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Hippocampal synaptic plasticity: role in spatial learning or the automatic recording of attended experience?

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SUMMARY

Allocentric spatial learning can sometimes occur in one trial. The incorporation of information into a spatial representation may, therefore, obey a one-trial correlational learning rule rather than a multi-trial error-correcting rule. It has been suggested that physiological implementation of such a rule could be mediated by *N*-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) in the hippocampus, as its induction obeys a correlational type of synaptic learning rule. Support for this idea came originally from the finding that intracerebral infusion of the NMDA antagonist AP5 impairs spatial learning, but studies summarized in the first part of this paper have called it into question. First, rats previously given experience of spatial learning in a watermaze can learn a new spatial reference memory task at a normal rate despite an appreciable NMDA receptor blockade. Second, the classical phenomenon of 'blocking' occurs in spatial learning. The latter finding implies that spatial learning can also be sensitive to an animal's expectations about reward and so depend on more than the detection of simple spatial correlations.

In this paper a new hypothesis is proposed about the function of hippocampal LTP. This hypothesis retains the idea that LTP subserves rapid one-trial memory, but abandons the notion that it serves any specific role in the geometric aspects of spatial learning. It is suggested that LTP participates in the 'automatic recording of attended experience': a subsystem of episodic memory in which events are temporarily remembered in association with the contexts in which they occur. An automatic correlational form of synaptic plasticity is ideally suited to the online registration of context–event associations. In support, it is reported that the ability of rats to remember the most recent place they have visited in a familiar environment is exquisitely sensitive to AP5 in a delay-dependent manner. Moreover, new studies of the lasting persistence of NMDA-dependent LTP, known to require protein synthesis, point to intracellular mechanisms that enable transient synaptic changes to be stabilized if they occur in close temporal proximity to important events. This new property of hippocampal LTP is a desirable characteristic of an event memory system.

1. INTRODUCTION

This paper outlines a new hypothesis about the function of associative synaptic plasticity in the hippocampal formation, namely that it is essential for what is referred to here as the 'automatic recording of attended experience'. This constitutes one component of a larger episodic memory system involving a number of brain regions (Tulving 1983; Tulving & Schacter 1994) and likely to be implemented by several neurophysiological mechanisms of plasticity. The idea is that this part of the episodic memory system of the brain is automatic in the sense that it cannot be switched off in a voluntary manner, although it can be subject to selective disruption by certain kinds of brain damage. Being automatic, it can potentially record everything to which attention is directed, including context, but this

recording may only be of markers that an event has happened at a particular place rather than a detailed encoding of sensory or perceptual information. To operate effectively, such a system needs a mechanism of neuronal plasticity that can register event–context associations rapidly in a strictly correlational manner, i.e. without regard to their consistency to an organism's goal-directed actions. *N*-methyl-D-aspartate (NMDA) receptor-dependent synaptic potentiation in the hippocampus is ideally suited to implementing the rapid online storage of such conjunctive associations. These would be retained temporarily, as changes in synaptic weights, by the early phase of long-term potentiation (LTP) after which they may decay to baseline (i.e. be forgotten). Their temporal persistence may, however, be stabilized by intracellular interactions with the plasticity-related proteins (PPs) that are synthesized by certain patterns of neuronal activation. This variable persistence may be thought of as a type of short-term

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consolidation of memory. Enhanced persistence of synaptic potentiation in the hippocampus extends the temporal window of opportunity for long-term memory formation by other brain structures that are also part of the episodic memory system, including the diencephalic and frontal lobe areas.

That the hippocampal formation might be part of the episodic memory system of the brain is hardly a new idea: it and structures within the medial temporal and frontal lobes have long been implicated in spatial, episodic and declarative memory (O'Keefe & Nadel 1978; Squire & Zola-Morgan 1991; Tulving & Schacter 1994). What is new, and thus the focus of this paper, is the suggestion that activity-dependent synaptic plasticity in the hippocampus (such as LTP) is functionally relevant to *episodic* memory rather than to the learning of spatial maps or associative conditioning with which it has more often been discussed (see, for example, Teyler & Discenna 1987; McNaughton & Morris 1987; Morris *et al.* 1990; Shors & Matzel 1997). Implicit in this proposal is the notion that episodic memory cannot, therefore, be unique to humans. As hippocampal LTP is present in mammals, 'elements of episodic memory' must exist in these animals also, a claim that is qualified below.

The structure of this paper is as follows. First, evidence implicating NMDA receptor-dependent hippocampal LTP in spatial learning and memory is reviewed. Second, two lines of evidence against this proposal are described: (i) circumstances in which spatial learning occurs in the presence of NMDA antagonists, and (ii) data indicating that the learning rule for the acquisition of a spatial map cannot, in practice, be isomorphic with the synaptic learning rule for LTP. Third, based on the notion that episodic memory builds upon a system used for spatial learning in animals (O'Keefe & Nadel 1978; Gaffan 1994), evidence is presented from a delayed-matching-to-place task consistent with this idea and it is shown that the results are exquisitely sensitive to an NMDA antagonist (AP5). Fourth, data pointing to a new property of protein synthesis-dependent LTP (sometimes called 'late-LTP') that would be desirable within an event-memory system are described. Finally, further aspects of the 'automatic recording' hypothesis are spelt out, including ideas about its neural basis, and a number of open issues and speculations that require further experimentation are identified.

2. NMDA RECEPTOR-DEPENDENT HIPPOCAMPAL LTP AND ITS ROLE IN SPATIAL LEARNING AND MEMORY

It has been known for over a quarter of a century that particular patterns of electrical stimulation in the hippocampal formation can lead to alterations in synaptic efficacy. The classic observations of Bliss & Lomo (1973), who studied the perforant path input to the dentate gyrus of anaesthetized rabbits, now referred to as long-term potentiation (LTP), have been replicated in other mammalian species, *in vitro* as well as *in vivo*, and in several pathways of the hippocampal formation. Contemporary studies have revealed that

potentiation of synaptic efficacy in different pathways can have different physiological properties, reflecting distinct underlying mechanisms. The best studied of these has been referred to as 'associative' or 'NMDA receptor-dependent LTP', to distinguish it from other forms of lasting synaptic change such as E-S potentiation, mossy-fibre potentiation, long-term depression, neurotrophin-induced potentiation, etc. Although these latter forms of neuronal plasticity are unquestionably important, this paper discusses only the associative NMDA receptor-dependent form, which is referred to, for simplicity, as 'LTP'. A distinction is made only between different temporal phases of its expression. Numerous reviews of LTP have been published (see, for example, Bliss & Collingridge 1993; Bear & Malenka 1994; Fazeli & Collingridge 1996) and the following general understanding of its properties, mechanisms and functional significance has emerged.

With respect to its physiological properties, LTP is defined as a rapidly induced, persistent enhancement in synaptic efficacy lasting at least one hour. Its induction is 'associative', in that weak patterns of stimulation insufficient to induce LTP on their own can none the less result in a persistent synaptic enhancement if they occur in association with depolarization of the target neurone(s) onto which the stimulated pathway is afferent. The resulting LTP is also 'input-specific' in that meeting the conditions for induction results in enhanced synaptic efficacy specific to the synaptic terminals of the activated pathway (or, at least, to closely neighbouring synapses). As noted many times, these properties of persistence, associativity and input-specificity are desirable properties of a physiological mechanism for storing information at synapses. Later (§6 below), a further property of hippocampal LTP is described, whereby the persistence of an induced change in synaptic efficacy can be extended by other heterosynaptic patterns of neural activity.

With respect to its underlying neural mechanisms, there is a consensus that activation of a subclass of excitatory postsynaptic glutamatergic receptors, the so-called *N*-methyl-D-aspartate (NMDA) receptor, is an essential first step in LTP induction. The NMDA receptor, now known to be a complex protein consisting of a number of individual subunits, has the intriguing property of being both ligand- and voltage-gated. When activated by glutamate and at a particular level of postsynaptic depolarization, calcium (Ca^{2+}) enters the dendrite via the NMDA receptor ion-channel, where it activates a chain of intracellular events leading to altered synaptic efficacy. Theories about how the resulting change in synaptic efficacy is achieved include activation of Ca^{2+} -dependent enzymes that phosphorylate receptors and trigger gene expression. Some of these biochemical events are responsible for short-lasting changes (often referred to as early-LTP); others cause the early change to be stabilized, i.e. made persistent (late-LTP), with the latter involving mechanisms activated by other than just glutamatergic inputs (see §7*c* below).

With respect to the functional significance of LTP, studies have been conducted exploring whether there is any correlation between behavioural learning and the occurrence or persistence of LTP (for recent reviews, see Alkon *et al.* 1991; Morris & Davis 1994; Barnes 1995; Jeffery 1997; Shors & Matzel 1997; Cain 1997). Inevitably, as LTP was first discovered in the hippocampus, such studies have tended to focus on types of learning broadly held to be 'hippocampal-dependent' (i.e. thought to engage hippocampal activity and/or be impaired by hippocampal lesions). Correlations have been observed between the persistence of LTP and how long such types of memory are retained, as well as between the occurrence of particular types of learning and the activation of the various Ca^{2+} -dependent enzymes. Studies with the use of drugs that antagonize the NMDA receptor, or targeted mutations of NMDA receptor subunits, have also revealed behaviourally selective learning impairments. The interpretation of many of these studies is very controversial: the techniques used to manipulate LTP generally have multiple effects on brain function.

Early support for the idea of a link between LTP and spatial learning came from several studies. One was the finding of Morris *et al.* (1986) that blockade of NMDA receptors by chronic intraventricular (ICV) infusion of the selective NMDA antagonist AP5 resulted in an impairment of spatial learning, but not of visual-discrimination learning, in the open-field watermaze. This inhibition of spatial learning is dose-related and occurs across a range of estimated extracellular concentrations of D-2-amino-5-phosphopentanoate (D-AP5) in the hippocampus *in vivo* comparable to those that block LTP *in vitro* (Davis *et al.* 1992). Application of AP5 after learning is without effect on performance (Morris 1989). Acute intrahippocampal infusion of nanomolar quantities of AP5, revealed radioautographically to be restricted to the hippocampus, are also sufficient to cause an impairment of spatial learning (Morris *et al.* 1989). Other pharmacological studies have also shown deficits in spatial learning with both competitive and non-competitive NMDA antagonists (Danysz *et al.* 1996; cf. Cain 1997).

A recent replication of the basic observation is shown in figure 1 (Bannerman *et al.* 1995, Experiment 1). Rats were trained to find the hidden escape platform over eight trials, at one trial per day, with transfer tests (platform absent) conducted before the first trial, half-way through training, and at the end. Before training, the animals were implanted with an osmotic minipump containing either artificial cerebrospinal fluid (aCSF) or D-AP5 (30 mM in aCSF). Connected via a catheter to a cannula implanted into the lateral ventricle, this pumped continuously into the brain of the rat at $0.5 \mu\text{l h}^{-1}$ (i.e. 15 nmol h^{-1}). The results were that aCSF animals showed a gradual decline in escape latency across training, reflecting learning of the platform's location, but the D-AP5-treated group did not (figure 1*a*). Similarly, in the transfer tests, the aCSF group gradually came to concentrate its search in the correct quadrant as training progressed (transfer tests TT2 and TT3), whereas the D-AP5 group did not

(figure 1*b*). These behavioural effects occurred at measured intracerebral concentrations of the drug sufficient to block dentate LTP under urethane anaesthesia.

Pharmacological studies such as this have been complemented by work using targeted molecular engineering. Deletion of the R2A subunit of the NMDA receptor causes both a blockade of NMDA receptor-dependent LTP and impairments of spatial learning in mice (Sakimura *et al.* 1995). Elegant experiments by Tonegawa and his colleagues have recently established that site-specific deletion of the NMDA-R1 subunit from CA1 pyramidal cells results in a blockade of LTP at the Schaffer collateral input to CA1, an impairment of spatial learning, and changes in the size and specificity of CA1 place-fields (Tsien *et al.* 1996*a,b*; McHugh *et al.* 1996). Collectively, these studies would appear to offer strong support for the notion that NMDA receptor-dependent synaptic plasticity is involved in spatial learning.

3. DISSOCIATION BETWEEN NMDA RECEPTOR-DEPENDENT AND NMDA RECEPTOR-INDEPENDENT COMPONENTS OF SPATIAL LEARNING

Some recent studies have, none the less, called into question the notion that NMDA receptor-dependent mechanisms are always necessary for spatial learning. In the authors' own work, for example, Bannerman *et al.* (1995, experiment 2) found that rats that had previously been trained a spatial task in one watermaze were relatively unaffected by AP5 when trained in a second watermaze in a different room. The thinking behind this study was twofold.

First, although learning in a watermaze is conveniently categorized as a 'spatial', it is misleading to think that spatial learning is the only type of learning that occurs in the apparatus. Multiple types of learning can occur simultaneously, coupled with the formation of distinct memories. Animals that are experimentally naive have to learn to swim away from the side walls to find the platform at all (i.e. overcome thigmotaxis) and to learn that climbing on the platform when they find it is the appropriate thing to do (i.e. incentive learning). These and other behavioural processes engaged by the watermaze task may also be AP5-sensitive. It follows that it cannot be unambiguously concluded that the failure of experimentally naive, AP5-treated animals to learn a spatial task (as in figure 1*a,b*) is necessarily because AP5 interacts directly with spatial learning mechanisms *per se*. Second, although animals may be 'experimentally naive', they will nevertheless have had previous experiences that could influence their subsequent learning. To explore this in a controlled way, the possibility was considered that spatial training of animals probably enables them to learn more than just the particular layout of cues in the training room. They may also learn behavioural or even abstract 'strategies' that could influence their performance in other spatial tasks in the future. For example, they may learn that there is a single place to escape and

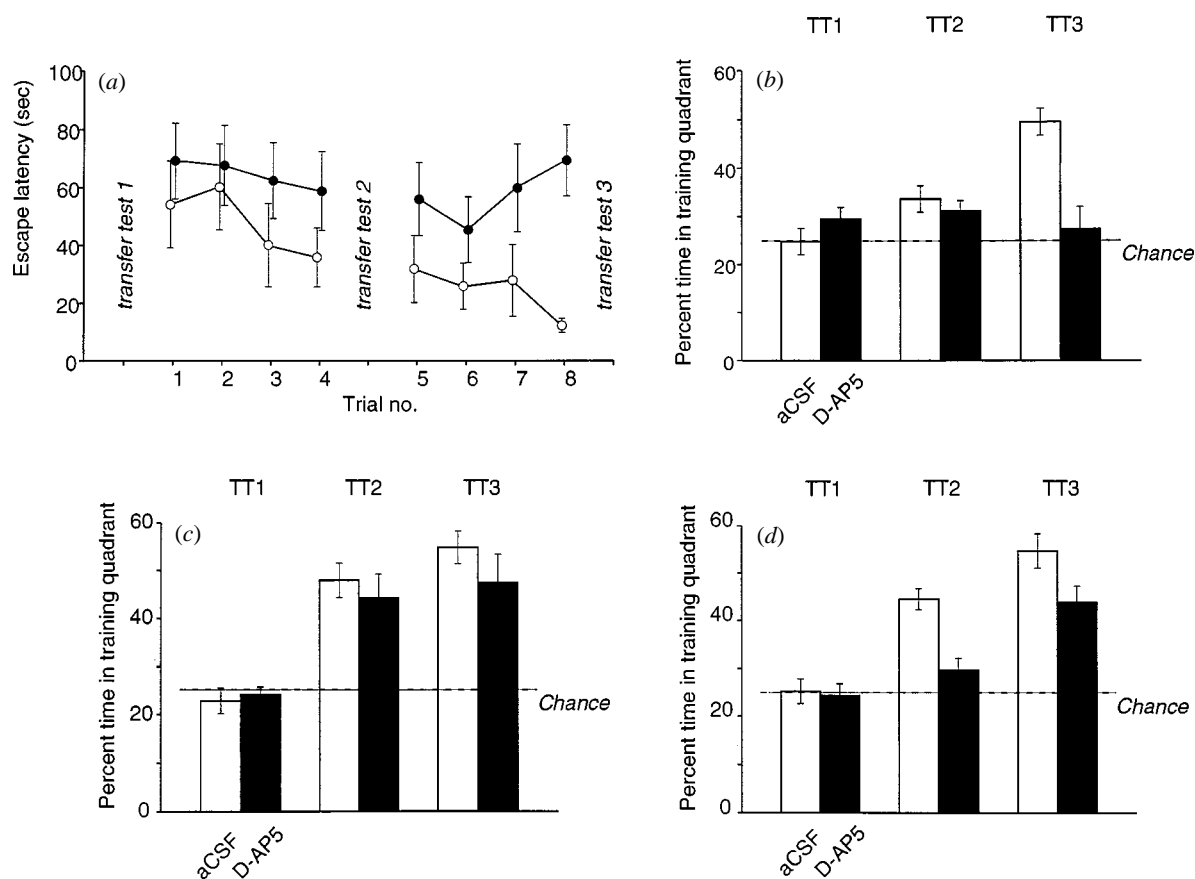


Figure 1. Dissociation between components of spatial learning by using an NMDA receptor antagonist. (a) Experiment 1. Escape latency ($s \pm 1$ s.e.m.) across training by the experimentally naive aCSF- (open symbols) and AP5-treated (filled symbols) groups. Note blockade of learning by the AP5-treated group. (b) Experiment 1. Percentage time (± 1 s.e.m.) spent in the training quadrant during TT1 (before training), TT2 (halfway through) and TT3 (after training). Note absence of searching in the training quadrant by the AP5-treated group. (c) Experiment 2. In animals given spatial pretraining in a watermaze in a separate room, AP5 has no significant effect on the percentage of time spent searching in the training quadrant during the second task. (d) Experiment 4. In animals given random search pretraining in a separate room, AP5 impairs learning of the platform location during the second task. The deficit is not as substantial as in experimentally naive animals (Experiment 1). Based on Bannerman *et al.* (1995).

that, once it is found, one should always approach that place. Such a strategy might generalize from one spatial environment to another. Learning a strategy, as distinct from learning a specific set of spatial cues, may also be sensitive to AP5.

To address both issues, additional experiments were conducted in which rats were first trained in one watermaze before drug treatment and then, under AP5 or aCSF, taken to a second laboratory room housing a different watermaze and trained in the same spatial task as the one described in figure 1. Bannerman *et al.* (1995, experiment 2) found, surprisingly, that AP5-treated animals then learned the second task remarkably well. Their escape latencies showed a steady decline across training (although they were slightly longer than those of aCSF-treated animals) and their performance in TT2 and TT3 was indistinguishable from that of controls (figure 1c). Control procedures were instituted to ensure that there was minimal generalization between the two laboratory rooms. At the end of training, the AP5-treated animals revealed a near-complete blockade of dentate LTP *in vivo*, together

with whole-tissue drug concentrations indistinguishable from those obtained in the earlier experiment.

In another study (Bannerman *et al.* 1995, experiment 4), the rats were first trained on a random search task. For this, curtains were drawn around the pool to occlude extramaze cues, and the hidden platform was moved to a different location in the pool between trials. There is little other than incentive learning in such a task; the rats search around randomly and learn to use the platform as a refuge when it is found. After the same number of trials as in the spatial pretraining used in experiment 2 above, the rats were given minipumps and trained in the second spatial task. A drug-induced deficit was now obtained (see also Morris 1989). Escape latencies during training were longer in AP5-treated rats and their performance during TT2 and TT3 was impaired relative to that of controls (figure 1d). The AP5-treated animals were, however, not as impaired as the experimentally naive animals of experiment 1.

These findings allow three separate points to be made. First, as non-spatial pretraining affected the

sensitivity of subsequent spatial learning to AP5, there must be aspects of watermaze training that are non-spatial and that depend on NMDA receptor activation. These may include learning that the platform is a refuge. Second, as spatial pretraining caused subsequent spatial learning to be insensitive to AP5, spatial learning may be dissociable into components that depend on NMDA receptor activation in the hippocampus and those that do not. Learning the spatial layout of an environment, which it had hitherto been thought would depend critically upon the associativity of LTP (e.g. representing the associative relationships between landmarks) appears to be insensitive to the drug with this training schedule of one trial per day. The animals have, presumably, acquired some kind of spatial strategy during spatial pretraining that can transfer to a new environment, and it is this component of spatial learning that is AP5-sensitive. Third, although these results are similar to Saucier & Cain's (1995) finding of normal spatial learning under AP5 in certain circumstances, they do not support their argument that the effects of NMDA antagonists on performance in spatial tasks can be explained exclusively in terms of whether they induce sensorimotor disturbances. Not only were these minimal in the one-trial-per-day procedure, but such disturbances cannot explain the differential effects of pretraining.

4. BLOCKING IN THE SPATIAL DOMAIN

The notion that allocentric spatial learning is divisible into a number of dissociable components is also suggested by a recent strictly behavioural study of landmark learning. The idea was to explore whether the incorporation of information into a spatial map of the environment obeyed a correlational rule or depended also on an animal's goal-directed expectations; the classic phenomenon of blocking was used to make this distinction.

The rationale was as follows. O'Keefe & Nadel (1978) claimed that two dissociable learning systems can be used for navigation: the 'locale' and the 'taxon' system. The former is the cognitive mapping system in which the locations of landmarks are rapidly encoded as a result of exploration of the environment. Exploration is triggered by novelty, such as mismatches between the animal's memory of the environment and its perception of it. This learning system is thought to be located in the hippocampal formation and critically depends on place cells (Burgess *et al.*, this volume). Importantly, it is not thought to be goal-driven; that is, learning about space is thought to be unaffected by the animal's needs or expectations. If this is correct, the incorporation of information into a spatial map may follow a Hebbian learning rule in being sensitive only to correlations between information about the relative locations of landmarks. This idea raises the intriguing possibility that the 'behavioural' learning rule determining the incorporation of information into an animal's representation of the environment may be isomorphic to the 'synaptic' learning rule underlying hippocampal LTP.

There are, however, at least two reasons to be suspicious of this idea. First, the experiments with AP5 described in §3 above suggest that NMDA receptor-dependent mechanisms are not critical for learning about the spatial layout of an environment even if they do play some unidentified role in spatial 'strategy' learning. Second, most forms of associative learning are sensitive to an animal's expectations about the availability of reward. Learning tends to take place only to the extent that an animal needs to learn. The well-studied phenomenon reflecting this selectivity is called 'blocking'.

Blocking refers to the ability of a previously trained stimulus (A) that predicts reinforcement R to prevent or 'block' conditioning to a second or added stimulus (B) when B is arranged to predict R as well (Kamin 1969). Learning about the B-R association fails to occur despite B being correlated with R and repeatedly presented before it at an appropriate interstimulus interval. This phenomenon has had an important influence on the formulation of modern associative learning theory (Rescorla & Wagner 1972; Dickinson 1980; Mackintosh 1983) according to which learning can be adequately described by the accumulation of associative connections between events, according to goal-driven error-correcting learning rules. It is widely accepted as a parsimonious account of animals' associative learning abilities.

To investigate whether blocking would occur in the spatial domain, Biegler & Morris (1997) trained two groups of rats to find food hidden at a particular location in a large arena (as in Biegler & Morris (1993, 1996)). The arena had several centimetres of sawdust on the floor and the food (hidden inside a small computer-activated feeder that could rise to the surface of the sawdust) was placed at a set distance from an array of landmarks. These were distinctive objects (such as white cylinders, a pyramid-shaped object, and a stack of golf balls glued together); they were placed in an array that was systematically changed across training and test phases.

At the start of training (phase 0, days 1-5), the location of the food (F+) was cued by two identical landmarks that, on their own, could not unambiguously specify the location of food (figure 2*a*). In the later phase 1 (days 6-28) and phase 2 (days 28-37) of a conventional blocking design, other landmarks were added to provide disambiguating directional information. The experimental group had one additional landmark added at the start of phase 2 (as shown); the control group was trained with a visually different landmark in a different geometric location during phase 1, but then given the same two landmarks as the experimental group at the start of phase 2 (not shown). Thus, the key difference between the groups in phase 2 was that, for the experimental group, the location of the hidden food was already cued by the landmark trained in phase 1, whereas for the control group, both landmarks added in phase 2 were novel. There were four training trials per day, of which one was non-rewarded and without landmarks. This schedule ensured that the landmarks served as conditional cues, signalling the availability of reward.

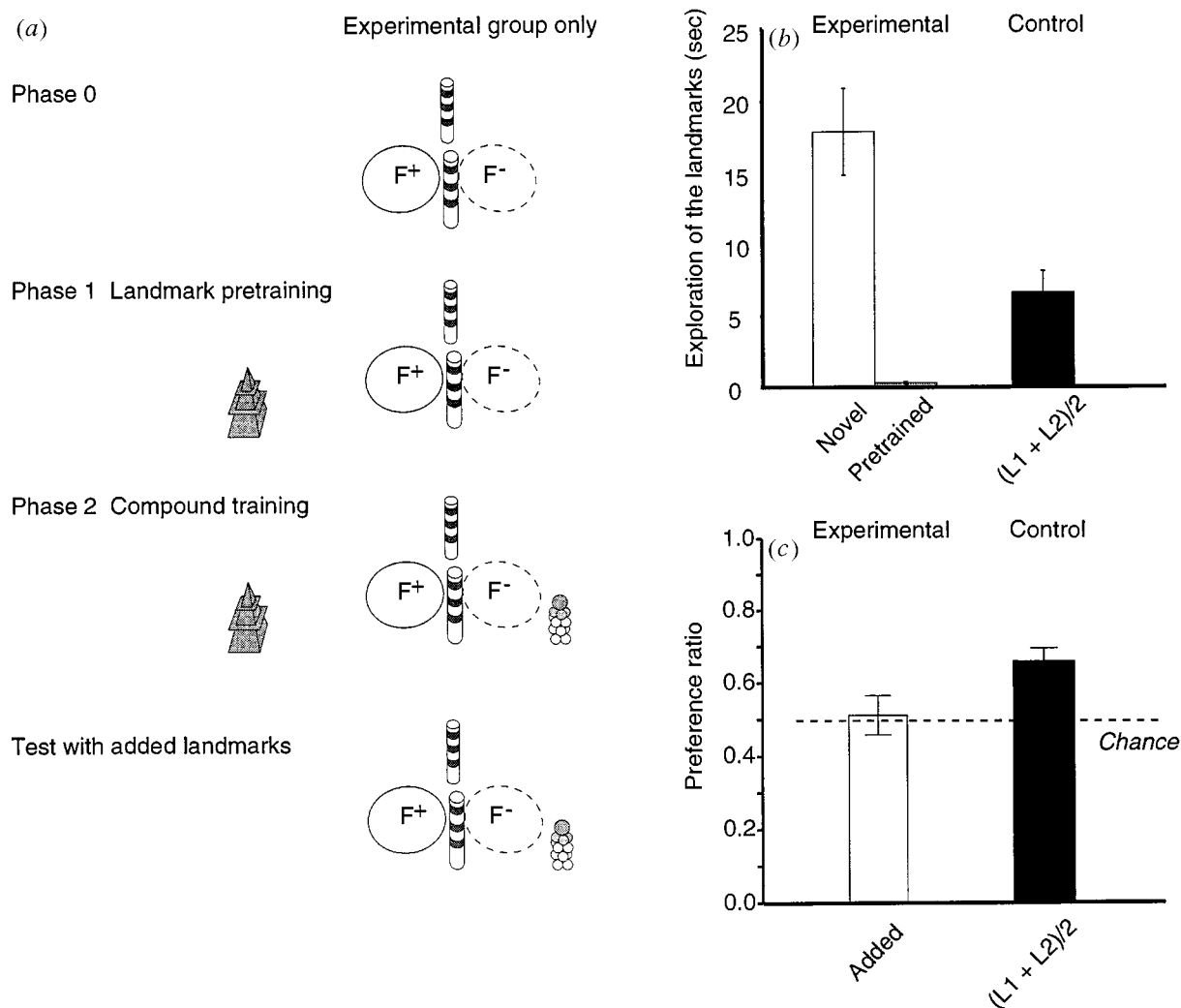


Figure 2. Blocking in the spatial domain. (a) The experimental design consisted of successive phases. For the experimental group (shown), the animals were first trained (phase 0) to find food (F+) in relation to two identical white towers. In phase 1, a landmark (grey pagoda symbol) was then added to disambiguate the situation and the animals trained until search was focused at F+ rather than F-; in phase 2, a second landmark was then added (stack of golf balls) and additional training given for several days; finally, a test was conducted with this added landmark (and the two identical landmarks). For the control group (not shown), the landmark used in phase 1 was visually distinctive and in a different geometric location. (b) Searching of the added landmarks during trial 1 of phase 2 (time spent (in seconds) in circle of radius 20 cm around each landmark ± 1 s.e.m.). The control group explores both added landmarks $(L1+L2)/2$; the experimental group directs search to the novel landmark added on that trial. (c) Searching during the transfer test with the landmark added at the start of phase 2 for the experimental group (preference ratio $= T_{F+}/(T_{F+} + T_{F-}) \pm 1$ s.e.m.). The control group shows a bias towards searching at F+ but the experimental group does not. Based on Biegler & Morris (1997).

The transition from phase 1 to phase 2 was one focus of attention: whether the experimental group would react to and explore the novel added landmark. The second focus of attention was whether this group would incorporate the added landmark into its spatial map of the landmark array. To measure this, a series of post-training probe tests were conducted at the rate of one test per two days, interleaved with additional training at asymptote. The key test among these examined how well the animals could search appropriately for the food with only the single landmark added in phase 2 (as well as the two identical landmarks present throughout training).

Two main findings were obtained. First, during the transition from phase 1, both groups explored the

added landmarks. Exploration was measured by recording the amount of time spent searching in a 20 cm radius around each of the landmarks during the first trial of phase 2. For the control group, both landmarks were novel and both were explored. For the experimental group, only one landmark was novel and only it was explored (figure 2b). In keeping with O'Keefe & Nadel's (1978) theory, exploration is triggered and guided by a mismatch between the animal's stored and perceived representations of space. The animals of the experimental group were not so intent on finding the food that they ignored the added landmark.

However, the second finding was that this exploration (which habituated rapidly over the course of the

next 1–2 trials) was insufficient for the location of the added landmark to be incorporated into the experimental group's spatial map. In the post-training test after the end of phase 2, the extent to which both groups searched preferentially in an area of 20 cm radius around the F+ and F– locations on either side of the two identical landmarks was measured (figure 2c). The control group learned about both landmarks that had been added together in phase 2 and used each of them to disambiguate the locations of F+ and F–. Both were incorporated into the animals' representation of the landmark array and either could be used alone to localize F+. In contrast, the experimental group noticed the added landmark and explored it, but then ignored it. It failed to search preferentially at F+. Thus, blocking occurs in the spatial domain. Spatial learning is influenced by the extent to which the animals need to learn about the location of landmarks to find a desired goal (see, also, Rodrigo *et al.* 1997).

There are several implications of these results for the study of spatial learning. The key point in the present context is that the incorporation of information into an animal's representation of space cannot be explained fully in terms of a simple Hebbian type of correlational rule. The learning rule must be more complex and probably involves at least two processes: (i) perception of mismatch followed by exploration and the short-term retention of information that could prove of value, followed by (ii) some decision-making process governing the incorporation of the temporarily stored information into the animal's long-term representation of the environment. The former process can be thought as a kind of novelty-detection, guided by the animal's existing and activated knowledge base (its spatial map in this case). The latter can be thought of a selective process, and perhaps as an aspect of memory consolidation in which errors are corrected as a function of need. A goal-driven error-correcting learning rule is engaged if the animal is required to alter its representation of the environment to find the goal. This study did not address the issue of whether hippocampal synaptic plasticity is engaged in either of these processes. However, to anticipate the argument, it is surmised that the 'automatic recording' process is likely to be involved in only the first of these two processes.

5. THE ROLE OF NMDA RECEPTORS IN DELAYED MATCHING TO PLACE: A FORM OF EVENT MEMORY?

Two distinctive features of 'event memory' are that it refers to memory for something that may happen once only (rather than repeatedly) and that singular events happen in specific spatial contexts. A memory system capable of keeping track of events must therefore have the ability to encode information very rapidly. Moreover, because it may be helpful to distinguish between similar events occurring in different spatial contexts, an event-memory system will disambiguate more effectively if it encodes where an event happened in addition to information about its nature. As Gaffan (1994, this volume) has cogently argued, episodic

memory may be fundamentally spatial in origin, although not necessarily linked to navigation through space or to the detailed geometric representation of space. Certain phenomena, such as food-caching (Sherry *et al.* 1992; Jacobs 1994), illustrate this 'episodic' aspect of spatial memory.

A complication in thinking about event-memory in animals arises from the fact that, in humans, the occurrence of events is normally reported via language. The question therefore arises of whether it is possible to devise tasks for animals that reflect event memory unambiguously. Broadly speaking, there are two views one can take on this question. One view holds that animals do not possess 'episodic memory' in 'quite' the same way as humans (Tulving 1983, p. 1). Thus such tasks cannot be devised. The present authors favour the alternative view that animals are capable of event memory, but that few laboratory tasks developed so far are unambiguous reflections of such a memory process. The watermaze, as it is usually run (i.e. as a reference-memory task), is a case in point. Animals are given repeated training trials to find a fixed hidden platform. The events that happen on each of these trials contribute, usually incrementally, to their eventual 'semantic' knowledge of the task. There is no obligation on the part of the animals to remember 'explicitly' any specific event that has happened during training. When placed into the water on trial *N*, there is no necessity for them to have a 'recollective experience' of what happened on trial *N*–1. All that is required is that they develop knowledge about the environment, about the location of the hidden platform, and some kind of behavioural strategy to perform the task. The animals may remember their previous experience in the pool, but this is not required. In animal learning theory, this idea is sometimes referred to as the 'independence of path assumption'.

To model episodic memory in animals more effectively, the challenge is therefore to devise new tasks in which having a 'recollective experience' would be helpful (or even required). More formally, such a task should distinguish between *changes in behaviour that occur because an animal remembers some prior event* and *changes in behaviour that merely happen because some prior event has occurred*. This distinction, although subtle, is absolutely fundamental to the claim that animals possess 'elements of episodic memory'. Such a task might also help in investigating comparative aspects of the character of event memory and its neural mechanisms.

Steele & Morris (1997) have recently developed a modification of the watermaze task that goes some way towards this. The procedure is as follows. Rats are trained to find the hidden platform in the pool at a rate of four trials per day. Importantly, the platform moves from one random location to another random location each day so that, on trial 1 of the day, the animals have no way of knowing where the platform is located. Having found the platform on trial 1, the animals may be able to remember the 'event' of having got out of the water at this location during the second and succeeding trials, and so use this trial-unique information to escape faster on trials 2–4. The results show that this is precisely what happens (figure 3a). Early in training,

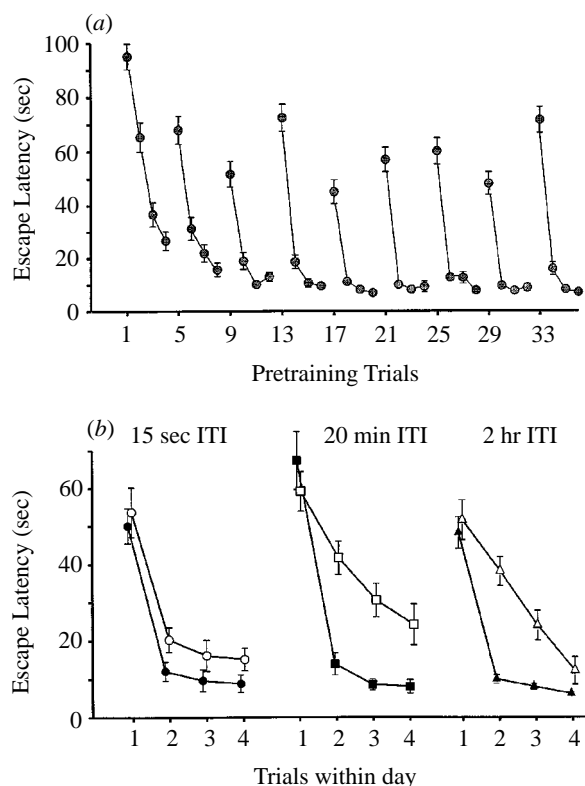


Figure 3. Delayed matching to place. (a) Escape latency (± 1 s.e.m.) over the nine days of pretraining, four trials per day, with the escape platform moving location each day. Note that latency on trial 1 stabilizes at around 60 s, whereas trial 2 latencies drop over the course of training from 65 s to less than 20 s. The saving between trial 1 and trial 2 reflects memory of platform location on trial 1. Normal animals shown as grey symbols. (b) Performance of the DMP task during the nine days of testing in the presence of AP5 (filled symbols) or aCSF (open symbols) when the data are subdivided as a function of the intertrial interval between trials 1 and 2 (the ITI between trials 2, 3 and 4 was always 15 s). Note the delay-dependent effect of AP5; savings are equivalent at the short ITI, but decline in the AP5-treated group as ITI is lengthened. Based on Steele & Morris (1997).

the escape latency on trial 2 is quite long. After a few days, trial 2 latencies drop substantially and stabilize at a level that improves no further. Trial 1 latencies average about 60 s. By this stage of training, the animals are familiar with the environment and have a stable spatial representation that could provide a framework in which to remember where events happen in the environment.

This delayed matching-to-place (DMP) task cannot, however, be unambiguously described as an event-memory task. It is different from strict 'working-memory' tasks of the kind described by Olton *et al.* (1979) because in these, information is retained and used within a single trial. In the DMP task, information acquired in one trial is used in subsequent trials, but is not necessarily of value for the purpose of creating a lasting long-term memory. However, what is unclear is whether the animals remember the recent

event of escaping at that place, or merely a recent place; moreover, recently visited places might simply acquire a relative increase in 'familiarity' compared with other places in the room, obviating the need for 'recollective experience'. However, in comparison with the spatial reference-memory task used in the earlier experiments, the capacity to remember selectively what has happened most recently is clearly a useful component of event memory. If so, disruption of the system responsible for encoding recent events would be expected to cause memory deficits, particularly if the interval between trial 1 and the subsequent trials was lengthened. It was therefore asked whether this DMP task was sensitive to the NMDA-receptor blockade in a delay-dependent manner.

To determine this, rats were first trained as normal rats (i.e. before drug administration) over nine days with four trials per day. The hidden platform was located in a different position each day (nine locations) and the animals were allowed 30 s on the platform after escaping from the water. This gave them an opportunity to encode the location where they escaped. During this pretraining, three different intertrial intervals (ITIs) were used between trials 1 and 2. On three days (randomly intermixed), the ITI was 15 s; on three days it was 20 min; on the remaining three days it was 2 h (these are averaged in figure 3a). The ITI between trials 2 and 3, and between 3 and 4, was always 15 s. The animals were then divided into two groups given AP5 or aCSF via minipumps as before. Both groups were then retrained on the task over nine days with nine new platform locations. As in pretraining, the ITI between trials 1 and 2 was varied between the three intervals.

The AP5-treated animals showed a striking delay-dependent pattern (figure 3b). When the interval between trials 1 and 2 was 15 s, they performed well and indistinguishably from the aCSF-treated animals. Both groups took approximately 1 min to find the platform on trial 1 but only 20 s on trial 2. This 'saving' in escape latency reflects their ability to remember, on trial 2, the location that the platform had occupied on trial 1. However, when the ITI between trials 1 and 2 was lengthened to 20 min and 2 h, the AP5-treated animals were impaired. Whereas the aCSF group continued to be able to remember back to trial 1 without difficulty, the drug-treated group showed much longer escape latencies on trial 2 and thus much less saving. The change in performance showed up in the analysis of both trial 2 latencies and T1-T2 savings scores as a highly significant statistical interaction between groups and delay interval, i.e. there was a true delay-dependent effect.

What are the implications of these findings? In §3 above, it was shown that prior spatial training on a reference-memory task resulted in subsequent spatial training in a new environment being insensitive to AP5. From this and other results (Saucier & Cain 1995), it might be supposed that NMDA receptor activation is not critical for spatial learning. However, it was also seen that changing the pretraining from a spatial task to a random search task (with extramaze cues obscured) had the effect of restoring, at least

partly, the sensitivity of subsequent spatial learning to AP5. The effects of AP5 on the new DMP task take this a step further, bearing out the notion that spatial learning is divisible into AP5-sensitive and AP5-insensitive components. The DMP task also uses pretraining of normal animals to develop the strategy, but, instead of requiring learning of a new environment under AP5, its performance requires memory of the most recently visited location within a now familiar environment (ie. a recent event–context association). On trial 2 of each day, the animals are attempting to remember what happened to them the last time they were in the pool. AP5-treated animals can only do this over a short period.

6. SYNAPTIC TAGGING AND THE VARIABLE PERSISTENCE OF HIPPOCAMPAL SYNAPTIC PLASTICITY

In describing the physiological properties of LTP (§2 above), its persistence for at least one hour was identified as the defining property of the phenomenon. It is clear that persistence is a necessary condition for a putative synaptic mechanism of information storage underlying any kind of long-term memory. A prominent characteristic of event memory is, however, that some events are remembered for a long time, others only for a short time. In fact, the human capacity to remember the inconsequential events of the day for any length of time is quite limited, although we are generally able to remember such events for a few hours. It follows that, if NMDA receptor-dependent plasticity is an essential prerequisite for event memory, factors contributing to the variable persistence of LTP could be of functional significance with respect to the strength or accessibility of memory ‘traces’.

The issue of variable temporal persistence is made more complicated by the possibility that events happening closely in time may be part of a single ‘episode’, where an episode is defined as a sequence of related events. It would clearly make sense for the encoding system to be organized in such a manner that most or all events associated with an episode are recalled together. Spatial context may be one important feature of this ‘binding’ process because, if events are remembered with respect to where they happen, this could provide a basis for considering them as part of a single episode. A common spatio-temporal context is, of course, likely to be only one of several determinants of this binding process.

These speculations form part of the intellectual context of a new series of experiments on the persistence of protein-synthesis-dependent late LTP (Frey & Morris 1997). The immediate aim of this study was to address the issue of how the input-specificity of late LTP is realized. The early phase of NMDA receptor-dependent LTP, lasting less than 3 h (early LTP), can be dissociated from LTP lasting longer (late LTP) by using inhibitors of protein synthesis. However, whether synthesized in the cell body (arguably the more important site (Frey *et al.* 1989)) or in dendrites (Feig & Lipton 1993; Steward & Wallace 1995; Torre & Steward 1996), the question arises of how the input-

specificity of late LTP is achieved without elaborate protein trafficking. One way might be via the creation of a short-lasting ‘synaptic tag’ at each activated synapse at the time of LTP induction (figure 4). This tag would have the potential to sequester plasticity-related proteins to stabilize early LTP at that synapse and so render it long-lasting. In the simplest case, a single strong input to a population of afferent fibres could (i) induce early-LTP, (ii) set synaptic tags locally in the postsynaptic compartment of each of the activated synapses, and (iii) trigger the biochemical cascades that increase the synthesis of plasticity-related proteins (PPs). The diffuse travel of these newly synthesized PPs inside the cell’s dendrites would result in tag–protein interactions only at previously activated synapses. This hypothesis makes an intriguing prediction. Provided the creation of these tags is independent of protein synthesis, there is no reason why tags set in the presence of drugs that inhibit protein synthesis should not ‘hijack’ PPs synthesized earlier and so stabilize any early LTP induced after protein synthesis has been shut down. Paradoxically, the synaptic-tag mechanism for realising input-specificity allows for the possibility that protein-synthesis-dependent LTP can be induced during the inhibition of protein synthesis.

Stimulation and recording were conducted in the stratum radiatum of area CA1 *in vitro* by using extracellular techniques. Figure 4*a* shows that when a strong tetanus was applied to a pathway (S2) in the presence of anisomycin, a decaying early LTP was induced but not late LTP. The cartoon insert shows that protein synthesis cannot be induced during the application of anisomycin. In figure 4*b*, S1 is strongly tetanized before anisomycin application. S2 is also strongly tetanized, but only after protein synthesis has been inhibited by the drug. Late LTP none the less develops on S2 because PPs synthesized in response to tetanization of S1 are captured by the tag set on S2. The same phenomenon can be displayed by using weaker patterns of stimulation that cannot, on their own, trigger protein synthesis. Figure 4*c* shows that weak tetanization of S2 only induces early LTP. In figure 4*d*, weak tetanization of S2 is preceded by strong tetanization of S1. Late LTP develops on pathway S2 because the tag set by weak stimulation of S2 sequesters proteins synthesized in response to the stimulation of S1. Further experiments of this series indicated that the putative ‘synaptic tag’ lasts less than 3 h (see Frey & Morris 1997).

There are three immediate implications of these findings. First, they support the synaptic-tag hypothesis. Second, the input-specificity and temporal persistence of LTP must be determined somewhat separately. Whereas input-specificity is determined by the local synaptic activation of NMDA receptors, temporal persistence appears to be determined, at least in part, by the history of activation of the neurone. Third, weak afferent events that usually only give rise to transient changes in synaptic efficacy can be made to cause lasting changes in neurones in which the synthesis of PPs has previously been upregulated. These findings are relevant to the general hypothesis of this paper, as discussed below.

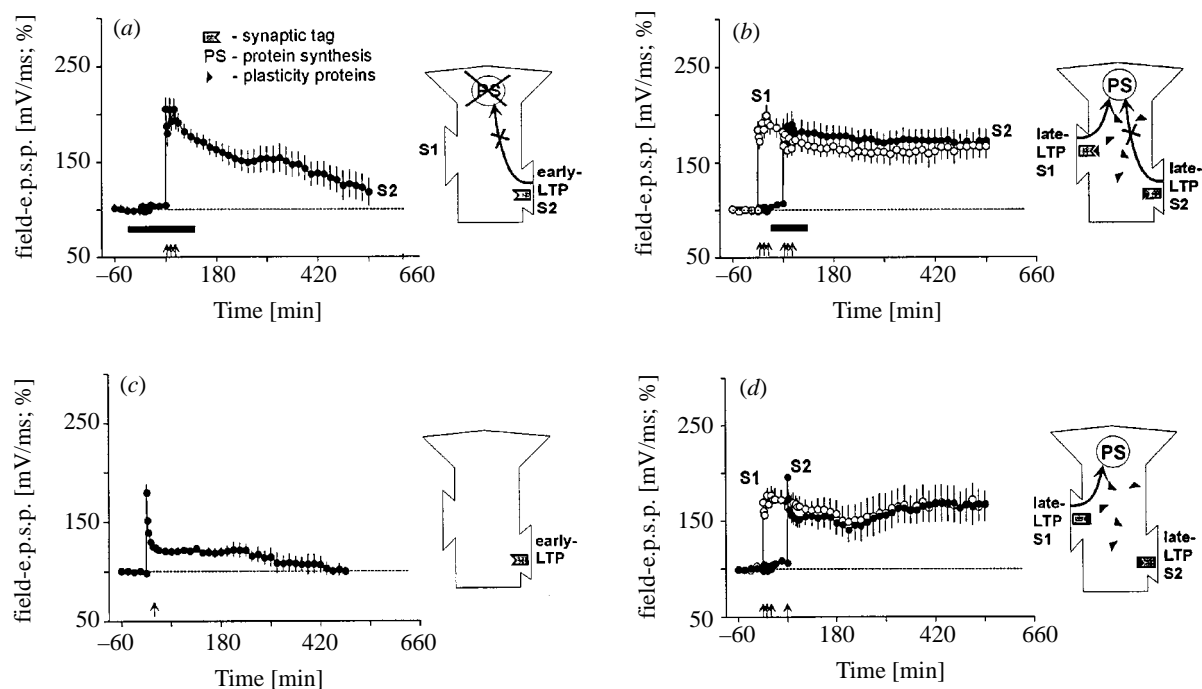


Figure 4. Synaptic tagging and long-term potentiation. (a) Induction of short-lasting long-term potentiation (early LTP) on pathway S2 in response to a strong tetanus (three trains of 100 Hz for 1 s, arrow symbols) given in the presence of anisomycin (black bar). The cartoon inset shows that a synaptic tag has been set on pathway S2 but protein synthesis is blocked (cross symbol). (b) Prior induction of late LTP on pathway S1 now allows late LTP to be induced on pathway S2 even when the strong tetanus is given in the presence of anisomycin. The cartoon inset shows synaptic tags set on both S1 and S2, and events at the synapses activated by S1 capable of triggering protein synthesis. Plasticity-related proteins (triangles) diffuse through the dendrites, where they are sequestered by the tags set at both pathways. (c) Induction of early LTP on pathway S2 in response to a single short tetanus (one train of 100 Hz for 200 ms). No drugs to limit protein synthesis are necessary. The early LTP induced decays over 3–4 h. (d) Prior induction of late LTP on pathway S1 also allows late LTP to be triggered in response to single-tetanus activation of S2. The tag set at S2 can sequester plasticity proteins synthesized in response to activation of S1. Based on Frey & Morris (1997).

7. GENERAL DISCUSSION

The aim of this paper has been to present a series of experiments that collectively point to a new way of thinking about the functional role of NMDA-dependent hippocampal synaptic plasticity. Specifically, in contrast to the current emphasis upon its serving a role in associative and/or spatial learning, this paper has summarized findings more consistent with its playing a role in one aspect of event memory.

(a) Summary of experimental findings

The evidence here summarized against a Hebbian correlational rule being sufficient to account for spatial learning is at two levels. First, varying the character of pretraining given before animals are later trained on a spatial reference memory task can change this second task from one that is sensitive to an NMDA antagonist (if no pretraining is given) to one that is insensitive (after spatial pretraining in a different environment). This differential sensitivity suggests, at a minimum, that spatial learning in a watermaze is more complex than previously recognized and that NMDA-receptor activation is not critical for learning the spatial relationships between extramaze cues (the usual way of

thinking about this type of learning). Second, at a purely behavioural level, the observation that ‘blocking’ occurs in the spatial domain also indicates that the determinants of spatial learning must be quite complex. The results here presented show that rats are sensitive to differences between their perception and stored representation of a landmark array, and that their reaction to mismatch is expressed in the form of exploratory behaviour. Exploration of a novel landmark is, however, no guarantee that its location will be incorporated into the animal’s spatial map. Incorporation only occurs to the extent that information is needed to locate a goal. That exploration of the novel landmark declines over trials indicates that some information about it is rapidly encoded; the possibility that this includes information about its location cannot be excluded. However, if this does happen, it is not in a form that can later be used to guide search behaviour. Our view is that the hippocampally based automatic recording system has access to the animal’s currently activated spatial map and that it triggers exploratory behaviour (directed attention) in situations where there is mismatch. If the information it then acquires is needed—for example to find the goal in a new place—the effortful components of the long-term memory system are engaged and the animal’s spatial

representation of the environment updated. When it is not needed to find the goal, there will be no 'reinforcement signal' of a goal-directed character and, thus, the error-correcting learning rule used for long-term memory need not be engaged.

The positive evidence in favour of hippocampal LTP playing a role in event-memory is also at two levels. First, it was shown that, after animals have been pretrained in the DMP task to a stable level of proficiency, chronic infusion of AP5 causes a severe delay-dependent impairment. This finding implies that blocking NMDA receptors does not affect the use of spatial information *per se*, but might impair the capacity to form or recall recent events in relation to a previously learned spatial framework. In this case, and unlike the study by Bannerman *et al.* (1995), the behavioural strategy that the animals acquire during pretraining is one that continues to call upon event memory for its deployment. Second, we have uncovered a novel property of LTP—synaptic tagging—that is suggestive of LTP playing a role in episodic memory. A synaptic tag provides a way of marking that an event has happened and has been recorded as a recent distributed alteration of synaptic strengths. It also extends the opportunity for creating a more lasting long-term memory as a function of other events happening around the same time. The determinants of persistence of synaptic enhancement extend beyond the particular pattern and strength of activation at the time of LTP induction; the history of activation of the neuron is also important.

(b) The automatic recording of attended experience

The theoretical proposal for integrating these findings is that the neural mechanisms underlying hippocampal NMDA-dependent synaptic plasticity underlie temporary information storage within a network responsible for the 'automatic recording of attended experience'. This recording system is part of a larger 'episodic memory' system of the brain (Tulving 1983). In making this proposal, a distinction is drawn between functions of the hippocampus itself and our proposed function of NMDA-dependent hippocampal synaptic plasticity. This is an important distinction: there may be other functions, including information retrieval from cortex, in which the hippocampus participates (and specifically, fast synaptic transmission) but in which changes in synaptic efficacy are unnecessary.

Beyond this, we make the following further comments about the hypothesis. First, the inclusion of 'automaticity' within the definition emphasizes the need to distinguish between automatic and effortful aspects of memory encoding. Many types of memory experiment in humans, such as remembering lists of words accurately, or recalling the details of complex pictures, require careful and deliberate scanning of the stimulus material and an effortful process of encoding. This type of memory requires the integrity of structures in the medial temporal lobe (Squire & Zola-Morgan 1991) and there is evidence from functional imaging studies that it also activates the frontal lobe (Shallice *et*

al. 1994; Kapur *et al.* 1994; Tulving *et al.* 1996). Our supposition is that 'episodic memory' might usefully be subdivided into an automatic subsystem involved in 'online' information capture (medial-temporal?) and a second subsystem involved in the deliberate creation of veridical memory traces as a function of task demand (frontal?). If a task requires accurate recall of a large amount of information, it is generally necessary to go over the stimulus information several times before a lasting veridical memory can be formed from the online record. This distinction has points of similarity to Moscovitch's (1995) important idea of a distinction within the domain of episodic memory between the conscious experience of an event (that he believes to be hippocampal) and the task of working with episodic memories during encoding and retrieval (involving the frontal lobes). Second, the reference to it as a recording of 'experience' constitutes a recognition that information cannot be processed automatically in a manner that is divorced from its spatiotemporal context (O'Keefe & Nadel 1978; Gaffan 1994). Events happen at particular places and particular times; human memory for events necessarily includes remembering where (and sometimes when) an event actually happened. Our supposition is that the system is tuned to record events with respect to the scenes or places where they occur, rapidly forming event-context associations. These associations serve the important function of helping to disambiguate similar stimuli occurring in different places. Third, we also consider 'automatic recording' a subsystem of episodic memory in which attended information is processed preferentially. Selective attention acts as a filter controlling the access of information to the system.

There are numerous facets of the hypothesis that need to be developed more formally if it is to be predictive. As we are proposing that hippocampal LTP plays a critical role in this type of temporary information storage, it follows that all mammals displaying LTP (with the properties we have described) should be capable of at least 'elements' of episodic memory. The extent to which this challenges Tulving's claim (1983, p. 1) that only humans are capable of this type of memory is largely one of emphasis. After all, his book recognized that certain phenomena studied in animals (such as the studies by Olton *et al.* (1979) of 'working memory' in the radial maze) may be analogous to episodic memory in humans. Our suspicion, guided in part by later writings (Tulving & Markowitsch 1994), is that Tulving has always been sceptical about whether animals are capable of remembering events in 'quite' the same way as humans (his emphasis). Underlying this scepticism may be the supposition that, because animals are unable to report events via the medium of language, they have no need of 'recollective experiences'. We prefer the alternative view that event memory evolved because it is useful to an organism in its own right, with the communication of information about events being a separate matter. The division of episodic memory into (i) a subsystem involved in the online capture of events, and (ii) a system for integrating information as a function of task demand could be valuable in all mammalian species.

The challenge for neuroscientists investigating memory in animals is, therefore, to devise ways of distinguishing between changes in behaviour that occur because of true memory for events and those that occur simply because an event has happened. We do not yet offer any solution to this important problem.

A separate point is that the proposal for subdividing episodic memory is in the tradition of seeing an important link between memory and understanding. This link is rarely discussed by proponents of declarative memory (cf. Squire *et al.* 1993), but has been a key aspect of the 'cognitive mapping' theory of O'Keefe & Nadel (1978). Briefly, we believe that the processing of information within the automatic recording system is strongly influenced by the current activated knowledge of the animal (or human). Animals do not just process attended information; they notice mismatches between what they perceive and what they know. In spatial learning, these mismatches immediately trigger exploration and such behaviour ensures that some record of the newly attended information is processed. In the delayed matching-to-place task, the capacity to respond appropriately to information acquired in a single trial relies upon the animal's having some activated representation of the space in which that event happens. Thus, the capture of new information is guided by what the animal already knows, focusing processing effort onto novel information. The notion that the memorability of information is importantly influenced by existing activated knowledge has long been appreciated in the human literature also (Bransford & Johnston 1972; Longuet-Higgins 1983). However, because we see a distinction between the automatic and effortful components of episodic memory, information captured temporarily may not be stored permanently. Memory consolidation is a selective process, guided in part by task demand and so by goal-directed error-correcting learning rules.

(c) *Neural implementation within the hippocampal formation*

The neural mechanisms of episodic memory are poorly understood. Pieces and patches are emerging from functional imaging studies, but these have so far been restricted to discoveries about localization within the brain and the sequence of mental processes involved, rather than underlying neural mechanisms. Our proposal is that NMDA receptor-dependent LTP in the hippocampus displays properties ideal for an 'automatic recording' subsystem (rapid associative induction using a correlational rule, input-specificity, variable persistence). The concept of the synaptic tag is relevant to this idea, as it affords a way of extending the persistence of synaptic changes induced by recent events as a function of their temporal proximity to other events. We conclude by focusing on the implications of synaptic tagging for event memory.

In physiological experiments designed to identify the mechanisms by which changes in synaptic efficacy are triggered, high-frequency stimulation of afferents can induce either a short or a prolonged increase in synaptic strength as a function of the prior (and perhaps

subsequent) activity state of the neuron. With respect to LTP, it has already been noted that an early phase can be dissociated from a late phase because only the latter requires the synthesis of new macromolecules. Activation of NMDA receptors and the subsequent influx of Ca^{2+} ions, possibly acting via the cytoplasmic tail of the NMDA receptor signalling complex, triggers several intracellular cascades. These are now thought to include the phosphorylation of kinases, of receptors and of target proteins as well as the synthesis of plasticity-related proteins (PPs) (Deisseroth *et al.* 1996; Malinow *et al.* 1988; O'Dell *et al.* 1991; Rostas *et al.* 1996; see Bliss & Collingridge 1993; Goelet *et al.* 1986; Schulman 1995; Walaas & Greengard 1991, for reviews).

The stimulation pattern that ordinarily results in early LTP activates only some of these intracellular processes. We have argued that they must also include, beyond expressing the change in synaptic efficacy itself, the setting of input-specific synaptic tags. The job of these tags is to sequester PPs to stabilize temporary synaptic changes. Identifying the molecule(s) that serve as synaptic tags is clearly a very important goal of future research. A parsimonious speculation, in the spirit of Goelet *et al.* (1986), is that such molecules are likely to be on the same biochemical pathway that gives rise to the synthesis of PPs. They are therefore likely to be downstream of the NMDA receptor, and possibly at, or upstream of, the protein kinase A (PKA) signalling pathway that activates transcription factors in the cell nucleus. The type of experiment needed to identify a candidate tag will, therefore, involve the two-pathway S1-S2 paradigm used by Frey & Morris (1997), with strong tetanization of S1 followed by tetanization of S2 during the application of selective enzyme-inhibiting drugs. Pharmacological studies would, of course, have to be complemented by relevant molecular and cell-biological work.

Increasing the strength of the stimulation needed to induce early LTP also activates mechanisms responsible for the synthesis of PPs. Identification of these PPs is also an important priority of current research. A clue to what might be involved is the finding of a transient increase in intracellular levels of cyclic AMP (cAMP) in CA1 after both strong tetanization that results in late LTP (Frey *et al.* 1993) and pharmacological activation of the NMDA receptor (Chetkovitch & Sweatt 1993). This increase probably then activates a somatically located cAMP-response element (CRE) that triggers immediate gene expression (Deisseroth *et al.* 1996). Interestingly, an input-*non*-specific late LTP can be induced by application of a membrane-permeable cAMP analogue which activates cAMP-dependent protein kinase A (PKA). This late LTP is prevented by simultaneous application of anisomycin, indicating the necessity for protein synthesis. Electrically induced, input-specific late LTP is also blocked by a PKA inhibitor applied during tetanization (Frey *et al.* 1993). Collectively, these data point to a multifunctionality of the cAMP-PKA pathway: it could be linked both to the synthesis of plasticity-related proteins and to the setting of synaptic tags. An additional point is that Frey *et al.* (1993) found that the increase in cAMP concentrations after strong

tetanzation was blocked by antagonists of the dopaminergic D1-receptor, a receptor that is positively coupled to adenylate cyclase. Late LTP is blocked by D1-receptor antagonists (Frey *et al.* 1990) and induced by D1 or D5 receptor agonists (Huang & Kandel 1995). Dopamine could have reinforcement properties, controlling the transformation of early LTP into late LTP. Other transmitter systems than just glutamate have to be brought into the picture in relation to the synthesis of PPs (see, also, Matthies 1989).

(d) Conclusion

Assuming these biochemical mechanisms can be identified, how might the synaptic tagging mechanism help the automatic recording system to achieve selectivity? We end with two speculations: the first concerned with a distinction between short- and long-term consolidation, the second with how episodes could be constructed from a succession of events.

First, variable persistence is important because it allows the duration of synaptic changes triggered by events to be influenced by other temporally adjacent events. We have argued that early LTP implements the on-line recording of information in an 'associative' manner, linking information presented to the hippocampal network about events (such as briefly presented stimuli, or an animal's own actions) to more stable information about the context in which they occur. The synthesis of PPs is likely to be increased if other events happening around the same time also trigger LTP in a common pool of neurons. This synthesis will, synergistically, increase the chance that temporally related events are sustained for longer in the hippocampal network (short-term consolidation). Long-term consolidation (stabilization of intracortical connections) also requires time; it is more likely to be successful if the automatic but temporary record is more persistent. Short-term consolidation extends the opportunity for the creation of lasting episodic memories or the incorporation of newly acquired information into an animal's or person's long-term semantic memory, a process that probably involves interaction with other brain areas (e.g. the frontal lobe).

Second, whereas synaptic tagging provides a mechanism for realizing variable persistence, it could also be useful in a number of distinct circumstances for enhancing the memorability of stimuli that might otherwise be poorly remembered. With respect to the circumstances surrounding emotionally significant events, it is not uncommon to remember numerous apparently trivial details. This phenomenon is sometimes referred to as 'flashbulb memory' (Brown & Kulik 1977). If emotionally charged events activate reinforcing inputs to the hippocampal formation (such as the dopaminergic system), incidental stimuli associated with these events could trigger changes in synaptic plasticity in the hippocampus and set synaptic tags against the background of this greater availability of PPs. Memory of these incidental stimuli would then be longer-lasting. A different way in which trivial events might be rendered more memorable would be if the neural representation of two (or more) events in the

hippocampus shared a common pool of neurones. This would be most likely if two events occurred in a common spatial location. For example, if events were represented as sparsely coded but orthogonal patterns of activation on glutamatergic input pathways to the hippocampus, the construction and binding together of 'episodes' might occur when these patterns activated a common pool of place cells. Under these circumstances, a weak event might innervate a substantially similar population of cells as a stronger event and so benefit from the latter triggering the synthesis of PPs. Place-event associations may thereby provide a way of constructing coherent episodes. As O'Keefe & Nadel (1978) and Gaffan (1994) before us have argued, spatial memory provides the evolutionary foundation upon which the elaborate scaffold of human episodic memory is built.

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