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Behavioral correlates of human hippocampal delta and theta oscillations during navigation

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Watrous AJ, Fried I, Ekstrom AD. Behavioral correlates of human hippocampal delta and theta oscillations during navigation. *J Neurophysiol* 105: 1747–1755, 2011. First published February 2, 2011; doi:10.1152/jn.00921.2010.—Previous rodent studies demonstrate movement-related increases in theta oscillations, and recent evidence suggests that multiple navigationally relevant variables are reflected in this activity. Human invasive recordings have revealed movement-related modulations in delta and theta activity, although it is unclear whether additional behavioral variables are responsible for modulating this neural activity during navigation. We tested the role of delta and theta oscillations during navigation by addressing whether spatial-related processing, in addition to speed and task variables, modulates delta and theta activity. Recording from 317 hippocampal intracranial electrodes in 10 patients undergoing seizure monitoring, we observed increasing delta and theta power with increasing virtual speed at significantly more electrodes than would be expected by chance, replicating previous findings in nonhuman mammals. Delta and theta power were more consistently modulated, however, as a function of spatial view, including when subjects looked at stores in the virtual environment both to find a relevant goal or for spatial updating. A significantly larger proportion of electrodes showed view-related effects than speed-related modulations. Although speed, task, and spatial view affected delta and theta activity, individual electrodes were most frequently modulated by only one variable, rather than a combination of variables. These electrodes likely sampled independent delta and theta generators, which reflected movement-related and allocentric processing, respectively. These results extend previous findings in nonhuman mammals and humans, expanding our knowledge of the role of human hippocampal low-frequency oscillations in navigation.

hippocampus; navigation

A TIGHT COUPLING between local field potential oscillations in the theta band (3–12 Hz) in the hippocampus and a variety of behaviors in rodents, including movement and spatial memory, has been suggested in previous reports (Winson 1978). Theta oscillations are known to coordinate the timing of place cell activity (O'Keefe and Recce 1993; Skaggs et al. 1996) and improve reconstruction of a rat's position when the phase of firing of place cells relative to the theta oscillation is considered (Jensen and Lisman 2000). These findings suggest that hippocampal theta oscillations play an essential role in coordinating neuronal ensembles during navigation (Buzsaki 2005; Mizuseki et al. 2009). Although previous work suggests that

movement similarly modulates human theta oscillations (Caplan et al. 2003; Ekstrom et al. 2005), significantly less is known about the behavioral correlates of these coordinated neural events in humans in deep structures such as the hippocampus.

Previous research in rodents suggests that two types of theta oscillations exist: one is elicited during movement and the other in response to salient sensory information (Kramis et al. 1975). An alternate account of rodent hippocampal function, the sensorimotor integration hypothesis (Bland 1986; Bland and Oddie 2001), posits that these two types of theta oscillations incorporate incoming sensory information with existing motor plans to guide movement. Central to this hypothesis is the observation that hippocampal theta amplitude increases linearly with movement speed such that more rapid traversals require faster sensorimotor transformations, a finding documented in rodents (McFarland et al. 1975), guinea pigs (Rivas et al. 1996), cats (Whishaw and Vanderwolf 1973), and dogs (Arnolds et al. 1979). To date, this phenomenon has not been demonstrated in humans.

In contrast to the sensorimotor integration hypothesis, lesion and functional MRI studies of the human hippocampus suggest it plays a primary role in episodic memory and spatial navigation (Bird and Burgess 2008; Burgess 2008). Hippocampal lesion patients do not typically have overt impairments in sensorimotor processing and are able to learn and perform new sensorimotor tasks (Corkin 2002; Shadmehr et al. 1998; Zola-Morgan and Squire 1986). Furthermore, functional MRI studies have found hippocampal activity during navigation tasks compared with a sensorimotor control task (Baumann et al. 2009; Bohbot et al. 2004; Ekstrom et al. 2009; Iaria et al. 2003; Suthana et al. 2009). Finally, a strong body of research suggests that parietal cortex, and not hippocampal, computations are a fundamental component of sensorimotor integration in primates (Andersen and Cui 2009). Thus the lesion and imaging results suggest that the human hippocampus plays a role in spatial navigation and episodic memory beyond sensorimotor integration.

Invasive recordings in humans have demonstrated movement-related theta oscillations in both the neocortex (Caplan et al. 2001; Caplan et al. 2003; Kahana et al. 1999) and hippocampus (Ekstrom et al. 2005). These findings could be taken to support the sensorimotor integration hypothesis (Bland 1986; Bland and Oddie 2001), although the specific factors responsible for modulating theta activity during virtual movement were not investigated. For instance, virtual movement

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requires subjects to process optic flow, to compute their location in space based on salient landmarks in the environment, and to initiate and maintain virtual movement toward the target location, all in a short span of time. Previous research has been unable to address which factors are responsible for modulating hippocampal theta activity during navigation in humans.

We have addressed the extent to which different factors might modulate oscillatory activity, particularly in the theta band, in the human hippocampus during navigation by recording intracranial EEG activity in patients undergoing seizure monitoring while they explore a virtual environment. Using a multivariate regression approach, we simultaneously compared speed, task, and spatial view to determine which of these (combinations of) variables provided the best fit for changes in oscillatory power on a hippocampal electrode. Because previous work on human theta activity has generally indicated comparable behavioral modulations in the delta band (1–4 Hz), all analyses consider both delta and theta modulations along with higher frequency modulations for comparison [i.e., alpha (9–12 Hz), beta (13–30 Hz), gamma (31–55 Hz)]. A final issue we have addressed regards recent evidence suggesting that local theta generators in the hippocampus can be modulated as a function of seemingly disparate navigational variables, such as a rodent's movement speed, location, and behavioral task (Montgomery et al. 2009). We hypothesized that different behavioral variables might also impact theta-band activity independently in the human hippocampus such that a greater number of electrodes would show effects of one behavioral variable compared with being modulated by more than one variable. We thus reasoned that although theta activity in the human hippocampus could be modulated by a variety of behavioral variables, activity at individual sites might not be simultaneously modulated by multiple behavioral variables.

METHODS

Behavioral paradigm and patient data. Subjects performed a navigation task similar to the Yellow Cab virtual taxi game, which we have employed previously to investigate human navigation (Ekstrom et al. 2009). This paradigm was administered on a laptop computer and alternated between navigation and baseline tasks. Each navigation block lasted 120 s. Subjects used a joystick to search for passengers (i.e., “searching for a passenger”; Fig. 1A) located in the center of a virtual environment and then delivered them to specific locations (“stores”) located around the edge of the environment (i.e., “searching for a store”; Fig. 1B). Passengers were always located in the center of

the city. During a baseline task that lasted 25 s, subjects moved the joystick in the direction of arrow cues on a black screen. We included the baseline task for use with a subset of patients who also received this task while undergoing functional magnetic resonance imaging (fMRI) to allow direct comparison between EEG and fMRI (Ekstrom et al. 2009); because this was not an a priori epoch of interest, we did not include these time periods in our analysis. A total of 32 deliveries occurred in total, with 4 deliveries to each of 8 different stores. Delivery order was randomized. To compensate for learning and memory effects, a different virtual environment was used for subjects who participated in multiple sessions. Unlike the original Yellow Cab task (Caplan et al. 2001; Caplan et al. 2003; Ekstrom et al. 2005), movement speed was not constant but was set to a maximum of ~6 pixels/s. Subjects accelerated at a rate of 0.008 pixels/s.

Electrophysiology and data analysis. We recorded from 317 hippocampal microelectrodes in 10 patients with pharmacologically intractable epilepsy across 20 recording sessions (summarized in Supplemental Table S1). (Supplemental data for this article is available online at the *Journal of Neurophysiology* website.) Electrode localization (Supplemental Fig. S1) was performed by registering a preoperative MRI with a postoperative computed tomography (CT) image (Ekstrom et al. 2008; Nelles et al. 2004). Although this allowed us to localize microelectrodes as a group along the anterior, middle, and posterior aspects of the hippocampus, we could not localize individual microelectrodes (or the group) to specific hippocampal subfields. This is because we only obtained high-resolution structural images for a subset of patients ($n = 6$) included in a previous report on this topic (Ekstrom et al. 2009), and thus we have restricted our consideration to locations along different thirds of the anterior-posterior hippocampus. Electrophysiological recordings were sampled at 28 kHz with depth electrodes using a Neuralynx 64-channel recording system. Eight microelectrodes were located on each depth electrode, with a ninth distal microwire serving as a reference for each electrode. Raw signals were downsampled to 1,000 Hz, band-pass filtered from 1 to 200 Hz, and notch filtered at 60 Hz (59.9–60.9 Hz) to minimize line noise artifacts during postprocessing. All analyses were performed using custom MATLAB code in conjunction with the EEG Toolbox (<http://memory.psych.upenn.edu/Software>). Spectral power estimates were computed from each recording site by convolving the local field potential (LFP) with Morlet wavelets (cycles = 6) at 31 logarithmically spaced frequencies from 1 to 181 Hz. Power values were collapsed into the canonical delta (1–4 Hz), theta (4–8 Hz), alpha (9–12 Hz), beta (13–30 Hz), and gamma (31–55 Hz) frequency bands. Because our primary hypotheses relate to theta oscillations, we have focused on data below 55 Hz.

Statistical analysis utilized multilinear regression (“regstats” MATLAB function; The Mathworks, Natick, MA). The log-transformed power value in each frequency band served as the dependent variable, whereas speed, task, and store viewing served as predictor



Fig. 1. Behavioral task. Subjects navigated to find passengers and deliver them to specific stores in a virtual environment. *A*: screenshot of task as subject searches for a passenger. *B*: screenshot of task as subject searches for a store (Burger City). Note that in this example, the subject would be viewing the goal store, and other stores (not shown) during this specific round of navigation are nongoal stores. *C*: example preoperative MRI image (MP-RAGE) used for electrode localization with patient 6. Circle indicates electrode localization in left middle hippocampus for this patient, determined by coregistering this preoperative MRI sequence with a postoperative CT sequence (not shown). *Inset* shows location of depth electrode with protruding microelectrodes.

variables. The speed predictor variable represented the subject's virtual linear speed in the environment. The task predictor variable corresponded to whether the subject was searching for passengers or stores, and the store viewing predictor variable (spatial view) represented whether the subject was viewing a goal store, nongoal store, or the background (i.e., no store). The goal store was defined as the virtual passenger's destination store, and nongoal stores were all other stores during a given delivery. Periods of navigation were subdivided into time points of goal store viewing, nongoal store viewing, and background viewing and were segmented into ~200-ms epochs. These epochs were used to create each type of predictor variable as well as the log-power-dependent variable. We deemed a store to have been viewed if it occupied more than 20% of the viewable area of the laptop screen. Speed values were prewhitened to account for temporal autocorrelation among temporally adjacent speed values.

To determine whether an electrode showed a statistically significant effect of a behavioral variable, we employed a bootstrap resampling procedure to estimate the null hypothesis distribution. This procedure involved shuffling the labels of each predictor variable 1,000 times at each electrode and recomputing the multilinear regression. This allowed us to produce a pseudo *t*-value distribution separately for each regressor by pooling the resulting *t*-values across electrodes within each frequency band. We then selected the pseudo *t*-value in the 99.99th percentile (i.e., bootstrap alpha threshold = 0.001) as the critical *t*-value for each predictor variable, and electrodes with *t*-values greater than the critical *t*-value were deemed significant.

We focused on three methods for quantifying the proportion of electrodes showing oscillatory modulations with behavioral variables. The first analysis assessed the most significant predictor of oscillatory power at each electrode. Thus, for our "exclusive" analysis of the population of electrodes, we calculated the proportion of electrodes significantly modulated by task, speed, and spatial view variables; electrodes modulated by multiple variables were classified according to the most significant predictor variable. The second analysis computed the proportion of electrodes showing narrowband (i.e., prediction for a behavioral variable specific to only one frequency band) effects for task, speed, and spatial view. This analysis was done to determine the extent to which navigation-related broadband vs. narrowband modulations were occurring. For instance, an electrode that showed behavioral modulations in delta, theta, and gamma would not be considered significant in this analysis because more than one frequency band showed modulations with behavior. To be considered a narrowband effect in the theta band in this analysis, for example, electrodes could only have a significant effect in the theta band. This second analysis thus allowed us to contrast narrowband with broadband effects determined in the first analysis to look for possible differences in modulation by behavioral variables of interest.

A third analysis computed the proportion of electrodes showing significant modulations for each combination of behavioral variables. Thus, in our "overlap" analysis of the population of electrodes, we tabulated the proportion of electrodes modulated by every combination of our predictor variables (i.e., all combinations of speed, searching for passengers, searching for stores, goal store viewing, nongoal store viewing, and background viewing). This analysis allowed us to compare electrodes that were modulated by more than one behavioral variables with electrodes that were modulated by only one behavioral variable.

We utilized an oscillatory detection method to characterize the most prominent rhythm in our recordings, which provides an estimate of the relative occurrence of oscillatory events within a frequency band (termed "P_episode"). This method has been used and detailed in numerous previous publications (Caplan and Glaholt 2007; Caplan et al. 2001; Caplan et al. 2003; Ekstrom et al. 2005). Briefly, this technique applies a power threshold, P_t , and a duration threshold, D_t , to the calculated power values to find significant increases in oscillatory activity. This procedure was applied at each hippocampal electrode individually and then pooled across electrodes. First, the

background spectrum was determined by fitting the observed power values to a chi-square distribution using linear regression. Second, consistent with parameters used in previous work (Caplan and Glaholt 2007; Caplan et al. 2001; Caplan et al. 2003; Ekstrom et al. 2005), we extracted the 95th percentile of this fit distribution at each frequency and used this as our power threshold. The duration threshold was set to three cycles, consistent with previous work. Third, we calculated the percent of recording time in which power values exceeded both the power and duration threshold for each frequency. Finally, the mean percentage of oscillatory time was computed by taking the mean at each frequency across electrodes. This method allowed us to determine the percent of recording time in which the signal exhibited significant oscillatory events at each frequency.

RESULTS

We analyzed navigation-related power modulations in 317 hippocampal electrodes across 10 patients with intractable epilepsy whose placement in the hippocampus was confirmed using each patient's coregistered CT and MRI (Supplemental Table S1). Our multivariate regression analysis revealed electrodes responding significantly to speed, spatial view, and task. Figures 2, 3, and 4 provide three examples of each type of modulation in the theta band. Although for these examples there is a clear "bump" at low frequencies in the power spectral density plot, we also observed broadband modulations (i.e., power increases across multiple frequency bands, Figs. 2A and 3B). We observed both electrodes that responded exclusively to one of these three variables and electrodes that responded to some combination of these variables. We quantified the total number of electrodes showing power modulations with increasing speed, task, or spatial view in each frequency band. This analysis showed significant numbers of electrodes responding to all three types of variables, which we consider below.

Exclusive analysis of most significant behavioral predictors. Our first report results from our exclusive analysis, in which we classified significant electrodes in each frequency band according to the most significant predictor variable (see METHODS). Considering first our group analysis of speed-related electrodes, significantly more electrodes showed power increases with increasing speed than chance levels (type 1 error rate < 1 electrode, Fig. 5A) in each frequency band. Furthermore, significantly more electrodes showed speed-related theta-band power modulations compared with other frequencies [$\chi^2(4) = 43.8$, $P < 10^{-8}$]. These data are consistent with studies showing speed-related modulation of theta power in nonhuman mammals (Arnolds et al. 1979; McFarland et al. 1975; Rivas et al. 1996; Whishaw and Vanderwolf 1973).

We then asked whether additional variables such as spatial view (Rolls and O'Mara 1995) significantly affected human hippocampal oscillatory activity in our population of recordings across patients. As shown in Fig. 5A, significantly more electrodes showed modulations of oscillatory activity as a function of store viewing than would be expected by chance in all frequency bands (type 1 error rate < 1 electrode). The proportion of significant electrodes across frequencies differed from uniformity; view-related modulations were significantly more prevalent in the delta and theta band, [$\chi^2(4) = 42.5$, $P < 10^{-7}$]. We next asked which of the three possible viewing variables the majority of the electrodes responded to across frequency bands: viewing a store when it was a goal, viewing a store when it was not a goal, or viewing the nonstore

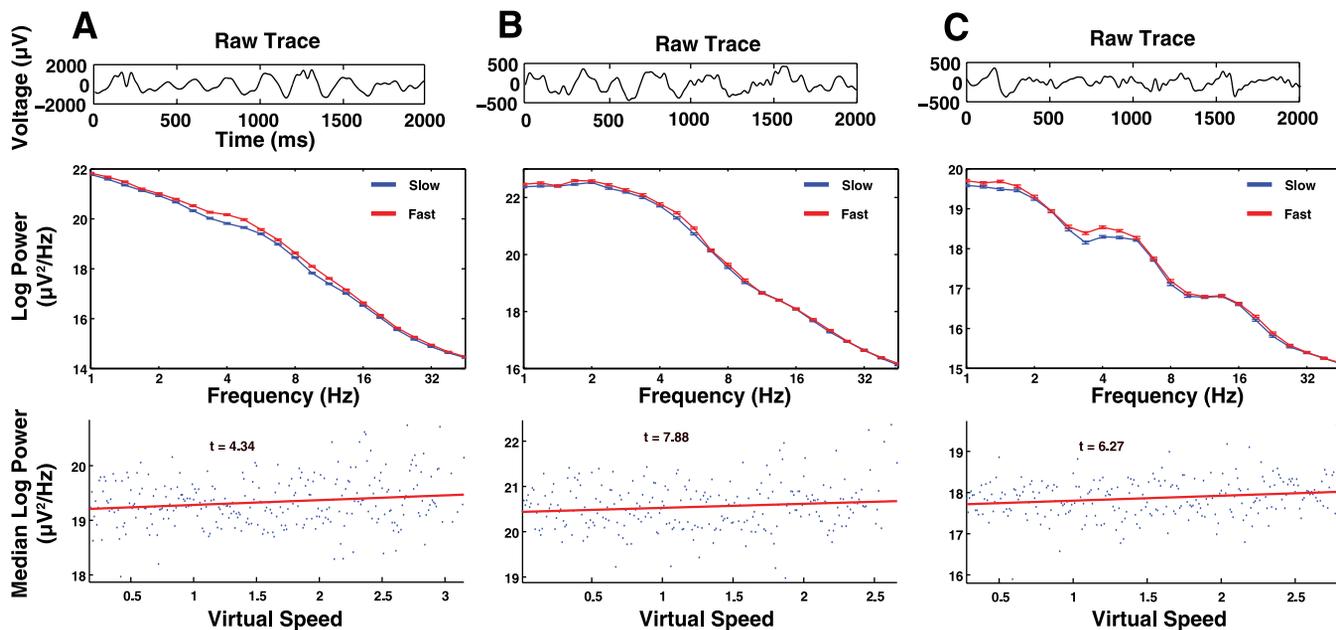


Fig. 2. Example of 3 different electrodes showing theta power modulated by increasing speed. *A, top*: raw trace taken from the right anterior hippocampus of *patient 4* during a period of movement. *Middle*: power spectral density plot for slow and fast epochs. *Bottom*: significant regression plot showing increasing log-theta power as a function of virtual speed. All power values were entered into the statistical analysis; however, median power is plotted as a function of speed for clarity. *B*: same as *A* except data are from the right anterior hippocampus of *patient 3*. *C*: same as *A* except data are from the right anterior hippocampus of *patient 10*. All error bars show standard error of the mean.

background. Figure 5B shows the proportion of electrodes modulated by each viewing variable. More electrodes were modulated by nongoal store viewing than goal or background viewing in all but the gamma band [all $\chi^2(2) > 27.4$; all $P < 10^{-5}$]. One interpretation of this finding is that the observed modulations during nongoal store viewing are related to spatial updating to facilitate locating the target store because nongoal stores could be used as a reference to locate the goal store.

Figure 5A also shows the proportion of electrodes modulated by the task variable (i.e., searching for passengers or stores). We found significantly more electrodes modulated by the task variable than expected by chance (type 1 error rate < 1 electrode). The proportion of electrodes showing task-related modulations was largest in the delta and theta frequency bands, and the distribution of modulated electrodes across frequency bands differed from uniformity [$\chi^2(4) = 28.6, P < 10^{-5}$].

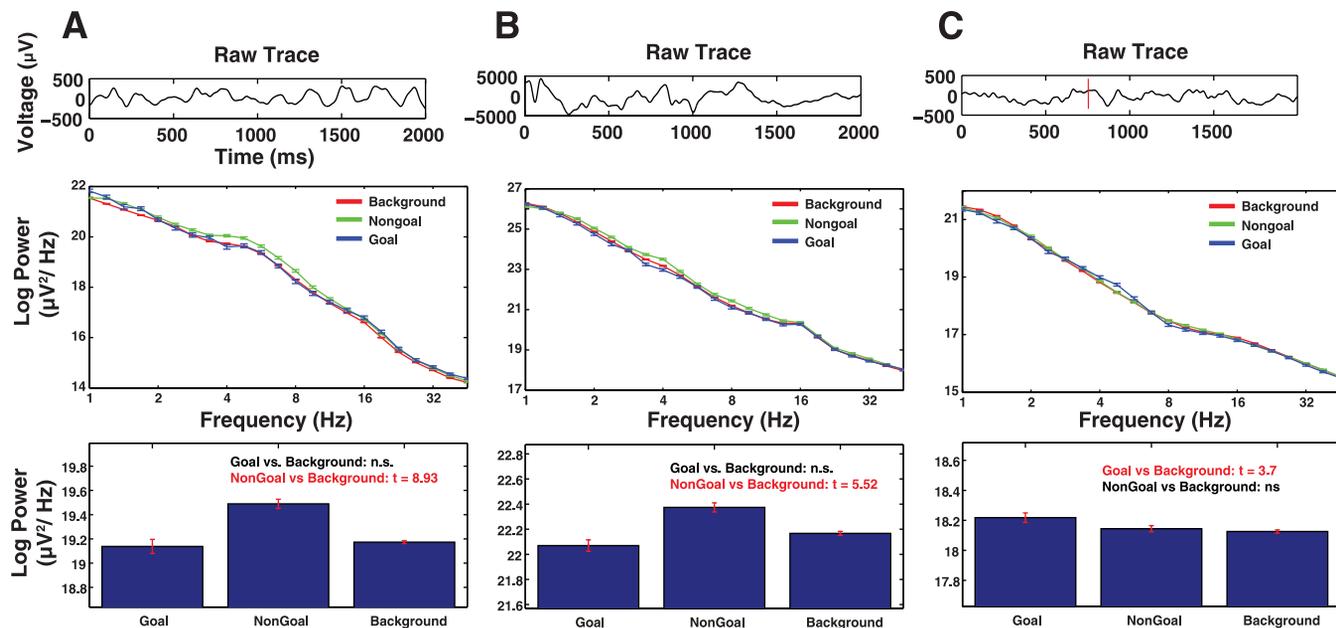


Fig. 3. Example of 3 different electrodes showing theta power modulated by view. *A, top*: raw trace taken from the right anterior hippocampus of *patient 4* during a period of nongoal building viewing epochs. *Middle*: power spectral density plot during background, nongoal, and goal store viewing. *Bottom*: bar plot of mean log-theta power for each viewing condition. *B*: same as *A* except data are from the left anterior hippocampus of *patient 3* during a period of nongoal viewing. *C*: same as *A* except data are from the right anterior hippocampus of *patient 3* during a period of goal viewing. The red tick mark in the raw trace indicates the onset of goal store viewing. All error bars show standard error of the mean.

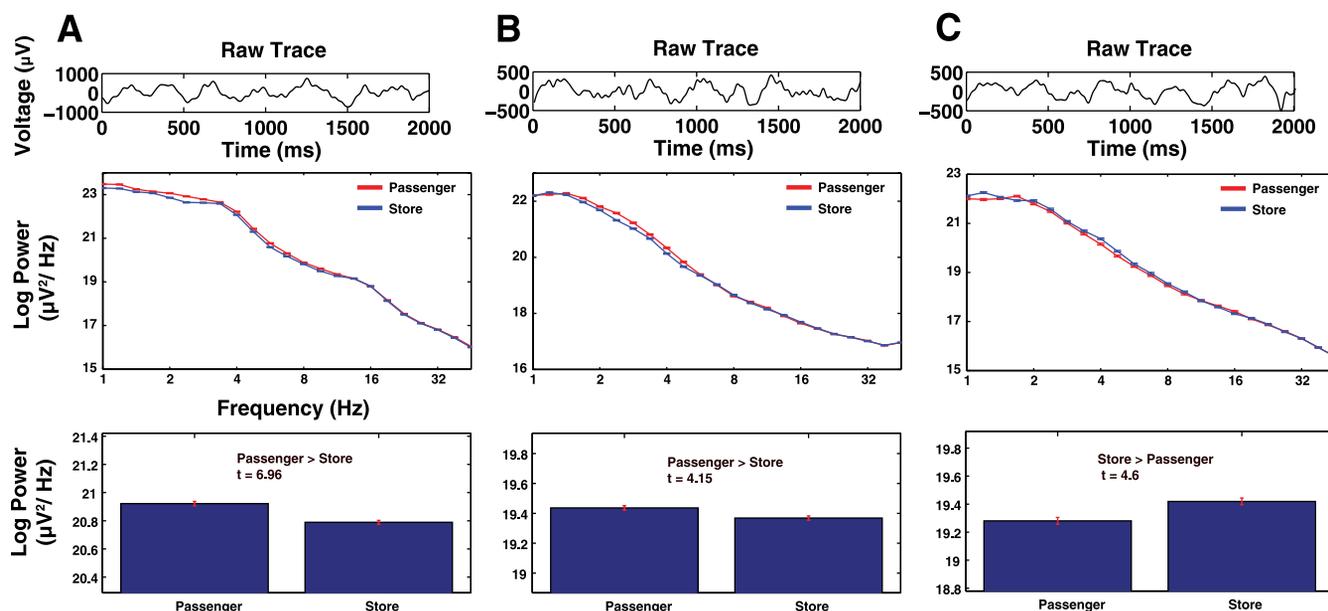


Fig. 4. Example of 3 different electrodes showing theta power modulated by task. *A, top*: raw trace taken from the left middle hippocampus of *patient 5* during a period of searching for passengers. *Middle*: power spectral density plot during searching for passengers and searching for store epochs. *Bottom*: bar plot of mean log-theta power for each task condition. *B*: same as *A* except data are from the right anterior hippocampus of *patient 9* during a period of searching for passengers. *C*: same as *A* except data are from the right anterior hippocampus of *patient 7* during a period of searching for a store. All error bars show standard error of the mean.

Prior studies using virtual navigation in human hippocampus (Ekstrom et al. 2005) and neocortex (Caplan et al. 2003) have shown that theta, as well as delta and higher-band activity is differentially modulated when subjects are searching for passengers compared with stores. As shown in Fig. 5C, we also found significantly more electrodes were modulated by searching for passengers than stores in all frequency bands but the beta band [all $\chi^2(1) > 10.7$, all $P < 0.005$]. Notably, the differential modulation of power during searching for passengers was largest in the theta band (64 vs. 17 electrodes showing theta-band modulations), replicating previous findings in humans (Caplan et al. 2003; Ekstrom et al. 2005).

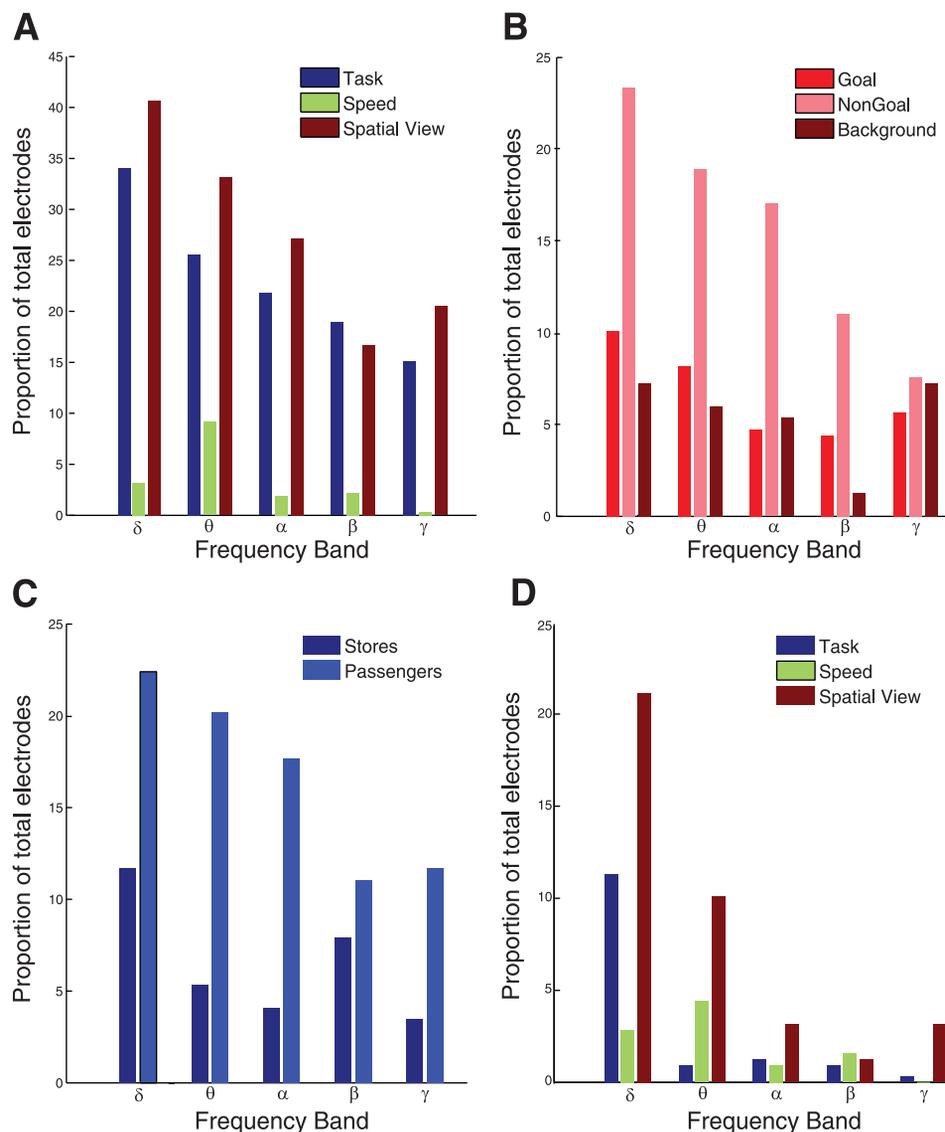
Next, we sought to determine whether a greater proportion of electrodes showed power modulations as a function of increasing speed or as a function of spatial view. This comparison allowed us to test two possible accounts of human hippocampal function taken from rodent findings. As shown in Fig. 5A, more electrodes were modulated by spatial view than increasing speed in all frequency bands [all $\chi^2(1) > 35$, all $P < 10^{-8}$], and as noted before, more electrodes were modulated during viewing of nongoal compared with goal stores (Fig. 3B). These results therefore support the possible involvement of human hippocampal theta oscillations in spatial processing.

Identification of both narrowband and broadband modulations. One interpretation of the data in Fig. 5, A–C, is that broadband shifts in power, rather than narrowband power increases, are exclusively associated with specific navigational variables. Although we found examples to the contrary (Figs. 2–4), we addressed this possibility by recomputing our exclusive analysis to identify narrowband modulations or effects specific to a single frequency band (e.g., theta). That is, we identified the proportion of electrodes responding to each behavioral variable in only one frequency band. Again, we found more electrodes showing narrowband effects for view, speed, and task than

expected by chance (Fig. 5D; type 1 error < 1 electrode). Narrowband effects were most prominent in the delta and theta band and were usually observed in a majority of our patient sample. Across our sample of 10 patients, narrowband delta effects for spatial view, speed, and task were observed in 10/10, 5/10, and 8/10 patients, respectively. Narrowband theta effects for spatial view, speed, and task were observed in 9/10, 6/10, and 2/10 patients, respectively. When we consider narrowband effects in either the delta band or theta band, 10/10, 7/10, and 8/10 subjects showed effects for spatial view, speed, and task, respectively. Narrowband modulations in the delta and theta band did not vary along the anterior-posterior extent of the hippocampus [anterior vs. middle vs. posterior; all $\chi^2(2) < 4.54$, all $P > 0.1$]. Overall, these results suggest that both narrowband and broadband power modulations occur with navigation-related variables.

Overlap analysis of combinations of behavioral predictors. Finally, we performed an overlap analysis and sought to determine the extent to which theta activity was modulated by multiple behavioral variables (see METHODS). This was not directly assessed in the preceding analyses because we previously categorized each significant electrode according to the most robust predictor variable in each frequency band. In contrast, this analysis tabulated the proportion of electrodes modulated by each combination of behavioral variables. Figure 6 shows the proportion of electrodes showing significant modulations by each combination of behavioral variables in the theta band. Forty percent of electrodes were modulated by a single behavioral variable, whereas 21% of electrodes were modulated by multiple behavioral variables. Significantly more electrodes were modulated by a single variable compared with multiple variables [$\chi^2(1) = 17.1$, $P < 0.00005$]. Twenty-three percent of electrodes were not modulated by any variables investigated in our experiment. These findings argue that a greater number of electrodes were modulated by a single

Fig. 5. *A*: proportion of 317 electrodes modulated by each behavioral variable in each frequency band (bootstrap alpha = 0.001, type 1 error rate < 1 electrode). More electrodes were modulated by spatial view than by speed in all frequency bands. *B*: breakdown of view effects in each frequency band. In all but the gamma band, the proportion of electrodes showing power modulations during nongoal viewing was greater than during goal and background viewing. *C*: breakdown of task effects in each frequency band. A greater proportion of electrodes were modulated when searching for passengers than when searching for stores in all but the beta band; this difference was largest in the theta band. *D*: proportion of 317 electrodes showing narrowband power modulations for each behavioral variable in each frequency band.



behavioral variable. Since this was true in the theta band, this argues for the presence of multiple theta generators rather than a single one, as outlined in the Introduction.

The above-described analyses sampled all electrodes regardless of whether these electrodes were subsequently determined to be ictal zones. Although it seems unlikely that ictal activity could be modulated by our behavioral task, we sought to rule out the possibility that our results were due to sampling potential ictal areas and analyzed the subset of 158 hippocampal electrodes from tissue outside of areas determined by the epilepsy team to be involved in seizure genesis. We thus re-ran our overlap analysis and assessed the proportion of electrodes showing theta-band modulations for combinations of our behavioral variables (i.e., goal viewing, nongoal viewing, searching for passengers, searching for stores, speed, and none). We found the same proportions of electrodes showing theta band modulations in our subsample of 158 electrodes as in our full sample [$\chi^2(5) = 7.8, P > 0.15$]. These data suggest that our results are not accounted for by epileptogenic activity and are consistent with the idea that disease-related activity does not cause power modulations in a behavior-specific manner.

Characterization of the prominent human hippocampal rhythm. Our behavioral results suggest that the majority of navigation-related oscillatory modulations occur in the delta and theta bands. The extent to which these same frequencies are the predominant rhythm in the human hippocampus, independent of behavior, remains controversial. To address this issue, we utilized the P-episode oscillatory detection method (see METHODS) to quantify the percentage of time that each hippocampal recording exhibited oscillatory activity at each frequency. We found that the most common oscillatory frequency observed across our population of electrodes occurred at 3.3 Hz (Fig. 7), which lies at the interface of the canonical delta and theta bands (Niedermeyer 1999). These results provide evidence that human hippocampal “theta” may exist at lower frequencies than the theta band (4–8 Hz) established previously using scalp EEG.

DISCUSSION

We capitalized on a rare opportunity to investigate theta oscillatory activity from the human hippocampus during virtual navigation. Whereas previous work has utilized macroelec-

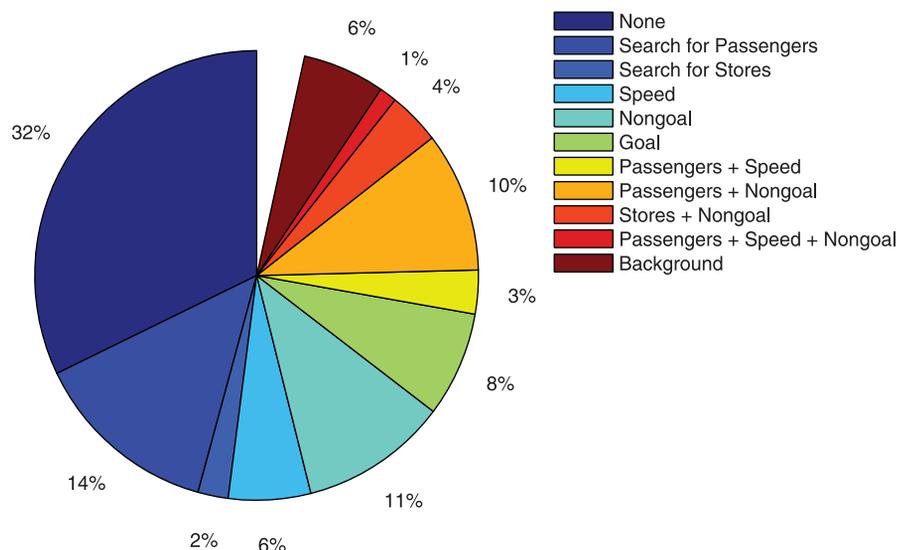


Fig. 6. Proportion of 317 electrodes showing theta (4–8 Hz) activity modulated by each combination of behavioral variables. To enhance clarity, only combinations with at least 1% of electrodes are shown. Thus the open portion represents all other variable combinations that accounted for <1% of electrodes. The majority of significant electrodes are modulated by a single variable, although ~20% are also modulated by multiple variables.

trode recordings (~1-mm electrode diameter, 13 electrodes) from a smaller patient sample (Ekstrom et al. 2005), the present study collected more focal LFP activity from more microelectrodes (40- μ m diameter, 317 electrodes) in more patients ($n = 10$). These recordings therefore allowed us to investigate more focal LFP activity in a much larger sample with finer resolution than that employed in previous studies. We also employed a navigation paradigm that involved acceleration, permitting us to look at theta activity over a range of speeds. Our behavioral paradigm thus allowed us to address our first objective: whether theta power increases with increases in speed, as shown previously in the rodent (McFarland et al. 1975).

Movement-related delta and theta power increases in the human hippocampus. Our results provide the first demonstration in the human hippocampus of proportional increases in delta/theta

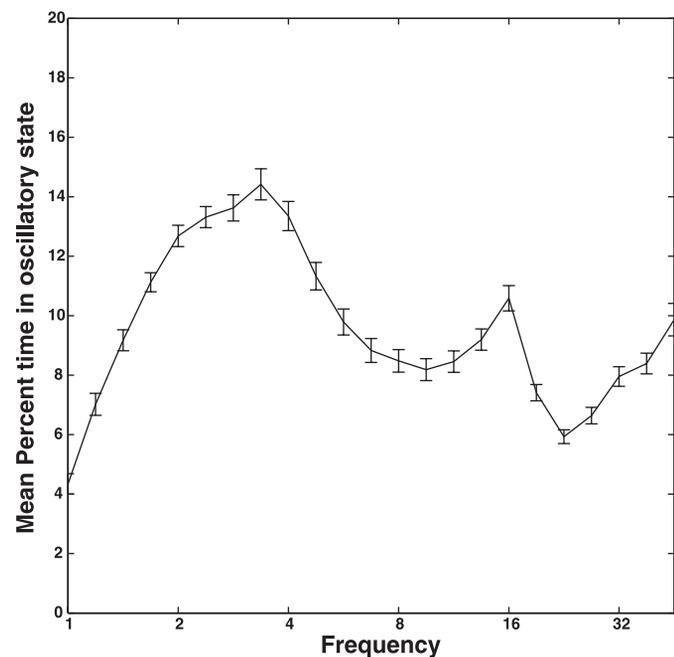


Fig. 7. Percentage of time significant oscillatory activity was detected as a function of frequency averaged across 317 hippocampal electrodes. Note the peak is at 3.3 Hz, below the canonical theta frequency band. Error bars indicate standard error of the mean across electrodes.

activity with increases in speed. Prior studies in rodents have shown general movement-related theta increases (Vanderwolf 1969), as well as theta amplitude increases with movement speed (McFarland et al. 1975). Although virtual movement and real movement are fundamentally different, a previous human study has shown movement-related modulations of hippocampal theta oscillatory activity (Ekstrom et al. 2005), suggesting that virtual navigation can be used as a proxy for real-world navigation to measure theta activity (see also Caplan et al. 2003; Harvey et al. 2009). However, Ekstrom et al. (2005) could not investigate continuous speed-related modulations because they used a constant virtual movement speed in their navigation task. Notably, this study also found modulations in other medial temporal lobe regions, such as the parahippocampal gyrus. Although we focus on hippocampal activity in this study, this is largely because we sampled this region most frequently. We therefore do not make specific claims about hippocampal function distinct from other adjacent regions.

Our results provide important links between the known electrophysiology in the rat hippocampus and the partially characterized electrophysiology of the human hippocampus. Our data suggest that delta/theta oscillations in the human hippocampus may serve a similar function to the rodent, possibly increasing as a result of increases in optic flow during navigation. Optic flow is largely tied to a sense of movement (Warren et al. 2001) and is independent of landmarks and other information that aided in spatial localizing. Thus speed-related changes, as suggested previously, might in turn play a role in timing of incoming information during navigation. Consistent with data in Fig. 5A, we speculate that the modest speed-related effects observed in this data set may reflect the fact that the human hippocampus is more involved in spatial processing than visual optic flow-related processing.

Increases in delta/theta power to viewing landmarks. Our data also provide additional insight into how we interpret delta/theta oscillations within the hippocampus. Speed-related increases in theta activity have often been taken to support a role for the hippocampus in sensorimotor integration (Bland 1986; Bland and Oddie 2001; Caplan et al. 2003). This hypothesis suggests that hippocampal theta increases in amplitude to allow integration of sensory input with motor output

during navigation. Our results from the spatial view analysis, in which we analyzed changes in oscillatory power based on what the subject viewed while navigating, provide a potentially contrary point of view. Compared with viewing the background, we found significant numbers of electrodes in the delta/theta band that increased in power when subjects viewed stores. We also found that significantly greater number of electrodes responded to view than to speed (Figs. 5, A and D, and 6). The fact that we observed significantly greater numbers of electrodes responding to view than to speed suggests that hippocampal delta/theta oscillations reflect more than speed-related and sensorimotor-related information.

With respect to the function of the view-related theta increases we observed, it is of particular interest that the greatest number of view-responsive electrodes increased in power during viewing of nongoal stores. On any given trial in our task, patients could view a store either because that was their navigational goal (the store they were searching for) or because they viewed it in the process of finding their goal. Thus nongoal stores likely served as a means for patients to localize themselves within the spatial environment because it provided information about the relative position of the goal store. What is perhaps then most striking in our view analysis is that the majority of delta/theta-related increases were to nongoal stores, suggesting that view-related changes in delta/theta oscillations may have served as a means of spatial updating. Because viewing of nongoal stores would seem easier to reconcile with a role in updating of spatial representations rather than a purely sensorimotor role, these results further strengthen the idea that human hippocampal delta/theta oscillations play a more direct role in spatial processing than previously considered.

Broadband vs. narrowband delta- and theta-related effects. Our primary aim was to address how hippocampal delta/theta activity is modulated by sensorimotor or cognitive variables. We observed narrowband power modulations, particularly in the delta and theta bands, to all of our behavioral variables of interest (Fig. 5D). Considering only electrodes showing narrowband effects did not change our overall results reported above. Fixing the type I error rate across frequency bands using our bootstrapping procedure allowed us to make direct comparisons between frequency bands and to compare narrowband and broadband modulations of oscillatory power in our paradigm. Although we observed significant numbers of electrodes specific to the delta and theta band that were effected by view, speed, and task, we also observed significant numbers of electrodes that responded to more than one frequency band, including modulations in higher frequency bands (i.e., alpha, beta, and gamma). One possible explanation for this finding is the presence, on a subset of electrodes, of broadband behavior-related shifts (He et al. 2008; Manning et al. 2009). These broadband shifts in power we observed could relate to underlying firing rate changes related to navigational processing in the hippocampus (Manning et al. 2009). For instance, hippocampal place cells are known to increase their firing rate while in their place field as a function of running speed (McNaughton et al. 1983; O'Keefe et al. 1998; Wiener et al. 1989). In addition, place cell firing is known to depend on the location of distal environmental cues (Muller and Kubie 1987), which may approximate nongoal stores in our task. We note, however, that our analyses suggested the presence of both focal changes within the delta and theta band to view, speed, and task as well as the possible presence of broadband shifts. Thus, although we found

little evidence for a difference in terms of behavioral modulation of narrowband vs. broadband frequency changes in our data set, future studies must be focused on addressing exactly how these two different types of changes in the $1/f$ spectrum may play different or comparable roles in navigation-related behavior in humans.

We observed the greatest modulatory effects in the delta and theta bands compared with higher frequency bands (Figs. 5D and 7). These findings are consistent with a number of other human intracranial studies of the hippocampus, which have also reported low-frequency (2–6 Hz) effects based on peak power, coherence, and neuronal phase-locking measures (Arnolds et al. 1980; Brazier 1968; Jacobs et al. 2007; Mormann et al. 2008; Rutishauser et al. 2010). Our data, coupled with previous studies, thus suggest the possibility that human navigation-related oscillatory effects may manifest in lower frequency bands (2–6 Hz) than is often reported in human scalp EEG studies (4–8 Hz). We note that because the canonical frequency bands were defined based on human scalp EEG studies (Niedermeyer 1999), they therefore may not accurately reflect human hippocampal dynamics. Although rodent delta and theta are often associated with different brain states, the similar pattern of results in these bands in our data does not allow us to draw conclusions about potential navigation-related differences between these bands.

Independent vs. global generator models of theta oscillations in the human hippocampus. One final issue we addressed was the extent to which multiple behavioral variables (view, speed, or task) affected oscillations on an individual electrode. Based on our analyses, we found that theta oscillatory activity was usually modulated either by view, speed, or task but significantly less frequently by combinations of these variables. An early influential model suggested that afferent input from the medial septum/diagonal band of Broca gives rise to a global hippocampal theta rhythm (Petsche et al. 1962; Stewart and Fox 1990). In this scenario, it would be unlikely that disparate behaviors could emerge from a global theta rhythm. However, recent *in vitro* evidence suggests that hippocampal theta is not a global rhythm (Lubenov and Siapas 2009) and may be generated without medial septal input (Goutagny et al. 2009; Lubenov and Siapas 2009) and that multiple theta dipoles can be modulated by different navigational variables in rodents (Montgomery et al. 2009). Consistent with this idea, previous reports have shown that local generators likely produce theta in humans (Mormann et al. 2008; Raghavachari et al. 2001). Our data also support the idea that independent generators exist for theta oscillations within the human hippocampus, which is also consistent with accounts of navigation-dependent modulation of independent theta generators in the rodent (Montgomery et al. 2009). We therefore speculate that the subsets of hippocampal electrodes showing theta-band modulations may be sampling independent theta generators that are serving a variety of behaviors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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