

Theta activity, virtual navigation and the human hippocampus

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The theta rhythm is a prominent oscillatory EEG pattern recorded from the mammalian hippocampus. It has been studied most extensively in the rat but is also known to exist in the rabbit, cat and dog. It consists of large amplitude sinusoidal oscillations with a frequency of 4–12 Hz, which are clearly visible in the unfiltered EEG. In the rat, theta usually occurs during movements that translate the animal's location relative to the environment: walking, running, swimming, jumping and exploratory sniffing. Beyond these behavioral correlates, there has been much recent progress in understanding the crucial role played by the theta rhythm in the organization and timing of neuronal activity. However, recordings of theta activity in the primate hippocampus including the human, have proved elusive.

Rare experiments using depth electrodes in the human hippocampus have observed activity at theta frequencies, although their behavioral correlates were not clear^{1,2}. This has led some authors to suggest that theta may not have the same behavioral correlates in humans as in other mammals. This is an important issue as the absence of theta, or a change in its behavioral correlates, in the human would suggest different neural mechanisms of hippocampal function in rats and humans, and would prevent the application of knowledge from animal electrophysiology to human cognition in this area. Another possibility is that the theta mechanism might exist in humans but not be expressed in the EEG (as is the case, for example, in the CA3 field of the rat hippocampus). However, it is also possible that human studies have not used the correct behavioral task.

Human theta recordings

A recent report provides some support for this third possibility³. It indicates that theta activity can be recorded in the human EEG and that it may occur predominantly under the same or similar circumstances to that seen in the rat: during movement through an environment. Kahana *et al.* recorded the EEG from subdural electrodes implanted over different cortical areas in three patients. They found theta activity on leads from many sites while the patients navigated through a virtual reality maze. More theta activity was seen during traverses through more difficult 12-choice mazes

than through simpler six-choice mazes. Although the authors do not emphasize the point, there appears to be more theta from the temporal lobe electrodes than from the others. Because surface electrodes were used, the present study could not identify the generator for this activity, much less localize it to the hippocampal formation. Furthermore the authors did not comment on the relationship between theta activity in different areas so it is difficult to tell whether one is dealing with one or more synchronizing mechanisms. It is also not clear from the paper how specific the theta activation was to the navigational task. Ideally these results need to be corroborated by investigations using depth electrodes and a wider range of behavioral tasks.

There has also been recent interest in the related field of frequency analysis of EEG recorded from scalp electrodes. For example, increases in the power present in the EEG at theta frequencies have been shown to be related to the successful encoding of new information (see Ref. 4 for a review). However, these

studies have not specifically addressed navigation, nor do they typically demonstrate the peak in the power spectrum at theta frequencies or the long continuous records trains of theta activity shown by Kahana *et al.* (see Fig. 1). Localizing the source of theta in scalp-recorded EEG is even more problematic than from subdural electrodes and, in one experiment where it was attempted, implicated the anterior cingulate rather than the hippocampus (in a task showing increased theta with increased working memory load⁵). In addition, spectral peaks at theta frequencies have been found in experiments using magnetoencephalography, and have been interpreted as consistent with a generator near the hippocampus⁶, although this technique also suffers from problems of accurate source localization. Nevertheless, these findings, and particularly the subdural recordings of Kahana *et al.*, clearly show that theta activity exists in the human brain and tempt one to speculate that it might be related to the hippocampal system.

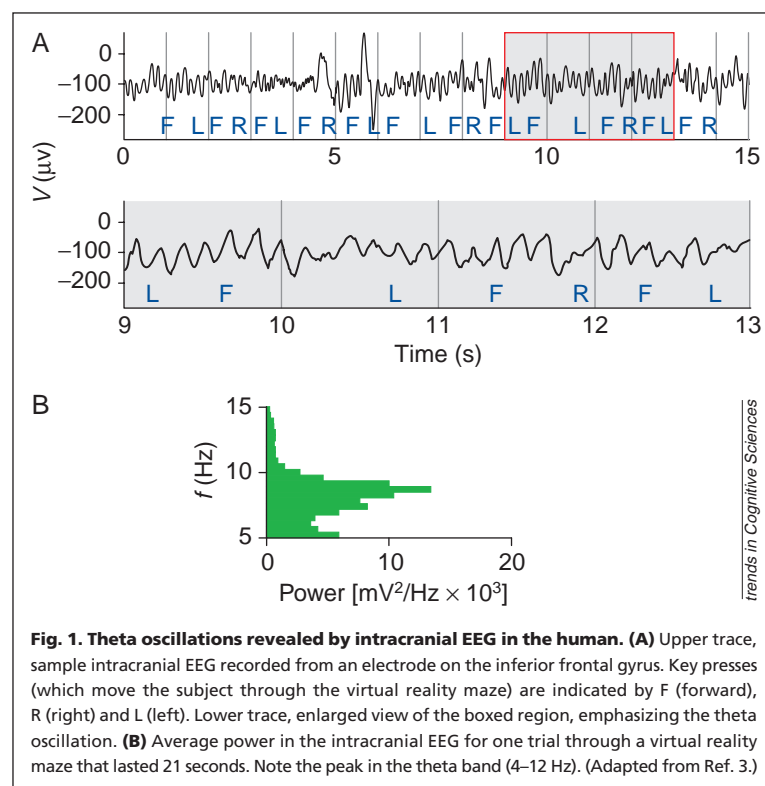
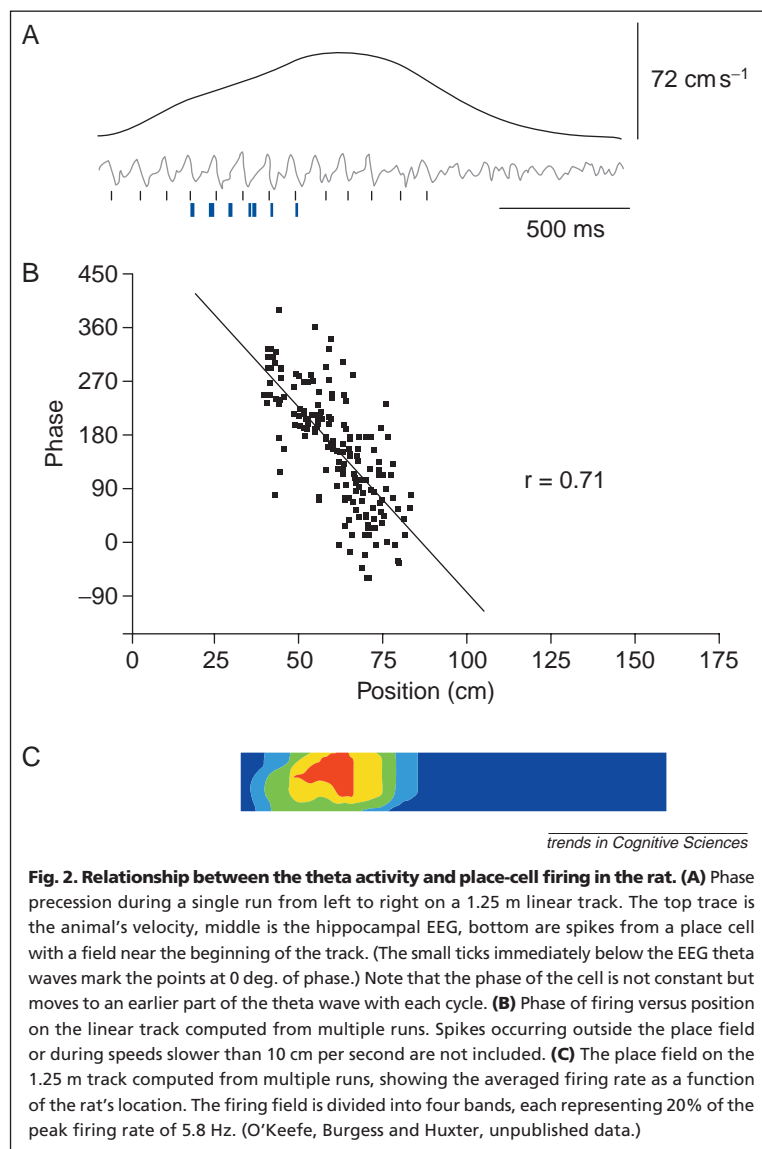


Fig. 1. Theta oscillations revealed by intracranial EEG in the human. (A) Upper trace, sample intracranial EEG recorded from an electrode on the inferior frontal gyrus. Key presses (which move the subject through the virtual reality maze) are indicated by F (forward), R (right) and L (left). Lower trace, enlarged view of the boxed region, emphasizing the theta oscillation. (B) Average power in the intracranial EEG for one trial through a virtual reality maze that lasted 21 seconds. Note the peak in the theta band (4–12 Hz). (Adapted from Ref. 3.)

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Functional implications

In the remainder of this article we explore the possible implications of this speculation for the neural basis of cognitive function in the human hippocampus. First we briefly review the relevant data from electrophysiology in rats.

In rats, there are two types of theta rhythm⁷. Both are dependent on the medial septum but they differ in their pharmacology and behavioral correlates. The predominant type does not depend on acetylcholine, is directly coupled to the motor system and conveys information about changes in direction and distance within an environment on the basis of motor efference copies, and perhaps also proprioceptive and vestibular inputs derived from the animal's own movements. The second type of theta in the rat is blocked by muscarinic antagonists and does not require actual movement but may instead be related to anticipated movement. One of the changes that might take place in the evolution of hippocampal function between rat and human is that the theta mechanism might become more easily activated by imagined movements⁸. A

major implication of the Kahana *et al.* result is that, in humans, theta might be associated with imagined and/or virtual movements as well as with actual movements through an environment. Indeed, there is a growing trend to study real-world spatial tasks in a more controlled fashion using virtual reality techniques (e.g. Ref. 9).

Work on the rat hippocampus allows us to ascribe at least two functions to theta. Firstly it acts as a global synchronizing mechanism, essentially locking the entire hippocampus into one single processing module and organizing its activity with respect to related brain areas. Simultaneous recordings of the EEG in different hippocampal locations have shown that theta activity is both in synchrony and coherent across large areas of the hippocampal formation¹⁰⁻¹². This means that if two cells have firing patterns that are systematically related to the theta cycle, they will have systematic temporal relations to each other, even if they are located far apart in the hippocampus. In the rat, the theta system is centred on the hippocampal formation, taken to include the septum, the subicu-

lar area and the entorhinal cortex¹³⁻¹⁵. However, there are also reports of EEG and cellular activity phase-locked to theta in the cingulate cortex¹⁶, perirhinal cortex¹⁷, posterior hypothalamus including the mammillary bodies¹⁸⁻²¹, brainstem reticular formation²², amygdala²³ and inferior colliculus²⁴. If the Kahana findings of widespread neocortical theta reflect the existence of several different generators, this might mean that the theta system in the human is at least as extensive as that found in lower mammals, raising the possibility that the synchronization of cortical neuronal processes to each other and to other brain structures is more widespread than has previously been realized.

A second function of the theta oscillations is to provide a periodic clocking system against which the timing of each spike can be measured. The phase relationship of each pyramidal cell measured against the concurrent theta activity is not constant but can vary from one cycle to the next^{25,26}. As a rat runs through the receptive field of a place cell, the place cell fires bursts of spikes at an interburst frequency slightly higher than that of the concomitant EEG theta. This leads to a precession of the phase of firing to earlier points on each successive cycle (see Fig. 2 A,B). Over the course of the 5-7 theta cycles that comprise the typical place field, the phase of the EEG at which the cell fires might precess through a full 360 degrees, although smaller amounts of precession are also seen. Furthermore, the phase of firing is highly correlated with the animal's location within the place field (more so than with the duration spent in the field). Thus temporal variation in spike firing conveys information about the animal's spatial location.

What are the implications of these roles for theta in the spatial functions of the hippocampus? First, it is clear that the timing of spike firing can convey more information than simply the number of spikes fired per unit time^{27,28}. These findings in the hippocampus are complementary to work on the mammalian neocortex suggesting that the different elements of a percept are bound together by the synchronous firing of the neurons underlying that percept²⁹. Second, some computations performed in the CNS have an internal clock and are not carried out by asynchronous elements as is often assumed. Third, the firing patterns of individual neurones might code for vectors and not scalars, with the one variable being coded by the amplitude of firing (i.e. the number of spikes per unit time) and a second variable coded by the phase of firing. O'Keefe suggested that hippocampal place cells might use a phasor notation in which the amplitude of place-cell firing might code for the proximity of an object or environmental landmark while the phase of firing might code for the angle of the landmark in allocentric or egocentric space^{30,31}. Fourthly, the time of firing might be useful for downstream

computations such as those necessary to extract the directional vector to a goal location³¹.

Role in navigation

The Kahana results also provide further evidence (albeit indirect) supporting the notion that the human hippocampus has an important role in the processing of spatial information, and in particular in supporting a representation of the environment suitable for guiding navigation³². Some studies of patients with damage to the medial temporal lobes show a selective deficit in spatial memory^{33–37}. Functional imaging studies show selective activation of the hippocampus or parahippocampal gyrus during spatial perception, spatial memory and spatial navigational tasks^{38–43}. In one PET study, which required the subject to navigate in a virtual reality environment, it was found that the amount of bloodflow through the right hippocampus was highly correlated with the accuracy of navigation⁴³. However, it is likely that the human hippocampus, and in particular the left hippocampus, is not restricted to purely spatial functions but also serves as the basis for an episodic memory system. This could be accomplished by the incorporation of a temporal component to the basic spatial mapping system, providing for a spatio-temporal framework³². A second enhancement would enable the left human hippocampus to act as the basis for a memory system for narratives through the inclusion of linguistic rather than physical markers for the entities within the map^{32,44}. It will be interesting to see whether the theta-related neural mechanisms of navigation in the rat can be applied to the understanding of human navigation in the first instance, and eventually extended to the understanding of episodic memory.

Acknowledgements

J.O'K. is supported by the Medical Research Council and N.B. by the Royal Society. We thank Mick Rugg for useful suggestions on an earlier draft and John Huxter for help with the figures.

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Using intracranial recordings to study theta

Response to J. O'Keefe and N. Burgess (1999)

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We are indebted to O'Keefe and Burgess for raising the issue of the use of intracranial recordings to study the human theta rhythm [O'Keefe, J. and Burgess, N. (1999) Theta activity, virtual navigation and the human hippocampus *Trends Cognit. Sci.* 3, 403–406]¹. Such recordings from patients with pharmacologically refractory epilepsy provide a unique opportunity for linking spatially distinct patterns of oscillatory brain activity with performance in behavioral tasks. Our recent work used this paradigm to demonstrate task-dependence of theta oscillations in humans during a virtual maze navigation task². In their thoughtful commentary on our work, O'Keefe and Burgess raise a number of important questions¹. Here we will elaborate on those questions, discuss some additional merits of our approach, and highlight some of its special challenges.

Two particularly valuable questions are raised by the preceding article. First, O'Keefe and Burgess quite rightly ask about task specificity: is task-dependent theta specific to spatial learning tasks, or is it a general property of human learning? Although our analyses of intracranial recordings were based on a spatial learning task, other reports using scalp electrodes (e.g. Ref. 3) suggest a role for theta in a variety of symbolic learning and memory tasks. Further evidence for task-related theta in *non-spatial* learning and memory tasks, particularly from direct cortical recordings, would suggest that theta plays a crucial role in the cognitive processes underlying a broad range of learning and memory functions in humans. This would also provide an important link with both *in vivo* and *in vitro* studies that demonstrate clear dependence of the induction of long-term potentiation on theta phase^{4,5}. Second, O'Keefe and Burgess quite naturally wonder to what extent human task-dependent theta, like theta in rodents, is primarily hippocampal. In our study, theta appeared at many of our recording sites, but none of our electrodes were directly in the hippocampal formation, leaving open the question of the source of theta and the possibility

that theta may be generated in multiple regions of cortex.

In an effort to address the specificity of human theta, and to pin down its precise function, we have begun to look at task-dependent oscillatory activity in a variety of other learning tasks. In recent collaborative work with J. Lisman and S. Raghavachari⁶, we found clear evidence for task-dependent theta in Sternberg's probe-recognition-memory procedure⁷. This preliminary evidence, from a single epileptic patient, reveals clear theta oscillations that begin near the onset of the first list item and end near the time of the subject's response. Although we recorded from 128 electrodes bilaterally covering frontal (anterior and orbital) and temporal (anterior and subtemporal) regions, this effect only appeared in a group of 10 electrodes near the inferior frontal gyrus⁶. This finding is consistent with models that implicate theta oscillations in maintaining activity in short-term memory (e.g. Refs 8,9).

In addressing the question of theta localization, it is important to keep in mind that the placement of electrodes is determined by the clinical team in order to identify the site or sites of seizure onset. When the seizure focus is unclear, large numbers of electrodes placed directly on the cortical surface can be especially informative. Because the focus is often in the temporal lobe, there is a sampling bias toward temporal regions. In cases where evidence points to a hippocampal source, depth electrodes are often used. O'Keefe and Burgess emphasize the preponderance of task-dependent theta that we recorded in temporal lobe electrodes. But necessary clinical bias in electrode placement did not allow us to test the hypothesis that task-dependent theta is localized primarily in the temporal lobes, in these three particular patients. O'Keefe and Burgess are correct to point out that our study could not clearly identify the generator or generators of task-dependent theta. Given the significant variability in electrode sampling across patients and the reorganization of cortical circuits that may accompany epilepsy, better

localization will be possible with larger numbers of subjects and with sophisticated source-localization techniques (e.g. Ref. 10).

Although O'Keefe and Burgess acknowledge the clear advantages of subdural recordings over scalp recordings, they stress that depth recording could be of much greater value in localizing the source of theta. We agree that depth electrodes could be of great value; however, it is important to note that depth electrodes record from a more limited and sparsely sampled volume than subdural electrodes and, hence, are often not selected for clinical purposes because they give a 'myopic' view. Selection of electrodes used depends on the potential foci that need to be resolved. Not only can subdural electrodes localize and resolve neocortical seizure foci, our data suggest that they can spatially resolve relevant oscillations. Thus, we find that with our intracranial subdural electrodes, activity in neighboring electrodes (spaced approximately 1 cm apart) can be highly correlated ($r = 0.80$) or quite independent ($r = 0.01$) with respect to the occurrence of task-related theta activity. This is consistent with the subdural electrode spacing being appropriate to resolve the spatial extent of the source or sources of theta. Ultimately, looking at both subdural and depth electrodes (which for ethical reasons must be determined by clinical needs for each patient) in a variety of cognitive tasks may enable us to identify multiple generators of task-related oscillatory activity. In more detailed analyses of our maze-learning data, we have seen that different groups of spatially clustered electrodes, each group exhibiting task-related theta oscillation, can have different characteristic frequencies within the theta range¹¹.

The exciting goal of this line of research is to link theta oscillations (as well as other neuronal activity observable intracranially) to the elemental operations of well-defined cognitive tasks. O'Keefe and Recce's discovery of a link between theta phase and place cell activity in rats, raises the possibility that human theta might be related to learning and/or navigation in very specific ways^{12,13}. Although our maze navigation task did evoke theta and yielded some clear task dependencies, it may be too complex a task at this stage to be decomposed into identifiable subtasks. For example, because subjects are not prevented from planning ahead, the timing of their keyboard responses might not directly reflect the timing of higher (non-motor) cognitive events. As such, this particular task does not lend itself to event-related potential (ERP) analyses.

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