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Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory

R. G. M. Morris[1*], E. I. Moser[2], G. Riedel[3], S. J. Martin[1], J. Sandin[4], M. Day[1,5] and C. O'Carroll[1]

[1]*Division and Centre for Neuroscience, The University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, UK*
[2]*Centre for the Biology of Memory, NTNU, 7489 Trondheim, Norway*
[3]*Department of Biomedical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK*
[4]*Department of Neuroscience, Section of Behavioural Neuroscience, Karolinska Institute, S-171 77 Stockholm, Sweden*
[5]*GSK Neurology Centre of Excellence for Drug Discovery, New Frontiers Science Park (North), Harlow, Essex CM19 5AW, UK*

The hypothesis that synaptic plasticity is a critical component of the neural mechanisms underlying learning and memory is now widely accepted. In this article, we begin by outlining four criteria for evaluating the 'synaptic plasticity and memory (SPM)' hypothesis. We then attempt to lay the foundations for a specific neurobiological theory of hippocampal (HPC) function in which activity-dependent synaptic plasticity, such as long-term potentiation (LTP), plays a key part in the forms of memory mediated by this brain structure. HPC memory can, like other forms of memory, be divided into four processes: encoding, storage, consolidation and retrieval. We argue that synaptic plasticity is critical for the encoding and intermediate storage of memory traces that are automatically recorded in the hippocampus. These traces decay, but are sometimes retained by a process of cellular consolidation. However, we also argue that HPC synaptic plasticity is not involved in memory retrieval, and is unlikely to be involved in systems-level consolidation that depends on HPC–neocortical interactions, although neocortical synaptic plasticity does play a part. The information that has emerged from the worldwide focus on the mechanisms of induction and expression of plasticity at individual synapses has been very valuable in functional studies. Progress towards a comprehensive understanding of memory processing will also depend on the analysis of these synaptic changes within the context of a wider range of systems-level and cellular mechanisms of neuronal transmission and plasticity.

Keywords: synaptic plasticity; event memory; early long-term potentiation; late long-term potentiation; synaptic tagging; memory consolidation

1. THE SYNAPTIC PLASTICITY AND MEMORY HYPOTHESIS

During learning, spatio-temporal patterns of neural activity that represent events cause long-lasting changes in the strength of synaptic connections within the brain. Later reactivation of these altered connections causes patterns of cell firing that collectively constitute the experience of memory for these events or the expression of learned changes in behaviour triggered by them. These statements are the essence of the SPM hypothesis. The discovery of LTP, whereby brief high-frequency stimulation can induce long-lasting increases in synaptic efficacy (Bliss & Lømo 1973), provided the first experimental analogue of these postulated learning-induced changes in synaptic connectivity in the mammalian brain. Thirty years later, evidence consistent with the hypothesis has accumulated to the point where few doubt the general principle to be correct.

In a series of review articles, we have outlined criteria by which this hypothesis might be judged, the experimental strategies that have been used to address it, and the evidence that supports or conflicts with it (Martin *et al.* 2000; Grimwood *et al.* 2001; Martin & Morris 2002). A key aspect of our approach is the need to think about both synaptic plasticity on the one hand and memory on the other. Recognition that there are different forms of each makes the claim that 'LTP equals memory' too general to be useful, even if a million dollars may be on offer (Stevens 1998). It is a hypothesis that has to be specified more precisely—what forms of synaptic plasticity, what brain structures and circuits, and what forms of learning and memory are being considered? Partly because of this, numerous variants of the SPM hypothesis have been advanced over the years pertaining to the study of memory in different species, networks and brain regions (e.g. Marr 1971; Kandel & Schwartz 1982; Lynch & Baudry 1984; Teyler & Discenna 1984; McNaughton & Morris 1987; Bliss & Collingridge 1993; Izquierdo & Medina 1995;

* Author for correspondence (r.g.m.morris@ed.ac.uk).

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

Maren & Baudry 1995; Jeffery 1997; Morris & Frey 1997). Notwithstanding important differences, the underlying core hypothesis is as follows.

> Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed.

In our reviews, we argued that this hypothesis should be tested in relation to four criteria: detectability, mimicry, anterograde alteration and retrograde alteration. The first and most intuitive of these criteria, detectability, states that the formation of memory must be associated with detectable changes in synaptic efficacy in relevant circuits of the nervous system. The main difficulty is deciding where to look. The second criterion, mimicry, is a critical test of whether changes in synaptic strength are sufficient for memory formation—sufficient, that is, within the context of a normally functioning nervous system. Our third and fourth criteria, anterograde and retrograde alteration, relate to whether synaptic plasticity is necessary for memory formation and expression respectively. We argued that, across a range of different types of learning and memory, including the experience-dependent reorganization of neural circuits, three of these criteria have largely been met. Work from our laboratories and those of many others provides relevant supporting evidence as summarized in our reviews. This evidence includes experiments documenting physiological, biochemical and structural changes during learning that are very likely to have been caused by activity-dependent synaptic plasticity (detectability criterion (e.g. Rioult-Pedotti *et al.* 2000)). Such experiments include physiological, pharmacological and gene-targeting interventions that alter or occlude the capacity to induce or express synaptic plasticity and simultaneously cause changes in learning (anterograde alteration criterion (e.g. Morris *et al.* 1986; Silva *et al.* 1992; Moser *et al.* 1998). We recognize that the dependent consequences of a single independent treatment are not necessarily causally related, a logical issue we have discussed at length, but the weight of evidence is very suggestive. Meeting the criteria also includes experiments in which memory retrieval is affected after learning by similar experimental manipulations (retrograde alteration criterion (e.g. Brun *et al.* 2001)).

The outstanding problem is mimicry. This is the sufficiency or 'engineering' criterion. The supposition is that, if it were possible artificially to engineer a particular spatial distribution of synaptic weight changes across a network of neurons, an experimental subject would genuinely behave as if it remembered something that had not in fact happened. Unfortunately, however logically desirable the sufficiency criterion may be, it is unclear that such an experiment would be feasible in many mammalian brain structures owing to the distributed nature of memory storage. Nevertheless, simpler mammalian brain structures, or the nervous systems of lower vertebrates or invertebrates, may offer a more promising substrate for a meaningful test of this criterion (Pittenger & Kandel 2003).

2. ELEMENTS OF A NEUROBIOLOGICAL THEORY OF THE HIPPOCAMPUS AND THE ROLE OF NMDA RECEPTOR-DEPENDENT SYNAPTIC PLASTICITY

A difficulty with this way of assessing the generic SPM hypothesis is that it is somewhat formal and abstract. Although attractive logically, it lacks specifics. It needs to be complemented by the examination of specific neurobiological theories of particular brain regions in which activity-dependent synaptic-plasticity serves an identifiable role. Accordingly, in this paper, we pursue a different approach by outlining some elements of what might eventually become a neurobiological theory of HPC function. We stress that our proposals fall short of a comprehensive theory at this stage, but they represent a synthesis of the published ideas of others and our own thinking about the specific role of activity-dependent synaptic plasticity in HPC memory function.

The mammalian HPC formation is a set of brain structures that, following neuropsychological research on patients with selective brain damage, functional imaging studies, and work using experimental lesions in animals, is widely held to serve an important function in certain types of memory. Its specific contribution to memory remains a matter of dispute. Rival theories include proposals for a role in spatial and cognitive mapping (O'Keefe & Nadel 1978; Gaffan 2001), declarative and relational memory (Squire 1992; Eichenbaum & Cohen 2001), episodic memory (Tulving 1983; Mishkin *et al.* 1997; Morris & Frey 1997; Vargha-Khadem *et al.* 1997; Aggleton & Brown 1999) and the rapid acquisition of configural or conjunctive associations (Sutherland & Rudy 1989; O'Reilly & Rudy 2001). Neural network modelling studies indicate that its intrinsic anatomy and synaptic physiology could mediate the rapid encoding and distributed storage of many arbitrary associations (Marr 1971; McNaughton & Morris 1987; McClelland *et al.* 1995; Rolls & Treves 1998). In all mammals—man, monkey and mouse—the HPC formation seems to be a particular kind of associative memory network. It does not operate in isolation; inputs from midbrain and other forebrain nuclei modulate its activity, and several excitatory inputs and outputs reflect important functional interactions with the neocortex (Amaral & Witter 1989).

A focus of our thinking has been that HPC memory includes the ability to remember events. Events happen in particular places at particular times, and their later recall generally includes the memory of where and when an event happened (Gaffan 1994). Thus, event encoding is necessarily associative in character. Many events cannot be anticipated, occur only once, and may contain distinct features that, in sequence, form short episodes. It is vital that traces representing information about such episodes are encoded and stored in real time—as they happen—a process that we have previously described as the 'automatic recording of attended experience' (Morris & Frey 1997; Morris 2001). Not all events are remembered for any length of time; indeed to do so is not only unnecessary but might also saturate the storage capacity of the brain. In addition, although paradoxical to some, it is far from clear that the hippocampus need receive via its extrinsic afferents the detailed sensory/perceptual information

pertaining to individual objects or events. Rather, all it needs to remember events and the sequence in which they happen are cartoons or 'indices' of the locations in the neocortex where this detail is processed and at least temporarily encoded. Our first proposition is as follows.

Proposition 2.1. *Some animals have episodic-like memory and the HPC is one group of brain structures mediating it.*

A prominent candidate for the neural substrate of event memory is HPC NMDA receptor-dependent synaptic plasticity. Such plasticity, assessed by the experimental phenomenon of LTP, exhibits many properties that are suitable for a role in memory formation (Bliss & Collingridge 1993; Martin *et al.* 2000), and a growing body of evidence offers support for this view (Riedel *et al.* 2003). Accordingly, our second proposition is as follows.

Proposition 2.2. *A form of activity-dependent, NMDA receptor-dependent synaptic plasticity in the hippocampus is the primary neural mechanism responsible for inducing the temporary storage of HPC 'indices' of event memory.*

If most automatically encoded event memories are temporary, there must be psychological processes and neural mechanisms for selecting the subset of traces that are to be rendered longer lasting or even permanent. These include the emotional significance of the event to be remembered itself (or of other events happening close together in time or space), and the relevance of the event to the existing knowledge structures of the organism witnessing it (Bartlett 1932; Bransford 1979). Underlying these psychological processes are two separate neuronal mechanisms of memory consolidation: cellular consolidation mechanisms that include the synthesis and synaptic capture of plasticity-proteins that stabilize memory traces within individual cells and at the level of the individual synapse; and systems-level consolidation mechanisms that reflect a dynamic interaction between populations of neurons within HPC and neocortex (Dudai & Morris 2001). These forms of consolidation are distinct but inter-dependent. This inter-dependence derives from the cellular consolidation mechanism enabling memory indices to last long enough in the HPC for the slower systems-level consolidation process to work. Reflecting new ideas about cellular consolidation, our third proposition is as follows.

Proposition 2.3. *An essential feature of cellular consolidation processes is the interaction between local 'synaptic tags' (set by glutamatergic activation), and diffusely targeted 'plasticity proteins' (that can be triggered by heterosynaptic activation of neuromodulatory inputs) (Frey & Morris 1997, 1998a; Dudai & Morris 2001).*

In contrast to cellular consolidation, systems-level consolidation refers to a process through which initially labile memory traces in the neocortex become gradually stronger through the strengthening of connections between cortical modules. Some theories hold that this requires a dynamic interaction between the HPC and neocortex that eventually enables the cortex to act as an associative memory, linking arbitrary items of information (Squire 1992). Other theories assert that long-lasting HPC traces may exist for certain kinds of memory (e.g. Nadel & Moscovitch 1997).

The defining functional characteristics of associative networks such as the HPC are believed by several theorists to include distributed representations, interleaved storage across multiple synapses and associative retrieval. These enable stored patterns of activity to be 'completed' from partial fragments of the original input (Marr 1971; McNaughton & Morris 1987; Paulsen & Moser 1998; Tonegawa *et al.* 2003). Several factors determine the operating characteristics and storage capacity of such networks. One, connectivity density (i.e. the number of connections per cell), provides an anatomical basis for understanding an important feature of the relationship between HPC and neocortex (McNaughton *et al.* 2003). Specifically, the average connectivity within the cortex is too low to support the encoding of arbitrary associations (Rolls & Treves 1998). The cortical mantle contains in the order of 10^{10} neurons, but each cortical principal neuron receives only about 10^4 connections. Thus, the average connection probability in the cortex is only $1 : 10^6$. To overcome this apparent biological limitation, mammals seem to have evolved an arrangement whereby distributed associative memory between items represented in different sensory modalities can be accomplished through indirect associations mediated by a hierarchical organization (McNaughton *et al.* 2003). In such a scheme, neocortical modules at the base of the hierarchy are reciprocally connected via modifiable synapses with one or more HPC modules at the apex. The HPC modules include CA3 as well as the dentate hilus, both characterized by high internal connectivity as well as modifiable synapses. In CA3, each pyramidal cell is contacted by *ca.* 4% of the pyramidal cells of the same subfield (Amaral 1990), implying that most CA3 pyramidal cells are connected via 2–3 synaptic steps (Rolls & Treves 1998). This high degree of internal recurrent connectivity is probably sufficient to allow autoassociation, or association among individual elements of a patterned input (Marr 1971). Activity patterns reflecting sensory detail in neocortical modules may generate a unique identifying pattern, a so-called 'index', in such a network (Teyler & DiScenna 1987). This higher-level index is no longer 'sensory' in any strict sense, but is stored associatively with other indices and the output fed back to lower level neocortical modules via modifiable synapses. Activation of a cortical pattern (e.g. a specific flavour of food) could then result in activation of its index in the hippocampus. In turn, this enables retrieval of associated indices and thence the complementary pattern in the other cortical modules (e.g. where the food is found). Indirect associations enable memory retrieval between cortical modules that are too sparsely connected to do this directly.

This principle of indirect association in memory places high demands on the synaptic storage capacity of the HPC that is otherwise in danger of becoming saturated. Once saturated, learning can no longer proceed effectively (McNaughton & Barnes 1986; Moser *et al.* 1998). One of several ways to limit this burden could, as already noted, be via the rapid decay of a high proportion of the traces that are automatically encoded online. Heterosynaptic depression may also serve a normalizing function and increase effective storage capacity (Willshaw & Dayan 1990). Another way, also an element of the ideas being described, would be to ensure that what is stored in the

HPC is merely an index of the neocortical sites of trace storage where the full sensory/perceptual details are encoded. A fourth way would be to enable HPC associations that are repeatedly recalled, often representing environmental regularities, to trigger the gradual development of low-level intermodular connections within the neocortex, a process that is likely to require cortical, but not HPC, synaptic plasticity. These connections would enable cortical retrieval in the absence of activity in the hippocampus. This is the process of systems-level memory consolidation. Identified originally through experiments on retrograde amnesia revealing that damage to the HPC and related structures can impair new memory encoding while leaving old memories relatively intact (Squire & Zola-Morgan 1991; Kapur 1999), it is unlikely that insensitivity to brain damage is the adaptive pressure that led to its evolution. Our theoretical framework implies that, in part, its function is to avoid the distracting 'recovery to consciousness' of irrelevant associations that could otherwise interfere with ongoing mental activities (Moscovitch 1995). To work, it is vital that the inter-modular connections that develop are appropriate to the associations represented. This requires the gradual interleaving of appropriate connections (McClelland *et al.* 1995), perhaps during sleep (McNaughton *et al.* 2003). Interestingly, the rate of consolidation may not be strictly time-dependent. The process may be 'cladistic', with the rate of consolidation affected by the frequency with which HPC indices are reactivated. Thus, a further set of propositions to investigate is as follows.

Proposition 2.4. *Systems-level consolidation requires both HPC and neocortical neural activity, and may therefore not be strictly time-dependent.*

Proposition 2.5. *Systems-level consolidation does not require HPC plasticity, but does engage neocortical plasticity.*

3. EXPERIMENTAL OBSERVATIONS

(a) *Propositions 2.1 and 2.2*

There has been considerable recent interest in the idea that the HPC is essential for episodic rather than all forms of declarative memory in humans (Vargha-Khadem *et al.* 1997, 2001; Duzel *et al.* 2001; Maguire *et al.* 2001). An immediate difficulty for neurobiological studies is that episodic memory is defined in a way that renders it difficult to study in animals, in particular, Tulving's (1983) insistence on concomitant 'autonoetic consciousness' (the sense of self). Notwithstanding this difficulty, there have been claims that vertebrates may possess an episodic-like memory system analogous to subcomponents of true human episodic memory. One-trial spatial working-memory tasks are of this character (Steele & Morris 1999; Aggleton & Pearce 2001; Brown & Aggleton 2001), but the argument is not watertight as these might be, and sometimes are, solved using familiarity (Griffiths *et al.* 1999; Brown & Aggleton 2001). A valuable breakthrough has been Clayton & Dickinson's (1998) food-caching paradigm with scrub-jays. They observed that jays can recall 'what, where and when' in appropriately securing, during cache retrieval, either a favoured foodstuff (mealworms) or, after several days, one that lasts better over time (peanuts).

Inspired by this experiment, Day & Morris (2003) have developed a one-trial paired-associate task (figure 1) in which rats recall (rather than merely recognize) in which of two locations a particular flavour of rat food is to be found within a large 1.6 m × 1.6 m event arena. In each of two sample trials on each day, a few minutes apart, rats exit a start box to find a single open sand well where they can dig for a flavoured food. On the daily choice trial, 5 to 20 min later, the rat is given one of the two flavours to eat in the start box (its recall cue) and, 30 s later, exits to choose between the two sand wells now available. A win–stay rule applies whereby going to the location recalled by the flavour cue is usually rewarded by more of that same flavour (non-rewarded probes are also run). Up to 30 different locations and flavours are paired in novel combinations at the rate of two pairs per day. Video clips showing a rat performing two successive sample trials (where it encodes flavour–location associations) followed by a choice trial are available at: http://neuroweb-2.cfn.ed.ac.uk/video/. This what–where paradigm, with one-trial encoding and recall as the expression of memory, constitutes evidence that rats are capable of episodic-like memory as proposed in proposition 2.1, and in a species more amenable to neurobiological study than jays. In keeping with proposition 2.2 above, we have also established that the encoding of one-trial memory of such paired-associates lasts more than 60 min before recall performance drops to chance. Encoding is sensitive to the acute intrahippocampal infusion of an NMDA receptor antagonist (D-AP5) without any effect on retrieval, whereas encoding and retrieval are sensitive to the AMPA receptor antagonist CNQX (figure 2).

These findings complement earlier work using the repeated one-trial learning paradigm in the water maze called DMP (Steele & Morris 1999). However, whereas DMP examines only spatial memory, this new training procedure looks at what–where associations and reveals that one-trial learning of such associations is possible and that they decay quite quickly (within a day). The training protocol does not (yet) incorporate the temporal 'when' component, as in Clayton & Dickinson (1998). However, from a neuropharmacological perspective, having even a what–where association is sufficient to point to a partial dissociation between the role of NMDA and AMPA receptors in the hippocampus with respect to memory encoding and memory retrieval respectively. A weakness of the experiment—as it stands—is that the deficit in choice behaviour observed when CNQX is infused before recall could be a strictly spatial deficit, rather than a deficit in the ability to recall a place given the cue of an appropriate flavour (the 'what–where' association). This ambiguity has been addressed in new work using overtrained flavour–place associations, but this weakness does not affect the interpretation of the AP5 experiments. Blocking HPC NMDA receptors *after* the daily sample trials but *before* a choice trial had no effect on choice accuracy relative to aCSF infusions. It follows that NMDA receptors are not critical for the recall of spatial information or place–flavour associations. In turn, this implies that the deficit in choice trials seen when AP5 is infused *before* sample trials also cannot be due to impaired spatial recall. Thus, the memory deficit in choice trials following pre-sample AP5 infusions must result from a failure of

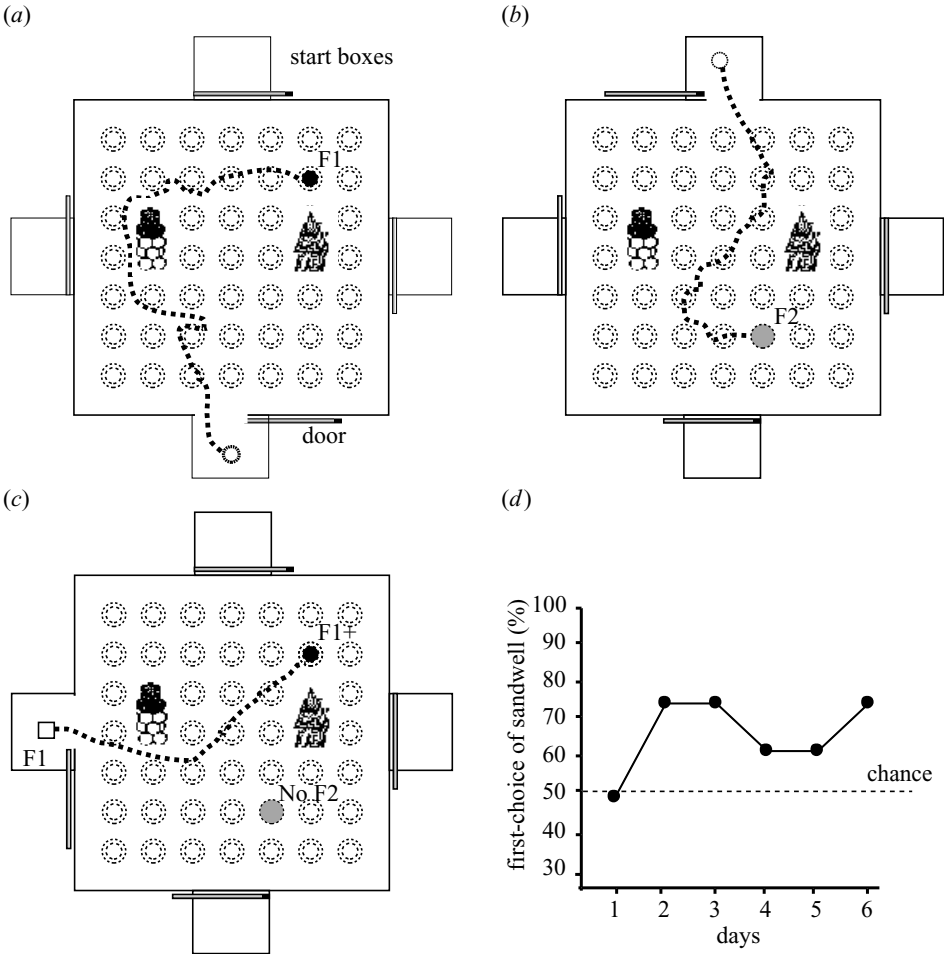

Figure 1. The event arena. The 1.6 m^2 arena made of Perspex consisted of 49 sand wells (open circles), the two intramaze landmarks, and the four start boxes. (*a*) On sample trial one, the door to a start box is drawn back and the rat runs out into the arena (dotted line) where it displays occasional lateral head-movements to find food (F1) at the single open well. (*b*) Sample trial two to a different food (F2) at a different location. Double-sample presentation rats had sample trials one and two repeated at this point. (*c*) The cued-recall choice trial begins with presentation of either of the two sample trial foods (food F1 is shown) followed by the rat being rewarded selectively for digging at the sand well containing this same food. (*d*) Proportion of choice trials in which the first chosen sand well had been cued in the start box. Single sample presentation rats ($n = 8$) were above chance over days 2–6 of training.

encoding and storage. As the representation of the environment has already been well learned at the time of the drug infusions, this must be a deficit in associating new information about flavours with information retrieved from the neocortex about locations within the familiar testing environment.

What, then, is the function of the hippocampus in the earlier stages of spatial memory and how might the spatial and non-spatial features of an event be put together? An important milestone in the understanding of spatial cognition was the discovery that most pyramidal cells in the hippocampus exhibit location-specific activity and that the activity of such place cells is influenced by the training history of the animal (O'Keefe & Dostrovsky 1971). The predominantly spatial nature of HPC neuronal activity led to the proposal that place cells form a distributed map-like representation of the spatial environment that an animal uses for efficient navigation (O'Keefe & Nadel 1978). When a rat is exposed to a new environment, pyramidal cells develop distinct firing fields within few minutes (Hill 1978; Wilson & McNaughton 1993). The place fields then remain stable for weeks or more if the environment is constant (Thompson & Best 1990; Lever *et al.* 2002), as predicted if these cells contribute to a particular spatial memory.

It is commonly believed that the development of HPC firing patterns, like HPC memory, might depend on LTP at HPC excitatory synapses. Studies have primarily investigated the contribution of LTP to spatial firing in HPC pyramidal cells. Surprisingly, interventions that abolish HPC LTP have only weak effects on the development of place fields. For example, blockade of NMDA receptors does not prevent the formation of new place fields in rats that explore a novel environment. Place fields recorded in CA1 in mice with mutations of NMDA receptors either in CA3 or CA1 are somewhat less distinct than in control mice under certain conditions, but the fields remain stable across repeated tests on the same day (McHugh *et al.* 1996; Nakazawa *et al.* 2002). Place fields also develop normally in rats treated systemically with an NMDA receptor antagonist at a dose that prevents new LTP in the hippocampus (Kentros *et al.* 1998). Despite blockade of the NMDA receptor, place fields were maintained between consecutive test sessions in the same environment for at

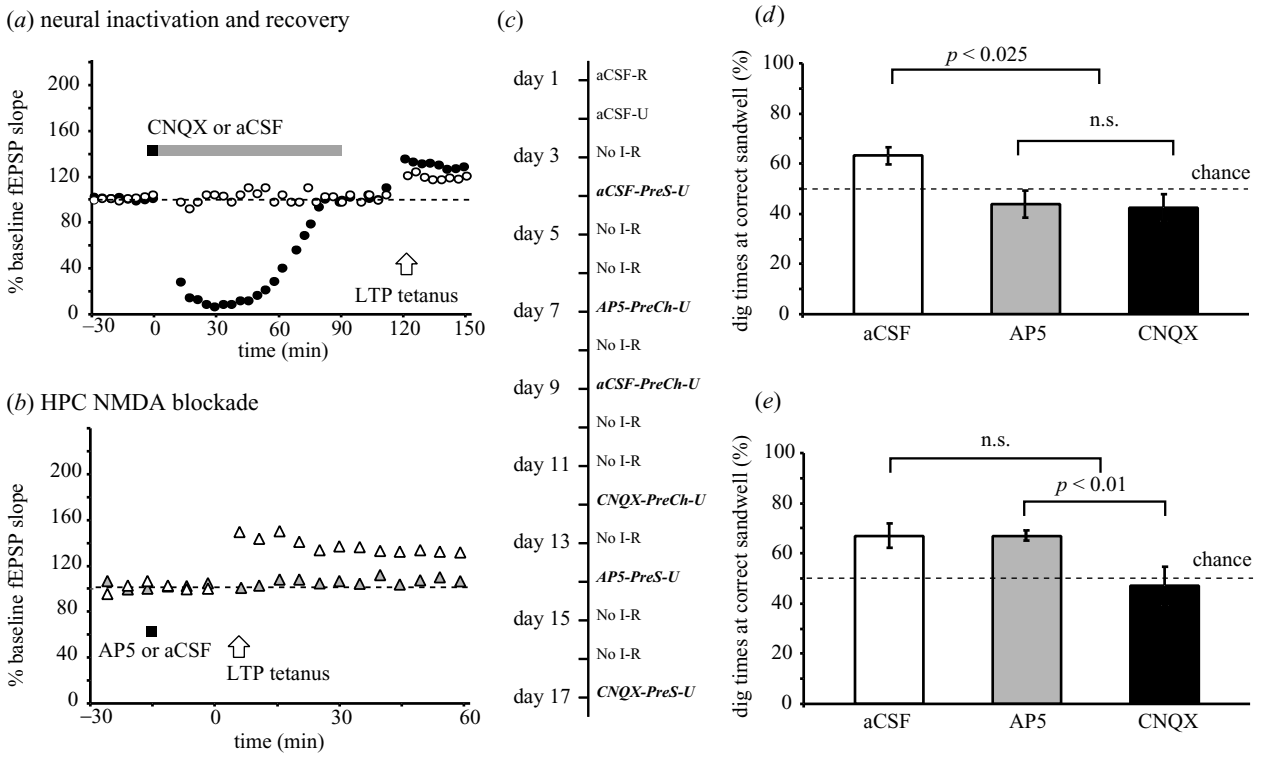

Figure 2. Role of HPC NMDA and AMPA receptors in encoding and retrieval of memory. (*a*) CNQX and electrophysiology. Maximal neural inactivation in the hippocampus occurs within 10–15 min of CNQX infusion and lasts for *ca*. 60 min. Open circles, aCSF; closed circles, CNQX. (*b*) AP5 and electrophysiology. AP5 infusions do not affect fast synaptic transmission but block LTP induction 15 min post-infusion. Open triangles, aCSF; closed triangles, AP5. (*c*) Representative sequence of the treatments given to an individual rat across 17 days. Different sequences were used to achieve counterbalancing of treatment order. AP5, CNQX, aCSF: bilaterally infused with respective treatment; R,U: choice trial rewarded or unrewarded (dig time data only available for unrewarded trials); Pre-S and PreCh: infusions before the sample or choice trials. Dig time data secured from days assigned in bold italic. (*d*,*e*) Drug-infusions before sample trials (*d*) and before choice trials (*e*). Separate analyses of days when the drugs (aCSF, AP5 and CNQX) were infused before sample trials revealed a significant drug effect. There was no difference between days with AP5 and CNQX treatment, but both better and above-chance performance on aCSF days than drug days. Analyses of days when the drugs were infused before choice trials revealed no difference between days with aCSF and AP5 treatment, but better and above-chance performance on these days compared with those with CNQX infusions.

least 1.5 h. Similar results were obtained when LTP was blocked by interference with Ca^{2+}/calmodulin-dependent protein kinase II (Rotenberg *et al.* 1996) or protein kinase A (Rotenberg *et al.* 2000). However, these interventions did decrease the long-term stability of the place fields, as measured 24 h after the initial exposure to the environment. Together, these studies suggest that NMDA receptor activation may not be necessary for the development or initial maintenance of place-related activity in HPC neurons, although it may contribute to the fine-tuning of place fields and aspects of the long-term stabilization of spatial representations. The latter function could involve the neocortex as well as the hippocampus.

The development of place fields during NMDA receptor blockade or other forms of disruption of LTP is consistent with several lines of work suggesting that spatial information can be generated and stored upstream of the hippocampus. First, location-specific firing is already expressed in the superficial layers of the entorhinal cortex (Quirk *et al.* 1992; Frank *et al.* 2000). The signal : noise ratio of these spatial signals is lower than in the hippocampus, but the fact that most principal cells in entorhinal cortex exhibit view-independent spatial modulation suggests that, by this stage, the fundamental computation may already have been made. It is possible, though, that spatial firing in superficial entorhinal neurons depends on spatial input from cells in deep layers, which in turn may rely on associative computations in afferent HPC structures. However, several studies suggest that place fields develop without the intrahippocampal trisynaptic circuitry. Pyramidal cells in CA1 exhibit spatial firing both after selective lesions of the dentate gyrus (McNaughton *et al.* 1989) and after disconnection of CA1 from CA3 (Brun *et al.* 2002; figure 3). In CA3-lesioned animals, CA1 pyramidal neurons receive cortical input only by the direct connections from the entorhinal cortex. The presence of place fields in these preparations suggests that direct entorhinal–HPC circuitry has significant capacity for transforming weak location-modulated signals from superficial layers of the entorhinal cortex into accurate spatial firing in CA1. Several simple filter mechanisms could accomplish such a transformation. For example, firing rates of perforant path fibres to CA1 could be thresholded by feed-forward inhibition, such that only the highest afferent firing rates, i.e. those in the centre of the entorhinal place field, are able to drive postsynaptic neurons in the hippocampus. Alternatively, single EPSPs in distal pyramidal-cell dendrites of CA1 may often not be

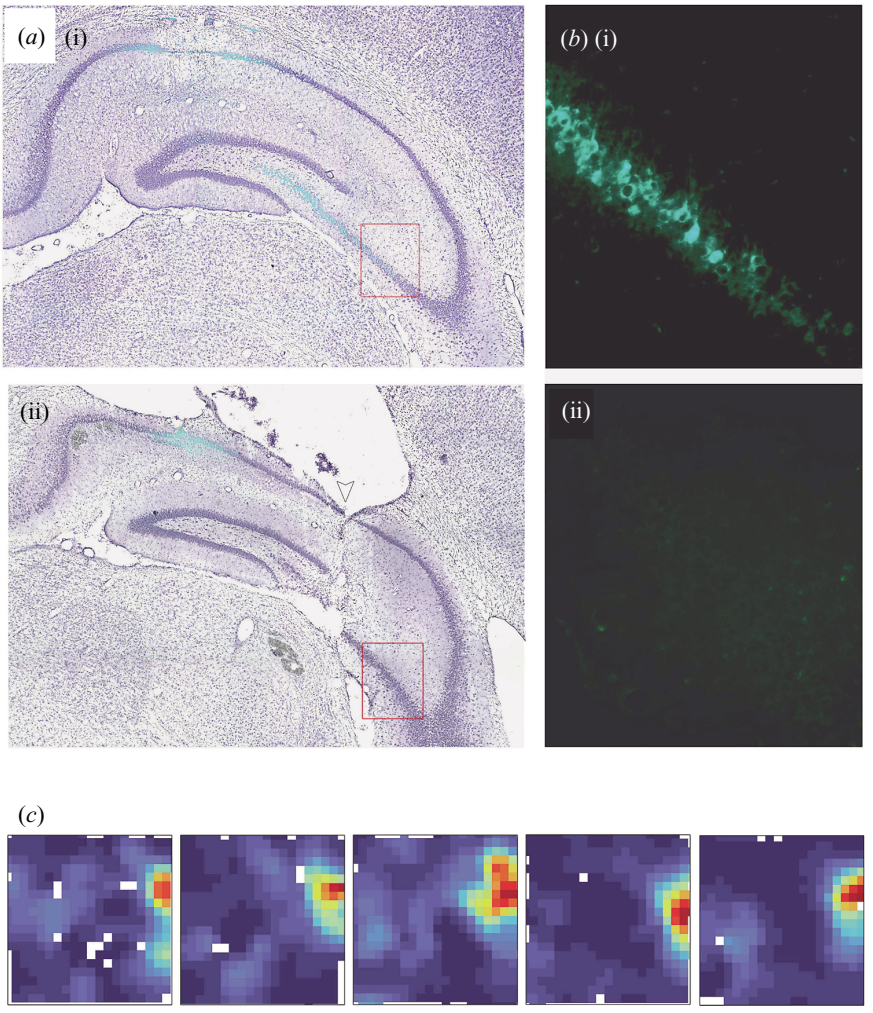

Figure 3. Intact place fields in area CA1 after transection of fibres from CA3 to CA1. (*a*,*b*) Cresyl violet and fluorescence images from an unlesioned control rat (*a*(i) and *b*(i)) and a rat with CA1 isolated from CA3 by a longitudinal cut (arrowhead) at the border between these subfields (*a*(ii) and *b*(ii)). A retrograde tracer (aminostilbamidine) was infused at the recording position in dorsal CA1 (green). Fluorescence images in (*b*) correspond to red boxes in adjacent left sections in (*a*). (*c*) Colour-coded firing rate map for a cell from the lesioned rat in ((*a*) and (*b*)). The cell was recorded for 5 consecutive days (left to right). Dark red indicates maximum rate (left to right: 8, 12, 12, 17 and 11 Hz).

sufficient to trigger somatic actional potentials in these cells; reliable discharge may require summation of EPSPs, i.e. high afferent firing rates (Golding & Spruston 1998; Golding *et al.* 2002).

It is important to note that the computation and storage of positional information outside the hippocampus does not preclude the processing, storage and use of spatial information (or indices of such information) within the hippocampus. Indeed, the internal recurrent connectivity of HPC area CA3 makes the region highly suitable for storage of just this type of patterned information, at least for an intermediate period of time. Recent results suggest that plasticity in associative synapses of CA3 is necessary for the successful encoding of spatial information in a manner that later allows recall with partial cues (Nakazawa *et al.* 2002; Tonegawa *et al.* 2003). Mice with targeted deletions of NMDA receptors in CA3 were trained in a reference memory task in the water maze. These mice were unable to localize the hidden platform on a recall trial with only a limited set of the landmarks used during training. When the full set of cues was available, retention was indistinguishable from that of control animals. Place fields in CA1 were more dispersed than in control mice in the limited-cue condition but not in the full-cue test. These findings suggest that the CA3 performs pattern completion during recall of spatial information. Longitudinal axon collaterals in CA3 may be important for successful retrieval of such information, as memory retention may be impaired by a single transversely-oriented cut through the dorsal CA3 region of each hippocampus (Steffenach *et al.* 2002).

The key novel feature of our argument and data is that the network of the hippocampus has the circuitry and the plasticity to store associations between locations and events. The location information that is encoded within these associations may be derived online from HPC spatial processing (e.g. that occurring during exploration of a novel environment) or retrieved via the direct entorhinal pathway (e.g. that concerning a familiar environment). To examine how HPC neurons respond to an unpredicted event in a well-consolidated environment, we trained rats to find a hidden platform at a fixed location in an annular water maze and then moved the platform to a new place (Fyhn *et al.* 2002). This movement of the platform consti-

tuted transferring a critical event (escaping from the water) from one location to another. Several cells fired vigorously at the new platform location, despite previously having been silent. Others that fired in different locations around the maze continued to do so after the platform relocation, arguing against spatial remapping. The new activity was paralleled by reduced discharge in a subset of simultaneously recorded interneurons. The pattern of activity largely returned towards its original configuration as the rat learned the new location. However, a few of the newly recruited neurons remained active. This persistent firing may reflect facilitated synaptic plasticity during the temporary reduction in inhibition (Wigstrom & Gustafsson 1983; Paulsen & Moser 1998; see also Lynch 2003). NMDA-receptor-dependent LTP may be necessary for these permanent modifications in firing patterns when novel events occur in a familiar environment.

(b) *Proposition 2.3*

The idea that HPC memory indices are encoded as distributed patterns of synaptic weights requires that changes in synaptic weight last long enough for the slower systems-level HPC/neocortical consolidation process to take place. E-LTP lasts at most 3–4 h. Protein-synthesis-dependent L-LTP lasts longer but perhaps not indefinitely (c.f. Abraham 2003). The difference between these two forms of synaptic potentiation reflects a long-recognized difference between STM and LTM: that *de novo* protein synthesis is required for a short-lasting trace to be converted into a long-lasting one. It draws upon experimental work in *Drosophila* (Belvin & Yin 1997), *Aplysia* (Montarolo *et al.* 1986), early learning in birds (Rose 1995), mammalian memory (Davis & Squire 1984), neural models of memory formation such as LTP (Krug *et al.* 1984) and theories about the relationship between STM and LTM (Goelet *et al.* 1986).

A new perspective on these ideas is the synaptic tagging hypothesis of memory trace formation (Frey & Morris 1997, 1998*a*,*b*; Morris & Frey 1997; Dudai & Morris 2001). This hypothesis accepts that plasticity proteins are critical for the persistence of synaptic memory traces, but argues against obligatory *de novo* synthesis of these proteins in response to the events that are to be remembered. Our idea is that LTM trace formation is at least a two-stage process (the systems–neuroscience framework above actually implies a three-stage process). In one step, the potential for a LTM is established locally at synapses in the form of rapidly decaying E-LTP accompanied by the setting of a synaptic tag. In the other, a series of biochemical interactions, including protein–protein interactions, are triggered to convert this synaptic potentiality into a longer lasting trace at those synapses at which tags have been set. The somatic events that lead to these interactions can be set in motion shortly before the event to be remembered, at the same time (as in most behavioural and *in vitro* brain slice experiments so far), or shortly afterwards. Critically, the persistence of memory does not have to be determined at the time of initial memory trace formation. Frey & Morris (1998*b*) proposed that patterns of afferent glutamatergic activation and postsynaptic spiking, which together induce LTP, set synaptic tags and induce short-lasting changes in synaptic weights. Heterosynaptic activation, which we proposed in 1998 occurs through neuromodulatory inputs (particularly DA afferent to areas CA1 and CA3 of the hippocampus, and the noradrenergic inputs to the dentate gyrus), is responsible for *de novo* protein synthesis. These proteins travel diffusely in dendritic compartments until sequestered locally by the synaptic tags whereupon they help induce synaptic stabilization.

At present, we still do not know whether synaptic tagging occurs *in vivo* and whether the principle also extends to behavioural memory as implied by proposition 2.3. That is, would it be possible to induce a long-lasting memory during the inhibition of protein synthesis if the synthesis and distribution of the relevant plasticity proteins had occurred earlier? Unlike brain slice or intracellular experiments, it would be necessary, *in vivo*, to ensure that the upregulation of protein synthesis occurred in a common population of neurons to those used by the animal later during learning. One way in which it may be possible to work towards this is to take advantage of the idea that heterosynaptic activation of neuromodulatory afferents, such as dopamine D1 and D5 receptors, is involved in the persistence of LTP (Swanson-Park *et al.* 1999) and, in particular, L-LTP (Frey *et al.* 1991). In new work, we have recently replicated the observation that the D1/D5 antagonist SCH23390 blocks L-LTP in HPC slices (figure 4*a*) and then explored the impact of this drug on STM and LTM.

The behavioural experiments used the DMP paradigm in the water maze. This is a repetitive one-trial learning protocol in which the hidden platform moves location each day, but remains in that day's location for each of four trials. The animals therefore have the opportunity to encode the new location on trial one of each day and so escape much more rapidly on trials two to four. The delay between trials one and two was varied between 20 min and 6 h. This study revealed that bilateral intrahippocampal infusion of the D1/D5 receptor antagonist SCH23390 causes a delay-dependent impairment of memory (figure 4*b*).

This study represents the first step of a systematic series of experiments in which we hope to test the implications of the synaptic tagging idea in behaving animals. As the critical predictions of the theory require protein synthesis to be triggered at one point in the sequence of events but not at another shortly thereafter (or shortly before), it is unclear whether gene-targeting techniques will be very useful. They will, as in the work of Barco *et al.* (2002) and Hédou & Mansuy (2003), help us identify many of the mechanisms of persistence of LTP and LTD at a genetic level. However, addressing the heterosynaptic issue will be more difficult as even inducible constructs require several days to work. By using physiological and pharmacological techniques, however, it may be possible to activate dopaminergic afferents to the hippocampus before a learning experience and then train in the presence of an antagonist. This and other related tests of the synaptic tagging hypothesis of the persistence of HPC indices are underway.

(c) *Propositions 2.4 and 2.5*

Our theoretical framework identifies the HPC as encoding indices linking disparate neocortical modules whose connectivity is too sparse to support the encoding of arbitrary associations. According to some, the HPC sub-

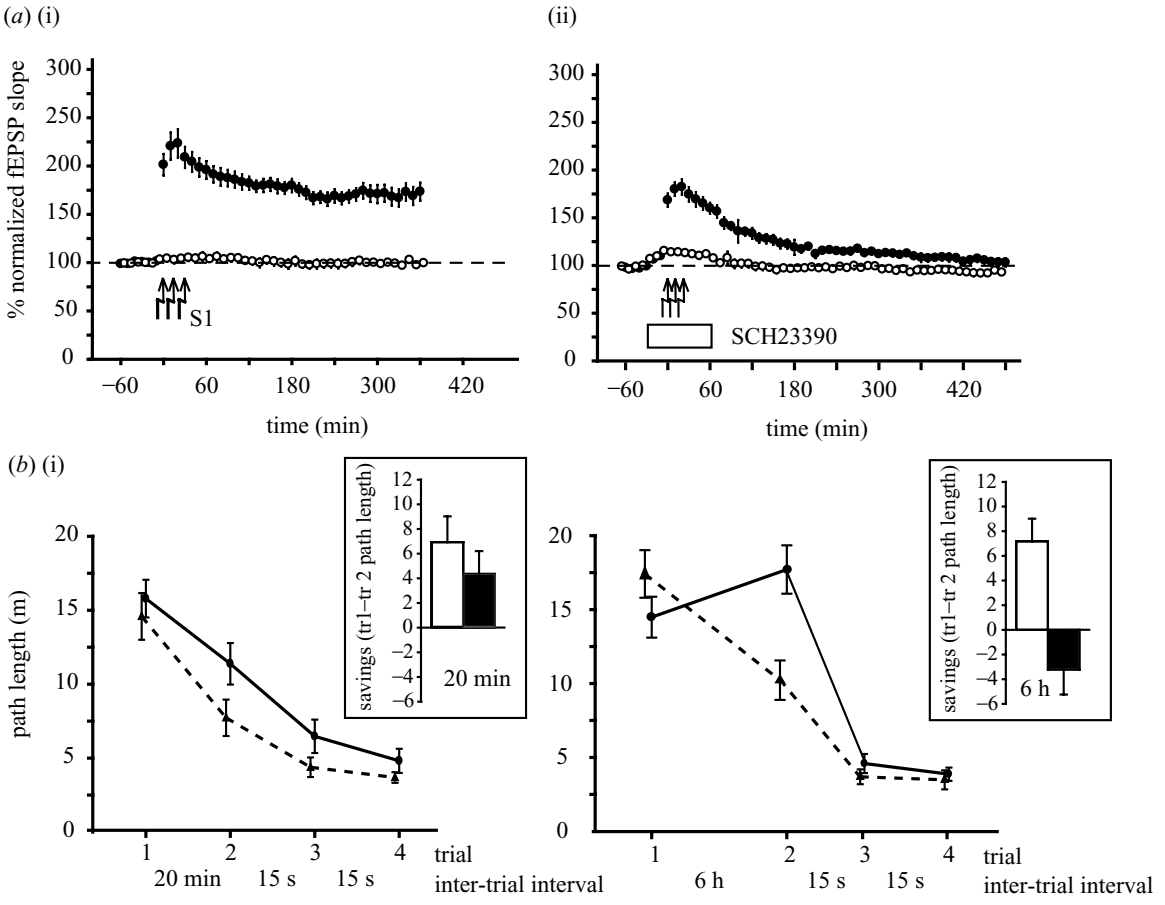

Figure 4. The D1/D5 receptor antagonist blocks L-LTP and LTM for a single event. (*a*) Electrophysiological brain slice experiments confirmed earlier studies showing that SCH23390 blocks L-LTP but not E-LTP. Note stability of simultaneously monitored control pathway (S2, open circles). LTP was induced by three bursts of tetanic stimulation at 100 Hz spaced 10 min apart in HPC slices maintained at 32 °C (S1, closed circles). (*b*) Behavioural studies used rats ($n = 36$) prepared for acute bilateral infusion of drugs into the dorsal hippocampus. After recovery, they were given 8 days of drug-free training (four trials per day, 30 s on the platform after each trial). The inter-trial interval was 15 s between most trials. However, between trials one and two, it was 20 min on half the days and 6 h on the other half (in an ABBA design). The DMP protocol was then continued with bilateral intrahippocampal infusions of aCSF or SCH23390 in aCSF on different days (30 min before trial one of each day). Averaged across the 8 days of training, rats infused with the D1/D5 antagonist showed good memory of the new platform location on trial two each day at the 20 min interval between trials one and two, but substantial forgetting at the 6 h interval. Path-length on trial two was lower on the drug-treatment days for 20 min than for 6 h. The savings between trials one and two are shown in the inserts.

sequently plays a time-limited role in memory by enabling the gradual development of intracortical connections that render the cortical memory traces enduring and self-sufficient, the process we have referred to as systems-level consolidation (Squire 1992; McClelland *et al.* 1995). Others argue that the HPC has a permanent role in memory storage for certain kinds of information and, thus, its retrieval (Nadel & Moscovitch 1997). Much of the conflicting evidence is derived from studies on patients with permanent brain damage (Kapur 1999) or animals with irreversible lesions. Such studies cannot easily dissociate the distinctive memory processes of storage, consolidation and retrieval.

Reversible pharmacological manipulations offer an alternative approach (Izquierdo & Medina 1998; McGaugh 2000). They have three advantages. (i) The experimental manipulation can be made after training during the consolidation period, but withdrawn during the next phase (e.g. retrieval). Any effects they then have cannot be on sensorimotor processes, or on memory encoding. (ii) They offer the opportunity of asking what aspects of neural activity are required because, in addition to studying the effects of regionally specific neural inactivation (induced by AMPA antagonists), one of our propositions (2.5) implies that HPC plasticity should play no role in guiding neocortical consolidation. There is a clear controversy on this issue, particularly between genetic (Shimizu *et al.* 2000) and pharmacological data (Day & Morris 2001; Villarreal *et al.* 2002). Finally, (iii) if the HPC guides consolidation by establishing relevant intracortical connectivity, reversible pharmacological manipulations might be applied to the neocortex as well as to the HPC during the putative consolidation period.

We have previously shown that 7 days' infusion of a GLUR1-5 antagonist to inactivate the HPC, starting 1 to 5 days after training, disrupts spatial memory in the water maze when tested 16 days after training (Riedel *et al.* 1999; figure 5). This finding is consistent with systems-level consolidation requiring HPC neural activity post-training, but raises two questions relevant to propositions

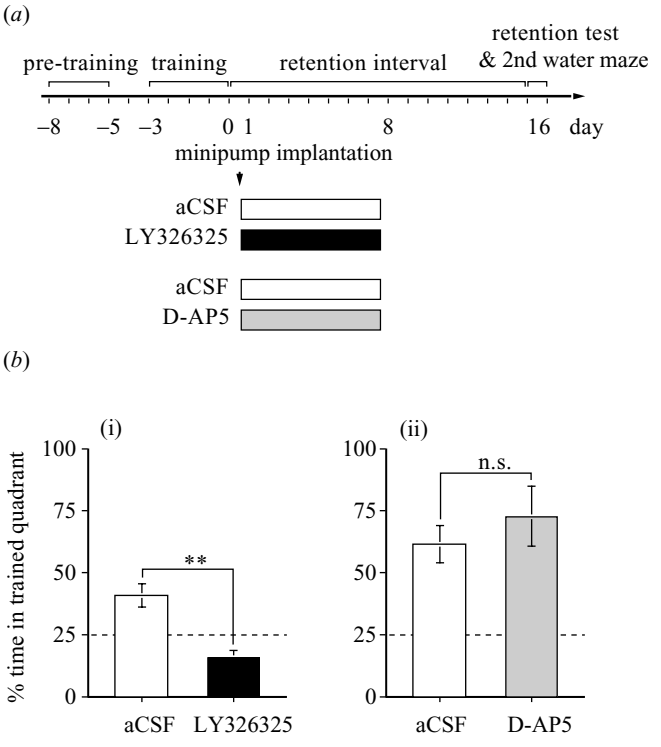

Figure 5. HPC neural activity but not NMDA receptor activity is involved in systems-level memory consolidation. (*a*) Experimental design shows training phases and periods when aCSF (n.s. = 17 and 5, respectively), the GLUR1-5 antagonist LY326325 ($n = 8$), and D-AP5 ($n = 7$) were chronically infused after spatial reference memory training using an Atlantis platform. Retention tests consisting of a 60 s swim with the platform absent were conducted 16 days after the end of training. (*b*) Selective impairment of spatial memory following AMPA receptor (i) but not NMDA receptor blockade (ii). The variation in performance of the two aCSF groups was unexpected and reflects variability in performance of rats tested at different times.

2.4 and 2.5. First, would a similar finding pertain if an NMDA antagonist were chronically infused into the hippocampus over the same time-period? This is a relevant follow-up of the work with the GLUR1-5 antagonist as this would, as a secondary effect, have also inhibited NMDA receptor mechanisms by preventing sufficient postsynaptic depolarization. Second, is interference with systems-level consolidation the only interpretation of the findings of Riedel *et al.* (1999)? We consider these two issues in turn.

New work using rats and mice indicates that chronic *post-training* infusion of D-AP5 into the dorsal hippocampus bilaterally has no effect on later memory (figure 5*b*). We put emphasis on both the location in the brain where the AP5 is infused (the hippocampus) and the time of administration of the drug (post-training) for our propositions do include that AP5 *during* learning disrupts memory encoding. In the rat studies, retrieval was tested 16 days after the end of training exactly as in Riedel *et al.* (1999), long after the 7 day minipumps implanted after training were exhausted. The concentration of D-AP5 used was sufficient to block dentate and CA1 LTP *in vivo* when this was tested during the period of drug infusion.

However, second, it is possible that the chronic blockade of AMPA receptors actually disrupts trace storage within the HPC itself rather than the HPC/neocortical consolidation process. This may happen by a breakdown in the quantitative scaling of homeostatic plasticity (Turrigiano *et al.* 1998). One way of distinguishing these possibilities would be to contrast HPC inactivation starting soon after training ('recent memory' group as in Riedel *et al.* (1999)) with inactivation starting several weeks later ('remote memory' group). If the recent memory group were to display amnesia while the remote memory group did not, the most parsimonious explanation would be in terms of a systems-level consolidation process. However, if an equivalent memory impairment is observed in both groups, suggesting that memory traces do not survive a prolonged period of AMPA receptor blockade, an HPC site of storage has likely been disrupted. These traces may be the 'indices' that are persistently required to link information in disparate neocortical modules, in the manner of Nadel & Moscovitch's (1997) theory. An experiment to test this prediction of our hypothesis is currently underway. Overall, the experimental philosophy is that use of reversible inactivation rather than conventional lesions should enable us to distinguish theoretically between a putative consolidation process and any contributions that HPC activity may be making to storage and retrieval processes. The data at hand point to a clear difference between post-training neural inactivation and post-training inhibition of NMDA receptor-dependent plasticity, and are inconsistent with recent gene-targeting experiments. We find no support for the notion that HPC NMDA receptor-dependent synaptic plasticity is involved in long-term consolidation.

However, the persistence of spatial memory after post-training blockade of HPC NMDA receptors leaves several questions unresolved. One is that other forms of activity-dependent plasticity may be engaged—our experiment is silent on this issue. Another relates to the role of synaptic plasticity during offline reactivation in neuronal ensembles that were active during the preceding behavioural experience. In the context of place cells, reactivation refers to the striking observation that cells with overlapping place fields continue to exhibit correlated firing during slow-wave and rapid-eye-movement sleep episodes subsequent to the behavioural session (Wilson & McNaughton 1994; Louie & Wilson 2001). Reactivation occurs throughout large areas of the posterior cortex (Hoffman & McNaughton 2002) and is seen particularly during sharp waves. Sharp waves are bursts of synchronous activity in HPC pyramidal cells that may be necessary for the induction of plasticity in downstream areas in behaving animals (Buszaki 1989; King *et al.* 1999). The poor long-term stability of place fields after blockade of HPC LTP suggests that HPC or neocortical plasticity during offline states may play a role in the modification of spatial representations. This modification may take place in the cortex, in the hippocampus, or both. Our proposition states only that HPC plasticity is unlikely to be involved in circumstances in which information that has been encoded online in the HPC network is to be protected from change during the course of systems consolidation. However, it remains to be determined whether there is a direct link between sharp-wave related reactivation and NMDA

receptor-dependent synaptic modifications in efferent synapses within the HPC formation (e.g. subiculum) or in neocortical target areas. Reactivation is strongest immediately after the behavioural session, during a time-period much shorter than that thought to underlie systems consolidation. This shorter time-course includes the very time-periods over which place field instability has been observed. Examining whether reactivation gives rise to NMDA receptor-dependent plasticity within the hippocampus would therefore require an experimental design in which the receptors were blocked almost instantly after termination of the training experience (Packard & Teather 1997).

4. CONCLUSION

Bliss & Lømo (1973, p. 355) ended their article on long-lasting potentiation with a somewhat embedded conundrum: 'whether or not the intact animal makes use in real life of a property which has been revealed by synchronous, repetitive volleys to a population of fibres the normal rate and pattern of activity along which are unknown, is another matter.' Thirty years later, our appraisal of the literature indicates that there is now overwhelming evidence that activity-dependent synaptic plasticity is engaged during learning, is required for learning and, if induced physiologically after learning, alters an animal's memory of past experience. Accordingly, three of the four formal criteria by which the SPM hypothesis can be assessed have been satisfied in one or more brain systems of learning and memory, although not always within a single brain system.

Beyond this abstract assessment of this hypothesis, we have also outlined some elements of an emerging neurobiological theory of the HPC formation together with new data pertaining to a series of specific propositions. Both behavioural and electrophysiological data are consistent with the idea that activity-dependent HPC synaptic potentiation is critical for the automatic recording of unique event–place associations. This involves both encoding and intermediate storage of memory traces that constitute indices of the locations in the neocortex where more detailed sensory/perceptual detail may be found. Many automatically encoded traces decay rapidly. However, if encoding happens around the time of the synthesis and dendritic distribution of plasticity-related proteins to activated synapses, the traces may persist long enough to enable, through a process of indirect association, the much slower HPC/neocortical consolidation process to build direct connections between relevant cortical modules. Retrieval of remote memories is a process through which this passive storehouse of cortically located traces can then be reactivated. With recent memories, HPC neural activity is likely to be involved; with more remote memories, it need not be. HPC LTP engages mechanisms used in some but not all of these processes that collectively enable the seamless execution of what we understand as memory.

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GLOSSARY

aCSF: artificial cerebrospinal fluid
AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
CA1–3: Cornu Ammonis areas 1–3
DMP: delayed matching-to-place
E-LTP: early long-term potentiation
EPSP: excitatory postsynaptic potential
HPC: hippocampal
L-LTP: late long-term potentiation
LTD: long-term depression
LTM: long-term memory
LTP: long-term potentiation
NMDA: *N*-methyl-D-aspartate
SPM: synaptic plasticity and memory
STM: short-term memory