



Variable specificity of memory trace reactivation during hippocampal sharp wave ripples

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Hippocampal sharp wave-ripples (SWR) are thought to mediate brain-wide reactivation of memory traces in service of memory consolidation. However, rather than the faithful replay of neural activity observed during a specific experience, reactivation in both the hippocampus and downstream regions is more variable. We suggest that variable reactivation is a unifying feature of recurrent brain circuits. In the hippocampus, self-organized activation during offline states is constrained by existing attractor manifolds, or maps, and may be biased toward particular mapped locations by salient experience, which results in the appearance of experience-specific replay. Similarly, the impact of SWR-associated reactivation on downstream regions is not a simple transfer of hippocampal representational content. Rather, the response of downstream regions depends on a transformation function, defined by both the feedforward and local circuit architecture, as well as the 'listening state' of the downstream region. We hypothesize that SWRs act as a multiplexed signal, the mnemonic specificity of which is largely determined by this transformation function, and discuss the implications of this framing for theories of systems consolidation.

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Introduction

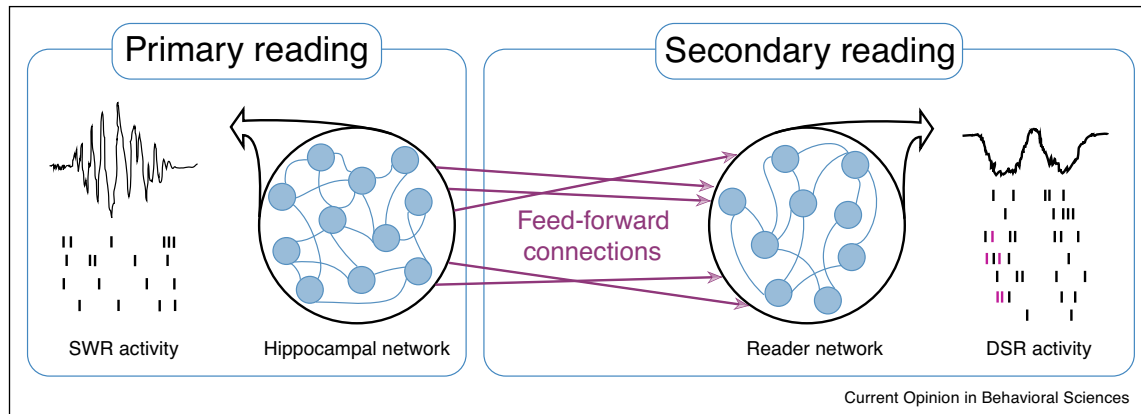
Current theories of memory posit that plasticity during experience results in the formation of a memory trace: a set of *de novo* physical changes to the nervous system that

allow information about that experience to persist beyond its duration. Extensive work has shown that for many behaviors, initial formation of a memory trace relies on the hippocampal system. Over time the memory trace is modified and distributed across the rest of the brain, or consolidated. While theories of memory consolidation differ in the extent to which memories remain dependent on the hippocampus, common across them is that reactivation of memory traces during waking rest and sleep, or 'offline' behavioral states, is a mechanism of consolidation.

In order for a memory trace to be consolidated, it must be 'read-out', or transformed from its physical substrate into patterns of neural activity. We consider the 'reading' of memory traces to occur in two conceptually separable steps (Figure 1). First, the memory trace shapes spontaneous neural activity in the circuit that stores the memory trace, which we refer to as 'primary reading'. Second, primary reading can affect activity in target brain regions, or downstream readers (DSR), which we refer to as 'secondary reading'. During offline behavioral states, primary reading is often considered to occur in hippocampal circuits during sharp wave-ripple complexes (SWRs): brief (~100 ms) population bursts that are associated with task-related patterns of activity and correlate with future task performance [1; additional relevant citations available in the Supplementary Note].

According to the Two-stage model of memory consolidation, hippocampal-dependent memories are replayed during offline states, which drives their coordinated reactivation in the neocortex and ultimately transfers the associated memory trace from the hippocampus to long-term storage in the neocortex [1,2]. While SWRs have been identified as the leading physiological candidate underlying consolidation, recent work has brought into question 1) the degree to which neural activity during SWRs resembles that during initial experience, and 2) the degree to which SWRs impact activity in downstream regions, particularly the extent to which the representational content in downstream regions reflects that in the hippocampus. We refer to these variations of degree as the specificity of primary and secondary reading (Figure 2). At one extreme, SWRs may replay specific experiences via neuronal patterns that act as letters of neural 'words', interpreted by downstream readers with letter-by-letter precision. At the other extreme, neural activity during SWRs may be unstructured with respect to

Figure 1



Reading from SWR activity.

Leveraging SWRs to broadcast information from the hippocampus assumes two stages of reading. In the primary reading stage, information from a memory trace existing in the hippocampal network is read out, in the form of a SWR. In the secondary reading stage, information is broadcast through feedforward connections to a DSR network. The information broadcast depends on the feedforward connectivity and its alignment with the SWR activity. This broadcast is received (purple spikes), and interacts with the ongoing local activity in the DSR network (black spikes). This interaction depends on local properties of the DSR network, including connectivity and state.

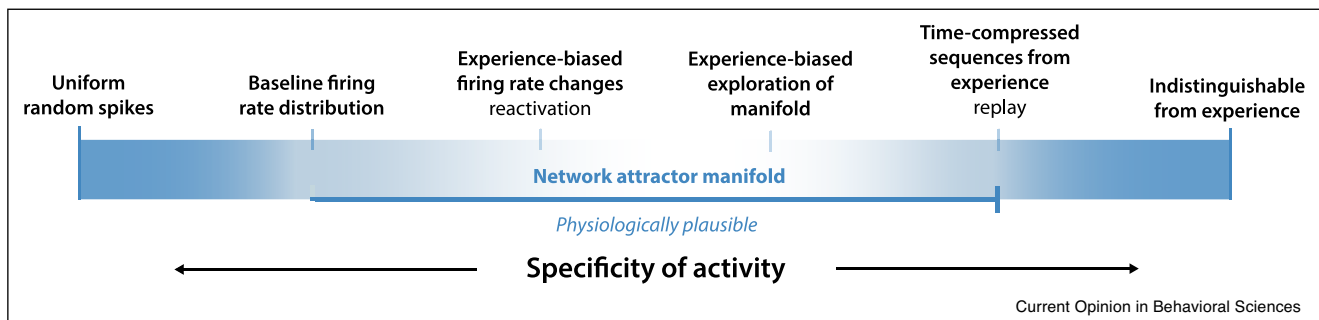
any representational content, and the exact spike sequences may be inconsequential to downstream readers. Rather than competing models of hippocampal physiology, we suggest that the varying degrees of specificity observed during primary and secondary reading events are a consequence of the biophysical mechanisms underlying spontaneous activity in the hippocampus and its downstream structures.

Primary reading: from memory trace to hippocampal dynamics

Neural activity during SWRs can be decoded by the experimenter to recapitulate spatial trajectories in

previously experienced environments [3], and has thus been proposed to correspond to neural replay of experience. This proposal aligns with classical views of memory consolidation, whereby the hippocampus replays specific experiences to transfer recent memories from fast-learning hippocampal to slower-learning neocortical networks [2]. This computational strategy has been modeled in machine learning applications [4], lending support to its feasibility as a mechanism for robust long-term memory formation. However, these models rely on the high-fidelity replay of specific experiences, whereas the brain engages noisy processes and intrinsically generated dynamics. Thus, how and even if the hippocampal system

Figure 2



Specificity of SWR activity.

The relevant information contained in a SWR exists on a theoretical spectrum of specificity: at the most general (left) the content of a SWR is completely random and unrelated to previous experience or local network architecture. At the most specific (right) the activity exactly replicates that which occurred during an experience. The range of possibilities is restricted to a physiologically plausible domain that accounts for the constraints imposed by the local network and SWR dynamical events. Towards the middle is a network attractor manifold subspace that acknowledges the low(er) dimensional space that activity is likely to occupy, which results from network architecture and local smooth manifolds corresponding to represented environmental variables. Experience may bias which or where an attractor is activated.

can replay previous experience with an analogous level of fidelity remains an open question.

Replay of specific experiences in the hippocampus?

To study offline replay, a method is needed to compare neural activity during rest with that recorded during behavior. Typically, a neural activity template is constructed based on hippocampal activity during a behavioral task, putative replay events are detected (e.g. SWRs or population bursts), and similarity to the template is calculated for each event [5]. Events with similarity above a statistically determined threshold are considered replay. Notably, studies often report that only 10–40% of SWR-associated population bursts meet statistical criteria for replay [3], raising a question about the representational content of the remaining events. While non-matched events may simply be replay of unobserved (and thus undecodable) experiences, distributions of replay scores are often continuous rather than bimodal. This suggests that activity during SWRs falls on a continuum of similarity to that during any one experience. Furthermore, a variety of similarity metrics have been used that each make their own assumptions about which aspects of neural activity to compare, such as precise sequences of spikes (often termed replay), general reactivation of task-related cell assemblies (often termed reactivation), or changes in pairwise correlations between cells [5]. Thus, not only is the majority of neural activity during offline states unaccounted for, but the variety of detection methods used result in conceptual ambiguity regarding what in fact constitutes replay.

In principle, neural activity during offline events could be considered on a spectrum of specificity (Figure 2). On one end, we find perfect specificity, where spiking is indistinguishable from that which occurred during a behavioral episode. We consider this to be idealized hippocampal replay — a veritable re-play of a previous experience. On the other, we find complete nonspecificity, where spiking activity is unstructured with respect to any behaviorally relevant representation. Rather than defined by a particular detection method, we consider reactivation to refer to any offline activity pattern that might be detected by a statistical technique used to identify similarity to waking activity. While this differs from the detector-based terminology often used in the field, we will see that it nicely captures a biophysical perspective — namely that transient activation events are inevitable in recurrent circuits during offline states, and that (re)activation is simply the biasing of those events towards specific activity patterns. Reactivation events can thus be considered to have a range of specificity, with an ambiguous lower bound that will need to be refined via future experimental studies on the biological relevance of low-specificity events, and a hard upper bound at perfect specificity (i.e. ideal replay).

Ideal replay appears untenable. SWRs impose unique temporal constraints on spiking compared to those during wake (for example, activity patterns during SWRs are compressed with respect to behavioral timescales [1]); thus perfect specificity is not physiologically realizable. On top of these temporal constraints, recent findings have suggested that less-specific reactivation may be more reflective of physiology. When decoded, spiking activity during SWRs was better characterized as representing a random walk in the behavioral arena rather than a representation of any specific experienced behavioral trajectory taken by the animal [6].

However, unstructured spiking is also not physiologically realizable. Neurons in the hippocampus are not isolated actors, but are embedded in a synaptic network that constrains which cells tend to fire together, and in what order [7,8]. Such constraints are a natural consequence of learning in recurrent neural networks like the hippocampal CA3 region [9,10]. Depending on the local circuit and statistics of the learned content, recurrent networks can contain embedded clusters that store specific cell assembly patterns [11], feedforward chains that store spike sequences [12], or low-rank structure that stores low-dimensional manifolds [13]. Originally termed a cognitive map [14], these learned patterns define attractors to which neural activity is constrained, forming the physiological basis of navigation [15,16] and content-addressable memory [17]. Further, behaviorally similar sequential activity is observed in the hippocampal system before behavioral training [18], which might reflect spontaneously emerging attractors or those generated during development [19]. Thus, any unfolding activity in the hippocampal network, including offline activity, is structured by the presence of existing network attractors.

Experience-biased spontaneous (re)activation

During offline states, the hippocampus is in an excitable regime, in which SWRs reflect transient activations of the hippocampal network [20]. Excitable regimes are seen in strongly recurrent networks when the level of external drive is low, and are characterized by relative inactivity with brief episodes of network activation induced by internal or afferent noise. Spiking activity during these activation events is maintained by local connectivity, and thus shaped by existing network attractors [21]. Spontaneous activation in recurrent network models can take a variety of forms [22], ranging from activation of discrete Hebbian-like assemblies [23] to synfire chain-like replay of specifically learned sequences [22]. Further, these types of near-critical dynamics can promote the activation of weaker attractors even in the presence of numerous well-established neuronal trajectories (e.g. those that correspond to older memories) [24]. We can thus consider that reactivation events correspond to those spontaneous activations that conform to any recently active attractors (such as those visited during behavior), and the replay

phenomenon corresponds to a tendency of the hippocampal network to re-visit the constellation of attractor states visited in a particular earlier experience during SWRs.

What then governs the spiking content of an activation event? A diverse array of studies have indicated reactivation is affected by salient aspects of behavior. Early work suggested that reactivation persists in only the first 10 to 30 min of sleep [3], but recent work shows that reactivation extends for many hours following learning in novel environments [25]. Reactivation is biased not only by novel experiences, but also by a variety of other conditions, such as reward prediction error [26] and active engagement in behavior [27]. Together, these results suggest that attractor manifolds in the hippocampal network are primed during experience to be activated during subsequent offline states, and that priming is facilitated by and biased toward specific manifold locations. The biasing of SWR-associated activation toward task-related patterns of activity is also seen during active behavior, and is not simply a direct reflection of recent experience [28,29]. In hippocampal models, replay generally relies on plasticity during spike sequences embedded in the theta oscillation during behavior [30], and this prediction is supported by recent experimental studies [29]. Priming might occur during theta activity linked to the encoding of salient experiences [31], due to enhanced theta coherence with prefrontal cortex [32], or due to neuromodulatory effects that enhance theta activity and modulate synaptic plasticity [33]. Thus, a wide variety of mechanisms exist by which neural activity during experience may bias activity during subsequent spontaneous network activations to reactivate recently encountered patterns.

As the hippocampus selects or learns different maps corresponding to different environments, subsequent (re)activation bias might take two forms. First, a bias only toward which map is activated (e.g. the one that matches a recently explored arena), or second, a bias specifically toward which locations or trajectories on those maps will be activated (e.g. those that were the site of particularly salient experiences). The ramifications of these biases for learning need to be explored. Experience could modify the structure of an existing manifold, warping the space that activity can occupy [34^{••}]. Alternatively, the structure could remain largely constant, but the occupancy of activity on the manifold could change [35^{••}]. This difference is analogous to redrawing a map versus moving to a new place on an existing map. Both of these scenarios could result from the changes in synaptic strength and intrinsic excitability associated with learning, but the behavioral implications may be quite different. For example, on-manifold learning in a brain-machine interface task [35^{••}] is more rapid than off-manifold learning [34^{••},36]. A parallel psychological literature on schemas supports this [37]. Additional experimental and computational work is needed to distinguish these forms of

learning, when they occur, and how they relate to variable specificity reactivation.

Thus far, we have proposed that reactivation events exist along a physiologically realizable spectrum of specificity, from nonspecific activation of neural patterns constrained by hippocampal attractor manifolds to specific activation of experienced patterns, under the temporal constraints of the SWR (Figure 2). Recent literature suggests that spontaneous attractor activation is a universal property of attractor networks such as the hippocampus and that the salience of an experience can bias subsequent spontaneous activation to be more specific to that behavior. Framing hippocampal reactivation as such suggests that the statistical methods used to detect reactivation may be capturing different aspects of (re)activation in the same underlying network.

Secondary reading: from hippocampal dynamics to downstream regions

SWRs have been proposed to act as *memory signals* that coordinate reactivation of memory traces across brain-wide networks [1,38]. Given the range of reactivation specificity observed during SWRs within the hippocampus, we next ask what features of SWRs can a downstream region actually read-out?

There is ample support for brain-wide perturbation by hippocampal SWRs. SWRs are correlated with modulation of brain-wide activity across spatiotemporal scales, from changes in the BOLD signal [39], to modulation of NREM-associated sleep rhythms [31], to changes in the firing rates of individual neurons across primary and association cortices, and subcortical regions [3]. Further, a number of studies have found a correlation between SWRs and reactivation of task-related activity in DSRs [3,40]. However, few studies have directly compared the informational content of simultaneously occurring SWRs and DSR spiking activity, and those that have reported mixed results (e.g. coordinated: [41,42]; not coordinated: [43,44]). In sum, although there is strong evidence of brain-wide perturbation by hippocampal SWRs, DSR responses that mirror the mnemonic content of concurrent SPWRs are variable.

We suggest the response of a given DSR can be theoretically characterized by a transformation function that maps SWR activity to that DSR's responses. The transformation function is defined by three components. First, the feedforward projections between the sending region and the receiving region determine which channels of SWR activity are broadcast from the sending network [45^{••},46]. Second, the local connectivity within a DSR determines which channels of the broadcast signal a DSR has access to, as alignment between the broadcast signal and predominant activity modes of the receiving network can amplify, while misalignment can suppress, any response

in the DSR [47]. Finally, the dynamical state of a DSR determines how incoming information is combined with ongoing local activity. Taken together, these three features determine the specificity with which a DSR reads hippocampal activity during a SWR — that is, the degree to which the DSR is impacted by, and reflects, hippocampal activity (Figure 3). The diversity of structures and dynamics observed across the brain demonstrates the large number of readers that are theoretically possible, and the broad responsiveness to SWRs indicates that a variety of reader mechanisms may be utilized to simultaneously access different aspects of SWR activity.

Feed-forward weights affect readout

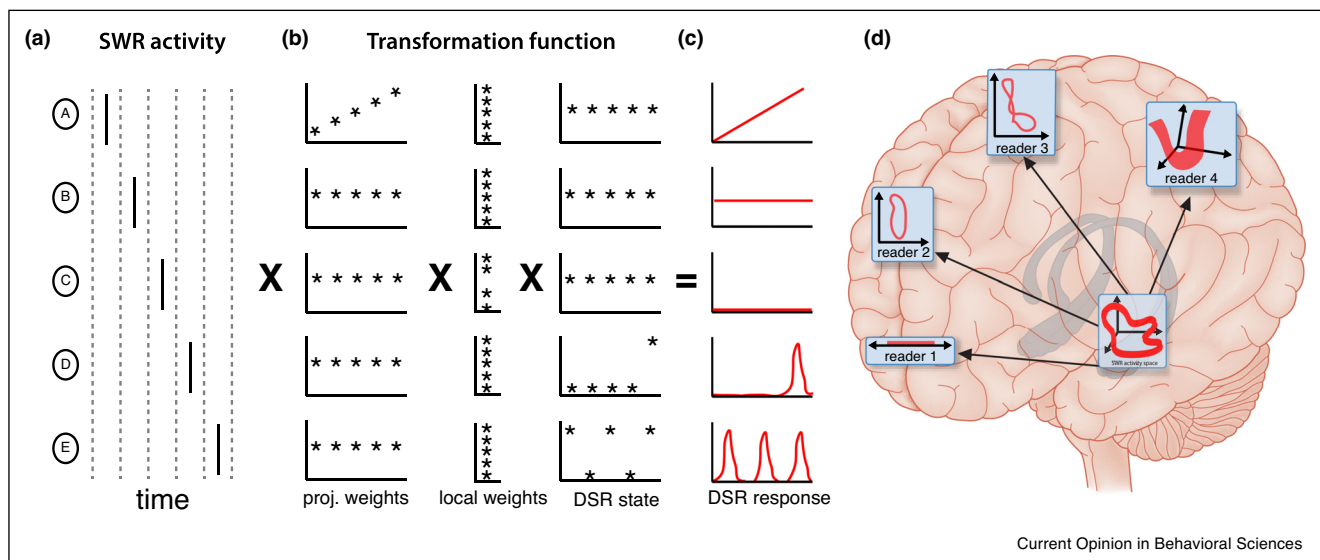
Projections from the hippocampus to DSRs can be qualitatively characterized by two anatomical motifs: convergent ‘fan-in’, and divergent ‘fan-out’ architecture. These opposing patterns of connectivity can achieve different functions: A DSR that receives highly convergent input may be sensitive only to the magnitude of a SWR, considered a nonspecific reader. In contrast, a DSR that receives divergent or distributed hippocampal inputs may be sensitive to more specific content in the SWR, for example, a sequence of spikes, considered a specific reader (Figure 3).

DSRs that receive strongly convergent inputs from the hippocampus would receive a high degree of synchronous excitatory input during a hippocampal SWR. As may be

expected from such a ‘fan-in’ architecture, such a DSR may have a limited ability to read out the spiking content of SWR-associated population bursts, but instead may be more capable of extracting the magnitude of upstream activity. Nonspecific transformation functions may be ideal for subcortical DSRs that perform functions regardless of the content of the SWR. For example, neurons in the lateral septum were found to respond to the magnitude of SWR-associated population synchrony, but not to their informational content [44]. Regulation of neuromodulatory systems that shape state and plasticity across the brain by SWRs may be another example of a nonspecific reader mechanism [48].

In contrast, divergent projection patterns (fan-out) may allow a DSR to tune in to unique dimensions of a given SWR. Experimental work has shown that a transformation function between two networks exists that allows the receiving network to read from a distinct ‘communication subspace’ of the sender’s activity [49]. The transformation function may result from specific projection subnetworks in the sending region [46] or the alignment of feed-forward inputs with specific dimensions of local network structure in the receiving region [47], resulting in the receiving region being sensitive only to fluctuations along certain dimensions of the sending region’s activity. Theoretical work has shown that even simple, anatomically plausible feed-forward connections are capable of recovering useful information from the complex

Figure 3



Reading multiple signals from one SWR.

(a) Series of spikes across a population during a SWR. (b) Set of filters implemented by properties of DSR. Feed forward projections determine signal broadcast from SWR. Local weights in DSR network filter the subspace of inputs accessible to a network. (Note: In this column, we do not depict the local DSR network weights themselves, simply the subspaces of SWR activity accessible to the DSR given the local weights). DSR state determines the DSR’s responsiveness to inputs. (c) Resulting DSR responses to single SWR event given diverse DSR features. (d) DSRs can access different channels of information contained in the same SWR. Numerous aspects of secondary reading can vary across DSRs, granting them unique access to information contained in a SWR. A unitary SWR event can thus broadcast unique information to each DSR.

dynamics of a network [45**]. This suggests that a DSR may read consistent information from varying patterns of activity as long as the activity evolves within the subspace of SWR activity that the DSR is tuned to. It follows that different transformation functions can be tuned to different subspaces, reading different streams of information from the same SWR. In this sense, the SWR is better characterized as a multiplexed network event, rather than a unitary broadcasting of mnemonic content. Multiple neocortical modules with distinct patterns of divergent inputs from the hippocampus could be a realization of this theoretical principle. Messages passed from hippocampal neurons to neocortical networks through SWR dynamics also depend on the attractor in which those dynamics unfold and the particular subspace a DSR is tuned to [50]. Thus, specificity of secondary reading might also depend on regional modality, with different cortical regions responding only when the SWR is related to modality-specific content.

Local connectivity in DSR affects readout

Specificity of secondary reading might also depend on specific memory traces contained locally within a DSR. Recent experimental evidence demonstrates that even upon initial learning, a memory trace is not restricted to the hippocampus, but is instead distributed across regions involved in the experience [51]. Furthermore, neocortical populations show local reactivation during spontaneous activity [52] which, like hippocampal reactivation, can be biased by recent behavior [53]. When replay events were detected independently in the superficial layers of the medial entorhinal cortex and hippocampus, only 6% of the events were found to be time-locked to hippocampal replay [43]. Thus, the medial entorhinal cortex and presumably any other sufficiently recurrent region is capable of reactivation independent of the hippocampus. This suggests that rather than cortical reactivation being driven exclusively by the hippocampus, SWR-neocortical interaction may be better characterized as the coordination between two systems capable of both independent reactivation and mutual influence, which depends in part on the degree of overlap of memory traces contained in both the hippocampus and any given DSR [54]. This coordination may be achieved by the local memory trace pushing primary reading in an extra-hippocampal region towards activity that is within the bounds of the DSR's transformation function. Experimental support for this scenario is sparse. Yet, it has been demonstrated that the presence of this extra-hippocampal memory trace is necessary for subsequent consolidation [55], even though the trace cannot initially support recall independently of the hippocampus [56]. Taken together, these studies suggest that secondary reading involves the interaction between hippocampal and neocortical memory traces [38], and that the neocortical trace may play a significant role in filtering the content of hippocampal activity during a secondary reading event. In sum, identifying the mnemonic content

of a given SWR has no meaning beyond its local effects unless considered in the context of a particular DSR, and further, that a single SWR can have many different effects, depending on DSR architecture and the nature of hippocampal to DSR projections (Figure 3).

State of DSR affects readout

DSRs are not passive readers, but rather have active ongoing dynamics that play a role in parsing input. During NREM sleep, hippocampal SWRs are coordinated with neocortical slow waves and thalamo-cortical spindles [31]. Slow waves are characterized by coordinated cessations in spiking activity, or transient DOWN states, whereas sleep spindles are brief thalamocortical 9–15 Hz oscillatory events [31]. Both patterns have been proposed to act as windows of opportunity for synaptic plasticity: slow waves due to the coincident increase in gamma band power, locus coeruleus input, and sequential spiking activity following the DOWN state [57,58], and thalamocortical spindles due to influx of dendritic calcium [31]. Both slow waves and spindles have a nuanced spatiotemporal relationship with hippocampal SWRs, and closed loop experiments indicate that such temporal coupling affects memory consolidation [58]. These sleep rhythms may act as neocortical 'listening states' during which neocortical regions can have distinct interactions with hippocampal SWRs.

Slow waves occur when the neocortex is in an excitable regime complementary to the hippocampus [20], in which synchronous hippocampal output during SWRs can trigger a slow wave [59], or prematurely end the DOWN state by initiating a DOWN to UP transition [60]. SWRs not only influence neocortical population dynamics, but can also influence spike sequences at DOWN → UP transitions [58,61]. Each DSR state has unique effects on local activity and thus plasticity. Sleep spindles often follow slow waves and SWRs, and can have SWRs nested in the troughs of individual spindle cycles. Importantly, this interaction is not unidirectional. Both UP states and thalamocortical spindles can invade entorhinal-hippocampal networks and time the occurrence of SWRs [62]. These triggered SWR events are likely important because the punctate hippocampal output can further enhance the activity of the same still-active neurons that initiated the SWR [62,63*].

Temporal coordination of these cortical rhythms also varies across regions. Hippocampal SWRs tend to precede slow waves in medial neocortical regions [59], but follow slow waves in parietal and entorhinal regions [62]. Spindles in frontal regions tend to follow SWR-slow wave complexes [58], while SWRs tend to couple to troughs of spindles in parietal cortex. Some of this variability in coupling between hippocampus and neocortex may be explained by taking into account the spatial and temporal properties of these patterns. Both slow waves and spindles

are traveling waves with distinct spatial characteristics. For example, slow waves tend to travel from frontal to posterior regions [64], while spindles tend to travel in spiral shaped patterns or remain locally restricted [65]. Despite these clear spatiotemporal dynamics, experimental evidence linking wave propagation patterns to topographic coupling between neocortex and hippocampus is lacking, although modeling work suggests that SWRs can synchronize slow waves across cortical regions and act to bias the propagation direction of traveling multi-regional UP states [61]. This observation is of particular interest, as memories are inherently multimodal and thus distributed across the brain, presumably requiring multi-regional interaction for reactivation. Supporting this hypothesis, projections from higher to lower order areas play a crucial role in consolidation [66**]. Further studies to unify the spatiotemporal properties of SWRs and thalamocortical sleep rhythms with the spiking content of hippocampal and neocortical reactivation as related to learning are sorely needed.

Specificity of brain-wide coordination of reactivation

Even if an SWR does not cause a response in a DSR, the local consequences of that spiking activity are important for sleep-associated functions. Spontaneous activity in attractor networks can on its own maintain assembly structure [23,67], even in the absence of explicit reactivation, through memory trace-induced correlations in spiking activity [68]. Further, lower specificity reactivation, like that observed in the hippocampus during NREM sleep, may aid in generalization via coincident activation of attractors that are similar, but were not coactivated during the behavior. Supporting this idea, low-specificity sleep-like reactivation improves the generalization ability of an artificial neural network in classifying images with various types of noise [69]

If any sufficiently recurrent circuit is on its own capable of maintaining local assembly structure, a natural question is — to what extent is hippocampal reactivation necessary for consolidation of memories in extra-hippocampal structures? We consider three observations. First, the anatomical connectivity of the hippocampus with association cortices and subcortical regions uniquely positions it to act as an associative hub [70], the connectivity of which may endow it with the ability to control large-scale brain networks [71]. Second, each region downstream of the hippocampus could listen to distinct specific (or nonspecific) aspects of the SWR, based on its transformation function. Third, DSR reading states are governed by slow oscillations and thalamocortical spindles that can be biased by external perturbation. Taken together, these observations promote a view that, rather than the spiking content of an SWR at a single location driving reactivation in a single DSR, the SWR is better considered as a ‘conductor’, that orchestrates reactivation in various

DSRs by virtue of the hippocampus’ role as an ‘index’ or ‘pointer’ [70,72]. Coordination of the spatiotemporal activation of disparate memory traces across DSRs [38] may occur by biasing the propagation of thalamocortical rhythms from association regions to their respective DSRs. Further, spontaneous reactivation of spike patterns in extra-hippocampal regions may bias hippocampal reactivation [63*], thus facilitating its role in multi-regional pattern completion [1,70]. This suggests a physiologically plausible mechanism by which multi-regional memories may be consolidated.

Unlike local reactivation-driven strengthening of a memory trace, as discussed above, semi-specific reactivation in a hippocampal pointer can induce spatiotemporal correlations that would not have been produced otherwise — perhaps because the pattern was not elicited by any one experience, or because the memory traces for a particular experience are spread across disparate brain regions. Even a nonspecific DSR response can be involved in consolidation. For example, if a SWR induces a conducive listening state (i.e. window of opportunity for plasticity) at the same time as activating specific memory traces in other connected regions, local traces could be pattern completed into a global, multi-regional memory schema. Thus, rather than the direct transfer of a veridical memory trace [2], or the storage of redundant memory traces in the hippocampus and extra-hippocampal regions, the hippocampus may serve as a content-free or content-limited spatiotemporal sequence generator that, given its unique intra-regional and inter-regional topography, can bias ongoing spatiotemporal listening states and drive local reactivation across modalities in service of generalization or formation of multi-modal memories.

Conclusions

Hippocampal SWR-mediated brain-wide reactivation of veridical memories during sleep is thought to be a mechanism for memory consolidation. In this review, we highlighted recent work indicating that the offline reading of memory traces is often less specific than the classical view of memory consolidation would suggest — both in hippocampal reactivation and in the coordination of reactivation with the rest of the brain. Rather than a faithful reproduction of recent experience, the available experiments suggest that activity during hippocampal SWRs can range from nonspecific (i.e. content-free) activation of neural patterns, to the sequential activation of patterns primed during a specific salient experience, under the temporal constraints of the SWR. Such self-organized activation is a universal property of attractor networks in the excitable regimes seen during offline states.

The impact of SWR-induced reactivation on DSRs is not simply a specific reflection of the spiking content of hippocampal activity, because the response of a

downstream region to a SWR depends on both feedforward and local circuit architecture, as well as the listening state of the DSR circuit. Given that local circuit architecture and state vary both across regions and within a given region across time, a single SWR may have multiple effects, depending on the DSR circuit under consideration and the temporal coordination of locally generated rhythms in relation to the SWR. From this perspective, SWRs act as a multiplexed signal, the mnemonic specificity of which is largely determined by a transformation function. Thus, instead of faithful read-out of a single experience, we suggest that specificity of both primary and secondary reading of SWR content is dynamically regulated over the course of sleep, governing which aspects of a learned experience are remembered, forgotten, or incorporated into an existing knowledge base.

Author contribution

None.

Conflict of interest statement

Nothing declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.cobeha.2020.02.008>.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Buzsáki G: **Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning.** *Hippocampus* 2015, **1188**:1073-1188.
2. McClelland JL, McNaughton BL, O'Reilly RC: **Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory.** *Psychol Rev* 1995, **102**:419-457.
3. Joo HR, Frank LM: **The hippocampal sharp wave – ripple in memory retrieval for immediate use and consolidation.** *Nat Rev Neurosci* 2018, **19**.
4. Kumaran D, Hassabis D, McClelland JL: **What learning systems do intelligent agents need? Complementary learning systems theory updated.** *Trends Cogn Sci* 2016, **20**:512-534.
5. Tingley D, Peyrache A: **On the methods for reactivation and replay analysis.** *Philos Trans R Soc B Biol Sci* 2019 <http://dx.doi.org/10.1098/rstb.2019.0231>.
6. Stella F, Baracska P, O'Neill J, Csicsvari J: **Hippocampal reactivation of random trajectories resembling Brownian diffusion.** *Neuron* 2019, **102**:450-461.e7.
Stella *et al.* investigated reactivated spatial trajectories in CA1 following exploration on a familiar open-field environment and found that reactivations resembled random trajectories with Brownian motion-like statistics, rather than replay of specific behavioral experiences.
7. Dragoi G, Tonegawa S: **Distinct preplay of multiple novel spatial experiences in the rat.** *Proc Natl Acad Sci U S A* 2013, **110**:9100-9105.
8. Stark E, Roux L, Eichler R, Buzsáki G: **Local generation of multineuronal spike sequences in the hippocampal CA1 region.** *Proc Natl Acad Sci U S A* 2015, **112**:10521-10526.
9. Hopfield JJ: **Neural networks and physical systems with emergent collective computational abilities.** *Proc Natl Acad Sci U S A* 1982, **79**:2554-2558.
10. Li XG, Somogyi P, Ylinen A, Buzsáki G: **The hippocampal CA3 network: an in vivo intracellular labeling study.** *J Comp Neurol* 1994, **339**:181-208.
11. Ocker GK, Litwin-Kumar A, Doiron B: **Self-organization of microcircuits in networks of spiking neurons with plastic synapses.** *PLoS Comput Biol* 2015, **11**:1-40.
Ocker *et al.* investigate how self-organized spontaneous activity and synaptic plasticity interact to determine network structure in a recurrent neural network. Spike initiation dynamics, spike-frequency adaptation, synaptic inhibition, and passive membrane properties can all drive emergent motif dynamics.
12. Izhikevich EM: **Polychronization: computation with spikes.** *Neural Comput* 2006, **18**:245-282.
13. Chaudhuri R, Gerçek B, Pandey B, Peyrache A, Fiete I: **The intrinsic attractor manifold and population dynamics of a canonical cognitive circuit across waking and sleep.** *Nat Neurosci* 2019, **22**:1512-1520.
Chaudhuri *et al.* demonstrate the existence of low-dimensional manifolds in population activity using the head direction system. They identify a one-dimensional ring attractor that can be parameterized and mapped to the external variable of head direction and persists across waking and REM states.
14. O'Keefe J, Nadel L: **The hippocampus as a cognitive map.** *Behav Brain Sci* 1979, **2**:487-533.
15. Recanatani S, Farrell M, Lajoie G, Deneve S, Rigotti M, Shea-Brown E: **Predictive learning extracts latent space representations from sensory observations.** *bioRxiv* 2019 <http://dx.doi.org/10.1101/471987>.
16. Low RJ, Lewallen S, Aronov D, Nevers R, Tank DW: **Probing variability in a cognitive map using manifold inference from neural dynamics.** *bioRxiv* 2018 <http://dx.doi.org/10.1101/418939>.
Low *et al.* developed an unsupervised learning algorithm to characterize hippocampal population activity as a trajectory on a nonlinear manifold during spatial and non spatial tasks. They found that the recovered manifolds were low-dimensional and smoothly encoded task-related variables.
17. Hopfield JJ: **Neural networks and physical systems with emergent collective computational abilities.** *Proc Natl Acad Sci U S A* 1982, **79**:2554-2558.
18. Pastalkova E, Itskov V, Amarasingham A, Buzsáki G: **Internally generated cell assembly sequences in the rat hippocampus.** *Science* 2008, **321**:1322-1327.
19. Farooq U, Sibille J, Liu K, Dragoi G: **Strengthened temporal coordination within pre-existing sequential cell assemblies supports trajectory replay.** *Neuron* 2019, **103**:719-733 <http://dx.doi.org/10.1016/j.neuron.2019.05.040>.
20. Levenstein D, Buzsáki G, Rinzal J: **NREM sleep in the rodent neocortex and hippocampus reflects excitable dynamics.** *Nat Commun* 2019, **10** <http://dx.doi.org/10.1038/s41467-019-10327-5>.
21. Cossart R, Aronov D, Yuste R: **Attractor dynamics of network UP states in the neocortex.** *Nature* 2003, **423**:283-288.
22. Chenkov N, Sprekeler H, Kempter R: **Memory replay in balanced recurrent networks.** *PLoS Comput Biol* 2017, **13** <http://dx.doi.org/10.1371/journal.pcbi.1005359>.
Chenkov *et al.* studied mechanisms of replay in balanced networks and showed how even small changes in synaptic weights can result in replay when combined with recurrent connectivity. They found that the relative strength of embedded feedforward and recurrent weights influences the nature of replay — with replay events ranging from synfire chains to assemblies or sequences of assemblies.

23. Litwin-Kumar A, Doiron B: **Formation and maintenance of neuronal assemblies through synaptic plasticity.** *Nat Commun* 2014, **5**.
24. Skilling QM, Maruyama D, Ognjanovski N, Aton SJ, Zochowski A: **Critical dynamics mediate stabilization of new distributed memory representations** Quinton. *arXiv* 2017.
25. Giri B, Miyawaki H, Mizuseki K, Cheng S, Diba K: **Hippocampal reactivation extends for several hours following novel experience.** *J Neurosci* 2019, **39**:866-875.
26. Roscow EL, Jones MW, Lepora NF: **Behavioural and computational evidence for memory consolidation biased by reward-prediction errors.** *bioRxiv Prepr* 2019 <http://dx.doi.org/10.1101/716290>.
27. Carey AA, Tanaka Y, van der Meer MAA: **Reward revaluation biases hippocampal replay content away from the preferred outcome.** *Nat Neurosci* 2019, **22**:1450-1459.
28. Gupta AS, van der Meer MAA, Touretzky DS, Redish AD: **Hippocampal replay is not a simple function of experience.** *Neuron* 2010, **65**:695-705.
29. Drieu C, Todorova R, Zugaro M: **Nested sequences of hippocampal replay during behavior support subsequent sleep replay.** *Science* 2018, **362**:675-679.
30. Nicola W, Clopath C: **The dance of the interneurons: how inhibition facilitates fast compressible and reversible learning in hippocampus.** *bioRxiv* 2018 <http://dx.doi.org/10.1101/318303>.
31. Klinzing JG, Niethard N, Born J: **Mechanisms of systems memory consolidation during sleep.** *Nat Neurosci* 2019, **22**:1598-1610 <http://dx.doi.org/10.1038/s41593-019-0467-3>.
32. Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, Battaglia FP, Wiener SI: **Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning.** *Neuron* 2010, **66**:921-936.
33. Atherton LA, Dupret D, Mellor JR: **Memory trace replay: the shaping of memory consolidation by neuromodulation.** *Trends Neurosci* 2015, **38**:560-570.
34. Oby ER, Golub MD, Hennig JA, Degenhart AD, Tyler-Kabara EC, Yu BM, Chase SM, Batista AP: **New neural activity patterns emerge with long-term learning.** *Proc Natl Acad Sci U S A* 2019, **116**:15210-15215.
- Monkeys learn to control the trajectory of a cursor in 2D space using recorded motor cortical population activity in a BMI task. This is a follow-up study to [54], and shows that if neural activity outside of a low-dimensional "intrinsic manifold" is required to control a cursor, this can be done but takes longer than on-manifold learning in the same task. This longer timescale learning leads to a systematic restructuring of pairwise population activity in motor cortex.
35. Golub MD, Sadtler PT, Oby ER, Quick KM, Ryu SI, Tyler-Kabara EC, Batista AP, Chase SM, Yu BM: **Learning by neural reassociation.** *Nat Neurosci* 2018, **21**:607-616.
- Monkeys learn to control the trajectory of a cursor in 2D space using recorded motor cortical population activity in a BMI task. Because the mapping between neural activity and behavior is precisely defined, authors demonstrate that on a short timescale, animals can more quickly learn to produce neural activity patterns on rather than off a low dimensional manifold, defined by co-activity patterns of the recorded cell population, demonstrating fast on-manifold learning.
36. Sadtler PT, Quick KM, Golub MD, Chase SM, Ryu SI, Tyler-Kabara EC, Yu BM, Batista AP: **Neural constraints on learning.** *Nature* 2014, **512**:423-426.
37. Tse D, Langston RF, Takeyama M, Bethus I, Spooner PA, Wood ER, Witter MP, Morris RGM: **Schemas and memory consolidation.** *Science (80-)* 2007, **316**:76-82.
38. Frankland PW, Bontempi B: **The organization of recent and remote memories.** *Nat Rev Neurosci* 2005, **6**:119-130 <http://dx.doi.org/10.1038/nrn1607>.
39. Logothetis NK, Eschenko O, Murayama Y, Augath M, Steudel T, Evrard HC, Besserve M, Oeltermann A: **Hippocampal-cortical interaction during periods of subcortical silence.** *Nature* 2012, **491**:547-553.
40. Norman Y, Yeagle EM, Khuvis S, Harel M, Mehta AD, Malach R: **Hippocampal sharp-wave ripples linked to visual episodic recollection in humans.** *Science (80-)* 2019, **365**.
41. Ólafsdóttir HF, Carpenter F, Barry C: **Coordinated grid and place cell replay during rest.** *Nat Neurosci* 2016, **19**:1-6.
42. Girardeau G, Inema I, Buzsáki G: **Reactivations of emotional memory in the hippocampus-amygdala system during sleep.** *Nat Neurosci* 2017, **20**:1634-1642.
43. O'Neill J, Boccarda CN, Stella F, Schoenenberger P, Csicsvari J: **Superficial layers of the medial entorhinal cortex replay independently of the hippocampus.** *Science (80-)* 2017, **355**:184-188.
44. Tingley D, Buzsáki G: **Routing of hippocampal ripples to subcortical structures via the lateral septum.** *Neuron* 2020, **105** 138-149.e5.
45. Heeger DJ, Mackey WE: **Oscillatory recurrent gated neural integrator circuits (ORGaNICs): a unifying theoretical framework for neural dynamics.** *PNAS* 2019, **116**:22783-22794 <http://dx.doi.org/10.1073/pnas.1911633116>.
- Created an LSTM style neural network that dynamically scales input and recurrence to model working memory and motor control. They demonstrate how information can be read from complex dynamics in a network and how different readers may access different information from the same ongoing activity.
46. Kim M-H, Znamenskiy P, Iacaruso MF, Mrcic-Flogel TD: **Segregated subnetworks of intracortical projection neurons in primary visual cortex.** *Neuron* 2018, **100**:1313-1321.e6.
47. Dayan P, Abbott LF: *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems.* MIT Press; 2005. Chapter 7.4..
48. Eschenko O, Magri C, Panzeri S, Sara SJ: **Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep.** *Cereb Cortex* 2012, **22**:426-435.
49. Semedo JD, Zandvakili A, Machens CK, Yu BM, Kohn A: **Cortical areas interact through a communication subspace.** *Neuron* 2019, **102**:249-259.e4.
50. Ciochci S, Passecker J, Malagon-Vina H, Mikus N, Klausberger T: **Selective information routing by ventral hippocampal CA1 projection neurons.** *Science (80-)* 2015, **348**:560-563.
51. Roy DS, Park Y-G, Ogawa SK, Cho JH, Choi H, Kamensky L, Martin J, Chung K, Tonegawa S: **Brain-wide mapping of contextual fear memory engram ensembles supports the dispersed engram complex hypothesis.** *bioRxiv* 2019 <http://dx.doi.org/10.1101/668483>.
52. Luczak A, Barthó P, Harris KD: **Spontaneous events outline the realm of possible sensory responses in neocortical populations.** *Neuron* 2009, **62**:413-425.
53. Contreras EJB, Gomez A, Schjettan P, Muhammad A, Bartho P, Mcnaughton BL, Kolb B, Gruber AJ, Luczak A: **Formation and reverberation of sequential neural activity patterns evoked by sensory stimulation are enhanced during cortical desynchronization.** *Neuron* 2013, **79**:555-566.
54. Khodagholy D, Gelinás JN, Buzsáki G: **Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus.** *Science (80-)* 2017, **372**:369-372.
55. Kitamura T, Ogawa SK, Roy DS, Okuyama T: **Engrams and circuits crucial for systems consolidation of a memory.** *Science* 2017, **78**:73-78.
56. Cowansage KK, Shuman T, Dillingham BC, Chang A, Golshani P, Mayford M: **Direct reactivation of a coherent neocortical memory of context.** *Neuron* 2014, **84**:432-441.
57. Levenstein D, Watson BO, Rinzel J, Buzsáki G: **Sleep regulation of the distribution of cortical firing rates.** *Curr Opin Neurobiol* 2017, **176**:139-148.
58. Maingret N, Girardeau G, Todorova R, Goutierre M, Zugaro M: **Hippocampo-cortical coupling mediates memory consolidation during sleep.** *Nat Neurosci* 2016, **19**.

59. Peyrache A, Battaglia FP, Destexhe A: **Inhibition recruitment in prefrontal cortex during sleep spindles and gating of hippocampal inputs.** *PNAS* 2011, **108**.
60. Battaglia FP, Sutherland GR, McNaughton BL: **Hippocampal sharp wave bursts coincide with neocortical “up-state” transitions.** *Learn Mem* 2004, **11**:697-704.
61. Sanda P, Malerba P, Jiang X, Krishnan GP, Cash S, Halgren E: **Interaction of hippocampal ripples and cortical slow waves leads to coordinated large-scale sleep rhythm.** *bioRxiv* 2019.
62. Isomura Y, Sirota A, Simal O, Montgomery S, Mizuseki K: **Integration and Segregation of Activity in Entorhinal-Hippocampal Subregions by Neocortical Slow Oscillations.** 2006 <http://dx.doi.org/10.1016/j.neuron.2006.10.023>.
63. Rothschild G, Eban E, Frank LM: **A cortical – hippocampal – cortical loop of information processing during memory consolidation.** *Nat Neurosci* 2016 <http://dx.doi.org/10.1038/nn.4457>.
- A cued memory consolidation paradigm is used in rodents to prompt reactivation of auditory cortex in response to a learned tone. This reactivation is demonstrated to bias subsequent hippocampal reactivation, which then impacts ongoing activity in A1 during rest. This is direct evidence of both the ability or activity in primary sensory cortices to bias hippocampal reactivation, and hippocampal reactivation to bias activity in sensory cortices many synapses removed from the structure.
64. Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G: **The sleep slow oscillation as a traveling wave.** *J Neurosci* 2004, **24**:6862-6870.
65. Piantoni G, Koller D, Cash SS, Halgren E, Sejnowski TJ, Muller L, Piantoni G, Koller D, Cash SS, Halgren E: **Rotating waves during human sleep spindles organize global patterns of activity that repeat precisely through the night.** *eLife* 2016 <http://dx.doi.org/10.7554/eLife.17267>.
66. Miyamoto D, Hirai D, Fung CCA, Inutsuka A, Odagawa M, Suzuki T, Boehringer R, Adaikkan C, Matsubara C, Matsuki N *et al.*: **Top-down cortical input during NREM sleep consolidates perceptual memory.** *Science* 2016, **352**.
- The inhibition of axons projecting from higher order secondary motor to lower order somatosensory cortex impairs reactivation of S1 neurons and memory. Asynchronous stimulation of both regions impaired memory and synchronous stimulation improved memory, demonstrating a direct role for synchronous top-down input in driving reactivation, supporting the mnemonic benefits of consolidation.
67. Fauth MJ, Van Rossum MCW: **Self-organized reactivation maintains and reinforces memories despite synaptic turnover.** *eLife* 2019.
68. Wei Y, Koulakov AA: **Long-term memory stabilized by noise-induced rehearsal.** *J Neurosci* 2014, **34**:15804-15815.
69. Krishnan GP, Tadros T, Ramyaa R, Bazhenov M: **Biologically inspired sleep algorithm for artificial neural networks.** *arXiv* 2019.
70. McNaughton BL: **Cortical hierarchies, sleep, and the extraction of knowledge from memory.** *Artif Intell* 2010, **174**:205-214.
71. Gu S, Pasqualetti F, Cieslak M, Telesford QK, Yu AB, Kahn AE, Medaglia JD, Vettel JM, Miller MB, Grafton ST *et al.*: **Controllability of structural brain networks.** *Nat Commun* 2015, **6**.
72. Teyler TJ, Discenna P: **The hippocampal memory indexing theory.** *Behav Neurosci* 1986, **100**:147-154.