No Evidence for Enhancing Prospective Memory with Anodal Transcranial Direct Current
Stimulation across Dorsolateral Prefrontal Cortex

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Abstract

A standard finding in the event-based prospective memory literature is that focal cues are more often detected than nonfocal cues. The multiprocess view of prospective memory accounts for this result by suggesting that dorsolateral prefrontal cortex (DLPFC) mediated executive processes are necessary for nonfocal cue detection while hippocampally mediated spontaneous retrieval processes support detection of focal cues. In agreement with the multiprocess view, previous studies have found that working memory capacity is predictive of prospective memory performance through detection of nonfocal cues, but non-predictive for focal cues. Because the DLPFC is known to support working memory maintenance, we predicted that anodal transcranial direct current stimulation (tDCS) of the DLPFC would increase prospective memory cue detection for nonfocal cues when compared with a sham condition. Critically, we also expected an interaction between prospective memory cue type and stimulation such that anodal stimulation would not influence focal cue detection. Our results replicated the standard effect of improved focal compared to nonfocal cue detection. However, there was no significant effect between the sham and active tDCS conditions. Furthermore, we did not find the expected interaction between cue type and stimulation. Not only do our findings add onto the growing literature of tDCS experiments that failed to find stimulation effects to DLPFC, but it is also one of the first studies to incorporate prospective memory with tDCS.

Keywords: prospective memory, working memory, tDCS, neural stimulation

Introduction

Prospective memory refers to the encoding, retention, and retrieval of intended future actions. A key component of prospective memory involves associating intended actions to environmental cues that may be encountered in the future. For example, imagine needing to remember to stop by the bank to make a deposit after work. In this example, a variety of cues that occur in the environment (i.e., writing a check, reading *The Economist*, leaving work, and even seeing a riverbank on the way home) may cue retrieval of the intended action from memory. Detecting prospective memory cues that are associated with intended actions and remembering to execute these actions is oftentimes difficult for healthy individuals as well as those with many important clinical deficits (i.e., individuals with frontal lobe deficits; Burgess et al., 2007). Given pronounced prospective memory deficits in clinical populations, it is an important goal to validate innovative techniques (e.g., neural stimulation) for helping people detect environmental cues, remember appropriate actions, and successfully fulfill their intentions (Basso et al., 2010).

Prospective memory performance is commonly measured with an event-based paradigm in which participants encode an intention to execute an action upon encountering cues in an ostensibly unrelated ongoing future task (Einstein & McDaniel, 1990). For example, participants are instructed to press a special key on the keyboard if they ever encounter a word with the syllable TOR (e.g., tortoise) in the context of an upcoming lexical decision task. Using this paradigm, Einstein et al., (2005) showed that cue focality is a critical determinant of whether or not individuals detect event-based cues and fulfill their intentions. Cue focality refers to the degree to which features of the event-based cue are highlighted by ongoing-task processing. In the example above, words or nonwords containing the syllable TOR that occur in the lexical

decision task would be considered *nonfocal* cues. This is because the ongoing task encourages stimulus processing at a semantic level (i.e., word versus nonword) but the features of the cue relevant for prospective memory detection must be processed at a syllabic level (i.e., does the word or nonword contain ‘TOR’). A focal cue in the case above would be if the participant had formed the intention to respond to the specific word “tortoise”, instead of the syllable TOR, which would benefit from being processed semantically and therefore have a higher likelihood of being detected. Einstein & McDaniel’s (2005) multiprocess view suggests that executive processes are used for successful detection of nonfocal cues while focal cue detection rely on spontaneous retrieval processes. Accordingly, previous studies have replicated this enhancement towards focal cue detection in older populations, clinical populations, and individuals with low working memory capacity (Brewer et al., 2010; Kliegel, Jaeger, & Phillips, 2008; Kliegel et al., 2011; Rose et al., 2010).

The present study aimed to provide further empirical evidence for the view that executive processes are critical for prospective memory by using neural stimulation to induce increased detection of nonfocal cues but not focal cues. Transcranial magnetic stimulation (TMS), theta burst stimulation (TBS) experiments, and transcranial random noise stimulation (tRNS) have been used to examine causal relationships between the DLPFC and working memory and have found conflicting results (Bisiacchi, Cona, Schiff, & Basso, 2011; Basso, Ferrari, & Palladino, 2010; Debarnot et al., 2015; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011). Basso et al. (2010) used TMS on right and left DLPFC during a dual prospective memory/working memory task and found deleterious effects on prospective memory performance and marginal negative effects on working memory task performance. Thus, the results of Basso et al., (2010) highlight a functional role of DLPFC in prospective memory. Beyond these TMS studies, very limited

research has explored neural stimulation of prefrontal tissue to facilitate prospective memory performance. Therefore, the current study contributes to the growing literature on DLPFC stimulation in the context of aiding prospective memory with noninvasive neural stimulation techniques.

Specifically, we investigated the effect of transcranial direct current stimulation (tDCS) on prospective memory performance. tDCS is a noninvasive neural stimulation technique used to enhance or inhibit neural activity (Woods et al., 2016). tDCS differs from TMS in that TMS administers a pulsing electrical current to a small region of the brain using a coil that is fixed above the participant's head. Alternatively, tDCS uses two electrodes (one anodal and one cathodal) that are placed on the scalp which apply a weak direct electrical current (e.g., 1-2 mA) to the underlying target cortex. While the current is being applied, individuals describe the sensation as that of an "itch" or "tickle". Both sham and active stimulation are used in these experiments to account for any possible demand characteristics. Anodal stimulation is thought to increase the probability of neural firing while cathodal stimulation is believed to inhibit the probability of action potentials (Paulus, 2003).

Other than prior work examining stimulation to motor cortex, the mechanisms of tDCS are not well understood (Stagg et al., 2018; Voroslakos et al., 2018). However, previous studies have produced positive results in enhancing working memory task performance (Fregni et al., 2005; Mulquiney et al., 2011). Fregni et al. (2005) used anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) at 1mA to determine a causal relationship between stimulation and working memory task performance. Using a within-subjects design, the participants completed a 3-back letter task undergoing either an active anodal tDCS or a sham. Participants made significantly more correct responses during active tDCS when compared with the sham

condition. Participants also made significantly more errors in the sham condition relative to the active stimulation. Another pair of tDCS stimulations were added to ensure that the effects of the tDCS were focal and polarity dependent. In this portion of the experiment, they found that stimulating the primary motor cortex (controlling for focality) and reversing the anode and cathode placement (controlling for polarity), had no impact on N-back performance. The results of Fregni et al. (2005) suggested that stimulation of the left DLPFC facilitated working memory. Thus, in the present study, we will also stimulate the left DLPFC to modulate theoretically specified executive processes that are thought to support nonfocal prospective memory cue detection.

We aim to further examine the effectiveness of tDCS by using an event-based prospective memory task embedded within an ongoing animacy task. We expect to replicate the standard finding that focal prospective memory cues are detected more often than nonfocal prospective memory cues (Einstein et al., 2005). By using tDCS, we also expect an increase in nonfocal cue detection when stimulating the left DLPFC when compared with a sham condition. We also expect an interaction between cue-type and stimulation, where stimulation would have a significantly stronger effect on nonfocal cue detection than on focal cue detection. This prediction emerges from the multiprocess view of prospective memory which specifies two possible neurophysiological routes of cue detection based on two independent sets of cognitive processes (executive versus spontaneous). Thus, beyond the value of exploring innovative techniques for improving prospective memory, the current study also provides an important theoretical test of current psychological theory. Finally, we would be remiss to not highlight the current debate regarding variability in previously reported effect sizes of tDCS stimulation across DLPFC tissue (Brunoni & Vanderhasselt, 2014; Hill, Fitzgerald, & Hoy, 2016). Given these

recent meta analyses, it is clear that both significant and null effects of tDCS stimulation on working memory, and prospective memory, must be reported and this is another important aspect of the current study.

Methods

This study was approved by the Human Research Institutional Review Board at Arizona State University.

Participants and Design

A total of 106 young adults (M age = 19 years) from Arizona State University completed the study and were used in the current analysis¹. After providing consent, each participant was tested individually in sessions that lasted approximately 1 hour. A 2 (Cue Type: Focal versus Nonfocal PM) x 2 (Stimulation: Active versus Sham tDCS) between-subjects design was used. Participants were randomly assigned to one of four experimental conditions: Focal - Sham (N=27), Focal - Active (N=26), Nonfocal - Sham (N=26), and Nonfocal - Active (N=27).

Stimulation Protocol

For our stimulation procedure we tried to most directly replicate the protocol of previous studies exploiting anodal tDCS stimulation to augment working memory task performance. Participants were fitted with a Soterix Medical 1x1 tDCS platform at the outset of the experiment. Two EASYpads (5x7 cm², 35cm²) were soaked in a physiologic saline and used for current delivery. The pads were secured with an EASYstrap. In both sham and active stimulation, the anodal electrode was placed over the the left DLPFC (around the electrode F3

¹ There were originally 116 participants in the sample, but 3 participants were removed from all analysis for having corrupted data files and 7 for failing to complete the task as instructed. We analyzed the data with these 7 subjects included, however, and there were no differences in the pattern of findings.

using the international 10-20 electrode system (EEG)) and the cathode was placed on the contralateral supraorbital area. After the appropriate placement of electrodes, prior to the application of the active/sham-stimulation, a pre-stim tickle of 0.5mA was applied to expose the participant to the sensation associated with the application of tDCS. Next, a gradual increase of electric current was applied until reaching 2mA in the active stimulation (electrode current density: 0.057 mA/cm^2). The increase to 2mA takes approximately 1 minute. The sham stimulation also initially gradually increased to 2 mA. However, the electric current quickly deteriorates until no current is being applied. The procedure for both active and sham tDCS was otherwise identical, and all participants were blind to stimulation assignment. The active and sham stimulation started before the experiment began and completed when the task was finished. tDCS stimulation was started before beginning the prospective memory task and lasted for the entire duration of the prospective memory task. Overall, the entire stimulation procedure and prospective memory task lasted less than 20 minutes.

Prospective Memory Materials and Procedure

Participants were first given instructions for the ongoing task. The ongoing task was a living-nonliving (LNL) animacy activity that has commonly been used in prospective memory studies. Participants were told that their task was to decide, as quickly and accurately as possible, whether a presented word was living (e.g., dog) or not living (e.g., book) by pressing “f” or “j” respectively on a standard keyboard. Words were presented one at a time and stayed on the center of the screen until participants responded. After making each LNL response, participants were instructed to press the spacebar (with their thumbs) when a “waiting” message appeared between each trial, which triggered presentation of the next LNL stimulus. After

receiving instructions for the LNL task, all the participants were presented with 100 words (i.e., ongoing task practice (OGT Prac)), half of which were living and half of which were non-living.

Following completion of the baseline LNL task, participants encoded their prospective memory intention. For both focal and nonfocal conditions, the participants were told that we were also interested in their ability to remember to perform a specific future action in the future. Therefore, in addition to performing the LNL animacy task, participants were instructed to make a special key press (“/” key) during the “waiting” message whenever they encountered a particular stimulus (i.e., the event-based cue). In the focal condition the cue was the word “DOCTOR” and in the nonfocal condition the cue was the syllable “TOR”. After the experimenter was satisfied that participants fully understood the instructions, participants completed a 4-minute distractor task (i.e., a decimal multiplication task). Instituting filled delays between intention encoding and execution is typically used to remove the intention from primary memory (Einstein & McDaniel, 1990). After 4 minutes of filled activity, the experimenter initiated the prospective memory LNL task without making any reference to the intention, cues, or intended action. For each condition, 420 LNL (ongoing task (OGT)) trials were presented with a total of 16 prospective memory cues. These cues occurred on trials 30, 55, 80, 105, 130, 155, 180, 205, 240, 265, 290, 315, 340, 365, 390, and 415. Prospective memory performance was defined as the proportion of cues successfully responded to with a “/” response during the “waiting” message immediately following the cue.

Results

We analyzed two primary dependent variables from the prospective memory literature. These include prospective memory performance (the proportion of focal or nonfocal cues successfully detected) and task interference to ongoing activities as a function of possessing an

intention which was quantified by measuring differences in reaction times (RTs) between experimental and baseline blocks of the LNL. For this task interference measure, only correct (non-cue) trials within 2.5 standard deviations of each participant's mean were included in the analysis (Brewer, 2011). For all statistical analyses, a conventional alpha level of .05 was used. Table 1 displays the means for all analyses.

Prospective memory performance was submitted to a 2 (Cue Type: Focal versus Nonfocal) x 2 (Stimulation: Active versus Sham tDCS) between-subjects (ANOVA). According to the multiprocess theory, executive processes support detection of nonfocal cues while spontaneous processes support detection of focal cues (Einstein et al., 2005). As expected, focal cues were detected ($M = .78$, $SD = .37$) more than nonfocal cues ($M = .53$, $SD = .37$), $F(1, 102) = 11.743$, $p < .001$, $\eta_p^2 = .103$. However, there was no significant effect of tDCS stimulation, such that cue detection between both active and sham tDCS conditions was equivalent, $F(1, 102) = .082$, $p = .765$, $\eta_p^2 = .001$. We also failed to see the expected interaction between Cue Type and Stimulation, $F(1, 104) = .113$, $p = .738$, $\eta_p^2 = .001$.

Consistent with previous research, participants exhibited less task interference in the focal condition ($M = -139.98$, $SD = 135.96$) than in the nonfocal condition ($M = 11.07$, $SD = 175.44$), $F(1, 102) = 24.571$, $p < .001$, $\eta_p^2 = .194$. Notably, the negative value reported in Table 1 for the focal condition task interference condition reflects a general speeding up of ongoing task decisions that is consistent with a practice effect. This type of practice effect was not observed in the nonfocal condition which is consistent with prior research. This result indicates that increased demands on executive control, or other related working memory processes, was present in the nonfocal conditions when compared with the focal condition. However, we found no main effect of tDCS stimulation on task interference, $F(1, 102) = .280$, $p = .598$, $\eta_p^2 = .003$.

We also found no significant interaction between Cue Type and Stimulation, $F(1, 102) = 1.448$, $p = .232$, $\eta_p^2 = .014$.

Table 1

Group performance for the proportion of prospective memory cues (PMP) correctly identified, mean reaction time for the ongoing task during the first 100 trials (OGT Prac), mean reaction time for the ongoing task during the 420 trials where the prospective memory cue was present (OGT), and the mean difference of the OGT Minus OGT Prac (Task Interference). Standard deviation in parentheses.

	N	PMP	OGT	OGT Prac	Task Interference
Focal – Sham	27	.76 (.38)	856.17 (159.31)	970.20 (187.65)	-114.03 (117.03)
Focal – tDCS	26	.80 (.36)	913.84 (184.40)	1080.77 (230.94)	-166.92 (150.74)
Nonfocal – Sham	26	.53 (.35)	1055.98 (230.54)	1034.80 (188.40)	21.18 (157.73)
Nonfocal – tDCS	27	.53 (.39)	1056.96 (230.95)	1056.38 (193.44)	.57 (194.75)

While we failed to find a significant effect of tDCS on cue detection, null effects are minimally informative from a frequentist statistical testing framework (Rouder, Morey, Verhagen, Swagman, & Wagenmakers, 2017). Therefore, the similar factorial ANOVA analyses were conducted using Bayes factors to provide a means of inferring evidence in favor of various models of the data (using default prior r scale on fixed effects = .5; JASP, 2018). Given our design there are five possible models, 1) the null model, 2) a model with the main effect of Cue Type, 3) a model with the main effect of Stimulation, 4) a model with the main effects of Cue Type and Stimulation, 5) a model with main effects of Cue Type and Stimulation, and the interaction between Cue Type and Stimulation. Specifically, Bayes factors represent the odds ratio in favor of one model (i.e., a model that accounts for variability in cue detection as a function of Cue Type) over another model (i.e., a null model with no structure to account for variability in cue detection). As expected, the Bayes factor for the model with a main effect of Cue Type was 35 times more likely than the null model ($BF_{10} = 35.331$) which represents strong evidence for an effect of Cue Type similar to the frequentist analyses reported earlier. The Bayes factor for the model with a main effect of Stimulation was 4.77 times less likely than the null

model ($BF_{10} = .210$) which represents negative evidence for an effect of Stimulation, similar to the frequentist analyses reported earlier. Neither the main effects ($BF_{10} = 4.932$ in favor of the Cue Type only model) nor the main effects plus interaction ($BF_{10} = 16.904$ in favor of the Cue Type only model) models garnered more evidence than the Cue Type only model. Taken together there is strong evidence for the effect of Cue Type on prospective memory cue detection and substantial to strong evidence against an effect of Stimulation and any interaction between Cue Type and Stimulation.

General Discussion

Our results replicated the standard effects found in the prospective memory literature regarding focal cues being detected more frequently than nonfocal cues (Brewer et al., 2010; Einstein et al., 2005). Additionally, we found significant task interference to ongoing activities when participants possessed a nonfocal intention compared with a focal intention. Critically, anodal tDCS stimulation across left DLPFC had no effects on cue detection nor task interference. Given that we replicated the known effects of cue focality on prospective memory behaviors, but failed to find tDCS effects, we contribute to the growing literature questioning the reliability of tDCS-guided improvements in working memory. Also, we cast doubt on the utility of tDCS stimulation for improving prospective memory abilities given the stimulation parameters used in the current study.

One possibility for the lack of significant results can be found within tDCS stimulation itself. tDCS remains a controversial neural stimulation technique, as some researchers claim that the technique can modulate cognition, while others fail to replicate their findings. A recent study by Robison, McGuirk, & Unsworth (2017) failed to find evidence for enhancing visual WM using tDCS. Nilsson, Lebedev, Rydström, & Lövdén (2017) and Lovden (2017) used tDCS to

modulate working memory training and also found no difference between active stimulation versus sham. A quantitative review by Horvath, Forte, & Carter (2015) found no significant evidence of enhanced cognitive effects in healthy populations from single-session tDCS. Our study adds to this growing body of literature.

tDCS is a subthreshold neuromodulatory technique, as opposed to actual brain stimulation. Therefore subtle differences in experimental designs (both the experimental task as well as the tDCS montage and dosage applied) might matter greatly. tDCS is also difficult to time-lock with stimulus presentation, given the need to ramp the electrical current up and down over some period of time, which may also limit our ability to develop reliable stimulation protocols. In addition, task-based practice effects such as reported in this study, may easily override the typically much more subtle effects of tDCS. Another limitation to the current study is that there was no data collected on the effectiveness of blinding the participants to sham versus stimulation conditions, thereby limiting our knowledge on whether or not the participants were aware if they were in the active or sham condition. It is recommended that future studies evaluate these possible limitations in addition to considering alternative stimulation parameters and stimulation techniques with more precise temporal and spatial resolution (e.g., transcranial focused ultrasound). Furthermore, a refinement of cognitive theory can also aid in the development of neuromodulatory studies in this domain.

For example, our findings are contradictory to the findings of Nelson et. al (2014) who reported that tDCS to DLPFC improved performance on a vigilance task. Vigilance and nonfocal prospective memory tasks both rely on proactive maintenance of task-relevant information in working memory (Ball & Brewer, 2018). In the vigilance tasks used by Nelson et al. (2014), participants were tasked with identifying whether a set of four planes separated into quadrants on

a radar display were going the same direction or whether one was going in the opposite direction (i.e., opposing motion was the critical signal demanding vigilant attention). Conversely, prospective memory tasks like the one used in the current study have both an ongoing task (i.e., complete lexical decisions) and a prospective memory task (i.e., detect low frequency cues that occur in the ongoing task). In order to properly detect the prospective memory cue, especially in the nonfocal condition, additional processing is required beyond what is required by the primary ongoing task. One possibility is that tDCS may aid in tasks where executive processes are entirely devoted to a single task (i.e., vigilance), but not tasks where executive resources are spread across multiple tasks (i.e., prospective memory). Insights of this nature are an important development from the usage of neural modulation across related research domains where similar theoretical mechanisms (e.g., vigilant attention, executive functioning, or working memory; see also Nelson et al., 2016) are hypothesized to support task performance. Discrepant findings demand cognitive psychologists and cognitive neuroscientists to be more precise regarding our specifications of the underlying mechanisms of behavior.

For future studies of neural stimulation and prospective memory, using HD-tDCS may be more effective as it is considered to be more focally constrained than traditional tDCS. Instead of using two larger sponge-based electrodes (one anodal and one cathodal electrode), HD-tDCS uses smaller EEG-like electrodes with the option of using more than two of such electrodes (e.g. a 4 x 1 montage) and which has been thought to increase focality. Gbadeyan, McMahon, Steinhauser, & Meinzer (2016) report significant effects using HD-tDCS. Also, multiple session tDCS has also been found to be effective in enhancing cognitive demands over time, which may provide another option for future research on this topic. In our study, we failed to find a significant stimulation effect and our participants only completed a single session (Talsma,

Kroese, & Slagter, 2017). However, there are many parameters that need to be systematically explored. Although HD-tDCS has improved focality, without neuronavigation for each individual and/or time-locked stimulation during the specific process or frequency of interest, tDCS is both spatially and temporally imprecise, relative to other forms of stimulation such as TMS, or even transcranial alternating current stimulation (tACS) when it modulates or entrains oscillations in a specific brain region whose frequency of an endogenous oscillation is known to be important for the process of interest.

While our study used a common prospective memory paradigm testing focal and nonfocal cue detection, it is important to note that this task has limited ecological validity and there is evidence that poor performance in this laboratory task does not predict poor prospective memory performance in the real world (Hering et al., 2018; Rose et al., 2010; Unsworth, Spillers, & Brewer, 2012). A task commonly used in the literature that has stronger ecological validity is the Virtual Week Task (Rendell & Craik, 2000). Rose, Thomson, Kliegel, & Rendell (under review) have recently conducted a similar tDCS experiment where they evaluated prospective memory performance in healthy older and younger adults during the Virtual Week Task while applying anodal stimulation to left DLPFC. The parameters of their tDCS stimulation were very similar to those found in the current study. Their experiment had similar null effects of anodal stimulation to left DLPFC and only showed reliable improvements between session 1 and session 2 (i.e., practice effects) irrespective of whether tDCS or sham stimulation was applied. In combination, the current study and the study reported by Rose et al., (under review) cast doubt on the utility of anodal tDCS stimulation to left DLPFC for improving either laboratory-based or naturalistic prospective memory.

Although we failed to find our expected effect using tDCS, it does not negate the importance of using neural stimulation to test theory and aid those with prospective memory deficits. As theory states, a dissociation should be found between stimulation effects on nonfocal versus focal cues and this is an important direction for future research. Although our study was not successful at finding the intended stimulation effect through tDCS, given some of the noted possibilities associated with HD-tDCS and multiple session experiments, there could be an effect of tDCS on prospective memory cue detection. Therefore, the present study provides a good basis, from which a series of experiments where individual or sets of stimulation parameters are systematically varied, rather than as a final word. More research needs to be done as it is important to improve tDCS guidelines to ensure reliable and significant stimulation effects with a manipulation check in the future (for a discussion of this issue and a new stimulation procedure see Voroslakos et al., 2018). The individuals tested in this experiment were, based upon self-report, healthy college age students, so applied interventions and treatments for clinical populations that suffer from prospective memory failures, such as patients suffering from TBI, stroke, and dementia, may greatly benefit from neural stimulation. Based upon our review of the literature, we are the first to test the effects of tDCS on prospective memory performance. This is the first step in examining the effects of tDCS in event-based prospective memory.

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