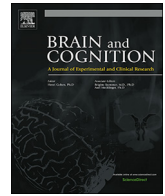




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Verbal long-term memory is enhanced by retrieval practice but impaired by prefrontal direct current stimulation

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ABSTRACT

Retrieval practice involves repeatedly testing a student during the learning experience, reliably conferring learning advantages relative to repeated study. Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex (dlPFC) has also been shown to confer learning advantages for verbal memory, though research is equivocal. The present study examined the effects of retrieval versus study practice with or without left dlPFC tDCS on verbal episodic memory. Participants (N = 150) experienced either retrieval practice or study practice, and active anodal, active cathodal, or sham tDCS while encoding word lists, and then returned two days later for a final recall test. Three primary patterns emerged: first, during encoding, tDCS did not influence recall rates in the retrieval practice group. Second, during final recall, participants in the retrieval practice groups recalled more than those in the study practice groups. Finally, during final recall, anodal tDCS decreased recall relative to sham and cathodal stimulation, suggesting that it interfered with developing highly detailed memories that could be relied upon for subsequent recollection. Data support existing research demonstrating the effectiveness of retrieval practice as a learning strategy, but also suggest that anodal dlPFC stimulation can induce long-term negative impacts on verbal episodic memory retrieval.

1. Introduction

Few reliable methods exist for enhancing the encoding and retention of long-term verbal memory. Among them, two specific techniques hold promise: retrieval practice and electrical brain stimulation. Retrieval practice is a behavioral technique involving repeatedly testing a student during learning (Roediger & Butler, 2011; Roediger & Karpicke, 2006a); for example, asking a student to recall and write down as much of the learning materials as they can, before continuing the study experience. Electrical brain stimulation is a neuroscientific technique involving the administration of low-intensity electrical current to cortical regions via electrodes mounted on the surface of the scalp (Bestmann, de Berker, & Bonaiuto, 2015; Herrmann, Rach, Neuling, & Strüber, 2013; Nitsche et al., 2008); for example, stimulating the prefrontal cortex to selectively enhance aspects of executive control (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). The latter technique, however, has been the subject of recent debate regarding its reliability and robustness for altering cognitive performance (Horvath, Forte, & Carter, 2015b; Price & Hamilton, 2015; Santarnecchi et al., 2015). Furthermore, these two techniques, retrieval practice and

electrical brain stimulation, have never been compared for their independent and interactive effects on learning. The present experiment used a between-participants design to compare the effects of retrieval practice (versus study practice alone) and electrical brain stimulation (anodal, cathodal, versus sham) on verbal episodic memory. To motivate this experiment, we review research from the learning sciences examining retrieval practice influences on long-term memory, and additional research examining electrical brain stimulation impacts on executive control and memory.

1.1. Retrieval practice

Originally referred to as the *consolidation effect* or *recitation effect*, educational psychologists reported that testing knowledge during learning aided retention, even in the absence of feedback (Gates, 1917; Jones, 1923; Laporte & Voss, 1975; Spitzer, 1939). Renewed attention to this phenomenon has emerged over the past few decades, aimed at understanding how to reliably induce the effect, whether it generalizes across learning materials, sourcing its underlying cognitive mechanisms, and detailing its translational value for learning contexts

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(Delaney, Verkoeijen, & Spiguel, 2010; Karpicke & Aue, 2015; Roediger & Butler, 2011). In contemporary literature, the pattern describing memory advantages that accrue through testing during learning (versus studying only) is typically referred to as *retrieval practice* or the *testing effect*. Herein we will refer to it as retrieval practice. A large body of research demonstrates that retrieval practice versus study practice can support a range of verbal learning contexts, including enhanced long-term memory for word lists and extended texts (Agarwal, Karpicke, Kang, Roediger, & McDermott, 2008; Roediger & Karpicke, 2006a), and accelerated foreign language learning (Karpicke & Roediger, 2008). Several putative mechanisms have been proposed to account for this effect, including: (1) retrieving information can cause elaboration of a memory trace when successfully retrieved, and provide more flexible routes for retrieval (Bjork, 1975; Kornell, Bjork, & Garcia, 2011; McDaniel & Masson, 1985; Roediger & Butler, 2011), (2) error correction learning can occur when participants are able to compare their retrieved memory to a subsequent learning experience (even without explicit feedback) (Carrier & Pashler, 1992), (3) the theory of disuse proposes that retrieval practice effects are inversely related to retrieval strength, such that circumstances involving low memory accessibility is most likely to benefit from retrieval practice (Bjork & Bjork, 1992), (4) the episodic context account suggests that retrieval practice benefits accrue due to an active reinstatement and updating of prior learning contexts that can guide and constrain retrieval (Karpicke, Lehman, & Aue, 2014), and (5) there is evidence that retrieval practice may enhance category-based clustering during learning that provides schemas to guide recall (Zaromb & Roediger, 2010). Regardless of its precise mechanism, retrieval practice is widely accepted as a reliable strategy for increasing long-term verbal and visuospatial memory in both experimental and instructional contexts (Agarwal et al., 2008; Roediger & Karpicke, 2006b).

1.2. Electrical brain stimulation

Transcranial direct current stimulation (tDCS) is a form of electrical brain stimulation involving the delivery of low intensity direct current to brain regions via electrodes arranged on the surface of the scalp (Bestmann et al., 2015; Nitsche et al., 2008; Woods et al., 2016). Several stimulation-related parameters can be manipulated, including electrode placement to target varied cortical regions, current polarity (anodal versus cathodal), current intensity (typically 1–2 mA), and current duration (Jacobson, Koslowsky, & Lavidor, 2012; Nikolin, Loo, Bai, Dokos, & Martin, 2015; Paulus, 2011). Originally used in clinical and neurorehabilitation contexts to stimulate motor cortical regions (Nitsche & Paulus, 2000), tDCS has recently gained popularity as a tool for temporarily modulating cortical excitability in brain regions directly tied to perceptual and cognitive functioning (Hsu et al., 2011; Jacobson et al., 2012; Price, McAdams, Grossman, & Hamilton, 2015). Mechanistic explanations relating tDCS influences at the levels of neurons, neural networks, functional brain activations, and cognitive performance are generally lacking (Bestmann et al., 2015). One mechanistic explanation proposes that tDCS induces transient and sub-threshold depolarizations of resting neuronal membrane potentials (Paulus, 2011). In this manner, tDCS does not induce neuronal activation, rather it induces small shifts in neuronal resting state; thus, brain regions underlying the anode are more likely to subsequently engage themselves in response to task demands (Bikson & Rahman, 2013; Lapenta, Minati, Fregni, & Boggio, 2013). Of course, this mechanistic explanation likely understates the complexity and dynamics of tDCS effects on brain and behavior; indeed, recent research has suggested the tDCS influences are further modulated by parameters such as the orientation of neurons relative to the electrical field, cell type and morphology, sham parameters, electrode positioning, and the intensity and duration of electrical stimulation (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Bestmann et al., 2015; Brunyé, Cantelon, Holmes, Taylor, & Mahoney, 2014; Rahman et al., 2013).

One popular tDCS method involves anodal stimulation of the left dorsolateral prefrontal cortex (dlPFC, 10/20 site F3) with the return electrode placed over the right supraorbital area; this method has been shown to improve response times and/or accuracy on several tasks involving the executive control of attention (Dedoncker et al., 2016). Executive function describes the ability to effectively control cognition and accomplish goals in a flexible manner, including processes such as planning, judgment, decision-making, reasoning, and inhibitory control (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Miyake & Shah, 1999). Substantial research has identified a diverse network of brain regions involved in attentional and cognitive control, including the dlPFC, anterior cingulate cortex, and the inferior parietal lobule (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). The left dlPFC in particular is thought to be involved in the implementation of control processes, particularly task setting and maintenance (MacDonald, Cohen, Stenger, & Carter, 2000). A recent review and meta-analysis of 233 published studies (Dedoncker et al., 2016) involving dlPFC stimulation demonstrated several related findings. First, cathodal tDCS of the dlPFC does not affect response times or accuracy on tasks demanding executive control, and no stimulation parameters affected this outcome. Second, anodal tDCS of the dlPFC can improve response times and accuracy on executive control tasks, and in general higher current intensity is related to larger response time advantages. While the neurobiological mechanisms underlying these effects are largely unknown, at the behavioral level anodal dlPFC stimulation is thought to upregulate domain-general executive control processes that are engaged during a wide range of perceptual and cognitive processes (Loftus, Yalcin, Baughman, Vanman, & Hagger, 2015).

1.3. Verbal episodic memory & brain stimulation

Verbal episodic memory, including the encoding, consolidation, retention, and retrieval of words, is one domain in which left dlPFC stimulation appears to hold potential for increasing memory performance (Javadi & Walsh, 2012). This possibility is grounded in several functional neuroimaging and transcranial magnetic stimulation (TMS) studies demonstrating the role of the prefrontal cortex in verbal episodic memory. Specifically, the left prefrontal cortex has been implicated in controlling the organization of verbal semantic information during encoding (Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003; Savage et al., 2001). To date, four experiments have examined the effect of dlPFC stimulation on verbal episodic memory, focusing on word list memory. In the first, the authors examined whether 1 mA anodal or cathodal stimulation of the left dlPFC during encoding would modulate immediate recognition memory for words either guessed during a word-stem completion task and then revealed, or simply presented to participants (Hammer, Mohammadi, Schmicker, Saliger, & Munte, 2011). Results demonstrated that anodal increased and cathodal decreased recognition memory for words learned during the word-stem completion task, but did not affect words learned through simple study presentation. Thus, it appears that anodal left dlPFC stimulation may hold value for enhancing verbal episodic memory over the short-term, but only when the learning task is effortful (i.e., more likely to engage dlPFC due to conflict and error monitoring (Ullsperger & Von Cramon, 2001)). More recently, two studies demonstrated that anodal left dlPFC stimulation can increase verbal episodic memory during a recognition test performed after a 1-hour retention interval, whether stimulation was administered during word list encoding or memory retrieval (Javadi, Cheng, & Walsh, 2012; Javadi & Walsh, 2012); note that in both studies the encoding was non-effortful. A similar result was found with a 5-minute retention interval (Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013).

Thus, there appears to be a growing consensus that anodal left dlPFC stimulation during encoding can impart positive long-term memory advantages. However, we do note that these studies all used either no retention interval, or one that was relatively short duration

(5–60 min). Furthermore, they all used a recognition rather than recall task, making it difficult to know whether these results will replicate under different retrieval demands. Free recall can be more demanding than recognition given its sole reliance on recollection processes, unlike recognition memory which can rely on recollection and familiarity (Yonelinas, 2002). In fact, some recent reports suggest that advantages of dlPFC stimulation effects on verbal episodic memory are only found during recall versus recognition tests (Leshikar et al., 2017; Matzen, Trumbo, Leach, & Leshikar, 2015; Zwissler et al., 2014). Also, we note that some studies using left dlPFC stimulation have reported no effects on verbal episodic memory (de Lara, Knechtges, Paulus, & Antal, 2017), or negative effects on memory including increased false alarm rates during recognition tests (Zwissler et al., 2014). In accounting for the latter effect, the authors suggested that left dlPFC stimulation can decrease detailed episodic memories (Zwissler et al., 2014); if so, then this effect could become more pronounced over longer retention intervals as memories become increasingly abstracted from their source (Schacter & Addis, 2007). It is important to point out, however, that the earlier research did not show decreased correct recognition (only increased false memory) (Zwissler et al., 2014). One additional study found negative effects of anodal posterior parietal stimulation on the recollection of musical melodies, suggesting that stimulation can sometimes induce paradoxical negative effects on memory (Schaal, Javadi, Halpern, Pollok, & Banissy, 2015).

Thus, current research is equivocal regarding the effects of brain stimulation on various verbal episodic memory processes, possibly due to differences in retention interval and retrieval demands. Furthermore, there have been recent debates regarding the reliability of tDCS effects on cognitive functions (Horvath, Carter, & Forte, 2014; Horvath, Forte, & Carter, 2015a; Mancuso, Ilieva, Hamilton, & Farah, 2016; Price & Hamilton, 2015; Price et al., 2015). Indeed, tDCS effects show high variability across participants and low reliability within participants, can interact in varied and possibly unknown ways with cognitive and motor tasks, and the underlying mechanisms for tDCS have yet to be fully elucidated. These limitations underscore the importance of continuing research to identify the circumstances under which it might prove advantageous, ineffective, or even disadvantageous.

1.4. The present study

While existing research provides compelling evidence that left dlPFC stimulation during encoding increases verbal episodic memory on recognition tasks after short durations, it is unknown whether similar effects will be found with recall tests performed after longer retention intervals. Furthermore, given the apparent role of effortful encoding in modulating tDCS effects on memory (Hammer et al., 2011), the nature of the learning experience may additionally alter the effects of stimulation on long-term memory. The present study explored these unanswered questions by crossing learning strategy (study only versus retrieval practice) with three types of left dlPFC tDCS (anodal, cathodal, sham) administered during encoding; as a final memory test, participants completed a free recall task after a 2-day retention interval. Note that existing research has shown verbal recall advantages of retrieval practice versus study practice after a 2-day retention interval (Zaromb & Roediger, 2010).

We made several hypotheses. First, we expected that retrieval practice would increase memory recall relative to the study condition, supporting a number of existing studies (Carrier & Pashler, 1992; Karpicke & Roediger, 2007; Roediger & Karpicke, 2006a). Second, we made contrasting hypotheses regarding the effect of tDCS targeting the dlPFC on recall performance. On the one hand, we might expect to support research suggesting positive effects of dlPFC on recognition memory (Javadi & Walsh, 2012; Manenti et al., 2013), which might translate to increased recall rates following anodal (versus cathodal or sham) stimulation. On the other hand, we might expect to support research suggesting that anodal left dlPFC can decrease highly detailed

episodic memory (Zwissler et al., 2014), which would be reflected in decreased recall rates following anodal (versus cathodal or sham) stimulation, particularly with our lengthy retention interval. Finally, we also explored whether any effects of stimulation might interact with whether learning involved study only or retrieval practice, given that some research suggests that stimulation may only impart benefits under conditions that demand relatively effortful learning (Ullsperger & Von Cramon, 2001).

2. Materials and methods

2.1. Participants

A total of 150 men ($n = 69$) and women ($n = 81$) participated for monetary compensation (mean age = 21.2). Participants were screened for history of seizure, head injury, brain injury, neurological or psychiatric disorders, metal implants in head, sensitive scalp, or adverse reactions to prior tDCS. Procedures were approved by the institutional review board at Tufts University, with secondary approvals by the U.S. Army.

2.2. Design

Participants were randomly assigned to one of six groups. These groups crossed learning condition (retrieval practice versus study practice) and stimulation type (anodal, cathodal, sham) in a 2×3 between-participants design. There were 25 participants in each group, except for the study practice – anodal stimulation group ($n = 24$), and study practice – cathodal group ($n = 26$). The target group size of 25 was based on existing research examining dlPFC tDCS influences on verbal episodic memory, which examined sample sizes ranging from 16 (Javadi & Walsh, 2012; Manenti et al., 2013) to 20 participants per group (Hammer et al., 2011).

2.3. Materials

For the verbal memory task, we used a set of 40 neutral words (e.g., *whistle, vase, spoon, flute, apple, ruler*) selected from published norms (Snodgrass & Vanderwart, 1980), and verified for neutral valence using the Affective Norms for English Words tool (Bradley & Lang, 1999). Simple and moderately difficult arithmetic problems were chosen from earlier research (Brunyé et al., 2013) for use in a filler task. Using the PsychoPy python software library (Peirce, 2007), we developed a program to display words during learning, collect word pleasantness ratings, collect recall responses, and present the arithmetic filler task. The software also collected and logged responses to pleasantness ratings, arithmetic tasks, and recall tasks.

For tDCS, we used the Soterix Medical, Inc. (New York, NY) M \times N system along with two sintered ring (Ag/AgCl) electrodes. The electrodes were secured to a 74-channel EasyCap electroencephalography (EEG) cap (EasyCap GmbH, Herrsching, Germany), properly sized to each participant using the 10/20 positioning system. Sigma gel was used to conduct current between the electrode and the surface of the scalp. This combination of electrodes and gel has proven effective for comfortably and effectively administering tDCS (Kuo et al., 2013; Minhas et al., 2010; Villamar et al., 2013).

2.4. Procedure

Participants were consented and then fitted with the cap appropriately sized for their measured head circumference. Two electrodes were secured to the cap, one positioned at 10/20 position F3 (over left dlPFC), and the other over the right supraorbital area (FP2). This electrode arrangement is commonly used for targeting the left dlPFC (Nitsche et al., 2008). Any hair underlying the electrode sites was parted and the scalp was cleaned using alcohol; conductive gel was

aged and reapplied until impedances were below 2 k Ω .

Stimulation then began, starting with a ramp-up of current intensity over 30 s to a target intensity of 1.5 mA (Javadi et al., 2012; Manenti et al., 2013). In the sham condition, stimulation was then ramped down over the next 30 s and remained off until the end of the session at which time it would ramp up and down again. In the anodal and cathodal stimulation conditions, stimulation was continued for a total of 20 min. For anodal stimulation, the anode was placed over F3 and cathode over the right supraorbital area, whereas for cathodal stimulation, this was reversed. Note that anodal, cathodal, and sham current intensity and polarity were verified with a digital multimeter prior to beginning the study.

One minute after the onset of stimulation, participants provided a perceived sensation rating on a scale from 0 (*Cold*) to 9 (*Hurts a lot*) to ensure they were comfortable (i.e., ≤ 7) with the stimulation (Clark et al., 2012). Five minutes after the onset of stimulation, participants began verbal memory encoding. They were presented with a list of 40 words, one at a time on a 24" computer monitor at 1920 \times 1080 resolution for 3 s each in random order; words were presented at 24-point Arial font. They were instructed to memorize each word for a subsequent test. To encourage depth of processing (Bower & Karlin, 1974), after each word we asked participants to rate the word's pleasantness on a scale from 1 (*very unpleasant*) to 5 (*very pleasant*); this was the only phase of the study in which the pleasantness ratings were used. After being presented with all 40 words, participants then completed 3 min of arithmetic tasks; during the task, a problem was presented on the screen (e.g., $12 \times 7 = 90$) and using labeled keyboard keys M and C, the participant responded *Yes* or *No* to indicate whether a correct or incorrect solution was provided. The arithmetic task was self-paced and automatically terminated after 3 min.

In the study practice group, the procedure then continued as follows: second exposure to the list of 40 words in a unique random order, 3 min of arithmetic, third exposure to the list of 40 words again in a unique random order, 3 min of arithmetic, fourth exposure to the list of 40 words again in a unique random order. In this manner, the study practice group was exposed to the list of words for a total of 4 times, with a total session duration of 20 min.

In the retrieval practice group, the procedure then continued as follows: two minutes of free recall by typing as many words as they could remember into a text box, 3 min of arithmetic, second exposure to the list of 40 words again in a unique random order, 3 min of arithmetic, two minutes of free recall by typing as many words as they could remember into a text box. In this manner, the retrieval practice group was exposed to the list of words twice and tested twice, with a total session duration of 20 min.

Stimulation completed at the same time as the memory task. Following these procedures, the tDCS cap was removed and participants were excused from the session and scheduled for a follow-up visit 2 days later. This second session was always scheduled two nights after the first session; most participants scheduled for the same time of day (48 h interval), whereas some participants changed the time of day, causing some minor variation in the retention interval (48 ± 4 h). During the second visit, participants were provided with a 5-minute final free recall test, involving typing any recalled words into a text box in the PsychoPy software. They were then excused from the study and compensated for their time.

2.5. Data scoring & analysis

Pleasantness ratings collected during the first exposure to the word list were analyzed to ensure there were no differences as a function of learning condition or stimulation condition, using a univariate analysis of variance (ANOVA). Mean accuracy during the arithmetic filler tasks was analyzed in the same manner.

Recall was scored by calculating the proportion of words recalled relative to the number of words originally studied (40). Instances of

pluralization were marked as correct (e.g., recalling *spoon* as *spoons*), but changes in parts of speech were marked as incorrect (e.g., recalling *whistle* as *whistling*). We also counted the number of incorrectly recalled words (i.e., intrusions). Thus, we ended up with two scores for each recall test: proportion of words correctly recalled, and number of words incorrectly recalled.

For recall performance, two primary analyses were conducted. First, we asked whether recall increased over the course of the two recall tests performed in the retrieval practice condition, and whether this varied as a function of stimulation condition. This first analysis was done using a mixed ANOVA with the two recall tasks as a repeated measure (Recall 1, Recall 2), and stimulation condition as a between-participants factor. Second, we analyzed recall rates on the final recall test in an omnibus 2×3 univariate ANOVA with two factors: learning condition (study practice versus retrieval practice) and stimulation condition (anodal, cathodal, sham). An alpha criterion of 0.05 was used for all tests, and effect sizes are provided as eta-squared (ANOVAs) or Cohen's *d* (t-tests).

3. Results

3.1. Word pleasantness ratings

Mean pleasantness ratings were overall moderate ($M = 3.2$, $SD = 0.46$), and did not vary significantly as a function of learning condition, $F(1, 144) = 1.88$, $p = .17$, $\eta^2 < 0.01$, or stimulation condition, $F(2, 144) = 0.04$, $p = .96$, $\eta^2 < 0.01$. The two factors did not interact, $F(2, 144) = 0.92$, $p = .40$, $\eta^2 < 0.01$.

3.2. Arithmetic filler test

Mean accuracy during the arithmetic task was overall moderate to high ($M = 0.88$, $SD = 0.10$), and did not vary significantly as a function of learning condition, $F(1, 144) = 0.09$, $p = .77$, $\eta^2 < 0.01$, or stimulation condition, $F(2, 144) = 2.42$, $p = .09$, $\eta^2 < 0.01$. The two factors did not interact, $F(2, 144) = 1.42$, $p = .24$, $\eta^2 < 0.01$.

3.3. Recall during retrieval practice

In the retrieval practice group, the mean proportion of words correctly recalled increased significantly from the first ($M = 0.29$, $SD = 0.10$) to the second ($M = 0.48$, $SD = 0.15$) recall test, $F(1, 72) = 188.58$, $p < .001$, $\eta^2 = 0.72$. There was no effect of stimulation condition, $F(2, 72) = 3.05$, $p = .053$, $\eta^2 < 0.01$, and the two factors did not interact, $F(2, 72) = 0.04$, $p = .96$, $\eta^2 < 0.01$.

The mean number of intrusions was less than 1 ($M = 0.84$, $SD = 2.5$) and did not vary as a function of recall test, $F(1, 72) = 2.67$, $p = .11$, $\eta^2 = 0.03$, or stimulation condition, $F(2, 72) = 0.48$, $p = .62$, $\eta^2 = 0.01$, and there was no interaction, $F(2, 72) = 1.8$, $p = .17$, $\eta^2 = 0.05$.

3.4. Final recall test

The overall pattern of final recall test performance is depicted in Fig. 1. The mean proportion of words correctly recalled differed significantly as a function of learning condition, $F(1, 144) = 7.86$, $p = .006$, $\eta^2 < 0.01$, and stimulation condition, $F(2, 144) = 5.94$, $p = .003$, $\eta^2 = 0.01$. There was no interaction, $F(2, 144) = 0.03$, $p = .97$, $\eta^2 < 0.01$. Thus, retrieval practice showed overall higher mean recall relative to study practice (Cohen's $d = 0.46$), and mean recall further differed as a function of stimulation condition.

To specifically compare stimulation conditions, we collapsed across learning conditions and conducted three independent samples t-tests comparing sham to anodal stimulation, $t(97) = 3.39$, $p = .001$, Cohen's $d = 0.68$, sham to cathodal stimulation, $t(99) = 1.41$, $p = .16$, Cohen's $d = 0.28$, and anodal to cathodal stimulation, $t(98) = 1.96$, $p = .053$, Cohen's $d = 0.39$. Thus, anodal stimulation significantly reduced mean

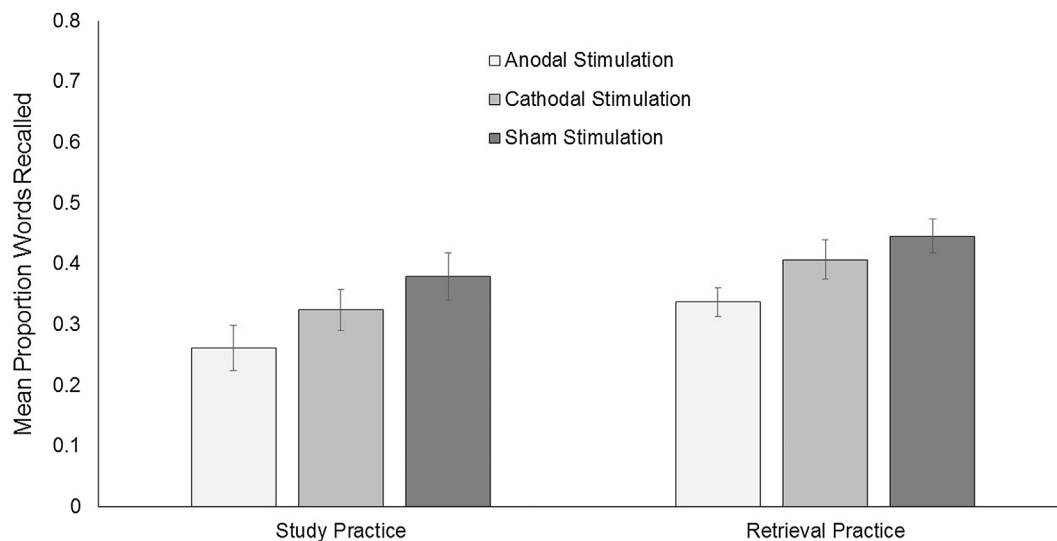


Fig. 1. Mean proportion of words recalled as a function of learning condition (study practice, retrieval practice) and stimulation condition (anodal, cathodal, sham). Error bars represent standard error of the mean.

proportion recall relative to the sham condition (with a medium effect size), and marginally relative to the cathodal condition (with a small effect size). Cathodal stimulation did not significantly modulate recall relative to sham.

The mean number of intrusions ($M = 2.21$, $SD = 3.69$) did not vary as a function of learning condition, $F(1, 144) < 0.01$, $p = .99$, $\eta^2 < 0.01$, or stimulation condition, $F(2, 144) = 0.96$, $p = .39$, $\eta^2 < 0.01$. There was also no interaction, $F(2, 144) = 1.36$, $p = .26$, $\eta^2 = 0.01$.

4. Discussion

This study investigated the independent and interactive effects of two learning strategies, study practice versus retrieval practice, and three non-invasive brain stimulation conditions, anodal, cathodal, and sham stimulation, on verbal episodic memory. During retrieval practice, we found evidence of increased word recall over the course of the two repeated tests, and this pattern was not modulated by stimulation condition. At the final memory test, we found evidence for recall advantages with retrieval practice versus study practice, with a medium effect size. There was also a main effect of stimulation condition, with anodal stimulation producing recall decrements relative to sham (and marginally relative to cathodal), with a medium effect size. Across all measures, there were no additional effects of learning or stimulation conditions, including word pleasantness ratings, arithmetic task performance, or false recall. Thus, we provide the first evidence that anodal tDCS centered over the dlPFC can produce significant verbal episodic memory decrements.

4.1. Retrieval practice effects

Our results replicate a large body of existing research demonstrating significant memory advantages associated with repeated testing (Karpicke & Grimaldi, 2012; Karpicke & Roediger, 2008; McDaniel & Fisher, 1991; McDaniel, Kowitz, & Dunay, 1989; Roediger & Karpicke, 2006a). The present design fits closely with earlier research involving word list learning under conditions of repeated testing versus repeated study (Hogan & Kintsch, 1971; Wheeler, Ewers, & Buonomano, 2003; Zaromb & Roediger, 2010). For instance, in one study the authors found that parametrically increasing the number of tests during learning produced linear increases in recall, whereas increasing the number of study opportunities similarly decreased recall after a 2-day interval (Zaromb & Roediger, 2010). In the present experiment, we found

similar evidence for enhanced recall rates after 2 days, following a learning experience involving two tests versus two additional study opportunities. An additional study with a similar design asked participants to study a prose passage and then either restudy or perform free recall; they then completed another recall test after 5-minute and 2-day retention intervals (Roediger & Karpicke, 2006a). The authors found that restudy increased recall at the 5-minute interval, but free recall during learning increased final recall at the 2-day interval. In both of these earlier studies, the authors reported effect sizes; in the first, there was a medium effect size (Cohen's $d = 0.50$) (Zaromb & Roediger, 2010), and in the second a large effect size (Cohen's $d = 0.95$) (Roediger & Karpicke, 2006a) when comparing repeated study versus retrieval practice. The present results fit squarely within the patterns of these earlier reports, with a medium effect size of approximately 0.5, providing a strong replication of existing effects reported in the literature.

4.2. Stimulation effects

An interesting pattern emerged when examining the effects of stimulation on recall rates after the 2-day retention interval, with anodal stimulation decreasing recall rates relative to the sham and cathodal (marginally) conditions. At the outset of this study we made two contrasting hypotheses. First, that tDCS targeting the dlPFC would increase recall of verbal materials. This hypothesis was based on research demonstrating the engagement of dlPFC during verbal memory encoding (Sandrini et al., 2003; Savage et al., 2001), and the apparent effectiveness of anodal tDCS targeting the dlPFC for enhancing recognition of verbal materials. However, we also noted that no studies have assessed dlPFC effects on recall of verbal episodic memory (Javadi & Walsh, 2012), and none has used a retention interval exceeding 1 h (Javadi & Walsh, 2012; Javadi et al., 2012). Second, our contrasting hypothesis was that anodal tDCS targeting the dlPFC would either not affect or reduce recall of verbal episodic memory.

These possibilities were based on three primary findings: that recall is more difficult than recognition, which can reduce overall recall rates and possibly diminish our ability to detect differences between conditions (Yonelinas, 2002), that some studies show no or negative effects of dlPFC stimulation on verbal episodic memory (de Lara et al., 2017; Zwissler et al., 2014), and that dlPFC might decrease detailed episodic memories (Zwissler et al., 2014). In the latter study, the authors suggested that anodal dlPFC stimulation may increase associative processing during word presentation, increasing noise during memory

encoding and leading to a more abstracted and less detailed memory trace (Zwissler et al., 2014). This type of explanation is in accord with theories suggesting that the neuronal excitability induced by tDCS increases neural noise (i.e., indiscriminate modulation) in stimulated brain regions, leading to uncertain interactions with task-induced neural activations (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Miniussi, Harris, & Ruzzoli, 2013). One behavioral result of introducing neural noise might be relative diverse and far-reaching neuronal activations that decrease the levels of detail associated with a given memory trace, particularly in a task that a participant is unfamiliar with (i.e., does not have consolidated neural network architecture for performing) (Dockery et al., 2009). This may be particularly the case during lengthy retention intervals when memory traces are already vulnerable to abstraction into relatively general thematic content (Brainerd & Reyna, 2008; Payne et al., 2006). Thus, the present result demonstrating a recall disadvantage following anodal stimulation may be attributable to these effects. Of course, this type of explanation might also predict higher false recall rates in the anodal stimulation condition, which we did not find. Continuing research will be valuable for disentangling these putative mechanisms underlying the present results.

It is important to point out that the neural noise explanation runs counter to traditional ways of conceptualizing tDCS influences on brain and behavior, particularly sliding scale models suggesting that anodal increases and cathodal decreases excitability in underlying brain regions (Bestmann et al., 2015; Bikson & Rahman, 2013). The present results demonstrated that neither anodal nor cathodal stimulation enhanced recall performance, both polarities induced numerical decreases in recall, and anodal significantly impaired recall relative to sham. In conjunction with recent research demonstrating that anodal stimulation may affect neuronal excitability in inhibitory neurons (Molae-Ardekani et al., 2013; Stagg et al., 2014, 2009), our results suggest that sliding scale models may over-simplify stimulation effects on the cognitive system (Berker, Bikson, & Bestmann, 2013; Bestmann et al., 2015). This adds to a growing body of evidence suggesting that tDCS is often unreliable in the extent and directionality of its effects.

We point out three examples of unreliable tDCS effects from the domains of visual perception, classical conditioning, and cognitive control. First, visual phosphene have been used for decades as a method for validating the influence of magnetic and electrical brain stimulation methods on visual cortex excitability (Antal, Kincses, Nitsche, & Paulus, 2003; Barker, Freeston, Jalinous, Merton, & Morton, 1985). But recent research has suggested that tDCS targeting the human visual cortex either does not modulate phosphene thresholds, has paradoxical effects on phosphenes, or phosphenes are modulated interactively across individuals and tasks (Antal, Ambrus, & Chaieb, 2014; Brückner & Kammer, 2016). Similarly inconsistent results have been found during perceptual learning tasks (Pirulli, Fertonani, & Miniussi, 2013) and orientation discrimination tasks (Pirulli, Fertonani, & Miniussi, 2014). Second, the eyeblink reflex is a classical conditioning task that has been extensively validated in the literature; in this task, participants learn to associate a tone with an air puff next to the eye and thus lower their eyelid in anticipation of its arrival (Thompson et al., 1997). The cerebellar cortex and nuclei have been consistently implicated in eyeblink conditioning (Thompson & Steinmetz, 2009; Thurling et al., 2015; Timmann et al., 2010), and repetitive transcranial magnetic stimulation (rTMS) of the cerebellum has been shown to reliably modulate performance on eyeblink conditioning tasks (Hoffland et al., 2013). However, research attempting to modulate eyeblink conditioned associative learning with tDCS have been equivocal, with a recent series of experiments suggesting no reliable polarity-specific effects of tDCS on eyeblink conditioning (Beyer, Batsikadze, Timmann, & Gerwig, 2017). Third, sense of agency (SoA) is the ability to understand and control one's own actions, and understand ourselves as causal agents acting within the world (Haggard, 2008, 2017). One way to examine SoA is by leveraging the phenomenon of intentional binding,

which describes the tendency for agents to compress time between their own voluntary actions and its perceived effects on the environment (Tsakiris & Haggard, 2003); in general, a higher sense of agency leads to stronger intentional binding. In a series of published papers, equivocal effects of brain stimulation on intentional binding have been reported. For instance, both anodal and cathodal stimulation of prefrontal brain regions (targeting the pre-supplementary motor area) have been shown to modulate intentional binding (Cavazzana, Penolazzi, Begliomini, & Bisiacchi, 2015). Another paper found that anodal but not cathodal stimulation of the angular gyrus modulated intentional binding (Khalighinejad & Haggard, 2015), and a recent review of brain stimulation effects on intentional binding suggested that results are equivocal and sometimes contrasting (Crivelli & Balconi, 2017).

Thus, there is emerging evidence from a diverse set of research domains and tasks suggesting that additional research is warranted to better specify the individuals, contexts, tasks, and brain regions that reliably elicit stimulation effects on human behavior (Berker et al., 2013; Bestmann et al., 2015; Brunyé, Hussey, Gardony, Holmes, & Taylor, 2018; Horvath et al., 2014, 2015b, 2015a; Nitsche, Bikson, & Bestmann, 2015). There is also an increasing need for comprehensive biologically-inspired models of brain stimulation influences on brain and behavior; several recent candidates are worth mentioning, such as models suggesting that tDCS: (a) modulates neuronal tuning curves during perceptual tasks (Javadi, Brunec, Walsh, Penny, & Spiers, 2014), (b) induces non-linear effects on neuronal firing rates and behavior (Bonaiuto & Bestmann, 2015), (c) differentially modulates neurons based on their orientation relative to the electrical field potential (Tranchina & Nicholson, 1986), and (d) introduces stochastic noise that is beneficial or detrimental based on its amount (Miniussi et al., 2013). More advanced computational models validated through *in vitro* and *in vivo* studies will likely provide deeper insights into the mechanisms underlying equivocal effects of non-invasive electrical brain stimulation on the brain and behavior (Bestmann et al., 2015).

4.3. Limitations

This was the first study examining the effects of dlPFC tDCS on verbal episodic memory after a lengthy retention interval, and as such there are a few limitations worth considering. First, it is entirely possible that recognition performance may be enhanced by dlPFC tDCS after the relatively lengthy retention interval. As we suggested above, recognition can rely on both familiarity and recollection, and the extent to which dlPFC tDCS might promote a relatively “gist” representation in verbal episodic memory could reasonably translate to higher familiarity during a recognition test (but not necessarily more precise recall). Such a finding would support and extend existing research demonstrating recognition advantages after relatively short retention intervals. Second, it is possible that administering tDCS during encoding versus retrieval would differently modulate verbal episodic memory. Indeed, some recent research demonstrates effects of anodal dlPFC tDCS when administered during encoding, but not retrieval (Javadi & Walsh, 2012), whereas other research shows the opposite effect (Manenti et al., 2013). It is also possible that any stimulation effects introduced during encoding could ostensibly modulate the consolidation phase, as suggested by some research examining prefrontal tDCS effects on memory reconsolidation (Javadi & Cheng, 2013; Sandrini, Censor, Mishoe, & Cohen, 2013). Finally, it is worth mentioning that recent research has shown the importance of understanding and leveraging individual differences to account for performance alterations due to tDCS (Berryhill & Jones, 2012; Brunyé et al., 2015; Brunyé, Moran, Holmes, Mahoney, & Taylor, 2017; Brunyé et al., 2014; Jones, Gozenman, & Berryhill, 2015; Sarkar, Dowker, & Cohen Kadosh, 2014; Slaby et al., 2015). For instance, poorer baseline performance on tasks related to a primary outcome measure can predict advantages due to tDCS. Thus, continuing research in this domain might consider better understanding inter-participant (and even intra-participant) variability in verbal episodic

memory to account for otherwise noisy data outcomes (Horvath et al., 2014).

5. Conclusions

Retrieval practice supports the development of verbal episodic memories that can be recollected after a relatively lengthy retrieval interval. Electrical brain stimulation in the form of anodal tDCS targeting the left dlPFC effectively reversed these advantages and produced an overall recall decrement relative to both sham and cathodal stimulation. We provide the first evidence of reliable recall decrements following dlPFC tDCS during encoding and a 2-day retention interval, and suggest that our specific methodology may decrease highly detailed memory and thus alter subsequent recollection processes. This possibility needs to be further explored in continuing research, to better ascertain the circumstances under which electrical brain stimulation may or may not prove advantageous for memory performance.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bandc.2018.09.008>.

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