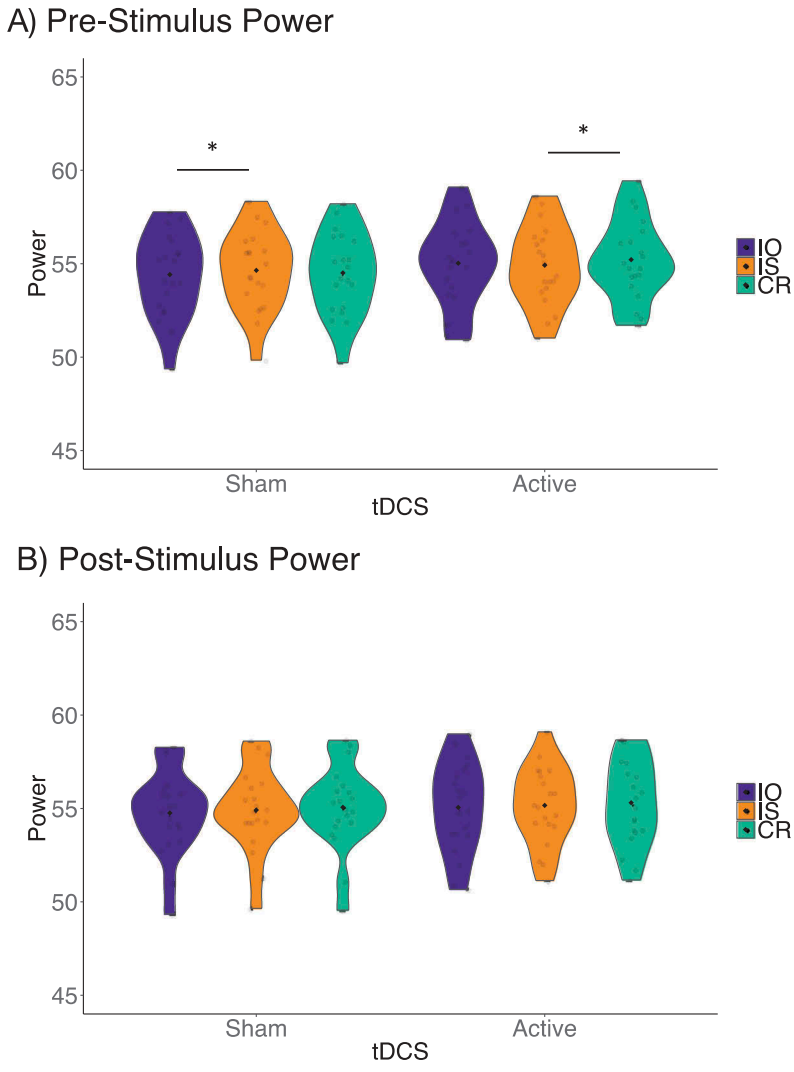

Figure 3. Pre-stimulus (a) and post-stimulus (b) power differences across item-only, item+source, and correct rejection trials for sham and active sessions. a) Significant pre-stimulus power difference observed between item+source and item-only for the sham session but not for the active session. b) Similar post-stimulus power values were observed across trial types for both sham and active sessions (averaged across regions of interest).The black dot in the middle represents the mean with individual data points plotted in the background. The colored area provides an overview of the shape of the distribution via vertically mirrored density plots.

retrieval, and instead altered pre-stimulus theta activity for both item+source and item-only trials (i.e., correct item recognition with incorrect source retrieval). These findings demonstrate, in a surprising way, that spontaneous theta activity may play a causal role in episodic memory retrieval.

There is disagreement in the literature on the relationship between theta power and memory performance. Some studies have reported that theta power is increased during successful episodic memory retrieval (Addante et al., 2011; Kaplan et al., 2014; Watrous et al., 2013; White et al., 2013). Other studies suggest that decreased power of low frequency oscillations during episodic memory retrieval, although these effects have not consistently been specific to the typical 4–8 Hz frequency range that is typical of frontal midline theta (Burke et al., 2014 (3–8 Hz); Lega, Germi, and Rugg (2017) (3–5 Hz); Michelmann, Bowman, and Hanslmayr (2016) (8 Hz)). Although the functional relationship between theta activity and memory performance seems to differ across paradigms, it is important to note that, in the sham stimulation condition, as in the study by Addante et al. (2011), theta activity was enhanced during successful source memory retrieval. Because the theta power difference between successful and

unsuccessful source memory retrieval trials was eliminated by stimulation, it is reasonable to conclude that the stimulation-induced change in neural activity was related to the detrimental behavioral effects of theta stimulation.

It is also important to note that our findings do not suggest there is a single function for theta oscillations. Although the present paper focused primarily on theta powers in IS and IO trials, one may find it counterintuitive that we also observed that post-stimulus theta power was higher for CR than IS/IO trials. If theta activity is strictly and uniquely associated with source memory retrieval, it should not be even numerically higher for CR trials—as correctly rejecting a new stimulus does not involve retrieval of remembered stimuli. One possibility is that theta power reflects cognitive control processes that generalize across encoding and retrieval. The engagement of memory monitoring and cognitive control processes during retrieval can affect neural activity during processing of new, as well as old items (Ranganath & Paller, 1999, 2000). There is considerable evidence that people incidentally encode novel foils during recognition testing (e.g., Buckner et al., 2001), particularly during tasks that engage cognitive control processes (Jacoby et al., 2005). Theta power is often enhanced during successful memory encoding, so it is possible that theta activity on correct rejection trials reflected incidental encoding of novel foils. Although this explanation is speculative, this raises a larger point—we do not want to assume that theta activity is somehow uniquely associated with source memory retrieval.

The observed changes in pre-stimulus theta due to otDCS demonstrate that aftereffects of otDCS persisted into the memory retrieval test phase. The data are consistent with the idea that theta stimulation led to a persistent, nonspecific enhancement in theta activity and weakening the functional link between endogenous theta states and source memory retrieval. The fact that otDCS had persistent, rather than transient effects might be related to synaptic plasticity. Findings from previous studies suggest that tDCS effects lasting beyond the stimulation duration may be mechanistically different from effects during the stimulation and may involve neuronal plasticity (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003). In both these studies, TMS-generated motor-evoked potentials (MEPs) were used as a measure of excitability of the motor cortex and its immediate and long-lasting changes induced by tDCS were assessed. Critically, they tested the effects of pharmacological manipulations on the effects of tDCS. Na+channel blocker (carbamazepine) and Ca +channel blocker (flunarizine) eliminated the excitability enhancement induced by anodal stimulation during and after tDCS (i.e., both the on-going and long-lasting effects were eliminated). In contrast, the NMDA-receptor antagonist dextromethorphan did not affect excitability changes during stimulation, but it selectively suppressed the long-lasting aftereffects of tDCS for both cathodal and anodal stimulation. Together, the results suggest that the aftereffects of anodal and cathodal stimulation are dependent on NMDA receptors. In addition, endogenous theta rhythms and TMS-induced changes in theta oscillations are also mediated by NMDA receptor activation (Barr, Lambert, Hoyt, Moore, & Wilson, 1995; Labedi, Benali, Mix, Neubacher, & Funke, 2014; Leung and Desborough, 1988) and in-vitro application of NMDA to hippocampal slices induces theta activity (Kazmierska & Konopacki, 2013; Larson and Lunch, 1988). Therefore, it is reasonable to speculate that otDCS manipulation in the present study might have enhanced the efficacy of NMDA receptors, thereby increasing overall theta activity and diminishing the kind of selective theta enhancement seen during successful source memory retrieval.

It is noteworthy that the observed changes in theta activity might have been induced by either AC or DC effects of stimulation, or more likely, by combined effects of both. The present study was not aimed at disentangling AC effects from DC effects induced by the stimulation, but instead to exploit the fact both AC and DC effects are associated with increased theta activity (Helfrich et al., 2014; Herrmann et al., 2013; Miller et al., 2015) and maximize the likelihood to effectively modulate theta activity. It is outside the aim or scope of the present study to answer whether and how DC and AC modulation differentially affects neural oscillations and the associated cognitive function, for which future research is needed.

It is an ongoing debate whether transcranial electrical stimulation effectively modulates neuronal and cognitive functions (Herrmann et al., 2013; Lafon et al., 2017). We think that it is futile to pursue this question, because it is overly broad and ill-posed. The parameter space for brain stimulation is massive—any given study can use a

different configuration of stimulation sites, polarity, current strength, electrode size, stimulation duration, and stimulation phase. Considerable evidence suggests that electrical brain stimulation can have aftereffects that persist up to an hour (Ardolino, Bossi, Barbieri, & Priori, 2005; Nitsche & Paulus, 2000, 2001). Thus, the timing of stimulation relative to cognitive performance may be another critical parameter. Current studies adopt widely varying parameter sets, and we currently have little understanding of the physiological consequences of particular parameter selections. Without knowing the physiological effects of different particular stimulation protocol, it difficult to interpret the mixed effects of stimulation on cognitive functions (Jantz et al., 2016; Kim et al., 2016; McKinley, Bridges, Walters, & Nelson, 2012; Nitsche et al., 2008; Nitsche & Paulus, 2011, for reviews).

The hypothesis of the present study was that otDCS would improve source memory retrieval via modulation of frontal theta activity, but the results went in the opposite direction. Without EEG data, we could have only speculated as to the physiological effects that might have driven the behavioral impairment. These findings underscore the point that collection of neurophysiological data can provide insights into effects of electrical brain stimulation that might not be readily interpretable otherwise.

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Disclosure statement

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