

Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval

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The hippocampus is required for the encoding, consolidation and retrieval of event memories. Although the neural mechanisms that underlie these processes are only partially understood, a series of recent papers point to awake memory replay as a potential contributor to both consolidation and retrieval. Replay is the sequential reactivation of hippocampal place cells that represent previously experienced behavioral trajectories and occurs frequently in the awake state, particularly during periods of relative immobility. Awake replay may reflect trajectories through either the current environment or previously visited environments that are spatially remote. The repetition of learned sequences on a compressed time scale is well suited to promote memory consolidation in distributed circuits beyond the hippocampus, suggesting that consolidation occurs in both the awake and sleeping animal. Moreover, sensory information can influence the content of awake replay, suggesting a role for awake replay in memory retrieval.

Our memories are central to our sense of self. We use past experiences to guide current decisions, an ability that requires episodic memory storage and retrieval. These memory processes engage the highly plastic hippocampal circuit, which is believed to be the initial site of encoding episodic memories. Evidence suggests that there is a subsequent process during which the hippocampus interacts with the rest of the brain to engrain stable, long-lasting representations in hippocampal-neocortical circuits¹⁻⁴. Although there is still debate about how long this consolidation process lasts and whether memories ever become truly independent of the hippocampus^{5,6}, it is clear that the hippocampus is essential in the initial encoding and subsequent stabilization of long term memories⁷⁻⁹. This stabilization is thought to depend on the hippocampally driven reactivation of previously encoded associations, a process that is thought to promote memory storage in the neocortex^{10,11}. Mechanisms underlying this process would need to have several properties. First, putative patterns of hippocampal activity supporting consolidation would need to repeatedly reactivate mnemonic representations in the absence of behavioral repetition. Further, as consolidation refers to the progressive stabilization of a memory trace over time, processes that support consolidation would need to persist for some time period after the experience. Finally, consolidation processes would need to promote plasticity in distributed neocortical circuits, allowing memories that initially depend on the hippocampus to become encoded in more distributed networks over time.

The reactivation of stored hippocampal representations during sharp wave ripples (SWRs) is a physiological pattern of activity that is thought to have all of these properties, suggesting a role for reactivation in consolidation¹¹⁻¹⁵. Reactivation of cell pairs after an experience was first studied during sleep^{13,16}, which reinforced the idea that sleep is a privileged state for memory consolidation processes^{14,17}. However, SWR reactivation has also been found to occur in the awake animal¹⁸. Recently it has become clear that hippocampal representations are replayed frequently and with high fidelity in the awake state, indicating that replay during both waking and sleep could support memory consolidation.

After initial learning, stored associations can be retrieved to guide ongoing behavior. Lesions of the hippocampus lead to severe deficits in the retrieval of recently stored associations, suggesting that the hippocampus plays a fundamental role in memory retrieval for at least a period of time after the experience^{3,19,20}. The patterns of hippocampal activity that support retrieval are likely to show several properties. First, retrieval events must occur during waking behavior and show the 'mental time-travel' associated with episodic memory recall²¹. In other words, retrieval should reactivate the internal representation of an experience in the absence of behavioral repetition. Second, memories can be recollected on a faster timescale than the original experience, suggesting that retrieval of stored representations can be compressed in time. Third, current sensory input should be able to influence which stored representations are retrieved, as in the case of cued memory recall. Finally, to retrieve a memory stored in distributed hippocampal-neocortical circuits, a retrieved hippocampal trace should either initiate or be part of a broader neocortical retrieval event that could be used to make memory guided decisions^{11,22,23}.

There is no consensus as to the specific patterns of hippocampal activity that support memory retrieval. We do know that theta coherence between the hippocampus and prefrontal cortex is greater

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BOX 1 MEASURING AWAKE REPLAY

Identifying replay requires both detection of sharp wave ripple (SWR) events and quantification of reactivated sequences. SWRs are detected in CA1 by identifying times when power in the ripple band (150–250 Hz) exceeds some threshold above the mean. Thresholds as high as 7 standard deviations^{46,50,80} and as low as 3 standard deviations above the mean have been used for SWR detection^{31,39,47,48,53}. There is no obvious bimodality in the SWR amplitude distribution, so there is no ‘correct’ threshold³⁹. Although using a lower threshold may lead to incorrect classification of some events as SWRs, high thresholds will lead to the exclusion of lower-amplitude SWRs. Depending on the question being asked, it is important to determine which type of error leads to more conservative estimates. SWRs can also be identified as periods with transient elevations in the multiunit activity, as these times are generally associated with increased ripple band power⁴⁸. In addition, to distinguish awake replay events from sequential firing occurring during movement-related phase precession, analyses are often limited to times when the animal is immobile and the theta to delta ratio is low.

Replay is marked by the ordered reactivation of hippocampal neurons reflecting previous behavioral experiences. Two methods have been used to detect awake replay when large ensembles of neurons are being recorded: template matching and decoding. Template matching quantifies the correlation between the sequence of firing observed during candidate events and the order of place cells as determined by the location of the place fields observed during locomotion^{46,47,49}. A variant of template matching that compares spike times during exploration and awake SWRs has been used to quantify awake replay in an open field⁵⁰. Template matching can reliably detect large replay events in which most cells with place fields are reactivated. However, because the correlation used to identify significant replay events is between one spike fired during each SWR and the relative location of place field centers, template matching is less effective when only a subset of neurons participate in the SWR event. Furthermore, because place fields are not always well defined by their center location, there can be ambiguity in defining the template sequence. Finally, in a novel environment, place cells tend to be active in both directions of motion along linear tracks⁸², making it difficult to construct unambiguous directional templates.

Bayesian decoding is a more powerful method of detecting sequential reactivation, partially because this approach uses all of the spiking during SWRs and the entire place field structure. Decoding translates the ensemble spiking during a period of time into an estimate of a series of positions^{31,48,80}. An event is considered to be a significant replay event if this series of decoded positions is more consistent with an ordered trajectory through the environment than is a large set of shuffled decoded trajectories. To avoid temporal smoothing across neighboring estimates, and thus the false detection of replayed trajectories, it is important that the decoding algorithm be memoryless^{31,48}.

Ensemble measures such as Bayesian decoding require that large populations of neurons be recorded simultaneously. When only a small population is sampled, pairwise measures can identify activity that is consistent with awake replay. For clarity, we refer to ensemble measures as replay and pair-wise measures as reactivation, although the two methods likely detect the same network events. Pairwise measures quantify the likelihood of two cells firing together during an awake SWR as a function of their coactivity during behavior^{38,39,53,54}. Enhanced coactivation during awake SWRs for pairs of cells that are coactive during behavior is consistent with awake replay. Furthermore, pairwise comparisons of the distance between place fields and the time between spikes within SWRs can reveal activity consistent with ordered replay of behaviorally relevant sequences^{31,53}.

at locations where animals must execute a memory-guided decision^{24,25}. As place field activity is prominent when the theta rhythm is prominent, theta coherence seems well suited to allow information from the hippocampus about the animal’s current position or current trajectory^{26–28} to trigger place-related associations in downstream regions such as the prefrontal cortex. Larger place fields in the ventral hippocampus may also provide information about the broader spatial context²⁹. Nonetheless, we would expect that only cells whose place fields overlap the animal’s current location will be activated at these times. Distinct environments are generally represented by distinct sets of place cells³⁰, suggesting that place cell activity in one environment is unlikely to be able to retrieve representations of a previously experienced environment. In contrast, as we argue below, awake replay is consistent with the patterns of activity necessary to support a hippocampal retrieval mechanism, indicating that hippocampal replay during the awake state could be a common neural mechanism for both consolidation and retrieval^{31,32}.

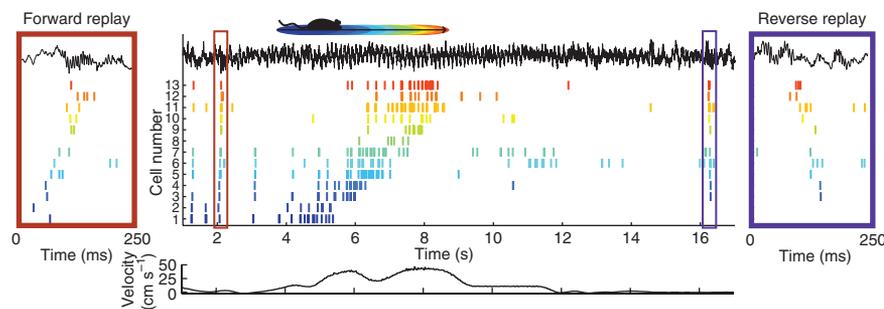
Hippocampal replay occurs during sharp wave ripples

SWRs originate in the hippocampus and are triggered by synchronized activation of pyramidal cells in its CA3 region, leading to characteristic negative potentials (sharp waves) in the stratum radiatum of the CA1 region^{12,33}. When recording in area CA3, this synchronized activation of CA3 pyramidal cells can be measured as

a 100–150 Hz oscillation³⁴. The population burst in the CA3 region recruits CA1 pyramidal cells as well as basket and chandelier cells, leading to a transient (~100 ms) ‘ripple’ oscillation (150–250 Hz) in the CA1 pyramidal cell layer³⁵. The short-latency bursts of CA3 and CA1 neurons during SWRs seems well suited to induce synaptic plasticity^{12,36}. SWRs are prominent during sleep as well as in the awake state during immobility, consummatory behavior and grooming^{12,37}, and can also be seen during running^{38,39}. Activity during SWRs propagates from CA3 to CA1, one of the main output areas of the hippocampus, and then out to neocortex^{40–42}.

The extensive excitatory recurrent connections among CA3 pyramidal cells⁴³ have led some to suggest that CA3 acts as an autoassociative pattern completion network^{44,45}. Thus the activation of a small subset of CA3 neurons could initiate a cascade of excitation across previously modified synapses, leading to reverberating activity that eventually settles into an attractor state corresponding to a previously stored memory. Reinstatement of stored representations in CA3 could then reinstate the corresponding representations in CA1 through feed-forward excitation. Hippocampal replay during SWRs is thought to reflect this type of autoassociative pattern completion in CA3 in conjunction with feed-forward recruitment of pyramidal cells and interneurons in CA1. This model is consistent with the observation that the fidelity of reactivation (measured across cell pairs) is higher in CA3 than CA1 (ref. 31).

Figure 1 Place cell sequences experienced during behavior are replayed in both the forward and reverse direction during awake SWRs. Spike trains for 13 neurons with place fields on the track are shown before, during and after a single traversal. Sequences that occur during running (center) are reactivated during awake SWRs. Forward replay (left inset, red box) occurs before traversal of the environment and reverse replay (right inset, blue box) after. The CA1 local field potential is shown on top and the animal's velocity is shown below. Adapted with permission from ref. 47.



Awake replay of the local environment

The first observation of sequential awake replay found that when animals stop and consume a reward after traversing a linear track, sequences of place cells originating at the animal's current location are reactivated in the reverse of the order experienced behaviorally⁴⁶ (see **Box 1** for discussion of methodological issues). Reverse replay is seen immediately after the very first traversal, demonstrating that the hippocampus can replay sequences that are experienced only once and indicating that replay could contribute to one-trial learning. Behaviorally relevant sequences are replayed repeatedly; in fact, sequences are replayed more often than the trajectories they represent were experienced.

Further examination of SWR activity revealed that awake replay can occur in either the same (forward) or the opposite (reverse) direction as that observed during behavior⁴⁷ (**Fig. 1**). Furthermore, the direction of replay is related to the animal's behavior. Reverse replay occurs preferentially at the end of runs when the animal reached the reward location, potentially linking behavioral trajectories to their outcomes⁴⁶. Forward replay occurs preferentially at the beginning of runs, perhaps providing information relevant for evaluating future trajectories⁴⁷.

Early studies focused on relatively small environments where replay occurring during the time frame of a single SWR (~100 ms) could represent an entire behavioral trajectory. It was therefore unclear whether SWR replay could recapitulate the extended sequences an animal might experience in a more naturalistic setting. Examination of hippocampal activity during exploration of a larger environment revealed that both forward and reverse replay events can span long distances and extend across multiple SWRs⁴⁸. These results indicate that the timescale of a single SWR event does not limit the extent of memory reactivation.

In all of these studies, animals traversed locations in both directions of motion, so forward replay in one direction was similar to reverse replay in the other (see **Box 1**). The presence of both forward and reverse replay was verified in a recent study in which the animal's direction of travel along the track was restricted, resulting in experience almost exclusively in one direction⁴⁹. Furthermore, activity consistent with forward and reverse replay has also been observed in an open-field maze⁵⁰, where animals do not traverse paths in a stereotyped fashion. These results suggest that replay reflects trajectories through a "cognitive map" that represents the relationships between locations or episodes⁵¹ rather than simply recapitulating recent experiences. This hypothesis is consistent with the observation that replay events can occasionally represent "short-cut" sequences made up of joined forward and backward sequences that were never experienced together⁴⁹.

Although the presence of awake replay has been conclusively established, there are several outstanding questions. First, it is unclear how sequences experienced in only one direction can be stored in such a way as to allow for both forward and reverse replay. It is also not clear

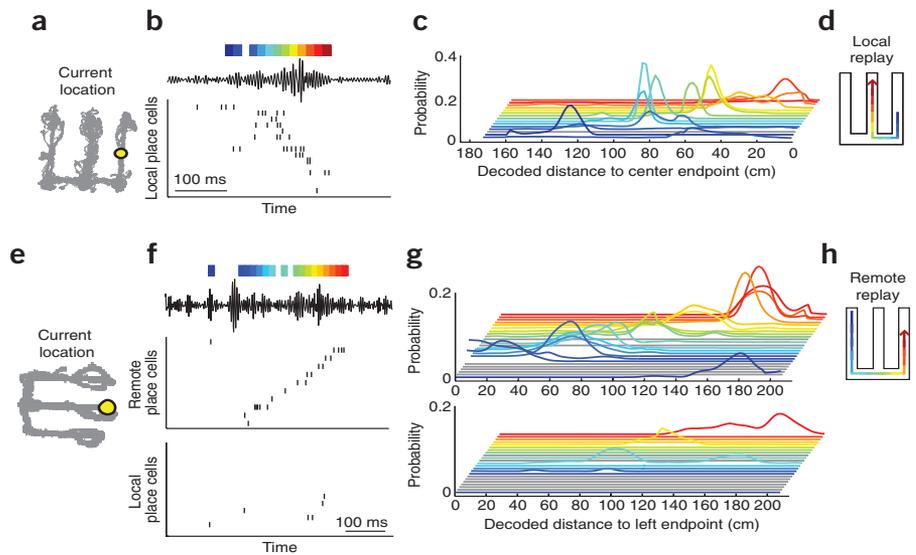
whether forward and reverse events serve similar or different roles. Intriguingly, reverse replay does not seem to be present during sleep⁵². This raises the possibility that the content of hippocampal replay is actively controlled and that different directions of replay serve different functions. Forward replay during both behavior and subsequent sleep seems well suited for consolidation of representations related to experienced trajectories, and forward replay during behavior may enable the retrieval of future paths to aid memory-guided decision making^{31,47}. Reverse replay during behavior seems well suited for linking recently experienced sequences to their outcome, which may promote task learning^{46,47,53}.

Awake replay can occur remotely

Sleep replay reinstates neural representations of previous experiences in the absence of associated sensory inputs¹³. In contrast, early observations of awake replay suggested that sensory input could explain the sequential reactivation during replay. One model posited that progressive depolarization during SWRs unmasks subthreshold place field, resulting in sequential reactivation^{46,47,50}. Although this model is appealing, recent observations of remote replay during awake behavior demonstrate that this subthreshold model cannot fully explain the occurrence of awake replay. Examination of the similarity of pairwise neural co-firing during awake SWRs and during awake exploration first suggested that activity during awake SWRs can reactivate past, rather than current, experiences⁵⁴. For some recording sessions, the same cell assemblies are active during awake SWRs as were activated during exploration in a previously experienced environment.

Further investigation demonstrated that sequential replay is not limited to trajectories through the animal's current environment. Entire sequences of neurons representing trajectories through a previously explored environment are replayed during subsequent experience in distinct environments³¹ (**Fig. 2a-h**). The reactivation of a distant memory during ongoing behavior raises the intriguing possibility that awake remote replay, in conjunction with local place-related input, could contribute to the formation of associations between past and current events. Remote replay can be detected in over 40% of the SWRs for which sufficient numbers of neurons with place fields in the remote environment are active, and remote replay persists throughout a 2-hour recording session. Replay of the local environment is similarly detected in more than 40% of the SWRs with sufficient levels of place field activity. Most replay events correspond to trajectories through either the local or the remote environment, but not both³¹ (**Fig. 2e-h**). Replay of the local environment can represent a sequence of locations distant from the animals' current position^{31,48,49}. Surprisingly, awake replay of a remote environment is a higher fidelity recapitulation of past experiences than replay seen during quiescent, sleep-like states³¹, indicating that awake replay could be particularly important for memory consolidation.

Figure 2 Awake replay reinstates representations of both current and past experiences. (a) The animal's physical location during a local replay event. (b) Sequential spiking of neurons with place fields in the current environment during an SWR. At top is the filtered CA1 local field potential. The color bar shows the colors associated with each 15-ms time bin used for decoding. (c) Probability distribution of decoded location for each time bin. Each color corresponds to the spiking in the associated time bin; gray indicates time bins where no spikes occurred. (d) A diagram of the local replay event, emanating away from the animal's current location. (e) The animal's physical location during a remote replay event. (f) Spiking of cells during the SWR for cells with place fields in either the remote (top) or local (bottom) environment. (g,h) Decoded locations reflect a coherent trajectory through the remote environment, but do not represent a coherent trajectory through the local environment (g, bottom). Adapted with permission from ref. 31.



The observation that a large proportion of replay events represent coherent trajectories through either the local or a remote environment raises the possibility that a complete sampling of all experienced environments would reveal that most SWR activity is consistent with experiences in some environment. Alternatively, some SWRs may represent patterns of activity generated as a result of anatomic and synaptic connectivity that does not reflect past experience. Future theoretical work on the structure of all SWRs and experiments that record place cell activity and replay across all of the environments an animal experiences on a daily basis will help determine the extent to which SWR activity reflects experience.

Salient experiences enhance awake replay

We form strong, long-lasting memories of salient experiences, suggesting that these experiences enhance memory consolidation processes. Memory encoding and consolidation are particularly important when new information needs to be learned, as in a novel environment, and awake replay is more prevalent in a novel environment than in a familiar one^{46,47}. In addition to being more prevalent, reactivation is more temporally precise in a novel environment, and as locations become more familiar, the precision of awake reactivation decreases³⁹. This enhanced precision may be important for consolidation processes, as precise co-firing of neurons is thought to drive synaptic plasticity^{55,56}. In addition, novelty increases the reactivation of neurons associated with new experiences during subsequent sleep⁵⁷.

Similar enhancement of reactivation is seen after reward. Although a reward is not necessary for awake replay to occur^{50,54}, SWRs occur frequently when animals are at rewarded locations. The relationship between reward and reactivation has been investigated in more detail in the context of a sequence-switching task where animals use changing reward contingencies to guide their behavior⁵³. SWRs are more prevalent and CA3 pyramidal cells are more active during SWRs at the end of rewarded trajectories than unrewarded trajectories. The activity during these SWRs is consistent with ordered replay of paths to and from rewarded locations. Although this sequence-switching task occurred in a familiar environment, reward-related SWR activity is enhanced when animals first learn a novel reward contingency, indicating that activity during awake SWRs could contribute to learning the associations between actions and their outcomes.

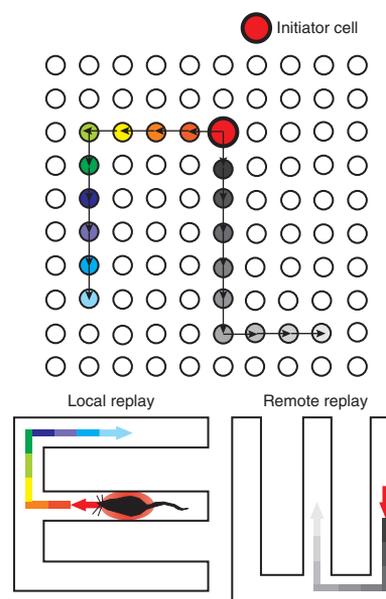
It is well established that salient events alter hippocampal activity in part through the activation of neuromodulatory inputs such as the dopaminergic⁵⁸, noradrenergic⁵⁹ and cholinergic systems⁶⁰, and that these neuromodulatory systems modify hippocampal synaptic plasticity (for reviews, see refs. 61–63). For example, both novelty and reward are associated with activation of midbrain dopaminergic neurons⁵⁸. Late-phase long-term potentiation (LTP) in the hippocampus is enhanced by dopamine agonists⁶⁴ and impaired by blockade of dopamine receptors⁶⁵. Furthermore, novelty leads to a dopamine-dependent reduction in the threshold for LTP induction at the CA3-CA1 synapse⁶⁶. These findings suggest that during exploration of novel environments and after receipt of reward, the hippocampus exists in a privileged state for the induction and maintenance of plasticity. As spiking during SWRs has a temporal structure similar to that used to induce LTP¹², replay events occurring during these highly plastic periods may contribute to consolidation by supporting the stabilization of representations within the hippocampal network. Furthermore, effects of neuromodulatory systems such as this may contribute to the preferential encoding of salient memories outside the hippocampus as well.

Sensory input can cue awake replay

The discovery of awake remote replay demonstrates that awake replay can reinstate stored representations that are not dependent on local place field activity. However, current sensory input can bias the initiation of awake replay of the animal's current environment. Awake replay often begins at the animal's current location and moves away from the animal in either the forward or reverse direction^{31,46–48}. At the onset of an awake SWR, neurons with place field centers near the animal's current location have a higher probability of firing and show a shorter latency to fire^{38,50}. The effect of location on firing probability decreases throughout the replay event⁵⁰. Cells active in the current location may influence the initiation of awake replay by acting as "initiator cells"³⁶ that trigger the reactivation of previously stored sequences. This is similar to a cued memory retrieval process whereby current sensory input triggers retrieval of relevant episodic sequences. The retrieval of relevant sequences may help evaluate future choices and enable memory-guided decision making.

Local spatial input can also influence remote replay. Place cells that initiate awake remote replay events have high local spatial firing

Figure 3 Spatial inputs could lead to retrieval of either local or remote sequences. Schematic illustrating how current sensory input could trigger either local or remote replay. Current sensory information relating to the animal's current location activates cells with place fields nearby. These cells act as "initiator" cells and lead to sequential reactivation of previously stored sequences. Because the initiator cell also has a place field in a spatially remote environment, this cell can initiate replay of either environment. The initiator cell leads to reactivation of stored sequences (top) through either the current environment (local replay, bottom left) or a previously experienced environment (remote replay, bottom right). The geometry of the neural ensemble is for illustration only and does not represent any actual topography of representations in the hippocampus.



rates³¹. This seems to be a result of the overlap in the set of cells that are active in any two distinct environments. In general, hippocampal place cells form unique maps of each experienced environment, and only about 40–50% of CA1 place cells are active in any given environment^{67,68}. As a result, if an animal has experienced two distinct environments, a subset of neurons that are active in one environment will also be part of the representation of the other. Local spatial input to cells that represent locations in both environments can therefore participate in replay of sequences from either environment³¹. These cells can act as “bridges” or “nodes” across multiple representations and may enable the retrieval of related past experience in order to guide behavior in the current environment (Fig. 3)¹¹.

Linking awake replay and memory consolidation

Awake replay has the potential to meet all of the criteria for a mechanism that supports memory consolidation. Awake replay repeatedly reactivates patterns associated with past experience on a timescale consistent with the induction of synaptic plasticity in the absence of behavioral repetition. Consistent with this possibility, a recent study demonstrated that the strength of awake reactivation predicts subsequent memory⁶⁹. Reactivation was examined both during and after experiences where animals learned novel associations between locations and rewards. The intensity of reactivation occurring during brief pauses in exploration was found to be related to subsequent performance, whereas the intensity of reactivation occurring during extended immobility was not. In addition, performance on this memory task correlated with reactivation during a rest period immediately after the experience.

Causal evidence for a role of awake replay in memory consolidation is still lacking, but two recent studies have used real-time disruption of SWRs during sleep to demonstrate the link between hippocampal SWRs during sleep and learning^{70,71}. These studies disrupted SWRs during a sleep session immediately after the training sessions and found that task acquisition was impaired. A similar study of the role of awake SWRs during spatial and task-related learning would clarify the link between awake SWRs and memory consolidation. Furthermore, appropriate controls must be done to demonstrate that disruption of SWRs does not cause synaptic plasticity or disrupt hippocampal representations.

During sleep, activity during SWRs propagates from the hippocampus to prefrontal cortex⁴² and entorhinal cortex^{40,72}, and replay of mnemonic activity during sleep has been observed in multiple brain areas^{73–77}. Similar studies of awake replay will be required to determine how awake replay events affect regions outside the hippocampus. Ideally these studies would also evaluate the effect of disrupting awake replay on representations in these distributed circuits. It will also be necessary to extend the investigation of replay beyond spatial sequences using multimodal behavioral tasks, since the hippocampus is known to be involved in transfer of rules and schemas

related to behavior⁷⁸. Replay is most prevalent immediately after an experience and decays with time; however, it persists at above chance levels even 18–24 hours after an experience^{18,31}. Future studies measuring and disrupting replay over longer periods of time in behavioral tasks for which the time course of consolidation has been worked out will be needed to address questions about whether replay persists and is necessary for the entire time course of consolidation. Finally, it is important to remember that consolidation is a complex process that involves neural activity, protein synthesis and gene expression⁷⁹. Understanding the associated patterns of neural activity will only address part of the consolidation process.

Linking awake replay and memory retrieval

Awake replay also seems well suited to supporting memory retrieval processes. Awake replay reactivates memory traces from past experience on a compressed timescale. Local input can bias the content of awake replay, suggesting that awake replay can act as a cue-triggered retrieval process. Awake replay is also very similar to “vicarious trial and error” events⁸⁰, in which the replay of possible future trajectories is seen in a multiple-T maze tasks where animals must make memory-guided decisions^{80,81}. Although these vicarious trial and error events were reported to occur outside of SWRs, this study used a very restrictive criterion to define SWR activity and examined SWRs in CA3, for which the criterion for identifying SWRs is less well established³⁴ (see **Box 1**). Thus it remains possible that these vicarious trial and error events are similar to awake replay events occurring during SWRs. In support of this idea, awake replay during SWRs has been seen frequently at the choice point in a similar task, where animals must make a memory-guided decision between two trajectories³¹. Further, these awake replay events frequently begin well before the choice point and extend out to the left or the right arms of the track, as would be expected if the animal were playing out possible upcoming choices, consistent with the activity observed in the vicarious trial and error events.

The link between awake replay and memory retrieval remains correlative, and several important questions remain to be answered. It will be essential to specifically disrupt awake SWRs at times when a memory-guided decision must be made. Further, future studies will need to investigate the relative contributions to memory retrieval processes of awake replay and place-related firing. We suggest that awake replay and place field activity support different types of

retrieval, with awake replay supporting the retrieval of spatially or temporally remote experiences and place field activity supporting the retrieval of associations related to the animal's current location.

We also need to understand how forward and reverse replay affect neocortical regions, in both animal models and humans. We are able to trace events backward in time, but the conscious experience of memory retrieval occurs forward in time. We speculate that forward and reverse replay are triggered at different times to support different types of memory processes. Finally, it is unknown whether the relatively short bursts of activity seen during single SWRs can trigger long-lasting reverberatory processes⁴⁸ in distributed circuits that correspond to the perceived timescale of memory retrieval processes.

Conclusions

The hippocampus contributes to the rapid encoding, subsequent consolidation and ongoing retrieval of stored memories. Both consolidation and retrieval are thought to depend on the reactivation of previously stored patterns of neural activity. However, as consolidation has been primarily associated with sleep and retrieval with waking behavior, the idea that a common process supports both functions is not widely accepted. Awake replay is robust and prevalent in brief periods of stillness during behavior and is enhanced during both novel and rewarding behaviors. The presence of remote awake replay suggests that animals do not have to sleep to consolidate memories of previous experiences and that the consolidation process begins as soon as new memories are encoded in the hippocampus. Moreover, awake replay may also be important in memory retrieval. Local inputs bias the content of both local and remote replay, suggesting that sensory input to the hippocampus serves as a cue for targeted memory retrieval. One particularly interesting possibility is that replay events that begin at the animal's current location provide information about possible upcoming trajectories to target brain structures such as the prefrontal cortex and nucleus accumbens. These downstream structures could then assess the value of different trajectories and make an informed choice about future actions. Similarly, awake replay of remote experience could reinstate previously learned associations in distributed hippocampal-neocortical circuits that are relevant for ongoing behavior. The possibility of replay as a common neural mechanism underlying the hippocampal contribution to memory retrieval and consolidation is parsimonious, but by no means established. We expect that efforts to address these issues will lead to a new and deeper understanding of the hippocampal contribution to memory processes.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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