Transcranial direct current stimulation modulates pattern separation

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Maintaining similar memories in a distinct and nonoverlapping manner, known as pattern separation, is an important mnemonic process. The medial temporal lobe, especially the hippocampus, has been implicated in this crucial memory function. The present study thus examines whether it is possible to modulate pattern separation using bilateral transcranial direct current stimulation (tDCS) over the temporal lobes. Specifically, in this study, pattern separation was assessed using the Mnemonic Similarity Task following 15-min offline bilateral temporal lobe tDCS (left cathode and right anode or left anode and right cathode) or sham stimulation. In the Mnemonic Similarity Task, participants studied a series of sequentially presented visual objects. In the subsequent recognition memory test, participants viewed a series of sequentially presented objects that could be old images from study, novel foils, or lures that were visually similar to the studied images. Participants reported whether these images were exactly the same as, similar to, or different from the studied images. Following both active tDCS conditions, participants were less likely to identify lures as 'similar' compared with the sham condition, indicating a reduction in pattern separation resulting from temporal lobe tDCS. In contrast, no significant difference in overall accuracy was found for participants' discrimination of old and new images. Together, these results suggest that temporal lobe tDCS can selectively modulate the pattern separation function without changing participants' baseline recognition memory performance. *NeuroReport* **00:000–000**

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Introduction

Maintaining specific and exclusive memories for similar external events is crucial for one to navigate in an ever-changing environment. This capability to store similar memory representations in a nonoverlapping manner is known as pattern separation [1]. A growing body of literature suggests the involvement of medial temporal lobe (MTL) structures, such as the hippocampus, perirhinal cortex, and parahippocampal gyrus, in pattern separation [2–4]. For instance, a recent high-resolution neuroimaging study shows that the perirhinal and parahippocampus are involved in pattern separation for domain-selective information (e.g. perirhinal for object information and parahippocampus for spatial information) [4], whereas the hippocampus serves as a general hub in separating mnemonic representations across domains [4, 5]. More importantly, pattern separation deficits often occur following hippocampus lesions [6] or psychiatric conditions that produce hippocampal abnormality, such as schizophrenia [7]. These empirical findings suggest that MTL structures, especially the hippocampus, are causally associated with pattern separation. In the current study, we therefore examine whether it is possible to modulate pattern separation using noninvasive stimulation of the temporal lobe with transcranial direct current stimulation (tDCS) in healthy observers.

A typical tDCS setup delivers a weak current to the brain through two electrodes, an anode and a cathode, placed on the scalp that are presumed to increase (anode) and decrease (cathode) the excitability of the underlying cortex [8]. tDCS effects are often attributed to modulation of the superficial cortex; however, the physics of current flow mandate that current crossing gray matter will continue through the brain to the return electrode. As a result, deep brain structures will also be polarized [9]. Imaging studies (not restricted to a cortical region of interest) suggest comparable neuromodulation of superficial and subcortical structures [10], such as the hippocampus as well as increased connectivity between the hippocampus and other brain regions [11]. The regions of cortical current flow, as well as the degree of deep penetration during tDCS, is dependent on the electrode montage [9]. Positioning electrodes lateralized across the head preferentially modulates the underlying cortex and also optimizes deep current flow to structures such as the hippocampus [12]. We therefore applied tDCS bilaterally across the temporal lobes in the present study.

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Recent research showed significant modulation of memory functions, which may critically depend on the MTL [13], using tDCS administered over temporal lobes [14]. For example, Chi *et al.* [14] reported that temporal lobe tDCS improved participants' memory accuracy. In this study, participants remembered sets of simple objects of varying shapes, sizes, and orientations. Items in each set were related by particular themes (e.g. combinations of small and large circles). In the test phase, items that were related to the studied items (e.g. recombination of features from different studied items), but were not included in the study set, were presented as critical lures. The application of temporal lobe tDCS led to an improvement in participants' discrimination of studied items from critical lures. In this study, it is crucial for participants to encode proper relational information (e.g. a small circle on the left and a right circle on the right) to distinguish studied items from lures (e.g. a small circle on the right and a right circle on the left). Failure in encoding relational memory will lead to falsely remembering critical lures as studied items. Given that memories for relational information are critically dependent on the hippocampus and surrounding structures in MTL (for a review, see the study by Eichenbaum *et al.* [13]), these results seem to suggest that temporal lobe tDCS may modulate MTL functions.

To directly assess pattern separation, items bearing more visual similarities to studied items, instead of recombining features from previous studied items as in Chi *et al.* [14], should be used as lures. Correspondingly, a response option where participants may report lure items as 'similar' to studied items should be included in addition to 'old' and 'new' response options [15]. The stimuli and tasks from Chi *et al.* [14] did not fulfill these requirements, given that experiments in Chi *et al.* [14] were designed to test relational memory and false memory. Therefore, we adopted the Mnemonic Similarity Task (MST; formerly known as the Behavioral Pattern Separation Task-Object Version, Fig. 2) to directly investigate pattern separation for real-world objects [15]. In this task, participants' pattern separation performance is evaluated using the pattern separation index (PSI), calculated as the difference between 'similar' responses on the lure trials and 'similar' responses on the foil trials [15]. This index has been shown to reliably capture individual differences in pattern separation ability across healthy and clinical populations [15].

The present study therefore investigated the effects of bilateral temporal lobe tDCS on pattern separation of real-world objects using the MST task. Assessment of pattern separation with the MST task was performed offline after a 15 min tDCS session. Bilateral stimulation, instead of unilateral stimulation, was chosen because of its effectiveness in polarizing superficial and deep MTL structures on the bases of computational modeling of current flow with tDCS (see the Methods section for details). We thus adopted similar stimulation montage, duration, and current intensity as used in previous studies [14,16]. Although we predict that temporal lobe tDCS will perturb MTL functions, there is no general consensus on which polarity will lead to the strongest effect [14,16]. Therefore, left cathode right anode (L − R +), left anode right cathode (L + R −), and sham conditions are all included and compared using a within-participant design. We hypothesize that bilateral temporal lobe tDCS should modulate pattern separation relative to sham stimulation. Given the difficulties in determining whether these tDCS montages will exert excitatory or inhibitory effects on MTL deep structures without neural imaging data (see the Methods section for details), the current tDCS protocol could lead to an increase or a decrease in pattern separation.

Methods

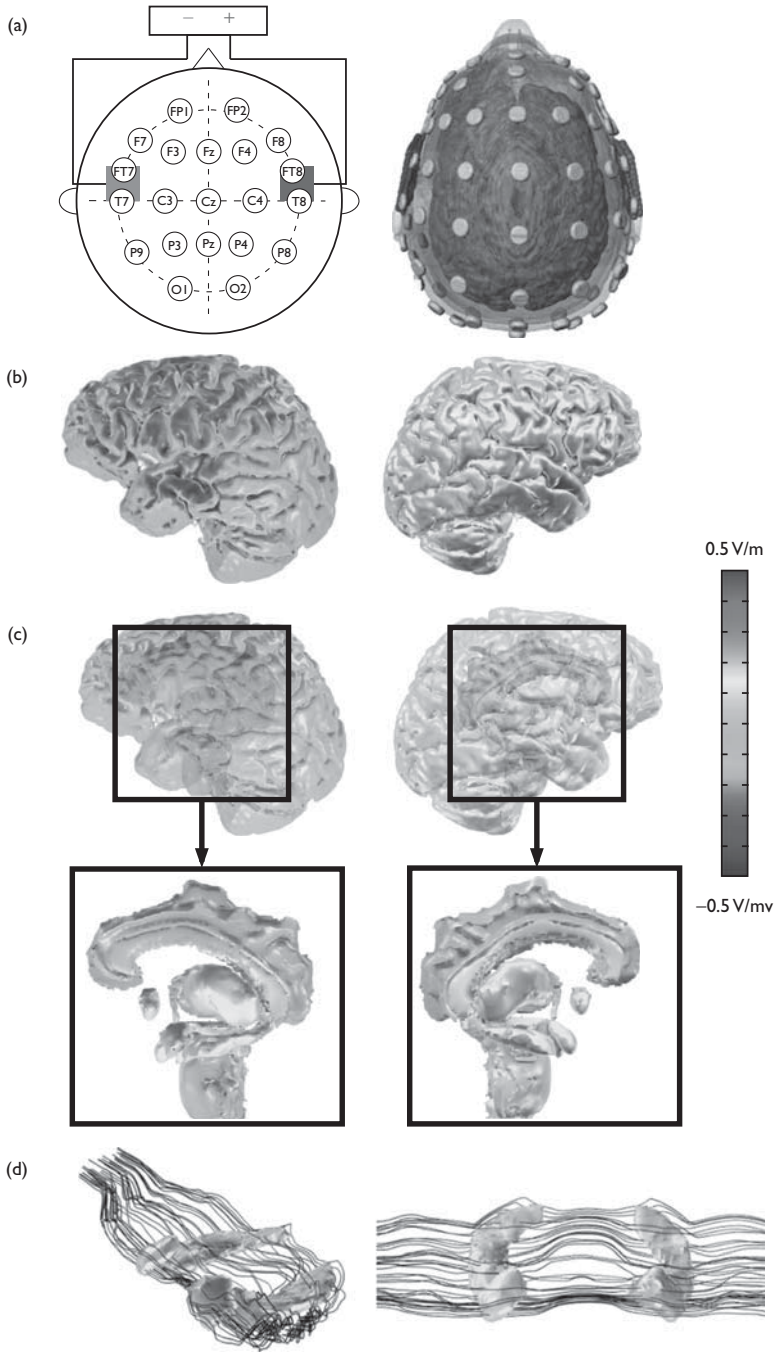
Participants

Twenty volunteers (20.0 ± 1.1 years old, 10 women) participated in the experiment for course credit at the University of California, Riverside. All had normal or corrected-to-normal visual acuity and reported having normal color vision. Informed consent was obtained at the beginning of the experiment.

Transcranial direct current stimulation

Before the study phase of the MST task in each session, participants received either a 15 min bilateral tDCS across the anterior temporal lobes (for L + R − and L − R + conditions) or a 15 s sham stimulation using a neuroConn DC-Stimulator Plus (neuroConn GmbH, Ilmenau, Germany). Stimulation protocols (stimulation montage, duration, and intensity) were modified from Chi *et al.* [14]. Direct current at 1.5 mA was delivered with two 5 × 5 cm saline-soaked surface sponge electrodes (yielding an average electrode current density of 0.06 mA/cm^2). Participants received three bilateral stimulations over the anterior temporal lobes (Fig. 1a) in three sessions separated by at least 1 day. For each session, participants received stimulation under one of three conditions. In the L + R − condition, the anode electrode was placed midway between T7 and FT7 (International 10–20 EEG System) and the cathode electrode was placed midway between T8 and FT8. The polarity of the electrodes was switched for the L − R + condition (the cathode electrode was placed midway between T7 and FT7 and the anode electrode was placed midway between T8 and FT8). In the sham condition, the placement of the electrodes was counterbalanced matching either the L − R + condition or the L + R − condition. The order of the three tDCS conditions was counterbalanced across participants. During stimulation, participants sat quietly for the entire 15 min period (including the sham condition).

Fig. 1



The bilateral temporal lobe tDCS montage (a) and estimated brain electric field amplitude distribution on the surface of the cortex including temporal lobes (b), estimated electric field amplitude distribution within deeper brain structures including the hippocampus (c), and estimated current flow through the hippocampus and amygdala. Only the L−R+ polarity condition is shown for illustrative purposes. (a) Positions of tDCS electrodes are shown for the L−R+ condition on a 10–20 system diagram (left) and a 3D model of a male brain (right). The cathode is placed between T7 and FT7 and the anode is placed between T8 and FT8. Another stimulation condition, L+R−, consisted of the opposite polarity, with the anode placed between T7 and FT7 and the cathode placed between T8 and FT8 (not shown). (b) Predicted current distribution on the temporal cortex for L−R+ condition is broadly distributed and clustered. Bidirectional current bar (−0.5 to 0.5 V/m) shows that currents are dominantly inward (positive) under the anode and outward (negative) under the cathode. The densest condensation of unidirectional peaks is in the temporal lobes. (c) Predicted electrical flow distribution in deep structures, including the hippocampus, transparently plotted beneath temporal lobes (top row) and in isolation with the temporal lobes removed (bottom row). The electrical flow intensity shown represents the unidirectional magnitude of current (0–0.5 V/m). Predicted electrical flow distribution in the hippocampus suggests peaks ~75% of maximum cortical intensity with local clustering. (d) The flux lines represent current flow through the hippocampus and amygdala from a lateral view (left) and a front view (right). tDCS, transcranial direct current stimulation. A color version of this figure can be found at *memory.ucr.edu*.

The Human Research Review Broad of University of California, Riverside approved the tDCS stimulation protocol in the present study. No adverse effects were reported by the participants or observed by the experimenters during or after the stimulation.

Modeling of transcranial direct current stimulation

To show that the current tDCS montage could be effective in delivering stimulation to deep MTL structures, two finite element models simulating bilateral stimulation of the temporal lobes were developed on the basis of previously described protocols [17,18]. A 3D 1 mm isotropic T1 MRI of an adult male was segmented into 20 different head regions using both automated and manual techniques. The electrodes were initially modeled as vertically aligned 5×5 cm saline-soaked surface sponge electrodes in a computer-aided design format and placed midway between FT7 and T7 and midway between FT8 and T8. They were imported into the segmentation model, where a volumetric mesh was then generated.

For both active stimulation conditions, the 20 segmented regions were assigned one of seven possible conductivities: skin, fat, skull, cerebral spinal fluid, gray matter, white matter, or air. For the first active condition, an inward current density of 0.06 mA/cm^2 was applied to the electrode between FT7 and T7 and ground was applied to the return. For the second active condition, an inward current density of 0.06 mA/cm^2 was applied to the electrode between FT8 and T8, with ground applied to the return. The Laplace equation was solved with these conditions using COMSOL Multiphysics 4.3 (COMSOL Inc., Burlington, Massachusetts, USA) to a relative tolerance of 1×10^{-6}. Cortical and deep structure electric field magnitudes and cortical radial electric field were plotted for the resulting solutions of each model (Fig. 1b and c).

As expected, symmetric bilateral stimulation across the head produced a symmetric pattern of current flow intensity (Fig. 1b), primarily in the temporal lobe. The direction of cortical flow depended on proximity to the anode (inward current) or the cathode (outward current) flow [19]. Consistent with previous models of tDCS using pad-electrodes, current flow was distributed across the cortex, but the lateralized montage produced maximal concentration (peak $\sim$0.7 V/m) under the electrodes. Inverting the polarity of stimulation (from L$-$R$+$ to L$+$R$-$) reversed the direction of current flow across the cortex, but did not alter peak intensity in any region because of the linearity of the electric current distribution (not shown).

Significant electrical stimulation was also estimated in both hippocampi (peak $\sim$0.24 V/m) with clustering within the hippocampi (Fig. 1c). Note that whereas cortical current flow was represented as either inward (positive, excitatory) or outward (negative, inhibitory) using a bipolar scale, current flow across the hippocampus was represented as electric field magnitude [19]. With typical tDCS montages, including the one used in the present study, electrical current predominantly flows in the tangential direction (relative to the cortical surface) in the cortex; thus, the polarity of the tangential field can be determined. However, only the intensity of radial current flow, which is perpendicular to the tangential field, can be modeled in deep structures [19]. Consequently, the activation shown in Fig. 1c and d represented the magnitude of the stimulation, ranging from 0 to 0.5 V/m.

Several additional deep structures in the MTLs, including those traditionally considered as parts of the limbic system, such as the amygdala, thalamus, hypothalamus, and basal ganglia, are also being stimulated using the present stimulation parameters (Fig. 1c). However, these structures are not involved in tasks targeting pattern separation as shown in a previous whole-brain neuroimaging study [20]. The present study thus focused on the effects of tDCS on MTL structures that are implicated in pattern separation, specifically the hippocampus.

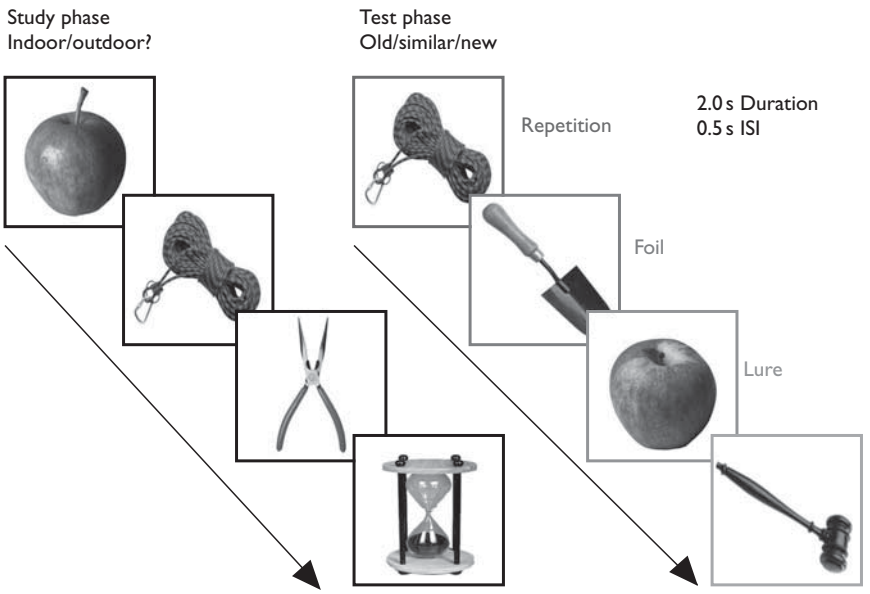
Stimuli

Three separate sets of images of everyday objects (Fig. 2) from the standard MST task [15] were used for three sessions for each participant. The order of the three image sets was counterbalanced across participants. Each image subtended a visual angle of 2.9° to 12.9° in width and 4.0° to 12.8° in height. All stimuli were presented on an LCD monitor (calibrated with an X-Rite I1Pro spectrophotometer; X-Rite, Grand Rapids, Michigan, USA) at a viewing distance of 57 cm using the Psychtoolbox in Matlab (Mathworks; Natick, Massachusetts, USA).

Procedure

Participants came in for three 1 h sessions at least 1 day apart. Following the 15-min offline temporal lobe tDCS at the beginning of each session, electrodes were removed and participants immediately began the MST task. As can be seen in Fig. 2, the MST task consisted of two separate phases administered in immediate succession: a study phase and a test phase. In the study phase, 128 images were sequentially displayed at the center of the screen for 2000 ms per image with a 500 ms interstimulus interval. Participants reported whether the image contained an indoor object or an outdoor object by pressing the 'V' and 'N' buttons on a standard keyboard, respectively. They were allowed up to 2500 ms to make such a response following the presentation of the object. Participants were asked to respond as accurately as possible within the given time window. If the participants were unsure, they were instructed to make the best guess possible and to attempt to provide a response for each image. No performance feedback was provided.

Fig. 2



Task structure of the Behavioral Pattern Separation Task-Object Version. Participants first performed an encoding phase in which they responded 'indoor' or 'outdoor' to a series of images. They were then given a recognition memory test in which they responded 'old','new', or 'similar' to a series of images that were the exact old images from study, novel foils, or lures that were visually similar to the studied images.

In the test phase, 192 images were sequentially displayed at the center of the screen for 2000 ms per image with a 500 ms interstimulus interval. One-third of these images were exact repetitions of images presented in the study phase (targets); one-third of the images were new images not previously seen (foils); and one-third of the images were similar to those seen during the study phase, but not identical (lures). Participants responded to whether they saw the image during the study phase (old), whether the image was similar to one seen in the study phase (similar), or whether the image was not seen in the study phase (new) by pressing the 'V', 'B', and 'N' keys, respectively. Accuracy was stressed as long as participants responded within the appropriate time window (2500 ms). A computer-generated beep was played as feedback when no response was made. On average, the MST task was about 20 min across sessions and participants.

Data analyses

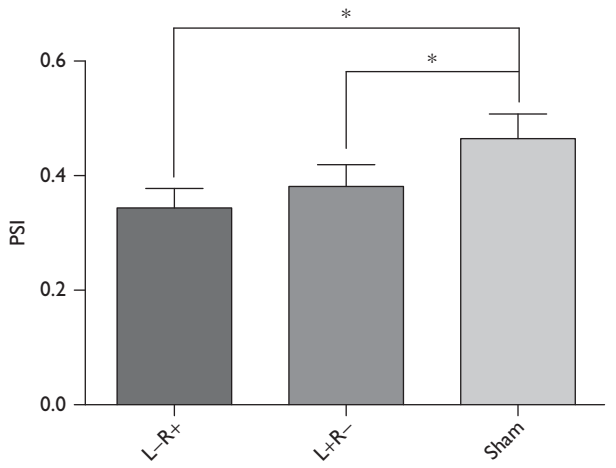
Pattern separation was assessed using the PSI, calculated as the difference between 'similar' responses on the lure trials and 'similar' responses on the foil trials [6], which has also been named the BPS score [15]. A high PSI indicates that participants often respond 'similar' on lure trials, showing a propensity for pattern separation (i.e. the ability to distinguish between the old image and a lure that is similar to the old image).

Results

On the basis of previous literature implicating the hippocampus in pattern separation [2], if the estimated electric current distribution in the hippocampus is large enough, we expect to observe a pattern separation modulation. As shown in Fig. 3, bilateral temporal lobe tDCS indeed reduced pattern separation assessed as PSI, relative to the sham stimulation. Repeated-measures analysis of variance yielded a significant difference in PSI across the three bilateral temporal lobe tDCS stimulation conditions [L − R +: 0.34 ± 0.15 (mean ± SD), L + R −: 0.38 ± 0.17, sham: 0.45 ± 0.19, $F_{(2,38)} = 5.59$, $P = 0.007$, $\eta_p^2 = 0.23$]. Planned comparisons showed significantly lower PSI for the L − R + condition [$t_{(19)} = 2.93$, $P = 0.009$, Cohen's $d = 0.67$] and the L + R − condition [$t_{(19)} = 2.15$, $P = 0.045$, Cohen's $d = 0.49$] compared with the sham condition. No significant difference in PSI was found between the L − R + and the L + R − conditions [$t_{(19)} = 1.25$, $P = 0.23$, Cohen's $d = 0.29$].

No significant difference was found in overall recognition memory accuracy [percent correct: L − R +: $86.9 \pm 10.8\%$, L + R −: $86.7 \pm 8.0\%$, sham: $86.7 \pm 9.2\%$, $F(2,38) = 1.06$, $P = 0.36$, $\eta_p^2 = 0.053$]. Planned comparisons verified that recognition memory accuracy was comparable between the L − R + condition and the sham condition [$t_{(19)} = 1.28$, $P = 0.22$, Cohen's $d = 0.29$], between the L + R − condition and the sham condition [$t_{(19)} = 1.60$, $P = 0.13$, Cohen's $d = 0.37$], and between the L − R + and the L + R − conditions ($t < 1$). Percent endorsed for each stimulus and response type is listed separately for each stimulation condition in Table 1. Taken together, these results suggested that bilateral temporal lobe tDCS

Fig. 3



Pattern separation index (PSI) for each stimulation condition. Error bars represent the SE (*$P < 0.05$).

degraded pattern separation without affecting overall recognition memory accuracy.

Discussion

The present study tested the causal relationship between the temporal lobes, presumably MTLs, and pattern separation with temporal lobe tDCS. We found that bilateral tDCS over the temporal lobes (both L − R + and L + R −) decreased pattern separation performance relative to sham stimulation. Specifically, temporal lobe tDCS decreased participants' ability to correctly identify similar lures as similar to studied items, relative to sham stimulation, even though participants' ability to correctly identify objects as old or new was comparable across the three conditions.

Although the stimulation used in the present study most likely affected temporal lobe tissues directly beneath the electrodes, some remote structures in MTL could also have been affected by temporal lobe tDCS on the basis of the modeling data. These remote MTL structures have been implicated in pattern separation. For example, hippocampal activities for lure and target items seemed to be more distinctive in CA3 and the dentate gyrus of the hippocampus than other sub-regions of the hippocampus [2]. Complementary to previous lesion studies [6], the specific effect of anterior temporal lobe tDCS on pattern separation in the present study thus provided further support for the causal role of the MTL in pattern separation in normal brain. To further establish more exclusive roles of the MTL in pattern separation, an active stimulation over another area (e.g. posterior parietal cortex) could be used as an active control condition to be compared with the anterior temporal lobe tDCS effects from the present study.

Table 1 Mean (SD) percentage of different responses for each experimental condition

		Stimulation conditions (%)		
Stimuli type	Response type	L−R+	L+R−	Sham
Targets	Old	74.9 (13.3)	76.6 (8.8)	80.3 (8.3)
	New	6.2 (3.9)	8.4 (4.0)	7.15 (3.8)
	Similar	16.2 (11.2)	12.6 (6.1)	10.9 (6.4)
Lures	Old	37.8 (10.9)	32.9 (7.5)	25.5 (10.5)
	New	12.3 (9.2)	12.7 (6.4)	16.1 (9.5)
	Similar	46.7 (9.7)	51.8 (8.8)	56.1 (12.5)
Foils	Old	2.5 (1.9)	3.28 (2.5)	3.4 (4.9)
	New	76.3 (11.0)	77.7 (7.3)	83.1 (7.7)
	Similar	12.9 (5.3)	14.4 (5.9)	10.8 (5.2)

Note: No-response trials were not included.

Two primary approaches are typically used in tDCS studies: a combination online/offline approach (continues stimulation into the task) or a purely offline approach (all stimulation occurs before the task). The combination online/offline approach makes it difficult to determine exactly what mechanism is behind any observed effects. Therefore, for the current study, we adopted a pure offline approach; thus, the mechanism behind the decreased pattern separation performance is only because of the after-effects of tDCS. These after-effects have been shown in the human cortex as examined using noninvasive techniques [8]. As for deeper structures, tDCS cannot have substantial effects unless the current penetrates the cortex immediately beneath the stimulation sites and continue through the cortex [9]. As shown in Fig. 1d, the bilateral stimulation in the present study maximizes the likelihood that deep MTL structures, including the hippocampus, are modulated by tDCS.

The offline tDCS protocol combined with the short duration (about 20 min) of the MST memory task in the present study make it possible that both memory encoding and retrieval are affected by tDCS. To isolate encoding effects [21], a sufficiently long delay between the study and the test could be introduced in future studies to ensure that the effects of tDCS wear off before the test starts. To isolate retrieval effects, tDCS could be applied between the study and the test so that memory encoding is not affected by tDCS.

Because of the limited understanding of the neural mechanisms and effects of tDCS, it is difficult to know exactly what anatomical structures the stimulation is affecting and how they are affected on the basis of computational modeling of tDCS effects alone [9]. Therefore, it remains possible that the decreased pattern separation may directly result from the modulation of anterior temporal lobe activities by bilateral tDCS. This alternative interpretation is in line with the functional roles of the anterior portion of the temporal lobe in long-term memory in general [22] and specifically in representing fine-grained details of complex objects [23]. Further research using deep brain stimulation or

combined temporal lobe tDCS and functional neuroimaging is needed to determine a more definitive mechanism behind the observed effects. Nonetheless, the present study has established that it is possible to alter pattern separation function using noninvasive brain stimulation, which may have implications in applied settings such as eyewitness memory.

Previous studies showed that temporal lobe tDCS improved visual memory by reducing false memory [14], which may seem to contradict the current finding of pattern separation impairment. However, these studies used a false memory paradigm in which all items in the memory sets were related to some extent [24]. In this task, a relational scheme across the entire study set has been learned and subsequently affects recognition. Specifically, the presence of the critical lure in the test that is consistent with the relational scheme allows for the provocation of false memories. In sharp contrast, there is no relationship between the memory items presented in the current study using the MST, and the lures are visually similar to one of the studied items. Therefore, performance in this task should be largely determined by item memory, specifically, the participant's ability to distinguish between memory representation of a studied item and a visually similar lure. As associative memory and item memory are dissociable [13], the effects of temporal lobe tDCS on associative memory in the two previous studies [14] and item memory in the current study could also be dissociable. Similar improvements were observed previously in verbal memory using bilateral anterior temporal lobe tDCS [25], supporting the functional role of anterior temporal lobe as the semantic hub. Given the current study's focus on visual memory and MTL, it is not straightforward to make direct comparisons between those previous studies on verbal memory and the present study. Further research is needed to understand the relationship between these effects of anterior temporal lobe tDCS on memory across paradigms and modalities.

Conclusion

The present study showed that pattern separation, an essential mnemonic process that was indexed by PSI in the MST task, decreased in the L − R + and L + R − temporal lobe tDCS conditions relative to the sham condition, adding to the growing literature on the modulation of memory functions using noninvasive brain stimulation.

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Conflicts of interest

There are no conflicts of interest.

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