Cognition and Behavior

# Electrical Stimulation Modulates High γ Activity and Human Memory Performance

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Visual Abstract
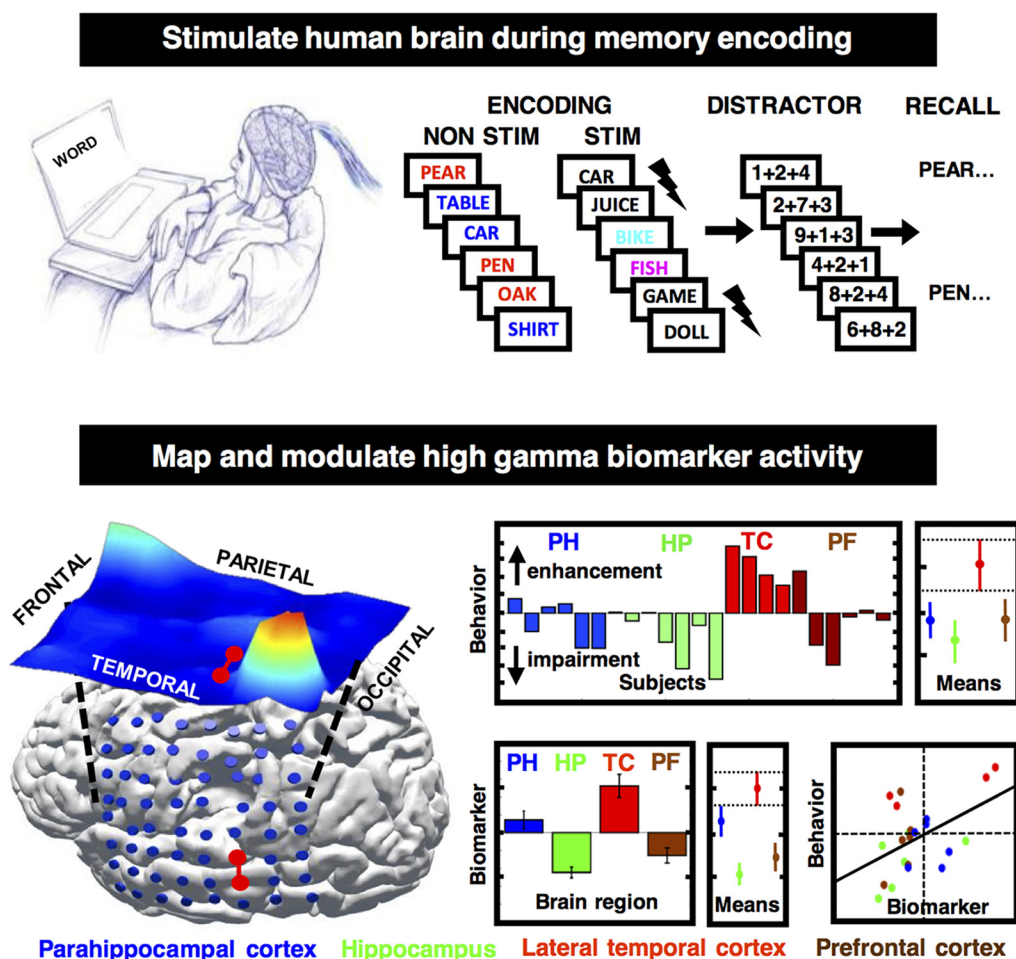
Significance Statement

Brain stimulation technologies for memory disorders can be advanced with improved understanding of the physiologic processes modulated by electrical current. In this study, intracranial EEG recordings from epilepsy patients performing memory tasks during direct brain stimulation revealed distinct changes in the induced high γ activity, particularly on the trials with poor memory encoding. Given that these physiologic changes were correlated with the effect of stimulation on task performance, we propose they may be useful as a biomarker to optimize brain stimulation parameters for memory enhancement. These findings could help accelerate development of brain-machine interface technologies to treat memory and cognitive disorders.

Direct electrical stimulation of the brain has emerged as a powerful treatment for multiple neurological diseases, and as a potential technique to enhance human cognition. Despite its application in a range of brain disorders, it remains unclear how stimulation of discrete brain areas affects memory performance and the underlying electrophysiological activities. Here, we investigated the effect of direct electrical stimulation in four brain regions known to support declarative memory: hippocampus (HP), parahippocampal region (PH) neocortex, prefrontal cortex (PF), and lateral temporal cortex (TC). Intracranial EEG recordings with stimulation were collected from 22 patients during performance of verbal memory tasks. We found that high γ (62–118 Hz) activity induced by word presentation was modulated by electrical stimulation. This modulatory effect was greatest for trials with "poor" memory encoding. The high γ modulation correlated with the behavioral effect of stimulation in a given brain region: it was negative, i.e., the induced high γ activity was decreased, in the regions where stimulation decreased memory performance, and positive in the lateral TC where memory enhancement was observed. Our results suggest that the effect of electrical stimulation on high γ activity induced by word presentation may be a useful biomarker for mapping memory networks and guiding therapeutic brain stimulation.

Key words: brain stimulation; cognitive enhancement; ECoG; γ-activity; high-frequency oscillations; intracranial EEG

Introduction

Studies of direct electrical stimulation of the human brain were pioneered in epilepsy patients undergoing surgery to treat drug resistant focal epilepsy. During the surgery when patients were awake and stimulated in specific areas of the neocortex, they reported conscious experience of past events (Penfield, 1958). This phenomenal effect of invoking declarative memory representations was more likely to occur when stimulating in a discrete range of spectral and temporal parameters, which led to a hypothesis that the electrical current that was passed through the neural tissue activated specific neurophysiological activity supporting memory (Bickford et al., 1958; Penfield and Perot, 1963). In the current study, free recall tasks were used to investigate how stimulation in specific brain regions modulated the electrophysiological activities induced by word presentation and their subsequent recall.

Recent attempts at human memory enhancement have primarily focused on the hippocampus (HP) and the associated mesial temporal lobe structures, with reports of positive outcomes described in small studies of individual brain regions (Suthana and Fried, 2014; Kim et al., 2016). In general, however, studies have shown inconsistent results for stimulation in mesial temporal lobe structures, including: HP (Coleshill et al., 2004; Suthana et al., 2012; Fell et al., 2013; Jacobs et al., 2016), entorhinal cortex (Suthana et al., 2012; Fell et al., 2013; Jacobs et al., 2016), and fornix (Hamani et al., 2008; Miller et al., 2015). The

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effect of stimulation on the neurophysiological activity associated with memory tasks was largely unexplored. The positive effects of stimulation on memory reported in some of these studies were observed either in a single case (Hamani et al., 2008) or at the level of a group of patients (Suthana et al., 2012; Miller et al., 2015) without a detailed analysis of the electrophysiological signals, which is often challenging because of the stimulation artifacts (Johnson et al., 2013). In summary, limitations in the sample size, number of brain regions tested, and analysis have impeded our understanding of the impact of direct human brain stimulation on memory processes.

γ activities in the local field potential present one plausible target for exploring the neurophysiology of memory processes and the effect of stimulation. These activities have been associated with cognitive functions, including perception, attention and memory (Singer, 1993; Tallon-Baudry and Bertrand, 1999; Fries, 2009; Düzel et al., 2010). γ activities in the high frequency ranges (40–150 Hz) were proposed to be generated by local neuronal assemblies underlying cognitive processing during task performance (Crone et al., 2006; Lachaux et al., 2012), and thus provide a potential biomarker for mapping brain functions. Recent studies of γ activity in humans and nonhuman primates showed discrete bursts of γ power induced by memorized stimuli (Kucewicz et al., 2014; Lundqvist et al., 2016). In these studies, the rate of high γ burst events was associated with memory performance and proposed to underlie the differences in average power induced between trials with remembered and forgotten items, i.e., the subsequent memory effect (Kahana, 2006; Sederberg et al., 2007). Although the physiologic source of γ activities, local field oscillations or firing of neuronal assemblies, and their role in cognitive function are actively debated (Crone et al., 2006; Waldert et al., 2013; Kucewicz et al., 2017), they may still be useful as a measure of neuronal processing and modulation.

There is growing evidence that γ activities can be modulated by external interventions. Optogenetic stimulation of distinct neuron types was shown to increase γ power in the local field potential and enhance neuronal network performance in rodents (Sohal, 2016). γ power can also be increased through neurofeedback training in specific brain regions, as reported in nonhuman primate recordings that showed synchronous neuronal firing and enhanced behavioral performance (Engelhard et al., 2013). Transcranial current stimulation is another approach used to modulate γ activities and, for instance, was shown to induce dream self-awareness in the human subjects (Voss et al., 2014). The effect of direct stimulation of the human brain on γ activities linked to memory performance has been largely unexplored. However, the reports of a positive effect on memory performance in humans were all stimulating at frequencies in the γ range (40/50/200 Hz; for review, see Kim et al., 2016), suggesting that the applied current presumably modulated similar frequencies of neuronal oscillations. Here, we tested the effect of 50-Hz electrical stimulation on γ activity and task performance in four brain regions supporting declarative memory.

Materials and Methods

Study participants

Patients undergoing intracranial electroencephalographic monitoring as part of their clinical treatment for drug-resistant epilepsy were recruited to participate in this multi-center collaborative study. Data were collected from the following clinical centers: (Mayo Clinic, Thomas Jefferson University Hospital, Hospital of the University of Pennsylvania, Dartmouth-Hitchcock Medical Center, Emory University Hospital, University of Texas Southwestern Medical Center). The research protocol was approved by the respective IRB at each clinical center and informed consent was obtained from each participant. Electrophysiological data were collected from standard clinical subdural and penetrating depth electrodes (AdTech Inc., PMT Inc.) implanted on the cortical surface and into the brain parenchyma, respectively. The subdural electrode contacts were arranged either in a grid or a strip configuration with contacts separated by 10mm. The depth electrode contacts were separated by 1.5–10 mm spacing. In each case, the placement of the electrodes was determined by a clinical team whose sole purpose was to localize seizures for possible epilepsy surgery. In this study, we identified 22 patients (nine males) with subdural or depth electrodes implanted in at least one of the four brain regions of the cortical-hippocampal declarative memory system (Eichenbaum, 2000), who completed at least two stimulation sessions in any of these regions (Tables 1, 2).

Anatomic localization and brain surface mapping

Cortical surface parcellations were generated for each participant from preimplant magnetic resonance imaging (MRI) scans (volumetric T1-weighted sequences) using Freesurfer software (RRID:SCR_001847; Fischl et al., 2004). The HP and surrounding cortical regions were delineated separately based on an additional 2-mm-thick coronal T2-weighted scan using the Automatic Segmentation of Hippocampal Subfields (ASHS) multi-atlas segmentation method (Yushkevich et al., 2015). Electrode contact coordinates derived from registered postimplant CT scans were then mapped to the preimplant MRI scans to determine their anatomic locations. For subdural strips and grids the electrode contacts were additionally projected to the cortical surface using an energy minimization algorithm to account for postoperative brain shift (Dykstra et al., 2012). For comparisons across subjects, coordinates were transformed to the MNI brain space, in which distance between bipolar electrode pairs was estimated using the shortest path from the stimulating electrode pair. Contact locations were reviewed and confirmed on surfaces and cross-sectional images by a neuroradiologist. For further visualization and presentation purposes, surfaces and contact coordinates were rendered using Blender (http://blender.org) and Blend4web (http://blend4web. org) open source software in a customized interactive web application.

Electrophysiological recordings

Intracranial data were recorded using one of the following clinical electrophysiological acquisition systems spe-

Table 1. Clinical profile of the study participants

Subject no.	Age	Gender	Handedness	SOZ	MRI	Brain pathology	Language laterality (method)	Stimulation mapping overlap	vIQ	Verbal memory deficits
1001	48	F	R	Right TC	Normal	Gliosis	L (fMRI)	-	81	None
1006	20	F	R	Right FC	MCD	Gliosis	L (fMRI)	-	91	None
1016	31	F	R	Left FC	Normal	Gliosis	-	None	71	None
1018	47	M	L	Left FC, left FPC	Normal	-	L (fMRI)	-	85	None
1020	48	F	L	Right TC, right FC	Abnormal	Gliosis	L (fMRI)	-	98	Mild
1022	24	M	R		Atrophy	Gliosis/ encephalomalacia	-	L (fMRI)	-	81	None
1024	36	F	R	Right OPC	Normal	Gliosis	L (unknown)	-	100	None
1026	24	F	R	Left aTC left OC	MTS, gliosis	-	Bilateral (Wada)	-	112	None
1027	48	M	R	Right TC right IC right/left FC	Abnormal	-	L (fMRI)	-	93	None
1028	27	F	R	Right MTL	Abnormal	CD, Gliosis	L (Wada)	-	103	None
1029	33	F	R	Left FC	Abnormal	-	-	-	108	Mild
1030	23	M	L	Left MTL	Normal	Gliosis	L (fMRI)	-	106	None
1031	24	M	R	Right FC right TC	Abnormal	-	L (aphasia)	-	110	Moderate
1033	31	F	R	Right TC	Atrophy	-	L (Wada)	-	85	None
1036	49	M	L	Left aTC, left MTL	MTS	HS	Bilateral (Wada)	-	93	Moderate
1042	27	F	L	Right TC	MCD	-	R (fMRI)	None	114	None
1050	20	M	R	Left PC	Neoplasm	DNET	Bilateral (Wada)	None	95	Mild
1060	36	F	R	Right TC	Normal	Gliosis	L (Wada)	-	95	Mild
1069	26	M	R	Left FC	MCD	-	L (Wada)	-	-	Mild
1111	20	M	R	Left TC left OPC left OC	Gliosis	Gliosis	L (fMRI)	-	108	None
1176	41	F	R	Right MTL right IC	MTS	-	L (Wada)	-	85	Moderate
1177	23	F	R	Left TC	TS	-	L (aphasia)	None	87	Moderate

Patient demographic data are presented together with clinical observations from structural MRI, clinically identified seizure onset zones (SOZs), pathology for those subjects who underwent respective surgery, hemispheric laterality of language functions together with the method of determination ("aphasia" means that the determination was done based on an identified lesion/pathology in a specific hemisphere), overlap of the stimulating electrodes with the language areas for patients who have undergone cortical stimulation mapping ("-" means that the stimulation mapping was not performed or the report was not available), verbal IQ (vIQ), and the clinical qualitative description of verbal memory deficits as concluded in the neuropsychological assessment. FC, frontal cortex; PC, parietal cortex; OC, occipital cortex; IC, insular cortex; aTC, anterior TC; MTL, mesial temporal lobe; TPC, temporo-parietal cortex; FPC, fronto-parietal cortex; OPC, occipito-parietal cortex; CD, cortical dysplasia; HS, hippocampal sclerosis; MCD, malformation of cortical development; MTS, mesial temporal sclerosis; PMG, polymicrogyria; DNET, dysembryoplastic neuroepithelial tumor.

cific to a given site of data collection: Nihon Kohden EEG-1200, Natus XLTek EMU 128, or Grass Aura-LTM64. Depending on the acquisition system and the preference of the clinical team, the signals were sampled at either 500, 1000, or 1600 Hz and were referenced to a common contact placed either intracranially, on the scalp, or on the mastoid process. For analysis all recordings using higher sampling rates were down-sampled to 500 Hz. A bipolar montage was calculated *post hoc* for each subject by subtracting measured voltage time series on all pairs of spatially adjacent contacts. This resulted in $N-1$ bipolar signals in case of the penetrating and the strip electrodes, and $N+x$ bipolar signals for the grid electrodes, where N is the number of electrode contacts and x is the number of extra combinations of bipolar contacts that resulted from the montage.

Memory tasks with brain stimulation

The tasks were based on classic paradigms for probing verbal memory (Kahana, 2012), in which subjects learned lists of words for subsequent recall (Fig. 1A). Subjects were instructed to study lists of individual words presented sequentially on a laptop computer screen for a later memory test. Lists were composed of 12 words chosen at random and without replacement from a pool of high frequency nouns (either English or Spanish, depending on the participant's native language; http://memory.psych.upenn.edu/WordPools). Each session had a set of 25 specific lists using words from the same general pool. The words on each list were either sampled from specific categories like vehicles, music instruments and vegetables, or they were sampled randomly. Each word re-

Table 2. Summary of the experiments used to assess effect of stimulation on encoding of word lists

Subject	Sessions	Localization	Region	Electrode	Amplitude
1001	2	Left HP	HP	Depth	1.0
1006	2	Right HP	HP	Depth	1.0
1016	2	Left PF	PF	Subdural	3.5
1018	2	Left PF	PF	Depth	1.5
1020	4	Right HP	HP	Depth	1.0
1022	2	Left HP	HP	Depth	1.0
1024	3	Left HP	HP	Depth	1.0
1026	4	Left EC	PH	Depth	0.5
1027	2	Left HP	HP	Depth	1.0
1028	3	Right EC	PH	Subdural	1.0
1029	2	Left PF	PF	Subdural	3.5
1030	4	Left PHC	PH	Depth	0.5
1031	2	Right PRC	PH	Depth	1.5
1033	2	Left PRC	PH	Depth	1.5
1036	4	Left PRC	PH	Depth	1.0
1042	2	Right PF	PF	Subdural	1.5
1050	2	Left TC	TC	Subdural	1.5
1060	3	Right PF	PF	Subdural	3.0
1069	2	Left PF	PF	Subdural	2.5
1111	3	Left PHC	PH	Depth	0.75
1111	3	Left TC	TC	Subdural	1.5
1176	3	Left TC	TC	Depth	1.0
1177	4	Left TC	TC	Subdural	1.0

Analysis was focused on 23 subject experiments that had at least two sessions with any one stimulation target in four of the studied brain regions. PHC, PH cortex; PRC, perirhinal cortex; EC, entorhinal cortex.

mained on the screen for 1600 ms, followed by a random jitter of 750- to 1000-ms blank interval between stimuli. Immediately following the final word in each list, participants performed a distractor task (20 s) consisting of a series of arithmetic problems of the form "A + B + C = ??", where A, B, and C were randomly chosen integers ranging from 1 to 9. Following the distractor task subjects were given 30 s to verbally recall as many words as possible from the list in any order. Vocal responses were digitally recorded by the laptop computer and later manually scored for analysis. Each session consisted of 25 lists of this encoding-distractor-recall procedure.

Stimulation was applied by passing electrical current between two adjacent electrode contacts using parameters from the study (Suthana et al. 2012) showing a positive effect of stimulation on memory performance (bipolar symmetric, charge-balanced, square-wave stimulation at a frequency of 50 Hz and 300-μs pulse width). Safe amplitude for stimulation was determined at the start of each session using a mapping procedure in which stimulation was applied at 0.5 mA while a neurologist monitored for after-discharges. This procedure was repeated, incrementing the amplitude in steps of 0.5 mA, up to a maximum of 1.5 mA for depth contacts and 3.5 mA for cortical surface contacts. These maximum amplitudes were chosen to be below the after-discharge threshold and below accepted safety limits for charge density (McCreery et al., 1990). The stimulation was delivered for 4600 ms during the presentation of two subsequent words (from 200 ms before the first word onset to 200–

450 ms after second word offset due to a random jitter in inter-stimulus interval) on every other word pair (three pairs on every list with first pair pseudorandomized across all lists in a given session). Stimulation was applied on 20 out of 25 randomly assigned lists of a full session. There were no more than two sessions a day of a given task separated by at least three hours. The target electrode pair for stimulation was selected based on the anatomic coverage of brain regions associated with declarative memory functions (Eichenbaum, 2000), including hippocampus (HP), parahippocampal region (PH), temporal cortex (TC), and prefrontal cortex (PF). Within these regions specific target electrode pairs for stimulation were selected based on anatomic localization in one the studied brain regions and based on mapping of active areas showing a subsequent memory effect (Kahana, 2006; Sederberg et al., 2007). Electrodes had to be localized outside the seizure onset zone, as defined by the local clinical team. Additional clinical data were collected about the localization of language functions relative to the stimulation sites and neuropsychological assessment of verbal memory (Table 1). Stimulation amplitude was determined using conservative limits for safe charge density (Gordon et al., 1990; McCreery et al., 1990) for subdural or depth electrode contact, not higher than 3.0 and 1.5 mA, respectively.

Electrophysiological analysis

Brain activity induced by word presentation was analyzed in this study, and comprised 1600 ms of word display on the screen and 200-ms blank interval before and after each word (total 2000 ms segments). Stimulated word pair epochs were excluded from analysis to prevent potential contamination of spectral analysis with the stimulus artifact. Hence, one complete session yielded electrophysiological signal from 60 nonstimulated list epochs (five lists × 12 words) and 120 stimulated list epochs (20 lists × six words). Every signal epoch was spectrally decomposed in 50-ms time bins using multi-taper Fast Fourier Transform (Chronux toolbox, RRID:SCR_005547; Bokil et al., 2010); taper parameters: 4-Hz bandwidth, 250-ms timewidth, one taper). To estimate power in distinct frequency bands (high γ: 62–118 Hz, low γ: 30–58 Hz, β: 14–26 Hz, θ/α: 6–14 Hz) signals were bandpass filtered between the corresponding cutoff frequencies (Barlett-Hanning, 1000 order) before spectral decomposition to reduce any possible influence of lower frequencies on the power estimate. The cutoff frequencies for the high γ band were chosen to minimize contamination of the 60-Hz line noise and its first harmonic at 120 Hz. The decomposed spectral power values in a given frequency band were log and z-score transformed in each frequency bin to account for the power law effect and obtain values that can be compared in the same scale across sessions and subjects. Frequency bands in the low θ and δ ranges between 1 and 5 Hz were not included in this study due to different high-pass filters applied in signal acquisition across the data collection centers. Average power estimates were calculated from all epochs of the studied words from nonstimulated lists.
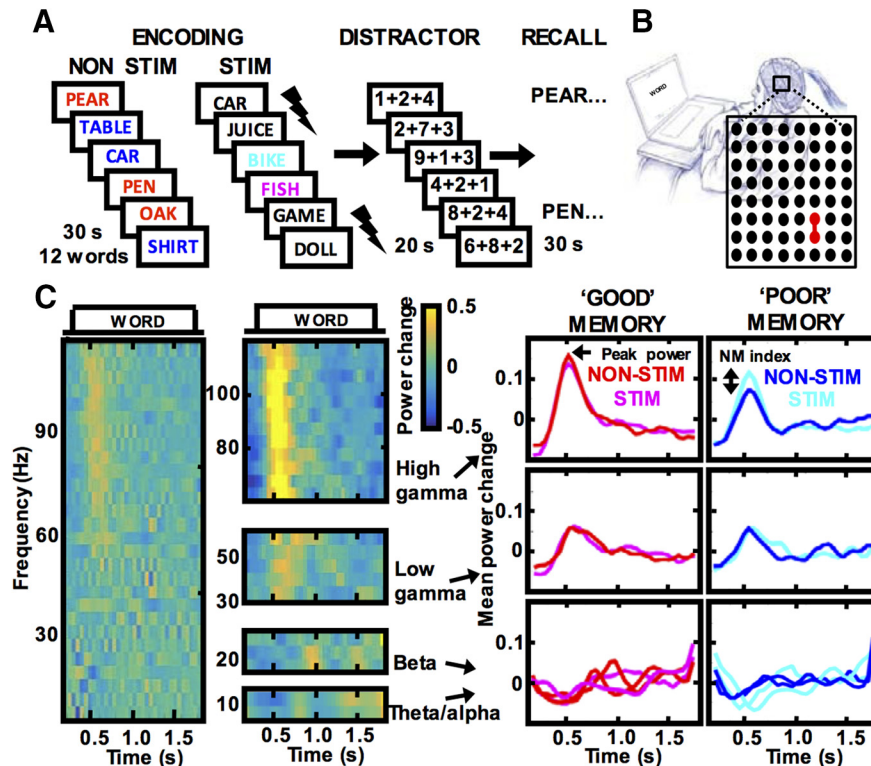
Figure 1. Free recall tasks to study electrophysiological modulation of verbal memory encoding. **A,** Diagram of the task design, in which subjects memorized word lists for subsequent recall. Thunderbolt marks the words with stimulation on the STIM lists. The remaining word trials were used for electrophysiological analysis and are labeled according to the lists type (NON-STIM or STIM) and their encoding based on subsequent recall (GOOD or POOR). **B,** Example of an 8×8 electrode grid implanted over the lateral TC highlights in red two adjacent contacts used for brain stimulation (connected red dots) in subject 1050. **C,** Broadband spectrogram (left column) shows trial-averaged power changes aligned to the time of word presentation for encoding, in contrast to the power changes in the signal prefiltered in the four studied frequency bands (middle column), as recorded from a representative electrode example from subject 1111. Line plots on the right summarize the mean power change response independently for the four bands (rows) and separately for the good and poor encoding trials (columns) in the two conditions of list stimulation, color-coded as in **A**. Notice the difference in peaks of the response (NM index) caused by stimulation in the poor encoding trials specifically in the high γ frequency band.

Exact time of memory encoding during the stimulus presentation is difficult to determine and can vary between subjects. We used the maximum peak value of the average power estimates as proxy for the brain response related to the memory encoding. This maximum value of the average power estimate was defined as peak power, and the difference between peak power values from the stimulated (P_{stim}) and nonstimulated (P_{non}) list condition was defined as the "neuromodulation (NM) index":

$$NM = P_{stim} - P_{non}$$

$$P_{stim} = f(t); 0 < t < 2000ms$$

$$P_{non} = f(t); 0 < t < 2000ms$$

$$f(t) = a_0 + \frac{\sum_{n=0}^{N} f(a_n)}{N}, \text{ where } f(a_n)$$

is the nth power estimate.

Surface plots were created using the peak power and the NM index values interpolated between all bipolar pairs

on an electrode grid. Active electrodes were selected by identifying outliers of the peak power value distributions above the upper adjacency value (UAV; > third quartile + $1.5 \times$ interquartile range), which were calculated from all nonstimulated list epochs for every electrode in a given patient. The identified active electrodes were used to determine mean value of the NM index across all electrodes in a given subject or brain region, which had active electrodes from at least two subjects.

Behavioral analysis

Memory performance was quantified as count of words recalled per list (with or without stimulation). To compare the effect of stimulation on performance across subjects the raw counts from all sessions in a given subject were normalized into z-scores. Difference between means of the scores on the stimulated and nonstimulated lists was defined as a measure of stimulation's effect on memory performance (Δ behavioral score). At least two sessions in a given stimulation target were required to be included in data analysis to ensure an accurate estimate of the mean for the nonstimulated lists, i.e., more than five scores were required to estimate the mean.

Table 3. Statistical tables for the analyses of variance

Source of variation	Sum od squares	Degrees of freedom	Mean squares	F ratio	Probability $> F$
		NM index in different frequency bands during the poor encoding trials			
Groups	0.10172	3	0.03391	14.79	<0.0001
Error	0.19262	84	0.00229		
Total	0.29434	87			
		NM index in different frequency bands during the good encoding trials			
Groups	0.01226	3	0.00409	1.71	0.1708
Error	0.20053	84	0.00239		
Total	0.21279	87			
		Effect of stimulation in different brain regions on memory performance			
Groups	1.83311	3	0.61104	7.31	0.0019
Error	1.58778	19	0.08357		
Total	3.4209	22			
		Effect of stimulation in different brain regions on NM			
Groups	0.26765	3	0.08922	23.27	<0.001
Error	0.74363	194	0.00383		
Total	1.01128	197			

Statistical analysis

All statistical tests were performed in Matlab (Math-Works Inc., RRID:SCR_001622) using built-in and custom written codes. One-way ANOVA test compared NM index calculated from the same set of electrodes from one subject in different frequency bands (Fig. 3C). The test was followed by Tukey–Kramer *post hoc* group comparison of the 95% confidence intervals of the means. Pearson's correlation was chosen to test dependence between NM index and: peak power value (Fig. 3D), distance from the stimulating electrode (Fig. 3D), and the behavioral effect of stimulation on memory performance (Fig. 5D). For the former two the correlation was additionally confirmed on the level of electrodes from individual patients. The correlation plots were complemented with least-squares lines to aid visual interpretation. ANOVA test was used to compare the effect of stimulating in the four studied regions on the NM index and on behavioral performance. The test was followed by Tukey–Kramer *post hoc* group comparison of the 95% confidence intervals of the means. Data are shown as mean ± SEM. ANOVA tables are summarized in Table 3. All data collected in this project are available at: http://memory.psych.upenn.edu/RAM_Public_Data.

Results

We investigated the effect of direct brain stimulation on electrophysiological activity and memory performance in epilepsy patients undergoing evaluation for surgery to treat refractory seizures. Each patient was implanted with intracranial subdural, depth, or subdural and depth electrode arrays in multiple cortical and subcortical brain regions selected based solely on the clinical considerations. We identified 22 patients who were implanted in one of the four brain regions of the declarative memory system (Eichenbaum, 2000) and completed at least two sessions of free recall tasks with stimulation (Tables 1, 2). The tasks were based on a classic paradigm for probing verbal short-term memory (Kahana, 2012), in which subjects learned lists of twelve words to be freely recalled in any order following a distractor (Fig. 1A). Electrical stimulation was applied between a pair of adjacent electrode

contacts during encoding of words for subsequent recall (Fig. 1B). Low amplitude stimulation (<1.5 mA, 50-Hz frequency, pulse width 300 µs; Table 2) was applied for 4.6 s during presentation of two consecutive words, followed by presentation of two other words without any stimulation to enable electrophysiological analysis without stimulus artifact (Fig. 1A).

We found that stimulation in the lateral TC modulated the spectral power specifically in the high γ band (62–118 Hz) on electrodes showing induced responses to word presentation (Fig. 1C), which was associated with enhanced memory performance (for behavioral analysis, see Fig. 5). The high γ response on trials with words that are subsequently not recalled ("poor" encoding) is known to be decreased relative to trials with the subsequently recalled words ("good" encoding), as previously described (Kahana 2006, Sederberg et al., 2007). Stimulation on the poor encoding trials increased this high γ response and restored it to the magnitude observed on the good encoding trials with words that were subsequently recalled (Fig. 1C). Thus, the subsequently forgotten words from the stimulated "STIM" lists had increased high γ response relative to the words from the "NON-STIM" lists that were not stimulated. Each experimental session comprised of both the STIM and the NON-STIM lists, which were randomly assigned in a double-blind fashion. The modulatory effect of stimulation was quantified as a difference between peaks of the power response in the STIM minus the NON-STIM condition, which we called the NM index (Fig. 1C). The peak response was thus used as proxy for brain activity related to memory encoding.

This NM effect was localized to "activated" areas of the brain showing the induced high γ response in the tasks. Figure 2 presents three exemplar cases of stimulation from subdural surface grid electrodes in the TC, which modulated the peak power responses. The top case depicts a single discrete area of the peak activation. The magnitude of this discrete high γ response is greater on the good than the poor encoding trials in the NON-STIM control condition. This disparity between the remembered and the forgotten word trials is not present in the STIM
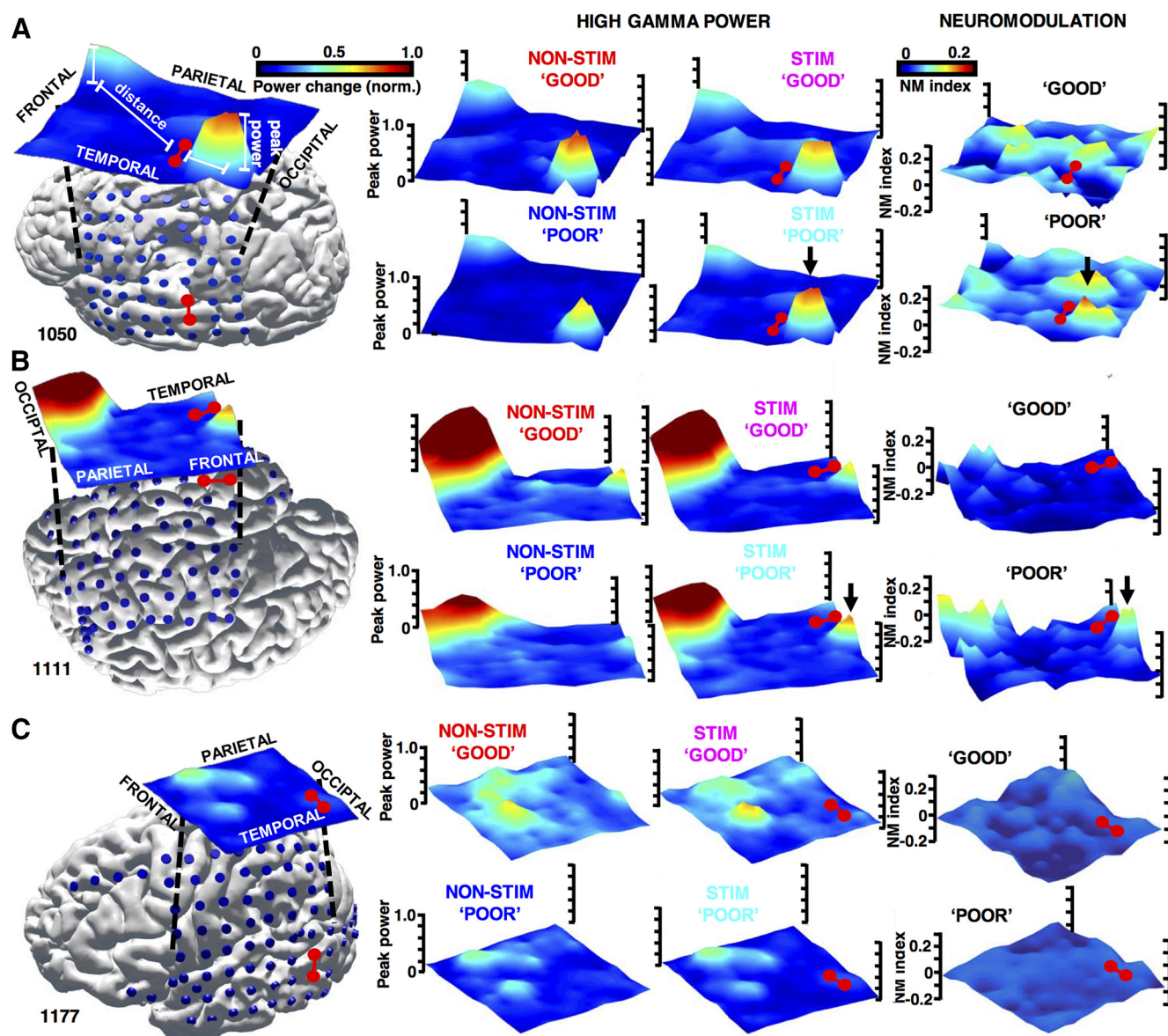
Figure 2. Stimulation modulates high γ responses in localized areas activated in the tasks. **A**, Values of the peak power of the γ responses and the NM index from all 8 × 8 grid electrodes (blue dots, stimulating electrodes in red) of subject 1050, as in Figure 1B, are interpolated and visualized as surface plots overlaid on this subject's brain surface (left side). The first two columns present peaks of the high γ power in the STIM (first) and the NON-STIM (second) conditions, the third column presents the NM index, i.e., the effective difference between the first two columns. Arrows point to a discrete area of peak power modulated by stimulation particularly in the poor encoding trials. **B**, **C**, Analogous plots from two other cases of subject 1111 (brain surface rendering was turned upside down to aid visualization) and 1177, respectively. Notice that the high γ modulation is observed also at a distance from the stimulation site in subject 1111 and is not observed in subject 1177.

condition with similar peaks on the two trial types (Fig. 2A). Stimulation therefore increased the high γ response on the poor encoding trials to the levels seen during good encoding, selectively in the area of the induced task activity. The middle case reveals that this effect was also observed in an activated area of the occipital cortex, which was distant from the site of stimulation located in the TC (Fig. 2B). We did not observe this neuromodulatory effect (quantified as the NM index) in the bottom case, where no area in the TC was activated in the tasks (Fig. 2C). Cortical stimulation mapping of language functions

was performed as part of the clinical evaluation in patients 1050 and 1177, which showed no overlap with the target stimulation electrodes (Table 1).

We quantified these observations for all electrodes in the activated brain areas ("active" electrodes) in the only stimulated subject who had more than ten such active electrodes (n = 22). The active electrodes were selected based on the distribution of the peak values of the high γ response from all available electrodes in a given patient (Fig. 3A,B). To test whether the observed modulation was specific to the high γ band we compared the NM index
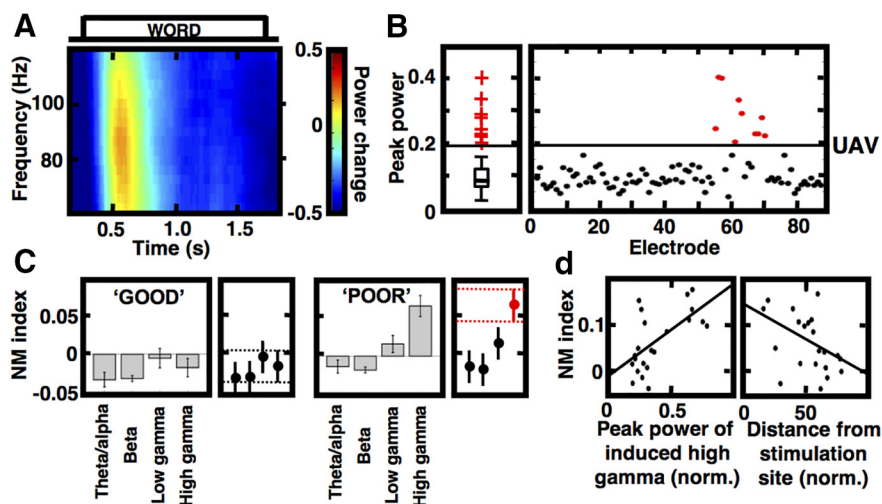
Figure 3. Stimulation selectively modulates task responses in the high γ frequency band. **A**, Spectrogram of trial-averaged high γ response to word presentations recorded on an electrode in the brain area activated in the tasks. **B**, Active electrodes showing this response were identified as positive outliers of the peak value distribution of this response (red data points above the solid line of UAV). **C**, Mean NM index of all active electrodes in one stimulated patient ($n = 36$) is compared among four frequency bands in the poor and good memory encoding conditions. Subplots on the right show *post hoc* comparison of the group means, dashed lines mark the 95% CI intervals (error bars) for the high γ group, and red indicates significant group with the intervals that do not overlap with any other group. **D**, Scatterplots with least-square lines show correlations of the NM index values in the poor encoding condition plotted against peak value of the task response (left) and against the distance from the stimulation site (right) for the active electrodes from **C**. Notice that NM index was proportional to the induced power response and inversely proportional to the distance from the stimulation site.

values in four nonoverlapping frequency bands (θ/α, β, low γ and high γ). A significant difference was found between the studied bands in the condition of poor memory encoding ($p < 0.0001$, ANOVA, $F = 14.8$, degrees of freedom = 3, 84) but not in the good memory encoding ($p = 0.171$, ANOVA, $F = 1.71$, df = 3, 84) in this subject. NM index values for the high γ band in the poor encoding condition were significantly more positive (Tukey–Kramer *post hoc* test, $p < 0.05$) than for any of the other bands (Fig. 3C). We further investigated whether these significantly more positive values of NM index were correlated with the amplitude of the high γ response and with the distance from the source of stimulation (Fig. 3D). The mean NM index was positively correlated with the mean amplitude of the high γ response (Pearson's correlation, $R = 0.627$, $p = 0.0018$) and negatively correlated with the distance from stimulation site (Pearson's correlation, $R = -0.429$, $p = 0.0461$). These correlations suggest that the strength of modulation was dependent on the electrode activity in the tasks and its proximity to the site of stimulation.

In the final part of this study, we asked whether this positive modulation of the high γ activities induced in the free recall memory tasks is specific to stimulation in the lateral TC. We observed an inverse pattern of modulation when the other studied brain regions were stimulated. Figure 4 shows two example electrodes showing a positive NM index with TC stimulation (top rows) and two negative index values with stimulation in the HP (bottom rows). The latter came from subject 1024, who noted decreased memory performance on the STIM relative to the NON-STIM lists.

To test this observed relationship between the behavioral performance and magnitude of the modulation in different brain regions, we compared the effect of stimulation in the four regions involved in the declarative memory system: PH (entorhinal/perirhinal and PH gyrus), HP (subiculum and HP proper), lateral TC (middle and superior temporal gyrus), and PF (middle and inferior frontal gyrus). Precise localization of all stimulation targets used in every subject ($N = 23$) is shown on a unified brain surface (Fig. 5A) and can be viewed online (to be identified if the article is published). We summarized the behavioral effect of stimulation across the studied brain regions to find that all four subjects stimulated in the lateral TC showed a positive effect on memory performance (Fig. 5B). There was a significant effect of the brain region ($p = 0.0019$, ANOVA test, $F = 7.31$, df = 3, 19) revealing a stronger positive modulation of memory performance in the TC stimulation group than any other brain region (Tukey–Kramer test, $p < 0.05$). Stimulating in the four regions also exerted different effects on the high γ modulation ($p < 0.001$, ANOVA test, $F = 23.27$, df = 3, 194). We found that the NM index, averaged over active electrodes from stimulation in a given region ($n = 198$), followed the same pattern (Fig. 5C) with a stronger positive NM in the TC group compared to any other group (Tukey–Kramer test, $p < 0.05$). Plotting the behavioral modulation score as a function of the mean NM index for every subject (Fig. 5D) confirmed that the electrophysiological effect of stimulation and memory performance were correlated (Pearson's correlation, $R = 0.50$, $p = 0.016$). Subjects 1050 and 1111, who noted the highest NM index values, demonstrated the
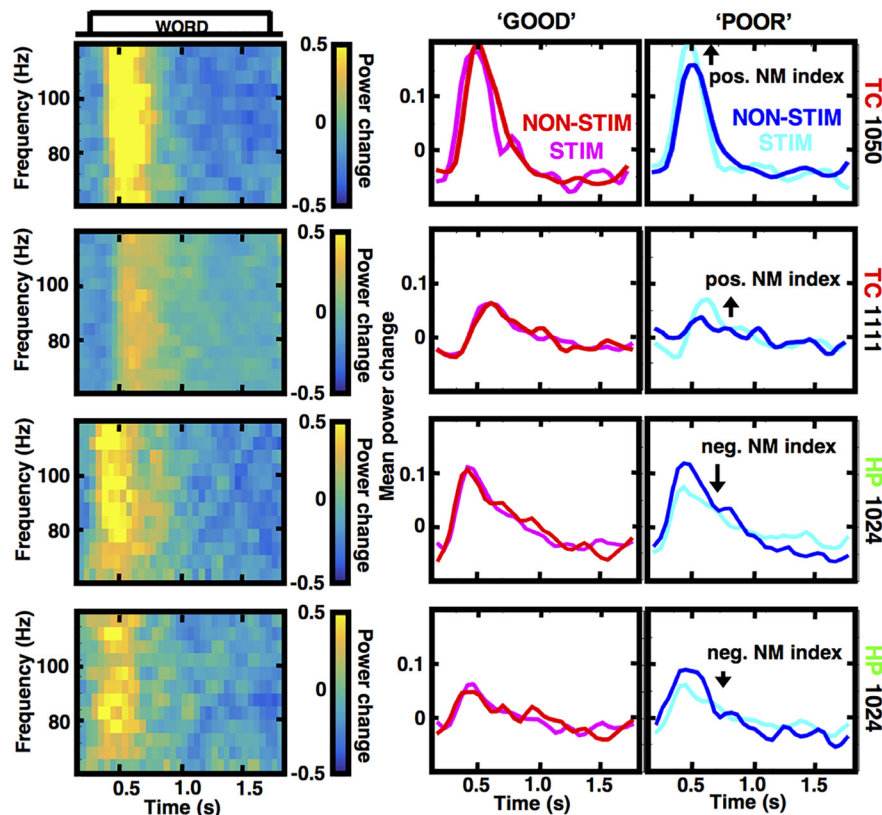
Figure 4. High γ responses are positively and negatively modulated in different brain regions. Four electrode examples show modulation of the task-induced high γ activities by stimulation in the lateral TC (red) and the HP (green), as presented in another example from Figure 1C. Arrows mark the positive and negative NM index changes in the three patients who showed the greatest positive (upper rows) and negative (lower rows) behavioral effects of stimulation (Fig. 5).

greatest memory enhancement (Fig. 5D). Conversely, subject 1024 with the lowest mean NM index, noted the greatest memory impairment.

Discussion

In this work, we found evidence that electrical stimulation in specific regions of the human brain modulates high γ activities induced during encoding of words for subsequent recall. Positive high γ modulation, as observed with stimulation in the lateral TC, was associated with the brain region showing enhanced memory performance with stimulation, whereas negative modulation was seen in the HP, a region where stimulation had the opposite effect on memory recall. Both structures have been proposed to play differential roles in the declarative memory. HP and the medial temporal lobe structures are thought to be critical for binding episodic memory representations from distributed regions in the neocortex, which process and store memory (Squire and Zola-Morgan, 1991; Eichenbaum, 2000). Previous studies using electrical stimulation in the medial temporal lobe during memory performance in human subjects showed mixed results (Kim et al., 2016). Our results corroborate a recent report of stimulation-induced impairment in a range of tasks, including the free recall of word lists, applied in a large number of patients stimulated in the HP and the entorhinal cortex (Jacobs et al., 2016). Much less is known about the effect of stimulation in the lateral TC. Since the original reports

of eliciting memory experience in individual epilepsy patients (Penfield and Perot, 1963), stimulation in this region of the human brain has been predominantly used for mapping language functions (Ojemann, 1991). Noninvasive stimulation (Tune and Asaridou, 2016) and imaging studies (Binder et al., 2009) support the role of brain regions in the lateral TC in processing semantic information. Another study with large number of epilepsy patients implanted with electrodes in various regions of the brain found that epileptiform discharges were impairing memory encoding of word lists specifically if they occurred in the lateral TC (Horak et al., 2017). Our results show that stimulation applied in the lateral TC enhanced the high γ activities in response to word encoding. In summary, there is a growing body of literature implicating the lateral TC in verbal memory functions.

Stimulation-related enhancement of the induced high γ activities was observed on trials with poor memory encoding and not on the good encoding trials. In fact, the average NM index for the high γ band during good encoding trials turned out to be negative (Fig. 3C). In a recent study of electrical stimulation applied during word encoding, the induced high γ activity was used to classify brain states into good and poor encoding states and predict that stimulating in the good state decreased the probability of recall and vice versa increased probability of recall when stimulating in the poor encoding state (Ezzyat
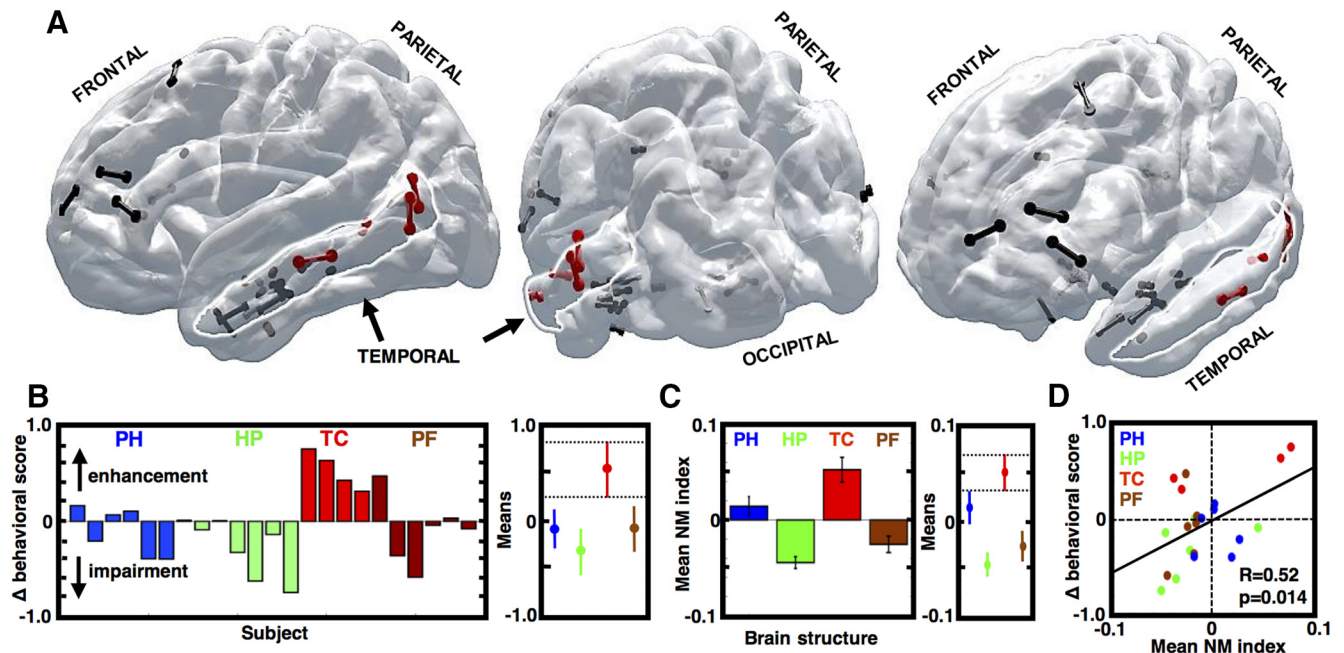
Figure 5. Modulation of high γ activity in different brain regions is correlated with behavior. *A*, Localization of the stimulation sites in the lateral TC (red contact pairs) and the other three brain regions studied (black contact pairs) is visualized in a unified transparent brain surface. *B*, Stimulation-induced change in memory performance for every subject (each bar is one subject) reveals that stimulation in the TC had a positive effect on performance compared to the other brain regions (PF). *Post hoc* group comparison (right side) shows that TC scores are greater than PH, HP, PF (dashed lines are 95% CI of the TC group). *C*, NM index values reveal the same pattern as in *B*, averaged from all active electrodes in a given group [$n = 38$ (PH), $n = 80$ (HP), $n = 36$ (TC), $n = 44$ (PFC)]. *D*, The behavioral and NM index scores averaged for each subject (color-coded dots) are correlated. Least-square line is added in black, crossing the two dashed lines at point 0 indicating no stimulation-induced changes.

et al., 2017). This interesting finding of good and poor encoding state-dependency is consistent with our observation of a positive stimulation-induced NM index during the poor encoding trials and a negative index during the good trials. Still, the positive effect of stimulation on the high γ activity was restricted to trials with words that were ultimately forgotten, making it challenging to explain the overall enhancement observed in the increased number of recalled words.

The outcome of stimulation was not only determined by the encoding brain state, but also by anatomic location. Our results show that both the neurophysiology and the behavior (recall performance) were differentially modulated depending on the brain region tested. The same stimulation pattern applied in the lateral TC versus the HP had opposite effects on the high γ responses and the associated recall performance (Fig. 5). The exact factors causing these differential effects on the neurophysiology and behavior remain unclear. The difference could be related to the qualitative differences in the electrode contacts used for stimulation, i.e., penetrating depth electrodes in the HP and subdural electrodes on lateral TC, but the surface area of the different electrodes is similar. In addition, five out of six subjects undergoing stimulation in the PF group were stimulated using subdural electrodes and did not show the same neurophysiological or behavioral effect as in the TC group. Further, the difference could be attributed to the range of stimulation parameters used. The original studies with epilepsy patients

found that only a given set of amplitude and frequency parameters elicited the memory experience (Bickford et al., 1958; Penfield and Perot, 1963). Stimulating the same regions of the brain with higher amplitudes is known to disrupt cognitive processing of, e.g., verbal information mapped in these patients (Ojemann, 1991) as applied in clinical language mapping. Therefore, our reported results may not necessarily generalize to other tasks or be replicable with different set of parameters, which could not be tested within the scope of this study. Nevertheless, the results hold promise for using high γ activities as a biomarker of NM to target optimal parameters, phases and sites for stimulation and support that the stimulated region in the posterior half of the middle and superior temporal gyrus is specifically important for modulating memory processes engaged in these tasks.

Regarding the possible target sites, within the lateral TC there were distinct focal areas where word encoding induced the high γ activity (Fig. 2). These "islands" of high frequency power have been reported in the intracranial recordings during tasks (Kucewicz et al., 2014, 2017), which may indicate local processing of neuronal assemblies (Crone et al., 2006; Lachaux et al., 2012) and be used to map target sites for stimulation. Interestingly, the precise localization of the foci of high γ activities was not exactly the same in the studied subjects even within the lateral TC, possibly due to different strategies employed by subjects in these tasks (e.g., remembering more semantic or visual representations). At this point we can only

speculate about the effects of stimulating in the focus or perimeter of these islands, over a gyrus or a sulcus, or at various scales of neuronal organization. Successful stimulation sites were localized on the middle temporal gyrus adjacent to the high γ island in two out of four subjects, who showed the strongest positive effect on neurophysiology and behavior (Fig. 5). Our study as well as others in the field (Suthana and Fried, 2014; Kim et al., 2016; Jacobs et al., 2016; Ezzyat et al., 2017) were performed with standard clinical electrodes with contacts of diameters ranging from 1 to 10mm^2 and separated by 5-10 mm. We speculate that future studies using combined macro- and micro-electrode arrays could provide additional information of the spatial scale of the neuronal networks underlying memory function (Le Van Quyen et al., 2010; Viventi et al., 2011; Worrell et al., 2012; Kucewicz et al., 2016).

With regard to the target phases and parameters for stimulation, there are many other possible approaches to enhance memory processing and task performance. We have focused on modulating the encoding of memorized stimuli during their presentation, which induces high frequency activities. Another approach is to modulate maintenance, consolidation or retrieval of memory for the encoded items, which are thought to engage oscillatory activities in the lower frequency bands, including the θ rhythm (Buzsaki, 2006; Düzel et al., 2010). These lower frequency oscillations were shown to be more widely spread than the focal γ responses (Burke et al., 2013; Kucewicz et al., 2014), thus possibly providing a viable target for noninvasive stimulation techniques. For instance, transcranial magnetic stimulation was employed to modulate θ oscillations mapped in parietal cortex to enhance retention of nonverbal memory (Albouy et al., 2017). Memory performance was increased in 13 out of 17 subjects and attributed to entrainment of the θ oscillations during the maintenance phase of the task. Other studies using noninvasive stimulation in similar tasks to probe active maintenance of memory in the PF showed mixed effects on reaction time and accuracy (Brunoni and Vanderhasselt, 2014). Although these studies are limited in terms of elucidating the ongoing neurophysiological activity, they complement the invasive intracranial recordings with insight into other measures of neural excitability and plasticity (Kincses et al., 2004; Fregni et al., 2005).

The precise memory processes that were modulated in our study are elusive. The observed NM did not directly enhance memory encoding per se since the high γ modulation was observed on the poor encoding trials with words that were subsequently forgotten. It could rather enhance memory performance through an associated process. Selective attention, perception and computation of sensorimotor information were all proposed as functions of γ oscillations (Singer, 1993; Tallon-Baudry and Bertrand, 1999; Jensen et al., 2007; Fries, 2009), which are essential to memory performance. If stimulation worked by increasing the level of attention and/or sensory processing of words, it would aid their encoding but not necessarily improve the retention and recall of all of them. In this scenario, the likelihood of successful memory encoding would be increased specifically on the trials with words that were not adequately attended and processed. As a result, more of these words would end up being recalled due to this enhanced attention or perception to the verbal stimuli, which is what we observed on the behavioral level. There would still be words that did not end up being recalled despite the stimulation-induced enhancement of these associated processes. In summary, stimulation would restore processing of these allegedly "less attended" words, increasing their subsequent recall probability that would lead some, but not all, to transition and add to the number of the recalled words (the good encoding group). Disentangling this challenging relationship between memory and the associated processes requires additional experiments that can track attention and sensory processing through other behavioral or autonomic measures, e.g., the eye movements or pupil dilation.

Another way to identify the cognitive processes modulated by electrical stimulation is to test the existing computational models of memory. One can look for example at the classic primacy and recency effect in remembering lists of stimuli (Murdock, 1962) or the temporal contiguity effect (Sederberg et al., 2010). The former model incorporates serial position of a word on the presented lists with a prior knowledge that the ones in the beginning and in the end of the list tend to be more attended, and thus better recalled, than the middle-list words. The latter is a model of the probability of recall based on temporal proximity of the presented words; words presented next to each other are more likely to be recalled together. In the current paper, we explored these possibilities and did not find compelling evidence for either; however, the current study is limited by a small number of trials to compare. Both of these models may prove useful in future for elucidating the effect of stimulation on memory processing with larger number of subjects.

Finally, physiologic mechanisms of the high γ modulation and how it is linked with the associated behavioral effect remain to be explored. Direct brain stimulation is thought to primarily activate neuronal axons rather than cell bodies (Perlmutter and Mink, 2006), which would provide one explanation for why the electrophysiological effects were observed and not only in the region of stimulation but also in more distant islands of high γ activity, presumably connected with each other. It could also account for the disparity between the frequency of stimulation (50 Hz) and the higher frequencies of the modulated high γ response. Axons of the stimulated white matter tracts may be depolarized and trigger a response of neuronal assemblies oscillating at other frequencies in the distant brain regions they connect. Supporting evidence for the role of axonal stimulation comes from micro-electrode stimulation combined with calcium imaging that shows wide-spread activation of sparsely distributed neurons instead of local depolarization of neurons surrounding the stimulating electrode (Histed et al., 2009).

We observed that the modulation was stronger on electrodes closer to the stimulation site and more active in the tasks. This may possibly reflect a small-world network organization of the brain (Bassett and Bullmore, 2006),

which proposes higher number of local and fewer long-distance connections. Therefore, more of the short-range local connections would be depolarized by the electric current and activate more proximal neuronal assemblies, relative to the longer-distance assemblies. In this network view of brain modulation, stimulation would also exert the strongest effect when applied to brain regions, which were critical nodes, i.e., hubs, with many connections to other active nodes in a given network. The lateral TC and the HP, where we observed the strongest positive and negative modulation of high γ activities respectively, are both considered critical hubs for declarative memory networks. Therefore, finding and targeting these critical connection hubs to modulate the whole network instead of a single brain region may be the most efficient strategy for enhancing memory processes (Kim et al., 2016). In our study, stimulation in the lateral TC could work by activating a network hub for verbal declarative memory. These network hubs can potentially be more effectively identified using various measures of connectivity and temporal interactions like spectral coherence or cross-frequency coupling. Future investigations of the brain connectomics data and modeling tools combined with high-density electrophysiological recordings promise to shed light on the mechanisms of electrical modulation for memory and cognitive enhancement.

References

Albouy P, Weiss A, Baillet S, Zatorre RJ (2017) Selective entrainment of theta oscillations in the dorsal stream causally enhances auditory working memory performance. Neuron 94:193–206.e5. CrossRef

Bassett DS, Bullmore E (2006) Small-world brain networks. Neurosci Rev J Bringing Neurobiol Neurol Psychiatry 12:512–523. CrossRef Medline

Bickford RG, Mulder DW, Dodge HW, Svien HJ, Rome HP (1958) Changes in memory function produced by electrical stimulation of the temporal lobe in man. Res Publ Assoc Res Nerv Ment Dis 36:227–240; discussion 241–243.

Binder JR, Desai RH, Graves WW, Conant LL (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 19:2767–2796. CrossRef

Bokil H, Andrews P, Kulkarni JE, Mehta S, Mitra PP (2010) Chronux: a platform for analyzing neural signals. J Neurosci Methods 192:146–151. CrossRef Medline

Brunoni AR, Vanderhasselt M-A (2014) Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 86:1–9. CrossRef Medline

Burke JF, Zaghloul KA, Jacobs J, Williams RB, Sperling MR, Sharan AD, Kahana MJ (2013) Synchronous and asynchronous theta and gamma activity during episodic memory formation. J Neurosci 33:292–304. CrossRef Medline

Buzsaki G (2006) Rhythms of the brain. Oxford, New York: Oxford University Press.

Coleshill SG, Binnie CD, Morris RG, Alarcón G, van Emde Boas W, Velis DN, Simmons A, Polkey CE, van Veelen CWM, van Rijen PC (2004) Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. J Neurosci 24:1612–1616. CrossRef

Crone NE, Sinai A, Korzeniewska A (2006) High-frequency gamma oscillations and human brain mapping with electrocorticography. Prog Brain Res 159:275–295. CrossRef Medline

Düzel E, Penny WD, Burgess N (2010) Brain oscillations and memory. Curr Opin Neurobiol 20:143–149. CrossRef Medline

Dykstra AR, Chan AM, Quinn BT, Zepeda R, Keller CJ, Cormier J, Madsen JR, Eskandar EN, Cash SS (2012) Individualized localization and cortical surface-based registration of intracranial electrodes. Neuroimage 59:3563–3570. CrossRef Medline

Eichenbaum H (2000) A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 1:41–50. CrossRef Medline

Engelhard B, Ozeri N, Israel Z, Bergman H, Vaadia E (2013) Inducing γ oscillations and precise spike synchrony by operant conditioning via brain-machine interface. Neuron 77:361–375. CrossRef Medline

Ezzyat Y, Kragel JE, Burke JF, Levy DF, Lyalenko A, Wanda P, O'Sullivan L, Hurley KB, Busygin S, Pedisich I, Sperling MR, Worrell GA, Kucewicz MT, Davis KA, Lucas TH, Inman CS, Lega BC, Jobst BC, Sheth SA, Zaghloul K, et al. (2017) Direct brain stimulation modulates encoding states and memory performance in humans. Curr Biol 27:1251–1258. CrossRef Medline

Fell J, Staresina BP, Do Lam ATA, Widman G, Helmstaedter C, Elger CE, Axmacher N (2013) Memory modulation by weak synchronous deep brain stimulation: a pilot study. Brain Stimul 6:270–273. CrossRef

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004) Automatically parcellating the human cerebral cortex. Cereb Cortex 14:11–22.

Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MTA, Paulus W, Pascual-Leone A (2005) Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166:23–30. CrossRef

Fries P (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu Rev Neurosci 32:209–224. CrossRef Medline

Gordon B, Lesser RP, Rance NE, Hart J, Webber R, Uematsu S, Fisher RS (1990) Parameters for direct cortical electrical stimulation in the human: histopathologic confirmation. Electroencephalogr Clin Neurophysiol 75:371–377. Medline

Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, Wennberg RA, Lozano AM (2008) Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 63:119–123. CrossRef Medline

Histed MH, Bonin V, Reid RC (2009) Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. Neuron 63:508–522. CrossRef Medline

Horak PC, Meisenhelter S, Song Y, Testorf ME, Kahana MJ, Viles WD, Bujarski KA, Connolly AC, Robbins AA, Sperling MR, Sharan AD, Worrell GA, Miller LR, Gross RE, Davis KA, Roberts DW, Lega B, Sheth SA, Zaghloul KA, Stein JM, et al. (2017) Interictal epileptiform discharges impair word recall in multiple brain areas. Epilepsia 58:373–380.

Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, Sharan A, Worrell G, Berry B, Lega B, Jobst BC, Davis K, Gross RE, Sheth SA, Ezzyat Y, Das SR, Stein J, Gorniak R, Kahana MJ, Rizzuto DS (2016) Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron 92:983–990. CrossRef Medline

Jensen O, Kaiser J, Lachaux J-P (2007) Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 30:317–324. CrossRef Medline

Johnson MD, Lim HH, Netoff TI, Connolly AT, Johnson N, Roy A, Holt A, Lim KO, Carey JR, Vitek JL, He B (2013) Neuromodulation for brain disorders: challenges and opportunities. IEEE Trans Biomed Eng 60:610–624. CrossRef Medline

Kahana MJ (2006) The cognitive correlates of human brain oscillations. J Neurosci 26:1669–1672. CrossRef Medline

Kahana M (2012) Foundations of human memory. Oxford, New York: Oxford University Press.

Kim K, Ekstrom AD, Tandon N (2016) A network approach for modulating memory processes via direct and indirect brain stim-

ulation: toward a causal approach for the neural basis of memory. Neurobiol Learn Mem 134:162–177.

Kincses TZ, Antal A, Nitsche MA, Bártfai O, Paulus W (2004) Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 42:113–117. Medline

Kucewicz MT, Cimbalnik J, Matsumoto JY, Brinkmann BH, Bower MR, Vasoli V, Sulc V, Meyer F, Marsh WR, Stead SM, Worrell GA (2014) High frequency oscillations are associated with cognitive processing in human recognition memory. Brain J Neurol 137: 2231–2244. CrossRef

Kucewicz MT, Michael Berry B, Bower MR, Cimbalnik J, Svehlik V, Matt Stead S, Worrell GA (2016) Combined single neuron unit activity and local field potential oscillations in a human visual recognition memory task. IEEE Trans Biomed Eng 63:67–75. CrossRef

Kucewicz MT, Berry BM, Kremen V, Brinkmann BH, Sperling MR, Jobst BC, Gross RE, Lega B, Sheth SA, Stein JM, Das SR, Gorniak R, Stead SM, Rizzuto DS, Kahana MJ, Worrell GA (2017) Dissecting gamma frequency activity during human memory processing. Brain 140:1337–1350. CrossRef Medline

Lachaux J-P, Axmacher N, Mormann F, Halgren E, Crone NE (2012) High-frequency neural activity and human cognition: past, present and possible future of intracranial EEG research. Prog Neurobiol 98:279–301. CrossRef Medline

Le Van Quyen M, Staba R, Bragin A, Dickson C, Valderrama M, Fried I, Engel J (2010) Large-scale microelectrode recordings of high-frequency gamma oscillations in human cortex during sleep. J Neurosci 30:7770–7782. CrossRef

Lundqvist M, Rose J, Herman P, Brincat SL, Buschman TJ, Miller EK (2016) Gamma and beta bursts underlie working memory. Neuron 90:152–164.

McCreery DB, Agnew WF, Yuen TG, Bullara L (1990) Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. IEEE Trans Biomed Eng 37:996–1001. Medline

Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS (2015) Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. Brain 138:1833–1842.

Murdock BB (1962) Serial position effect in free recall. J Exp Psychol 64:482–488. CrossRef

Ojemann GA (1991) Cortical organization of language. J Neurosci 11:2281–2287. Medline

Penfield W (1958) Some mechanisms of consciousness discovered during electrical stimulation of the brain. Proc Natl Acad Sci USA 44:51–66. Medline

Penfield W, Perot P (1963) The brain's record of auditory and visual experience. Brain 86:595–696. Medline

Perlmutter JS, Mink JW (2006) Deep brain stimulation. Annu Rev Neurosci 29:229–257. CrossRef Medline

Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, McCarthy DC, Brandt A, Tully MS, Kahana MJ (2007) Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cereb Cortex 17:1190–1196.

Sederberg PB, Miller JF, Howard MW, Kahana MJ (2010) The temporal contiguity effect predicts episodic memory performance. Mem Cogn 38:689–699. CrossRef Medline

Singer W (1993) Synchronization of cortical activity and its putative role in information processing and learning. Annu Rev Physiol 55:349–374. CrossRef Medline

Sohal VS (2016) How close are we to understanding what (if anything) γ oscillations do in cortical circuits? J Neurosci 36:10489–10495. CrossRef Medline

Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253:1380–1386. Medline

Suthana N, Fried I (2014) Deep brain stimulation for enhancement of learning and memory. Neuroimage 85:996–1002. CrossRef Medline

Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I (2012) Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 366:502–510. CrossRef Medline

Tallon-Baudry C, Bertrand O (1999) Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 3:151–162. Medline

Tune S, Asaridou SS (2016) Stimulating the semantic network: what can TMS tell us about the roles of the posterior middle temporal gyrus and angular gyrus? J Neurosci 36:4405–4407. CrossRef Medline

Viventi J, Kim DH, Vigeland L, Frechette ES, Blanco JA, Kim YS, Avrin AE, Tiruvadi VR, Hwang SW, Vanleer AC, Wulsin DF, Davis K, Gelber CE, Palmer L, Van der Spiegel J, Wu J, Xiao J, Huang Y, Contreras D, Rogers JA, et al. (2011) Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. Nat Neurosci 14:1599–1605. CrossRef Medline

Voss U, Holzmann R, Hobson A, Paulus W, Koppehele-Gossel J, Klimke A, Nitsche MA (2014) Induction of self awareness in dreams through frontal low current stimulation of gamma activity. Nat Neurosci 17:810–812. CrossRef Medline

Waldert S, Lemon RN, Kraskov A (2013) Influence of spiking activity on cortical local field potentials. J Physiol 591:5291–5303. CrossRef Medline

Worrell GA, Jerbi K, Kobayashi K, Lina JM, Zelmann R, Le Van Quyen M (2012) Recording and analysis techniques for high-frequency oscillations. Prog Neurobiol 98:265–278. CrossRef Medline

Yushkevich PA, Pluta JB, Wang H, Xie L, Ding S-L, Gertje EC, Mancuso L, Kliot D, Das SR, Wolk DA (2015) Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. Hum Brain Mapp 36:258–287. CrossRef Medline