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tDCS over the prefrontal cortex alters objective but not subjective encoding

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Abstract

Previous research has implicated the prefrontal cortex (PFC) in successful associative encoding and subjective awareness of one's memory performance. We tested the causal role of the PFC in these processes by applying transcranial direct current stimulation (tDCS) during a verbal associative encoding and judgment-of-learning task. TDCS over the PFC impaired associative encoding compared to sham and parietal tDCS, as showed fewer hits on a subsequent associative recognition test. There were no effects of tDCS on the magnitude or accuracy of judgments-of-learning. These results suggest the PFC plays a causal role in objective measures of encoding, and that objective and subjective aspects of associative encoding are separable.

Keywords

tDCS; memory; encoding; metamemory; judgments of learning; prefrontal cortex

Introduction

Self-directed learning involves both forming new associations, and subjectively knowing whether that information has been encoded. Inaccurate awareness of one's own memory impairments may result in a failure to alter behaviors to compensate for these impairments or seek appropriate help. Populations with various clinical disorders, including schizophrenia and Alzheimer's disease, have shown deficits in both memory and memory awareness (known as "metamemory"), and the goal of this experiment is to understand the role of the prefrontal cortex in both memory and metamemory.

Previous studies have demonstrated the role of prefrontal regions in forming inter-item associations necessary for successful associative encoding (Blumenfeld & Ranganath, 2007). Similarly, neuroimaging and lesion studies have demonstrated that prefrontal regions have a role in judgments-of-learning (JOLs), which are subjective metamemory judgments made at study about the ability to later remember currently retrievable items (Do Lam et al., 2012; Vilkki, Surmaaho & Servo, 1999). However, neuroimaging studies are correlational, and

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cannot establish causal relationships between brain activity and cognitive performance. In contrast, lesion studies can provide causal evidence, but are limited by significant variation in lesion sizes and locations, often making inferences about specific roles of cortical regions difficult. Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) provide a cost-effective way for researchers to test causality by directly manipulating cortical activity in healthy subjects (Fregni et al., 2005). Given that the prefrontal cortex (PFC) has been associated with both objective and subjective memory, we tested whether tDCS over the PFC would alter associative encoding, JOLs, or both.

tDCS typically involves passing a weak current through the scalp from a positive electrode (“anode”) to a return electrode (“cathode”), and is thought to alter the resting membrane potential and/or alter synaptic transmission (Nitsche et al., 2003). However, tDCS effects may be state-dependent; for example, anodal stimulation has been shown to increase neuronal excitability when subjects are at rest, but slightly decrease excitability if applied during a cognitive or motor task (Antal et al., 2007) and tDCS effects have been shown to increase with task difficulty (Jones & Berryhill, 2012), leading to the hypothesis that tDCS may only show behavioral effects when performance is suboptimal (Horvath, Forte & Carter, 2015). Because young adults typically reach optimal memory performance in the afternoon (Yoon, May & Hasher, 1999), we used time of day as a potential state-dependent factor in the effects of tDCS on our college-aged sample.

To examine the role of the PFC in objective and subjective associative memory, tDCS was applied during a verbal paired-associate encoding and JOL task. Subjects received active tDCS over the prefrontal or parietal cortex, or sham stimulation while studying word pairs and making JOLs. One day later, subjects took a recognition test. Changes in associative recognition following prefrontal stimulation would suggest the PFC has a stronger role in objective memory performance, whereas altered JOLs would indicate a causal role of the PFC in subjective memory awareness.

Methods

Participants

72 young adults from the Brooklyn College community (41 F, ages 18–31 years, $M = 20.8$, $SD = 3.3$ years) participated for course credit or \$15/hour. All participants were fluent English speakers, had no contraindications to tDCS, and gave written informed consent as approved by the Human Research Protection Program of the City University of New York.

Transcranial direct current stimulation

Current was delivered through a battery-driven constant current stimulator (1×1 tDCS Low-Intensity Stimulator, Soterix Medical, USA) via rubber electrodes encased in saline-soaked sponges (5cm × 7cm).

Participants were randomly assigned to sham ($n=24$), prefrontal ($n=24$) or parietal ($n=24$) groups. To stimulate the PFC, the anode was placed over F3, with the return over the contralateral supraorbital ridge (Fregni et al., 2005). We stimulated the parietal cortex by placing the anode over CP3 and return over CP4 to determine whether tDCS effects were

regionally specific, or if tDCS to any cortical region would produce similar effects compared to sham (Pergolizzi & Chua, 2015). Active stimulation consisted of a constant current of 2mA for 20 minutes. During sham tDCS, the stimulator ramped up to 2mA and down to 0.1mA, which was maintained for the duration of the 20-minute period, followed by a final ramp up and down. After completing the study, participants were asked if they believed they had received active or sham tDCS; 52% of participants in the sham condition believed they had received active stimulation, compared to 41% in prefrontal and 48% in parietal groups, suggesting that blinding to condition was successful.

Stimuli and procedure

Stimuli were presented using Psychopy (Peirce, 2007). Stimuli consisted of 384 words from the MRC Psycholinguistic Database (Wilson, 1988), matched on frequency and imageability, sorted into 192 pairs of unrelated words. During study, subjects were instructed to create a mental image using the paired words, and to memorize them. Each pair was presented for 3s, followed by a self-paced JOL on an 11-point scale from 0–100% in 10% increments, indicating their confidence that they would remember that pair later. TDCS was administered beginning ~5 minutes before the start of study and continued for 20 minutes. Previous research has shown that this duration of stimulation, particularly when it is initiated at least five minutes prior to the task, is sufficient to produce after effects for several minutes, ensuring all participants received effects of stimulation even if they took longer than 20 minutes to complete the behavioral task (Stagg & Nitsche, 2011). On average, subjects completed the task in 21.7 minutes ($SD = 6.77$), with no difference in duration between groups. One day later, at test, participants viewed 192 word pairs; half had been paired together at study (“intact”), and half were word pairs created from different study pairs (“rearranged”). Test sessions were scheduled as close as possible to 24 hours after each participant’s study session ($M = 24.08$ hours, $SD = 2.35$). Subjects indicated whether each pair was “intact” or “rearranged” via keypad.

Data analyses

To examine associative memory performance, recognition trials were categorized as associative hits (intact pairs called ‘intact’), false alarms (rearranged pairs called ‘intact’), misses (intact pairs called ‘rearranged’), and correct rejections (rearranged pairs called ‘rearranged’). JOL accuracy was calculated by backsorting the response to each test item with the JOL rating given at study. Backsorted JOLs were used in computing Goodman Kruskal Gamma Coefficients (γ) and d_a , which are measures of relative metamemory accuracy. The gamma coefficient is a commonly used measure based on the difference between concordant pairs (P) and discordant pairs (Q), and is calculated by the equation $(P - Q)/(P + Q)$. Concordant pairs are ranked in the same order for accuracy and JOLs, whereas discordant pairs are ranked in reversed orders on accuracy and JOLs. D_a is thought to be more sensitive than gamma, and is considered a signal-detection based measure of metamemory accuracy (Benjamin & Diaz, 2008; Spellman, Bloomfield & Bjork, 2008). To compute d_a , we used the procedure described by Benjamin and Diaz (2008), wherein the probability of a metacognitive hit, such as giving a high JOL to a later-remembered item, is plotted against the probability of a metacognitive false alarm, and d_a is calculated using the formula $2y_0/(1+m^2)$, where y_0 is the y intercept and m^2 is the slope of a normal deviate

isosensitivity function, such that d_a represents the distance between this isosensitivity plot and chance performance.

Analyses used linear regressions to examine effects of tDCS and time of day on associative hits, false alarms, JOL ratings, and JOL accuracy, and were considered significant at $p < 0.05$. Stimulation condition was dummy coded into two variables with sham as the reference.

Results

Subsequent Associative Memory

Participants had reasonable associative hit rates, and relatively high associative false alarm rates (Table 1). Both prefrontal stimulation and time of day were significant predictors of associative hits ($R^2 = 0.133$; $R^2_{adjusted} = 0.095$; $F(3,68) = 3.49$, $p < 0.05$; Prefrontal vs. Sham: $B = -0.068$, $p < 0.5$, 95% CI $[-0.136, -0.001]$; Parietal vs. Sham: $B = -0.011$, $p > 0.09$, 95% CI $[-0.080, 0.059]$; Time of Day: $B = 0.063$, $p < 0.05$, 95% CI $[0.006, 0.121]$). In other words, the frontal stimulation group had a mean decrease of 0.068 in associative hit rates as compared to sham (Figure 1), and there was no difference in parietal compared to sham stimulation. When directly comparing parietal and frontal stimulation groups there was no significant difference in associative hits between groups ($p > 0.3$). In terms of time of day, afternoon stimulation (defined as after 12pm, $M = 2:27pm$, $SEM = 0.16$) predicted an average increase of 0.063 in associative hit rate as compared to morning stimulation (defined as before 12pm, $M = 10:27am$, $SEM = 0.07$). Stimulation and time of day were not, however, predictive of subsequent associative false alarms ($R^2 = 0.026$; $R^2_{adjusted} = -0.017$; $F(3,68) = 0.608$, $p = 0.612$).

Judgments of Learning

For JOLs, participants in each group gave a range of responses (Table 1); 68 participants had 0, 4 had 10, 1 had 20, and 1 had 30 as their minimum response; 65 had 100, 5 had 90, and 2 had 80 as their maximum response. JOLs showed some predictive value with participants giving higher JOLs to subsequent associative hits ($M = 53.60$, $SD = 12.42$) compared to associative false alarms ($M = 47.82$, $SD = 13.01$; $F(1,69) = 59.49$, $p < 0.001$), and there was no main effect of tDCS on JOL ratings [$F(2,69) = 1.55$, $p > 0.22$], nor was there a tDCS by accuracy interaction [$F(2,69) = .945$, $p > 0.39$; see Table 1]. JOL accuracy was low (Table 1), as is typical for immediate JOLs (Dunlosky & Metcalfe 1991). Neither prefrontal nor parietal stimulation compared to sham, nor time of day, were significant predictors of JOL ratings ($R^2 = 0.041$; $R^2_{adjusted} = -0.001$; $F(3,68) = 0.978$, $p = 0.41$). Similarly, our model did not explain significant variance in metamemory accuracy, measured by gamma ($R^2 = 0.017$; $R^2_{adjusted} = -0.027$; $F(3,68) = 0.386$, $p = 0.763$), or d_a ($R^2 = 0.030$; $R^2_{adjusted} = -0.013$; $F(3,68) = 0.696$). See Table 1.

Discussion

Both memory and metamemory have essential roles in self-directed learning, and there is a need for a greater understanding of how different cortical regions contribute to both objective and subjective memory processes. With the growing interest in using non-invasive brain stimulation as a tool in cognitive remediation, it is important to understand the effect

of tDCS over different brain regions on either objective and subjective memory processes, or perhaps both. The prefrontal cortex has been implicated in successful encoding and metamemory (Blumenfeld & Ranganath, 2007; Do Lam et al., 2012), and here we showed that tDCS over the PFC reduced associative encoding, as evidenced by significantly lower associative hits. In contrast, there were no effects of tDCS on judgments-of-learning, suggesting the role of the PFC at encoding is more related to associative processing than metamemory.

Because tDCS has limited focality, our results are most accurately interpreted as the effects of stimulation over broad areas of the PFC. However, the montage we used is thought to stimulate the dorsolateral prefrontal cortex (DLPFC) (Fregni et al., 2005). Our findings are therefore consistent with the idea that the DLPFC is crucial to successful associative encoding (Blumenfeld & Ranganath, 2007). However, because tDCS is relatively nonfocal, it is also possible that stimulation of cortical regions beyond the DLPFC may have contributed to our results (Nitsche et al., 2007).

We showed worse associative encoding with tDCS over the PFC, and this direction may seem surprising because other tDCS research has shown that “anodal” tDCS tends to enhance memory performance (Matzen, Trumbo, Leach & Leshikar, 2015). However, several other studies have shown that “anodal” stimulation does not always improve performance (Jacobson, Koslowsky & Lavidor, 2012). For example, for individuals with less education, anodal stimulation to the DLPFC impaired working memory (WM) performance, whereas anodal tDCS improved performance in adults with higher education (Berryhill & Jones, 2012). Although we tested associative memory not WM, DLPFC activity during WM tasks predicts subsequent long-term memory, likely through strengthening inter-item associations (Blumenfeld & Ranganath, 2007). Thus, individual differences may predict who benefits from tDCS, and may explain our finding that “anodal” tDCS impaired associative encoding.

An alternative explanation for why we showed worse associative encoding, whereas other work has shown improved associative encoding (Matzen et al., 2015), is related to the tDCS montage used. For example, Matzen et al. (2015) showed that anodal stimulation to the PFC during associative encoding led to better recall but not associative recognition performance, whereas our results showed poorer performance. However, Matzen et al. (2015) used a different montage, in which the anode was placed at F9 and the return electrode on the contralateral upper arm. Although the spatial resolution of tDCS is relatively poor, the montage used by Matzen et al. (2015) targets a much more ventral region of the PFC, and likely accounts for the differences in performance seen across studies.

In contrast to a causal role of the PFC in associative encoding, there were no effects of tDCS on immediate JOLs, showing that encoding and metamemory are dissociable. The lack of effect of prefrontal tDCS on JOLs is consistent with a recent TMS study that showed no effect of TMS to the DLPFC on immediate JOLs (Ryals, Rogers, Gross, Polnaszek & Voss, 2015). The same study did show that TMS to the frontopolar cortex influenced JOL accuracy. Given that the tDCS cathode serves as a functionally effective reference electrode, placing the cathode over the supraorbital ridge may have inhibited more anterior PFC

regions, and it is possible that the combination of the anode over the DLPFC and the cathode over the anterior PFC contributed to the lack of tDCS effects on JOLs (Nitsche et al., 2007). However, based on our results and those of Ryals et al. (2015), it seems more likely that the role of the DLPFC in immediate JOLs is minimal, especially in comparison to other PFC regions. Notably, this lack of effect may be specific to immediate JOLs, and may differ for other types of metamemory judgments; a recent study showed improved metamemory accuracy using feeling-of-knowing judgments with High-Definition tDCS (HD-tDCS) over the DLPFC (Chua & Ahmed, 2016), suggesting other metamemory judgments, likely those that occur at retrieval, may rely on the DLPFC.

Another potential explanation for the lack of an effect on JOLs relates to how poor JOL accuracy was in our study. The relative accuracy of immediate JOLs tends to be poor (Dunlosky & Metcalfe 1991), particularly as compared to JOLs made after a delay between study and judgment (Nelson and Dunlosky, 1991). Immediate JOL accuracy was also low in our study, although participants did give higher JOLs to associative hits compared to false alarms, and gamma coefficients were above chance [$t(71)=13.57$, $p<0.001$]. Nevertheless, it is possible that if JOL accuracy were better, then stimulation would affect JOL accuracy. We believe this is unlikely based on analyses of JOL accuracy for intact and rearranged pairs by tDCS, which showed significantly higher gamma coefficients for intact pairs ($M=0.37$, $SD=0.18$) than rearranged pairs ($M=-0.02$, $SD=0.13$; $p<0.001$). If tDCS had an effect on JOL accuracy when JOL accuracy was higher, then we would expect an effect of stimulation on JOL accuracy for intact pairs, which had better JOL accuracy, but no effect of tDCS on rearranged pairs; however, there was no difference in the effects of tDCS on JOL accuracy for intact compared to rearranged pairs [$F(2,69) = 0.713$; $p > .45$]. Another reason low metamemory accuracy is less likely to be an explanation is that a different tDCS study of metamemory showed improved metamemory accuracy, using a feeling-of-knowing task, during HD-tDCS over the dorsolateral prefrontal cortex compared to over the anterior temporal lobe, even though metamemory accuracy was low in the sham and anterior temporal lobe conditions (Chua & Ahmed, 2016). Thus, the effects of tDCS may be more dependent on the type of metamemory task rather than differences in metamemory accuracy.

It is worth noting that the current study is somewhat limited by a between-subjects design, in that we are unable to account for baseline differences in memory and metamemory and make conclusions about the influence of tDCS on individual performance. We chose to use a between subjects design out of concern that in a within-subjects design subjects would be more likely to detect relative differences in sensations between sham and active conditions, which could influence their task performance. Future work may benefit from using within subjects or mixed designs in a similar paradigm.

The growing use of tDCS has allowed researchers to test the causal role of cortical regions in various cognitive tasks, and may serve as a promising intervention for enhancing various cognitive abilities in populations with deficits, but mixed findings warrant further exploration into when tDCS enhances memory processes (Horvath, Forte & Carter, 2015). Although we showed that tDCS over the PFC worsens associative encoding, further research is needed to understand how tDCS parameters interact with individual differences to facilitate or inhibit memory formation. Non-invasive brain stimulation methods with greater

spatial focality, such as HD-tDCS or TMS, may allow us to further elucidate how more precise subregions of the PFC causally contribute to both objective and subjective associative memory.

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Figure 1.
Mean associative hit and false alarm rates by tDCS group. Error bars represent standard errors of the means. * $p < 0.05$

Table 1

Mean (*SD*) associative hit rates, false alarm rates, JOL ratings, minimum JOL rating (JOL Min), maximum JOL rating (JOL Max), JOLs for associative hits and false alarms, Gamma Coefficients, and d_a for sham, prefrontal, and parietal tDCS groups, and collapsed across groups.

tDCS Group	Sham	Prefrontal	Parietal
Associative Hits	0.66 (0.10)	0.59 (0.13)	0.63 (0.12)
Associative False Alarms	0.34 (0.15)	0.29 (0.10)	0.29 (0.13)
Overall JOL Ratings	48.07 (11.28)	44.72 (12.50)	50.5 (11.74)
JOL Min	2.50 (6.76)	0.00 (0.00)	1.25 (4.48)
JOL Max	97.92 (5.09)	98.75 (4.48)	99.58 (2.04)
JOLs for Associative Hits	56.11 (12.95)	50.88 (12.65)	55.91 (11.65)
JOLs for Associative False Alarms	47.70 (12.60)	44.19 (12.86)	51.57 (13.07)
Gamma Coefficients	0.17 (0.12)	0.19 (0.11)	0.19 (0.12)
d_a	0.25 (0.19)	0.22 (0.19)	0.29 (0.18)