The medial temporal lobe organizes memory across time and space: Causal evidence from brain stimulation

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Abstract

The medial temporal lobe (MTL) is widely implicated in supporting episodic memory and navigation, but its precise functional role in organizing memory across time and space remains elusive. Here we examine the specific cognitive processes implemented by MTL structures (hippocampus and entorhinal cortex) to organize memory by using electrical brain stimulation, leveraging its ability to establish causal links between brain regions and features of behavior. We studied neurosurgical patients who performed spatial-navigation and verbal-episodic memory tasks while brain stimulation was applied in various regions during learning. During the verbal memory task, stimulation in the MTL disrupted the temporal organization of encoded memories such that items learned with stimulation tended to be recalled in a more randomized order. During the spatial task, MTL stimulation impaired subjects' abilities to remember items using view-independent (allocentric) navigation strategies. These stimulation effects were specific to the MTL. Our findings thus provide the first causal demonstration in humans of the specific memory processes that are performed by the MTL to encode when and where events occurred.

Significance Statement

Numerous studies have implicated the medial temporal lobe (MTL) in encoding spatial and temporal memories, but they have not been able to causally demonstrate the nature of the cognitive processes by which this occurs in real-time. Electrical brain stimulation is able to demonstrate causal links between a brain region and a given function with high temporal precision. By examining behavior in a memory task as subjects received MTL stimulation, we provide the first causal evidence demonstrating the role of the MTL in organizing the spatial and temporal aspects of episodic memory.

Introduction

The medial temporal lobe (MTL) plays a key role in encoding episodic memories for various types of spatial and temporal information (Eichenbaum, 2004; Cohen & Eichenbaum, 1993; Ekstrom et al., 2011). The importance of the MTL for memory is now well accepted, as researchers have reported concordant evidence from multiple methods, including observational studies of lesion patients (Scoville & Milner, 1957), experiments in rodents (O'Keefe & Dostrovsky, 1971), and, more recently, with noninvasive neuroimaging work (Henson, 2005). However, although we know that the MTL is vital for episodic memory in general, we do not precisely understand the computational nature of the processes that the MTL employs to encode individual episodic memories in various contexts (Howard & Eichenbaum, 2015; Guderian et al., 2015; Maguire et al., 2015; Douglas et al., 2016).

Traditional methods for investigating the anatomical basis of human cognitive processes, such as lesion and neuroimaging approaches, have provided a plethora of information regarding the role of the MTL in memory (Bohbot et al., 2004; Copara et al., 2014; Suthana et al., 2009; Kolarik et al., 2017), but are unable to demonstrate causal links between a given brain region and a set of functions with high temporal precision. Localization of lesions is often uncontrolled, and the permanent nature of brain injury results in poor temporal resolution; one cannot use lesion studies to perfectly identify the specific circumstances under which a given brain region is necessary for a given behavior (Rorden & Karnath, 2004). Analogously, neuroimaging studies are correlational, and are therefore unable to provide conclusive evidence about the necessity of a given brain region for a specific task in human subjects (Rorden & Karnath, 2004; Friston et al., 2002; Ramsey et al., 2010).

A different approach for probing brain function in humans is neuromodulation. Neuromodulation is promising because it can establish causal relationships between a brain region and the functions that it supports (Knotkova & Rasche, 2014; S. H. Lee & Dan, 2012). Neuromodulation techniques such as optogenetics, transcranial magnetic stimulation (TMS), and electrical brain stimulation (EBS) allow researchers to transiently alter processing in a region and determine the effects of this modulation on task performance. By showing that a cognitive process is transiently altered when a particular region is specifically stimulated, a causal link is demonstrated. Optogenetics is currently only implemented in animals, and TMS is only able to target neocortical structures

(Klomjai et al., 2015). However, EBS is a viable research approach for certain neurosurgical patients, as it can target subcortical structures such as the hippocampus, making it a useful approach to selectively explore cognitive function in human subjects.

Previous work has shown that MTL stimulation impairs spatial and temporal memory overall (Jacobs et al., 2016). We move beyond the results of this work by using an improved analytic approach to identify the specific features of memory that were perturbed by stimulation. To foreshadow our results, we find that in the verbal domain, MTL stimulation specifically disrupted the temporal ordering of episodic memory and impaired the recall of items from early list positions. Analogously, we found that stimulation specifically disrupted spatial memories that were likely encoded via view-independent (allocentric) strategies rather those encoded with boundary-assisted (view-based) strategies. By performing quantitative item-level analyses of behavioral data collected during brain stimulation, our findings serve as the first causal and temporally precise demonstration of the specific cognitive processes that the MTL utilizes to organize episodic memories across time and space.

Methods

We analyzed data from 49 epilepsy patients who had surgically implanted electrodes for localization of seizure foci. Patients performed verbal-episodic and spatial memory tasks, which were adapted such that direct brain stimulation was applied during some learning trials.

In each session, a selected electrode pair was connected to an electrical stimulator (Grass Technologies or Blackrock Microsystems). Stimulators were configured to deliver bipolar stimulation current between a pair of electrodes, each with a surface area of 0.059 cm^2. MTL structures were stimulated using depth electrodes, while strip and grid electrodes targeted other neocortical structures. Stimulation was applied at 50 Hz with a balanced biphasic stimulation pulse of 300 μs per phase. Under clinical supervision, we began each session by manually testing a range of currents for each site, beginning at 0.5 mA and slowly increasing to a maximum of 1.5 mA (depth electrodes) or 3.0 mA (surface electrodes). The final stimulation current that was used for the cognitive experiments was the maximum current for each site that could be applied without inducing epileptiform afterdischarges or seizures.

The anatomical location of each implanted electrode was determined via an MRI scan that provided a high resolution image of the hippocampus and MTL (0.5 mm x 0.5 mm x 2 mm resolution). Depth electrodes within the MTL were localized via a semi-automatic process. First, MTL subregions were labeled within the MRI image using a multi-atlas based segmentation technique (Wang et al., 2013; Yushkevich et al., 2015). A neuroradiologist then identified each electrode contact using a thin-section post implant CT scan. The scan was co-registered with the MRI image (Avants et al., 2008), and the anatomic label for each contact was automatically generated. Finally, the neuroradiologist visually confirmed the accuracy of the location of the implant (Jacobs et al., 2016; Suthana et al., 2012). We designated stimulation sessions to be targeting a particular region if at least one electrode of the bipolar pair was in the region.

Each subject provided informed, written consent prior to participation. Our multisite study was approved by local IRBs, the IRB of the University of Pennsylvania (data coordination site), and the Human Research Protection Official (HRPO) at the Space and Naval Warfare Systems Center Pacific (SPAWAR/SSC). The raw data are publically available (`http://memory.psych.upenn.edu/`) and were analyzed previously (Jacobs et al., 2016) but the results presented here are novel.

Verbal Task. 39 patients (23 with MTL stimulation) performed the Free Recall task (Sederberg et al., 2003) while stimulation was applied during the learning of some items. Figure 1A presents a timeline of this task. During each trial, subjects were asked to memorize a list of 12 words sequentially presented as text on the computer screen. After a 20-s math distractor task, subjects were given 30 s to verbally recall the words in any order. Vocal responses were recorded and scored manually later. Each word was presented for 1600 ms, followed by a blank screen for 750–1000 ms. Lists consisted of high-frequency nouns (http://www.memory.psych.upenn.edu/WordPools).

Lists consisted of two types: stimulated lists, in which half of the words on the list were delivered simultaneously with electrical brain stimulation, and control lists, in which all 12 words were presented without stimulation. Each session consisted of 25 lists, 20 stimulated lists and 5 control lists, randomly ordered. For stimulated lists, stimulation occurred in a blocked pattern: the stimulator was active for a pair of consecutive words and then inactive for the following pair, resulting in the stimulator being active for half the total words on each such list. When the stimulator activated, it was timed to occur 200 ms prior to the presentation of the first word in each

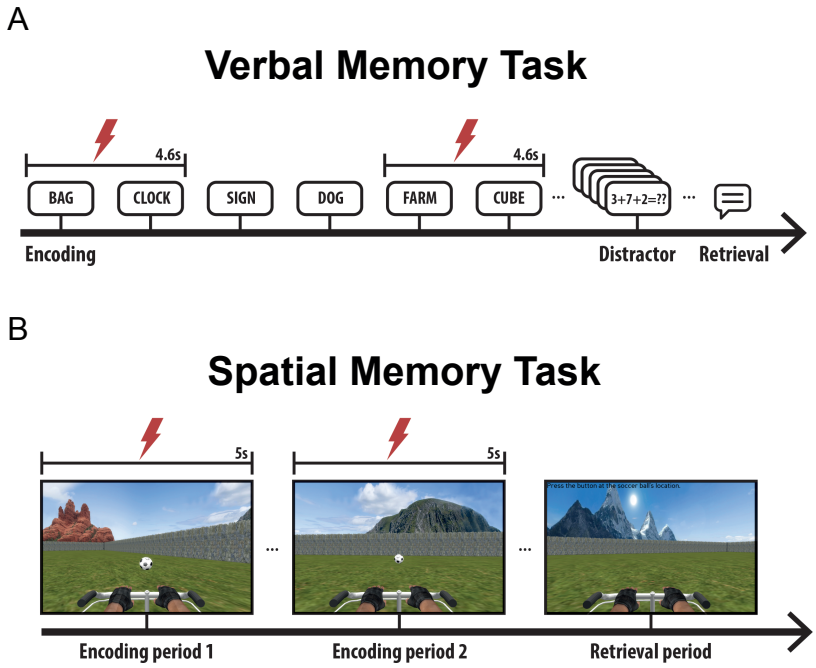

Figure 1: **Overview of verbal and spatial memory tasks A.** Timeline of the verbal memory task. Half of the words on stimulated lists are encoded with the stimulator active. **B.** Overview of the spatial task. Half of the trials occurred with the stimulator active during both encoding periods. Taken from Jacobs et al. (2016) with permission.

block, continuing for 4.6 s until the disappearance of the second word. The timing of stimulation onset was balanced. Half of the lists were randomly chosen to begin with a non-stimulated block, while the other half began with a stimulated block.

Data Analysis: Free Recall Task. Our analyses of data from the Free Recall task followed methods used in other studies (Sederberg et al., 2003; Kahana, 1996; Polyn et al., 2009b; Jacobs et al., 2016), adapted for examining the behavioral effects of stimulation. When a subject recalled a word from the previously encoded list, its serial position on the encoded list, as well as its stimulation condition, were recorded. Serial position curves were calculated by dividing the number of times words at a given serial position were recalled by the number of total words presented in that position, for each stimulation condition. Overall recall probabilities for each subject were computed as the average across all serial positions.

To explore the time scale of the effect of stimulation, we tested whether recall probability depended on position within the stimulated blocks (first stim item vs. second stim item, e.g.). To

remove the confound of list position, we compared each position with position-matched controls of the same phase. Specifically, performances on stimulated lists and control lists were averaged across subjects for each serial position in that phase ("first stim" would be positions 1, 5, and 9 for a list that began with a stimulated block, for example). Each control position was then subtracted from each stimulated list position. The positions were then averaged together.

To test that stimulation reduced the degree to which items remain in memory, we examined the probabilities that subjects recalled items from the previously encoded list while attempting to recall items from the current list. Such false recalls are termed "prior list intrusions" (PLIs) (Darley & Murdock, 1971). The stimulation condition of the item from the previous list that intruded into the current recall was noted. If the item was an item on a control list, this would be termed a "stimulated list to control item" transition. The number of transitions in each condition were tallied for each subject. The number of times a control list preceded a stimulated list, and the number of times a stimulated list preceded a stimulated list, were also tallied. The number of transitions were then divided by the appropriate number of possible transitions (stimulated list to control item transitions were divided by the number of times a control list preceded a stimulated list, etc.) for each subject. The data were then averaged across subjects. As many of the probabilities were close to 0, we could not assume them to follow a normal distribution. We therefore elected to utilize the nonparametric Wilcoxon Signrank Test to compare PLI probabilities across conditions.

We then examined the relationship between the order in which items were encoded and the order in which they were recalled. The probability that the first encoded item was recalled first was calculated as the number of times the first encoded item was recalled first divided by the total number of lists presented to the subject. Identical analyses took place for the probability that any encoded item was recalled in a given output position. Statistical tests (paired t tests) were conducted between control lists and stimulated lists (by averaging the values for stimulated items and non-stimulated items) for each position.

In Free Recall, subjects exhibit a strong tendency to cluster their recall sequences based on the temporal proximity of the items during study. We examined the effect of stimulation on this "temporal contiguity effect" by comparing the temporal clustering factor (Polyn et al., 2009b) and conditional response probabilities (Kahana, 1996) between stimulation conditions. The temporal clustering factor (TCF) is a measure of the tendency of the subject to make recall transitions to

nearby items. A TCF of 1 indicates perfect temporal contiguity, with the subject only making transitions to adjacent items, while a TCF of 0.5 indicates that the subject is making transitions randomly (Polyn et al., 2009a). CRPs plot the probabilities that a certain item will be recalled given that another item was just recalled. These conditional probabilities are plotted as a function of lag, where a $+i$ lag would indicate that the subject recalled the item at serial position n, followed by the item at position $n + i$ (Kahana, 1996).

All temporal factor and CRP statistical comparisons were tested through a Mann-Whitney Rank sum test, as we could not assume normality for either calculation. The temporal clustering factors were all skewed towards higher values, while the CRPs were skewed towards lower values.

Finally, to test if the particular effects of stimulation were restricted to the MTL, we examined recall probabilities and temporal dynamics separately for MTL and non-MTL regions by repeating the above analyses for subjects that were stimulated in the temporal neocortex, cingulate, fusiform gyrus, or the frontal lobe. These were termed "neocortex" regions.

Spatial Task. In the spatial memory task (Fig. 1B), 26 subjects participated in a virtual navigation paradigm that is reminiscent of the Morris (1984) water maze. The environment was rectangular (1.8:1 aspect ratio), and was surrounded by a continuous boundary. There were four distal visual cues (landmarks), one on each side of the rectangle, to aid with orienting. Each trial started with two 5-s encoding periods, during which subjects were driven to an object from a random starting location. At the beginning of an encoding period, the object appeared and, over the course of 5 s, the subject was automatically driven directly towards it. The 5 second period consisted of three intervals: first, the subject was rotated towards the object (1 s), second, the subject was driven towards the object (3 s), and finally, the subject paused while at the object location (1 s). After a 5 second delay, the same process was repeated from a different starting location. Alternating trials (24 out of the 48) were designated as stimulation trials, during which stimulation was applied throughout the 5 s of time while the object was visible to the subject for both encoding periods.

After both encoding periods for each item, there was a 5-s pause followed by the test trial period. The subject was placed in the environment at a random starting location with the object hidden and then asked to freely navigate using a joystick to the location where they remembered the object had been hidden. When they reached their chosen location, they pressed a button

to record their response. They then received feedback on their performance via an overhead view of the environment showing the actual and reported object locations. Between stimulation and non-stimulation trials, starting location, starting orientation, and object location were all counterbalanced. This was achieved by creating a set of location triads for the stimulated conditions and transposing them across the environment's diagonal for use in non-stimulation trials, ensuring that the geometric relationship between the start and object locations was matched in stimulation and non-stimulation trials.

Data Analysis: Spatial Memory Task. Performance in the spatial task was measured by computing the distance between the reported and actual locations for each object. In the same manner as Jacobs et al. (2016), we normalized this euclidean distance metric into a memory score (MS) between the range of 0 and 1, where a value of 1 indicates a perfect response and a value of 0 indicates the worst possible response given the object's location. This normalization took the form of ranking the subject's actual response compared to all other possible responses. This unbiased measurement adjusts for the fact that the distribution of possible response error distances varies according to the object's distance from the boundaries; it also corrects for the rectangular shape of the environment. Namely, objects near boundaries had a larger maximum possible error distance than objects in the interior. Subjects with an average MS of less than chance (0.5) were excluded from all analyses.

Previous studies have shown that boundaries play a crucial role in guiding navigational behavior (Chan et al., 2012; S. A. Lee, 2017), so we chose to analyze the effect of object location on subject performance. To this end, the environment was divided into equal-sized "boundary" and "interior" areas by creating an inner rectangle with an identical aspect ratio to the environment itself. Each trial was labeled for data analysis according to the region in which the object was located.

We analyzed whether certain subjects utilized different navigation strategies at the boundaries as opposed to the interior. Certain strategies, such as scene recognition, rely on facing the same direction during encoding and recall to ensure accuracy. To test whether such a strategy was used, the directions that subjects faced at the end of the learning trials and the test trials were converted into "headings" based on their angle from a defined zero degree line. The circular mean of the two learning headings was then subtracted from the test learning heading, and the results were averaged across each subject/location population. All circular statistics tests were drawn from the

MATLAB Circular Statistics Toolbox (Berens, 2009).

Finally, we examined the effects of stimulation on subject performance, and whether this was affected by location. For each subject/location population, we subtracted the average MS of stimulated trials from the average MS of non-stimulated trials.

Results

We sought to determine the effects of MTL (hippocampus and entorhinal cortex) stimulation on the temporal and spatial organization of memory to elucidate the cognitive processes implemented by the MTL in maintaining these representations. We first describe, as before, that MTL stimulation impairs spatial and episodic memory overall (Jacobs et al., 2016). We then expand on this work by reporting a new set of analyses that measure the effects of MTL stimulation on specific features of memory. We show that MTL stimulation selectively disrupts the recall of items learned earlier, the ability to maintain a temporal ordering of past episodic events, and the ability to encode locations in an environment using view-independent (allocentric) spatial representations.

Verbal Episodic Memory

In the verbal memory task, subjects learned and recalled two types of lists, stimulated lists and control lists. On stimulated lists the stimulator was cycled on and off for blocks of two items, so that the items on these lists were either delivered with stimulation ("stimulated items") or delivered without ("non-stimulated items on stimulated lists"). Control lists were delivered entirely without stimulation. We classified each item based on its stimulation condition during encoding and then analyzed whether or not it was subsequently recalled.

Effect of Stimulation on Primacy Recall. We first computed mean recall probability for items from each MTL (hippocampus + entorhinal cortex) stimulation condition (Figure 2A). These analyses reproduce the results of Jacobs et al. (2016), showing that recall rates were lower for stimulated items relative to non-stimulated items ($t_{22} = -2.29$, $p = 0.04$, paired t-test). This indicates that MTL stimulation *impairs* the encoding of episodic memories at the population level.

Going beyond earlier work, we separately computed recall performance for non-stimulated

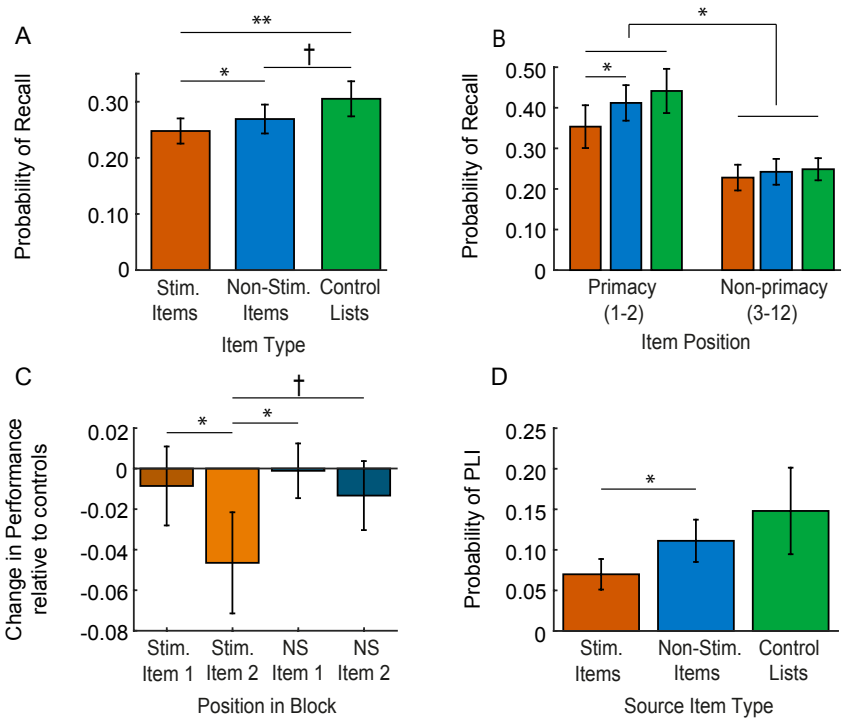

Figure 2: **Effect of MTL stimulation on recall probability in Free Recall. A.** Probability of item recall in Free Recall averaged across all serial positions, separately computed for stimulated items (red), non-stimulated items on stimulated lists (blue), and control lists (green), then averaged across subjects. **B.** Recall probabilities separately computed for primacy (items 1–2) and non-primacy items (items 3–12) in the same way as **A. C.** Recall probabilities within stimulation lists, separately computed by the position relative to the timing of stimulation onset and then averaged across subjects. **D.** Probabilities of making a prior-list intrusion to a specific item type while trying to recall items from a stimulated list. *: $p \leq 0.05$, **:$p < 0.01$, † : $p < 0.1$. Error bars are SEM.

items on stimulated lists and control lists. We find that recall for stimulated items was impaired relative to both non-stimulated items on stimulated lists ($t_{22} = -2.29$, $p = 0.04$, paired t test) and to items on control lists ($t_{45} = -2.83$, $p = 0.007$, unpaired t test). Non-stimulated items on stimulated lists showed a trend towards impairment compared to control lists ($t_{45} = -1.73$, $p = 0.09$, unpaired t test).

Brain recording studies have suggested that different neural patterns underlie the encoding of items from different list positions (Serruya et al., 2014; Sederberg et al., 2006; Manning et al., 2011). We tested the role of the MTL in memory for items from different positions by assessing the impact of stimulation on encoding across the course of each list. To do this, we computed mean recall probabilities for each stimulation condition separately for primacy items (items 1 &

2) and non-primacy items (items 3–12) (Figure 2B). As expected (Murdock, 1962), overall recall probabilities for primacy items were higher than for non-primacy items. However, the effects of MTL stimulation varied over the course of the list. Stimulation significantly impaired recall of primacy items ($t_{45} = -1.95$, $p = 0.05$, paired t test), but not later list positions ($p's > 0.8$). We performed a two-way repeated-measures ANOVA with factors list position and stimulation condition. The interaction between the two factors was significant ($p = 0.047$), indicating that MTL stimulation specifically impaired the recall of items at early rather than late positions. To confirm the results, we performed the same analysis for recency items (items 11 & 12), and found no difference for stimulated items ($p's > 0.8$).

We also examined how the effect of stimulation on memory varied across each phase of the two-on-two-off stimulation cycle by comparing memory performance across this cycle relative to position-matched controls (Figure 2C). The first stimulated item showed significantly less reduction of average recall probability compared to the second ($t_{22} = -2.10$, $p = 0.042$, paired t test), indicating that the impairment of memory from stimulation accumulates gradually.

Examining task errors is an additional method for assessing the properties of memory encoding (Darley & Murdock, 1971). To test whether stimulation influenced subjects' incorrect recalls, we examined the rates at which subjects recalled items from a previous list (prior-list intrusions; PLIs) while attempting to recall items from a list that had been presented with stimulation (Darley & Murdock, 1971). We found that items that were viewed on control lists were more likely to be the sources of PLIs, compared to items on stimulated lists (Figure 2D). On stimulated lists, non-stimulated items were more likely to be the source of PLIs compared to stimulated items ($z = -2.12$, $p = 0.034$, sample sizes = 23, Wilcoxon Signed Rank Test). Because items from stimulated lists less frequently generated PLIs, it suggests that stimulation had diminished the strengths of their representations in memory.

Effect of Stimulation on the Temporal Organization of Memory. We next examined whether MTL stimulation altered the temporal structure of memory. In a standard delayed free recall task without stimulation, there is a tendency for items to be recalled in the order that they were encoded (Howard & Kahana, 1999). We hypothesized that stimulation might interfere with the temporal structure of memory, disrupting this phenomenon. To examine this issue, we present the results

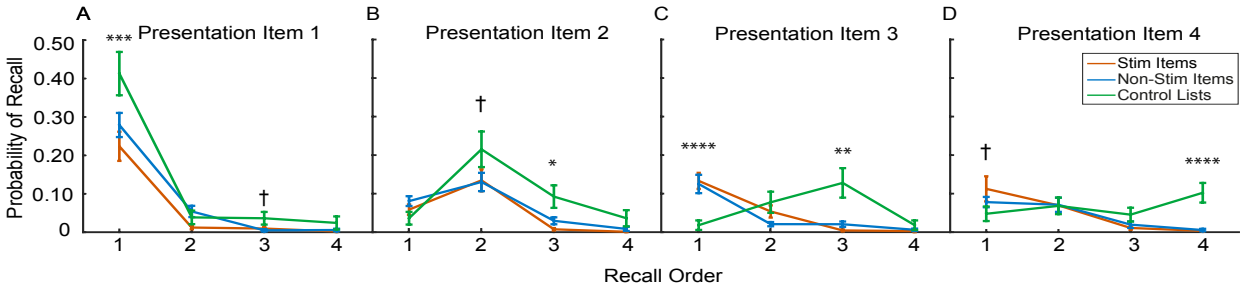

Figure 3: **Effect of MTL stimulation on recall ordering for primacy items.** Plots show the probability of recall at different recall-output positions. Probabilities were averaged within each subject and then averaged across subjects. Plots from left to right show results separately for items that were presented at positions 1–4. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 10^{-3}$, ****: $p < 10^{-4}$, † : $p < 0.1$

of two separate analyses of the temporal structure of episodic memory recalls, beginning with a specific exploration of whether items were recalled in the order that they were viewed (Howard & Kahana, 1999) at the beginning of each list, followed by a broader analysis of the overall order of responses across the complete list (Polyn et al., 2009a).

To examine the effects of MTL stimulation on recall order, we computed the mean probability of recalling an item from each learned list position for each of the first four output positions (Figure 3). On control lists, the results were consistent with earlier work, showing a tendency for items to be recalled in the order they were viewed (i.e., items learned at list position n have the highest recall probability in the nth output position). However, this pattern was disrupted when MTL stimulation was applied. We compared recall rates at each position between control and stimulation lists. There were significant decreases in the probabilities for recalling each of the first two items in their proper orders (Figure 3A & B; $t_{21} = -3.17$, $p = 0.0046$ and $t_{21} = -1.85$, $p = 0.078$, paired t-tests). When subjects recalled three or more items on stimulated lists, the third item was often recalled first, while subjects tended to recall the third item third on control lists (Figure 3C; $t_{21} = 5.33$, $p = 0.00003$ and $t_{21} = -2.96$, $p = 0.0074$ paired t-tests). These results show that items on stimulated lists were less likely to be recalled sequentially, implying that stimulation hinders subjects from encoding the temporal structure of the items they encounter.

We performed a follow-up control analysis to ensure that these apparent disruptions in temporal order were not a trivial result from the overall reduced recall rates for stimulation lists. Here, for analyses of recall for each presentation position n, we included only trials where subjects recalled

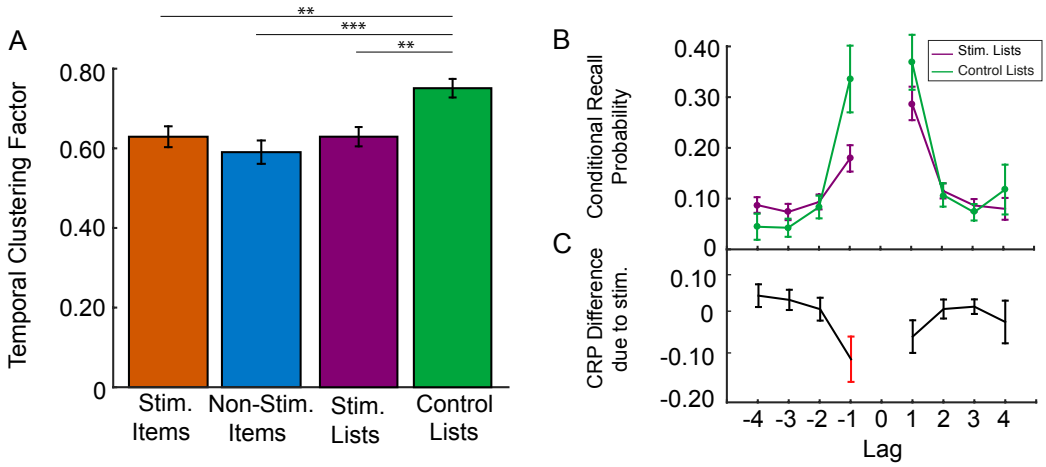

Figure 4: **Analysis of the effect of MTL stimulation on temporal clustering of item recalls. A.** Temporal Clustering Factors (TCF) for items from each stimulation condition, averaged across subjects. **B.** Conditional Recall Probability (CRP) plot for control and stimulated lists, averaged across subjects. **C.** Difference in recall probability from stimulation (Stim List – control). **: $p < 0.01$, ***: $p < 10^{-3}$

at least n items. The item ordering effects found previously continued to be disrupted at output positions 1, 3, and 4 ($p's < 0.05$, paired t-tests).

When normal subjects perform the Free Recall task without stimulation, they exhibit a tendency for their recalls to be temporally clustered, such that items consecutively recalled were likely to have been learned from nearby list positions (Howard & Kahana, 2002). We examined the effect of stimulation on this clustering by computing two measures of list-wide temporal contiguity—the temporal clustering factor (TCF) (Polyn et al., 2009a) and the lag conditional recall probability (CRP) function (Kahana, 1996)—and testing if they changed with MTL stimulation. The TCF measures the correlation between item ordering during encoding and recall. Our analyses show that MTL stimulation significantly disrupts the temporal structure of memory. TCFs were higher for unstimulated control lists compared to conditions with stimulation ($p's < 0.05$, Mann-Whitney Rank sum tests), implying that MTL stimulation disrupted the temporal organization of remembered list items (Figure 4A).

Despite the theoretical insensitivity of the TCF to recall counts (Polyn et al., 2009a), to rule out the possibility that the temporal factor was lowered by lower recall rates for stimulated lists, we reperformed this analysis after matching recall counts between control and stimulated lists with random subsampling. After matching recall counts of control lists to stimulated lists with 2 recalls

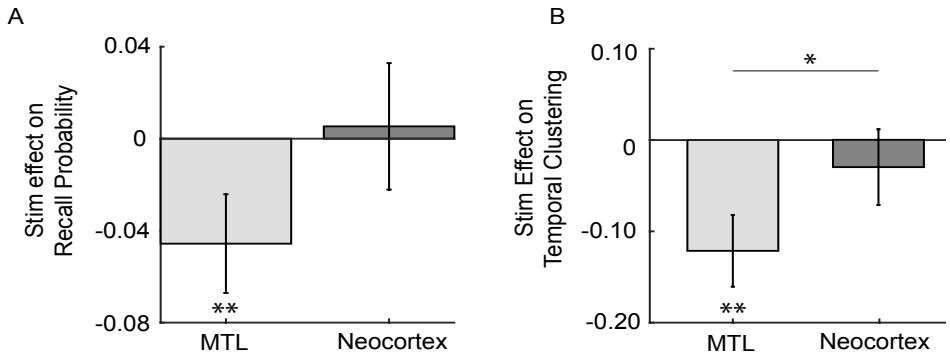

Figure 5: **Comparison of effects of stimulation in different regions during Free Recall. A.** Change in recall probability due to stimulation (stimulated lists - control lists). This measure was separately computed for stimulation that was applied in hippocampus/entorhinal cortex (labeled "MTL") or in neocortex (labeled "Not MTL"). **B.** Change in temporal clustering factor (stimulated lists - control lists) for stimulation that was applied in MTL and non-MTL regions. *: $p < 0.05$

and then to 3 recalls, we recapitulated the same results, again finding that temporal factor was significantly decreased with MTL stimulation ($p = 0.014$ and $p = 0.017$, respectively, Mann-Whitney Rank sum tests).

To visualize the effect of MTL stimulation on the dynamics of memory, we computed the lag-CRP for each list condition. Overall, both stimulated and control lists show higher recall probabilities at short lags, as expected (Kahana, 1996). However, CRPs for stimulated lists were flatter than for control lists (Figure 4B). In particular, there was a significant decrease in recall probability for item transitions with lag=-1 ($p = 0.032$, Mann-Whitney Rank sum test; Figure 4C). These results are consistent with MTL stimulation disrupting the temporal order of memory, by decreasing subjects' tendencies both to recall items in their viewed order and to make temporally contiguous recalls.

An unexpected feature of our data was that the CRPs for control lists were rather symmetric, as opposed to showing a moderate asymmetry (Kahana, 1996). To explain this pattern, we separately examined CRPs for items from different list positions. The CRP for the first half of each list showed a normal forward asymmetry for both control and stimulated lists, including a significantly lowered recall probability at lag=-1 during stimulation ($p < 0.05$, Mann-Whitney Rank sum test). In contrast, the CRP for the second half of the list was symmetric and showed no significant differences between stimulation and control conditions ($p > 0.1$). Thus the symmetry of the aggregate CRP was caused by recalls in the second half of lists tending to deviate from expected patterns in our dataset.

Stimulation outside the MTL. To compare whether the memory modulation patterns we observed were specific to stimulation in the MTL, we compared recall patterns between sessions where stimulation was applied in MTL (hippocampus and entorhinal) regions versus sessions with stimulation outside the MTL (neocortex). Recapitulating past results (Jacobs et al., 2016), we found that recall rates were not meaningfully impaired for stimulation in the neocortex (Fig. 5A; $p > 0.1$, one-sample t test). We expanded upon this analysis by contrasting the effects of stimulation on temporal clustering in the MTL and neocortex (Figure 5B). We found that stimulation impairs the temporal clustering of item recalls within the MTL significantly more than within the neocortex ($t_{31} = -2.31$, $p = 0.029$, unpaired t test). These results indicate that stimulation's ability to disrupt the temporal organization of memory is not a brain-wide phenomenon but is instead specific to the MTL.

Spatial Memory

Our spatial memory task tested subjects' ability to remember the locations where items had been observed in a virtual reality environment. By analyzing subjects' response patterns during this task, we were able to distinguish subsets of trials where subjects were more likely to have used MTL-mediated view-independent (henceforth shortened to "allocentric") strategies, such as path integration (Wolbers et al., 2007), or view-based response strategies (O'Keefe, 1979; Rondi-Reig et al., 2006). Allocentric representations are hypothesized to rely on an internal "cognitive map" that represents the spatial structure of the environment and the items it contains (Tolman, 1948). By examining stimulation's effects on the accuracy of memory responses, we show that MTL stimulation selectively disrupts performance on trials where subjects were relatively more likely to have used an allocentric spatial representation, suggesting a causal link between the MTL and view-independent spatial encoding strategies.

Assessing spatial memory strategies. Because multiple brain systems have been proposed to underlie spatial cognition (Doeller et al., 2008; Squire, 1992; Iaria et al., 2003), we hypothesized that individual subjects might utilize different spatial location encoding strategies during the task, utilizing view-based spatial representations in the presence of salient cues such as visible nearby boundaries, and otherwise using their more global, allocentric representation of space (O'Keefe &

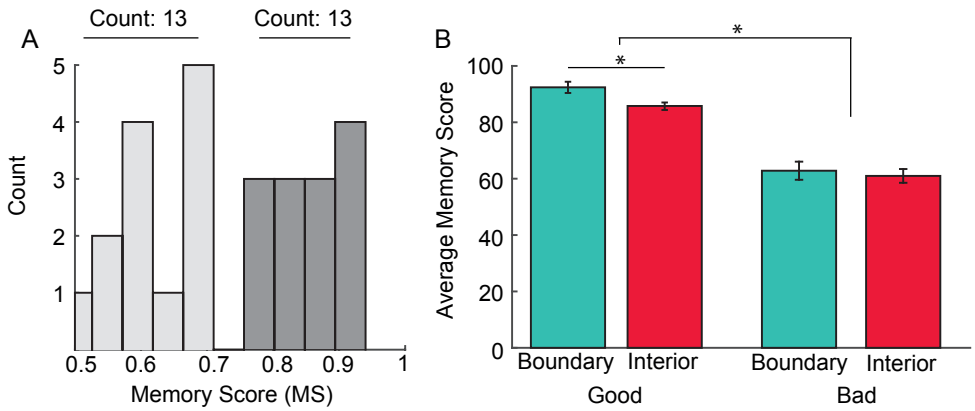

Figure 6: **Behavioral analysis of memory performance in the spatial memory task without MTL stimulation. A.** Histogram of memory scores across subjects with electrodes in the MTL. **B.** Average memory score for good- and bad-performing subjects, separately computed for remembered locations near and far from boundaries, then averaged across subjects. *: $p < 0.05$

Nadel, 1978; Hartley et al., 2003; Wolbers & Buchel, 2005). We began our analyses by examining overall task performance for subjects with electrodes localized to the MTL, as measured by our memory score (MS) measure. Patients showed a range of mean memory scores, ranging from 0.51 to 0.95 (Fig. 6A). The data is significantly bimodal ($p < 10^{-11}$, one-sample Kolmogorov-Smirnov test). We thus considered the possibility that this performance diversity reflected a difference in subject ability to effectively utilize the appropriate encoding strategy for a given object location. Thus, we divided subjects into two groups—good-performers and bad-performers—based on a median split at MS=0.75.

We moved to examine whether good-performers perform better because they are more adept at utilizing the presence of nearby boundaries to assist with encoding object locations. Examining trials without MTL stimulation, we found that good-performers showed improved memory performance for items located near boundaries, compared to their ability to remember the locations of items in the interior of the environment ($t_{12} = 2.61$, $p = 0.03$, paired t test). Bad-performers did not show this boundary-related improvement ($t_{12} = 0.52$, $p = 0.61$, paired t test), as shown in Figure 6B. A two-way ANOVA confirmed that good performers showed a significantly larger improvement in performance near boundaries compared to bad-performers (ANOVA interaction $p = 0.018$).

The fact that good-performers showed differential performance that depended on object location suggested that they may use different strategies for remembering items in the different regions. For

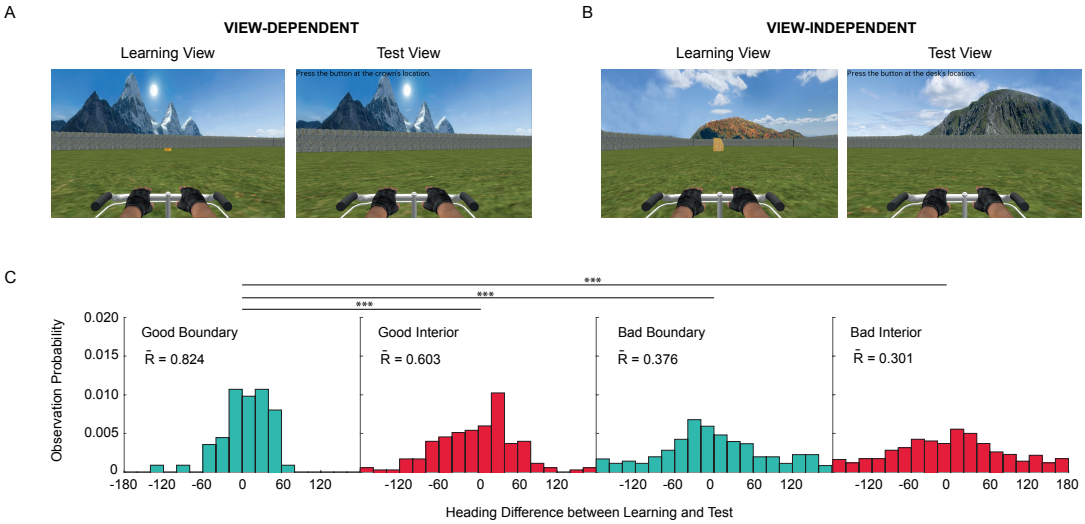

Figure 7: **Analysis of navigational strategies used by subjects independent of MTL stimulation** **A.** First-person visualization of a subject utilizing scene recognition on a trial where they remembered a location near a boundary. **B.** Same, but for a trial where the subject does not utilize scene recognition on a trial where they remembered a location near the interior. **C.** Probability density functions of differences in headings between learning and test trials. Length of resultant vector for the differences between learning and test headings for each category are also indicated. Large values imply significant clustering about 0. Heading differences were averaged across subjects in each category. ***: $p < 0.001$

objects in interior locations, subjects may have relied on utilizing distances and directions provided by the place and grid cell network in the hippocampal formation to encode spatial location due to the lack of proximity to visual landmarks or boundaries to assist encoding (O'Keefe & Nadel, 1978). Memory for objects near boundaries, on the other hand, is supported by visual scene representations in the parahippocampal place area, retrosplenial cortex, and occipital place area (Epstein et al., 2007; Park & Chun, 2009; Park et al., 2011; Julian et al., 2016). To explain our hypotheses, figure 7A presents a visualization of how view-based scene recognition could occur in this task, whereby the navigation to the remembered object location was aided by the subject matching the visual scene, including walls and background landmarks, between learning and test trials. Figure 7B displays a separate set of learning and test trials where the object is in the interior region of the environment. Because the subject is able to recognize the same location even though the final views are different, the subject likely made use of an MTL-dependent allocentric representation.

Thus, we hypothesized that view-based and allocentric spatial strategies would each be relatively more effective in the boundary and interior parts of the environment, respectively. To test this

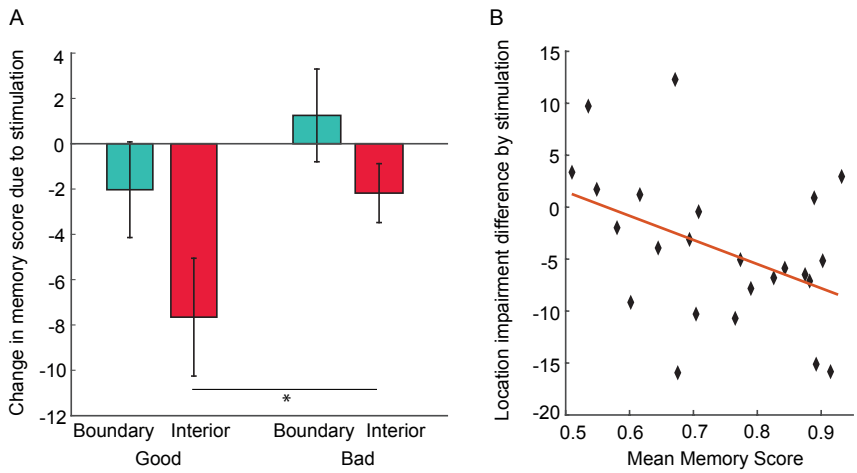

Figure 8: **Analysis of effect of hippocampal/entorhinal stimulation on memory for objects from different locations. A.** Difference in memory score (x 100) from MTL stimulation for different object locations and subject types. Negative values indicate impairment from stimulation. Impairments were first averaged across trials and then across subjects. *: $p < 0.05$ **B.** Scatter plot for individual subjects of the differences in memory score between stimulated and non-stimulated and between boundary and interior trials. Each point represents by how much stimulation impairs boundary trials more than interior trials. A negative value indicates increased impairment for interior trials. Line represents best-fit trend line from linear regression.

hypothesis, we estimated the spatial strategy used on each trial by measuring the difference between their headings at the end of each learning and test trial. If they showed a similar direction between learning and test, it was evidence that they used a view-based memory strategy. In contrast, a dissimilar heading between learning and test suggested use of an allocentric spatial strategy.

The results for each subject group are depicted by the histograms in Figure 7C. In this analysis, an angle of 0°indicates that a similar heading was present for both learning and test. In Figure 7C, the histograms are all concentrated around 0°(κ-test, $p < 0.001$), but the good-performing boundary group was significantly more concentrated compared to each of the other groups (k tests between groups, all p's< 0.001). This clustering pattern suggested that good-performing subjects were relatively more likely to utilize a scene recognition strategy at the boundaries and a view-independent (allocentric) strategy at the interior. The result that the bad-performing population did not see an increased clustering around 0°for boundary trials is a statistical control that indicates that this effect in the good-performing population is not a result of the nature of the task design, such as an asymmetry of the environment.

Effect of Stimulation. Given this evidence that we can distinguish between task strategies, we next assessed the effects of MTL stimulation separately for the conditions where we estimated different strategies were prevalent. We hypothesized that allocentric strategies, which are thought to be mediated by the MTL (O'Keefe, 1979), would be more strongly disrupted by MTL stimulation than view-based strategies. We separately assessed the effect of MTL stimulation on memory score for each subject type and environment area (Fig. 8A). Here, negative values indicate that stimulation impaired memory. For memory items located near boundaries, neither subject population is significantly affected ($p's > 0.1$). At the interior, however, stimulation significantly impaired performance for good-performing subjects (Mean MS change = -7.9, $p = 0.010$, one-sample t test). Good-performing subjects showed significantly greater impairment from stimulation compared to bad-performers in this same area ($t_{24} = -2.36$, $p = 0.03$, unpaired t test), showing that, across subjects, the degree to which MTL-based strategies are effectively employed is correlated with overall task performance.

Figure 8B visualizes this interaction between mean memory score and interior impairment. Here, the presence of a negative slope ($t_{24} = -2.21$, $p = 0.038$, one-sample t test) indicates that, with increasing subject performance, stimulation caused greater memory impairment for items near the center of the environment. These results support the view that allocentric representations, which subjects likely use to remember items in the environment's interior, where assistive visual cues are scarce, were specifically impaired by MTL stimulation, and that better performance on the task is due to the ability to utilize the correct strategy to meet task demands.

Discussion

By identifying the precise changes in memory performance that related to direct electrical brain stimulation, we have provided causal evidence to suggest that the human MTL supports memories by organizing them into a spatiotemporal network. This bolsters our understanding of the specific cognitive processes implemented by the MTL to allow humans to maintain a framework of when and where past events occurred. By using causal and temporally-restricted methods to causally identify the means by which the MTL maintains episodic memory representations, our results provide strong evidence that are consistent with the interpretations derived from previous lesion

(Bohbot et al., 1998, 2004; Kolarik et al., 2017; Spiers, Maguire, & Burgess, 2001; Spiers, Burgess, Maguire, et al., 2001), imaging (Copara et al., 2014; Suthana et al., 2009; Staresina & Davachi, 2009) and intracranial EEG studies (Watrous et al., 2013; Ekstrom & Bookheimer, 2007; Miller et al., 2013; Howard et al., 2012; Foster et al., 2013). Future work may incorporate ongoing neural recordings to understand precisely which electrophysiological mechanisms are disrupted by brain stimulation as a means to determine the neural mechanisms mediating spatiotemporal memory encoding.

Theoretical models have suggested that the medial temporal lobe (MTL) plays a role in supporting episodic memory coding with place cells and time cells (Howard & Eichenbaum, 2015). Place cells activate to encode an animal's presence at a specific location in a given environment, representing that location in an allocentric manner, relative to the overall constellation of the environment's spatial geometry (O'Keefe & Nadel, 1978). Analogously, time cells activate at particular moments in temporally structured intervals, relative to the overall scaling of the event sequence (Eichenbaum, 2014). Based on the properties of place and time cells, it has been suggested that the role of the MTL, and specifically the hippocampus, in memory is to neurally represent the overall spatiotemporal context for memory coding (Squire et al., 2004; Howard & Eichenbaum, 2015; Ekstrom & Ranganath, 2017). Our findings are consistent with the view that the MTL supports this process, as the pattern of behavior we observed after stimulation is what would be expected if these contextual associations were disrupted.

There is evidence from rodents that the fidelity of time-cell representations is important for memory (Manns et al., 2007). Moreover, the rate of time-cell representation shifts decrease over the course of an interval, with faster shifts occurring early in an interval (Eichenbaum, 2014). These changes may correspond to differences between the encoding of primacy and non-primacy items, with the former being represented by more dynamic time-cell patterns. The dynamics of time cells provide a potential explanation for our result that items at the beginning of the list were selectively impaired by stimulation, as the period of rapidly shifting time cell representations coincides with item encoding periods in those instances when stimulation preferentially caused impairment. This suggests that the primacy period for each list is a particular critical period where the hippocampus is important for encoding, and thus it is especially susceptible to disruption from stimulation. Inversely, non-primacy periods, when the rates of time-cell drift rates are slower, are less hippocampally dependent (and less impacted by stimulation).

It is important theoretically to note that stimulation caused decreased temporal clustering (Figure 4), as evidenced by a flattened lag-CRP curve for items learned while the stimulator was active. The clustering of item recalls based on the times when they were encoded is a key element of retrieved-context models of episodic memory (Howard & Kahana, 1999); our results therefore support these models generally and indicate that the MTL has a key functional role in the neural instantiation and encoding of episodic contexts (Howard et al., 2005). Notably, stimulation in our task occurred during encoding whereas the item clustering changes we measured were during recall. This causally shows that clustering of recalls is a result of neural signals during encoding, perhaps due to the construction of associations between each viewed item to the current temporal context represented in MTL activity.

In a similar way to how our findings suggest that MTL stimulation disrupted memory for items with distinctive time-cell representations, the results from our spatial task indicated that stimulation disrupts memories for items based on place and grid cells. The data from our spatial memory task indicate that the types of memories that were disrupted were more likely to have been encoded allocentrically than remembered with a view-based strategy. Hippocampal place cells and entorhinal grid cells provide an allocentric cognitive-map representation of a given environment (Moser et al., 2008), providing a potential explanation for this phenomenon. MTL stimulation is likely to disrupt place- and grid-cell firing patterns. Because encoding of items in the center of the environment (farther from boundaries) most likely relies on these allocentric representations, our findings could explain why those items are encoded less strongly, as their requisite representations were disrupted by stimulation. Inversely, the encoding of objects near boundaries was less reliant on allocentric signals, as they were perhaps memorized based on visual scene information. Consistent with this interpretation, there is evidence from fMRI studies that spatial scene recognition is mediated by non-MTL structures, such as the striatum, parahippocampal place area, retrosplenial cortex, and occipital place area (Epstein et al., 2007; Park & Chun, 2009; Park et al., 2011; Julian et al., 2016; Doeller et al., 2008), and that MTL damage leaves scene recognition intact (Spiers, Burgess, Hartley, et al., 2001).

Our primary finding is that by leveraging the causal and temporally reversible nature of electrical brain stimulation, we show that the MTL is responsible for encoding episodic memories based on temporal and allocentric cognitive representations. A potentially surprising feature of

our results is that good- but not bad-performing subjects exhibited differential spatial-memory performance according to the location of an object. This emphasizes that strategy selection may be an important element of memory, for settings where multiple memory systems could potentially accomplish a task (Doll et al., 2014; Squire, 1992; Iaria et al., 2003). In addition to being important for our fundamental understanding of brain function and memory systems, this result has implications for guiding the future use of brain stimulation for cognitive enhancement. Memory includes a diverse range of cognitive and neural processes. Our findings suggest that to develop brain stimulators for memory enhancement, it might be useful to tune these devices to a specific memory or behavioral process. Neuromodulation in the MTL may be useful for modulating memories based on the activity of place and time cells. Enhancement of other types of learning could be optimized different methods, such as neuromodulation in the striatum for procedural learning (Barnes et al., 2005). One approach that could be useful for such enhancement is to utilize a closed-loop approach to stimulation by measuring ongoing neuronal activity in real-time and dynamically varying the nature of the stimulation that will be applied (Ezzyat et al., 2017). Given the complexity of human memory and cognition, this type of dynamic approach would be useful by allowing stimulation to vary according to instantaneous internal neural states as well as external environmental demands.

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