Review

CellPress

Memory trace replay: the shaping of memory consolidation by neuromodulation

Laura A. Atherton[1], David Dupret[2], and Jack R. Mellor[1]

[1] School of Physiology and Pharmacology, University of Bristol, Bristol, BS8 1TD, UK
[2] Medical Research Council Brain Network Dynamics Unit at the University of Oxford, Department of Pharmacology, Oxford, OX1 3TH, UK

The consolidation of memories for places and events is thought to rely, at the network level, on the replay of spatially tuned neuronal firing patterns representing discrete places and spatial trajectories. This occurs in the hippocampal-entorhinal circuit during sharp wave ripple events (SWRs) that occur during sleep or rest. Here, we review theoretical models of lingering place cell excitability and behaviorally induced synaptic plasticity within cell assemblies to explain which sequences or places are replayed. We further provide new insights into how fluctuations in cholinergic tone during different behavioral states might shape the direction of replay and how dopaminergic release in response to novelty or reward can modulate which cell assemblies are replayed.

What is memory trace replay?

What determines which memories are retained and which are lost is an absorbing topic for scientists and nonscientists alike, yet the mechanisms underlying the persistence of some pieces of information and the forgetting of others remain to be identified. Well-established theories propose that memories are encoded during wake behavior, with information being represented in the coordinated activity of subsets of neurons forming cell assemblies [1–4]. However newly encoded memories are typically fragile and, because they may decay, require additional maintenance processes. At the network level, one such process is the off-line reactivation of assembly firing patterns observed during active behavior. This process is best illustrated by the location-specific firing of principal cells [5–8] in the hippocampus. These place cells (see Glossary) are activated sequentially as an animal runs through an arena. Subsequently, co-active place cells representing a discrete place or sequential place cell activation representing a trajectory are reactivated or replayed during SWRs (Boxes 1 and 2), which intermittently occur in slow wave sleep (SWS) (sSWRs), long periods of awake immobility (iSWRs), or brief pauses in exploration (eSWRs) (reviewed in [9,10]).

Sequential replay can occur in both a forward [11–15] and backward [11,13–16] direction, with the directional balance proposed to be dependent on the ongoing behavioral state of the animal [17]. Similar to theta-phase precession [18], these replayed sequences are temporally compressed compared with those observed during wake

Glossary

Acetylcholine: a neuromodulator and neurotransmitter with numerous functions, including attention, learning, arousal, and synaptic plasticity, which mainly exerts its actions via nicotinic and muscarinic receptors.
Current sinks and sources: subdomains along the neuronal membrane where net positive charge flows into (sinks) or out of (sources) neurons. The location of sinks and sources is inverted for a net negative charge.
Dopamine: a neuromodulator classically implicated in reward or reward-prediction error; it exerts its actions via G-protein-coupled receptors.
Hippocampus: a structure within the medial temporal lobe that is important for episodic memory, spatial learning, and associational recollection. It comprises CA1–3 and the DG. Input to the hippocampus comes primarily from the entorhinal cortex via axons of the perforant pathway and temporoammonic pathway, which connect the entorhinal cortex with the DG and CA3, or CA1 respectively. Hippocampal mossy fibers are axons connecting the DG to CA3, while axons of the Schaffer collateral pathway connect CA3 to CA1. CA1 axons then project out of the hippocampus to the subiculum.
Medial septum/basal forebrain: primary source of cholinergic fibers innervating the neocortex and hippocampus.
Place cells: hippocampal principal cells increasing their discharge of action potentials in a specific location (place field) of the environment.
Reactivation/replay: the reoccurrence during off-line states of the firing patterns of hippocampal principal cells previously observed during active waking behavior. These waking activity patterns can either represent discrete places or extended sequences of place cell activity.
Sharp wave ripples (SWRs): hippocampal transient network events manifest as negative potentials (sharp waves) in the CA1 stratum radiatum superimposed with short-lived, fast (140–250 Hz) frequency oscillations (ripples) in the CA1 stratum pyramidale. SWRs mainly occur during long periods of behavioral awake immobility and SWS.
Synaptic plasticity: an activity-dependent change in the efficiency of synapses. If occurring for an extended period of time, an increase in synaptic strength is referred to as long-term potentiation (LTP), while a decrease is referred to as long-term depression (LTD).
Theta phase precession: the phenomenon whereby a place cell spikes at progressively earlier phases of a theta cycle during movement through the place field of that cell.
Ventral tegmental Area (VTA): midbrain structure containing the dopaminergic cell bodies of the mesocorticolimbic dopamine system. The VTA targets a large number of structures, including not only the accumbens, olfactory tubercle, orbitofrontal cortex, motor cortex, striatum, lateral septum, ventral pallidum, extended amygdala, subventricular zone, and lateral habenula, but also the entorhinal cortex and hippocampus.

Corresponding author: Atherton, L.A. (LA.Atherton.2009@my.bristol.ac.uk).
Keywords: hippocampus; sharp-wave ripples; replay; synaptic plasticity; dopamine; acetylcholine.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2015.07.004

Box 1. Sharp wave ripples in the hippocampus

Sharp wave ripples (Figure I) are transient hippocampal network events observed in a variety of species, including humans [43,113–115]. They comprise negative potentials (sharp waves) in the CA1 stratum radiatum superimposed with short-lived, fast frequency oscillations (ripples) in the CA1 stratum pyramidale. Sharp waves have a current sink in the stratum radiatum of CA1 and CA3 and a current source in the pyramidal cell layer [55,72,116,117], whereas ripples have sink–source pairs at the level of the stratum pyramidale [43,117]. The frequency of the ripple oscillations in CA1 spans a large frequency range [118] that is positively correlated to the amplitude of the sharp wave, with frequencies ranging from 140 to 250 Hz for large sharp waves down to the fast gamma range of 90–140 Hz for smaller sharp waves [55,119], a frequency that is more akin to those of ripples in CA3 [43,117]. Given the absence of CA3–CA1 ripple coherence [117], CA3 units firing in an uncorrelated manner to CA1 ripples [118], incoherent interhemispheric CA1 ripples [43,120], and decreasing ripple coherence with distance along the septotemporal hippocampal axis [119], ripples are likely to be generated locally within CA1. Indeed, recent work suggests that SWRs occur when a build-up of excitation drives a population of parvalbumin-positive basket cells to fire. Reciprocal inhibition synchronizes this firing at ripple frequency and creates critical windows for alternate basket cell and pyramidal cell firing [121,122]. Approximately 10–20% of hippocampal pyramidal cells fire in any given SWR, but notably usually only with a single action potential each [43,117].

Despite the lack of widespread ripple coherence, SWRs nevertheless occur simultaneously throughout the hippocampus, subiculum, pre- and parasubiculum cortices, and entorhinal cortex, creating temporal windows of heightened neuronal firing [120,123] and widespread changes in activity throughout the cortical network [124]. As such, they have been proposed as an ideal candidate to transfer labile hippocampal memories to more stable neocortical sites during offline states [72,90] and also to downstream structures, including the ventral striatum [125,126].

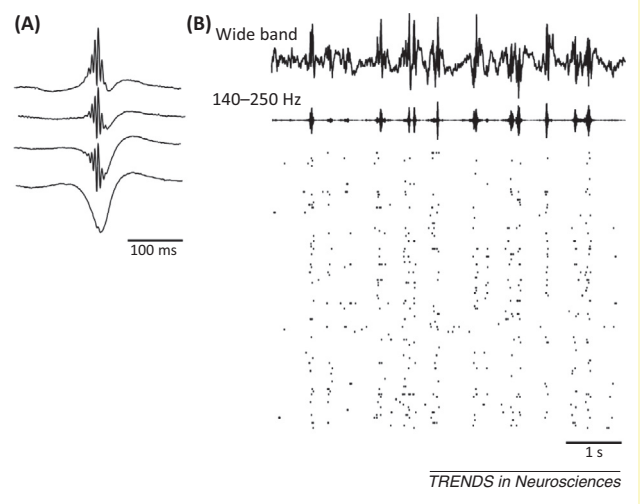

Figure I. Hippocampal network activity during sleep epochs. **(A)** Mean sharp wave ripple (SWR)-triggered local field potential from four separate tetrodes located just above and within the stratum pyramidale (first three waveforms) and below in the stratum radiatum (bottom waveform). **(B)** SWR firing responses of CA1 pyramidal cells during sleep. Top trace, wide-band (1 H–5 kHz) local field potential recorded in the pyramidal cell layer. Bottom trace, 140–250 Hz band pass-filtered local field potential highlighting ripple frequency events. Raster plots, spike times (vertical tics) of simultaneously recorded CA1 pyramidal cells (one cell per row). Note the firing synchrony during ripple events. Data from [69].

behavior [12,13,19,20]. Consequently they have been posited to provide the appropriate temporal neural activity for the Hebbian synaptic modification occurring downstream in neocortical networks during memory consolidation [1,12,21,22]. Although direct support for this hypothesis is currently lacking, intact NMDA receptor (NMDAR) activity during learning and intrahippocampal synaptic transmission during consolidation are at least necessary for unimpaired memory consolidation and place cell reactivation during SWRs [23,24]. Moreover, evidence suggests the hippocampus and neocortex are actively engaged during SWRs and SWS. Cortical and hippocampal sequences, reflecting the same experiences, replay together during SWS [20] and, during SWRs, prefrontal neurons consistently fire within tight temporal windows <100 ms after hippocampal pyramidal cells, which could plausibly drive plasticity at the level of single cell pairs [25].

Concordantly, a growing body of literature has linked SWRs to learning and memory. SWR incidence during SWS is increased following training on a place-reward association task [26]. Conversely, electrically interrupting SWRs during post-training sleep impaired spatial learning [27,28], while interrupting SWRs during training on a spatial alternation task selectively impaired spatial working memory, but not spatial reference memory [29]. Critically, it remains to be determined whether the ongoing hippocampal network activity during SWRs (i.e., global transient changes in interneuron and pyramidal cell activities) or specifically the reactivation or replay of place cell activity during SWRs is the more important for spatial learning and memory. Indeed, SWR activity content can be biased towards newly learnt firing patterns and predict memory performance [24]. Moreover, recent work also showed the induction of an artificial place-preference behavior following intracranial stimulation, triggered by single-place cell activity during sleep. This further suggests that replay of place cell activity serves an important role in spatial memory [30], although how this applies to the coordinated neuronal ensemble activity during SWRs remains to be investigated.

By contrast, replay, particularly during awake SWRs, has also been proposed to have functional roles other than for spatial memory consolidation; for example, in temporal credit assignment to reward locations (particularly backward replay) [16,31]; formation of goal-relevant or novel environment place-related assemblies [24,32–34]; evaluation of trajectory choices for decision making on spatial working memory tasks for prospection and planning (particularly forward replay) [29,35–38]; and representation of unexplored trajectories [15,39]. Preplay of trajectories yet to be experienced has been proposed to facilitate, at least in part, the selection of subsequent place cell representations in a novel environment [40].

Despite over a decade's worth of literature describing hippocampal replay during SWRs, several questions remain. How is neuronal coordination during SWRs controlled? What selects which trajectories will be replayed within a given SWR? Do these mechanisms differ for SWRs in different behavioral states, or under different neuromodulators? In this review, we provide a critique of

Box 2. Replay of place cell activity

As a rodent follows a spatial trajectory, place cells are sequentially activated. In subsequent SWRs, this sequence of place cells may be reactivated in a time-compressed manner in either a forward or a backward direction. The directional bias is dependent on the behavioral state of the animal, with more backward replay in eSWRs, a similar occurrence probability of forward and backward replay in iSWRs, and more forward replay in sSWRs [11,17] (Figure I).

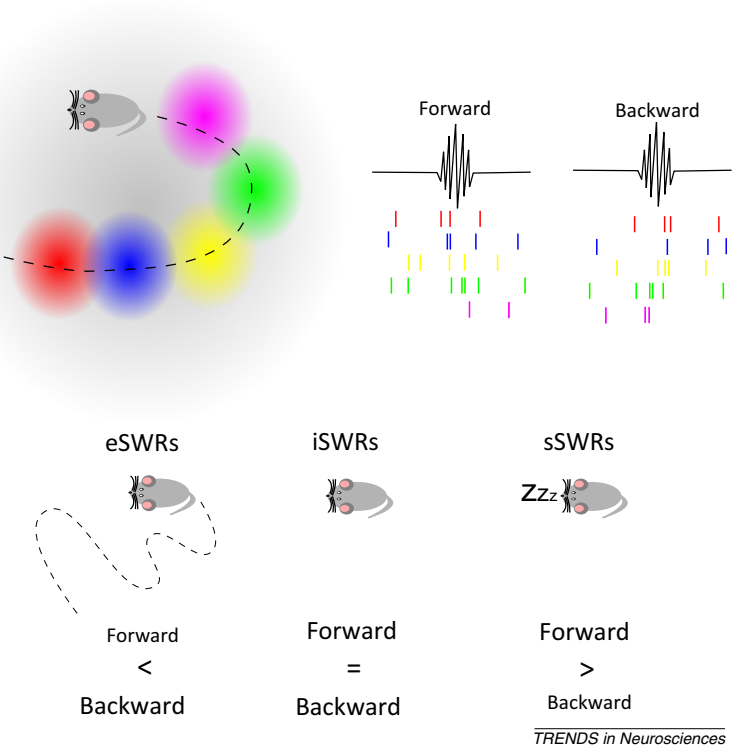

Figure I. Replay of place cell activity in sharp wave ripples (SWRs).

the evidence surrounding two current theories on how replay occurs, namely by lingering place-related excitability or as a result of synaptic plasticity. Given the limitations of both models, we then outline how neuromodulatory factors are likely to influence the mechanisms underlying replay and impart selection onto which trajectories are replayed. Finally, we propose an integrated model for replay in SWRs that takes into account the behavioral state of the animal and the underlying neuromodulatory tone.

Replay by lingering place-related excitability

Replay in a forward or backward direction during awake iSWRs at the ends of linear tracks and in a reverse direction during eSWRs in an open-field environment has been proposed to occur via a residual, place-selective, spatial tuning drive [11,14,16]. In this model, place cells receive subthreshold inputs as a function of the distance of the animal from the place field center of each cell [41,42]. During SWRs, pyramidal cells have a higher firing probability and their waking patterns are reactivated [43–45]. However, the replay firing content *per se* is lingered in an order dictated by the subthreshold spatial inputs onto place cells at the current position of the animal (Figure 1). This effectively represents a nonassociative bias that can influence the spontaneous SWR response of hippocampal cell assemblies [46]. Concordantly, on a linear track, there is a preference for reverse replay at the end of the track following even the first lap [16], while there is a preference for forward replay at the start of the track in anticipation of the run [14].

In support of this model, the firing probability of place cells in eSWRs increased the closer the animal was to the place field center, suggesting that the momentary, place-related, excitatory drive directly contributes to reverse reactivation in an open-field environment [11]. This is consistent with a large proportion of awake replays starting from the current location in a maze, where the spatial inputs would be stronger [13,37,47]. Therefore, the model predicts that sequential activation of place cells in awake SWRs should not only reflect the actual path taken or future path from the current position, but also the cascades of spatially tuned activities dictated by the hippocampal map representation of the entire environment. In line with this suggestion, forward reactivation during eSWRs in a 2D open-field environment was not anticipatory to future path taken [11]; reactivation in SWRs on a spatial alternation task were equally representative of actual and alternative past–future paths [35]; and replay initiated from current location on a long linear track was not biased towards future and past trajectories [13]. However, when the task is goal driven, trajectory sequences in awake SWRs strongly represent the path to the future goal location [37].

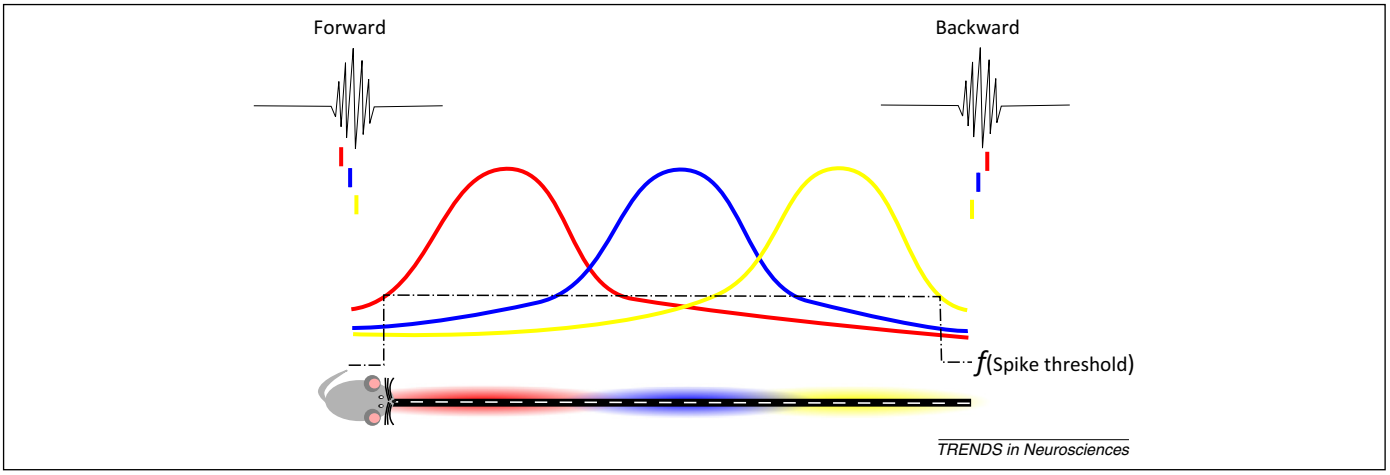

Figure 1. Lingering excitability model. The firing rate of a place cell (colored distributions) can be considered as a symmetrical distribution centered on the middle of the place field of the cell [41,83]. Normal spike thresholds along the track mean that the firing of each cell is turned on and then off as an animal traverses the place field of the cell. However, at the end of the track, where sharp wave ripples (SWRs) may occur as the animal slows down, the hippocampal network moves into a state where inhibitory inputs impinging onto pyramidal cells are temporally redistributed; inhibition at the axon initial segment is removed, effectively reducing the spike threshold of pyramidal cells compared with waking periods outside of SWRs [127]. This then reveals the tails of the firing distributions of the spatially tuned cells so that, during SWRs, the cells fire in an order dictated by these distributions (i.e., forward if the animal was at the start of the trajectory sequence but in reverse if the animal was at the end of the trajectory sequence).

Evidence that challenges this model comes from *in vitro* studies showing that somatic depolarization does not dramatically increase pyramidal cell spiking in SWRs [48,49] and that there was no difference in resting membrane potential between the pyramidal cells that spike during SWRs and those that do not [48]. However, this potentially did not account for the role of synaptic inhibition, which can act to hyperpolarize the membrane (at membrane potentials above the inhibitory reversal potential) or as a shunt at the inhibitory reversal potential. Pyramidal cell spiking is dampened during SWRs by strong perisomatic inhibition [48,50,51], likely from parvalbumin positive basket cells, which are strongly active in SWRs [45,52]. The prolonged somatic depolarization that was used [48,49] would have also increased the size of this hyperpolarizing inhibition by increasing inhibitory drive, as the membrane potential was moved further from the inhibitory reversal potential, and this may explain the absence of a facilitating effect on pyramidal cell spiking. By contrast, the phasic depolarization induced by a dendritic spatial drive from excitatory synapses, in the lingering excitability model, with neurons at resting membrane potential and perisomatic inhibition acting as a shunt [51], may still be sufficient to depolarize pyramidal cells beyond action potential threshold.

Nevertheless, this standalone model cannot explain how goal-directed but not random foraging and/or navigation biases trajectory sequences in awake SWRs to strongly represent the path to the future goal location [37]. Neither does it explain how awake replay occurs in the absence of local sensory drive to place cells. For example, nonlocal forward and backward replay has been observed for trajectories that were either not experienced for more than 10 min [15], or which originated some distance away from the current position of the animal [13]. Moreover, it has been observed that activity in a previous environment is remotely replayed during awake SWRs while the animal is exploring a new environment [53]. Although the first active cell in these remote replays had a higher local firing rate outside of SWRs in the new environment than the last active cell [53], which is consistent with reverse replay depending on the recent firing history of cells [11], this model does not explain how the firing of one initiator cell drives the replay of entire ordered sequences of trajectories from another environment. Clearly, the model also does not explain forward and backward replay during sleep [12,17], where any residual place selective drive has dissipated.

Replay as a result of synaptic plasticity

A different model for the generation of sequential replay posits that place cells active during a given trajectory are coupled together by associative synaptic plasticity during exploration. An autoassociative network is required for this model, which may either be provided by the Cornu Ammonis (CA)-3 network alone, or by rapid interactions between CA3 and the dentate gyrus (DG) [54], considering the potential involvement of the DG in promoting SWR activity [55]. Once a given initiator cell in CA3 becomes active during subsequent SWRs, the entire trajectory sequence is reactivated along the path of least resistance, dictated by the internal connectivity and potentiated synapses between cells [9,12,46,56] (Figure 2). The effect of this can then be read out downstream in CA1 through Schaffer collateral connectivity. This can be considered as being similar to how the internal organization of CA3 has been proposed to underlie internally generated theta sequences [57] and preplay activity [40], or indeed how down to up state transitions during the neocortical slow oscillation might initiate spontaneous sequential cortical activity [58]. Since the likelihood of synaptic plasticity is increased following a repeated number of spike pairings, this model would explain how full replay sequences during iSWRs were not visible until at least one, but sometimes

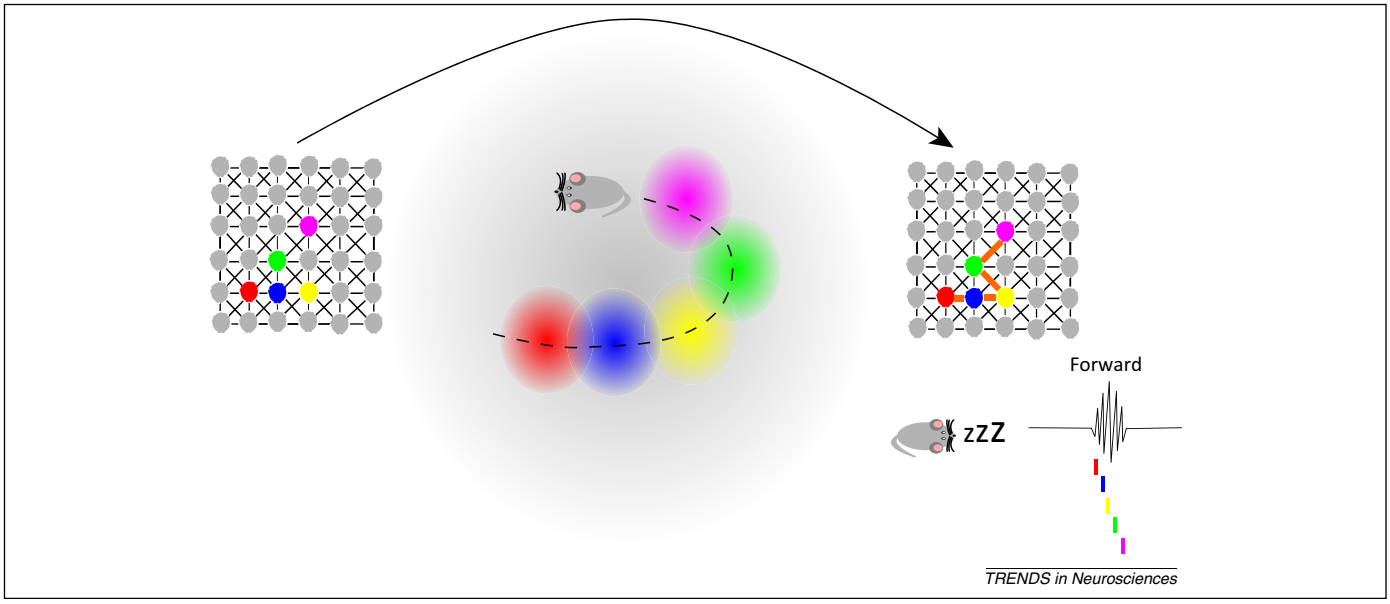

Figure 2. Synaptic plasticity model. In this model, the spatial overlap between the place fields mapping a trajectory in an environment facilitates the strengthening of the excitatory synaptic connections between the transiently co-active place cells. Subsequently, when pyramidal cells are disinhibited during sharp wave ripples (SWRs), the firing of an initiator cell (e.g., the red one) leads to replay of the entire sequence of cells (e.g., the blue, yellow, green, and pink ones) that were previously paired together.

several, laps on a track were completed [16,47]. This model is also supported by computational work showing that CA1 pyramidal cell spiking in SWRs is dependent on the strength of their Schaffer collateral connections [59,60].

If synaptic plasticity is a necessary prerequisite of replay, manipulations that induce plasticity should facilitate SWR replay, while manipulations that prevent plasticity within the hippocampus should not. This prediction has received relatively little support so far, possibly due to methodological considerations, although it has been shown that sSWR-associated unit firing increases following a plasticity-inducing protocol [61]. One approach to blocking plasticity has been to manipulate NMDARs, which are critical for the induction of long-term potentiation at Schaffer collateral and CA3 autoassociational synapses [62,63]. In one study, the NMDAR antagonist CPP was injected before the learning of new goal locations within an already familiar environment [24]. While any synaptic plasticity engaged in encoding the environment would have likely already occurred, the specific reconfiguration of CA1 place cell representations caused by the learning phase [24] would still be liable to perturbation [64]. Consistently, while the mean firing response within eSWRs was not impaired under CPP, the learning-enhanced sleep reactivation of co-activity patterns observed at goal locations was prevented [24]. It would be interesting to know whether the specific blockade of hippocampal NMDARs, rather than systemic CPP injections, has the same effect.

In another study that seemingly challenges the synaptic plasticity model, mice with NMDAR1 knockout (KO) specifically in CA3 pyramidal cells and, therefore, with an absence of NMDAR-dependent long-term potentiation (LTP) at CA3 autoassociational synapses, were found to show stronger, less variable replay of CA1 place cell activity compared with control mice [65]. In this experiment, the mice did not have prior exposure to the environment. During familiarization, lap-by-lap correlations in spiking activity between place cells increased [65], which is a measure of cell assembly formation [66]. This increase and subsequent plateauing was still observed in the KO mice, but at a reduced rate compared with controls [65], not only indicating a role for CA3 synaptic plasticity, but also suggesting that an alternative, potentially plastic, compensatory mechanism, possibly via an alternative autoassociative network, such as DG-CA3, was engaged in binding place cells into coordinated assemblies in these mice. The alternative mechanisms engaged by the NMDAR1 KO mice may have led to the stronger cascading replay activity observed. Therefore, while CA3 NMDAR-dependent synaptic plasticity may not be necessary for the expression of replay *per se*, these studies suggest that NMDAR activity and, as a by product, hippocampal synaptic plasticity, are critically involved in dynamically configuring the hippocampal network into a state that can subsequently bias the SWR activity content. In line with this, while the blockade of NMDARs during learning of new goal locations impaired the sleep reactivation of new place cell representations, it unexpectedly promoted that of old representations [24].

This model is supported by evidence suggesting that reactivation in SWRs is expressed as a function of potentially plasticity-inducing experience. For example, co-activation during awake and sleep SWRs is stronger for cell pairs with overlapping place fields [22,32], which is a requirement that is critical for the induction of long-term potentiation at Schaffer collateral synapses [67]. Indeed, reactivation in iSWRs improves with experience during exploration [32], in a manner dependent on the repetitiveness of the task and, therefore, the likelihood of place cells to be co-active [68]. Consistently, reactivation during sleep was found to be dependent on the number of times place cells

fired together in short windows (<50 ms) during exploration, that is, windows compatible with spike timing-dependent plasticity [56]. Although, since asymmetrical cross-correlations during exploration between cell pairs were not required for reactivation in SWRs, it is debatable whether spike timing-dependent plasticity *per se* is the plasticity mechanism utilized by such a model [32]. By contrast, another carefully designed study found no relation between awake replay and experience. Poorly and extensively experienced trajectories were replayed in similar proportions, never-experienced shortcut sequences were observed during SWRs, and replay was more representative of a scenario independent of experience [15].

This latter observation casts doubt on whether this model alone can sufficiently explain all observable replay phenomena. It is difficult to reconcile a plasticity mechanism that could bind ensembles of cells together in a manner that would enable backward replay preferentially during exploratory behaviors but forward replay during sleep [11,17,32]. Moreover, the preferential reactivation in SWRs of novel locations or environments over familiar ones [33,56,69] (although see [11]), the stronger reactivation on rewarded trials over unrewarded trials [31], and the enhanced reactivation of firing patterns surrounding reward sites [24,31] are incompatible with the above model when considered in the absence of neuromodulatory drive.

How does neuromodulation impact SWR activity?

The hippocampus receives constant inputs related to the behavioral state of the animal, including those leading to the release of neuromodulators, which dramatically transform the functional output of neural circuitry [70]. Acetylcholine and dopamine are two such factors whose action within the hippocampus bears particular relevance when considering hippocampal processing during spatial navigation and memory tasks. Here, we propose that these neuromodulatory factors during specific behavioral epochs can explain the observed activity of place cells within SWRs that may otherwise be considered inconsistent with the lingering excitability or synaptic plasticity models when viewed in isolation. Given their different spatiotemporal profiles of release, we propose acetylcholine and dopamine to have different functional roles for the processes underlying memory consolidation. However, at times of simultaneous cholinergic and dopaminergic release, these roles likely occur concomitantly.

Acetylcholine

Microdialysis measurements of hippocampal acetylcholine levels show variation throughout the sleep–wake cycle, with acetylcholine high during rapid eye movement (REM) sleep and active wakefulness but decreasing levels during quiet wakefulness and SWS [71]. SWRs are generally believed to be initiated when subcortical, particularly cholinergic, drive to the hippocampus is reduced [1,72]. Accordingly, optogenetic stimulation of cholinergic medial septal neurons strongly suppressed SWRs in awake and anaesthetized animals [73], while muscarinic receptor activation suppressed SWRs *in vitro* [74,75]. This could explain why exploratory eSWRs observed during periods of high cholinergic tone occur at a reduced rate compared with awake immobility iSWRs, when the cholinergic tone is reduced [32]. These findings suggest that firing activity during eSWRs and i/sSWRs is differentially modulated by acetylcholine.

Within the hippocampus, acetylcholine exerts wide-ranging cellular and synaptic effects [76]. At the pyramidal cell level, acetylcholine causes membrane depolarization, increased input resistance [77–79], and enhanced NMDAR currents [80,81] specifically via the inhibition of SK channels [79,82]. Since somatic depolarization facilitates the emergence of place cell spiking in previously silent CA1 pyramidal cells [83], during eSWRs (but to a lesser extent in iSWRs and not in sSWRs), cholinergic-mediated depolarization would be predicted to facilitate the contribution of subthreshold place-related drive and, thus, the lingering excitability model, to the reactivation of place cell activity. Indeed, place cells have reduced firing rates following pharmacological inactivation of the medial septum [84,85] or pharmacological blockade of muscarinic receptors [86].

In addition, muscarinic receptor activation by endogenously released acetylcholine *in vivo* [87,88], or by pharmacological manipulations *in vitro* [79,89], lowers the threshold for long-term potentiation of excitatory synaptic transmission in the hippocampus. Notably, overlapping CA1 place cell activity was able to engage LTP in CA1 only if sufficient cholinergic tone was present *in vitro* [67]. Therefore, during exploratory activity, acetylcholine likely has a permissive role in the coupling of place-related cell assemblies by synaptic plasticity. It is also possible that the exploration-related cholinergic tone during eSWRs promotes the ability of intra-SWR place cell activity (i.e., replay activity itself) to generate synaptic plasticity. Accordingly, an interesting prediction from this framework is that sSWR activity, while still important for memory consolidation [27,28], may have a reduced likelihood of inducing plasticity compared with waking SWRs, because cholinergic tone declines. Surprisingly, however, while SWRs have long been posited to provide temporal windows for synaptic plasticity within the hippocampus and in downstream areas [1,90], few studies have tested whether SWR-driven spiking can induce synaptic plasticity [61].

Clearly, the impact of acetylcholine on place cell activity during exploration and SWR activity is complex and deserves further investigation by experimentation and computational modeling. Meanwhile, the available literature, outlined above, points towards a model whereby the behavioral state of the animal influences how the hippocampus engages both the lingering excitability and synaptic plasticity mechanisms to initiate replay activity, in a manner strongly shaped by the cholinergic tone (Figure 3). This new framework may go some way to explain the directional bias of replay in different behavioral states [11,17].

Dopamine

The hippocampus is also innervated by dopaminergic mesencephalic neurons from the ventral tegmental area (VTA) and substantia nigra [91], although this innervation is sparse [69], with hippocampal dopamine concentrations

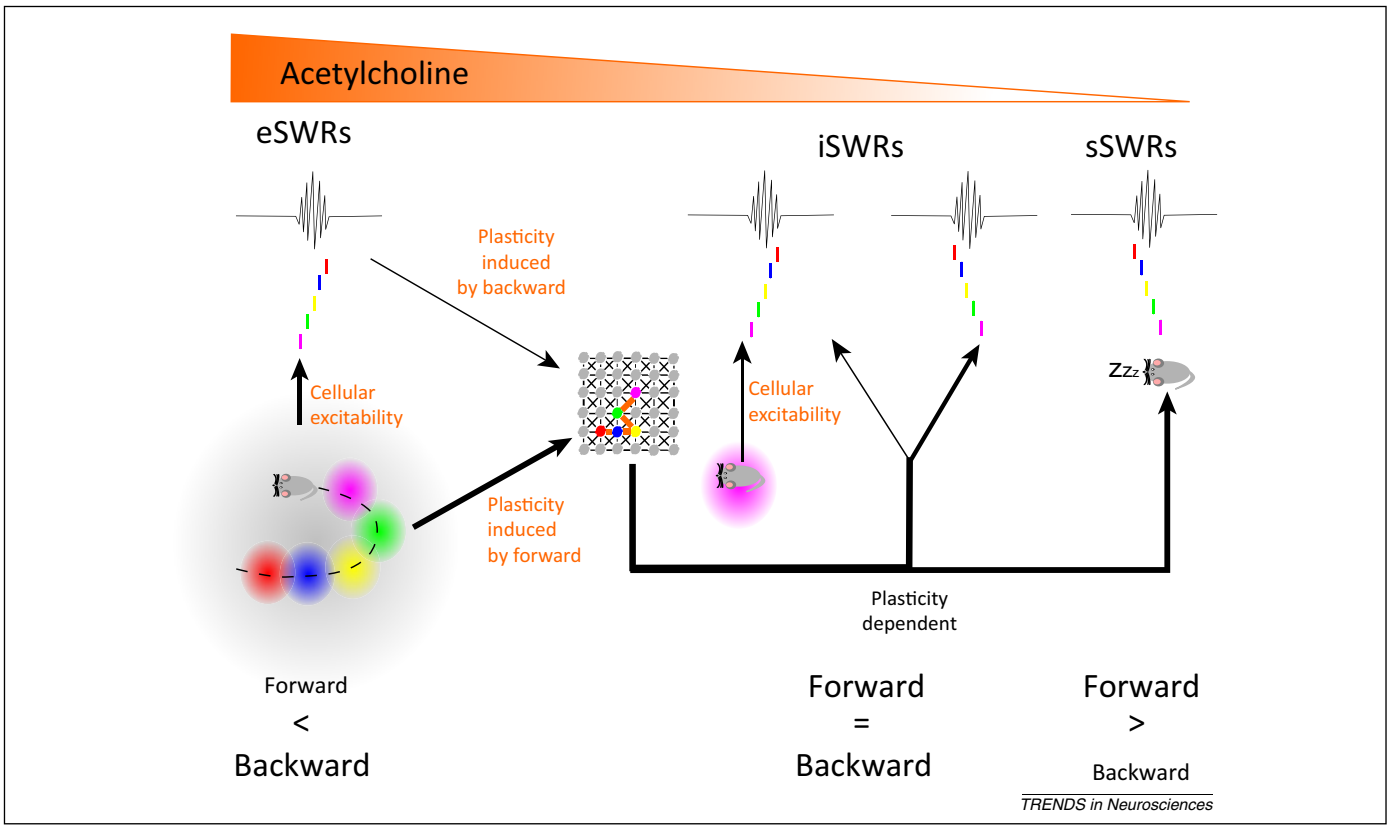

Figure 3. Behavioral state model. During exploration, there are sensory inputs to the hippocampus, place cells are active, and the high cholinergic tone depolarizes cells. These factors all favor predominantly backward replay in exploration sharp wave ripples (eSWRs) [11,32], in accordance with the model of lingering excitability. It is predicted that this backward replay in eSWRs and the forward activation of place cells during exploration, in the presence of high cholinergic tone, both lead to synaptic plasticity between the active place cells with overlapping place fields [67]. An important assumption is that plasticity induced from environmental exploration is greater than that induced by activity in eSWRs and, therefore, there is a bias in subsequent SWRs for forward replay over backward replay. During longer periods of immobility, this plasticity-dependent forward replay bias is balanced by the lingering excitability of place cells, which, although reduced due to slightly lower levels of acetylcholine [71] and a longer time spent immobile, is still capable of providing an initiation bias to the current position [13,37,47] that can drive backward replay. Consequently, during immobility (i)SWRs, there is an equal balance of forward and backward replay [17]. However, since there is a lower level of cholinergic tone, it is predicted that replay during iSWRs induces less plasticity than the replay in eSWRs. Hence, the plasticity-dependent bias for forward replay is maintained. Thus, when the animal sleeps and the lingering excitability and sensory drive to place cells are removed, replay now occurs solely through the plasticity-dependent mechanism and there is more forward than backward replay [12,17].

much lower than in other brain areas, such as the striatum [92]. Notable recent work also suggests that hippocampal dopamine can be released from noradrenergic neurons from the locus coeruleus [93]. VTA neurons exhibit bursting in response to reward or reward-prediction stimuli [94] (reviewed in [95]) and display increased firing, with a higher propensity to fire in bursts, during exposure to novel environments [69]. This is associated with increased dopamine release in downstream areas, including the hippocampus [92].

Interestingly, place cell ensembles are more reactivated in sleep SWRs following the exploration of novel locations and/or environments [33,56,69] and following reward-driven learning tasks [24,31]. During SWRs at reward locations, there is also a higher probability of pyramidal cell firing on rewarded versus unrewarded trials [31], and cells with place fields surrounding the reward site have an increased likelihood of firing in both these reward SWRs and subsequent sSWRs [24,31]. Moreover, sequential replay has been shown to be biased towards goal and/or reward sites, with forward and backward replay preferentially representing sequences approaching or ending at the reward site, respectively [15,37].

Therefore, it is tempting to make the conjecture that dopamine release during exposure to spatial novelty or rewarded outcomes biases the content of subsequent SWR activity for the purpose of memory to represent locations spanning the entire novel environment or the particular behaviorally salient location, respectively. Concordantly, a recent study has shown that burst stimulation of VTA dopaminergic neurons, during exposure to a novel environment (to further enhance novelty-increased VTA firing [69]), subsequently enhanced hippocampal reactivation in a D1/D5 receptor-dependent manner [69]. Neither the general activity of CA1 pyramidal cells during the awake and sleep periods (mean firing rate, SWR-firing rate response, or preferred theta phase) nor the sSWR incidence were modified by such an intervention. These findings suggest that dopamine promotes the consolidation of new memories by the sleep reactivation of newly formed firing patterns. Along this line, it has been further shown that, during the memory retention test of a hippocampal-dependent goal-directed task on a crossword maze, CA1 place maps formed during learning were only partially reinstated and behavioral performance was degraded. However, photostimulation of VTA dopaminergic fibers

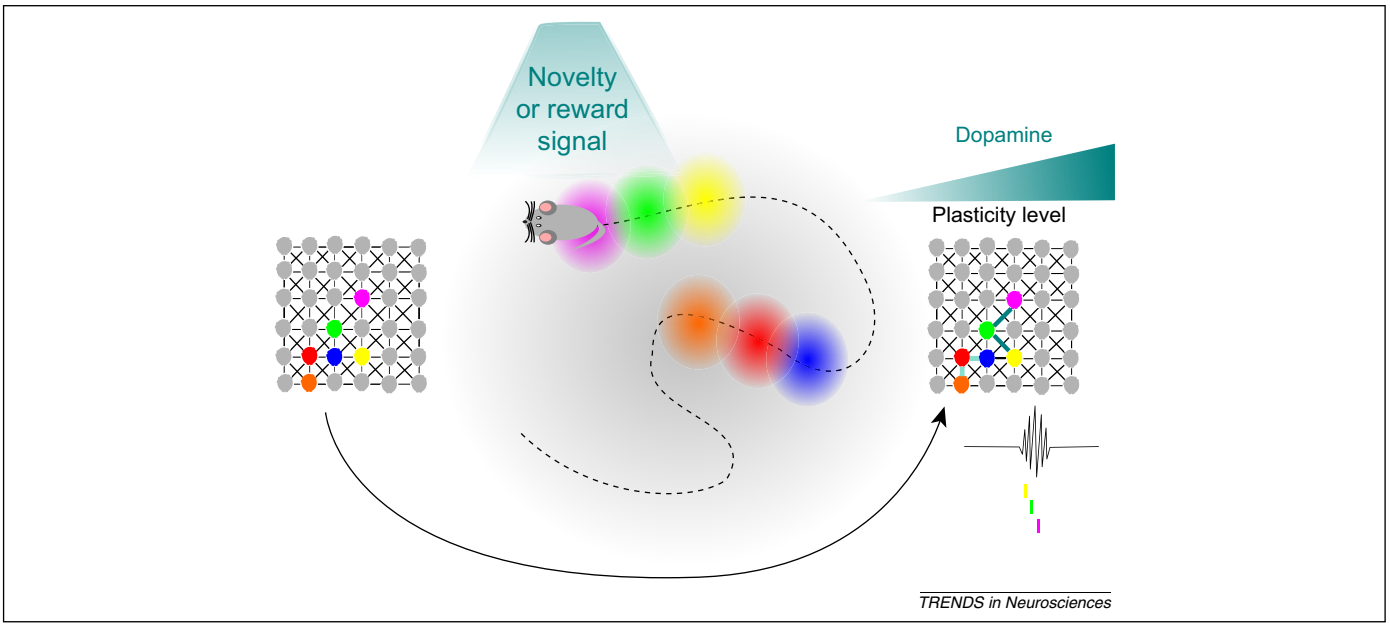

Figure 4. Novelty and/or reward based model. Dopamine release in response to novelty or reward facilitates the formation of stable place cell assemblies through synaptic plasticity (note the stronger connection within the network between the yellow, green, and pink fields compared with the orange, red, and blue fields). This increases the likelihood of replay of cell assemblies active during novel or rewarding environments via the synaptic plasticity model.

in dorsal CA1 during learning enhanced SWR reactivation of newly established place cell assemblies. This was accompanied by improved reinstatement of these firing patterns in the retention test and a stable behavioral performance [69]. These findings are consistent with other previous findings showing that midbrain dopaminergic neurons can promote hippocampal place cell dynamics related to memory processing (e.g., [96–98]) and numerous findings providing additional support at the behavioral level (e.g., [99–101]).

It is unclear how dopamine may bias SWR activity through the lingering excitability model since the effects of dopamine on hippocampal pyramidal cell excitability are mixed, with some studies reporting a decrease in excitability, for example by hyperpolarizing the membrane potential and augmenting the spike after hyperpolarization [102], while others report an increase in excitability [103]. However, in both novel environments, and during learning on a goal-driven spatial navigation task, hippocampal place cells remap their activity [8,24,104]. The stability of these new place cell representations, but not the initial formation, is NMDAR dependent [24,64] and can be facilitated by D1/D5 receptor activation [98] or optogenetic stimulation of VTA dopaminergic terminals in CA1 [69]. Indeed, pharmacological inhibition of VTA neurons has been shown to impair CA1 place cell stability [97]. These results support a model where dopamine release in novel environments or during reward-driven spatial learning facilitates synaptic plasticity, which then stabilizes place cell activity. Specifically, this may occur via the permissive role of dopamine in the transition from early to late long-term potentiation, potentially through the synaptic tagging and capture hypothesis, as reviewed elsewhere [105,106]. It should also be noted that increased CA1 pyramidal cell firing and changes in CA1 interneuron firing during novel exploration could also contribute to enhanced synaptic plasticity [8,9,11,104,107]. In agreement, novel environment exposure facilitated the induction of LTP at Schaffer collateral synapses to a weak conditioning stimulus *in vivo* and this facilitatory effect was abolished by D1/D5R antagonists or mimicked by D1/D5R agonists [108]. Consequently, via the synaptic plasticity model, dopaminergic modulation likely biases replay to preferentially reactivate cell assemblies relevant to novelty or reward (Figure 4).

How the brain informs the dopaminergic systems about spatial novelty or rewarded outcomes remains to be investigated. This likely involves a complex network of multiple brain circuits [38,109,110]. For instance, it has been recently shown that VTA dopaminergic cells receive spatiocontextual inputs from the hippocampus via the lateral septum [111]. Moreover, how dopamine release and the firing activity of dopaminergic neurons also relates to aspects of motor actions [112], in addition to reward prediction and spatial novelty, remains to be disentangled.

Concluding remarks

In conclusion, we have proposed a new conceptual framework for understanding the ordered sequential activation of prior waking activity in SWRs. This likely occurs via a combination of mutually nonexclusive mechanisms, since none of these can explain the available literature in isolation. While many questions remain (Box 3), our current understanding leads us to suggest that the lingering excitability model largely dictates local replaying sequences during awake behavior, while the synaptic plasticity model contributes to subsequent nonlocal awake replays and replaying activity during future rest. Within this framework, we have proposed that cholinergic tone is important for shaping the direction of replay in different behavioral

Box 3. Outstanding questions

- The ability of replay activity to drive excitatory synaptic plasticity within the hippocampus and between the hippocampus and neocortical sites, a central concept to the proposed function of SWRs in memory consolidation, has received limited experimental attention [61]. Can *in vivo* patterns of SWR-related firing drive excitatory synaptic plasticity *in vitro* at specific synapses? How does cholinergic tone impact how SWR activity induces synaptic plasticity?
- Similarly, evidence testing whether synaptic plasticity can drive pyramidal cell firing in SWRs is limited [61]. By artificially inducing synaptic plasticity onto specific cells and within cell assemblies, can the content of SWR activity be biased? What type of synaptic plasticity is required and at which synapses?
- Given the role of inhibition in limiting pyramidal cell spiking in SWRs, how might activity-dependent interneuron plasticity influence SWR pyramidal cell spiking? Could this provide another mechanism for selecting which place cell ensembles are replayed?
- We have assumed that the action of acetylcholine on membrane depolarization and input resistance can facilitate the contribution of subthreshold place-related drive and, thus, the lingering excitability model, to the reactivation of place cell activity. This could be tested similarly to [83] by asking whether optogenetic stimulation of cholinergic input to the hippocampus can determine the emergence of new place cell representations in previously silent CA1 pyramidal cells.
- The behavioral state model could be tested computationally by incorporating rules governing how cholinergic tone influences spiking and synaptic plasticity (both by theta activity and SWR activity) into a model of forward and backward replay during SWRs (e.g., [128,129]). The model could then be used to ask whether cholinergic input could explain the transition in replay direction preference between eSWRs, iSWRs, and sSWRs.
- We have proposed that dopamine release during exploration biases subsequently replaying trajectories via the synaptic plasticity model. Our behavioral state model predicts that this could bias forward over backward replay when dopamine is present. This could be tested by assessing the replay direction of place cell activity at a reward site on rewarded versus unrewarded trials. In addition, can physiological optogenetic stimulation of dopaminergic terminals bias the content of replay to represent an artificial and/or pseudo-reward site?
- Given the involvement of the DG in SWR activity [55] and the influence of the spatially tuned entorhinal cells (e.g., grid and boundary cells) on place cell activity [130], how might activity in the DG and entorhinal cortex influence replay activity?

states. Meanwhile, we have identified dopaminergic release during, for example, novel environments and reward-driven spatial tasks, as being important for biasing the content of subsequently replaying trajectories, potentially to strengthen new place cell assemblies and place-reward associations. Testing this new framework experimentally and computationally will be an important step forward for our understanding of the field.

Acknowledgments

L.A.A. is supported by the Engineering and Physical Sciences Research Council UK and Eli Lilly & Company; D.D. is supported by the Medical Research Council UK; J.R.M. is supported by the Wellcome Trust, Biotechnology and Biological Sciences Research Council UK and Medical Research Council UK. We thank M. Jones for initial discussion and the reviewers for their constructive and helpful comments.

References

1 Buzsaki, G. (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* 31, 551–570
2 McGaugh, J.L. (2000) Neuroscience – memory – a century of consolidation. *Science* 287, 248–251
3 Hebb, D.O. (1949) *The Organisation of Behavior*, Wiley
4 Harris, K.D. *et al.* (2003) Organization of cell assemblies in the hippocampus. *Nature* 424, 552–556
5 O'Keefe, J. and Dostrovsky, J. (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res.* 34, 171–175
6 Leutgeb, S. *et al.* (2005) Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science* 309, 619–623
7 Muller, R.U. *et al.* (1987) Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. *J. Neurosci.* 7, 1935–1950
8 Wilson, M.A. and McNaughton, B.L. (1993) Dynamics of the hippocampal ensemble code for space. *Science* 261, 1055–1058
9 O'Neill, J. *et al.* (2010) Play it again: reactivation of waking experience and memory. *Trends Neurosci.* 33, 220–229
10 Carr, M.F. *et al.* (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat. Neurosci.* 14, 147–153
11 Csicsvari, J. *et al.* (2007) Place-selective firing contributes to the reverse-order reactivation of CA1 pyramidal cells during sharp waves in open-field exploration. *Eur. J. Neurosci.* 26, 704–716
12 Lee, A.K. and Wilson, M.A. (2002) Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36, 1183–1194
13 Davidson, T.J. *et al.* (2009) Hippocampal replay of extended experience. *Neuron* 63, 497–507
14 Diba, K. and Buzsaki, G. (2007) Forward and reverse hippocampal place-cell sequences during ripples. *Nat. Neurosci.* 10, 1241–1242
15 Gupta, A.S. *et al.* (2010) Hippocampal replay is not a simple function of experience. *Neuron* 65, 695–705
16 Foster, D.J. and Wilson, M.A. (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* 440, 680–683
17 Wikenheiser, A.M. and Redish, A.D. (2013) The balance of forward and backward hippocampal sequences shifts across behavioral states. *Hippocampus* 23, 22–29
18 Skaggs, W.E. *et al.* (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6, 149–172
19 Nadasdy, Z. *et al.* (1999) Replay and time compression of recurring spike sequences in the hippocampus. *J. Neurosci.* 19, 9497–9507
20 Ji, D.Y. and Wilson, M.A. (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci.* 10, 100–107
21 Kruskal, P.B. *et al.* (2013) Circuit reactivation dynamically regulates synaptic plasticity in neocortex. *Nat. Commun.* 4, 2574
22 Wilson, M.A. and McNaughton, B.L. (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265, 676–679
23 Nakashiba, T. *et al.* (2009) Hippocampal CA3 output is crucial for ripple-associated reactivation and consolidation of memory. *Neuron* 62, 781–787
24 Dupret, D. *et al.* (2010) The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nat. Neurosci.* 13, 995–1002
25 Wierzynski, C.M. *et al.* (2009) State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. *Neuron* 61, 587–596
26 Ramadan, W. *et al.* (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. *PLoS ONE* 4, e6697
27 Girardeau, G. *et al.* (2009) Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci.* 12, 1222–1223
28 Ego-Stengel, V. and Wilson, M.A. (2010) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus* 20, 1–10
29 Jadhav, S.P. *et al.* (2012) Awake hippocampal sharp-wave ripples support spatial memory. *Science* 336, 1454–1458
30 de Lavilleon, G. *et al.* (2015) Explicit memory creation during sleep demonstrates a causal role of place cells in navigation. *Nat. Neurosci.* 18, 493–495
31 Singer, A.C. and Frank, L.M. (2009) Rewarded outcomes enhance reactivation of experience in the hippocampus. *Neuron* 64, 910–921

32 O'Neill, J. *et al.* (2006) Place-selective firing of CA1 pyramidal cells during sharp wave/ripple network patterns in exploratory behavior. *Neuron* 49, 143–155
33 Cheng, S. and Frank, L.M. (2008) New experiences enhance coordinated neural activity in the hippocampus. *Neuron* 57, 303–313
34 Csicsvari, J. and Dupret, D. (2014) Sharp wave/ripple network oscillations and learning-associated hippocampal maps. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 369, 20120528
35 Singer, A.C. *et al.* (2013) Hippocampal SWR activity predicts correct decisions during the initial learning of an alternation task. *Neuron* 77, 1163–1173
36 Yu, J.Y. and Frank, L.M. (2014) Hippocampal-cortical interaction in decision making. *Neurobiol. Learn. Mem.* 117, 34–41
37 Pfeiffer, B.E. and Foster, D.J. (2013) Hippocampal place-cell sequences depict future paths to remembered goals. *Nature* 497, 74–79
38 Pezzulo, G. *et al.* (2014) Internally generated sequences in learning and executing goal-directed behavior. *Trends Cogn. Sci.* 18, 647–657
39 Molter, C. *et al.* (2007) Reactivation of behavioral activity during sharp waves: a computational model for two stage hippocampal dynamics. *Hippocampus* 17, 201–209
40 Dragoi, G. and Tonegawa, S. (2014) Selection of preconfigured cell assemblies for representation of novel spatial experiences. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 369, 20120522
41 Harvey, C.D. *et al.* (2009) Intracellular dynamics of hippocampal place cells during virtual navigation. *Nature* 461, 941–946
42 Epsztein, J. *et al.* (2011) Intracellular determinants of hippocampal CA1 place and silent cell activity in a novel environment. *Neuron* 70, 109–120
43 Buzsaki, G. *et al.* (1992) High-frequency network oscillation in the hippocampus. *Science* 256, 1025–1027
44 Csicsvari, J. *et al.* (1999) Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat. *J. Neurosci.* 19, 274–287
45 Klausberger, T. *et al.* (2003) Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature* 421, 844–848
46 Shen, B. and McNaughton, B.L. (1996) Modeling the spontaneous reactivation of experience-specific hippocampal cell assembles during sleep. *Hippocampus* 6, 685–692
47 Wu, X. and Foster, D.J. (2014) Hippocampal replay captures the unique topological structure of a novel environment. *J. Neurosci.* 34, 6459–6469
48 Bähner, F. *et al.* (2011) Cellular correlate of assembly formation in oscillating hippocampal networks in vitro. *Proc. Natl. Acad. Sci. U.S.A.* 108, E607–E616
49 Maier, N. *et al.* (2003) Cellular and network mechanisms underlying spontaneous sharp wave-ripple complexes in mouse hippocampal slices. *J. Physiol.* 550, 873–887
50 Hajos, N. *et al.* (2013) Input-output features of anatomically identified CA3 neurons during hippocampal sharp wave/ripple oscillation in vitro. *J. Neurosci.* 33, 11677–11691
51 English, D.F. *et al.* (2014) Excitation and inhibition compete to control spiking during hippocampal ripples: intracellular study in behaving mice. *J. Neurosci.* 34, 16509–16517
52 Tukker, J.J. *et al.* (2013) Distinct dendritic arborization and in vivo firing patterns of parvalbumin-expressing basket cells in the hippocampal area CA3. *J. Neurosci.* 33, 6809–6825
53 Karlsson, M.P. and Frank, L.M. (2009) Awake replay of remote experiences in the hippocampus. *Nat. Neurosci.* 12, 913–918
54 Lisman, J.E. *et al.* (2005) Recall of memory sequences by interaction of the dentate and CA3: a revised model of the phase precession. *Neural Netw.* 18, 1191–1201
55 Sullivan, D. *et al.* (2011) Relationships between hippocampal sharp waves, ripples, and fast gamma oscillation: influence of dentate and entorhinal cortical activity. *J. Neurosci.* 31, 8605–9616
56 O'Neill, J. *et al.* (2008) Reactivation of experience-dependent cell assembly patterns in the hippocampus. *Nat. Neurosci.* 11, 209–215
57 Pastalkova, E. *et al.* (2008) Internally generated cell assembly sequences in the rat hippocampus. *Science* 321, 1322–1327
58 Luczak, A. *et al.* (2007) Sequential structure of neocortical spontaneous activity in vivo. *Proc. Natl. Acad. Sci. U.S.A.* 104, 347–352
59 Taxidis, J. *et al.* (2012) Modeling sharp wave-ripple complexes through a CA3-CA1 network model with chemical synapses. *Hippocampus* 22, 995–1017
60 Taxidis, J. *et al.* (2013) Influence of slow oscillation on hippocampal activity and ripples through cortico-hippocampal synaptic interactions, analyzed by a cortical-CA3-CA1 network model. *Front. Comput. Neurosci.* 7, 3
61 King, C. *et al.* (1999) Hebbian modification of a hippocampal population pattern in the rat. *J. Physiol.* 521, 159–167
62 Collingridge, G.L. *et al.* (1983) Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. *J. Physiol.* 334, 33–46
63 Zalutsky, R.A. and Nicoll, R.A. (1990) Comparison of two forms of long-term potentiation in single hippocampal neurons. *Science* 248, 1619–1624
64 Kentros, C. *et al.* (1998) Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. *Science* 280, 2121–2126
65 Dragoi, G. and Tonegawa, S. (2013) Development of schemas revealed by prior experience and NMDA receptor knock-out. *Elife* 2, e01326
66 Dragoi, G. and Buzsaki, G. (2006) Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron* 50, 145–157
67 Isaac, J.T.R. *et al.* (2009) Hippocampal place cell firing patterns can induce long-term synaptic plasticity in vitro. *J. Neurosci.* 29, 6840–6850
68 Jackson, J.C. *et al.* (2006) Hippocampal sharp waves and reactivation during awake states depend on repeated sequential experience. *J. Neurosci.* 26, 12415–12426
69 McNamara, C.G. *et al.* (2014) Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nat. Neurosci.* 17, 1658–1660
70 Marder, E. (2012) Neuromodulation of neuronal circuits: back to the future. *Neuron* 76, 1–11
71 Marrosu, F. *et al.* (1995) Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Res.* 671, 329–332
72 Buzsaki, G. *et al.* (1983) Cellular bases of hippocampal EEG in the behaving rat. *Brain Res.* 287, 139–171
73 Vandecasteele, M. *et al.* (2014) Optogenetic activation of septal cholinergic neurons suppresses sharp wave ripples and enhances theta oscillations in the hippocampus. *Proc. Natl. Acad. Sci. U.S.A.* 111, 13535–13540
74 Norimoto, H. *et al.* (2012) Muscarinic receptor activation disrupts hippocampal sharp wave-ripples. *Brain Res.* 1461, 1–9
75 Zylla, M.M. *et al.* (2013) Cholinergic plasticity of oscillating neuronal assemblies in mouse hippocampal slices. *PLoS ONE* 8, e80718
76 Teles-Grilo Ruivo, L.M. and Mellor, J.R. (2013) Cholinergic modulation of hippocampal network function. *Front. Synaptic Neurosci.* 5, 2
77 Cole, A.E. and Nicoll, R.A. (1984) Characterisation of a slow cholinergic post-synaptic potential recorded in vitro from rat hippocampal pyramidal cells. *J. Physiol.* 352, 173–188
78 Madison, D.V. *et al.* (1987) Voltage clamp analysis of cholinergic action in the hippocampus. *J. Neurosci.* 7, 733–741
79 Buchanan, K.A. *et al.* (2010) Facilitation of long-term potentiation by muscarinic M-1 receptors Is mediated by inhibition of SK channels. *Neuron* 68, 948–963
80 Markram, H. and Segal, M. (1990) Acetylcholine potentiates responses to N-methyl-D-aspartate in the rat hippocampus. *Neurosci. Lett.* 113, 62–65
81 Marino, M.J. *et al.* (1998) Activation of the genetically defined m1 muscarinic receptor potentiates N-methyl-D-aspartate (NMDA) receptor currents in hippocampal pyramidal cells. *Proc. Natl. Acad. Sci. U.S.A.* 95, 11465–11470
82 Giessel, A.J. and Sabatini, B.L. (2010) M1 muscarinic receptors boost synaptic potentials and calcium influx in dendritic spines by inhibiting postsynaptic SK channels. *Neuron* 68, 936–947
83 Lee, D. *et al.* (2012) Hippocampal place fields emerge upon single-cell manipulation of excitability during behavior. *Science* 337, 849–853
84 Koenig, J. *et al.* (2011) The spatial periodicity of grid cells is not sustained during reduced theta oscillations. *Science* 332, 592–595
85 Brandon, M.P. *et al.* (2014) New and distinct hippocampal place codes are generated in a new environment during septal inactivation. *Neuron* 82, 789–796

86 Brazhnik, E.S. *et al.* (2003) Muscarinic blockade slows and degrades the location-specific firing of hippocampal pyramidal cells. *J. Neurosci.* 23, 611–621
87 Leung, L.S. *et al.* (2003) Cholinergic activity enhances hippocampal long-term potentiation in CA1 during walking in rats. *J. Neurosci.* 23, 9297–9304
88 Ovsepian, S.V. *et al.* (2004) Endogenous acetylcholine lowers the threshold for long-term potentiation induction in the CA1 area through muscarinic receptor activation: in vivo study. *Eur. J. Neurosci.* 20, 1267–1275
89 Shinoe, T. *et al.* (2005) Modulation of synaptic plasticity by physiological activation of M-1 muscarinic acetylcholine receptors in the mouse hippocampus. *J. Neurosci.* 25, 11194–11200
90 Buzsaki, G. (1996) The hippocampo-neocortical dialogue. *Cereb. Cortex* 6, 81–92
91 Gasbarri, A. *et al.* (1994) Mesolimbic dopaminergic-neurons innervating the hippocampal formation in the rat: a combined retrograde traceing and immunohistochemical study. *Brain Res.* 668, 71–79
92 Ihalainen, J.A. *et al.* (1999) Comparison of dopamine and noradrenaline release in mouse prefrontal cortex, striatum and hippocampus using microdialysis. *Neurosci. Lett.* 277, 71–74
93 Smith, C.C. and Greene, R.W. (2012) CNS dopamine transmission mediated by noradrenergic innervation. *J. Neurosci.* 32, 6072–6080
94 Cohen, J.Y. *et al.* (2012) Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* 482, 85–88
95 Schultz, W. (2007) Behavioral dopamine signals. *Trends Neurosci.* 30, 203–210
96 Tran, A.H. *et al.* (2008) Dopamine D(1) Receptor modulates hippocampal representation plasticity to spatial novelty. *J. Neurosci.* 28, 13390–13400
97 Martig, A.K. and Mizumori, S.J.Y. (2011) ventral tegmental area disruption selectively affects CA1/CA2 but not CA3 place fields during a differential reward working memory task. *Hippocampus* 21, 172–184
98 Kentros, C.G. *et al.* (2004) Increased attention to spatial context increases both place field stability and spatial memory. *Neuron* 42, 283–295
99 Furini, C.R.G. *et al.* (2014) D1 and D5 dopamine receptors participate on the consolidation of two different memories. *Behav. Brain Res.* 271, 212–217
100 Rossato, J.I. *et al.* (2009) Dopamine controls persistence of long-term memory storage. *Science* 325, 1017–1020
101 Bethus, I. *et al.* (2010) Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. *J. Neurosci.* 30, 1610–1618
102 Benardo, L.S. and Prince, D.A. (1982) Dopamine action on hippocampal pyramidal cells. *J. Neurosci.* 2, 415–423
103 Pedarzani, P. and Storm, J.F. (1995) Dopamine modulates the slow $Ca2^{+}$-activated K^{+} current I-AHP via cyclic AMP-dependent protein kinase in hippocampal neurons. *J. Neurophysiol.* 74, 2749–2753
104 Frank, L.M. *et al.* (2004) Hippocampal plasticity across multiple days of exposure to novel environments. *J. Neurosci.* 24, 7681–7689
105 Lisman, J. *et al.* (2011) A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends Neurosci.* 34, 536–547
106 Takeuchi, T. *et al.* (2014) The synaptic plasticity and memory hypothesis: encoding, storage and persistence. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 369, 20130288
107 Nitz, D. and McNaughton, B. (2004) Differential modulation of CA1 and dentate gyrus interneurons during exploration of novel environments. *J. Neurophysiol.* 91, 863–872
108 Li, S.M. *et al.* (2003) Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nat. Neurosci.* 6, 526–531
109 Battaglia, F.P. *et al.* (2011) The hippocampus: hub of brain network communication for memory. *Trends Cogn. Sci.* 15, 310–318
110 Pennartz, C.M.A. *et al.* (2011) The hippocampal-striatal axis in learning, prediction and goal-directed behavior. *Trends Neurosci.* 34, 548–559
111 Luo, A.H. *et al.* (2011) Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. *Science* 333, 353–357
112 Jin, X. and Costa, R.M. (2010) Start/stop signals emerge in nigrostriatal circuits during sequence learning. *Nature* 466, 457–462
113 O'Keefe, J. and Nadal, L. (1978) *The Hippocampus as a Cognitive Map*, Clarendon Press
114 Le Van Quyen, M. *et al.* (2008) Cell type-specific firing during ripple oscillations in the hippocampal formation of humans. *J. Neurosci.* 28, 6104–6110
115 Skaggs, W.E. *et al.* (2007) EEG sharp waves and sparse ensemble unit activity in the Macaque hippocampus. *J. Neurophysiol.* 98, 898–910
116 Buzsaki, G. (1986) Hippocampal sharp waves: their origin and significance. *Brain Res.* 398, 242–252
117 Ylinen, A. *et al.* (1995) Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. *J. Neurosci.* 15, 30–46
118 Csicsvari, J. *et al.* (1999) Fast network oscillations in the hippocampal CA1 region of the behaving rat. *J. Neurosci.* 19, RC20
119 Patel, J. *et al.* (2013) Local generation and propagation of ripples along the septotemporal axis of the hippocampus. *J. Neurosci.* 33, 17029–17041
120 Chrobak, J.J. and Buzsaki, G. (1996) High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. *J. Neurosci.* 16, 3056–3066
121 Schlingloff, D. *et al.* (2014) Mechanisms of sharp wave initiation and ripple generation. *J. Neurosci.* 34, 11385–11398
122 Stark, E. *et al.* (2014) Pyramidal cell-interneuron interactions underlie hippocampal ripple oscillations. *Neuron* 83, 467–480
123 Chrobak, J.J. and Buzsaki, G. (1994) Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. *J. Neurosci.* 14, 6160–6170
124 Logothetis, N.K. *et al.* (2012) Hippocampal-cortical interaction during periods of subcortical silence. *Nature* 491, 547–553
125 Pennartz, C.M.A. *et al.* (2004) The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. *J. Neurosci.* 24, 6446–6456
126 Lansink, C.S. *et al.* (2009) Hippocampus leads ventral striatum in replay of place–reward information. *PLoS Biol.* 7, e1000173
127 Somogyi, P. *et al.* (2014) Temporal redistribution of inhibition over neuronal subcellular domains underlies state-dependent rhythmic change of excitability in the hippocampus. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 369, 20120518
128 Cutsuridis, V. and Hasselmo, M. (2011) Spatial memory sequence encoding and replay during modeled theta and ripple oscillations. *Cogn. Comput.* 3, 554–574
129 Vladimirov, N. *et al.* (2013) Synaptic gating at axonal branches, and sharp-wave ripples with replay: a simulation study. *Eur. J. Neurosci.* 38, 3435–3447
130 Bush, D. *et al.* (2014) What do grid cells contribute to place cell firing? *Trends Neurosci.* 37, 136–145