The medial entorhinal cortex keeps Up

David Dupret & Jozsef Csicsvari

A study reveals that medial entorhinal cortex layer III spiking dynamics shape the neocortical-hippocampal dialog during Up-Down state fluctuations in slow-wave sleep that may contribute to memory consolidation.

Higher order functions rely on cooperative computations of multiple brain regions. Understanding how these spatially distributed neuronal circuits work together remains an important question. Neocortical-hippocampal interactions lay the foundation of information processing for several forms of memory[1,2]. During slow-wave sleep, when memory consolidation is thought to occur, neocortical networks spontaneously fluctuate at slow frequencies between persistently active Up states and quiescent Down states[3]. However, as the hippocampus is only weakly tied to this Up-Down state–related neocortical activity, how might activity be synchronized across circuits? A study by Hahn and colleagues[4] in this issue of *Nature Neuroscience* provides a clue to resolving this paradox. The study identifies the medial entorhinal cortex (MEC), where layer III neurons often continue to fire during cortical Down states, as the source of neocortical-hippocampal decoupling. This neuronal response excites hippocampal circuits at times when neocortical neurons are silent, suggesting that the MEC firing described may gate the information flow needed for the consolidation of different types of memories.

The hippocampus receives highly processed information from the neocortex and can therefore act as a hub for certain types of memories. It is thought that the hippocampus coordinates memory consolidation by replaying information during sleep[5,6]. Given that the hippocampus indirectly receives a major source of excitatory inputs from the neocortex, one might expect coordinated neocortical firing to correspond to similar levels of hippocampal synchrony. However, neocortical-hippocampal circuit interactions during slow-wave sleep do not work this way. Although Up-Down state fluctuations represent the dominant neocortical network pattern during slow-wave sleep, the hippocampus exhibits only brief periods of excitation, which are weakly tied to the neocortical Up state. Hahn *et al.*[4] found that the source of this desynchronization lies upstream, in the MEC. Here, layer III neurons exhibit persistent excitatory activity that spans several cycles of the neocortical Up-Down state, skipping entire Down states. As the entorhinal cortex stands as the main gateway between the neocortex and the hippocampus, the persistent excitation of MEC layer III neurons appears to drive the activation of neurons in the CA1 region of the hippocampus during cortical Down states, even though neocortical neurons are silent at that point.

Hahn and colleagues[4] measured *in vivo* both the intracellular membrane potential of entorhinal cortex neurons in mice during Up-Down states and local field potentials in parietal neocortex. Consistent with previous work, they found that membrane potentials of MEC and lateral entorhinal cortex (LEC) layer III neurons exhibited Up-Down state fluctuations. Critically, the depolarization of MEC layer III pyramidal neurons often outlasted the neocortical Up states over several Down states, although the onset of their depolarization remained coupled to the neocortical Down-to-Up transitions with some delay (**Fig. 1**). Moreover, this effect was restricted to the MEC; the membrane potential of LEC layer III neurons closely matched the neocortical Up-Down state. This persistent MEC layer III activity was also found to drive downstream hippocampal multi-unit activity recorded in CA1. CA1 responses exhibited even longer delays relative to the Down-to-Up state transitions than those of MEC neurons. Unexpectedly, CA1 activity was occasionally even further boosted during Up-to-Down state transitions in association with persistent activation of MEC layer III cells. Notably, these effects were observed not only under anesthesia, under which cortical Up-Down states have been primarily studied, but also during natural sleep.

The persistent Up states and delayed Up-to-Down transitions were observed for both pyramidal and nonpyramidal neurons in MEC layer III. Moreover, the persistent Up activity did not vary with the dorso-ventral location of the neurons, even though MEC superficial layer neurons exhibit changes in their membrane potential properties along this axis[7]. These findings suggest that the Down-state skipping behavior is a network phenomenon and not directly driven by the intracellular properties of single cells. Indeed, previous *in vitro* work in acute brain slices has shown that isolated circuits of both neocortex and MEC can generate

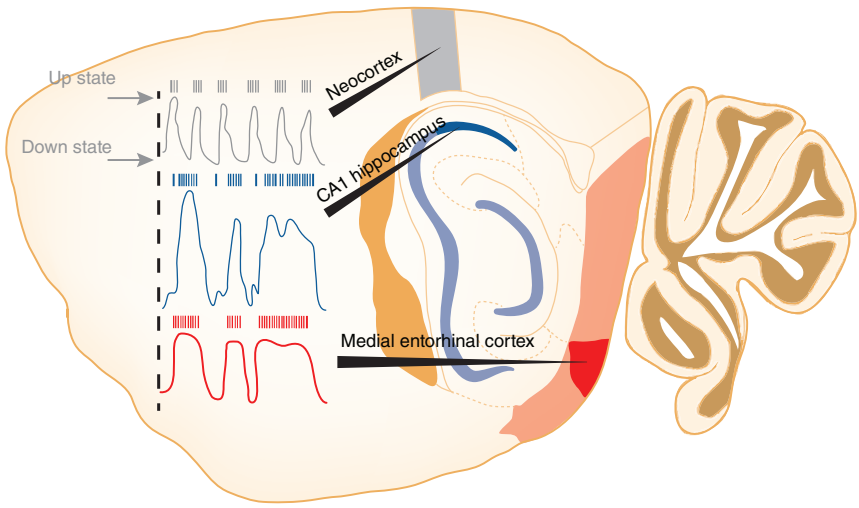

Figure 1 MEC layer III neurons exhibit persistent Up states. Illustration showing the Up-Down state fluctuations of the neocortical local field potential, the membrane potential of a layer III MEC neuron and the envelope of summed CA1 hippocampal multi-unit activity. Rasters illustrate spike times in these three regions. The location of different brain regions is illustrated on a sagittal section of a mouse brain.

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synchronized Up-and-Down states[3,8,9]. The findings of Hahn *et al.*[4] therefore suggest that both neocortex and MEC can act as rhythm generator circuits for cortical slow oscillations. The mechanism underlying the synchronization of cortical slow oscillations has been an important question in the field of network physiology[3,10]. One idea is that transitions between Up and Down states propagate as traveling waves across partially coupled oscillators. However, the work by Hahn *et al.*[4] argues against this scenario, as it suggests that the MEC generator can gain independence from the neocortical generators by skipping Down states. It is also possible that other cortical generators may show similar decoupling, thereby making the temporal dynamics of slow oscillations more complex.

Whether the decoupling effect of the MEC on cortical slow oscillations is restricted to the hippocampus or occurs elsewhere remains unknown. Such MEC-related decoupling may also extend to other cortical structures, such as the postrhinal cortex. But what is the functional role of such a release? And how can a hippocampal dialog during neocortical Down states be beneficial? Many MEC neurons exhibit firing patterns that are spatially tuned to the location of the animal in its environment, whereas most neurons in the LEC display a weak spatial selectivity that indicates the possible influence of nonspatial sensory inputs[11–13]. Because of this, it has been suggested that MEC-postrhinal-retrosplenial cortices may represent a spatial information stream, whereas the LEC-perirhinal-anterior cingulate cortices may represent a nonspatial information pathway[14,15]. Thus, during active waking behavior, CA1 hippocampal neurons may encode a combination of spatial and nonspatial information through the integration of MEC and LEC inputs, respectively. However, during off-line periods, at times when memory traces are thought to be consolidated, the temporal dynamics between the LEC Up-Down states and the MEC persistent Up states might differentially channel the reactivation of spatial and nonspatial memory traces.

Hippocampal sharp wave ripple (150–250 Hz) events have been implicated in the reactivation of waking firing patterns and memory consolidation[5]. In light of the study from Hahn *et al.*[4], hippocampal sharp wave ripple events during neocortical Down states might favor the reactivation of spatial information, whereas those in the Up states might act to bind space and events. This would provide a mechanism that emphasizes spatial information at times when the hippocampus is decoupled from the neocortex and allows the selective communication of cortical areas involved in the spatial information stream. Such regions could include the postrhinal and the retrosplenial cortices, if these regions prove similarly capable of decoupling from neocortical Down states via MEC-moderated influence. In contrast, sharp wave ripple events that occur during neocortical Up states could enable the integrated binding of spatial and nonspatial information by simultaneously recruiting not only the spatial stream but also the nonspatial stream. This hypothesis is but one example of how the work of Hahn *et al.*[4] could stimulate pertinent follow-up work to test the influence of MEC Down-state skipping on other cortical areas and eventually reveal its broader function. Further work could also investigate whether reactivation patterns are different during neocortical Up and Down states to test whether the possible binding of spatial and nonspatial information occurs in the hippocampus or only in higher cortical areas.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Buzsáki, G. *Cereb. Cortex* **6**, 81–92 (1996).
2. McClelland, J.L., McNaughton, B.L. & O'Reilly, R.C. *Psychol. Rev.* **102**, 419–457 (1995).
3. Steriade, M. & Timofeev, I. *Neuron* **37**, 563–576 (2003).
4. Hahn, T.T.G., McFarland, J.M., Berberich, S., Sakmann, B. & Mehta, M.R. *Nat. Neurosci.* **15**, 1531–1538 (2012).
5. O'Neill, J., Pleydell-Bouverie, B., Dupret, D. & Csicsvari, J. *Trends Neurosci.* **33**, 220–229 (2010).
6. Rasch, B. & Born, J. *Curr. Opin. Neurobiol.* **17**, 698–703 (2007).
7. Giocomo, L.M., Zilli, E.A., Fransen, E. & Hasselmo, M.E. *Science* **315**, 1719–1722 (2007).
8. Cunningham, M.O. *et al. Proc. Natl. Acad. Sci. USA* **103**, 5597–5601 (2006).
9. Mann, E.O., Kohl, M.M. & Paulsen, O. *J. Neurosci.* **29**, 7513–7518 (2009).
10. Crunelli, V. & Hughes, S.W. *Nat. Neurosci.* **13**, 9–17 (2010).
11. Fyhn, M., Molden, S., Witter, M.P., Moser, E.I. & Moser, M.B. *Science* **305**, 1258–1264 (2004).
12. Hafting, T., Fyhn, M., Molden, S., Moser, M.B. & Moser, E.I. *Nature* **436**, 801–806 (2005).
13. Hargreaves, E.L., Rao, G., Lee, I. & Knierim, J.J. *Science* **308**, 1792–1794 (2005).
14. Witter, M.P. & Moser, E.I. *Trends Neurosci.* **29**, 671–678 (2006).
15. van Strien, N.M., Cappaert, N.L. & Witter, M.P. *Nat. Rev. Neurosci.* **10**, 272–282 (2009).

Two layers of neural variability

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Variability in neuronal firing rates and spike timing can be modeled as doubly stochastic. A study now suggests that these phenomena could arise from a network built of deterministic neurons with balanced excitation and inhibition.

The principal mode of neural communication is the action potential: a stereotyped spike in voltage across the membrane of a neuron. Neural circuits represent and process information through the temporal and spatial patterns of their spikes. However, these patterns of spikes are surprisingly variable, even across trials in which an animal is experiencing identical stimuli or performing a nominally identical action. A common practice is to treat such variability as arising from the stochastic (Poisson) generation of spikes on the basis of a firing rate. There is debate regarding the degree to which deviations from stochastic spiking (for example, synchrony and spike-timing effects) encode additional information beyond the rate. Putting that debate aside, it is widely agreed that the rate carries a good deal of information and that much of the recorded spiking variability is effectively noise. Many of our most successful models and hypotheses are couched entirely in terms of firing rates. Notably, such models often allow firing rates themselves to be variable across trials (for example, this might be necessary to explain behavioral variability). Thus, the observed data is often modeled as 'doubly stochastic'[1]: a variable firing rate gives rise to variable spiking[2] (**Fig. 1**). Although such models provide good descriptions of the data, they seem to be at variance with the known biophysics of neurons. Nowhere inside a neuron is there a biophysical quantity that corresponds to a

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