Memory trace reactivation in hippocampal and neocortical neuronal ensembles

Gary R Sutherland* and Bruce McNaughton[†]

During active behavior, patterns of hippocampal and neocortical neuronal activity reflect ongoing inputs and their contexts. Recent neurophysiological investigations have shown that during 'off-line' periods, traces of these experiences are spontaneously reactivated in both structures. Although the functional importance of this phenomenon remains to be demonstrated, it does provide clues about the nature and mechanisms of memory retrieval and consolidation.

Addresses
Arizona Research Laboratories, Division of Neural Systems, Memory and Aging, 384 Life Sciences North Building, PO Box 24-5115, Tucson, AZ 85724-5115, USA
*e-mail: grs@nsma.arizona.edu
[†]e-mail: bruce@nsma.arizona.edu

Abbreviations

AMPA	2-amino-3-hydroxy-5-methyl-4-isoxazole proprionate
EEG	electro-encephalogram
LIA	large irregular activity in hippocampal EEG
LTD	long-term depression
LTP	long-term potentiation
NMDA	N-methyl-D-aspartate
REMS	rapid eye movement (paradoxical) sleep
SWS	slow-wave sleep

Introduction

'Memory consolidation' is generally used in two distinct ways in the neuroscience literature. One sense of the term implies a putative cascade of cellular and molecular events that is initiated by an experience and eventually culminates in a durable form of synaptic alteration. In this manner, the biophysical substrates for modified neuronal interactions underlying the initial storage of memories may be established and stabilized [1–8,9•]. The other sense is that of a post-processing of memory traces, during which the traces may be reactivated, analyzed and gradually incorporated into the brain's long-term event-memory and general knowledge base [10].

This review focuses on recent observations that patterns of neural activity in hippocampus and neocortex, expressed during a behavioral episode, are spontaneously re-expressed during subsequent 'off-line' states, such as quiet wakefulness and slow-wave sleep (SWS). Theoretical concepts originating with Marr (see [10–16]) suggest that such spontaneous reactivation of memory traces, occurring while the brain is not processing external input, may be a necessary step in the gradual selection of a synaptic weight distribution that is appropriate for the incorporation of recent experiences into the brain's long-term knowledge base.

The hippocampus and memory consolidation

Scoville and Milner's [17] report of the patient HM indicated that bilateral damage to the hippocampus and related temporal lobe structures may cause a severe anterograde amnesia (the inability to form new memories after a lesion) and a temporally graded retrograde amnesia (where more recent memories appear to be more seriously disrupted than older ones). Clinical observations in humans [18,19••] and numerous lesion studies in animals [20–23] have reinforced the concept that the hippocampus is necessary for the initial acquisition of certain memories but only temporarily necessary for their retrieval; although the phenomenon is not without controversy [24]. In certain clinical cases, for example, retrograde amnesia may extend many years into the past. This has led to recent proposals that the hippocampus may play a more permanent role in some forms of memory [24]. These proposals nevertheless call for a prolonged interaction between the hippocampus and the neocortex, during which there may be a gradual reshaping of the stored information.

One formulation of the consolidation hypothesis is that during an extended period following the initial experience, hippocampal neuronal activity somehow 'orchestrates' the spontaneous, coordinated retrieval of the diverse components of a given experience, which have putatively been stored as patterns distributed across sparsely interconnected neocortical modules [25]. These retrieval episodes would then serve as supplementary training trials through which the network would gradually select an optimal encoding pattern for the experience, as part of either an existing class of events or a novel class [10,14,15]. The hypothesis that consolidation involves reactivation and recoding has by no means been fully verified, but it has recently been bolstered by both behavioral and neurophysiological studies, some of which are reviewed here.

A popular theory regarding the assembly of a long-term memory from the initial experience is the two-stage model [26], which takes its origins in the work of Marr [10]. In this model, the hippocampus toggles between a recording mode, supported by a cholinergically mediated theta rhythm, and a playback mode (identified with sharp-waves), during which the hippocampus is relieved of external input and cholinergic control [27], and reverts to its previously stored memory states. The retrieved memory states during the playback mode are broadcast, via widely diverging hippocampal formation efferents, to the neocortex during 'offline' periods. There can be two versions of this theory. In one, what is stored in the hippocampus is actually a compact representation of the current external input, and there is an invertable, relatively stable relationship between the hippocampal and

neocortical 'representations'. In the other version, which is based on the 'index theory' of Teyler and Discenna [25], the patterns in the hippocampus comprise arbitrary labels with no intrinsic meaning in terms of representation of external events. In this case, the labels must be associatively stored in the neocortical modules at the time of the original event in order for hippocampal output during the playback phase to elicit recall in the neocortex. In the former model, the rest of the brain need not 'listen' to the hippocampal output during recording, whereas in the latter model it must.

Two different but complementary experimental approaches can be taken in the study of hippocampal function in memory. Either one may ask, "what can the rest of the brain do without a hippocampus?", or one may ask "what does the hippocampus do?". The former is in the domain of neuropsychology and the latter, which is the subject of this review, is in the domain of neurophysiology.

Reversible blockade of hippocampal activity

A convincing new demonstration of the existence of a hippocampal-dependent consolidation process has been enabled by the development of a water-soluble AMPA receptor antagonist (LY326325). Riedel *et al.* [28••] delivered LY326325 via osmotic minipumps implanted into rats, thereby inducing a prolonged but reversible hippocampal inactivation at specific times during or following water maze training. Animals that underwent continuous hippocampal inactivation during a 7 day time block, beginning either 1 or 5 days after learning, were impaired on a retention test 16 days later. On the same day, however, they were unimpaired at learning a new spatial problem in a different room. These results indicate that AMPA receptor activity in the hippocampus during the consolidation interval is necessary for the subsequent expression of long-term spatial memory. This is consistent with the notion that outflow of stored information from the hippocampus is a critical component of the consolidation of spatial memory.
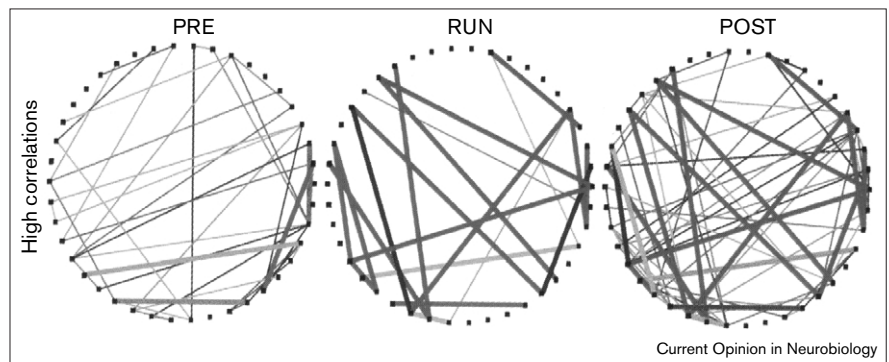
Reactivation of hippocampal activity patterns

O'Keefe *et al.* [29] discovered that cells of the hippocampus fire at unique locations within an environment; these locations are referred to as the 'place fields' of that cell. In the first study of reactivation of experience-specific neuronal activity in the hippocampus [30], rats were confined for an extended time within the 'place field' of one hippocampal cell, causing that cell to fire robustly. During the time in which the rat was confined to this particular place, a second recorded neuron was essentially silent. The cell that was active during the awake state displayed elevated firing during subsequent sleep, while the non-active cell remained quiescent. The fact that only one active cell and one location were studied at a time, however, precluded making any conclusions about the retrieval of experience-specific population codes. The alternative possibility is that intense activity during waking causes cells to undergo some intrinsic process resulting in elevated firing that is not correlated with the firing of other cells participating in the same encoding event. This would not constitute memory retrieval.

Wilson and McNaughton [31] recorded simultaneously from 50 to 80 neurons in hippocampal area CA1. Cells that were active together during waking behavior — due to overlap of their place fields — also tended to fire together during SWS immediately following the maze running task. This effect was detectable for about 20–30 min following the maze running activity. Pairs of neurons were artificially classified as being 'correlated' or 'uncorrelated' depending on how much their place fields overlapped (see Figures 1 and 3a); however, when considering how well the patterns of neural ensemble activity during the maze and subsequent SWS epochs resemble one another, the fact that two cells that were

Figure 1

During running behavior on a maze (RUN), the fact that hippocampal CA1 neurons express place-specific activity imposes an experience-specific pattern of firing-rate correlations among a population of simultaneously recorded hippocampal CA1 neurons. This pattern persists during subsequent sleep (POST), but is essentially absent from sleep immediately preceding the experience (PRE). Each node represents one of 42 cells that had 'place fields' in the experimental apparatus. Lines connecting the nodes represent correlations greater than an arbitrary cut-off of 0.05. The bold lines represent those above-threshold correlations that were present during RUN and also during either PRE or POST. It is clear that most of the higher correlations that emerge during the experience persist, whereas few of them could have been predicted from the activity pattern occurring before the experience. Thus, the hippocampal ensemble expresses spontaneous retrieval of recently stored activity patterns. Data from Wilson and McNaughton [31].

Figure 2
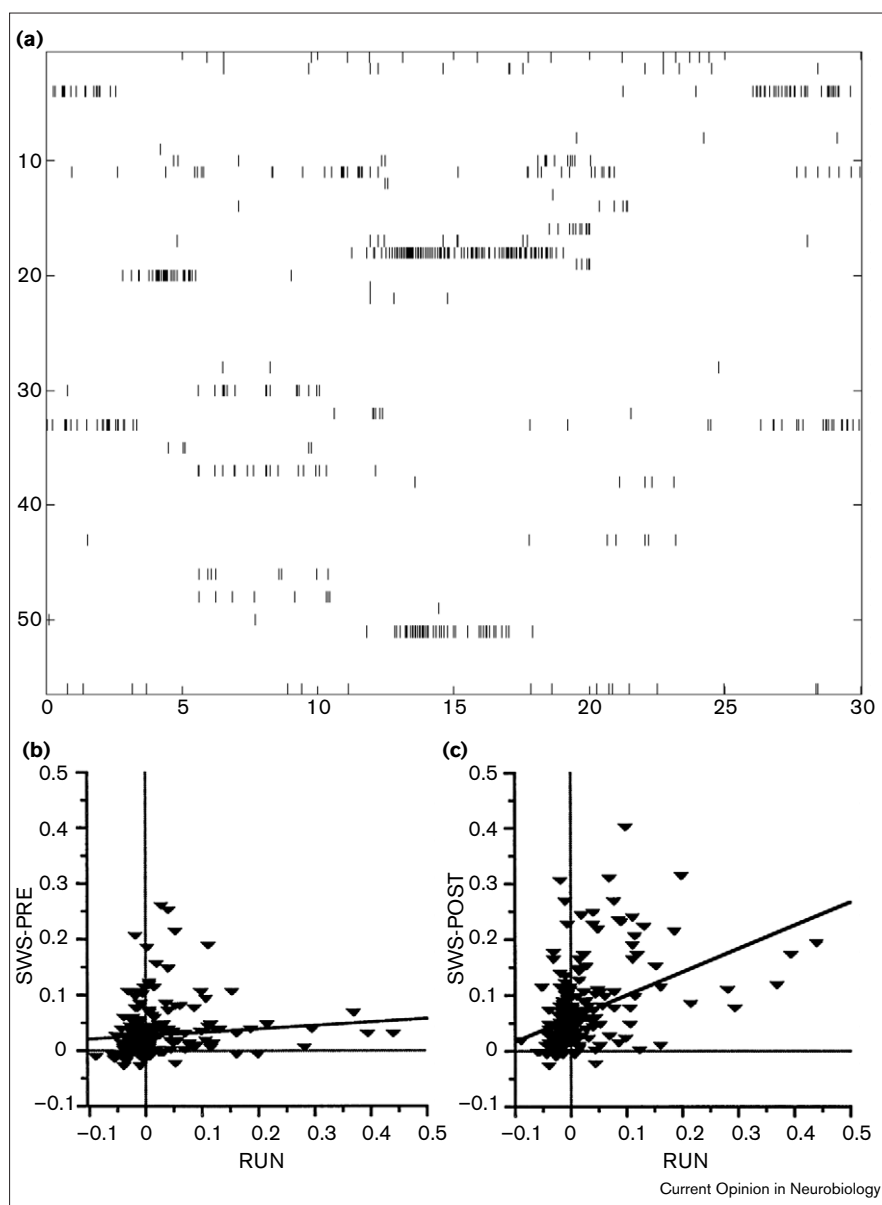
Regression analysis of the reactivation of neuronal firing-rate correlations during sleep. **(a)** For such an analysis, the raw data consist of a matrix of firing rates, typically binned in some small time interval (e.g. 20–100 ms). The x-axis refers to cell number and the y-axis is time in seconds. Each tick mark represents a spike from the corresponding cell. Each row represents the firing of one of N simultaneously recorded cells (55 in this case). For N cells, there are N(N−1)/2 pairwise correlations. These are computed for each behavioral epoch. SWS-PRE, RUN, SWS-POST refer to sleep before the experience, the waking experience, and sleep after the experience, respectively, and their relationships were compared by partial regression analysis. The simple scatter plots of cell-pair correlations during sleep versus during behavior shown in **(b)** and **(c)** exhibit the typical effect: the correlation values expressed during POST sleep (c) match those observed during behavior better than the values expressed during PRE sleep (b). It is also possible to perform analyses on the population vectors themselves [i.e. the columns of (a)] to assess whether instantaneous patterns that occur during behavior are more probable in subsequent sleep [69•]. Because of the sparsity of hippocampal population codes, this approach requires a larger number of neurons. Data from [32••].

uncorrelated remain uncorrelated is just as important as the fact that two correlated cells remain correlated. A more appropriate measure of memory trace reactivation would thus be a measure of the similarities of the firing rate correlations for all pairs of simultaneously recorded cells (Figure 2).

Kudrimoti *et al.* [32••] developed a partial regression analysis which quantified the amount of variance in the firing rate correlations during sleep and/or quiet wakefulness following a maze running experience that could be accounted for by the pattern of correlations during the experience itself. The analysis statistically controlled for the correlations that already existed during sleep prior to the experience. Thus, the residual 'explained' variance

(10–30%) could be taken as a measure of mnemonic reactivation. Although the reactivation strength substantially declined over about 30 min, there was evidence for occasional reactivation at least 24 h after the experience. The strongest reactivation occurred during the hippocampal sharp-wave/ripple events (i.e. irregularly occurring bursts of cellular discharge, also known as large irregular activity, or LIA) [33] as opposed to during the inter-ripple intervals; indeed, it was found that the presence of sharp waves in the EEG was sufficient for reactivation. Actual sleep was not essential. In the same study it was found that traces of two separate spatial experiences appeared within the same SWS episode. It has been suggested that such interleaving of retrieval events may play an important role in memory consolidation [14].

Hippocampal–neocortical interactions

It is known that the topographic distribution of mnemonic representations in neocortex can change spontaneously over time [34], and that the development of correlated feature detectors for paired associates in inferotemporal cortex depends on reciprocal projections from the hippocampal area [35]. The hypothesis that the hippocampus orchestrates neocortical memory retrieval during consolidation implies that the reactivation of previous events should also be readily observable in neocortical neuronal ensembles. It was found that neurons in rat posterior parietal cortex also undergo a period of pattern reactivation following a behavioral episode, similar to that observed in the hippocampus [36]. Moreover, simultaneous recording of groups of neurons in the hippocampus and the neocortex revealed that the reactivation process is coherent between the two regions. In other words, the neuronal correlation states for any given hippocampal–neocortical cell pair also tended to be preserved. This is a necessary, but not a sufficient, condition for the hypothesis. It remains to be determined whether a normally functioning hippocampus is necessary for coherent reactivation of events over disparate neocortical areas.

Where is the reactivation process initiated? Most hippocampal theories suggest that area CA3 is the likely site because of its dense recurrent connections [10,12,37–39], and this idea is consistent with the apparent origin of sharp waves in the CA3 field [40]; however, coherent retrieval states appear to occur throughout much of the neocortical–hippocampal axis [32••,36,41••], and it remains possible that there is no single site of origin.

Temporal patterns

An episode of experience includes the evolution of events in time, thus the temporal order of firing within a neural ensemble is a relevant parameter in considering memory-trace reactivation. During a repetitive route-following task, the temporal asymmetry (bias) of the cross correlation of two place cells reflects the asymmetry of spatial overlap of their place fields (see Figure 3). It was found [42] that this temporal asymmetry was significantly preserved during subsequent sleep, indicating that relative firing order within a given short time interval was preserved. This effect was restricted to neurons with overlapping place fields during behavior. During sleep, the widths of the cross-correlation peaks were compressed by about 10–20-fold, even though the relative magnitude and sign of their asymmetry was maintained. At least three interpretations have been suggested for this effect. The first is that segments of memory sequences are replayed during sleep at a much faster rate than real-time (as a result of temporal compression) [42–44,45••]. The second is that redundant spikes in a sequence may simply be omitted, thus optimizing the information transmission and shortening the overall sequence. Finally, the replayed sequence segments are very short — about the duration of sharp-waves (80–100 ms) — and hence any long-range temporal order could be abolished.

Figure 3

Current Opinion in Neurobiology
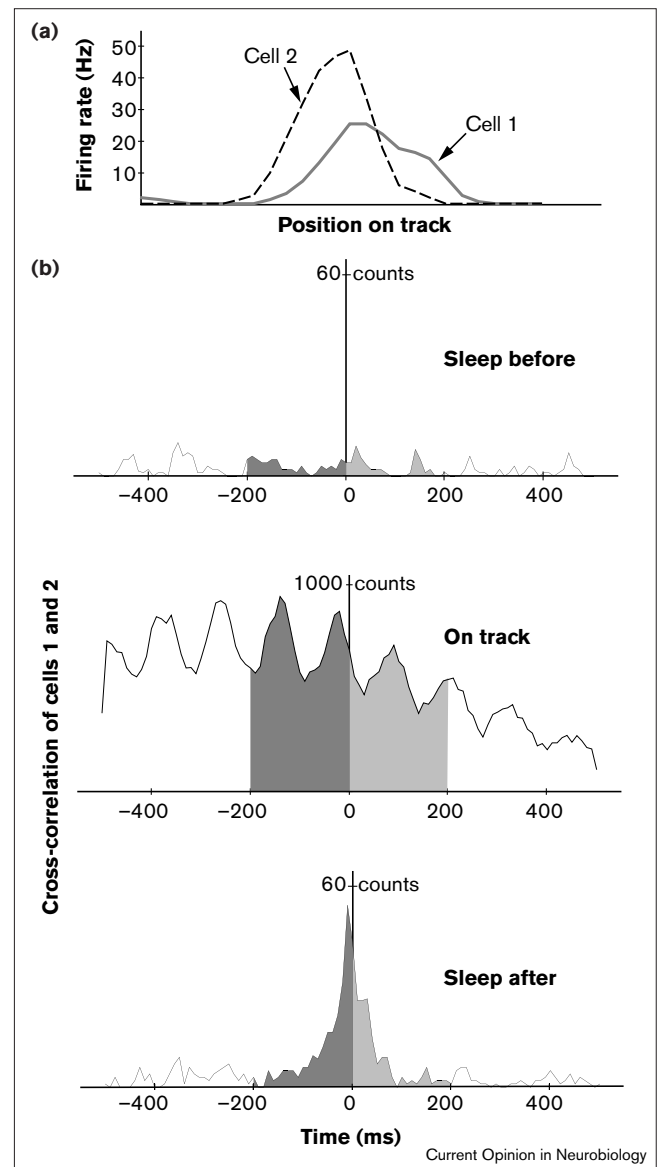
Temporal asymmetry of cross-correlations between two cells with partially overlapping place fields in a spatial task involving repeated, unidirectional movement around a triangular track. As the rat runs down the track, cell 2 will fire before cell 1. **(a)** Firing rates for two cells. **(b)** Cross-correlations for the cells in (a) before, during and after the spatial experience. The histograms were constructed by taking each spike in cell 1 as reference and summing the number of occurrences (counts) of spikes in cell 2 that appeared within a temporal range of −400 ms to +400 ms of the reference spike. The difference between the sum of the correlations up to 200 ms prior to zero (dark shading) and the 200 ms following zero (light shading) reflects the temporal bias. Although no discernible correlations or asymmetry appeared between the two cells during sleep before the maze experience, both the correlations and the amount of temporal bias increased while on the track. Note that during behavior, asymmetry occurs both on a broad time-scale (1–2 s), reflecting the asymmetry of place field overlap, and on a short time-scale (50–100 ms), which results from the phase precession phenomenon (see text), which gives rise to the ~140 ms oscillations in the cross-correlation. During theta cycles, during which both cells are active, the phase precession results in cell 2 typically firing earlier than cell 1. Only a short time-scale component is frequently preserved in subsequent sleep. Data from [42].

These interpretations are not mutually exclusive. In addition, the apparent temporal compression that is expressed during sharp-waves may actually already be present during the experience itself. At normal running speeds of the rat, a typical place cell fires throughout 10–15 cycles of the theta rhythm (i.e. for about 2 s). Because the firing phase advances with successive cycles (the 'phase precession' effect [46]), the spatial displacement of any two overlapping place fields is reflected in the firing order of the cells within the theta cycle (see Figure 3b). Thus, temporal firing order, on the time-scale of seconds, is already expressed in compressed form (tens of milliseconds) during any given theta cycle. The mechanism of this real-time compression effect is unknown but, functionally, it may serve the encoding of event sequences by making the neural activity pattern change rapidly within the effective time-window of NMDA-receptor-dependent asymmetric long-term potentiation (LTP), which is about the duration of a theta cycle [47]. Without compression, the patterns that become associated over this short time-scale would be so similar to each other that retrieval of sequences would be impossible because of interference. The apparent time-compression during sharp-waves may thus reflect a compression effect that was already present at the time of encoding.

To gain further insight into the precision of spike timing replay in groups of cells, Nádasdy *et al.* [45••] explored the spatiotemporal spike patterns of small ensembles of hippocampal CA1 cells using either a template-matching method or a joint-probability mapping of spikes. A large number of repeating spike triplets was observed both while the rat was running on a wheel and during sleep. Approximately 5% of the spike triplets were the same during sleep prior to the task and during the running task, whereas significantly more (9%) were the same during the running task and during sleep following the task.

The role of REM sleep

As noted earlier, sleep *per se* is not necessary for memory trace reactivation — the presence of sharp waves in the EEG appears to be sufficient. However, there is a long history of research suggesting that sleep, and REM sleep (REMS) in particular, is necessary for (or at least beneficial to) the process of memory consolidation ([48–56], but see [57]). In addition, dream experiences reported after wakening from REMS often contain elements that can be linked directly to recent events. Thus, it is of interest to know whether recent activity patterns expressed during awake theta states can reappear during REMS when sharp waves in the EEG are replaced by the theta rhythm.

Using the partial regression methods described above, however, Kudrimoti *et al.* [32••] were unable to observe significant reactivation of recent ensemble patterns in hippocampus during REMS. This was surprising in view of the two facts: first, that the dynamics of hippocampal neuronal firing more closely resemble active waking during REMS than during SWS [58•,59•]; and second, that the expression of plasticity-related immediate early genes in the brain is enhanced during REMS following learning [60].

There are several reasons why it would be premature to conclude that reactivation does not occur in REMS, however. Behavioral studies [50,61] suggest that consolidation of recent memories is more susceptible to disruption by interruption of later rather than earlier REM epochs during a given sleep period. Thus, it is possible that the last experiences before sleep may not show up until the later REM bouts, which, for technical reasons, were not recorded by Kudrimoti *et al.* [32••].

Stickgold *et al.* [54–56] have bolstered this idea by showing that spontaneous improvement on a visual perceptual learning task depends on both the amount of SWS during the early part of the night and the amount of REMS during the late part. Finally, a relatively small percentage of the sleep cycle is spent in REMS, especially in the early portion of a given sleep episode, and hence the amount of data that has thus far been available may not have been sufficient to detect significant trace reactivation.

Nevertheless, information processing may occur during REMS [62]. During REMS following an experience in a familiar environment, cells that had expressed place fields fire weakly and at a mean phase of the theta rhythm 180° from their preferred firing phase during behavior. Cells that expressed place fields in a novel environment, however, fire more robustly, and at the same phase as during behavior. It is known that the balance of long-term potentiation and depression (or depotentiation) of hippocampal synapses is sensitive to theta phase, with LTP being favored at the normal peak firing phase and long-term depression (LTD) being favored at the opposite phase [63–66]. These observations lead to the speculation that during REM sleep there may be a process of selective weakening of hippocampal synapses allocated to older (presumably already consolidated) memories, and a selective strengthening of those synapses allocated to new memories. These findings are also consistent with an earlier proposal that REM sleep facilitates selective forgetting [67]. Clearly, however, much remains to be learned about the dynamic patterning of neural ensemble activity during REM sleep and its functional significance (if any) with respect to memory consolidation.

Conclusions

Hippocampal neural activity is characterized essentially by two global states, each identified by their predominant waveforms: theta and LIA. During the former state (at least during waking), the information expressed in hippocampal and neocortical neural activity typically appears to be driven by external input. During the LIA state, patterns that were expressed in the preceding awake theta state reappear spontaneously in both hippocampal and neocortical circuits. Simulation studies have shown that any recurrent network endowed with an associative mechanism for

synaptic strengthening may exhibit spontaneous retrieval of stored patterns when presented with random inputs [68]. Thus, it is not very surprising that such an effect can be observed in the brain while it is not attending to external sensory inputs. Whether this effect is of any functional significance or simply a by-product of the memory storage process itself is open to further investigation.

Acknowledgements

References and recommended reading

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

- • of special interest
- •• of outstanding interest

1. Reymann KG, Frey U, Jork R, Matthies H: **Polymyxin B, an inhibitor of protein kinase C, prevents the maintenance of synaptic long-term potentiation in hippocampal CA1 neurons.** *Brain Res* 1988, **440**:305-314.

2. Otani S, Marshall CJ, Tate WP, Goddard GV, Abraham WC: **Maintenance of long-term potentiation in rat dentate gyrus requires protein synthesis but not messenger RNA synthesis immediately post-tetanization.** *Neuroscience* 1989, **28**:519-526.

3. McGaugh JL: **Involvement of hormonal and neuromodulatory systems in modulating memory storage.** *Annu Rev Neurosci* 1989, **12**:255-287.

4. Yin JC, Tully T: **CREB and the formation of long-term memory.** *Curr Opin Neurobiol* 1996, **6**:264-268.

5. Bernabeu R, Bevilaua L, Ardenghi P, Bromberg E, Schmitz P, Bianchi N: **Involvement of hippocampal cAMP/cAMP-dependent protein kinase signalling pathways in a late memory consolidation phase of aversively motivated learning in rats.** *Proc Natl Acad Sci USA* 1997, **94**:7041-7046.

6. Izquierdo I, Medina JH: **Memory formation: the sequence of biochemical events in the hippocampus and its connection to activity in other brain structures.** *Neurobiol Learn Mem* 1997, **68**:285-316.

7. Roullet P, Sara S: **Consolidation of memory after its reactivation: involvement of β noradrenergic receptors in the late phase.** *Neural Plasticity* 1998, **6**:63-68.

8. Lisman JE, Fallon JR: **What maintains memories?** *Science* 1999, **283**:339.

9. Sweatt DS: **Toward a molecular explanation for long-term**
•   **potentiation.** *Learn Memory* 1999, **6**:399-416.
A comprehensive review of the current status of our understanding of the machinery of LTP. Particularly helpful was his organization of tables and figures to highlight the molecular mechanisms of LTP with respect to their temporal functions, such as early versus late phase, or induction versus maintenance or modulation.

10. Marr D: **Simple memory: a theory of archicortex.** *Philos Trans R Soc Lond B* 1971, **262**:23-81.

11. Hinton GE, Sejnowski TJ: **Learning and relearning in Boltzmann machines.** In *Explorations in the Microstructure of Cognition,* vol 1: *Foundations.* Edited by McClelland J, Rumelhart D. Cambridge: MIT Press; 1986:282-317.

12. Buzsáki G: **Two stage model of memory trace information: a role for 'noisy' brain states.** *Neuroscience* 1989, **31**:551-570.

13. Sejnowski TJ: **Sleep and memory.** *Curr Biol* 1995, **5**:832-834.

14. 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.

15. Squire LR, Alvarez P: **Retrograde amnesia and memory consolidation: a neurobiological perspective.** *Curr Opin Neurobiol* 1995, **5**:169-177.

16. Sejnowski TJ: **The computational neuroethology of sleep: new neuroethology on the move.** *Proc 26th Gottingen Neurobiol Conf* 1998, Gottingen, Stuttgart: Georg Thieme Verlag; **1**:127-144.

17. Scoville WB, Milner B: **Loss of recent memory after bilateral hippocampal lesions.** *J Neurol Neurosurg Psychiatry* 1957, **20**:11-21.

18. Squire LR, Knowlton B, Musen G: **The structure and organization of memory.** *Annu Rev Psychol* 1993, **44**:453-495.

19. Teng E, Squire LR: **Memory for places learned long ago is intact**
•• **after hippocampal damage.** *Nature* 1999, **400**:675-677.
An important new addition to the human neuropsychological literature on memory consolidation. This paper presents the case of a patient (EP) with severe bilateral hippocampal and temporal lobe damage. EP's recollection of the spatial layout of the town in which he grew up, and to which he had not returned for more than 50 years, was as good as that of an age-matched control subject who grew up in the same region. EP had no knowledge, however, of the neighborhood to which he had moved after he became amnesic.

20. Winocur G: **Anterograde and retrograde amnesia in rats with dorsal hippocampal or dorsomedial thalamic lesions.** *Behav Brain Res* 1990, **38**:145-154.

21. Zola-Morgan S, Squire LR: **The primate hippocampal formation: evidence for a time-limited role in memory storage.** *Science* 1990, **250**:288-290.

22. Kim JJ, Fanselow MS: **Modality-specific retrograde amnesia of fear.** *Science* 1992, **256**:675-677.

23. Kim JJ, Clark RE, Thompson RF: **Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses.** *Behav Neurosci* 1995, **109**:195-203.

24. Nadel L, Moscovitch M: **Memory consolidation, retrograde amnesia and the hippocampal complex.** *Curr Opin Neurobiol* 1997, **7**:217-227.

25. Teyler A, Discenna P: **The hippocampal memory indexing theory.** *Behav Neurosci* 1986, **100**:147-154.

26. Buzsáki G: **Two stage model of memory trace information: a role for "noisy" brain states.** *Neuroscience* 1989, **31**:551-570.

27. Hasselmo ME, Wyble BP: **Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus.** *Hippocampus* 1996, **6**:693-708.

28. Riedel G, Micheau J, Lam AGM, Roloff EVL, Martin SJ, Bridge H,
•• deHoz L, Poeschel B, McCulloch J, Morris RGM: **Reversible neural inactivation reveals hippocampal participation in several memory processes.** *Nat Neurosci* 1999, **2**:898-905.
The authors temporarily inactivated the hippocampus by blocking AMPA receptors during water maze training, and were able to demonstrate that the hippocampus is necessary for the encoding and retrieval of spatial memories. It was revealed that a time window exists, during which memory consolidation is dependent on a functional hippocampus.

29. O'Keefe J, Dostrovsky J: **The hippocampus as a spatial map: preliminary evidence from unit activity in the freely-moving rat.** *Brain Res* 1971, **34**:171-175.

30. Pavlides C, Winson J: **Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes.** *J Neurosci* 1989, **9**:2907-2918.

31. Wilson MA, McNaughton BL: **Reactivation of hippocampal ensemble memories during sleep.** *Science* 1994, **265**:676-679.

32. Kudrimoti HS, Barnes CA, McNaughton BL: **Reactivation of**
•• **hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics.** *J Neurosci* 1999, **19**:4090-4101.
The authors explored the reactivation of novel versus repeated experiences and discovered that both types were present simultaneously. Neither sleep nor REM epochs were necessary for reactivation, while sharp-wave/ripple episodes were sufficient. This also supports the notion that sharp wave/ripples are the carriers of the reactivated neural patterns observed in CA1. Sharp waves are thought to originate as a result of attractor dynamics in CA3. A more quantitative analysis of reactivation (explained variance) was also introduced.

33. Ylinen A, Bragin A, Nádasdy Z, Jandó G, Szabo I, Sik A, Buzsáki G: **Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms.** *J Neurosci* 1995, **15**:30-46.

34. Freeman JH, Gabriel M: **Changes of cingulothalamic topographic excitation patterns and avoidance response incubation over time following initial discriminative conditioning in rabbits.** *Neurobiol Learn Mem* 1999, **72**:259-272.

35. Higuchi S, Miyashita Y: **Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions.** *Proc Natl Acad Sci USA* 1996, **93**:739-743.

36. Qin Y-L, McNaughton BL, Skaggs WE, Barnes CA: **Memory reprocessing in corticocortical and hipocampocortical neuronal ensembles.** *Philos Trans R Soc Lond B* 1997, **352**:1525-1533.

37. McNaughton BL, Morris RGM: **Hippocampal synaptic enhancement and information storage within a distributed memory system.** *Trends Neurosci* 1987, **10**:408-415.

38. Levy WB: *A Computational Approach to Hippocampal Function.* New York: Academic Press; 1989.

39. Treves A, Rolls ET: **A computational analysis of the role of the hippocampus in memory.** *Hippocampus* 1994, **4**:374-391.

40. Chrobak JJ, Buzsáki G: **High frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat.** *J Neurosci* 1996, **16**:3056-3066.

41. Shen J, Kudrimoti HS, McNaughton BL, Barnes CA: **Reactivation of**
••   **neuronal ensembles in hippocampal gyrus during sleep after spatial experience.** *J Sleep Res* 1998, **7** (Suppl 1):6-16.
This study shows that spontaneous reactivation of recent patterns occurs in the dentate gyrus, which, at least in the anterior hippocampus, is 'upstream' from CA3. This finding is, at least superficially, inconsistent with the concept of the reactivation process originating in CA3 and propagating to output structures. Contrary to the unidirectional theories of hippocampal flow, the dentate gyrus could also be considered downstream of CA3 because, more ventrally, CA3 also projects to the dentate gyrus.

42. Skaggs WE, McNaughton BL: **Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience.** *Science* 1996, **271**:1870-1873.

43. August DA, Levy WB: **Temporal sequence compression by a hippocampal network model.** *International Neural Networks Society World Congress on Neural Networks* 1996, San Diego, CA. Mahwah, NJ: Lawrence Erlbaum Associates; 1299-1304.

44. Skaggs WE, McNaughton BL, Wilson MA, Barnes CA: **Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences.** *Hippocampus* 1996, **6**:149-172.

45. Nádasdy Z, Hirase H, Czurkó A, Csicsvari J, Buzsáki G: **Replay and**
••   **time compression of recurring spike sequences in the hippocampus.** *J Neurosci* 1999, **19**:9497-9507.
The authors used multi-electrode recordings and conducted a mathematically sophisticated analysis of the recurrence of exact temporal sequences of neural ensemble activity in the hippocampus during sleep. Their analysis suggests that the hippocampus can replay spike train sequences and that those sequences are temporally compressed.

46. O'Keefe J, Recce ML: **Phase relationships between hippocampal place units and the EEG theta rhythm.** *Hippocampus* 1993, **3**:317-330.

47. Levy WB, Steward O: **Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus.** *Neuroscience* 1983, **8**:791-797.

48. Fishbein W, Tusa RJ, McGaugh JL: **The effects of REM sleep deprivation during the retention interval on long-term memory of a discrimination task.** *Psychophysiology* 1970, **7**:298-299.

49. Fishbein W, Gutwein BM: **Paradoxical sleep and memory storage processes.** *Behavioral Biol* 1977, **19**:425-464.

50. Smith C, Butler S: **Paradoxical sleep at selective times following training is necessary for learning.** *Physiol Behav* 1982, **29**:469-473.

51. Smith C: **Sleep states and learning: a review of the animal literature.** *Biobehav Rev* 1983, **9**:157-168.

52. Smith C, Kelly G: **Paradoxical sleep deprivation applied two days after end of training retards learning.** *Physiol Behav* 1988, **43**:213-216.

53. Karni A, Tanne D, Rubenstein BS, Askenasy JJM, Sagi D: **Dependence on REM sleep of overnight improvement of a perceptual skill.** *Science* 1994, **265**:679-682.

54. Stickgold R: **Sleep: off-line memory processing.** *Trends Cog Neurosci* 1998, **2**:484-492.

55. Stickgold R, Scott L, Rittenhouse C, Hobson JA: **Sleep-induced changes in associative memory.** *J Cogn Neurosci* 1999, **11**:182-183.

56. Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA: **Visual discrimination learning: a multi-step process requiring both slow wave and REM sleep.** *J Cogn Neurosci* 2000, **11**:in press.

57. Vertes RT: **Memory consolidation in REM sleep: dream on.** SRS Bulletin, 1: www.srssleep.org/srs/vertes.htm.

58. Skaggs WE, McNaughton BL: **Neuronal ensemble dynamics in**
•   **hippocampus and neocortex during sleep and waking.** In *Neuronal Ensembles.* Edited by Eichenbaum H, Davis JL. New York: Wiley; 1998:235-246.
This chapter illustrates the methods of ensemble recording and analysis of neural firing patterns during various EEG/behavioral epochs to explore hippocampal and neocortical reactivation and temporal bias.

59. Buzsáki G: **Memory consolidation during sleep: a**
•   **neurophysiological perspective.** *J Sleep Res* 1998, **7** (Suppl 1):17-23.
This is a very readable and concise review on the role of sleep in memory consolidation from a neurophysiological perspective. Particularly useful are the explanations of memory theories originating from hippocampal EEG patterns.

60. Ribeiro R, Goyal V, Mello CV, Pavlides C: **Brain gene expression during REM sleep depends on prior waking experience.** *Learn Memory* 1999, **6**:500-508.

61. Plihal W, Born J: **Effects of early and late nocturnal sleep on declarative and procedural memory.** *J Cogn Neurosci* 1997, **9**:534-547.

62. Poe GR, Nitz DA, McNaughton BL, Barnes CA: **Experience-dependent reversal of theta phase discharge profiles in REM sleep.** *Brain Res* 2000, **855**:176-180.

63. Pavlides C, Greenstein YJ, Grudman M, Winson J: **Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm.** *Brain Res* 1988, **439**:383-387.

64. Huerta PT, Lisman JE: **Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1** *in vitro*. *Neuron* 1995, **15**:1053-1063.

65. Huerta PT, Lisman JE: **Low-frequency stimulation at the troughs of θ-oscillation induces long-term depression of previously potentiated CA1 synapses.** *J Neurophysiol* 1996, **75**:877-884.

66. Hölscher C, Anwyl R, Rowan RJ: **Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1** *in vivo*. *J Neurosci* 1997, **17**:6470-6477.

67. Crick F, Mitchison G: **The function of dream sleep.** *Nature* 1983, **304**:111-114.

68. Shen B, McNaughton BL: **Modeling the spontaneous reactivation of experience-specific hippocampal cell assemblies during sleep.** *Hippocampus* 1996, **6**:685-692.

69. McNaughton BL: **The neurophysiology of reminiscence.** *Neurobiol*
•   *Learn Mem* 1998, **70**:252-267.
This is a review of the technical concepts required in the analysis of memory reactivation. It describes, at length, the spike rate matrices, temporal correlation matrices and the state correlation matrices that are an integral part in studying cell–cell cross-correlations and temporal compression of hippocampal and neocortical neuronal ensembles.