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Hippocampal sharp-wave ripples in waking and sleeping states

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Abstract

Waking and sleeping states are privileged periods for distinct mnemonic processes. In waking behavior, rapid retrieval of previous experience aids memory-guided decision making. In sleep, a gradual series of reactivated associations supports consolidation of episodes into memory networks. Synchronized bursts of hippocampal place cells during events called sharp-wave ripples communicate associated neural patterns across distributed circuits in both waking and sleeping states. Differences between sleep and awake sharp-wave ripples, and in particular the accuracy of recapitulated experience, highlight their state-dependent roles in memory processes.

Introduction

The ebb and flow of waking and sleeping states imposes structure and periodicity on all mammalian life. In addition to the state of awareness, neural states that accompany waking and sleeping differ drastically in several dimensions, including the level of neuromodulators, widespread synchronization, and responsiveness to input from external stimuli [1]. These features dissociate the neural context of waking and sleeping states and manifest in distinct memory processing [2–4]. While awake, rapidly retrieved memories influence prediction, deliberation, and evaluation. Often, a decision must be made following only a short period of deliberation, suggesting a need for rapid and precise memory retrieval. In sleep, fresh memories are gradually strengthened, transformed, and integrated into the ensemble of amassed knowledge in the process of system-level consolidation [5,6]. Here, the need for rapidity and precision may be relaxed, and indeed a high fidelity representation may not be optimal for building more generalized representations.

Memory reactivation, serving both retrieval and consolidation, entails repetition of previously experienced episodic associations. Reactivation is commonly detected in the context of patterns of activity in spatially selective cells in subregions of the hippocampus [7]. The hippocampus is essential for all aspects of spatial memory, including encoding, consolidation, and retrieval [8,9]. Hippocampal pyramidal neurons that are active during a

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given experience are often referred to as ‘place cells’ because a large fraction of them fire in a location-dependent manner - preferring certain ‘place fields’ as animals explore space. Plasticity mechanisms associate cells with neighboring place fields, enhancing neighbor coactivity following their activation during exploration [10]. During a pause in active exploration or while asleep, bursts (100–200 ms) of place cell activity occur within distinct high-frequency (150–250 Hz) fluctuations in the hippocampal local field potential, called sharp-wave ripples (SWRs; Fig 1a; [11]). Sequences of simultaneously recorded place cells, whose collective place field assemblies reflect trajectories through space, are often reactivated in a time-compressed cascade during hippocampal SWRs (Fig 1a,b). The timescale of SWRs aligns with the optimal window for inducing synaptic plasticity, and therefore could influence the encoding of memory traces in synaptic weights [12,13].

SWRs have garnered significant attention as a common phenomenon for broadcasting mnemonic messages, in both waking and sleeping states [7,14]. However, the processing demands of waking and sleep are distinct, and differences in sleep and awake SWR replay events may support these distinct functions. Here we review recent developments addressing this issue and discuss the hypotheses that SWR replay during the waking state serves to mediate awake memory retrieval [7] and update navigational planning with respect to current perceptual input, whereas SWR replay during sleep is fundamentally geared to gradually consolidate a memory trace into a broader framework of existing memories.

The Role of Awake SWR Replay

The vicarious representations of spatial paths extending beyond an animal’s current position could be an efficient component for deliberating and evaluating possible routes to reach a goal [7,15–17]. In a causal test of a role for awake SWR events, Jadhav et al. [18] found that waking SWR activity was necessary for navigational memory-guided decision making in rats. The authors employed a spatial alternation task with a ‘W’ shaped maze on which the animals were rewarded at each arm’s end for navigating in the following order: outbound-left, inbound-center, outbound-right, inbound-center, and so on (Fig 1c). Brief pulses of electrical stimulation, delivered immediately upon awake SWR onset, selectively disrupted SWRs and lead to a highly significant impairment in performance of the outbound alternation rule, which depends on integrating immediate past experience with the task rule. Parallel results came from a study in which awake SWR detection during learning triggered a bright light which led to an impairment in trace eyeblink conditioning in rabbits, likely because the light disrupted neocortical activity associated with SWRs [19].

Subsequent studies have begun to identify a relationship between the content of SWRs and behavior [20,21]. Using the ‘W’ maze spatial alternation task (Fig. 1c), Singer and colleagues [21] found a greater degree of coordination in the pairwise firing of place cells in the waking state during SWRs that preceded a correct outbound decision, compared to an incorrect decision, on a trial-by-trial basis. This suggests that failure to reactivate the appropriate assembly representing possible future paths may lead to errors in navigational decision making. Interestingly, they did not find a consistent bias for the reactivated trajectory representation to reflect the subsequent navigational choice of the animal. This latter finding is in line with recent arguments positioning hippocampal replay as primarily

communicating possible trajectory options for downstream circuits to evaluate [15,16,22]. In contrast, another study, employing an ‘open field’ foraging task, did detect a bias for the content of awake replay events to represent space in the general direction of the subsequent behavior – although there were still many replay events sweeping toward alternate locations. The relative hippocampal involvement in prediction, deliberation, and evaluation is likely influenced by task, learning stage, and environment.

Finally, we note that awake replay occurs in both the forward direction, consistent with the animal’s experience, as well as in the reverse direction, with the relative prevalence and control of these sequences likely reflecting different processes [23–28]. For instance, reverse replay in the waking state commonly occurs when the animal has arrived at a goal location, potentially supporting on-line reinforcement learning [7,24–26]. Forward replay in the waking state is more prevalent in anticipation of a trajectory, when deliberation of future paths and spatial working memory is critical [7,25]. The task-location specificity of forward and reverse awake replay suggests an actively controlled retrieval system related to ongoing behavior.

The Role of Sleep SWR Replay

In contrast to the role of memory retrieval for active planning, replay in sleep is a component of system consolidation, which is thought to involve a quantitative and qualitative transformation of representations, stabilizing, decontextualizing, and integrating associations into distributed hippocampal-cortical circuits according to the statistical structure of experienced episodes [5,29–33]. Consistently, evidence indicates that sleep promotes mnemonic flexibility in inference tasks that are enriched by the inductive capacity to link remote fragments of episodic representations [34–39].

Memory stabilization and integration in sleep is thought to require reactivation of awake neural patterns, serving to direct synaptic modifications across hippocampal-neocortical networks [1,30,40,41]. Hippocampal SWR replay and cortical reactivation primarily occurs during periods of slow-wave sleep (SWS) [42–44]. Evidence of a direct link between SWR-related replay in sleep and memory processes has been provided by a number of studies employing a spatial memory task [20,45–47]. If SWR replay assemblies percolate mnemonic messages across distributed circuits, a significant swath of the brain’s activity should be temporally aligned with SWRs. Such evidence was recently reported in a study showing globally coordinated response patterns from monkey whole-brain functional magnetic resonance imaging at the time of hippocampal SWRs while the subjects alternated between sleeping and waking [48].

Additionally, SWR sequences in the sleeping state have been shown to favor the forward direction, maintaining the overall temporal structure of the animals’ actual experience [27,49–52]. In order to infer future events based on previous exposure to a particular instance, preserving the appropriate overall temporal order of episodic fragments may be a crucial feature in the face of decontextualization processes. Fittingly, sleep has been shown to selectively strengthen the forwardly learned associations of word or picture sequences during post-sleep waking retrieval [53,54].

The Fidelity of Replay

A critical feature of awake SWRs is the fidelity of recapitulated experience, as accurate portraits of established trajectories are crucial for rapid memory-driven behavioral performance. Karlsson and Frank [55] recorded from principal neurons in hippocampal areas CA1 and CA3 while rats performed the W-track alternation task (Fig 1c) flanked by ‘sleep-box’ sessions. Strikingly, their analyses reveal that awake SWRs contained overall higher fidelity recapitulations of previously experienced traversals through place fields than SWRs recorded in sleep-like states (Fig 2).

Furthermore, recent evidence couples fidelity of replay with an additional level of coherence across hippocampal areas within and across hemispheres. Carr et al. [56] found that increased synchrony of ‘slow’ gamma oscillations (20–50 Hz) across CA3 and CA1 regions was predictive of replay fidelity in the waking state, suggestive of an internal clocking mechanism to coordinate sequential reactivation across the hippocampal network. In contrast, spiking during SWRs in sleep-like states was less modulated by slow gamma with no clear relationship between gamma synchrony and the fidelity of replay.

Beyond the coupling of hippocampal slow gamma oscillations in the waking state, sleep SWRs are temporally coordinated with oscillating ‘Up’ and ‘Down’ states of widespread activation and suppression of cortical activity, respectively [1,57–60]. These oscillations are linked to the retention and integration of new learning into existing knowledge structures [61,62]. Synchronized interaction between the hippocampus and prefrontal cortex (PFC), one of the major sites of hippocampal output, is critical for system consolidation [63], occurs largely coincident with SWRs during SWS [42,64], and specifically includes reactivated cortical patterns of awake experiences [43,65]. Recording in the PFC, Peyrache et al. [43] found that the temporal dynamics of reactivation strength, or the accuracy with which population activity in sleep corresponded to waking experience, peaked immediately preceding a transition from Down to Up states, which is temporally aligned with a prevalence of SWRs [43,66]. Given that hippocampal SWRs can occur during both Up and Down states [66,67], this raises an intriguing possibility that the phase of certain cortical oscillations are linked with the relative fidelity of replay transmission in the hippocampal-cortical axis. For instance, widespread activation or suppression of cortical activity, respectively associated with Up or Down states, could either influence the cortical receptivity to input patterns from the hippocampus, or variably infuse noise into an ensuing hippocampal replay assembly. Additionally, recent work demonstrated that the medial entorhinal cortex, part of the main input and output structure between the hippocampus and neocortex, contains persistent Up states that can span multiple quantized neocortical Up/Down states and influence the activity levels of the hippocampus, potentially gating the form of transmission across the hippocampal-neocortical axis around the time of SWR replay [68].

A Role for ‘Noisy’ Replay

It seems intuitive that high fidelity replay would promote effective decision-making during waking, but how could lower fidelity, ‘noisy’ recapitulations of experience serve the

mnemonic functions of sleep? Importantly, sleep allows the brain to consolidate sparse data and store the statistics of the environment into a semantic memory system, allowing for inductive predictions about the future. Inspired by computational linguistics, Battaglia and Pennartz [69] advance an illustrative approach of how memory networks, trained by ‘noisy’ episodic replay, could become schematized and generative, constructing episodes based on past experience and allowing for prediction in the face of uncertainty. In this way, the comparatively more random organization of sleep SWR replay may be a feature rather than a bug, serving to fulfill the transformational consolidation process and supporting the capacity to build rich schemata from only a limited number of episodic associations.

Recent evidence is consistent with the idea that adding ‘noise’ to the relevant neural circuits during sleep consolidation alters the specificity, but not necessarily the strength, of learning. Barnes and Wilson [2] conditioned electrical stimulation in the rat olfactory bulb (OB) with a foot-shock, an established paradigm for subsequently eliciting the rat’s natural fear response to the conditioned olfactomimetic stimulation. However, in intervening SWS bouts between conditioning and testing, they stimulated a naive (not previously conditioned) OB site, likely eliciting a very different activity pattern than that which was conditioned. Surprisingly, this manipulation, which consisted of introducing novel and seemingly irrelevant activity during the period of memory consolidation, did not decrease the strength of the trained memory association. Instead, this manipulation led to memory generalization, as observed by fear response to previously unpaired odors. Together, these studies suggest that the level of interference during periods of consolidation can influence the precision of memory expression, and furthermore predicts that over-rigidity in sleep replay, relative to awake, may impair the ability to flexibly use past memory in a novel context.

Conclusion

SWRs may be a common neurophysiological phenomenon for broadcasting mnemonic messages in both waking and sleeping states, the importance of which is underscored by recently documented impairments of sequence reactivation in models of schizophrenia [60,70], dementia [71,72], and aging [73]. Causal manipulations lend strong support to this role for SWRs, but elucidation of their intrinsic features is necessary to understand the mechanisms supporting distinctive memory processes. Awake SWRs proceed both forward and reverse, entail a more veridical account of experience, and can predict future behavior. Sleep SWRs mainly unfold in the forward direction, are generally more noisy depictions of past actions, and are tightly coordinated with cortical oscillations. Together, the evidence supports the hypotheses that SWR replay during the waking state serves to support retrieval and planning, whereas SWR replay during sleep is geared to gradually consolidate a memory trace into a broader framework of existing memories.

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Highlights

- Hippocampal SWRs contain neural activity reactivations in both waking and sleeping.
- SWRs in waking and sleeping entail distinct features, particularly replay accuracy.
- Features of awake SWRs suggest a role in rapid navigational planning.
- Features of sleep SWRs suggest a role in gradual memory consolidation.

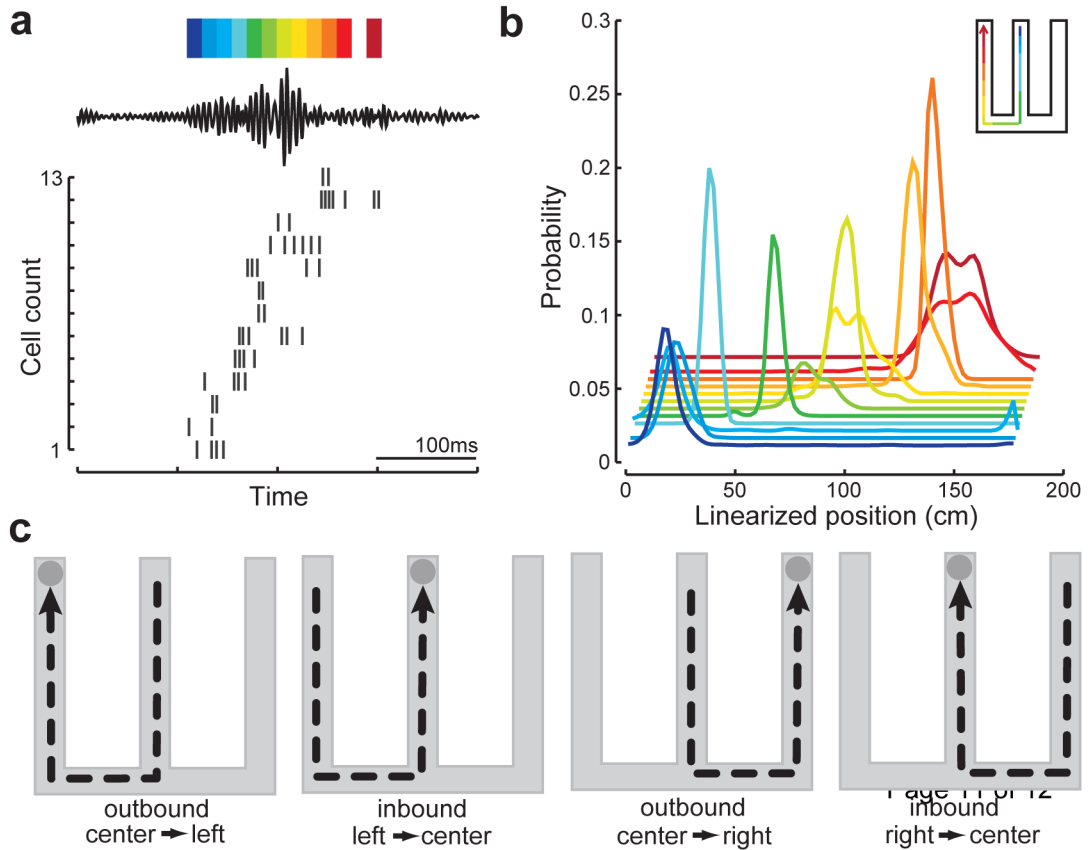


Figure 1.

SWR Reactivation of Spatial Sequences. **(a)** Sequential spiking from place cells during an awake SWR. Bottom, rows depicting the spiking of individual place cells in CA1 or CA3 activated during the SWR. Top, the filtered local field potential signal (150–250 Hz) from one tetrode with the color bar showing the separation of each 15-ms decoded bin. **(b)** Probability distributions of decoded locations for the spiking in each associated colored bin in **a**. Inset shows a cartoon of the replayed trajectory. **(c)** Schematic depicting the rewarded behavioral sequence of the ‘W’ track task. Adapted with permission from ref. [56].

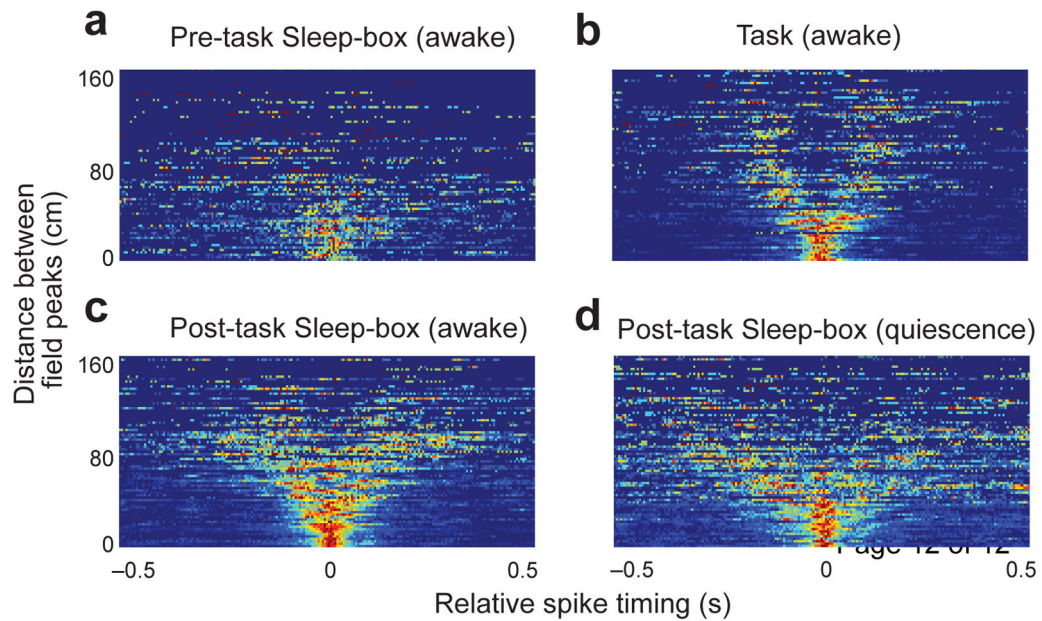


Figure 2.

The quality of SWR replay of remote task trajectories is higher during awake than quiescent periods. Karlsson and Frank [55] calculated the extent to which the linear spatial distance between the peaks of place field pairs belonging to a remote ‘W’ environment predicted the relative timing of their SWR spikes for all place cell pairs. The normalized cross-correlation histograms of all the pairs is shown in order of their place field distances, with the signature of the degree to which the place-field distances are linked to their SWR timing being represented by the emergent ‘V’ shape centered at 0-ms latency. **(a)** Awake SWRs during the first sleep-box session of the day, prior to the daily exposure of the ‘W’ track task ($R^2 = 0.025$). **(b)** Awake SWR replay during task performance shows the most robust remote replay ($R^2 = 0.1736$; see ref. [55] for further explanation of behavioral paradigm). **(c)** SWRs during waking bouts in the post-task sleep-box, after exposure to the ‘W’ maze task ($R^2 = 0.1164$). **(d)** SWRs during quiescent, sleep-like states in the sleep-box, after exposure to the ‘W’ maze task ($R^2 = 0.0693$). R^2 values were computed by taking the correlation of the distance between place field peaks and the absolute value of the relative spike timing measure. Adapted with permission from ref. [55].