Report

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Spatiotemporal Neural Pattern Similarity Supports Episodic Memory

Highlights

- EEG STPS during encoding predicted later memory
- Item-specific STPS occurred around 500 ms after stimulus onset
- LPFC anodal tDCS enhanced subsequent memory and item-specific STPS

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In Brief

Using EEG and tDCS, Lu et al. examined the neural mechanisms of memory formation. They found that greater item-specific STPS during encoding predicted better later memory. Anodal tDCS over the left LPFC specifically enhanced STPS and memory.

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Report

Spatiotemporal Neural Pattern Similarity Supports Episodic Memory

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Summary

Formal computational models of human memory posit a central role of feature representations in episodic memory encoding and retrieval [1–4]. Correspondingly, fMRI studies have found that, in addition to activity level [5, 6], the neural activation pattern similarity across repetitions (i.e., self-similarity) was greater for subsequently remembered than forgotten items [7–9]. This self-similarity has been suggested to reflect pattern reinstatement due to study-phase retrieval [7, 10, 11]. However, the low temporal resolution of fMRI measures could determine neither the temporal precision of study-phase reinstatement nor the processing stage at which the reinstatement supported subsequent memory [12]. Meanwhile, although self-similarity has been shown to correlate with the activity level in the left lateral prefrontal cortex (LPFC) [10, 13], a causal link between left LPFC function and pattern similarity remains to be established. Combining transcranial direct current stimulation (tDCS) and EEG, we found that greater spatiotemporal pattern similarity (STPS) across repetitions of the same item (i.e., self-STPS) during encoding predicted better subsequent memory. The self-STPS located in the right frontal electrodes occurred approximately 500 ms after stimulus onset, reflected item-specific encoding, and contributed to memory above and beyond the effects of ERP amplitude and global pattern similarity (i.e., similarity to all other items in memory space). Anodal stimulation over the left LPFC specifically enhanced memory performance and item-specific STPS in the right frontal electrodes. These results support a causal role of LPFC in enhancing STPS and memory and contribute to a mechanistic understanding of memory formation.

Results

Previous fMRI research has shown that neural activation pattern similarity during encoding predicted subsequent memory [7–9, 13–15]. However, due to its limited temporal resolution, fMRI data cannot pinpoint the time point during encoding when neural activation pattern similarity starts to matter. Moreover, no experimental manipulation of pattern similarity has been used to establish its causal role in subsequent memory. These issues were addressed in the current study by combining electroencephalography (EEG) and transcranial direct current stimulation (tDCS).

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We recorded EEG while 20 participants were studying the visual forms of 120 novel visual symbols (i.e., Korean Hangul characters), using a visual structure judgment task (Figure 1A). Each character was repeated three times, with an inter-repetition-interval (IRI) of 4–7 trials. Their recognition memory was probed 1 day later using a six-point old or new judgment task (Figure 1B). Participants finished two sessions of the same task (1 week apart): once after 20 min anodal tDCS over the left lateral prefrontal cortex (LPFC) and once after sham stimulation (Figure 1C). The order of the two sessions was counterbalanced across participants. We targeted the left LPFC because it has been consistently implicated in memory encoding [5, 10, 16, 17], including evidence from tDCS studies [18, 19], and because this region's activity is positively correlated with neural activation pattern similarity in the posterior regions [10, 13].

Anodal tDCS Selectively Enhanced Memory Performance

Memory performance was indexed by the hit rate and d′. Because participants finished two sessions of the task, we first confirmed that there was no significant practice effect in memory performance for either the hit rate ($t(19) = 0.16$, $p = 0.87$) or d′ ($t(19) = 0.33$, $p = 0.75$). Compared to sham stimulation, anodal tDCS over the LPFC significantly increased the number of remembered items (scored 4 and above) ($t(19) = 3.63$, $p = 0.002$) and d′ ($t(19) = 2.28$, $p = 0.03$) (Figure 1D). There was no difference in false alarm (FA) rate ($t(19) = -0.57$, $p = 0.57$). Further examination of the confidence distribution indicated that the tDCS effect on memory performance was achieved by a shift from misses to hits (Table S1), but not by an increase from low to high confidence.

We also examined behavioral performance during encoding where subjects were asked to judge the visual structure (left-right versus top-bottom) of the characters. Two-way (stimulation by repetition) ANOVA revealed no significant interaction for either reaction time ($F(2,38) = 1.15$, $p = 0.33$) or accuracy ($F(2,38) = 0.48$, $p = 0.62$). Across repetitions, the reaction time decreased ($F(2,38) = 62.86$, $p < 0.001$) and accuracy increased ($F(2,38) = 3.43$, $p = 0.043$), but tDCS did not affect the reaction time ($F(1,19) = 0.03$, $p = 0.871$) or accuracy ($F(1,19) = 0.06$, $p = 0.807$) (Figures 1E and 1F). Together, these results demonstrate that anodal tDCS selectively enhanced subsequent memory without affecting behavioral performance during encoding.

Subsequently Remembered Items Showed Greater Item-Specific STPS

We hypothesized that subsequently remembered items would show greater spatiotemporal pattern similarity (STPS) across the three repetitions (i.e., self-STPS) [7]. The self-STPS reflects the distinctiveness and reproducibility of item-specific encoding. It is calculated for single-trial EEG epochs following Kriegeskorte et al. [20] (Figure S1 and Supplemental Experimental Procedures). To improve STPS's spatial resolution, we divided the 64 electrodes into six regions (Figure 2A). Within each region, the EEG responses from all channels within 100 ms sliding windows (with a step size of one sampling point) were chosen as features. Several temporal clusters in the late time window showed greater self-STPS for remembered items than for forgotten items (Figure 2B). Two temporal clusters,

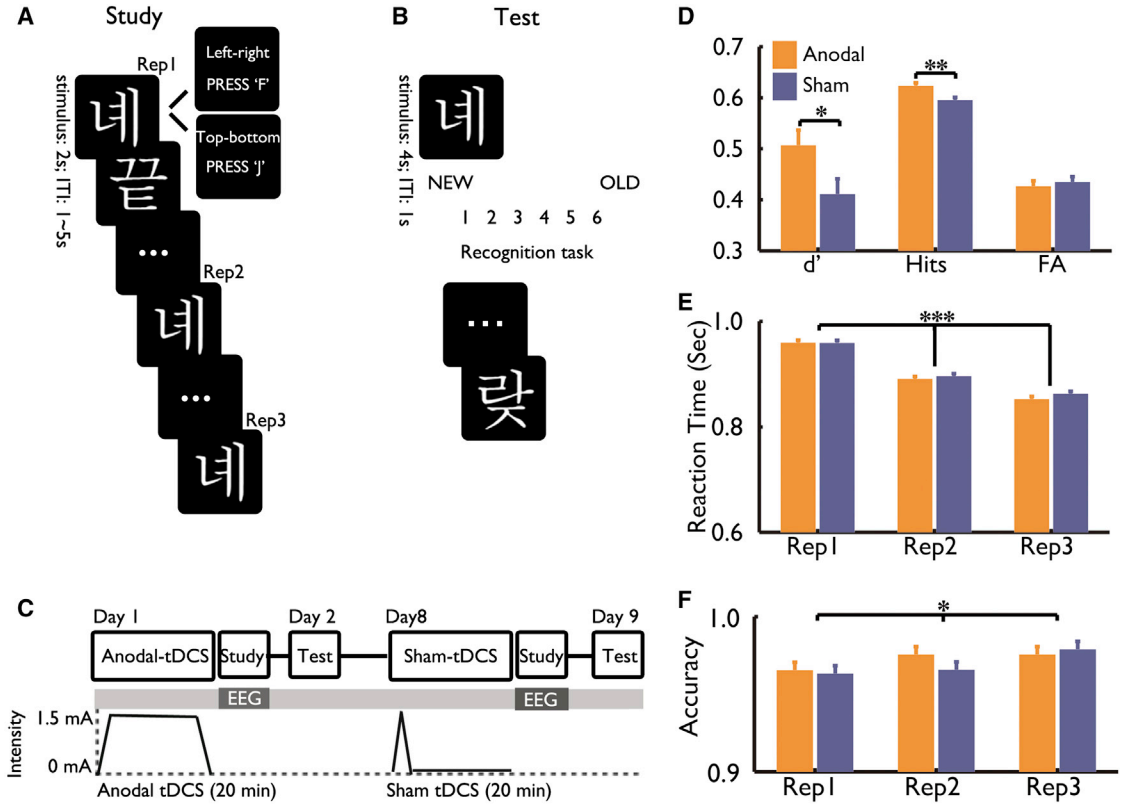

Figure 1. Experimental Paradigm and Behavioral Results

(A) The memory encoding task. Each of the 120 novel Hangul characters was presented three times with an IRI of 4–7 trials. Participants were asked to memorize each character and perform a visual structure (left-right or top- bottom) judgment task.

(B) The recognition test. Participants were asked to decide whether they recognized each character on a six-point scale, with 1 indicating "definitely new" and 6 indicating "definitely old."

(C) The tDCS procedure. Participants completed the tasks under two conditions (anodal tDCS and sham), separated by 5–7 days.

(D) The effect of LPFC anodal tDCS on subsequent memory performance.

(E and F) Accuracy (E) and reaction time (F) during memory encoding as a function of stimulation condition and repetition.

Error bars represent within-subject SE. **$p < 0.01$; *$p < 0.05$.

one in the right frontal region (region 2, 500–656 ms: $t(19) = 3.34$, $p = 0.003$; corrected $p = 0.036$), and the other in the left posterior region (region 5, 547–684 ms: $t(19) = 3.72$, $p = 0.002$; corrected $p = 0.056$), survived cluster-based multiple comparison correction (see Supplemental Experimental Procedures) (Figures 2C–2F), whereas the other two clusters did not (all $p > 0.195$).

This STPS's item specificity was supported by a significant interaction between subsequent memory and item specificity in the right frontal region (547–668 ms: $F(1,19) = 10.468$, $p = 0.004$; corrected $p = 0.029$) (Figures 2C and 2D). Post hoc t tests showed significantly greater within-item than between-item STPS for remembered items ($t(1,19) = 2.08$, $p = 0.05$) but greater between-item STPS than within-item STPS for forgotten items ($t(1,19) = 2.16$, $p = 0.04$), suggesting that only subsequently remembered items showed item-specific STPS during repeated learning.

Self-STPS Did Not Reflect Contextual Drift

The computational models of memory often assume a slow drift of internal context, which can explain many observations in memory, such as the spacing effect [21] and the temporal clustering effect [4, 22]. We found that the IRI during learning was comparable for subsequently remembered and forgotten items under both the anodal ($t(19) = -1.61$, $p = 0.12$) and sham ($t(19) = -0.88$, $p = 0.39$) conditions (Figure S2A), suggesting our results were not due to the spacing effect. Furthermore, we examined whether the recognized items were temporally clustered by comparing the average distance (in terms of the number of intervening items during the learning stage) between remembered items with the average distance between remembered and forgotten items [23]. This analysis revealed no evidence of temporal clustering for either anodal ($t(19) = -0.79$, $p = 0.44$) or sham ($t(19) = -0.71$, $p = 0.48$) condition (Figure S2B). It should be noted that since the current study used a recognition test and the sequence of old and new items were randomly mixed, it did not have enough statistical power to take the sequence of test order into consideration and to calculate the conditional response probability (CRP) as a function of lag (i.e., lag-CRP) [23].

We then examined whether the spatiotemporal responses also carried contextual information. If they did, the between-trial STPS would show a decline with increasing lag [24, 25]. We found no lag effect for between-item STPS in the two regions showing the subsequent memory effect (Figures S2C and S2D). Together, our analysis revealed no evidence that contextual drift contributed to STPS or subsequent memory (See Supplemental Discussion).

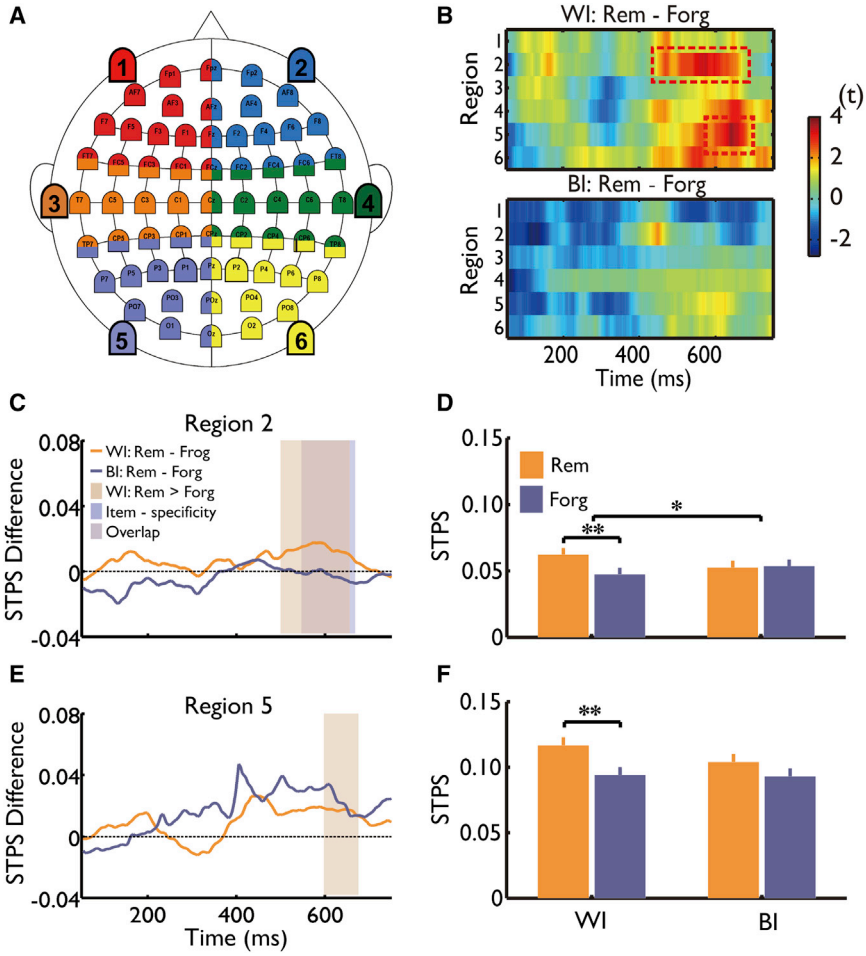

Figure 2. Self-STPS Predicted Subsequent Memory

(A) The 64 electrodes were grouped into six regions. To obtain more stable spatial patterns, we included the electrodes in the border of two regions in both regions.

(B) The statistics of the subsequent memory effect based on within-item (WI) STPS (top) and the between-item (BI) STPS (bottom). The x axis represents time, and the y axis represents the spatial locations.

(C) Plot of STPS differences, as a function of time and subsequent memory (remembered versus forgotten items) in Region 2. The shaded areas mark the temporal clusters showing significant effects after correction for multiple comparisons using cluster-based permutation.

(D) Bar graph of mean pattern similarity in the corresponding temporal cluster in Region 2, as a function of subsequent memory, separately for within-item and between-item STPS.

(E) Plot of STPS differences, as a function of time and subsequent memory (remembered versus forgotten items) in Region 5.

(F) Bar graph of mean pattern similarity in the corresponding temporal cluster in Region 5.

Error bars represent within-subject SE. **p < 0.01; *p < 0.05.

Controlling Signal Amplitude and Feature-Level and Trial-Level Variability

The above analyses suggested that subsequently remembered items showed greater item-specific STPS. Meanwhile, we also found a significant univariate effect in the event-related potential (ERP) amplitude (Supplemental Results). Although the Pearson correlation coefficients we used to calculate STPS were insensitive to the absolute amplitude and variance of the EEG response, existing simulation work suggests that feature-level (within-trial) variability, trial-level (cross-trial) variability [26], and mean signal amplitude [14] could all affect the pattern similarity estimation. Several control analyses were thus conducted, and the results confirmed that our conclusions were not affected by these factors (Supplemental Results and Figure S3).

Anodal tDCS Enhanced Item-Specific STPS

To test our hypothesis that LPFC tDCS could enhance item-specific STPS, we compared the self-STPS between anodal and sham stimulation for each of the six regions (Figure 3A). This analysis revealed that the right frontal region showed greater self-STPS under the anodal than under the sham stimulation condition in the 414–750 ms time window ($F(1,19) = 11.37$, $p = 0.003$; corrected $p = 0.015$) (Figure 3C). It is worth noting that this spatiotemporal cluster completely covered the cluster that showed the subsequent memory effect (500–656 ms). Furthermore, there was a significant interaction between tDCS condition and item specificity in the 480–656-ms time window ($F(1,19) = 16.24$, $p < 0.001$; corrected $p = 0.024$), suggesting that anodal tDCS significantly enhanced the self-STPS ($F(1,19) = 11.37$, $p < 0.001$), but not the between-item STPS ($F(1,19) = 2.02$, $p = 0.17$) (Figure 3D). A 480–601-ms temporal window in the right posterior region also showed a tDCS effect ($F(1,19) = 6.07$, $p = 0.023$), but this effect was not significant after correction ($p = 0.21$).

TDCS also enhanced univariate ERP amplitude (Supplemental Results) but did not affect the feature-level or trial-level variability in the regions showing significant tDCS effects on self-STPS (Figure S3). Simulation results confirmed that the tDCS effects were not due to differences in feature-level or trial-level variability (Figure S3). Linear mixed-effect model revealed that after controlling for the ERP amplitude, the tDCS effect on self-STPS in the right frontal region remained significant ($p = 0.001$).

Subsequent Memory Was Associated with Greater Global STPS

Existing computational models and fMRI studies suggest that self-similarity and global similarity might reflect different cognitive and neural processes related to subsequent memory [14, 15]. The global similarity reflects how similar the mental representation of one item is to those of other items in the memory space. To calculate the neural global STPS, we first averaged the EEG responses for each item across three repetitions. Global STPS was obtained by averaging the z-transformed similarity index (from Pearson correlation coefficients) with all other studied items [14]. Two posterior regions showed higher global STPS for subsequently remembered items than forgotten items (Figure 4A). The right occipital region survived the multiple comparison correction (422–582 ms, $t(19) = 2.902$,

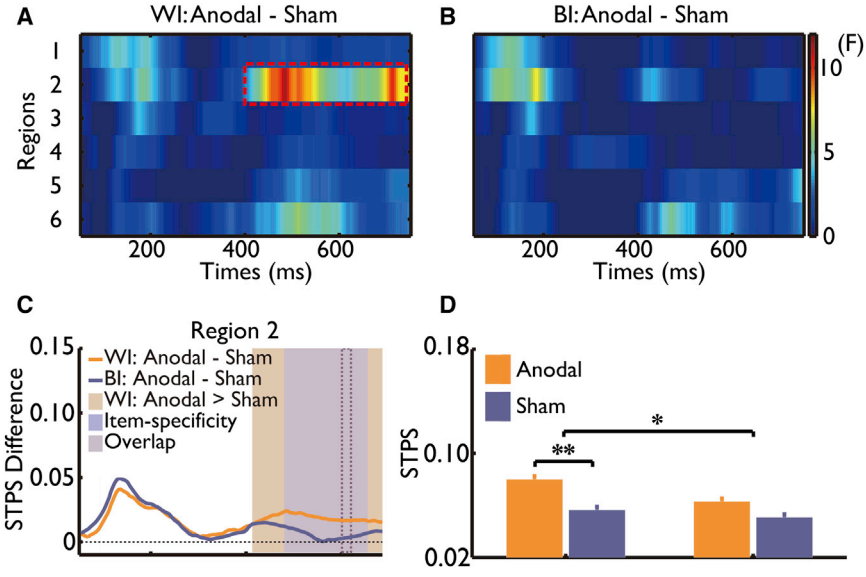

Figure 3. TDCS Effect on Self-STPS

(A) The statistics of the tDCS effect on within-item (WI) STPS.

(B) The statistics of the tDCS effect on between-item (BI) STPS.

(C) STPS differences as a function of time and stimulation condition (anodal versus sham stimulation), in Region 2.

(D) Mean STPS in the corresponding temporal clusters as a function of stimulation condition, separately for within-item and between-item STPS. Error bars represent within-subject SE. **p < 0.01; *p < 0.05. See Figure 2 for spatial location of the right frontal region.

p = 0.009; corrected p = 0.027) (Figures 4C and 4D), whereas the left occipital region did not (504–586 ms, t(19) = 3.367, p = 0.003; corrected p = 0.097). Linear mixed-effect model revealed that after controlling for the EEG amplitude, the effect remained marginally significant (p = 0.06) in the right occipital region.

As both self-STPS and global STPS contributed to subsequent memory, we also examined their unique contributions using the linear mixed-effect model. Results showed that self-STPS in the right frontal region (p = 0.015) and global STPS in the right occipital region (p = 0.078), which showed a robust subsequent memory effect after controlling for the EEG amplitude, remained significant after controlling for each other, suggesting they had independent effects on subsequent memory.

Anodal stimulation only had a marginally significant effect on global STPS, which was found in the right posterior region in the time window of 433–543 ms (F(1,19) = 7.145, p = 0.015; corrected p = 0.079) (Figures 4B and 4D). However, after controlling for the EEG amplitude, this effect was no longer significant (p = 0.17). Together, our results showed that self-STPS played a unique role in successful memory encoding and that tDCS over the left LPFC mainly enhanced self-STPS.

Control Experiment: The tDCS Effect Was Specific to LPFC

We did a control experiment to examine whether the tDCS effect was region specific. Since the encoding task required detailed visual analysis, we stimulated the posterior visual cortex to examine whether it could also enhance memory performance and pattern similarity. Seventeen additional subjects were recruited to perform the same experimental task, once under anodal stimulation and once under sham stimulation. We found that anodal tDCS, as compared to sham, significantly improved the accuracy (F(1,16) = 4.77, p = 0.04) during visual structure judgment (Figure S4A). Nevertheless, it did not change the reaction time (F(1,16) = 0.37, p = 0.55) (Figure S4B) or the memory performance as measured by the number of correct hits (t(16) = 1.01, p = 0.33) or d′ (t(16) = 0.41, p = 0.69)(Figure S4C).

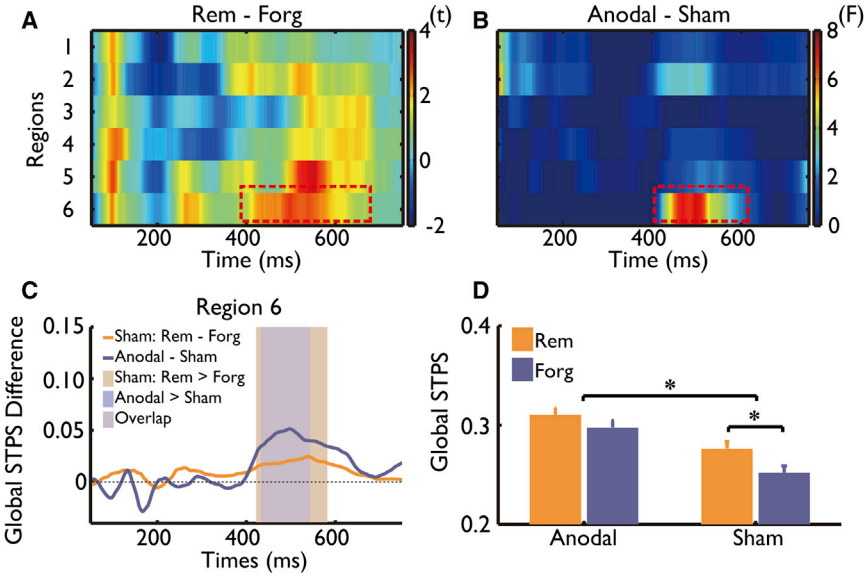

Figure 4. Global STPS and Subsequent Memory

(A) The statistics of the subsequent memory effect on global STPS.

(B) The statistics of the tDCS effect on global STPS.

(C) Global STPS differences as a function of time, subsequent memory, and stimulation condition in Region 6.

(D) Mean global STPS in the corresponding temporal clusters as a function of subsequent memory and stimulation condition. Error bars represent within-subject SE. **p < 0.01; *p < 0.05. See Figure 2 for spatial location of the right occipital region.

Consistently with our main experiment, EEG data indicated that two temporal clusters in the right frontal electrodes, one between 238 and 496 ms ($F(1,16) = 13.83$, $p = 0.004$; corrected $p = 0.04$) and the other between 527 and 746 ms ($F(1,16) = 8.66$, $p = 0.01$; corrected $p = 0.05$), showed greater STPS for subsequently remembered than forgotten items (Figures S4D–S4F). Notably, the temporal window of the second cluster showed much overlap with the cluster found in the main experiment. Again, STPS in the second cluster only reflected item-specific encoding as indicated by the significant subsequent memory by item specificity interaction ($F(1,16) = 5.46$, $p = 0.03$) (Figure S4F). Further analysis suggested that only remembered items showed greater within-item than between-item similarity ($F(1,16) = 11.45$, $p = 0.004$), whereas forgotten items did not ($F(1,16) = 0.08$, $p = 0.78$). Nevertheless, there was no significant main effect of tDCS ($F(1,16) = 1.23$, $p = 0.28$) or tDCS by subsequent memory interaction ($F(1,16) = 2.75$, $p = 0.12$) in this time window. If anything, we found that stimulation over the visual cortex slightly reduced STPS in the early time window ($F(1,16) = 5.96$, $p = 0.03$; corrected $p = 0.11$) (Figures S4G–S4I).

Discussion

Combining EEG with noninvasive brain stimulations via tDCS, the present study examined (1) the STPS's contributions to subsequent memory and (2) the LPFC's role in enhancing STPS and memory. Using representational similarity analysis on features from distributed electrodes and extended time windows, the current study replicated and extended the previous observation [27, 28] that the amplitude of neurophysiologic responses reflects item-specific encoding. Importantly, the STPS that contributed to successful memory encoding occurred at approximately 500 ms post-stimulus, most reliably in the right frontal scalp. This component was unlikely to be related to semantic processing [29], as the novel Korean characters contained no explicit semantics to the participants, and the latency was obviously later than the typical N400 component that peaks at around 350 ms. Instead, it has been consistently linked to memory retrieval in the literature [30]. Moreover, it could index memory reinstatement as this response differed according to the prior encoding history of the same stimuli [31–33].

The above finding suggests that one important source of the item-level STPS is the reactivation or reinstatement of existing memory trace, i.e., study-phase retrieval. Behavioral and computational studies have consistently suggested that during repeated studies, subsequent study episode serves as a retrieval cue to reactivate and strengthen the memory representation of the information stored during earlier study episodes [34, 35]. Imaging studies suggest that this study-phase retrieval is accompanied by the reactivation of early neural activation pattern [10, 11] that is similar to pattern reinstatement during recall [36, 37] or recognition [38].

The tDCS results showed a causal relationship between left LPFC activity and STPS. The left LPFC supports goal-directed top-down attentional control [39], and left LPFC stimulation can enhance selective attention [40] and reduce the vigilance decrement over time [41]. This improved attentional control can enhance task-relevant feature representations [42], leading to greater pattern similarity across repetitions [43]. In addition, due to the dense anatomical connectivity between the prefrontal cortex (PFC) and medial temporal lobe (MTL) [44], anodal tDCS can enhance their functional connectivity [45], resulting in stronger pattern reinstatement and thus greater pattern similarity [7, 9].

Although fMRI studies have often reported reinstatement in the posterior regions associated with perception, the current study, together with several previous ERP studies have consistently found reinstatement over the right anterior scalp [31–33]. Interestingly, we found that tDCS over the left LPFC enhanced the STPS in the right frontal electrodes. This functional asymmetry appears to be consistent with the hemispheric encoding/retrieval asymmetry (HERA) model [17], which posits that the left PFC regions are critically engaged in memory encoding, whereas the right PFC regions are involved in memory retrieval. Nevertheless, due to the poor spatial resolution and the methodological challenges in accurate source localization, the source of the EEG effect requires further examination (Supplemental Discussion).

Taken together, our results suggest that greater STPS during repeated study underlies successful memory encoding, probably by creating unique yet consistent inputs to the hippocampus, which facilitates pattern separation and avoids interference in later retrieval [46]. This STPS is partially contributed by study-phase retrieval in the late time window and can be enhanced by increasing the prefrontal cortex function via tDCS. These results help to deepen our understanding of the role of neural activation pattern similarity in memory formation. Future studies should examine whether and how other types of information, including context, can affect pattern similarity and memory (Supplemental Discussion).

Supplemental Information

Supplemental Information includes Supplemental Results, Supplemental Discussion, Supplemental Experimental Procedures, four figures, and one table and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.01.055.

Author Contributions

Y.L. and G.X. designed the experiment. Y.L. performed the experiment. Y.L., C.W., and G.X. analyzed the data. Y.L., C.C., and G.X. wrote the manuscript.

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Current Biology

Supplemental Information

Spatiotemporal Neural Pattern Similarity Supports Episodic Memory

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Supplementary Information for

Spatiotemporal neural pattern similarity supports episodic memory

Figures S1-S4

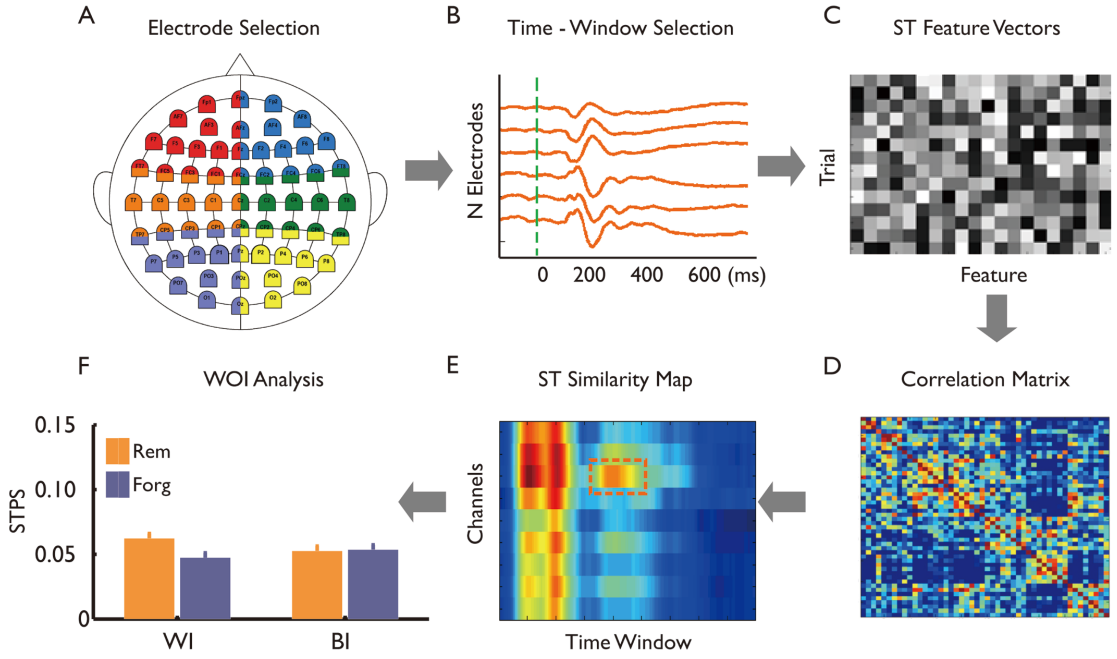

Figure S1. Data analysis pipeline (related to Figures 2, 3 and 4). Diagram of the spatiotemporal pattern similarity analysis. (A) Selection of spatial locations, which could include either all 64 electrodes or electrodes in one of the 6 regions of interest for better spatial specificity. (B) Selection of the temporal window, which was defined as a 100ms sliding window. (C) Vectorization, which converts the spatiotemporal features of a given trial into a vector. (D) Correlation, which calculates the pattern similarity (Pearson correlation) across trials. (E) Statistical analysis, which compares the pattern similarity across different conditions and generates a statistical map. (F) Window of interest (WOI) analysis, which extracts and analyzes the averaged STPS from certain spatiotemporal windows.

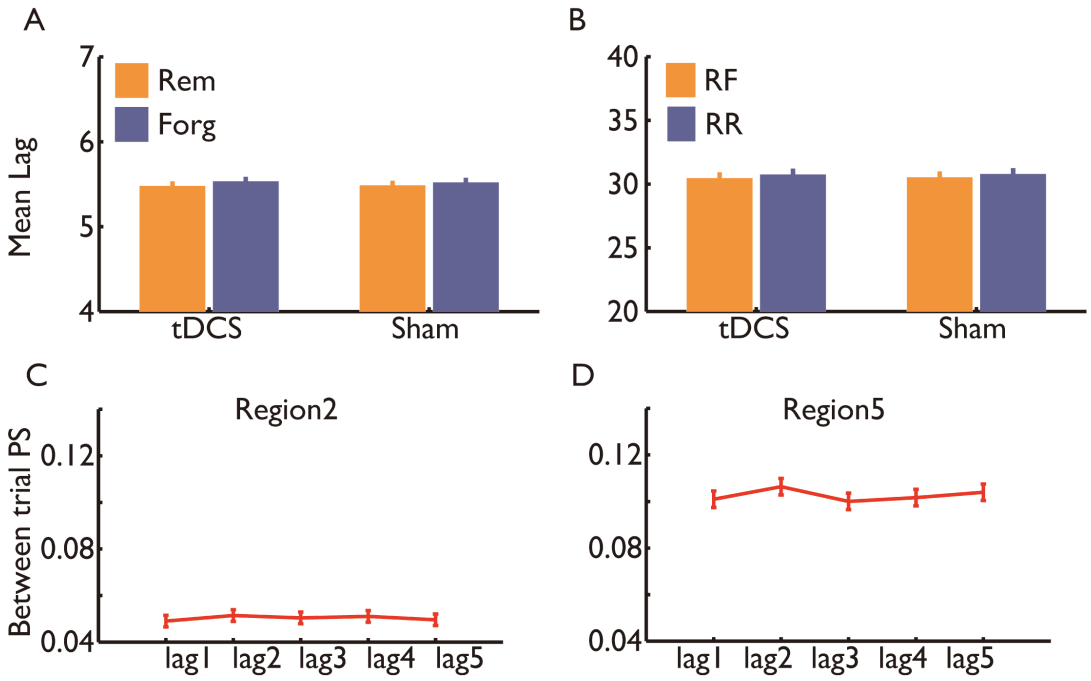

Figure S2. Temporal cluster and the lag effect (related to Figures 1, 2 and 3). (A)The averaged inter-repetition-interval (IRI) or lag for subsequently remembered and forgotten items, separately plotted for the tDCS and sham conditions. (B) The mean lag between remembered items (RR) and that between remembered items and forgotten items (RF), for the tDCS and sham conditions. As each item was repeated 3 times, forming 9 pairs for any two given items, the smallest lag of the 9 pairs was used for this calculation. The absence of significant differences suggests that there was no temporal clustering in the recognition performance. Error bars represent within-subject standard error. C-D show the between-trial STPS as a function of lag in Region 2 and Region 5 respectively. Error bars represent within-subject standard error. The absence of a lag effect suggested that the spatiotemporal pattern carried no information of neighboring items.

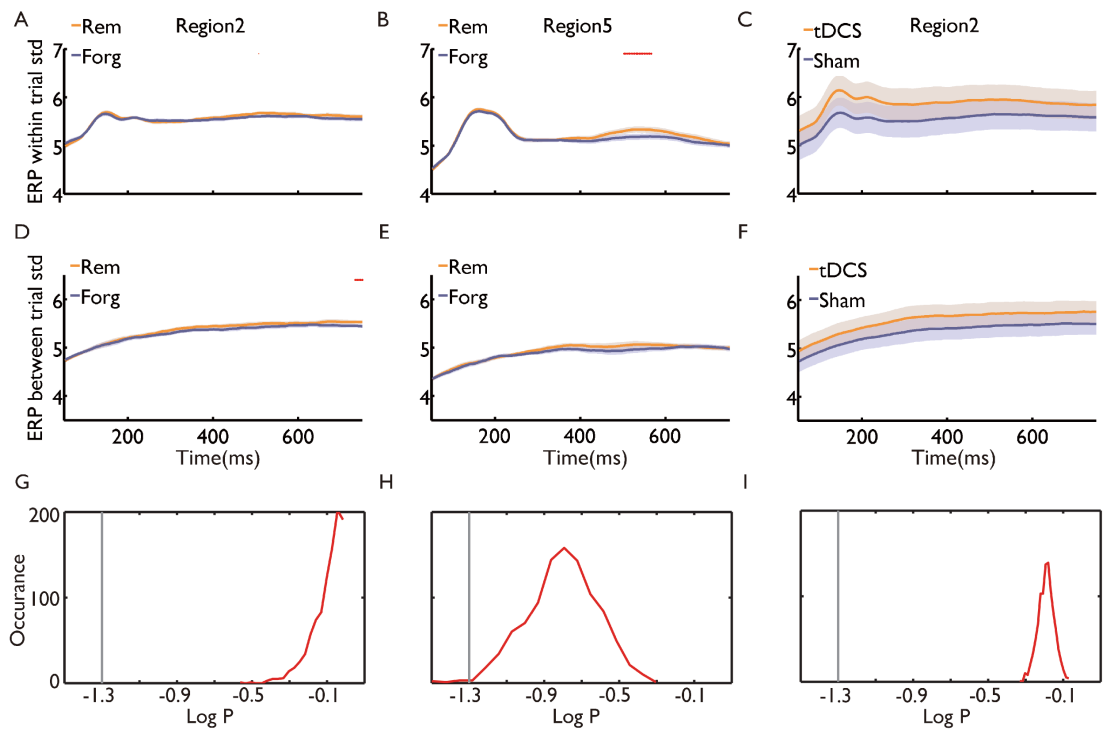

Figure S3. Controlling feature- and item-level variability (related to Figures 2 & 3). The top row shows the plots of the feature-level variability for subsequently remembered (Rem) and forgotten (Forg) items in the two regions showing the subsequent memory effect (A, B) and for anodal and sham stimulation in Region 2 showing the tDCS effect (C). The middle row shows the plots of the trial-level variability for subsequently remembered (Rem) and forgotten (Forg) items in the same regions showing the subsequent memory effect and tDCS effect. The line shows the mean SRN and the shade indicates the standard error. The red dots on the top indicate significant differences ($p < .05$) between the two conditions. The bottom row shows the distributions of the log transformed p values of 1000 simulations comparing pattern similarity for subsequently remembered (Rem) and forgotten (Forg) items. The simulation used estimated feature-level and trial-level variability above. The simulation result was mostly on the right side of the grey line, indicating a p value larger than .05. This suggests that the differences in feature- and trial-level variability could not have contributed to significant

differences in self-STPS.

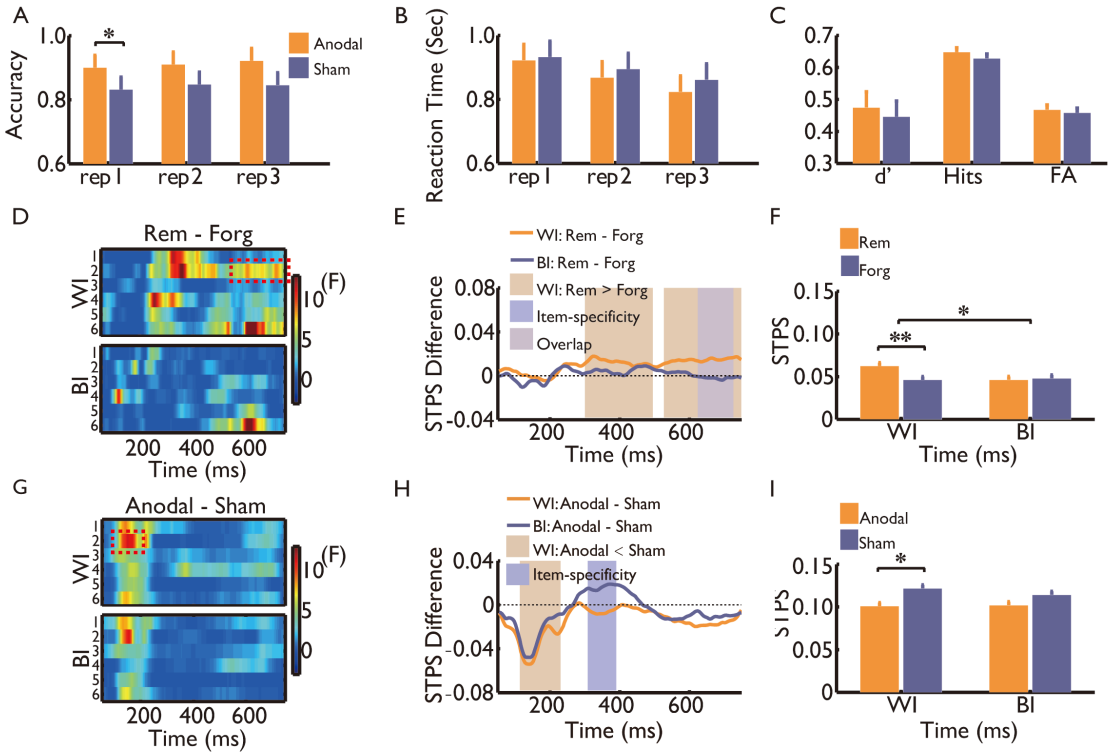

Fig S4. The control experiment (related to Figures 1, 2 & 3). (A) Accuracy and (B) Reaction time during memory encoding as a function of stimulation condition (V1 anodal stimulation or sham stimulation) and repetition. (C) The effect of anodal tDCS on subsequent memory performance. (D) The statistics of the subsequent memory effect based on within-item (WI) STPS (top panel) and the between-item (BI) STPS (bottom panel). The x-axis represents time and the y-axis represents the spatial locations. (E) Plot of STPS differences between remembered vs. forgotten items in Region 2, as a function of time and subsequent memory and item-specificity. The shaded areas mark the temporal clusters showing significant effects after correction for multiple comparisons using cluster-based permutation. (F) Bar graph of mean pattern similarity in the corresponding temporal cluster in Region 2, as a function of subsequent memory. Error bars represent within-subject standard error. G, H, and I show results for the tDCS effect.

Table S1. Distribution of confidence level in recognition test (Mean ± S.E.) (Related to Figure 1)

Confidence		1	2	3	4	5	6
Old	Anodal	3.9±1.2	14.0±1.6	18.7±2.5	24.6±2.6	24.7±1.6	13.0±2.8
	Sham	4.4±1.5	16.6±2.1	18.1±2.6	24.6±3.0	23.1±2.3	11.9±2.3
New	Anodal	10.8±2.6	22.3±1.8	22.6±3.1	20.8±2.1	16.1±1.4	5.8±1.4
	Sham	11.4±2.7	23.2±2.4	20.3±3.2	21.1±2.5	16.1±2.0	6.3±1.7

Supplementary Experimental Procedures

Participants

Twenty healthy college students (7 males, 20.6 ± 1.3 years), and another 17 students (7 males, 19.9 ± 1.7 years), completed the main experiment and control experiment, respectively. All participants were right-handed, had normal or corrected-to-normal vision, and had no history of neurological or psychiatric diseases. They were all native Chinese speakers with no experience of Korean language. Informed written consent was obtained before the study. The study was approved by the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University.

Experimental materials

Four hundred and eighty Korean Hangul characters were used in this study. They were divided into four groups matched by the number of strokes (2 to 14), number of units (2 to 4), and spatial structures (left-right vs. top-bottom) (Figure 1). Characters were in 170*170 pixel size and presented in the center of the computer screen.

Orthographic memory task

The behavioral task was programmed with Psychtoolbox 3

(http://psychtoolbox.org) and administered on an IBM-compatible computer. The computer resolution was set to 1024 * 1680 and vertical refreshing rate was 60 Hz. In each session, participants were asked to memorize the visual forms of 120 Korean characters, which would be tested one day after learning. To help with memory encoding, they were asked to pay attention to the characters and make judgment on the visual structure, that is, whether each character had a left-right structure or a top- bottom structure (Figure 1A). Each character was presented three times, with an inter-repetition-interval of 4-7 trials.

The recognition test was conducted 24 hours after the study phase. The 120 studied characters and 120 new Korean characters (used as foils) were pseudorandomly mixed. Participants were asked to decide whether they recognized each character on a 6-point scale, with 1 = “definitely new” and 6 = “definitely old” (Figure 1B). The materials used for the two conditions (anodal and sham stimulation) were counterbalanced across participants.

TDCS Procedure

Each participant completed both the anodal tDCS and the sham conditions, separated by 5 to 7 days between the conditions. The order of the conditions was counterbalanced across participants. For the main experiment, a pair of electrodes housed in the 5×5 cm saline-soaked sponge coverings were separately placed over the left inferior frontal gyrus (FC5 in the international 10/20 system) and the contralateral orbitofrontal cortex. For the control experimental, the stimulation site was the visual cortex (Oz in the international 10/20 system). For both experiments, the anodal condition applied 20 min (15 sec ramping up, 15 sec ramping down) current with an intensity of 1.5 mA, or 0.06 mA/cm^2. The total charge in the anodal condition was 0.072 C/cm^2. Both the intensity and total charge in the experiment were substantially below the safety criteria of 25 mA/cm^2 for density and 216 C/cm^2 for total charge [S1]. During sham stimulation, the current was applied with 15 sec of current ramping up and ramping down. The sham tDCS condition could elicit the same sensation as real

stimulation but no real stimulation, thus served as an appropriate control condition. All participants were tDCS naïve and were not aware of the effect of tDCS stimulation. After the experiment, we interviewed every participant whether they felt anything different between the two stimulation conditions, and none of them reported any noticeable differences. Finally, for the control experiment, subjects were also given a forced choice test as to which session was the actual stimulation, the results indicated that they could not tell the difference between real and sham stimulation (Chi^2 =1.63, p = .20).

EEG Recording

EEG data were collected during the encoding stage, after the anodal or sham tDCS stimulation. Participants were seated approximately 100 cm away from the computer screen in a soundproof, light adjustable room. Continuous EEG data were recorded with a sampling rate of 512 Hz using the 64-channel Biosemi ActiveTwo EEG system (Biosemi, Inc). Ag–AgCl electrodes were mounted according to the 10–10 system and the impedances of all the electrodes were kept below 5 kΩ before recording.

Behavioral data analysis

TDCS effects on reaction time and accuracy were examined with stimulation condition by repetition two-way ANOVAs. For memory performance, items scored 4 and above were considered as subsequently remembered items, and those scored 3 or below were considered as subsequently forgotten items. The ratios of hits, false alarms, and discriminability (d') were compared between the two stimulation conditions using paired sample t tests.

EEG data analysis

EEG data preprocessing was implemented using a Matlab-based toolbox EEGLAB (http://www.sccn.ucsd.edu/eeglab/). The EEG data were down sampled to the rate of 256 Hz, re-referenced to the common average reference and filtered with a band-pass filter of 0.1-60 Hz. Eye movement or blink noises were

identified and corrected using the independent component analysis (ICA) algorithm. The continuous sample EEG data were then epoched into 1.2-second segments (-200~1000ms relative to trial onset), and the pre-stimulus interval (-200 ms ~ 0 ms) was used as the baseline for baseline removal procedure. Trials contaminated by any remaining eye movement or blinks were rejected by visual inspection. To obtain the ERP response, the remaining trials were averaged as a function of memory performance, stimulation condition, and repetition.

Spatiotemporal pattern similarity analysis (STPS)

We developed a method of calculating the spatiotemporal pattern similarity for single-trial EEG epochs (Figure S1). The spatial features were scalp voltages from one of the six regions for better spatial specificity, and the temporal features were selected using a 100 ms (26 time points) sliding window from the epoched EEG data. The step size of the sliding window is one time point. Then a vector containing both the spatial and temporal features was formed for each single trial. Similarity between trials was calculated using Pearson correlation coefficients, which are insensitive to the absolute amplitude and variance of the EEG response. The correlation coefficients were then converted to Fisher's Z scores for subsequent statistical analysis.

The within-item STPS (i.e., self-STPS) was obtained by calculating the averaged similarity across three repetitions of the same item, which were then separately averaged according to subsequent memory performance (remembered vs. forgotten) or stimulation condition (anodal vs. sham). To further examine whether this within-item similarity reflected item-specific representations or common cognitive processes related to memory, we further calculated the similarity for between-item pairs that matched the within-item pairs on memory performance, number of repetitions (1, 2 or 3), and repetition lag. It should be noted that since the same EEG responses were used for within- and between-item similarity comparison, a greater within-item than between-item response should reflect item-specific encoding rather than other confounding factors, such as the

differences in amplitude or variance, or artifacts of the recorded EEG response.

For the global-STPS, we first average the EEG responses across the three repetitions for a given item. The similarity index (Pearson correlation coefficients) between a given item with all other studied items was z-transformed, and then averaged [S2]. They were then separately averaged according to subsequent memory performance (remembered vs. forgotten) or stimulation condition (anodal vs. sham).

Focusing on the STPS, we did the following hypothesis-driven contrast analyses. First, to link spatiotemporal similarity to subsequent memory performance, we examined whether the remembered items showed greater spatiotemporal pattern than forgotten items. We then tested whether this pattern similarity reflected item-specific encoding by examining the interaction between subsequent memory and item-specificity. Finally, we tested whether tDCS could enhance item-specific spatiotemporal pattern similarity by examining the effect of tDCS on within-item similarity. To examine the item-specificity of the tDCS effect, we examined the interaction between tDCS and item-specificity.

Permutation test for multiple comparisons

To correct for multiple-comparison problems that may potentially result in false positive results in this study, we employed a nonparametric statistical method based on cluster-level randomization testing to control the family-wise error rate [S3]. This method is implemented in an open source software Fieldtrip (http://fieldtrip.fcdonders.nl/). For STPS analysis, statistical analysis was conducted for every time point, and the time points whose statistical values were larger than a threshold ($p = 0.05$) were selected and clustered into connected sets on the basis of temporal adjacency. The observed cluster-level statistics were calculated by taking the sum of the statistical values within a cluster. Then, condition labels were permuted 10,000 times based on their exchangeability to simulate the null hypothesis and the maximum cluster statistics over all six

regions were chosen to construct a distribution of the cluster-level statistics under the null hypothesis. The nonparametric statistical test was obtained by calculating the proportion of randomized test statistics that exceeded the observed cluster-level statistics.

Feature- and trial-level variability estimation and simulation analysis

Following recent simulation results [S4], we also examined the effect of feature- and trial-level variability on our self-similarity results. For each subject, the feature-level variability was represented by the standard deviation across all spatiotemporal features of a trial (separately for each region and 100ms temporal window), which was then averaged across trials, separately for remembered and forgotten items, and for anodal and sham conditions. The trial-level variability was represented by the standard deviation from the three repetitions of the same item, and then averaged across all features within an item. Similarly, the trial-level variability was then averaged across trials, again by memory performance and tDCS condition. Paired-sample t tests were then conducted to examine the differences between conditions (Figure S3).

To calculate the feature- and item-level variability for global pattern similarity, a different method was used. Specifically, since the three repetitions of a given item were averaged, the feature-level variability was then calculated within each item and across time points, whereas the trial-level variability was calculated across all studied items. Again, we found no differences in trial-level or feature-level variability between remembered and forgotten items, or tDCS and sham.

In the simulation analysis, we created an activation pattern containing 500 features (approximately matching the features in our STPS analysis) with a within-trial variability from the estimated value for each condition and individual. This represents the spatiotemporal pattern for a single item. We created three copies of this pattern, and different random noises with a SD from the estimated between-trial variability were added to each copy to represent the neural patterns

of the three repetitions of the same item. Pattern similarity was calculated using Pearson correlation coefficients, which were then transformed to Fisher's Z. For each subject (20 in total), this procedure was repeated 60 times for remembered vs. forgotten items or 120 times for tDCS vs. sham conditions. Paired-sample t test was then conducted to obtain the statistical significance. We conducted 1000 simulations for each comparison and the distribution of the log transformed P values was plotted (Figure S3).

Supplementary Results

Subsequently remembered items showed greater ERP response

Existing studies using conventional univariate analysis have revealed the subsequent memory effect in ERP response amplitude [S5-8]. Based on these studies, we examined the subsequent memory effect on the three components of interest, i.e., N170 (150~200ms) [S5], N400 (300~500ms) and LPC (500~800ms) [S6-8]. Compared to forgotten items, remembered items showed stronger N170 amplitudes in the left central region ($t(19) = 3.07$; $p = .006$), more positive going N400 in the central frontal region ($t(19) = 3.28$, $p = .004$), but more negative going N400 in the left posterior region ($t(19) = -3.22$, $p = .005$). The LPC was more positive going for remembered items than for forgotten items in the right central region ($t(19) = 4.45$, $p < .001$).

TDCS enhanced EEG responses related to memory encoding

We then analyzed the effect of anodal tDCS on ERP response. We found a greater N170 response for anodal stimulation relative to the sham condition in the right frontal region ($t(19) = 3.60$, $p = .002$) and the central region ($t(19) = 2.39$, $p = .027$). Meanwhile, anodal tDCS also elicited more positive going N400 in the frontal central region ($t(19) = 2.82$, $p = .011$) and more negative going N400 in the left posterior region ($t(19) = -2.85$, $p = 0.01$). Finally, anodal stimulation also elicited more positive going LPC in the frontal central region ($t(19) = 3.79$, $p = .001$), and more negative going LPC in the posterior region ($t(19) = -4.07$, $p < .001$). The electrode locations overlapped with those showing the subsequent

memory effect for the N400 component, but not for the N170 or LPC component.

Controlling the effect of confounding factors on self-STPS

Three analyses were conducted to control for potential confounds. First, we estimated the feature- and trial-level variability, separately for subsequently remembered and forgotten items. This analysis revealed overall comparable feature-level and trial-level variability between remembered and forgotten items, in the time window showing the subsequent memory effect of self STPS. Only several time points in the left occipital regions showed significantly greater feature-level variability for subsequently remembered items than for forgotten items (Figure S3).

Second, using the estimated feature- and trial-level variability, we conducted a simulation analysis to examine whether the differences in feature- and trial-level variability could have jointly led to differences in pattern similarity. Assuming identical representations across repetitions for both remembered or forgotten items (the ground truth), the differences in feature- and item-level variability did not yield significant differences between conditions in 1000 simulations (Figure S3). These results suggested that our results in these regions could not be attributed to feature- or trial-level variability; they instead reflected different degrees of reproducibility across repetitions.

Third, to examine whether our key findings of pattern similarity were due to differences in univariate signal amplitude, generalized linear mixed models were constructed to predict later memory. In these models, pattern similarity scores of the spatiotemporal clusters that previously showed the subsequent memory effect in self-STPS and the corresponding mean EEG amplitude were used as predictor variables. Models included intercept terms for participants and slope terms for each predictor variable. We found that the right frontal region ($p = 0.005$), left occipital region ($p = 0.013$) remained significant after controlling for the EEG amplitude.

Finally, it should be noted that the item-specific STPS (greater within- than between-item similarity) could not be attributed to the above confounding factors because the between- and within-item STPS were calculated based on the same signals.

Supplementary Discussion

The location of the pattern similarity effect

Beside the content-independent recollection effects, several EEG studies have investigated the time course of content-dependent differences in retrieval-related activity [S9-11]. They found that the retrieval-related EEG responses differed depending on the specific materials that were retrieved [S11], the task that subjects had performed during study [S9], as well as the type of perceptual information paired with the items during encoding [S10]. Maximal differences were consistently found in the frontal electrodes, in a later time window typically linked to the electrophysiological correlates of recollection (400–700ms) rather than the familiarity-based recognition (300–400ms, i.e., FN400) [S10]. This effect is in contrast to the parietal old-new effect that is insensitive to the encoding manipulation [S9-11]. Our results were very consistent with those observations, as we found strong old-new effect in the centro-parietal electrodes, but item-specific STPS in the frontal region. In addition, the content-dependent effects were enhanced for memory judgments accompanied by recollection as opposed to judgments made based on familiarity alone [S9].

Together, these findings suggest that the frontal content-dependent neural activity may index processes involved in the online recovery of specific contents (i.e., reinstatement). However, unlike the fMRI studies [S12-14], existing EEG studies did not examine the encoding-retrieval similarity, so their findings of category- or task-level differences in the anteriorly distributed effect may also index content-specific processes operating on the products of retrieval. Our

pattern similarity results provide strong evidence for the reinstatement account, as we found greater within- than between-item STPS for remembered items.

One interesting issue is that although content-specific reinstatement has been consistently observed in the frontal electrodes [S9-11], fMRI studies often revealed reinstatement in the posterior regions associated with perception [S13, 14]. In an fMRI study [S15] that employed a very similar paradigm to the EEG study [S9], Johnson and Rugg found that brain regions exhibiting content-dependent neural activity during recollection were a subset of the regions where encoding-related activity also differed, including the occipital and fusiform cortex. Thus, it is possible that the content-dependent ERP effects in the frontal lobe partly reflect the scalp projections of the neural activity identified by the fMRI study. Certainly, due to the poor spatial resolution and the methodological challenges in accurate EEG source localization, conclusions regarding the functional location of the EEG results should be considered very tentative. Although simultaneous EEG and fMRI studies could help to address this issue, it is also possible that EEG and fMRI may have captured different aspects of memory reactivation.

Reinstatement of the temporal context

Previous research has found that reinstatement is not only specific to an individual item but also to its temporal context [S16, 17]. However, our results showed that memory performance in our task did not benefit from the temporal context. Several possible reasons can be offered. First, we used a recognition task, which has been found to reduce the reliance on contextual information. Consequently, we did not find significant temporal clustering during the recognition test. Second, the learning materials used in our study lacked semantic information. It has been found that only during intentional study of words that are grouped by semantic category (i.e., semantically clustered), did the oscillatory signal at multiple bands reflect the integrative coding of both items and their context [S18]. Third, the context was not explicitly changed or manipulated in our study, so changes in

context would have been minimal and likely have resulted from a slow drift in context representation [S19]. Fourth, the sequence was randomized, so under each repetition the words were surrounded by different items. Existing evidence shows that brain regions such as the hippocampus carry information about the temporal positions of objects when they are learned in fixed sequences, but not when they are learned in random sequences [S20]. Finally, we focused on the neural components that carried strong item-specific information. Consequently, we found that STPS that contributed to memory showed no overlapping representations with adjacent items (i.e., no lag effect).

Differential roles of self and global pattern similarity

Existing studies further suggest that self and global similarity might reflect different cognitive and neural processes related to subsequent memory. These two types of similarity have been shown to independently influence subsequent memory [S21]. Whereas global similarity reflects how similar the mental representation of one item is to those of other items in the memory space, self similarity reflects the distinctiveness and reproducibility of the item-specific encoding, as well as the reinstatement of the prior encoding. Consistently, the two types of neural similarity measures have been shown to independently influence subsequent memory [S21]. Our results are consistent with this observation. Furthermore, we found that anodal LPFC tDCS significantly enhanced self-STPS, but barely global-STPS, further suggesting that they are modulated by different factors.

Questions for future research

Several questions remain to be addressed in future studies. First, the current study used novel symbols as learning material to avoid the influence of prior knowledge/semantics on memory encoding, and a long study-test delay (24 hours) to increase the subsequent memory effect. Future studies should replicate our finding by using different learning materials and study-test delay.

Second, several study-phase retrieval mechanisms have been proposed to account for the empirical data [S22-27], and there are debates regarding how multiple studies of the same items are integrated at the neural level and what roles contextual drift and reinstatement play. To test these models with neural data, future studies should examine the exact nature of context (identity, semantic, temporal position, or their combinations) as processed by the brain [S18, 20], the modulatory role of the learning condition [S18, 20], and the effect of context on different types of memory [S28, 29]. In particular, it would be fruitful to examine how spacing and contextual change affect neural pattern similarity and subsequent memory.

Finally, regarding the content and time course of memory trace reinstatement, although several studies found evidence of reinstatement in the time window of around 500ms, other studies found that contextual information entrained during encoding rapidly reemerged within 300ms during a later memory test [S30], and the early encoding processes at around 180ms could be replayed at 400ms after retrieval cue [S31]. It is thus possible that multiple types of information are reactivated at different time points, and the underlying mechanisms and their contributions to memory certainly need further examination.

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