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## Behavioral significance of hippocampal theta oscillations: looking elsewhere to find the right answers

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**Young CK.** Behavioral significance of hippocampal theta oscillations: looking elsewhere to find the right answers. *J Neurophysiol* 106: 497–499, 2011. First published May 11, 2010; doi:10.1152/jn.00358.2011.—The function of hippocampal theta oscillations has been subjected to constant speculation. Dynamic coupling of theta field potentials and spiking activity between the hippocampus and extra-hippocampal structures emphasizes the importance of theta-frequency oscillations in global spike-timing precision in the brain. Recent advances in understanding theta coupling between distant brain structures are discussed and explored in this article.

brain; theta coupling

THETA OSCILLATIONS ARE PROMINENT local field potential signals recordable in many parts of the brain, particularly in the rodent hippocampus. Many support the notion that theta oscillations, as well as other forms of brain oscillatory activity, may participate in contextual binding and the exchange of information in the brain to allow emergent properties such as complex behavior and cognition to occur. Accumulating evidence has shown that structures outside of the hippocampus exhibit locally generated theta oscillations, and these oscillations may undergo coupling with the hippocampus during specific epochs of behavior. However, very little effort has been focused on the cellular correlates of such transitions. Over the past year, significant contributions from different laboratories have provided insights to the importance of theta oscillations within and beyond the hippocampus, and how theta rhythms mediate the exchange in information with other regions of the brain in a behaviorally meaningful manner.

The seminal account of hippocampal theta oscillations by Green and Arduini (1954) triggered the surge of interest on the subject. With more than five decades of studying theta oscillations in the hippocampus, many more behavioral correlates have been described (see Buzsáki 2005 for a review), yet there is no consensus regarding the behavioral relevance of hippocampal theta oscillations. Robert Miller proposed that theta oscillations are crucial in the coordination of behavior through cortico-hippocampal dialogues (Miller 1991). The evidence for cortico-hippocampal interactions through theta oscillations was scarce at the time, with many accounts of recordings outside of the hippocampus deemed to be solely volume conducted from the hippocampus itself. The interest in cortico-hippocampal interactions through theta oscillations was rekindled when Siapas and colleagues (2005) documented the en-

trainment of prefrontal cortical neurons to ongoing hippocampal theta oscillations, which was later found to be correlated with decision making (Jones and Wilson 2005). At around the same time, behavior-dependent theta coupling between the hippocampus and many other brain regions, such as the amygdala (Seidenbecher et al. 2003), was also described in the literature. These observations have revitalized the quest to understand the role of theta oscillations in the hippocampus, as well as their role in other brain areas where theta field potential and entrained cell activity can be recorded.

In many studies it has been reported that extra-hippocampal theta oscillations can occur independently of hippocampal oscillations, and vice-versa, in brief periods. These observations suggest that brain regions which oscillate at theta frequencies do not do so in an all-or-none fashion; therefore, mechanisms must exist to control not only periods of oscillatory synchrony in local circuits, but also how interregional oscillatory synchrony waxes and wanes as a function of behavior. For example, it is known that when rats need to make a correct choice in a T-maze working memory task, theta oscillations in the hippocampus and the prefrontal cortex can become synchronized, with prefrontal cell activity also entrained to ongoing hippocampal theta oscillations (Jones and Wilson 2005). The described interaction has been implicated in the transfer of information from the hippocampus to the neocortex as part of the consolidation process. However, it has also been reported that hippocampo-prefrontal theta coherence can be observed during spontaneous behaviors in the open field, increasing between behavioral transitions from immobility to ambulation, with further increases during rearing (Young and McNaughton 2009). So, does hippocampo-prefrontal synchrony reflect some internal construct such as attention, or does it reflect an experience-dependent process that establishes hippocampo-cortical Hebbian ensembles? The recent study by Benchenane and colleagues (2010) set out to answer these questions by recording ensemble and field potential activities from the medial prefrontal cortex of the rat, while correlating these recordings with simultaneously recorded field potentials from the intermediate/ventral hippocampus, which directly projects to the medial prefrontal cortex. The authors were able to show that a Y-maze-based choice task evokes hippocampo-prefrontal synchrony in the central arm, prior to the decision making point, as shown previously (Jones and Wilson 2005). They were able to further the observation by demonstrating that when a new rule had to be learned, theta coherence between the hippocampus and prefrontal cortex increased. The increased synchronization is reflective of synchronization at the single cell level, where the phase preference and entrain-

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ment increased after the acquisition of the new rule. Importantly, not all cells displayed this increased entrainment to theta oscillations. The selective population of pyramidal cells that were entrained by theta oscillations appear to form a functional ensemble that displays increases in correlated activity during theta coherence, increased probability of correlated firing after learning a new rule, and preference of coreactivation during sleep. To examine how hippocampal inputs entrain prefrontal theta coherence at the single cell level, the authors used parameters based on spike waveforms they recorded to classify whether the recorded cells were presumed principal cells or interneurons. Consistent with the idea that interneurons shape local network activities, the authors found that the presumed prefrontal interneurons always fired action potentials at the same hippocampal theta phase during periods of high or low theta coherence. Instead, the presumed pyramidal cells converged to the same hippocampal theta phase preference in response to transition from low to high theta coherence, suggesting that the increased spike-to-field coupling was due to an increase of pyramidal cell entrainment.

If the increase in theta coherence is related to an increased entrainment of presumed principal cells but not local interneurons, is the increased pyramidal entrainment due to increased synaptic input from the hippocampus? Or is another mechanism at play that can account for such an increase? Since the behavioral task in the study is reward based, Benchenane et al. (2010) hypothesized that the reward-related release of dopamine may drive theta neural synchrony. Remarkably, dopamine injection in anesthetized animals brought on the same changes observed in behaving animals when they transitioned into the decision area, increased theta synchrony and the entrainment of pyramidal cells through phase reorganization without modification of interneuron response. With virtually no change in theta power recorded from either structure, it is perhaps reasonable to assume that dopamine did not change the net synaptic currents at theta frequencies in either structure. Then, it is likely that dopamine-mediated changes are modifying how pyramidal cells respond to interneuronal modulation but not increasing afferent synaptic inputs, since there was no detectable increase in theta entrainment of local interneurons and no changes in local theta oscillation power.

In this single study, Benchenane and colleagues (2010) were able to demonstrate that increases in theta oscillation coupling between the hippocampus and the prefrontal cortex can be experience dependent and are gated by the neuromodulator dopamine. Hippocampal input to the prefrontal local interneurons appears to provide theta rhythmic inhibition and the selective synchronization of specific principal cell ensembles during periods of increased dopamine. This selective recruitment of principal cells during decision making is strengthened by reactivation during slow-wave sleep, providing support for the formation of a cortico-hippocampal Hebbian ensemble.

As mentioned, the hippocampus and the prefrontal cortex are only two of many brain structures that exhibit theta oscillation and entrained cell activities. The amygdala also exhibits theta oscillations that become coherent with hippocampal theta oscillations during conditioned freezing in fear-conditioning paradigms (Seidenbecher et al. 2003). Specifically, it was demonstrated that hippocampal and lateral amygdala theta oscillations became highly correlated during the presentation of the conditioned fear stimulus, which elicited freezing be-

havior. Do the hippocampo-amygdalar theta interactions mirror those observed between hippocampo-prefrontal interactions? Popa and colleagues (2010) examined hippocampal, amygdalar, and prefrontal theta field potential synchrony in a fear-conditioning paradigm. Recordings were made before and after the conditioning, across different behavioral states, including sleep. The authors found intermittent coherent theta oscillations and field potential entrained theta-rhythmic spiking across all structures examined. When correlating theta coherence across all examined structures with the strength of foot-shock conditioning, it was shown that increases in coherence were selectively increased during paradoxical sleep between the amygdala and the hippocampus or the prefrontal cortex, but not between the hippocampus and the prefrontal cortex. Using a multivariate approach, Popa and colleagues applied Granger causality analysis to examine possible dynamic interactions between coherent theta oscillations recorded from the structures of interest. Granger causality analysis is a way to estimate how much predictive value one signal holds over another; hence, it is a statistical method that provides clues to the directionality of interactions between areas. By using this approach, the authors reported that, as a general rule, hippocampal theta oscillations seem to drive theta oscillations in the basolateral amygdala and the prefrontal cortex. However, when the directionality of theta interaction during paradoxical sleep was examined based on the amount of freezing during fear recall tests across all animals, it appeared that the hippocampus preferentially drives the basolateral amygdala, which then in turn drives the prefrontal cortex at theta frequencies without detectable correlates between hippocampo-prefrontal interactions.

The results from Popa et al. (2010) show the consolidation of fear-related memory may be preferentially cemented during paradoxical sleep rather than slow-wave sleep, and such interaction may be initiated from the hippocampus, relayed through the amygdala, and finally routed to the prefrontal cortex. However, only theta frequency interactions were investigated in this study; therefore, it is possible that hippocampo-prefrontal interactions during sleep may occur selectively during sharp wave/ripple activities, which may also contribute to the consolidation of long-term fear memories (Benchenane et al. 2010; Quinn et al. 2008). These results also suggest that apart from dopamine, other neuromodulators and/or mechanisms may be involved in gating theta synchrony in general, since at least during paradoxical sleep, increased hippocampo-amygdalar or amygdalo-prefrontal theta synchrony can increase independently of hippocampo-prefrontal interactions which appear to be dependent on dopamine.

As the two discussed studies have shown, to truly understand the functional significance of hippocampal theta oscillations in the context of brain circuitries, it is important to understand how oscillatory coupling is regulated and controlled among all components of a functional circuit. To achieve this, novel techniques to perturb neuromodulator transmission and ways to simultaneously sample from many structures from a functional circuit is necessary. Dzirasa and colleagues (2010) have pioneered this approach by developing transgenic animals with impaired neuromodulator transmission and obtaining multisite recordings using a multi-electrode array. In their most recent report, a noradrenergic depletion in freely moving mice was achieved by injecting a drug that

inhibits catecholamine synthesis into a transgenic line that lacked noradrenaline transporter. Using this approach, the authors were able to reduce the availability of noradrenaline in the animal to <5% compared with wild-type animals. With this manipulation and recording from 10 interconnected structures in the mesolimbic circuitry, the authors show complex, bidirectional changes in single-unit firing rates, as well as theta and delta oscillatory coherence between the recorded areas. These observed changes were coupled with behavioral anomalies such as hyperactivity and stereotypy. Remarkably, treatment with noradrenergic precursors or catecholamine reuptake inhibitors attenuated some of the behavioral abnormalities, as well as partially reversed delta/theta coherence changes in select mesolimbic circuits examined brought on by the noradrenergic depletion challenge. Although the relationship between single-cell and field potential activities in these areas and the changes induced by noradrenergic depletion were not examined, the study demonstrates that it is possible to probe the role of modulators in gating-coupled activities simultaneously in many distant but functionally interacting circuits.

Collectively, these studies suggest that neuromodulators play a crucial role in gating theta-related coupling between brain structures across different behavioral states. The flexibility and control of interregional theta coupling mediated by neuromodulators may underlie the fast dynamics of consciousness and cognition. Of course, the assumption that field potential level coupling is meaningful is based on its usefulness as a measure of local ensemble activity. Volume conduction can be problematic when recording from neighboring brain areas or in the vicinity of a strong oscillatory current source (Sirota et al. 2008); hence, it is of great importance to demonstrate a clear and robust spike-to-field relationship to demonstrate the relevance of local field potential as a second order measure of local ensemble activity (e.g., Popa et al. 2010), especially if such relationships have not been demonstrated previously. Even when these relationships are established, it is important to elucidate what activity changes are brought upon the different cell types in the recorded ensemble to understand the cellular relevance of oscillatory coupling in behavior (e.g., Benchenane et al. 2010).

These recent advances in hippocampal theta oscillation research have allowed us to truly integrate and understand the function of the hippocampus as part of the brain, instead of looking at it as an omnipotent integrator that is assumed to carry out all higher order functions of the brain. The characterization of new brain regions that also oscillate at theta frequencies is a growing field of research. It is likely that as more studies on behavioral correlates of theta coupling across structures emerge, more behavioral correlates will be found for increased theta coherence between the same structures, as has been done in the hippocampus. Then, efforts must be focused

on examining how theta coupling is gated, modulated, and coordinated among structures involved to understand how brain states emerge. Of equal importance, understanding how the activity of different cell types change in relation to the ongoing field potential as a function of the strength of interregional coupling will reveal the role of local computation during whole brain synchronization. The papers mentioned here represent the first important step towards the goal of not only understanding the significance of the hippocampal oscillations, but also technical and theoretical advances that could provide a clearer picture as to how information is exchanged and processed in the brain.

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#### DISCLOSURES

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