Review

# Play it again: reactivation of waking experience and memory

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**Episodic and spatial memories each involve the encoding of complex associations in hippocampal neuronal circuits. Such memory traces could be stabilised from short- to long-term forms by consolidation processes involving the 'reactivation' of the original network firing patterns during sleep and rest. Waking experience can be replayed in many different brain areas, but an important role for the hippocampus lies in the organisation of the 'reactivation' process. Emerging evidence suggests that sharp wave/ripple (SWR) events in the hippocampus could coordinate the reactivation of memory traces and direct their reinstatement in cortical circuits. Although the mechanisms remain uncertain, there is a growing consensus that such SWR-directed reactivation of brain-wide memory traces could underlie memory consolidation.**

## The hippocampus and consolidation

Learning and memory processes are crucial for an organism to adapt its behaviour to ever-changing environments, enabling it to use prior experience to anticipate the future. The establishment of stable memories of places and events is not a single process. Initially, episodic memories are labile and are vulnerable to degradation during ongoing experience. With time, such memories become resistant to the compromising effects of interference and, finally, can last for decades. Understanding the neural mechanisms underlying these processes remains an important objective in neuroscience.

Since the observation that patients with hippocampal damage show deficits in forming new memories [1], a number of studies have shown that the hippocampus participates in the formation of episodic and spatial memories at all stages of memory processing, namely encoding, consolidation and recall [2–6]. Current theories propose that, after the initial encoding, the hippocampus has a time-limited role, where the transfer of the memory trace to a permanent neocortical store is associated with hippocampal disengagement [5–7] or, alternatively, that the hippocampus is never disengaged and the memory retrieval will continue to be associated with activation of both hippocampal and cortical representations of the original experience [8,9]. Regardless, newly encoded information is stabilised through consolidation processes that involve hippocampal–cortical interactions.

Several studies conducted in humans and rodents suggest that sleep could play a role in such a system-level consolidation [10–13]. However, understanding these processes is complicated by the fact that both sleep and memory are not unitary phenomena, the former being composed of multiple systems [14] and the latter of several stages [15]. Converging evidence from rodents suggests that network events termed the sharp wave/ripple (SWR, Box 1) play a key role in hippocampus-dependent memory consolidation. These SWRs are most prominently present during rest and during sleep intervals that are not associated with rapid eye movement (non-REM sleep), and these periods represent the times of highest firing-synchrony between hippocampal neurones, thereby providing the conditions for both plasticity within the hippocampus and for communication between the hippocampus and other brain structures [16–18].

Hippocampus-dependent memory formation is likely to take place in two main stages. First, the hippocampus rapidly encodes memories during alert wakefulness. Then, during 'offline periods', memory traces are 'reactivated' by the hippocampus, facilitating either transfer to longer term storage in cortical networks, or strengthening associations between traces in different brain regions, within and outside the hippocampus [18,19] .

Reactivation of waking neural activity during SWRs has been observed by a number of groups. Here we review the extensive work using single-unit recordings in rodents that demonstrates reactivation in the hippocampus and other brain regions, and assess the progress in placing this phenomenon in the context of memory. In doing so we discuss how reactivated patterns reflect the behaviour of the animal. We also summarise data pointing to coordinated reactivation across brain regions.

## Reactivation of waking sharp wave/ripple (SWR) firing patterns during sleep

The firing patterns of excitatory neurones in the CA1 and CA3 regions show characteristic differences during network oscillations in active waking periods and rest (Box 1), and these are thought to play distinct roles in memory processing. During exploration, each cell shows sparse firing that tends to be restricted to a discrete region of the environment, known as a 'place field' [20,21] (Box 1, Figure Ic). Subsets of these 'place cells' fire in different locations, collectively forming a patchwork of overlapping fields that cover an entire environment (Box 1, Figure Id). As a consequence, the firing patterns of groups of place cells are organised in time, according to the behaviour of the animal. That is, as the animal explores, different

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**Box 1. Hippocampal firing patterns during exploration and sleep**

Waking exploration and rest periods are accompanied by different patterns in the local field potential (LFP). During alert wakefulness and exploration, hippocampal LFP is marked by theta-band oscillations (5–12 Hz, Figure Ia) (Ref. [94]). In rodents, sleep can be broadly subdivided into rapid eye-movement (REM) (that is again marked by theta oscillations) and non-REM epochs. Non-REM sleep is dominated by SWR events (Figure Ia,b). The two components of the SWR are the negative 'sharp waves' in the CA1 stratum radiatum [95] and the transient fast 'ripple oscillations' (150–250 Hz) in the CA1 pyramidal layer [16,21]. These events are initiated by the synchronous discharge of CA3 cells, that in turn promotes both ripple oscillations and the synchronous (~5 fold increase in synchrony relative to theta epochs) discharge of cells in the CA1 (Refs [17,27,96,97]). Whereas both CA1 interneurones and pyramidal cells show a marked increase in firing rate, the increase in pyramidal cell firing is greater [97]. In turn, these events lead to depolarisation and increased network activity in the entorhinal cortex and subiculum [91,98], as well as coordinated firing across several brain regions. Although mainly characterised through rodent studies, SWR activity has also been identified in primates and humans, although at a slower frequency [99,100].

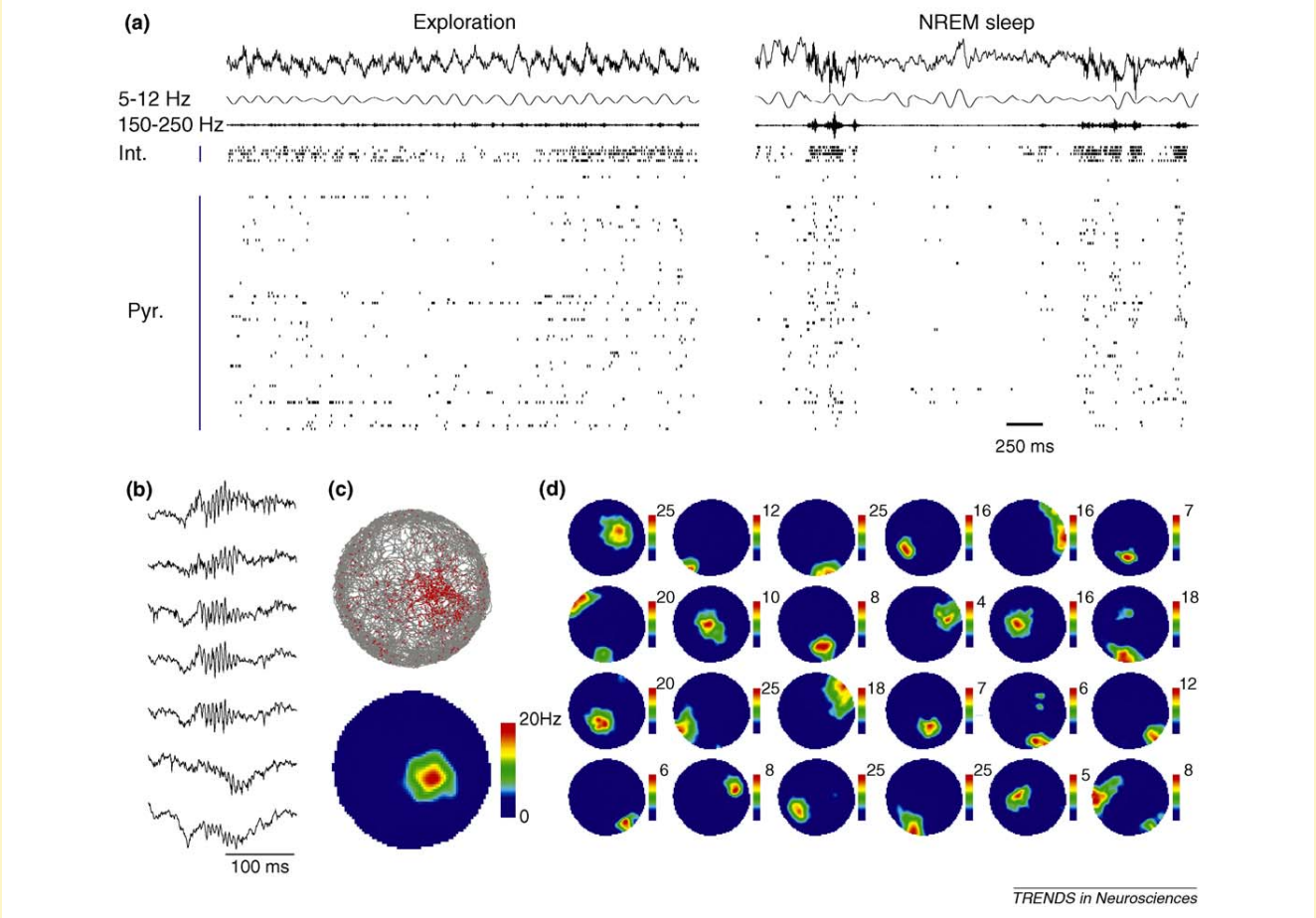


**Figure I.** Hippocampal network activity during waking and sleep periods in the rodent. **(a)** Illustration of network activity in the CA1 region of the hippocampus during exploration and non-REM (NREM) sleep [97]. Top traces: wide band (1 Hz – 5 kHz) and band-pass filtered local field potentials recorded in the pyramidal cell layer. The exploratory period is marked by rhythmic theta band activity (5–12 Hz, middle trace) whereas non-REM is accompanied by sporadic bursts of ripple oscillations (150–250 Hz, lower trace) [16,21]. The raster plots show the spike timing of simultaneously recorded CA1 pyramidal cells and interneurones during the two behavioural periods. The vertical lines indicate the action potential times of cells. Int, CA1 interneurons; Pyr, CA1 pyramidal cells. As described in Ref. [17], CA1 neurones show high synchrony clustered around ripple activity during sleep. **(b)** Wide band (1 Hz – 5 kHz) traces of a ripple oscillation from 7 different electrodes placed in the CA1 pyramidal cell layer. **(c)** Illustration of the place-selectivity of a CA1 neuron [20,21]. Top panel: red dots mark the locations of action potentials fired by an individual cell whereas the grey trace shows the path taken by the animal during exploration. Note that the cell discharges in a specific part of the circular arena. Bottom panel: the firing rate of the cell is shown as a function of location. High firing-rate regions (marked by warm colours: red > orange > yellow) indicate the 'place field' of that cell. **(d)** Illustration to show how different CA1 place cells express firing fields in different regions of the environment, covering the whole recording arena [21].

groups of cells fire together in specific locations within the environment. Retaining the spatial and temporal organisation of these firing patterns could provide the basis of a memory trace of waking experience. One potential repository of such a trace is the CA3 region, that is endowed with intense recurrent connectivity and highly modifiable synapses [22,23]. Here, groups of jointly firing cells can form associations through changes in synaptic weight. Thereafter, firing by only a subset of these cells would tend to recruit the whole group (or 'assembly') through their recurrent connections, thereby recalling the entire 'pattern' [23–25]. In such networks, previously stored patterns could spontaneously recur [26] when the coincident activation of some cells ('initiator cells' [18]) triggers the completion of an entire assembly pattern. Therefore, pattern completion in the CA3 region could promote the replay of waking patterns during rest and sleep.

Immobility and non-REM sleep are marked by sporadic bursts of synchronous firing in the CA1 and CA3 regions, coordinated by SWR events. These events are thought to be initiated within the CA3 region [17,27], and therefore ensemble activity during SWR is primarily governed by the established synaptic weights within the CA3 area, and between the CA3 and CA1 regions. Thus, firing patterns during SWR could be shaped by pattern completion so as to promote the joint firing of hippocampal assemblies representing a memory trace. In turn, this rehearsal-like 'reactivation' of stored memory traces could facilitate their consolidation [28].

The development of large-scale multi-channel recording techniques in behaving rodents [29] has provided physiological evidence in support of this conjecture. Using these techniques, the experimenter can record the firing patterns of large ensembles of cells in the animal while it explores and sleeps, making it possible to test whether the waking activity patterns of place cells are reactivated in subsequent sleep. First shown by Wilson and McNaughton, CA1 pyramidal cells with overlapping place fields show a greater tendency to fire together during sleep following exploration than do cells encoding different locations. Moreover, this relationship was strongly reduced in the sleep preceding the exploration [30] . Thus, different groups of cells fire together from one sleep to another according to the configuration of place fields in the intervening exploration [31–33] (Figure 1). Importantly, sleep reactivation was strongest during SWR [31,33,34]. These techniques have been used extensively to demonstrate how patterns of waking activity are reflected in sleep SWR, utilising different kinds of analyses [35]. An important next step was to show that reactivated patterns reflect more than just the configuration of place fields in the previously explored environment.

## Reactivated hippocampal firing patterns reflect exploratory behaviour

If reactivation of hippocampal firing patterns underlies the consolidation of hippocampus-dependent memories, reactivated patterns ought to reflect not only the environment the animal explored, but also its recent behaviour. Several studies have shown that sleep firing patterns reflect the path taken by the animal during exploration. When animals run for food on a narrow track, place cells fire in a controlled order while the animal traverses each place field in turn. Under these conditions most place cells tend to fire in one direction only, so that pairs of these cells show a temporal bias in their joint firing patterns (i.e. one cell tends to fire before the other). This temporal bias during exploration is retained into subsequent sleep [36]. Moreover, further studies have demonstrated that entire firing sequences of cells active during track running are replayed in following sleep-SWR, but on a faster timescale than during the track running [37,38] (as represented by the schematic in Figure 2). It should be noted that such sequence replay also takes place during REM sleep [39].

Ensemble activity during SWR in rest periods also reflects the behaviour of the animal in 'open field' environments, where the animal is free to explore an arena and does not follow a stereotyped path. Here, waking firing patterns are more reliably reactivated during SWR when the animal has spent a longer time exploring the recording arena [32]. Moreover, reactivation improves even on the linear track if the animal spends more time shuffling back and forth on the path [40], collectively suggesting that reactivation improves with experience.

A further indication that SWR firing patterns reflect behaviour, and not simply the environment, comes from the fact that more frequently visited places are reactivated more strongly in subsequent sleep. It was shown that, during subsequent sleep, the firing synchrony of cells encoding a particular location increased as a function of the time spent in that location during the previous exploration period [33]. Thus, reactivated patterns were biased towards the most visited places (Figure 3).

Together, these findings argue that firing patterns associated with exploration are reactivated during sleep. The caveat to all these studies is that no specific learning paradigm has been performed in these experiments. Recent work has shown that inhibiting synaptic release in CA3 pyramidal neurons after learning suppresses both reactivation in the CA1 region and the consolidation of context-dependent memory, indicating that these

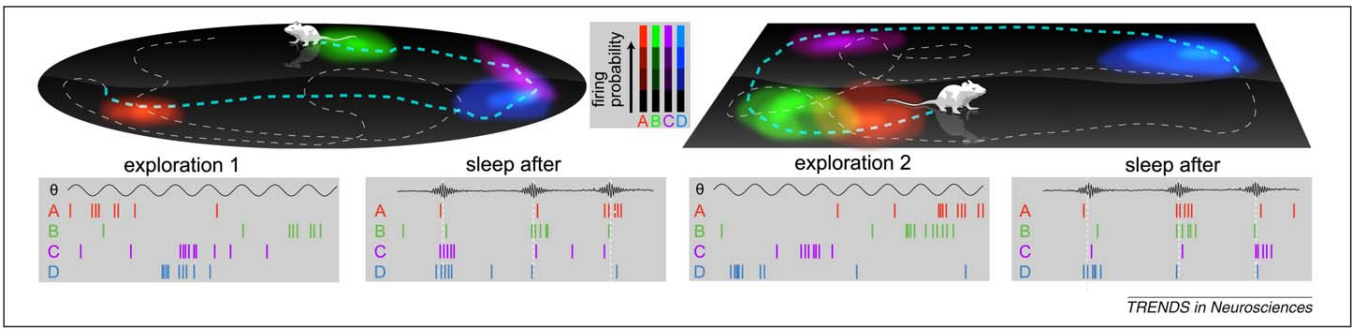


**Figure 1.** Reactivation of place-related waking firing patterns. The figure provides a schematic illustration of how neuronal firing patterns associated with visited places are reactivated during sleep [30,33]. Panels show the location of firing fields from four hippocampal pyramidal cells in two environments. Note that in the circular arena, cells C and D show overlapping place fields, whereas in the rectangular environment cells A and B overlap. The bottom panels show raster plots for the same 4 cells during a sequence of exploration and sleep periods in the circular arena and then the rectangle environment. Note that during theta periods in the circular arena, cells C and D fire together within a single theta cycle, and continue to rigorously fire together during SWR in subsequent sleep. However, during exploration in the rectangle environment, cells C and D no longer fire together, and consequently do not fire together during the next sleep session. Conversely, cells A and B do fire together in this environment and fire together in the following sleep session. Thus, the tendency of cells to fire together is reorganised between sleep sessions, depending on the spatial firing patterns of the pyramidal cells during exploration.

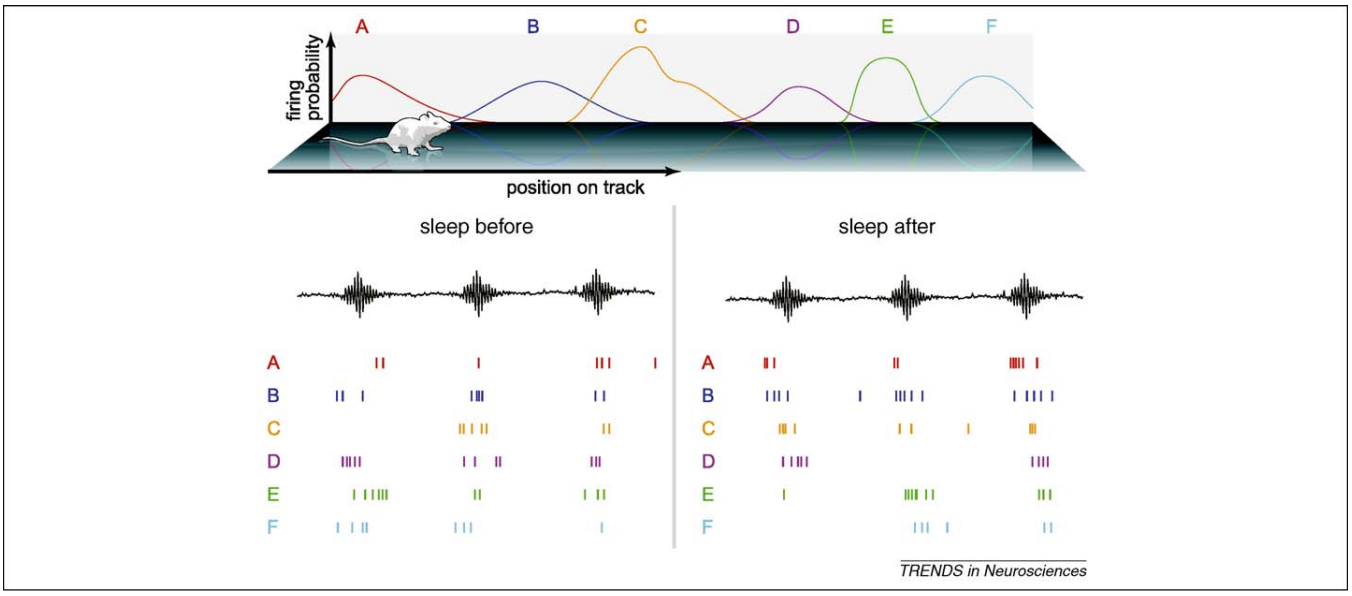


**Figure 2**. Reactivation of spike sequences. This figure shows a schematic illustration of how CA1 pyramidal cells tend to fire in the same order during sleep as during a prior track running session [37,38]. Upper panel: firing probability of six hippocampal pyramidal cells A–F as a function of the location of the rat as it traverses the linear track. Bottom panels: spike times of the same cells during sleep before and after the track running. Note that in the first sleep (the sleep before track running), cells fire in an order that is unrelated to ensemble firing patterns during subsequent track running. However, in sleep after exploration, the order of cell firing during an SWR reflects the order in which the cells fired during track running.

phenomena are related [34]. Additional evidence linking reactivation to memory comes from the fact that memory-impaired aged rats exhibit impaired sequence reactivation [41]. Finally, two recent reports indicate that SWR emission during rest periods is associated with consolidation. By real-time detection of SWR it was possible to stimulate afferents to the CA1 region at the beginning of SWR, thereby preventing the full expression of SWR. Rats with disrupted SWR during rest following a spatial memory task showed a weak impairment in learning over days [42,43]. Such data indicate a role for SWR in the consolidation of spatial memory. However, there is a possibility that electrical stimulation during SWRs could have altered CA3–CA1 synaptic connections in these experiments, so disrupting learning [44,45]. Moreover, it is also not clear whether SWRs alone, or reactivation during SWRs, promote consolidation. Therefore, it has not been directly shown so far that reactivated patterns represent memory traces in the process of consolidation. Even so, we know that reactivated patterns represent previous waking experience that first require their storage within the hippocampus. The putative mechanisms underlying these processes are discussed in the following section.

## Does synaptic plasticity underlie reactivated patterns?

Donald Hebb was the first to speculate that memories could be encoded by the coordinated, 'reverbatory', activity of cell populations and that such activity packets might be stabilised into more permanent constructs (Hebbian cell assembly) due to the 'persistence or repetition' of this activity. This would tend to induce 'lasting cellular changes that add to its stability' [26]. The discovery of long-term potentiation (LTP) [46] provided a potential physiological mechanism, and LTP can be induced through the frequent pairing of pre- and post-synaptic action potentials (i.e. a Hebbian learning rule). Many forms of synaptic plasticity are dependent on NMDA-type glutamate receptors (NMDARs), including LTP at the synapses between pyramidal cells in the CA3 and CA3–CA1 areas [47,48]. Blocking NMDARs has been shown to impair both spatial learning [49,50] and the consolidation of certain hippocampus-dependent memories [51]. Thus, NMDAR-dependent synaptic plasticity could underlie the storage of memory traces for subsequent reactivation.

### *Spike timing dependent plasticity (STPD) and sequence replay*

The replay of place cell sequences after exploration of one dimensional (1D) environments could be explained by the formation of asymmetric associations between place cells during track running, such that, during sleep, cells tend to fire in the same order as during exploration. These asymmetric associations could be established following a form of Hebbian mechanism known as STDP. In this NMDAR-dependent process, potentiation only occurs when the presynaptic cell fires before the postsynaptic cell; if the postsynaptic cell fires first then depression results [52,53]. During track running, place fields expand backwards relative to the direction in which the animal is running, a process that is NMDAR-dependent [54–56]. Such an effect could be explained by the formation of stronger associations between cells with neighbouring place fields, so that each cell strengthens its connection weight with those postsynaptic cell pairs that lie next in the direction that the animal is running. These asymmetric associations could bias cells to fire earlier on the next traversal of the track and potentially contribute to the formation of assembly sequences for subsequent reactivation.

### *Synaptic plasticity in the reactivation of places*

Conversely, in 2D environments the animal can take many different paths while it explores its environment. Here, cell

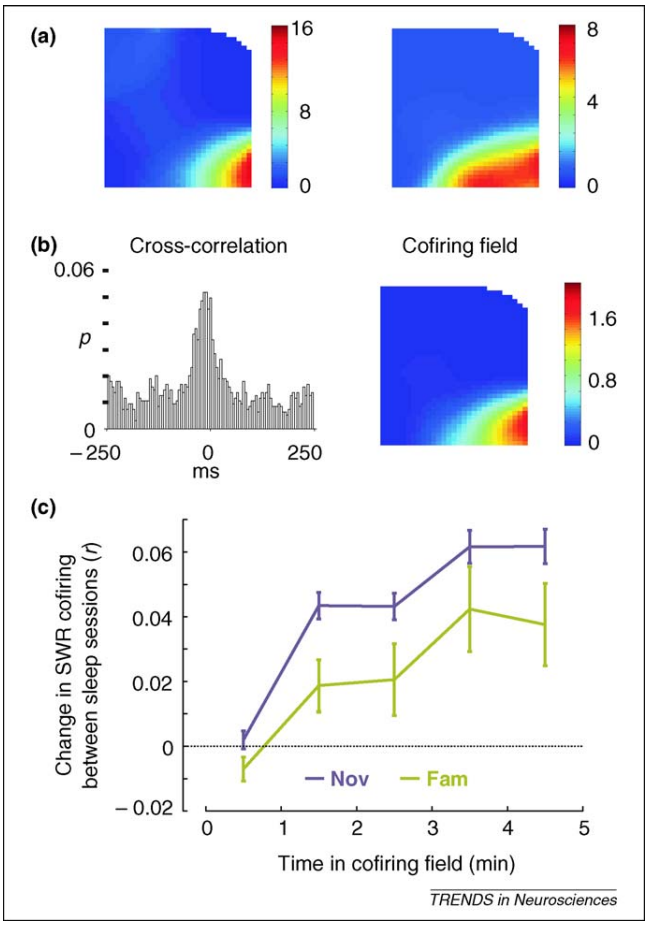


**Figure 3**. Behaviour-dependency of sleep reactivation following exploration of 'open field' environments. **(a)** Representative examples of two CA1 place cells with overlapping fields recorded in a square environment. **(b)** Cross-correlation between the spike times of the same cells with the region of the environment where both cells fired together, referred to as their 'cofiring field' [33]. **(c)** Change in sleep SWR cofiring between pairs of cells as a function of the time spent in their cofiring field. Note that the more time spent during exploration in the 'cofiring field' of a cell pair, the bigger the increase in their SWR cofiring in sleep after exploration relative to control sleep before. This change in SWR cofiring was larger for novel (Nov, marked in purple) than familiar (Fam, marked in green) environments. Figure adapted from Ref. [33].

pairs with overlapping fields will not necessarily fire in a set pre–post order because the animal will not consistently cross one field before another. Yet reactivation of places occurs even if cells do not exhibit a temporal bias in their waking firings needed for STDP [32]. The firing rates of cells are correlated between waking and sleep sessions, and changes in rate between sleep sessions could thus promote the joint firing of different subsets of cells [57,58]. However, this 'rate-reactivation' alone cannot explain the cofiring of cells observed during reactivation [33], and associative changes involving synaptic plasticity between cells are likely to be required. A recent report indicates that the joint firing tendency (cofiring) of cells during subsequent sleep depends on how many times they fired together during exploration. In addition, these cells must fire together within short (<50 ms) time intervals in order to observe reactivation [33], reminiscent of the coactivity required by Hebb's learning rule. Indeed, recent data suggest that precise pre–post order is not required to induce LTP at CA3–CA1 region synapses [59,60], suggesting that LTP can occur at synapses between cells that repeatedly fire together, and even if they do not fire in a set temporal order.

Incorporating labile representation of novel waking experience into pre-existing representations could require additional processes to prevent their degradation through interference with already existing representations.

### *Reactivation after exploration of novel environments*

Spatial learning often involves forming internal representations of newly encountered environments. The stabilisation of new place representations requires NMDAR-dependent plasticity. NMDAR blockade does not prevent the recall of place maps representing familiar environments, or the formation of new context-specific place maps that emerge upon entry to a novel environment. However, when administered prior to experience in the novel environment, NMDAR blockade prevents the subsequent reinstatement of these newly-established place maps 24 hours later [61], implying that encoding and/or consolidation are disrupted rather than retrieval processes. Thus, synaptic plasticity within the hippocampus could be upregulated in novel environments, thereby facilitating encoding of new places and events. Tulving and colleagues proposed the 'novelty-encoding hypothesis' whereby the probability of long-term storage of information varies directly with the novelty of the information [62]. In this way, enhanced reactivation following novel experience could preferentially facilitate the consolidation of memory traces representing those events. Consistent with this hypothesis, reactivation is stronger following exploration of novel than familiar environments [33,63] (Figure 3). Exploration of novel environments is associated with increases in the firing rate [64,65] and coordination of CA1 pyramidal cells [66], that could promote neuronal plasticity. Moreover, exposure to novel environments results in a lower threshold in CA1 for LTP induction facilitated by dopaminergic D1/D5 receptor activation [67]. In addition, exposure to novelty promotes increases in hippocampal levels of acetylcholine [68] and noradrenaline [69], both of which can facilitate LTP [59,70].

### *Plasticity during exploration-associated SWRs*

SWR emission is not restricted to sleep or waking periods of long immobility. Exploration-related SWR (eSWR) can occur during pauses in locomotion at the border of theta oscillations, or even while the animal is still moving [32,66].

CA1 and CA3 pyramidal cell firing patterns exhibit reduced place-selective firing as a function of the time elapsed following theta oscillations [32,71], so that SWR-related firing during periods of long immobility is less influenced by the location of the animal [32]. By contrast, during eSWR, cells within their place field fire more robustly than outside (Figure 4a). This enhanced firing represents an overlap of spatial inputs – presumably originating in the entorhinal cortex [72,73] – and the SWR-related firing of the CA3 region. The combination of these two inputs produces a greater-than-sum firing of CA1 area pyramidal cells [32] (Figure 4b). Thus, during these events, cells with place fields in the location where

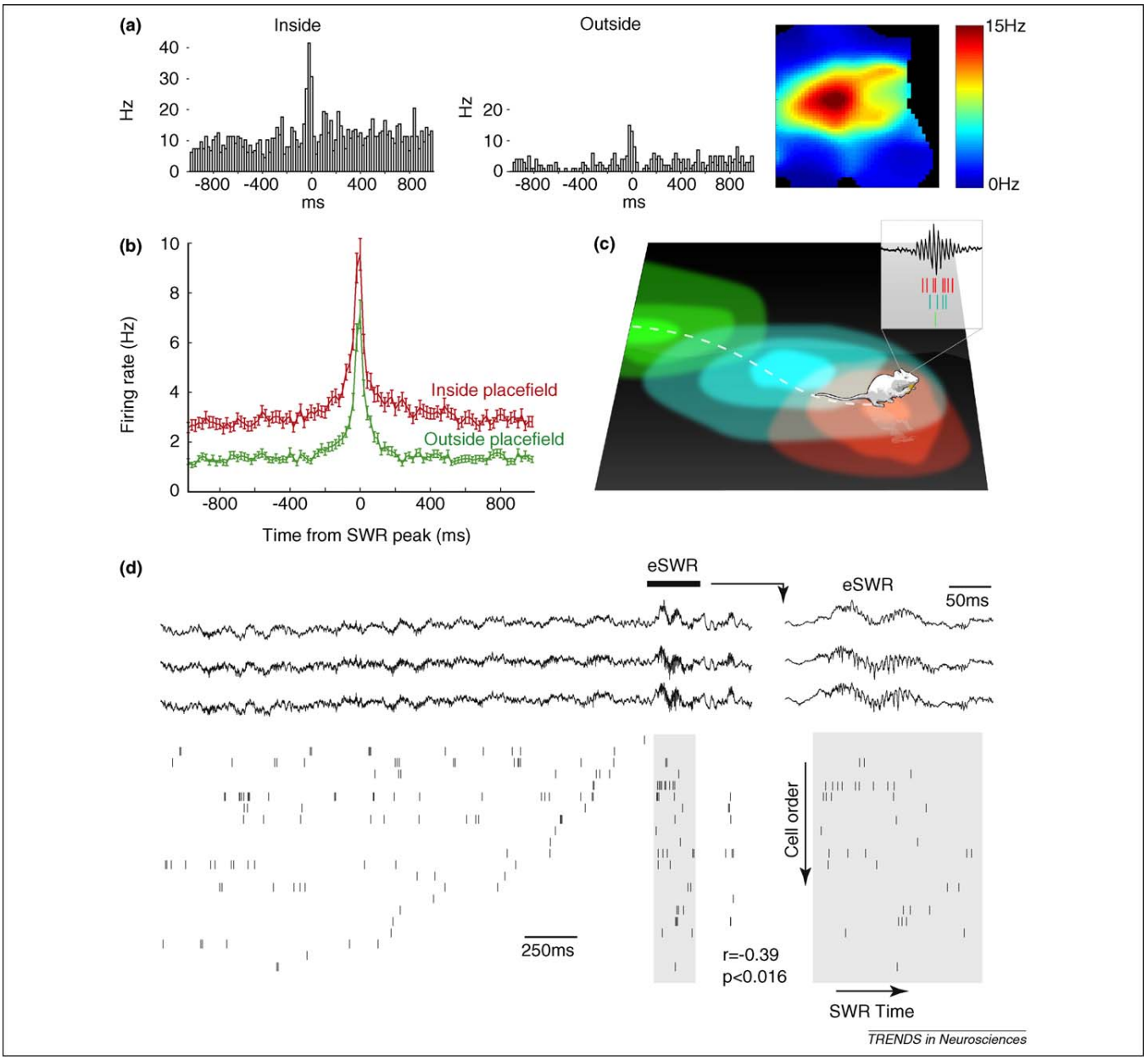


**Figure 4**. SWR-related firing patterns of CA1 pyramidal cells during brief pauses in exploration. **(a)** SWR firing response of a CA1 place cell during SWRs that occurred during or near to theta periods (eSWR). The eSWR firing response was calculated separately for eSWRs that occurred inside or outside the place field of the cell depicted in the right panel. The cell's peak firing response is larger for eSWRs that occur inside its place field [32]. **(b)** The eSWR network response of CA1 pyramidal cells is greater inside than outside of their place fields [32]. **(c)** Organisation of spatial firing patterns during eSWR. The figure shows a schematic illustration of a scenario where a rat traverses three place fields (green, blue and red) before pausing for a food reward, where an eSWR occurs. The red cell exhibits the strongest firing during eSWR because the eSWR occurs at the centre of its place field, whereas the green cell, having a place field outside the eSWR field, fires the weakest. Stronger-firing cells tend to start firing earlier during eSWRs, hence recently firing cells with infield eSWR location tend to fire first, whereas cells with a place-field outside the eSWR location will fire last [65]. **(d)** An example of reverse-order reactivation of pyramidal cells during eSWR. The upper panels show wide-band (1 Hz–5 kHz) traces from three different recording sites within the pyramidal cell layer; the lower panels show a raster plot of the simultaneous activity of CA1 pyramidal cells. Each line shows the activity of a different cell, with vertical lines marking spike-times. Cells were sorted according to the time of their last spike before the leading eSWR border. Note that pyramidal cells show a tendency to fire in a reverse order during the eSWR window relative to their previous ranked firing. The eSWR window is marked in grey. The top horizontal bar marks the time interval shown in the expanded traces in the second panel. Panels (a) and (b) are adapted from Ref. [32]; panel (d) is adapted from Ref. [65].

the eSWR was emitted fire together strongly, providing the conditions for a further strengthening of associations between them [32]. Spatial inputs therefore select which CA3 and CA1 cell assemblies are active during eSWR. Some studies have reported that the incidence of eSWR-like high-frequency oscillations could be higher in a novel environment than in a familiar environment, suggesting that these are involved in the boosted reactivation of patterns associated with the novel environment [66]. These data suggest a dual role for SWR, both in facilitating initial trace acquisition during active exploration and in promoting the replay of memory traces. Indeed, recent data indicate that the hippocampus can rapidly switch between coding and replay modes.

## Reactivation during brief pauses in exploration

An assumption in the two-stage model of memory formation is that trace reactivation occurs during sleep, so

as to reduce interference caused by ongoing trace formation. However, recent findings show that reactivation also occurs during SWR in brief pauses of exploration [63,74,75].

Ensemble firing is organised into sequences during SWR at reward locations (Figure 4c) [63,65,73,75]. The first demonstration of this was made during SWRs recorded at reward locations at either end of a linear track. In these SWRs, place cells fired in an order that reflected the position of their place field on the track. However, this 'replay' of track running occurred in reverse order, such that the most recently visited locations were replayed first [74,75]. It was subsequently shown that both forward and reverse replay can take place in these SWRs, and it was proposed that the order of replay depends on whether the animal is just about to leave the food reward location (forward replay) or has recently arrived (reverse) [74], although this remains to be confirmed (but see Ref. [76]). Sequences that are replayed in reverse order are unlikely to be established during locomotion through asymmetric synaptic modification because STDP should lead to replay firing in the same order as during track running (i.e. forward), as described above. In such a case, forward replay could be similar to that seen in sleep, reflecting asymmetric associations formed between place cells during exploration. On the other hand, reverse replay is likely to be driven by recent network activity prior to the SWR [65]. Such replay is likely to take place during eSWRs, when place-selective drive itself can promote reverse replay [65] (Figure 4c). This idea is supported by the fact that, in open-field exploration where the animal can follow varied trajectories, firing during eSWR shows reverse replay of recent activity (Figure 4d), whereas no reverse replay is observed during SWR in longer periods of immobility [65]. Moreover, there is little anticipatory forward replay of open-field exploration during eSWR [65]. In fact, several models of reverse replay assume increased depolarisation for recently firing cells with place fields at the SWR location [74,75,77].

Thus the hippocampus can rapidly switch between encoding and replay modes during waking activity. During exploration, reverse replay might serve to coordinate recent spiking activity, and perhaps facilitate associations between cells representing salient features in the environment, such as a reward. In 1D environments, forward replay could represent the early stages of consolidation. Some forward replay could represent an anticipatory context-appropriate retrieval that prepares for subsequent route-taking, as in the theta-based forward-sweeping of successive locations that occurs at decision points [78]. Such 'retrieval' is not mutually exclusive with the process of consolidation.

## Reactivation occurs throughout the brain

Whereas it remains controversial whether the hippocampus is the final repository of spatial/episodic-like memory, joint reactivation between hippocampus and cortex remains central to the concept of systems consolidation. Several lines of evidence suggest that reactivation is coordinated throughout the brain. Initially, Qin *et al.* showed in both the hippocampus and parietal cortex that pairs of cells that expressed joint activity during behaviour continued to fire together in subsequent sleep [79]. This reactivation occurred between the two regions, as well as within each individually, suggesting that reactivation is a global and coordinated phenomenon. This finding has been extended by work showing that similar reactivation occurs between groups of neurones from several different cortical regions that are not necessarily monosynaptically connected [80]. This coordinated and brain-wide reactivation is consistent with the replay of a memory trace that is distributed across different brain regions, with each area contributing a component of the trace that reflects its role in waking processing. In support of this idea, Pennartz and colleagues report that reactivation of basal ganglia waking activity is strongest for reward-related neurones and that hippocampal–striatal ensembles are reactivated together during sleep, suggesting a putative mechanism for the consolidation of place–reward associations [81,82]. In addition, recent data taken from recordings in the hippocampus and visual cortex showed that coherent reactivation of behaviourally relevant sequences tends to co-occur in both structures [37]. Using a similar paradigm as described above, sequences of hippocampal cells were established during track running. However, some visual cortical cells also showed firing that was restricted to segments of the track (probably firing in relation to visual cues), and thus also fired in a set order. During slow-wave sleep, segments of these sequences in both visual cortex and hippocampal cells were replayed. Although this sequence replay was infrequent, they tended to co-occur. Finally, recent data demonstrated that reactivation in the prefrontal cortex preferentially occurs during hippocampal SWRs [83].

## Hippocampal–neocortical dialogue during sleep

In the previous section we described how reactivation is coordinated between the hippocampus and other cortical areas. However, a description of the physiological mechanism behind this coordinated replay is still lacking. The network interactions between the hippocampus and the neocortex have been examined in detail. Much of this work aimed to describe the temporal relationship of hippocampal SWRs to neocortical network oscillations. It has been shown that SWR are temporally aligned with cortical spindles (10–18 Hz), slow-wave oscillations and slow-wave-associated delta waves [84–87], and these could indeed favour hippocampal–neocortical dialogue. Synchronisation of hippocampal network patterns to neocortical slow oscillations has drawn special attention. Neocortical slow oscillations are related to up and down states: during slow-wave sleep and anaesthesia, the membrane potentials of neocortical neurones show a bimodal distribution and fire spikes in blocks of increased firing (known as the 'up state'), followed by periods of quiescence ('down state') [88]. Several studies have demonstrated that SWR activity is modulated by cortical up and down states although the findings of these studies do not converge. Some studies indicate that SWRs tend to occur in the up state [37,84,86] whereas others suggest that they preferentially occur during the down-to-up state transition [89,90]. These differences are possibly due to the different methods (and different brain

regions) used to estimate the occurrence of up and down states. Some studies suggest that reactivation during SWRs occurs later than neocortical up-state transitions [37]. This temporal relationship could potentially allow cortical firing, acting via the entorhinal cortex, to influence which patterns are reactivated in the hippocampus. Such inputs could provide partial triggers, enabling CA3 pattern completion to reinstate the closest stored trace. In turn, these completed CA3 patterns during SWR firing can recruit the subset of specific cortical assemblies, via the CA1 region. Indeed, it has been shown that, in some brain areas receiving direct input from hippocampus, units discharge consistently after hippocampal SWRs – such regions include the entorhinal cortex [91], the prefrontal cortex [92] and the ventral striatum [82].

## Conclusions

In many cortical areas, if not all, waking patterns of neuronal activity spontaneously recur during subsequent sleep. Indeed, any cortical circuits that possess excitatory recurrent collateral systems could potentially store waking patterns to be reactivated.

The hippocampus seems especially prepared to orchestrate brain-wide reactivation: it is at the end of a cortical hierarchy of associational processing, giving it access to highly-refined multimodal representations. Moreover, pyramidal cell assemblies in hippocampal CA3 are densely interconnected, enabling it to associate, store and recall vast numbers of complex patterns [23]. Finally, it has the capacity to switch rapidly between online and offline modes, seemingly ideal for memory formation and consolidation, respectively. This is in agreement with the idea that waking experience, initially processed by modality-specific neocortical circuits, can be associatively bound in the hippocampus such that a long-term link is established between the different components of a memory trace. It is this complete association of components that constitutes an episodic memory, and it seems that the long-term consolidation of such an association requires reactivation by the hippocampus in order to coordinate the progressive recruitment of the interrelated components in downstream cortical areas. SWR network burst patterns in the hippocampus, and cortical events associated with them, could reflect the mechanism of such recruitment, and could thus provide the substrate for controlled consolidation of complex memory traces.

Although many questions remain (Box 2), the evidence reviewed above strongly suggests that SWR-associated hippocampal reactivation is a robust phenomenon that has the attributes necessary to implement episodic memory consolidation. The greater temporal control over hippocampal processing provided by optogenetics [93] should yield more definitive evidence for the role of reactivation in consolidation, as well as the mechanisms underlying this phenomenon.

### Box 2. Outstanding questions

- Although studies have shown that reactivated patterns are related to the prior behaviour of the animal, and that SWR emission could facilitate spatial learning, no study has yet shown whether reactivation itself reflects acquired memory traces or plays a role in consolidation. One must therefore ask:

i). Specifically, in a complex memory task, does reactivation reflect what has been learned?
ii). For example, in a task where a number of items must be learned, are representations of the recalled items reactivated more strongly or frequently than the poorly-learned items?
iii). In general, can reactivation predict future recall of acquired information?

- No data as yet shed light on *how* reactivation might facilitate consolidation; whether reactivation might result in the *transfer* of information from the hippocampus, and/or strengthen the associations between mnemonic items across different brain regions?
- Does reactivation play a role in the consolidation of all types of hippocampus-dependent memories, or of only certain types?
- A further outstanding issue is related to the mechanism behind reactivation. While synaptic plasticity is likely to be required for the storage of reactivated patterns, it is not clear what kind of network events bring about plastic changes and what changes occur at the cellular and synaptic levels.
- Finally, the factors that govern the reactivation of specific patterns are also not understood. Do extrahippocampal inputs control which patterns are reactivated?

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