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Task-dependent effects of intracranial hippocampal stimulation on human memory and hippocampal theta power

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ABSTRACT

Background: Despite its potential to revolutionize the treatment of memory dysfunction, the efficacy of direct electrical hippocampal stimulation for memory performance has not yet been well characterized. One of the main challenges to cross-study comparison in this area of research is the diversity of the cognitive tasks used to measure memory performance.
Objective: We hypothesized that the tasks that differentially engage the hippocampus may be differentially influenced by hippocampal stimulation and the behavioral effects would be related to the underlying hippocampal activity.
Methods: To investigate this issue, we recorded intracranial EEG from and directly applied stimulation to the hippocampus of 10 epilepsy patients while they performed two different verbal memory tasks – a word pair associative memory task and a single item memory task.
Results: Hippocampal stimulation modulated memory performance in a task-dependent manner, improving associative memory performance, while impairing item memory performance. In addition, subjects with poorer baseline cognitive function improved much more with stimulation. iEEG recordings from the hippocampus during non-stimulation encoding blocks revealed that the associative memory task elicited stronger theta oscillations than did item memory and that stronger theta power was related to memory performance.
Conclusions: We show here for the first time that stimulation-induced associative memory enhancement was linked to increased theta power during retrieval. These results suggest that hippocampal stimulation enhances associative memory but not item memory because it engages more hippocampal theta activity and that, in general, increasing hippocampal theta may provide a neural mechanism for successful memory enhancement.

Introduction

The hippocampus is a pivotal structure in episodic memory [1] and has been one of the main target structures of electrical brain stimulation aimed at manipulating the neural circuits underlying memory formation and, ultimately, at improving memory performance [2]. Surprisingly, however, previous studies using direct hippocampal stimulation have broadly converged on the finding that stimulation has adverse effects [3–5] or no effect [6] in enhancing memory, with only a few having reported favorable effects [7–9] including in our own recent study [10]. These human and animal studies have underscored the causal role of the hippocampus in memory but raised many questions in the field regarding the factors that determine the efficacy of its stimulation.

One prominent theory of hippocampal function postulates that the hippocampus has a special role in relating or binding different attributes together to form memory for prior episodes into an

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integrated memory trace [11,12]. As such, the hippocampus is often characterized as a hub of information, engaged to a greater extent for associations among memory elements than it is for individual elements [2,13,14]. Amnesic patients with selective hippocampal lesions exhibit greater impairment in item-item associative memory than in memory for the items themselves [15–17], and similar findings have also been reported in studies of primates [18,19] even within the same individual [20]. Underlying the differential behavioral effects could be a difference in hippocampal neuronal responsiveness in the two types of memory tasks employed [21]. Indeed, neuroimaging studies demonstrated greater hippocampal activation during encoding of associative than item information [22,23] and claimed that the hippocampus preferentially contributes to associative memory [17,24].

If the effect of applying direct electrical current to the hippocampus is dependent on its latent activity [25], then it is possible that tasks that differentially engage the hippocampus (e.g., item vs. associative memory) may be differentially influenced by hippocampal stimulation. To explore this issue, the present study added patients with different memory tasks to compare the effect of direct hippocampal stimulation on a word pair associative memory task for which we previously reported positive stimulation effects [26] and a single word item memory task that was slightly modified from previous studies that reported negative effects of stimulation [3,4].

More importantly, unlike our recent study [26], the present study aims to investigate the underlying hippocampal activity elicited by the task at hand. The relevance of the hippocampal theta rhythm on cognition is well-documented [27–29], and past findings on human iEEG indicate that hippocampal theta rhythm enhances context-dependent retrieval of sequences [30,31]. Thus, we hypothesized that associative memory and item memory would be differentially affected by hippocampal stimulation, and that stimulation-induced memory enhancement would be related to an increase in hippocampal theta power.

Materials and Methods

Subjects and electrode localization

Ten intractable temporal lobe epilepsy patients [4 males and 6 females; average age, 30.5 ± 10.5 years; Memory Quotient (MQ) > 60]. Data were collected in a numerical order (Table 1) using the same methods at Seoul National University Hospital (Seoul, South Korea) had hippocampal depth electrodes implanted (Fig. 1A) and then performed two different verbal memory tasks (i.e., word pair associative memory and single word item memory) with or without stimulation to the hippocampus. The local IRB approved the study protocol (H-1407-115-596) and all subjects provided written informed consent to participate in the present study.

All electrodes were implanted for clinical purpose only. Electrodes (AdTech Medical Instrument Corporation, Racine, WI, USA) targeting medial temporal structures were depth electrodes (platinum, surface area of 0.059 cm^2, placed 6 mm apart). Depending on clinical need, subdural grid electrodes were placed on the cortical surface (diameter of 4 mm, placed 10 mm apart) with stainless steel contacts. Prior to electrode implantation, each patient underwent a magnetic resonance (MR) imaging in a Magnetom Trio, Magnetim Verio 3-tesla (Siemens, München, Germany) or Signa 1.5-tesla scanner (GE, Boston, MA, USA). Computed tomography (CT) images were recorded using a Somatom sensation device (64 eco; Siemens München, Germany). Additional MRI and CT scans were performed following electrode implantation.

Target hippocampal electrodes for stimulation were inserted into the mid-body of the hippocampus gray matter using a temporo-lateral approach. A neuroradiologist identified each electrode contact using a thin section postimplant CT scan. The brain model and implanted electrodes were reconstructed from individual preoperative MR images and postoperative CT images using CURRY 7.0 (Compumedics Neuroscan, Charlotte, NC, USA). A neuroradiologist and neurosurgeon then confirmed the hippocampal electrodes within the medial temporal lobe (MTL). Each patient had at least one hippocampal electrode in the region of interest. The stimulation was applied between two adjacent contacts on the same depth electrode. Given that the electrodes within the MTL were 6 mm apart, the adjacent two stimulation target electrodes were identified as the hippocampal gray matter and in the temporal white matter and that the anode/cathode was assigned accordingly.

Memory tasks

To assess the effect of stimulation on task-dependent memory, we asked each subject to perform the two different verbal memory tasks, both of which are known to recruit the medial temporal lobe including the hippocampus during memory encoding [32], using STIM2 software (Compumedics Neuroscan, Victoria, Australia).

Table 1
Demographics and clinical characteristics of patients.

Subject	Demographics		Clinical characteristics				Stimulation parameter	
	Age	Sex	Seizure type	Pathology	Resection	Seizure onset	Anode	Cathode
Sub1	31	F	TLE	HP neuronal loss	aTG, aHP	STG	L.mHP	LWM
Sub2	55	F	TLE	DG dispersion	HP	PHG	L.mHP	LWM
Sub3	27	F	TLE	Temporal lobe FCD	ITG	TP, STG	L.mHP	LWM
Sub4	27	M	TLE	PHG reactive gliosis	PHG	aTG,	R.mHP	LWM
Sub5	28	F	TLE	FCD heteropia	PHG, AMY	AMY	R.mHP	LWM
Sub6	21	M	TLE	HP neuronal loss	AMY, PHG	OFC	R.mHP	LWM
Sub7	24	F	TLE	Temporal lobe FCD,	aTG, AMY	AMY	R.mHP	R. mHP
Sub8	25	F	TLE	left occipital lobe FCD	Occipital gyrus, HP	occipital lobe	L.mHP	LWM
Sub9	46	M	TLE	Temporal lobe FCD	aTG, AMY, aHP	temporal lobe	L.mHP	LWM
Sub10	20	M	TLE	AMY neuronal loss	aTG, AMY, HP	AMY	L.mHP	LWM

Abbreviations: R. = Right; L. = Left; HP = hippocampus; mHP = mid-hippocampus; aHP = anterior-hippocampus; AMY = amygdala; LWM = limbic white matter; PHG = parahippocampal gyrus; DG = dentate gyrus; aTG = anterior temporal gyrus; STG = superior temporal gyrus; ITG = inferior temporal gyrus; TP = temporal pole; TLE = temporal lobe epilepsy; FCD = Focal cortical dysplasia; OFC = orbitofrontal cortex.
Subject demographic data are presented together with clinical observations from clinically identified seizure onset zones, and pathology in subjects who underwent corresponding surgery. Anode and cathode indicate brain regions of stimulation in each subject. In all subjects, the stimulation location was either the left or the right mid-hippocampus, the mean current was 2 mA, and the mean charge density was 360 μC/cm^2/phase.

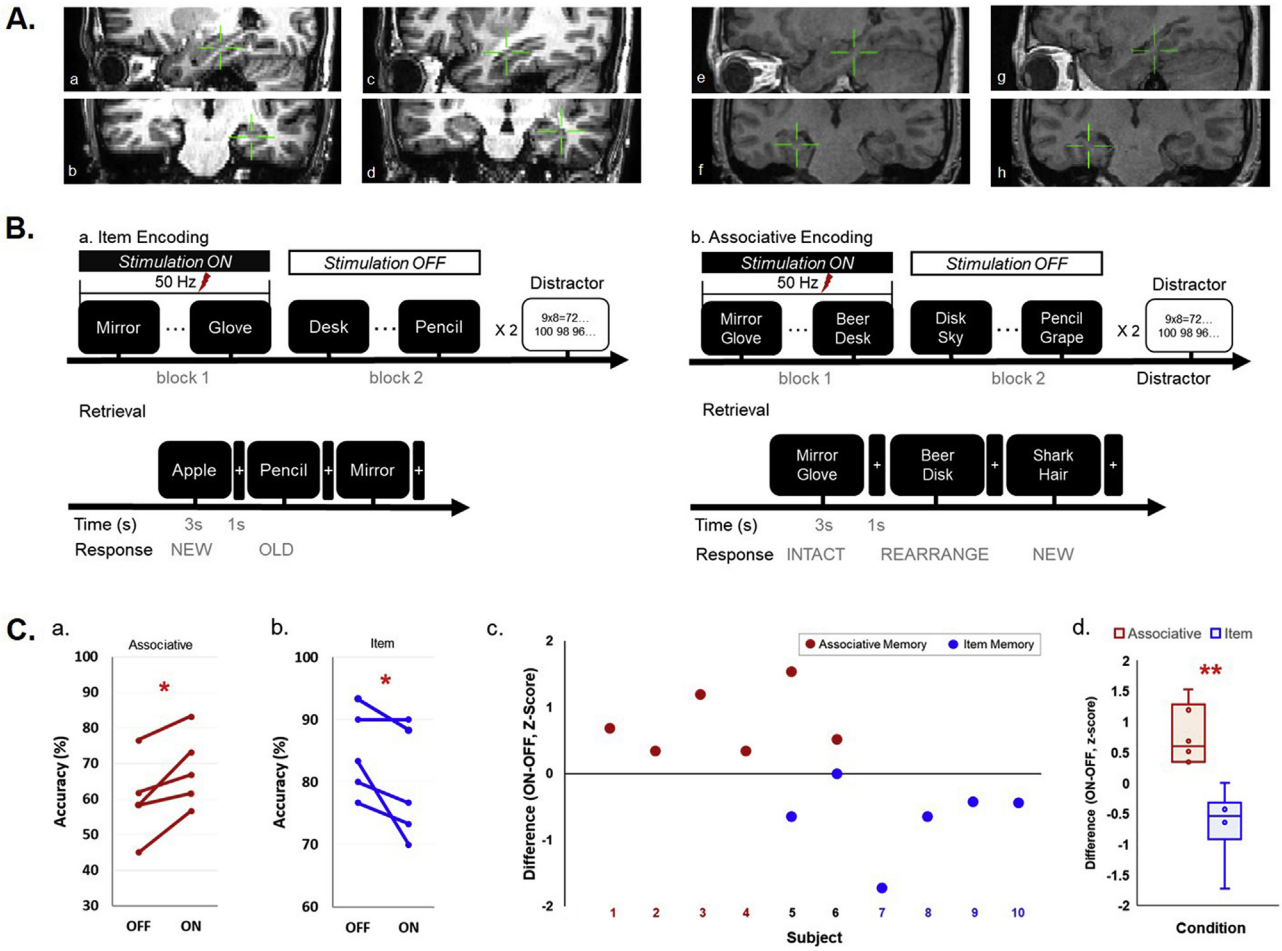

Fig. 1. A. Location of stimulation contacts in the medial temporal lobe. Preoperative high-resolution MR imaging co-registered with a postoperative CT scan (not pictured) showing the location of depth electrodes. The green crosshair denotes the location of the stimulation electrode in the right middle hippocampus in sagittal anode (a), sagittal cathode (b), coronal anode (c), and coronal cathode (d) sections in Subject 4. (e–h) The left middle hippocampus electrode in Subject 3. **B. Paradigms of verbal memory tasks with stimulation.** Example of the timeline of (a) word item memory and (b) a word pair associative paradigm. The 50 Hz stimulation was delivered in 5 s trains only at the encoding phase and was randomly assigned to two of four blocks. Lightning bolts denote periods when stimulation may be applied. **C. Effects of stimulation on verbal memory performance.** (a–b) The proportions of correctly recognized words under the *stimulation-off* and *-on* conditions. Accuracy differences between the two conditions were significant across subjects (Wilcoxon signed-rank test, $^{*}p < .05$). Colors denote associative task (red) and item task (blue). (c) The Z-score difference accuracy in between *stimulation-on* and *-off* in each individual subject. Note that Subjects 5 and 6 performed both tasks. (d) Mean difference accuracy across conditions for each task (Mann-Whitney *U* test, $^{**}p < .01$). Error bar indicates standard error of mean (SEM). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Each memory task comprised three successive stages: encoding, distractor, and retrieval (Fig. 1B). For word pair associative memory, six subjects completed sequentially 120 word pairs modified based on previous studies [33]; the pairs consisted of two Korean concrete nouns with a mean frequency of 105.11 (SD = 3.35, IQR = 122.5). For word item memory, six subjects performed 120-word items of one concrete noun, randomly shown one at a time.

During encoding, a word pair was visible for 4 s, followed by a white fixation with a black screen of 1 s. To ensure a deep encoding, we used previously reported encoding feedback [34] in which participants were encouraged to respond by pressing with their index finger if they judged the appeared word on the screen as "pleasant" or "unpleasant". Following the final word of the encoding block, subjects took a 10 min break and then performed a 30 s math distractor task consisting of a series of arithmetic problems for "A-B = ?", where A and B were randomly chosen integers ranging from 1 to 100.

In retrieval, a word pair associative test that was visible for 3 s, the subjects were asked to press one of three keyboard buttons as accurately and quickly as possible, depending on whether the word pairs had been presented before in the same pair ("intact"; button #1), whether the two words had been presented before but as parts of different pairs during encoding ("rearranged"; button #2) or whether both words were all new (button #3). No words pairs appeared twice. In retrieval on the item task, subjects were to respond whether the word had been presented before ("old"; button #1) or was new ("new"; button #2) or the subject was not sure ("familiar"; button #3). For the main experimental session, no patients were exposed to the same experimental task more than once.

Brain stimulation

Stimulation was given only in the encoding phase by passing an electrical current between two adjacent electrodes using biphasic symmetric squared wave pulse of 300 μs per phase, at a frequency of 50 Hz, which was reported to have a positive effect on memory performance in past studies [6]. A Grass S12X stimulator (Natus, RI, USA) delivered a cycle of 5 s trains using 2.0 mA current equally in all subjects. Total energy was between 30 and 57 ($\mu C/cm^2/ph$) of

Table 2
Results of neuropsychological memory test of patients.

Subjects	Neuropsychological memory test		
	Full Scale IQ	MQ	WMS word associative memory
Sub1	91	90	11
Sub2	77	94	30
Sub3	78	81	12
Sub4	97	112	18
Sub5	85	111	9
Sub6	110	60	22
Sub7	57	66	5
Sub8	65	74	10
Sub9	97	89	17
Sub10	101	79	24
Average	85.8 (15.8)	86.2 (20.2)	15.8 (7.4)

Data presented as mean (SD).
Subject pre-operative neuropsychological results. A clinical psychologist employed the Wechsler Adult Intelligence Scale-Korean version (K-WAIS-IV) for Full Scale Intelligence Quotient (IQ). The Rey-Kim Memory test was used to assess Memory Quotient (MQ) and the Wechsler Memory Scale (WMS) IV was used for word associative memory.

charge per phase and square centimeter that was demonstrated to be safe and well tolerated in patients with epilepsy.

The encoding phase consisted of two sessions, with two blocks in each session. Stimulation was given during one of the two blocks in each session. During the *stimulation-on* block, the stimulator was active during the learning of a word (or a word pair), turned on or off for each trial. The stimulation was activated at the presentation of the word and lasted continuously for 5 s, extending until the following fixation; the stimulator was then inactive for the following word and fixation. The stimulation was randomized to occur during one of the two blocks in each session. Note that for the present study, we compared stimulation effects between the *stimulation-on* and *stimulation-off* blocks.

Neuropsychological memory test

Neuropsychological assessments were conducted on all subjects before surgery (within one month) as part of routine clinical practice [35]. We measured the Memory Quotient (MQ) using the verbal immediate and delayed recall subtests from the Korean version of the Rey auditory verbal learning test (RAVLT). The RAVLT requires immediate recall a list of 15 words presented audibly at intervals of 1 s, and this procedure is repeated five times (verbal immediate recall) after 20 min' recall for the list of words (verbal delayed recall). We measured WMS word associative memory using the verbal paired associates subtest from the Wechsler memory scale fourth Edition (WMS-IV). The WMS requires that patients learn seven pairs of unrelated words presented audibly and then listen to the first word of each pair and recall immediately the other word in the pair (verbal paired associates immediate, VPA1). After 30 min, the first word of the pair was presented and then the patient was required to recall the other word in the pair (verbal paired associates delayed, VPA2). For the purpose of revealing the relationship between individual memory capacity and the memory performance with hippocampal stimulation, we used the subjects' FSIQ, MQ, and WMS word associative memory in this study. Details of neuropsychological test scores are presented in Table 2.

Analysis of memory performance and electrophysiological data

Behavioral data were analyzed with SPSS 23 (IBM, Armonk, NY, USA). We quantified the stimulation-on memory performance in this task by computing the proportion of learned words that were successfully recognized during *stimulation-on* versus those words learned during *stimulation-off*. To test whether items learned during stimulation were remembered more accurately than items learned without stimulation, we compared the accuracy of memory scores between *stimulation-on* and *stimulation-off* trials within blocks; we used the Wilcoxon signed-rank test and assessed the statistical significance of changes. Then, we compared memory differences with neuropsychological memory scores using the Spearman's rank correlation analysis with bootstrap confidence intervals calculated using 1000 resamples with a significance level of 95 %.

Intracranial EEG data including depth and ECoG were recorded using a 128-channel digital video monitoring system (Telefactor Beehive Horizon with an AURA LTM 64- & 128- channel amplifier system) digitized at a sampling rate of 1600 Hz. The impedance of the electrodes was between 0.3 and 1 kΩ when implanted. Analyses of intracranial EEG focused on oscillations in iEEG of field potentials recorded from the hippocampus in two patients who performed both the word pair associative and word item memory tasks. Our main interests were whether oscillatory activity in the iEEG of field potentials would differ between the two task conditions and further testing the characteristics in successfully recognized words. To this end, iEEG data were recorded during experimental testing from the same targeted hippocampal electrodes for stimulation. Given the electrical stimulation produced substantial electrical artifacts in the recording channels, and volume conduction effects in nearby channels, iEEG data were not recorded when stimulation was given. We investigated the neural mechanism underlying the effects of hippocampal *stimulation-on* by analyzing iEEG data from memory retrieval as well as *stimulation-off* phase during encoding in the two subjects who performed both the tasks.

Analyses of iEEG data were conducted with MATLAB (Mathworks, Natick, MA, USA). Prior to data processing, all channels clinically identified within the ictogenic zone, or those electrodes observed as corrupt during recordings, were excluded from all data analysis. Electrodes were also excluded from subsequent analyses if there were any motion artifacts. All data preprocessing was performed at a single electrode level. For each subject, all non-excluded electrodes were first digitally filtered with a low-pass filter of 100 Hz. To attenuate 60 Hz line noise, a notch filter at 60 Hz was applied. The recorded data were then re-referenced to the common average reference (CAR).

To quantify specific changes in different frequency ranges in the hippocampal gray matter with a continuous time complex value representation of the signal, we conducted a time-frequency analysis. We performed spectral decomposition (1 frequency from 1 to 10 Hz, 2 frequencies from 10 to 20 Hz, and 4 frequencies from 30 to 100 Hz, logarithmically spaced; Morlet wavelets; wave number = 2.48) for the 0–4 s epoch relative to word onset in the encoding phase and 0–3 s epoch relative to word onset in the retrieval phase. Mirrored buffers (length = 2 s) were included before and after the interval of interest and then discarded to avoid convolution edge effects. Transformed single trial data were squared for calculating power and then normalized by the mean and standard deviation of the baseline power (−1 to 0 s of word presentation onset) of each frequency.

To test the significance between *stimulation-on* versus *stimulation-off* during memory retrieval phase, we extracted *t*-values using the means and SDs with the independent two sample *t*-test. For visualization of time frequency map, epoched single trials were averaged across all trials. Then, to investigate the theta power changes in the hippocampus, we analyzed the signal across three different frequency ranges that have been implicated in episodic memory and plotted time series data with averaged *t*-value in each of the three frequency bands. To obtain hippocampal power during

the encoding phase, we performed the same procedure and same spectral decomposition method described above.

For statistical analysis, trials were split into 2 groups based on whether the stimulus was associative memory or item memory. The averaged *t*-value across the presentation for stimuli (0–3 s) in all trials of each three frequency bands was compared between associative memory and item memory. This result was then used to perform group-level comparison in each of 6 subjects (Fig. 2C). For the analysis of encoding phase, we performed the same procedure and same spectral decomposition methods described above. Note that the independent two sample *t*-test for encoding phase was conducted with all trials between two different memory tasks within subject (Fig. 3C and D right panel).

For Power spectral density (PSD) analysis, analyses for each patient, and state were calculated separately in Matlab. PSD analysis used the Welch method (*pwelch* function in Matlab with a 512 ms window, 256 ms of overlap, see Fig. 3A for an example of PSD in Subject 5). We determined significance using non-parametric statistics that controlled for multiple comparisons [36].

Results

Hippocampal stimulation improves associative memory but impairs item memory

In our study, 10 subjects including two within-subjects with implanted electrodes performed two different verbal memory tasks while hippocampal stimulation was applied during some encoding trials (Fig. 1A). We designed these tasks specifically to assess the differential effects of electrical stimulation in the hippocampus on memory encoding (Fig. 1B). We assessed the effect of stimulation on memory by examining behavior in the subsequent recognition phase of each task. In the item task, we defined successful memory as correctly identifying old items as "old". The mean percentage of correct responses across all trials was 83.6 ± 7.3%. We defined successful memory in the associative task as the combined accuracy in the "intact" and "rearranged" trials because in order to correctly identify a pair as "rearranged", the subject must not only recognize that the words are all familiar but, they also recognize that the words are not in the correct pairing arrangement. The mean percentage of correct responses on the associative task was 63.5 ± 9.8%. Note that the behavioral result of the associative task is the same as in our recent study [26].

We then assessed individual memory performance for the two memory tasks on *stimulation-on* blocks compared with *stimulation-off* blocks and conducted nonparametric statistical within-subject's comparison of mean accuracy between *stimulation-on* and *stimulation-off* trials to measure significance (Fig. 1C). For associative memory, the average accuracy in the six subjects improved significantly with hippocampal stimulation (*off* = 59.3 ± 10.1 %; *on* = 67.3 ± 9.7%; Wilcoxon signed-rank test, $df = 5$, $p = .027$). In contrast, for item memory, the average accuracy in the six subjects was significantly lower with hippocampal stimulation (*off* = 86.1 ± 6.5%; *on* = 81.1 ± 8.0%; Wilcoxon signed-rank test, $df = 5$, $p = .042$). Crucially, we conducted a comparison analysis of the effect of stimulation (i.e., the difference scores for *stimulation-off* and *-on* transformed to Z-scores) across the two conditions and found + 0.77 ± 0.45 for associative memory, but - 0.65 ± 0.53 for item memory (Mann-Whitney *U* test, $Z = -2.9$, $p = .004$); this statistically significant difference confirmed a task-dependent effect of stimulation.

Stimulation-induced memory enhancement is reflected in increased theta power during retrieval

We next sought to identify neural correlates of the observed memory enhancement in the hippocampus during memory retrieval. In this analysis, we used neural oscillations during the 3 s

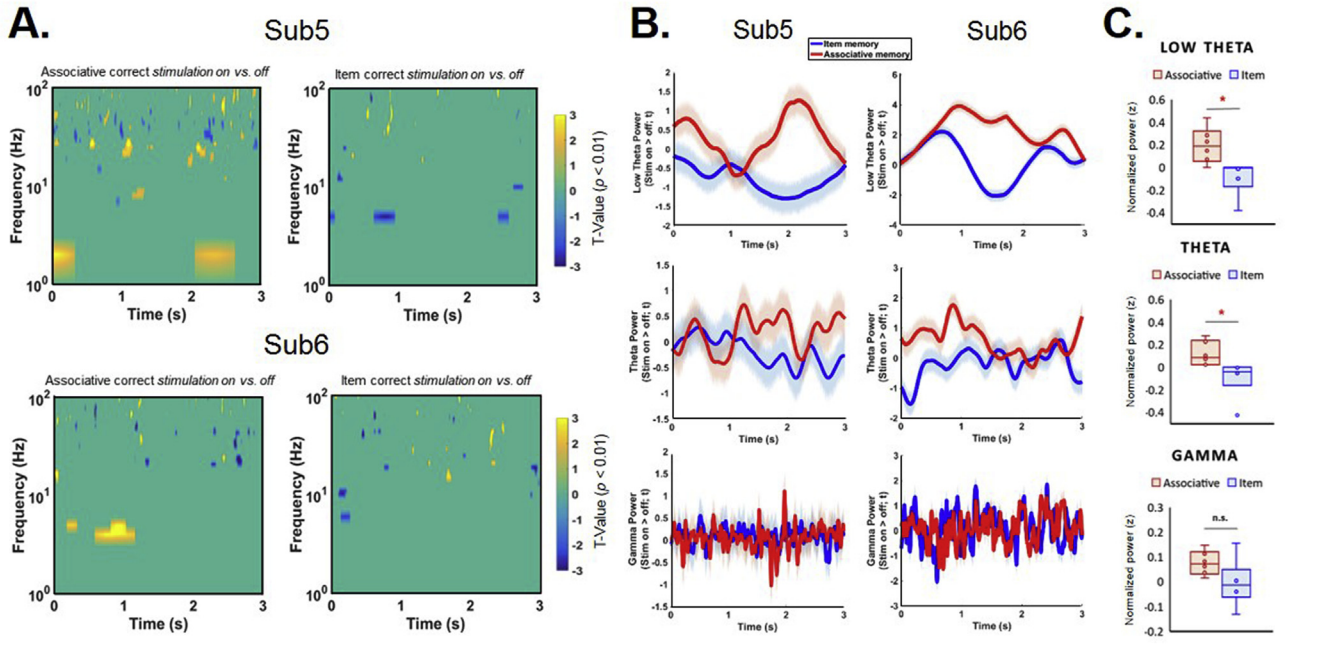

Fig. 2. Memory effect in the hippocampus during retrieval. A. Individual within-subject time-frequency maps for Subjects 5 and Subject 6; a mean difference is shown in normalized power in correctly recognized trials between *stimulation-on* and *-off* during encoding. Baseline normalized power changes at each of 10 log-spaced frequencies between 1 and 100 Hz during the associative memory (left) and item memory (right) tasks in each subject. Colored regions indicate significance at $p < .01$ resulting from two-sample *t*-test comparing *t*-valued power. **B.** hippocampal time courses of 2–4 Hz (low theta), 4–10 Hz (theta), and 30–100 Hz (gamma) power during word presentation. **C.** Group-level comparison of baseline normalized theta power changes across six patients in each task. The results showed significant differences in the low theta and theta ranges but not in the gamma range (Mann-*Whitney U* test, $p < .05$ adjusted *p* value with *post-hoc*, n = 6).

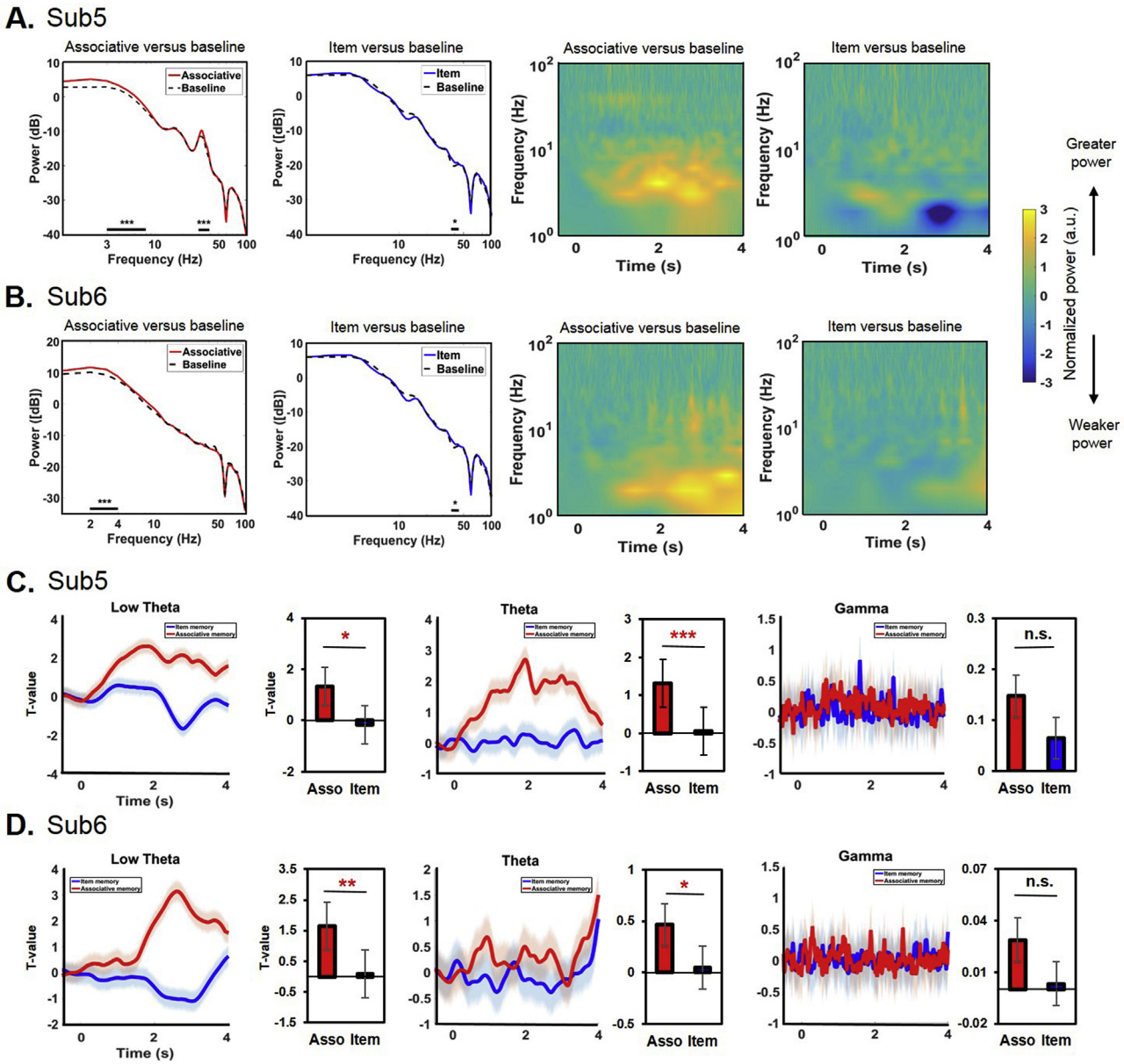

Fig. 3. Neural evidence of verbal memory encoding. A-B. The left two panels show frequency spectrograms for the associative memory (red) and item memory (blue) tasks, respectively, for Subjects 5 and 6, showing mean difference in power between task and baseline ($^{*}p < .05$, $^{***}p < .001$). The right two panels indicate baselined power changes shown at each of 10 log-spaced frequencies between 1 and 100 Hz for the associative memory and item memory tasks. **C-D. Memory-related oscillatory activity of verbal memory encoding.** Time courses of 2–4 Hz, 4–10 Hz, and 30–100 Hz power in the hippocampus during word presentation for the two subjects who performed both tasks (Subject 5 and Subject 6, respectively). All power values are baseline normalized to the pre-stimulus baseline. Shaded error regions are ± 1 within-subject SEM. The bar represents averaged power during item presentation, shown with 95% confidence intervals ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$). n.s. indicates not significant. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of stimulus presentation during retrieval trials to investigate how prior hippocampal stimulation during the encoding phase affected subsequent hippocampal oscillatory activity during retrieval. We first looked at two subjects who performed both tasks for within-subject comparisons. Fig. 2A shows the baseline normalized spectral power in the hippocampus for both subjects, calculated by the oscillatory activity difference between correctly remembered words in the *stimulation-on* and *stimulation-off* conditions in both the associative and the item memory tasks. The overall results exhibited that oscillatory power in the theta range (2–10 Hz) increased significantly in the associative memory task but not in the item memory task. Successful recognition in associative memory but not in item memory exhibited increased power in the theta frequency range for remembered words previously followed by stimulation compared with remembered words without stimulation (two-sample *t*-test, $p < .01$).

We next analyzed the signal across three frequency ranges that have been previously implicated in episodic memory [3,28,30,37–41], 2–4 Hz ("low theta" or "delta"), 4–10 ("theta"), and 30–100 Hz ("gamma"). We averaged the oscillatory power in each of the frequency bands and plotted during the retrieval period (0–3s) in which the word stimulus was visible on the screen. Associative and item memory showed a significant power difference in the low theta and theta ranges but not in the gamma range (two-sample *t*-test, $p < .01$, Fig. 2B).

In addition, we also found that the memory effect in each of the other subjects who performed the associative memory task showed significant theta power increase but that did not occur with the item memory task (Supplementary Fig. S1). Group-level theta power comparison between the associative and item memory tasks, after correction for multiple comparisons, confirmed significance difference (Mann-Whitney *U* test, 2-4 Hz: Z = −2.69, $p = .004$; 4–10 Hz: Z = −2.88, $p = .002$; 30–100 Hz: Z = −1.92, $p = .065$, adjusted *p* value with *post-hoc*, n = 6, Fig. 2C). These results indicate that hippocampal stimulation during associative encoding may promote subsequent memory retrieval by influencing theta activity in the hippocampus, which is important for memory association.

Associative memory elicits higher theta power than item memory during encoding

As we started with the assumption that in our study based on past studies, the associative memory would elicit higher theta activity than would item memory. Although the site of stimulation and patient characteristics (such as sex and cognitive ability) were largely matched across the two conditions, it is possible that the difference across the two task conditions could be due to a factor other than task. Because two of our subjects (Subject 5 and 6) participated in both tasks, we were able to make a closer, within-subject comparison between neural activities during the two tasks for these subjects.

To address the hypothesis that underlying neural signals during each task may correlate with the variations in the behavioral outcomes of hippocampal stimulation, we analyzed the brain activity in the *stimulation-off* trials during encoding. First, to determine whether there were reliable differences in hippocampal activity between the two tasks, we calculated changes in power during encoding relative to the pre-trial baseline, in which the patients were gazing at the white fixation cross. In general, the trend across the subjects' data showed that the theta range (2–10 Hz) power were significantly elevated for the associative task, but not for the item task (Fig. 3A and 3B).

We also calculated the power in each of three bands and averaged across the 0–4 s of the encoding period during which the word stimulus was visible on screen. There was a significant increase in power following the onset of stimuli in the low theta and theta but not the gamma range on the associative task, but not on the item task (two-sample *t*-test, Subject 5, 2–4 Hz: $t(98) = 1.67$, $p = .04$; 4–10 Hz: $t(98) = 3.51$, $p = .001$; 30–100 Hz: $t(98) = 1.07$, $p = .29$, Fig. 3C; Subject 6, 2–4 Hz: $t(73) = 3.17$, $p = .002$; 4–10 Hz: $t(73) = 2.03$, $p = .04$; 30–100 Hz: $t(73) = .51$, $p = .61$, Fig. 3D). Taken together, these results demonstrate a fundamental difference in hippocampal oscillatory activity between the two tasks.

Successful memory encoding elicits higher theta power in both memory task

Past studies of verbal item memory [29,42] reported that hippocampal theta power during memory encoding was higher for subsequently remembered trials than for forgotten trials (a positive subsequent memory effect). Supplementary Fig. S2 shows the subsequent memory effect in each of our subjects, labeled according to whether the learned stimuli were correct or incorrect. Replicating past studies, we found that correct items in both the associative and item memory tasks showed higher theta power during encoding (both two-sample *t*-tests, $p < .05$). These results add to the existing literature that successful memory encoding in the hippocampus is positively correlated with the strength of theta oscillations.

Stimulation-mediated memory effect is greater in subject with poorer baseline cognitive function

We further considered the possibility that stimulation effects could be related to baseline memory function, and thus analyzed the correlations between the hippocampal-mediated memory effect and baseline cognitive capacity including memory in all patients (Fig. 4). Overall, the patients with poorer baseline cognitive performance tended to improve much more with stimulation on the associative memory during retrieval. Conversely, the patient with higher baseline cognitive performance tended to show the greater stimulation-mediated impairment in item memory. Across all subjects, the magnitude of the associative memory enhancement showed negative correlations with three different baseline neuropsychological performance, showing that only the correlation with WMS associative memory task presented as significance. (Spearman's *rho*, Full-Scale IQ, associative; $r(6) = -.145$ $p = .784$; MQ, associative: $r(6) = -.203$, $p = .7$; WMS word associative memory, associative: $r(6) = -.841$, $p = .036$). On the contrary, although the correlation with MQ is not statistically significant (item: $r(6) = -.116$, $p = .827$), the memory impairment for item memory showed significantly positive correlations with baseline performance measures (Full-Scale IQ, item: $r(6) = .928$, $p = .008$; WMS word associative memory, item: $r(6) = .812$, $p = .05$).

Discussion

Summary

With the present study, we demonstrated that direct 50 Hz electrical stimulation of the human hippocampus improved a word pair associative memory but impaired single-item memory. The task-specific memory modulation may be related to the fact that the associative task elicited stronger theta oscillations than the single-item task. During retrieval, memory enhancement was accompanied by neural oscillations that reflected increased theta activity in the hippocampus. Altogether, our findings indicate that cognitive effects of brain stimulation are dependent on the tasks employed and suggest that theta oscillations may provide a mechanism by which hippocampal stimulation enhances memory performance.

The present study provides for the first-time direct evidence of task specificity on the efficacy of direct hippocampal stimulation on memory in humans and demonstrates that theta activity is linked to this stimulation-induced memory enhancement. This finding extends prior non-invasive stimulation studies that implied the specific role of the hippocampus on associative memory [43–45], and the selective stimulation influence on associative memory success in contrast with item memory [46]. Notably, our data reveal that hippocampal stimulation specifically influenced theta-dependent task in the hippocampus, and that this task-dependent neural activity associated with memory enhancement was observed even within the same subjects.

Task-dependent effects of hippocampal stimulation on memory

Our behavioral finding of impaired item memory by stimulation corresponds with prior findings of observed item memory impairment by hippocampal stimulation [3,4]. Interestingly, however, we also found enhancement in associative memory [26]. There are several differences, not necessarily mutually exclusive, that may underlie these behavioral discrepancies. One potential explanation is that the brain's encoding state could have an impact on the behavioral outcome of the stimulation. That is, the memory tasks that recruit different neuronal processes may be differently

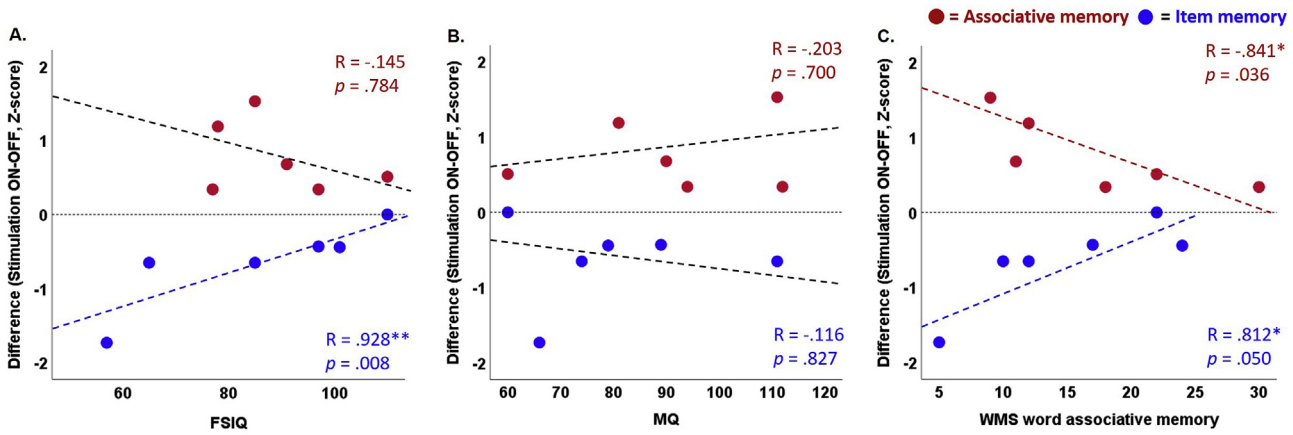

Fig. 4. Correlation coefficient between the hippocampal stimulation mediated memory effect and baseline cognitive capacity. A. Full-Scale Intelligence Quotient (IQ), **B.** Memory Quotient (MQ), and **C.** WMS word associative memory were selected because they relate to the verbal memory task used in the study. The patients with worst baseline cognitive performance tended to show the greatest stimulation-mediated improvements in associative recognition and the greatest stimulation-mediated impairment in item recognition (Spearman's *rho*, $^{*}p < .05$, $^{**}p < .01$).

affected by stimulation through the activation of different neuronal pathways [47]. A robust body of previous evidence indicates that the hippocampus supports encoding associative or relational information whereas item memory can be supported by extra-hippocampal structures [11,48–51]. The preferential engagement of the hippocampus for associative memory rather than item memory (i.e., non-associative memory) has been found in humans at the level of single hippocampal neurons in a recent study [52], which reported elevated hippocampal firing selectively during successful associative memory retrieval. In fact, we showed in our behavioral results a selective influence on a word pair associative memory task compared with single-item memory. We further confirmed that the underlying neural activation levels differed depending on the tasks applied even within the same individuals during memory encoding (Fig. 3), indicating that the stimulation generated differing behavioral effects depending on its targeted underlying neuronal activities.

This reliance of stimulation effect on different brain activity is in line with the MTL single unit activity in primates: A small difference in the specific neuronal population of the MTL could produce opposite behavioral effects through stimulating certain stimulus (i.e., task) selective neurons [53]. In similar reasoning, prior human iEEG study explored brain's encoding state-dependent modulation, showing that the effect of the stimulation on brain function depend on the state of neural activity at the time the stimulation is applied [25]. This study estimated, unlike in the present study for which we focused on local hippocampal activity, global brain encoding states derived from whole-brain patterns of neural activity and showed that decoding the latent brain states can improve the chances of influencing memory outcomes through stimulation methods. On a related note, a non-invasive transcranial magnetic stimulation (TMS) study exhibited that the effect of stimulation is strongly reliant on the state of the stimulated region [54], suggesting that the difference in excitability of neurons could have a critical role in determining the behavioral outcomes of stimulation [47].

Besides the differences in underlying hippocampal activity, the effects of stimulation could be sensitive to several stimulation parameters. In the present study, stimulation characteristics of phase, frequency and pulse width were similar to those in previous studies [4,6]; however, there were still minor differences in factors such as stimulation sites, amplitudes, and duration. The stimulation sites in our study (i.e., cathodes) were located in temporal white matter together with the hippocampus gray matter; hence we hypothesize that the net effect of stimulation was to increase the activation of neurons projecting from the site of stimulation that preferentially mediated axons rather than the cell bodies [55]. Accordingly, this may have driven hippocampal activity by eliciting excitatory responses upon electrical stimulation [56]. In addition to the stimulation site, our protocol was of slightly higher stimulation amplitude and of longer stimulation duration, which could have increased the total energy delivered to the tissues [57]. Previous studies on animal and human deep brain stimulation exhibited that brain structures respond differently to stimulation parameters [58,59]. Thus, setting precise parameters is an important factor for consistent effects of brain stimulation [60].

Theta activity as a neural signature for memory enhancement

In our iEEG data, theta activity increased only during associative memory and during successful memory encoding of item memory. Our findings are consistent with those from several prior neuroimaging studies, suggesting more activity in the hippocampus for associative than for item memory [17,61–63] and increased theta activity during encoding for successfully remembered memory [42,64].

Could the increase in theta power for associative retrieval be a result of exciatory activity by stimulation, resulting in subsequent memory improvement? As aforementioned, stimulation's effect on physiology depends on the excitability of the targeted neuron [65]; therefore, cognitive effects of stimulation could be modulated by the ongoing neural activity at the time [25]. Particularly, hippocampal stimulation could alternately incur either long-term potentiation or depression depending on whether the theta phase is at the peak or at trough at the time of stimulation delivery [66,67]. As such, stimulating the hippocampus may respect intrinsic brain states (i.e., theta activity) and dynamics accordingly, suggesting that the hippocampal theta oscillations may play a role in stimulation-induced memory enhancement.

In the context of our study, we might speculate that the higher theta power in associative memory, which is generally associated with better memory performance, reflects a high level of hippocampal engagement in memory encoding; consequently, electrical stimulation when the brain is active in this manner might have induced positive stimulation effects on memory performance.

Clinical implications

Patients with epilepsy often exhibit cognitive deficits as a consequence of chronic seizures, antiepileptic medications, and associated neural dysfunction [4,25]. Thus, an important question was whether the benefit of hippocampal stimulation was attenuated in patients with poorer baseline cognitive function. We found that the patients with poorer baseline cognitive performance tended to improve in memory much more with stimulation, while the enhancement effect was more limited in patients with higher baseline cognitive scores. This implies that those who have poor cognitive function and therefore need help might benefit the most from brain stimulation.

The neuropsychological test in which the patterns of test scores illustrate profiles of cognitive strength and weakness [68] was designed to examine a variety of cognitive abilities. Because the tests we referred to covered verbal item memory, verbal associative memory, or general Intelligence Quotient (IQ; see **Materials and Methods, Neuropsychological test**), the correlations between the neuropsychological test and the effects of stimulation on memory performance may reflect the task specificity of the two different verbal memory tasks. For instance, our result was that the effect of stimulation on item memory was positively correlated with the Full-Scale Intelligence Quotient (FSIQ) score. In contrast, the stimulation effect on associative memory was negatively correlated with the Korean Wechsler Memory Scale (K-WMS) associative memory scores. Given the differential task characteristics, it seems rather obvious that these differences in correlation are apparent, and in fact, the FSIQ score reflect the attributes of verbal item memory function rather than associative memory function.

Addressing these issues can potentially translate into clinical practice, as the finding that electrical stimulation in the hippocampus might provide a hint regarding why some patients with bilateral hippocampal lesion showed worse performance on the associative memory task than with item memory [69] and why some patients who undergo surgical removal of this region have associative verbal memory deficits.

Limitations

As in any study examining the effects of direct electrical stimulation in patients undergoing intracranial electrode monitoring, our study necessarily included patients with intractable epilepsy. Therefore, because of clinical constraints across patients including idiosyncratic variables (e.g., seizure locus, etiology, specific location of stimulation electrode), the present study raises several technical considerations. First, since the electrodes were implanted only for clinical purpose as part of pre-surgical evaluation for drug-resistant seizure, our study did not directly test a control region for stimulation. However, the selective modulation effect of hippocampal stimulation has been demonstrated previously in non-invasive studies [43,46]. For example, while non-invasive primary motor cortical stimulation did not exhibit any reliable changes in cortical-hippocampal connectivity or associative memory performance [43], targeted hippocampal stimulation demonstrated a selective influence on associative memory success [46].

Second, we investigated a small number of subjects, and thus, we cannot claim with any certainty that the statistical power was sufficient. However, despite these limitations, we observed a consistent memory effect of stimulation in all six subjects following each memory task. In addition, although not all subjects performed both memory tasks, we accounted for the differential effect of stimulation on memory tasks across patients by using a within-subject design and comparing two patients' performance and electrophysiological responses during the memory process. We note, however, that although the subjects' cognitive level was largely matched, it is possible that variability in other factors such as memory strategy or task difficulty may have interacted with hippocampal stimulation-induced memory modulation. To further investigate such issues, future work will aim to independently manipulate such factors from the stimulation itself.

Given that invasive stimulation is highly localized and given the heterogeneous nature of neural responses at small scales, further study using smaller electrodes or micro-stimulation is needed to understand more precisely the relationship between stimulation parameters and the response elicited from small pieces of neuronal tissue [70]. Furthermore, considering the importance of mechanically characterizing the causal effects of stimulation on brain activity during memory encoding, it is crucial for the entire field that new and improved methods to minimize stimulation artifacts be developed.

Conclusion

By depicting that hippocampal stimulation is most likely to improve memory when the underlying hippocampal activity is specifically related to theta activity, our data offer valuable insights into the inconsistencies reported in behavioral effects of hippocampal stimulation so far and provides the foundation for future work that maximizes the effectiveness of brain stimulation for treating memory disorders.

Ethics

Human subjects: This study was approved by the in the Institutional Review Board of Seoul National University Hospital (H-1407-115-596). All subjects provided written informed consent to participate the present study.

Declaration of competing interest

All authors have no conflict of interest to disclose. The authors declare no competing financial interests and there are no personal relationships with other people or organizations that could have inappropriately influenced the work.

CRediT authorship contribution statement

Soyeon Jun: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Sang Ah Lee:** Writing - original draft, Writing - review & editing, Supervision. **June Sic Kim:** Methodology, Formal analysis, Supervision. **Woorim Jeong:** Methodology. **Chun Kee Chung:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.01.013.

References

[1] Tulving E, Markowitsch HJ. Episodic and declarative memory: role of the hippocampus. Hippocampus 1998;8(3):198–204.
[2] Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. Annu Rev Neurosci 2007;30:123–52.
[3] Goyal A, Miller J, Watrous AJ, Lee SA, Coffey T, Sperling MR, et al. Electrical stimulation in Hippocampus and entorhinal cortex impairs spatial and temporal memory. J Neurosci 2018;38(19):4471–81.
[4] Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, et al. Direct electrical stimulation of the human entorhinal region and Hippocampus impairs memory. Neuron 2016;92(5):983–90.
[5] Lacruz ME, Valentin A, Seoane JJ, Morris RG, Selway RP, Alarcon G. Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. Neuroscience 2010;170(2):623–32.
[6] Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, et al. Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 2012;366(6):502–10.
[7] Fell J, Staresina BP, Do Lam AT, Widman G, Helmstaedter C, Elger CE, et al. Memory modulation by weak synchronous deep brain stimulation: a pilot study. Brain Stimul 2013;6(3):270–3.
[8] Berger TW, Hampson RE, Song D, Goonawardena A, Marmarelis VZ, Deadwyler SA. A cortical neural prosthesis for restoring and enhancing memory. J Neural Eng 2011;8(4):046017.
[9] Hampson RE, Song D, Chan RH, Sweatt AJ, Riley MR, Gerhardt GA, et al. A nonlinear model for hippocampal cognitive prosthesis: memory facilitation by hippocampal ensemble stimulation. IEEE Trans Neural Syst Rehabil Eng 2012;20(2):184–97.
[10] Jun S, Kim JS, Chung CK. Direct stimulation of human Hippocampus during verbal associative encoding enhances subsequent memory recollection. Front Hum Neurosci 2019;13:23.
[11] Battaglia FP, Benchenane K, Sirota A, Pennartz CM, Wiener SI. The hippocampus: hub of brain network communication for memory. Trends Cognit Sci 2011;15(7):310–8.
[12] Eichenbaum H, Cohen NJ. From conditioning to conscious recollection : memory systems of the brain, x. Upper Saddle River, NJ: Oxford Univ; 2001. p. 583.
[13] Squire LR, Zola SM. Episodic memory, semantic memory, and amnesia. Hippocampus 1998;8(3):205–11.
[14] Eichenbaum H, Otto T, Cohen NJ. 2 functional components of the hippocampal memory system. Behav Brain Sci 1994;17(3):449–72.
[15] Kroll NEA, Knight RT, Metcalfe J, Wolf ES, Tulving E. Cohesion failure as a source of memory illusions. J Mem Lang 1996;35(2):176–96.
[16] Turriziani P, Fadda L, Caltagirone C, Carlesimo GA. Recognition memory for single items and for associations in amnesic patients. Neuropsychologia 2004;42(4):426–33.
[17] Giovanello KS, Verfaellie M, Keane MM. Disproportionate deficit in associative recognition relative to item recognition in global amnesia. Cognit Affect Behav Neurosci 2003;3(3):186–94.
[18] Baxter MG, Murray EA. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus 2001;11(1):61–71.
[19] Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 1986;6(10):2950–67.
[20] Pascalis O, Bachevalier J. Neonatal aspiration lesions of the hippocampal formation impair visual recognition memory when assessed by paired-comparison task but not by delayed nonmatching-to-sample task. Hippocampus 1999;9(6):609–16.
[21] Kreiman G, Koch C, Fried I. Category-specific visual responses of single neurons in the human medial temporal lobe. Nat Neurosci 2000;3(9):946–53.
[22] Brown MW, Aggleton JP. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2001;2(1):51–61.
[23] Giovanello KS, Schnyer DM, Verfaellie M. A critical role for the anterior hippocampus in relational memory: evidence from an fMRI study comparing associative and item recognition. Hippocampus 2004;14(1):5–8.
[24] Mayes AR, Holdstock JS, Isaac CL, Montaldi D, Grigor J, Gummer A, et al. Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. Hippocampus 2004;14(6):763–84.
[25] Ezzyat Y, Kragel JE, Burke JF, Levy DF, Lyalenko A, Wanda P, et al. Direct brain stimulation modulates encoding states and memory performance in humans. Curr Biol 2017;27(9):1251–8.
[26] Jun S, Kim JS, Chung CK. Direct stimulation of human Hippocampus during verbal associative encoding enhances subsequent memory recollection 2019;13(23).
[27] Rutishauser U, Ross IB, Mamelak AN, Schuman EM. Human memory strength is predicted by theta-frequency phase-locking of single neurons. Nature 2010;464(7290):903–7.
[28] Buzsaki G, Moser EI. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat Neurosci 2013;16(2):130–8.
[29] Lega BC, Jacobs J, Kahana M. Human hippocampal theta oscillations and the formation of episodic memories. Hippocampus 2012;22(4):748–61.
[30] Hasselmo ME. The role of hippocampal regions CA3 and CA1 in matching entorhinal input with retrieval of associations between objects and context: theoretical comment on Lee et al. Behav Neurosci 2005;119(1):342–5. 2005.
[31] Hasselmo ME. Arc length coding by interference of theta frequency oscillations may underlie context-dependent hippocampal unit data and episodic memory function. Learn Mem 2007;14(11):782–94.
[32] Axmacher N, Schmitz DP, Weinreich I, Elger CE, Fell J. Interaction of working memory and long-term memory in the medial temporal lobe. Cerebr Cortex 2008;18(12):2868–78.
[33] Atri A, Sherman S, Norman KA, Kirchhoff BA, Nicolas MM, Greicius MD, et al. Blockade of central cholinergic receptors impairs new learning and increases proactive interference in a word paired-associate memory task. Behav Neurosci 2004;118(1):223–36.
[34] de Vanssay-Maigne A, Noulhiane M, Devauchelle AD, Rodrigo S, Baudoin-Chial S, Meder JF, et al. Modulation of encoding and retrieval by recollection and familiarity: mapping the medial temporal lobe networks. Neuroimage 2011;58(4):1131–8.
[35] Shin MS, Lee S, Seol SH, Lim YJ, Park EH, Sergeant JA, et al. Changes in neuropsychological functioning following temporal lobectomy in patients with temporal lobe epilepsy. Neurol Res 2009;31(7):692–701.
[36] Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 2007;164(1):177–90.
[37] Jacobs J. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. Philos Trans R Soc Lond B Biol Sci 2014;369(1635):20130304.
[38] Watrous AJ, Tandon N, Conner CR, Pieters T, Ekstrom AD. Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. Nat Neurosci 2013;16(3):349–56.
[39] Nyhus E, Curran T. Functional role of gamma and theta oscillations in episodic memory. Neurosci Biobehav Rev 2010;34(7):1023–35.
[40] Lee SA, Miller JF, Watrous AJ, Sperling MR, Sharan A, Worrell GA, et al. Electrophysiological signatures of spatial boundaries in the human subiculum. J Neurosci 2018;38(13):3265–72.
[41] Hasselmo ME. What is the function of hippocampal theta rhythm?–Linking behavioral data to phasic properties of field potential and unit recording data. Hippocampus 2005;15(7):936–49.
[42] Sederberg PB, Kahana MJ, Howard MW, Donner EJ, Madsen JR. Theta and gamma oscillations during encoding predict subsequent recall. J Neurosci 2003;23(34):10809–14.
[43] Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, et al. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 2014;345(6200):1054–7.
[44] Wang JX, Voss JL. Long-lasting enhancements of memory and hippocampal-cortical functional connectivity following multiple-day targeted noninvasive stimulation. Hippocampus 2015;25(8):877–83.
[45] Matzen LE, Trumbo MC, Leach RC, Leshikar ED. Effects of non-invasive brain stimulation on associative memory. Brain Res 2015;1624:286–96.
[46] Tambini A, Nee DE, D'Esposito M. Hippocampal-targeted theta-burst stimulation enhances associative memory formation. J Cognit Neurosci 2018;30(10):1452–72.
[47] Silvanto J, Cattaneo Z. Common framework for "virtual lesion" and state-dependent TMS: the facilitatory/suppressive range model of online TMS effects on behavior. Brain Cognit 2017;119:32–8.
[48] Davachi L. Item, context and relational episodic encoding in humans. Curr Opin Neurobiol 2006;16(6):693–700.
[49] Mayes A, Montaldi D, Migo E. Associative memory and the medial temporal lobes. Trends Cognit Sci 2007;11(3):126–35.
[50] Diana RA, Yonelinas AP, Ranganath C. Imaging recollection and familiarity in the medial temporal lobe: a three-component model. Trends Cognit Sci 2007;11(9):379–86.
[51] Olsen RK, Moses SN, Riggs L, Ryan JD. The hippocampus supports multiple cognitive processes through relational binding and comparison. Front Hum Neurosci 2012;6:146.
[52] Staresina BP, Reber TP, Niediek J, Bostrom J, Elger CE, Mormann F. Recollection in the human hippocampal-entorhinal cell circuitry. Nat Commun 2019;10(1):1503.
[53] Tamura K, Takeda M, Setsuie R, Tsubota T, Hirabayashi T, Miyamoto K, et al. Conversion of object identity to object-general semantic value in the primate temporal cortex. Science 2017;357(6352):687–92.
[54] Silvanto J, Muggleton N, Walsh V. State-dependency in brain stimulation studies of perception and cognition. Trends Cognit Sci 2008;12(12):447–54.
[55] Perlmutter JS, Mink JW. Deep brain stimulation. Annu Rev Neurosci 2006;29:229–57.
[56] Ranck JB. Which elements are excited in electrical-stimulation of mammalian central nervous-system - Review. Brain Res 1975;98(3):417–40.
[57] Moro E, Esselink RJA, Xie J, Hommel M, Benabid AL, Pollak P. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. Neurology 2002;59(5):706–13.
[58] Hescham S, Lim LW, Jahanshahi A, Blokland A, Temel Y. Deep brain stimulation in dementia-related disorders. Neurosci Biobehav Rev 2013;37(10 Pt 2):2666–75.
[59] Hamani C, Temel Y. Deep brain stimulation for psychiatric disease: contributions and validity of animal models. Sci Transl Med 2012;4(142):142rv8.
[60] Hamani C, Diwan M, Isabella S, Lozano AM, Nobrega JN. Effects of different stimulation parameters on the antidepressant-like response of medial prefrontal cortex deep brain stimulation in rats. J Psychiatr Res 2010;44(11):683–7.

[61] Davachi L, Wagner AD. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. J Neurophysiol 2002;88(2):982–90.
[62] Jackson 3rd O, Schacter DL. Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. Neuroimage 2004;21(1):456–62.
[63] Kirwan CB, Stark CE. Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. Hippocampus 2004;14(7):919–30.
[64] Molle M, Marshall L, Fehm HL, Born J. EEG theta synchronization conjoined with alpha desynchronization indicate intentional encoding. Eur J Neurosci 2002;15(5):923–8.
[65] Pollen DA. Responses of single neurons to electrical stimulation of the surface of the visual cortex. Brain Behav Evol 1977;14(1–2):67–86.
[66] Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J Neurosci 2003;23(37):11725–31.
[67] Pavlides C, Greenstein YJ, Grudman M, Winson J. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. Brain Res 1988;439(1–2):383–7.
[68] Lezak MD. Neuropsychological assessment. third ed. New York: Oxford University Press; 1995. p. 1026. xviii.
[69] Gold JJ, Hopkins RO, Squire LR. Single-item memory, associative memory, and the human hippocampus. Learn Mem 2006;13(5):644–9.
[70] Titiz AS, Hill MRH, Mankin EA, Z MA, Eliashiv D, Tchemodanov N, et al. Theta-burst microstimulation in the human entorhinal area improves memory specificity. Elife 2017;6.