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SYNAPTIC PLASTICITY AND MEMORY: An Evaluation of the Hypothesis

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■ **Abstract** Changing the strength of connections between neurons is widely assumed to be the mechanism by which memory traces are encoded and stored in the central nervous system. In its most general form, the synaptic plasticity and memory hypothesis states that "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." We outline a set of criteria by which this hypothesis can be judged and describe a range of experimental strategies used to investigate it. We review both classical and newly discovered properties of synaptic plasticity and stress the importance of the neural architecture and synaptic learning rules of the network in which it is embedded. The greater part of the article focuses on types of memory mediated by the hippocampus, amygdala, and cortex. We conclude that a wealth of data supports the notion that synaptic plasticity is necessary for learning and memory, but that little data currently supports the notion of sufficiency.

INTRODUCTION

The role of activity-dependent synaptic plasticity in learning and memory is a central issue in neuroscience. Much of the relevant experimental work concerns the possible role of long-term potentiation (LTP) in learning, with the majority of studies focusing on *N*-methyl-D-aspartate receptor-dependent forms of LTP. The aim of such research is caricatured by the question—does LTP equal memory (Stevens 1998)? However, this is widely recognized as an oversimplification—even by the interrogator. Qualifications include the following: what type of LTP is involved; which properties of LTP are really relevant to memory; whether long-term depression (LTD) or depotentiation is involved; what types of learning are involved and in which brain area; and whether LTP is relevant to encoding, storage, consolidation, and retrieval or to only a subset of these memory processes. In short, thinking about LTP's putative role in memory has moved on from a relatively simple hypothesis (Hebb 1949) to a set of more specific ideas

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about activity-dependent synaptic plasticity and the multiple types of memory that we now know to exist (Kandel & Schwartz 1982, Lynch & Baudry 1984, McNaughton & Morris 1987, Morris & Frey 1997). These distinct hypotheses do, however, share a common core, which we will call the synaptic plasticity and memory (SPM) hypothesis: *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.*

This hypothesis is rooted in the fact that synaptic plasticity is a physiological phenomenon whereby specific patterns of neural activity give rise to changes in synaptic efficacy and neural excitability that long outlast the events that trigger them. Having the biophysical and biochemical machinery to perform this trick is potentially useful to neurons for all sorts of purposes and is vital for memory.

The argument we present is that the properties of synaptic plasticity, including several of the newer properties that have recently been discovered, make LTP particularly suitable in several memory systems for (*a*) the initial encoding and storage of memory traces and (*b*) the initial phases of trace consolidation (or stabilization) over time. We also argue that LTP is unlikely to be involved in retrieval.

However, we qualify these points in two ways. First, the memory processing achieved by LTP (or LTD) is likely to be network specific. LTP may serve a universal function in the encoding and storage of memory traces, but what gets encoded and how is an emergent property of the network in which this plasticity is embedded, rather than of the mechanisms operating at the synapse in isolation. For example, the character of information processing in the hippocampus is different from that in the amygdala and would remain so even if the mechanisms of plasticity utilized in each brain area were conserved.

A second qualification is that if synaptic plasticity is involved in encoding and storage, distinct patterns of neural activity may be necessary at the read-in and read-out stages. The difference may reflect the presence or absence of sharp waves (Buzsáki 1989), alterations in neuromodulatory input (e.g. Hasselmo et al 1995), or opportunities afforded by pattern-completion during retrieval (but not encoding) in certain kinds of distributed networks (Churchland & Sejnowski 1992).

The SPM hypothesis should be distinguished from others about LTP or LTD. These include the null hypothesis, which states that synaptic plasticity has nothing to do with memory; the plasticity/pathology continuum hypothesis (McEachern & Shaw 1996); and the notion that synaptic plasticity plays a role in attentional rather than memory processes (Shors & Matzel 1997). Distinguishing between these and alternative hypotheses about the functions of LTP is not always easy. The SPM and null hypotheses are easy to contrast, but much of the evidence thought to support the SPM hypothesis could also be said to support the view that an LTP-like mechanism underlies cognitive processes, such as attention, which are essential prerequisites for learning rather than integral to encoding or storage processes per se. The thrust of the critique by Shors & Matzel (1997),

with which we have a measure of sympathy, is that few experiments have yet been conducted that can unambiguously distinguish these rival hypotheses.

ASSESSMENT CRITERIA AND EXPERIMENTAL STRATEGIES

The SPM hypothesis has to fulfill four logical criteria (Table 1). The first of these criteria, detectability, states that, in association with the formation of memory lasting any length of time, LTP or LTD must occur at certain synapses in one or more brain areas and should, in principle, be detectable. The paucity of synapses that change with any one learning experience, and their spatial distribution, may make this criterion difficult to meet experimentally. With respect to the mimicry criterion, if changes in synaptic weight are the neural basis of trace storage, then their artificial induction in a specific spatial pattern should give rise to "apparent" memory for some (nonoccurring) experience. Satisfying this mimicry criterion would establish that changes in synaptic weights are sufficient to induce memory. Induction of LTP (or LTD) at an appropriate subset of hippocampal synapses to achieve an apparent memory of an event that never occurred is unlikely to be feasible in the near future. It may, however, be easier in brain areas such as the amygdala or in simpler vertebrate (or invertebrate) systems. For example, in the case of the goldfish escape reflex, it is known that repeated acoustic stimuli induce LTP at inhibitory synapses onto the Mauthner cell and that they also cause behavioral desensitization of this reflex (Oda et al 1998). It follows that our mimicry criterion might be met by examining whether inducing LTP at this synapse artificially is sufficient to induce behavioral desensitization.

Necessity would be established by the anterograde alteration and retrograde alteration criteria. Blocking the mechanisms that induce or express changes in synaptic weights should have the anterograde effect of impairing new learning, whereas altering the pattern of synaptic weights after learning should affect the

TABLE 1 Four formal 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: Conversely, if it were possible to induce the same spatial 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 wieghts induced by a prior learning experience (see detectability) should alter the animal's memory of that experience.

animal's memory of past experience. An asymmetry about anterograde alteration should be recognized. Treatments that definitively block synaptic plasticity in a brain area are predicted to have deleterious effects on learning mediated by that brain area; however, treatments shown to affect learning need not. This asymmetry arises because there are many additional aspects of central nervous system function that influence learning and memory beyond synaptic plasticity.

Our review of the literature indicates that research, to date, has followed five basic strategies (Table 2): correlation—the behavioral parameters of learning should be correlated with some but not necessarily all of the properties of synaptic plasticity; induction—learning should be associated with the induction of measurable changes in synaptic efficacy at synapses in appropriate networks of the brain, and the induction of such changes at relevant synapses (were this to be feasible) should result in apparent memories; occlusion—saturation of synaptic plasticity in a network should destroy the pattern of trace strengths corresponding to established memories and occlude new memory encoding; intervention—blockade or enhancement of synaptic plasticity, achieved by pharmacological, genetic, or other manipulations, should have commensurate effects on learning or memory; and erasure–erasure of synaptic plasticity should, at least shortly after learning, induce forgetting.

Two of these strategies, correlation (weakly) and induction, are relevant to the idea that synaptic plasticity must occur during learning (detectability) and be sufficient (mimicry) for a memory trace to be established; and three others—occlusion, intervention, and erasure–are relevant to the claim that synaptic plasticity is necessary for subsequent memory trace formation (anterograde and retrograde alteration). Certain strategies are pertinent to two criteria. For example, attempting to saturate LTP (occlusion) has the potential of providing data relevant to both the anterograde and retrograde criteria. Similarly, other strategies go beyond the formal criteria in interesting and important ways. For example, exper-

TABLE 2 Five experimental strategies that have been used to assess the SPM hypothesis

CORRELATION: The behavioral parameters of learning should be correlated with some but not necessarily all of the properties of synaptic plasticity.
INDUCTION: Learning should be associated with the induction of measurable changes in synaptic efficiency at synapses in appropriate networks of the brain; and the induction of such changes at relevant synapses (were this to be feasible) should result in apparent memories.
OCCLUSION: Saturation of synaptic plasticity in a network should destroy the pattern of trace strengths corresponding to established memories and occlude new memory encoding.
INTERVENTION: Blockade or enhancement of synaptic plasticity, achieved by pharmacological, genetic or other manipulations, should have commensurate effects on learning or memory.
ERASURE: Erasure of synaptic plasticity should, at least shortly after learning, induce forgetting.

iments establishing that pharmacological or genetic interventions that enhance LTP also improve learning indicate that the SPM hypothesis may lead to discoveries about how to improve memory. However, the hypothesis is not required to make this prediction, as synaptic plasticity may ordinarily be so finely tuned to the optimum that any disturbance of the balance between LTP and LTD would be deleterious. New genetic evidence provides some support for this conjecture.

We consider these criteria and strategies in relation to the role of synaptic plasticity in hippocampus-, amygdala-, and cortex-dependent learning in vertebrates. Excluded are studies of the role of LTD in the cerebellum and cortical receptive field plasticity. We have also limited our discussion of the effects of stress on plasticity, gene-targeting studies, and the role of cAMP response element-binding protein (CREB) in memory (Linden & Connor 1995, Chen & Tonegawa 1997, Buonomano & Merzenich 1998, Silva et al 1998, McEwen 1999). Our exclusion of invertebrate studies is unfortunate, as many of the conceptual issues overlap, but there are too many differences of detail to be discussed in the space available.

PROPERTIES OF LTP AND LTD: THE OLD AND THE NEW

There are various forms of synaptic plasticity differing with respect to their persistence over time and their underlying induction and expression mechanisms. The best known of these is long-term potentiation (LTP) (Bliss & Lømo 1973), in which synaptic potentials, evoked by low-frequency stimulation, are observed to increase in amplitude as a consequence of brief patterns of high-frequency stimulation or the pairing of presynaptic activity with postsynaptic depolarization (Figure 1*A*). LTP occurs in many pathways of the brain (not just the dentate gyrus and hippocampus, where it was first observed). Most forms of LTP are glutamatergic and the most prominent form is induced following activation of the *N*-methyl-D-aspartate (NMDA) receptor. Numerous reviews concerning the neural mechanisms of both NMDA-dependent and NMDA-independent LTP have been published, to which the interested reader should refer for details of pre- and postsynaptic mechanisms, signal transduction pathways, and molecular mechanisms (e.g. Johnston et al 1992, Bliss & Collingridge 1993, Nicoll & Malenka 1995, Fregnac 1997).

Long-term depression (LTD) is a lasting activity-dependent decrease in synaptic efficacy that was first discovered in CA1 in vitro by Lynch et al (1977). Both hetero- and homosynaptic forms of LTD can be induced in various pathways of the hippocampal formation in vivo (Levy & Steward 1979, Thiels et al 1994, Heynen et al 1996, Thiels et al 1996) (Figure 1*B*) and in vitro (Dunwiddie & Lynch 1978, Dudek & Bear 1992, Derrick & Martinez 1996). Like its LTP counterpart, it may be NMDA-receptor dependent or independent. LTD is also

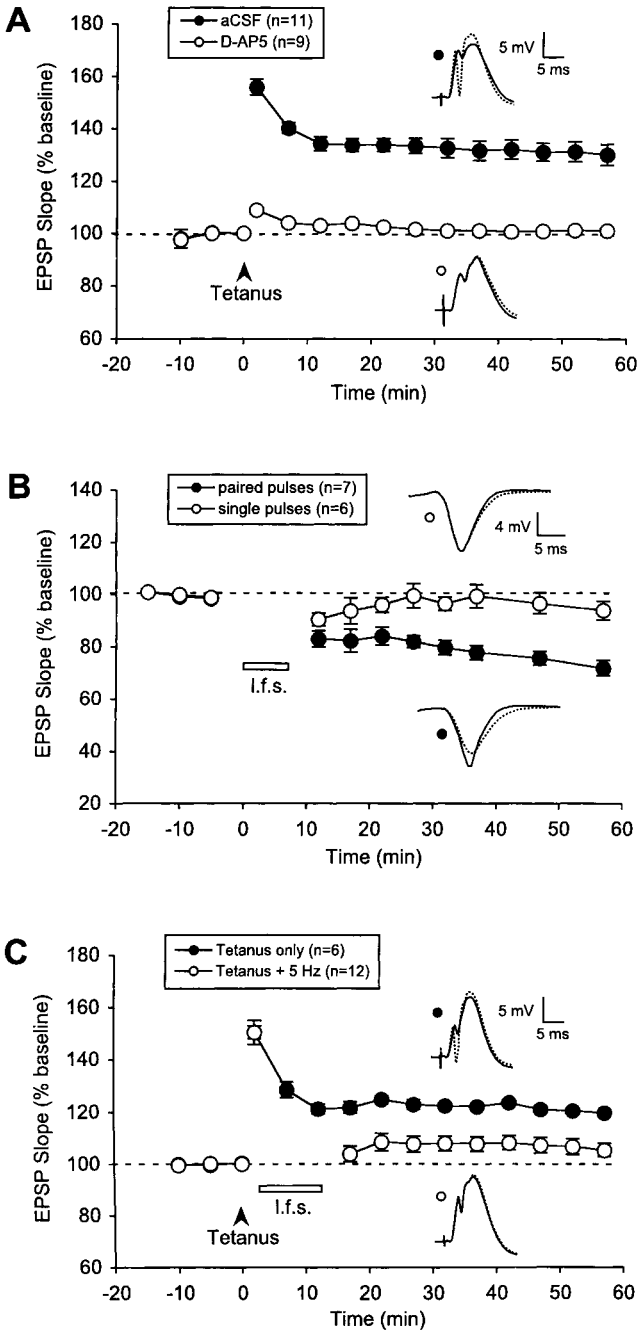

Figure 1 (*A*) Excitatory postsynaptic potential (EPSP) slope long-term potentiation (LTP) in the dentate gyrus in vivo recorded during chronic minipump infusion of artificial cerebrospinal fluid (aCSF) or 30 mM D-2-aminophosphonopentanoic acid (D-AP5). Superimposed waveforms from each group are shown before the tetanus (*solid lines*) and 37 min afterward (*dotted lines*). LTP was completely blocked by AP5 infusion (SJ Martin, unpublished data). (*B*) Long-term depression (LTD) in area CA1 in vivo. Low-frequency stimulation (l.f.s.) consisted either of 200 pairs of pulses delivered at 0.5 Hz with a 25-ms interstimulus interval or 400 pulses at 1 Hz. Only the former protocol induced robust LTD. [From Thiels et al (1994).] Sample waveforms are illustrated as described in *A*. (*C*) The reversal of dentate LTP by l.f.s. in vivo. Rats received either a tetanus only or a tetanus followed 2 min later by a 10-min period of 5-Hz stimulation. Note that posttetanic stimulation was equivalent in both groups prior to l.f.s. [From Martin & Morris (1997).]

observed in the amygdala (Li et al 1998) and cortex (Artola et al 1990, Kirkwood & Bear 1994). Depotentiation (Figure 1*C*), the reversal of LTP, is also observed in vivo (Barrionuevo et al 1980, Stäubli & Lynch 1990) and in vitro (Fujii et al 1991, Bashir & Collingridge 1994).

Having the capacity to bidirectionally modify synaptic efficacy improves the potential fidelity of memory recall in associative memory matrix models (Willshaw & Dayan 1990). This theoretical argument is not based on assigning different functions to LTP and LTD (such as learning and forgetting, respectively); rather, they complement each other with respect to signal-to-noise ratio and hence storage capacity. A complication in accepting an important role for homosynaptic LTD in memory processing is that the phenomenon has, with rare exceptions (Doyère et al 1996, Manahan-Vaughan 1997), proved remarkably elusive in freely moving animals (Errington et al 1995).

Here we use the terms LTP and LTD to refer, respectively, to any input-specific up- or down-regulation of synaptic strength that lasts at least 1 h, including both NMDA receptor-dependent and -independent forms. There are other forms of activity-dependent neuronal plasticity, such as excitatory postsynaptic potential (EPSP)-spike potentiation and changes in membrane properties (e.g. after-hyperpolarization); these are not, in general, input specific. We recognize, but also exclude from detailed discussion, experience-dependent alterations in neurogenesis or cell survival (Kempermann et al 1997, Gould et al 1999, van Praag et al 1999). These may reflect the nervous system creating the neural space for subsequent learning rather than the on-line encoding of the specific experiences that trigger this change.

Properties of Synaptic Plasticity Suggest a Role in Learning

It has often been pointed out that synaptic plasticity displays physiological properties that are highly suggestive of an information storage device (McNaughton 1983, Lynch & Baudry 1984, Goelet et al 1986, Morris et al 1990, Bliss & Collingridge 1993, Barnes 1995, Jeffery 1997, Shors & Matzel 1997). These classical properties include, at least for NMDA receptor-dependent LTP, that its induction is associative, and that its expression is both input specific and persistent over time. These may be relevant (*a*) to associative or relational features of learning and memory (because associative induction implies the capacity to relate two arbitrary patterns of pre- and postsynaptic neural activity); (*b*) to storage capacity (because a synapse-specific mechanism endows greater storage capacity than would changes in cell excitability); and (*c*) to the permanence of memory (because the synaptic enhancement must last as long as the memory).

These assertions beg the question of whether the properties of synaptic plasticity are likely to be homologous to characteristics of learning at the behavioral level. Some properties will be directly reflected in memory—such as persistence over time. Others are less likely to be, because the overt manifestations of memory are not solely due to synaptic properties—they also depend on the properties of

the network in which that plasticity is embedded (see below). An example of mismatch is that the temporal contiguity requirements for presynaptic glutamate release and postsynaptic depolarization in the induction of NMDA receptor-dependent LTP are much tighter than those governing various forms of associative conditioning. This has sometimes been presented as a weakness of the SPM hypothesis (Diamond & Rose 1994). However, until more is known about how information is represented as spatiotemporal patterns of activity on pathways in the higher nervous system, and about the relative timescales of neural events within the brain and those of overt sensory stimuli and motor output, it is difficult to do more than speculate about the degree of isomorphism to be expected.

Some Newly Discovered Properties of LTP with Potential Implications for a Role in Memory

Various newly discovered properties of synaptic plasticity have added implications for the SPM hypothesis. These include metaplasticity, the induction of LTP and LTD by naturalistic patterns of stimulation and the role of propagative postsynaptic dendritic action potentials, synaptic gain or redistribution, the degree of input specificity, the possibly digital nature of potentiation at individual synapses, the concept of silent synapses, and the variable persistence of LTP following identical induction conditions.

Metaplasticity The magnitude and direction of change in synaptic efficacy can be influenced by the prior history of synaptic activity. Such prior activity need not itself induce a change in synaptic efficacy but can alter the capacity of a synapse to undergo plastic changes in future. This phenomenon has been termed metaplasticity (Abraham 1996, Abraham & Bear 1996). For example, prior tetanization can inhibit subsequent LTP (Fujii et al 1991, Huang et al 1992, Abraham & Hugget 1997) and facilitate LTD (Wagner & Alger 1995, Holland & Wagner 1998).

According to a theoretical account of metaplasticity [the Bienenstock-Cooper-Munro (BCM) model (Bienenstock et al 1982)] (Figure 2*A*), low levels of postsynaptic activity result in LTD and high levels of activity result in LTP. However, the modification threshold θ_M can "slide" in a manner determined by the prior history of postsynaptic activity. High levels of activity result in a rightward shift in θ_M, thus favoring LTD, whereas low levels of activity result in a leftward shift favoring LTP. Such a variable threshold might serve a normalizing function, helping to limit excessive and potentially epileptogenic levels of LTP and, conversely, reducing the likelihood of synaptic efficacy falling to zero.

Measurement of synaptic plasticity over a range of tetanus frequencies (at least in CA1 slices) yields a frequency/plasticity function with the same form as the BCM curve in which metaplasticity constitutes a shift in θ_M (Dudek & Bear 1992). However, there is the important difference that synaptic plasticity is plotted as a function of presynaptic activity experimentally, but of postsynaptic activity in the

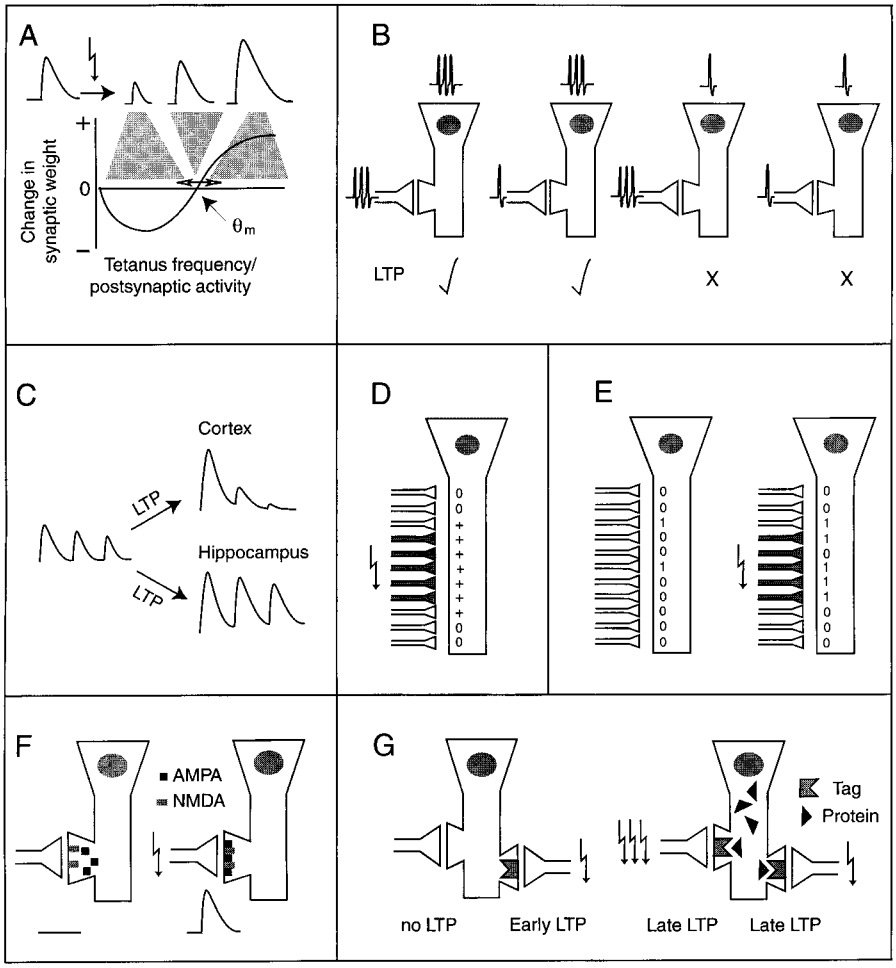

Figure 2 Cartoons summarizing several newly discovered properties of long-term potentiation (LTP) and long-term depression (LTD) likely to have functional implications. These cartoons oversimplify the experimental data but are each intended to convey a key idea about a new property of LTP or LTD. See text for references. (*A*) Metaplasticity—the BCM function implies that low-frequency tetani cause LTD whereas higher frequencies cause LTP. The threshold separating these slides up or down in response as a function of prior activity. (*B*) The induction of LTP and LTD by naturalistic patterns of stimulation. LTP is induced if and only if there is postsynaptic bursting. (*C*) Synaptic gain or redistribution. When a train of potentials occurs, synaptic plasticity can cause a temporal redistribution of excitatory postsynaptic potential amplitudes in the cortex but an increase in gain in the hippocampus. (*D*) The degree of input specificity. Presynaptic activation of a restricted number of afferents during postsynaptic depolarization can cause a spread of LTP to neighboring synapses. (*E*) The possibly digital and noncumulative nature of potentiation at individual synapses (0, nonpotentiated; 1, potentiated). (*F*) The concept of silent synapses. One model supposes that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are inserted into the postsynaptic membrane during LTP. (*G*) The variable persistence of LTP following identical induction conditions. LTP seen on a pathway tetanized at a strength that ordinarily induces early LTP can nonetheless result in late LTP against a background of strong tetanization of other afferents. NMDA, *N*-methyl-D-aspartate.

model. The two functions are only equivalent if presynaptic activity is the main determinant of postsynaptic firing, a situation that may not hold true in vivo (TVP Bliss, personal communication).

Autophosphorylation of calcium/calmodulin-dependent protein kinase (CaMKII) has been implicated in metaplasticity (Bear 1995; Mayford et al 1995, 1996; Tompa & Friedrich 1998). Some forms are NMDA receptor dependent (Christie & Abraham 1992), whereas other forms depend on the activation of metabotropic glutamate receptors (mGluRs) both in vitro (Bortolotto et al 1994, Cohen & Abraham 1996) and in vivo (Manahan-Vaughan 1998). Neuromodulators, including stress hormones, are found to induce metaplastic changes. Stressed animals exhibit impaired LTP and facilitated LTD, an effect that is dependent on glucocorticoid receptor activation (Xu et al 1997, 1998b; see Kim & Yoon 1998). Metaplasticity also occurs outside the hippocampus, for example in the amygdala (Li et al 1998).

The phenomenon of metaplasticity brings with it some potential pitfalls for the SPM hypothesis. The biochemical correlates of metaplasticity might easily be mistaken for correlates of LTP or LTD (Abraham & Tate 1997). The existence of the frequency/plasticity function also illustrates the importance of assessing LTP over a range of tetanus frequencies if valid conclusions about an animal's capacity for synaptic plasticity are to be drawn (see later discussion of Migaud et al 1998).

Naturalistic Patterns of Induction The traditional methods of inducing LTP and LTD, involving long bursts of presynaptic stimuli at high frequencies, or prolonged periods of continuous low-frequency stimulation, respectively, almost certainly do not emulate natural patterns of neuronal activity. Previous variations of the SPM hypothesis have often been strongly criticized for this reason. However, LTP, LTD, and depotentiation can, at least in the hippocampus, be induced using stimulation that mimics firing patterns associated with the hippocampal theta rhythm that occurs as animals move around and explore the world.

LTP lasting for several weeks in vivo occurs following the delivery of short bursts of 100-Hz stimulation at intervals of 200 ms (Larson et al 1986, Rose & Dunwiddie 1986, Stäubli & Lynch 1987). It has also been reported that LTP is preferentially induced by burst stimulation on the positive phase of the theta rhythm in urethane-anaesthetized rats (Pavlides et al 1988). Similar findings have been reported in CA1 slices bathed in carbachol to elicit a theta rhythm: Delivery of trains of single pulses each locked to a positive theta peak was sufficient to induce LTP, whereas stimulation on the negative phase had no effect or, occasionally, induced LTD (Huerta & Lisman 1993). Depotentiation of existing LTP was convincingly shown following the delivery of either a single burst or a train of single pulses phase-locked to the negative phase of theta (Huerta & Lisman 1995, 1996). Similar results are found in CA1 in vivo (Hölscher et al 1997). Additional studies have revealed that LTD can be induced by very brief episodes of 1-Hz stimulation paired with mild postsynaptic depolarization (Wang et al

1997). Thus, bidirectional modifications of synaptic strength can be induced by brief periods of physiologically realistic stimulation.

A number of recent papers using intracellular recording techniques have highlighted the requirement of back-propagating dendritic action potentials for the induction of synaptic plasticity (Magee & Johnston 1997, Markram et al 1997). Interest has focused on the role that timing of postsynaptic action potentials plays in the induction of synaptic plasticity in the cortex (Markram et al 1997). Synaptic efficacy between bidirectionally connected neurons in slices of neocortex was potentiated when the EPSP preceded the back-propagating spike (by 10 ms), but depressed when the spike preceded the EPSP. In the CA1 region of hippocampus, it has been found that bursts of postsynaptic action potentials are necessary for the induction of synaptic potentiation in vitro (Thomas et al 1998, Pike et al 1999) (Figure 2*B*). The implication of this finding is that the use of presynaptic bursts in extracellular recording studies is a convenience, but mechanistically misleading.

Synaptic Gain or Temporal Redistribution If tetanization paradigms can be criticized for being unphysiological, we should recognize that the parameters of test stimulation may also not reflect natural activity patterns. Generally, presynaptic fibers are stimulated with single low-frequency pulses, whereas many hippocampal and cortical neurons often fire in high-frequency bursts. Postsynaptic responses to a train of action potentials, mimicking such bursts, typically show frequency-dependent short-term depression in the neocortex. Following LTP induction, the first EPSP is potentiated but the degree of depression within the train is also enhanced such that the overall throughput is unchanged (Markram & Tsodyks 1996). It has been argued that this redistribution of synaptic efficacy changes the content rather than the gain of the signal (Figure 2*C*). At CA3-CA1 synapses, by contrast, LTP induction results in a similar potentiation of EPSPs throughout a train, irrespective of the level of short-term depression, and thus overall gain is increased (Selig et al 1999). The difference between cortical and hippocampal synapses may reflect differences in LTP expression mechanisms.

Input-Specificity Another "new" property of LTP, and one that challenges one of its classical properties, is the observation that the input specificity of LTP need not imply a true synapse specificity (Engert & Bonhoeffer 1997). Organotypic cultures were bathed in low-calcium solution containing cadmium to prevent synaptic transmission throughout the hippocampal slice; focal application of a high-calcium solution was then used to permit activity at localized synapses. Induction of LTP occurred at active synapses but also, strikingly, at nearby (<70 μm) inactive synapses to that same cell (Figure 2*D*). Why LTP should obey a local-volume rule and be distributed to nearby inactive terminals is unclear, although it may be important in the formation of cortical columns (Montague & Sejnowski 1994, Stetter et al 1998).

Digital Nature of Synaptic Change and Silent Synapses Petersen et al (1998) have found that LTP can sometimes be expressed in an all-or-none manner at individual synapses. When LTP was induced by occasional pairings of presynaptic activity and postsynaptic depolarization, the population response showed the expected gradual increase in synaptic efficacy over time. However, using minimal stimulation, individual synapses showed a "digital" change that occurred once only, at different thresholds, during the sequence of pairings (Figure 2*E*). This finding was interpreted in relation to neural network models as advantageous, for two reasons. It is a better way of coping with the noise problem inherent in maintaining a memory over time despite the turnover of synaptic proteins. And the existence of a sharp threshold at which individual synapses flip from the not-potentiated to the potentiated state helps to separate the circumstances in which information is or is not stored. The observations of Petersen et al (1998) may be related to the suggestion that LTP is expressed via the transformation of synapses from a "silent" to a "communicative" state by the insertion of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Kullmann 1994, Isaac et al 1995, Liao et al 1995) (Figure 2*F*), an idea that echoes earlier theoretical proposals about the expression of LTP (Lynch & Baudry 1984). Detailed quantal analysis of mini amplitudes in other studies does, however, suggest there are circumstances in which quantal size at individual fibers is more complex than a binary function.

Variable Persistence and Synaptic Tagging The temporal persistence of LTP has been linked to the intensity of NMDA receptor activation (Malenka 1991) and to the necessity for protein synthesis (Krug et al 1984, Goelet et al 1986). One idea is that there is a temporal window shortly after LTP induction during which protein synthesis-independent LTP (sometimes called early LTP) can be consolidated by plasticity-associated proteins (Nguyen et al 1994). This idea raises the puzzle of how these proteins are selectively targeted to synapses activated during tetanization. A possible resolution of this issue was suggested by Frey & Morris (1997), who introduced the concept of synaptic tagging. They reasoned that plasticity proteins, probably synthesized in the cell body in response to dendritic activation from various inputs (and not necessarily the glutamatergic activation associated with the tetanus), would be distributed in a relatively non-targeted manner. Instead of individual proteins being trafficked to recently potentiated synapses, it would be simpler if, at the time of LTP induction, such synapses also set a "tag" whose function is to sequester diffusely targeted proteins. Once sequestered, these proteins could then contribute to consolidating the synaptic potentiation in an input-specific manner. To test this idea in adult brain slices, one pathway was potentiated strongly to induce protein synthesis–dependent LTP (sometimes called late LTP). A second input was tetanized 60 min later, but not until protein synthesis had been shut down by bath application of anisomycin. The paradoxical (but predicted) result was that late LTP was seen both on the pathway tetanized prior to inhibition of protein synthesis and on the one tetanized

during the inhibition of protein synthesis. Similar findings prevailed if the second input was stimulated too weakly to induce late LTP on its own and when it was stimulated weakly up to 2 h prior to the induction of late LTP on the other pathway (Frey & Morris 1998a).

An implication of the findings of Frey & Morris is that the persistence of LTP over time depends on the prior and future history of activation of the entire neuron, and not just the conditions prevailing at the time of LTP induction (Frey & Morris 1998b) (Figure 2*G*). That is, LTP can display variable persistence to a common induction protocol. A speculative implication for the SPM hypothesis is as follows. As an animal attends to novel events, it is likely that LTP will be induced at a subset of hippocampal synapses and decay relatively rapidly over time. It will only be stabilized, or consolidated, at those synapses that are potentiated shortly before or shortly after occurrence of those patterns of neuronal activation to that cell that have triggered the synthesis of plasticity-related proteins. This might be most likely when an emotionally significant event has occurred (amygdala input?) or when an animal is, for whatever reason, highly motivated to learn (inputs from frontal cortex?). The discovery by Seidenbecher et al (1995) that LTP in freely moving thirsty rats can be reinforced by water reward shortly after its induction is a phenomenon that might, therefore, be understood within a synaptic tagging framework, as could several classical experiments on posttrial drug administration and electrical stimulation (McGaugh 1966).

Behavioral studies of variable persistence and synaptic tagging are clearly on the agenda, such as whether long-lasting behavioral memory can be induced during the inhibition of protein synthesis under certain circumstances. Unlike in vitro slice experiments, the complication will be to establish the synergistic use of a common pool of neurons in two successive behavioral tasks while minimizing task interference. That exploratory behavior can induce c-*fos* activation (Zhu et al 1995, Gall et al 1998) and fear conditioning can activate CREB (Impey et al 1998) across, in each case, a relatively large number of neurons suggests that the input specificity of interactions between plasticity proteins and synaptic tags is determined primarily by synaptic rather than somatic events. CREB activation may reflect the potential to induce a lasting change, rather than the commitment to do so, a view consistent with its regulation by extrinsic neuromodulatory inputs traveling in the fornix (Taubenfeld et al 1999).

SYNAPTIC PLASTICITY, NEURAL CIRCUITRY, AND THE REPRESENTATION OF INFORMATION STORED BY DIFFERENT MEMORY SYSTEMS

Recognition that synaptic plasticity occurs in different memory-related brain regions points to the possibility that even a single type, such as NMDA-dependent LTP, will likely encode and store different types of information as a function of

the network in which it is embedded. In simple networks, the direction of change of synaptic plasticity often reflects the direction of change of overt behavioral output. For example, conditioning procedures result in the strengthening or weakening of responses, and synaptic facilitation and depression, respectively, are widely held to be the basis of such changes (Hawkins & Kandel 1984). However, in more complex networks, such isomorphism may not prevail. It is a big leap from the synapse to the behaving animal—and the chasm in between is the neural network. What synaptic plasticity achieves is not just a consequence of the direction of change and properties of synaptic plasticity itself but an emergent property of the expression of that plasticity within a network (Morris 1990). O'Reilly (1998) has recently summarized six general principles governing the operation of biologically based computational models of cognition—biological realism, distributed representations, inhibitory competition, bidirectional connectivity, error-driven task learning, and Hebbian learning (Figure 3*A*). The importance of all these principles in relation to the possible cognitive functions of LTP and LTD, not just the synaptic learning rule, needs to be recognized.

Consider a reflex network that can do no more than increase or decrease the throughput of neural signals (Figure 3*B*). Although such networks can, in practice, be quite complicated, involving excitatory, inhibitory, and facilitatory neurons in various arrangements (e.g. Frost et al 1988), their common property is that they encode information about experience in a nonpropositional manner. Nonpropositional learning results in changes in behavioral output that are adaptive, to be sure, but such learning does not represent the specific experiences that give rise to these changes in a manner that would later enable them to be explicitly recalled. Rather, changes in synaptic efficacy are thought to occur whose function is to increase the probability of behavioral output appropriate for dealing with similar circumstances in future. Certain types of nonassociative (habituation, sensitization) and associative (classical and operant conditioning) conditioning can be understood in terms of the up- or down-regulation of neural reflexes (Kandel 1978, Hawkins & Kandel 1984). In classical conditioning, for example, a neutral conditional stimulus (CS) is repeatedly paired with a biologically significant unconditional stimulus (US). The CS gradually comes to evoke a conditioned response and the mechanism mediating this change in response probability and magnitude could involve increases in either synaptic efficacy (such as presynaptic facilitation or LTP) or neuronal excitability (such as EPSP-spike potentiation). Even higher forms of conditioning, such as second-order conditioning, may be explicable in such terms (Hawkins et al 1998a).

However, modern psychological theories of associative conditioning actually take a more sophisticated view of the psychological processes involved. Specifically, conditioning is now recognized as a set of procedures that could, potentially, engage several different learning processes. These differ with respect to the manner in which information is represented, the learning rule, and other parameters. First, information may be represented in a distributed manner enabling multiple associations to be overlaid within a matrix of synaptic connec-

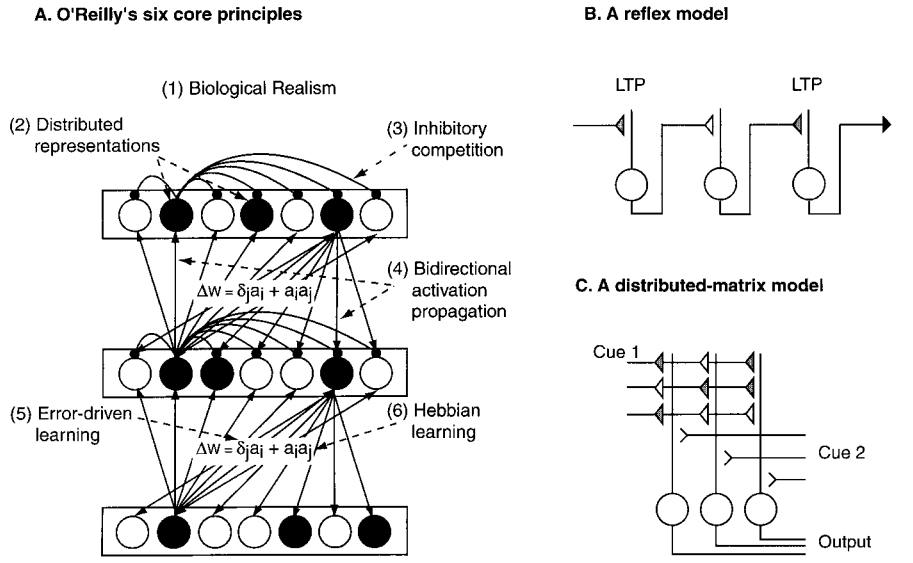

Figure 3 Different ways of thinking about how changes in synaptic strength might subserve information storage. (*A*) Layers of input, hidden, and output neurons connected by pathways displaying Hebbian and error-correcting learning rules can accomplish a wide variety of different learning tasks. The information processing capacity of such networks is an emergent property of network architecture and synaptic learning rules. Six key principles have come from their analysis. [After O'Reilly (1998).] (*B*) The simplest reflex model presupposes that stimulus and response are linked by a chain of neurons. Augmenting synaptic strength along that neural pathway enables firing threshold to be reached more easily, such that a stimulus more reliably evokes a postsynaptic response. (*C*) An example of a heteroassociative distributed matrix in which information is associated within networks during conjunctions between spatiotemporal patterns of neural activity. Input-specific alterations of synaptic strength enable numerous traces to be overlaid in a single matrix such that one stimulus (Cue 1) can evoke the memory of another with which it has previously been arbitrarily paired (Cue 2). LTP, Long-term potentiation.

tions. This form of representation is well suited to many features of brain processing in sensory/perceptual, motor, and learning-related circuits. Second, some of these learning processes are capable of representing the association between two arbitrary stimuli (or events) in a propositional rather than a nonpropositional manner. This enables encoded information to be used inferentially and the events that enter into the association to be recalled explicitly. Third, the associative process may be guided by a "teacher" requiring an error-correcting learning rule [such as the rule due to Rescorla & Wagner (1972)]. Even the simplest distributed matrix (Figure 3*C*) is robust because it enables content-addressable recall with partial cues (pattern completion) and sustained performance in the face of neuronal damage.

In contrast to reflex networks, even the simplest heteroassociative distributed matrix can learn that black is associated with white when these two stimuli are presented together—an arbitrary association that is different from learning to respond more or less strongly to "black" following conditioning. The representational aspects of fear conditioning thought to be mediated by the amygdala, although often described in reflex terms as increases in freezing or heart rate, are likely to be mediated by a distributed matrix of some form. Complexities that this network has to deal with include the multiple sources of CS and US information arriving at different times over different pathways.

Most neural networks in the brain are surely carrying out algorithms more complicated than the mere up- or down-regulation of stimulus-response efficacy. The hippocampus, for example, is widely thought to be involved in information processing functions related to spatial memory (O'Keefe & Nadel 1978), declarative/relational memory (Squire 1992, Cohen & Eichenbaum 1993), and episodic memory (Vargha-Khadem et al 1997). Debate about the relative merits of these differing theories continues. The neural architecture of the hippocampal formation is more complex than that envisaged even in complex neural networks, with O'Reilly's (1998) principle of biological realism a key issue that we will have to approach gradually. The role that synaptic plasticity could play within this network to help implement these psychological processes has rarely been specified explicitly, but one can envisage it helping, respectively, to store information about spatial variables, about individual facts or events and the relationships between them, or about events and the contexts in which they occur. In keeping with aspects of the episodic framework, Morris & Frey (1997) have suggested, on the basis of such new properties of LTP as variable persistence, that LTP could subserve the rapid, automatic encoding of attended events. This is a component of episodic memory.

The key implication of this discussion is that, with distributed representations and a variety of synaptic learning rules, there is unlikely to be any simple isomorphism between the pattern, extent, or direction of synaptic changes and the behavioral output observed as a result of conditioning (or other forms of learning). Accordingly, we must interpret experiments on higher forms of learning relevant to the detectability criterion above with caution and recognize the inherent difficulties in doing experiments addressing the mimicry criterion. Studies addressing the necessity criteria (anterograde and retrograde alterations) are more straightforward, but we look on experiments searching for global changes in extracellular field potentials following learning as, at best, unpromising.

Over the past 30 years, neural-network research has explored various computational features of Hebbian synaptic plasticity, beginning with Marr's (1971) classic model of the hippocampus. McNaughton & Morris (1987) outlined how several features of the intrinsic anatomical circuit of the hippocampal formation are analogous to the kinds of neural architectures required for heteroassociative and autoassociative network processing. Recent more formal models include those of Hasselmo et al (1995) and Paulsen & Moser (1998), in which cholinergic

and GABAergic neuromodulation are, respectively, incorporated into the picture; Levy (1996) and Wallenstein et al (1998), in which the importance of sequences with respect to episodic memory is emphasized; Rolls & Treves (1998), in which pattern separation (orthogonalization) and pattern completion are implemented by different components of the hippocampal network; and McClelland et al (1995), in which a mixture of fast and slow synaptic weight changes helps prevent catastrophic interference when interleaving new information during memory consolidation. Lisman (1999) has taken the analysis of biologically realistic types of network a step further with an intriguing model consisting of reciprocal interconnecting autoassociative (dentate gyrus) and heteroassociative (CA3) networks. In this, synaptic potentiation in area CA3 of the hippocampus encodes traces relevant to sequences of events occurring within episodes, maintaining sequence order despite the essentially passive nature of trace storage at synapses of the longitudinal-association pathway. During retrieval, CA3 neurons are, speculatively, held to project information retrieved in response to items earlier in a sequence back to the mossy cells the of dentate gyrus, where pattern completion corrects recall errors, the corrected recall pattern being then projected forward to CA3 to retrieve the next item in the sequence, and so on. Lisman's model also allows a role for context to bias the firing of CA3 cells (achieved by the direct perforant path input to CA3), with recoding of the hippocampal representation back into a form that the cortex can understand being accomplished by area CA1.

To summarize, our main point is that emergent properties of memory arise within certain networks that cannot be understood in relation to the properties of synaptic plasticity alone. An adequate circuit-level description of the information processing within a specific brain area will be essential to bridge the gap between synapse and behavior. Without this level of description, a satisfactory test of the mimicry criterion is impossible. A secondary point is that memories should not be confused with the traces that subserve them. Trace encoding can be thought of as the momentary collective activity of large numbers of neurons whose patterns of firing give rise to increases and decreases of synaptic strength that then outlast these very patterns. Memory retrieval is the process of passing neural activity through the network to create patterns of firing that constitute a memory. The SPM hypothesis asserts that activity-dependent synaptic plasticity is the fundamental mechanism responsible for creating and storing traces. In this sense, LTP enables memory, it does not equal it.

SYNAPTIC PLASTICITY AND HIPPOCAMPUS-DEPENDENT LEARNING

The cell types and neural network of the hippocampal formation have been reviewed by Amaral (1993) and Freund & Buzsáki (1996). LTP at perforant path-dentate gyrus granule cell synapses and Schaffer collateral-CA1 pyramidal cell

synapses is NMDA receptor dependent. LTP at synapses of the perforant path onto CA3, and interconnecting CA3 neurons via the longitudinal-commissural pathway, is also NMDA receptor dependent, whereas that at mossy fiber synapses onto CA3 neurons is NMDA receptor independent. In vivo, different tetanization frequencies are optimal on these different pathways (Yeckel & Berger 1998).

Correlation: Is the Expression of Properties of LTP in Individual Animals Correlated with Characteristics of Learning or Memory?

The first studies implicating LTP in memory were correlational. Barnes (1979) and Barnes & McNaughton (1985) observed, in the course of work on the impact of aging, that the persistence of LTP was statistically correlated with the rate of learning and/or the degree of retention of spatial memories over time. Similar correlations have been observed many times over the past 20 years. A recent example is the report that overexpression of mutant amyloid precursor protein (APP) in a murine model of Alzheimer's disease (Hsiao et al 1996) is associated with an age-related decline in performance in a delayed spatial alternation task (Chapman et al 1999). The decline in performance was correlated with a corresponding decline in LTP, assessed both in vivo and in vitro.

Such correlations are hardly to be expected on the null hypothesis, but they clearly represent only a first step in understanding. This is because the link reflects a statistical correlation rather than a mechanistic connection. Work on APP transgenics is a case in point because not enough is yet known about the normal function of beta amyloid for the link to mechanisms of induction or expression of LTP to be completely clear (Seabrook & Rosahl 1998). It is interesting to note that one study of APP knockout mice revealed an impairment in watermaze performance but no overall difference between groups with respect to LTP induction. A careful factor analysis of the behavior identified three main factors that contributed to the poor performance of the mutants—including alterations in swim speed, persistent swimming near the side walls (thigmotaxis), and variation in spatial memory. Once the contributions of the first two factors were removed, it was found that the magnitude of LTP in both mutants and controls correlated with the third factor—spatial memory (Lipp & Wolfer 1998). This work illustrates the importance of careful behavioral analysis.

Occlusion: Does Saturation of LTP or LTD Prevent the Retrieval of Old Information or the Encoding of New Memory Traces?

In thinking about occlusion studies, it is important to distinguish between the cumulative induction of LTP (or LTD) and the saturation of either process. Successive episodes of LTP may have a cumulative effect, at least at a population

level (cf Petersen et al 1998), but not saturate the plasticity available on the pathway being stimulated (Jeffery 1997). Cumulative LTP should enhance neural throughput and so, in a reflex system, improve learning; Berger (1984) obtained just such a result. In contrast, a true saturation of LTP prior to behavioral training should prevent new learning because no further LTP would be possible. Similar considerations would apply to saturation of LTD, which can be achieved with three successive trains of stimulus pairs (Thiels et al 1998), but preliminary experiments (V Doyère, personal communication) indicate inconsistent behavioral effects of such stimulation in a radial maze task.

The concept of saturation of LTP is poorly defined. It is most commonly viewed as a state in which every synapse on a pathway has been potentiated such that both the probability of transmitter release at every axonal terminal and the postsynaptic receptor efficacy are maximal. But is this the right way to think about saturation? In our view, such a state of affairs would be most unphysiological and might even put the network at risk of seizure activity. An alternative definition is that saturation is a neural state in which, at least for a period of time, no further LTP is possible. Whether 10%, 20%, or a very high proportion of the synapses have been subject to maximal LTP is irrelevant; the point is that saturation is defined as occurring when no further LTP can be induced, even though the Hebbian induction criterion is met (i.e. a form of metaplasticity).

Research on the behavioral effects of LTP saturation reached an impasse in 1993 when a series of papers (Cain et al 1993, Jeffery & Morris 1993, Korol et al 1993, Sutherland et al 1993) reported an inability to replicate earlier findings indicating that saturation induced a reversible occlusion of subsequent spatial learning (Castro et al 1989). Jeffery & Morris (1993) and Korol et al (1993) both conducted exact replications of part of the experiment by Castro et al (1989). In neither study was any learning deficit observed. Reid & Stewart (1997) did succeed in replicating the findings, including the decay of the effect over time, but they used electroconvulsive seizures, which cause, among other effects, indiscriminate induction of LTP rather than explicit saturation on a single pathway.

Bliss & Richter-Levin (1993) pointed to several reasons why, apart from the SPM hypothesis being wrong, negative results were obtained: (*a*) Cumulative LTP of perforant path terminals may not have reached a true state of saturation; (*b*) perforant path terminals may have been sufficiently saturated, but not those of other extrinsic or intrinsic hippocampal pathways that are also critical for learning (e.g. CA3-CA1 terminals); (*c*) appropriate saturation of the full septotemporal axis of the hippocampus may not have been achieved with stimulation at a single site within the angular bundle. Evidence for the latter possibility was presented by Barnes et al (1994), who found up-regulation of the immediate early gene *zif-268* restricted to the dorsal (septal) hippocampus after stimulation at one site within the angular bundle. They also note differences in the sensitivity of different learning tasks to LTP saturation.

The study by Moser et al (1998) was designed with these issues in mind. There were three key features: (*a*) the use of an array of cross-bundle stimulation elec-

trodes designed to maximally activate the perforant path, with the cathode switched frequently between active electrodes; (*b*) the use of a separate probe-stimulating electrode to test whether the asymptotic LTP induced by the electrode array was a true saturation of LTP on that pathway; (*c*) the use of animals given unilateral hippocampal lesions (Mumby et al 1993). Subsequent to multiple high-frequency trains or control low-frequency stimulation, the rats were trained in a standard watermaze task. Controls learned normally. The high-frequency group showed a bimodal distribution, with some animals learning where the platform was located and with others failing to learn. When all animals were subsequently tested for the induction of LTP from the probe site within the perforant path, those high-frequency animals in which it was impossible to induce further LTP (i.e. the saturated subgroup) were the ones that failed to learn the watermaze, whereas those in whom LTP could still be induced did learn a little about where the platform was located. Thus, a true saturation of LTP in the perforant path does impair spatial learning. These findings vindicate the earlier claims of McNaughton et al (1986) and Castro et al (1989). The further observation by McNaughton et al (1986) that immediate posttraining LTP saturation occludes the retrieval of recently learned spatial information has not, to our knowledge, been reexamined.

Despite these positive findings, there remains skepticism about the analytic potential of saturation experiments. One concern is that repeated tetanization may result in acute pathological phenomena, such as seizure-like after-discharges, that would cause learning deficits (McEachern & Shaw 1996). However, Moser et al (1998) found no after-discharges during tetanization. Learning was also only impaired in the animals with saturated LTP, despite all rats having received the same course of tetanic stimulation. A second point concerns homeostatic compensatory changes—such as alterations in inhibitory transmission, synapse formation, and reductions in postsynaptic sensitivity. These compensatory changes are considered in a recent review article by Moser & Moser (1999), primarily as factors contributing to the difficulty often experienced in saturating LTP. Even when LTP saturation is successful, it might still be argued that such changes, rather than saturation itself, are responsible for the learning impairment. A third disquiet is that LTP saturation does, of course, increase synaptic weights; a global increase in the efficacy of synaptic transmission might, on its own, disrupt normal hippocampal information processing. However, the number of studies reporting normal learning despite the induction of substantial LTP suggests that a cumulative increase in synaptic weights does not in itself disrupt the encoding of new information. In fact, Moser et al (1998) found no correlation between the magnitude of LTP induced by cross-bundle tetanization and subsequent learning.

The study by Moser et al (1998) is unlikely to be the last word. Saturation might also be realized by bilateral stimulation of the ventral hippocampal commissure, to potentiate the commissural/associational pathway in CA3 and CA1 (Bliss & Richter-Levin 1993). A pharmacological rather than an electrophysiological approach should also be considered, using drugs such as agonists of aden-

ylate cyclase, protein kinase A, or mitogen-activated protein kinase to induce a slow-onset but asymptotic synaptic potentiation.

Pharmacological and Genetic Intervention: Does Blockade or Enhancement of the Neural Mechanisms Responsible for LTP and LTD Have Commensurate Effects on Learning and Memory?

Many behavioral studies have been conducted with NMDA antagonists that block both LTP and LTD. Other drugs acting downstream of the NMDA receptor have also been used to isolate the possible contribution of the various biochemical cascades that underlie plasticity. This work has been complemented by studies using genetically manipulated animals, in which glutamate receptors or associated signal transduction pathways have been targeted. Drugs and genetic manipulations that enhance plasticity have also been examined. These strategies are relevant to the anterograde alteration criterion.

Pharmacological Blockade of NMDA Receptors Impairs Some Types of Hippocampus-Dependent Learning Following the original observations of Morris et al (1986), who showed that the NMDA antagonist AP5 blocked spatial but not visual discrimination learning, numerous studies have found that competitive NMDA antagonists impair hippocampus-dependent learning. Learning paradigms used include spatial learning, T-maze alternation, certain types of olfactory learning, contextual fear conditioning, delayed reinforcement of low rates of response, and other operant tasks (Danysz et al 1988, Tonkiss et al 1988, Stäubli et al 1989, Shapiro & Caramanos 1990, Tonkiss & Rawlins 1991, Bolhuis & Reid 1992, Cole et al 1993, Lyford et al 1993, Caramanos & Shapiro 1994, Fanselow et al 1994, Li et al 1997; for review, see Danysz et al 1995). The impairment is dose related and occurs over a range of intrahippocampal drug concentrations comparable to those that impair hippocampal LTP in vivo and in vitro (e.g. Davis et al 1992). These data strongly support the SPM hypothesis, but there are problems associated with drug diffusion, sensorimotor side effects, and the fact that NMDA antagonists could affect neuronal processes other than LTP. Further issues include the role of NMDA receptors in encoding versus retrieval, the duration of memory traces under NMDA receptor blockade, and the use of other drugs to block or enhance LTP.

Drug Diffusion The intracerebroventricular method of infusing AP5 used by a number of laboratories results in drug diffusion to many regions of the forebrain (Butcher et al 1991). This route of drug administration, and that of intraperitoneal injections, is therefore likely to block sensorimotor, cognitive, and NMDA receptor-dependent learning processes in all these structures. Greater regional selectivity can be achieved by local acute infusions. For example, Morris et al (1989) found that, at a dose that blocks LTP, acute infusions of nanomolar quantities of

AP5 into the dorsal hippocampus are sufficient to impair spatial learning in the watermaze.

Sensorimotor Side Effects A number of sensorimotor disturbances are sometimes, although not always, observed during watermaze training with diffuse NMDA receptor blockade. These include falling off the platform during a "wet-dog" shake, thigmotaxis, and failure to climb onto the platform (Cain et al 1996, Saucier et al 1996; RGM Morris, RJ Steele, SJ Martin & JE Bell, submitted for publication). Disturbances are also seen in other tasks. Such abnormalities could be due to diffusion of drug from the ventricle to the thalamus disrupting the normal transmission of somatosensory and visual information (Sillito 1985, Salt 1986, Salt & Eaton 1989), or to the striatum causing motor disturbances such as flaccidity (Turski et al 1990). Clearly learning cannot proceed when animals cannot see, feel, or move properly. Many laboratories have noted that animals treated with noncompetitive NMDA-antagonists (such as MK-801) show sensory inattention and motor stereotypies (Koek et al 1988, Tricklebank et al 1989, Keith & Rudy 1990, Tiedtke et al 1990, Mondadori & Weiskrantz 1991, Danysz et al 1995, Cain et al 1996). At high doses, AP5-treated animals also display stereotypies, but these doses are substantially higher than those necessary to block LTP in vivo following regionally restricted infusion.

Cain et al (1996) showed that the impairment of spatial learning in a watermaze is correlated with the degree of sensorimotor impairment. It is therefore tempting to look on the sensorimotor deficit as primary and the learning deficit as secondary. Recently, however, the massed trial training protocol of Cain et al (1996) was used (RGM Morris, RJ Steele, SJ Martin & JE Bell, submitted for publication) and it was found that AP5-induced sensorimotor disturbances were modest on the first trial but gradually built up across trials. The correlation that Cain et al observed between sensorimotor disturbances and learning could, therefore, have arisen because the AP5-induced failure to learn resulted in fatigue, which then exacerbated the situation. That is, the direction of causality could, at least in part, be the opposite of what Cain et al (1996) surmise.

Saucier & Cain (1995) also observed that the impairment in watermaze learning that normally occurs following intraperitoneal (i.p.) administration of a competitive NMDA antagonist disappears if the animals are given sufficient pretraining to prevent the drug-induced sensorimotor disturbances seen in experimentally naive animals. Their pretrained animals showed a clear block of LTP, no sensorimotor impairment, and normal rates of spatial learning. Other data indicate, however, that a deficit in spatial learning can still be observed, relative to appropriate control groups, following nonspatial pretraining (Morris 1989, Bannerman et al 1995). Bannerman et al (1995) discovered that the usual AP5-induced learning deficit all but disappeared in animals trained first as normal animals in one watermaze (downstairs) before later being trained in a second watermaze (upstairs) under the influence of the drug. However, if training in the downstairs watermaze was nonspatial in character, with sight of extramaze cues

occluded, an AP5-induced deficit in spatial learning was again seen in the second task. Bannerman et al (1995) suggested that blocking NMDA receptors dissociated different components of spatial learning: It may impair an animal's ability to learn the required strategy rather than the map of landmarks in the room in which the watermaze is situated. This explanation is apparently refuted by the report by Hoh et al (1999) that watermaze strategy learning is unaffected by i.p. administration of the NMDA antagonist CGS19755 at a dose that successfully blocks LTP in freely moving animals in both CA1 and the dentate gyrus. Drug-treated rats learned nonspatial strategies adequately and showed equivalent performance in subsequent spatial learning and spatial reversal to controls. Hoh et al (1999) suggest that relative task difficulty may explain the different outcome of their study compared with Bannerman et al (1995) and Steele & Morris (1999). However, the use of i.p. drug administration is problematic, as many of the 10 trials per session with a 5-min intertrial interval would have been completed before adequate penetration of CGS19755 into the brain. Resolving these discrepancies will not be easy. The procedural simplicity of the watermaze task belies an underlying complexity that is inadequately captured by the notion of task difficulty; rats learn several qualitatively different things in the task and dissociable components of spatial learning can be revealed with different protocols.

The Persistence of Memory Traces Under NMDA Receptor Blockade Using single-unit recording to study the effects of the NMDA antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) on hippocampal place fields, Kentros et al (1998) have shown that following drug infusion (*a*) previously established firing fields remain unchanged and (*b*) place fields are apparently acquired normally when rats are placed into a new environment, but (*c*) these fields are unstable over time. Temporal instability of place fields was also observed in transgenic mice with altered LTP (Rotenberg et al 1996). This temporal instability could account for the finding by Bannerman et al (1995) of poor learning by naive animals trained with one trial per day, but not the observation that spatially pretrained AP5-treated animals learned normally in a new environment. It has been suggested (C Kentros, personal communication) that there may be cryptic generalization between the two watermazes in the study by Bannerman et al, with the animals able to use a "cognitive map" acquired in the first task when trained in the second. Alteration in the spatial geometry of the two learning tasks would be one way to investigate this suggestion.

However, poor memory over time in the presence of NMDA receptor blockade is unlikely to be specific to novel environments. Steele & Morris (1999) trained rats in a delayed matching-to-place task in the watermaze; in this variant of the task, the platform is hidden in a different location each day and stays there for four trials. Normal rats show long escape latencies on the first trial (when they do not know where the platform is hidden) but much shorter latencies on subsequent trials (when they do). Most of the "savings" in escape latency occur

between the first two trials, indicative of one-trial learning. Infusion of AP5 had no effect on performance at a short memory delay (15-s intertrial interval) but caused a pronounced impairment at 20 min and 2 h. This delay-dependent deficit occurred irrespective of whether the animals stayed in the training context throughout the memory delay or were returned to the room where they lived, and irrespective of whether the drug was infused chronically intracerebroventricular or acutely into the hippocampus. If the AP5-induced impairment of matching-to-place performance were sensorimotor or attentional in nature, a deficit would be expected at all delays. The delay-dependent memory impairment is also inconsistent with the proposal by Kentros et al (1998) that temporal instability occurs only in a novel context.

Encoding and Retrieval In the hippocampus, NMDA receptor antagonists leave AMPA receptor-mediated fast synaptic transmission relatively unaffected. Accordingly, although such drugs should freeze the spatial distribution of synaptic weights throughout the intrinsic circuitry of the hippocampal formation, neurons in the network should still be able to fire and transmit information. NMDA antagonists may therefore impair the encoding of memory traces but have no effect on retrieval.

Consistent with this idea, Stäubli et al (1989) found that administering AP5 to animals after they had been trained in odor discrimination learning had no effect on retention, although the drug did impair new learning. Entorhinal cortex lesions, on the other hand, cause rapid forgetting of olfactory information (Stäubli et al 1984). Likewise, Morris (1989) and Morris et al (1990) found that AP5 had no effect on the retention of a previously trained watermaze task, whereas lesions of the hippocampal formation were disruptive when given shortly after the end of training. Similar deficits in encoding but not retrieval were noted in the delayed matching-to-place task of Steele & Morris (1999).

Effects of NMDA Antagonists on Neuronal Processes Other than LTP Even if it were accepted that blocking hippocampal NMDA receptors selectively disrupts memory encoding and storage, this could still be unrelated to LTP. Leung & Desborough (1988) showed that acute intracerebroventricular infusions of AP5 disrupt the hippocampal theta rhythm. Effects on the firing of complex spike cells (Abraham & Kairiss 1988) and a decrease in population spike amplitude have been reported (Errington et al 1987, Abraham & Mason 1988). NMDA currents contribute to normal synaptic transmission at somatosensory and visual relays in the thalamus (Salt 1986, Salt & Eaton 1989, Sillito et al 1990); and in lamprey spinal cord, they contribute to the rhythmical neuronal repolarization that underlies swimming by turning on a Ca^{2+}-dependent K^+ current (Grillner et al 1998). NMDA currents may contribute to more than just plasticity in the hippocampus also.

One way to finesse the problem that these observations present might be to conduct behavioral studies with drugs that interact with other sites on the NMDA

receptor (such the glycine or polyamine site), with metabotropic glutamate receptors, or with inhibitors that act downstream of the NMDA receptor on second-messenger cascades. Such compounds might leave certain NMDA-mediated processes intact while still blocking LTP. A complementary approach is to use gene-targeting.

Before considering these, note should be made of several studies indicating that low doses of NMDA receptor antagonists can, paradoxically, enhance the learning of certain tasks, such as step-down inhibitory avoidance (Mondadori et al 1989) and social learning (Lederer et al 1993). These findings embarrass but do not really challenge the SPM hypothesis because the effects are observed at doses too low to block LTP in vivo, and different mechanisms are likely to be involved in the antagonist-induced facilitation of learning. For instance, the facilitation of inhibitory avoidance by low doses of NMDA antagonists is sensitive to pretreatment by such steroids as aldosterone or corticosterone, whereas the impairment of inhibitory avoidance caused by high doses is steroid insensitive (Mondadori & Weiskrantz 1993, Mondadori et al 1996). Work with the noncompetitive antagonist memantine has led to counterintuitive findings by virtue of its rapid on- and off-channel blocking kinetics. At therapeutic doses, memantine impairs neither learning nor LTP, but it does limit neurotoxicity and so prevents impairments in cognitive function (Parsons et al 1999).

Drugs Acting at Sites Other than the NMDA Receptor Affect LTP and Learning Experiments using the mGluR antagonist, α-methyl-4-carboxyphenylglycine (MCPG), are interesting because some data suggest that it blocks LTP while leaving STP unaffected both in vitro (Bashir et al 1993) and in freely moving rats (Riedel et al 1995). It should, therefore, cause a sensitivity to memory delay different from that induced by AP5 in the study of Steele & Morris (1999). Unfortunately, its reliability in blocking LTP has been called into question, blocking it under some circumstances (Bashir et al 1993, Richter-Levin et al 1994, Riedel et al 1995, Breakwell et al 1996) but not others, either in hippocampal slices or in vivo (Chinestra et al 1993, Manzoni et al 1994, Bordi & Ugolini 1995, Martin & Morris 1997, Anwyl 1999). The mGluR subtype involved in LTP also remains unknown (see Breakwell et al 1998, Fitzjohn et al 1998). Nonetheless, MCPG and the group I selective drug AIDA have been reported to impair spatial learning and contextual fear conditioning in rats (Richter-Levin et al 1994, Riedel et al 1994, Bordi et al 1996, Nielsen et al 1997), but effects on tasks with varying memory delay are yet to be reported.

There have been several reports that interfering with the synthesis of the putative intercellular messenger nitric oxide (NO) can cause impairments of spatial learning and olfactory recognition (Chapman et al 1992, Böhme et al 1993, Hölscher et al 1996, Kendrick et al 1997). However, these findings are controversial because the precise role of NO in LTP is unresolved (Hawkins et al 1998b). Nor is it clear whether the alterations in behavioral performance that occur with broad-spectrum NOS inhibitors can ever be fully independent of the cerebrovas-

cular consequences of inhibiting endothelial NOS (e.g. high blood pressure) (see Bannerman et al 1994). Studies using an inhibitor of neuronal rather than endothelial nitric oxide, such as the compound 7-nitro indazole, could illuminate this issue. Hölscher et al (1996) reports that 7-nitro indazole does impair learning in a radial maze at a dose that has been shown to block LTP in area CA1 in vivo, but the effect he obtained is not a robust one.

In summary, there is now an overwhelming body of data indicating that blockade of hippocampal NMDA receptors during learning disrupts the acquisition but not the retention of hippocampus-dependent memory tasks. Such results support the SPM hypothesis. They also take us further in suggesting that NMDA receptor-dependent plasticity is necessary for memory encoding but not for memory retrieval. However, support for the hypothesis must be qualified: Sensorimotor effects of NMDA antagonists are frequently observed, and even where they are minimal, there is the unsolved problem that blocking hippocampal NMDA receptors may have physiological effects beyond the inhibition of LTP and LTD.

Do Drugs that Enhance Hippocampal LTP Improve Memory? We suggested earlier that the SPM hypothesis is not required to predict that drugs that enhance LTP must also enhance learning. Ironically, that such drugs can be developed would not only be icing on the cake for the SPM hypothesis but, potentially, of clinical significance. Perhaps the best known are the ampakines, which decrease the rate of AMPA receptor desensitization and slow the deactivation of receptor currents after agonist application (Arai et al 1994, 1996). Ampakines facilitate the induction of hippocampal LTP (Stäubli et al 1994), and there is now a considerable body of evidence that they can enhance the encoding of memory in a variety of tasks (see Lynch 1998). A number of other compounds have also been reported to enhance both learning and hippocampal LTP, including benzodiazepine inverse antagonists (Fontana et al 1997, Letty et al 1997, Marchetti-Gauthier et al 1997, Seabrook et al 1997).

Gene-Targeting Offers an Alternative Way of Investigating the Relationship Between Synaptic Plasticity and Memory An alternative interventionist approach includes targeted deletion of specific genes (knockouts), site-directed mutagenesis (mutation of specific amino acids), and transgenesis (gene overexpression). Knocking out genes was the first of these techniques to be used systematically to look at synaptic plasticity and learning. Silva et al (1992a,b) and Grant et al (1992) made mutant mice deficient in the alpha subunit of CaMKII and of *fyn* tyrosine kinase, respectively. These early studies revealed intriguing correlations between LTP and hippocampus-dependent learning. They set the pattern for a host of subsequent studies in which homologous recombination was used to delete genes in all cells of the body for the lifetime of the animal (Capecchi 1989). The approach is typically characterized by evidence that the deletion has been successful, followed by electrophysiological and behavioral analyses of the phenotype of the mutant progeny.

At the outset, such animals were presented as offering "definitive" confirmation of the obligatory role of certain genes in LTP, LTD, and/or learning—a claim based on the fact that the receptor or kinase in question is completely absent and not merely reduced in effectiveness. The array of generally positive findings obtained from about 60 relevant knockout animals developed since 1992 lends general support to the SPM hypothesis. Numerous problems were, however, soon identified. For certain critically important proteins, there can be a catastrophic outcome, such as embryonic or perinatal lethality. Other mutants display the opposite problem, a null phenotype, but it is hard to believe that key brain enzymes have no function. Either inappropriate tests have been used or there has been biochemical compensation by other closely related genes (see Grant et al 1995). Additionally, that some slices of the αCaMKII mutants from Silva et al (1992b) showed normal LTP whereas the majority showed none is also puzzling, unless parallel biochemical pathways can be activated in a probabilistic fashion. Hinds et al (1998) report a yet higher proportion of αCaMKII mutants showing normal LTP and suggest that the ß enzyme may have been up-regulated. The study by Hinds et al (1998) involved animals crossbred with mice of C57/BL6 strain. The issue of genetic background is very important: The embryonic stem cells most widely used to make mutants are derived from a specific strain of mice—the Sv129 strain—and when these mice are crossbred with such strains as C57/BL6, a number of flanking genes derived from the 129 strain will still be expressed alongside the mutated gene for several generations. Aspects of the resulting phenotype may reflect these flanking genes (Gerlai 1996). Residual L129 genes have unpredictable effects and are undesirable because the L129 strain is notoriously poor at learning (Lipp & Wolfer 1998). Recommendations about the desirability of back-crosses into more suitable strains (such as C57/BL6) have now been discussed in the gene-targeting community and guidelines have been published (Anonymous 1997).

Nonetheless, gene targeting is such a powerful approach and the technology is developing so quickly, it is rightly having an impact on the field. Second-generation mutants are now being made in which cAMP response element recombinase is expressed downstream of specific promoters in one line of mice that, on being crossbred, target genes flanked with *loxP* sites in another. The resulting progeny enable the development of mutant strains in which a target gene is deleted (or mutated) in only one area of the brain. This approach was used to knock out the R1 subunit of the NMDA receptor in area CA1 of the hippocampus only (Tsien et al 1996a, Mayford et al 1997)—an illustrative example, as the standard knockout of this important receptor subunit resulted in a mutant that died shortly after birth (Chen & Tonegawa 1997). Region- and cell-type–specific interventions are very powerful, as they carry the potential to investigate gene function in specific cells, to manipulate pre- or postsynaptic sites of synapses independently, and to intervene in biochemical pathways for which there is no known pharmacological ligand. The CaMKII promoter is very suitable for these experiments because it is not activated until around day 20 (obviating certain developmental

problems). However, numerous lines have had to be developed of which only some show useful expression patterns. We anticipate that promoters for specific regions of the hippocampus and amygdala, selected areas of the neocortex, and other brain regions will prove of great interest (see Steel et al 1998).

Achieving regional specificity does not, on its own, enable the same temporal precision as can be achieved with pharmacological interventions. Above, experiments were described in which animals were normal in one phase of an experiment but treated in another. This enabled dissociations between encoding and retrieval processes of memory to be addressed. The way forward, using genetic intervention, is via third-generation mutants in which inducible promoters are engineered to put gene activation or inactivation under experimental control [such as tetracycline transactivator systems rtTA and tTA (see Furth et al 1994, Kistner et al 1996)]. This should also finesse the complications of altered neuronal development that can occur with standard knockouts (Lathe & Morris 1994, Mayford et al 1997), which can, to date, only be addressed using "rescue" experiments.

Because it is impossible to target a drug to area CA1 (along its full axis) without also invading the dentate gyrus, a good example of the use of these techniques concerns the role of LTP in subregions of the hippocampal formation. Although no clear answer is yet apparent, some ingenious studies show the way forward. Tsien et al (1996a,b) made mutants in which NMDAR1 was restricted to area CA1 of the hippocampus. They showed no LTP in area CA1, normal LTP in the dentate gyrus and neocortex, and a modest learning impairment in the watermaze. Using multiple single-unit recording, McHugh et al (1996) discovered that these mice had abnormal place fields and a reduction in the correlated firing of cells with overlapping place fields. In contrast, recent work by Zamanillo et al (1999) targeting AMPA receptors has found that a comparable inhibition of LTP in area CA1, but not the dentate gyrus, is unaccompanied by any change in rate of learning in the watermaze. It is not clear what to make of this contradiction, though note should be made of the extensive pretraining (13 days) given to the mice in the latter study; we saw in the earlier work of Bannerman et al (1995) and Saucier & Cain (1995) using normal rats that pretraining would, at best, limit the sensitivity of the standard watermaze assay. A separate consideration concerns the value of looking at LTP in vivo. Using standard knockout techniques, Nosten-Bertrand et al (1996) found that *thy-1* mutants had normal LTP in area CA1 but no LTP in the dentate gyrus when measured in anaesthetized animals in vivo. Further studies revealed, however, that normal LTP could be obtained in dentate slices when bicuculline was added to reduce inhibition, implying that the machinery for inducing LTP must still be present in *thy-1* mutants. When bicuculline was infused locally in vivo in small quantities (to avoid seizure activity), the now disinhibited area of the dentate showed normal LTP. Errington et al (1997) also found that LTP in freely moving *thy-1* mutants was compromised but not totally abolished. In fairness to Zamanillo et al (1999), they did investigate the effects of bicuculline and found no effect. Still, the important general message of the

thy-1 study is that electrophysiological results in brain slices are not infallible predictors of what might happen to synaptic plasticity in the whole animal.

Using inducible techniques, Mayford et al (1996) described a transgenic mouse in which the overexpression of a constitutive CaMKII was under the control of tetracycline. This study built upon previous work using standard transgenic mice that overexpress the autophosphorylated form of CaMKII through a point mutation of Thr^{286} (Mayford et al 1995). These animals had exhibited normal CA1 LTP in response to high-frequency stimulation at 100 Hz, but stimulation in the 5- to 10-Hz range (encompassing theta) preferentially resulted in LTD rather than LTP—a shift of θ_M in the BCM function of Figure 2*A*. Hippocampus-dependent learning was impaired: The mice showed impaired spatial learning using a Barnes maze, but normal contextual fear conditioning (Bach et al 1995), a finding clarified by later lesion work establishing that contextual fear conditioning is not always hippocampus dependent in mice (Frankland et al 1998). Mayford et al (1996) replicated the learning impairments and deficits in LTP found by Bach et al (1995) and Mayford et al (1995), with suppression of the transgene by administration of doxycycline relieving the impairment of both learning and synaptic plasticity.

Work by Giese et al (1998) complements these studies. Instead of using transgenic techniques, they introduced a point mutation into the gene encoding CaMKII to block autophosphorylation at Thr^{286}, thereby preventing the transition of this kinase into a CaM-independent state without disrupting its CaM-dependent activity. CA1 LTP could not be elicited in the mutant mice across a range of stimulation frequencies, a slightly different profile from that shown by Mayford's transgenic mouse. The mice of Giese et al also had profound deficits in spatial learning in the watermaze and showed an altered dependence on extramaze versus intramaze cues in single-unit recording studies of place cells (Cho et al 1998). However, Giese and his colleagues have not yet used inducible techniques to control this site-directed mutation.

The first studies to use both the tTA and rtTA techniques are those of Mansuy et al (1998a,b) and Winder et al (1998). They report that transgenic mice overexpressing a truncated form of the phosphatase calcineurin display normal early LTP and short-term memory, but defective late LTP and long-term memory. However, evidence that the latter deficit was secondary to some other problem came from behavioral work showing that a change in training protocol could rescue the impairment in long-term memory. This suggested that the deficit in these animals was more likely in the transition from short- to long-term memory than in the mechanisms underlying either on its own. Regulation of calcineurin overexpression using the rtTA technique was examined in animals tested in the watermaze (Mansuy et al 1998b). In the latter study, animals completed training and were first tested with the transgene off. They learned the platform location, as indexed by good performance in a posttraining probe test. When the transgene was then turned on, performance in a second probe test fell to chance, and aston-

ishingly, when it was later turned off again, performance recovered. These results suggest that calcineurin contributes to retrieval mechanisms and/or performance.

Good temporal control can also be achieved using antisense techniques. These lie somewhere between the genetic and pharmacological approaches—possessing certain advantages and certain disadvantages of both. Relevant examples of their use include studies in which the expression of mRNA for two different potassium channels was reduced by repeated intracerebroventricular injections of oligodeoxyribonucleotides to reveal a dissociation between learning and plasticity. Antisense disruption of the presynaptic A-type potassium channel, Kv 1.4, eliminated both early and late phases of CA1 LTP, without affecting LTP in the dentate gyrus in rats (Meiri et al 1998). However, this antisense knockdown of plasticity had no effect on spatial learning. Given that threshold changes have been seen with some genetic manipulations (Kiyama et al 1998), the fact that Meiri et al (1998) used different intensities to induce LTP significantly strengthens their conclusion that CA1 LTP was successfully blocked in the antisense group. However, this study did not include in vivo observations, a range of tetanization frequencies (Mayford et al 1995, Migaud et al 1998), or information about the regional spread of the antisense oligo. This latter point is important, as LTP may have been monitored in an area along the longitudinal axis of the hippocampus that was affected by the oligo, whereas learning may have utilized neurons along the full length of this axis. It should be recognized, however, that antisense disruption of Kv 1.1, a different potassium channel that is highly localized within dendrites of CA3 neurons, had no effect on LTP in either the CA1 subfield or the dentate gyrus but did cause profound deficits in spatial learning (Meiri et al 1997). Clearly the longitudinal axis objection cannot apply here. Despite our criticisms, we recognize the potential significance of both these data and the approach.

Before concluding this section, note should be made of studies in which genetic techniques have achieved an enhancement of LTP and/or learning. Using standard knockout techniques, Manabe et al (1998) report that mice lacking the nociceptin/orphanin FQ receptor show enhanced LTP in area CA1 (possibly also due to a change in K^+ channel function), and both a modest but significant decrease in escape latency in the watermaze and enhanced memory consolidation in step-through avoidance learning. In contrast, Migaud et al (1998) have found that a PSD-95 mutant that shows enhanced hippocampal LTP and decreased LTD across a range of induction frequencies displays a profound impairment of watermaze performance (Migaud et al 1998). It is unclear how to explain this discrepancy. Migaud et al (1998) suggest that deletion of PSD-95 has shifted θ_M of the BCM function well to the left of its optimal position for bidirectional plasticity. LTD was not investigated by Manabe et al (1998). Finally, a thorough behavioral analysis by Tang et al (1999) has revealed that overexpression of the juvenile 2B subunit of the NMDA receptor facilitates LTP across a range of induction frequencies and enhances memory in a novel object recognition task, in cue and context fear conditioning, and in a probe test performance in the earliest stages

of learning a watermaze. The multiple determinants of LTP and LTD offer numerous sites at which genetic mutations to enhance function will be explored in coming years.

What are we learning from these genetic techniques? While highlighting certain limitations, we share the optimism of many neuroscientists that these should be kept in perspective. A "small industrial revolution in the construction of mice with mutated neural genes" (Morris & Kennedy 1992) is now upon us, providing the opportunity to explore issues outside the realms of other techniques. Network theorists are also showing interest in such techniques to explore features of their models that are impossible using other techniques, of which Lisman's (1999) request for a mouse with an inducible excision of mossy cells of the polymorphic (hilar) region of the dentate gyrus is a case in point. The use of reporter genes activated during LTP to drive markers that can be detected using confocal microscopy in living brain slices (Impey et al 1998) is also an opportunity that, but a few years ago, would have seemed like science fiction. It promises to shed light on the relationships between synapse and nucleus that are so critical to such hypotheses as the synaptic tagging idea of Frey & Morris (1998a,b).

Erasure: Does Reversal of LTP Cause Forgetting?

If traces related to a recent learning experience are temporarily stored within the hippocampus, procedures that successfully reverse LTP should cause forgetting (retrograde alteration). Erasure might be achieved (*a*) using trains of suitable depotentiating (e.g. low frequency) stimulation or (*b*) using the application of drugs or enzyme inhibitors that interrupt the expression of LTP when given shortly after its induction (such as kinase inhibitors).

Depotentiation can be induced using continuous trains of single pulses at 1–5 Hz (Barrionuevo et al 1980, Stäubli & Lynch 1990, Bashir & Collingridge 1994). Stäubli & Chun (1996) report that a few minutes of 5-Hz stimulation can depotentiate recently induced LTP in area CA1 in vitro. The efficacy of depotentiation declines rapidly as the interval between tetanus and 5 Hz is increased, with little effect being obtained 30 min after LTP induction. Dentate LTP in vivo can also be reversed by 5-Hz stimulation when delivered up to 2 min after tetanization (Figure 2*C*), but such stimulation has little effect after 10 min or 30 min (Martin 1998). The ability to preferentially erase recently induced LTP, while sparing established LTP, might provide a novel tool for future behavioral studies of the SPM hypothesis.

However, none of the protocols for inducing depotentiation have yet been tested for their ability to cause forgetting in behaving animals. One problem with doing so is that it may be difficult to induce depotentiation on all relevant pathways of the hippocampal formation. The same practical difficulties that beset the saturation approach lurk menacingly here also. Arguably, it would not be necessary to depotentiate very many hippocampal synapses after an individual learning experience because if LTP-like changes are sparsely distributed at specific

synapses, only some terminals may have to be depotentiated to disrupt a stored trace. An added worry is that long trains of 1- or 5-Hz stimulation can cause seizures, although this problem might be avoided by the use of naturalistic patterns of stimulation (see above).

A pharmacological approach would have the advantage that it is easier to target all the relevant synapses with a drug, but at the cost of unknown side effects. For example, Stevens & Wang (1993) reported that bath application of zinc protoporphyrin IX, an inhibitor of haem oxygenase (the enzyme that makes carbon monoxide in the brain), could bring a recently potentiated pathway back to its pre-LTP baseline without effect upon an independent nonpotentiated pathway. Unfortunately, the reliability of the erasure results of Stevens & Wang (1993) has been called into question (Meffert et al 1994), and it may, therefore, be necessary to await newer drugs before this approach can be satisfactorily explored. A promising compound is the integrin antagonist Gly Arg-Gly Asp-Ser-Pro (GRGDSP) that has been reported to reverse LTP in a pathway-specific manner within a time window of up to 10–15 min after LTP induction (Stäubli et al 1998).

An intriguing finding that Xu et al (1998a) have reported is that exposing freely moving animals to a novel but nonstressful recording chamber can reverse recently induced LTP without affecting a control pathway. They speculate that exposure to novelty has the effect of erasing hitherto unconsolidated information. Support for this interpretation is offered in a report by Izquierdo et al (1999), in which exposure to novelty limited the ability of an animal to remember a one-trial inhibitory avoidance task carried out up to 1 h previously. Exploration of novelty shortly before or long after the training trial was without effect. The effect appears to be NMDA receptor and CaMKII dependent.

Induction: Is Hippocampus-Dependent Learning Associated with the Induction of LTP?

The SPM hypothesis requires that synaptic changes must occur during learning. As Morris & Davis (1994) put it, "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 & Davis 1994:368). The experimental design is ostensibly straightforward: Synaptic efficacy is compared before and after a variety of different learning experiences, the prediction being that a persistent increase in synaptic transmission should occur at appropriate synapses following certain types of learning. Types of learning that engage the hippocampal formation should be associated with such changes; other types of learning should not. What is less clear is whether such changes would be readily detectable. The key problem is to monitor the appropriate synapses.

Exploration and Learning Induce Changes in Hippocampal Field Potentials and Transmitter Release Considerable excitement surrounded the discovery of what appeared to be a striking short-term modulation of perforant-path evoked EPSPs in the dentate gyrus during spatial exploration (Sharp et al 1989, Green

et al 1990). Exploratory activity was accompanied by an increase in the dentate field EPSP (fEPSP) and a decrease in both amplitude and latency of the population spike.

However, Moser et al (1993a) discovered that this unusual pattern of electrophysiological change during exploration is largely, although not exclusively, due to changes in brain temperature caused by the associated muscular activity. Application of radiant heat was sufficient to induce changes in fEPSPs. If, during exploration, the animal's brain was temperature clamped by intermittent infrared heating, exploratory motor activity was no longer associated with changes in the fEPSP. The fact that the brain is less homeothermic than had been thought previously means that in similar future studies, it would be wise to check that changes in fEPSPs are independent of brain temperature. Moser et al (1993b) worked out the calibration functions relating brain temperature to fEPSP magnitude before placing animals into an environment containing six landmarks. A small temperature-independent component of the increase in fEPSP associated with exploration was observed. This increased rapidly at the start of exploration and declined gradually to baseline over approximately 15 min. With so much focus on LTP in this field, the observation of a short-lasting change is a timely reminder that other forms of plasticity in the hippocampus may be functionally important [indeed, genetic studies have shown that mice with mutations of presynaptic proteins display impaired short-term potentiation and profound learning difficulties in the absence of any known deficit in LTP (Silva et al 1996)]. There are a number of unanswered questions about exploration-induced potentiation. Would a cumulative effect be seen across a population of synapses if additional novel objects were added over time? Is it saturable? What factors control its time course? Is it NMDA receptor dependent?

The induction of an LTP-like effect during learning has also been observed in the extrinsic connections of the hippocampal formation. Mice trained in two different tasks in a radial arm maze exhibited task-dependent potentiation of the connection of the fimbria to lateral septum (Jaffard et al 1996). Three observations reduce the likelihood that these changes were temperature induced: The potentiation developed gradually over the course of training; it was positively correlated to learning as assessed by the probe trial; and it was not seen with a control task involving comparable muscular activity on a treadmill. Similarly, Ishihara et al (1997) found that population spiking in the CA3 region induced by mossy fiber stimulation became potentiated during learning in a radial arm maze. A correlation was seen between changes in population spike amplitude and performance. Several observations suggest that this correlation is unlikely to be due to temperature.

Complementing these studies of fEPSPs in behaving animals have been studies comparing brain tissue in vitro from animals that have been exposed to a learning situation with tissue from animals that have been left unattended. For example, Green & Greenough (1986) saw enhanced dentate fEPSPs in response to perforant path stimulation in slices taken from adult animals that had been reared in complex environments. This study was particularly sophisticated in showing no

changes in antidromic potentials or the presynaptic fiber volley. However, before accepting that the enhanced dentate fEPSP is uniquely due to synaptic potentiation, one should also bear in mind the possibility that experience can alter the absolute number of neurons in the dentate gyrus. Studies of environmental enrichment have shown that mice kept in social groups with the opportunity for physical and exploratory activity can show dramatic increases in neurogenesis and cell survival in the dentate gyrus (Kempermann et al 1997, 1998; Gould et al 1999; van Praag et al 1999). These changes could account for the results of Green & Greenough (1986); enhanced fEPSPs may not, on their own, indicate a change induced by synaptic as distinct from other forms of neuronal plasticity.

Some studies have used markers of synaptic plasticity other than changes in field potentials—such as alterations in transmitter release or receptor sensitivity. For instance, an increase in glutamate release has been reported following both LTP (e.g. Dolphin et al 1982, Bliss et al 1986; but see Aniksztejn et al 1989, Diamond et al 1998, Lüscher et al 1998) and watermaze learning (Richter-Levin et al 1995, McGahon et al 1996). Richter-Levin et al (1997) trained rats in a spatial watermaze task for varying numbers of trials, then induced LTP in vivo on one side of the brain and finally examined veratridine-induced glutamate release in synaptosomes prepared from the hippocampus of the trained animals. Learning was associated with an increase in glutamate release. Tissue prepared from the hemisphere in which LTP had been induced showed that when taken from rats at an early stage of training, the increase in glutamate release was greater than when taken at a later stage. Thus, not only were both LTP and learning associated with an increase in glutamate release, but the learning-associated increase occluded the increase normally seen after LTP. This striking result would accord with the SPM hypothesis, were it not for the further finding that the amount of perforant path–induced LTP in vivo was the same in both the undertrained and the extensively trained groups. This is puzzling. That the magnitude of electrophysiologically induced LTP is unaffected by prior spatial learning is consistent with the storage capacity argument outlined above; learning may have only enhanced a small proportion of synapses in the dentate gyrus. However, if this is the case, why was the LTP seen after extensive learning not associated with an increase in glutamate release? Perhaps learning is associated with a shift in the relative expression of presynaptically mediated and postsynaptically mediated LTP.

Why Changes in Synaptic Efficacy Associated with Learning Might Be Difficult to Detect Why is it so difficult to see learning-associated synaptic changes? And does their absence in numerous experiments favor the null hypothesis? There are at least three points to consider—where to look, information storage capacity, and LTD.

There is little to say about the problem of where to look, beyond capitalizing on knowledge derived from lesion and unit-recording studies of functional localization. Regional differences in the behavioral modulation of neural gene expres-

sion provide additional clues. Hess et al (1995a,b) and Gall et al (1998) have found that the immediate early gene c-*fos* and the dendritically localized mRNA arc (or Arg3.1) (see Link et al 1995, Lyford et al 1995) are both up-regulated during exploration and odor-discrimination learning with, it is interesting to note, the regional pattern of activation reflecting different stages of learning. CA3 activation of c-*fos* was seen during the earliest stages of odor learning, whereas both exploratory activity and overtrained responding to discriminated odors were reflected in higher CA1 activation. Similarly, Wan et al (1999) report differential regional patterns of c-*fos* expression in animals observing novel stimuli and novel spatial arrangements of stimuli. These studies imply that type of task and stage of learning are likely determinants of when and where LTP-like changes may occur. However, the immediate early gene c-*fos* is not an unambiguous marker of activity-dependent synaptic plasticity, being regulated by various patterns of neural activity (Kaczmarek 1992). The discovery of genes more tightly coupled to the induction of late LTP would be helpful.

Second, with respect to storage capacity, long-term increases in synaptic efficacy should occur, at near optimal signal-to-noise efficiency (Willshaw & Dayan 1990), in proportion to the product of the probability of activity on afferent fibers (P_{pre}) and the probability of sufficient depolarization in this same population (P_{post}). If it is assumed that discrete events are represented as spatiotemporal patterns of activity with a relatively sparse code to maximize storage capacity (i.e. that P_{Pre} is small), the proportion of synapses potentiated following an individual learning experience will be a very small fraction of the whole (it will be proportional to the product P_{Pre} x P_{Post}). It follows that changes in population measures, such as fEPSPs, should be difficult to detect.

One way to get round this problem might be to use multiple single-unit recording. Wilson & McNaughton (1994) succeeded in finding nonrandom cross-correlation functions between the firing patterns of place cells with overlapping firing fields, and an increase in the cross-correlation when episodes of sleep followed repeated running through the relevant place fields. Such changes may be due to the consolidation of synaptic associations established during the earlier running. An extension of this kind of experiment might be to examine whether the learning of a simple hippocampus-dependent task is also associated with changes in cross-correlation functions. However, the chances of finding connected pairs of CA3 and CA1 cells is remote, even at the border of these areas. Moreover, pairs of cells connected prior to learning may, as implied by the findings of Petersen et al (1998), be the very cells at whose connections LTP has already occurred. If so, finding increases in the cross-correlation function would only be possible between cells that, before learning, are anatomically connected by non-functional synapses. Ironically, observing LTD in cell pairs might be easier because the nonrandom cross-correlation function might decrease. In our view, multiple single unit recording is an extremely important new approach to the problem but the design of analytically informative experiments is formidably difficult.

A third reason why LTP-like changes might be difficult to detect after learning would be if heterosynaptic depression (LTD) occurred at other synapses during learning. LTD might serve a normalizing function by ensuring that the sum of the synaptic weights on any given neuron remains roughly constant; fEPSP amplitude would thus remain unchanged. A useful analogy here is to the suspension system of a car: The passengers get a smooth ride, even over the bumpiest road, but a great deal of "plasticity" is going on in the suspension system to achieve this end.

In summary, although refuge in the assertion that a key prediction of a hypothesis is difficult to test is the territory of the rogue, new approaches involving visualization of genes specifically implicated in LTP and multiple single-unit recording promise to shed light on the issue.

SYNAPTIC PLASTICITY AND AMYGDALA-DEPENDENT LEARNING

The amygdala has been implicated in many forms of learning (Aggleton 1992, Holland & Gallagher 1999). The strongest evidence for an involvement of LTP-like processes in amygdala-dependent learning and memory has emerged from studies of conditioned fear. In classical fear conditioning, an innocuous conditioned stimulus, such as a tone or light, is paired with an aversive unconditioned stimulus, such as footshock. After a small number of pairings, the CS alone evokes responses such as freezing, increases in heart rate, and the potentiation of startle reflexes, previously associated only with the occurrence of the US (Davis et al 1993, LeDoux 1995). The expression of these indices of conditioned fear is sensitive to lesions of the lateral amygdala (LeDoux et al 1990, Sananes & Davis 1992), leading to the view that this structure is the sole site of long-term storage. However, others remain skeptical of this view (e.g. Cahill et al 1999; but see Fanselow & LeDoux 1999), in part because the lateral/basolateral amygdala does not seem to be involved in cognitive/explicit aspects of conditioned fear (Vazdarjanova & McGaugh 1998). One interpretation is that multiple brain circuits are involved in fear conditioning (see Kagan 1998). In this review, we limit our discussion to studies of conditioned freezing and fear-potentiated startle because these have been studied most closely in relation to LTP and its underlying mechanisms. An attractive feature of this research is that the CS and US can be clearly identified, as can the anatomical pathways along which this information is projected. Correlations with LTP are thus easier to identify than with hippocampus-dependent learning. For reasons of space, we do not discuss the extensive literature concerning inhibitory avoidance learning but note that evidence is mounting for the recruitment of a sequential biochemical cascade by this form of learning, which is strikingly similar to that implicated in the induction and expres-

sion of LTP (e.g. Kim & McGaugh 1992, Izquierdo & Medina 1995, Izquierdo et al 1997).

The Circuitry and Synaptic Plasticity of the Amygdala

Sensory information from the thalamus and cortex enters the amygdala mainly via the lateral and basolateral nuclei. Lesion studies have suggested that either the cortical or the thalamic pathway alone is sufficient for the acquisition of fear conditioning (Romanski & LeDoux 1992). The basolateral/lateral amygdala projects to many other brain areas, including the cortex and striatum, but for the indices of fear conditioning we are considering, the projections of these nuclei to the central nucleus of the amygdala appear to be critical (see Davis et al 1994, Pitkanen et al 1997). The numerous projections from the central nucleus to the brainstem are believed to mediate the many autonomic and behavioral components of the fear response.

Anatomical tract tracing studies have revealed an extensive projection to the lateral amygdala from areas of the auditory thalamus, such as the medial division of the medial geniculate nucleus (MGm), and the posterior intralaminar nucleus (LeDoux et al 1985). The latter region conveys pain information from the spinal cord, as well as auditory inputs from the inferior colliculus (LeDoux et al 1987). The lateral amygdala thus receives convergent CS and US information via its thalamic inputs. Indeed, most of the acoustically responsive cells in the dorsal subregion of the lateral nucleus of the amygdala are also responsive to noxious somatosensory stimulation, which suggests a possible locus for the formation of CS-US associations (Romanski et al 1993). The routes by which information about a visual CS reaches the amygdala are less well characterized, but the lateral geniculate and lateral posterior nuclei of the thalamus are believed to be involved (M Davis, personal communication). However, the lateral amygdala may not be the sole site of information storage. Receptive field plasticity at such upstream relays as the MGm is observed following fear conditioning (Edeline & Weinberger 1992), and evidence suggests that convergence of CS and US information may also occur in this region (for discussion, see Weinberger 1998). Nevertheless, synaptic plasticity has been most intensively studied in the amygdala itself, and our discussion of the literature necessarily reflects this bias.

As required by the SPM hypothesis, LTP can be induced in the lateral amygdala by high-frequency stimulation of thalamic afferents (Clugnet & LeDoux 1990). However, it has recently been reported that the induction of LTP in this pathway may be independent of NMDA receptors, at least under certain circumstances (Weisskopf et al 1999). In addition, application of AP5 reveals an NMDA receptor-mediated component of normal, low-frequency synaptic transmission (Li et al 1995), which suggests that NMDA receptors are involved in the routine transmission of sensory information from the thalamus. A route for the transmission of cortical information to the lateral amygdala is via the external capsule. LTP induced by high-frequency stimulation of this input has been reported to be

NMDA receptor independent (Chapman & Bellavance 1992), although a recent study has provided evidence that LTP in this pathway may depend on NMDA receptor activation under certain stimulus conditions (Huang & Kandel 1998). However, low-frequency transmission in this pathway, unlike that in the thalamic input, is mediated solely by AMPA receptors (Li et al 1996). The implication of these findings is that the use of NMDA antagonists during learning may not control all forms of plasticity in this network and that they may also have additional performance effects.

Pharmacological and Genetic Intervention: Does Blockade of the NMDA Receptor or Downstream Pathways Impair Fear Conditioning?

Many studies of conditioned fear involving intraamygdala application of NMDA receptor antagonists were carried out before currently available electrophysiological data. The hypothesis behind such studies was simple: If NMDA receptor-dependent LTP is the induction mechanism underlying the association of CS and US information within the amygdala, then infusion of AP5 into the amygdala ought to block the acquisition, but not the expression, of fear conditioning. Exactly this result was obtained using fear-potentiated startle to visual and auditory CSs (Miserendino et al 1990, Campeau et al 1992). Similar results have been obtained in several other amygdala-dependent conditioning tasks, including second-order fear conditioning (Gewirtz & Davis 1997) and discriminated approach to an appetitive CS (Burns et al 1994). However, it has recently been reported that, in addition to impairing the acquisition of conditioning in naive and pretrained rats, AP5 can also impair the expression of conditioned fear to both auditory and visual stimuli (Lee & Kim 1998; cf Bannerman et al 1995). A similar impairment of the expression of conditioned fear was previously reported by Maren et al (1996). These latter results suggest that amygdalar NMDA receptors may have a role in memory retrieval or nonmnemonic processes related to task performance (e.g. attention, cf Shors & Matzel 1997).

Considering the role of NMDA receptors in normal, low-frequency synaptic transmission in the thalamic input to the amygdala, it is perhaps not surprising that AP5 infusion can result in deficits in the expression of conditioned fear. However, information also reaches the amygdala via the cortex. The attenuation of LTP in the cortical input following AP5 infusion, such as that reported by Huang & Kandel (1998), should also impair those components of fear conditioning mediated by this pathway. However, the expression of fear responses conveyed by this route should be unaffected by AP5, as routine synaptic transmission here is NMDA receptor independent (Li et al 1996). Selective lesioning of either the cortical or thalamic pathways (cf Romanski & LeDoux 1992) coupled with NMDA receptor blockade might resolve this issue. Nevertheless, the potential role of NMDA receptor-mediated synaptic transmission and/or plasticity in other inputs to the amygdala, or in intraamygdala circuits, should not be overlooked.

Infusion of the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) into the basolateral amygdala blocks the expression of fear-potentiated startle (Kim et al 1993). It is interesting to note that facilitation of AMPA receptor-mediated transmission by infusion of the ampakine BDP-12 results in faster acquisition of fear conditioning, but it does not affect the final level of conditioned fear attained (Rogan et al 1997a). As Rogan et al note, this result parallels the effect of the drug on LTP induction, in which the rate of potentiation with successive tetani is increased but the asymptotic level remains unchanged.

The potential for genetic intervention in amygdalar synaptic plasticity is becoming a focus of interest. Mayford et al (1996) created a number of strains of transgenic mice in which the autophosphorylated form of CaMKII was under the control of tTA. In one of these strains, expression was moderate in the hippocampus, subiculum, striatum, and amygdala; but in another strain, there was little expression in the hippocampus and neocortex, but prominent expression in the striatum and the lateral and anterior nuclei of the amygdala. The former strain was impaired in a hippocampus-dependent spatial learning task but unimpaired in fear conditioning, whereas the latter strain was unimpaired in spatial learning but showed a severe impairment in fear conditioning. Acquisition of conditioned fear was normal after suppression of the transgene by doxycycline. In a further experiment, mice were trained in the presence of doxycycline, then tested for retention of fear conditioning after doxycycline withdrawal and the resumption of transgene expression. A retention deficit was obtained that, after control experiments, could not be attributed to differences in the perception of the US, or to changes in the performance of the conditioned response. This ingenious use of genetic engineering techniques suggests that the CaMKII signaling pathway in the amygdala is also involved in the consolidation or retrieval of conditioned fear.

Other signaling pathways have also been implicated in amygdala-dependent synaptic plasticity and fear conditioning. Brambilla et al (1997) created mice deficient in Ras-guanine nucleotide-releasing factor (Ras-GRF), one member of a protein subfamily normally associated with the control of cell proliferation and differentiation. Ras-GRF is specific to cells of the central nervous system and is involved in the activation of the Ras–mitogen-activated protein kinase pathway in response to postsynaptic calcium influx. Knockout mice showed normal retention of fear conditioning when tested 30 min after acquisition, but they were impaired relative to controls when tested 24 h later, which suggests that Ras signaling may be involved in memory consolidation. Subsequent experiments revealed that slices from knockout mice exhibited deficient LTP in the basolateral amygdala in response to tetanization of the external capsule. Despite the high expression of Ras-GRF in wild-type CA1, in addition to the amygdala, hippocampus-dependent spatial learning was normal in knockout animals, as was CA1 LTP in vitro. As noted by Orban et al (1999), the apparent differential dependence of hippocampal and amygdalar synaptic plasticity and memory on Ras signaling could reflect either the compensatory actions of other regulatory molecules within the hippocampus or a difference in LTP induction mechanisms between the two

structures. With respect to the second point, Orban et al (1999) note that muscarinic receptors, which are known to activate Ras-GRF, are highly expressed in the amygdala, and the antagonism of these receptors blocks the induction of LTP.

Induction: Does Fear Conditioning Induce LTP?

In recent work, LeDoux and colleagues have sought to relate LTP to learning in the manner required by our first criterion (detectability). In the first of a series of studies, a stimulating electrode was lowered into the MGm/posterior intralaminar nucleus of anaesthetized rats while a recording electrode was placed in the lateral amygdala. In addition, a small audio speaker was placed in the ear canal. Using this arrangement, it is possible to record amygdalar responses to both electrical stimulation of the auditory thalamus, and to natural acoustic stimuli. The delivery of a high-frequency tetanus to the MGm-LA projection increased the amplitude of both electrical- and auditory-evoked potentials (Rogan & LeDoux 1995), revealing that the induction of tetanic LTP can enhance the transmission of natural sensory information.

In a further experiment, evoked potentials elicited by an auditory CS were monitored in the lateral amygdala before and after fear conditioning (Rogan et al 1997b). Paired presentations of the auditory CS and footshock resulted in an increase in freezing behavior and a parallel potentiation of the CS-evoked potential. Furthermore, presentation of the CS in the absence of footshock led to the extinction of conditioned fear, and the fall of the CS-evoked response back to baseline levels. It has been reported, however, that footshock stress alone, rather than fear conditioning, causes a long-term enhancement of auditory-evoked responses in the basolateral nucleus of the amygdala (Garcia et al 1998). However, Rogan et al (1997b) trained unpaired CS-US controls, finding neither fear conditioning nor an increase in auditory-evoked potentials. There is as yet no evidence that the increase in the CS-evoked response is mechanistically equivalent to electrically induced LTP or is selective for the specific CS used, although such experiments will no doubt be forthcoming.

A complementary study lends support to the idea that fear conditioning can induce a phenomenon resembling LTP. McKernan & Shinnick-Gallagher (1997) prepared brain slices from fear-conditioned rats 24 h after behavioral testing. Control groups received either unpaired CS-US presentations or were experimentally naive. EPSCs were recorded from neurons in the lateral amygdala in response to stimulation of afferents from the auditory thalamus. Those from fear-conditioned rats were potentiated relative to those recorded from either of the control groups. This potentiation was accompanied by a decrease in paired-pulse facilitation. However, EPSCs elicited in the lateral amygdala by stimulation of the endopyriform nucleus projection to the lateral amygdala, a pathway not believed to be involved in fear conditioning, did not differ between fear-conditioned and control groups.

These studies suggest that fear conditioning induces a form of LTP, thus fulfilling the detectability criterion. However, it remains to be seen whether the artificial induction of LTP can induce behavioral responses analogous to conditioned fear, i.e. the mimicry criterion (cf Stevens 1998). Such an experiment would have the power to resolve the current controversy surrounding the site of storage of fear memories. For example, would pairing of stimulation in specific CS and US pathways to the amygdala result in potentiation of the CS pathway and would behavioral testing reveal that this LTP constitutes the engineering of an emotional memory? It is unlikely such a mimicry experiment could be carried out in the hippocampus in the near future, but in the amygdala at least, we may not have so long to wait.

SYNAPTIC PLASTICITY AND CORTICAL LEARNING

The neocortex is the repository of many kinds of information, reflecting different facets of experience, at various stages of life. Early sensory experience, particularly during so-called sensitive periods, contributes to activity-dependent self-organization. The representation of sensory experience in the cortex is dynamic; reorganization of cortical receptive fields occurs throughout life in response to behaviorally important experiences, albeit to a more limited extent than during early development. The role of synaptic plasticity in receptive field plasticity has recently been reviewed (Buonomano & Merzenich 1998).

Here we focus on research concerning the possible role of synaptic plasticity in cortical learning in adult animals. The cortex is widely assumed to store traces of experience underlying both explicit (declarative) and implicit (procedural) learning. In the former case, it is generally assumed that structures within the medial temporal lobe, including the hippocampus, are involved in the earliest stages of encoding and storage, somehow guiding the eventual consolidation of information in the cortex to a point where the obligatory participation of the hippocampal formation is no longer required. In the latter case, the cortex is thought to learn on its own—laying down a trace that later enables information to be called to mind but in a manner that disallows the capacity for constructive recollection. This important dissociation between the types of information laid down in cortical traces is not easy to get at using animal studies; but such work is essentially the only way to reveal the neural mechanisms responsible for the forms of long-term storage that last a lifetime.

Bidirectional activity-dependent synaptic plasticity with properties similar to hippocampal synaptic plasticity has been observed throughout the adult cortex in vitro (Artola & Singer 1987, Iriki et al 1989, Aroniadou & Keller 1995, Castro-Alamancos et al 1995, Kirkwood et al 1996) and in freely moving animals (Jay et al 1995, Trepel & Racine 1998). The enhancement of LTP through repeated daily tetanization (Trepel & Racine 1998) is reminiscent of the neocortical memory theory of McClelland et al (1995), according to which a slow consolidation

process enables new memories to be interleaved with others. One property of cortical LTP in particular—its NMDA receptor dependence—enables a similar pharmacological approach to that pursued in hippocampus and amygdala. However, the use of NMDA antagonists is only as good as their selectivity in blocking plasticity while leaving routine transmission intact. An ideal experiment would use a combination of local infusion of an NMDA antagonist, electrophysiology, and behavior. Few studies meet this ideal. Compared with literature on the hippocampus and amygdala, there is a paucity of information concerning synaptic plasticity and memory processes in the cortex. This is surprising given widespread interest in the idea that hippocampus and amygdala each contribute to consolidation processes.

Pharmacological Intervention: Does NMDA Receptor Blockade Impair Conditioned Taste Aversion?

We begin with a paradigmatic instance of implicit learning, conditioned taste aversion (CTA), in which a rat learns to avoid a novel taste when it is followed by digestive malaise (usually through LiCl injections). This involves multiple brain regions, including the central part of the insular cortex (see Bures et al 1998). In rats, taste information arrives in the insular cortex from thalamic nuclei and the basolateral nucleus of the amygdala.

Acquisition but not retention of CTA is impaired by local infusion of NMDA receptor antagonists into the insular cortex without significant impairment of sensory, motivational, or motor abilities necessary to acquire or express the behavior (Rosenblum et al 1997, Escobar et al 1998, Gutierrez et al 1999). However, CTA is sensitive to AP5 injections up to at least 2 h after the acquisition trial (Gutierrez et al 1999). This time delay is intriguing, as it suggests that the critical associative events can occur long after ingestion. It is thought that upon feeling ill a few hours postingestion, the animal forms an association between the retrieved memory of the taste and the then-current state of malaise. This would be an instance of what Holland (1990) calls mediated associative learning and it is consistent with NMDA receptors serving to detect stimulus conjunctions. But one of the stimuli is a memory.

In a separate series of experiments, Escobar et al (1998) found that i.p. injections of CPP blocked LTP in the insular cortex following high-frequency stimulation of the basolateral amygdala. In addition to blocking NMDA receptors, molecules downstream of the NMDA receptor have also been locally targeted to examine the effects on CTA. Inhibitors of protein kinase C (Yasoshima & Yamamoto 1997) and mitogen-activated protein kinase (Berman et al 1998) each impair CTA. Both kinases are thought to be required for various forms of LTP (Lovinger et al 1987, English & Sweatt 1997, Impey et al 1999). Further support for a role of LTP in CTA is correlational in nature. LTP in the dentate gyrus (Rosenblum et al 1996) and the learning of a novel taste (Rosenblum et al 1997) are both associated with phosphorylation of the NMDA receptor 2B subunit.

Thus, an NMDA receptor-triggered mechanism appears to be necessary for both the induction of LTP in the insular cortex and the encoding (but not retrieval) of CTA. However, it is premature to conclude that an LTP-like mechanism underlies the learning-related functions of the insular cortex during CTA because local infusion of AP5 dramatically blocks taste responses in cortical taste areas (Otawa et al 1995). The lack of effect of AP5 on retention of CTA, although not conclusive, argues against a major sensory effect of the drug. Nonetheless, even if NMDA receptor-dependent LTP must occur in the insular cortex during CTA, it is unlikely to be the only mechanism of trace formation. Changes occur elsewhere in the brain. Novel tastes evoke long-lasting bursting activity in the nucleus of the solitary tract (McCaughey et al 1997) and larger responses in the parabrachial nucleus (Shimura et al 1997). NMDA receptor blockade (Yamamoto & Fujimoto 1991, Tucci et al 1998), protein kinase C inhibition (Yasoshima & Yamamoto 1997), and CREB disruption (Lamprecht et al 1997) in the amygdala all impair CTA. Trace formation in CTA is clearly more complex than a simple up-regulation of synaptic strength in a single brain region. This will make satisfying our mimicry criterion difficult to meet in subsequent research.

Induction Studies

Does Cortical Learning Induce LTP? Our detectibility criterion asserts that LTP must occur during learning. Roman et al (1993) found that learning an odor-discrimination task, possibly a form of explicit learning, was associated with synaptic plasticity within the piriform cortex. The pathway concerned was the monosynaptic connection of olfactory bulb neurons within the lateral olfactory tract onto cells in the piriform cortex—a pathway previously shown to support NMDA receptor-dependent LTP (Jung et al 1990). Rats were trained to discriminate between a true odor and olfactomimetic stimulation of the lateral olfactory tract (electrical odors). The key finding was that LTP occurred during learning but not control pseudoconditioning. A roughly parallel potentiation of the polysynaptic field potential occurs in the dentate gyrus during a similar odor-discrimination protocol (Chaillan et al 1996). These data provide demonstrations of learning being associated with measurable synaptic plasticity in both a neo- and an allocortical structure. However, satisfying our first criterion for the SPM hypothesis is also consistent with the attentional hypothesis (Shors & Matzel 1997).

It has recently been reported that the learning of a motor skill is associated with the strengthening of horizontal connections within layers II/III of the primary motor cortex (Rioult-Pedotti et al 1998). Rats were trained to reach for food using a single forelimb, and 20–45 h later electrophysiological recordings were made from slices of motor cortex taken from these and untrained animals. An enhancement of the fEPSP was observed only in the hemisphere controlling the active forelimb in trained animals, consistent with reports of learning-induced functional cortical reorganization (Nudo et al 1996, Kleim et al 1998). The enhancement of

the fEPSP was associated with the occlusion of tetanus-induced LTP, which suggests that an LTP-like mechanism is involved in learning-related cortical plasticity. These data beg the intriguing question of whether the learning of a new skill would also be occluded, as might be expected if LTP is indeed necessary for skill acquisition.

Not all attempts to observe enhancement of synaptic efficacy following learning have been successful. Beiko & Cain (1998) examined the effect of spatial training of rats in a watermaze on transcallosal evoked field potentials in the posterior parietal cortex—one of several neocortical areas implicated in aspects of spatial learning (Sutherland et al 1988, Kolb et al 1994). Rats showed robust learning of several different platform locations, yet the amplitude of the transcallosal-evoked potentials was unaffected. These findings contrast with the experiments of Roman et al (1993). At the price of artificiality, Roman et al (1993) specifically select inputs that are necessarily involved in the learning process; the choice by Beiko & Cain (1998) of the transcallosal pathway may have been an inappropriate one. We also reiterate our concern that in a distributed network, such as cortex, global effects on field potentials are not necessarily to be expected.

Cellular Conditioning Studies Reveal LTP-Like Changes in Neuronal Connectivity Functional connectivity studies in the monkey auditory cortex, using cross-correlation histograms, reveal several interesting features of cortical plasticity (Ahissar et al 1992, 1998; Ahissar & Ahissar 1994). Two functionally connected neurons were selected, the degree of contingency between which could be altered by a sound. Further, the sound was, in one group, part of a behavioral discrimination task that required the animal to attend to the sound. Two important points arise from these data. First, the connectivity between neurons was strengthened when the contingency was increased above the steady state level, depressed when the contingency was decreased, and unaltered when it remained unchanged. Second, the magnitude of plasticity was much greater in monkeys performing the task. That is, the plasticity is a function not just of the contingency but also of the behavioral relevance of the activity. It should, however, be stressed that this plasticity was short lived and its similarity to LTP is unclear.

CONCLUSION

It has been three decades since Kandel first discovered that synaptic plasticity occurs during nonassociative conditioning of reflex behavior. Fuelled by the report of Bliss & Lømo (1973) about the discovery of LTP, the elucidation of NMDA receptor physiology and pharmacology, improved intracellular recording techniques, and advances in genetic engineering, much progress has been made in trying to understand the cellular basis of learning and memory. Advances in our understanding of multiple memory systems have occurred in parallel.

Throughout this time, variants of what we here refer to as the SPM hypothesis have proved useful in probing these cellular mechanisms. Varying degrees of enthusiasm and skepticism surround such hypotheses, and clearly we are among the enthusiasts.

We began by asserting that there are multiple types of memory and that the exact role of synaptic plasticity in trace storage would depend very much on the neural network in which it was embedded. It is difficult to build upon this bald assertion because serious testing of neural network models of memory is likely to require the simultaneous recording of hundreds (perhaps thousands) of single cells. One would look for alterations in neuronal connectivity and establish whether these were mediated by LTP-like changes and/or could be blocked by suitable pharmacological and genetic manipulations. Experimental research would, in addition, be guided by the very specific predictions of particular models. The field has not yet reached this state of sophistication.

What we were able to do, however, was to outline a set of formal criteria by which to judge a more generalized SPM hypothesis. To reiterate, this states that "activity dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for information storage underlying the type of memory mediated by the brain area in which that plasticity is observed." We also outlined four criteria: detectability, mimicry, anterograde alteration, and retrograde alteration (Table 1). These criteria have been met to varying degrees in the studies we highlighted.

In the hippocampus, detectability has proved difficult to meet. One study found only short-term temperature-independent changes in dentate field potentials during behavior. However, more persistent behavioral LTP induced by learning has been found in projections to the lateral septum and in the hippocampus. Anterograde alteration has been the main focus in studies of hippocampus-dependent learning. Three experimental approaches—saturation, pharmacological intervention, and genetic intervention—have each provided strong support for the SPM hypothesis. Retrograde alteration has not yet been reliably met, whereas meeting the mimicry criterion seems unlikely given the distributed nature of hippocampal processing. Of the two remaining criteria, satisfying retrograde alteration seems more feasible.

A not dissimilar picture exists with respect to amygdala-dependent learning and memory. Detectability has been met, arguably in a much more convincing way than in the hippocampus, and it constitutes some of the strongest data supporting the SPM hypothesis. Anterograde alteration has also been met in pharmacological studies, subject to problems arising from the NMDA dependence of routine transmission, and is complemented by supportive genetic studies. Neither the retrograde alteration nor the mimicry criteria have been met, although satisfying the latter is conceivably more likely than in the hippocampus.

Study of the neural mechanisms underlying cortical-dependent learning is much less well developed. Arguably, the detectability criterion has been met in

studies of odor discrimination learning, whereas anterograde alteration is being addressed in studies of conditioned taste aversion. However, the potential side effect of NMDA receptors on routine transmission is a recurring problem in the cortex, where our knowledge of neuropharmacological aspects of local circuitry is still in its infancy.

A thorough evaluation of the SPM hypothesis requires experiments addressing both necessity and sufficiency. The current shortfall is that sufficiency has barely been tested. To do so requires the artificial induction of synaptic changes to create what would constitute an apparent memory of an event that did not occur. Consequently, the SPM hypothesis is not yet secure, and exploring whether synaptic plasticity is sufficient for memory remains an enticing if somewhat intangible goal to add to the already large body of supportive evidence.

What of the future? We doubt there is any single definitive experiment yet to be done. Rather than being accepted or rejected, we expect the SPM hypothesis to be replaced by a variety of specific hypotheses focusing on the information processing functions of different networks in the brain and the role synaptic plasticity plays in these. Currently, progress is hampered by our lack of knowledge about what and how information is represented as spike trains across extrinsic and intrinsic pathways of memory processing areas. We anticipate ever more interest in the technology of multiple single-unit recording and the possibility of combining this with pharmacological or genetic intervention. The sophisticated nature of the field means that few laboratories can marshal, within their walls, the myriad of multidisciplinary techniques that are necessary to advance our understanding. Such diverse technological requirements dictate a collaborative approach. We can learn from our colleagues working on allied problems in sensory/perceptual systems, before designing appropriate experiments relevant to what we have referred to as the detectability and mimicry criteria. There is also growing interest in the role of the neocortex in memory storage, and in its interactions with such allocortical areas as the hippocampus and amygdala during memory consolidation. We anticipate that tackling this issue will be a particular focus of future research.

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