

## Theta returns

Michael J Kahana\*, David Seelig and Joseph R Madsen

Recent physiological studies have implicated theta – a high-amplitude 4–8-Hz oscillation that is prominent in rat hippocampus during locomotion, orienting and other voluntary behaviors – in synaptic plasticity, information coding and the function of working memory. Intracranial recordings from human cortex have revealed evidence of high-amplitude theta oscillations throughout the brain, including the neocortex. Although its specific role is largely unknown, the observation of human theta has begun to reveal an intriguing connection between brain oscillations and cognitive processes.

### Addresses

Volen Center for Complex Systems, Brandeis University, Waltham, MA 02254-9110, USA and Department of Neurosurgery, Children's Hospital Boston, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA;  
\*e-mail: kahana@brandeis.edu

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### Abbreviations

<b>EEG</b>	electroencephalograph
<b>ERPs</b>	event-related potentials
<b>iEEG</b>	intracranial EEG
<b>LTP</b>	long-term potentiation
<b>MEG</b>	magnetoencephalograph
<b>MS-DBB</b>	medial septum/diagonal band of Broca
<b>NMDA</b>	<i>N</i> -methyl-D-aspartate
<b>REM</b>	rapid eye movement

### Introduction

Theta is a 4–8 Hz oscillation that is observed in electrophysiological recordings at many levels of neural organization — from individual pyramidal cells in rodents [1,2] to the synchronous activity of large neural networks, as seen in scalp-recorded electrical signals [3,5,6•].

In this review, we begin by summarizing evidence from studies in rodents that point to theta's role as an important biological rhythm, and to theta's involvement in learning and memory processes. We also discuss studies of human theta that use electrical signals recorded from the scalp. Finally, we turn to recent work using human intracranial recordings that offer an important bridge between studies of animal theta and the indirect evidence for neocortical oscillations provided by scalp measurements in humans.

### Rodent theta

The hippocampal theta rhythm in rat is one of the most well-studied biological rhythms. It appears with striking regularity when the animal engages in exploratory behavior, which includes movement, sniffing and orienting, and in rapid eye movement (REM) sleep [7]. Pioneering work by Vanderwolf [8] demonstrated that rat hippocampal theta can be either tightly coupled to the motor activity and

independent of cholinergic input, or it can be of the type readily blocked by muscarinic antagonists. In the first case, it is modified by environmental inputs, whereas in the second, it is more related to anticipated movement [8].

Hippocampal theta, which can be recorded from local field potentials and can be seen at the frequencies at which individual pyramidal cells fire [9•,10], depends strongly on the inputs that it receives from the medial septum/diagonal band of Broca (MS-DBB). Lesions of MS-DBB both eliminate the hippocampal theta rhythm and induce memory impairment [11]. In contrast, adding muscarinic agonists to MS-DBB increases the activity of hippocampal theta [12], and enhances learning and memory processes [13]. Recent findings suggest that muscarinic agonists might achieve this effect by exciting septohippocampal  $\gamma$ -amino butyric acid (GABA) neurons, which could trigger disinhibition of pyramidal cells via hippocampal interneurons [14].

Theta's functional importance derives from several lines of evidence. First, long-term potentiation (LTP) is highly sensitive to the phase of the theta rhythm, with potentiation favored at the peak of the cycle and depotentiation favored at its trough. This finding, which has been observed both *in vitro* [15] and *in vivo* [16], suggests that theta acts as a windowing mechanism for synaptic plasticity.

If the phase of theta is crucial for LTP, then one might expect that stimulus events would produce a reset or phase shift in ongoing theta. Consistent with this hypothesis, the activity of hippocampal theta appears to be phase locked to stimuli in a working memory condition, but not in a reference memory condition [17]. Viewed in light of the findings of phase-dependent synaptic plasticity, these observations help to explain how important sensory input undergoes neural encoding [18•]. Alternatively, phase reset may explain how patterns of neural activity are maintained in working memory, facilitating the formation of long-lasting synaptic connections [19].

Second, theta appears to play a role in the neural coding of place. As a rat traverses a place field, hippocampal place cells fire at a progressively earlier phase of the ongoing theta oscillation [1,2]. This information significantly improves accuracy in reconstructing the animal's position in space (beyond rate-coded information alone) [20•], providing additional support for the hypothesis that the phase of theta at which cells fire plays an important role in the coding of place information in the rat hippocampus.

Phase precession is not altered by blockade of the *N*-methyl-D-aspartate (NMDA) receptor, though NMDA blockade does prevent experience-dependent place field expansion, a process possibly important for fine tuning

spatial information during learning. This result suggests that the relative phase of theta on which a cell fires may be a fundamental aspect of the spatial code, not dependent on experience [21\*].

Third, theta's functional importance has been demonstrated through attempts to block theta. As mentioned earlier, theta can be blocked by lesioning the medial septum. Such lesions, in addition to blocking theta, produce severe impairments in memory function (e.g. see [22]). Although neither prior learning of spatial information nor hippocampal place representations are impaired by septal lesions, such lesions do impair the acquisition of new spatial information [23]. This evidence suggests that theta has a role in memory, but it is difficult to dissect the specific effect on theta from the concomitant cholinergic loss. Adaptive electric-field feedback, which can accentuate or minimize a specific frequency band in generated field potentials [24], may be used to directly assess the effects of theta manipulation in the rat.

Although most studies of rodent theta have focused on hippocampal theta and its MS-DBB generator, prominent theta activity has been recorded from many extrahippocampal regions, including cingulate cortex, hypothalamus, superior colliculus, entorhinal cortex, perirhinal cortex and prefrontal cortex [25–32]. Because these recordings of theta sample small regions, it is more likely that they reflect the presence of theta generators other than the MS-DBB, rather than the alternate hypothesis of volume conduction from the MS-DBB and hippocampus, which might make theta appear to be generated in regions that are simply conducting signals generated from MS-DBB.

### Oscillatory contributions to scalp-recorded EEG signals

The crucial role of theta oscillations in neural plasticity and information coding, as indicated in the animal studies reviewed above, has sparked interest in the role of theta in human cognition. Human electroencephalograph (EEG) and magnetoencephalograph (MEG) recordings at the scalp have provided a means of investigating theta oscillations in the human brain. Although these recordings have a very low signal-to-noise ratio (relative to direct brain recordings), oscillations can nonetheless be detected at the scalp provided they are synchronous over large regions of cortex and high in amplitude.

Periods of intense cognitive activity may indeed serve to synchronize theta in human cortex. Consistent with this hypothesis, many researchers have observed that theta increases in power during cognitive tasks [7,10,33–35]. For example, theta power increases with memory load during both verbal and spatial *n*-back tasks [34,35]. In these tasks, subjects are presented with a series of items, and must indicate whether the current item matches an item that occurred *n*-items back in the series, thus involving simultaneous encoding, maintenance, and retrieval of information.

Coherence analysis permits the detection of small oscillatory effects by looking for shared variance of signals in the frequency domain. This method has shown significant long-range theta-band coherence between prefrontal and posterior electrodes during the retention interval of both a verbal and a visuospatial working memory task, but not during a perceptual control task [36].

Recent findings suggest that theta synchronization across distant brain regions is characteristic of 'top down' processes (which use higher-level expectations and strategies to coordinate lower level perceptual and encoding processes), whereas gamma synchronization, which was found between more local brain regions, reflects 'bottom-up' processes (the interaction of perceptual inputs that drive higher order mental activities) [37].

If theta is related to synaptic plasticity, as suggested by physiological studies in rats, one might expect to find that increased theta activity during encoding would predict successful retrieval on a test of subsequent memory. Although such an effect has yet to be documented for theta activity *per se*, there have been reports of increased theta-band coherence after the study of items that are later recalled [38,39].

Most scalp EEG and MEG studies do not look at spectral changes that are correlated with cognitive variables. Rather, a majority of studies have focused on the effects of various manipulations on event-related potentials (ERPs) or event-related fields), which represent the average of many EEG (or MEG) signals, temporally aligned at the occurrence of specific stimulus events. These studies show that different cognitive processes are associated with changes in the form of the ERP at different points in time.

There is evidence that certain components of the evoked potential result from the superposition of oscillations that are phase locked to stimulus presentation. In rodents presented with an auditory discrimination task, rare tones associated with water elicit a much stronger and more widespread P300-evoked response than frequent, task-irrelevant, tones [40]. Analysis of oscillatory activity reveals that the maxima of the P300 amplitude — the positive deflection in the ERP that appears between 300 and 400 ms post-stimulus — and theta-frequency power are significantly correlated in all recordings. The connection between ERPs and oscillatory activity is one that is only beginning to be examined in human studies [6\*]. Such investigations hold the promise of integrating these two fields of EEG research.

### Using intracranial recordings to study task-dependent theta in humans

Until very recently, a seemingly insurmountable gap separated the two levels of EEG oscillation analysis described above: on one level rodent studies, which used field potential and single-unit recordings from the

hippocampus; and on the other level human studies, which focused on subtle changes in the scalp-recorded EEG spectrum that result from the modulation of large-scale, synchronous, neocortical oscillations. The failure of human scalp EEG measurements to demonstrate oscillations in raw traces or to show clear theta peaks in spectral distributions led many to question the evidence for the existence of a human theta rhythm.

Intracranial EEG (iEEG) provides a tool for bridging the gap between these two levels of analysis. By measuring the electrical activity generated by much smaller neuronal networks [41], iEEG recordings allow the observation of brain signals that would be invisible at the scalp. Such recordings may be ethically obtained from individuals with pharmacologically refractory epilepsy who are undergoing invasive monitoring for the localization of seizure foci.

Because the clinical procedure of locating seizure foci requires electrode placement on regions that are only thought to be epileptogenic, there are typically far more electrodes covering nonepileptogenic ('control') areas than areas that will eventually prove to be the focus. The high signal-to-noise ratio characteristic of iEEG recordings helps to locate the areas of steep voltage gradients indicative of signal sources in the human brain. Although there have been clinical reports of hippocampal theta using this technology [42–45], only recently has iEEG been used to study task-dependent brain oscillations in well-controlled experiments.

One such experiment extended the finding of theta involvement in rat spatial function by revealing prominent theta oscillations in the human brain during a virtual, 3D-rendered maze-learning task [5]. These recordings showed theta in raw iEEG traces and as large peaks in the power spectra, at numerous cortical sites distributed over many brain regions. The study also demonstrated that during maze navigation, intermittent bouts of theta activity appear with greater probability during longer mazes, even when controlling for degree of mastery [5].

A subsequent study presents a more comprehensive analysis of theta during this maze-learning task [46••]. Refined analytic techniques that allow oscillatory episodes to be compared across frequencies show that the effect of maze length on theta does not reflect the increased difficulty of encoding or retrieval at individual choice points. Rather, it reflects a more global difference between long and short mazes. Unlike theta, gamma power increases with increasing difficulty of individual choices at maze junctions. These studies, in tandem, suggest that theta increases during complex cognitive tasks, but not in a highly specific manner [5,46••].

Recent iEEG studies have found task-dependent theta scattered across many brain locations, even within individual subjects [46••]. These oscillatory patterns were sometimes highly correlated across nearby (1 cm) sites, but were

often only very weakly correlated (S Raghavachari *et al.*, unpublished data). The latter findings suggest that human neocortical theta does not reflect volume conduction from the hippocampus or the MS-DBB, but instead may represent the presence of local generators within cortex. Finding high amplitude neocortical theta in iEEG suggests that theta recorded at the scalp reflects generators near the surface of the brain.

The high amplitude theta activity reported during human maze learning appears very much like the theta seen in rodents during spatial exploration. Some investigators have suggested that these observations may be specific to tasks that involve a spatial component [47]; however, the discovery of rodent theta during non-spatial learning tasks [18,21] and scalp-recorded theta during verbal working memory tasks, as reviewed in this section, suggest that theta may play a far more general role in human cognition.

To test this hypothesis, a recent study examined iEEG recordings during working memory for lists of 1–4 consonants [48•]. At 36 out of 306 cortical sites, the amplitude of theta oscillations increased between two- and ten-fold at the beginning of the trial, remained elevated until the end of the trial, and decreased markedly thereafter. The high signal-to-noise ratio (>100  $\mu$ V) of iEEG recordings made it possible to analyze recordings at the level of individual trials — a feature that is generally not possible with the much weaker (1–10  $\mu$ V) EEG or MEG signals recorded at the scalp. An analysis of the ten sites with the largest amplitude theta revealed that theta activity was roughly continuous for over 90% of the individual trials.

These analyses of iEEG recordings during spatial and non-spatial memory tasks do not necessarily prove there to be a specific involvement of theta in memory function. In every case, it is most parsimonious to see these results as reflecting theta's increase with attention or cognitive control. This interpretation is also generally true of rodent theta and analyses of theta-band power recorded from human scalp EEG signals. What is clear, however, is that theta is a feature of cognitive control across species. This raises the stakes for understanding its role in the physiology of attention, memory and cognition.

In rodents, hippocampal theta activity seen during REM sleep has been linked to processes of memory consolidation [49]. Using iEEG, we can examine whether hippocampal theta is also seen during REM sleep in humans. Indeed, using electrodes with direct contacts in the parahippocampal gyrus along the hippocampal formation, Bódizs *et al.* [50•] have recently observed rhythmic hippocampal activity (1.5–3 Hz) during REM sleep. This pattern of oscillation was not found during waking or other sleep stages, and no other frequency significantly correlated with sleep stages or showed high rhythmicity. Although the frequency of oscillation observed during human REM sleep is slower than that found in rodents, the finding of

REM-specific slow-wave oscillations in humans provides another interesting analog of oscillations found in rodents.

## Conclusions

The past few years have seen increased interest in brain oscillations, and their possible role in perceptual and cognitive processes. The two oscillations that have received the most attention are the theta rhythm (4–8 Hz) and the gamma rhythm (30–50 Hz). In this review, we have summarized the current state of knowledge about the role of theta in memory and cognition by linking rodent and human work. Studies in rodents have clarified theta's involvement in neural plasticity [15,16] and information coding [1,2,17]. These studies, in particular, have demonstrated the importance of the phase relations between theta activity, as seen in the field potential and single-unit activity.

Until recently, theta's involvement in primate [51], and especially human, cognition had been a subject of considerable debate [47]. Although the spectral properties of scalp-recorded EEG signals had been studied for many years, there was little evidence that these properties reflected the presence of high-amplitude oscillations in the brain. In particular, scalp-recorded signals would not allow the observation of oscillations in deep brain structures, such as the hippocampus. Recent studies using implanted depth and cortical surface electrodes in humans has changed this situation by demonstrating a task-related high-amplitude activity of theta. These studies have shown that theta increases during both verbal and spatial memory tasks. Furthermore, human theta does not appear to be restricted to hippocampal sites, but rather appears over widespread regions of neocortex. These neocortical theta oscillations, when synchronized over large regions, may account for the changes in oscillatory power that can be observed using non-invasive scalp EEG techniques.

Despite this progress, there is still much to be learned about the precise behavioral correlates of the theta rhythm. It is unlikely, for instance, that theta has a single role in cognitive function. Theta in different neuronal networks may reflect the different types of information processing for which those networks are specialized. Furthermore, it may be that theta's role can best be seen in its varying patterns of coherence as a function of task demands and in its relationship to other brain rhythms, such as gamma. Finally, studies in rodents suggest that information is carried by the phase of the theta rhythm. Analyses of the relationship between theta and stimulus events may provide a bridge between the analysis of task-related oscillations and evoked potentials [40]. All of these issues remain largely unexplored in relation to human cognition.

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