

Reading the hippocampal code by theta phase-locking

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Both the prefrontal cortex and the hippocampus are crucial for memory encoding and recall. However, it remains unclear how these brain regions communicate to exchange information. Recent findings using simultaneous recordings from the hippocampus and prefrontal cortex of the behaving rat have demonstrated that prefrontal cells' firing is phase-locked to the hippocampal theta rhythm. This suggests that phase synchronization clocked by the theta rhythm could be crucial for the communication between hippocampal and prefrontal regions.

It is well established that the hippocampus plays an essential role in the encoding of new episodic information whereas the prefrontal cortex (PFC) has been shown to undertake executive operations in working memory and episodic memory tasks. This is supported by lesion and brain imaging studies [1,2]. It is therefore highly likely that successful memory operations require the exchange of information between the hippocampus and PFC; however, the dynamics of the mechanism responsible for the communication remains unknown. In a recent paper Siapas *et al.* [3] performed simultaneous recordings in PFC and the hippocampus in behaving rats. They found that a large proportion of prefrontal cells fires phase-locked to the hippocampal theta rhythm (5–10 Hz) (Figure 1). This finding suggests that phase synchronization clocked by theta oscillations could play an important role in controlling the neuronal dynamics required for the communication between memory structures.

Simultaneous measurements of prefrontal and hippocampal cells

In their study Siapas *et al.* implanted tetrodes [4] in the medial PFC and the CA1 subfield of four rats. This allowed the researchers to measure spiking activity from 411 hippocampal and 316 prefrontal cells in total. They also recorded local field potentials (LFPs), which allow the detection of population activity like the theta rhythm. Although a large fraction of hippocampal cells have been shown to exhibit place-specific firing (hence 'place cells') [5], much less is known about cells in PFC. Also, spontaneous theta activity is typically not seen in the LFP of PFC. Siapas *et al.* correlated the firing of the prefrontal cells with the phase of the hippocampal theta rhythm. Surprisingly, they found that ~40% of the prefrontal cells fired phase-locked to the hippocampal

theta rhythm (Figure 1). Given that the firing of both the hippocampal and prefrontal cells is phase-locked to the theta rhythm, it should also be possible to observe a correlation in the spike time of the two groups of neurons. This was confirmed by calculating the cross-covariance between the two groups of neurons. About 10% of the PFC neurons fired phase-locked to the population firing of hippocampal neurons. The cross-covariance function also makes it possible to assess temporal directionality by asking whether the firing in the hippocampus correlates with slightly delayed firing in the PFC, or vice versa. The authors showed that the firing of hippocampal cells on average preceded the prefrontal firing by ~50 ms (Figure 1). This supports the notion that information flows mainly from the hippocampus to PFC.

A role for theta phase coding?

Although the results of Siapas *et al.* provide evidence of information flowing from the hippocampus to PFC, the findings do not directly address the nature of the neuronal code being exchanged. The relationship between place cells and the hippocampal theta rhythm has been the subject of many studies. It is well established that as a rat enters a place field, the respective place cell fires late in the theta cycle. As the rat progresses through the place field, the firing advances to earlier and earlier phases (Figure 2a) [6]. This so called 'theta phase precession' has led to the notion of phase coding, namely that information is represented by the phase at which a cell fires. Indeed, it has been demonstrated that when estimating a rat's position from the firing of multiple place cells alone, the accuracy of estimation can be improved by up to 40% by taking the theta phase of firing into account [7]. Experimental data suggest that late firing in the theta cycle predicts upcoming positions on the rat's path whereas early firing in the cycle represents the rat's current position [8]. Thus, according to this scheme the firing of place cell 2 (Figure 2a) in the 6th theta cycle reflects a prediction of the rat's position 5–6 cycles later. The firing of cell 1 on cycle 8 reflects the rat's actual position.

If one accepts the notion of theta phase coding, the next question to ask is how structures receiving hippocampal inputs make use of the phase-coded firing patterns. One simple requirement is that the receiving structure also receives information about the hippocampal theta rhythm. In a theoretical paper, a model has been proposed that explores a physiological mechanism for decoding phase-encoded information from firing patterns arising

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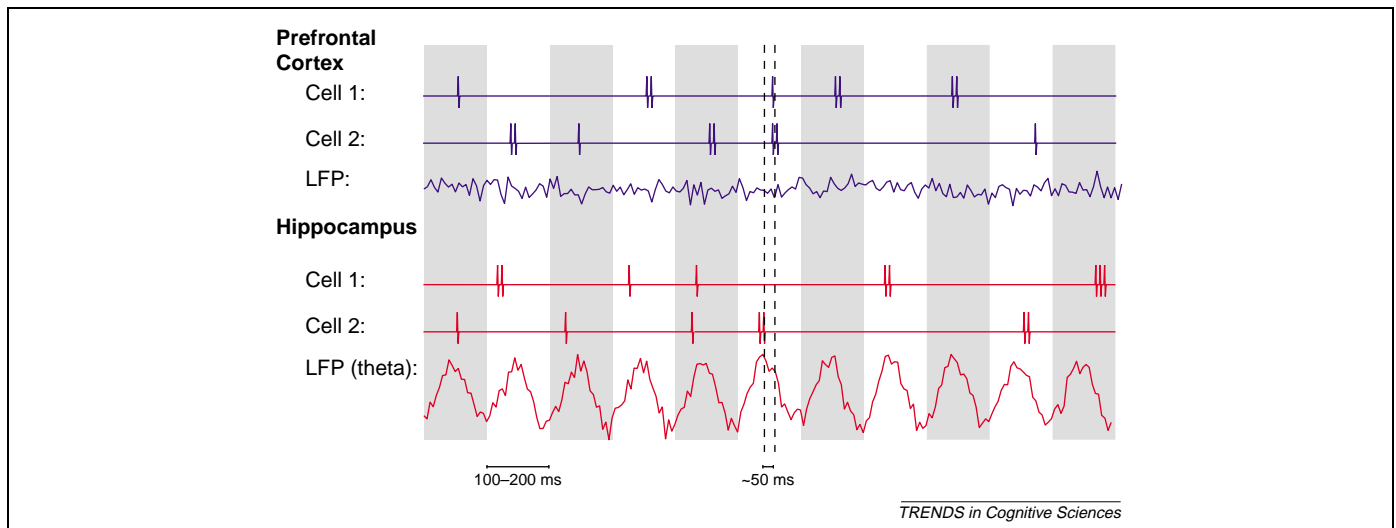


Figure 1. Prefrontal cortical cells fire phase-locked to the hippocampal theta rhythm (schematic illustration of the experimental findings of Siapas *et al.* [3]). Single unit activity was recorded from both prefrontal (blue) and hippocampal cells (red) simultaneously, together with the local field potentials (LFPs). Only the hippocampal LFP was dominated by strong theta oscillations. Hippocampal cells tended to precede the firing of prefrontal cells by ~ 50 ms.

from the theta phase precession [9]. The decoding network functions as follows: decoding neurons receive a subthreshold theta input together with afferent inputs from the hippocampus (Figure 2b). Only if the timing of the hippocampal input coincides with a theta peak does a neuron in the decoder fire. By changing the phase of the theta input, the decoding neurons will be sensitive to hippocampal firing from different phases of the theta cycle. In short, the model predicts that neuronal firing in the decoding network will fire phase-locked to the hippocampal theta rhythm. This prediction is consistent

with the findings of Siapas *et al.* [3]. The PFC is one of several regions that could serve as a phase decoder. Multiple other regions also have neuronal activity phase-locked to the hippocampal theta rhythm (see [10,11] for reviews), including the cingulate cortex, entorhinal cortex, the mammillary bodies and the anterior nuclei of the thalamus.

Taking the notions of phase coding and decoding for granted one could speculate on the concrete role of such a scheme for neuronal processing. One simple possibility is that the information flowing from hippocampus to PFC is

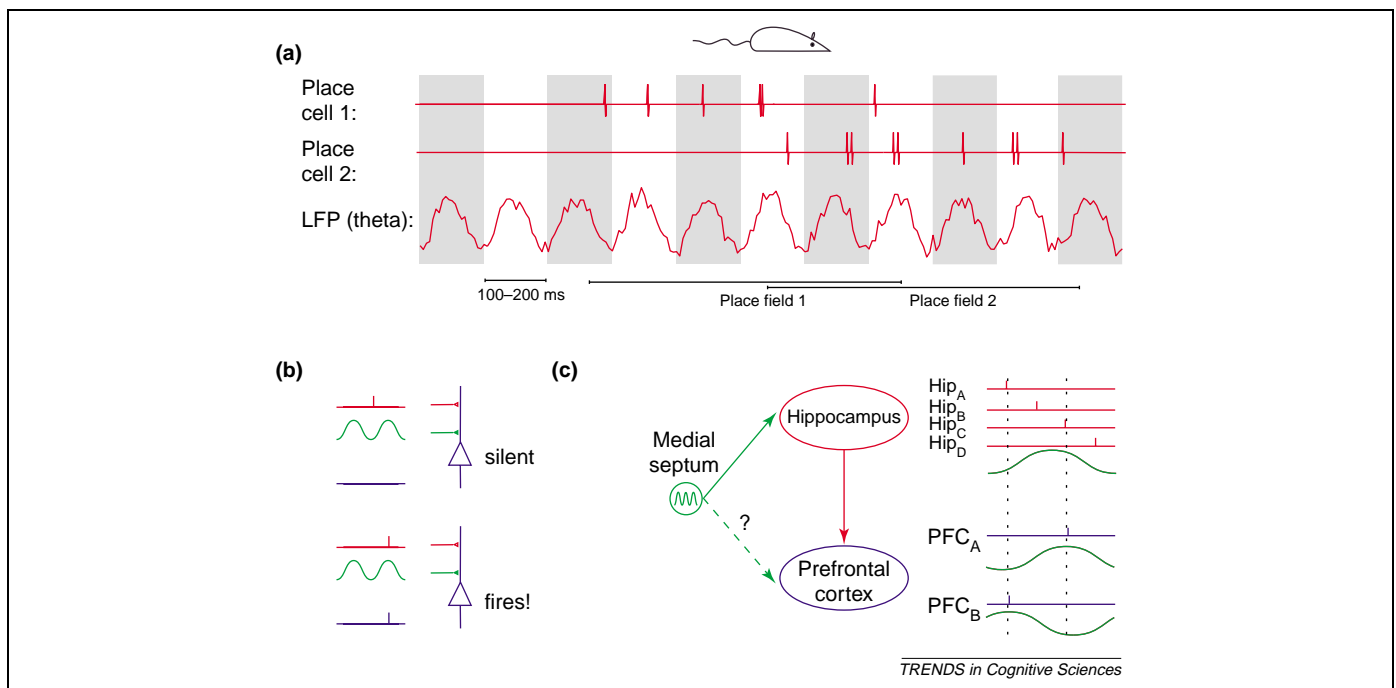


Figure 2. (a) The theta phase precession of hippocampal place cells in the rat. A given place cell fires when the rat is in a specific region of the spatial environment. When the rat enters this place field, the firing occurs late in the theta cycle. As the rat progresses, the phase of firing advances to earlier phases [6]. This phenomenon has led to the notion of phase coding. (b) A simple mechanism for phase decoding. The neuron fires (blue) when an afferent input (red) coincides in time with the peak of a depolarizing oscillatory input (green) [9]. (c) Exchange of phase coded information between the hippocampus and PFC. In the particular example, the prefrontal cell PFC_A will be driven by hippocampal firing late in the hippocampal theta cycle (Hip_C) whereas cell PFC_B will be driven by hippocampal firing at early phases (Hip_A). A theta input to PFC phase-shifted with respect to the hippocampal theta input determines which firing patterns are transmitted. This principle allows different neuronal populations in PFC to integrate hippocampal firing patterns dependent on the phase of the theta input to PFC [9].

being gated by turning on and off the phase locking. Another possibility is that PFC filters relevant information by systematically integrating firing patterns from specific phases of the theta rhythm, depending on the task the rat is performing [9] (Figure 2c). Whatever the actual mechanism, the findings of Siapas *et al.* open up the possibility that communication and information processing involving the hippocampus and PFC is achieved by the exchange of phase coded information.

Open questions

The experimental findings by Siapas *et al.* lead to several new questions that deserve to be addressed experimentally. For example, the phase locking of PFC neuronal firing to the hippocampal theta rhythm was found in rats performing a variety of spatial tasks. It would be interesting to know if specific parameters of the tasks predict the degree of phase locking: for instance, is the phase locking more prevalent during recall than during encoding? Another important question pertains to the hippocampal theta phase precession. Given that it is a highly robust phenomenon in the hippocampus, could one also identify task parameters that correlate with phase specific firing in PFC? Interestingly, theta activity was not identified in the LFPs of PFC. This is surprising given the strong theta modulation of the prefrontal cells. One explanation might be that the spatial arrangement of the PFC pyramidal cells is such that their fields do not summate; however, the question deserves to be experimentally addressed. One last question relates to the theta modulation of PFC cells. The hippocampal theta activity is clocked by a phasic drive from the medial septum [10]. Is the theta modulation in PFC a consequence of the hippocampal input or is it paced by other structures (e.g. the basal forebrain [12])?

The findings reported by Siapas *et al.* suggest that theta activity is important for setting up the functional connectivity between hippocampus and PFC. The mechanism might generalize to other brain structures in both humans and animals. It is possible that functional connectivity between brain structures involved in memory processing can be assessed by measures of phase-locking in the theta band. This is directly testable in humans using electrophysiological measurements such as EEG and MEG in healthy subjects and intracranial recordings in epileptic patients. Indeed theta activity in humans

has been found to relate to episodic encoding and retrieval [13,14]. However, there is much work to be done in the investigation of theta phase-locking between brain structures.

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Feelings you can't imagine: towards a cognitive neuroscience of alexithymia

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