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Human Hippocampal Theta Oscillations and the Formation of Episodic Memories

Bradley C. Lega,[1]* Joshua Jacobs,[2] and Michael Kahana[3]

ABSTRACT: The importance of the hippocampal theta oscillation (4–8 Hz) to memory formation has been well-established through studies in animals, prompting researchers to propose comprehensive theories of memory and learning that rely on theta oscillations for integrating information in the hippocampus and neocortex. Yet, empirical evidence for the importance of 4–8 Hz hippocampal theta oscillations to memory formation in humans is equivocal at best. To clarify this apparent interspecies discrepancy, we recorded intracranial EEG (iEEG) data from 237 hippocampal electrodes in 33 neurosurgical patients as they performed an episodic memory task. We identified two distinct patterns of hippocampal oscillations, at ~3 and ~8 Hz, which are at the edges of the traditional 4–8 Hz human theta band. The 3 Hz "slow-theta" oscillation exhibited higher power during successful memory encoding and was functionally linked to gamma oscillations, but similar patterns were not present for the 8 Hz "fast-theta" oscillation. For episodic memory, slow-theta oscillations in the human hippocampus appear to be analogous to the memory-related theta oscillations observed in animals. Both fast-theta and slow-theta oscillations exhibit evidence of phase synchrony with oscillations in the temporal cortex. We discuss our findings in the context of recent research on the electrophysiology of human memory and spatial navigation, and explore the implications of this result for theories of cortico–hippocampal communication. © 2011 Wiley Periodicals, Inc.

KEY WORDS: episodic memory; free recall; hippocampus; oscillation; subsequent memory effect; theta rhythm

INTRODUCTION

The theta rhythm in the rodent hippocampus represents a striking link between neuronal physiology and complex behavior. Hippocampal theta has been implicated in synaptic plasticity, information coding, and memory function in several species (Buzsáki, 2002, 2005; Dragoi et al, 2003; Dragoi and Buzsáki, 2006; Sirota et al, 2008; Montgomery et al., 2008, 2009; Tort et al., 2008; Mizuseki et al., 2009). Theta activity is thought to bind brain regions together during memory encoding and retrieval based on detailed animal experiments recording from cortical and subcortical locations (Vertes et al., 2001; Hasselmo, 2005; Hyman et al., 2005; Vertes, 2005). For memory-related theta activity in particular, experimental evidence in animals has reliably demonstrated that successful memory encoding is accompanied by increases in theta oscillatory power (Berry and Thompson, 1978; Seager et al., 2002; Nokia et al., 2008), and that pharmacologic or lesional disruption of theta is correlated with impaired learning function (Winson, 1978; Givens and Olton, 1995). Increases in theta power also occur during animal navigation (Vanderwolf, 1969; Buzsáki, 2005), and during the storage and retrieval of working memory items (Givens, 1996; Jensen and Colgin, 2007). In rodents, theta exists separately as 6–8 Hz Type 1 (atropine-resistant) theta and 4–6 Hz Type 2 theta (Kramis et al., 1975). The slower-frequency Type 2 oscillation has been preferentially implicated in memory during learning, while Type 1 theta is more closely associated with locomotion (Macrides et al., 1982; Berry and Swain, 1989; Miller, 1991; Seidenbecher et al., 2003).

In humans, evidence for the functional significance of theta oscillations has come from intracranial electroencephalographic (iEEG) recordings from neurosurgical patients engaged in cognitive tasks. These studies reliably find that "neocortical" 4–8 Hz theta oscillations play a role in episodic-memory encoding, working memory, and navigation [for reviews, see Kahana et al. (2001); Buzsáki (2005); Jacobs and Kahana (2010)]. However, studies exclusively analyzing "hippocampal" recordings report more checkered results, without a consistent 4–8 Hz effect. For working memory, data from behavioral studies describe functional properties for oscillations in the 4–8 Hz frequency range that include inter-region coherence, phase reset, and theta phase modulation of gamma band and single unit activities (Mormann et al., 2005; Babiloni et al., 2008; Fell et al., 2008; Axmacher et al., 2010; Rutishauser et al., 2010). Yet, these studies often report stronger memory-related effects for oscillations outside the 4–8 Hz range (especially <4 Hz) (Babiloni et al., 2008; Fell et al., 2008; van Vugt et al., 2010), and there is little evidence of a correlation between 4–8 Hz power changes and memory encoding performance as one might expect from the animal literature (Berry and Thompson, 1978; Nokia et al., 2008).

[1] **Department of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania;** [2] **School of Biomedical Engineering, Science, and Health Systems, Drexel University;** [3] **School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, Pennsylvania, USA**
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*Correspondence to: Bradley Lega, University of Pennsylvania, 3401 Walnut St (Entrance C), Room 303, Philadelphia, PA 19104. E-mail: bradlega@gmail.com
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Sederberg et al. analyzed cortical and hippocampal iEEG recordings from patients engaged in an episodic memory task (Sederberg et al., 2007b). At the hippocampal electrodes, they found that successful memory encoding was associated with increased gamma band activity but found no matching effect at lower frequencies, including the theta and delta (1–4 Hz) bands (Sederberg et al., 2007b). The only evidence for 4–8 Hz oscillatory power changes in the hippocampus related to episodic-memory formation has come from non invasive studies, in which it can be difficult to localize hippocampal oscillations (Tesche and Karhu, 2000; Stephen et al., 2005; Guderian et al., 2009). Using a visual memory task, Rutishauser et al. have identified single-unit activity locked to the phase of 3–8 Hz theta oscillations that predicts recognition memory performance (Rutishauser et al., 2010). However, their data include evidence of spike-field coherence below 4 Hz and they report no 4–8 Hz theta power difference that correlates with successful encoding akin to animal theta.

Studies of hippocampal oscillatory activity from humans engaged in spatial navigation have revealed similarly mixed results. While navigation-related changes in 4–8 Hz oscillations have been reported [for a review, see Jacobs and Kahana (2010)], many studies identify oscillations at frequencies below 4 Hz that have functional roles more similar to animal theta (Ekstrom et al., 2005; Cornwell et al., 2008; Jacobs et al., 2007, 2010). Finally, research on human hippocampal oscillatory activity during REM sleep has reported prominent oscillations in the <4 Hz band, rather than the traditional 4–8-Hz range (Bódizs et al., 2001; Clemens et al., 2009).

Taken together, existing human data do not unequivocally identify a critical role for 4–8 Hz hippocampal theta oscillations for navigation and memory, in contrast to studies in animals (Berry and Thompson, 1978; Buzsáki, 2002, 2005; Niedermeyer, 2008; Nokia et al., 2008). We sought to probe this discrepancy through a systematic analysis of human hipppocampal electrophysiological activity, in particular comparing oscillatory power across the frequency spectrum during episodic-memory encoding and retrieval. We identified two distinct oscillations that appear at the edges of the traditional 4–8-Hz theta band. Our findings show that the lower-frequency oscillation, at ∼3 Hz, is analogous to Type 2 hippocampal theta oscillations in animals, because it demonstrates increased power during successful episodic-memory. This power increase is correlated with gamma power changes that predict memory formation.

METHODS

Intracranial Recordings

We examined data from intracranial depth electrodes in 33 patients undergoing surgical treatment for intractable epilepsy who had hippocampal depth electrodes implanted due to clinical concerns. Of these, 12 patients were from the USA (Boston, MA and Philadelphia, PA) and 21 were from Freiburg, Germany. The presence of specific contacts within the hippocampus proper, rather than in the entorhinal cortex, subiculum, parahippocampal gyrus, or amygdala, was confirmed via careful examination of high resolution magnetic resonance images by qualified members of the clinical team. If an electrode was not unequivocally located in the hippocampus, it was excluded from our analyses. Electrodes thought to be located in the entorhinal cortex and subiculum were excluded. Analysis of contacts outside of the hippocampus was not performed as part of this investigation, although previous results (on a smaller dataset) are reported in Sederberg et al. (2007b).

We recorded from these electrodes while participants studied and recalled lists of words in a delayed free-recall task. Recordings from 18 of these patients were used in prior studies (Sederberg et al., 2003, 2007b). All protocols were approved by the relevant institutional review boards and conformed to accepted standards of ethical experimentation. The signal from each electrode was amplified and sampled at a minimum of 200 Hz. The signals were selectively notch filtered at either 60 Hz or 50 Hz, depending upon the location of the recordings (USA or Germany, respectively). We used the Morlet wavelet transform (wave number of 6) to compute the spectral power as a function of time for all iEEG signals. Frequencies were sampled logarithmically between 2 Hz and 100 Hz, total of 48 frequencies (van Vugt et al., 2007).

We sought to check our results for the effects of epileptogenic brain tissue. The patients in this study suffered seizures that suggested a temporal onset, but none had mesial temporal sclerosis or a well-defined radiographic lesion. As such, no electrodes were located in radiographically abnormal brain tissue. We excluded any recordings in which the iEEG signal contained evidence of interictal spiking activity. Furthermore, as a control, our analysis was performed separately on electrodes that were adjacent to putative epileptogenic cortex, and we confirmed that our findings did not hinge upon unusual signal characteristics emanating from these contacts.

All analyses were performed separately on electrodes implanted into the language dominant and non dominant hemispheres. All but two patients were right-handed, and for these two the side of language dominance had been determined by pre-implantation functional imaging and/or Wada testing (Woermann et al.; 2003).

Experimental Task

Participants performed between 1 and 7 sessions of the free-recall task (median number 2). For each session, participants attempt to remember words on 15 to 20 different lists. Each list within the free-recall task consists of four epochs. At the beginning of each list, in the orientation epoch, participants quietly view a fixation cross at the center of a computer screen for 1600 msec this was meant to alert participants to the upcoming word presentations. Next, during the encoding epoch, participants are asked to memorize lists of words. The lists are composed of 15 or 20 common nouns chosen at

random from a pool of high-frequency words in the participants' native language (English or German), with no repetitions. A change in the list length (reduction from 20 to 15) was made to accommodate the wishes of our clinical collaborators to reduce the amount of time required to complete a single testing session. Each word is onscreen for 1600 ms and the screen is blank for 800 to 1200 msec before the presentation of the next word (ISI). The 2000 msec that follows item presentation is considered the "encoding epoch". After the list, the participants perform a distraction task (simple arithmetic problems performed for a total of 20 sec). This is followed by a row of asterisks that appear on the screen for 300 msec signaling the participants that they will be asked to recall the presented item. Participants are given 45 sec to verbally recall as many of the items as they remember. The recall period is audio recorded, and the times at which participants verbalize each memory item are carefully annotated in a post-processing step along with whether or not each presentation item was successfully recalled. By annotating the recall times, we were able to divide the recall period into two different epoch types centered on the verbalization of a memory item. The 700-msec period immediately preceding each recalled word was considered the retrieval epoch. This time point was chosen because previous work determined that it is a critical window prior to recall at which overall brain activity begins to recapitulate the pattern of activation that was present during initial word encoding (Manning et al., 2009b; Polyn and Kahana, 2008). The 800 msec period preceding each retrieval epoch (i.e., −1500 to −700 msec relative to each word's verbalization) was the deliberation epoch. (See Fig. 5 for an illustration of all epochs.) Only correct responses were included in the analysis of the deliberation and retrieval epochs given the rarity of incorrect recalls (i.e., intrusions, which on average comprise less than 5% of recalled items for each participant).

Oscillation Detection Algorithm

We designed an oscillation detection algorithm to identify and characterize the neuronal oscillations that reliably appeared in the power spectra. We applied this algorithm to recordings from the 2-second time window following the presentation of each word. At each frequency, we log-transformed the measured oscillatory power at each sample, computed the mean log power for each word presentation, and then computed the mean power across all word presentations. This provided a power spectrum that characterized the overall oscillatory activity at each site related to memory encoding. When plotted in logarithmic coordinates, these power spectra appeared as a straight line with positive deviations (i.e., peaks) at particular frequencies, consistent with previous findings that iEEG power has a $1/f^a$ distribution (Freeman et al., 2003; Miller et al., 2007). To identify these peaks quantitatively, we fit a line to this power spectrum for each electrode using robust regression (Holland and Welsch, 1977; Manning et al., 2009a). Robust regression is suitable for this purpose because, the fitted line is relatively unaffected by peaks at particular frequencies. The regression line was then subtracted from the power spectrum, generating a curve that clearly showed the peaks where the observed power spectrum diverged from the $1/f^a$ background. We then identified the local maxima in these curves to find the exact frequencies of the peaks; these were frequencies at which narrowband oscillations appeared. The power spectra were smoothed with a four-frequency boxcar function to avoid spurious, small peaks.

Phase Analysis

We sought to verify the origins of the oscillations detected by our algorithm to confirm that they were not attributable to volume conduction from cortical sources. We analyzed phase synchrony between cortical and hippocampal electrodes that exhibited slow or fast theta oscillations. Volume conduction is expected to occur (1) between nearby electrodes within 2 cm of each other and (2) that exhibit significant phase synchrony with a phase difference centered at zero degrees (Lachaux et al., 1999; Melloni et al., 2007). To identify cortical sources of slow and fast-theta, we applied the oscillation detection algorithm to temporal-cortex electrodes in the same set of 33 patients. We identified pairs of electrodes in individual patients, one from the temporal cortex and one from the hippocampus, in which both exhibited an oscillation in the slow-theta or fast-theta range (excluding electrodes that showed both). We compared the distribution of the phase difference between the two oscillations, selecting a 1 Hz frequency window around the peak of the oscillation and a time point 1 sec after word onset to limit the number of comparisons. Phase synchrony was assessed using the Rayleigh test in the manner of Lachaux et al. (1999). We identified the phase value in the frequency-time window for all memory item presentation events for both electrodes from the hippocampal-cortical pair being compared. Phase differences were obtained for all events, subtracting the hippocampal phase value from the cortical value. The distribution of these phase differences was tested for non uniformity using a permutation procedure with a P threshold of 0.01. For such synchronous pairs, the mean phase differences across all trials were computed. The distance between synchronous pairs was calculated. Of significant electrode pairs, hippocampal electrodes that demonstrated an average phase difference of 0° (+/− 15°) and were less than 40 mm from the cortical electrode with which they were synchronous were separately counted (Lachaux et al., 1999). We performed this analysis separately for electrodes that showed fast-theta or slow-theta oscillations. Volume conduction was assessed by looking for the total number of electrodes that exhibited zero degree phase synchrony and not the total number of pairs identified by this method. Each electrode was counted once even if it exhibited synchrony with multiple cortical electrodes.

Subsequent Memory Effect (SME) Analysis

We performed a series of analyses to identify electrodes exhibiting changes in oscillatory power at particular frequencies in relation to memory-encoding performance in the free-recall

task (Sederberg et al., 2003, 2007b). We compared power during encoding for words that were successfully recalled versus power for words that were unsuccessfully recalled. For this, we performed a Wilcoxon rank-sum at each frequency. We used a permutation procedure (1,000 iterations) to identify the *P* threshold to use for the rank-sum tests, which ensures that our Type 1 error rate is fixed at 5% across all comparisons in each frequency bin. Counts of electrodes that yielded significant differences between recalled and non recalled encoding events were compiled in a histogram. To ease data interpretation, for some analyses we pooled together counts of electrodes at individual frequencies into counts for the entire frequency band. The demarcations for these bands were: slow theta, 2.5–5 Hz; fast theta, 5.5–10 Hz; alpha, 10–19 Hz; beta, 19–32 Hz; and gamma, 34–100 Hz. Significance testing for the counts of electrodes in each band were performed with the binomial test with a Bonferroni correction for the number of wavelet frequency bins that went into each band. Comparisons of counts between bands were performed using the χ^2 statistic with Yates correction when appropriate. Correlations among electrode counts from different frequency bands and counts in the same band between retrieval and encoding epochs were assessed using Yule's Q. The use of counts of electrodes to quantify effects during memory encoding and retrieval have been developed by our laboratory as a robust means to account for heterogeneity among oscillatory activity at different brain sites, even within a particular region (Raghavachari et al., 2006; van Vugt et al., 2007). The multi-faceted electrographic correlates of human cognitive states require a method that describes the broad range of observed responses.

To visualize the timecourse of the SME effect across multiple electrodes (Fig. 2), we used a permutation procedure to produce a single *P* value that combined the results of statistical tests separately conducted at individual electrodes (Sederberg et al., 2007b). In this procedure, we applied the inverse-normal transformation to compute a *z* value corresponding to the *P* value computed at each time/frequency. Then we summed these *z* values across all electrodes, at each time/frequency. We also performed the same series of steps on 1000 sets of surrogate data that were generated by randomly shuffling the trials in each dataset (permuting trials for recalled and non recalled words). We determined a final *P* value for each time/frequency by identifying the position of the summed *z* score in the distribution of *z* scores from the surrogate datasets.

We sought to determine if the location of an electrode within the hippocampus affected our SME results. Taking advantage of high-resolution MR images, we addressed this question by dividing the hippocampus into four quadrants. The anterior-posterior boundary was drawn on axial slices at the level of the sulcus lateralis of the adjacent midbrain, the connection point between the peduncle anteriorly and the colliculi posteriorly. The lateral geniculate nucleus, previously cited as a possible landmark for radiographic orientation (Bernasconi et al., 1999), was not unquestionably visible on a sufficient number of hippocampal axial slices to use it as a landmark. In the medial/lateral direction, axial and coronal images were used to draw an imaginary sagittal bisector of the hippocampus, assigning electrodes on either side to different categories. High resolution images were only available for more precise anatomic localization for 155 of the 237 electrodes in the dataset, so intra hippocampal analysis is limited to these data. Electrodes were divided into four groups: anterior-medial, posterior-medial, anterior-lateral, and posterior-lateral based on these anatomic boundaries. Comparisons of counts of electrodes in each region were made separately for positive and negative SMEs via χ^2.

RESULTS

We analyzed recordings from 237 electrodes implanted in the hippocampi of 33 epilepsy patients undergoing invasive monitoring to identify seizure foci. Our initial goal was to identify sustained theta band oscillations from these hippocampal electrodes. The power spectra from individual electrodes revealed peaks at specific frequencies (Fig. 1, second row), and we surmised that these peaks corresponded to narrow-band oscillations. To better visualize and quantitatively identify these peaks, we "whitened" the power spectra by using robust non linear regression to subtract the $1/f^{\alpha}$ background signal (see Methods). The abscissal coordinates where peaks occurred in the "whitened" spectra were identified as the frequencies of underlying narrow-band oscillations (Fig. 1, third row). To assess the frequencies at which these oscillations were clustered, we tabulated the number of electrodes at each frequency at which these local maxima were detected. We compared the results across different conditions using electrode counts as a means to characterize the entire breadth of electrographic correlates of cognitive processes. The heterogeneity of brain responses at different sites makes this technique especially useful (Raghavachari et al., 2006; van Vugt et al., 2007). The resultant histogram from these electrode counts (Fig. 1, panel E) reveals that hippocampal oscillations appeared in three distinct frequency groups: ~3 Hz (e.g., Fig. 1A), ~8 Hz (e.g., Fig. 1B), and ~20 Hz (e.g., Fig. 1D). Some electrodes exhibited oscillations at multiple frequencies, as in Figure 1, panel C, which depicts an electrode that shows oscillations centered at 3 and 9 Hz.

Notably, this histogram shows that we did not observe a large number of electrodes exhibiting oscillations in the center of the 4–8-Hz traditional human theta band. Rather, we detected oscillations at the edges of this range, at 3 and 8 Hz. Given their origin at the edges of the theta band, we call the ~3-Hz oscillation "slow theta" and the ~8 Hz oscillation "fast theta." The histogram was used to identify the lower and upper boundaries of the frequency bands for slow and fast theta (2.5–5 Hz, 5.5–10 Hz, respectively). Out of 237 hippocampal electrodes, an oscillation in the slow theta band was detected in 51 electrodes, fast theta activity was identified in 68 electrodes, and oscillations in both the slow- and fast-theta bands were observed in 90 electrodes (as in Fig. 1C).

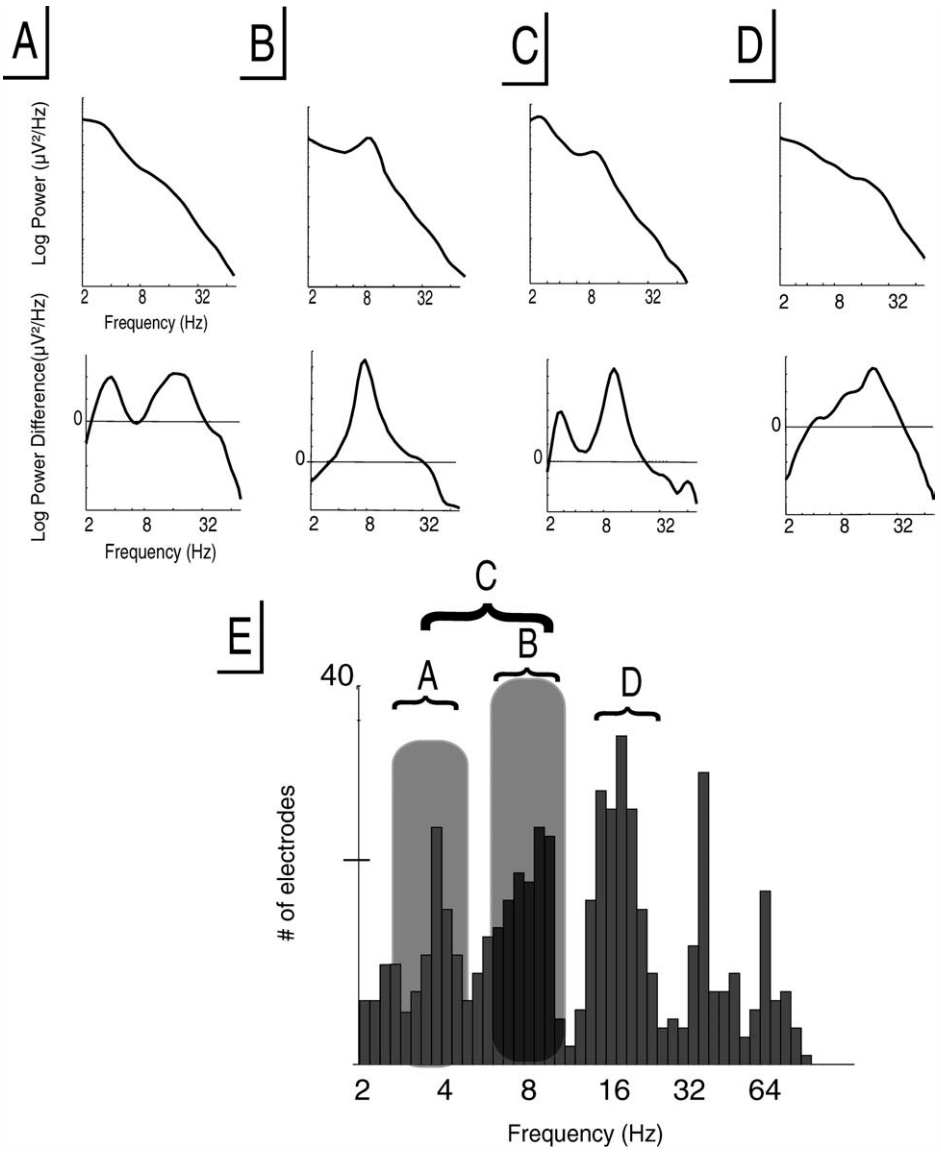

FIGURE 1. Application of Frequency Detection Algorithm. A: An electrode that showed oscillations at ~3 Hz and ~22 Hz. Top row shows mean power spectra for this electrode across all trials (recalled and non recalled), with peaks located at 3 and 22 Hz. Bottom row shows power spectra after subtraction of a robust-fit regression line (see Methods), which accentuates narrowband oscillatory peaks. Local maxima identified after robust regression line subtraction were used to identify oscillations in the signal. B: An electrode with an oscillation at 8.5 Hz. C: An electrode exhibiting both ~3 and ~9-Hz oscillations. D: An electrode with an oscillation at ~22 Hz. E: A histogram showing the results of applying our peak-detection algorithm to all electrodes in our dataset. The height of each bar indicates how many electrodes demonstrated an oscillatory peak at each frequency. The shading implies the limits of the slow-theta (2.5–5 Hz) and fast-theta (5.5–10 Hz) frequency bands. Labels on the histogram refer to the panels describing individual electrodes that show oscillations within the relevant band.

To characterize the functional properties of these oscillations, we analyzed how their power varied in relation to memory encoding during the free-recall task. Free recall is a standard test of episodic memory and successfully performing this task requires the hippocampus (Polyn and Kahana, 2008). We separated iEEG signals gathered at the time of item presentation according to whether or not a participant successfully recalled the presented word (i.e., successful memory encoding). By comparing oscillatory power at each frequency, we identified the frequencies at which each electrode exhibited a significant difference in oscillatory power for successful versus unsuccessful encoding, if any (rank-sum test; see Methods for details). This phenomenon, a SME, indicates that a power difference at a particular frequency predicts a subject's ability to successfully encode an episodic memory. When power is elevated during successful encoding, it is termed a positive SME, while a power decrease with successful encoding is termed a negative SME. An electrode can exhibit a positive SME at one frequency and

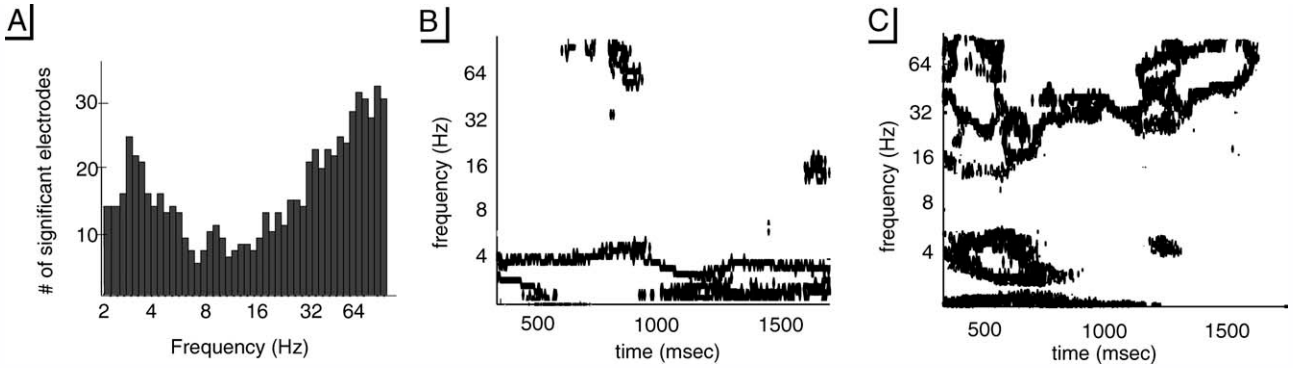

FIGURE 2. Positive subsequent memory effects (SMEs). A: Histogram indicating the counts of electrodes at each frequency that demonstrated positive SMEs (i.e., greater power during encoding of successfully recalled words). B: For all electrodes that exhibit positive slow-theta SMEs, this plot illustrates the prevalence of positive SME across all frequencies and timepoints. Time is relative to each item presentation. Black coloring indicates that the presence of a significant positive SME. C: Same analysis, for electrodes exhibiting gamma band positive SMEs. A concomitant slow-theta power increase is visible.

a negative SME at another, but not both a positive and negative SME at the same frequency.

Figure 2A shows the number of electrodes that exhibited positive SMEs at each frequency. Positive SME's appeared to be clustered in the gamma band (>32 Hz) and in the slow-theta band at ~3 Hz. In particular, the slow-theta positive SME occurred at the same frequency range where we detected activity with our oscillation-detection algorithm; the SME was likely attributable to a power change in this oscillation. To illustrate the temporal and spectral properties of the positive SME effects, we pooled the power data from the specific electrodes that exhibited significant SME effects in the slow-theta and gamma bands (Fig. 2B and C). The plots demonstrate all the timepoints at which power differs significantly ($P < 0.01$, rank sum test with permutation procedure) between recalled and non recalled words during encoding (separately for the sets of slow-theta and gamma electrodes). This analysis revealed that both the slow-theta and gamma SME effects persist throughout the encoding epoch (2 sec after item presentation).

Overall, we identified at least one electrode exhibiting a positive SME in the slow-theta band (2.5–5 Hz) in 17 of 33 patients. 44 out of 237 total hippocampal electrodes showed a positive SME in this band, a number that far exceeds the 5% of electrodes that would be expected to exhibit this pattern by chance ($P < 0.001$, binomial test, Bonferroni corrected). Sixty-four electrodes in seventeen different patients showed a gamma positive SME. Positive SME electrodes were more prevalent in the slow theta and gamma bands than any other frequency band ($\chi^2 = 63.823$, $P < 0.001$). Counts of electrodes with SME effects in other frequency bands were not significantly different from the numbers expected by chance (binomial tests, P's all > 0.05). The number of participants who exhibited at least one electrode at which we detected an SME was higher for the slow theta and gamma bands (17) than for all other frequency bands (9, 11, and 9 for the fast theta, alpha, and beta bands respectively, $\chi^2 = 8.627$ for comparison of proportions of participants in each band, $P = 0.07$). Previous human and animal data have pointed to correlations between theta- and gamma-band oscillatory activity (Bragin et al., 1995; Chrobak and Buzsáki, 1998; Csicsvari et al., 1999; Sirota et al., 2008; Axmacher et al., 2010). We tested for such an association and found that the electrodes that exhibited slow-theta positive SMEs also tended to show gamma-band positive SMEs (Yule's $Q = 0.57$, $P < 0.001$). This association was present for the number of subjects as well ($|Q| = 0.682$, $P < 0.001$). This correlation was absent when comparing the association of gamma SMEs with positive SMEs in other frequency bands for either the number of electrodes or the number of participants ($|Q| < 0.15$, p's > 0.1).

The number of electrodes with gamma band negative SMEs (32) was significantly lower than the number of electrodes with negative SMEs in all other frequency bands except beta (χ^2 for all comparisons > 5.243, $P < 0.02$; Fig. 3). This finding is in line with previous data (Sederberg et al., 2007b), in which the negative effect often spares the gamma band within a brain region but encompasses multiple low-band frequencies. The numbers of participants exhibiting negative SME effects did not differ significantly across frequency bands ($\chi^2 = 1.329$, $P = 0.24$). At frequency bands slower than gamma, many electrodes exhibited negative SME effects simultaneously at multiple frequency bands (Yule's $Q > 0.42$, P's < 0.01).

Taken together, these data support the conclusion that during successful encoding, the human hippocampus exhibits increases in oscillatory power preferentially in the slow-theta and gamma frequency bands. The positive SME that we observed in the gamma band is consistent with previous studies that reported similar patterns of memory-related gamma activity in both cortex and hippocampus in humans and animals (Sederberg et al., 2003, 2007b; Jensen et al., 2007; Jutras et al., 2009). However, the slow-theta positive SME has not been previously identified in humans. The unique correlation between slow-theta and gamma band power changes suggest a role for slow-theta in modulating gamma activity. The epistolary nature of the free recall task prompted us to analyze SMEs from the language-dominant and non-dominant hemispheres separately. We were able to identify the hemisphere of language

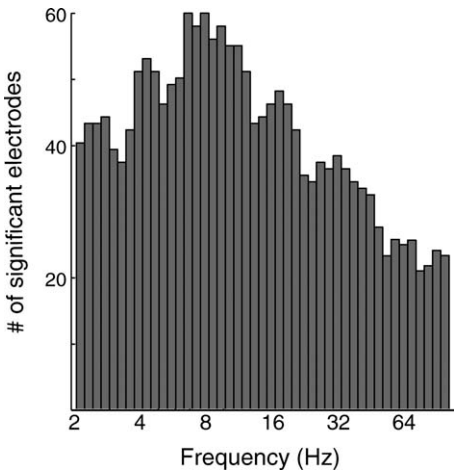

FIGURE 3. Negative SMEs. Counts of electrodes exhibiting negative SMEs (significantly lower power during successful encoding) for each frequency.

dominance for each of the 33 patients. Thirty-One patients were right-handed with left-sided language function. For the remaining two subjects, pre-operative testing (fMRI and/or Wada) confirmed that the right hemisphere was the side of language dominance. Overall, there were 112 language-dominant electrodes and 125 language-non dominant electrodes. Quantifying the number of electrodes exhibiting a positive SME at each frequency yields the histograms in Figure 4. We tested for differences in effects between dominant and non dominant hemispheres by comparing the electrode counts in each frequency band (slow-theta, fast-theta, alpha, beta, and gamma) directly. We identified no significant differences (χ^2's < 3.01, P's > 0.25). Thus, it seems that the slow-theta positive SME is present both in the language-dominant and the non dominant hemisphere.

We sought to examine the spatial distribution of hippocampal sites exhibiting SMEs, based on findings in animals that the hippocampus exhibits multiple distinct oscillations and is differentiated along the anterior/posterior and cranial/caudal axes (Moser and Moser, 1998; Kocsis et al., 1999; Bannerman et al., 2004; Montgomery et al., 2009). We classified each electrode into one of four hippocampal sub-regions (anterior/superior, posterior/superior, anterior/inferior, posterior/inferior) and compared the prevalence of SMEs between these areas. However, we did not observe any significant differences in the prevalence of positive or negative SMEs in any frequency band between these groups ($\chi^2 < 2.55$; P's > 0.2).

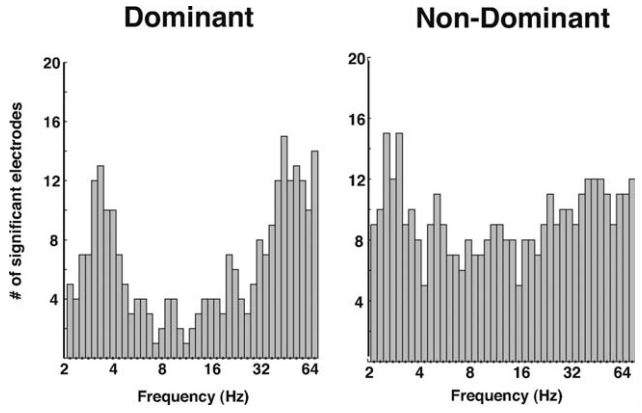

FIGURE 4. Dominant versus non dominant hemispheres. The prevalence of positive SMEs in each patient's dominant and non dominant hemispheres.

We sought to determine if the differences in activity that occur as a subject is encoding memory items are similar to those that occur as a subject approaches the recall of a memory item. We analyzed the time before the vocalization of recalled items, dividing this time period into two epochs, the 700 msec immediately before a word is verbalized (the "retrieval epoch") and the 800 msec before that (the "deliberation epoch," 1.5 sec before recall occurs). Figure 5 illustrates a timeline of these epochs. We compared power between these two epochs, looking for evidence of power increases or decreases (akin to positive and negative SMEs) that occur in the hippocampus as a subject is remembering a memory item.

As shown in Figure 6A and B, we tabulated the number of electrodes that showed a significant power difference between these epochs at each frequency (rank-sum test with permutation procedure, $P < 0.05$). This analysis revealed that the transition from deliberation to retrieval is associated with a significant increase in gamma and slow-theta power (33 and 34 electrodes respectively, $P < 0.001$, binomial test, Bonferroni corrected). The pattern matches that of positive SMEs, with a concentration of effects in both the slow theta and gamma bands for electrodes that exhibited power increases.

Counts of electrodes that exhibited power increases in other bands were not significantly different than that expected by chance (binomial tests, $P > 0.05$). The pattern of electrodes exhibiting power decreases as subjects approached item recall (comparing deliberation to retrieval) included a narrow, prominent 14–16-Hz power decrease in the alpha band. A power decrease in this specific range is not observed in negative SMEs during encoding (for which the effect is distributed among many frequency ranges and not as tightly concentrated), suggesting a change in oscillatory pattern unique to item retrieval. Taken together, the pattern of electrodes exhibiting power increases during retrieval was similar to the pattern of positive SME electrodes, but the pattern of power decreases did not match that of negative SMEs.

We looked for a possible relationship between the group of electrodes that exhibited SMEs and the group that exhibited significant power changes during retrieval, testing the hypothesis that the same electrodes that exhibited positive and negative SMEs also exhibited power increases and decreases during retrieval, respectively. However, there was no correlation between these groups: electrodes that showed a slow-theta positive SME (during encoding) and those that showed a slow-theta power increase during retrieval were not correlated ($Q = 0.12$, $P = 0.29$). The same was true for the gamma band ($Q = 0.11$, $P = 0.30$). Similarly, electrodes at which power decreased during item retrieval were not correlated with those that exhibited

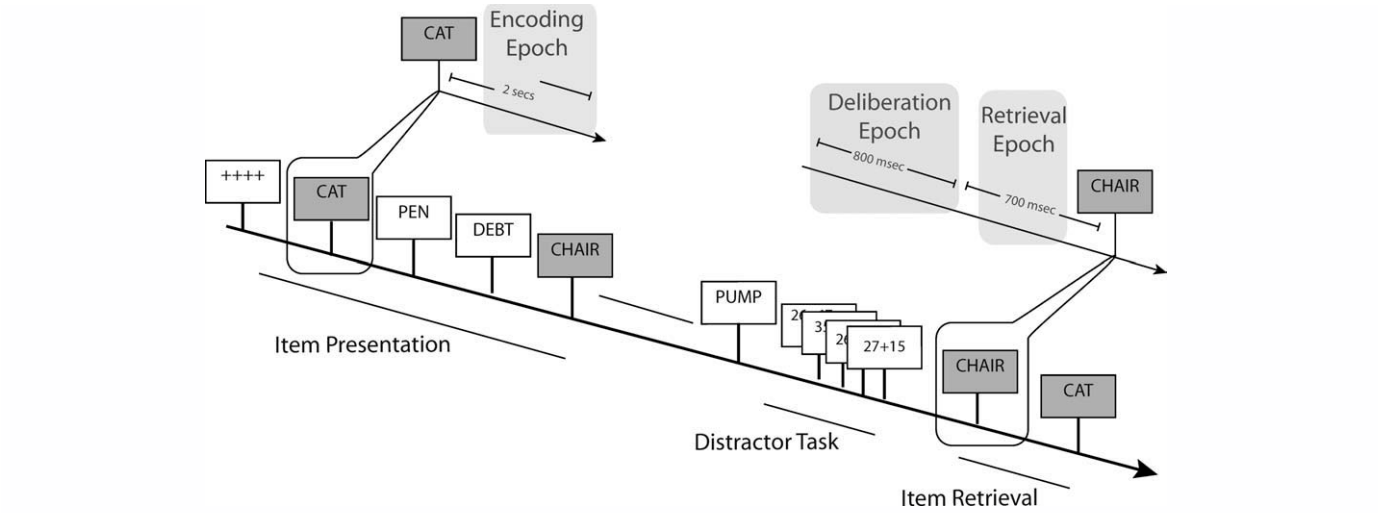

FIGURE 5. The free-recall task. Before each trial, fixation crosses appear on the screen for 1600 msec while the room is held quiet, alerting the participant that stimuli will be presented. Next, each trial consists of a series of "encoding epochs"; in each of these the participant tries to memorize a different word. The word is on screen for 1600 msec and then a blank screen is presented for 400–800 msec. For analysis, a 2 second window after word presentation was used (encompassing the entire period when the word was visible plus 400 msec of black screen). After the presentation of all stimuli, a 20-second distraction task consisting of simple arithmetic problems is presented. Retrieval is cued by a tone after the distractor task period. During item retrieval, the participant attempts to recall the presented words, saying them aloud. "Deliberation epochs" are defined as the 800-ms period 1500–700 ms before each successfully recalled word. The "retrieval epoch" is the 700-ms period immediately preceding each recalled word.

lower power during encoding in any frequency band ($|Q| < 0.13$, $P > 0.10$). These results imply encoding and retrieval networks are overlapping but not necessarily identical and provide fertile ground for further experimentation.

The results of our oscillation detection algorithm and SME analysis were unexpected: it was surprising to detect two oscillations at the edges of the traditional 4–8-Hz theta band. We therefore wanted to confirm that both emanated from the hippocampus itself, rather than from adjacent neocortex (detected by volume conduction of the iEEG signal rather than due to local generation of the oscillation). To address this possibility, we first applied our oscillation detection algorithm to surface electrodes in temporal cortex. The resultant histogram (Fig. 7A) demonstrated prominent fast-theta and beta oscillations commensurate with our results for hippocampal electrodes, though fewer electrodes with prominent slow theta oscillations. Next, we used a synchrony analysis to look for evidence of volume conduction (see Methods for full details). In brief, volume conduction is characterized by a zero degree phase difference between oscillations of the same frequency at two different

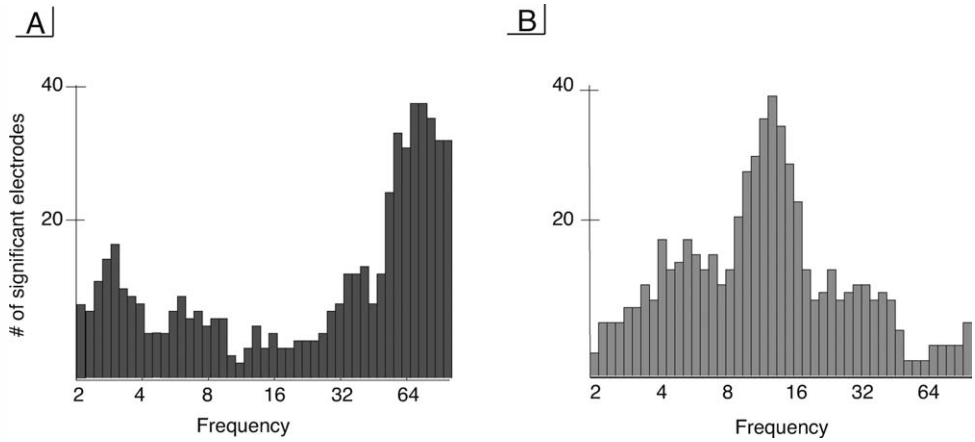

FIGURE 6. Hippocampal oscillations related to memory retrieval. A: A histogram showing the number of electrodes that showed significantly higher power during retrieval as compared to deliberation, at each frequency. Power increases occur in a significant number of electrodes only in slow-theta and gamma ranges B: Counts of electrodes exhibiting significantly decreased power during retrieval. Many electrodes exhibit this pattern at 14–16 Hz.

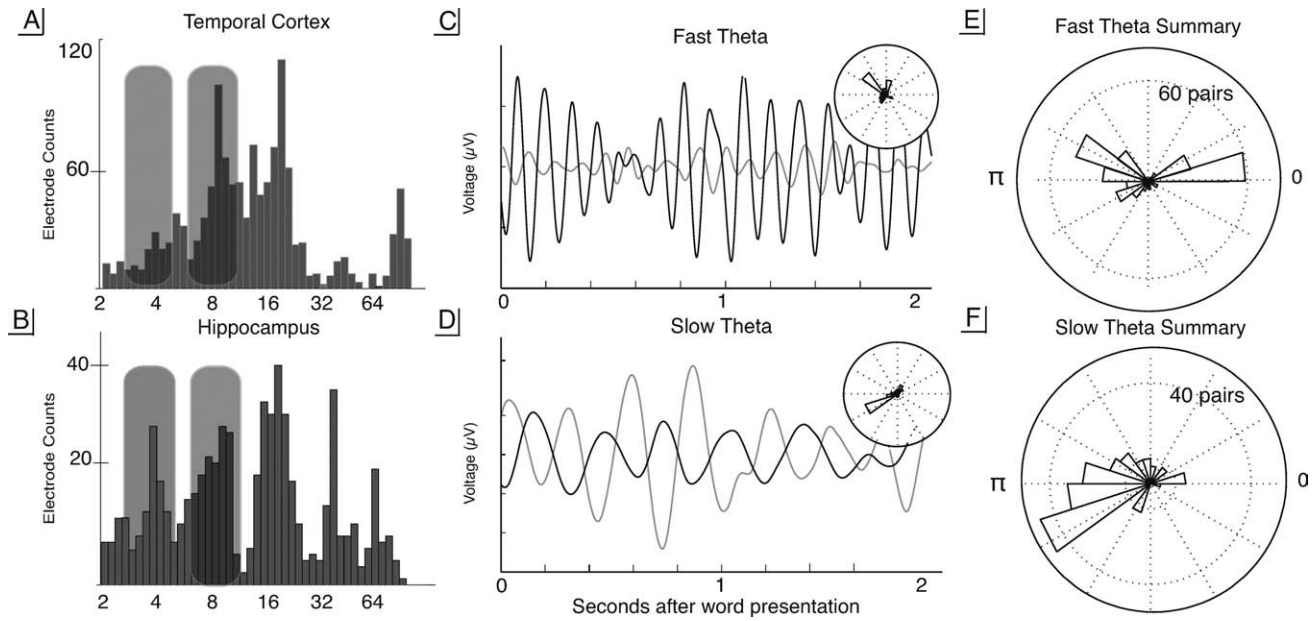

FIGURE 7. Phase synchrony between temporal surface and hippocampal electrodes. A: Histogram indicating the counts of "temporal cortex" electrodes that demonstrate an oscillatory peak at each frequency (see description of peak-detection algorithm in Methods). This analysis revealed that many sites exhibited fast-theta oscillations at 9 Hz. B: Oscillatory peaks detected in the hippocampus, shown for comparison to A. Note the prominence of slow theta in hippocampus as compared to temporal cortex. C: iEEG tracing (bandpass filtered) showing hippocampal (black) and cortical (gray) fast theta oscillations from a synchronous electrode pair. Inset shows histogram of instantaneous phase differences for these two electrodes at each time sample within this 2-second interval, revealing significant phase synchrony with a phase difference of 150°. D: Same as C, but for hippocampal and cortical electrodes exhibiting slow theta (3 Hz) oscillations and significant phase synchrony with a 200-degree phase shift. E: Summary histogram of the mean phase differences across all electrode pairs exhibiting fast-theta phase synchrony between hippocampus and temporal cortex. This plot reveals one group of electrode pairs that exhibit phase synchrony with a phase difference of 0°, which is potentially caused by volume conduction. Another group of electrode pairs exhibits a phase difference of 150° which cannot be attributable to volume conduction. F: Same azs E but for slow-theta oscillations.

locations. Two centimeter is considered the upper limit of the distance over which volume conduction can occur (Lachaux et al., 1999), however we used a more liberal definition of volume conduction (4 cm distance).

To analyze fast-theta volume conduction, we first identified pairs of electrodes in individual patients that exhibited prominent fast-theta oscillations in both the hippocampus and temporal cortex. 41 hippocampal and 147 temporal cortex intracranial electrodes were compared (463 total pairs, Fig. 7B). Of the hippocampal electrodes, 10 met criteria for possible volume conduction: 0° phase synchrony (+/− 15°) within 4 cm of a cortical electrode that exhibited a fast-theta oscillation. The pattern of average phase differences between cortex and hippocampus for fast-theta oscillations is shown in Figure 7E. The cluster of electrode pairs exhibiting ∼0° synchrony includes those in which the oscillation may be attributable to volume conduction. Even with the liberal criteria we used, fewer than 25% (10 of 41) of the hippocampal fast-theta electrodes exhibited possible volume conduction.

As such we concluded that there is significant fast-theta activity in the hippocampus that is separate from neocortical oscillations (Lachaux et al., 1999; Raghavachari et al., 2006; Melloni et al., 2007). However, there is another group of synchronous pairs centered at 150°. This includes seven hippocampal electrodes that exhibited significant synchrony with a cortical electrode ($P < 0.01$, Rayleigh test with permutation procedure). The average distance between electrode pairs at this phase difference was 7.7 cm. For an oscillation at 8.5 Hz (period of 118 msec), a phase lag of 150° implies a conduction time of ∼50 msec. Over an average 7.7 cm distance, this calculation entails a conduction velocity of 1.54 m/sec, in line with the calculated range for conduction in the human temporal lobe (Wilson et al., 1990).

We applied the same analysis to slow-theta oscillations, although these oscillations were less commonly detected over temporal cortex than over the hippocampus (Fig. 7A). We identified 51 hippocampal and 60 cortical electrodes that exhibited slow-theta oscillations using the peak detection algorithm (342 total electrode pairs). Thirty hippocampal electrodes exhibited significant phase synchrony with 24 different cortical electrodes. The distribution of phase differences is visible in Figure 7F. The largest cluster of phase differences occurs at 160° this consists of five hippocampal electrodes that were on average 5.4 cm from the temporal electrode with which they were synchronous. Only 2 of the 30 hippocampal electrodes that exhibited phase synchrony showed a phase difference near 0° between cortex and hippocampus. This result is not consistent with volume conduction of slow theta. We concluded that

there was strong evidence for the involvement of both fast and slow theta oscillations in hippocampal-cortical communication based on the synchrony of these oscillations over relatively long distances (Miller, 1991).

DISCUSSION

Our results demonstrate that the human hippocampus contains two distinct theta oscillations that have different functional roles, one at ~3 Hz and the other at ~8 Hz. Of the two, the 3-Hz slow-theta oscillation bears properties similar to the memory-related theta oscillations observed in animals (Berry and Thompson, 1978; Nokia et al., 2008), as we observed that the amplitude of this oscillation is positively correlated with memory formation. These slow-theta oscillations were also linked to gamma oscillations: electrodes that showed slow-theta SMEs showed significant gamma SMEs as well. The trend towards slower hippocampal theta in larger animals has been noted, and we think our results in humans are in line with the decreased hippocampal theta frequency in dogs, cats, and monkeys relative to rodents (Miller, 1991). Human hippocampal data have not demonstrated unequivocal 4–8 Hz oscillations, although there is evidence of sub-4 Hz changes in oscillatory activity correlated with behavior in classical iEEG studies in which oscillatory changes at such frequencies occurred as subjects performed tasks such as reading (Arnolds et al., 1980).

We observed a different hippocampal oscillation centered at 8 Hz, which is the upper bound of the traditional 4–8 Hz human theta band. However, this fast-theta oscillation showed a consistent power decrease during successful memory encoding, suggesting it has complementary properties to the 3 Hz oscillation. The non specific pattern of power decreases across the frequency spectrum at electrodes exhibiting negative SMEs may be consistent with a type of default network that is deactivated during successful encoding performance [for review, see Fair et al. (2008)]. The existence of two unique hippocampal oscillations in the theta range has precedence in the animal literature. In rats, a 6–8 Hz theta rhythm occurs during locomotion and a 4–6 Hz theta rhythm occurs preferentially during stationary activity, including memory encoding (Vanderwolf, 1969, 1988; Kramis et al., 1975; Macrides et al., 1982; Berry and Swain 1989; Miller, 1991; Seidenbecher et al., 2003). In rodents, faster movements alter the frequency of the higher frequency oscillation. The fast-theta oscillation, which we observed, was at a higher frequency than traditional 4–8 Hz theta and was faster than the frequencies at which rodent Type 1 theta typically occurs.

Fast-theta was detectable over the temporal cortex, suggesting slow-theta is more specific to the hippocampus. A rhythm between the traditional 4–8 Hz band and the alpha band has been identified over the temporal cortex via analysis of iEEG by previous authors (Niedermeyer, 1990, 1991; Shinomiya et al., 1999). Their data demonstrate that the rhythm is unrelated to epileptic activity.

Existing literature supports our contention that functionally important human hippocampal oscillations exist below 4 Hz. Previously, these sub-4 Hz effects have mostly been referred to as "delta" oscillations and 4–8 Hz patterns as "theta" oscillations. We hold that within the hippocampus, it is more appropriate to call many of these lower frequency oscillations "slow-theta" (rather than "delta"), because they share functional properties with descriptions of theta oscillations from studies of animal brain recordings (Berry and Thompson, 1978; Seager et al., 2002; Buzsáki, 2005). For working memory, <4 Hz hippocampal theta oscillations have been observed to vary in amplitude with memory load (van Vugt et al., 2010) and to exhibit phase reset while viewed stimuli are remembered (Fell et al., 2008). Analyzing human hippocampal oscillations during sleep, two studies identified sub-4 Hz oscillations that appear as subjects transition from slow-wave to REM sleep; these proved to be linked with gamma activity (Bódizs et al., 2001; Clemens et al., 2009). The frequency and functional role of these oscillations are consistent with the slow-theta oscillation we describe. From spatial navigation data, Jacobs et al. observed phase locking between neuronal spiking and navigation-evoked hippocampal oscillations at ~3 Hz, and even as slow as ~1 Hz, but not in the standard 4–8-Hz band (Jacobs et al., 2007). Their findings support a role for slow theta rather than fast theta in human spatial processing, a conclusion supported by the results of Cornwell et al. who found that the power of hippocampal oscillations at ~3 Hz correlated with navigation accuracy (Cornwell et al., 2008). Other studies examining human hippocampal recordings during navigation observed power changes correlated with spatial memory function both in the sub-4 Hz band and in the traditional 4–8 Hz range (Ekstrom et al., 2005; Jacobs et al., 2010). These observations may be partially attributable to fast-theta oscillations, for which functional properties may exist for spatial navigation.

Two recent studies using a recognition memory paradigm identified 4–8 Hz effects from hippocampal recordings in humans. Axmacher et al. report ~7 Hz phase modulation of gamma oscillations that predicts memory load and task performance, though they found no 4–8 Hz power changes to accompany the phase relationships (Axmacher et al., 2010). Rutishauser et al. recorded single unit activity along with field potentials from nine patients implanted with hippocampal electrodes (Rutishauser et al., 2010). They used a visual recognition memory task, and report significant differences in single unit phase locking properties for recalled and non recalled words centered at an average of ~5 Hz, but no theta-band power changes to predict recall. There are several possible explanations for discrepancies between our results and those seen in this pair of studies. The first is that evidence of functional properties from Axmacher et al., and especially, Rutishauser et al. extend well below 4 Hz. The memory effects of single unit locking to the oscillatory phase was most prominent at ~3 Hz in the latter article, consistent with the oscillation we identified. Further, the pattern they reported is bimodal, with separate groups of electrodes exhibiting this effect both above and below ~6 Hz. This is consistent with our result that differ-

ent electrodes within the hippocampus do not always demonstrate both fast and slow theta; phase locking may occur preferentially at the slow-theta oscillation in one area and fast-theta in another. As such, combining data across electrodes and patients may have changed the apparent frequency range(s) where the effect was most prominent. Finally, it is possible that the recognition-memory tasks used in these studies elicit different oscillatory dynamics compared with the free recall task we used.

More generally, the frequency range where slow-theta appears (2.5–5 Hz, which spans the traditional 4-Hz delta–theta boundary) may have encumbered efforts in these and other investigations to identify human effects analogous to animal theta (power changes to predict memory). Our data suggest that, researchers should carefully determine the frequency range at which particular electrophysiological phenomena occur (Jacobs and Kahana, 2010). Using the traditional 4-Hz boundary for delta–theta demarcation may split the human slow-theta band and diminish its apparent functional significance.

Sederberg et al. previously analyzed a subset of the data we examined and did not report a positive slow-theta SME (Sederberg et al., 2007b). Two important methodological differences account for this discrepancy. First, the dataset we examined included more patients with hippocampal contacts (33) than Sederberg et al. studied (18). Because prominent theta oscillations do not appear in all human hippocampal recordings (Niedermeyer, 2008), the additional statistical power provided by the larger dataset may have helped to identify the slow-theta SME. Second, Sederberg et al. combined data from all hippocampal electrodes to identify the cumulative direction of the SME in the hippocampus. Because some hippocampal electrodes exhibit positive and others negative SME effects, the positive SME may have been masked by other electrodes exhibiting negative SMEs.

Studies analyzing "neocortical" electrodes reliably demonstrate theta oscillations at 4–8 Hz that show power increases during working memory, episodic memory, and navigation (Jensen and Tesche, 2002; Caplan et al., 2003; Rizzuto et al., 2003, 2006; Canolty et al., 2006; Jacobs et al., 2007; Jacobs and Kahana, 2009). Our findings suggest that hippocampal power changes during memory encoding occur in a separate slow-theta oscillation, and that the temporal cortex shows a more traditional 4–8 Hz oscillation (as in Fig. 7, panel A). This raises the question of the relationship between cortical theta and hippocampal theta. Specifically, whether fast or slow theta (or both) is involved in hippocampal-cortical communication (Miller, 1989, 1991; Eichenbaum, 2000; Hasselmo, 2005, 2007)? Theories of memory encoding based on connections between the cortex and hippocampus predict that recurrent "loops" of neuronal activity exist between the two sites, and hypothesize that the time constant of these loops is synchronized to the hippocampal theta cycle. Empiric evidence for the loop time in rats implies that faster, Type 1 theta is preferentially involved (Miller, 1991), although our data point to both slow and fast theta synchrony for these connections.

In addition to memory encoding, slow-theta oscillations also appear to be related to memory retrieval, as we observed increased slow-theta power ~700 msec before the verbalization of a recalled item. A gamma power increase that discriminates between correct and incorrect items has been identified during the recall period, but the slow-theta effect we identify is novel (Sederberg et al., 2007a). This suggests that slow-theta oscillations play a role in reinstating features of the brain state present during memory encoding that is thought to occur in widespread brain regions before memory retrieval (Sederberg et al., 2007a; Gelbard-Sagiv et al., 2008; Polyn and Kahana, 2008; Manning et al., 2009b). While the overall pattern of oscillatory changes during encoding and retrieval was similar, the exact electrodes exhibiting slow-theta and gamma power increases differed in the two epoch. Our results imply that hippocampal sites that participate in encoding and retrieval networks may be different. This finding has some precedence in human fMRI studies (Small et al., 2001; Zeineh et al., 2003), in which different hippocampal activity patterns are observed for encoding and recall periods within a task. The analysis of datasets obtained from recording techniques with improved spatial resolution (i.e., LFP from microelectrodes) would hep disambiguate the roles of the subiculum, entorhinal cortex, and hippocampal subfields during encoding and retrieval. Spatial differences in hippocampal activity may complement the role of theta phase coding to disambiguate these processes (Rizzuto et al., 2006; Manns et al., 2007).

We observed the unique 14–16 Hz power decrease during retrieval looks distinct from the oscillations detected during encoding period in the 8–30 Hz range (fast-theta and beta oscillations, see Fig. 1, bottom panel). The 14–16 Hz oscillation exhibited a power decrease; this may represent the deactivation of a resting hippocampal oscillation akin to the abolition of posterior alpha or motor cortical mu rhythms, as those regions are activated during visual or motor actions, respectively. The functional role of the faster ~20 Hz beta oscillation we observed during encoding remains an unanswered question. One possibility is that hippocampal beta oscillations are associated with the processing of sensory information. Beta power bursts immediately following sensory input have been observed from human neocortical recordings (Caplan et al., 2003; Sehatpour et al., 2008), and they are elicited in parietal cortex by behavioral stimuli in non-human primates (Siegel et al., 2009).

CONCLUSION

Through the analysis of 237 hippocampal electrodes implanted in 33 neurosurgical patients, we found that an increase in the power of 3-Hz "slow theta" oscillations predicts successful episodic-memory encoding. This is the first such demonstration in humans. Notably, the theta oscillation, which we identified, is centered at 3 Hz, which is below the traditional 4–8 Hz human theta band. We also identified an ~8 Hz "fast theta" hippocampal oscillation, but it exhibited a relative decrease in amplitude during successful memory encoding, which indicates that it is functionally distinct from slow theta. The discovery of two different theta oscillations should prompt analyses of iEEG data during other types of behavioral tasks examining the conditions that elicit func-

tional variations in each of these separate rhythms. We found evidence of phase synchrony between the cortex and hippocampus for both oscillations, suggesting that both may have a role in cortical-hippocampal communication.

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