Behavioural significance of hippocampal theta oscillations: Looking elsewhere to find the right answers

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Abstract

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 review.
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 behaviour 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 behaviour. 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 behaviourally 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 behavioural correlates have been described (see Buzsaki 2005 for a review), yet there is no consensus regarding the behavioural relevance of hippocampal theta oscillations. Robert Miller proposed that theta oscillations are crucial in the coordination of behaviour 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 re-kindled when Siapas and colleagues documented the entrainment of
prefrontal cortical neurons to ongoing hippocampal theta oscillations (Siapas et al. 2005), which was later found to be correlated with decision making paradigm (Jones and Wilson 2005). At around the same time, behaviour-dependent theta coupling between the hippocampus and many other brain regions, such as the amygdala (Seidenbecher et al. 2003), were 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 independent 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 inter-regional oscillatory synchrony waxes and wanes as a function of behaviour. 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 behaviours in the open field, increasing between behavioural transitions from immobility, ambulation to 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 entrainment 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 co-reactivation 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 behavioural 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 anesthetised animals brought upon 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 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 re-activation 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 becomes 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 behaviour. Do the hippocampo-amygdalar theta interactions mirror those observed between hippocampo-prefrontal interactions? Popa and colleagues examined hippocampal, amygdalar and prefrontal theta field potential synchrony in a fear conditioning paradigm (Popa et al. 2010). Recordings were made before and after the conditioning, across different behavioural states, including sleep. The authors found intermittent coherent theta oscillations and field potential entrained theta-rhythmic spiking across all structures examined. Correlating theta coherence across all examined structures with the strength of footshock 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 independent 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 amongst all
components of a functional circuit. To achieve this, novel techniques to perturb
neuromodulator transmission and ways to simultaneously sample from as many structures
from a functional circuit is necessary. Dzirasa and colleagues have pioneered this
approach by developing transgenic animals with impaired neuromodulator transmission
and obtaining multi-site 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 (Dzirasa et al. 2010). Using this approach, the authors were able to reduce the
availability of noradrenaline in the animal to <5% compared to wild-type animals. With
this manipulation and recording from ten interconnected structures in the mesolimbic
circuitry, the authors show complex, bi-directional changes in single unit firing rates, as
well as theta and delta oscillatory coherence between the recorded areas. These observed
changes were coupled with behavioural anomalies, such as hyperactivity and stereotypy.
Remarkably, treatment with noradrenergic precursors or catecholamine re-uptake
inhibitors attenuated some of the behavioural abnormalities, as well as partially reversing
delta/theta coherence changes in select mesolimbic circuits examined brought upon by
the noradrenergic depletion challenge. Although the relationship between single-cell and
field potential activities in these areas and the changes induced by noradrenergic
deposition 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 behavioural states.
The flexibility and control of inter-regional 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 neighbouring 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 in order to understand the cellular relevance of oscillatory coupling in behaviour (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 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 behavioural correlates of theta coupling across structures emerge, more behavioural 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 are gated, modulated and coordinated amongst structures involved in order 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 inter-
regional coupling will reveal the role of local computation during whole-brain
synchronization. The papers reviewed 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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