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# Hippocampal ripples and memory consolidation

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During slow wave sleep and quiet wakefulness, the hippocampus generates high frequency field oscillations (ripples) during which pyramidal neurons replay previous waking activity in a temporally compressed manner. As a result, reactivated firing patterns occur within shorter time windows propitious for synaptic plasticity within the hippocampal network and in downstream neocortical structures. This is consistent with the long-held view that ripples participate in strengthening and reorganizing memory traces, possibly by mediating information transfer to neocortical areas. Recent studies have confirmed that ripples and associated neuronal reactivations play a causal role in memory consolidation during sleep and rest. However, further research will be necessary to better understand the neurophysiological mechanisms of memory consolidation, in particular the selection of reactivated assemblies, and the functional specificity of awake ripples.

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## Introduction

Memory consolidation refers to a process by which labile newly formed memory traces are progressively strengthened into long term memories and become more resistant to interference, although they may remain susceptible to further updating and modification [1,2]. In effect, recently acquired information is reorganized and progressively integrated into networks of pre-existing memories in a time-dependent manner. This is thought to take place preferentially during sleep (see [3]). Early clinical studies and subsequent experimental work on animal models established the hippocampus as a brain structure prominently involved in encoding, consolidation and early retrieval phases of episodic and spatial memory ([4]; its necessity for remote memories is still under debate, see e.g. [5]). An influential theory of memory consolidation [6,7] posits that information is transferred between the hippocampus and neocortex during sleep or quietful rest ('off-line' states), inducing long-lasting cellular and network modifications responsible for memory stabilization (see Box 1 for an alternative theory). Here we review recent evidence for the underlying neurophysiological mechanisms. We focus on hippocampal field potential and neuronal firing patterns, namely *sharp wave-ripple* (SPWR) complexes and associated *neuronal replay*, which are believed to play a prominent role in off-line consolidation.

## The two-stage model of memory trace formation

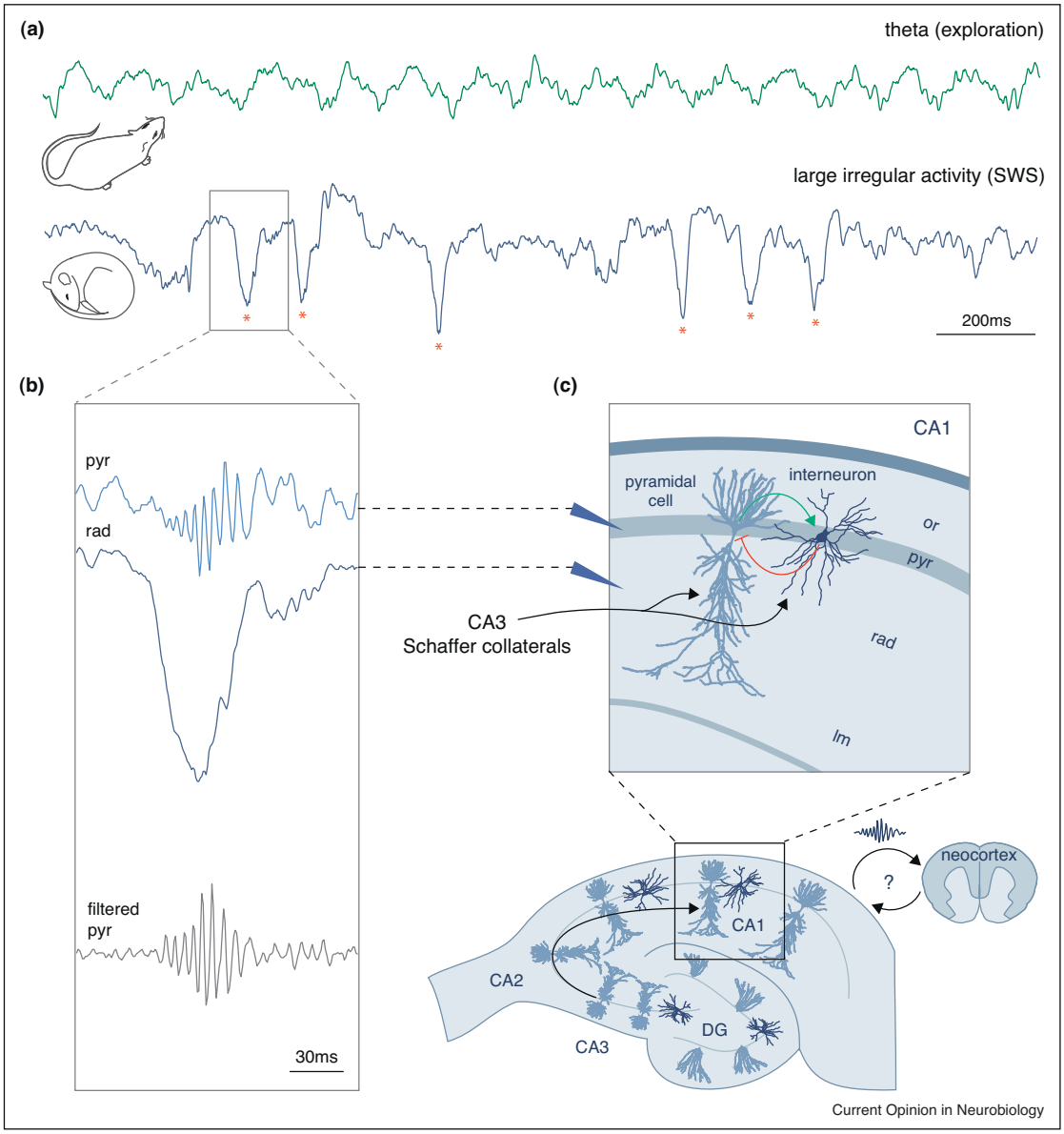
New memory formation was proposed to involve a two-step process [6,7], wherein novel information is first encoded during the waking state, then consolidated during subsequent sleep. During alert wakefulness, higher levels of neuromodulators such as acetylcholine in the hippocampus enhance the influence of external inputs relative to intrinsic activity, likely favoring sensory processing and predominant information flow from the neocortex to the hippocampus [8]. In rodents exploring their environment, hippocampal pyramidal cells, known as *place cells*, selectively fire when the animal is located in restricted zones of space ('place fields'), possibly constituting the brain basis of a cognitive map [9]. Place cells have also been identified in non-human [10] and human primates [11], in which the role of the hippocampus seems to have generalized to broader functions, such as episodic memory ([4]; for non-spatial correlates of hippocampal activity in rodents, see e.g. [12]). Importantly, place cell discharges are temporally organized in time-compressed sequences [13–16] embedded in the ongoing theta rhythm (7–14 Hz). As a result, cells fire in close temporal proximity, which would trigger plastic changes in the synapses between cells with nearby place fields [14,17,18], providing a cellular mechanism for initial sequence learning in the hippocampal network [14,19]. Subsequently, during the sleep period following exploration, the brain is isolated from external stimuli and lower levels of acetylcholine in the hippocampus enhance recurrent effective connectivity [8]. This favors endogenous activity, and previously encoded information (e.g. place cell sequences) is reactivated, strengthened, and potentially transferred to the neocortex. Specifically, during slow wave sleep (SWS) and quiet wakefulness, the hippocampus displays large irregular activity, characterized by recurring occurrences of SPWRs, caused by massive endogenous activation of large neuronal populations. Because these bursts of activity provide the strong synaptic bombardment necessary for the induction of long term synaptic changes believed to form the cellular

and molecular basis of memory, they were proposed as a candidate mechanism for off-line consolidation [7].

## Mechanisms of sharp wave-ripples

Hippocampal SPWR complexes [9,20] (Figure 1) are transient field events occurring during slow-wave sleep and non-exploratory wake states (eating, drinking, grooming and quiet wakefulness) at an occurrence rate ranging from 0.01 to 2 Hz. SPWRs have also been recorded in macaques [21] and humans [22,23]. *Sharp-waves* result from massive non-rhythmic depolarization of the apical dendrites of CA1 pyramidal cells in stratum radiatum by synchronous bursts of large ensembles of CA3 cells (up to 10–20%, [24]) via the Schaffer collaterals. CA1 interneurons are also widely recruited and start firing synchronously at a high population frequency (150–250 Hz),

**Figure 1**




Hippocampal local field potentials (LFPs) during exploration and rest/sleep. **(a)** During exploration, the hippocampus displays a strong 7–14 Hz oscillatory activity, known as the *theta* rhythm (green trace). During sleep and quiet wakefulness, theta is replaced by large irregular activity (blue trace) characterized by the occurrence of *sharp wave* events (red stars). **(b)** Detailed view of the LFP trace. Simultaneous with the sharp wave recorded in stratum radiatum (rad), a high frequency (~200 Hz) *ripple* oscillation is recorded in stratum pyramidale (pyr). The filtered signal is also shown below (ripple-band filtering between 150 and 250 Hz). **(c)** Sharp waves in stratum radiatum reflect massive excitation of CA1 neurons by CA3 pyramidal cells via the Schaffer collaterals. The concomitant synchronization of the interneuron network at ~200 Hz generates a ripple in the pyramidal layer (or: stratum oriens, lm: stratum lacunosum moleculare, CA1–3: cornu ammonis subfields of the hippocampus, DG: dentate gyrus).

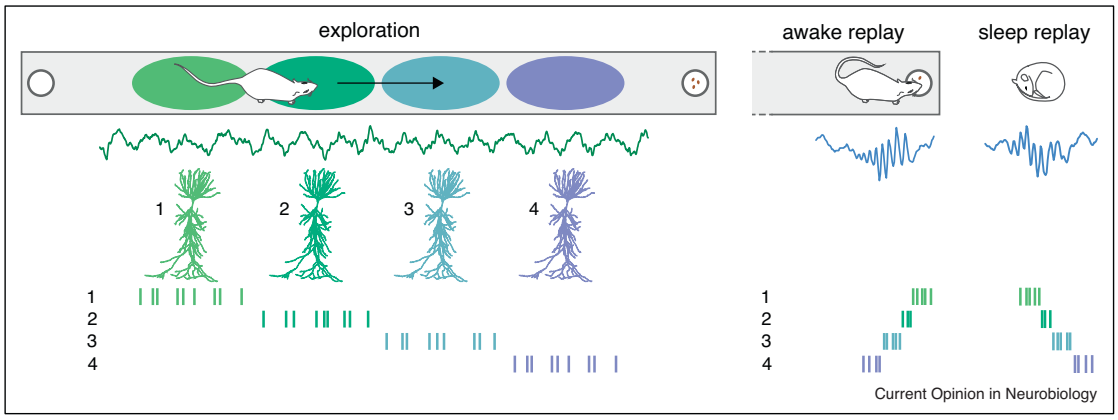
likely because of their widespread interconnectivity and intrinsic membrane properties [25,26]. In the CA1 pyramidal layer, the interaction between this oscillating proximal inhibition and the strong distal excitation from CA3 results in fast field oscillations called *ripples* (150–250 Hz), which pace the spike timing of recruited pyramidal cells (10–15% of the population) [20,27]. The waveform of a given SPWR is related to the actual subset of activated pyramidal cells [28]. SPWRs are synchronous along the longitudinal axis of the hippocampus, except in the ventral part [29], and occur simultaneously, but not phase-locked, in both hemispheres [27]. Although recent data indicate that perisomatic interneurons may play an important role in selecting the assembly of CA3 cells that participate in each particular SPWR [30•], how these cells are preselected or 'primed' during exploration remains unknown.

## Neuronal replay and synaptic plasticity

An increasing number of studies support the view that SPWRs are involved in off-line memory consolidation. First, the intrinsic ripple frequency is ideal to trigger synaptic modifications in downstream neurons, for example via long term potentiation (LTP, [31]) or spike time dependent plasticity (STDP, [32,33]), which have recently been confirmed to underlie certain forms of memory [34,35]. Notably, experimental induction of LTP in the hippocampus can artificially impose a new configuration of place fields in space [36], consistent with the idea that in physiological conditions SPWR-induced plasticity could stabilize newly formed place maps (see also [37•]). In this scenario, the coordinated activation of a subset of CA3 cells weakly potentiated during exploration would provide the strong synaptic excitation necessary for the enhancement of synaptic efficacy in CA3, targeted pyramidal cells of CA1 and possibly downstream cortical areas. Indeed, it was shown that depolarizing CA1 pyramidal cells during SPWRs induces LTP [38].

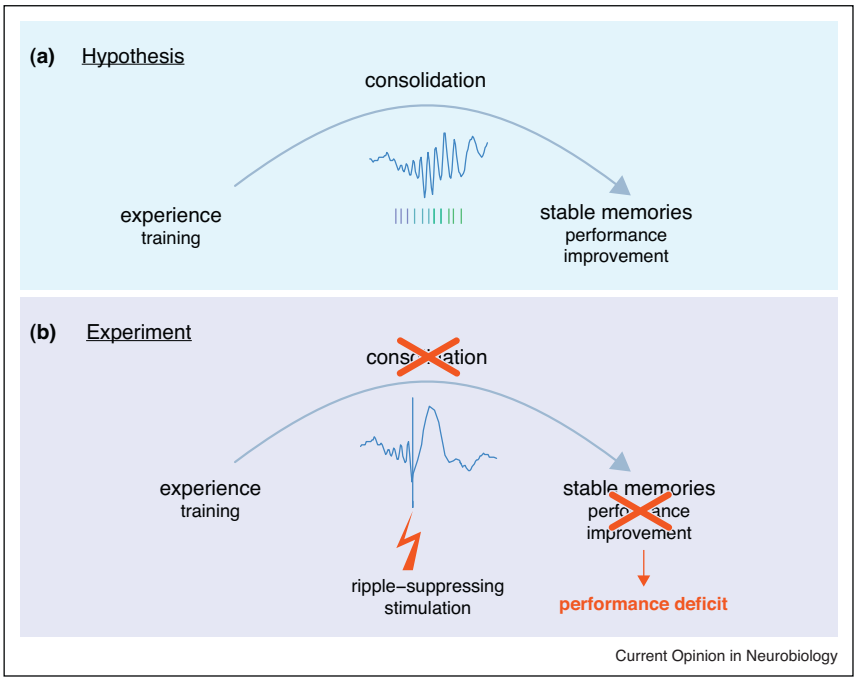
A second argument is that hippocampal activity elicited during awake experience is later reinstated during SWS, when SPWRs abound. Reactivation of neuronal firing patterns ('replay') has been extensively studied in rodents (for related studies at the structural and cognitive level in humans, see e.g. [39,40]). The first indication that neuronal off-line activity reflects previous waking experience was provided in a study where single place cells that were activated during awake behavior were shown to increase their firing rate during subsequent sleep compared to other cells [41]. This result was later confirmed and extended using pioneering simultaneous recordings of large cell ensembles [42], revealing that the correlations between spike trains of numerous pairs of place cells observed during exploration were later replicated during sleep [42,43]. Subsequent studies further showed that the order of activation of place cell pairs during exploration was preserved during sleep [44], and as a consequence that whole sequences of place cells repeatedly activated in the same order during exploration (trajectories) could later be replayed during sleep [45,46] (Figure 2). Importantly, these replay events occurred predominantly during SPWRs [45], in a temporally compressed manner compatible with the typical time windows of synaptic plasticity [46] (note that reactivations were also reported during rapid eye movement sleep at a decelerated rate [47]). Reactivations involving broader brain regions, including the thalamus and neocortex, were also observed [48]. However, with the notable exception of three experiments where novelty was shown to modify individual firing rates [49], cofiring of cell pairs [50], and

**Figure 2**




Sharp wave-ripple (SPWR)-associated neuronal replay. When a rat is running on a linear track, the hippocampus oscillates at theta frequency (green trace) and place cells are successively activated as the rat enters their respective place fields (colored ellipses), yielding a neuronal sequence (vertical ticks). Upon arrival at the food well, the rat stops to consume a reward and the place cell sequence reactivates in reverse order (reverse replay) during SPWRs (blue trace). In subsequent slow wave sleep and quiet rest periods, place cells reactivate in the same order as during exploration (forward replay).

**Figure 3**




Working hypothesis. If ripples are critically involved in memory consolidation, enabling the strengthening of newly acquired information into stable memories, then suppressing ripples is expected to impair consolidation and induce a memory deficit. This can be experimentally measured as a decreased performance on a spatial reference memory task [57••,58••].

ensemble reactivation rates [43] during subsequent sleep, these studies were all performed on highly trained animals that were not actually learning. Thus, the significance of place cell reactivations for learning and memory remained unclear.

## Sharp-wave ripples and memory consolidation

More recently however, several studies have revealed a correlation between SPWRs and memory. Ripple occurrence rates were shown to increase during the hour following a training session on an odour-reward association task [51]. A similar increase was observed in rats learning a radial maze task, concomitant with a significant improvement in performance [52••]. Also, the intrinsic ripple frequency increased after a change in the task contingency, such as a variation in the minimum delay to receive a new reward by lever pressing [53]. Taken together, these results suggest that SPWRs may be modulated by learning-related regulatory processes (conversely, coupling stimulus presentations with ripples facilitates trace eyeblink conditioning [54]). In addition, ripple characteristics were altered in mutant mice in which inducible inactivation of the CA3–CA1 pathway impaired consolidation of contextual fear conditioning [55]. Similarly, in older rats, impaired place cell reactivations paralleled performance deficits in the water maze task [56]. These are further indications of the important role of ripples and associated reactivations in memory consolidation.

The first direct evidence for a causal role of SPWRs in memory consolidation was provided in a study where ripples were selectively suppressed to impair consolidation [57••] (Figure 3). Each day, rats were trained on a hippocampus-dependent spatial memory task, then allowed to sleep for one hour during which ripples were automatically detected and suppressed by timed electrical stimulation. Critically, potential uncontrolled effects of the stimulation were ruled out by stimulating a control group outside SPWR events. Ripple suppression induced a significant performance impairment, comparable to that reportedly observed in hippocampal-lesioned animals. This was independently confirmed by a different group using a slightly different task and stimulation protocol [58••]. These two studies have thus confirmed the causal involvement of SPWR and associated replay in off-line memory consolidation, but still leave two questions unanswered. First, it is not clear whether the observed deficit was induced by the absence of ripples, the disruption of place cell reactivations, or both. Second, one can only speculate whether ripple suppression prevented the hypothesized hippocampo-cortical transfer of the memory traces, rather than the reinforcement of intra-hippo-

**Box 1 Synaptic downscaling during sleep**

An alternate theory of the role of sleep in memory posits that SWS promotes a global synaptic downscaling necessary to avoid saturation of synaptic strengths [90,91]. We propose that this view can be reconciled with the theory of off-line memory consolidation, assuming that a limited number of selected synapses is potentiated on a background of global downscaling. This idea is supported by the finding that in novel environments the firing rates of CA1 pyramidal cells are initially elevated, then progressively decrease, on average, over the course of several days. This decrease is not uniform, as the most highly spatially selective subpopulation of cells increase its firing rates while the less spatially selective cells become less active, resulting in an enhanced sparsity of the spatial code [92]. One potential difficulty with the downscaling hypothesis is that it would predict a progressive increase in firing rates during the awake state, followed by a commensurate decrease during sleep. Yet, the overall firing rate in the hippocampus is maintained over time [93], even after experimental *in vivo* LTP induction [36]. Further work will thus be necessary to better integrate these two theories of sleep function.

campal connections, although these are not mutually exclusive possibilities.

## Hippocampo-neocortical information transfer

Several lines of evidence support the idea of a gradual transfer of labile information from the hippocampus to form more permanent traces in the neocortex. Following the description of temporally graded amnesia in patients with hippocampal lesions, animal studies have provided anatomical and functional evidence that over time, retrieval of remote memories becomes relatively independent of the hippocampus. Instead, successful retrieval becomes increasingly dependent on necortical areas, in particular the prefrontal and anterior cingulate cortices [59,60]. Eventually, according to the standard theory, the consolidation process leads to a complete transfer of memory traces to neocortical areas, and a concomitant erasure from the hippocampus. However, this is still an unresolved issue, as certain types of remote memories may remain dependent on the hippocampus, for example those retaining detailed information or episodic features ([61,62]; for a comprehensive review of this topic, see [5]). Another widely held view, namely that hippocampo-cortical consolidation is a slow, progressive process, has recently been challenged in a study where rats demonstrated very rapid (one day) memory consolidation in a paired flavor-place association task, when new information was presumably incorporated into a pre-existing cortical network of similar traces, referred to as a 'schema' [63].

The physiological mechanisms underlying the hypothesized hippocampo-neocortical transfer would involve several brain structures and rhythms related to memory consolidation. Consistent with the view that the hippocampus initially encodes incoming information during theta oscillations, and then transfers it to neocortical areas during off-line states, principal neurons in the superficial layers of the retrohippocampal (entorhinal, subicular, presubicular and parasubicular) cortices, which project to the hippocampus, are modulated by the theta rhythm during exploration. Conversely, neurons in the deep layers of the retrohippocampal cortices, which relay hippocampal outputs to the neocortex, are modulated by SPWRs during which their firing rates increase dramatically [64]. At the field level, hippocampal SPWRs synchronously propagate to retrohippocampal cortices.

In addition, hippocampal SPWRs have been shown to be coordinated with neocortical sleep rhythms [65–67]. During SWS, neocortical field potentials oscillate at 0.1–4 Hz. This *slow oscillation* reflects the synchronous alternation of widely distributed populations of neocortical neurons between depolarized ('up') and hyperpolarized ('down') states, corresponding to periods of high activity and almost complete silence [68]. Experimental induction of slow oscillations by transcranial magnetic stimulation enhances memory performance, indicating that neocortical slow oscillations are also critically involved in memory consolidation [69]. Slow oscillations are accompanied by faster (7–15 Hz) transient oscillations, termed thalamo-cortical *spindles* [68], which have also been linked to learning and memory both in humans and animals [70,71]. Slow oscillations and spindles are correlated with hippocampal large irregular activity. Hippocampal SPWRs are more likely to occur at the transition between down and up-states [66,67,72,73] and coincide with neocortical spindles, preferentially phase-locked to spindle troughs [23,65,66,74].

Consistent with the transfer hypothesis, hippocampal neuronal activity tends to precede downstream neocortical activity [65,75•,76•]. The inverse relationship is observed for sensori-motor cortical areas [66,77]. Because it is inherently difficult to disentangle temporal relationships between weakly coupled oscillatory events, the causal relationships between neocortical and hippocampal activity are still incompletely understood. Nonetheless, at a coarser timescale, reactivations of ensemble firing patterns in neocortical areas coincide with hippocampal SPWR events [75•,77]. Interestingly, a recent study showed that as soon as a rat has learned a behavioral rule, prefrontal neurons self-organize into cell assemblies coordinated with the hippocampal theta rhythm, and that the same assemblies are then preferentially reactivated during sleep [78•]. This is consistent with a study in humans showing that sleep can promote the discovery of a hidden rule in a simple cognitive task [79], and suggests that coordinated hippocampo-prefrontal reactivations could participate in selective reinforcement of relevant traces. Taken together, these studies support the idea that memory consolidation may involve a transfer of information initially stored in the hippocampus toward neocortical areas via the SPWR-related reactivation of neuronal ensemble activity. However, experimental

proof of a causal link between the SPWRs and hippocampo-neocortical transfer is still missing.

## A complementary role for awake replay?

Following the prediction that neuronal replay during immobility at reward sites should occur in temporally reversed order [7], a growing number of studies have focused on awake SPWRs and reactivations [37,80–86,87••,88••]. Not only was it confirmed that most reactivations during awake SPWRs occur in reverse order when the animal receives a water reward at the end of a trajectory [80], reactivations were also found to anticipate the subsequent trajectory (in forward order) when the animal was about to start running again [84]. This suggests that awake replay could play a different role complementary to sleep replay, for instance by linking reactivated sequences to motivational signals triggered by reward consumption. Indeed, awake replay is enhanced following receipt of a reward in rats engaged in spatial memory tasks [87••], and behavioral performance is correlated with the number of goal-related reactivations at reward points [37•]. It is not yet known whether hippocampal place cells and reward-related cells in ventral striatum tend to reactivate together in the awake state, as has been reported during sleep [89]. More generally, the role of awake SPWRs may not be confined to replay of recent experience. Neuronal sequences corresponding to remote trajectories [86] as well as routes never experienced before ('shortcuts', [88••]) have also been reported. Awake reactivation could thus contribute to building a broader mental representation of space.

## Conclusion

Recent studies have provided experimental evidence that sleep SPWRs and associated neuronal reactivations play a critical role in memory consolidation. However, it remains unclear how SPWR-associated cell assemblies are preselected during the awake state, then selectively activated during sleep. Also, whether SPWRs are implicated in the transfer of memory traces from the hippocampus to the neocortex remains to be confirmed, and further multiple-site recording studies will be necessary to better understand the complex relationships between the hippocampus and other reward-related and memory-related brain structures, such as the amygdala or striatum. Finally, a growing amount of evidence suggests a different, maybe complementary role of awake SPWRs compared to sleep SPWRs. Further research will be required to better understand their specific contribution to memory encoding and consolidation, and their precise relationship with sleep SPWRs.

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