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Review

The rodent hippocampus and spatial memory: from synapses to systems

S. J. Martin[a,*] and R. E. Clark[b]

[a] Laboratory for Cognitive Neuroscience, Centre for Cognitive and Neural Systems, University of Edinburgh, 1 George Square, Edinburgh, EH8 9JZ (UK),
Fax.: +44 131 650 4579, e-mail: stephen.martin@ed.ac.uk
[b] Department of Psychiatry, 0603, UCSD and Veterans Affairs Medical Center, San Diego, La Jolla, California 92093 (USA)

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Abstract. Although its operations are not limited to the spatial domain, there is a near consensus that the hippocampus plays a critical role in memory for place. This review aims to explore this role, with a particular emphasis on the functions performed by distinct hippocampal subregions. The use of innovative lesioning techniques, localized pharmacological treatments, and molecular genetic interventions is offering increasingly precise brain-regional specificity and temporal control. Together with the electrophysiological recording of neuronal activity, these techniques are beginning to shed light on the functioning of specific components of the hippocampal circuitry in the different phases of memory – encoding, storage, consolidation, and retrieval. In view of these developments, we examine the involvement of the hippocampus in the encoding versus retrieval of spatial memory, before turning to the issue of long-term information storage and the role of 'cellular' and 'systems' consolidation processes in the formation of lasting memories.

Keywords. Rat, mouse CA1, CA3, dentate, learning, LTP, LTD.

General introduction

The hippocampal formation, a structure whose surface area rivals that of the neocortex in rats [1], is perhaps the most intensively researched structure in the central nervous system. Extending caudally between the neocortex and diencephalon before curving ventrally toward the temporal lobe, the hippocampus receives polymodal sensory information via its inputs from the entorhinal cortex and enjoys extensive afferent and efferent connectivity with subcortical and frontal cortical structures [2]. Perpendicular to its long axis, the hippocampal formation can be divided into distinct subfields based on morphological and cytoarchitectonic criteria: in this review, we use the term 'hippocampus' to refer only to the subfields of CA1, CA2, and CA3, plus the dentate gyrus. Numerous theories of hippocampal function have been advanced over the past few decades, and a near consensus has been reached that the structure plays a role in memory. But the specific nature of this role remains uncertain.

In their seminal synthesis, O'Keefe and Nadel [3] made a highly convincing case that the hippocampus encodes maps of space in a literal Euclidean sense.

* Corresponding author.

This view was supported by multiple lines of evidence, but the discovery of hippocampal 'place cells' [4] – neurons that exhibit place-specific firing – was especially influential. O'Keefe and Nadel argued that extra-hipppocampal 'taxon' systems are capable of acquiring and processing stimulus-response associations and egocentric spatial information, such as 'turn left at the end of the alley.' The hippocampus, in contrast, was held to be unique in supporting an 'allocentric' map of space – i.e., one based on the relationships of external spatial cues and not tied to any internal reference frame. Building on early maze-learning studies dating back at least as far as the 1950s [see ref. 4 for a review], experimental damage to the rodent hippocampal formation has been found to cause severe deficits in learning and memory in a wide range of spatial tasks conducted in the radial-arm maze [5], watermaze [6–8], and T-maze [9], to name just a few. Although several authors have emphasized the participation of the hippocampus in non-mnemonic functions [10–17], a role for the structure in spatial memory is in little doubt for most researchers; the issue is whether place memory is simply one example, or one component, of a broader category of memory for which the hippocampus is required [see refs. 18, 413]. Suggestions include declarative memory [19], episodic memory [20–22, 414, 415], configural or conjunctive memory [23, 24], relational memory [25], contextual memory [26, 27], the acquisition of arbitrary visuomotor mappings [28], and the association of temporally discontiguous events [29, 30]. We likewise feel that there is compelling evidence for a hippocampal role beyond memory for place; thus, although the present review focuses on studies of the rodent hippocampus and spatial memory, we do not intend to imply that its operations are limited to this domain.

In preparing this review we have not attempted to present a systematic overview of theories of hippocampal function [see 31–36]. Our aim is to highlight a few lines of contemporary research that, in our view, are beginning to offer mechanistic insights into the operations performed by the rodent hippocampus during the different phases of spatial memory – encoding, consolidation and retrieval. The scope of this article regrettably excludes a vast body of relevant work in humans and non-human primates, and, for the most part, the rodent literature concerning several non-spatial behavioral paradigms, including recognition memory, contextual fear conditioning [37–43], inhibitory avoidance [44–47], and several others. Our focus is perhaps more systems orientated than might be expected, but the multi-disciplinary nature of memory research makes this difficult to avoid: many of the same issues are equally relevant to molecular, cellular, and systems-level analyses of learning and memory.

Evidence for a hippocampal role in place learning and memory

The hippocampus and incremental place learning

Hippocampal damage often causes severe impairments in the ability of rodents to learn and remember a location in space defined by distal visual cues (see the Introduction). For example, in the watermaze reference memory task commonly used to assess learning and memory in rodents [48, 49] (see box 1), hippocampal lesions severely limit the rate of learning [6, 7]. However, after extensive training, lesioned rats can gradually learn to navigate to a particular place, and to search accurately in this location during probe trials [50, 51] (see Fig. 1). In other words, spatial memories can eventually be acquired by extrahippocampal brain structures alone.

In addition to overtraining, certain cueing or shaping procedures can be effective in establishing place memory in hippocampally lesioned rats [52–54]. But without the hippocampus, spatial memories are not merely acquired more slowly, there is also evidence that they are qualitatively different from 'normal' memories [50, 55]. Indeed, hippocampus-independent place memory in the watermaze is often characterized by its inflexibility [54, 56, 57], and a reliance on egocentric strategies – i.e., turning in a particular direction – is sometimes indicated in plus-maze tasks [58, 59]. Such findings are consistent with the idea that the brain can employ alternative strategies and neural substrates for solving certain spatial tasks after the hippocampus is removed.

Box 1. The watermaze reference memory task

In the watermaze spatial reference memory task, animals learn to find a submerged escape platform occupying a fixed location in a large pool of water based on its location relative to extra-maze cues located in the testing room. These typically include curtains, posters, equipment racks, etc. Testing usually begins with one or more days of pretraining, in which animals learn to swim to a randomly located, visually cued platform. After this, training to find a single hidden platform in an unchanging location proceeds for several days, with multiple trials conducted in each daily session. Performance can be assessed by recording latency to reach the escape platform during acquisition, and also by the measurement of time spent in the correct area of the pool during occasional probe trials conducted with the platform absent [see ref. 60].

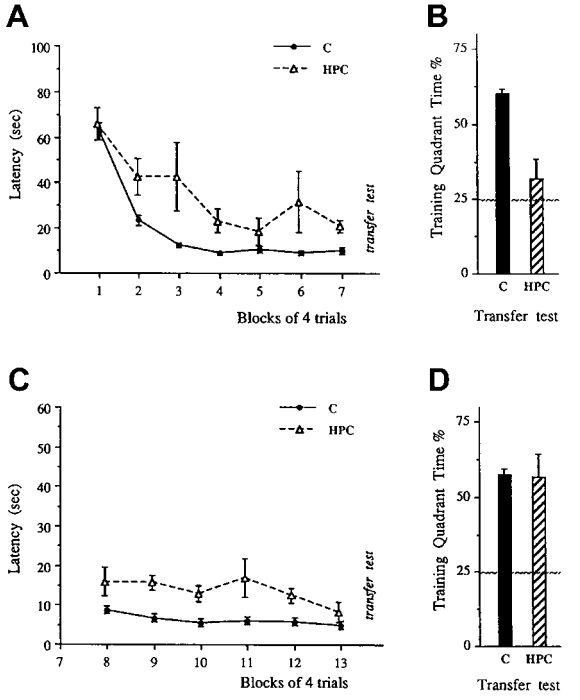

Figure 1. The hippocampus and incremental place learning. Hippocampal lesions reduce the rate of incremental learning in a spatial reference memory task, but normal levels of place memory can be attained after extensive training. (A; left-hand panel) The acquisition of a watermaze reference memory task (see box 1) by rats with ibotenic lesions of the hippocampus, compared to sham-lesioned animals. Hippocampal lesions did not prevent a decline in escape latencies over trials, but this phenomenon might simply have reflected the acquisition of an effective search strategy, such as circling at the correct radius from the pool walls. In fact, lesioned rats performed at chance levels in a probe trial conducted after the first 28 trials, despite the accurate searching observed in shams (A; right-hand panel). After the first probe trial, rats were overtrained for a further 24 trials (B; left-hand panel). In a second probe trial conducted after overtraining, the performance of lesioned rats was substantially above chance, and equivalent to that of sham-operated controls (B; right-hand panel). [Figure reprinted with permission from ref. 50; copyright 1990, Blackwell Publishing.]

Rapid, one-trial learning

Although incremental learning of place information over multiple trials is possible without a hippocampus, the structure is critically important for rapid encoding, particularly of trial-unique spatial information. One-trial memory is often assessed using a delayed matching-to-place version of the watermaze procedure [52, 61–63] (see box 2 and Fig. 2). Performance in this version of the task is severely impaired in animals with large hippocampal lesions [52, 63–65], and extensive task experience does not alleviate the deficit. For example, Steele and Morris [63] found that rats given complete hippocampal lesions after 8 days of pre-training (4 trials per day), still failed to show any improvement in escape latency between trials 1 and 2 after a further 8 days of postoperative training, even when the inter-trial interval was as short as 15 s (see Fig. 2).

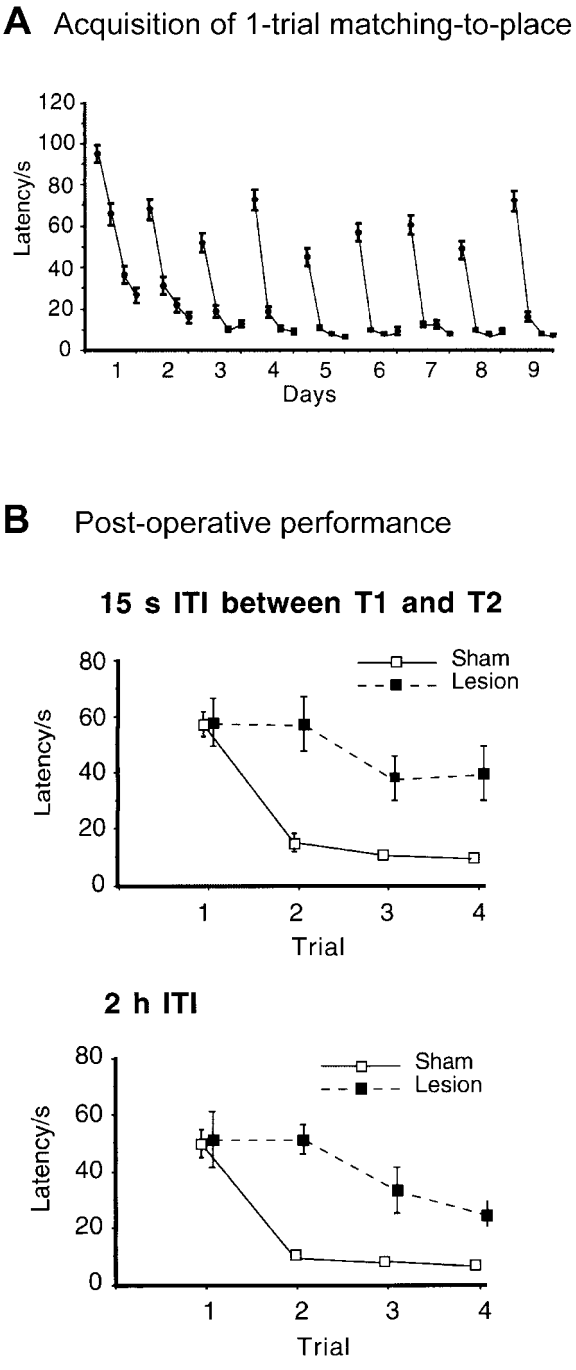

Figure 2. The hippocampus and one-trial learning. Rapid, one-trial spatial learning is impossible without a hippocampus. (A) The acquisition of matching-to-place performance over the 9 days of pretraining in a DMP task (see box 2). Note the development of a sharp fall in latency between trials 1 and 2, indicating one-trial learning of each novel platform location. (B) The subsequent mean performance of rats with ibotenic acid lesions of the hippocampus versus sham-operated animals as a function of the interval between trials 1 and 2 (i.e., 15 s or 2 h) over the 9 days of postoperative training. Each data point was generated by averaging the latency scores obtained during successive presentations of the same inter-trial interval. In the lesioned group, no improvement was evident between the first two trials, irrespective of the delay between them. [Figure reprinted with permission from ref. 63; copyright 1999, Wiley-Liss, Inc.]

Box 2. The watermaze delayed matching-to-place task
In contrast to the spatial reference memory paradigm, the watermaze delayed matching-to-place (DMP) task (see Fig. 2) requires the learning of a novel platform location on each testing day. A critical performance measure is the improvement in escape latency between the first and second trials of a particular day – an index of the one-trial acquisition of spatial information. However, the occasional addition of a probe trial with the platform temporarily absent on the second trial of a day can provide a more sensitive measure of memory than escape latency alone [66]. Although the difference in latency between trial 1 and 2 ('savings') is usually the primary measure of memory, four or more trials are often conducted in an effort to reinforce the matching-to-place rule, and to avoid potential carry-over effects from one day to the next.

The impact of lesions made before or after learning

In the studies discussed so far, learning and memory were always assessed following a brain lesion. This kind of experiment can tell us whether a particular structure is necessary for a specific form of learning. But interventions made after learning provide additional information: they permit targeting of a putative memory substrate after a memory has been formed. This prevents the development of compensatory strategies and the recruitment of alternative brain areas, and allows the time course of a memory's dependence on a particular brain structure to be assessed.

A striking example of the difference between pre- and post-training damage is provided by a study in which dorsal hippocampal lesions (occupying 40% of the total hippocampal volume) were made either before, or immediately after, place learning in a watermaze [67]. Whereas lesions made before training had no effect on new learning, lesions made after training disrupted memory retention. These results suggest that partial hippocampal damage prior to training spares sufficient hippocampal tissue to support near-normal task acquisition; conversely, a memory trace formed in the intact hippocampus, and distributed widely within the structure, is substantially degraded when even a small part of the hippocampus is subsequently removed. In later studies, the longitudinal fiber system within CA3 was transected using small knife cuts; this manipulation produces a striking impairment of preoperatively acquired place memory, but the impact on new spatial learning is minimal [68, 69]. These findings indicate that longitudinal hippocampal connectivity is involved in the storage and/or retrieval of recently formed spatial memory, a result that would have been missed using a purely anterograde design (see 'Memory encoding and retrieval' below).

Findings such as these extend the notion of hippocampus dependence and illustrate the need for caution in interpreting the results of an intervention that disrupts the normal functioning of a brain structure prior to behavioral testing. In fact, the study of retrograde memory impairments has been a cornerstone of research into memory consolidation and the formation of stable, long-term memories, a theme that will be further explored in 'Systems consolidation'.

The role of distinct hippocampal subregions

The use of regionally specific lesions. In addition to large hippocampal lesions targeting both the dentate gyrus and CA subfields, there is a substantial literature on the effects of more selective hippocampal damage. Early studies indicated that kainic acid lesions of CA3 can impair spatial working memory in the 8-arm radial maze [70, but see 71]; such lesions also impair matching-to-place performance [64]. Colchicine lesions of the dentate gyrus have likewise been reported to impair spatial tasks, with the largest deficits again observed in one-trial learning [64, 72]. Permanent lesion studies have since been complemented by the use of reversible subfield-specific inactivation [73–75]. In recent years, we have begun to see the development of ever more selective manipulations, driven by the wealth of ideas about the significance of various components of the hippocampal circuitry. The 'classical' view of the hippocampal trisynaptic loop (entorhinal cortex – dentate gyrus – CA3 – CA1) focuses on functional connectivity in a transverse direction, perpendicular (approximately) to the long axis of the structure [76, 77]. Current thinking is further informed by an appreciation of the existence of extensive intrinsic connectivity along the long axis of the hippocampus [78], the longitudinal heterogeneity of extrinsic afferent and efferent connections (see box 3), and the existence of substantial direct entorhinal input to areas CA3 and CA1 [see ref. 2 for review]. A schematic view of the intrinsic connectivity of the hippocampus is provided in Figure 3.

The dentate gyrus. A topic of long-standing interest is the role of the dentate-CA3 network in pattern separation versus pattern completion [see ref. 79]. The latter refers to the orthogonalization or decorrelation of overlapping input patterns, a process that may be critical for efficient learning. In more concrete terms, pattern separation might serve to disambiguate places with overlapping features – a situation that is

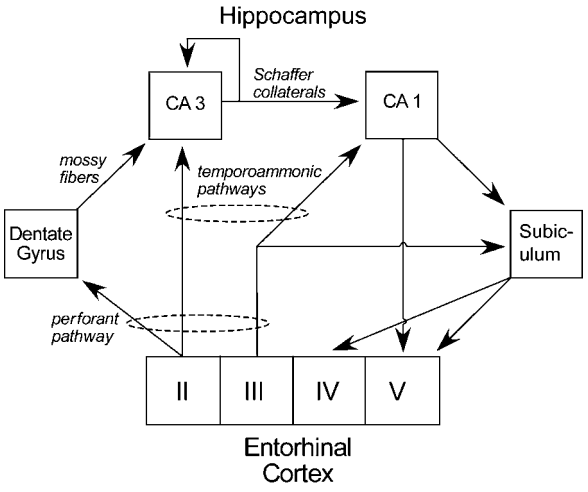

Figure 3. The hippocampal circuit. The hippocampus, defined here as the dentate gyrus (DG), CA3, CA2, and CA1, is anatomically situated to receive highly processed information from widespread neocortical regions through three temporal cortical areas known as the entorhinal, perirhinal, and postrhinal cortices, and through other direct projections from extra-temporal areas. The hippocampus can be viewed as part of a hierarchically organized system of structures in the temporal lobe that is important for the formation of long-term memory. The main relay station for the transmission of sensory information to the hippocampus is the entorhinal cortex; layer II of this structure provides the major input to the hippocampus. This unidirectional projection, forming part of the perforant pathway, provides a substantial input to the DG, which, in turn, provides the major input to CA3 via the mossy fiber projection. There is also a smaller unidirectional projection to CA3 from layer II of the entorhinal cortex. CA3 provides the major input to CA1 via the Schaffer collateral/commissural pathway, but there is a substantial recurrent associational projection back to the CA3 field. CA1 also receives a direct temporoammonic projection from layer III of the entorhinal cortex (as does the subiculum). Both Schaffer collateral and temporoammonic projections to CA1 are unidirectional. CA1 primarily projects to the subiculum, but also sends a projection to entorhinal cortex layer V. The subiculum sends a prominent projection primarily to the entorhinal cortex layers IV and V [see ref. 2 for review]. The figure shows a simplified view of the way in which information enters the hippocampus from the superficial layers of the entorhinal cortex and then flows in a largely unidirectional, feed-forward, clockwise direction to ultimately return predominantly to the deep layers of the structure. From here, processed information can then be sent to widespread neocortical areas.

likely to be common in real-world environments. A role in pattern separation has long been attributed to the dentate gyrus, based, among other considerations, on the divergence of entorhinal inputs to the granule cell layer, the sparse connectivity of the mossy fiber projection to CA3 pyramidal cells, and the desirability of decorrelated inputs to the putative autoassociative network of CA3 [e.g. ref. 80, 81]. This notion has some behavioral support: lesions of the dentate gyrus impair performance in a spatial matching-to-sample task, but only when the spatial separation between the target location and an unrewarded foil is small [82–84]. During the 1990s, growing evidence led to a widespread belief that neurogenesis occurs in several regions of the adult brain, including the dentate gyrus [85]. Although in recent years the formation of new granule cells in this region has been implicated in learning and memory under some circumstances [see ref. 86 for review], it should be emphasized that it is far from clear whether the impairments are related to neurogenesis *per se* or to some non-specific effect of the method used to disrupt neurogenesis. Interestingly, a recent computational model of hippocampal functioning implicates dentate neurogenesis in the creation of distinct memory traces for very similar items or events occurring at different times – effectively a process of pattern separation [87].

CA3. In contrast to the dentate gyrus, the extensive recurrent connectivity of CA3 appears ideally suited to pattern completion – the reconstruction of a complete output pattern from a degraded input. This is a basic property of many associative neural networks, and may be useful for maintaining stable representations in the face of incomplete sensory data, or trivial alterations of an otherwise stable environment. The idea that CA3 comprises an autoassociative network specialized for the rapid encoding of new information has a long history [80, 84, 88, 89]. CA3 pyramidal cells make multiple recurrent connections with other pyramidal cells in the subfield – an arrangement reminiscent of re-entrant neural network architectures that are capable of pattern completion [80] – and these recurrent synapses exhibit associative, NMDA-receptor-dependent long-term potentiation (LTP). There is now considerable behavioral and physiological evidence for this hypothesis, work that will be discussed in the 'Memory encoding and retrieval' section.

CA1. The dentate-CA3 network might not be necessary for all aspects of hippocampus-dependent memory: CA1, the final station in the trisynaptic loop, receives a substantial glutamatergic input from layer III of the entorhinal cortex via the direct temporoammonic projection, in addition to the Schaffer collateral input from CA3 (see Fig. 3; note that CA3 also receives a direct perforant path input from layer II of the entorhinal cortex). It has often been suggested that CA1 acts as a 'novelty detector,' detecting mismatches between cortical information concerning the current situation, with the stored predictions arriving from CA3 [e.g., refs. 11, 90–93]. The resulting novelty signal might then trigger the updating of stored information to eliminate the mismatch [94] (and see 'Cellular consolidation' below). A recent study of the temporal gating of temporoammonic inputs to CA1 by activity in the Schaffer collateral pathway offers an intriguing glimpse of how this match/mismatch signal

Box 3. Functional differentiation along the longitudinal axis of the hippocampus

Throughout much of this review, the dentate and CA subfields are discussed as if they were homogeneous entities throughout the entire length of the hippocampus. However, there is considerable evidence for functional heterogeneity along the long axis of the structure [2]. An examination of the effects of partial hippocampal lesions of varying sizes, sparing either the septal (dorsal) or temporal (ventral) portions of the hippocampus, revealed that septal lesions have a greater impact on spatial learning than temporal ones [103–106]. This is consistent with the fact that the septal two-thirds of the hippocampus receives most of the structure's visuospatial input, whereas the temporal third (or ventral hippocampus) is extensively connected with a range of brain regions implicated in motivation, emotion, and executive functions, including the prefrontal cortex and a number of subcortical structures [see refs. 2, 105, 107, 108 for reviews]. In a recent study, lesions of the dorsolateral band of the entorhinal cortex, a region that projects to the dorsal hippocampus, resulted in a disruption of spatial memory; conversely, lesions of the ventromedial band that projects to the ventral hippocampus impaired fear-related behavior in an elevated plus-maze [109]. Moreover, CA place fields exhibit progressively broader spatial tuning as one moves from the dorsal pole toward the intermediate [110, 111] and ventral [112] hippocampus.The initial findings of the Moser laboratory have since been confirmed by others [113–115]. It has been suggested that the ventral hippocampus might be more important for non-spatial memory or innate information processing, such as fear-related behavior and anxiety [16, 108, 113, 116–119], sensorimotor processes [16], or the utilization of internal cues [120, 121]. However, there is evidence that the temporal hippocampus might play a substantial role in spatial learning and memory under some circumstances [122, 123]. An alternative idea emphasizes the importance of sensorimotor integration along the longitudinal axis of the hippocampus, i.e., the linking of information received and processed at different septotemporal levels with the executive connections of the temporal hippocampus [16]. The observation of coherent longitudinal theta oscillations [124, 125] may be significant in this regard. According to this view, the septal and temporal poles of the hippocampus do not mediate entirely different forms of memory or information processing, but may play complementary but distinct roles in a single memory process.

might be calculated [95]. However, the role of CA1 versus other hippocampal subregions in novelty detection remains uncertain [11, 14, 96, 97].

In order to isolate the contributions of the direct cortical input to CA1, Brun and colleagues [98] disconnected CA1 from CA3 using a series of continuous knife cuts between the two subregions. Surprisingly, place fields formed normally, although their sharpness was slightly reduced, consistent with a prior study of the consequences of reducing CA3 activity [99]. Despite this, the acquisition and retention of a standard open-field watermaze reference memory task was impaired, although lesioned animals exhibited substantial place memory by the end of training. A subsequent test of spatial recognition memory yielded a different pattern of results, however. Rats were trained to swim around a narrow annular insert within a watermaze in order to find a hidden escape platform [100]. On probe trials, the platform was removed; recognition memory was then expressed as slower swimming in the target area of the corridor. Although performance in this task is disrupted by complete hippocampal lesions, no impairment was evident following disconnection of CA3 from CA1. These findings suggest that whereas the direct cortical projection to CA1 is sufficient for place recognition, the CA3-CA1 pathway is necessary for the rapid learning and recall of a spatial location and/or navigation towards it, an idea to which we will return in the following section. Moreover, these data were the first to show conclusively that CA1 is capable of generating place-specific firing based solely on information contained in the entorhinal input, without the need for further processing via the trisynaptic circuitry. This result is perhaps not as surprising as it might seem – the pyramidal cells of the dorsocaudal medial entorhinal cortex are now known to exhibit substantial spatial modulation, with individual 'grid cells' displaying multi-peaked firing fields that form a regular lattice across the recording arena [101, 102].

Memory encoding and retrieval

Alternatives to brain lesions: the use of reversible and selective interventions

The lesion work discussed above has been complemented by pharmacological interventions that offer far greater temporal control, while sacrificing, to some extent, the spatial precision offered by current lesion techniques. Over the past two decades, a wealth of data has been accumulated indicating that pharmaco-

logical blockade of hippocampal NMDA receptors impairs memory formation [see refs. 126–129 for reviews]. Although the present review focuses on NMDA-dependent mechanisms, other receptors and their associated signaling pathways have also been implicated in synaptic plasticity and memory. Examples include the metabotropic glutamate receptors (mGluRs) [130–135], and L-type calcium channels [136] (see also 'Cellular consolidation' below).

In recent years, the use of transgenic and knockout animals has begun to offer opportunities beyond the scope of traditional techniques. In principle, the development of animals with conditional knockouts of selected genes can combine the excellent temporal control of pharmacological studies with a spatial selectivity – in terms of specific brain regions and even cell types – that greatly exceeds the potential of conventional lesions. Although many pioneering studies did not aim for this level of sophistication, genetic interventions have provided substantial evidence that disruption of key elements of the hippocampal plasticity machinery has commensurate effects on spatial memory [see refs. 137–146].

Synaptic plasticity and the rapid encoding of spatial information

The effects of inhibiting plasticity are not identical to the effects of large hippocampal lesions. First, blockade of hippocampal NMDA receptors results in a delay-dependent impairment in the watermaze matching-to-place task [63]. Memory is normal at a 15-s inter-trial interval, but severely impaired at delays of 20 min or more. In contrast, complete hippocampal lesions impair memory at all delays. These results imply that hippocampal NMDA-receptor-dependent processes – such as changes in synaptic efficacy – are unnecessary for the transient retention even of trial-unique place information, but are essential for the encoding of a lasting memory trace. Intriguing data have recently been obtained concerning the role of different hippocampal subregions in the intermediate-term retention of spatial memory [147]. Local infusion of AP5 targeting the dentate gyrus or CA1 was sufficient to impair spatial working memory in a familiar environment at a training-test interval of 5 min, but no effect was observed at a 10-s delay. CA3 infusion, in contrast, had only a transient effect that disappeared with further training. However, definitive conclusions about the differential role of specific subregions may be premature. The longitudinal extent of drug diffusion achieved by Lee and Kesner [147] is likely to be somewhat limited owing to the requirement for subregional selectivity in the transverse plane – a problem that may be difficult to avoid with pharmacological interventions.

Second, we argued earlier that the hippocampus is particularly important for rapid learning, but this is true to an ever greater extent for hippocampal synaptic plasticity. Treatments that prevent NMDA-receptor-dependent plasticity can result in substantial deficits in the acquisition of spatial reference memory tasks – this is true of both pharmacological blockade of NMDA receptors [126, 127], electrophysiological saturation of LTP [148], and CA1-specific deletion of the NR1 subunit of the NMDA receptor [149]. However, rats pretrained in certain ways exhibit little or no impairment in incremental learning of a spatial reference memory task after LTP induction is limited by pharmacological means [150, 151] or electrophysiologically [152]. The same pretraining procedures do not benefit rats with hippocampal lesions [150]. However, one-trial spatial matching-to-place in the watermaze remains very severely impaired by intra-hippocampal D-AP5 infusion, despite an extended period of pretraining prior to the start of drug infusions, suggesting that synaptic plasticity might only be absolutely necessary when information must be acquired rapidly [63]. A more recent study employed a delayed non-matching-to-place protocol in a radial maze, in which a rat had to choose between a previously visited arm, and an unvisited one [147]. AP5 infusions targeting CA3 had no effect on performance in a familiar spatial environment, but were highly disruptive in a novel environment. Although there are many differences in detail between the data of Lee and Kesner [147] and Steele and Morris [63], both sets of findings are consistent with a role for CA3 in the rapid acquisition of spatial information.

A similar selectivity for rapid learning has since been obtained using a variety of gene targeting approaches. For example, mice with a deletion of the gene coding for the GluR-A subunit of the AMPA receptor exhibit impaired Schaffer collateral–CA1 (LTP), but no deficit in spatial reference memory [153–156]. This is true even in the absence of extensive pretraining, perhaps reflecting a milder impact of the manipulation compared to hippocampus-wide pharmacological blockade or genetic deletion of the NMDA receptor – although the selectivity of the manipulation for plasticity at Schaffer collateral synapses versus other populations has not been determined. But robust impairments are obtained in tests of spatial working memory, such as non-matching-to-place in a T-maze [154, 155, 157]. Deficits are also found in a task that requires spatiotemporally discontiguous events to be associated [158]. The reduction in LTP and the working memory impairment can be rescued by the addition of a forebrain-specific GluR-A expression system to the knockout mice [159]. However, this

story is complicated by the finding that theta-burst stimulation – an arguably more physiologically realistic pattern of stimulation than a 'conventional' tetanus – can induce LTP even in the absence of GluR-A.

Despite the frequent focus on LTP-like increases in synaptic efficacy, it is possible that long-term depression (LTD)- or depotentiation-like decreases in synaptic strength are just as important as synaptic potentiation, particularly when old, irrelevant information must be forgotten, and new information quickly added. Exposure to a novel environment, for example, can reverse existing LTP [160] and facilitate the induction of LTD [161] see also ref. 133]. Mice with a forebrain-specific calcineurin knockout exhibit a substantial deficit in Schaffer collateral LTD, but normal, or slightly enhanced LTP [162]. These mice are unimpaired on a watermaze reference memory task, but perform very poorly on a matching-to-place version of the task. Performance in the spatial working memory version of the 8-arm radial maze is also impaired. These results support the idea that bidirectional synaptic plasticity is critical for spatial working memory, but the possible effects of enhanced LTP – a phenomenon with an uncertain relationship to memory [for example, see refs. 163, 164] – should also be considered.

More recent work has taken these ideas even further, employing genetic techniques to target very specific components of the hippocampal circuitry. Nakazawa and colleagues created a conditional knockout mouse with a CA3-specific deletion of the gene coding for the NR1 subunit of the NMDA receptor; as expected, LTP at CA3 recurrent collateral synapses was impaired [165]. Nonetheless, these mice were able to learn a spatial reference memory version of the watermaze task over repeated trials (see 'The role of pattern completion in memory retrieval'). However, subsequent testing revealed that watermaze DMP performance was substantially impaired in knockout animals, but no deficit was evident if a platform location was repeated [166]. This is consistent with the idea that plasticity in the recurrent network of CA3 is critical for the rapid encoding of novel place information, although a role for NMDA receptor-dependent plasticity in other populations of CA3 synapses cannot yet be ruled out. A subsequent analysis of the place-specific firing of CA1 pyramidal neurons revealed the formation of normal place fields in familiar surroundings, but place fields were more broadly tuned upon initial exposure to a novel area of the testing environment.

The simplest explanation for all of the above findings is that synaptic plasticity in specific pathways (e.g., CA3-CA3, CA3-CA1, and probably others) is critical for the encoding of information in a trial-unique manner. When this plasticity is abolished, one-trial place learning is impossible, but other mechanisms are sufficient to support incremental learning. However, the build-up of proactive interference as successive platform locations are introduced is an additional factor that distinguishes matching-to-place from reference memory tasks. Accordingly, plasticity-dependent mechanisms might be critical in some way for remembering the location experienced most recently, rather than the many now incorrect locations encountered on previous days [see ref. 167]. As we have discussed, it is attractive to assign a key role to both increases and decreases in synaptic strength under these circumstances.

Dissociating memory retrieval from encoding processes: the role of AMPA and NMDA receptors

In much of the work discussed in the previous section, it is difficult to dissociate the impact of a manipulation on memory encoding versus retrieval. However, several studies have attempted to address this issue. Early work indicated that blockade of hippocampal NMDA receptors with AP5 has no effect on the retention of previously learned place information [63, 126, 168, 169]. These findings have recently been confirmed in a one-trial dry-land version of the matching-to-place task, in which rats search for food buried in recessed sand-wells (Fig. 4A); as expected, performance at a 20-min delay was impaired by AP5 infusion prior to the encoding trial [170] (see Fig. 4B). Similar results were obtained in a flavor-place paired associate task in the same apparatus [171]. However, performance in both studies was unaffected by NMDA receptor blockade prior to a retention test (see Fig. 4B). In other words, once formed, the retrieval of an existing memory does not require further NMDA receptor activation. The retrieval of a recently formed memory is, however, dependent on hippocampal activity: blockade of hippocampal AMPA receptors before retention testing brought performance close to chance levels [66, 171] (see Fig. 4C). Hippocampal lesions made before retrieval have a similar impact in a spatial reference memory task [50].

The role of pattern completion in memory retrieval

Speculation concerning the mechanisms of memory retrieval has often centered on the process of pattern completion [see ref. 79]. The idea is that specific synapses within a recurrent network (e.g., CA3) undergo NMDA receptor-dependent changes in synaptic strength that collectively comprise a memory trace. Once established, these changes can be read out during retrieval without the need for further NMDA

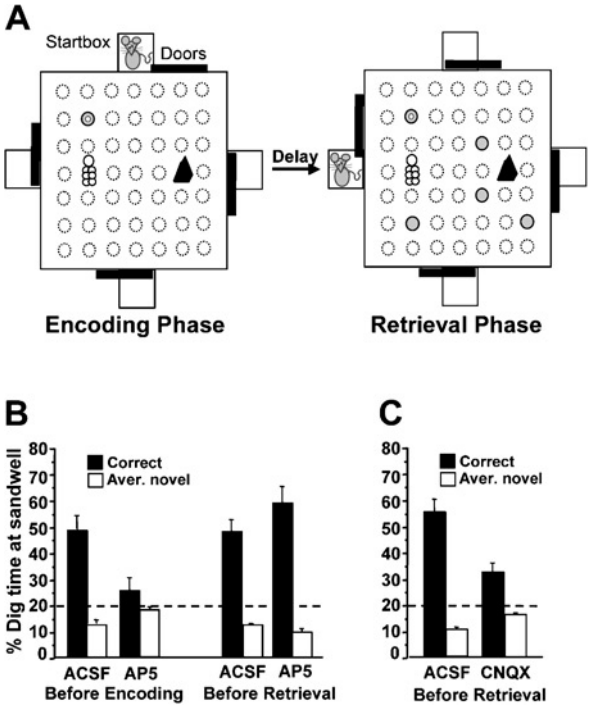

Figure 4. Memory encoding and retrieval. Hippocampal NMDA receptor activation is necessary for the encoding, but not retrieval, of one-trial place memory in a dry-land, arena-based task. Retrieval is, however, impaired by AMPA receptor blockade. (A) The open-field event arena comprises a grid of recessed sand-wells, covered with sawdust. In the encoding phase of a spatial matching-to-place task (lefthand panel), the rat must search for a food pellet located in a single, open well. In the retrieval phase (righthand panel), the rat must locate the previously rewarded well in order to collect another reward. Four additional unrewarded wells are also open during this phase. Encoding and retrieval phases are conducted in a single day, 20 min apart, and the location of the rewarded well is always changed between days. The task is therefore analogous to trials 1 and 2 of the watermaze matching-to-place task (see Box 2 and Fig. 2). (B, C) Once the task had been learned, occasional probe trials were conducted in which no reward was available during the retrieval phase. On these occasions, rats were given intrahippocampal infusions 15 min prior to encoding or retrieval via chronically implanted cannulae. Graphs indicate the percentage time spent digging in the correct sand-well versus the average time spent digging in the four incorrect wells. Infusion of D-AP5 (30 mM; 1 µl/side) 15 min before the encoding trial resulted in a severe memory impairment, relative to aCSF-infused controls; but AP5 infusion prior to retrieval had no effect (B). In contrast to AP5, the AMPA antagonist CNQX (3mM; 1 µl/side) disrupted memory when infused 15 min before retrieval (C). [Figure reprinted with permission from ref. 170; copyright 2005, the Society for Neuroscience.]

receptor activation – hence the absence of an effect of AP5 on retention. (But although synaptic changes may not be necessary for memory retrieval, it is likely that such changes do normally occur [see refs. 172, 173 and Box 4].) Importantly, the existence of extensive recurrent connections between different cells of the network allows a complete output pattern to be reconstructed from a partial or degraded input, a feature that might be critical in many real-world situations.

Experimental evidence for such a process was recently obtained using mice with a CA3-specific knockout of the gene encoding the NR1 subunit of the NMDA receptor [165] (see also 'Synaptic plasticity and the rapid encoding of spatial information'). After training in a standard watermaze reference memory task, knockout mice were able to remember the location of a hidden platform during a probe trial when all distal cues were present; but when only a subset of cues was presented, the mutant mice were markedly impaired. These findings suggest that NMDA receptors at recurrent CA3 synapses are necessary for the encoding of memory traces in such a way that pattern completion can occur during retrieval. Behavioral data consistent with those of Nakazawa et al. [165] have recently been reported in an analogous dry-land task in which rats learned to locate a food reward hidden in a sand-well on the basis of four extra-maze cues [174]. Following neurotoxic lesions of area CA3, rats were given probe trials with a variable number of cues removed. Cue removal had only minor effects in normal rats, but performance declined steeply in lesioned animals, consistent with impaired pattern completion [see also ref. 175].

A recent comparison of the firing properties of CA3 and CA1 has provided further support for the pattern completion hypothesis. Lee et al. [176] recorded place fields as rats ran around a circular track. In this case, comparisons were made following changes to the environment made by rotation of proximal and distal cue sets in opposite directions. Most CA1 neurons exhibited a remapping as the mismatch increased, but CA3 place fields tended to retain their coherence consistent with a pattern completion operation, perhaps serving to identify the environment as the same despite changes in the relationships between cue sets. In contrast to these findings, Leutgeb et al. [177] presented evidence for the opposite process of pattern separation in CA3. Instead of manipulating cues within a single environment, they recorded the firing of CA3 and CA1 neurons in separate environments whose geometrical similarity could be varied by moving the walls of the enclosures. In CA1, there was substantial overlap between active neuronal populations in different environments, and the degree of overlap grew larger with increasing environmental similarity. In CA3, however, very little overlap was observed between the subsets of cells activated in each environment, even when the enclosures were identical. It was suggested that this orthogonalized representation may help to reduce interference and maintain distinct representations of similar but distinct environments.

A possible resolution of the apparent discrepancies between the two studies has been presented, based on

a hypothesized non-linear transformation of input patterns as the change in an environment increases [178]. In other words, CA3 responds to small environmental alterations with pattern completion, but shifts to pattern separation mode when differences become larger, or if different environments are employed. This interpretation draws on an immediate early gene activation imaging study in which changes were made either to a single environment or two different environments [179]. The predicted pattern of neuronal activity was observed: small environmental changes resulted in overlapping activity patterns, but larger changes caused a shift toward a non-overlapping pattern of activity. Findings such as these might have important implications for our understanding of the role of the hippocampus in the context-specific retrieval of memory [see refs. 26, 27].

Nevertheless, the story is far from complete. First, the role of CA3 versus upstream processing in the dentate gyrus – a structure traditionally associated with pattern separation – remains unknown. Second, it is difficult to see how information processed by the dentate-CA3 network can leave the hippocampus if similar information is not represented in CA1. Interestingly, in contrast to the earlier findings [see also refs. 180], a recent study has reported both pattern separation and pattern completion in the firing patterns of CA1 neurons: cells exhibited an abrupt shift in their representations as a square arena was 'morphed' into a circular one, with intermediate shapes presented in semi-random order [181], a finding that is consistent with the suggestions made by Guzowski et al. [178] concerning CA3. But a continuous remapping has also been observed when one environment is gradually morphed into another, suggesting that an incremental coding of environmental changes can also occur [182]. A further complexity – perhaps relevant to this apparent discrepancy – is introduced by the observation that two separate indices, the place-specific firing characteristics of neurons and their firing rate [see refs.183], can exhibit independent remapping in CA3 [184]. For further discussion of these issues, see refs. [185, 186].

Theories of memory retrieval versus encoding

Rather than simply transforming a pattern of inputs, it has been suggested that the hippocampus might exhibit distinct encoding and retrieval 'modes' and/or that distinct neural mechanisms are engaged during the two processes. One suggestion is that the direct cortical input to the CA subregions and the intrinsic hippocampal circuitry play distinct roles in encoding and retrieval processes [89, 92, 187]. For instance, based on physiological data, it has been proposed that the hippocampal theta rhythm serves to separate encoding from retrieval, with encoding occurring at the troughs of the rhythm (recorded at the hippocampal fissure) and retrieval occurring at the peaks [188]. This model is inspired, in part, by evidence that the direct cortical input to CA3 and CA1 is strongest at theta troughs, perhaps providing a 'teaching signal'; conversely, intrahippocampal pathways, and the output to entorhinal cortex – perhaps conveying stored information – predominate at the peaks of the rhythm [189].

Other models make somewhat different predictions about the role of the direct cortical input. There is evidence, for example, that dopamine selectively depresses the perforant path input to CA1; the activation of dopaminergic projections from the VTA might inhibit this input when novel information is received, while facilitating plasticity at CA3-CA1 synapses [92; see also ref. 94 and 'Cellular consolidation' below]. Thus, dopamine might provide a signal that instructs the hippocampus to enter a transient encoding state. Conversely, there is considerable experimental evidence that activation of the noradrenergic system can facilitate memory retrieval [172, 190, 191]. Alternative possibilities include the idea that acetylcholine provides the novelty signal that switches the hippocampus from retrieval to encoding modes [192, 193]. Others have suggested that inhibitory interneurons might control this switching function [194]. Although many of these ideas are very preliminary, there is enormous scope for the parallel development of computational and empirical approaches to hippocampal function. Aided by the increasing selectivity of the tools available for disrupting and monitoring the functions of specific components of the hippocampal network, the work described in this section is beginning to close the gap between neuroanatomy and function, bringing us gradually closer to a circuit-level description of hippocampal operations.

Memory retrieval: beyond the hippocampus

A degree of caution is appropriate at this point: we should not assume that memory retrieval is a solely intrahippocampal process acting on memory traces located within the structure. In fact, successful retrieval involves the conjoint activation of multiple brain regions, including the prefrontal cortex [195–198]; neuromodulatory and endocrine systems also play key regulatory roles, [172, 190, 199–202]. Moreover, it is generally thought that the neocortex is the final site of long-term storage for many kinds of information. A major function of the hippocampus is thought to be the 'binding' of memory traces stored in the cortex into a coherent representation: after a process of memory consolidation, this representation

can be retrieved without hippocampal involvement. These ideas are considered in detail in 'Memory consolidation' below.

Memory consolidation

Introduction

It has been suggested that the hippocampus records a continuous transcript of attended events [203]. If so, there must be mechanisms for selecting those memory traces that are worthy of long-term storage, while discarding the rest. Entry into long-term storage is likely to be gated in many ways at different levels of organization – relevant factors might include the motivational significance of the memory (or of other events occurring shortly before or after [204]), its compatibility with existing semantic knowledge structures [205], and the amount of reminding and rehearsal that occurs after learning. At the neuronal level, the stabilization of selected memory traces is thought to be mediated by a range of consolidation processes, involving many different substrates and operating over differing timescales [206]. These processes are sometimes divided into interdependent 'cellular' and 'systems' components [207]. The former is thought to encompass a range of local intracellular events – occurring over a period of several hours – that lead to the formation of stable changes in synaptic connectivity and/or neuronal excitability. The latter refers to a postulated systems-level reorganization of the memory trace that involves interactions between brain structures and the extensive refinement and remodeling of patterns of synaptic weight changes. This process may take days, weeks, or even years in humans [208], although an extended time course should not necessarily be regarded as a defining feature of this form of consolidation.

Cellular consolidation

The role of NMDA receptors and downstream signaling pathways. It is generally thought that long-term memory formation requires both hippocampal and neocortical activity and synaptic plasticity during initial encoding, followed by local 'cellular' consolidation processes within these two structures [see ref. 209 for review] – although research to date has focused largely on the hippocampal side of the story. Consistent with this, the long-term retention of place memory (i.e., >24 h) is impaired by the blockade of NMDA receptor-dependent synaptic plasticity either before (see 'Synaptic plasticity and the rapid encoding of spatial information'), or soon after, acquisition [210, 211]. The latter finding suggests that the early stabilization of a memory requires additional 'offline' episodes of NMDA receptor activation after the initial encoding event [see also refs. 212, 213]. Such findings may account for the reduced long-term stability of CA1 place fields observed after NMDA receptor blockade [214]. In contrast, as discussed above, short-term spatial memory (e.g., with a 20-min acquisition-retention interval) is unaffected by post-training NMDA receptor blockade, despite a marked impact of blockade during acquisition [170]. Taken together, these findings suggest that NMDA receptor activation makes distinct but complementary contributions both to the encoding, and the early stabilization, of memory.

However, the existence of cellular consolidation processes is most commonly inferred from the consequences of interventions targeting processes downstream of the NMDA receptor. Sensitivity to inhibitors of macromolecular synthesis [204, 207, 215] (Fig. 5) is often regarded as a defining feature of cellular consolidation, but a large number of other interventions can interfere with the consolidation of hippocampus-dependent memory in the minutes to hours after its formation. The list – by no means an exhaustive one – includes disrupting the activity of a range of protein kinases [216, 217], such as CaMKII [218], MAPK/ERK [219–222], tyrosine kinases [223], PKA [224], and PKC [225]; other manipulations include the inactivation of CREB [226–232], the deletion or disruption of the expression of certain genes, such as those coding for Zif268 [233, 234], Arc [235], or BDNF [236], temporary neuronal inactivation [75, 237, 238], and interference with cell adhesion processes [239–241]. There is also growing interest in the possibility that epigenetic mechanisms – such as DNA methylation and histone modification – might play a critical role in information consolidation and storage at the cellular level [see ref. 242 for review].

Late-LTP and synaptic tagging. The induction of late LTP (lasting > 4 h) is sensitive to a similar range of interventions to those that impair long-term memory formation, consistent with the idea that lasting changes in synaptic efficacy underlie lasting memories. For example, the inhibition of protein synthesis has a minimal effect on LTP in the first hour or more following its induction, but little potentiation persists after 4–6 h [see ref. 204 for review]. Paradoxically, protein synthesis need not be initiated at the same time as the induction of LTP. For example, strong tetanization of the Schaffer collateral input to CA1 in the presence of the protein synthesis inhibitor anisomycin normally results in a transient early LTP. But if drug infusion and LTP induction are preceded by strong tetanization of an independent input to the

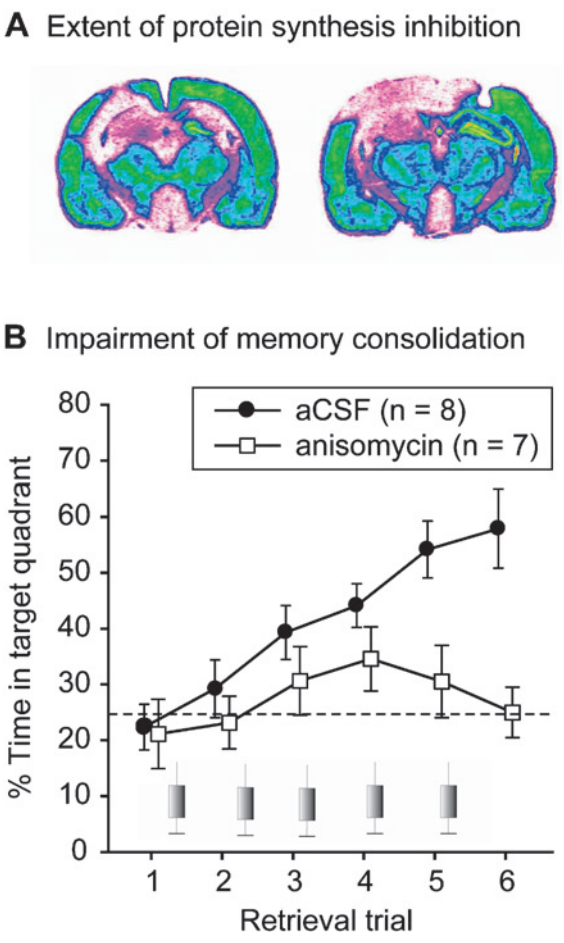

Figure 5. Inhibition of protein synthesis and cellular consolidation. (A) Unilateral infusion of anisomycin into the dorsal hippocampus results in a local reduction in protein synthesis. Autoradiographic images from two different rats are shown. Inhibition of protein synthesis is indicated by a reduction in the uptake and incorporation of [^{14}C]L-leucine (white areas). (B) Bilateral post-training infusion of anisomycin (250 mg in 2 ml per side) into the dorsal hippocampus impaired memory consolidation in a watermaze reference memory task. Rats were trained over 6 days, with four trials/day, to find a hidden platform in a fixed location. The first trial of each day was a 'rewarded' probe in which the platform was made available after 60 s, providing repeated measures of 24-h memory retention. Anisomycin or aCSF was infused immediately after the end of each daily testing session. The percentage time spent in the training quadrant during the first 60 s of each daily probe trial is plotted. Rats that received anisomycin were never able to retain a spatial memory over the 24-h period between testing sessions, indicating a disruption of memory consolidation. [Figure reprinted with permission from ref. 304; copyright 2006, Elsevier.]

same population of neurons, a stable, late LTP is induced [243]. These and subsequent findings suggest that a high-frequency tetanus sets synaptic 'tags' that enable the sequestration of plasticity proteins that are currently available owing to past activity, or those that become available in the near future [204, 243, 244]. In fact, if proteins are scarce, a competitive interaction can be observed between tagged synapses [245]. Under normal circumstances, the activity of neuromodulators such as dopamine in CA1, norepinephrine in the dentate gyrus, or stress hormones, may be a critical factor in regulating protein availability (see below).

During memory formation, a dual requirement for protein synthesis and tag setting provides a plausible mechanism for the interaction of diffuse neuromodulatory signals – indicating, for example, novelty, reward, or punishment – with specific patterns of synaptic weight changes; the former might lead to a widespread upregulation of protein synthesis [246], and the latter might set synaptic tags that reflect the encoding of ongoing experience. Such a scheme might explain the facilitation of memory often observed for the incidental details surrounding emotionally significant events, and the related phenomenon of 'flashbulb memory' [203, 204].

The role of dopamine. There is increasing interest in the idea that the activation of dopaminergic inputs might provide the diffuse trigger required by the above model, particularly in CA1. The firing of dopaminergic neurons in the VTA has been linked to the prediction of motivationally significant events and reward, and to the occurrence of novel events and stimuli [see refs. 94, 247 for reviews]. This information is potentially available to the hippocampus: CA1, for example, receives dopaminergic projections from the VTA that terminate predominately within the stratum lacunosum moleculare [248]. Consistent with a role in upregulating protein synthesis, dopamine D1/D5 receptors are positively coupled to the cAMP/PKA cascade that activates MAPK and CREB [223, 249]. However, the possibility of a MAPK-mediated upregulation of translation – perhaps in dendrites – should not be overlooked [221]. In fact, the activation of D1/D5 receptors can stimulate the translation of local dendritic mRNAs [250], a process that is sometimes sufficient for the induction of persistent LTP [251, 252].

There is good evidence that dopaminergic activity modulates the persistence of LTP. Strong tetanization of the Schaffer collaterals causes dopamine release in the hippocampal slice preparation [253], and the blockade or knockout of dopamine D1/D5 receptors impairs late LTP in CA1 [253–258] – although modest effects on early LTP are also often observed. Conversely, dopamine agonists can enhance the magnitude and persistence of CA1 LTP [257, 259, 260]. Consistent with the proposed role of dopamine in stimulating protein synthesis, tagging experiments have the same outcome if a dopamine receptor antagonist is substituted for anisomycin: strong tetanization of one input can rescue L-LTP in an

independent input that has been tetanized in the presence of SCH23390 [261]. In fact, the activation of dopamine receptors can sometimes induce a slow-onset late LTP in the absence of early LTP [204, 255, 262]. An enhancement of LTP is also observed following the exposure of a rat to novelty [263–265], an effect that is dependent on the activation of D1/D5 receptors [263, 265]. Unit recording data are consistent with these effects of dopaminergic manipulations on synaptic plasticity. For example, the long-term stability of CA1 place fields is increased when the behavioral significance of environmental cues is increased. This effect can be mimicked by the systemic administration of a dopamine agonist, and stability can be reduced by the administration of an antagonist [266], although dopaminergic actions outside the hippocampus may also play an important role. A similar reduction in long-term place field stability is seen after inhibition of protein synthesis [267].

The manipulation of dopaminergic activity can also have corresponding effects on memory. Post-training administration of dopamine agonists has been reported to enhance memory in both spatial [260, 268] and non-spatial tasks [269]. Conversely, treatments that decrease hippocampal dopaminergic activity impair memory [226, 270]. In the watermaze, intrahippocampal infusion of the D1/5 antagonist SCH23390 impairs the retention of one-trial place memory in the watermaze at a 6-h interval, but has no effect on retention after 20 min [271] (Fig. 6). This time course is consistent with the effects of dopaminergic interventions on the persistence of LTP and place field stability discussed above. It is tempting to speculate that the firing of dopaminergic neurons in response to the reward or novelty of locating an escape platform in a new location leads to an upregulation of hippocampal protein synthesis, and the subsequent stabilization of synaptic changes 'tagged' by glutamatergic stimulation. In the presence of a D1/D5 receptor antagonist, the initiation of this cellular consolidation process would be disrupted, leading to a selective loss of long-term memory.

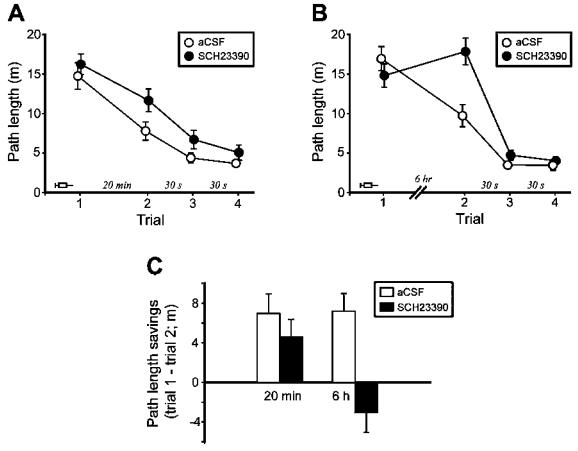

Figure 6. Dopamine receptor activation as a trigger for cellular consolidation. Blockade of dopamine D1/D5 receptors during learning impairs the formation of long-term but not short-term, memory, suggesting that dopamine receptor activation provides a trigger for the initiation of cellular consolidation. Rats with chronically implanted intrahippocampal infusion cannulae were pretrained for 8 days in a matching-to-place version of the watermaze task (see Fig. 2 and Box 2), after which a further 8 days of training were conducted. Prior to trial 1 of each training day, rats received a bilateral intrahippocampal infusion of SCH-23390 (5 μg in 1 μl per side) or aCSF. The interval between trial 1 and 2 was either 20 min or 6 h. Both drug condition and interval were varied in a counterbalanced within-subjects manner. The mean distance traveled in order to find the platform during training is plotted in A and B. Both drug- and vehicle-treated groups showed a marked improvement between trials 1 and 2 at the 20-min ITI (A), but drug-treated rats failed to remember the platform location at the 6-h ITI (B). An analysis of the difference between path lengths on trials 1 and 2 (savings) confirms this picture – the drug-treated condition exhibits a marked impairment only at the 6-h ITI (C). [Data adapted from ref. 271 with permission from the authors.]

The role of norepinephrine. Dopamine is not the only neuromodulator implicated in both synaptic plasticity and memory. Norepinephrine, for example, acts on beta-adrenergic receptors that are coupled to the same cAMP-PKA cascade that is activated by dopamine D1/D5 receptor stimulation. And the hippocampus receives a noradrenergic projection from the locus coeruleus, whose neurons, like those of the VTA, can respond to novelty [272; see ref. 273 for review]. There is considerable evidence that beta-adrenergic manipulations can modulate early LTP in several hippocampal pathways [257, 274–279]. Moreover, activation of the locus coeruleus causes a slow-onset dentate LTP *in vivo* [280], and the application of adrenergic agonists can result in the conversion of early LTP to protein synthesis-dependent late LTP in CA1 *in vitro* [281], and in the dentate gyrus of freely moving rats [282, 283], an effect that is mimicked by exposure to a novel environment [284]. Reminiscent of heterosynaptic rescue and synaptic tagging in CA1 *in vitro*, these findings are consistent with an earlier report that water reward given after weak tetanization can rescue decaying dentate potentiation, leading to stable late LTP [285]. In both the Straube et al. [284] and Seidenbecher et al. [285] studies, the rescue effect was blocked by the application of propranolol, a beta-adrenergic antagonist. However, the importance of intrahippocampal beta-adrenergic mechanisms in these phenomena remains uncertain: the modulation of hippocampal plasticity and memory in the intact animal is also thought to depend critically on the activation of beta-adrenergic receptors within the amygdala.

In support of the latter view, there is a wealth of evidence that the amygdala facilitates memory for

emotionally arousing experiences or material [237, 286–289]. Although severe stress is detrimental to memory [290], moderate concentrations of stress hormones such as glucocorticoids within the hippocampus can facilitate memory – an action that depends on noradrenergic activation of the basolateral amygdala [see refs 291, 292 for reviews]. Moreover, post-training infusion of norepinephrine into the basolateral amygdala can enhance the long-term retention of watermaze spatial reference memory, whereas memory is impaired by the infusion of propranolol [293]. Consistent with these findings, the amygdala enjoys extensive connectivity with the hippocampus and entorhinal cortex [294, 295], and the activation of inputs from the lateral amygdala can facilitate the spread of neural activity from the perirhinal cortex to the entorhinal cortex and hippocampal formation [296]. Moreover, stimulation of the basolateral amygdala can facilitate the induction of dentate early LTP under some circumstances [297–301], and can convert early LTP into protein-synthesis-dependent late LTP [299]. The latter phenomenon is observed following BLA stimulation within a specific time window either before or after tetanization of the perforant path, and is blocked by propranolol. The authors speculate that a 'motivation' or 'arousal' signal from the basolateral amygdala can interact with synapse-specific tags in the hippocampus, resulting in the stabilization of an otherwise decaying memory trace.

Box 4: Reconsolidation

Until recently, the prevailing view was that memory traces become stabilized after a single episode of cellular consolidation that occurs over a period of hours to days following encoding. Despite this, over the past few decades, there have been occasional reports that reactivated memories could become newly vulnerable to some of the same treatments that interfere with the initial consolidation process – results that imply the existence of 'reconsolidation' processes [see ref. 172 for review]. A recent revival of interest in reconsolidation began with the finding that infusion of anisomycin (an inhibitor of protein synthesis) into the lateral amygdala could disrupt a consolidated auditory fear memory, but only if drug administration was preceded by re-exposure to the conditioning tone – in other words if the memory was first reactivated [303]. Since then, similar phenomena have been documented in many brain areas, in many different species, and for a variety of behavioral tasks, including the watermaze [304, 305; for reviews, see refs. 306, 307]. A current focus of interest is whether reconsolidation is simply a recapitulation of consolidation, or whether distinct mechanisms are involved in the two phenomena. Although the cellular mechanisms of reconsolidation overlap with those of consolidation [302], some important dissociations have been observed [236; see ref. 308 for a review]. But despite a growing research effort, a number of problems remain unresolved [see for example ref. 309]. One such issue concerns the occasional reports that the amnesia following memory reactivation is sometimes temporary, implying a failure of memory retrieval rather than storage [310, 311]. However, it is worth noting that this storage verses retrieval debate was never entirely resolved for 'conventional' consolidation either. Nonetheless, when one considers work from humans, monkeys, rodents, and the invertebrate, where neurons and synapses can be examined and related to behavior, a compelling case can be made for storage impairment as the root of long-term memory loss [see ref. 312 for a review].In addition to cellular processes, systems-level examples of reconsolidation have also been reported. Remote contextual fear memory can become independent of the hippocampal formation, but re-exposure to the conditioning context can sometimes render the memory newly vulnerable to protein synthesis inhibitors or hippocampal lesions [313, 314]. However, such effects are not always observed [315], and the issue has not yet been fully resolved [see ref. 316 for discussion]. Some commentators have suggested that systems-level consolidation might simply reflect the cumulative effects of multiple rounds of cellular reconsolidation during the 'offline' reactivation of cortico-hippocampal memory traces – a process that might occur by reminding or rehearsal during wakefulness, and/or during sleep [308, 310, 317]. This position is reminiscent of the 'multiple trace' hypothesis of systems-level memory consolidation [318], in which each reactivation of a memory generates a new trace, or a new component of the trace. In support of this view, the vulnerability of reactivated memory to protein synthesis inhibitors is sometimes found to decline as a function of the strength and/or age of the memory [319–321], suggesting that very strong, or old and well-established traces do not always undergo reconsolidation. Despite these controversies, the resurgence of research into the reconsolidation phenomenon has brought new vigor to the memory consolidation field and continues to drive new insights into the processes that stabilize memory.

Summary. As we have discussed, the activity of neuromodulatory inputs, and interactions between the hippocampus and other brain structures, can determine the fate of recently induced synaptic changes and newly formed memories in the hours and days following their formation – a scenario that perhaps challenges the term 'cellular' consolidation. Nonetheless, once changes in synaptic efficacy have become stabilized, there is still no guarantee that the resulting memory trace will persist indefinitely; the entry of memory into very long-term storage is further gated by the higher-order process of systems consolidation discussed in the following section. Moreover, the idea that cellular and systems consolidation have clearly defined end-points has been increasingly questioned in recent years with the resurgence of interest in 'reconsolidation' processes: the reactivation of established and presumably consolidated memories sometimes renders them newly vulnerable to certain interventions, some of which also impair consolidation (see Box 4). Nonetheless, reconsolidation, despite its name, is not simply a faithful repeat of the consolidation process, and notable differences are observed between the two phenomena [236, 302].

Systems consolidation

Introduction. Despite the vast body of evidence documenting the critical role of the hippocampus in the rapid encoding of memory, long-term information storage may not always depend on the structure. Via its projections to various cortical areas, the hippocampus is thought to facilitate the gradual off-line development of intracortical connections, perhaps through mechanisms similar to LTP and LTD. According to the 'standard model' of memory consolidation, this process, sometimes known as 'systems' consolidation [207], eventually confers self-sufficiency on the cortical memory trace. Several models emphasize the possibility that the hippocampus encodes 'indices' or 'pointers' that temporarily link activity in relevant neocortical areas until new intracortical connections are established [322–324]. Computational considerations also support a dual-systems view of memory formation and storage. Marr [80, 325] proposed that the hippocampus rapidly encodes ongoing events, before passing the information on to the neocortex for categorization and long-term storage. Subsequent models have emphasized the utility of having a hippocampal system for the rapid encoding of ongoing experience, and a cortical system that slowly integrates this information with existing knowledge structures [326, 327]; this arrangement might overcome the problem of "catastrophic interference" that plagues certain connectionist networks – unless two sets of patterns are presented in an interleaved fashion, training with the second set will often cause 'forgetting' of the first set [for a review, see ref. 328; but see also ref. 329].

Evidence for the standard model of memory consolidation.

1) *The role of the hippocampus*

Consistent with the idea that the hippocampus is a temporary storage device, damage to the temporal lobes or hippocampus in humans and animals often results in a preferential impairment of recently acquired memory, with sparing of remote memory acquired long before the intervention [330, 331]. This pattern of memory loss is known as temporally graded retrograde amnesia, or a 'Ribot' gradient – named after the author of the first detailed account of the phenomenon in humans [332]. The phenomenon has been observed in a wide range of behavioral tasks in rodents and rabbits, including contextual fear conditioning [333–335], social transmission of food preference [336–339], visual discrimination [340], trace eyeblink conditioning [341, 342], and some tests of spatial memory [343, 344; but see 'Remaining issues concerning theories of memory consolidation' below]. Consistent with these findings, the use of a range of pharmacological interventions, including AMPA receptor blockade, confirms the temporally limited role of the hippocampus in memory for inhibitory avoidance, and the growing importance of cortical regions with the passage of time [128, 345]. The evidence from intervention studies is complemented by functional imaging data in rodents indicating that, as predicted, the hippocampus is engaged during the recall of recently acquired contextual, spatial, or non-spatial memory, but is less active during the recall of remote information learned several weeks earlier [339, 346–349].

Evidence that an extended period of hippocampal activity is critical for the consolidation process is provided by studies in which the hippocampus is reversibly inactivated after training [128, 350]. In the study by Riedel et al. [350], rats received a week-long intrahippocampal infusion of an AMPA receptor antagonist starting 1 or 5 days after training in a watermaze reference memory task; when subsequently tested in the drug-free state, rats were unable to remember the previously learned location, but new spatial learning was unaffected. However, the possibility remains that inactivation simply disrupts hippocampal information storage, rather than the cortico-hippocampal interactions involved in the formation of a stable neocortical trace.

As an alternative to blocking AMPA-receptor-mediated transmission, some studies have investigated the

role of NMDA-receptor-dependent synaptic plasticity in systems consolidation. Shimizu et al. [351] created mice with an inducible, CA1-specific knockout of the NR1 subunit of the NMDA receptor. Reversible deletion of this subunit for a 1-week period after training in a watermaze reference memory task significantly impaired subsequent retention. However, chronic pharmacological blockade of NMDA receptors for a comparable period had no effect in a similar task [352; for discussion of this discrepancy, see refs. 146, 353, 354]. In fact, an enhancement of memory retention has been reported following chronic, post-training NMDA receptor blockade, perhaps owing to a reduction in the retroactive interference that might normally occur after learning as a result of NMDA receptor activation during ongoing experience [355].

2) *The role of the neocortex*

Our understanding of the cortical mechanisms involved in memory consolidation, and the storage and retrieval of remote memories, is still at a very early stage – partly because of the difficulty in selecting the right area of cortex to study. But important clues are beginning to emerge. Recent evidence suggests that mice with a heterozygous null mutation of alpha-CaMKII exhibit normal CA1 LTP, but potentiation in slices of temporal cortex rapidly decays back to baseline values [356]. Consistent with these findings, place memory in the watermaze is normal 3 days after training, but forgetting occurs far more rapidly than in wild-type controls, approaching chance levels after 10 days or more. In other words, impaired cortical function can result in a selective deficit in remote memory, with a complete sparing of recent memory – an inverse Ribot gradient – consistent with the idea that the hippocampus only supports memory for a limited period of time, until cortical mechanisms take over.

In fact, studies of metabolic activity and immediate early gene activation in mice have revealed that a network of cortical regions, including executive regions of the limbic neocortex (including anterior cingulate, infralimbic, and prelimbic areas) is engaged by the retrieval of remote, but not recent, spatial memory [331, 347, 348, 357, 358; see ref. 331 for a review]. Interestingly, a marker for synaptogenesis, GAP-43, was elevated in the anterior cingulate cortex a few weeks after spatial training or contextual fear conditioning [347]. Further clues regarding the cellular mechanisms of memory consolidation were provided by a laminar analysis of cortical activity. Comparison of Zif-268 activity following the retrieval of recent and remote memory revealed a shift in expression from deep to superficial layers of the parietal cortex with the passage of time [347]. As most intra-cortical projections arise from – and terminate within – the superficial layers, the finding is consistent with the development of intracortical connections that is postulated to occur as consolidation proceeds. Evidence that these brain areas are not only activated by the retrieval of remote memory, but are also necessary for the process, has also been reported; inactivation of the anterior cingulate cortex with lidocaine caused a severe impairment in remote memory for the baited arm of a five-arm radial maze, but had no effect on the retention of recent memory [347]. Conversely, hippocampal inactivation disrupted only recent memory. Similar results have recently been obtained for spatial reference memory in the watermaze except that hippocampal inactivation disrupted recent and remote memory [358].

At face value, the double dissociations between hippocampal and cortical roles reported in the above studies are puzzling. Most versions of consolidation theory hold that the hippocampus and neocortex act in concert during the initial encoding and storage of memory. But it is possible that the cortical regions identified in these studies are not sites of memory encoding and storage per se, but executive areas responsible for the integration of consolidated neocortical traces distributed across a number of brain areas – a function initially dependent on the hippocampus. It remains possible that continuing intracortical consolidation processes, operating over an even longer time scale, might, in turn, relieve these areas of their integrative role [see ref. 331 for discussion]. Alternatively, the reduction in hippocampal activity over time might reflect forgetting or the loss of 'episodic' detail [359]. Conversely, increased prefrontal activity during remote memory retrieval might simply indicate a greater dependence on effortful processes for the retrieval of a distant weak memory compared to a recent strong memory [360]. As Rudy et al. [360] point out, this hypothesis is consistent with data from a recent human imaging study in which activity in the anterior cingulate cortex (ACC) was negatively correlated with hippocampal activity during the retrieval of a weak visual association [361]. This suggests that the ACC may be preferentially engaged when memory trace strength is low. The potential confounding of memory strength with age in consolidation studies has not yet been addressed.

3) *Sleep and memory consolidation*

Systems memory consolidation is often portrayed as a gradual process of stabilization that, once started, simply requires the passage of sufficient time to reach completion. However, the formation of a lasting

memory is likely to be a far more dynamic process, with continuous remodeling of patterns of cortico-hippocampal synaptic weights [362], as newly acquired information is incorporated into existing memory frameworks. This process may depend on multiple episodes of reminding during wakefulness, and/or the replay of encoding-related activity during sleep – an idea with growing experimental support [363]. Building on earlier work [364], it was discovered that place cells that tended to fire together during exploration of an environment exhibited similarly correlated firing during subsequent slow-wave sleep [365]. This reactivation occurred preferentially during high-frequency network oscillations known as 'ripples' (see below).

Subsequent evidence pointed to the replay of temporal sequences of unit activity during sleep. For example, the temporal order of CA1 pyramidal cell firing during behavior is found to be preserved during sleep [366]. A similar preservation of temporal correlations during sleep has been observed in simultaneous recording from CA1 and posterior parietal cortex [367]. There is recent evidence that sequences of place cell firing occurring during awake behavior are replayed in temporally compressed bursts during slow-wave sleep [368, 369], and almost in real time during REM sleep [370]. Slow-wave sleep is characterized by the occurrence of bursts of hippocampal network activity: large-amplitude sharp waves originate in CA3 and lead to high-frequency (140–200 Hz) field oscillations, known as ripples, in the CA1 pyramidal cell layer [371, 372]. These ripples are coupled to the occurrence of lower-frequency (7–14 Hz) thalamocortical EEG events known as sleep spindles [373, 374]. The occurrence of sharp waves is also associated with cortical 'up state' transitions [375], and slow oscillations in the prefrontal cortex [376]. It has been suggested that the coupling of patterns of neocortical and hippocampal activity might play a role in the inter-structure transfer of information, or the formation of intra-cortical connections that may underlie the systems consolidation process [377–379]. Replay is not limited to sleep, however: a 'reverse replay' phenomenon has recently been observed following spatial experience in awake rats [380].

Remaining issues concerning theories of memory consolidation. Despite compelling evidence from multiple convergent lines of research, some findings are not easily accommodated by conventional theories of memory consolidation. Graded retrograde amnesia is frequently not observed in studies of rodent spatial memory, for example. This is particularly true in studies of retrograde amnesia for a platform location in the watermaze after large hippocampal lesions: in at least six such studies conducted to date, no evidence for a sparing of either recent or remote memory has been obtained [381–386] (Fig. 7A). Similar results have been obtained following reversible hippocampal inactivation with lidocaine prior to retention testing [358, 387]. Several possible explanations have been advanced to explain these anomalous findings; we consider each in turn.

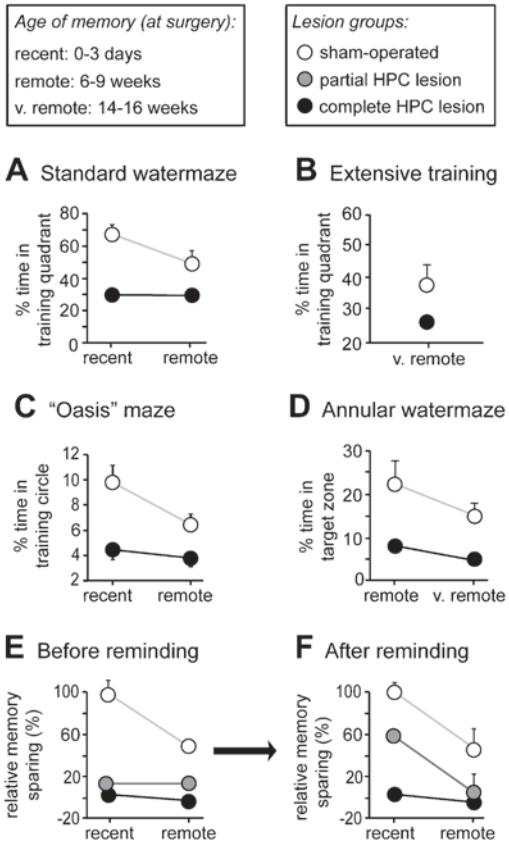

Figure 7. Systems consolidation. Large hippocampal lesions result in temporally ungraded retrograde amnesia in a range of spatial tasks. All panels indicate the degree of spatial bias towards the target location in a retention test, or probe trial, conducted in the absence of reward. (A) Rats were trained in a standard watermaze reference memory task (see Box 1), and given hippocampal lesions at different time points afterwards (see key). Neither recent nor remote memory was spared in lesioned rats, as indicated by performance in a probe trial conducted after recovery from surgery [385]. (B) Very extensive overtraining in a watermaze reference memory task, starting from a young age, still did not result in spared performance following hippocampal damage [386]. (C) Performance on a dry-land, water-reinforced analog of the watermaze – the 'Oasis maze' – was similar to that observed in the watermaze itself [385]. (D) Sparing of remote memory was still not observed after reducing the navigational demands of the watermaze task by limiting swimming to a narrow annulus [385]. (E, F) Consistent with A, both partial and complete hippocampal lesions resulted in temporally ungraded retrograde amnesia in a watermaze reference memory task (E); after a reminder treatment [408], some recovery of recent memory was evident in the partial-lesion group, but remote memory remained at chance (F) [384]. [Data adapted from refs 384–386 with permission from the authors.]

1) *The hippocampus might play a permanent role in the storage of certain forms of memory*

Spatial memory traces – or some component of such traces – might simply remain in the hippocampus indefinitely. The occasional observation of temporally ungraded retrograde amnesia has led to the proposal of an alternative to consolidation theory. According to the 'multiple trace' hypothesis [388, 389], memories are permanently mediated by hippocampo-cortical traces. Each reactivation of a memory is hypothesized to lead to the formation of additional memory traces. Temporally graded retrograde amnesia can thus be explained by the proliferation of traces over time. Assuming that hippocampal damage is incomplete, remote memories supported by large numbers of redundant traces will be more likely to survive than recent memories supported by very few traces. Despite this prediction, neither partial nor complete destruction of the rat hippocampus in rats reveals a Ribot gradient of retrograde amnesia on spatial memory tasks [384, 385].

However, a revised version of the multiple trace hypothesis [390, 391] attempts to explain why some memories never become independent of the hippocampus; contextually rich memories are proposed to remain dependent on the hippocampus indefinitely; those that acquire a context-free or semantic character become hippocampus-independent over time as the standard consolidation theory predicts. In support of the 'sematicization' view of memory consolidation [392, 393], it is sometimes observed that the remote autobiographical memories that survive in human temporal lobe amnesics are impoverished in detail and richness, and qualitatively different from those in neurologically intact subjects [for reviews, see refs. 390, 391, 394, 395], but it is also possible that these impoverished details are a result of the extratemporal lobe damage that is present in these patients. Similar suggestions have been made with regard to spatial memory in rodents [344, 390]. Importantly, other studies have failed to find qualitative or quantitative differences between healthy participants and amnesic patients with damage confined to the medial temporal lobe. For example, six patients with damage limited primarily to the hippocampal region were able to recollect successfully remote autobiographical memories [396]. The memories of the patients were indistinguishable from the memories of 25 controls with respect to the number of details recalled, the duration of the narratives, and the number of prompts needed to begin a narrative. In a related study [397], five patients with damage limited mainly to the medial temporal lobe not only produced detailed, well-formed remote autobiographical memories that resembled the recollections of the control group, they also produced recollections that were qualitatively normal by three different measures. First, autobiographical memories were classified using the remember/know method – i.e. whether recall included a feeling of being able to re-experience the original event ('remember'), or did not include this feeling ('know'). Both controls and patients labeled the majority of their remote autobiographical memories as 'remember,' and both groups had similar proportions of 'remember' and 'know' responses. Second, the rated vividness of autobiographical memories was similar for controls and patients. Third, both groups experienced the imagery in their recollections from a first-person perspective. These findings suggest that recollective ability and richness of context is qualitatively normal in patients with damage limited mainly to the medial temporal lobe [397].

Nevertheless, it is reasonable to suppose that context-free or 'gist' memories might develop after extensive experience in an environment, whereas memories formed after comparatively brief periods of training might remain contextually rich. (Although there is no reason to expect a universal relationship between duration of training and memory type – humans can form semantic memories very rapidly.) In support of this view, rats that are reared in a complex environment exhibit spared spatial memory within the same environment after large hippocampal lesions [398]. The authors argue that this experimental design is a more accurate model for the experiences of human amnesics who often show a relative sparing of spatial memory for neighborhoods in which they spent much of their youth [399, 400]. Consistent with the data of Winocur et al. [398], semantic-like memory resulting from extensive training on a flavor-place paired associate task is unaffected by temporary inactivation of the hippocampus with an AMPA receptor antagonist, despite the fact that the task has a spatial component that is critical for successful performance [171]. Nonetheless, place memory in the watermaze does not become hippocampus independent, even after a greatly extended period of training starting in the first few weeks of a rat's life. Rats were trained in a watermaze reference memory task from the 21st to the 90th day of life, and hippocampal or sham lesions were made 100 days after the end of training – but lesioned animals still performed at chance [386] (Fig. 7B). In fact, if one defines the time of 'learning' as the time when performance first reached above chance levels (the second training day), then the learning-surgery interval in this study was more than 5 months. Thus, in the watermaze, even a massively overtrained spatial memory that was formed many months prior to brain damage remains hippocampus dependent. The reasons for the continued involvement of the hippo-

campus remain uncertain; a non-mnemonic possibility is considered in the following section.

2) *The hippocampus has a role in navigation or spatial information processing, in addition to its role in spatial memory*

There is good evidence that the hippocampus plays a role in non-mnemonic aspects of spatial information processing. As an alternative to calculating position allocentrically via distal spatial cues within an environment, it is possible to navigate by dead reckoning or path integration – i.e. by using self-motion cues to calculate current position or to return to a previously visited location. There is evidence that rats are able to use path integration strategies, and that the hippocampus plays a key role [53, 401–405]. This form of navigation is thought to depend on the subcortical and prefrontal connections of the hippocampus because lesions of the fornix are found to impair the path integration abilities of rats [406]. Related to this, it has been suggested that the demands of watermaze probe trials, requiring the constant updating of positional information, and the continuous generation of new trajectories toward the former platform location, might place higher demands on a navigational system than dry-land spatial tasks [407]. Interestingly, evidence for a temporal gradient of retrograde amnesia was obtained in two such studies [343, 344], but the use of reacquisition as an index of retention complicates the interpretation of these findings. Clark and colleagues [385] recently trained animals in a dry-land water-reinforced analogue of the watermaze task, in an explicit attempt to address this issue. However, rats with large hippocampal lesions failed to show any sparing of place memory formed up to 3 months prior to surgery (Fig. 7C). In fact, a recent study of spatial memory in a cross-maze reported no evidence for sparing of place information, even when memories were acquired more than 9 months before hippocampal lesioning [412].

An alternative strategy is to reduce the navigational demands of the watermaze. Building on earlier tasks, Hollup et al. [100] developed an annular version of the watermaze apparatus in which a rat swims around a circular corridor within the pool, and learns to find a hidden escape platform. Memory can be assessed in probe trials with the platform absent; successful memory is indicated by slower swimming in the goal area of the annulus. Despite the fact that this task merely requires recognition of the correct place upon arrival, rather than navigation towards an invisible goal, rats with hippocampal lesions made before training were unable to learn the task, suggesting that the role of the hippocampus is not limited to spatial navigation. Nonetheless, the navigational demands of the open-field watermaze task might still explain the dependence of remote spatial memory on the hippocampus. In order to test this possibility, Clark et al. [385] made hippocampal lesions either 9 or 14 weeks after training in an annular watermaze task. But, as in the open-field version, rats with hippocampal lesions performed at chance regardless of the age of the memory (Fig. 7D). Thus the requirement to generate trajectories toward a hidden goal is not sufficient to explain the temporally ungraded retrograde amnesia typically observed in studies of spatial memory. It should be noted, however, that although the annular maze removes the requirement for navigation, it remains possible that rats nonetheless approach the task in the same manner as the standard watermaze.

3) *The hippocampus might play a role in memory retrieval, regardless of the site of long-term memory storage*

It is possible that hippocampal lesions disrupt the retrieval rather than (or in addition to) the storage of remote spatial memory. Although the possibility of retrieval failure is difficult to eliminate in any study of memory, the use of reminding techniques can sometimes be useful to assess the possibility that an intact memory initially fails to be expressed. Nonetheless, the use of a reminding procedure that results in a limited recovery of recent place memory following partial hippocampal damage [408] did not reveal any evidence for sparing of remote memory in a watermaze reference memory task [384] (see Fig. 7E, F).

Toward a resolution of the consolidation debate? The neural substrates of very long term place memory remain uncertain, and we cannot rule out the possibility that the hippocampus plays a lasting role in the storage, retrieval, or expression of at least some component of the spatial memory trace. If the hippocampus is involved in memory retrieval, or plays a non-mnemonic role in spatial behavior, large lesions of the entire hippocampal formation are likely be relatively uninformative in analyzing the processes that underlie memory consolidation. However, it is possible that selective disruption of relevant components of the hippocampal circuitry might yield insights into the time-dependent reorganization of memory, without resulting in a catastrophic disruption of hippocampal functioning. One such intervention has recently been developed by Remondes and Schuman [409], who made lesions targeting the direct layer III entorhinal input to CA1. This manipulation impaired memory retention if made soon after training, but had no effect if delayed for 3 weeks after learning. The same lesion had no effect on new learning. These

findings suggest that the temporoammonic input to CA1 is involved in the intermediate- to long-term stabilization of memory, but that the intrinsic hippocampal circuitry is sufficient to support normal learning and the retrieval of consolidated memory. Preliminary evidence suggests that another selective hippocampal intervention – the transection of longitudinal fibers in CA3 [68] – preferentially impairs recent memory [69], although it is not yet known whether the interruption of long-range CA3-CA3 or CA3-CA1 projections, or both, is critical for this phenomenon.

A recent study of hippocampal Arc/Arg3.1 mRNA expression after the retrieval of recent versus remote memory is consistent with both of the above sets of findings [349]. The retrieval of recent spatial memory in the watermaze resulted in increased activity in the dorsal CA3, and to a lesser extent in dorsal CA1. However, the most pronounced activation of CA1 occurred in a separate region of the ventral hippocampus. These findings are consistent with a report that metabolic activity in CA1 – assessed using (^{14}C)-2-deoxyglucose autoradiography – occurs over a wider portion of the septo-temporal axis than CA3 activation during early acquisition of a spatial task [410]. After remote memory retrieval (1 month after training), Gusev et al. [349] reported an overall reduction in hippocampal activity, consistent with previous imaging studies of remote place memory. Persistent activity was still observed in dorsal CA3, however, but little activity remained in dorsal or ventral CA1. As the authors note, the time-limited activation of CA1 is consistent with the findings of Remondes and Schuman [409] concerning the role of the direct cortical input to this area (although the data raise interesting questions concerning the relevant efferent pathways from CA3). Moreover, the existence of prominent clusters of activity in dorsal CA3 and ventral CA1 after recent memory retrieval suggests a potential role for longitudinal CA3-CA1 projections in the integration of information along the septotemporal axis of the hippocampus – consistent with the disruptive effect of transecting longitudinal projections on recent spatial memory [68, 69]. The time-dependent reorganization of hippocampal activity revealed by these experiments might reflect the operation of early intrahippocampal consolidation processes, or a reorganization of cortico-hippocampal traces seen from a hippocampal perspective. Although our understanding of the mechanistic basis of memory consolidation remains limited, we are optimistic that a focus on specific components of the hippocampal circuitry – in conjunction with the use of reversible inactivation techniques [350]) – will remedy this situation, and ultimately resolve the 'paradox' of long-term spatial memory.

Finally, systems-level memory consolidation might not be the slow incremental progression towards neocortical trace stability that is often supposed; there is evidence that, under some circumstances, memory with a spatial component can become independent of the hippocampus very rapidly [205, 411]. We anticipate that future work will focus to an increasing extent on the interplay between the existing contents of long-term memory and the encoding and consolidation of ongoing experience. Few animal studies have attempted to probe these interactions between newly encoded and permanently stored traces that may well be critical for the admission of new information into long-term memory.

Conclusion

As we acknowledged in the 'Introduction', there is abundant evidence that the hippocampus – even in rodents – does not limit its operations to place memory. But the use of spatial memory tasks still provides a convenient way to engage the structure in studies probing the neural mechanisms of learning and memory. Indeed, much of what we know about how the hippocampus operates stems from such tasks. In this review, we have attempted to draw together some emerging insights into the substrates of encoding, consolidation, and retrieval of spatial memory. The techniques employed in this work range from increasingly specific molecular neurobiological interventions, to the electrophysiological recording of neuronal activity, computational modeling, and ultimately the analysis of behavior. The effort to integrate our understanding at these multiple levels of organization – molecules, cells, circuits, and systems – is only just beginning; but the analysis of memory for place has provided a useful starting point.

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