Report

Neuron

Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory

Highlights

- Deep brain stimulation in the entorhinal region and hippocampus impairs memory
- Stimulation at 50 Hz impairs both spatial and verbal memory encoding
- A causal role for the human medial temporal lobe in memory encoding is demonstrated

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In Brief

Jacobs et al. found that electrical stimulation in the entorhinal region and hippocampus impaired spatial and verbal memory. These findings show that these regions have a causal role in memory but suggest we need improved stimulation protocols for memory improvement.

Jacobs et al., 2016, Neuron *92*, 1–8
December 7, 2016
http://dx.doi.org/10.1016/j.neuron.2016.10.062

CellPress

Please cite this article in press as: Jacobs et al., Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory, Neuron (2016), http://dx.doi.org/10.1016/j.neuron.2016.10.062

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Report

Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory

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http://dx.doi.org/10.1016/j.neuron.2016.10.062

SUMMARY

Deep brain stimulation (DBS) has shown promise for treating a range of brain disorders and neurological conditions. One recent study showed that DBS in the entorhinal region improved the accuracy of human spatial memory. Based on this line of work, we performed a series of experiments to more fully characterize the effects of DBS in the medial temporal lobe on human memory. Neurosurgical patients with implanted electrodes performed spatial and verbal-episodic memory tasks. During the encoding periods of both tasks, subjects received electrical stimulation at 50 Hz. In contrast to earlier work, electrical stimulation impaired memory performance significantly in both spatial and verbal tasks. Stimulation in both the entorhinal region and hippocampus caused decreased memory performance. These findings indicate that the entorhinal region and hippocampus are causally involved in human memory and suggest that refined methods are needed to use DBS in these regions to improve memory.

INTRODUCTION

Deep brain stimulation (DBS) has gained attention in recent years as a potential treatment for a range of neurological disorders (Perlmutter and Mink, 2006; Lozano and Lipsman, 2013). Patients suffering from various ailments such as Parkinson's disease, tremor, and psychiatric disorders experience significant relief after DBS therapy (Ressler and Mayberg, 2007). DBS offers hope for treating disorders that do not have a well-characterized molecular pipeline for pharmacological intervention. For this reason, DBS has been seen as a potential avenue for treating a large number of neurological disorders that can be localized to a particular brain region or neural circuit (Lozano and Lipsman, 2013).

Several studies attempted to use DBS to modulate human memory by targeting the entorhinal and hippocampal regions, which are brain areas regarded as having a critical role in declarative memory (Squire, 1992). These studies produced a range of results (Suthana and Fried, 2014). Suthana et al. (2012) reported that entorhinal DBS improved spatial memory. Other studies found that hippocampal DBS impaired verbal memory (e.g., Coleshill et al., 2004; Lacruz et al., 2010). A growing number of people experience memory impairment or navigational difficulty due to brain injury or neurological disease (Hebert et al., 2003). Thus, given the potential impact of DBS for cognitive enhancement, we decided to study this approach more closely.

The hippocampus and entorhinal cortex are best understood in terms of their role in spatial navigation and memory because these regions contain place and grid cells, which represent the current location during navigation (O'Keefe and Dostrovsky, 1971; Hafting et al., 2005; Jacobs et al., 2013). The 50 Hz stimulation that was suggested for memory enhancement (Suthana et al., 2012) was shown in other research studies to silence neurons near the stimulating electrode (Chkhenkeli et al., 2004; Kinoshita et al., 2005; Logothetis et al., 2001) and to reliably disrupt function in clinical mapping procedures (Ojemann et al., 1989). Given the complexity and balance underlying place- and grid-cell computations (Couey et al., 2013), we thought there was a possibility that stimulation might disrupt this system's representation of location, as well as other memory-related information (MacDonald et al., 2011), causing spatial disorientation and memory deficits.

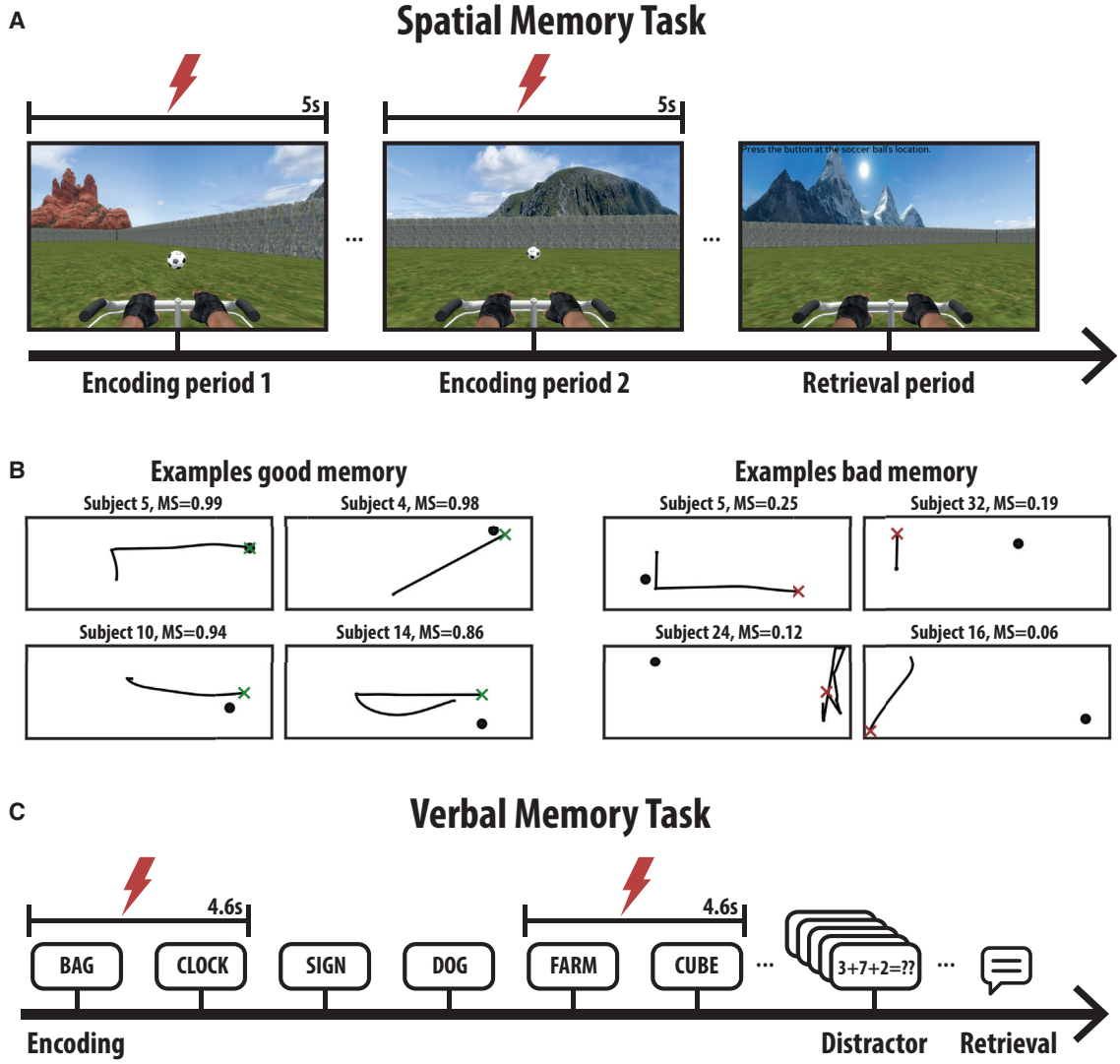

Figure 1. Spatial and Verbal-Episodic Memory Tasks with Integrated Brain Stimulation

(A) Timeline of a trial in the spatial memory task. Lightning bolts denotes periods when stimulation may be applied.

(B) Examples of good (left) and bad (right) spatial memory responses. Circle denotes the true object location, × denotes the response location, and black line denotes the subject's path. Memory score (MS) indicates the accuracy of each response relative to the true object location.

(C) Timeline of a trial in the verbal memory task.

We performed a multisite study to systematically investigate the impact of stimulation at 50 Hz in the hippocampus and entorhinal region on performance in spatial and verbal-episodic memory tasks. Our work relied on electrodes that were surgically implanted in patients who were undergoing a seizure-localization procedure to identify the anatomic source of drug-resistant epilepsy. Our study included several distinctive features: a relatively large dataset, separate tests of both spatial and verbal memory, and refined methods for behavioral tasks and for data analyses.

RESULTS

In our study, 49 subjects with implanted electrodes performed spatial and verbal memory tasks while brain stimulation was applied during some learning trials (see Figures 1 and S1 and Movie S1). We designed these tasks specifically to assess the effects of electrical stimulation in particular brain regions on the efficiency of memory encoding. During the encoding phases of each task, on some trials each subject received brain stimulation at one electrode pair. Across subjects the electrodes were positioned in several areas, which included the entorhinal region (16 sites in 12 subjects) and hippocampus (43 sites in 28 subjects). We assessed the effect of stimulation on memory by examining behavior in the subsequent recall phase of each task when the stimulator was off. Here we compared recall performance between trials in which subjects did and did not receive stimulation while a stimulus was learned.

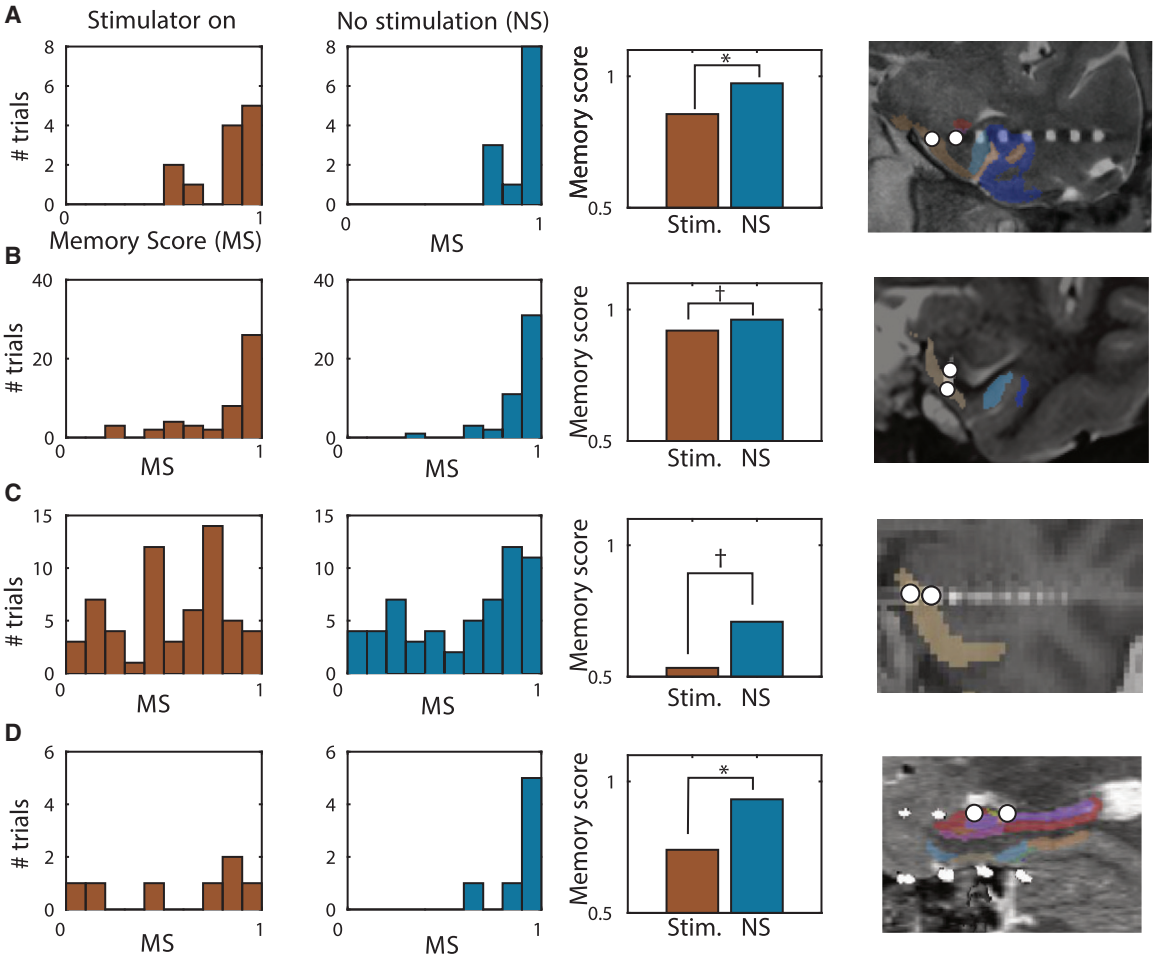

Figure 2. Effect of Stimulation on Individual Subjects' Spatial Memory Performance

(A) Data from subject 44, who received stimulation in the left entorhinal region. (Left) Distribution of spatial MSs observed across trials with stimulation (''Stim.'') and without stimulation ("NS"). (Left middle) Distribution of spatial MSs observed on trials without stimulation. (Right-middle) Median MSs in each condition. †$p < 0.1$, one-sided rank-sum test; *$p < 0.05$. (Right) Coronal brain image indicating the location of the stimulation electrodes (white circles) relative to the anatomy of the medial temporal lobe (MTL). Colors represent MTL subregions (Wang and Yushkevich, 2013); entorhinal region is depicted in beige.

(B) Data from subject 5, who received stimulation in the left entorhinal region.

(C) Data from subject 6, who received stimulation in the left entorhinal region.

(D) Data from subject 26, who received stimulation in the left hippocampus. Note that this brain image has a sagittal orientation.

In the spatial memory task on each trial the patient learned the location of an object that was hidden within a large virtual environment. We then assessed the accuracy of the patient's memory for each object's location by computing the memory score (MS) for its subsequent recall. The MS is a quantitative measure of how accurately the subject remembered an object's location, which we computed based on the distance from the subject's response to the object's actual location. Overall, subjects performed this task well, with a median MS of 0.80, which is above the chance level of 0.5. Figure 2A illustrates the performance of one subject who performed this task while receiving stimulation in the entorhinal region. Stimulation impaired memory in this subject. This subject's median MS was 0.82 with the stimulator on, compared to 0.92 with the stimulator off ($p < 0.05$, one-sided rank-sum test, $n_1 = n_2 = 12$, W = 178). Thus the presence of entorhinal stimulation impaired the accuracy of this subject's spatial memory, causing them to mark their responses at positions farther from the true object location compared to trials without stimulation. Similar patterns wherein entorhinal stimulation impaired memory accuracy were also present in other subjects (e.g., Figures 2B and 2C).

In the verbal task, we assessed the effect of stimulation on memory performance by having patients learn and recall lists of words (Sederberg et al., 2003). We measured memory performance on each trial by computing the MS as the proportion of presented items that the patient was able to subsequently recall. Here we again found that entorhinal stimulation during encoding impaired memory. Figure 3A illustrates data from a subject who performed this task while receiving entorhinal stimulation. This subject recalled 17% of items that were learned

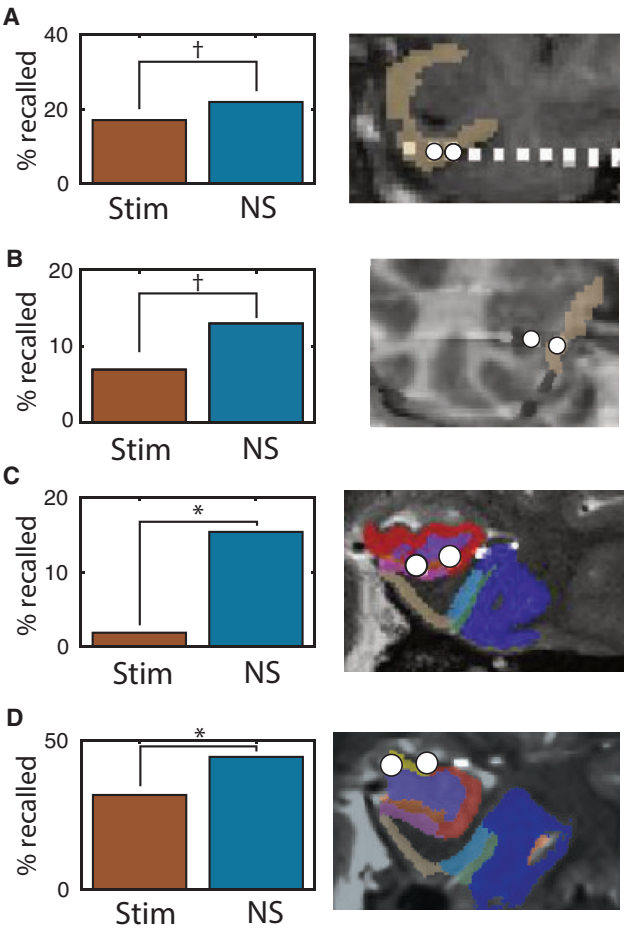

Figure 3. Example Subject Stimulation Data from the Verbal Memory Task

(A) Data from subject 48, who received stimulation in the left entorhinal region. (Left) Percentage of items recalled in lists when stimulation was applied (''Stim'') and lists without stimulation (''NS''). (Right) Brain image indicating the location of the stimulation electrodes (white circles) relative to the anatomy of the medial temporal lobe. †$p < 0.1$; *$p < 0.05$ one-sided z test.

(B) Data from subject 41, who had stimulation in the right entorhinal region.

(C) Data from subject 38, who was stimulated in the left hippocampus.

(D) Data from subject 14, who had stimulation in the left hippocampus.

with stimulation versus 22% without stimulation ($p = 0.07$, one-sided z test).

Across all patients and both tasks, entorhinal stimulation impaired memory accuracy (as measured by MS) by an average of 9% (permutation $p < 0.02$; $t[15] = 2.3$, $p < 0.02$). Entorhinal stimulation impaired memory in both the spatial task (permutation $p = 0.03$; $t[5] = 1.7$, $p = 0.08$) and the verbal task (permutation $p = 0.09$; $t[9] = 1.49$, $p < 0.09$). Aggregating across both tasks, the memory impairment from stimulation was robust in the subset of patients who had stimulation electrodes in the entorhinal region white matter (permutation $p < 0.02$; $t[8] = 2.6$, $p < 0.02$; Figure S2).

We also examined the effects of stimulation in other regions (Figure 4). Stimulation in the hippocampus significantly impaired performance by 8% overall across both tasks (permutation $p = 0.002$; $t[42] = 2.97$, $p < 0.003$.) This impairment was present separately in both the spatial task (permutation $p < 0.05$; $t[22] = 1.94$, $p < 0.05$) and the verbal task (permutation $p < 0.001$; $t[19] = 2.3$, $p < 0.02$). In each of the two tasks, entorhinal and hippocampal stimulation caused memory impairment when it was applied both in the left hemisphere and in the right hemisphere (Figure 4A). Notably, this bilateral effect persisted when we restricted our analyses to patients with clinical localization of language function to the left hemisphere (right-hemisphere stimulation, spatial permutation test $p = 0.038$, verbal $p = 0.018$; left-hemisphere stimulation, spatial $p = 0.11$, verbal $p < 0.01$).

Some stimulation sessions targeted the nonentorhinal parts of the parahippocampal gyrus (PHG), as well as regions outside the parahippocampal formation. In PHG there was a hint that stimulation improved MS. The MS enhancement from PHG stimulation was not robust statistically (mean MS increase, 4.2% across both tasks; permutation $p = 0.77$; $t[20] = -0.7$, $p = 0.76$), but a post hoc test showed that MSs from PHG stimulation were significantly greater than from hippocampal stimulation ($t(54) = 2.2$, $p < 0.05$). We also examined the effects of stimulation outside the hippocampal formation (Figure 4A), including sites in cingulate and prefrontal cortex (see Table S1). Across these areas there was a hint that stimulation caused memory impairment across both tasks, although the results were not statistically robust (permutation $p = 0.16$; $t[20] = 1.25$, $p = 0.11$).

Because our tasks provided each subject with a sizable number of independent memory-encoding trials, it allowed us to separately analyze the effect of stimulation for each session. Stimulation at entorhinal or hippocampal sites caused significant memory impairment ($p < 0.05$) in eight sessions individually. There were no sessions where stimulation in these areas caused significant memory improvement. This session-level asymmetry was statistically significant ($p < 0.01$, $n_1 = 8$, $n_2 = 0$, sign test).

To explain their findings mechanistically, Suthana et al. (2012) hypothesized that entorhinal stimulation improved memory by resetting the phase of ongoing hippocampal theta oscillations. To test this idea, we analyzed the effect of EC stimulation on hippocampal phase at various time points (Figure S3). We found that EC stimulation did not cause a sustained phase reset pattern of true hippocampal theta oscillations. Instead, stimulation only produced a brief phase alignment at the moment when stimulation was turned on or off. The transient nature of this pattern suggests it may be the result of an abnormality, such as a stimulation artifact, rather than the result of a theta oscillation with sustained phase consistency (Suthana et al., 2012).

DISCUSSION

By analyzing data from 49 subjects across seven hospitals who performed our hybrid cognitive-stimulation experiments, we demonstrated that brain stimulation at 50 Hz in the entorhinal region or hippocampus significantly impaired spatial and verbal memory encoding. Although memory is a complex process that involves widespread brain regions (Squire, 1992; Kim et al., 2016), these findings provide key additional evidence that the entorhinal region and hippocampus have a critical role in supporting memory function (Abrahams et al., 1997; Scoville and Milner, 1957). While the magnitude of the effect we observed

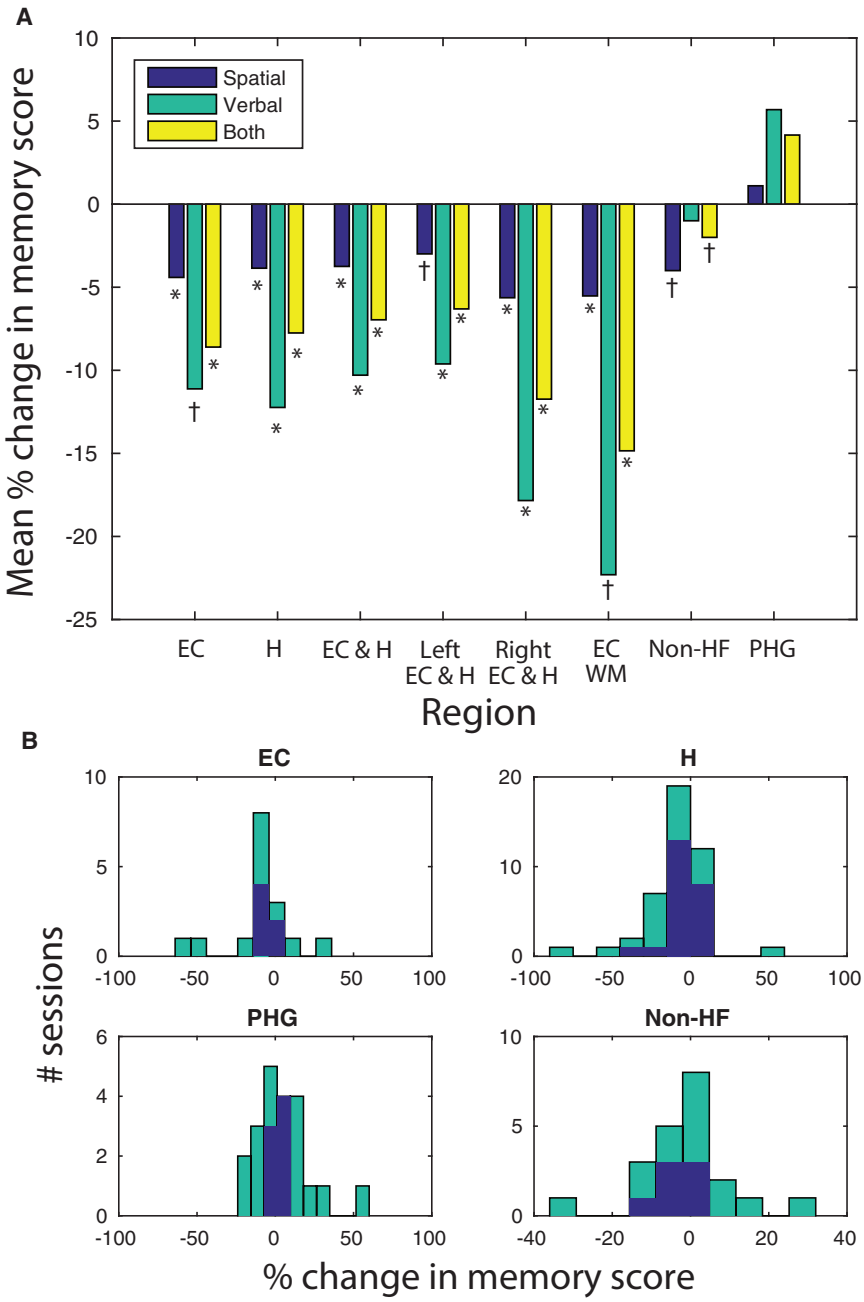

Figure 4. Population Analysis of the Effect of Stimulation on Memory Performance

(A) Mean percent change in MS as a result of stimulation, across tasks and stimulation regions. (Non-HF) Stimulation outside the hippocampal formation; see Table S1 for detail. *$p \leq 0.05$, permutation test; †$p < 0.1$.

(B) Histogram of percent changes in MS from stimulation in different brain regions in individual sessions. Colors denote spatial and verbal task sessions.

might be considered modest (~5%–20%), our finding that stimulation impaired memory might be unexpected in light of the report of Suthana et al. (2012) showing 64% memory improvement from entorhinal stimulation.

It should be noted that our study had key methodological differences compared to Suthana et al. (2012). Most notably, we analyzed a larger number of patients, and our tasks were designed to provide a larger number of independent observations, which provided us additional statistical power, including the ability to assess stimulation effects on a per-session basis. Unlike the task used by Suthana et al. (2012), our spatial memory experiment had a design that was similar to that of the Morris water maze (Morris, 1984), including an open arena with distant landmarks, hidden target locations, and randomized starting positions. This design encouraged subjects to encode spatial memories allocentrically, based on the arrangement of the target location relative to boundaries and external landmarks, which is thought to be supported by the medial temporal lobe (Burgess, 2006). In contrast, the Suthana et al. (2012) task had a visible target destination and a fixed starting location, which could allow the use of nonallocentric strategies that were not viable for our task, such as visually searching for the target during retrieval or route-based learning. In light of these differences, it is conceivable that the divergent results between our studies occurred because stimulation specifically impaired allocentric processing while having the opposite effect for nonallocentric processes.

An additional methodological difference between the two experiments concerns the duration of stimulation. In our spatial-memory experiment, stimulation was applied for exactly 10 s per trial (divided over two 5 s intervals), whereas in Suthana et al. (2012) a variable duration of stimulation was applied according to the length of time that the patient spent navigating on each manually controlled learning trial. As a result of this difference, it is likely that patients in Suthana et al. (2012) were stimulated for a longer total duration. Despite these task differences, it still might be considered striking that our experiments found memory impairment from both entorhinal and hippocampal stimulation, whereas Suthana et al. (2012) found neither of these patterns. In the Supplemental Experimental Procedures we explore these differences further.

Our findings have implications for understanding the neuroanatomical basis of memory. By eliciting memory impairment from stimulation in the entorhinal region and hippocampus during learning, our findings demonstrate that the medial temporal lobe is directly involved in memory encoding. In this way, brain

stimulation can provide causal evidence to support studies that had implicated these regions in memory encoding on the basis of lesions (e.g., Scoville and Milner, 1957; Kolarik et al., 2016) or correlations between neural activity and behavior (e.g., Lega et al., 2012). However, because stimulation can be applied with a fine temporal precision and is reversible, the types of findings that can be derived from this approach go beyond those from lesion studies because they can distinguish specific temporal intervals during complex behaviors when each brain region is functionally important.

Our finding of memory impairment from stimulation in the hippocampus proper differs from that of Suthana et al. (2012), who did not report that hippocampal stimulation reliably altered memory. However, our findings are consistent with a set of earlier studies that did in fact observe memory impairment from hippocampal stimulation (Coleshill et al., 2004; Lacruz et al., 2010). A question that emerged from this latter body of work is the potential relation between behavior and the hemisphere of hippocampal stimulation. Lacruz et al. (2010) found memory impairment only when both hemispheres were stimulated simultaneously, whereas Coleshill et al. (2004) found different types of impairment according to the stimulated hemisphere. Our results differ from both of these studies because we showed similar patterns of both spatial and verbal memory impairment irrespective of which hemisphere was stimulated. Because this effect persisted in a homogeneous population of patients who all had left-lateralized language function, it suggests that aspects of memory processing are supported in a holistic, network fashion (Kim et al., 2016). Further support for this network model of spatial cognition comes from our finding of a trend toward memory impairment from stimulation outside of the hippocampal formation (Figure 4). It might be unexpected that we found verbal memory impairment from entorhinal stimulation, due to the literature emphasizing this area's role in spatial processing (Hafting et al., 2005; Jacobs et al., 2013). However, there is evidence for nonspatial signals in the entorhinal region (e.g., Hargreaves et al., 2005), supporting the view that the entorhinal region supports the encoding of both spatial and nonspatial memories.

DBS is a powerful approach to disease treatment that has transformed aspects of neurology and neurosurgery (Perlmutter and Mink, 2006; Lozano and Lipsman, 2013). Given the success of DBS in other areas, we were disappointed to find that our approach to entorhinal and hippocampal DBS did not improve memory performance. Nonetheless, it may be possible to learn from our results to derive more effective stimulation protocols. Our findings support the general approach of choosing the entorhinal region and hippocampus as stimulation targets for memory modulation by showing that these sites are part of a network that can be used to causally modulate memory (Kim et al., 2016). However, going forward to achieve memory improvement it may be helpful to refine the types of stimulation parameters that are used, perhaps by measuring ongoing brain activity or by refining stimulation targets on the basis of individualized interregion connectivity patterns (Wang et al., 2014).

The domains where DBS has proven efficacious thus far have generally included regions where stimulation produces a predictable functional change (Lozano and Lipsman, 2013). The hippocampus and entorhinal cortex have a diverse functional anatomy, including heterogeneous neurons with widespread projections (Freund and Buzsáki, 1996) that represent different types of behavioral information, including time-varying coding patterns (Brandon et al., 2011). This complexity suggests that dynamic, responsive protocols may be necessary for hippocampal or entorhinal DBS to improve cognition and memory consistently.

EXPERIMENTAL PROCEDURES

The subjects in our study were 49 epilepsy patients who had electrodes surgically implanted to localize seizure foci and guide potential surgical treatment (Table S1). Each subject provided written informed consent prior to participation. Our multisite study was approved by local institutional review boards (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 Command Systems Center Pacific (SPAWAR/SSC).

In each testing session, a selected electrode pair was connected to an electrical stimulator (Grass Technologies or Blackrock Microsystems). The stimulators were programmed to activate during selected memory-encoding intervals of each task using a customized software and hardware interface. Our methods for electrical brain stimulation (see Supplemental Experimental Procedures) were modeled after the approach used in earlier work (Suthana et al., 2012).

Spatial Memory Task

Subjects performed a virtual-reality spatial memory task that is a variant of the Morris (1984) water maze procedure, adapted for use with brain stimulation in humans (see Movie S1). In each of the 48 trials in each task session, subjects learned the location of an object hidden in a rectangular arena. The virtual arena environment (1.8:1 aspect ratio) was surrounded by four walls and had four distal visual cues for orienting. Each trial included two encoding periods that each lasted exactly 5 s (Figure S1A). During each encoding period, the subject was placed at a random location and heading in the environment with the object invisible. Then the target object became visible, and over the course of 5 s, they were automatically moved toward the object. This automatic movement included first being rotated in place toward the target object (1 s), then driving straight toward the target (3 s), and finally pausing at the target location (1 s). The two encoding periods were separated by a 5 s pause. Alternating learning trials (24 of the 48) were designated as stimulation trials. During a stimulation trial, stimulation was applied continuously throughout both encoding periods.

After the two encoding periods, there was a 5 s delay and then the retrieval phase of the trial began (Figure 1B). The subject was placed randomly in the environment with the true object location unmarked and asked to remember the location where the object was located. The subject was instructed to drive to that location using the joystick and then press a button. The subject then received feedback on their response, by showing the actual and remembered object locations on an overhead map of the environment. We assessed response accuracy by computing the MS for each response (see Supplemental Experimental Procedures).

Between stimulation and nonstimulation trials, there was counterbalancing of the starting location, the starting orientation, and the object location. This counterbalancing was performed by creating a single set of location triads for the stimulation conditions and transposing them across the environment's diagonal for use in nonstimulation trials. This procedure ensured that the geometric relations between the start and object locations were perfectly matched between stimulation and nonstimulation trials.

Verbal Memory Task

To assess the effect of stimulation on verbal episodic memory, we asked each subject to perform the Free Recall task (Sederberg et al., 2003). In each list of this task, subjects studied 12 sequentially presented words and, after a distractor, attempted to recall them by speaking into a microphone. During

encoding, words were sequentially presented as text on the computer screen. Each word was visible for 1,600 ms, followed by a blank screen of 750–1,000 ms (Figure S1B). Lists were chosen from a pool of high-frequency nouns (available at http://memory.psych.upenn.edu/WordPools). Following the final word in each list, participants performed a 20 s math distractor task, and then participants were given 30 s to speak aloud as many words from the list that they could remember. Vocal responses were recorded on a microphone and later scored manually.

Each session of this task consisted of 25 lists, including 20 stimulation and 5 nonstimulation lists. On a stimulation list, the stimulator was active during the learning of half of the words on a list, such that it was turned on or off for two consecutive words at a time. When a given word pair was stimulated, the stimulation activated 200 ms prior to the presentation of one word and lasted continuously for 4.6 s, extending until after the second word in the pair disappeared from the screen. The stimulator was then inactive for the following two words. Across stimulation trials, the list position when the stimulator was activated was jittered randomly so that it began on either the first or the third word. We quantified the effect of stimulation on memory performance in this task by computing the MS as the proportion of viewed words that were successfully recalled while the stimulator was active versus those words learned while the stimulator was inactive. For this comparison, the nonstimulation group included all words on nonstimulation lists as well as unstimulated words on stimulation lists.

Statistical Analysis

We conducted parallel statistical analyses across both the spatial and verbal tasks, testing the hypothesis that items learned during stimulation were remembered more accurately than items learned without stimulation (Suthana et al., 2012). To statistically compare MSs between stimulation and nonstimulation trials within each session, we used a rank-sum test (spatial task) or a z test for proportions (verbal task). We used two approaches to assess the statistical significance of changes in MS with stimulation at the group level, a permutation procedure and a paired one-sided t test. Both methods generally provided comparable results and had the same degrees of freedom. For the permutation statistic, we first summarized the effect of stimulation for each session by computing a t statistic comparing the distribution of MSs for the stimulation or nonstimulation conditions. We then summed the z score from this test across sessions to compute a group-level test statistic. We assessed statistical significance by comparing the true group test statistic to a distribution of surrogate group test statistics from 10,000 iterations of shuffling procedure. The surrogate test statistics were generated by randomly shuffling the original dataset, randomly permuting the identities of the trials within each session that did and did not receive stimulation. We computed a p value for the hypothesis that stimulation significantly improved memory by measuring the rank of the true test statistic relative to the distribution of 10,000 surrogate test statistics.

SUPPLEMENTAL INFORMATION

Supplemental Information includes four figures, one table, one movie, and Supplemental Experimental Procedures and can be found with this article at http://dx.doi.org/10.1016/j.neuron.2016.10.062.

AUTHOR CONTRIBUTIONS

J.J. wrote the manuscript. J.J., J.M., and A.W. analyzed the data. J.J., J.M., S.A.L., T.C., Y.E., M.J.K., and D.S.R. designed the experiments. M.S., A.S., G.W., M.T.K., B.L., B.J., K.D., T.L., R.G., S.S., and C.S. performed the experiments. S.D. and J.S. processed the neuroimaging data. All authors edited the manuscript.

ACKNOWLEDGMENTS

This work was supported by the DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032). The views, opinions, and findings expressed are those of the authors and should not be interpreted as representing the official views or policies of the Department of Defense or the U.S. Government. We thank Marc Howard, Jeremy Manning, and Herbert Kaplan for helpful discussions. We thank Blackrock Microsystems for providing neural stimulation equipment.

Received: April 28, 2016
Revised: August 30, 2016
Accepted: October 31, 2016
Published: December 7, 2016

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Supplemental Information

Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory

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Supplemental Information: Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory

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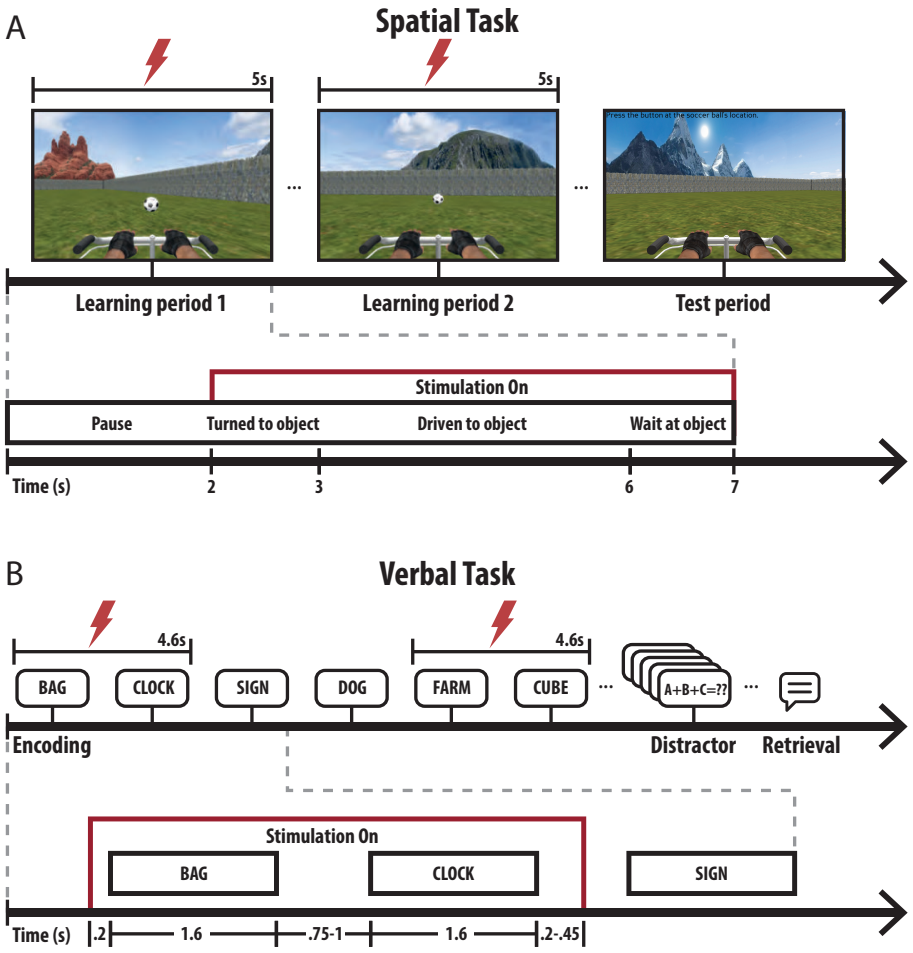
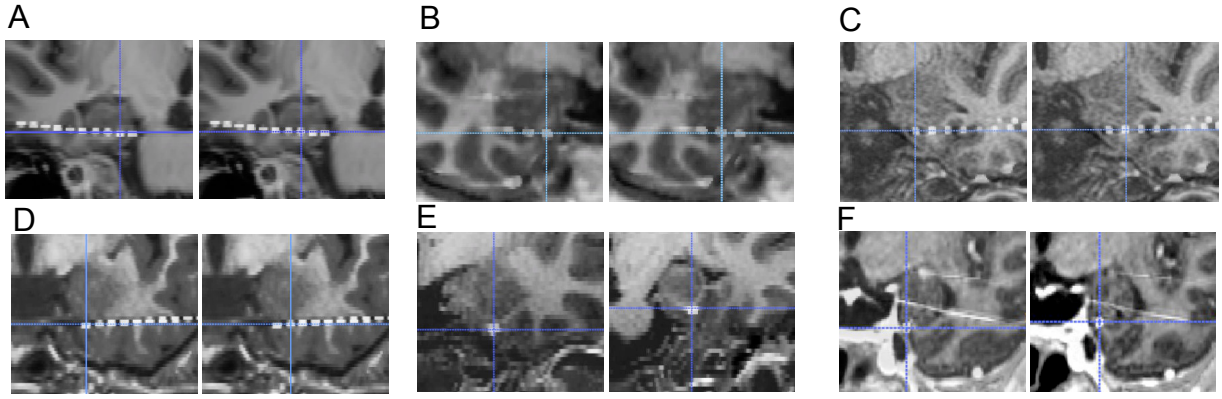
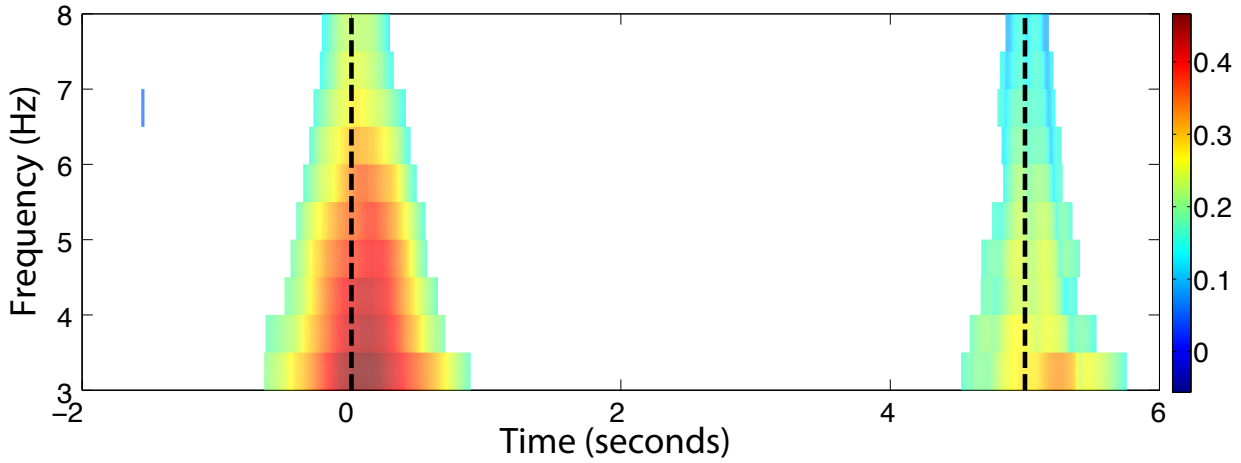


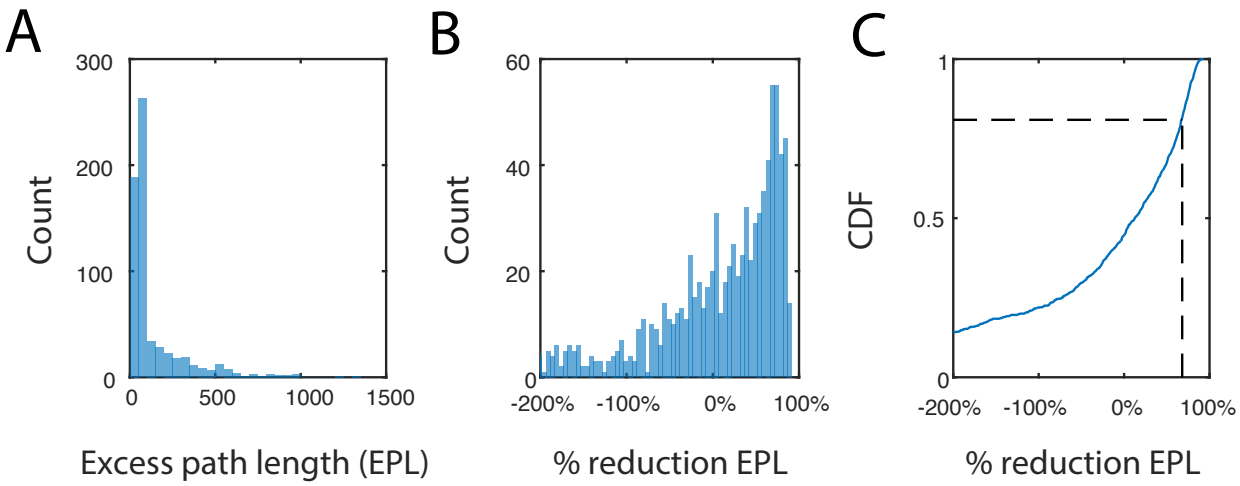
Supplemental Figure S1: **Detailed timeline of behavior and stimulation in spatial (Panel A) and episodic memory tasks (Panel B). Related to Figure 1.**



Supplemental Figure S2: **Images showing the positions of stimulation electrodes in patients who were stimulated in entorhinal white matter. Related to Figure 4.** These images are generated from thresholded computed-tomography images that were overlaid on coregistered high-resolution magnetic resonance images. **A.** Patient 47. **B.** Patient 41. **C.** Patient 44. **D.** Patient 46 **E.** Patient 15. **F.** Patient 5.



Supplemental Figure S3: **Analysis of entorhinal stimulation on hippocampal theta phase consistency in the spatial memory task. Related to Experimental Procedures.** Plot indicates the difference in magnitude of theta phase resetting in the hippocampus during the period when entorhinal stimulation was applied compared to unstimulated trials. The color indicates the mean circular vector length ($\bar{r}$; Fisher, 1993). Colored regions indicate $p < 0.0001$ (t test, uncorrected) at each timepoint and frequency. Dotted lines indicate timepoints when stimulation was turned on ($t = 0$ s) and off ($t = 5$ s).



Supplemental Figure S4: **Simulation of statistical methods employed by Suthana et al. (2012). Related to Experimental Procedures. A.** Distribution of excess path lengths from a similar spatial memory task where the data were made publicly available (Manning et al., 2014). **B.** Distribution of excess path lengths observed by chance, generated by applying random labels to the excess path length data illustrated in Panel A. **C.** Cumulative distribution function (CDF) from data in Panel B. Dotted line indicates the position in this distribution (i.e., 0.81) that corresponds to the 64% reduction identified by Suthana et al. (2012).

Subject characteristics				Spatial Memory Task				Verbal Memory Task			
Subject #	Sex	Age	Language	Average MS	Stim. region	Current (mA)	MS change due to stim.	Average MS	Stim. region	Current (mA)	MS change due to stim.
1	F	48	L					15	H	1.5	-0.1
2	F	49	L					38	A, A	1.5, 1.5	-12.4, 4.4
3	F	39	L					36	H	1.5	-1.1
4	F	20	L	71	H, H	1.5, 0.5–1.5	-2.1, -4.0	26	H	1	3.3
5	F	36	-	87	E	1.5	-7.3				
6	F	54	L	62	E, H, H	1, 1, 1	-5.8, -1.3, -6.9				
7	F	31	-					32	F	3.5	-3.7
8	M	57	-	61	H	1	2.4				
9	M	47	L					23	F, F	1.5, 1.5	0.6, -2.5
10	F	34	-	52	P, H, HP, H	0.5, 0.5, 0.5, 0.5	-0.1, -10.4, -0.3, -0.4				
11	F	48	L	80	H	1.5	-8.5	35	H, H	1.5, 1.5	2.0, -8.8
12	M	24	L					17	H	0.5–1	-5.6
13	M	32	L	79	C	1.5	-6.7	28	C, C	1.5, 1.5	-0.4, 0.8
14	F	36	-	80	H, H, H	1, 1, 1.5	5.8, 3.4, 1.0	38	H	1	-12.8
15	F	24	B	77	EP, EP	0.5, 0.5	2.6, -5.7	29	EP	0.5	3.5
16	M	48	L	25	H, C	1, 1	1.4, -0.1	19	H, HP	1, 1	3.0, -0.5
17	F	27	-					70	E, E (strip)	1, 1	2.1, -4.7
18	M	33	L	93	P, P	0.5, 0.5	1.3, 8.2	22	P, P, HP	1, 1, 1	-0.3, 2.8, 12.5
19	M	40	-					16	P	1.5	-1.7
20	F	19	L	74	H	1.5	6.2				
21	F	31	L	56	H	1	-3.9	17	P, H	1, 1	1.3, -3.6
22	F	45	L					16	HP	0.5	2
23	M	49	B					18	EP	1	4.8
24	M	47	L	57	H, H	1.5, 1.5	0.2, -1.4				
25	F	28	-	93	F	1.5	0.1	34	F	1.5	-1.9
26	F	39	L	74	H	1	-31.7				
27	M	22	-					40	P	1.5	-4.2
28	M	20	B	83	T	1.5	1.2	32	T	1.5	-2.8
29	F	19	-					32	H	1.5	-13.9
30	F	39	-					24	P	1	-3.6
31	M	34	L	92	H	0.5	-3.5	51	H	1.5	-9.3
32	F	36	-	68	F	3	-8.2	25	F	3	3.1
33	M	21	-	90	H	1	4.2				
34	F	34	-	95	P	0.5	1.5				
35	M	26	L	95	F	2.5	-2.2	40	F	2.5	4.2
36	F	40	L					21	P	0.5	3.9
37	M	24	-	82	C	1	-1.8	15	C	1	4.2
38	F	47	-					9	H	1	-13.5
39	F	30	L	85	H	1.5	-5.5	25	H	1.5	-5.8
40	F	26	R					27	H	0.5	-2.5
41	F	29	-					10	E	0.5	-6
42	M	47	L					41	I	0.5	0.3
43	F	58	L	69	E	1.5	3.5				
44	M	50	-	83	H, HE	1.5, 1.5	-8.3, -9.3	24	HE	1.5	-3.1
45	F	22	-					33	M	1	0
46	F	23	L					8	HE	1.5	-6.7
47	F	30	L					32	E, HE	1, 1	-1.5, -2.6
48	F	38	L					20	EP	1	-4.9
49	F	38	L					30	P	1	-7.8

Supplemental Table S1: **Subject summary table. Related to Figure 4.** *Average MS* indicates the patient's mean memory score (MS) averaged across both stimulation and non-stimulation conditions. MS scores reported in this table are multiplied by 100. *Stim region* indicates the brain regions where each subject received stimulation. Abbreviations: H, Hippocampus; E, entorhinal region; P, parahippocampal gyrus; C, cortex, T, temporal cortex; F, prefrontal cortex;, M, fusiform cortex; I, insula. Commas distinguish the regions from patients who participated in multiple stimulation sessions at different locations. Sessions where the bipolar pair of stimulation electrodes spanned two regions are denoted by two letters. *MS change due to stim.* indicates the difference in mean memory scores for stimulated versus unstimulated trials.

Supplemental Movie: Video of several trials of the Spatial Memory task. Related to Figure 1. This movie shows four trials of the spatial memory task from patient 5, who was stimulated in the entorhinal cortex. Lightning bolt and text in the upper-left corner of the screen indicate moments when stimulation was applied. This labeling was added to the movie for descriptive purposes and was not visible to the patient.

Supplemental Experimental Procedures

Participants. The subjects who participated in our study had electrodes implanted in various brain regions as dictated by clinical needs, including the hippocampus and entorhinal region. These subjects were selected to be aged between 18 and 65 and to have an IQ of at least 70. Data were collected using the same methods at seven hospitals: Thomas Jefferson University (Philadelphia, PA), Mayo Clinic (Rochester, MN), University of Texas Southwestern (Dallas, TX), Geisel School of Medicine at Dartmouth (Hanover, NH), University of Pennsylvania Medical Center (Philadelphia, PA), Emory University Hospital (Atlanta, GA), and Columbia University Medical Center (New York, NY).

Brain Stimulation. After receiving a trigger from the behavioral task, the stimulators were configured to provide a bipolar stimulation current between a pair of neighboring electrodes. Each depth electrode had a 0.059 cm^2 surface area. Electrodes targeting medial temporal structures were depth electrodes as in Suthana et al. (2012), with one exception noted in Table S1. Strip and grid electrodes were used to target other regions. Stimulation was applied with a frequency of 50 Hz and a balanced biphasic stimulation pulse of 300 μs per phase. We determined the stimulation current for each site on the basis of a pretesting monitoring procedure (Suthana et al., 2012), by manually applying a range of currents at each site, which began at 0.5 mA and slowly increased to a maximum level of 1.5 mA (depth contacts) or 3.0 mA (surface electrodes). The stimulation current used during each task was taken as the maximum level that could be applied to a given site without eliciting epileptiform afterdischarges or seizures. Neurologists continually monitored each subject's brain signals throughout pre-testing and experimental sessions. Subjects did not report that they could tell when stimulation was applied.

Assessing spatial memory accuracy. In the spatial task we quantified memory accuracy by first measuring the distance between the object's true location and the location of the subject's response. We used this raw error distance to compute the *memory score* (MS) for each trial. The MS is an unbiased measure of the subject's memory accuracy on each trial, which is computed as the rank of the subject's actual response location out of all the possible response locations. The MS is thus normalized to treat all target locations equally, by adjusting for the fact that the distribution of possible response error distances varies according to the object's distance to the environment's boundaries (e.g., objects near boundaries have a larger maximum possible error distance compared to objects in the center). MS=1.0 corresponds to a perfect response, MS=0 corresponds to the worst possible response (i.e., the location in the environment that is furthest from the true object location). MS=0.5 would be expected on average from purely random responses. Note that the MS is not based on excess path length as in Suthana et al. (2012).

Electrode localization. We used a multiphase procedure to determine the location of each stimulation electrode. Prior to electrode implantation each subject underwent an MRI scan with imaging parameters that provided a high-resolution image of the hippocampus and medial temporal lobe (0.5 mm $\times$ 0.5 mm $\times$ 2 mm resolution). Depth electrodes in the medial temporal lobe were localized using a semi-automated process. First, medial temporal lobe (MTL) subregions, including hippocampal subfields and extra-hippocampal cortical regions were automatically labeled in the high-resolution MRI acquired prior to electrode implantation using a multi-atlas based segmentation technique (Wang et al., 2013; Yushkevich et al., 2015). A neuroradiologist identified each electrode contact using a thin-section post-implant CT scan. This scan was then co-registered with the MRI (Avants et al., 2008) and the anatomical label for each contact was automatically generated. Finally, the neuroradiologist visually confirmed the output of the automated pipeline and provided additional detail on localization within MTL subregions. We designated each stimulation session as targeting a particular region if at least one electrode in the bipolar pair was in the region of interest, similar to earlier work (Suthana et al., 2012). We followed standard approaches for labeling each electrode's location within the medial temporal lobe. The entorhinal region is categorized as the antero-medial part of the parahippocampal gyrus and we use the term "parahippocampal region" as the posterior aspect of the parahippocampal gyrus. Within the entorhinal region, we distinguished contacts between white and gray matter similar to Suthana et al. (2012) (Fig. S2).

Effect of entorhinal stimulation on hippocampal theta phase. We sought to determine if entorhinal stimulation caused a phase reset of the hippocampal theta oscillation (Suthana et al., 2012). To this end, we examined electrophysiological recordings from the patients in our dataset who performed the spatial task with a stimulating electrode in the entorhinal region and a recording electrode in the hippocampus. Then we used Morlet wavelets (wave number = 7) to measure the phase on the hippocampal contact at 3–8 Hz in the encoding periods of stimulation and nonstimulation trials. We used circular statistics to measure the magnitude of phase locking ($\bar{r}$) (Fisher, 1993; Rizzuto et al., 2003) at each timepoint during this 5-s interval and compared the result between stimulation and nonstimulation trials.

As illustrated in Figure S3, this analysis indicated that phase resetting was a transient effect limited to the moments of stimulation onset ($t = 0$) and offset ($t = 5$), rather than extending throughout the stimulation interval as suggested by the data analyses of Suthana et al. (2012). This type of transient could be an artifact from turning the stimulator on or off. Therefore to exclude the possibility that our results were affected by these transients, we tested for changes in phase resetting over the middle 3 s of this interval, excluding these transients. This analysis revealed that when the transients were removed, there is no measurable change in mean hippocampal phase consistency ($\bar{r}$) between stimulation and nonstimulation trials (Wilcoxon sign-rank test, n=54, W=659, $p > 0.4$).

Simulation of statistical methods from Suthana et al. (2012). Suthana et al. (2012) reported that entorhinal stimulation improved spatial memory by 64%, as measured by the decrease in excess path length (EPL) during navigation with stimulation compared to the EPL during navigation without stimulation. To understand the nature of this finding we conducted a simulation of that study's analytical methods. We obtained raw data on subject's EPL from a paper by Manning et al. (2014) (data available online at `http://memory.psych.upenn.edu/`). The Manning et al. (2014) study examined 120 subjects in an experiment that is a close variant of the task used by Suthana et al. (2012). Critically, all of the key behavioral task characteristics of the Suthana et al. (2012) experiment are present in the Manning et al. (2014) protocol, including a similar task structure and environment layout.

We analyzed the data from Manning et al. (2014) following the methods from Suthana et al. (2012). We calculated EPL as the actual length of the subject's path on each navigation trial, subtracted from the minimum possible path from the trial's start location to its destination. As illustrated in Figure S4A, EPLs in this type of goal-directed navigation task are not distributed normally and are instead non-negative, positively skewed, and long-tailed. The long-tailed nature of this distribution is the likely result of a participant wandering randomly as a result of becoming "lost" during navigation.

Suthana et al. (2012) measured the effect of stimulation on memory by measuring the % reduction in EPL between stimulation and non-stimulation trials according to this formula:

$$\%EPL\ reduction = 100\% \times \frac{EPL_{NS} - EPL_{stim}}{EPL_{NS}}$$

EPL_{stim} and EPL_{NS} correspond to the mean excess path lengths in the stimulation and non-stimulation conditions of the task, respectively. Using this formula and the observed EPL distribution, we simulated the *% EPL reduction* that would be expected by chance by using a permutation procedure. Here, for each of 10,000 iterations, we randomly labeled each observation as "stimulated" or "unstimulated", and computed the observed % EPL reduction. Figure S4B shows the results of this analysis, illustrating that the chance level distribution of % EPL reduction is negatively skewed and has a maximum value near 100%.

The mean % EPL reduction that Suthana et al. (2012) observed for stimulation in the entorhinal region was 64%. By examining the cumulative distribution function of % EPL reduction expected by chance (Fig. S4C), it indicates that this value occurs at the 81st percentile in this distribution (i.e., one-sided $p = 0.19$). In conclusion, our simulation of their methods, using data of a similar size and type, indicates that an effect at least as big as the 64% EPL reduction they observed is found in 19% of randomly shuffled data.

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