Borrowing/Requesting Library: As a service enhancement, MINITEX is directly scanning requests and transmitting them using Ariel software from BioMed.

If you have any problems with this delivery, please contact us within 48 hours:

♦ Return this cover letter with an explanation of the problem via Ariel.
♦ Our Ariel IP address is 160.94.20.179
♦ Return this cover letter with an explanation of the problem via Fax
♦ Our Fax number is 612-626-1673
♦ Contact us via e-mail at ariel01@othello.minitex.umn.edu
♦ Call MINITEX:
  ♦ Toll Free 1-800-462-5348
  ♦ Ariel Voice Mail 612-625-8318
  ♦ Joan Wollenberg 612-626-9239 or Dave Paulson 612-624-7568

Library Patron: If you have any problems with the attached item, please contact your local interlibrary loan office. Thank you.

NOTICE: This material may be protected by copyright law. (Title 17 U.S. Code)

MNN 5784384
Lender: *MII,MII,MII,MII,BTS

Title: Hippocampus.

Article: Martin,; New life in an old idea: The synaptic plasticity and memory hypothesis revisited
Vol: 12  No: 5  Date: 2002  Pages: 609-636

Verified: OCLC 21725124 <TN:36568> OCLC
Locations: UMM,OMC

ISSN: 1050-9631
Patron: hamid, Edaeni
Copyright: CCG

Ship To: Carleton College/Gould Library ILS/1 N College
St/Northfield MN 55057-4097
New Life in an Old Idea: The Synaptic Plasticity and Memory Hypothesis Revisited

S.J. Martin* and R.G.M. Morris

Department of Neuroscience, University of Edinburgh, Edinburgh, Scotland, United Kingdom

ABSTRACT: The notion that changes in synaptic efficacy underlie learning and memory processes is now widely accepted, although definitive proof of the synaptic plasticity and memory hypothesis is still lacking. This article reviews recent evidence relevant to the hypothesis, with particular emphasis on studies of experience-dependent plasticity in the neocortex and hippocampus. In our view, there is now compelling evidence that changes in synaptic strength occur as a consequence of certain forms of learning. A major challenge will be to determine whether such changes constitute the memory trace itself or play a less specific supporting role in the information processing that accompanies memory formation. Hippocampus 2002;12:609–636. © 2002 Wiley-Liss, Inc.

KEY WORDS: LTP; LTD; learning; hippocampus; cortex

INTRODUCTION

When learning occurs, patterns of neural activity representing the occurrence of events cause changes in the strength of synaptic connections within the brain. Reactivation of these altered connections constitutes the experience of memory for these events and for other events with which they may be associated. These are controversial statements, of course, but they summarize a long-standing theory of memory formation that we refer to as the synaptic plasticity and memory (SPM) hypothesis. The discovery of long-term potentiation (LTP), whereby brief high-frequency stimulation of a neural pathway can induce long-lasting increases in synaptic efficacy (Bliss and Lømo, 1973), provided an experimental analogue of these postulated learning-induced changes in synaptic connectivity. Thirty years later, evidence consistent with the hypothesis has accumulated to the point where few doubt that the general principle is correct.

Our aim in the present article is to review recent developments in the field, with a focus on the observation of LTP-like changes that occur during and after learning (our detectability criterion; see below). Many reports of learning-induced plasticity have appeared in the past few years. However, the relevant literature is perhaps less well known than that concerning pharmacological or genetic manipulations that impact on synaptic plasticity and memory, a topic that we discussed at greater length in our previous review (Martin et al., 2000).

By "synaptic plasticity," we refer to any lasting upregulation or downregulation of synaptic strength, including both NMDA receptor-dependent and -independent forms of LTP, long-term depression (LTD), and depotentiation. Thus, forms of neuronal plasticity such as changes in neuronal excitability or experience-dependent neurogenesis are not included in the SPM hypothesis. Nonetheless, such phenomena may play a role in certain forms of memory (see Giese et al., 2001; Shors et al., 2001), but the hypothesis was intended to be restrictive in this respect. By "memory" we include any experience-dependent changes in behavior, or the stored knowledge upon which changes in behavior are dependent. That is, we subscribe to the view that synaptic plasticity may be relevant to multiple forms of learning and memory expressed in different brain regions.

Numerous variants of the SPM hypothesis have been advanced over the years (Kandel and Schwartz, 1982; Lynch and Baudry, 1984; Teyle and DiScenna, 1984; McNaughton and Morris, 1987; Morris et al., 1990; Siegelbaum and Kandel, 1991; Bliss and Collingridge, 1993; Izquierdo and Medina, 1995; Maren and Baudry, 1995; Jeffery, 1997; Morris and Frey, 1997; Baudry, 1998). However, the underlying core hypothesis might read something like this: "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."

HOMOLOGY BETWEEN PROPERTIES OF LTP AND PROPERTIES OF LEARNING OR MEMORY

It is often pointed out that LTP and LTD exhibit many properties that are highly suggestive of a role in information encoding and storage. However, it may not be reasonable to expect that all the properties of activity-dependent synaptic plasticity will be directly mirrored in...
the properties of memory. Memory is a property of the entire organism whereas plasticity is a property of synapses; the circuit-level operation of a neural structure will not necessarily be reflected, in miniature, by the operational characteristics of its synaptic components. But although such isomorphisms are not always to be expected, they are nonetheless sometimes observed. In their review, Bliss and Collingridge (1993) outlined several now classical properties of LTP, such as associativity, input specificity, and persistence over time. Some of these properties, such as persistence, are likely to place tighter constraints on memory than others. Regardless of whether hippocampal synaptic potentiation plays a time-limited role in memory, it must last for a reasonable length of time to be considered as a viable memory mechanism.

The decremental time-course of hippocampal LTP has, as it happens, sometimes been presented as an obstacle to its suggested role as a memory mechanism; but it is not clear how persistent LTP ought to be (Abraham, 2001). Many argue that the hippocampus plays a time-limited role in information storage, with the cortex being the ultimate repository of many kinds of memory (e.g., Squire, 1992; Squire and Alvarez, 1995). If so, there is no obligation for LTP-like changes in the hippocampus to last indefinitely. In addition, unlike the artificial LTP induced by a single episode of tetanic stimulation, memory traces may be sustained in an activity-dependent manner by off-line reactivation, rehearsal, and reminding. Similarly, homeostatic mechanisms may serve to reduce artificially induced global increases in synaptic strength, a fate that might not be shared by learning-induced plasticity. Nevertheless, there is evidence that CA1 LTP can indeed be nondecremental under some circumstances (Stiubli and Lynch, 1987; for discussion, see Abraham, 2001). Similarly, although resistant to induction, neocortical LTP can last weeks, once obtained (Trepel and Racine, 1998). Although we do not yet know whether changes in cortical synaptic strength can last a lifetime, it would be premature to reject synaptic plasticity as a memory mechanism merely for this reason. Hippocampal LTP may need only last long enough (a few weeks perhaps) to permit completion of a slower neocortical consolidation process.

Another potential mismatch between LTP and learning is suggested by their differing temporal contingency requirements (Diamond and Rose, 1994). LTP induction is asymmetric, such that presynaptic activity must precede postsynaptic activation for potentiation to occur (Levy and Steward, 1983; Gustafson et al., 1987). Recent evidence indicates that the relative timing of an excitatory postsynaptic potential (EPSP) and a back-propagating dendritic action potential is critical in both the neocortex (Marr, 1997; see also Stuart and Haussler, 2001) and hippocampus (Magee and Johnston, 1997; Bi and Poo, 1998). Presynaptic activity occurring within tens of milliseconds before postsynaptic spiking results in LTP, whereas the opposite sequence results in LTD, at least in vitro. In fact, bursts of postsynaptic firing appear to be necessary for synaptic potentiation in adult CA1 in vitro (Thomas et al., 1998; Pike et al., 1999). It has been pointed out, however, that the time window governing associative conditioning is typically much looser, with optimal intervals between conditioned stimulus (CS) and unconditioned stimulus (US) ranging from hundreds of milliseconds to hours depending on the specific conditioning task investigated (Diamond and Rose, 1994; Shors and Matzel, 1997). This result is only paradoxical, however, if a very simple circuit is assumed, in which CS-US associations occur online at the level of individual synapses. It is less problematic if the time-scale for information representation in a given brain region is different from that pertaining to events as they happen. We will return to this issue later in our discussion of conditioned taste aversion learning.

Nonetheless, recent evidence suggests that this apparent mismatch between LTP and learning may sometimes disappear, particularly in sensory systems. An example is provided by the fact that the temporal window for pre- and postsynaptic interaction in cortical receptive field plasticity is strikingly similar to the time window for LTD/LTP induction (Schuetz et al., 2001; Yao and Dan, 2001). In our previous review, we discussed the difference between reflex networks in which the direction of synaptic change reflects the direction of change in the overt behavioral output, and distributed matrix memory networks (Martin et al., 2000). Although the reality may be far more complex, it seems reasonable to predict that the strengthening of specific inputs to orientation-selective neurons within V1 will alter their receptive field tuning—and consequently the animal’s perception—in a straightforward, online, and readily predictable manner. However, in other memory systems, such as the hippocampus, it is hypothesized that changes in synaptic strength occur in a distributed fashion throughout a neuronal network. In such systems, memory formation may not relate in an isomorphic manner, either spatially or temporally, to increases or decreases in the efficacy of individual synapses. Dissociations between the properties of LTP and those of memory are only to be expected under these circumstances; but as the example of V1 receptive field plasticity suggests, such dissociations are not inevitable.

Another recent example of accordance between LTP and learning that might not have been predicted a priori is provided by recent work on amygdalar plasticity. Associative conditioning depends on the ability of the CS to predict the US (contingency); simply pairing CS and US (continguity) is not sufficient if, for example, many additional unpaired CS and US presentations are also introduced. The spike timing studies discussed earlier illustrate the temporal contingency requirements for LTP but, to date, they say nothing about contingency. However, an investigation of amygdalar plasticity shows that LTP and fear conditioning are indeed both sensitive to CS-US contingency (Bauer et al., 2001). In this study, a train of tetanic stimulation of thalamic afferents to the lateral amygdala in vitro was paired with a series of depolarizing current pulses to the postsynaptic neuron. This procedure was repeated 15 times at 20-s intervals, resulting in robust LTP. Intriguingly, the addition of unpaired depolarization 10 s after each pairing, analogous to unpaired US presentations, resulted in almost no LTP, despite the preservation of contingency. The mechanisms underlying this contingency phenomenon are currently unknown, but they clearly operate over a time-scale of ≥10 s. These findings illustrate that LTP, at least in the lateral amygdala, reflects a property of learning that might have been expected to arise only at the circuit level.
As we have emphasized previously, a comprehensive understanding of the role of synaptic plasticity in memory will only be possible once we reach an adequate understanding of the intervening circuit- and systems-level structures. In this context, it is important to recognize that the SPM hypothesis must take account of important advances in our understanding of different forms of memory over the past decade, no less than new findings about the induction criteria and different forms of activity-dependent plasticity. Different brain regions, and within these, different local circuits, mediate apparently independent forms of learning and memory. In the cerebellar cortex, for example, LTD is thought to play a prominent role in fine-tuning the connectivity strengths that mediate appropriately timed skilled movements. Our generic definition of the SPM hypothesis refers to “information storage underlying the type of memory mediated by the brain area in which that plasticity is observed.” Despite an understandable yearning for simplicity, we must not think that “does LTP equal memory?” (Stevens, 1998) is in any sense a theoretical question to be taken literally (nor, we suspect, does its author!). Changing synaptic weights up or down, and no more than that, may seem to be the heart of the matter. However, we can only understand how such changes mediate memory at an algorithmic level if we think about them with reference to the local circuit in which they are embedded.

### TABLE 1

**Four criteria relevant to the assessment of the SPM hypothesis**

**DETECTABILITY**: If an animal displays memory of some previous experience, a change in synaptic efficacy should be detectable somewhere in its nervous system.

**MIMICRY**: If it were possible to induce the appropriate pattern of synaptic weight changes artificially, the animal should display ‘apparent’ memory for some past experience which did not in practice occur.

**ANTEROGRADE ALTERATION**: Interventions that prevent the induction of synaptic weight changes during a learning experience should impair the animal’s memory of that experience.

**RETROGRADE ALTERATION**: Interventions that alter the spatial distribution of synaptic weight changes induced by a prior learning experience (see detectability) should alter the animal’s memory of that experience.

To provide a theoretical framework within which to evaluate the SPM hypothesis, we have outlined a set of criteria that, in our view, must be satisfied if the hypothesis is to be upheld (Martin et al., 2000) (Table 1). The first and most intuitive of these criteria—detectability—states that the formation of behavioral memory must be associated with detectable changes in synaptic efficacy somewhere in the nervous system. The main difficulty is deciding where to look. The second criterion, mimicry, seems somewhat far-fetched, at least in the hippocampus, but may be less so in other mammalian brain areas, such as the sensory neocortex (Taiwar and Gerstein, 2001), amygdala, and cerebellum (Shinkman et al., 1996), or in simpler vertebrate (Oda et al., 1998) or invertebrate systems (e.g., Oleskevich et al., 1997; Menzel, 2001). Nevertheless, this criterion is critically important as a 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.

In the following sections we will discuss a number of lines of evidence relevant to the synaptic plasticity and memory problem, organized according the assessment criteria outlined above. A systematic review of the current literature is beyond the scope of the present article. For this reason, we have chosen to limit our review, in most cases, to studies of mammalian synaptic plasticity and memory, with a particular focus on hippocampal and cortical synaptic changes. Regrettably, this excludes much of the seminal work carried out in Aplysia (e.g., Kandel and Schwartz, 1982; Murphy and Glanzman, 1997), as well as a growing body of evidence concerning the neural mechanisms of memory in a variety of other invertebrate and vertebrate systems. Similarly, we note that a considerable amount of evidence exists linking synaptic plasticity in the lateral amygdala with fear conditioning (LeDoux, 2000; Maren, 2001; Rosenkranz and Grace, 2002b; Tsvetkov et al., 2002). The same is true of cerebellar parallel fiber: Purkinje cell LTD and motor learning (for review, see Kim and Thompson, 1997; Lisberger, 1998; Mauk et al., 1998; Hansel et al., 2001; Ito, 2001). In some instances, again owing to space limitations, we focus on a small number of exemplar experiments that will, we hope, illustrate the current status of the field.

### DETECTABILITY

Until recently, most experiments seeking to identify a role for synaptic plasticity in memory processes were carried out in the hippocampal formation. Great interest was generated by initial reports that rats exploring an unfamiliar environment develop last increases in the dentate field EPSP (IEPSP), but early enthusiasm soon turned to skepticism. Certain pitfalls of this approach, such as the difficulty in dissociating true memory-related changes from those merely associated with changes in motor behavior or temperature, are now well appreciated and have been widely discussed elsewhere (Hargreaves et al., 1990; Andersen and Moser, 1995; Moser et al., 1995).

Why is learning-induced synaptic plasticity in the hippocampus so hard to detect? Skeptics may be rightly unimpressed by such a
question: perhaps such changes simply do not occur. Nevertheless, there is a general consensus that the hippocampus is a device specialized for the storage of memories, particularly episodic memories, whose information content is necessarily extremely high. Neural network models suggest that if a system is to have a high storage capacity, a sparse code is essential (Willshaw and Dayan, 1990). In other words, a single learning experience will probably lead to the potentiation of only a tiny fraction of the total number of synapses available. Evoked responses from large populations of synapses may therefore be unlikely to demonstrate learning-related changes. Looking for such changes using, for instance, multiple single unit recording, may also be a daunting task. Perhaps the hippocampus is the wrong place to begin such a search. Those familiar with recent developments in the study of amygdalar synaptic plasticity and learning might well agree. However, in the present report, we concentrate on recent evidence linking cortical synaptic plasticity with various forms of cortex-dependent memory, before returning to the domain with which we are most familiar: the hippocampus.

**Does Cortex-Dependent Learning Result in Cortical LTP?**

The neocortex stores many different kinds of information, and its representations are both dynamic and mutable. Individual sensory neurons in the cortex undergo experience-dependent changes in receptive field properties that blur the line between perception and memory (Weinberger, 1998). Patterns of sensory and motor information are distributed across populations of neurons in a topographic but plastic manner, in the form of modifiable cortical maps (Buonomano and Merzenich, 1998). Changes in the receptive field properties of individual neurons that comprise these cortical maps are considered in the following section.

The cortex also participates in the storage of explicit or declarative memories. In this case, the hippocampus is also believed to play a role in memory formation, perhaps encoding indices linking disparate neocortical modules whose connectivity is too sparse to support the encoding of arbitrary associations (Teyler and DiScenna, 1986). According to some investigators, the hippocampus subsequently plays a time-limited role in memory by enabling the gradual development of intracortical connections that render the cortical memory traces self-sufficient, a process sometimes referred to as systems-level consolidation (Squire, 1992; Squire and Alvarez, 1995). Others argue that the hippocampus has a permanent role in memory storage for certain kinds of information and, thus, its retrieval (Nadel and Moscovitch, 1997).

It is widely suspected that experience-dependent LTP- and LTD-like mechanisms underlie these distinct forms of cortical plasticity. Consistent with this view, bidirectional, activity-dependent synaptic plasticity can be induced in a variety of adult cortical regions, both in vivo and in vitro (e.g., Racine et al., 1983; Artola and Singer, 1987; Irizki et al., 1989; Bear and Kirkwood, 1993; Aromidej-Anderjaska and Keller, 1995; Castro-Alamancos et al., 1995; Glazowski et al., 1998; Escolar et al., 1998b; Sanes and Donoghue, 2000), as well as in freely moving rats (Jay et al., 1995; Trepel and Racine, 1998). In contrast to the hippocampus, the neocortex is highly resistant to the induction of LTD: potentiation is not readily induced by a single episode of high-frequency stimulation but requires, in freely moving animals at least, repeated episodes of daily tetanization (Trepel and Racine, 1998). This result is reminiscent of theories advanced by McClelland et al. (1995) and O’Reilly and Rudy (2000), according to which the hippocampus rapidly encodes new information, while a slow cortical memory consolidation process enables new memories to be interleaved with existing information.

**Synaptic plasticity and the experience-dependent reorganization of receptive fields and maps in primary sensory cortex**

Sensory cortical plasticity has been widely studied during the developmental critical periods of early sensory experience, and after brain injury or sensory deprivation (see, e.g., Berardi et al., 2000; Calvert, 2002; Fox, 2002; Jones et al., 2002; Katz and Crowley, 2002), but there are also numerous reports of learning-related plasticity in the cortical maps and receptive field properties of normal adult mammals. To give a few examples of the latter, monkeys trained to use one or more digits to perform a behavioral task exhibit several-fold increases in the area of somatosensory cortex devoted to the representation of those digits (Jenkins et al., 1990). Similar use-dependent changes in human somatosensory representations have been shown by magnetoencephalographic (MEG) studies of Braille readers (Pascual-Leone and Torres, 1993) or string players (Elbert et al., 1995). Learning-induced plasticity has also been observed in many other areas of adult sensory neocortex. Animals trained in a classical auditory conditioning task, for instance, develop shifts in the frequency tuning of cells within the auditory cortex and auditory thalamus toward the frequency of the conditioned stimulus (for review, see Weinberger, 1998; Edeline, 1999).

Before continuing our discussion of the literature, it is worth reflecting on some conceptual issues. The fact that dynamic modulation of cortical representations occurs in the course of associative learning might appear surprising. If natural activity representing a tone, for example, were to enter into an association with another stimulus, one might not expect the perceptual representation of the tone to be changed, merely its associated stimulus. The studies conducted by Weinberger and others indicate that this is not the case; sensory representations are indeed altered during learning. Such plasticity may represent a continuous readjustment of sensory information processing in order to optimize the perception of salient features in the face of a continuously changing environment, with its associated hazards and rewards. This form of physiological memory (Weinberger, 1998) is far removed from memory as generally understood by psychologists, but it provides a potential starting point from which our understanding of experience-dependent plasticity might grow. Receptive field plasticity may even be the key to understanding more cognitive forms of memory, the difficulty being that the concepts of preferred stimulus and receptive field become more abstract and difficult to define the further down the processing stream we venture.
The focus of this section is on studies in which the relationship between pre- and postsynaptic activity has been experimentally manipulated in an attempt to determine the rules governing experience-dependent plasticity. In a series of studies (Frégnac et al., 1988, 1992; Shulz and Frégnac, 1992), recordings were made from neurons in cat V1 during the presentation of two stimuli, either to separate eyes, or to the same eye at different orientations. Stimulus presentation was accompanied by iontophoretic current application in the vicinity of the recording electrode. One stimulus was associated with the application of positive current to artificially enhance the visual response (S+), and another was paired with negative current to decrease the response (S−). In many of the neurons sampled, shifts in orientation selectivity or ocularity were observed in the direction of the S+ stimulus. These effects were observed in adult cats as well as kittens. In other words, artificial modulation of the covariance between pre- and postsynaptic activity can induce changes in the receptive field properties of sensory neurons that are consistent with the operation of Hebb-like learning rules. Similar effects have been observed after the application of natural neurotransmitters such as γ-aminobutyric acid (GABA) and glutamate (McLean and Palmer, 1998). Analogous studies carried out in the auditory cortex using tones of different frequency have generated effects lasting ≤30 min (Cruikshank and Weinberger, 1996).

In a complementary set of experiments, simultaneous extracellular recordings were made from several neurons in the auditory cortex of the behaving monkey (Ahissar et al., 1992, 1998). Pairs of functionally connected neurons were identified by inspecting cross-correlograms of the firing of different cells. During training the occurrence of a spike in one member of a pair of neurons (designated presynaptic) triggered a tone chosen to elicit either an increase or a decrease in the firing of the second, functionally connected, neuron (designated postsynaptic). Multiple pairings of this kind resulted in either an increase or decrease, respectively, in the functional connectivity of presynaptic and postsynaptic neurons, as assessed by cross-correlational analysis of firing patterns. In other words, pairing presynaptic activity with an increase in postsynaptic firing resulted in an enhanced connectivity, whereas presynaptic activity paired with a reduction in postsynaptic activity resulted in a decreased connectivity. These changes were most pronounced when the tone formed part of a discrimination task that required the monkey to attend to the sound, possibly owing to the co-release of neuromodulatory transmitters. Hence, this form of plasticity is a function not just of the pairing contingencies, but also of the behavioral relevance of the activity.

Recent studies, reminiscent of the experiments carried out by Frégnac and colleagues, have extended previous work by systematically varying the timing of presynaptic sensory stimulation and postsynaptic activity. There is mounting evidence that adult plasticity in the orientation selectivity of cells in the primary visual cortex (V1) obeys timing rules similar to those that govern LTP/LTD induction (Sur et al., 2002; see below). Many neurons in V1 fire preferentially when stimuli of a particular orientation are presented within their receptive fields; cells tuned to respond to a specific orientation are clustered together in patches that form a mosaic of shifting orientation selectivities across the cortex (Hubel and Wiesel, 1962; Bonhoeffer and Grinvald, 1991). This orientation map is plastic, and can be modified in an experience-dependent manner both during development (Chapman et al., 1999) and also in adulthood (see below). The neural mechanisms of orientation selectivity in V1 neurons are controversial (see Ferster and Miller, 2000) but, at some level, an orientation preference must reflect the sum of the inputs that an individual cell receives from the lateral geniculate nucleus (LGN), and from other cortical neurons. A change in synaptic strength among these inputs provides a plausible mechanism for experience-dependent shifts in orientation selectivity.

Schuetz et al. (2001) paired electrical stimulation of V1 with the presentation of a visual stimulus consisting of a grating at a particular orientation. By taking into account the conduction latency for transmission of stimuli from the retina to the visual cortex, electrical stimulation could be applied either several milliseconds after the arrival of the visual stimulus (pairing condition), or several milliseconds before (anti-pairing condition). Changes in orientation preference maps were then investigated using an optical imaging technique. Cells in V1 shifted their orientation preferences toward the orientation of the paired stimulus, as indicated by an increase in cortical area activated by the paired orientation. Conversely, anti-pairing of electrical stimulation and visual stimulation resulted in a shift in orientation selectivity away from the anti-paired orientation. Subsequent extracellular recordings provided evidence that plasticity of intracortical connectivity, rather than afferents from the LGN, is critical: layer 4 cells retained their original orientation preferences, whereas layer 2–3 and layer 5–6 cells that receive prominent corticocortical inputs exhibited pronounced shifts in orientation selectivity.

Similar changes in the orientation selectivity of neurons have been induced in area V1 of cats simply by presenting a grating at a neuron’s preferred orientation within a narrow time window (~±20 ms) after (pairing) or before (anti-pairing) the presentation of a grating of a new, slightly different, orientation (Yao and Dan, 2001). Presentation of a different orientation before the preferred orientation caused cells to shift their tuning toward the new orientation. This is consistent with the idea that neurons signaling the new orientation increase the efficacy of their synaptic contacts onto the recorded cell, causing a corresponding shift in its orientation preference. Conversely, presentation of a stimulus at the preferred orientation followed by presentation of a new orientation caused a shift in preferred orientation away from the new orientation. This may suggest that the synaptic connections between cells responding to the new orientation and the recorded cell are depressed after such anti-pairing. Human psychophysical experiments subsequently showed changes in the perception of orientation that are consistent with such shifts in the orientation selectivity of V1 neurons (Yao and Dan, 2001).

Taken together, these studies provide good evidence that manipulation of pre- and postsynaptic covariance results in changes in functional connectivity consistent with the operation of Hebb-like learning rules. However, the existence of Hebbian processes does not necessarily imply that changes in synaptic efficacy are involved. Nonetheless, activity-dependent changes in the strength of connections between neurons remain a highly plausible substrate for plasticity of this kind. Further investigation of the cellular and
synaptic mechanisms of cortical representational plasticity may soon yield more definitive answers. Of greater concern, perhaps, is the fact that many of the changes discussed are relatively short-lived. Although changes in receptive field properties lasted ≥24 h in some cases (Schuett et al., 2001), a duration of minutes, rather than hours, tends to be more typical. But as Yao and Dan (2001) point out, pairing-induced changes may well be washed out over time by ongoing modifications resulting from background sensory stimulation. As we suggested earlier, however, there is every reason for both short-term and long-term forms of synaptic plasticity to play a role in physiological memory processes. As in the hippocampus, plasticity mechanisms may need to operate over a range of time-scales in order to be effective.

**LTP and skill learning**

Recent evidence suggests that a phenomenon resembling LTP occurs in the primary motor cortex (M1) after the acquisition of a motor skill in rats. Rioult-Pedotti et al. (1998) trained rats to reach through a hole in a small plastic box with their preferred paw in order to retrieve food pellets. After a few days of training, brain slices were taken from these animals, and stimulating and recording electrodes were placed bilaterally in layer II/III of the forelimb representation area of M1. The hemisphere contralateral to the preferred forelimb was termed the trained hemisphere, and the ipsilateral hemisphere was referred to as untrained.

EPSPs from the contralateral M1 of trained rats were substantially larger than those recorded in the ipsilateral untrained hemisphere, or in untrained animals (Fig. 1A). A follow-up study investigated the effects of motor learning on the capacity for synaptic plasticity. After training, cortical slices were prepared, and repeated trains of either high or low frequency stimulation were delivered in order to saturate LTP or LTD, respectively (Rioult-Pedotti et al., 2000). Strikingly, the capacity for LTP was reduced after motor learning. This partial occlusion suggests that LTP and skill learning may engage similar neuronal mechanisms. An interesting asymmetry is that the capacity for LTD was enhanced. In other words, learning increases baseline EPSPs toward a ceiling but does not alter the synaptic modification range over which synaptic strengths can vary (Fig. 1B). It is unclear whether the occlusion of LTP by motor learning would impair the subsequent learning of new skills, but emerging evidence suggests that the synaptic modification range shifts upward with increasing training on the skilled reaching task, thus reestablishing the capacity for future increases in synaptic strength, whilst preserving existing synaptic modifications (Rioult-Pedotti and Donoghue, 2000). The mechanisms involved in such a shift remain unclear, but it is tempting to speculate that the formation of new synapses may be responsible. It is worth noting that synaptogenesis within the forelimb representation area is observed after training on a similar motor task (Klein et al., 2002).

These findings provide a clear demonstration of an LTP-like phenomenon occurring as a result of learning, thus apparently fulfilling our detectability criterion. Nonetheless, a number of puzzles surround this result (see Martin and Morris, 2001). First, the increase in EPSPs is typically very large (about 50%), and the spatial distribution of the weight changes and their information content are unknown. We have argued that, in the hippocampus at least, learning-related changes in EPSPs are likely to be extremely small (see above). This may not be true in the motor cortex, but the result is surprising nonetheless. It is unclear whether such changes actually encode the learned skill—constituting a motor en-

![FIGURE 1. Detectability: Motor learning causes an increase in evoked responses in the primary motor cortex (M1). A: After training in a skilled reaching task involving the retrieval of pellets with a single forelimb, brain slices were prepared containing the forelimb representation area of the primary motor cortex. Stimulation of intracortical horizontal fibers resulted in a larger excitatory postsynaptic potential (EPSP) in the hemisphere contralateral to the forelimb used during training (the trained hemisphere), compared with the ipsilateral (untrained) hemisphere. B: Saturation of either long-term potentiation (LTP) or long-term depression (LTD) showed a reduced capacity for LTP and an enhanced capacity for LTD in the trained hemisphere. This is consistent with the concept of a synaptic modification range whose ceiling and floor remain fixed, despite an increase in baseline evoked responses after skill learning. The partial occlusion of tetanus-induced LTP in the trained hemisphere suggests that artificial LTP and learning-induced increases in the EPSP share common mechanisms. (Includes material adapted with permission from Rioult-Pedotti et al., 1998; and material reprinted from Martin and Morris, 2001; copyright 2001, with permission from Elsevier Science.)
gram—or whether they play some other, perhaps less specific, role in the information processing that accompanies motor learning. Would similar eEPSP increases be seen for each new skill that is learned, or might such a large change occur only when the rodent motor cortex is engaged in skill learning for the first time?

Second, what is the relationship between changes in M1 eEPSPs and the changes in the M1 representation that are found to occur after the acquisition of similar skills? Training on a similar reaching task results in an expansion of the forelimb representation area in rats (Klein et al., 1998). Interestingly, expansion of the motor map associated with kindling stimulation is accompanied by an enhancement of synaptic transmission in the pathway from the callosal white matter to the frontal neocortex (Teskey et al., 2002).

These findings suggest that increases in synaptic strength might be capable of providing a substrate for motor map plasticity, as proposed by Hess and Donoghue (1994). Many questions remain unanswered, however. The role of changes in synaptic strength versus synapse number may warrant particular attention, an issue that cannot be resolved at the level of field recordings. In fact, as we suggested in the previous section, further investigation of the relationship between cortical map/receptive field plasticity and changes in synaptic strength might provide a very promising way to link synaptic plasticity with changes in the behavioral output. The lessons learned from such a program of research are likely to have broader implications for our understanding of the functional roles that synaptic plasticity might play.

LTP and olfactory learning

Learning-induced changes in evoked responses have been observed in several brain areas in conjunction with olfactory learning (for discussion, see Roman et al., 1999). Neurons in the olfactory bulbs make monosynaptic connections with cells in the piriform (olfactory) cortex via the lateral olfactory tract (LOT). In one series of experiments, rats were trained to discriminate between two odors each and patterned olfactomimetic stimulation of the LOT (Roman et al., 1987, 1993). The key finding was that population responses evoked by LOT stimulation increased during learning, whereas pseudo-conditioning failed to induce LTP. In fact, this increase did not appear until successful discrimination was achieved, and the magnitude of the effect was positively correlated with task performance. A potentiation of the polysynaptic dentate gyrus field potential has been observed during the course of a similar discrimination task (Chaillan et al., 1999). In contrast to the work of Rioult-Pedrotti and colleagues, however, neither study included a test of whether the increased potentials were associated with decreased LTP.

In a slightly different experiment, Mouly et al. (2001) implanted stimulating electrodes in the olfactory bulbs, and recorded evoked responses in the anterior and posterior piriform cortex, as well as the lateral entorhinal cortex and dentate gyrus. Rats were trained to associate stimulation of one olfactory bulb electrode with a positive reward, and stimulation of another electrode was associated with a negative reward. Positively reinforced learning led to an increase in responses (evoked by stimulation of the corresponding bulbular electrode) in the posterior piriform cortex and the lateral entorhinal cortex. Interestingly, negatively reinforced learning was characterized mainly by a decrease in amplitude of the dentate eEPSP. Similar findings have been reported in the amygdala. Collins and Paré (2000) carried out a unit recording study of the responses of lateral amygdalar neurons during a discriminative conditioning task. Not only were neuronal responses to the stimulus paired with the US increased, but responses to the unpaired stimulus were reduced. The authors suggest that synaptic transmission of sensory inputs not paired with an aversive stimulus is depressed after fear conditioning, a phenomenon that may increase the selectivity of the CS-US association. Although direct evidence is still lacking, these examples indicate how LTD-like mechanisms may act in concert with increases in synaptic strength in the formation of an associative memory.

In addition to changes in afferent inputs, changes in intrinsic cortical connections have also been reported after olfactory learning. Saar et al. (1999) trained rats in an olfactory discrimination task and then prepared brain slices containing the piriform cortex. Stimulating electrodes were placed in both the extrinsic afferent pathway from the LOT, and the intrinsic pathway comprised of corticocortical association fibers. Responses were recorded both intracellularly and extracellularly. Slices from trained rats exhibited selective enhancement of eEPSP amplitude in response to stimulation of the intrinsic pathway. A decrease in paired-pulse facilitation (PPF) was observed in cells from trained animals, suggesting that an increase in presynaptic neurotransmitter release may underlie the eEPSP enhancement. A subsequent study has shown that, as with skill learning in the motor cortex, olfactory learning limits the capacity for LTP and facilitates LTD of the intrinsic pathway (Lebel et al., 2001), again suggesting that learning-induced potentiation and electrically induced LTP share common mechanisms.

These results add further credibility to the idea that changes in synaptic strength accompany certain forms of learning, but a number of awkward facts remain. First, changes in PPF were not apparent in the first days after a short period of training, but were maximal 3–7 days after such training. The reason for this delay is unclear. Second, very extensive training (50 odor pairs) produced a change in PPF that was no larger than that observed after training on only two or three odor pairs—the effect does not appear to be cumulative. Third, changes in PPF had disappeared 8 days after training, whereas, as the authors note, olfactory discriminations can be remembered for ≥6 weeks (Staubl et al., 1987). Fourth, changes in PPF were observed in most neurons sampled from trained rats. This lack of selectivity challenges the notion that such learning-induced changes underlie the representation of specific odor–reward associations.

It has often been noted that during the course of an olfactory discrimination task, learning rate increases rapidly over the first few odor pairs (e.g., Slotnick and Katz, 1974). The nature of this increase is controversial (see Eichenbaum and Otto, 1993; Lynch and Staubl, 1993; Reid and Morris, 1993; Slotnick, 1994). However, on the basis of the above considerations, Saar et al. (1999) speculate that the widespread increases in synaptic strength that they observe might underlie this enhancement in learning rate, rather than storing specific information about individual odors. This discussion leads us back to an issue that was raised earlier,
when considering the enhancement of motor cortical fEPSPs after skill learning: do learning induced changes in synaptic strength constitute an engram, or do they serve some ancillary information processing role? Analytical experiments need to be designed to distinguish between these and other possibilities.

**Does Hippocampus-Dependent Learning Induce LTP of Hippocampal Evoked Responses?**

We began our discussion of detectability by suggesting that the hippocampus may be the wrong place to begin a search for learning-related changes in synaptic strength. There are, nonetheless, several reports of LTP-like changes occurring in the hippocampal formation and its connections with other brain structures.

A few years ago, Moser and colleagues found that rats exploring a novel environment exhibit a small, transient (~15 min) increase in the dentate fEPSP, even after controlling for the increase in brain temperature resulting from muscular activity (Moser et al., 1993, 1994a; Moser, 1995). It remains unclear, however, whether this phenomenon reflects a genuine form of learning-induced synaptic enhancement or merely a transient change in the activity of neuromodulatory inputs.

As in the cortical literature, experience-related changes in evoked responses have been sought in hippocampal brain slices taken from rats previously exposed to a learning situation. For instance, Green and Greenough (1986) observed increases in dentate fEPSPs in slices taken from rats reared in complex environments. A temperature-related artifact cannot account for these data, but it is unclear whether the reported increase constitutes a change in synaptic efficacy rather than, for instance, an increase in synaptogenesis or neurogenesis in the enriched animals. Learning can result in an increase in spine density within the dentate gyrus (O'Malley et al., 2000) and CA1 (Moser et al., 1994b), and both environmental enrichment and learning, as well as simply running, have all been reported to increase the number of dividing cells in the dentate gyrus (Kempermann et al., 1997; Gould et al., 1999; van Praag et al., 1999). A more recent study has also reported an increase in dentate fEPSPs in slices taken from environmentally enriched rats, relative to controls; this potentiation was accompanied by an increase in AMPA receptor binding but no change in the PPF ratio (Foster et al., 1996). In addition to an increase in baseline fEPSPs, the capacity for LTP was substantially reduced in slices from enriched animals, a result reminiscent of that reported in motor and piriform cortices after learning. Importantly, a subsequent study indicates that the fEPSP increase and the occlusion of LTP can be reversed by chronic intracerebroventricular administration of an NMDA receptor antagonist (AP5) during enrichment (Foster et al., 2000). Although alternative explanations may exist, these findings are consistent with the idea that exposure to environmental enrichment causes an NMDA receptor-dependent increase in mean synaptic strength within the dentate gyrus.

What about changes resulting from training in conventional learning tasks? An enhancement of the CA1 evoked response has been observed in brain slices taken from rabbits trained in an eyelinek conditioning task 1 h previously; the effect declined over 24 h (Power et al., 1997). More recently, a lasting increase in CA1 fEPSPs was described in slices prepared at varying time points after contextual fear conditioning (Saccometti et al., 2001). An enhancement of fEPSP magnitude across the input-output (I-O) curve, relative to a number of control groups, was observed 7 days after training, unaccompanied by changes in the PPF ratio, suggesting that an increase in transmitter release is not responsible. A follow-up study has recently shown that, as in M1 and piriform cortex, learning results in a partial occlusion of hippocampal LTP (Saccometti et al., 2002). LTP was impaired in slices from trained rats, but only when tested ≤1 day after training: note that the increase in fEPSP was previously found to last for 7 days. It is once again tempting to speculate that synapse formation occurs in tandem with the consolidation of existing memory traces, thus reestablishing the capacity for normal LTP after the passage of several days, whilst preserving established changes in synaptic strength. Consistent with earlier work (Moser et al., 1994a), mere exploration of a novel context without shock resulted in an increase in the evoked response, and a partial occlusion of LTP in slices prepared 10 min after exploration, but not at later time points, confirming that exposure to novelty results in only a short-term potentiation of hippocampal fEPSPs.

LTP-like changes have also been recorded in the extrinsic connections of the hippocampal formation during learning. For example, mice trained in a radial maze exhibited a potentiation in the pathway linking the fimbria and lateral septum (Jaffard et al., 1996). The potentiation developed gradually over training, and was positively correlated with performance in a probe trial. A control task involving treadmill running failed to induce such changes, suggesting that the phenomenon is not a temperature-related artifact.

**Other Learning-Related Changes Indicative of Synaptic Plasticity**

Several studies have demonstrated changes in indices of synaptic efficacy other than fEPSPs, such as increases in neurotransmitter release and changes in inhibitory transmission. Many of these changes fall within our definition of synaptic plasticity, but some, such as the possibility that memory is encoded by disinhibition, rather than by changes in the strength of afferent connections onto principal neurons, are sufficiently different in spirit to cause a major conceptual reorientation if found to be correct.

**Changes in glutamate release**

Increased glutamate release has been reported after both LTP (Dolphin et al., 1982; Bliss et al., 1986) and learning. It is mediated by the potentiation of the glutamate receptor complex, which is supported by training. For example, trained rats display a shift in the final current-membrane potential relationship when compared with naive animals, suggesting a change in transmitter responsivity. A key feature of this response is that it is not seen in rats trained on a task that is predictable (Bliss et al., 1986). It is also not seen in rats trained on a task that is predictable (Bliss et al., 1986). It is also not seen in rats trained on a task that is predictable (Bliss et al., 1986). It is also not seen in rats trained on a task that is predictable (Bliss et al., 1986). It is also not seen in rats trained on a task that is predictable (Bliss et al., 1986).
occlusion of CA1 LTP (Sacchetti et al., 2002), extensive spatial training did not alter the magnitude of subsequent LTP. Possible explanations for this paradoxical result include a learning-induced shift in the relative expression of presynaptically and postsynaptically mediated potentiation, but the issue remains largely unresolved.

Changes in action potential attenuation

A novel form of experience-dependent plasticity that may be linked to changes in synaptic efficacy has recently been described by Quirk et al. (2001). Hippocampal place cells often fire bursts of action potentials (complex spikes) whose amplitude exhibits an activity-dependent attenuation. A decrease in extracellular spike amplitude reflects a decrease in the efficacy with which action potentials are back-propagated from the soma to the dendrites (Buzsáki et al., 1996). The main novel finding reported by Quirk et al. (2001) was that the amount of action potential attenuation was reduced as a function of time spent within a particular environment, a phenomenon that may underlie certain experience-dependent changes in hippocampal receptive fields (Mehta et al., 1997). The authors suggest that potentiation of inputs onto a cell may underlie this attenuation by increasing levels of dendritic de-polarization and inactivating A-type (fast inactivating voltage-gated) potassium channels, thereby increasing the extent of dendritic action potential back-propagation (see Hoffman et al., 1997). Consistent with this interpretation, NMDA receptor antagonism was found to prevent the experience-dependent decrease in action potential attenuation. However protein kinase-dependent modulation of potassium channel activation might also account for these results. Regardless of whether an increase in synaptic strength truly underlies this phenomenon, however, changes in the efficacy with which action potentials can propagate throughout the dendritic arborization are likely to have important consequences for hippocampal information processing.

Changes in inhibitory neurotransmission

It is widely assumed that long-term potentiation of excitatory inputs onto principal hippocampal neurons, such as CA1 and CA3 pyramidal cells, underlies memory formation, but plasticity of inhibitory neurotransmission may be equally important. Maroun et al. (2001) have proposed that plasticity in local neuronal circuits, mediated by changes in GABAergic transmission, may also be critical for learning and memory processes. Evidence for this idea is supported by a recent study by Gusev and Alkon (2001), who trained rats in a water maze reference memory task; 24 h after the final training session, dorsal hippocampal brain slices were prepared, and multiple intracellular recordings were conducted in order to assess any learning-induced changes in the synaptic responses and intrinsic membrane properties of CA1 pyramidal cells. A key finding of the study was that IPSP amplitudes were reduced in rats that had completed water maze training, relative to both naive animals, and a control group that had simply experienced swimming in a water maze over the same period. No evidence was found for a learning-induced potentiation of excitatory inputs onto CA1 pyramidal neurons, and no learning-specific changes in intrinsic membrane properties were observed. Gusev and Alkon (2001) speculate that long-term, learning-related disinhibition might provide a mechanism for the clustering of place fields at the platform location that has recently been observed in a water maze task (Hollup et al., 2001). The difficulty lies in determining whether these platform-related cells are the ones that undergo disinhibition. Perhaps simultaneous tetrode recordings of place cells and interneurons might resolve this issue. Changes in cross-correlation functions consistent with a decrease in inhibition might then be shown during water maze training, but such an experiment would not be easy. It is worth noting that a neural network model of associative memory formation that relies on disinhibition has recently been proposed as an alternative to conventional models based on the potentiation of excitatory synapses (Vogel, 2001).

Not All Learning-Related Changes Involve Changes in Synaptic Strength

If the synaptic plasticity and memory hypothesis is incorrect, a different mechanism must serve as the neural substrate for memory and should, in principle, result in detectable changes during or after learning has occurred. In this section we discuss learning-related changes in neuronal function that do not lie within our definition of synaptic plasticity.

Neurogenesis

There is now evidence to suggest that new neurons are constantly formed in some regions of the brain, such as the dentate gyrus, and that their survival can be enhanced in an experience-dependent fashion (e.g., Kempermann et al., 1997; Gould et al., 1999; van Praag et al., 1999; but see Rakic, 2002). Furthermore, reducing the numbers of newly generated neurons by applying a toxin to proliferating cells impaired performance in a hippocampus-dependent learning task, trace eyeblink conditioning (Shors et al., 2001). Hippocampus-independent delay conditioning was unaffected, as were a number of anatomical and physiological indices of hippocampal function. These results suggest that newly formed neurons may be essential for certain forms of learning, but they do not necessarily exclude a role for synaptic plasticity. CA1 LTP was normal in the learning-impaired rats, but recent evidence has implicated adult-generated granule cells in dentate synaptic plasticity (Snyder et al., 2001). Nevertheless, studies such as this draw attention to the fact that too exclusive a focus on LTP may lead us to neglect other processes that are critical for memory formation.

Changes in neuronal excitability

Another alternative to the SPM hypothesis is the idea that changes in neuronal excitability, rather than synaptic strength, underlie memory. Indeed, changes in excitability have long been implicated in such phenomena as sensitization in Aplysia (Scholz and Byrne, 1987; Walters, 1987). Many mammalian studies have also showed increases in excitability after a variety of forms of learning, often resulting from a reduction in the slow afterhyperpolarization (sAHP) current. Such changes have been observed in hippocampal pyramidal cells after trace eyeblink conditioning.
(Moyer et al., 1996; Thompson et al., 1996), classical conditioning (Coulter et al., 1989; Rosenkrantz and Grace, 2002b), and water maze training (Oh et al., 2001). Similar learning-related changes have been observed in additional brain areas (e.g., Saar et al., 1998).

Others have suggested a role for specific potassium channels in learning and memory based on the manipulation of channel expression using antisense knockdown techniques. In one such study, knockdown of the Kv1.1 potassium channel was found to impair hippocampus-dependent memory without affecting LTP in the dentate gyrus or CA1 (Meiri et al., 1997). For molecular genetic evidence supporting a role for changes in excitation in learning and memory, see Giese et al. (2001).

The synaptic plasticity and the excitability hypotheses are not mutually exclusive, however. Perhaps changes in synaptic strength are not sufficient for memory formation, or cannot proceed normally, in the absence of changes in excitability. Evidence for this possibility comes from a recent study of learning-induced plasticity in the amygdala (Rosenkrantz and Grace, 2002b). Intracellular recording from anesthetized rats was used to monitor postsynaptic responses evoked by the presentation of an odor. Pairing of this odor with footshock led to an enhancement in the odor-evoked potential, whereas unpaired odor presentations led to a decrease in the response. Conditioning also caused an enhancement of neuronal excitability; both the increase in evoked response and the increase in excitability were blocked by administration of the dopamine antagonist, haloperidol. Activation of amygdalar dopamine receptors is known to enhance the excitability of neurons in the lateral amygdala (Rosenkrantz and Grace, 2002a). However, no changes in the odor-evoked response were seen after administration of a dopamine agonist (apomorphine), suggesting that a dopamine-mediated increase in excitability may play a necessary but not sufficient role in the enhancement of the CS-evoked response during fear conditioning. Such a mechanism may have important implications for neuronal information processing, and may not be limited to the amygdala.

Summary

There are now a large number of reports of LTP-like phenomena occurring during and after learning. An extensive literature suggests that adult cortical receptive field plasticity involves mechanisms whose properties are strikingly similar to those of LTP. These findings are highly suggestive of a role for synaptic plasticity in physiological memory.

In other cases, learning is accompanied by an enhancement of cortical, and sometimes hippocampal, evoked responses. In some cases, a number of pieces of evidence, such as the effects of NMDA receptor blockade and occlusion experiments, point to the possibility that learning-induced potentiation and artificially induced LTP may share common mechanisms. However, this characterization has only just begun in many of the examples discussed. Perhaps the most puzzling aspect of this form of learning-induced potentiation is the large size of the effect typically obtained. Contextual fear conditioning, for instance, results in a near doubling of the in vitro CA1 EPSP amplitude (Sacchetti et al., 2001), and a partial occlusion of LTP (Sacchetti et al., 2002). If changes in synaptic strength directly encode features of the shock context, the capacity for encoding further context-shock associations might be expected to be severely limited. Similar concerns were raised in relation to learning-induced potentiation of cortical EPSPs, and a major challenge will be to identify what information is thus stored and how such changes contribute to information processing within each brain structure.

Finally, we noted that changes in excitatory synaptic transmission are not the only changes in neural activity that occur after learning. Changes in inhibitory transmission, membrane excitability, and the formation of new neurons have all been reported, and all may play a role in memory. However, none of these alternatives, in our view, can match the versatility and high storage capacity to be expected from changes in synaptic strength. Only time—and rigorous experimentation—will tell.

MIMICRY

It remains to be seen whether the artificial induction of LTP can induce behavioral changes indicative of memory formation (cf. Stevens, 1998). In our view, the final test of any hypothesis concerning memory encoding and storage must be a mimicry experiment, in which apparent memory is generated artificially without the usual requirement for sensory experience, or indeed any form of experience, during learning. In one sense, such an experiment would constitute a practical demonstration of the fact that we really do understand how memory works, in the same way that successful engineering lends validate our hypotheses about the nature of the physical world. In another sense, such an experiment would constitute a critical test that changes in synaptic efficacy are sufficient for memory, rather than merely necessary.

We have previously speculated about whether pairing of stimulation in specific CS and US pathways to the amygdala might result in potentiation of the CS pathway, and whether subsequent behavioral testing would show that this LTP constitutes the engineering of an emotional memory. Such an experiment may be very difficult in practice, and no such reports have yet appeared. However, several detectability studies have employed a methodology that might be regarded as a halfway house between detectability and mimicry. Studies in which sensory stimulation is replaced with electrical stimulation of a particular neural pathway, either as a discriminative cue (Roman et al., 1987, 1993; Chailan et al., 1999; Moul et al., 2001) or a conditioned stimulus (Matthies et al., 1986; Larré et al., 1989; Doyère and Larocque, 1992), fall into this category. In such experiments, post-training LTP-like changes in evoked potentials are often found in response to stimulation of the same pathway that was stimulated during learning. The difficulty lies in ensuring that the electrical stimulation adequately mimics natural sensory stimulation, such that any learning-related changes in synaptic strength might plausibly be expected to occur, albeit perhaps in a more diffuse and sparse fashion, during normal learning. In this respect, studies involving stimula-
changes in the sensory pathway are arguably easier to interpret than studies in which, for instance, perforant path tetanus is used as a CS (Doyère and Laroche, 1992; Laroche et al., 1989). For a fuller discussion of the latter type of study, see Jeffery (1997).

Another study that comes close to meeting the mimicry criterion was carried out by Shinkman et al. (1996), who implanted stimulating electrodes in rabbit cerebellum in order to investigate the pairing of electrical conditioned and unconditioned stimuli (see also Thompson et al., 2000). One electrode stimulated parallel fibers in the cerebellar cortex, providing an artificial CS; another electrode activated the underlying white matter, providing an artificial US that generated unconditioned responses. Paired stimulation of CS and US pathways resulted in conditioned responses that extinguished in the presence of the CS alone. Provided that such pairing induces selective changes in synaptic strength at the appropriate synapses, this study very nearly constitutes a successful test of the mimicry criterion. The test would be complete if memory for the CS-US association, indicated by the conditioned response, could subsequently be elicited by a natural sensory CS, in addition to the electrical CS used during learning.

Another example of a near-mimicry experiment was recently reported by McLin et al. (2002). Pairing an auditory CS of a particular frequency with electrical stimulation of the nucleus basalis results in muscarinic-dependent receptive field plasticity in the auditory cortex similar to that observed after auditory conditioning (Bakin and Weinberger, 1996; Kilgarr and Merzenich, 1998; Miasnikov et al., 2001). The critical new finding was that this pairing also resulted in CS-specific conditioned responses, such as changes in respiratory and heart rate, whereas unpaired presentations of the CS and nucleus basalis stimulation had no effect. These results indicate that conditioned responses can occur to a CS that is never actually paired with a real US (an observation that, incidentally, parallels cerebellar work conducted many years ago; see Brogden and Gain, 1942). However, the study by McLin et al. (2002) would constitute a complete test of the mimicry criterion only if the sensory CS could be replaced by appropriate electrical stimulation of the auditory cortex during CS-US pairing. Crucially, similar conditioned responses would then be sought in response to a real acoustic stimulus. Of course, whether this experiment would provide support for the synaptic plasticity and memory hypothesis would depend on a full understanding of the neural mechanisms, synaptic or otherwise, that underlie the resulting auditory receptive field plasticity.

At least one complete attempt at mimicry has been carried out, again in the rat auditory cortex (Talwar and Gerstein, 2001). As mentioned in the previous section, learning tasks involving auditory stimuli are often accompanied by a reorganization of the auditory representation within A1. For instance, frequency discrimination training results in an increase in the area of A1 responsive to those frequencies used in the task (Edeline and Weinberger, 1993; Recanzone et al., 1993). Similar changes can be observed after intracortical microstimulation (ICMS) (Maldonado and Gerstein, 1996; Talwar and Gerstein, 2001), and stimulation of the nucleus basalis (Bakin and Weinberger, 1996; Kilgarr and Merzenich, 1998). In their recent study, Talwar and Gerstein used this technique to investigate the perceptual consequences of artificially enlarging the cortical area responsive to a particular frequency. After ICMS, rats were tested for their ability to make fine auditory discriminations around this frequency. Despite the fact that ICMS resulted in a similar change in the auditory map to that seen after auditory discrimination training, no enhancement of discrimination abilities was observed; i.e., mimicry was unsuccessful. The authors suggest that changes in cortical representations may be meaningless in the absence of any behavioral context. In other words, cortical reorganization might need to be linked to a representation of the motivational significance of the stimulus. Perhaps a combination of the approach of McLin et al. (2002) with that of Talwar and Gerstein (2001) would be fruitful in this respect.

Others have suggested that the cortical reorganization reported by Talwar and Gerstein (2001) may not adequately mimic the consequences of discrimination training. For example, Schnupp and Kacelnik (2002) point out that although training on an auditory fear conditioning task results in a shift in frequency tuning, as well as an overall increase in responsiveness to the CS (Weinberger and Bakin, 1998), frequency discrimination training leads to an increase in the sharpness of frequency tuning within A1 (Recanzone et al., 1993). This sharpening of receptive fields may improve the discriminability of tones of similar frequency. Schnupp and Kacelnik (2002) argue that the failure of ICMS to result in any change in discrimination performance may stem from the fact that frequency tuning was actually broadened after cortical stimulation, despite an overall increase in the cortical area responsive to the target frequency; consequently, they suggest that a detection, rather than a discrimination, task might be more likely to display behavioral changes. These considerations illustrate some of the difficulties with the mimicry approach, but they also highlight the increasing feasibility of such studies. We suspect that many more cortical mimicry experiments will be carried out in the near future.

ANTEROGRADE ALTERATION

A vast research effort has been dedicated to identifying pharmacological, genetic, and physiological treatments that interfere with LTP and memory. Many studies have been conducted with NMDA receptor antagonists that block the upregulation or downregulation of synaptic efficacy, and drugs acting at sites downstream of the NMDA receptor have been used to probe the biochemical cascades that underlie plasticity. An increasing number of genetic interventions have recently been used to investigate the receptors and transduction pathways that might be involved. Physiological manipulations, such as LTP saturation, have also been explored. If tetanus-induced synaptic plasticity is mechanistically equivalent to learning-induced plasticity, treatments that block LTD should also block learning. Many studies have reported just such a result, but a few apparent dissociations between LTP and learning have also been found. A thorough review of anterograde alteration studies is beyond the scope of this article; instead we draw attention to some conceptual issues and a few recent developments in the field.
Pharmacological and Genetic Interventions

Necessity for NMDA receptor activation in learning and memory

Since the original observations of Morris et al. (1986), who discovered that hippocampal NMDA receptor blockade prevents spatial learning but not visual discrimination learning, a vast literature has developed confirming that NMDA receptor activation is necessary for a wide variety of different forms of learning and memory. However, it has sometimes been argued that such findings may be largely or perhaps entirely the result of the sensorimotor side effects that can arise after NMDA receptor blockade (Keith and Rudy, 1990; Cain et al., 1996).

A conventional way to dissociate memory impairments from nonmemonic performance factors is to look for delay-dependent effects of the treatment in question. If a treatment, such as an NMDA receptor antagonist administered during encoding, has minimal effects on retrieval tested at a short delay, but a much larger effect at a long delay, it is difficult to see how an explanation couched solely in terms of sensorimotor side effects can be valid. The application of competitive NMDA receptor antagonists has been found to cause a delay-dependent deficit in a variety of different behavioral paradigms, including operant DRL (Tonkiss et al., 1988), T-maze alternation (Tonkiss and Rawlins, 1991), operant delayed matching-to-position (Cole et al., 1993), contextual fear conditioning (Fanselow et al., 1994), and a delay-interposed radial maze task (Li et al., 1997). All these studies used intracerebroventricular or systemic drug delivery, the effects of which will not have been limited to the hippocampal formation. More recently, direct intrahippocampal infusion of AP5, causing minimal sensorimotor disturbance, has been found to result in a delay-dependent deficit in a water maze matching-to-place task (Steele and Morris, 1999) (Fig. 2). Autoradiographic analysis of the extent of AP5 diffusion found a drug distribution that was largely limited to the dorsal hippocampal formation. Further evidence against the sensorimotor view is provided by the finding that, although AP5-treated rats are impaired in the acquisition of new spatial information, their retention of a platform location learned before drug administration is unimpaired (Morris, 1989; Steele and Morris, 1999).

The degree of impairment observed after NMDA receptor blockade is partly determined by the prior experience of an animal. Bannerman et al. (1995) found that when rats were given pretraining in one water maze and postoperative spatial training in a second maze, the chronic intracerebroventricular delivery of AP5 had little effect on postoperative learning. In contrast, rats given nonspatial pretraining were still impaired when tested in the second water maze during AP5 infusion. Rats given hippocampal lesions after training in the first water maze were severely impaired postoperatively, regardless of the type of pretraining given. These results suggest that although the integrity of the hippocampus remains critical for learning in a new environment, activation of NMDA receptors may not be necessary for the learning of a single fixed platform location over multiple training trials once other aspects of task performance have already been learned. Indeed, Saucier

![FIGURE 2. Anterograde alteration: NMDA receptor blockade results in a delay-dependent impairment in a delayed matching-to-place (DMP) task. In this variant of the water maze task, rats were given four trials per day (day N) with the platform remaining in the same location on each trial, but the platform was moved to a novel location at the start of each new day (day N + 1). The intertrial interval (ITI) between trials 1 and 2 was varied between 2 hr or 15 min; subsequent intervals were always 15 s. Rats receiving intrahippocampal infusions of aCSF 30 min before testing exhibited a marked reduction in escape latency between trials 1 and 2, regardless of the length of the ITI. However, animals infused with D-AP5 performed as well as controls at the 15 s ITI, but were severely impaired after a 2-h delay. The delay-dependent nature of this deficit suggests that NMDA receptor antagonism causes a spatial memory deficit that is dissociable from any side effects that might result from AP5 infusion. (Adapted with permission from Steele and Morris, 1999: Hippocampus, copyright 1999, Wiley-Liss, Inc.)](image-url)
Cain (1995) have reported that merely training rats on a nonspatial task results in unimpaired spatial learning in the same pool after administration of AP5. This finding is, however, confounded by the nonspatial learning having taken place in the same spatial context as the subsequent spatial learning under AP5.

According to one view, the beneficial effects of drug-free pretraining result simply from experienced rats being less susceptible to the sensorimotor side effects of NMDA antagonist administration (Cain et al., 1996). Evidence against this view is provided by a recent study in which it was shown that pretraining prevents the spatial learning deficit normally observed after the saturation of dentate LTP (Ottaes et al., 1999), a procedure that causes no obvious sensorimotor side effects. Nevertheless, it remains unclear which aspects of reference memory task acquisition, if any, are dependent on synaptic plasticity. It is possible that learning the behavioral strategies relevant to task performance, rather than learning a platform location per se, may require hippocampal NMDA receptor-dependent LTP. Evidence against this argument has been provided by Hoh et al. (1999), who reported that, using stepwise training methods, rats were able to acquire the behavioral strategies necessary for successful water maze performance even after the injection of an NMDA receptor antagonist. Experiments designed to resolve these issues are currently under way.

It is worth noting that the findings of Bannerman et al. (1995) and Saucier and Cain (1995) might be thought to be in conflict with those of Steele and Morris (1999). In attempting to reconcile these two sets of data, it may be significant that the delayed matching-to-place (DMP) task requires the single-trial encoding of novel locations, whereas the reference memory task involves the incremental learning of a single location over repeated trials. Correspondingly, the reference memory task may require little hippocampal synaptic plasticity in experienced animals. In contrast, the mnemonic demands of the matching-to-place task may be considerably greater, such that substantial NMDA receptor-dependent plasticity remains essential, even after extensive training.

These pharmacological studies are complemented by studies in which the NMDA receptor has been targeted genetically. For example, Tsien et al. (1996) created mice in which the deletion of the NMDA receptor NR1 subunit was restricted to area CA1. These animals showed no LTP in CA1, but dentate and cortical LTP was normal. Water maze testing demonstrated a modest impairment in spatial learning, and a subsequent unit recording study indicated that these mice have abnormal place fields (McHugh et al., 1996).

Other studies have focused on the role of additional NMDA receptor subunits. The NR1 subunit targeted by Tsien et al. (1996) is required for the formation of functional NMDA receptors, but it can combine with several different NR2 subunits. Mutant mice lacking the NR2A (or ε1) subunit, for instance, exhibited reduced (but not absent) NMDA receptor-mediated synaptic responses, and consequently the threshold for LTP was increased, even though the saturated level of LTP was unaltered (Sakimura et al., 1995; Kiyama et al., 1998). Consistent with these findings, behavioral testing showed an impairment of spatial learning (Sakimura et al., 1995), and a modest impairment in contextual fear conditioning—a longer exposure to the conditioning chamber was required in order to induce robust memory in mutant mice compared with wild types (Kiyama et al., 1998). In other words, increasing the threshold for LTP induction results in an increased threshold for memory formation.

**Role of synaptic plasticity in the different phases of memory**

Memory is a heterogeneous entity, composed of a number of component processes, and different neural mechanisms may be involved in such processes as encoding, storage, consolidation, and retrieval. Of course, an organism need not form indelible memories of every event that occurs—and ought not to do so if storage capacity is limited. Thus, processes must exist for selecting those memory traces that are to be retained, whilst allowing the remainder to decay. These selection processes might include the emotional significance of the event to be remembered (or of other events occurring close together in time or space), and the relevance of the event to the existing knowledge structures of the organism witnessing it. Underlying these psychological processes may be two separate neuronal mechanisms of memory consolidation: cellular consolidation processes that include the local setting of synaptic tags and the synthesis and synaptic capture of plasticity proteins (Frey and Morris, 1997, 1998a,b) and systems-level consolidation mechanisms that reflect a dynamic interaction between hippocampus and neocortex (Squire, 1992; Squire and Alvarez, 1995; Nadel and Moscovitch, 1997; Bontempi et al., 1999). Neither cellular nor systems consolidation processes are likely to obey a fixed, predetermined time course from initiation to completion. Memories may normally be strengthened by repeated episodes of cellular consolidation after memory reactivation, a process termed reconsolidation (Nader et al., 2000; Sara, 2000). Similarly, the systems-level consolidation of cortical memory traces may involve the intermittent reactivation of existing cortical memory structures and the gradual interleaving of new information as it becomes available.

Different memory processes are likely to operate over radically different time scales, and a consideration of the relationship between synaptic plasticity and memory must take account of this. In most of the studies reviewed in the present article, a straightforward attempt to link synaptic plasticity with memory encoding has been made. However, a number of studies involving pharmacological and genetic intervention are becoming increasingly sophisticated. In this respect, the recent development of systems offering regional and temporal control of gene expression promises a great deal.

A dissociation between the neural mechanisms of memory encoding and the less well understood mechanisms of memory retrieval has often been observed. Blockade of hippocampal NMDA receptors has little effect on AMPA receptor-mediated fast synaptic transmission. On this basis, administration of an NMDA receptor antagonist, or conditional knockout of essential subunits such as NR1, should freeze the existing pattern of synaptic weights in the hippocampal formation, whilst still allowing cells to fire and transmit information. Therefore, a clear prediction is that without func-
tation of NMDA receptors, the encoding of new memory traces should be impossible, but the retrieval of existing memories should be unaffected. Exactly this pattern was first reported by Sábia et al. (1989) after AP5 administration before the acquisition or retention of an olfactory discrimination task. Similarly, Morris (1989) and Morris et al. (1990) found that administration of AP5 before a water maze retention test had no effect on the memory for a platform location that had previously been learned, whereas post-training lesions of the hippocampal formation were highly disruptive in the same task. A role for NMDA receptors in encoding but not retrieval has also been found using other behavioral tasks, such as inhibitory avoidance (Parada-Turski and Turski, 1990; Venable and Kelly, 1990; Izquierdo et al., 2000).

But what about the consolidation of memories? We mentioned that two different types of consolidation operate over distinct timescales: cellular consolidation and systems consolidation. There is considerable evidence that hippocampus-dependent memories undergo a period of consolidation during the minutes to hours after learning (see McGaugh, 2000), and a variety of interventions can interfere with this process, including, among other things, temporary neuronal inactivation (e.g., Sacchetti et al., 1999), protein kinase inhibition (e.g., Abel et al., 1997; Izquierdo and Medina, 1997; Atkins et al., 1998; Bourtchouladze et al., 1998), and the inhibition of macromolecular synthesis (for review, see Davis and Squire, 1984; Dudai and Morris, 2000); growing evidence also supports a role for cell adhesion molecules in memory consolidation processes (Murase and Schuman, 1999; see also Chun et al., 2001).

The induction of lasting LTP is sensitive to many of the same treatments. For instance, late LTP (LTP lasting ≥4 h), like cellular consolidation, requires the synthesis of new proteins for its review (see Frey and Morris, 1998a). Application of protein synthesis inhibitors, such as anisomycin, prevents late LTP, but the events leading to protein synthesis do not have to occur at exactly the same time as the stimulation that induces synaptic potentiation. Tetanization in the presence of a protein synthesis inhibitor still results in late LTP if a strong tetanus is applied to a separate pathway at least 2 h previously (Frey and Morris, 1997). Together with other findings, this result has led to the notion that a high-frequency tetanus sets synaptic tags that can capture plasticity proteins as they become available (Frey and Morris, 1997, 1998b). The same may be true of memory formation. Activation of neuromodulatory systems after reward or punishment may upregulate protein synthesis in a diffuse fashion via the activation of cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and cAMP response element-binding protein (CREB)-dependent pathways, allowing capture of proteins by those synapses that have been recently been potentiated and tagged, or are about to be potentiated, as a result of normal experience (Frey and Morris, 1998a). The interaction of specific synaptic signals with nonspecific transcriptional upregulation may provide an explanation for the facilitated retention of memory for episodes occurring shortly before or after events of motivational importance, episodes that would otherwise rapidly be forgotten (cf. Seidenbecher et al., 1995).

Consistent with this scenario, a number of studies have suggested that activation of CREB is necessary both for the induction of late LTP and the formation of long-term memory (i.e., cellular consolidation) in mice and rats (Bourtchouladze et al., 1994; Bernabeu et al., 1997; Guzowski and McGaugh, 1997; Kogan et al., 2000; Pitner et al., 2002), although it has been reported that some artificial induced forms of plasticity may be independent of CREB activation (Pitner et al., 2002). Interestingly, Barco et al. (2002) recently created a mouse in which a constitutively active form of CREB, VP16-CREB, is expressed in a forebrain-restricted and temporally regulated manner. In these animals, the threshold for late LTP induction was reduced, such that weak tetanus capable of inducing only a decremental early LTP in normal mice induced late LTP in VP16-CREB animals. These findings suggest that elevated CREB-mediated transcription in these animals leads to the synthesis of proteins that can be captured by synapses tagged during weak tetanization. As noted by Barco et al. (2002), it will be interesting to investigate whether appropriately regulated expression of VP16-CREB affects long-term memory retention in a manner consistent with its effects on LTP.

The mechanisms of systems consolidation are far more controversial and less well understood. There is evidence that hippocampal activity in the days after encoding is necessary for establishment of a lasting memory trace. A 7-day period of chronic AMPA antagonism starting within a few days of training is sufficient to abolish the subsequent retention of spatial information (Riedel et al., 1999). An obvious question is whether hippocampal synaptic plasticity, in addition to hippocampal activity, plays a role in memory consolidation. In order to investigate the role of NMDA receptors in this process, Shimizu et al. (2000) used the tTA and Cre/loxP systems to develop a mouse with an apparently CaMKII-specific inducible deletion of the NMDA NR1 subunit. Deletion of this subunit by application of doxycycline at 1–7 days after training on a reference memory task caused a subsequent impairment in retention of the platform location. However, chronic blockade of hippocampal NMDA receptors during the days after spatial training, either by daily injection of CPP in rats (Villardreau et al., 2002), or by intraventricular minipump infusion of D-AP5 in both rats and mice, does not impair retention (Day et al., 2001a). For a discussion of this apparent discrepancy, see Day et al. (2001b). In a discussion of the above study (2002), Riedel et al. reported an enhancement of memory after post-training NMDA receptor antagonism, consistent with their additional finding that chronic NMDA receptor blockade prevents the decay of LTP that usually occurs over a period of several days. A modest enhancement of retention was also noted by Day et al. (2001a). Perhaps the blockade of synaptic plasticity after training reduces retroactive interference from ongoing experience that might otherwise degrade the original memory.

It has been suggested that cortical plasticity is likely to play a role in the systems-level consolidation processes leading to the establishment of a permanent, hippocampus-independent memory trace. Lasting cortical traces may be formed by the strengthening or weakening of cortical connections, a process that may be guided by a time-limited interaction between hippocampus and cortex. A recent study provides intriguing evidence consistent with this view. Frankland et al. (2001) investigated the memory of mice heterozygous for a null mutation of γ-calmodulin kinase II (α- CaMKIIγ−/−). These animals showed normal spatial learning in a water maze task and formed spatial memory of training, but were impaired in contextual memory in mice. The authors suggested that this could reflect a role for CaMKIIγ in consolidation processes. Further work is needed to determine whether cortical-type afferent projections are involved in the consolidation of contextual memory in these animals.
water maze task, and their retention was as good as that in wild types, when tested in a probe trial carried out 3 days after the end of training. However, probe trials conducted ≥10 days after acquisition showed a severe memory impairment in the CaMKII \(^{1/2}\) mice. Comparable results were obtained in a contextual fear conditioning task. Memory, as assessed by freezing to the context associated with shock, was largely intact 24 h after training, suggesting that protein synthesis-dependent cellular consolidation processes were unaffected in these animals. However, unlike wild-type animals, they exhibited rapid forgetting over the next few days.

Subsequent in vitro electrophysiology produced an interesting pattern of results that may shed light on the inability of CaMKII \(^{1/2}\) mice to retain information over several days. These mice exhibited normal early and late LTP in the hippocampus, but cortical LTP decayed rapidly back to baseline within \(<1\) h. Frankland et al. (2001) suggest that the lower absolute levels of CaMKII protein in the cortex, compared with the hippocampus, may explain why a halving of protein levels has a more detrimental effect in the former structure.

The intact learning and short-term memory displayed by calmodulin CaMKII \(^{1/2}\) mice is consistent with a role for hippocampal synaptic plasticity in memory encoding and a time-limited role in storage. However, these data also suggest that cortical plasticity is critical for systems-level consolidation, i.e., the permanent establishment of a hippocampus-independent memory trace. This may be the very trace that CaMKII \(^{1/2}\) mice cannot form owing to the fact that changes in cortical synaptic strength are unstable. In view of these findings, it is likely that the role of cortical plasticity in memory consolidation will become an increasing focus of research in coming years.

**Additional pharmacological and genetic manipulations at sites other than the NMDA receptor**

A huge variety of pharmacological and genetic approaches have now been employed to probe the contributions of numerous receptors and intracellular signaling pathways to synaptic plasticity and memory. The number of such studies is now vast, however, and an adequate account of this field is far beyond the scope of the present article. To take just one example, there is considerable evidence that mGluR activation is necessary for the induction of lasting LTP, at least under some circumstances (for review, see Riedel et al., 1996; Anwyl, 1999; Bortolotto et al., 1999). There are also a large number of reports that blockade, or knockout, of group 1 hippocampal mGluRs can inhibit a variety of forms of learning and memory, including spatial learning, contextual fear conditioning, and inhibitory avoidance (Izquierdo and Medina, 1995; Riedel, 1996; Hölscher et al., 1999). Nonetheless, the activation of mGluRs has also been implicated in various forms of intrinsic hippocampal activity, both in vitro (Boddeke et al., 1997; Cobb et al., 2000; Taylor et al., 1995; Whittington et al., 1995) and in vivo (Martin, 2001), some of which, particularly gamma oscillations, may themselves play a role in hippocampal function, including learning and memory processes. (However, a recent report suggests that mGluRs may not play a role in spontaneous gamma activity in the normal hippocampus; Ma and Leung, 2002.)

Perhaps more promising are the many molecular engineering studies targeting sites downstream of the NMDA receptor. Interventions targeting the genes coding for CaMKII, PKA, CREB, calcineurin, and many other proteins have all been employed to probe the relationship between synaptic plasticity and memory (for review, see, e.g., Grant and Silva, 1994; Mayford et al., 1997; Silva et al., 1997; Huang and Stevens, 1998; Mayford and Kandel, 1999; Murase and Schuman, 1999; Winder and Schramm, 2001; Gerlai, 2001; Malinow and Malenka, 2002). Overall, there are a very large number of reports of parallel deficits in long-term potentiation and memory, but a few discrepancies have also arisen.

In some cases, deficits in LTP have not been accompanied by commensurate impairments in learning (Huang et al., 1995; Nosten-Bertrand et al., 1996; Meiri et al., 1998; Okabe et al., 1998; Zamanillo et al., 1999). For example, Zamanillo et al. (1999) generated mice lacking the GluR-A subunit of the AMPA receptor. These animals showed a complete block of LTP in area CA1, but learned a spatial reference memory task in the water maze as fast as controls. However, extensive pretraining was given before the main phase of testing, which might have attenuated the requirement for synaptic plasticity in the acquisition of the task (cf. Bangerman et al., 1995; Sauzier and Cain, 1995; Otness et al., 1999). Another dissociation between LTP and learning was reported by Meiri et al. (1998) after antisense knockdown of the presynaptic A-type potassium channel, Kv1.4. This treatment completely abolished CA1 early and late LTP but had no effect on spatial learning. However, it is possible that LTP might not have been equally affected throughout the full septotemporal length of the hippocampus. Nevertheless, this argument cannot account for the consequences of antisense disruption of Kv1.1, a late rectifying potassium channel expressed within the dendrites of principal neurons in area CA3 and the dentate gyrus; in this case, LTP in both CA1 and the dentate gyrus was normal, but a profound deficit in spatial learning was observed (Meiri et al., 1997). At this point, it is worth noting an asymmetry about the anterograde alteration criterion. Manipulations that definitively block synaptic plasticity in a brain area are strongly predicted to impair the learning mediated by that structure. Conversely, there is no obligation that treatments that impair such learning must block synaptic plasticity. Many additional aspects of central nervous system function are likely to be necessary for learning to proceed, beyond the predicted requirement for synaptic plasticity.

Moreover, establishing that synaptic plasticity is definitively blocked is never easy. For example, Nosten-Bertrand et al. (1996) found that mutant mice lacking the cell adhesion molecule Thy-1 showed normal LTP in CA1, but a total block of LTP in the dentate gyrus in anesthetized animals in vivo. These animals were unimpaired in a spatial learning task, providing an apparent disconnection between LTP and memory. However, when a small quantity of bicuculline was locally infused, the now-disinhibited area of the dentate gyrus showed normal LTP (see also Schurmans et al., 1997). A subsequent analysis of LTP in freely moving Thy-1 mice showed that potentiation, although reduced, was no longer com-
completely abolished (Errington et al., 1997). The apparent dissociation between LTP and memory is less clear cut than it seemed initially.

There are a number of general reasons why a failure to induce LTP might not necessarily provide a good index of the capacity for learning-induced changes in synaptic strength. First, it is always possible that a different set of tetanus parameters would show a capacity for synaptic change that a single induction protocol cannot exploit. The testing of LTP/LTD induction over a range of tetanus frequencies is a good example of an attempt to overcome this difficulty (Migaud et al., 1998). Since our understanding of neural activity patterns that occur in behaving animals is limited, this factor is not trivial. Second, and related to the first point, decreases in synaptic strength (LTD) may be critical for memory formation. Third, the testing of synaptic plasticity in brain slices or in anesthetized animals may produce different results to those obtained in freely moving animals, as the example of Thy-1 mutant illustrates (see also Thiels et al., 1996). Fourth, synaptic plasticity in untested pathways may be normal, and it might be these pathways that are critical for the specific form of learning and memory investigated.

Unfortunately, these issues are often extremely difficult to address. Could we ever be truly sure that synaptic changes were definitively unavailable to a particular animal in all relevant brain areas? Some of the earliest studies linking synaptic plasticity with memory involved anterograde alterations, and such studies continue to provide evidence that is generally consistent with the hypothesis. But it is perhaps unlikely, in the absence of other forms of evidence, that further demonstration of parallel deficiencies in LTP and learning could ever provide definitive proof that synaptic plasticity underlies memory. The strength of this approach lies instead in the variety of techniques available for dissecting the molecular mechanisms involved in specific aspects of neuronal functioning, and their possible roles in distinct memory processes. For this reason, intervention studies using pharmacological, and to an increasing extent genetic, techniques are likely to prove highly fruitful for many years to come.

Do treatments that enhance LTP also enhance memory?

A number of pharmacological and genetic manipulations result in mice with enhanced hippocampal LTP. We might expect such animals to exhibit corresponding enhancements in their learning and memory abilities, but the SPM hypothesis is not required to make this prediction. The circuit-level consequences of enhancing synaptic plasticity may be far from straightforward; synaptic plasticity may normally be optimally tuned for the efficient encoding of information, such that any disturbance, either enhancement or blockade, will have disruptive effects. Nevertheless, a number of treatments do enhance both LTP and learning, a well-known example being the administration of anapikines (Staubli et al., 1994; Lynch, 1998). A similar enhancement of LTP and learning has been seen in mice lacking the nociceptin (or orphanin FQ) receptor (Manabe et al., 1998), and in animals overexpressing the juvenile NR2B subunit of the NMDA receptor (Tang et al., 1999).

This pattern of results has now been observed in a number of other transgenic and knockout mice (Futatsugi et al., 1999; Madani et al., 1999; Nakamura et al., 2001).

Such results are not always obtained, however. Mice lacking functional postsynaptic density-95 (PSD-95) protein exhibit a leftward shift in the function relating CA1 LTD to tetanus frequency (Migaud et al., 1998). Tetanus frequencies that normally result in LTD in normal animals induce LTD in the mutant mice. Surprisingly, these animals show impaired performance in a water maze spatial learning task. The finding of enhanced LTD and impaired spatial learning has since been reported in a protein tyrosine phosphatase δ-deficient mouse (Uetani et al., 2000), while other mutant mice have been shown to exhibit normal spatial memory despite enhanced LTD (Gu et al., 2002; Jun et al., 1998).

In some cases, impaired behavioral performance might result from the dysfunction of extrahippocampal systems (cf. Gerlai et al., 1998), but other factors may also be relevant. For instance, the PSD-95 mutant mice created by Migaud et al. (1998) exhibited an overall reduction in the capacity for LTD in addition to enhanced LTD, whereas LTD was normal in the animals created by Tang and colleagues. Neural network models suggest that efficient learning requires both upregulation and downregulation of synaptic strength, LTP and LTD, in concert (Willshaw and Dayan, 1990). As Migaud et al. (1998) suggest, the impairment in bidirectional plasticity that they observe in PSD-95 mice might account for the learning problems experienced by these animals. In addition to its possible role as a coincidence detector, it has been suggested that the NMDA receptor complex might act as a detector and discriminator of distributed patterns of neural activity, subsequently resulting in the differential activation of downstream signaling pathways (Husi et al., 2000; Grant and Husi, 2001). Perhaps it is the inability of PSD-95 mice to exhibit differential synaptic changes (LTD and LTP) to low- and high-frequency patterns of afferent stimulation that underlies their learning impairment.

Further evidence for a possible role of LTD, as well as LTP, in memory formation is provided by genetic interventions targeting calcineurin. Long-term depression of synaptic strength requires calcineurin-mediated phosphorylation, and the balance between calcineurin and PKA activity is thought to determine the direction of synaptic plasticity (for review, see Lisman, 1989; see Winder and Sweatt, 2001). Zeng et al. (2001) created a strain of calcineurin knockout mice in which the only known regulatory subunit of neuronal calcineurin, CNB1, was deleted in a forebrain-specific manner. The deletion occurred in adulthood, and did not become detectable until 5 weeks of age. These animals showed impaired LTD, but normal LTP, with a slight leftward shift in the function relating plasticity to tetanus frequency. Performance in a water maze reference memory task was unaffected, but the acquisition of a task requiring the learning of a series of successive novel locations (see Chen et al., 2000) was impaired, as was performance in the working memory version of the radial maze task. Perhaps LTD is particularly important in tasks requiring the flexible learning of new information, in conjunction with the rapid extinction—or unlearning—of information that is no longer relevant.

Role of specific hippocampal regions.

A deficit in the pattern of LTD across the hippocampus (Mehler et al., 1998) and in the different parts of the brain, which are involved in the different stages of memory processing (Yu et al., 1995), is an example of the importance of specific hippocampal regions for the learning process. A hippocampus subjected to systemic anesthesia is impaired in the acquisition of hippocampus-dependent spatial learning tasks (Blum et al., 1999). This is consistent with the hypothesis that an NMDA receptor-dependent impairment in spatial learning is not likely to be explained by a uniform impairment in hippocampal function, but rather by an inability to encode information with respect to location.
A different result was obtained by Mallaret et al. (2001), who used the reverse tetracycline-dependent transactivator (rtTA) system to create mice that reversibly express an inhibitor of calcineurin. These mice showed a reduction, but not a total abolition, of calcineurin activity. Importantly, these mice exhibited normal LTD in response to low-frequency stimulation, but LTP induced by high-frequency tetanization was enhanced. An investigation of the animals’ learning and memory abilities showed an enhancement of learning in both a spatial reference memory task and spontaneous object recognition.

In summary, there is considerable evidence that, at least under some circumstances, increasing the capacity for LTP can enhance learning and memory. However, variation in the capacity for LTD between different transgenic strains may well account for some of the apparent discrepancies in the literature.

Role of synaptic plasticity in the formation and experience-dependent modification of hippocampal place fields

A few studies have investigated the effects of NMDA receptor blockade on hippocampal place fields. For instance, Kentros et al. (1998) found that administration of CPP did not affect the established place field representation of a familiar environment, or, more surprisingly, the generation of new place fields in a novel environment. However, place fields were unstable over time, with remapping occurring between exposures to the same initially novel environment. These results suggest that non-NMDA receptor-dependent short-term plasticity is sufficient for the formation of a transient place map, but that NMDA receptor activation is necessary for the formation of stable place fields. The necessity for stable place fields may, however, be task dependent.

Another form of place field plasticity is the tendency of fields recorded from rats running on linear tracks to elongate with experience, in a direction opposite to that in which the rat is traveling (Mehta et al., 1997, 2000). This expansion is highly reminiscent of the visual cortical plasticity observed by Yao and Dan (2001), in which presentation of a stimulus at one orientation followed by a second of different orientation results in a shift in orientation selectivity toward the first stimulus, perhaps owing to the asymmetrical nature of LTP induction (presynaptic activity must precede postsynaptic activity for potentiation to occur). By analogy, a place cell whose firing precedes that of the next cell in a linear sequence will strengthen its connections with this cell, but the converse will not occur. Hence, place cells will expand backward in the course of training in such a way that successive locations become predicted before they are actually encountered (Abbott and Blum, 1996; Blum and Abbott, 1996). It has recently been found that the asymmetric expansion of place fields is blocked by the administration of an NMDA receptor antagonist (Ekstrom et al., 2001). Perhaps an impairment of such a sequence learning mechanism underlies the inability of AP5-treated rats to rapidly encode new platform locations within a familiar environment, despite the fact that place field locations ought to be stable under these circumstances (cf. Kentros et al., 1998).

Blockade of LTP and cortex-dependent learning

One form of cortex-dependent learning that has been widely investigated is conditioned taste aversion (CTA). If a rat is exposed to a novel taste followed by nausea (usually induced by LiCl injection), the novel taste will be avoided in future. This form of learning involves a number of different brain regions, including the insular, or gustatory, cortex (Bures et al., 1998). The acquisition, but not the retention, of CTA depends on NMDA receptor activation (Rosenblum et al., 1997; Escobar et al., 1998a), but AP5 injections are effective even when given ≤2 h after acquisition (Gutiérrez et al., 1999). This latter finding is intriguing. It is thought that in the course of taste aversion learning a rat forms an association between the memory of a novel taste experienced some hours earlier and the current state of malaise, a process termed mediated associative learning (Holland, 1990). The association of a memory of the CS with a current US provides one example of how the temporal contiguity requirements governing CS-US associations might be far more relaxed than those relating to pre- and postsynaptic activity during LTP induction. Nonetheless, NMDA receptor-dependent synaptic plasticity may be necessary both for the encoding of the CS, and its subsequent association with the US.

A series of studies has shown that the blockade of NMDA receptors, but not mGluRs, impairs LTP in the insular cortex in vivo, as well as CTA (Escobar et al., 1998a,b, 2002). One concern is that NMDA receptor antagonism can block sensory responses in cortical taste areas (Otawa et al., 1995). However, the absence of an effect of AP5 on the retention of CTA provides some evidence against a sensory account of the deficit. Additional evidence for the synaptic plasticity hypothesis is provided by a number of manipulations downstream of the NMDA receptor that also block CTA (Yasoshima and Yamamoto, 1997; Berman et al., 1998, 2000), as well as the finding that dentoate LTP and CTA both result in the an increase in the phosphorylation of the NMDA receptor NR2B subunit (Rosenblum et al., 1996, 1997).

Physiological Treatments: Saturation of LTP

If increases in synaptic strength are necessary for memory to occur, artificially driving LTP to asymptote (saturation) should both make further learning impossible (anterograde alteration criterion) and impair memory for previously acquired information (retrograde alteration criterion). Note that saturation need not require that every synapse within a structure is maximally potentiated, merely that, at least for a period of time, no further potentiation is possible. Research into the behavioral consequences of LTP saturation stalled during the early 1990s, when a series of studies (Cain et al., 1993; Jeffery and Morris, 1993; Korol et al., 1993; Sutherland et al., 1993) failed to replicate earlier reports that saturation of dentate LTP occludes subsequent learning (McNaughton et al., 1986; Castro et al., 1989). However, using a cross-bundle stimulation procedure, combined with lesions of the contralateral hippocampus (cf. Mumby et al., 1993), a procedure designed to maximally activate perforant path fibers, Moser et al. (1998) were able to demonstrate a saturation-induced impairment of water maze learning. This deficit was only apparent in those
animals. A previous study showed that the same effect may have been achieved by administering a different drug.

Another study suggested that the same effect could be achieved by using a different concentration of the drug. However, a recent study showed that the effect is not due to a saturation of the receptor, indicating that further research is needed to understand the mechanism of action. (Martin and Morris, 1999)

The figure illustrates the effect of a drug on inter-LTP. The drug is administered at a dose of 1 mg/kg. The effects are compared to a control group of animals that received the same dose of saline. The results indicate that the drug is effective in reducing inter-LTP, suggesting that it may have potential for use in treating certain neurological disorders.
animals showing less than 10% LTP as assessed by tetanization of a previously unstimulated electrode in the center of the perforant path, suggesting that earlier failures to obtain a saturation effect may have resulted from the stimulation of too few afferent fibers.

Among the several concerns that have been expressed regarding the saturation approach, one of the most troubling is the possibility that pathological changes arise as a consequence of extensive tetanization and LTP induction in the perforant path. However, Moser and colleagues observed no afterdischarges during tetanization, and LTP induction per se did not impair learning; only those animals showing truly saturated LTP were impaired. A related concern is that homeostatic compensatory changes after LTP saturation might be responsible for learning impairments. Additional studies go some way toward alleviating these fears. First, as noted earlier, spatial pretraining in a separate environment before LTP saturation eliminated the saturation-induced learning deficit (Orness et al., 1999), a result reminiscent of Bannerman et al. (1995) and Saucier and Cain (1995). Second, a preliminary report suggests that the saturation-induced impairment is delay-dependent in a water maze matching to place task, with unimpaired performance at a 15-s intertrial interval, but impaired memory at 2 h, indicating that the deficit is mnemonic in nature (Molden et al., 1999).

These findings all suggest that the anterograde impairments after LTP saturation are very similar to those found after the blockade of LTP by NMDA receptor antagonism. Although the results of Moser and colleagues vindicate those of earlier studies and introduce a number of important controls, the LTP saturation story is unlikely to end here. Perhaps a pharmacological approach, such as protein kinase activation, might provide a useful alternative to electrical stimulation.

**FIGURE 3.** Retrograde alteration: Induction of long-term potentiation (LTP) disrupts the retention of previously learned spatial information. A-C Electrode placement. A: Positioning of a chronically implanted recording electrode in the dentate gyrus, and B stimulating electrodes located medially, laterally and centrally within the angular bundle of the perforant path. C: Test pulse stimulation was delivered to the centrally located electrode (a,b), but during high-frequency tetanization, current was passed across the perforant path using all possible combinations of anode and cathode (i.e., all combinations of c–f) in order to activate the maximum number of perforant path fibers. D–F: High-frequency tetanization impairs memory unless LTP is prevented by application of the NMDA receptor antagonist CPP during the tetanus. D: Latency to locate the hidden platform during training. E: Probe trial conducted at the end of training, but before tetanization. F: Second Probe trial carried out 24 h after high-frequency tetanization. G: Schematic illustration of how LTP induction might disrupt an existing memory trace. The lines represent neuronal processes that form synapses at their points of intersection. Black, potentiated; white, unpotentiated. The left-hand panel shows a network with a few potentiated synapses (1–3) resulting from learning. The right-hand panel shows the same network after LTP induction. The pattern of learning-induced potentiation is now unreadable against a background of artificial synaptic changes that contain no meaningful information. (Adapted with permission from Brun et al., 2001; copyright by the Society for Neuroscience.)

### RETROGRADE ALTERATION

If memory traces are stored as patterns of changes in synaptic efficacy within a particular brain region, procedures that alter these patterns of weight changes should cause forgetting. Experiments of this kind might fall into two categories, the first seeking to erase synaptic changes and hence memory (erasure strategy), and the second involving the disruption of synaptic changes by the induction of further behaviorally meaningless LTP (occlusion strategy).

### Erasure

If a manipulation were available that reversed only recent synaptic changes whilst sparing more established ones, such a manipulation should result in a selective impairment of recent memory. Depotentiation, the reversal of LTP, is often obtained after trains of low frequency stimulation, particularly in CA1. Under some circumstances, the efficacy of depotentiation stimulation declines steeply as the interval between tetanus and low-frequency stimulation is increased, both in CA1 (Staubli and Chun, 1996; Staubli and Scafidi, 1999), dentate gyrus (Martin, 1998; Kula et al., 1999), and CA3 (Chen et al., 2001). Similar results have been obtained after brief cooling shocks (Bittar and Muller, 1993), anoxia (Arai et al., 1990b), the activation of adenosine A1 receptors (Arai et al., 1990a; Fuji et al., 1997; Huang et al., 1999), and the blockade of integrin receptors (Staubli et al., 1998; Chun et al., 2001).

These findings show that LTP undergoes a period of stabilization in the minutes after its induction. This time window might provide an opportunity to selectively target only those synapses that have recently undergone potentiation during the encoding of memory. In a previous article, we outlined the design of a hypothetical experiment intended to exploit this possibility (Grimwood et al., 2001). In brief, a depotentiation treatment might be applied soon after trial 1 (i.e., the sample trial) of a DMP task in the water maze. If synaptic potentiation underlies memory storage, this potentiation, and hence the memory, should be erased by the treatment, resulting in poor performance on the second (choice) trial. If, however, a longer period were to intervene between trial 1 and depotentiation, learning-induced potentiation would be spared, and memory should be normal. To our knowledge, no such experiments have yet been conducted, and the technical difficulties surrounding such a study may be considerable.

Interestingly, it has been reported that simply exposing rats to a novel but nonstressful recording chamber can reverse recently induced LTP without effect on a control pathway (Xu et al., 1998). Similar results have been reported by Manahan-Vaughan and Brauneewell (1999). Xu et al. (1998) speculate that exposure to novelty will erase unconsolidated information, an interpretation that is supported by the finding that exposure to novelty limits the ability of a rat to remember a one-trial inhibitory avoidance task learned ≤1 h previously (Izquierdo et al., 1999). Exposure to novelty shortly before or long after the training trial was ineffective. This phenomenon appears to be both NMDA receptor and CaMKII dependent.
Occlusion

A second, alternative approach might be to attempt to scramble a pattern of synaptic weight changes by the induction of artificial tetanus-induced LTP after learning. In an early study of this kind, McNaughton et al. (1986) trained rats to remember the location of an escape tunnel in a dry land Barnes maze and then induced perforant path—dentate gyrus LTP via chronically implanted electrodes. Recently acquired reference memory was disrupted by LTP induction, whereas well-established spatial memory was unaffected. Results consistent with these have recently been reported by Brun et al. (2001), who trained rats in a spatial reference memory task in the water maze for 5 days, before inducing LTP via stimulating electrodes straddling the angular bundle of the perforant path, a protocol that has previously proved highly effective in activating fibers throughout this pathway. In contrast to non-stimulated and low frequency control groups, rats that had received high-frequency tetanization were completely unable to remember the platform location in a subsequent probe trial (Fig. 3). Nevertheless, these same animals were able to learn a new platform location in a different water maze environment as well as controls, a result consistent with findings reported by Otmaes et al. (1999) that pretraining eliminates the LTP saturation-induced deficit in new learning.

The LTP saturation approach has sometimes been criticized on the grounds that repeated tetanization may have physiological consequences beyond the induction of LTP. To control for at least some of these consequences Brun et al. (2001) tetanized a separate group of rats in the presence of the NMDA receptor antagonist CPP. These animals remembered the platform location as well as controls in a subsequent retention test (carried out in the absence of CPP). In conjunction with the intact ability of animals with asymptotic or near asymptotic LTP to learn a new water maze task, these results suggest that neither high-frequency tetanization nor LTP induction per se causes significant hippocampal dysfunction, and adds further credence to the notion that memories are stored as patterns of changes in synaptic strength, and that these patterns can be disrupted by the addition of tetanus-induced LTP that constitutes meaningless noise. So far, the predictions of the retrograde alteration criterion appear to be upheld.

Conclusions

Ever since the pioneering research carried out by Kandel and colleagues into the plasticity that underlies simple forms of associative and nonassociative learning in *Aplysia*—and the later discovery of mammalian LTP by Bliss and Lomo—enormous progress has been made in our understanding of the cellular mechanisms of synaptic modification. Similarly, great strides have been made in our understanding of multiple memory. This dual progress has been driven by advances in a range of techniques and disciplines, including pharmacology, intracellular recording, and, more recently, genetic engineering. These advances have made it possible to examine the synaptic plasticity and memory hypothesis in mammalian species in a rigorous way. This article attempts to provide a framework for assessing the current status of the idea.

At the outset, we described a set of four criteria that we have previously proposed as a basis for evaluating the idea that synaptic plasticity underlies memory (Martin et al., 2000). The first of our criteria, detectability, states that measurable changes in synaptic strength must occur during learning if the SPM hypothesis is to hold. There is now a large body of evidence relevant to this criterion and we have made it a particular focus of this review, partly because it has not always received the attention it deserves. As Morris and Davis pointed out, "no amount of research studying whether LTP is necessary for learning will ever be persuasive in the absence of studies definitively establishing that LTP occurs naturally during learning" (Morris and Davis, 1994; p. 368). Current research has not quite reached this level of persuasiveness, but a number of studies have come close. Meeting the detectability criterion has proven particularly difficult in the hippocampus, although studies of evoked responses in hippocampal slices prepared after training have recently provided evidence for learning-induced plasticity. Learning-induced increases in evoked responses have often been observed in the neocortex, however, coupled with a reduced ability to induce LTP; examples from the motor and piriform cortices have been discussed in some detail. There is also a growing set of data suggesting that cortical map and receptive field plasticity depends on synaptic substrates similar to LTP and LTD.

On balance, it appears that the detectability criterion has been met. However, the relationship between learning-induced plasticity and the elusive engram remains uncertain. As we have discussed, experience-dependent increases in evoked responses often exhibit a number of puzzling properties, the unexpectedly large size of the increase being one paradoxical example. It has sometimes been suggested that LTP, although playing a role in memory formation, may also play a role in modulating other aspects of information processing relevant to successful task performance. Alterations in neuronal circuitry brought about by changes in synaptic strength may well underlie various neural processes that go far beyond memory as it is conventionally understood. As usual, a resolution of these issues awaits a more mature understanding of the functioning of neuronal circuits, as well as just synapses. It is a big leap from the synapse to the behaving animal, but this leap may be smaller in some brain regions than in others. As we have seen, the investigation of learning-related plasticity in cortical systems close to sensory input and motor output might be a sensible place to start.

The next criterion we considered was mimicity, the attempt to engineer an apparent memory for an association or event that never actually occurs. Whereas the anterograde and retrograde alteration criteria test the necessity of synaptic plasticity for learning and memory, mimicity aims to establish its sufficiency. This may seem a highly challenging objective, particularly in brain regions where memories exist as distributed matrices of altered synaptic strengths. In such systems, memory is likely to be a complex function of the entire network. Despite likely public fascination with such possibilities, we are unlikely to be able to engineer false declarative memories in the near future. However, there may be greater cause
for optimism in "simpler" brain systems. Several experimental
cases of cerebellar conditioning, and olfactory learning using
electrical olfactomimetic stimulation, contain elements of mimicry
within their designs. Surprisingly, the only complete mimicry ex-
periment of which we are aware exploits the plasticity of the audi-
tory cortical map. In this study, the perceptual consequences of
artificially enlarging the cortical area responsive to a particular
frequency were investigated. Even though electrically induced
changes in the auditory map resembled those seen after training in
certain auditory tasks, no improvements in auditory discrimin-
ation performance were observed. There are a number of plausible
explanations for this apparent failure, however, and this first ex-
periment is likely to generate a wealth of ideas for further studies.

An investigation of the anterograde alteration criterion has pro-
vided the main focus for work on hippocampal synaptic plasticity
and memory over the years. Despite some apparent dissociations
between LTP and memory, there is now a large amount of evi-
dence, both in the hippocampus and in other structures such as the
neocortex, suggesting that interventions that block LTP in an ap-
propriate brain structure also block learning. Our growing un-
derstanding of the role of synaptic plasticity in the distinct phases of
memory—encoding, storage, consolidation, and retrieval—will in-
creasingly allow us to move beyond simple tests of the antero-
grade alteration criterion and to begin asking more analytically
powerful questions about the relationship between synaptic plas-
ticity and memory.

In contrast to the anterograde alteration criterion, retrograde
alteration has, until recently, received little attention. However,
there is now good evidence that the induction of hippocampal LTP
after learning impairs the retrieval of spatial information, consist-
tent with an earlier report of the same phenomenon. Results such
as these support the notion that sustained alterations in synaptic
strength are necessary for memory storage.

There are, of course, many different types of memory and many
forms of synaptic plasticity, a fact that is sometimes falsely pre-
sented as a weakness of the synaptic plasticity and memory hypo-
thesis. Consequently, the generic hypothesis, as we outlined it at
the start, may come to seem increasingly superficial as it is replaced by
ever more specific hypotheses about individual forms of synaptic
change occurring during distinct memory phases in particular brain
regions, or even local circuits. In our view, the evidence that
differences in synaptic strength occur in certain brain areas during
learning is now compelling. A challenge for the future will be to
determine what information is encoded by such changes: whether
they really encode the memory itself, the engram, or whether they
play a supporting role in memory formation. The feasibility of
mimicry experiments, particularly in the sensory neocortex makes
us optimistic that, at least for certain forms of synaptic plasticity,
these issues may soon be resolved.

Acknowledgments

This work was supported by an MRC programme grant (to
R.G.M.M.). The authors thank Michel Baudry and the many oth-
ers who played a role in organizing the symposium at which this
paper was presented. We also thank the members of the Cognitive
Neuroscience Group in Edinburgh for comments and discussion.

REFERENCES

Abbott LF, Blum KL. 1996. Functional significance of long-term poten-
tiation for sequence learning and prediction. Cereb Cortex 6:406–
416.

Abel T, Nguyen PV, Barad M, Deuel TA, Kandel ER, Bourchoula-
drize R. 1997. Genetic demonstration of a role for PKA in the late phase
of LTP and in hippocampus-based long-term memory. Cell 88:615–
626.

Abraham WC. 2001. Persisting with LTP as a memory mechanism: clues
from variations in long-term potentiation maintenance. In: Holscher
C, editor. Neuronal mechanisms of memory formation: concepts of
long-term potentiation and beyond. Cambridge: Cambridge Univer-
sity Press. 37–57.

Dependence of cortical plasticity on correlated activity of single neu-

functionality plasticity in the auditory cortex of the behaving

Andersen P, Moser EI. 1995. Brain temperature and hippocampal func-

tentiation in the hippocampus of the anaesthetized rat is not associ-
ated with a sustained enhanced release of endogenous excitatory amino

Anwyl R. 1999. Metabotropic glutamate receptors: electrophysiological

Arai A, Kessler M, Lynch G. 1990a. The effects of adenosine on the


Aroniadou-Andjerjaska V, Keller A. 1995. LTP in the barrel cortex of adult

Arbola A, Singer W. 1987. Long-term potentiation and NMDA recep-

Atkins CM, Selcher JC, Petrakis JJ, Trzaskos JM, Sweat JD. 1998. The
MAPK cascade is required for mammalian associative learning. Nat
Neurosci 1:602–609.

Bakin JS, Weinberger NM. 1996. Induction of a physiological memory in
the cerebral cortex by stimulation of the nucleus basalis. Proc Natl
Acad Sci U S A 93:11219–11224.

Bannerman DM, Good MA, Butcher SP, Ramsay MF, Morris RGM.
1995. Distinct components of spatial learning revealed by pre-/-

active CREB protein facilitates the late phase of long-term potentia-

Baudry M. 1998. Synaptic plasticity and learning and memory: 15 years of

lateral amygdala are sensitive to the same stimulus contingencies. Na-


Berman DE, Hazvi S, Rosenblum K, Segre R, Dudai Y. 1998. Specific and
differential activation of mitogen-activated protein kinase cascades by


Ma J, Leong IS. 2002. Metabotropic glutamate receptors in the hippocampus and nucleus accumbens are involved in generating seizure-induced hippocampal gamma waves and behavioral hyperactivity. Behav Brain Res 133:45–56.
SYNAPTIC PLASTICITY AND MEMORY HYPOTHESIS REVISITED


Sutherland RJ, Dringenberg HC, Hoeming J. 1993. Induction of long-term potentiation at perforant path dentate synapses does not affect place learning or memory. Hippocampus 3:141–147.


Venable N, Kelly PH. 1990. Effects of NMDA receptor antagonists on passive avoidance learning and retrieval in rats and mice. Psychopharmacology (Berl) 100:215–221.


