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CHAPTER 11

Hippocampal–cortical interactions and the dynamics of memory trace reactivation

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Abstract: The formation of memory and extraction of knowledge from it is the basis of intelligence. It is believed that, during slow-wave sleep, the brain reorganizes its connectivity matrix so as to store new information optimally. As the probability of direct synaptic connection between arbitrarily chosen neurons in the cortex is extremely low (on the order of 10^{-6}), a combination of modular and hierarchical organization appears to be necessary to enable rapid association of arbitrary items. During waking, an "index" of the neural pattern in lower order cortical modules may be created and stored in the highest order association cortex, the hippocampus, and broadcast back to the relevant cortical modules, where it is stored with the local data. In this manner, the pattern can be spontaneously reactivated and reinstated in all modules to enable the establishment of crossmodular connections, and replay of such patterns of neural activity or "phase sequences" has been observed in hippocampus and neocortex. In prefrontal cortex, the playback of "phase sequences" is associated with periods of intense upstate/downstate transitions and can be accelerated five- to eightfold relative to the waking state. The playback speed declines over time as does the strength of the replay, which is consistent with a simple decay of an asymmetric component of the synaptic weight matrix induced during the experience itself. Since the hippocampal events associated with memory reactivation (sharp-wave ripple events) tend to be correlated with up transitions in the neocortex, hippocampus may coordinate reactivation in neocortex, at least under some conditions.

Keywords: replay; slow oscillations; sharp waves; memory consolidation; indexing theory; slow-wave sleep.

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Cortical modular organization and memory indexing

The ability to remember facts and episodes is a critical component of thought and intelligence. Hebb (1949) proposed that memory is based on the formation of assemblies of cells that are mutually connected with strengthened synapses. The problem with this general idea is that the average connectivity of the cortex is extremely sparse (less than about 10^{-6}), and therefore, the cortex cannot support the acquisition of new, arbitrary associations by modifying preexisting connections alone; however, activity in two neurons that are not themselves directly connected can, nevertheless, be associated by virtue of their common reciprocal connections with a third, higher order neuron. Thus, by organizing the cortex into functional modules that are reciprocally connected and arranged in a hierarchical structure, sparsely distributed connections may be sufficient to organize the acquisition and storage of information effectively. Within this conceptual framework, the lowest level modules are represented by primary cortices, the level above by association cortices, and at the top resides the hippocampal formation, which has been recognized as the highest order association cortex (Fig. 1, left; Swanson, 1983). This organizational principle links neurons that are receiving and processing similar information to form modules that subserve a common function. Connectivity within modules is presumably high, enabling local (within module) associations, whereas connectivity between modules is very sparse. Therefore, slow growth and rearrangement of connections would be required to connect cells of different modules that together represent an experienced episode. The pattern of "vertical" information flow, from primary to higher order association cortices, would ultimately give rise to a unique pattern that is stored in the hippocampus. In addition, the hippocampal output pattern at the time of the experience would also be stored in the lower level modules as part of their "current input." In this manner, each module would store module-specific information plus a small component of common information that it receives from the hippocampus. The common information could thus serve as an index pattern that could be used to coordinate retrieval and memory trace reactivation. Recreating the index pattern would evoke the corresponding patterns in the lower level modules, thus completing the retrieval of the whole memory (Fig. 1, right). The trace reactivation theory of memory consolidation holds that reactivation of cortical modules that were involved during the original encoding of the pattern provides a training trial through which the modules can become appropriately connected

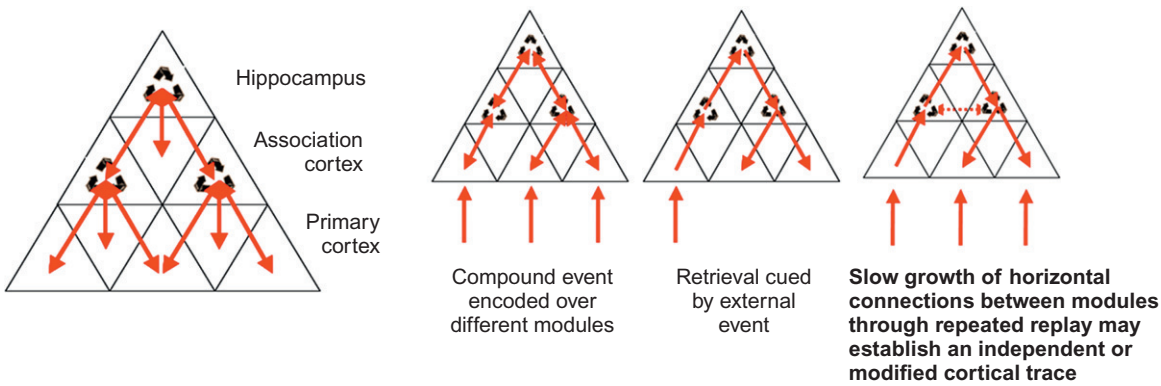

Fig. 1. Hierarchical organization of cortex and hippocampus and the indexing encoding principle.

through growth and rearrangement of horizontal, intermodular connections. In this manner, a cortical representation could be established which is independent of the hippocampus. Presumably, this representation would differ in some ways from the original form.

In the foregoing theoretical framework, rapid plasticity (Long term potentiation) in different encoding stages supports the indirect association of modules via an "index" pattern generated in the hippocampus. The ascending input from sensory areas to association cortices and hippocampus, mainly entering the hippocampus through entorhinal cortex layers II and III, and also the descending outputs from the hippocampus (Swanson and Kohler, 1986), should undergo rapid plasticity (Insausti et al., 1997). The hippocampal output is predominantly directed back to the NMDA-receptor rich (Monaghan and Cotman, 1985), superficial layers of almost the entire neocortical mantle either directly through the deep layers of the entorhinal cortex or indirectly via the perirhinal cortex (Insausti et al., 1997). Within-hippocampus and within-module plasticity processes would also be essential to enable the formation of local cell assemblies that can be retrieved autoassociatively. Through lengthy and slow plasticity processes, involving the rearrangement of intermodular connections, the modules would become directly linked.

In patients with anterograde amnesia, the ability to form new memories and to incorporate information from these into the existing semantic knowledge base is dramatically impaired. Such patients almost always have severe damage to the hippocampus and are therefore missing the module that, according to theory, enables indirect association among lower cortical modules. After hippocampal damage, however, some remote memories, cognitive functionality and categorized knowledge are left intact. According to the Standard Consolidation Theory, the hippocampus supports memory storage and recall only for a limited amount of time, after which the memory or the links are thought to be transferred to neocortical sites and protected from hippocampal damage through a process of systems consolidation. Accumulating evidence calls this theory into question (for review, see Sutherland et al., 2010) because, in many studies with hippocampal lesions or temporary inactivations, the memory deficits are not graded, meaning that memories that have been acquired further back in time are impaired as much as recent ones (Martin et al., 2005; Sutherland et al., 2008). This phenomenon seems to be independent of the extent of hippocampal damage and the memory task used. Only a small number of studies make an exception to this observation (Clark et al., 2002; Tse et al., 2007). Although episodic memory recall seems to depend on the hippocampus at all time intervals measured, it is unlikely that the memory persists in its original form throughout life. More likely, information may be extracted from these memory traces and incorporated into what is generally called "semantic memory" or knowledge (McClelland et al., 1995). Thus, whereas the hippocampal code represents direct associations of details that compose the experienced event, the cortical code represents the knowledge and general information that can be educed from it. "Consolidated" information is no longer necessarily linked to specific space and time information, but probably incorporated into the preexisting semantic knowledge about the world through a classification process (see also Marr, 1970, 1971).

It is now generally believed that the process of extracting knowledge from memory occurs mainly during sleep, when the brain is not occupied with processing current sensory information and is essentially functionally disconnected from the environment (Marr, 1971). A way to accomplish the postlearning resorting of information would be to "replay" the episodic information interleaved with knowledge representations from past experience (McClelland et al., 1995; McCloskey and Cohen, 1989). Indeed, there is abundant evidence in rats that behavioral activity patterns are reexpressed during postbehavioral sleep episodes

(Dupret et al., 2010; Euston et al., 2007; Karlsson and Frank, 2009; Kudrimoti et al., 1999; Lansink et al., 2008, 2009; O'Neill et al., 2008; Wilson and McNaughton, 1994). Such synchronous reactivation of various subcomponents of the memory that may be stored in different cortical modules may enable the rearrangement and strengthening of selective connections at this time. After the gradual formation and/or reorganization of the horizontal connections, the memory might be sustainable through the new associations (possibly in "semanticized" form) without the top-down linkage from the hippocampus. However, multiple reinstatements of the experience that trigger replay episodes are likely a requirement to establish a hippocampus-independent memory trace. If the amount of replaying episodes does not suffice to establish a strong enough extrahippocampal representation, the memory will likely not be spared after inactivation of the hippocampus.

Most of the experimental data which give clues about memory consolidation in the mammalian cortex are derived from electrophysiological ensemble recordings, mainly from the rat brain. In this chapter, we discuss how these data are acquired, organized, and analyzed, as well as what is our current knowledge about memory trace reactivation in the hippocampo-neocortical circuit during slow-wave sleep.

Sparse versus distributed coding to maximize storage capacity

The degree of sparsity in coding appears to differ systematically as one ascends in the hierarchy of cortical modules and peaks in the hippocampus. In a sparse code, the proportion of units used to store a memory (α) is minimized to maximize the number of distinct patterns that can be stored. In low-level modules, such as primary sensory or motor cortex, where high resolution and smooth generalization are emphasized rather than rapid information storage, coding is not sparse but rather fully distributed ($\alpha = 0.5$). In some areas of the hippocampus, coding appears to be optimized to store a maximal number of patterns rapidly in the network, thus α must be minimal. Electrophysiological recordings and immediate early gene (IEG) studies together confirm that the proportion of hippocampal neurons active at any given location is, in general, extremely small and that sparsity is greatest in DG and becomes progressively less in CA3, CA1, subiculum, and deep entorhinal cortex (Barnes et al., 1990; Guzowski et al., 1999; Leutgeb et al., 2004; Vazdarjanova and Guzowski, 2004; see, however, Alme et al., 2010).

Although sparse coding maximizes the number of items that can be stored, it does so at a cost of reduced information transmission per neuron. Thus, where only transmission and not storage is required, it is more economical to use a more distributed code so that the same amount of information can be sent over fewer channels. It appears that the hippocampal formation exploits this possibility by compressing the CA3 and CA1 output to a less sparse code prior to transmission back to the neocortex via the subiculum and deep layers of the entorhinal cortex (Barnes et al., 1990).

The main outputs of the hippocampal formation target the superficial layers of the neocortex. Recent evidence based on activity-dependent IEG activation indicates that, whereas the deep layers of the neocortical modules express purely domain-specific information (e.g., touch, taste, vision, movement, etc.), neurons in the superficial layers express the conjunction of spatial context and the domain-specific information (Burke et al., 2005). Although further study is needed, these observations are consistent with the "indexing" theory which postulates that the pattern transmitted from the hippocampus back to the neocortex is stored in the superficial layers of neocortex along with information about the current experience or motor output, thus serving as a means of top-down associative retrieval. Also consistent is the fact that the superficial layers possess the highest density of NMDA receptors

(Monaghan and Cotman, 1985) and thus may be more susceptible to rapid plasticity.

Basic data structure and analysis of ensemble recordings

In order to present the neurophysiological evidence for memory trace reactivation, it is useful first to discuss some general ways that neural ensemble recording data can be conceptualized and analyzed. In single-unit extracellular recordings (and, more recently, in optical imaging studies), spike trains (i.e., lists of action potentials over an arbitrary time interval) of a sample of a few hundred cells can be obtained with today's available technology. These lists comprise a matrix (i.e., $N \times T$ spike rate matrix Q, where N is the number of cells and T is the number of time intervals) that contains information about the animal's brain state at various time points (Fig. 2a). Each row corresponds to one cell's activity across the recorded time intervals (rate vector, reflecting the firing rate of one neuron), and each column corresponds to the ensemble activity of all neurons at a certain moment (state vector, reflecting the brain state by the ensemble activity at a given time). Summation along the first dimension would result in a vector containing the mean firing rates of all neurons. Summation along the second dimension would result in a time series of the mean population activity, which is sometimes considered to be reflected in the filtered local field potential trace.

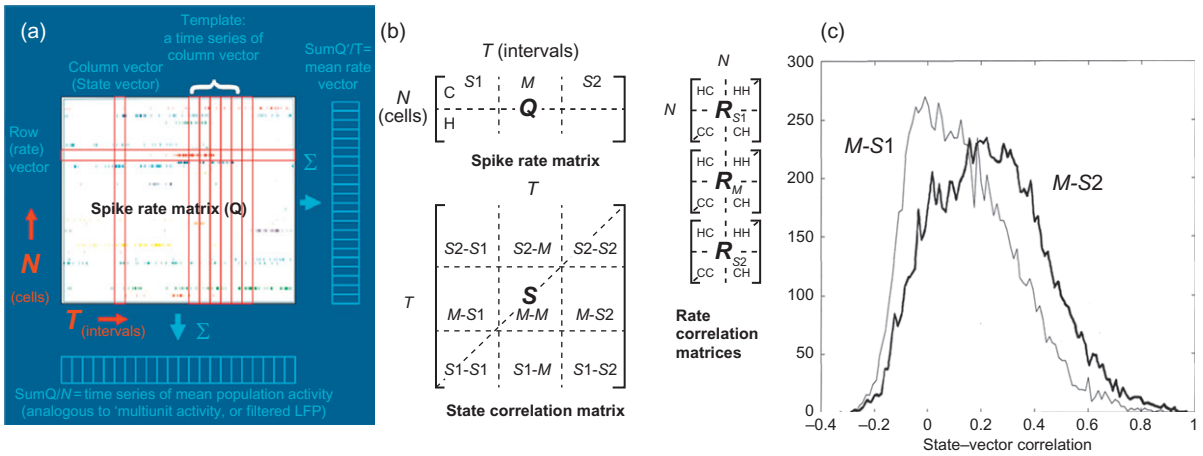

Fig. 2. (a) Modern neurophysiologic methods allow the simultaneous recordings of about a few hundred neurons. In this plot, the spike activity (colored vertical ticks) of about 50 neurons is plotted for about 10 s. This constitutes the $N \times T$ spike rate matrix (Q), where each row represents the spike activity of an individual neuron and the columns can be considered as time, binned into regular intervals of arbitrary size. Columnwise correlation measures similarity of brain states, while rowwise correlation detects cofiring between neuron pairs. (b) Data analyses of multiunit recordings. The columnwise correlation of the Q-matrix yields the $T \times T$ state correlation matrix (S-matrix). The S-matrix can be divided into subdivisions corresponding to the different epochs correlated with each other. Along the diagonal, within-epoch correlations will be high on average if the behavior is repetitive. The subdivisions $S1$-M and M-$S2$ are of main interest in terms of reactivated patterns in sleep. The rowwise correlation of the Q-matrix results in separate R-matrices (rate correlation matrices) for each epoch. (c) Distribution of state-vector correlation values. Correlation values between posttask sleep and behavior are higher than correlation values between pretask sleep and behavior, which peak around 0. The shift toward higher values of the state-vector correlation distribution of M-$S2$ indicates that behavioral firing patterns are reexpressed in sleep after behavior (McNaughton, 1998).

The simple correlation between any two rate vectors (temporal correlation) represents the correlation of firing between two neurons over a certain time interval, while the correlation between any two states of vector (state correlation) estimates the similarity of the global states of the system at the corresponding times.

An established method to quantify memory reactivation is to express the Pearson correlation coefficients of the temporal correlations (rate vector correlations) between neuron pairs for each epoch (pretask sleep, task, posttask sleep) and assemble them into single matrices. Memory trace reactivation is measured by computing how much of the variance in the firing rate correlation matrix in posttask sleep can be accounted for by the variance in the correlation matrix of the firing patterns established during the task, when controlling for all effects that were already present in the active cell population in pretask sleep (Kudrimoti et al., 1999; Tatsuno et al., 2006).

Another way to assess memory reactivation is to compare state vectors between epochs to identify patterns that emerge during behavior and are reexpressed during posttask sleep. If there is increased probability of a state vector to reappear in sleep after its appearance in a behavioral episode, either because of the formation of new cell assemblies through associative synaptic modifications or because they were already defined in the synaptic matrix before the behavioral epoch, it suggests that there is some form of memory being reactivated. By constructing a $(T \times T)$ correlation matrix S of all state-vector correlations, which will consist of different submatrices (Fig. 2b), of which $S1$-M and M-$S2$ are of main interest, one can compare the means of the correlation distribution for the $S1$-M and M-$S2$ matrix. If activity states of the preceding behavior are being reexpressed in $S2$, then we expect the average of the elements of the M-$S2$ matrix to be significantly larger than of $S1$-M. Consequently, the distribution of state-vector correlations for M-$S2$ is shifted toward higher values than the distribution of M-$S1$ (Fig. 2c).

A more sophisticated and elegant approach to determine state-vector similarities among task and sleep epochs is to define a series of state vectors during behavior as a template and shift it across a target period (pretask and posttask sleep, respectively) to identify matching episodes (Louie and Wilson, 2001). Unlike the previously described analytic methods, the template matching procedure is sensitive to the temporal sequence of state vectors and also to possible temporal compression of the template pattern (Tatsuno et al., 2006).

Using place cells to study memory

The dominant characteristic of neuronal activity in the rodent hippocampus is selectivity for spatial location, a discovery which led to the term "place cells" (Fig. 3; O'Keefe and Dostrovsky, 1971). This feature makes them particularly suitable to study memory because it is generally the case that simply being in different locations leads to distinct patterns of neuronal activity which can subsequently be identified during potential retrieval periods such as sleep. How could we tell if memory traces were being reactivated during sleep after a behavioral episode? Cells that fired together during the task should also fire together during subsequent sleep (Wilson and McNaughton, 1994), whereas cells that did not fire together during the task should not do so afterward (Fig. 4). By recording a large ensemble of cells in the hippocampus during task and sleep, a multiple regression analysis of pairwise firing rate correlations can be used to quantify memory trace reactivation (Fig. 4b; Kudrimoti et al., 1999). The spike rate correlation structure has been observed to persist during rest for up to 30–60 min following an episode of behavior, such as track running. This phenomenon is dependent on NMDA-receptor activation, as the correlation persistence disappears when NMDA receptors are blocked (Stanis et al., 2004) during the behavioral epoch. Reactivation can also be observed

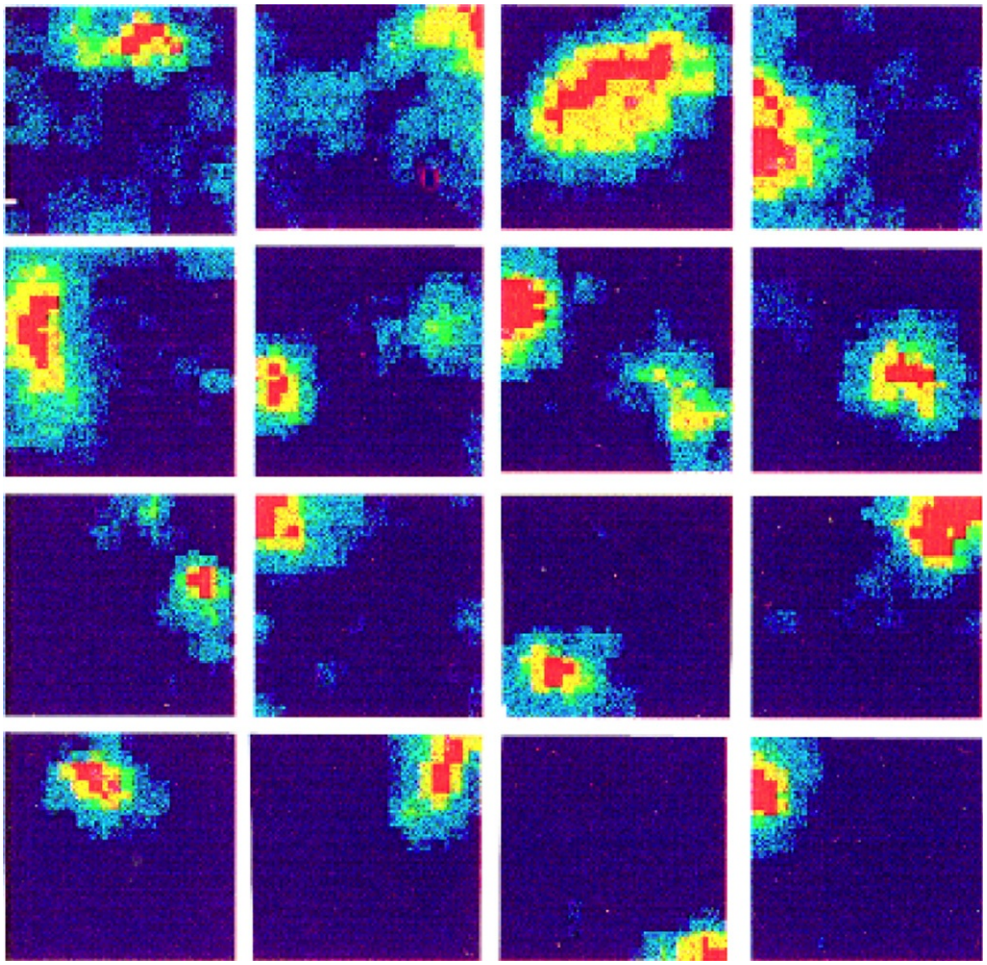

Fig. 3. Place cells in the hippocampus. Sixteen firing rate maps from representative dorsal hippocampal neurons (CA1) which had "place fields" in a 70×70 cm enclosure while the rats foraged for randomly scattered food pellets are depicted (Jung et al., 1994).

using the state-vector approach. In a typical maze running task, a rat runs laps repetitively, so the same states in the hippocampus repeat periodically at a rate that is dependent on the animal's speed. This repetitive pattern is reflected in high correlation values along the diagonal of a state-vector correlation matrix for the behavioral episode. If one compares the similarity of each state vector in sleep to each state vector during behavior (Fig. 2), then it is observed that there is generally a higher similarity of *S*2 vectors to the behavior than there is for *S*1, which is what one would expect if memories were retrieved during *S*2.

Experiences and memories for them are not typically discrete events but rather play out as temporal sequences. The neural basis for this temporal evolution was first proposed by Hebb (1949), who proposed the concept of "phase sequences," which he envisioned as sequences of cell assemblies which become directionally (i.e., asymmetrically) linked by strengthening connections from cells active earlier in the

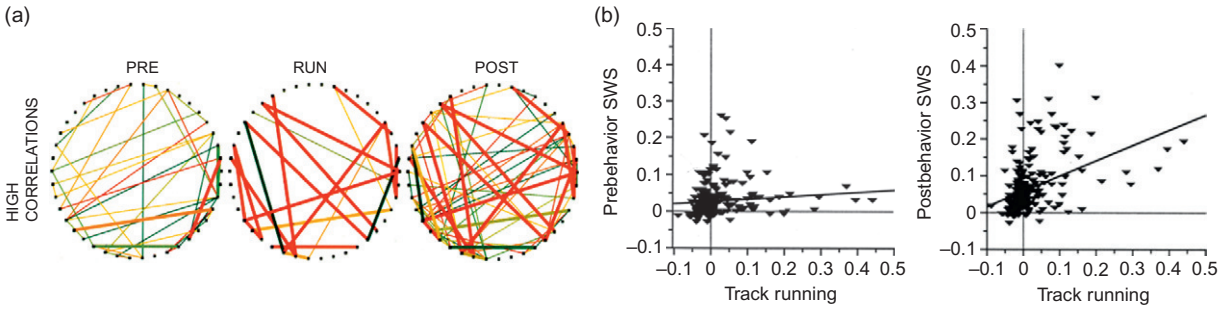

Fig. 4. (a) Diagram of synaptic connections among simultaneously recorded hippocampal neurons during pretask sleep, behavior, and posttask sleep. Lines indicate positive correlations between neuron pairs with the magnitude of the correlations coded in false colors (red: max; blue: min). Bold lines indicate pairs that were correlated during RUN and also correlated during either PRE or POST. Cell pairs that are strongly correlated during RUN are mostly also correlated during POST but generally absent in the pretask sleep (Wilson and McNaughton, 1994). (b) Scatterplots to illustrate the relationships of hippocampal pairwise correlations between track running and pretask sleep and between track running and posttask sleep, respectively. A simple linear regression line can be fit to the correlation data between run and posttask sleep (Kudrimoti et al., 1999).

sequence onto cells active later. One prediction of this concept is that, due to the rapid forward spread of neural activation, subsequent activation of cells earlier in the sequence would lead to activity in the cells at later points, before those points were actually reached. This phenomenon has been observed in hippocampal place cells which expand their fields with experience in the direction opposite to the rat's movement (Mehta et al., 1997). If cells have become sequentially linked during behavior, one might expect to see evidence of this linkage during off-line retrieval. A simple test would be to compute the temporal cross-correlograms of cells during sleep and compare their symmetry characteristics to the preceding behavior. For example, if cell A leads cell B in its firing during behavior, it should also tend to lead cell B during sleep after behavior. This was indeed observed by Skaggs and McNaughton (1996), and the reactivation of sequence data during sleep has now been documented using several different analytical approaches and in several different brain regions (Dupret et al., 2010; Euston et al., 2007; Hoffman and McNaughton, 2002; Karlsson and Frank, 2009; Kudrimoti et al., 1999; Lansink et al., 2009; Louie and Wilson, 2001; O'Neill et al., 2008; Tatsuno et al., 2006). Explained variance has proven to be a fairly robust measure of memory reactivation. The reason for this is that the measurement is based on pairwise correlations of binned spike trains of neurons within the time window of interest without taking into account complex fine timescale sequences expressed by the ensemble of neurons. Therefore shuffling the "population vectors" (i.e., columns in the *Q*-matrix), which equals segmented or incomplete replay of sequences, would not affect the correlation values. Sequences replayed at speeds different from the original encoding do not compromise the strength of the multiple correlations, but they do affect results obtained from template matching. Template matching, a powerful method to identify matching sequences of population vectors in two recording epochs, would need to employ an exhaustive and computationally expensive search to identify compression factors.

Coherent reactivation of memory traces in hippocampus and neocortex

The trace reactivation theory of memory consolidation requires that the reactivation of subcomponents of an experience is coherent across

all the modules in which these subcomponents are stored. Such coherence is necessary to ensure that the correct features are associated with one another. Here, we summarize the evidence supporting this requirement and review the current knowledge about the dynamics of the process.

Whereas during behavior and REM sleep, the hippocampal EEG is dominated by 8–12 Hz oscillations (theta), during slow-wave sleep, the hippocampal EEG is characterized by "sharp waves" and "ripples." Sharp waves reflect strong depolarizations of the CA1 dendrites due to synchronous activation of many Schaffer collaterals of CA3 pyramidal cells which make excitatory synapses there. These sharp waves often have high frequency oscillations called ripples (synchronous population discharge of CA1 pyramidal cells at ~150 Hz) superimposed on them. It is predominantly, if not exclusively during these synchronized population events, that memory traces are reactivated in the hippocampus (Fig. 5; Kudrimoti et al., 1999). The temporal relationships of the reactivating ensemble in sleep after behavior are preserved (Skaggs and McNaughton, 1996). If the hippocampus orchestrates the reinstatement of experience-specific patterns in the neocortex, as suggested by consolidation theories, then coordinated firing between hippocampal and neocortical units should emerge. Evidence supporting this hypothesis was obtained by recording from hippocampus and parietal cortex simultaneously (Qin et al., 1997). Simple correlation analyses of spike trains within and between areas showed that cofiring during behavior has effects on cofiring during subsequent sleep when taking into account preexisting correlations during prebehavioral sleep. The indexing theory postulates that hippocampal memory retrieval would coordinate reactivation of the relevant information in lower level modules to establish the necessary connections for pattern completion to occur without the indirect hippocampal associations. Consistent with this prediction, coherent reactivation among widespread neocortical modules has been observed following a simple reaching task in monkey (Hoffman and McNaughton, 2002). Activity patterns in motor, somatosensory, and parietal cortex were significantly reactivated. Contrary to at least the simple version of the theory, however, Ji and Wilson (2007) observed that during spontaneous retrieval in primary visual cortex and hippocampus, short sequences in the cortex may precede sequences in the hippocampus by about 50 ms after running on a highly familiar

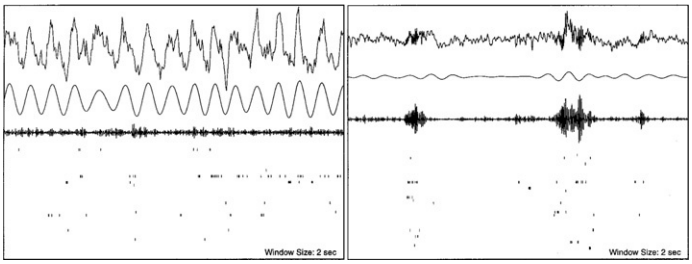

Fig. 5. Hippocampal EEG and concurrent spike activity during an REM (left) and slow-wave sleep (right) episode. The size of the windows is 2 s. The top trace in both panels is the raw EEG trace (sampling rate 200 Hz), the two traces below are the EEG band pass filtered between 6 and 10 Hz (second trace) and between 100 and 300 Hz (third trace). Below, each row represents the spiking activity of a hippocampal pyramidal neuron. Each tick mark represents a spike (left). Theta activity is prominent in the EEG during REM sleep but is absent in slow-wave sleep (right, missing 7–8 Hz component in filtered hippocampal trace). The third EEG trace shows 100–300 Hz components (ripples) in slow-wave sleep, which entail increased spiking activity of pyramidal neurons that are essentially silent in the absence of ripples. Adapted from Kudrimoti et al. (1999).

figure-8-shaped maze. Similarly, preliminary data suggest that in sleep after performing a highly familiar sequence task, medial prefrontal unit activity tends to lead hippocampal unit activity (Euston et al., 2008). However, direct pairwise correlations between hippocampal and prefrontal neurons during sleep after various spatial tasks reveal a consistent lead of hippocampal neurons during sharp wave events (Wierzynski et al., 2009). Although it is unclear how familiar the tasks are in the latter study, these data may suggest that the direction of interaction in initiating replay events in sleep after behavior might depend on the degree of "consolidation" of the memory. Reactivation of recent memory may be led by the hippocampus, while reactivation of already established memory traces may be coordinated by the medial prefrontal cortex, at least in certain cases. These observations remain to be studied and analyzed in more detail to allow for further interpretations. Since the actual memories are thought to be stored over multiple neocortical modules, it is also possible that reactivation of even a novel memory may be initiated within one of the relevant modules, which would trigger the reactivation of the hippocampal index code and lead to the synchronous reactivation of the entire memory.

Spontaneous memory trace reactivation has also been observed in subcortical structures, such as the ventral striatum (Pennartz et al., 2004). Neurons in that area also engage in memory trace reactivation, but only those neurons whose activity is modulated by sharp waves in the hippocampus, suggesting a close coordination between structures (Pennartz et al., 2004). This is consistent with the idea that the hippocampus acts as the coordinating module during spontaneous reactivation episodes in its projection areas. Further, only neurons coding for motivationally relevant information (such as reward) in the ventral striatum exhibited reactivation with hippocampal place units in a forward direction (Lansink et al., 2008, 2009).

Despite the accumulating data on reactivation in different brain regions, there is still no compelling evidence that memory trace reactivation is beneficial or critical for correct memory retrieval. Individual differences in reactivation scores in rats explain significant variance of performance in the water maze spatial task and therefore provide a piece of evidence suggesting that there is a direct relationship between reactivation and memory performance (Gerrard et al., 2008). This idea is further supported by the observation of impaired performance of a spatial reference task after selective interruption by electrical stimulation of hippocampal ripples in sleep after behavior (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009). Nevertheless, the more direct evidence for this hypothesis remains a major challenge in the field.

Memory trace reactivation dynamics during slow-wave sleep

Slow-wave sleep is characterized by a bimodal distribution of spike activity after the onset of slow oscillations and K-complexes (Johnson et al., 2010) and has become more strongly associated with memory reactivation than other sleep stages (Euston et al., 2007; Johnson et al., 2010; Louie and Wilson, 2001). Memory reactivation in the prefrontal cortex during slow-wave sleep is dynamically modulated by various patterns in the cortical EEG. One prominent pattern associated with reactivation is the K-complex. K-complexes are rapid voltage transitions that typically appear when the down- to upstate transition is extremely synchronized among a number of pyramidal neurons and are typically followed by a low voltage spindle (LVS, 6–20 Hz in rat; Fig. 6a). Periods of frequent K-complexes, LVS, and the down- to up-state transitions are correlated with strong cortical memory reactivation as measured with EV and template matching (Fig. 6b; Johnson et al.,

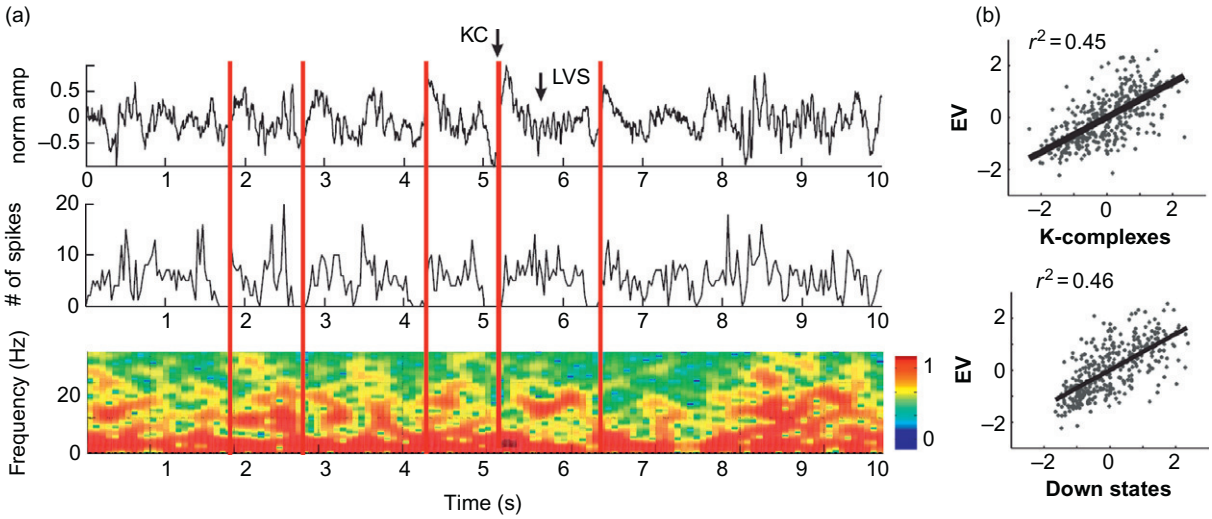

Fig. 6. (a, top) K-complex/LVS epochs occur during periods of low-frequency, high-amplitude activity in the local field potential (LFP; first panel).These periods correspond to periods of upstate/downstate fluctuations in the total spike activity (124 cells, 30 ms bins, second panel). A clear example of LVS preceded by a K-complex is marked by the arrow in the top panel. Each K-complex in the LFP is matched by a network down state in the total spike activity (red bars). In the spectrogram of the LFP (third panel), the K-complexes correspond to high power in the 2–6 Hz range, while LVSs correspond to a peak in the 10–20 Hz range. (b) Linear regression plot showing the relationship between memory reactivation, measured with explained variance, and the number of down states and K-complexes, respectively. The data points for sleep and behavioral epochs are compiled. Memory reactivation strength is positively correlated with the number of K-complexes (top) and down to up transitions (bottom) in a given epoch. Adapted from Johnson et al. (2010).

2010). During high voltage spindles (HVS, 6–8 Hz in rat), however, reactivation appears to be fairly weak (Johnson et al., 2010). In the prefrontal cortex, replay of activity patterns of a highly stereotyped behavior is compressed by a factor of six to seven (Euston et al., 2007), which can be inferred from similarly shaped cross-correlations of neuron pairs of the task and the posttask sleep epoch, with the only difference being the temporal scale (Fig. 7). This observation is consistent with the notion that memory replay speed is not constrained to real-time parameters during encoding but rather proceeds at speeds determined by network parameters such as synaptic strength and connection asymmetry, dendritic integration times, and conduction speeds. During a prolonged sleep session concomitant, the compression factor declines with a reduction of reaction strength (Tatsuno et al., 2008). This is consistent with the hypothesis of a gradual decline of the synaptic potential underlying the memory.

Memory replay in the prefrontal cortex and that in the hippocampus are most likely not isolated events, but may influence each other. This assumption is based on the observation that hippocampal sharp waves are most likely to occur at down- to upstate transitions in the cortex during slow-wave sleep (Fig. 8; Battaglia et al., 2004; Mölle et al., 2006). It is possible to detect frequently reactivated patterns in the prefrontal cortex with a high temporal precision and relate their times of occurrence to hippocampal sharp-wave ripple events (Peyrache et al., 2009). This is achieved by applying principal component analysis, a statistical tool to identify the structure of

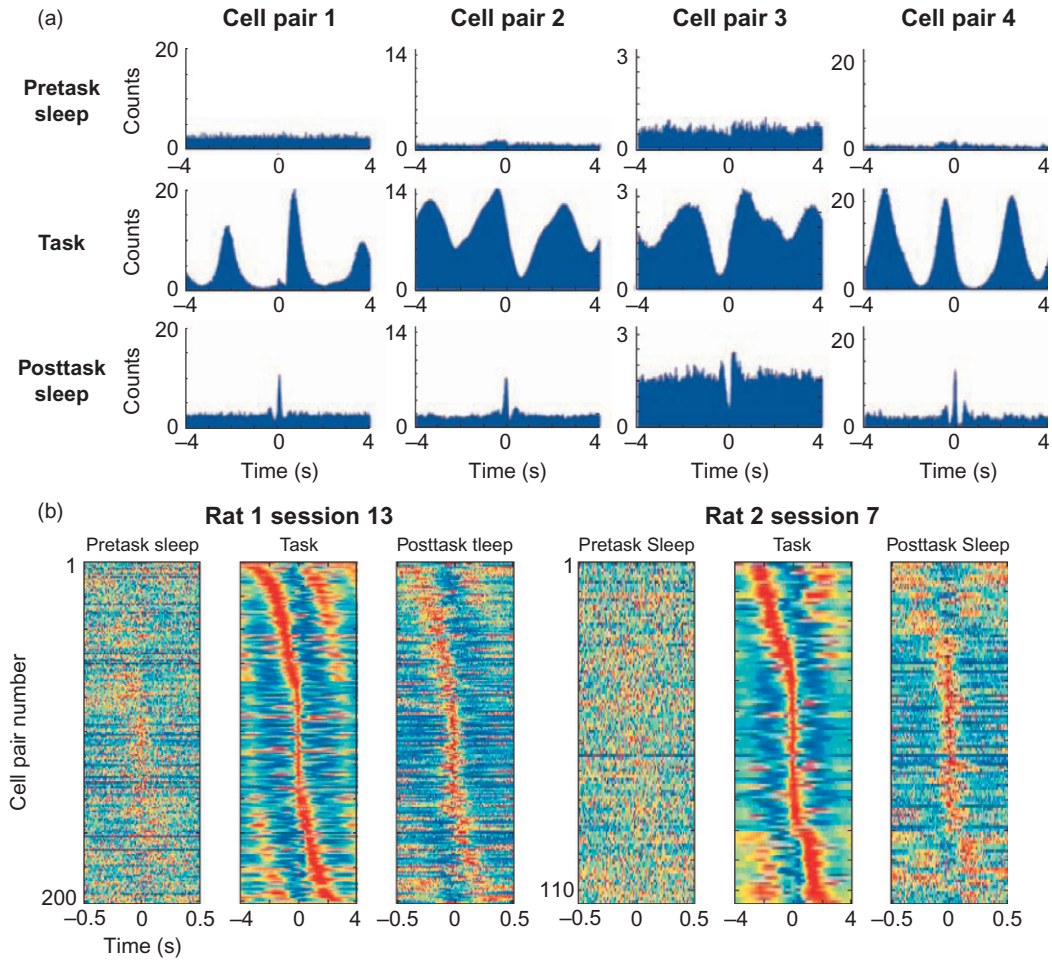

Fig. 7. (a) Cross-correlations of neuron pairs in the rat medial prefrontal cortex. Each row corresponds to a different behavioral epoch (pretask sleep, task, and posttask sleep). Each column corresponds to a different cell pair. Note that the peaks of the correlogram of the task epoch are reexpressed in posttask sleep in a compressed fashion but are not identifiable in pretask sleep. This suggests that cells that have been active together during the behavioral epoch reactivate together during sleep after behavior. (b) In each panel, cross-correlations are sorted according to the peak in their correlogram for the task epoch. For two rats, the cell pairs are depicted for pretask sleep, task, and posttask sleep. Note that the patterns of the peaks in the correlograms are similar in task and posttask sleep, but the temporal scale varies. Activity seems to be sped up by a factory of six to seven in posttask sleep compared to behavior (Euston et al., 2007).

the data by converting a number of correlated variables into a smaller number of uncorrelated values. In fact, principal components representing sequences of replayed firing patterns from the behavioral episode of a highly familiar task are reinstated as often in pretask sleep as in posttask sleep. However, during posttask sleep, the principal components have a stronger correlation with the appearance of sharp waves in the hippocampus. This suggests the conclusion that, after consolidation, the reactivation of familiar events has become relatively independent of the

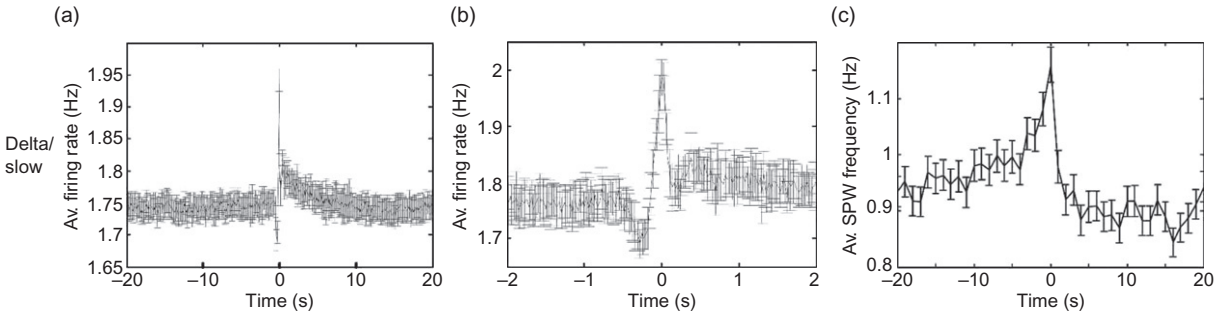

Fig. 8. Relationship between neocortical neural activity and hippocampal sharp waves. (a) Perievent time histogram (PETH) of cortical neural population activity during identified delta/slow-wave oscillations, centered on hippocampal sharp wave events. At the time of sharp waves, there is a transient increase of cortical activity and a subsequent increase in firing rates as compared to before the sharp waves. The sharp peak in the cortical activity is preceded by a dip (200–400 ms) as can be seen in the same PETH with a finer timescale. (b) This transient decreased activity could be entailed by delta oscillations that are occurring in phase. (c) PETH of hippocampal sharp wave events centered on the transitions from cortical down- to upstates. Sharp wave occurrence was maximal at down- to upstate transitions of cortical population activity. Baseline activity is higher during down (left of 0) than during up states, indicating that sharp waves are more likely to occur during down- than during up states. Adapted from Battaglia et al. (2004).

hippocampus, but when the memory is reinstated, new bouts of reactivation episodes are triggered in the hippocampus.

Memory trace reactivation is a process with complex dynamics that are not yet fully understood. The power of the analysis methods that are currently in use to assess reactivation processes increases with the number of units recorded, and substantial increases in this number can be expected to result from ongoing technical developments in many laboratories, including the application of optical recording methods. With the existing evidence, we can already attempt to make some speculations about how the cortex and hippocampus interact to replay memories. During sharp-wave ripple events in the hippocampus, events experienced in the immediate past are either spontaneously retrieved or their retrieval may be triggered by partial recall of the event in a cortical module. The hippocampal outflow during sharp waves coordinates reactivation of the relevant information distributed over multiple neocortical modules. Sharp waves tend to coincide with the down to up fluctuations in the cortical slow rhythm but tend to be of shorter duration than the up states. Thus, hippocampal reactivation may simply initiate the retrieval of neocortical sequences which play back during the remainder of the up state. During the up state, reactivated cortical neurons may strengthen or rearrange their synaptic connections with other neurons that were engaged in the sequence that is being replayed. This could be a mechanism through which knowledge is extracted from acquired memory and established in horizontal intermodular cortical connections.

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