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Permalink https://escholarship.org/uc/item/4d50d7jt

Journal Journal of Cognitive Neuroscience, 31(9)

ISSN 0898-929X

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Publication Date

2019-09-01

DOI

10.1162/jocn_a_01421

Peer reviewed

Anodal Transcranial Direct Current Stimulation to the Left Rostrolateral Prefrontal Cortex Selectively Improves Source Memory Retrieval

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Abstract

■ Functional neuroimaging studies have consistently implicated the left rostrolateral prefrontal cortex (RLPFC) as playing a crucial role in the cognitive operations supporting episodic memory and analogical reasoning. However, the degree to which the left RLPFC causally contributes to these processes remains underspecified. We aimed to assess whether targeted anodal stimulation thought to boost cortical excitability—of the left RLPFC with transcranial direct current stimulation (tDCS) would lead to augmentation of episodic memory retrieval and analogical reasoning task performance in comparison to cathodal stimulation or sham stimulation. Seventy-two healthy adult participants were evenly divided into three experimental groups. All participants performed a memory encoding task on Day 1, and then on Day 2, they performed continuously alternating tasks of episodic memory retrieval, analogical reasoning, and visuospatial perception across two consecutive 30-min experimental sessions. All groups received sham stimulation for the first experimental session, but the groups differed in the stimulation delivered to the left RLPFC during the second session (either sham, 1.5 mA anodal tDCS, or 1.5 mA cathodal tDCS). The experimental group that received anodal tDCS to the left RLPFC during the second session demonstrated significantly improved episodic memory source retrieval performance, relative to both their first session performance and relative to performance changes observed in the other two experimental groups. Performance on the analogical reasoning and visuospatial perception tasks did not exhibit reliable changes as a result of tDCS. As such, our results demonstrate that anodal tDCS to the left RLPFC leads to a selective and robust improvement in episodic source memory retrieval.

INTRODUCTION

Rostrolateral prefrontal cortex (RLPFC) has been theorized to be the highest order cognitive control center in the reputed rostrocaudal hierarchy of the lateral prefrontal cortex (PFC; Badre & D'Esposito, 2009; Koechlin & Hyafil, 2007; Ramnani & Owen, 2004) and has been implicated in functional neuroimaging studies examining cognitive control processes in episodic memory (Simons, Henson, Gilbert, & Fletcher, 2008; Simons, Gilbert, Owen, Fletcher, & Burgess, 2005; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Ranganath, Johnson, & D'Esposito, 2000) and relational reasoning (Cho et al., 2010; Green, Kraemer, Fugelsang, Gray, & Dunbar, 2010; Wendelken & Bunge, 2010). More generally, RLPFC appears to be critical for the integration or comparison of highly structured representations, regardless of domain (Westphal, Reggente, Ito, & Rissman, 2016; Bunge & Wendelken, 2009). For the RLPFC to perform its role in goal-directed cognition across a diverse set of cognitive tasks, it needs to be able to flexibly couple with neural systems that process the domain-specific

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information relevant to the behavioral goals of each task. Indeed, research from Westphal et al. (2016) showed that RLPFC exhibited particularly robust coupling with domainspecific brain regions for each task, as it coupled with the internally oriented default mode network (DMN) during episodic source memory retrieval, while also exhibiting connectivity with the externally oriented dorsal attention network (DAN) during visuospatial perception and Broca's area during verbal analogical reasoning.

RLPFC is composed of brain regions that belong to two major neural systems, the frontoparietal control network (FPCN) and the DMN. The DMN is critical for memory tasks as it has an important role in the internally oriented attentional focus required to retrieve episodic and semantic memories, in addition to activating for other introspective tasks, such as prospectively envisioning future scenarios (Andrews-Hanna, 2012). The FPCN is heavily involved in dynamic cognitive control, and it contains many of the lateral prefrontal regions implicated in the rostrocaudal hierarchy (Power et al., 2011; Badre & D'Esposito, 2009; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). The FPCN has also been shown to be able to flexibly couple as a system with either the DMN or DAN, depending on whether one's

> Journal of Cognitive Neuroscience 31:9, pp. 1–12 doi:10.1162/jocn a 01421

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current task goals prioritize attention to internal or external attributes (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). FPCN regions are anatomically distributed in such a way to promote flexible coupling, as they are typically spatially juxtaposed between DMN and DAN regions (Spreng et al., 2010). However, within the RLPFC, the FPCN component regions are not spatially proximate to any DAN component regions, but rather are primarily spatially positioned next to neighboring DMN component regions (Power et al., 2011). Moreover, the FPCN component of the left RLPFC is relatively close to the anterior aspect of Broca's area, which we previously found to be functionally connected to the RLPFC during analogical reasoning (Westphal et al., 2016). Therefore, the RLPFC appears to be a sensible target for brain stimulation aimed at improving memory and reasoning performance as it contains task-relevant FPCN and DMN regions that can be simultaneously stimulated using transcranial direct current stimulation (tDCS).

Although tDCS stimulates a relatively large patch of underlying cortex, a series of studies have shown that tDCS is "activity selective" (Bikson & Rahman, 2013), such that tDCS preferentially augments neural systems that are already endogenously activated by cognitive tasks. This property may make the effects of tDCS more focal than previously assumed (Lapenta, Minati, Fregni, & Boggio, 2013). Although the neurophysiological effects of anodal and cathodal stimulation are complex and still not fully understood, one prominent model suggests that a region's excitability and plasticity will be enhanced if it lies under the anode and decreased if it lies underneath the cathode (De Berker, Bikson, & Bestmann, 2013). This model emphasises modulation of the radial currents that run inward through the cerebral cortex, which are more highly concentrated beneath the electrodes than the surrounding areas and produce the excitability changes primarily in the neuron somas (Rahman et al., 2013).

Based on RLPFC findings and tDCS stimulation properties, we hypothesize that anodal tDCS to the left RLPFC will exhibit activity selectivity under the electrode for task-relevant FPCN and DMN areas in the RLPFC, which should result in improved episodic memory retrieval. We also hypothesize that anodal tDCS to the RLPFC has the potential to improve analogical reasoning performance due to the role of the RLPFC in integration processes in relational reasoning (e.g., Cho et al., 2010; Bunge, Helskog, & Wendelken, 2009) and due to the proximity of Broca's area (Westphal et al., 2016), which may be close enough to the electrode to exhibit net depolarization effects. Indeed, prior tDCS research has indicated that anodal tDCS of nearby dorsolateral PFC (DLPFC) during postencoding memory consolidation can augment subsequent retrieval (Gray, Brookshire, Casasanto, & Gallo, 2015) and during retrieval can improve memory monitoring (Chua & Ahmed, 2016). Anodal tDCS of the left RLPFC has been associated with improved creative analogical mapping (Green et al., 2016).

The design of the present study follows that of our previous fMRI study (Westphal et al., 2016), which included episodic retrieval, analogical reasoning, and visuospatial perception tasks that were matched for bottom-up perceptual stimulation (i.e., all trials presented participants with four-word stimulus arrays) and response demands (i.e., all trials forced participants to select between four response options). The inclusion of the visuospatial perception task allows us to evaluate the possibility that anodal tDCS leads to generalized cognitive improvement. Importantly, our experimental protocol always begins with a sham stimulation session to establish baseline performance and allow for within-subject examination of stimulation effects. This sham stimulation session is immediately followed by either anodal stimulation, cathodal stimulation, or additional sham stimulation of the left RLPFC (a between-subject manipulation). The group receiving sham stimulation during both the first and second sessions provides an assay of how task performance changes over time (i.e., due to potential practice effects and/or fatigue), and the group receiving cathodal stimulation provides an important test of whether the general application of electrical brain stimulation leads to task improvements or whether the polarity of stimulation is a critical factor.

METHODS

This study is a follow-up to a previous fMRI study conducted on an independent sample of participants; for a more comprehensive report on the design of the cognitive tasks, please refer to Westphal et al. (2016). Important features of the paradigm are described below.

Participants

Eighty-one participants were recruited from the University of California, Los Angeles, and the greater Los Angeles community. Data from nine participants were excluded for the following reasons: Four participants had extremely poor performance in the memory task, indicative of a lack of understanding of the task instructions (i.e., their false alarm rate equaled or exceeded their hit rate); one participant failed to understand and/or comply with task instructions during the memory encoding task; one participant was unable to master the button responses to any cognitive tasks; one participant found the tDCS stimulation to be unpleasant and elected to terminate the session; and two participants were excluded due to technical problems with the tDCS device. The final data set included 72 participants across three experimental groups (n = 24 per group), with each group averaging 20 years of age and consisting of 13 women and 11 men; group assignment was randomized, but with modifications made during recruitment to enforce sex balance. Participants were required to be 18-30 years old, be native English speakers, be right-handed, have normal or corrected-to-normal vision, have no neurological or psychiatric disorders, have no history of brain damage, and not consume illegal drugs or more than four alcoholic drinks per day. All participants provided written informed consent in accordance with operations approved by the University of California, Los Angeles, institutional review board (IRB 14-000814) and received monetary compensation.

Procedure

The experimental protocol was carried out over two consecutive days. On the first day, participants completed a memory encoding task where a sequence of 80 words was presented. Each word was preceded by a mental imagery context cue (3 sec) that specified, whether the participants should spend the next 10 sec visualizing themselves ("Self") or another person ("Other") interacting with the referent of that word. For instance, if the context cue was "Other" and the word was "moon," the participant might imagine an astronaut on the moon. Participants were informed at the beginning of the experiment that their memory would later be tested for both the studied words and their encoding context. Following encoding of all 80 words, which were evenly split between contexts, participants learned the instructions and the associated button-press response options for the memory, reasoning, and perception tasks that they would be performing the next day (see Figure 1). After completing a computerized training regimen to facilitate learning of the button mappings, participants performed a brief practice run of each of the three tasks.

On the second day, participants performed the three tasks while undergoing the tDCS procedure. Task order was pseudorandomized such that the same cognitive task was never presented twice in a row and that exactly two other tasks intervened before any given cognitive task was presented again. The tDCS procedure on the second day consisted of two consecutive sessions, with four runs per session, each consisting of nine 49-sec blocks (three blocks of each task). Each block included the 6-sec presentation of a task set cue indicating the task to be performed ("M" for memory, "R" for reasoning, and "P" for perception), followed by a fixation cross for 2 sec, four task trials, and a final 5-sec fixation cross. Each trial included a 7-sec presentation of a four-word stimulus array and was followed by a 2-sec fixation cross. Participants were allowed to respond at any point throughout the trial by pressing one of four buttons with their right hand. Each session lasted approximately 30 min and consisted of 144 trials, with 48 trials for each cognitive task.

The cognitive tasks all used four-word stimulus arrays to equate visual input, yet required distinct cognitive processing to perform each task and had independent response options. All word stimuli were either concrete or abstract nouns, which were displayed in lower case Geneva font. In the memory task ("M" cue), participants were instructed to scan the words and identify if they had studied one of the words in the first day memory encoding task (75% of trials had one word from the memory encoding task, whereas 25% of trials had all novel words). Participants were told to specify the encoding context if they remembered it. The response options were as follows: (1) remember one of the words from SELF context, (2) remember one of the words from OTHER context, (3) recognize one of the words but don't recall source, and (4) all words are novel. In the reasoning task ("R" cue), participants were instructed to evaluate if the top row and bottom row word pairs constituted an analogical relationship (50% of trials contained analogies). If not, they were told to specify how many semantic relationships were presented (50% of trials were equally divided into two, one, or zero semantic relationship trials [16.7% each]). The response options were as follows: (1) valid analogical relationship, (2) two valid semantic relationships, (3) one valid semantic relationship, and (4) no semantic relationships. An example of a valid analogy

Figure 1. Schematic of the cognitive tasks. The memory, reasoning, and perception tasks all had unique cognitive goals, used four-word stimulus arrays, and had four distinct response options. A task block begins with the presentation of a task cue ("M," "R," or "P"), which informs the participant of which task to perform for the next four trials, after which a new cue would be presented to indicate a switch to a different cognitive task for the next four trials.

Cognitive Tasks

- **Memory (M)**: identify if any of the 4 words had been previously encountered during the memory encoding task and indicate the context of the memory, if possible
- **Reasoning (R)**: judge whether the top and bottom word pairs constitute an analogical relationship or specify how many semantic relationships were present
- Perception (P): identify which of the 4 words contained the greatest number of straight lines

Trial Example			Response Options			
moon team		Memory Task	Reasoning Task	Perception Task		
			1) Remember word from SELF context	1) Analogical relationship	1) Top left word	
	+		2) Remember word from OTHER context	2) Two semantic relationships	2) Bottom left word	
			3) Remember word but don't recall source	3) One semantic relationship	3) Bottom right word	
prism		taxi	4) All words are novel	 No semantic relationships 	4) Top right word	

would be moat : castle :: firewall : computer (in both pairs, the former entity protects the latter from hostile invasion). An example of a trial with two valid semantic relationships (but no analogy) would be fragrance : odor :: engine : car. In the perception task ("P" cue), participants were instructed to select the word containing the greatest number of straight lines in its printed lettering. The correct answer, which always had two more straight lines than the next best answer, was equally likely to appear in each of the four quadrants. The response options were as follows: (1) top left word has the most straight lines, (3) bottom right word has the most straight lines, and (4) top right word has the most straight lines.

Transcranial Direct Current Stimulation

TDCS was applied using a 9-V battery-powered, constant direct current 1×1 stimulator (Soterix Medical, Inc.) through two separate conductive carbon rubber electrodes inside of 5×7 cm (35 cm²) sponges. Sponges were saturated with a saline solution (0.9%) and attached to the scalp by plastic straps. During conditions with active tDCS at 1.5 mA, the maximum current density was 0.043 mA/cm^2 , which is comfortably in the safe range for human participants (Nitsche et al., 2003). The international 10-20 EEG system was used to identify the stimulation sites. The primary stimulation site was the left RLPFC (see Figure 2A), which was defined from a previous fMRI study using this same task paradigm (Westphal et al., 2016). In that study, we identified a group-level left RLPFC cluster (MNI coordinates: -42, 42, 6) that not only showed elevated BOLD activity during correctly performed trials of the reasoning and memory tasks, relative to the perception task, but also contained sufficient representational information within its local BOLD activity patterns to facilitate robust decoding (using a multivoxel pattern classification approach) between trials of the reasoning and memory tasks. The right motor cortex was used as the reference site as this area is commonly paired with supraorbital stimulation in tDCS studies (Amadi, Ilie, Johansen-Berg, & Stagg, 2014; Nitsche et al., 2008) and is unlikely to play an important role in our cognitive tasks, especially because participants used their right hand to respond (which is controlled by the left motor cortex). However, we must note that there is a possibility that the right RLPFC may be influenced by the tangential currents that run parallel to the cerebral cortex and produce pathway-specific stimulation effects (De Berker et al., 2013). Based on projections of both 10-20 EEG sites into MNI space, the left RLPFC area was defined as being the midpoint between the Fp1 and F7 sites (Vitali et al., 2002), whereas the right motor cortex was specified as the C4 site (see Figure 2B). Visualization of the targeted left RLPFC region on the cortex and scalp region was done using MRIcroGL (www.mccauslandcenter.sc.edu/ mricrogl/), and visualization of the 10-20 EEG sites was done using a figure adapted from Malmivuo and Plonsey (1995).

The first session always involved sham stimulation as a baseline performance condition, whereas the immediately ensuing second session included either anodal stimulation of the left RLPFC ("Anode group"), cathodal stimulation of the left RLPFC ("Cathode group"), or further sham stimulation ("Sham group"); see Figure 3 for a schematic of the group design. Real stimulation was never applied during the first session: tDCS facilitation effects may persist for up to 90 min (McKinley et al., 2013), so a group receiving real stimulation during the first session would likely still be influenced by the stimulation during the second session. Concurrent stimulation was chosen to maximize activity-selectivity mechanisms (Bikson & Rahman, 2013), such that neuronal systems that are already highly active during the performance of a task are more likely to be modulated by tDCS than less active regions. Stimulation was administered at an intensity of 1.5 mA, as we believed that this intensity would be strong enough to modulate neuronal activity in the underlying cortex while ensuring high tolerability and safety for participants. Stimulation sessions began with 30 sec of ramping up to 1.5 mA followed by 30 min of stimulation

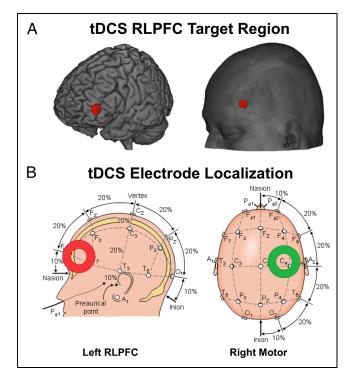
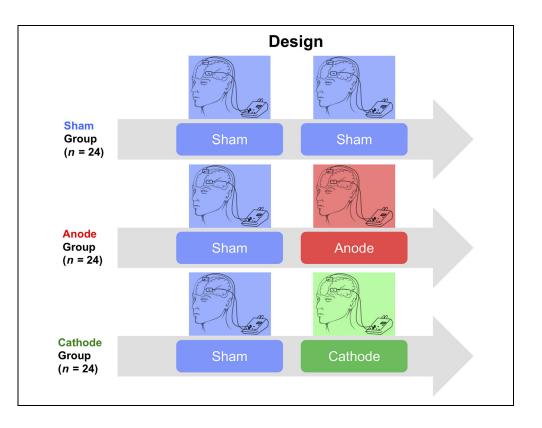


Figure 2. Representations of the tDCS stimulation sites. (A) Depiction of the left RLPFC stimulation target, derived based on fMRI findings from Westphal et al. (2016), rendered on a template brain and then projected onto a template head. (B) Illustration of the sponge electrode locations on a schematic of the 10–20 EEG system. For participants in the Anode group, the anode (red circle) would be positioned over the left RLPFC site, which was between the Fp1 and F3 locations, and cathode (green circle) would be placed over the right motor cortex site, situated on C4.

Figure 3. Portrayal of the tDCS experimental group design. Each experimental group began with sham stimulation (shown in blue) for the first session, whereas the second session varied depending on stimulation group. The Sham group received additional sham stimulation during the second session, whereas the Anode group received anodal stimulation (shown in red) and the Cathode group received cathodal stimulation (shown in green) of the RLPFC during the second session.



at 1.5 mA and end with 30 sec of ramping down. Sham stimulation sessions also began with 30 sec of ramping up to 1.5 mA (to induce the subjective sensation of stimulation) but were immediately followed by 30 sec of ramping down and 28 min of no stimulation, ending with another ramp up/down cycle in the final minute. After the tDCS procedure was completed, participants were surveyed on what they perceived to be the strength of stimulation for each experimental session, using a 3-point scale (with 1 =*weak stimulation* and 3 = strong stimulation). The mean perceived stimulation ratings (\pm SE values) across the groups and sessions were as follows: Sham Group Session 1 = 2.13 (0.17), Sham Group Session 2 = 2.17 (0.18), Anode Group Session 1 = 1.96 (0.11), Anode Group Session 2 =2.71 (0.09), Cathode Group Session 1 = 1.96 (0.11), and Cathode Group Session 2 = 2.63 (0.13).

Item Analysis

After the collection of data from all eligible participants, an item analysis was performed to screen for and remove any problematic trials. Trials were removed if more than 50% of participants showed poor performance for that specific trial, with poor performance defined as choosing an incorrect response in the reasoning task, failing to identify the best or second-best response in the perception task or as misses or false alarms in the memory task. This analysis flagged eight trials in the reasoning task and two trials in the perception task, and these trials were removed from all participants' data before statistical analysis. No trials were flagged for removal in the memory task, and this is favorable given that there was no a priori reason that certain memory trials would end up being consistently harder for participants than others (unlike analogies, which were created by the experimenters and varied more widely in their difficulty).

Statistical Analysis

Memory task performance was assessed by calculating the source retrieval hit rate (the proportion of trials containing a studied item for which participants reported the correct source context), as well as the source retrieval false alarm rate (the proportion of trials not containing a studied item for which participants erroneously reported a source context). Reasoning task performance was assessed by calculating the analogy hit rate (the proportion of trials containing a valid analogy for which participants correctly reported the presence of an analogy), as well as the analogy false alarm rate (the proportion of nonanalogy trials for which participants erroneously reported the presence of an analogy). For both tasks, subtraction of the false alarm rate from the hit rate yielded a corrected recognition (Pr) measure that inherently adjusts for potential response biases (Snodgrass & Corwin, 1988). Perception task performance was assessed by calculating the proportion of trials for which participants correctly identified the word containing the largest number of straight lines. Pr scores were not calculated for the perception task as there was no false alarm rate equivalent.

RESULTS

Effects of Experimental Group on Task Performance

Mean performance values for each task and session are presented in Table 1. The effects of tDCS were examined on performance metrics for each of the cognitive tasks using mixed model ANOVAs with Session (first session vs. second session) as the within-group factor and Experimental group (Anode vs. Cathode vs. Sham) as the between-group factor. The mixed model ANOVA for the memory task source retrieval Pr scores produced a significant main effect of Session, F(1, 69) = 15.28, p < .001, anonsignificant effect of Group, F(2, 69) = 0.79, p = .46, and a significant interaction, F(2, 69) = 4.06, p = .022, with the results visualized in Figure 4. The mixed model ANOVA for the reasoning task Pr scores resulted in a significant main effect of Session, F(1, 69) = 18.53, p < .001, a nonsignificant effect of Experimental group, F(2, 69) =0.57, p = .57, and a significant interaction, F(2, 69) =4.41, p = .016. The mixed model ANOVA for the perception task did not result in a significant main effect of Session, F(1, 69) = 2.41, p = .125, effect of Experimental group, F(2, 69) = 0.17, p = .84, or the interaction between them, F(2, 69) = 0.79, p = .46. The three ANOVAs were not corrected for multiple comparisons here, given our a priori hypotheses that only the memory and reasoning tasks would be affected by anodal tDCS. The significant interactions for the memory and reasoning tasks were followed up by post hoc Student-Newman-Keuls tests examining the effect of session between experimental groups. In memory, the increase in source retrieval Pr scores from the first to second session was significant both for the Anode group over the Cathode group (p = .032) and for the Anode group over the Sham group (p = .025), showing that source retrieval performance was reliably improved from anodal stimulation. In reasoning, the increase in Pr scores from the first to second session was significant for the Cathode group over the Anode group (p < .012), but was only trending for the Cathode group over the Sham group (p = .071). No further analysis was performed, as the improvement in reasoning for the Cathode group was not reliably better than the practice effects in the Sham group.

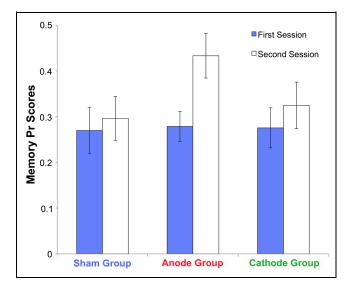


Figure 4. Memory source retrieval Pr scores across experimental groups. The first session was sham stimulation for each group, whereas the stimulation of the RLPFC in the second session depended upon experimental group. The Anode group demonstrated improved source memory retrieval relative to both the Cathode (p = .032) and Sham (p = .025) groups. Error bars specify \pm *SE* values.

Change in Memory Task Performance for Anode Group

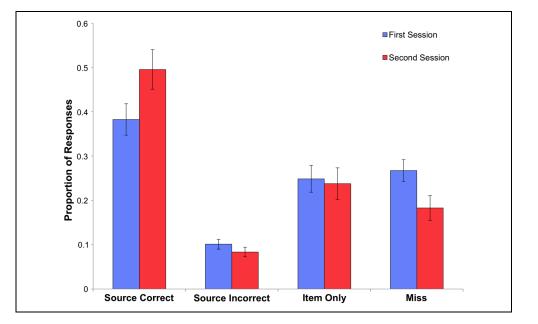
After finding that the Anode group showed a reliable improvement in memory source retrieval, measured by Pr scores, we aimed to identify how participants' responses to studied memory items changed as a result of the left RLPFC anodal stimulation. Responses to these items can be categorized as correct source retrieval, incorrect source retrieval, item recognition, or misses. Post hoc paired t tests, with Bonferroni correction, between the first session (sham stimulation) and the second session (anodal stimulation) showed that source retrieval hits $(p < .001; \alpha_{crit-Bonferroni} = .0125)$ were significantly elevated whereas misses (p = .001; $\alpha_{crit-Bonferroni} = .0125$) were significantly reduced; source incorrect responses (p = .076) and item recognition (p = .566) were unchanged (see Figure 5). These results show that anodal tDCS to the RLPFC in comparison to sham stimulation appears to increase correct source retrievals, while simultaneously reducing misses.

Table 1. Mean Values for Memory Task Source Retrieval Pr, Reasoning Task Pr, and Perception Task Proportion Correct, Shown for the First and Second Experimental Session in the Sham, Anode, and Cathode Experimental Groups

	Sham	Group	Anode Group		Cathode Group	
Task	Session 1	Session 2	Session 1	Session 2	Session 1	Session 2
Memory	0.270 (0.050)	0.296 (0.048)	0.279 (0.033)	0.433 (0.049)	0.275 (0.044)	0.325 (0.051)
Reasoning	0.650 (0.048)	0.701 (0.046)	0.696 (0.049)	0.710 (0.051)	0.684 (0.040)	0.797 (0.029)
Perception	0.605 (0.026)	0.575 (0.032)	0.603 (0.026)	0.606 (0.024)	0.627 (0.024)	0.589 (0.009)

Standard error values are presented in parentheses.

Figure 5. Change in memory performance between sham and the RLPFC anodal stimulation in the Anode group. Response distributions are shown for those trials where a studied word was reencountered during either sham stimulation (shown in blue) in the first session or anodal stimulation to the RLPFC (shown in red) during the second session. Post hoc paired t tests comparing between sessions showed that anodal stimulation of the RLPFC led to increased proportion of trials with correct source memory retrieval (p < .001) and a decreased proportion of misses (p = .001), with no change in the proportion of trials with incorrect source retrieval or item-only retrieval responses. Error bars specify $\pm SE$ values.



Control Analyses

Three additional control analyses were performed to test for potential confounds affecting the tDCS results. First, to determine if there could be group differences from participant sample effects, we assessed each of our task metrics at the first experimental session, which was always sham stimulation. We performed one-way repeatedmeasures ANOVAs for memory task source retrieval Pr scores, reasoning task Pr scores, and perception task scores. The effect of Experimental group was nonsignificant for the memory task, F(2, 69) = 0.01, p = .99, the reasoning task, F(2, 69) = 0.27, p = .77, and the perception task, F(2, 69) = 0.27, p = .76. Second, to ensure that our effects were not altered by the exclusion of the four participants with extremely poor performance on the memory task, we reran the mixed model ANOVA and post hoc Student-Newman-Keuls tests with these participants included, and none of the results were changed (i.e., significant effects remained significant, and nonsignificant effects remained nonsignificant). Third, to investigate the effect of participants' awareness of stimulation, we ran a generalized estimating equation model to assess the degree to which participants' ratings of perceived strength of stimulation could be predicted by experimental session, experimental group, and their interaction. This model type was chosen because it is well suited for the analysis of correlated response data (Hanley, Negassa, Edwardes, & Forrester, 2003). The model resulted in a significant intercept (p < .001); nonsignificant effects of Anode group (p = .410), Cathode group (p = .410), and experimental session (p = .410) .864); and significant Anode by experimental session (p = .012) and Cathode by experimental session (p = .012).034) interactions. Therefore, participants were able to detect an increase in stimulation strength in the Anode

and Cathode groups, potentially due to the experimental sessions being consecutive. However, the Cathode group is an active control for the Anode group in this study, so the effects of anodal stimulation improving memory performance are likely to be due to the tDCS itself rather than to expectation of improved performance.

DISCUSSION

Our study examined the effects of tDCS to the left RLPFC during episodic memory retrieval, analogical reasoning, and visuospatial perception in three distinct experimental groups. We obtained data from sham stimulation as a baseline session for all groups and then applied anodal, cathodal, or sham stimulation to the RLPFC. We did not observe any reliable changes in behavior due to tDCS in the experimental group solely receiving sham stimulation nor did we observe reliable task performance enhancements as a result of cathodal tDCS to the RLPFC. The group that received anodal RLPFC stimulation exhibited a reliable increase in source memory retrieval performance in comparison to the other two experimental groups but did not exhibit any improvements during the analogical reasoning task. Furthermore, when assessing the memory performance of participants who received anodal stimulation to the RLPFC in comparison to sham stimulation, there was a clear increase in the proportion of source memories retrieved and concomitant reduction in the proportion of missed items (i.e., trials where participants failed to recognize that one of the words in the array had been studied). This pattern of results suggests that rather than merely increasing participants' ability to recognize the presence of the studied word in a given trial (which would have been manifest as a shift from misses to item recognition hits), anodal

tDCS is actually serving to help participants recollect the source context. That is, trials where the studied item might have otherwise been forgotten are being converted to trials with successful recollection with tDCS intervention.

Previous studies have attempted to manipulate memory performance using tDCS, though most have targeted the DLPFC or ventrolateral PFC (VLPFC). Many of these studies have involved the application of tDCS during memory formation (encoding phase) or shortly thereafter (postencoding consolidation phase), and these efforts have yielded mixed results. One set of studies examining the effects of tDCS applied to the left DLPFC during the encoding of word stimuli showed improved subsequent recognition when anodal stimulation was applied and impaired performance when cathodal stimulation was applied (Javadi, Cheng, & Walsh, 2012; Javadi & Walsh, 2012). In contrast, a later study found that anodal stimulation to the left DLPFC during the associative encoding of word pair stimuli actually impaired participants' performance on a subsequent recognition memory test, while sparing metamemory judgments (Gaynor & Chua, 2017). This result appears to be consistent with another study examining tDCS to the left DLPFC during the encoding of scene/object stimuli, which were instructed to be either remembered or forgotten immediately after the stimulus presentation (Zwissler et al., 2014). Anodal stimulation led to increased false recognition of lure items that were individually matched to the encoded items on gist, regardless of the initial encoding instruction. In contrast, cathodal tDCS actually reduced false recognition of the lure items for stimuli marked to be remembered. These results suggest that tDCS modulation of memory encoding may also affect the balance of detail and gist in these memories, depending on the polarity of stimulation, and largely depends on ongoing encoding strategies. A study examining the effects of anodal tDCS to the left VLPFC found that intentional, but not incidental, encoding of verbal material was improved from stimulation, but this effect was only observed when stimulation was applied concurrently with encoding and not when stimulation was applied immediately before encoding (Medvedeva et al., 2018). This study also included a sample of older adults and found that they too benefited from concurrent stimulation during intentional memory encoding. Another study of older adults found that anodal stimulation of the left DLPFC during encoding improved free recall when memory was tested 3 days later, but the benefit was no longer observed when recall was tested 30 days later (Sandrini et al., 2016). In contrast, a study examining anodal tDCS to the left DLPFC during face-name associative encoding only observed subsequent recall and recognition memory benefits in younger adults but no such improvements in older adults (Leach, McCurdy, Trumbo, Matzen, & Leshikar, 2018). Given that older adults are typically poorer performers on memory tasks, this result is seemingly at odds with that of another study involving

anodal tDCS to the left DLPFC that found that verbal episodic memory performance was most improved in those participants who were initially poor performers (Habich et al., 2017). In an effort to leverage the power of converging methodologies, Lu, Wang, Chen, and Xue (2015) combined EEG and tDCS and found that greater spatiotemporal neural pattern similarity for repeated presentations of individual items measured with EEG at encoding could be used to predict subsequent memory performance. Intriguingly, anodal tDCS to the left DLPFC immediately before memory encoding led to greater item-specific spatiotemporal neural pattern similarity during encoding and improved recognition memory 1 day later, which the authors speculate is due to consistent and unique information being sent to the hippocampus for pattern separation, suggesting a potential mechanism whereby anodal tDCS can augment memory encoding.

To our knowledge, no prior tDCS study with a prefrontal stimulation site has been able to significantly improve retrieval performance with stimulation applied concurrently during the retrieval phase, although retrieval performance has been modulated with tDCS applied subsequent to memory encoding. One such study that involved anodal stimulation of the left DLPFC during a postencoding reconsolidation period (where participants performed a recognition task for previously encoded verbal material) reported memory improvements on a subsequent recognition test, but no acute retrieval improvements were seen in the recognition memory task performed during stimulation (Javadi & Cheng, 2013). Another study found improved source memory retrieval performance, specifically for word stimuli with a font color encoding context, when anodal stimulation was administered to either the left or the right DLPFC after encoding but before retrieval (Gray et al., 2015). Research in older adults has shown that anodal tDCS to DLPFC after consolidation 24 hr after encoding improved performance at retrieval 3 and 30 days after encoding paired with reduced forgetting (Sandrini et al., 2014). A follow-up study found that providing the encoding context reminder with anodal tDCS to DLPFC after consolidation led to the most robust memory improvement at recall up to 30 days later and that those with more subjective memory complaints showed a larger reduction in forgetting from stimulation 3 days after encoding (Manenti, Sandrini, Brambilla, & Cotelli, 2016). Studies involving stimulation applied during retrieval have yielded inconsistent results. One study that applied anodal stimulation to left DLPFC during retrieval found that both younger and older adults exhibited faster response times, relative to sham stimulation. Although this was interpreted as evidence of facilitated performance, analysis of the accuracy data actually showed that tDCS impaired recognition of concrete words and had no effect on recognition of abstract words (Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013). Another study found that anodal tDCS to the left DLPFC during retrieval improved metacognitive

monitoring accuracy for semantic knowledge questions while actually trending toward worse recall performance in another study (Chua & Ahmed, 2016). Furthermore, a study examining anodal tDCS to the left VLPFC did not show any benefits from stimulation immediately before or concurrently during retrieval of verbal material (Medvedeva et al., 2018). Considering that prefrontal tDCS administered during post-encoding consolidation of retrieval has not led to consistent mnemonic improvements, what mechanisms could make stimulation of a spatially proximate region like RLPFC able to yield the improvements in source memory retrieval demonstrated in the present study?

One reason why the RLPFC may be an ideal stimulation target for augmenting episodic memory retrieval performance is that an electrode placed over the RLPFC may simultaneously boost the cortical excitability of underlying prefrontal components of both the FPCN and DMN, both of which are known to be activated during episodic retrieval. This may in turn lead to increased functional connectivity within and between nodes of the DMN and the FPCN, a phenomenon that our previous work found to be linked to improved memory task performance (Westphal, Wang, & Rissman, 2017). A recent fMRI study by Amadi, Ilie, Johansen-Berg, and Stagg (2014) examined the consequences of anodal tDCS stimulation on the right RLPFC (with cathodal stimulation of the left motor cortex) and discovered that the resting state functional connectivity within the DMN was increased, while also showing further strengthened functional connectivity in a large cluster, which included motor areas and extended into FPCN and DAN regions (Power et al., 2011). Considering that our electrode montage was a hemispherically mirrored version of that used by Amadi et al. (2014) and that the left and right RLPFC tend to exhibit strong functional connectivity with each other (e.g., Vincent et al., 2008), it is likely that our left RLPFC anodal stimulation would similarly induce increased functional connectivity in the DMN and the FPCN systems. This interpretation is supported by another study examining fMRI functional connectivity changes due to tDCS, which used an electrode montage with the anode over left DLPFC (fairly close to our RLPFC target region) and the cathode over right RLPFC (Keeser et al., 2011). That study found strengthened resting state connectivity both within and between the DMN and the FPCN, especially near the left DLPFC anode.

However, two other studies with a similar electrode montage have had mixed effects, as one showed increased connectivity within the FPCN, but not DMN (Peña-Gómez et al., 2012), whereas another showed increased FPCN and DMN connectivity but solely in the right hemisphere (Park et al., 2013). Although these electrode montages have the cathode placed on right RLPFC, a functional near-infrared spectroscopy study examining the effects of tDCS on hemodynamic responses of underlying cortex with a left RLPFC anode and right RLPFC cathode electrode montage demonstrated a significant increase in oxyhemoglobin

near the anode but only a negligible effect from the cathode (Merzagora et al., 2010). As increased oxyhemoglobin typically accompanies increased neural activity (Devor et al., 2005), this may suggest that anodal, as opposed to cathodal, stimulation is potentially producing the observed increases in fMRI functional connectivity in these studies. Considering that anodal tDCS appears to significantly strengthen functional connectivity across task-relevant brain regions during the resting state, it is possible that the activity selectivity of tDCS (Bikson & Rahman, 2013) could further enhance functional coupling between these already active neural networks, which may explain the strength of the memory augmentation effects in this study. This may also explain why reasoning performance was not improved by tDCS, as previous neuroimaging work with this same cognitive task did not show increased coupling between the FPCN and DMN during analogical reasoning (Westphal et al., 2016, 2017). These data suggest that analogical reasoning heavily relies upon prefrontal circuitry, and the Broca's area cluster that did couple with the RLPFC during reasoning may have been too far from the RLPFC sponge electrode to receive net depolarization or activity selectivity effects.

Our finding that anodal tDCS to the left RLPFC improves memory retrieval performance builds upon prior research finding a significant role for the RLPFC in memory processes. Specifically, RLPFC may be important for the maintenance of a specific attentional state that has been deemed "retrieval mode," whereby the RLPFC would putatively facilitate attention to internally generated information obtained from goal-oriented episodic search (Velanova et al., 2003; Lepage et al., 2000). Others have posited that RLPFC is critical for implementing retrieval strategies to obtain and monitor contextual details (Simons et al., 2008; Dobbins & Wagner, 2005). Our prior work suggests that RLPFC is potentially important in this memory paradigm for the comparison of episodic representations generated at retrieval to those that were generated at memory encoding (Westphal et al., 2016).

Another candidate mechanism to explain these findings is that it is possible that our tDCS-induced improvement in source memory retrieval is attributable to an altered balance of excitatory and inhibitory connections. In a recent study by Barron et al. (2016), tDCS was used to reduce GABA concentrations underneath the anode at the right occipital-temporal cortex (cathode at the left RLPFC), measured by magnetic resonance spectroscopy, which led to a correlated reexpression of dormant associative memories between visual shape stimuli, 1 day after encoding. The associative memories in Barron's study were already becoming dormant after 24 hr, which is the same window between sessions in our study, but anodal tDCS was able to reduce inhibitory masking of these dormant memories to facilitate recall. It is possible that anodal tDCS to the RLPFC in our study is also altering this balance between excitatory and inhibitory connections to help facilitate the recovery of source context associations that might have otherwise been inaccessible.

An additional explanation for the memory effects in our study is referred to as stochastic resonance, which is the concept that, in nonlinear systems, the introduction of small amounts of noise, such as that from tDCS, can improve performance when the signal is small (De Berker et al., 2013). With respect to episodic retrieval, when the representation of an individual memory is weak, it may receive a disproportionate boost from tDCS, which could facilitate the recovery of the associated source details.

Our study was limited by not having a double-blind data collection procedure, although all researchers collecting tDCS data were blinded to experimental hypotheses throughout the duration of the study. Additionally, because many participants were able to detect increased stimulation strength during anodal and cathodal stimulation, we cannot fully rule out that some memory boosting effects may be due to perceived stimulation strength. That being said, it is unlikely that the observed improvement in episodic source memory retrieval from anodal stimulation to the left RLPFC in this study can be explained by expectation effects as cathodal stimulation was perceived equally strongly without leading to reliable memory enhancement outcomes. Another limitation for our memory findings is that participants were not asked to identify the specific word at retrieval that they studied at encoding, so it is possible that the participants were not explicitly recollecting the studied item on every trial (i.e., some of the correct source retrieval trials may have involved lucky guesses). Furthermore, we were limited by not having concurrent neuroimaging data on the study participants, which could have offered further insights into the mechanisms resulting in improved source memory retrieval from anodal tDCS to the RLPFC. Potential future studies could examine fMRI functional connectivity during the performance of a memory task immediately after anodal tDCS to the RLPFC to examine if more widespread connectivity between the DMN and the FPCN is responsible for the improved memory effects seen in this study. This could also be done at rest for the left RLPFC site, as this area could potentially boost coupling between the DMN and the FPCN without needing endogenous activation. Additional tDCS studies examining episodic memory processes at retrieval with different stimulation targets and reference locations, as well as stimulation parameters, could provide a richer understanding of the specificity of how electrical stimulation from tDCS influences memory retrieval. Furthermore, our analogical reasoning task heavily involved semantic processing in addition to relational integration, so it is possible that the anodal tDCS to the left RLPFC could improve relational integration but not semantic processing, which led to no improvements in this study. However, Green et al. (2016) did find that anodal tDCS of the left RLPFC augmented performance when participants were cued to find creative analogical

mappings, so further research examining anodal tDCS to the left RLPFC during analogical reasoning with a different task structure may be more successful. It would also be worthwhile for future studies to examine whether targeting of a different prefrontal region might be equally if not more effective for facilitating analogical reasoning performance, as the particular localization of our RLPFC stimulation sponge may not have been ideally suited to enhance the networks needed for relational integration and semantic processing.

Acknowledgments

We would like to thank Dr. Ladan Shams and Dr. Marco Iacoboni for their useful insights on the design and analysis of this project. We appreciate that Dr. Shams allowed us to use her lab's tDCS device to perform this research.

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