characteristics? Finally, LTP is triggered through calcium-dependent mechanisms. Does calcium regulate endosomal trafficking in spines, and if so, what are its downstream effectors? Long-term depression (LTD), which is in some sense the opposite of LTP and is induced by different patterns of synaptic activity, is linked to spine shrinkage (Zhou et al., 2004). Does LTD involve changes in endosomal recycling in spines and/or translocation of recycling compartments (see Brown et al. [2005])? Spines may be avid recyclers, but there is still much to be learned about their local ecology.

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Sleepy Dialogues between Cortex and Hippocampus: Who Talks to Whom?

During NREM sleep, neocortical neurons undergo near-synchronous transitions, every second or so, between UP states, during which they are depolarized and fire actively, and DOWN states, during which they are hyperpolarized and completely silent. In this issue of *Neuron*, Isomura et al. report that slow oscillations of membrane potential occur near-synchronously not only in neocortex but also in entorhinal cortex and subiculum. Within the hippocampus proper, pyramidal neurons lack the bistability of UP and DOWN states, but their firing is strongly modulated by cortical activity during the UP state. Intriguingly, many hippocampal neurons fire during the cortical DOWN state. Thus, during sleep UP states, the cortex can talk to the hippocampus, but it is unclear whether the hippocampus talks back.

The slow oscillation (SO)—a near-synchronous alternation of UP and DOWN states at around 0.8 Hz that occurs in virtually all excitatory and inhibitory cortical neurons—underlies the most pervasive and powerful of all EEG rhythms: the slow waves of NREM sleep (Steriade, 2006). The SO has several intriguing features. First, it is the default mode of activity of cortical circuits: it is seen not only in the sleeping cortex, but it persists after thalamectomy, in isolated cortical slabs, and even in cortical slices, being initiated, maintained, and terminated through the interplay of intrinsic currents and intracortical network interactions.

Second, the SO enforces a unique state of near-absolute synaptic stillness, for a good fraction of a second, over the entire cortical mantle. This forced inactivity, which invariably follows any form of activation of cortical neurons into an UP state, spontaneous or triggered by stimuli, is a remarkable expression of the intrinsic bistability of cortical networks in states of reduced consciousness, such as deep NREM sleep and certain forms of anesthesia.

Third, the SO behaves like a traveling wave: an UP state is ignited locally by the activation of local populations of neurons, more often than not in prefrontal cortex, after which it invades progressively other cortical areas over tens to a few hundred milliseconds (Massimini et al., 2004). Indeed, though born and discovered in the neocortex (Steriade, 2006), in recent years the SO has traveled steadily to conquer many other brain regions. Currently, we know that the SO also entrains the thalamus, the basal ganglia, the paleocortex, and the hippocampus. And now, using multiple intracellular and field potential recordings in the rat, Isomura et al. (2006) have nicely demonstrated a sequential propagation of cortically generated UP and DOWN states through the entorhinal cortex and the subiculum down to the dentate gyrus. Exactly how the SO might travel from one area or structure to the next is still unclear. Although corticocortical and corticofugal connections acting upon already primed neuronal targets are a likely mechanism, it is possible that subcortical structures, such as the thalamic reticular nucleus, may also play a role.

Fourth, the slow oscillation is responsible for grouping most other sleep rhythms (Steriade, 2006). Thus, the onset of the UP state in the cerebral cortex sends a strong volley of spikes down to the GABAergic neurons of the reticular thalamic nucleus, which in turn trigger recurring sequences of spindle oscillations in thalamocortical neurons. Similarly, the depolarized UP state of the SO favors the intermittent appearance of wakefulness-like fast rhythms during sleep. Isomura et al. (2006) as well as Mölle et al. (2006) have now shown that this grouping role extends to the hippocampus, where sharp wave-ripple complexes reliably follow cortical SO after a delay of tens of milliseconds.

Fifth, though SO are the largest of neural waves, and though they invade the cortex a thousand times a night, it is not clear whether they serve any function at all—apart from making us less conscious. However, we know that SO underlie EEG slow wave activity (0.5–4.5 Hz)—a reliable indicator of sleep need that increases with time awake and decreases during sleep. Thus, an attractive function for the SO itself, or for the

spindle, gamma, and ripple oscillations that are grouped by it, could be triggering plastic changes in cortical and subcortical circuits. In this way, sleep could potentiate synapses offline, as many think, or lead instead to generalized synaptic depression, as suggested by the decreasing amplitude of cortical SO (Tononi and Cirelli, 2006) and hippocampal correlation strength (Kudrimoti et al., 1999; see also Colgin et al., 2004) during sleep episodes. Certainly, the effects on synaptic plasticity of the peculiar patterns of firing of the sleeping brain should now become a focus of research. But then, what should one make of Isomura's demonstration that most hippocampal cells do not exhibit UP and DOWN states (CA1 interneurons do, however [Hahn et al., 2006])? Does this mean that they can do without the purported benefits of the sleep SO? Or perhaps what matters is not the alternation of UP and DOWN states but some other feature of sleep firing patterns, such as high-frequency bursts during UP states or ripples (Czarnecki et al., 2006)?

Whatever the answer, the study of the interplay of cortical and hippocampal structures, exemplified by the Isomura et al. report, is important for another reason, having to do with clarifying the direction of the cortico-hippocampal dialog. An influential suggestion has been that the flow of information goes from cortex to hippocampus during wakefulness, and from hippocampus to cortex during sleep (Buzsáki, 1998). In line with the role of the hippocampus in declarative memory, during wakefulness hippocampal circuits would rapidly store associations between signals originating in disparate cortical areas. However, declarative memories become progressively more resistant to hippocampal damage, so it is thought that the hippocampus slowly transfers the memories to the cortex. Since patterns of activity learned during wakefulness can be "replayed" during sharp wave-ripple complexes in sleep (Lee and Wilson, 2002), this transfer of information may actually occur during sleep. In this view, the hippocampus would act much like a remedial teacher during sleep, repeating facts to the cortex night after night until eventually the cortex remembers and the memories become independent of the hippocampus.

To be plausible, this classic scenario will have to meet some key requirements. If playback to cortex is supposed to be a major function of sleep, it should occur selectively during sleep, otherwise why should animals pay the price of relative unconsciousness of the environment? And yet, similar patterns of reactivation are seen also during quiet wakefulness (Kudrimoti et al., 1999). Also, the "replay" of learned activity patterns should be sufficiently high fidelity to ensure that ensuing neocortical storage captures the learned associations while avoiding spurious ones. Merely showing a statistical relationship between learned activity patterns and those occurring in subsequent sleep is insufficient; any "reactivation" of neural circuits, in sleep or wake, is bound to show some trace of synaptic changes induced by learning. And of course, there should be evidence that hippocampal replay can cause plastic changes consistent with the strengthening of cortical associations. In any case, there should be strong evidence for a flow of neural signals from hippocampus to cortex during sleep.

It is thus remarkable that a series of recent papers has now shown that, during sleep, neural activity clearly propagates in the opposite direction—from the neocortex to the hippocampus. Indeed, hippocampal spikes and field potentials always lag behind cortical ones by several tens of milliseconds. And in the report by Isomura et al., it is especially intriguing that the activation of hippocampal output layers often occurs in the DOWN state, when it has little or no effect on neocortex. At this point, evidence for signal flow in the hippocampal-neocortical direction during NREM sleep is comparatively meager. Conversely, there are reliable indications that the hippocampus can influence cortex during wakefulness, for example many neurons in the medial prefrontal cortex are phase locked to hippocampal theta rhythm (Siapas et al., 2005). In short, during wakefulness the dialog between cortex and hippocampus can proceed both ways. During sleep, we now know, the cortex certainly talks to the hippocampus. But can the hippocampus talk back loud enough? In other words, can it ripple the stormy sea of the sleeping cortex?

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