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Theta Oscillations Mediate Interaction between Prefrontal Cortex and Medial Temporal Lobe in Human Memory

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The medial temporal lobe (MTL) and the prefrontal cortex (PFC) are known to be critical structures for human memory processes. Furthermore, it has been suggested that they are part of a memory network. Although memory-modulated interaction between PFC and MTL has been observed at the hemodynamic level, it remains unclear what the neuronal process is that mediates the communication between these 2 areas. Experiments in rodents suggest that field oscillations in the theta band (4–8 Hz) facilitate PFC–MTL interaction. No such evidence has been reported in humans. To address this problem, cortical electrical activity from MTL, PFC, and lateral temporal lobe was recorded from implanted electrode grids in 3 epilepsy patients performing a verbal free recall task. The data were analyzed using a parametric spectral method to obtain estimates of power, coherence, and Granger causality. A task-modulated increase in coherence values between PFC and MTL was seen during free recall as opposed to a baseline condition. Concurrently, the number of coherent PFC–MTL site pairs was significantly increased during recall. Granger causality analysis further revealed that the increased coherence is a consequence of higher bidirectional information flow between the 2 regions, with a generally greater driving from MTL to PFC, namely, (MTL → PFC) > (PFC → MTL).

Keywords: coherence, electrocorticogram, Granger causality, intracranial EEG, verbal recall

Introduction

Two brain areas consistently implicated in human memory are the medial temporal lobe (MTL) and the prefrontal cortex (PFC). The role of the MTL in memory processes was well established in work of Scoville and Milner (1957) on patient HM, whose bilateral MTL lesions led to anterograde amnesia. Subsequent functional neuroimaging (Cohen et al. 1999; Daselaar et al. 2001) and electrophysiological studies (Fell et al. 2001) have further elucidated the MTL's role in episodic encoding and retrieval. Similarly, lesions in the PFC are known to cause impaired memory functions, such as free recall (Shimamura 1995; Wheeler et al. 1995) and working memory (Petrides and Milner 1982; Bechara et al. 1998). Positron emission tomography and functional magnetic resonance imaging studies have reported reproducible activations of the PFC in a broad array of memory processes (McIntosh et al. 1997; Fletcher and Henson 2001; Bunge et al. 2004; Dove et al. 2006). The hypothesis that both structures are part of a unified memory network is supported by the direct anatomical pathways linking PFC and MTL in monkeys and rats (Goldman-Rakic et al. 1984; Squire et al. 1989; Burwell et al. 1995; Suzuki 1996; Degenetais et al. 2003). In humans, functional connectivity analysis of fMRI data has revealed correlations between the lateral PFC and MTL in working memory (Gazzaley et al. 2004), episodic encoding (Grady et al. 2003), and episodic retrieval (Nee and Jonides 2008). These functional connectivity results suggest that not only are PFC and MTL both involved in memory, their task-related activity is statistically correlated, which can be taken to imply interaction. However, analyses at the hemodynamic level do not provide direct insight into how these interactions are mediated physiologically. Additional details of the interaction, including directions of information flow, remain not known.

What are the possible neuronal processes that could mediate the interaction between these 2 areas? Animal studies have long suggested that the theta rhythm, a prominent 4–8 Hz oscillatory phenomenon in the limbic system, is closely linked to the formation, storage, and retrieval of memory (Miller 1991; Kahana et al. 2001; Buzsaki 2002; Vertes 2005). More recent work postulates that during memory processes, theta oscillations mediate interactions between MTL and other cortical areas (Jensen and Lisman 2005), including PFC (Jones and Wilson 2005). In humans, theta activity has been observed in MTL (Meador et al. 1991; Kahana et al. 1999; Tesche and Karhu 2000; Ekstrom et al. 2005) as well as in frontal areas (Asada et al. 1999; Jensen and Tesche 2002; Sederberg et al. 2003). Furthermore, these theta activities were shown to correlate with memory performance. The issue of whether or not theta is a physiological process that mediates PFC–MTL interaction in humans remains unresolved. A recent study by Raghavachari et al. (2006), utilizing human intracranial recordings, found a lack of coherent theta activity between distant cortical sites during working memory. This finding suggests 2 implications: 1) there is a significant species difference in the processes that mediate cortical interaction during memory or 2) experimental or analytical issues have prevented the observation of the role of theta activity in human interareal interaction.

To examine this problem, 3 patients undergoing presurgical evaluation for intractable epilepsy were recruited to perform a free recall memory task. Intracranial electroencephalogram (iEEG), also known as electrocorticogram (ECoG), was recorded from multiple implanted electrode grids. The subjects were first given a series of words to remember. Then, following a distraction period, the subjects were asked to recall the words from memory. Data from the period of recall were compared with that from a baseline period of eyes open fixation. Consistent with the hypothesis that theta acts to mediate memory-related interaction between PFC and MTL, greater theta-band coherence was found during recall between electrodes in the prefrontal and in the medial temporal areas.

Granger causality analysis was used to estimate the directionality of this theta interaction, further defining the role played by each area.

Materials and Methods

Subjects and Electrode Placement

Three epilepsy patients gave informed consent and participated in the study. The experimental and recording protocol was approved by the Institutional Review Board of the University of Florida and the affiliated Shands Hospital at the University of Florida. Figure 1 illustrates the approximate positions of the implanted electrode grids in each of the 3 subjects. Two subjects had electrodes placed on the left hemisphere, and the remaining subject had electrodes placed on the right hemisphere. All 3 subjects had grids covering the lateral PFC and the lateral temporal lobe (LTL), as well as strips of electrodes on the ventral surface of the temporal lobe. The 2 most medial electrodes on the ventral strips, henceforth referred to as subtemporal grids, were treated as proxies of MTL activity due to their proximity to the parahippocampal region. In each grid, the electrodes were 3 mm in diameter with a spacing of 10 mm between neighboring electrodes. Depending on the subject, additional grids were implanted but were not included in the analyses for lack of corresponding coverage in all subjects.

Experimental Paradigm

The experimental paradigm was a verbal free recall and recognition task. An LCD monitor placed 3 feet in front of the subject was used to present the stimuli. A fixation cross remained in the center of the screen throughout the experiment. As illustrated in Figure 2, the experiment consisted of multiple blocks, with each block starting with the sequential presentation of 20 words (encoding period) chosen from the Kucera and Francis (1967) word pool. Each word was displayed on the screen for 2 s with a delay between words randomly selected from between 1 and 2 s (mean 1.5 s). The subject was instructed to try to remember as many of the words as possible. Next, in order to minimize recency effects and to discourage verbal rehearsal, the subjects were asked to count aloud, backward by 3's, starting at a random number for 30 s (distraction period). Following this distraction period, subjects were given 50 s to recall aloud as many of the previously presented words as they could remember (free recall period). After this free recall period, another set of 20 words was presented, which was followed by another distraction period and another recall period. Finally, an additional distraction period was given followed by a presentation of 80 words sequentially on the screen, consisting of the 40 previously presented words along with 40 words that had not been seen previously (recognition period). The subjects were asked to respond by button presses to indicate whether or not they recognized the word as being a previously presented word or a new word. The word stayed on the screen until the subject responded. Each response was followed by a delay of between 1 and 2 s (mean 1.5 s) before the appearance of the next word. The subjects each performed 3 blocks. At the end of each block, a 1-min baseline period during which the subject maintained their gaze on the fixation cross was recorded. The subjects were then allowed a short break before beginning the next block. The current analyses were focused on the data from 2 conditions: free recall and baseline fixation. Analysis of a third condition, the mental arithmetic (counting backward) during the distraction period, is included as Supplementary Material.

Data Analysis

Data were sampled at 400 Hz by a Nicolet amplifier system, band-pass filtered from 0.16 to 30 Hz, and downsampled to 200 Hz. Data segments contaminated by artifacts were excluded from further analysis. The remaining artifact-free data were divided into nonoverlapping epochs of 500 ms in length. Epochs from different blocks but within the same condition (free recall or fixation baseline), after a bipolar treatment (see below), were combined and treated as realizations of an underlying stochastic process to be characterized by power, coherence, and Granger causality spectra. Physiological differences in these variables between the 2 conditions were then assessed.

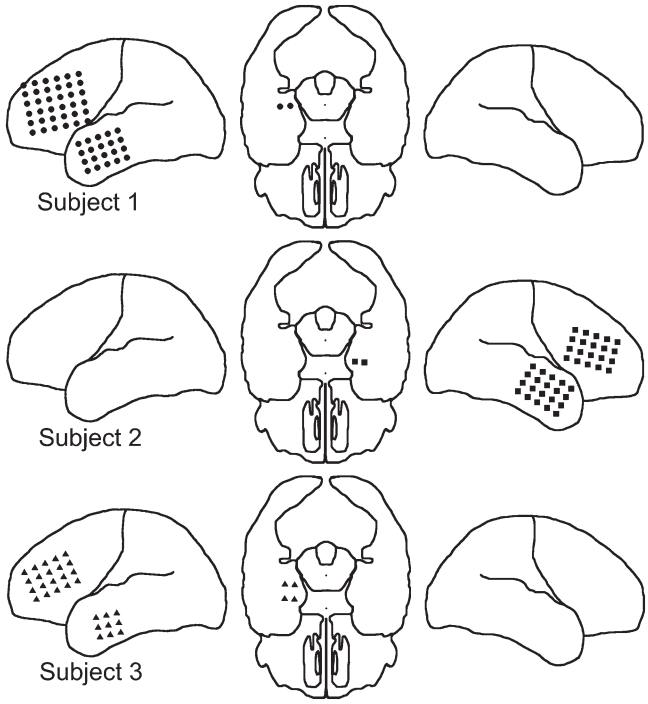

Figure 1. Approximate placement of electrode grids for each of the 3 subjects.

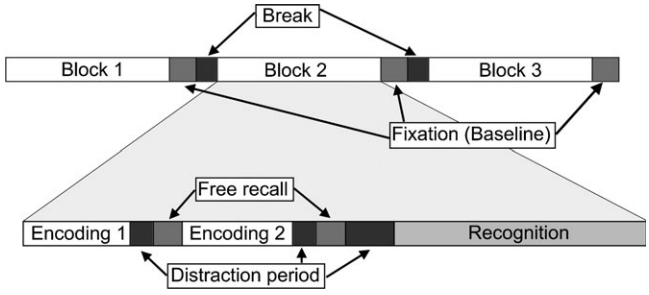

Figure 2. Schematic of the experimental paradigm.

Bipolar Derivations

The raw data in each implanted electrode grid were recorded against a common reference electrode fixed to the scalp of the subject contralateral to the hemisphere of grid placement. The reference electrode is not free of neural activity, which may potentially confound functional connectivity measures such as coherence and Granger causality, as the activity underlying this electrode will appear in all recorded channels. Volume conduction presented a further complicating factor. To overcome these problems, the data were rereferenced as bipolar signals. Specifically, for the 2 most medial electrodes in the subtemporal grid, their difference was treated as a representation of MTL activity. For the frontal and lateral temporal grids, the differences between all pairwise combinations of horizontally, vertically, and diagonally neighboring electrodes were used to represent activity in the respective brain regions. These difference signals will henceforth be referred to as bipolar signals or bipolar derivations. Table 1 gives the number of such signals in each of the 3 recording grids for all 3 subjects. For intergrid analysis, 3 combinations are possible: PFC–MTL, LTL–MTL, and PFC–LTL. Bipolar derivations from every grid were pairwise combined with bipolar derivations from another grid, and coherence and Granger causality were computed for each such pair.

Table 1
Total number of bipolar derivations in each area and total number of intergrid pairwise combinations of bipolar signals for each grid pair

Subject numbers	Number of bipolar derivations and intergrid pairwise combinations for each subject					
	Number of bipolar derivations			Number of intergrid combinations		
	PFC	LTL	MTL	PFC–MTL	PFC–LTL	LTL–MTL
1	110	55	1	110	6050	55
2	55	55	1	55	3025	55
3	55	20	2	110	1100	40

The total number of such pairs is given in Table 1 for each of the 3 intergrid combinations in each subject.

Spectral Analysis
Each pair of bipolar signals was subjected to autoregressive (AR) spectral analysis (Ding et al. 2000, 2006; Rajagovindan and Ding 2008). Briefly, let the pair of bipolar signals at time t be denoted by $\mathbf{X}_t = (x_{1t}, x_{2t})^{\mathrm{T}}$ where T stands for matrix transposition. Assume that the data can be described by the following AR model:

$$\sum_{k=0}^{m} \mathbf{A}_k \mathbf{X}_{t-k} = \mathbf{E}_t, \quad (1)$$

where $\mathbf{E}_t$ is a temporally uncorrelated residual error series with covariance matrix Σ, and $\mathbf{A}_k$ are 2×2 coefficient matrices to be estimated from data (Ding et al. 2000, 2006). The model order m was determined by the Akaike information criterion (Akaike 1974) and was further verified by comparing the spectral estimates from the AR model with that from the Fourier method. For the data analyzed in this study, $m = 17$ was chosen as a trade off between sufficient spectral resolution and overparameterization. Once the model coefficients $\mathbf{A}_k$ and Σ are estimated, the spectral matrix can be evaluated according to:

$$\mathbf{S}(f) = \mathbf{H}(f)\boldsymbol{\Sigma}\mathbf{H}^{*}(f), \quad (2)$$

where the asterisk denotes matrix transposition and complex conjugation, and $\mathbf{H}(f) = \left(\sum_{k=0}^{m} \mathbf{A}_k e^{-2\pi i k f}\right)^{-1}$ is the transfer function. The power spectrum of channel l is given by $\mathbf{S}_{ll}(f)$, ($l = 1$ or 2), which is the l-th diagonal element of the spectral matrix $\mathbf{S}(f)$. The coherence spectrum between channel l and channel k is:

$$C_{lk}(f) = \frac{|S_{lk}(f)|}{(S_{ll}(f)S_{kk}(f))^{1/2}}, \quad (3)$$

with l, $k = 1,2$ and $l \neq k$. The value of coherence ranges from 1 to 0, with 1 indicating maximum interdependence between the 2 bipolar signals at frequency f, and zero indicating no interdependence. The Granger causality spectrum from x_{2t} to x_{1t} is defined as (Geweke 1982; Brovelli et al. 2004; Ding et al. 2006):

$$I_{2\to 1}(f) = -\ln\left(1 - \frac{\left(\Sigma_{22} - \frac{\Sigma_{12}^2}{\Sigma_{11}}\right)\left|H_{12}(f)\right|^2}{S_{11}(f)}\right), \quad (4)$$

which can be interpreted as the proportion of x_{2t}'s causal contribution to the power of the x_{1t} series at frequency f. The logarithm is taken to preserve certain favorable statistical properties. Similarly, the causality spectrum from x_{1t} and x_{2t} can be obtained by switching the indices 1 and 2 in equation (4). In the present work, Granger causality analysis was carried out for those pairs of bipolar signals whose coherence in the theta range was deemed statistically significant (see below).

Interpretation of Granger Causality
Statistically, for 2 simultaneously measured time series, one series can be called causal to the other if we can better predict the second series by incorporating past knowledge of the first one (Wiener 1956). This concept was later adopted and formalized by Granger (1969) in the context of linear regression models of stochastic processes (see eq. [1]). Specifically, if the variance of the prediction error for the second time series at the present time is reduced by including past measurements from the first time series in the linear regression model, then the first time series can be said to have a causal (directional or driving) influence on the second time series. Reversing the roles of the 2 time series, one repeats the process to address the question of causal influence in the opposite direction. Here, directions of causal influence are equated with directions of synaptic transmission of neuronal activity (Ding et al. 2006; Bollimunta et al. 2008).

Random Permutation Test for Statistical Significance
To test the significance of intergrid coherence, the following procedure was followed (Brovelli et al. 2004), the aim of which is to create a null hypothesis distribution for the peak coherence values in the theta range for both conditions. 1) The 500-ms epochs were numbered from 1 to N, where N is the total number of epochs for a given condition (free recall or baseline). 2) The epoch index from each brain region was permuted randomly to create a synthetic data set where it is reasonable to assume that no interdependence exists between any pair of bipolar derivations. 3) All pairwise coherence was calculated for the synthetic data set, and the single largest peak coherence value among all coherence values in the theta range (4–8 Hz) from all channel pairs was selected. 4) Steps 2 and 3 were repeated many times. 5) The null hypothesis distribution was estimated by fitting an extreme value distribution to the peak coherence values (Wang et al. 2007). Calculated coherence values from the experimental data were considered significant if they exceeded the 99.9th percentile value of the maximum null hypothesis distribution between conditions ($P < 0.001$). The analysis of a frequency range as opposed to that of a single-frequency point and the simultaneous comparison of many intergrid channel pairs present a multiple comparison problem. The traditional Bonferroni correction is not applicable here as the underlying variables may not be independent. Choosing the maximum value in step 3 is a way to account for this problem (Nichols and Holmes 2002).

Results

All subjects completed the task according to instructions. Subjects sustained attention throughout the experiment and actively attempted to recall the presented words throughout the free recall periods. The mean percent of words correctly recalled was 27.8 ± 4.7% that is in line with previously reported results in healthy subjects (Fernandez et al. 1998). During the recognition phase of the task, subjects correctly recognized a mean of 92.7 ± 5.5% of the words presented.

Power

Spectral power was estimated for all the bipolar signals in each of the 3 implanted grids using the parametric AR approach, and the result from Subject 3 (for approximate electrode locations, see Fig. 1) is shown in Figure 3. A small peak in the range between 4 and 8 Hz was seen in most bipolar derivations, indicating synchronized local theta oscillations (Kahana et al. 1999; Raghavachari et al. 2001; Sederberg et al. 2003; Canolty et al. 2006). The power spectra for the remaining 2 subjects are similar (see Supplementary Material). The average peak theta frequency between all subjects was as follows: 7.41 Hz for MTL, 7.78 Hz for LTL, and 7.35 Hz for PFC. The larger spectral peaks at the lower frequencies (~2 Hz) are an artifact of combining the band-pass filtering (0.16–30 Hz) with the 1/f spectral characteristic of the electroencephalography signal (Slutsky 1937; Pritchard 1992; Demanuele et al. 2007). The thick solid curves are the averages of the bipolar power in each grid for each condition. For all 3 subjects, no consistent difference in theta power between the 2 conditions was found in any of the 3 regions; see average power spectra for all subjects, grids, and conditions, including the counting backward condition, in the Supplementary Material available online.

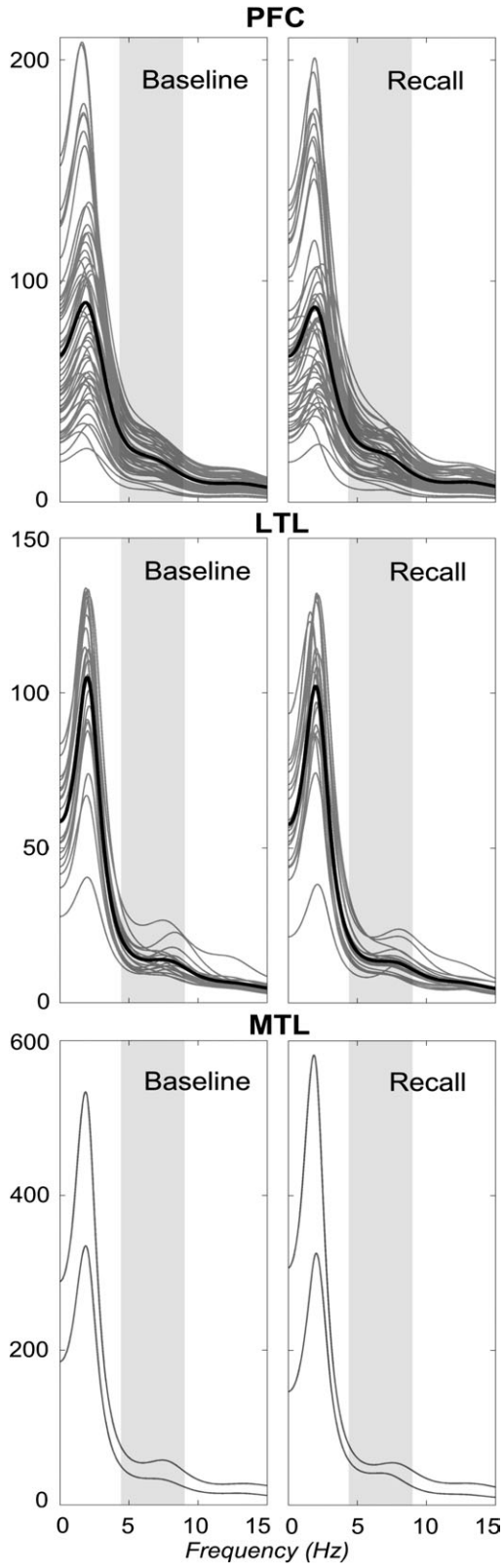

Figure 3. Power spectra in each of the 3 areas for Subject 3. Gray curves: spectra from individual bipolar derivations. Thick curves: average spectra. The large peak seen at the low frequency range (~2 Hz) is an artifact resulting from combining the high-pass action of the band-pass filter (0.16–30 Hz) with the 1/f type spectral characteristic of electroencephalography data. Theta frequency range is indicated by shaded background.

Coherence

To investigate the level of interaction between the cortical areas, coherence spectra between all possible pairwise combinations of bipolar derivations between a given pair of grids were estimated, and the result for PFC–MTL from Subject 3 is shown in Figure 4*A*. In contrast to the power spectra in Figure 3, where the theta peak is rather modest, coherence peaks in the theta range were much more prominent,

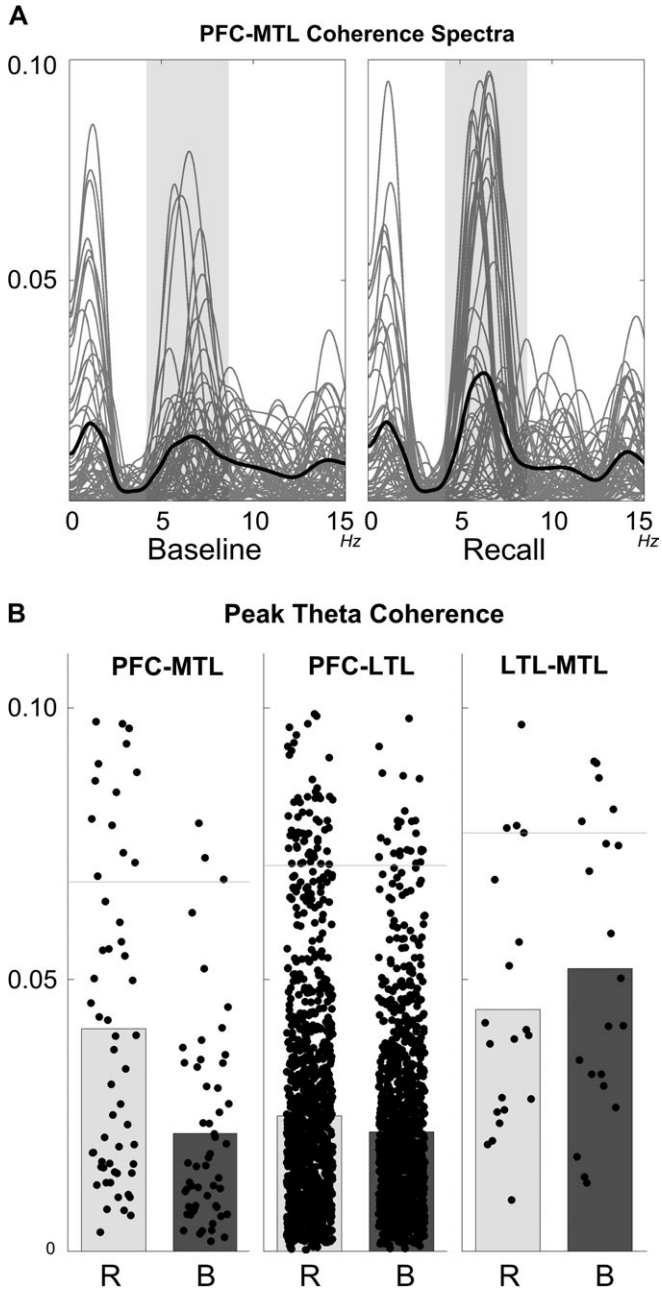

Figure 4. Intergrid coherence results for Subject 3. (*A*) Coherence spectra of all pairwise combinations of bipolar derivations between PFC and the posterior MTL electrodes (gray curves; see Fig. 1). Thick curves: averages of the gray curves. Theta frequency range is indicated by shaded background. (*B*) Coherence peak values in the theta range. Individual peaks are plotted as black dots. The horizontal placements of the dots within each bar are random. From left to right: PFC–MTL, PFC–LTL, and LTL–MTL. Each bar represents the mean of the peak coherence values in one condition with "B" denoting baseline and "R" denoting recall. The gray horizontal lines indicate the significance threshold corresponding to $P = 0.001$ for different grid pairs.

Table 2

P values from Wilcoxon signed rank test for difference in theta coherence peak values between free recall and baseline

Subject numbers	*P* values for difference in peak theta coherence between recall and baseline		
	Grid pairs		
	PFC–MTL	PFC–LTL	LTL–MTL
1	0.00009	0.0007	0.52
2	0.00019	0.0021	0.39
3	0.00002	0.0089	0.77

indicating communication between the 2 brain regions via theta-band oscillations. Moreover, the average theta coherence (thick solid curves) is higher for free recall than for baseline. This impression is confirmed in Figure 4*B* where peak coherence values in theta range are plotted for the 2 conditions. The height of the rectangular bars is the mean. A Wilcoxon signed rank test revealed that the interaction between PFC and MTL was significantly higher when the subject actively recalled words compared with baseline ($P = 0.00002$). No systematic spatial patterns were seen in frontal electrodes that showed increased coherence with MTL. For PFC–LTL, the coherence is slightly higher during free recall ($P = 0.0089$). There is no significant difference between the 2 conditions for LTL–MTL ($P = 0.77$). This pattern of interaction is found in all 3 subjects, as summarized in Table 2 below.

Another way of quantifying the task-related modulation of interareal theta synchrony is the number of pairwise bipolar combinations whose peak theta coherence values exceed the estimated 99.9% confidence thresholds (horizontal lines in Fig. 4*B*; see Materials and Methods) that corresponds to a significance level of $P < 0.001$. Because the number of channels in each grid varied between subjects, the percentages of pairwise combinations above threshold were calculated and averaged across subjects. As seen in Figure 5, there is a highly significant ($P = 0.002$) task-related increase in the percentage of theta coherent bipolar pairs for PFC–MTL. For PFC–LTL, a smaller increase in the number of coherent pairs is observed ($P = 0.02$). For LTL–MTL, although the percentage of pairs exhibiting significant theta coherence is high, the difference between the 2 conditions is not significant ($P = 0.31$).

Granger Causality

Coherence is a symmetric interdependence measure. Namely, when A is coherent with B, B is equally coherent with A. To gain insight into the information flow pattern between the PFC and MTL during memory performance, Granger causality analysis was carried out on the pairs of bipolar signals that showed significant theta coherence during recall. The results for the 3 subjects are shown in Figure 6. The peak Granger causality values in the theta band from MTL to PFC, denoted MTL→PFC, were significantly greater than those in the opposite direction, PFC→MTL, for all subjects and both conditions. This suggests that MTL theta plays a greater role in driving PFC–MTL synchrony than PFC theta. Reciprocal causal influence from PFC to MTL is also seen, indicating that the communication is bidirectional. Consistent with the task-related increase of coherence in Figures 4 and 5, Granger causality values in both directions show an increase for the free recall condition compared with the baseline fixation condition. For Subjects 1 (left panel) and 3 (right panel), the increase is

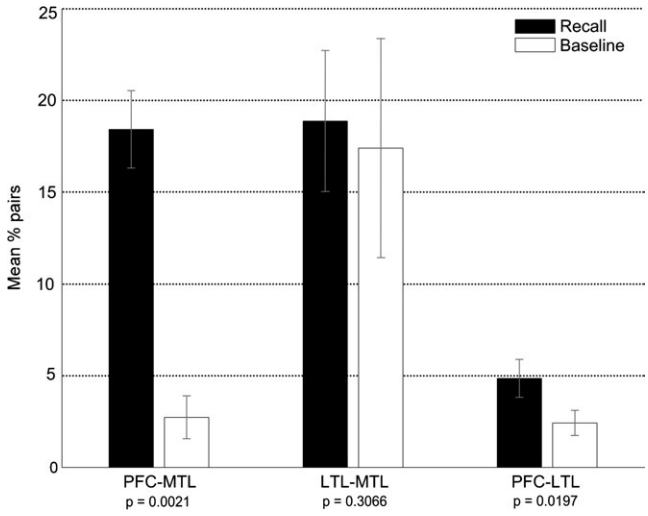

Figure 5. Average percent of intergrid bipolar signal pairs whose theta coherence exceeds the significance threshold for both baseline (white bars) and free recall (black bars) conditions. The standard errors are plotted as error bars. The one-sided *t*-test *P* values are included below each plot.

significant at $P < 0.01$. For Subject 2 (middle panel), the *P* value cannot be assessed, the reason being that no Granger causality value is available during the baseline period due to the fact that the number of bipolar signal pairs exhibiting significant theta coherence for this subject during baseline is zero. These results, schematically summarized in Figure 7, suggest that the increased coherence between the PFC and MTL in Figures 4 and 5 is a consequence of increased communication in the theta band in both the PFC→MTL and MTL→PFC directions.

Discussion

In this manuscript, we investigated whether theta oscillations play a role in mediating the interaction between the PFC and the MTL in human memory processes. Cortical electrical activity from 3 brain areas (lateral PFC, MTL, and LTL) was recorded from implanted electrode grids in 3 epilepsy patients performing a verbal free recall task. The multielectrode data, after a bipolar treatment, were analyzed using an AR spectral method to obtain estimates of spectral power, coherence, and Granger causality. Coherent theta activity was found in all pairwise combinations of the 3 cortical regions. When the free recall condition was compared with the baseline fixation condition, a large task-modulated increase in the overall coherence values between PFC and MTL was seen. At the same time, the number of coherent site pairs between PFC and MTL was also significantly increased during recall. Granger causality analysis of the coherent site pairs further revealed that the increased coherence is a consequence of higher bi-directional information flow between the 2 brain regions, with a generally greater driving from MTL to PFC.

Theta and PFC–MTL Interaction

The importance of theta activity in the hippocampus and other limbic system structures is well recognized (Buzsaki 2002; Vertes et al. 2004). Recent experiments with rats have begun to provide evidence in support of the notion that PFC–MTL interaction is mediated through theta oscillations and that this interaction is relevant for memory. Data in rats demonstrate

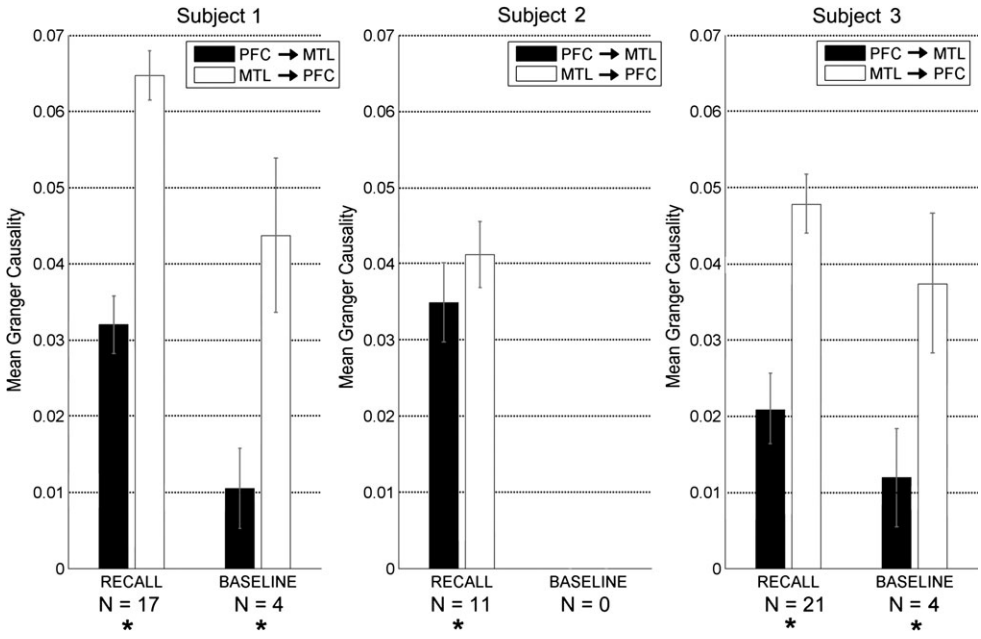

Figure 6. Mean Granger causality values for the coherent pairs of bipolar signals for PFC–MTL in each subject. The number of such pairs is given below each condition. White and black bars represent MTL → PFC and PFC → MTL, respectively. Standard errors are plotted as error bars. Conditions where MTL → PFC is larger than PFC → MTL at $P = 0.05$ level using a one-sided paired *t*-test are marked by an asterisk. Such comparison was not done for the baseline condition for Subject 2 as no coherent bipolar pairs were found for that subject in the baseline condition. Results from both subtemporal grids are combined for Subject 3.

that medial PFC neuronal firings are phase locked to hippocampal theta, and this entrained firing is modulated by animal behavior (Hyman et al. 2005). In addition, increased local field potential theta coherence between these 2 areas has been observed in rats during voluntary behaviors (Young and McNaughton 2009) and during decision making (Jones and Wilson 2005).

In humans, in spite of extensive evidence implicating PFC and MTL in memory-related functions, the questions of whether they work together as part of a network and what physiological processes might mediate their interaction remain unanswered. This lack of understanding could be in part attributable to the difficulty of noninvasive electrophysiological access to MTL structures. Recording of iEEG (ECoG) from patients undergoing presurgical monitoring to determine epileptic seizure foci partly overcomes this limitation. A recent study by Raghavachari et al. (2006) used this recording technique to investigate the coherence of theta oscillations between sites throughout the brain during a working memory task. It is reported that significant levels of coherence occurred only between nearby (<20 mm) sites, whereas distant sites very rarely showed coherent theta activity. Consequently, it was concluded that, in different brain areas, cortical theta oscillations are generated independently. In this regard, our study can be seen as the first to report PFC and MTL interaction in the theta band in humans. Although the theta coherence values between the 2 brain areas are generally low and are not statistically significant in most site pairs (>80%), these values, as well as the number of coherent pairs between PFC and MTL, are nevertheless significantly higher during free recall of remembered words as opposed to a baseline condition. This task-related modulation provides the key evidence for the role of PFC–MTL interaction in memory performance and suggests that theta activity is an underlying physiological process that

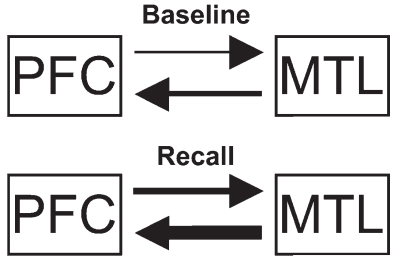

Figure 7. Schematic representation of the causal relationship for theta activity between PFC and MTL.

may mediate this interaction. It should be noted that the memory-related increase in PFC–MTL communication is observed for both hemispheres (see Fig. 1). Although hemispheric asymmetry of memory functions is commonly found (Tulving et al. 1994; Nyberg et al. 1996; Habib et al. 2003), functional imaging studies have shown PFC activation during verbal-free recall in both the left and the right hemispheres (Petrides et al. 1995; Fletcher, Shallice, Frith, et al. 1998). Hippocampal activation during verbal episodic retrieval has been found bilaterally in multiple imaging studies as well (Lepage et al. 1998).

Theta and Neuronal Communication

Neuronal ensembles interact and communicate with one another through the transmission of action potentials that carry information. Increased theta coherence during memory recall is a reflection of increased theta phase locking (Bressler and Kelso 2001). Siapas et al. (2005) hypothesize that, over short timescales, theta phase locking could be a mechanism for directing information flow between brain regions. They found that neurons constantly fire action potentials at restricted

phases of local theta (see also Lakatos et al. 2008). An offset in theta phase between 2 neurons would allow the neuron with the earlier phase preference to drive the neuron with the later phase preference. Over longer timescales, these consistent relationships would strengthen synaptic connections through spike timing–dependent plasticity. This could also lead to the formation of resonant phase-locked loops between regions with activation and transmission delays summing to around 150 ms, which corresponds to the estimated delays between PFC and MTL in humans (Miller 1991). Along another line of reasoning, Jensen (2001) suggests that cortical theta activity that is synchronous, yet out of phase, with hippocampal theta could allow decoding of phase-encoded hippocampal output. This "phase decoder" could be driven by neurons that fire out of phase, yet entrained to the hippocampal theta rhythm. With respect to the present experiment, 2 other considerations are relevant. First, field potential oscillations are accompanied by rhythmic bursts of action potentials. Lisman (1997) pointed out that bursting is a more reliable means of transmitting information over long distance than single-action potentials. Second, Lengyel et al. (2005), using computational modeling, shows that memory retrieval might occur in a theta rhythmic fashion. Thus, the idea of theta serving as information carrier during memory recall can be seen as grounded in both theoretical and empirical considerations. This is in further agreement with proposals where the role of theta oscillations in facilitating communication between the cortical and MTL structures has been emphasized (Miller 1991; Jensen 2005; Johnson 2006).

Generation and Propagation of Cortical Theta

Extensive evidence in animal studies as well as the evidence presented here for humans suggests that theta oscillations may facilitate communications between PFC and MTL. The question remains as to where these oscillations are generated and how they propagate. The hippocampal theta rhythm is generally believed to be caused by input from rhythmically bursting γ-aminobutyric acid (GABA)ergic and cholinergic neurons in the medial septum (Vertes and Kocsis 1997) as well as through recurrent connections within the hippocampus proper (Kocsis et al. 1999). The mechanisms underlying the generation of cortical theta are less understood. Cortical neurons have the ability to generate theta activity through the action of GABAergic interneurons (Blatow et al. 2003). Cholinergic input from structures in the basal forebrain is another important contributor (Liljenstrom and Hasselmo 1995; Jones 2004). Using phase analysis in rats, Siapas et al. (2005) proposed that PFC theta is the result of unidirectional theta input from the hippocampus. This idea is supported by Tierney et al. (2004), who found that hippocampal activity directly influences prefrontal interneurons that, as mentioned above, can create rhythmic cortical theta activity. These results seem to imply a passive role for the PFC in memory performance, a viewpoint at variance with work postulating an active role of the PFC in both memory encoding (Fletcher, Shallice, and Dolan 1998) and retrieval (Fletcher, Shallice, Frith, et al. 1998; Buckner and Wheeler 2001). Our Granger causality analysis shows that the PFC–MTL interaction is bidirectional, and during free recall of verbal information, the causal driving in both directions (PFC → MTL and MTL → PFC) is significantly increased compared with a baseline condition, with a generally greater causal influence from MTL to PFC, (MTL → PFC) > (PFC → MTL). This result supports an active role for the PFC in the present experimental paradigm. It is also in agreement with the prevailing notion that, at the top of the executive control hierarchy, the PFC coordinates posterior brain areas for goal-oriented behavior (Knight et al. 1999; Fuster 2001; Miller and Cohen 2001). It should be cautioned, however, that the bidirectional PFC–MTL interaction inferred from Granger causality, although consistent with the recurrent anatomical pathways existing between the 2 areas, cannot rule out the possibility that a third structure drives both PFC and MTL (Kaminski et al. 2001). Further investigations with more extensive spatial sampling are needed to elucidate the exact network mechanism.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

Conflict of interest: None declared.

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