

Distinct Patterns of Brain Oscillations Underlie Two Basic Parameters of Human Maze Learning

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Caplan, Jeremy B., Joseph R. Madsen, Sridhar Raghavachari, and Michael J. Kahana. Distinct patterns of brain oscillations underlie two basic parameters of human maze learning. *J Neurophysiol* 86: 368–380, 2001. We examine how oscillations in the intracranial electroencephalogram (iEEG) relate to human maze learning. Theta-band activity (4–12 Hz in rodents; 4–8 Hz in humans) plays a significant role in memory function in rodents and in humans. Recording intracranially in humans, we have reported task-related, theta-band rhythmic activity in the raw trace during virtual maze learning and during a nonspatial working memory task. Here we analyze oscillations during virtual maze learning across a much broader range of frequencies and analyze their relationship to two task variables relevant to learning. We describe a new algorithm for detecting oscillatory episodes that takes advantage of the high signal-to-noise ratio and high temporal resolution of the iEEG. Accounting for the background power spectrum of the iEEG, the algorithm allows us to directly compare levels of oscillatory activity across frequencies within the 2- to 45-Hz band. We report that while episodes of oscillatory activity are found at various frequencies, most of the rhythmic activity during virtual maze learning occurs within the theta band. Theta oscillations are more prevalent when the task is made more difficult (manipulation of maze length). However, these oscillations do not tend to covary significantly with decision time, a good index of encoding and retrieval operations. In contrast, lower- and higher-frequency oscillations do covary with this variable. These results suggest that while human cortically recorded theta might play a role in encoding, the overall levels of theta oscillations tell us little about the immediate demands on encoding or retrieval. Finally, different patterns of oscillations may reflect distinct underlying aspects of memory function.

INTRODUCTION

Oscillatory activity is found in the electroencephalogram (EEG) of many mammals while they perform numerous cognitive tasks. Rhythmic activity at a variety of frequencies has been studied extensively, and certain oscillations may be important for memory function. For example, oscillations in the theta band appear in the raw, unfiltered signal from field potential recordings (Bland 1986; Jung and Kornmüller 1938; Vanderwolf 1969). Researchers have linked theta oscillations in rodents and properties of theta to moving within an environment (Vanderwolf 1969), orienting (Gavrilov et al. 1995), conditioning (Adey et al. 1960, 1962; Elazar and Adey

1967a,b; Grastyán et al. 1959, 1966), memory performance (Givens and Olton 1990; Kinney et al. 1999; Landfield 1977; Landfield et al. 1972; Mizumori et al. 1990; Winson 1978), speed of learning (Berry and Thompson 1978), and degree of learning of an environment (Pan and McNaughton 1997). The phase within the theta cycle may also be important for memory function; in addition to findings showing motor behavior phase-locked to the theta rhythm (Buño and Velluti 1977; Forbes and Macrides 1984; Komisaruk 1970; Macrides 1975), O'Keefe and Recce (1993) showed that hippocampal place cells fired in a consistent phase relationship to the theta rhythm and that this phase varies systematically with the animal's path through the environment. Givens (1996) demonstrated reset of the phase of the theta rhythm with stimulus presentation during a rodent working memory task. These findings suggest that both the presence and properties of the theta rhythm are intimately involved in both spatial and nonspatial memory in rodents.

While most extensively studied in the hippocampus, theta oscillations have also been observed in the cingulate gyrus (Leung and Borst 1987), hypothalamus (Slawinska and Kasicki 1995), superior colliculus (Routtenberg and Taub 1973), entorhinal cortex (Błaszcyk et al. 1996), and neocortex (Biedebach 1966; Nakamura et al. 1992; Silva et al. 1991). Thus theta-band oscillatory activity is a phenomenon that has relevance beyond hippocampal function.

Theta oscillations also influence long-term potentiation (LTP) induction, a proposed mechanism of synaptic plasticity, both in vitro and in vivo (Hölscher et al. 1997; Huerta and Lisman 1993; Larson and Lynch 1986, 1989; Larson et al. 1986; Pavlides et al. 1988), suggesting that theta acts as a windowing mechanism for synaptic plasticity. Taken with the behavioral results discussed in the preceding text, these findings support the notion that theta could be involved in specific modes of synaptic plasticity that have important implications for learning and memory at the behavioral level.

Theta oscillations have been far less extensively investigated in primates than they have been in other mammals. Stewart and Fox (1991) recorded rhythmic theta-band activity from anesthetized monkeys. This finding suggested that theta oscillations might also be observable in invasive recordings from the human brain; however, invasive recording from the human

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brain is only possible in certain special cases. Human EEG is normally recorded from the scalp; this signal is noisier and of lower spatial and temporal resolution than intracranially recorded signal. Consequently, robust, task-related theta activity in raw, unfiltered scalp EEG traces has not been reported. Instead, frequency-domain analyses of human scalp EEG have focused on measures like theta-band power averaged across trials and have successfully related these measures to memory function in humans (Burgess and Gruzelier 1997; Klimesch 1999; Klimesch et al. 1994). It should be noted that these analyses can proceed even when oscillations cannot be seen in the raw signal and when the average power spectrum does not show a peak in the theta band. These results suggest that, while task-related rhythmic activity may not be apparent in unfiltered human scalp EEG signal, analyses of average EEG power in the theta band may reflect *underlying* rhythmic oscillations that are related to memory function.

In addition to quantitatively analyzing average task-related spectral power, researchers recording human scalp EEG have extensively characterized *evoked potentials* and their correlation with memory function (Rugg 1995; Rugg and Allan 2000). During a task, if rhythmic oscillations vary in phase across the cortex, phases might only align for brief periods of time relative to a measurable task variable (e.g., presentation time of a stimulus). Coupled with the spatial averaging of the skull and scalp, this could appear as a single (nonrhythmic) EEG deflection. Certain evoked potentials might even result from momentary phase resetting of underlying rhythmic activity (Basar-Eroglu et al. 1992; Brankack et al. 1996; Demiralp and Basar 1992; Intrilligator and Polich 1994; Spencer and Polich 1999; Yordanova and Kolev 1998). Direct findings of momentary stimulus-evoked phase resetting (Givens 1996; Tesche and Karhu 2000), like those mentioned in the preceding text lend further credence to this possibility. This kind of argument further highlights the utility of obtaining invasive recordings from human participants while they perform memory tasks.

In previous work, we analyzed invasive recordings from epileptic patients undergoing long-term monitoring for planning of subsequent resection surgery. In the unfiltered intracranial electroencephalographic (iEEG) signal, striking rhythmic activity in the theta band was seen both during a virtual maze learning task (Caplan et al. 2000; Kahana et al. 1999) and during a verbal working memory task (Raghavachari et al. 1999). Further, these episodes of oscillatory activity covaried with task variables, suggesting that, like similar rodent theta, they may be related to cognitive function. This ability to record, in humans, rhythmic slow-wave activity that is visually similar to oscillatory activity recorded in rodents during similar tasks provides a crucial link between studies of human and nonhuman theta-band activity. These new iEEG findings provided evidence that theta-band oscillations are involved in human memory function.

Oscillations outside the theta band are also of interest. For instance, high-frequency oscillations in the gamma range (above 30 Hz) have been implicated in perception both in animals (Eckhorn et al. 1988; Gray and Singer 1989; Gray and Viana Di Prisco 1997; Neuenschwander and Singer 1996) and in humans (Demiralp and Basar 1992; Gruber et al. 1999; Keil et al. 1999; König et al. 1995; Miltner et al. 1999; Tallon-Baudry et al. 1996–1998) and in motor behavior in rodents (Hamada et al. 1998). Researchers have also proposed that

high- and low-frequency activity may work together during certain forms of cognition (Buzsáki 1996; Csicsvari et al. 1999; Jensen and Lisman 1998; Lisman and Idiart 1995). We were therefore interested in examining the relationship of oscillations at many different frequencies with task variables. We also sought to determine how theta-band oscillations compare with oscillations at other frequencies during virtual maze learning. It is of interest to know whether task-related oscillatory episodes are a uniquely theta-band phenomenon or an EEG signature that is also present at other frequencies.

As elaborated in the preceding text, theta bears a relationship to tasks involving movement within an environment as well as to tasks involving a memory component. Recently, interest in spatial memory and way-finding has been revived with numerous behavioral and functional neuroimaging studies in humans (Aguirre et al. 1996; Berthoz 1997; Kahana et al. 1999; Maguire et al. 1996–1998). We were specifically interested in multiple T-junction mazes. Extensively studied in animals (Stone and Nyswander 1927) and in some cases in humans (Miles 1928), T-junction mazes are useful for their simplicity and uniformity. Additionally, a path through a T-junction maze is a sequence of left and right turns; hence, it could be treated purely as a symbolic list-learning task. However, the maze paradigm additionally includes visual cues. The task, then, can be thought of as a serial learning task embedded within a spatial navigation task. Given these properties, it is of interest to study the learning of multiple T-junction mazes in humans. Recent innovations have made it possible to design virtual reality experiments in which participants navigate and learn a virtual environment (Gillner and Mallot 1998; Tlauka and Wilson 1994) and to detect changes in human cortical activity during virtual navigation (Maguire et al. 1998). As in previous work (Kahana et al. 1999; Kirschen et al. 2000), our participants learned to navigate three-dimensional rendered, virtual, multiple T-junction mazes (Fig. 2). This task has been shown to involve the processing of spatial cues and has a significant memory component. It was shown that the presence of optic flow, a visual cue, helps participants learn T-junction mazes, even though optic flow in itself contains no information about the maze path (Kirschen et al. 2000). This suggested that the spatial cues interact with memory function in a complex way. We sought to determine how oscillations at various frequencies relate to virtual maze learning.

In this paper, we present a new method for detecting episodes of EEG oscillations. This method enables us to ask how bouts of rhythmic activity at a given frequency are related to cognitively relevant variables. This oscillatory episode detection algorithm takes advantage of the high signal-to-noise ratio and good spatial and temporal resolution of intracranially recorded signal. It is designed to pick out rhythmic features in the raw signal. One advantage of the algorithm is that it is applicable across a broad range of frequencies. Combined with the fact that intracranial recordings bypass the low-pass filtering of the skull and scalp, this allows us to apply the same analyses over the 2- to 45-Hz range. We first take advantage of the method by comparing the incidence of oscillatory episodes at different frequencies. We show that electrodes tend to have a specific “characteristic” frequency (sometimes more than one; sometimes none), but most of the oscillations during a virtual maze learning task occur within the theta band. We improve on the maze-length analysis reported in earlier work (Kahana et al.

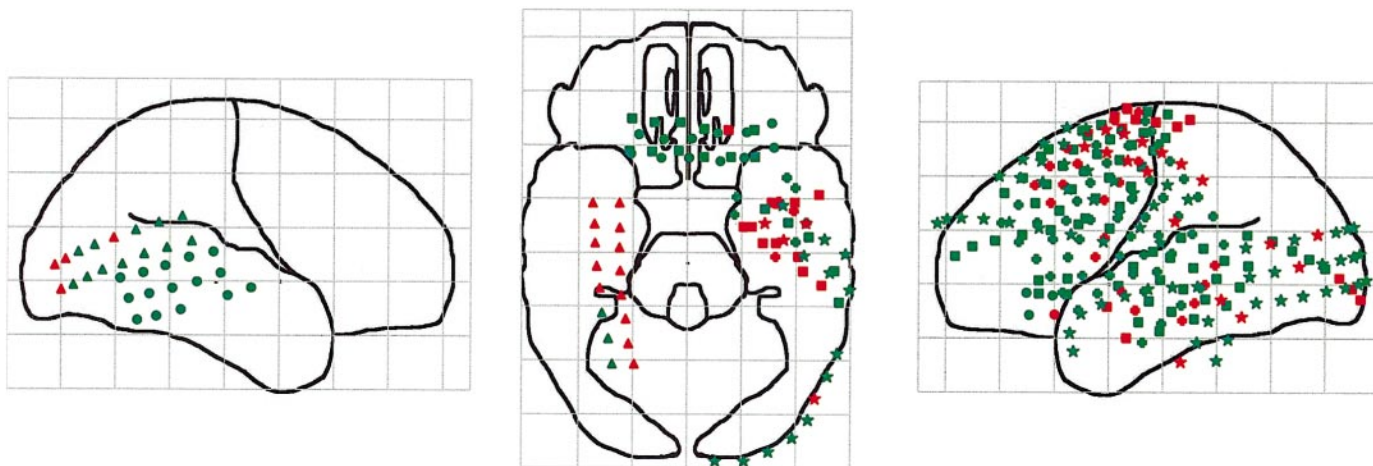


FIG. 1. All sites recorded from in all 5 participants. These topographic maps show electrode locations on 3 views of a standard brain. *Left*: right lateral view. *Middle*: inferior view. *Right*: left lateral view. Each shape denotes an electrode location. Different shapes denote different participants. Red-filled shapes were excluded from our analyses; green-filled sites were included.

1999). In these studies, we confined ourselves to the 4- to 8-Hz theta band, and our analyses could not be used to compare across frequency. With the new oscillatory episode detection algorithm, we are able to apply the maze-length analysis similarly across a broad range of frequencies and show that the maze-length effect occurs primarily within the theta band.

A limitation of the maze-length analysis is that maze length was an experimental *manipulation* of task difficulty. It is desirable to examine the electrophysiological correlates of behavioral measures that relate to learning. Therefore we examined participants' response times as they navigated through the mazes. This measure of response time, mean decision time per trial, has already been shown to correlate with learning (Kirschen et al. 2000). Mean decision time has also been shown to be a better correlate of learning than the number of errors committed (Kirschen et al. 2000) (also see RESULTS). We show that the patterns of oscillations that correlate with decision time are different from those that correlate with maze length.

METHODS

Participants and recording

We recorded from five patients with drug-resistant epilepsy. When the location of the seizure focus is unclear, patients undergo invasive monitoring to localize the focus. Intracranial platinum electrodes (3-mm diam) are placed subdurally in many brain regions to test hypotheses about the localization of the seizure focus as well as mapping functional regions to be avoided in surgery. By participating in our studies, these patients incurred no additional medical or surgical risk and informed consent was obtained from the patients and their guardians. The protocol was approved by the Institutional Review

Board at Children's Hospital, Boston. We sampled a total of 345 electrodes across five participants. iEEG signal was sampled at 200 Hz (Telefactor apparatus, band-pass filter: 0.5–100 Hz) for *participants 1–4* and at 256 Hz (BioLogic apparatus, band-pass filter: 0.3–70 Hz) for *participant 5*. The locations of the electrodes were determined from co-registered computed tomograms and magnetic resonance images by an indirect stereotactic technique (Talairach and Tournoux 1988). Electrodes overlying regions of known lesions or seizure onset zones were excluded from analysis (a total of 91 such electrodes were excluded).

All recording sites are plotted in Fig. 1, and further information about our patients is given in Table 1.

Task and procedure

Participants learned to navigate multiple T-junction mazes consisting of T junctions linked by corridors (Fig. 2). All corridors were of equal length. The sequences of successive turns were constrained to prevent the path from crossing itself (this happens with 3 successive left turns or right turns). We also eliminated paths that contained the subsequence right-left-right-left-right-left (or its complement) to avoid especially easy paths. Invisible walls prevented participants from moving down incorrect corridors.

Participants navigated the maze in a highly constrained fashion—one keystroke (up arrow) moved the participant's view down a corridor (the participant's virtual position was always on the midline of the corridor) and one keystroke (left or right arrow, respectively) turned the view 90° to the left or right. The keyboard buffer was cleared following each movement so that holding down a key had the same effect as pressing it once briefly. Turns immediately followed the keystroke, while forward movements occurred over 280 ms. In some cases, this delay was filled with optic flow (the view was redrawn multiple times as the participant's view moved along the corridor, simulating virtual movement); in others, there was no illu-

TABLE 1. *Participant demographics*

Participant	Age	Gender	Resection	No. of Electrodes	No. of Excluded Sites
1	16	F	R frontal	31	1
2	14	M	R inferior occipital	32	17
3	19	M	Anterior L temporal	108	27
4	23	M	L lateral frontal	78	23
5	22	F	L lateral frontal	96	23
Total				345	91

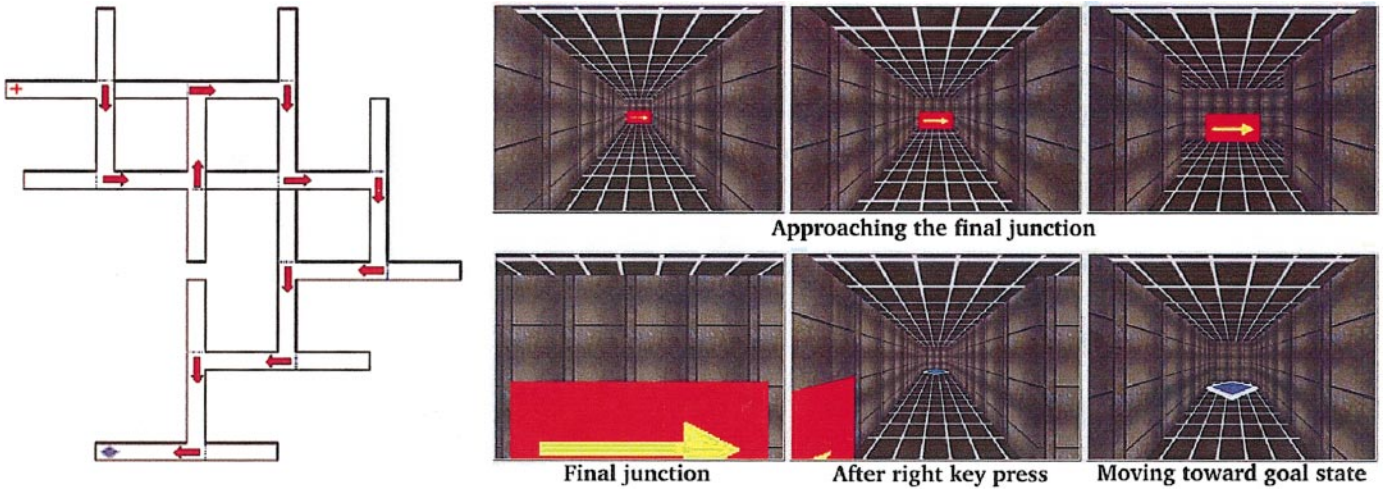


FIG. 2. The virtual maze learning task. *Left*: blueprint of a sample multiple T-junction maze. The red plus sign marks the start position and the blue diamond marks the end point. Arrows denote the correct path. Dotted lines represent invisible walls that prevented participants from going down incorrect corridors. *Right*: snapshots of the participants' perspective within the virtual maze, *study mode*, at the final junction of a sample maze.

sion of motion and the participant's view moved to the T junction following the delay.

Participants traversed a maze in two distinct *cueing modes*: initially, four consecutive trials were presented in *study mode*, in which arrows were placed on the walls to indicate the correct path. Participants then traversed the same maze in *test mode*, with the arrow cues removed, forcing them to rely on a learned representation of the maze. Participants navigated a maze repeatedly until they reached a performance criterion: namely, three consecutive errorless traversals. Task difficulty was manipulated by varying path length, which we term *maze length*. After a practice block of four eight-junction mazes (we excluded these mazes from our analyses), maze length was either *short* (sequences of 6 left and right turns) or *long* (sequences of 12 left and right turns) mazes.

Detecting oscillatory episodes

We designed the oscillatory episode detection algorithm to identify times within the signal that exhibited high-power rhythmic activity at a particular frequency, lasting a few cycles. We therefore defined an *oscillatory episode* at a particular frequency, f^* , as a duration longer than a time threshold, D_T , during which power at frequency f^* exceeded a power threshold, P_T . We selected the two parameters, P_T and D_T , as follows.

We moved to the frequency domain by wavelet transforming the raw traces [Morlet wavelet, window = 6 cycles (Grossmann and Morlet 1985)]. Frequency was sampled logarithmically because with wavelets, the relative bandwidth is preserved; 24 frequency steps were used in the range 1–54 Hz. The wavelet transform gave us wavelet power as a function of time at each frequency of interest.

To select the threshold, P_T , separately for each frequency at each recording site, we first assumed that the background spectrum was “colored noise,” with the form $Af^{-\alpha}$, a general property of natural, autocorrelated signals (Schlesinger and West 1988). We wanted to set P_T in such a way as to exclude this background signal. We therefore fit the theoretical $\text{Power}(f) = Af^{-\alpha}$ function to the actual power spectrum over the 1- to 54-Hz range at each electrode. The curve fitting was done by log-transforming the average wavelet spectrum and then computing a linear regression on these values. The intercept is then equal to $\log(A)$ and the slope is equal to the exponent, $-\alpha$. The fit value at frequency f^* was taken to be the mean of the $\chi^2(2)$ distribution of wavelet power at that frequency (Percival and Walden 1993). The parameter, P_T , at a given frequency, was set to the 95th

percentile of the cumulative distribution of this fit $\chi^2(2)$ function to exclude 95% of the background signal.

The duration threshold, D_T , at frequency f^* was set to three cycles [i.e., $3(1/f^*)$] to eliminate artifacts and physiological signatures that were nonrhythmic.

Finally, we introduce the measure: $P_{\text{episode}}(f)$, percent trial time in episodes. $P_{\text{episode}}(f)$ was defined as the total amount of time during which episodes occurred at frequency f divided by the total time in trial. P_θ was defined as the union of all $P_{\text{episode}}(f)$ time in the 4- to 8-Hz band (5 logarithmically spaced frequency values).

In subsequent analyses, we excluded frequencies at the ends of the 1- to 54-Hz range; our range of interest was 2–45 Hz. This was done to keep clear of the band-pass filtering of the amplifiers at the low-frequency end and to avoid contamination by the 60-Hz line noise artifact at the high end.

RESULTS

In all analyses, significance thresholds were chosen to obtain a low estimated *Type I* error (false positive) rate. Between-subject variability in electrode placement and possible reorganization of function due to the pathology of the subject pool make it meaningless to average over anatomical regions with only five participants. Therefore it is not possible to generalize the localization of the task dependencies; however, at this stage, we are primarily interested in the overall pattern of results; hence, we ensured that the hit rate exceeded by far a conservative estimate of false positive rate.

Behavioral data

Participants learned to navigate virtual, multiple T-junction mazes. Participants were first presented with four *study-mode* trials, where an arrow (a visual cue) appeared at each junction, denoting the correct path. Then participants were required to navigate the maze in *test mode* without the aid of the arrow cues. They continued until they reached a criterion of three perfectly navigated consecutive test trials. We manipulated the number of junctions in the maze, a variable that has a profound effect on task difficulty (Kirschen et al. 2000). Across participants, mean number of test trials required to reach the learning

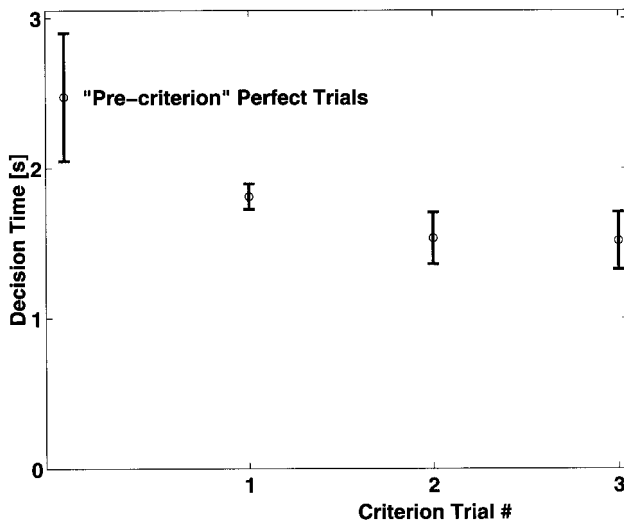


FIG. 3. The decision time measure. Plotted is the dependence of decision time on test trial number, for long (—) and short (---) mazes. Error bars denote SE across participants.

criterion (not including the three criterion trials) was 8.66 ± 3.31 (mean \pm SE) for long (12 junction) mazes and 0.58 ± 0.10 for short (6 junction) mazes.

To test the hypothesis that oscillations are related to learning, we wanted a sensitive measure of degree of learning. The first candidate is the number of erroneous turns committed. However, in a T-junction maze-learning task, or any binary sequence-learning task, the guess rate for each element of the list/path is 50%. Furthermore, once a wrong turn is made, the participant either corrects the error by making two successive turns in the opposite direction or turns around and becomes

disoriented in the maze and makes many more errors. Thus, after the first error it is hard to evaluate the quality of memory for the subsequent choice points (Kirschen et al. 2000). For two-alternative forced choice tasks, measures of inter-response times (IRTs) are especially useful for tapping performance levels even when response accuracy is perfect, and have been applied extensively in the literature (Kahana and Loftus 1999). We therefore chose to use the mean response time at choice points, *decision time*, as a measure of performance (Fig. 3). Consistent with the foregoing reasoning, earlier work demonstrated decision time to be a more sensitive measure of learning than the number of errors committed; learning curves that were significant in decision time were nonsignificant in number of error turns (Kirschen et al. 2000). Finally, the decision time measure allows us to compare perfect traversals of mazes, which, while they vary in demands on encoding, are matched for number of keystrokes.

Oscillatory episodes

As reported previously (Kahana et al. 1999), theta oscillations appear in the raw, unfiltered human iEEG signal. Figure 4 shows sample traces that show theta-band oscillations in selected electrodes from each of the five participants. We developed an algorithm to detect such episodes of oscillatory activity with two significant objectives in mind. First, we wanted the algorithm to tag signals that looked like rhythmic activity in the raw trace (as does theta activity in rodents). Second, we developed our method to be unbiased across frequency to be able to compare oscillatory activity at different frequencies. Previous analyses of oscillatory activity in humans and in rodents have tended to focus on measures of

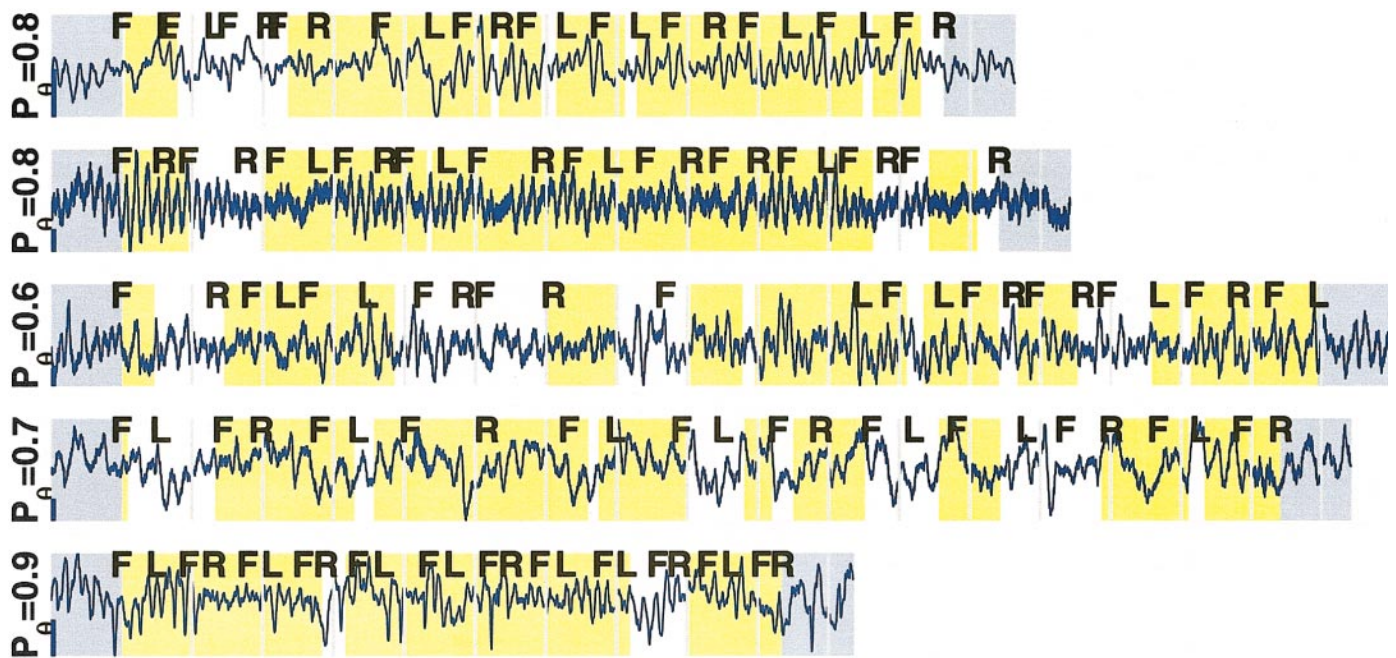


FIG. 4. Detecting theta-band oscillatory episodes. Theta is seen in raw signal (blue traces) recorded in electrodes in all 5 participants. Vertical gray lines mark 1-s intervals. The yellow-shaded regions denote theta-band oscillatory episodes identified by the algorithm (see text). The gray-shaded regions denote out-of-trial periods; these were utilized in the detection of episodes but excluded from the calculation of P_θ . F, R, and L, participants' keystrokes (forward, right, and left, respectively). Rows 1–5 represent traces from participants 1–5, respectively. Talairach coordinates (L-R, A-P, I-S) mm: participant 1, (–31.6, 19.1, –15.5); participant 2, (52.6, –49.5, 10.3); participant 3, (–52.1, –67.6, 12.6); participant 4, (–39.0, –4.4, –16.3); participant 5, (–56.1, –24.3, 23.4). Vertical scalebars (to the left of the traces) denote 100 μ V.

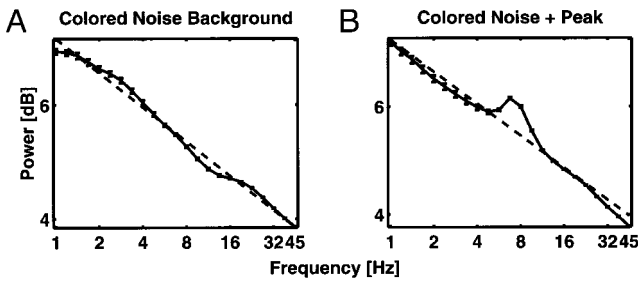


FIG. 5. Wavelet power spectrum for 2 example recording sites. A: *participant 5*, Talairach coordinates (L-R, A-P, I-S): (−41.4, 24.5, 38.0) mm. B: *participant 5*, (−60.1, −19.1, 15.4) mm. Error bars denote SE of the mean. ---, the $A \times (1/f^{-\alpha})$ (colored noise) spectrum fit.

average power (Benington et al. 1994; Mendelson et al. 1980; Pradhan et al. 1993; Roncagliolo and Vivaldi 1991; Smith et al. 1979). These methods have been applied without controlling for the levels of oscillatory activity that one would expect by chance. We present an oscillatory-episode detection algorithm that exploits the fact that theta episodes, runs of several cycles of theta-band activity, appear visibly in the unfiltered signal (see METHODS). By taking advantage of the known properties of background EEG and using these to tailor the method in the same way at each frequency, the method allowed us to fairly compare oscillatory episodes across frequencies. First, this allowed us to demonstrate that oscillatory episodes within the theta band are a prominent feature of our signal at many electrode locations. Second, we were able to compare incidences of the identified oscillatory episodes with task variables.

We designed our oscillatory episode detection algorithm to be able to identify times within the iEEG record that exhibited high-power rhythmic activity lasting a few cycles. We wanted the algorithm to be relatively insensitive to sharp transients as found in epileptic EEG. The method requires two parameters. An *oscillatory episode* at a particular frequency, f^* , was defined as a duration longer than D_T cycles during which power at frequency f^* exceeded P_T (see METHODS).

We selected the threshold, P_T , separately for each frequency at each recording site to make the method comparable across frequency, brain region, and subject. This selection of P_T relied on the ubiquitous property of background EEG—that the background power spectrum is colored noise, with the form $Af^{-\alpha}$, where f is frequency and A and α vary. The exponent α generally takes on values between 1 and 2; in our case, mean value, compiled across participants, was 1.69 ± 0.31 (mean $\pm \sigma$). Colored noise is a common property of a wide range of natural (including biological) signals (Schlesinger and West 1988). Power spectra indeed show this kind of background (Fig. 5A, —), and sometimes have superimposed peaks (Fig. 5B, —). These peaks likely occur because oscillations are present in the signal. Therefore we fit the function $Af^{-\alpha}$ to the wavelet power spectrum (e.g., Fig. 5, ---). The duration threshold, D_T^1 , at frequency f^* was set to three cycles [i.e., $3(1/f^*)$]. This biased the algorithm to tag oscillations consisting of sustained runs of rhythmic activity.

By choosing the thresholds in this manner, we could estimate the effect of the episode detection algorithm on “background EEG.” A power threshold $P_T = 95$ th percentile should, on average, eliminate 95% of the background signal. This would set an upper limit (on average) on the value that

$P_{\text{episode}}(f^*)$ could take—namely, 5%. However, by adding the duration threshold, $D_T = 3$ cycles, this 5% high power not only has to be present, but it has to *cluster* in time to be able to surpass the D_T . Therefore a good benchmark for identifying a significantly high amount of oscillatory episodes at a given frequency is $P_{\text{episode}}(f^*) > 5\%$.

The oscillatory episode detection algorithm agreed well with visual inspection. Figure 4 also illustrates the performance of the algorithm. Note that the algorithm picked out oscillatory episodes with the parameters used in this example ($P_T = 95$ th percentile, $D_T = 3$ cycles).

Frequency tuning of oscillatory episodes

If oscillations are present at particular “characteristic” frequencies, this should be evident as a local peak in the incidence of oscillatory episodes relative to nearby frequencies. In the episode-detection method we used, the parameters are selected for each wavelet frequency and electrode location individually, in a manner that is minimally biased with respect to the actual (experimental signal) distribution of wavelet coefficients. This makes it possible to compare the amount of oscillatory activity at one frequency to nearby frequencies.

By plotting the function $P_{\text{episode}}(f)$ (Figs. 6 and 7), one can see that there is indeed a significant peak at certain electrode locations, in the theta band (Figs. 6 and 7, A–C) as well as outside the theta band (Fig. 7, D–F). In some cases, multiple peaks can be seen (Fig. 7, G and H). While it is possible that multiple peaks are evidence of the fine spectral structure of a complex waveform, this is not always the case. For instance, P_{episode} at the two peak frequencies at the site in Fig. 7G shows statistical independence over maze trials [$r(114) \pm -0.022$, NS]. In still other sites, there is no pronounced peak (Fig. 7I). Figure 6 also illustrates the robustness of the frequency dependence to the choice of the two analysis parameters (P_T and D_T).

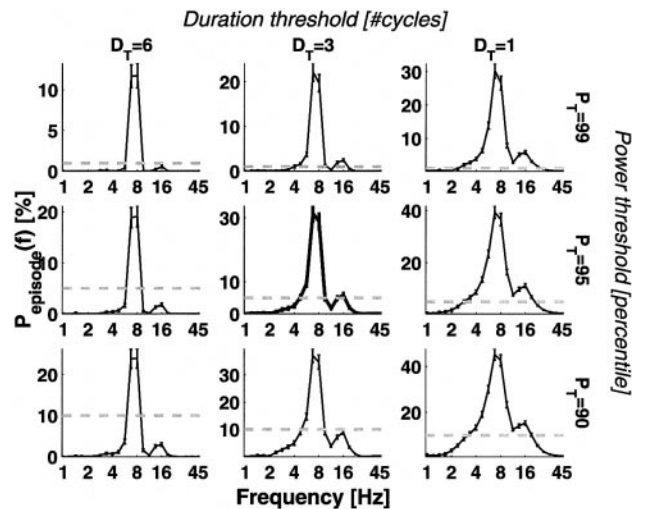


FIG. 6. Frequency dependence of oscillatory episode activity. Each plot shows P_{episode} as a function of frequency for an example location that shows both significant amounts of oscillatory theta-band activity and task dependence [*participant 1*, right inferior frontal cortex, Talairach coordinates (L-R, A-P, I-S): (9.8, 15.2, −18.9) mm]. The different plots illustrate the robustness of this pattern to the episode detection parameters, with the duration threshold varying by column and the wavelet coefficient threshold varying by row. The central thick plot indicates the standard parameter set used throughout the paper. Error bars denote SE.

We next addressed the question of whether oscillatory episodes occur predominantly within the theta band or comparably across the broad band examined. We simply evaluated the mean $P_{\text{episode}}(f^*)$ against the value 5% (the estimated maximum P_{episode} value for background signal). Figure 8 shows how many electrodes show significantly high $P_{\text{episodes}}(f^*)$ at each frequency (2-tailed t -test, $P < 0.001$). It is evident that oscillatory episodes are most prevalent within the theta band. The nonuniformity of the distribution of P_{episode} by frequency is significant for all participants [$\chi^2(22) = 223, 103, 588, 162$, and 520 for participants 1–5, respectively; $P < 10^{-14}$].

Because we controlled for the background colored noise spectrum, the predominance of oscillatory activity in the theta band cannot be explained by the general tendency for lower frequencies to exhibit larger amplitudes. The episode-detection algorithm successfully identifies episodes of oscillatory activity at different frequencies and is robust to the choice of parameters. Different brain regions show different dominant frequencies, and in some cases show multiple “active” frequencies. Still, at this stage, the theta band is the most well represented band at the electrode locations sampled.

Dependence of theta episodes on task parameters

We have found significantly elevated levels of both theta and non-theta oscillations during this task (Figs. 4–8). If it can be shown that these oscillations are correlated with variables known to have a strong influence on behavior, this would suggest that theta oscillations reflect an important feature of human cognition. We therefore examined the dependence of P_{episode} on two important task variables, *maze length* and *decision time* (see behavioral results in the preceding text).

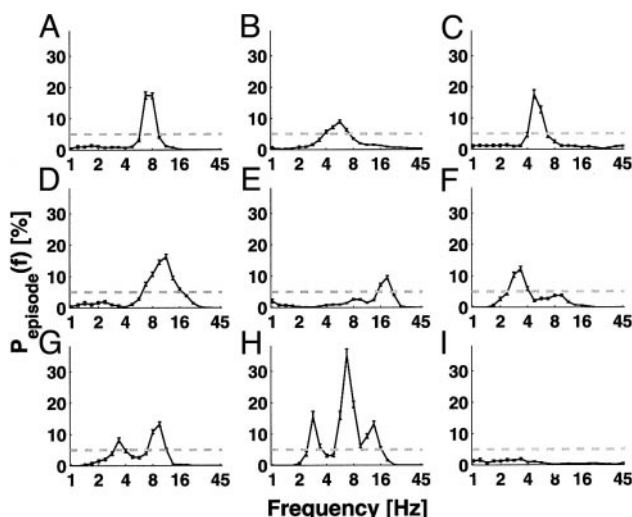


FIG. 7. Examples of different ways oscillatory episodes vary with frequency. Each plot shows P_{episode} as a function of frequency (error bars denote SE). Shown are electrodes with preferred frequency in the theta (A–C), alpha (D), beta (E), and delta (F) bands as well as an electrode with 2 (G) and 3 (H) preferred frequencies and 1 with no significant levels of oscillatory episodes (I). Dashed gray lines mark the 5% level, a benchmark for assessing significance (see text). Talairach coordinates (L-R, A-P, I-S) are: A (participant 2), (55.8, –32.1, 15.1) mm; B (participant 4), (–23.8, 15.1, 10.0) mm; C (participant 5), (–12.5, 15.7, 58.1) mm; D (participant 3), (–24.9, 8.0, 55.2) mm; E (participant 4), (–45.5, –15.1, 38.7) mm; F (participant 3), (–53.3, –18.9, 1.8) mm; G (participant 3), (–53.9, –42.6, 9.0) mm; H (participant 5), (–42.8, –21.1, –34.3) mm; I (participant 4), (–31.6, –13.2, 60.6) mm.

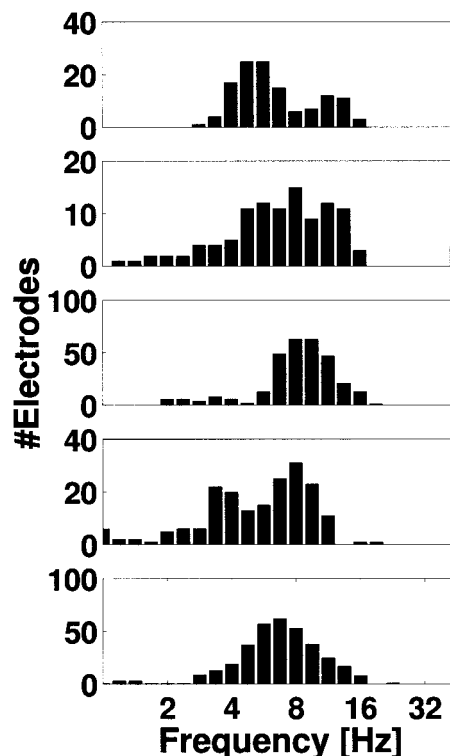


FIG. 8. Significant levels of oscillations. Histograms reveal the number of electrodes showing significantly high P_{episode} as a function of frequency, f . From top to bottom, the histograms represent participants 1–5, respectively.

MAZE-LENGTH EFFECT. We examined how P_{episode} varied with maze length (number of junctions) during perfect traversals of mazes, in both the training phase and test phase. Trials containing errors were excluded from this analysis because these trials were virtually absent in the short mazes, and thus, any difference observed between the short and long mazes could be carried by these error trials. Furthermore, on a significant number of error trials, participants became lost in the maze, and rather than trying recall or learn the sequence spent their time trying re-orient themselves.

As shown in Fig. 9, many sites showed significantly greater P_{episode} during long mazes than during short mazes ($P < 0.0005$ by a 2-tailed Mann-Whitney U test). This maze-length effect is seen for study trials as well as test trials¹ and at a broad range of frequencies; however, the effect is predominantly found in the theta and alpha bands. It is striking that only one electrode exhibited more theta-band oscillatory activity in short mazes than in long mazes.

The locations of all electrodes showing these effects within the theta band are plotted in Fig. 10. Due to the electrode sampling bias (a result of clinical considerations) and possible reorganization of function in epileptic brains (Fried et al. 1994; Margerison and Corsellis 1966; Sass et al. 1990), one should be cautious in generalizing the localization of these task effects.

¹ Because the task is self-paced and participants are directed through the maze during the first four trials, the task blurs the distinction between study and test. On each maze traversal after the very first, participants are engaged in both learning the maze sequence and attempting to retrieve the information learned on previous traversals from memory. We nonetheless analyzed these trials separately and found no systematic differences. Therefore, we do not plot analyses of study and test trials separately in the figures.

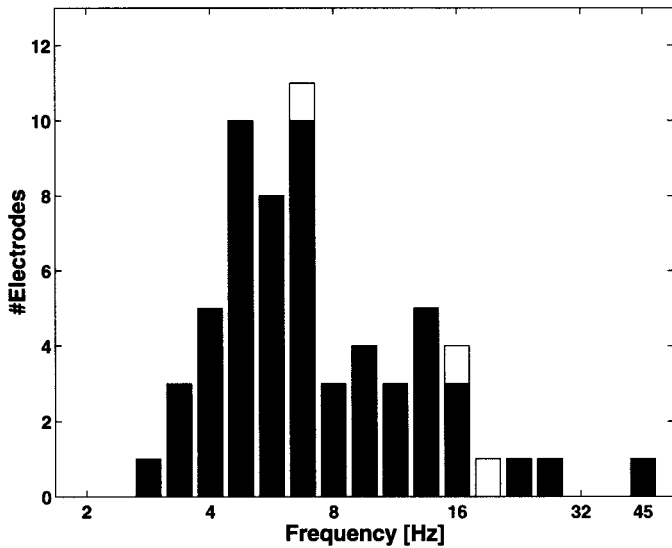


FIG. 9. Frequency characteristics of the maze-length effect. Histogram of the number of electrodes showing the maze-length effect as a function of frequency summarized across all 5 participants. ■, frequency-electrode pairs showing higher P_{episode} in long than short mazes ($P < 0.0005$); □, the opposite effect. Conservative estimate of *Type I* error rate is 0.22 sites at each frequency.

Nonetheless, it is of interest that the theta-band maze-length effect is observed in many brain regions. The widespread distribution of the maze-length effect might be a result of the fact that maze length in turn covaries with many task parameters. The presence of maze-length dependent theta in different regions may reflect different underlying functions for theta.

The maze-length effect extends previous findings (Kahana et al. 1999) to a larger population and to non-theta frequency bands. It indicates that oscillatory activity (primarily theta-band) is not only *present* during virtual maze learning but can be influenced by a manipulation of task difficulty, tying oscillatory episodes closely to cognition. The finding that in almost all cases of the maze-length effect within the theta band, oscillations are more prevalent in long than in short mazes,

suggests that theta is related to the increased cognitive demands of longer mazes.

DECISION-TIME EFFECT. The average amount of time a participant takes at a maze junction, *decision time*, is a good measure of learning at a given maze length and is a more sensitive probe of learning than the number of wrong turns a participant makes (Kirschen et al. 2000) (also see *Behavioral results*). We sought to determine whether this variable was related to oscillatory activity, independent of maze length. If the maze-length dependent theta we observed were directly related to the amount of encoding or retrieval difficulty during a trial, we should see an increase in theta per unit time with increasing decision time.

We were specifically interested in looking at perfect test trials during long mazes. Long mazes took participants numerous test trials to learn. We included all perfect test trials so that the trials would be controlled for the overall number of keystrokes. By including both criterion and precriterion perfect trials, we analyzed trials during which participants spanned a range of demands on encoding and retrieval. We therefore computed the Pearson correlation between $P_{\text{episode}}(f)$ and decision time across trials and selected a significance cutoff threshold of $P < 0.0005$ to equate the estimated Type I error rate with that for the maze-length effect [this corresponds to $r(75) \geq 0.40$, $r(92) \geq 0.36$, $r(57) \geq 0.45$, $r(72) \geq 0.40$, $r(32) \geq 0.59$ for *participants 1–5*, respectively].

Figure 11A shows the number of electrodes at each frequency showing this effect ($P < 0.0005$). In almost all cases meeting the significance criterion, the correlation was *positive*—oscillatory episodes occurred more of the time during trials with greater mean decision time. Quite surprisingly, however, in contrast to the maze-length effect, this task dependency appears relatively *absent* in the theta band. Instead, the decision-time effect is especially pronounced in the gamma and delta frequencies. This directly contradicts the hypothesis that the amount of theta in a given trial reflects either the encoding or retrieval difficulty during that trial.

It could be that while theta oscillations do not occur a greater percentage of *time* with increased demands on encoding or

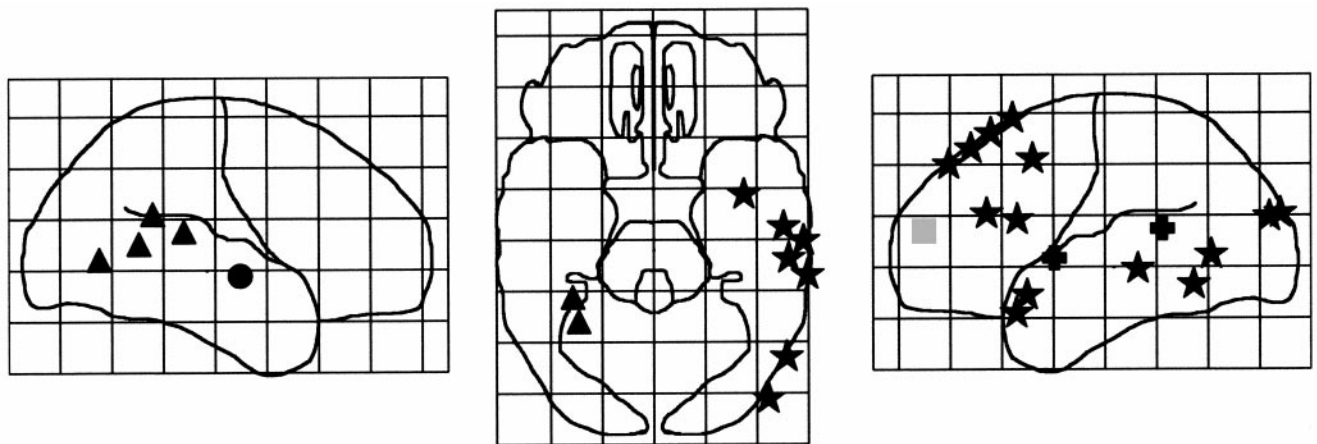


FIG. 10. Brain regions showing maze-length related theta episodes. These topographic maps show electrode locations on 3 views of a standard brain. *Left*: right lateral view. *Middle*: inferior view. *Right*: left lateral view. Each shape denotes an electrode location. Different shapes denote different participants. Filled shapes denote electrodes that show the maze-length effect to $P < 0.0005$ at any frequency within the theta band (4–8 Hz). Electrodes are filled black if they show more P_{episode} during long mazes than short mazes. The 1 electrode filled light gray showed the opposite effect. Conservative estimate of *Type I* error rate is 1.3 electrodes.

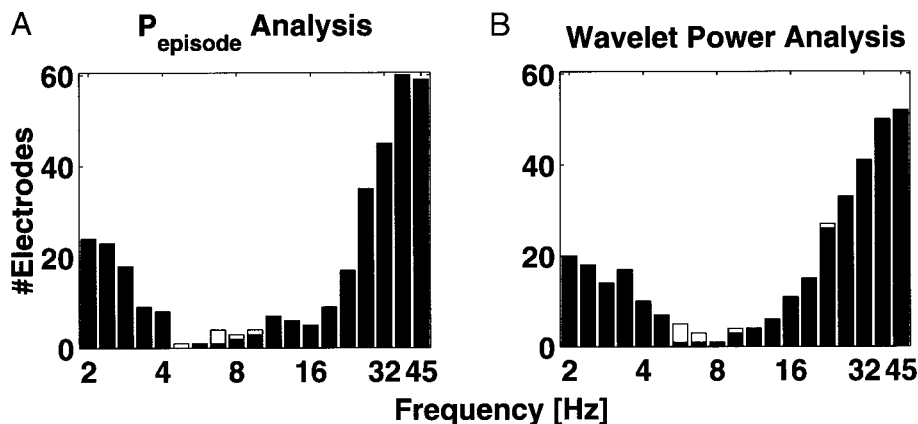


FIG. 11. Frequency characteristics of the decision-time effect. *A*: histograms of the number of electrodes showing the decision-time effect ($P < 0.001$) in perfect test trials during long (12 junction) mazes. ■, frequency-electrode pairs showing more P_{episode} as decision time increased; □, the opposite effect. *B*: the same analyses using average wavelet power as the measure. Conservative estimate of Type I error rate is 0.22 sites at each frequency.

retrieval, their *amplitude* might be larger. Following this alternate hypothesis, we predict that while P_{episode} does not in general covary with decision time, *average wavelet power* for a given trial should. We therefore repeated the decision-time analysis using average wavelet power as the measure. These results showed a highly similar frequency dependence (Fig. 11*B*). This suggests that the decision-time effect is found in the theta band neither in the predominance nor the amplitude of the oscillations. We discuss how to resolve the apparent contradiction between the maze-length and decision-time effects in DISCUSSION.

The decision-time effect is a finding of task dependence of oscillatory activity that is distinct from the maze-length effect—it is present even when maze length is fixed. The frequencies at which this effect occurs, however, are quite different from those at which the maze-length effect occurs. The decision-time effect appears *not* to be a theta-band phenomenon but rather, is prominent in the gamma and delta bands. We consider a specific example in Fig. 12. The first thing one notices is that the $P_{\text{episode}}(f)$ plot for this electrode shows a theta peak but no significant gamma peak (Fig. 12*A*). In contrast, the decision-time effect is nonsignificant at this peak theta frequency but highly significant ($P < \sim 10^{-7}$) in the gamma band at 38 Hz (Fig. 12, *B* and *C*). By inspecting the vertical scales in *B* and *C*, one can see that the 38-Hz oscillations take up a small percentage of the overall task time. Conversely, theta oscillations are found a much greater proportion of the time. This explains why theta oscillations dominate the overall $P_{\text{episode}}(f)$ plot. Nonetheless, the relatively less frequent 38-Hz oscillations are found significantly more of the time during trials with longer decision time.

DISCUSSION

Distinct patterns of task-related oscillations

We have shown that oscillatory episodes occur in relation to two task variables—maze length, a manipulation of task complexity, and decision time, a measure of encoding/retrieval demands. We found both effects at many different frequencies and at a variety of brain regions. The maze-length effect was found primarily within the theta and alpha bands, while the decision-time effect was primarily found in the delta, beta, and gamma bands, with relatively little effect found in the theta band. The different frequency characteristics of the two effects suggests that the two analyses are functionally distinct—that they tap quite different cognitive operations.

Possible roles of theta oscillations

Our findings rule out a number of competing accounts of the role of theta in our maze-learning task. According to one hypothesis, increases in the rate of key presses produce increased theta activity. Because the key-press rate and associated virtual movement is faster in short mazes than in long mazes, this would produce the opposite maze-length effect—namely, more theta in short mazes than in long mazes. Furthermore this account would predict a negative correlation between decision time and theta activity, and again, little support was found for this effect.

A follow-up account is that theta is related not to key presses or virtual movement but to time spent in encoding and retrieval, specifically when the participant is not moving through the maze. This account would predict the strong positive maze-

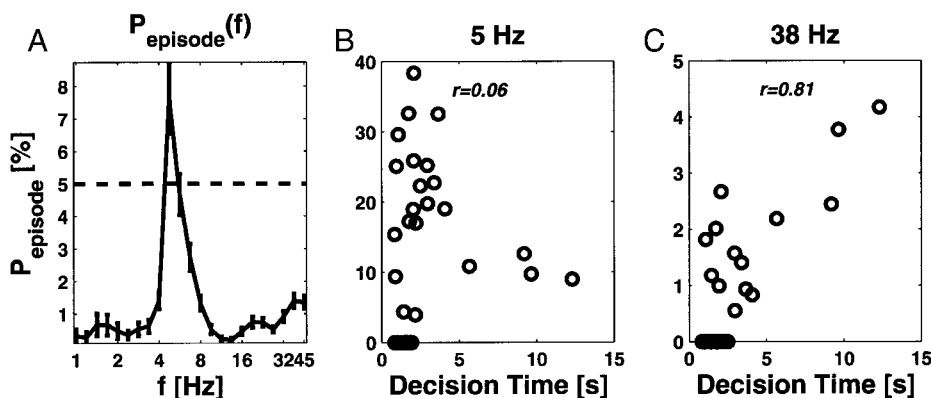


FIG. 12. Frequency specificity of the decision-time effect. The decision-time analysis is illustrated for a single sample recording site [participant 5, Talairach coordinates $(-62.6, -14.5, -1.7)$ mm]. *A*: the $P_{\text{episode}}(f)$ curve showing a theta peak but no gamma peak. ---, the 5% benchmark level (see text for details). Error bars denote 95% confidence intervals. *B*: scatter plot of P_{episode} (5 Hz) against decision time showing no significant decision-time effect. The r value denotes the Pearson correlation between these 2 variables. *C*: same as *B* for 38 Hz at the same recording site, showing a highly significant decision-time effect.

length effect which we observed. However, it would also predict an even stronger positive decision-time effect, which was not found.

Further supporting evidence comes from analyses of oscillatory activity during a symbolic working memory task that failed to relate theta-band oscillatory activity to keystrokes or stimulus presentation alone (Raghavachari et al. 2001).

The finding of a robust theta-band maze-length effect led us to hypothesize that the presence of theta oscillations were related to the encoding or retrieval demands on the participant. However, the notable *absence* of a decision-time effect (both in P_{episode} and in average power) contradicted this hypothesis. While it is possible that properties of theta that we have not analyzed (e.g., frequency, phase-locking of behavior) might covary with demands on encoding or retrieval, the results still present a problem. We propose the following resolution. We suggest that theta oscillations are *conductive* to specific types of encoding (Hölscher et al. 1997; Huerta and Lisman 1993; Larson and Lynch 1989; Larson et al. 1986; Pavlides et al. 1988). However, theta oscillations are invoked not by the *immediate* demands of the task but by the overall demands of the task. It is plausible that the brain cannot anticipate the cognitive demands at the time scale of hundreds of milliseconds. We suggest that instead, theta oscillations are invoked by the general demands of the task at hand, on the time scale of learning a maze. This would account for the presence of a maze-length effect combined with the relative lack of a decision-time effect in theta. This account is also consistent with theta being present in rodents during diverse types of exploratory behavior; the presence of theta tells us only that encoding and retrieval are facilitated, but tells us little of *how much* of these cognitive operations is achieved.

Interpreting task-related oscillations in patients with epilepsy

Recording intracranially from epileptic patients affords a number of significant advantages over scalp-recorded EEG in normal participants (Sperling 1997), including freedom from eye-movement artifacts, improved spatial resolution, and absence of the filtering of the skull and scalp as well as access to ventral brain regions. Other groups have successfully used intracranial recordings from human participants to investigate cognitive function including memory (Fernandez et al. 1999; Guillem et al. 1996) and language (McCarthy et al. 1995) as well as mapping the topography of the oddball (P300) potential (Halgren et al. 1980; Smith et al. 1990). However, there are some important caveats to iEEG research.

First, in addressing the issue of localization, it is important to keep in mind that the placement of electrodes is determined by the clinical team in order to identify the locus of seizure onset. When the seizure focus is unclear, large numbers of subdural electrodes, placed directly on the cortical surface, can be especially informative. Because the focus is often in temporal lobe, there is a sampling bias toward temporal regions. The necessary clinical bias in electrode placement means that the data obtained from any given patient give limited information about the locations associated with a cognitive function. To obtain a complete picture of the topography of brain activity associated with cognitive function, one must assess patterns across a large number of participants with varying electrode coverage. For the results presented here, therefore, it is pre-

ture to draw conclusions as to the general loci of human task-related oscillations.

It is also crucial to ask whether our results might be a direct result of the pathology of the subject pool. This is especially pertinent given that epilepsy is a disorder of rhythmic activity, and it is precisely rhythmic activity that we focus on in this paper.

There are several arguments against the possibility that our findings are related to epilepsy. First, we excluded sites involved in seizure onsets as well as electrodes placed over known lesions. Second, at a large number of sites, the incidence of oscillations covaried with the task, and these sites showed a high degree of spatial localization, a pattern quite the opposite of what one would expect from an uncontrolled process like epilepsy. Third, participants performed the task at levels similar to university undergraduates, indicating that the brain regions responsible for performing the maze learning task were functioning well. Fourth, sleep spindles, a different kind of theta-band oscillatory activity, have been recorded intracranially in epileptic patients and shown to be both similar to spindles in normals and unrelated to epilepsy (Malow et al. 1999), demonstrating that it is possible to observe rhythmic activity in epileptic participants that is not a result of their pathology. Finally, some evidence suggests that theta oscillations may in fact act to *inhibit* seizure onset in vivo (Miller et al. 1994) and that theta in vitro is insensitive to osmolality, a variable that affects patients' susceptibility to seizures (Osehobo and Andrew 1993). This kind of evidence dissociating theta oscillations and seizure activity supports the notion that the task-related rhythmic activity observed in our patients is not a consequence of their pathology.

Episode detection algorithm

Previous algorithms have been developed for analyzing oscillatory activity in rodents or theta-band power in humans as well as for analyzing sleep (both human and nonhuman), where rhythmic activity can be seen in raw scalp EEG signal. These algorithms have focused on measures of average power (Basar-Eroglu et al. 1992; Benington et al. 1994; Gavrilov et al. 1995; Intrilligator and Polich 1994; Klimesch et al. 1994; Yordanova and Kolev 1998) or zero-crossing algorithms (Berry and Thompson 1978; Roncagliolo and Vivaldi 1991) or measures not directly related to the rhythmic nature of the signal—or else have assumed that an underlying oscillation is present and proceeded to analyze its phase relative to task variables (Burgess and Gruzelier 1997; Givens 1996; O'Keefe and Recce 1993; Tesche and Karhu 2000; Yordanova and Kolev 1998). Instead, we developed an algorithm that would allow us to ask whether a site expressed significant levels of oscillatory episodes at a given frequency, relative to a reference spectrum. In this way, we could analyze oscillatory episodes in a manner that was not biased across frequency, electrode location, or subject.

The algorithm presented here makes use of known properties of the background EEG to identify significantly elevated runs of oscillatory activity. It has the desired properties and, importantly, agrees with visual inspection (Fig. 4) and is robust to choice of analysis parameters (Fig. 6). Our method takes advantage of the relative clarity of the signal obtained from invasive recordings in humans and the fact that the rhythmic

activity can be seen in the unfiltered trace. Additionally, the algorithm is simple in that it is an extension of average power analyses but overcomes some important biases of power spectrum analyses, including estimating background levels (Plett 2000) and requiring a sustained run of elevated power. The algorithm allows us to compare oscillatory activity across frequencies and favors frequencies that show spectral peaks.

Oscillatory episodes at different frequencies

When interpreting analyses of oscillatory episodes at different frequencies, it is important to consider the following. The iEEG is dominated by a colored noise background spectrum, which means that activity at lower frequencies will tend to be of higher amplitude than activity at higher frequencies and will therefore dominate the unfiltered trace. We applied the analysis methodology at each frequency using an estimate of the background spectrum. This is similar to “prewhitening” the signal or weighting the analyses equally across frequency. Therefore, results obtained at higher frequencies may be just as statistically significant as those obtained at lower frequencies; however, the higher-frequency oscillations will not tend to dominate the raw signal. Depending on the theoretical questions being addressed, one may wish to favor either oscillations of large amplitude or oscillatory activity that shows a highly significant relationship to the experimental paradigm. At present we are more interested in how oscillatory activity might be related to cognition, rather than the physiological mechanisms by which it might be generated; therefore we focused on oscillations that covary significantly with important task variables. Nonetheless, we found that oscillations occurred more in the theta band than at other bands in general during the task (Fig. 8). Further, the theta band appears to be the predominant band at which oscillations covary with maze length (Fig. 9) but not decision time (Fig. 11). Hence, oscillations that do in fact tend to be large in amplitude are also the most prevalent and dominate one of the task dependencies analyzed here.

Summary and conclusions

We analyzed oscillatory episodes in human iEEG signal recorded during a virtual maze-learning task. We asked whether the oscillations recorded intracranially in humans bore a consistent relationship to two basic task variables, maze length and decision time. We presented an algorithm to detect episodes of oscillatory activity. This algorithm and the clarity of the iEEG recordings made it possible to demonstrate that oscillatory episodes in our experiment occurred *predominantly* in the theta band (Figs. 6 and 8), tying our observations more closely to studies of both rodent and human theta-band results.

At a large subset of recording sites, the incidence of theta episodes increased with maze length (Fig. 10). However, inconsistent with the notion that these theta oscillations reflect the amount of encoding or retrieval, theta oscillations did not tend to covary with decision time, a measure of the immediate demands on encoding and retrieval. This suggested to us that theta oscillations might be a physiological state that is *conductive* to certain types of encoding but that theta is invoked to differing degrees based on the general demands of the task (e.g., how difficult the task is) but not by the immediate cognitive demands. Gamma and delta oscillations *did* covary

with decision time. These oscillations may reflect specific cognitive operations involved in integrating new information into memory.

The precise functions of patterns of oscillations during virtual maze learning remain unknown. Based on the rodent literature, one might expect that theta-band oscillations in particular are related to movement within the virtual space. As human theta oscillations have been observed in a symbolic working memory task using intracranial recordings (Raghavachari et al. 1999) and theta has been shown to be related to a similar task using MEG recordings (Tesche and Karhu 2000), this activity could not be *exclusively* related to the virtual navigation aspects of the task; however, it is still possible that theta plays an additional, unique role in tasks that rely on spatial cognition.

In the rat, theta has been shown to act as a dynamic window for the induction of long-term potentiation and depression at the synaptic level (Hölscher et al. 1997; Huerta and Lisman 1993, 1996; Larson and Lynch 1989; Pavlides et al. 1988). This raises the possibility that oscillations, especially in the theta band, are related to encoding and/or retrieval operations. However, in any memory task, including our maze-learning task, these operations are impossible to separate; learning strategies may in fact *actively* confound encoding and retrieval as in the case of rehearsal. Therefore we cannot distinguish oscillations related to encoding versus retrieval.

Oscillations at high frequencies (beta and gamma bands) are thought to play a role in perception (Demiralp and Basar 1992; Eckhorn et al. 1988; Gray and Singer 1989; Gray and Viana Di Prisco 1997; Gruber et al. 1999; Keil et al. 1999; König et al. 1995; Miltner et al. 1999; Neuenschwander and Singer 1996; Tallon-Baudry et al. 1996–1998), motor behavior (Hamada et al. 1998), and memory (Buzsáki 1996; Csicsvari et al. 1999; Jensen and Lisman 1998; Lisman and Idiart 1995). The high-frequency oscillations we observed might be related to perception or to memory operations or possibly to complex motor programming (although we eliminated the hypothesis that these oscillations are simply related to key pressing).

Finally, oscillations of varying frequencies may act together to perform multiple complex cognitive functions.

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