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Long-term potentiation: What's learning got to do with it?

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Abstract: Long-term potentiation (LTP) is operationally defined as a long-lasting increase in synaptic efficacy following high-frequency stimulation of afferent fibers. Since the first full description of the phenomenon in 1973, exploration of the mechanisms underlying LTP induction has been one of the most active areas of research in neuroscience. Of principal interest to those who study LTP, particularly in the mammalian hippocampus, is its presumed role in the establishment of stable memories, a role consistent with "Hebbian" descriptions of memory formation. Other characteristics of LTP, including its rapid induction, persistence, and correlation with natural brain rhythms, provide circumstantial support for this connection to memory storage. Nonetheless, there is little empirical evidence that directly links LTP to the storage of memories. In this target article we review a range of cellular and behavioral characteristics of LTP and evaluate whether they are consistent with the purported role of hippocampal LTP in memory formation. We suggest that much of the present focus on LTP reflects a preconception that LTP *is* a learning mechanism, although the empirical evidence often suggests that LTP is unsuitable for such a role. As an alternative to serving as a memory storage device, we propose that LTP may serve as a neural equivalent to an arousal or attention device in the brain. Accordingly, LTP may increase in a nonspecific way the effective salience of discrete external stimuli and may thereby facilitate the induction of memories at distant synapses. Other hypotheses regarding the functional utility of this intensely studied mechanism are conceivable; the intent of this target article is not to promote a single hypothesis but rather to stimulate discussion about the neural mechanisms underlying memory storage and to appraise whether LTP can be considered a viable candidate for such a mechanism.

Keywords: arousal; attention; calcium; classical conditioning; Hebbian synapses; hippocampus; memory systems; NMDA; spatial learning; synaptic plasticity; theta rhythm

1. Introduction

Few topics in neurobiology have attracted as much attention or resources over the past 20 years as the phenomenon of LTP (long-term potentiation), a putative mechanism for the induction of stable memories in the mammalian brain. Long-term potentiation is typically expressed as an increase in synaptic efficacy lasting from hours to days following brief tetanic (high-frequency) stimulation of an afferent pathway. [See Vanderwolf & Robinson's "Reticulo-Cortical Activity and Behavior. *BBS* 4(3) 1981.] Thus, following LTP induction, a fixed amount of presynaptic stimulation induces a "potentiated" postsynaptic response, for example, an increase in EPSPs (excitatory post-synaptic potentials). The phenomenon of LTP was initially observed in 1966 by Terje Lomo, then working in the laboratory of Per Andersen. In 1973, the first full article described LTP in the hippocampus of the rabbit, a collaborative effort between Lomo and Timothy Bliss (see also Bliss & Gardner-Medwin 1973). By 1989, the U.S. National Library of Medicine listed some 312 articles with the term "long-term potentiation" in the title, and, in the 1990s alone, over 1,000 additional articles have appeared. This search vastly underestimates the research effort, insofar as many articles that address LTP do not use "long-term potentiation" in the title or they refer to the same phenomenon by a different name (e.g., "long-term enhancement"; McNaughton et al. 1986).

The concerted attention that LTP has attracted over time perhaps carries no surprise for those familiar with the search for the engram (a neural memory store) and the associated mechanism that could account for its formation. Prior to the observation of LTP, the search had produced virtually no viable candidate mechanisms, at least for the vertebrate nervous system (cf. Kandel & Tauc 1965a; 1965b). In this regard, LTP has been and still may be the best candidate. In several recent reviews, various authors have concluded not only that LTP is a *viable* mechanism for the induction and storage of memories but that it is the most promising candidate (e.g., Morris et al. 1991). In one article (Martinez & Derrick 1996), the authors review recent evidence suggesting that the link between LTP and memory is in some cases tenuous, and in others even contradictory. Nevertheless, they conclude that "most evidence firmly supports a role for LTP in learning and memory" (see also Eichenbaum & Otto 1993). This conclu-

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sion is based, in part, on a commonly echoed assertion that, although no *direct* evidence links LTP to memory, no better mechanism has been postulated. This assertion is encompassed by the broader argument that a good theory should not be abandoned until a better one replaces it, an approach with obvious merit. On the other hand, explicit confidence in the validity of a prevailing theory can interfere with the development of viable alternatives and new approaches to a problem. Einstein once stated that "it is the theory which decides what we can observe" (see also Kuhn 1973). A flawed theory, the explanatory value of which is outweighed by the inconsistencies that it introduces, can serve only as a detriment to empirical progress. To the extent that a theory is maintained by popular consensus, "what we can observe" will necessarily be obscured by the convictions that a theory's advocates embrace.

Given the vast amount of attention that LTP has generated over the past 20 years, it seems an appropriate time to review the cellular and behavioral characteristics of LTP that led us to consider it as a memory device in the first place. We should evaluate whether these properties remain viable features of a memory device and, if so, whether LTP remains the most viable mechanism to serve that broader function. Of particular concern here is a distinction that we will draw between LTP and the formation and storage of memories versus a link between LTP and the processes that "influence" the formation and storage of memories. By "influence," we mean that LTP may be neither a necessary nor a sufficient condition for the actual storage of memories, but LTP or an endogenous equivalent could act to facilitate and maintain learning indirectly by altering the organism's responsiveness to, or perception of, environmental stimuli. In this target article, we first review a number of the cellular properties intrinsic to LTP, with a particular emphasis on hippocampal LTP and the characteristics most commonly presented as evidence for its relationship to memory. It is important to stress that, even if hippocampal LTP was the "learning mechanism," we would not expect individual synapses to express characteristics of learning and memory *processes*. Nevertheless, we discuss them because they are the features commonly cited as evidence for the role of LTP in learning, and this will allow us to evaluate the overall consistency of the evidence supporting LTP as a mechanism of memory storage. Second, we review the behavioral evidence that links LTP in the hippocampal formation to learning and memory in the behaving animal. Finally, we present an alternative hypothesis, that LTP is not a memory device per se but, rather, that it can influence the ultimate formation of memories by enhancing attention and the processing of sensory information.

2. Cellular properties of LTP and their relationship to memory

2.1. Distribution throughout the nervous system. The idea that LTP might serve as a memory storage device arose, at least in part, from its discovery in the hippocampus, a structure critical to the formation of certain types of memories. Not only was LTP discovered in the hippocampus, but its distribution, in various forms, is evident at the three major synaptic connections of the structure. It is induced in the dentate gyrus granule cells by stimulation of the perforant pathway as originally described by Bliss and Lomo (1973), in the CA3 pyramidal cells by stimulation of the mossy fibers (see, e.g., Alger & Teyler 1976; Yamamoto & Chujo 1978), and in the CA1 pyramidal cells by stimulation of the Schaffer collateral branches of the CA3 neurons (Andersen et al. 1977; Schwartzkroin & Wester 1975). The initial description of LTP in the hippocampus was probably fortuitous for memory research; had LTP first been identified in a brain region with less of a historical link to memory formation (see, e.g., Olds 1955; Scoville & Milner 1957), it might not have received such focused attention. Since 1973, however, LTP has been found to occur in many brain regions, including the piriform (Stripling et al. 1988), entorhinal (Wilhite et al. 1986), and prefrontal (Laroche et al. 1989) cortices, the septum (Racine et al. 1983), the autonomic (Libet et al. 1975) and superior (Brown & McAfee 1982) cervical ganglia, and the ventral horn of the spinal cord (Pockett & Figurov 1993). Furthermore, LTP is not limited to the mammalian brain but has been described in other vertebrates as well, such as the goldfish (Lewis & Teyler 1986; Yang et al. 1990), bullfrog (Koyano et al. 1985), bird (Scott & Bennett 1993), and lizard (Larson & Lynch 1985) and also in some invertebrates (Glanzman 1995; Walters & Byrne 1985). Because negative findings are usually not definitive, it cannot be said with certainty that LTP *cannot* be induced in a particular brain region, but it is safe to say that phenomena fitting the general description of LTP occur ubiquitously throughout the nervous system. If LTP is a ubiquitous feature of the nervous system, what might that mean with respect to its potential role in learning and memory? Moreover, if LTP is indeed a learning and memory device, what would such a wide distribution tell us about the neural mechanisms of memory formation?

Most researchers would agree that memory formation requires, or at least utilizes, wide and distributed brain regions, and the hippocampus is clearly not the only "storage" site for memory; humans and infrahumans do not require a hippocampus to acquire many forms of memory, and, even in tasks dependent on the hippocampus for acquisition, the structure is typically not required for later retrieval. If we begin with the premise that many memories are not actually stored in the hippocampus, then what function might LTP serve there? Before discussing the role of LTP in memory or any behavioral processes, however, we must first form an operational (and functional) definition of LTP.

2.2. Multiple definitions of LTP. A serious impediment to determining or even discussing LTP's putative role in learning is the confusion regarding its definition. As operationally defined by Bliss and Lomo (1973), LTP is a persistent (hours to days) enhancement of an EPSP following brief high-frequency (tetanic) stimulation of afferent pathways. This definition (or a close variant of it) still predominates at least formally. For instance, several major textbooks, in describing LTP, essentially reiterate the earlier definition of Bliss and Lomo (e.g., Kandel et al. 1991; Nicholls et al. 1992). Similarly, one extensive review states that LTP is "an increase in synaptic efficacy, at monosynaptic junctions, occurring as a result of afferent fiber tetanization" (Teyler & DiScienna 1987).

Although these definitions are generally accepted and are often used, they do not capture the range of conditions considered sufficient for the induction to reflect the induction of LTP. For this reason and others, a number of

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researchers have either implicitly or explicitly narrowed the definition since its inception. This is, in part, understandable; a number of the properties of LTP were unknown at the time when Bliss and Lomo (1973) first described the phenomenon. For instance, much of the research aimed at elucidating the role of LTP in memory has focused on the hippocampal formation, presumably because LTP was discovered there and for some time was considered to be unique to that region. In addition, at the time of Bliss and Lomo's original observation, the NMDA (N-methyl-D-aspartate) receptor had not yet been identified and thus did not enter into either the conceptualization or the operational definition of the phenomenon. Since then (see, e.g., Collingridge et al. 1983; Harris et al. 1984), it has been determined that LTP at two of the major synaptic regions in the hippocampus (the dentate gyrus and area CA1) is, in part, dependent on calcium influx through the NMDA type of glutamate receptor and channel (details of this mechanism are described below). As a result, some researchers focus on the role of NMDA-dependent forms of LTP in memory (often stating that LTP *is* an NMDA-dependent phenomenon) despite the numerous instances in which long-lasting increases in synaptic efficacy occur in the absence of NMDA receptor activation (Castillo et al. 1994; Jaffe & Johnston 1990; Johnston et al. 1992; Komatsu et al. 1991). To add to the confusion, even in the dentate gyrus and CA1, LTP can be induced in the absence of NMDA-receptor activation provided that there is an alternate means of intracellular calcium accumulation, such as strong depolarization and subsequent influx of calcium through voltage-dependent channels (Kullmann et al. 1992; Malenka 1992; Malenka et al. 1988; Wierazko & Ball 1993) or release of Ca^{2+} from intracellular storage pools (Bortollotto et al. 1995). Thus, defining LTP based on its NMDA dependence seems unnecessarily limiting and may be misleading with regard to a role for LTP in memory. We are not attempting to draw merely a semantic distinction; the significance will become apparent in the discussion below of pharmacological manipulations presumed to affect both LTP and memory.

An antithetical, yet potentially more serious, impediment to evaluating the link between LTP and memory formation is that the definition of LTP is often expanded to encompass virtually any observation of increased synaptic efficacy. By most accounts, memory storage is likely to involve a strengthening of specific synaptic connections (though these modifications need not be limited to synapses [see, e.g., Tesauro 1988]), but, in addition to high-frequency stimulation, a number of mechanisms have been identified through which such synaptic strengthening can occur (see Hawkins et al., 1993, for an integrative review). Many of these mechanisms are physiologically relevant and have been linked to memory formation. Thus, the observation of enhanced synaptic efficacy during learning does not necessarily indicate that the enhanced efficacy was induced by a mechanism similar or identical to the mechanism evoked by high-frequency stimulation. For example, in one study (Weisz et al. 1984), rabbits were chronically implanted with stimulating electrodes in the perforant pathway and recording electrodes in the dentate gyrus. The rabbits were subsequently trained to associate a tone (= CS; conditioned stimulus) with an aversive air puff to the eye (= US; unconditioned stimulus), eventually eliciting a CR (conditioned response) to the tone. The results indicated that neuronal efficacy in the dentate gyrus was enhanced during acquisition of the conditioned response. Although it is tempting to conclude that the potentiation in the dentate gyrus reflected an LTP-like mechanism (cf Teyler & DiScienna 1987), there is no evidence that it arose from a stimulation pattern similar to that inducing LTP. Moreover, given that the increase in learning and neural efficacy was correlational, it cannot be said that the potentiation contributes directly to the expression of the learned response. In fact, extensive experimentation by Thompson and his colleagues (see, e.g., Knowlton & Thompson 1992; Krupa et al. 1993; Lavond et at. 1993; McCormick et al. 1982; Swain et al. 1992; see also Berthier & Moore 1986; Yeo et al. 1986) suggests that the necessary and sufficient circuitry for the acquisition of the classically conditioned nictitating membrane response resides in the cerebellum. One mechanism for generating the conditioned response is thought to be a reduction in the activity of Purkinje neurons in response to stimulation of afferent mossy fibers/parallel fibers, the presumed pathway of the conditioned stimulus. This observation is consistent with Ito's (1984) hypothesis that LTD (long-term depression), rather than LTP, is the relevant mechanism underlying memory storage in the cerebellum (see also Lavond et al. 1993). However, were one simply to record activity induced by the conditioned stimulus in the interpositus or red nucleus (loci in the CR pathway efferent to the Purkinje neurons), an increase in the magnitude of the EPSP would be observed, owing to a release from presynaptic Purkinje cell inhibition. Such an observation could easily lead one to conclude that "LTP" underlies learning in this system, when quite the opposite appears to be true.

It has been suggested that the term "LTP" actually refers to a presumed endogenous phenomenon and that the laboratory phenomenon is simply a tool to study a more general class of neuronal plasticity. Such an approach is entirely reasonable, but it should be made explicit so that the *operation* that produces LTP in the laboratory is not considered a mechanism for storing memories in vivo. Many researchers recognize that the term "LTP" is generic, but written accounts of the role of LTP in memory storage often suggest a more specific function. Statements such as "LTP underlies learning and memory" should perhaps be replaced by "enhanced synaptic efficacy underlies memory storage." Conversely, if the term "LTP" is simply intended to describe an increase in synaptic efficacy related to learning, then perhaps the discovery of LTP should be credited to Kandel and Tauc (1965a; 1965b), who first described heterosynaptic facilitation, an increase in synaptic efficacy related to behavioral sensitization. If enhanced synaptic efficacy is, in fact, the mechanism underlying memory formation (a topic that we cannot fully address here), and all forms of enhanced synaptic efficacy are deemed to be LTP, the hypothesis that LTP underlies memory formation cannot be disproved and serves no heuristic value. In the end, "LTP" would become no more than a synonym for memory formation.

Use of the term "LTP" to describe all forms of enhanced synaptic efficacy might lead a casual observer to conclude that a common mechanism is shared by all. In 1987, Teyler and DiScienna constructed a partial list of 51 compounds (or manipulations that induce, prevent, or reverse LTP. Since then, the list has expanded tremendously, with particular emphases on modulators of protein kinases

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(Fukunaga et al. 1993; Kaczmarek 1992; Malinow et al. 1988; 1989; O'Dell et al. 1991b; 1992) and diffusible second messengers, such as arachidonic acid and nitric oxide (Bohme et al. 1991; Haley et al. 1992; Clements et al. 1991; Lynch et al. 1991; Schuman & Madison 1991; Williams & Bliss 1989; Williams et al. 1993), as well as platelet-activating factors (Goda 1994; Kato et al. 1994). Given the ever-expanding list of agents reported to induce an increase in synaptic efficacy referred to as "LTP," one might reasonably ask whether all these agents influence a common mechanism. For instance, PKC (protein kinase C) has been reported to play a role in LTP, based on findings that antagonists of the kinase block the induction of LTP (Akers et al. 1986; Malinow et al. 1988). Exogenous application of phorbol ester, a synthetic activator of the kinase and potent tumor promoter, can also induce potentiation (Malenka et al. 1986; Reymann et al. 1988). Likewise, it has been noted that D-alpha-tocopherol (vitamin E) induces synaptic potentiation, purportedly through its antioxidant, or tumor-*inhibiting*, properties (Xie & Sastry 1993). It seems likely that the synaptic potentiation induced by phorbol ester and that induced by D-alpha-tocopherol are regulated by different underlying substrates. However, both are referred to as "LTP" in the titles or abstracts of the respective articles. There are also reports of enhanced LTP through caloric restriction (Hori et al. 1992) and prevention of LTP induction by the sugar substitute saccharin (Morishita et al. 1992) as well as by cocaine (Smith et al. 1993). Again, the common denominator linking these observations is the term "long-term potentiation" in the title of the reports. Our point is that one should not assume that a single mechanism is shared by all; rather, the length and breadth of the list of modulators suggest that they could not influence a single mechanism or even a single class of mechanisms.

In summary, there are at least two approaches to establishing an acceptable definition of "LTP." One is to allow the term to encompass all long-lasting forms of potentiation. This approach renders the term almost meaningless and makes the presumed connection between LTP and memory an unfalsifiable construct. The second approach is to limit the definition partially. For the purposes of this target article, we have taken the position that all forms of synaptic modifications related to learning and memory are not equivalent. Nevertheless, with regard to experiments that attempt to link LTP to behavior, we review articles that describe manipulations that the various authors suggest influence "LTP." We recognize that this is not much of a limitation and, on occasion, dispute the authors' claims in an attempt to illustrate the necessity for a more precise nomenclature. Moreover, we focus our discussion on LTP in the hippocampal formation. This is necessary owing to space limitations and also because LTP in the hippocampus has been studied the most intensely with respect to learning and memory.

2.3. NMDA receptors and postsynaptic calcium. One defining feature of LTP is its dependence on high levels of postsynaptic calcium, a common feature of most experience-induced neuronal modifications. In and of itself, a definition that includes "calcium dependence" provides little insight insofar as a wide range of cellular functions require calcium, and still more are dependent on elevations of intracellular Ca^{2+} above basal levels. Although the exact role of calcium in LTP induction is a matter of debate, elevation of postsynaptic calcium is clearly necessary, and may even be sufficient, for the induction of hippocampal LTP. Induction of LTP is prevented by a pretetanus injection of calcium chelators into the postsynaptic cell (Lynch et al. 1983; Malenka et al. 1988), and induction occurs when the postsynaptic cell is artificially loaded with the ion (Malenka et al. 1988). A great deal of evidence (see, e.g., Collingridge et al. 1983; Harris et al. 1984; Jahr & Stevens 1987) indicates that the primary source of calcium influx during the induction of hippocampal LTP occurs through an ion channel that is coupled to the NMDA subtype of glutamate receptor. This receptor is unique in that stimulation of the channel ionophore requires glutamate binding as well as a moderate level of depolarization. At normal resting potentials (approximately −70 mV), the channel is blocked by magnesium, and glutamate binding is insufficient to open it. However, at depolarized membrane potentials (greater than −40 mV), magnesium is expelled from the channel, which can then be opened by glutamate and which displays a high selectivity to calcium ions. Thus, the NMDA receptor complex is said to be dually regulated by two factors, ligand and voltage. These cofactors can be recruited through several means. First, a relatively long, high-intensity presynaptic burst of activity (such as a high-frequency train of stimulation) can induce LTP by releasing glutamate onto the postsynaptic receptor, while depolarizing the postsynaptic cell through stimulation of the non-NMDA type of glutamate receptors (AMPA). Second, shorter and more physiologically relevant levels of presynaptic activity can induce hippocampal LTP by stimulating the NMDA receptor with glutamate, while the postsynaptic cell is depolarized via an alternative means such as an input from a second afferent pathway. Other forms of LTP, such as that induced in CA3 pyramidal cells following mossy fiber tetanization, occur independently of the NMDA receptor and are instead dependent on Ca^{2+} influx through voltage-gated channels, although there is some debate regarding whether the critical Ca^{2+} signal occurs presynapticaly (Castillo et al. 1994; Weisskopf et al. 1994) or postsynaptically (Johnston et al. 1992; Williams & Johnston 1989). As was mentioned above, even in area CA1, LTP can be induced without the participation of NMDA receptors, provided that the tetanus (or postsynaptic depolarization) is of sufficient intensity to activate voltage-dependent calcium channels (Grover & Tyler 1990; Kullman et al. 1992). In conclusion, activation of the NMDA receptor may be critical to many forms of LTP, but it is not necessary for all. In contrast, intracellular calcium appears to be a necessary element for the induction of LTP. A necessary role for calcium in LTP is consistent with LTP's presumed role in learning; calcium plays a critical role in many cellular modifications thought to underlie conditioned behavioral responses (see, e.g., Abrams & Kandel 1988; Falk-Vairant & Crow 1992; Matzel & Rogers 1993; Walters & Byrne 1985). However, it must be reiterated that calcium is necessary for a wide range of cellular functions.

2.4. Synaptic efficacy, specificity, and memory. The search for the engram has been guided by a number of expectations regarding the features that a memory mechanism *should* possess. Some of these expectations have been strengthened through experimentation, whereas others were ultimately discarded (cf. Chapouthier 1989; Gaito

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1976). One reasonable expectation is that learning is accompanied by an increase in the efficiency of communication between neurons, a concept with extensive historical antecedents (see, e.g., James 1892; Spencer 1870; Tanzi 1893). The formalization of this idea is usually attributed to Donald Hebb. In 1949, Hebb wrote in his book *The Organization of Behavior*, "when an axon of cell A . . . excite[s] cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased." This particular line from Hebb's treatise, subsequently referred to as "Hebb's Rule," closely resembles the operational definition of LTP and is frequently offered as a theoretical foundation for the presumed role of LTP in learning.

In addition to its expected basis in a modulation of synaptic efficacy, the search for the engram is based on a second expectation, that of synapse specificity. Besides its intuitive appeal, strong empirical support exists for synapse-specific changes that accompany the learning process (Clark & Kandel 1993; for review, see Hawkins et al. 1993), and hippocampal LTP itself is considered to be synapse specific (Andersen et al. 1977; Dunwiddie & Lynch 1978). However, as with the definition of LTP, the term "synapse specificity" is often used to describe very different phenomena. Under some circumstances, synapse specificity implies that the modifications underlying LTP are limited to synapses. This type of synapse specificity has intuitive appeal because it provides the necessary structure for a huge memory capacity, well beyond what could be achieved through somatic potentiation. However, the modifications induced by LTP are rarely, if ever, *limited* to synapses. For instance, in the original description of LTP, Bliss and Lomo (1973) reported a phenomenon since referred to as E/S potentiation. Following LTP induction, an increase in population spike amplitude (S) and a reduced threshold for cell firing can be observed even if the magnitude of the excitatory postsynaptic potential (E) is held constant, indicating that the tetanus-induced modification is not limited to the synapse. With use of an extracellular population spike as a dependent measure, an increase in efficacy can reflect changes that occur exclusively in the soma, along the entire membrane, at synaptic terminals, or with some combination of the three. Using an extracellular EPSP as the dependent measure, on the other hand, does not allow one to measure the changes that might occur at other cellular loci. Thus, changes at the soma, such as the nonsynaptic forms of potentiation that typically accompany an increase in synaptic efficacy, are virtually ignored (Andersen et al. 1977; 1980; Bliss et al. 1987). Given that there is no a priori reason to require that a memory mechanism be limited to modifications of synaptic terminals, these observations do not reflect on the validity of LTP serving this function. Neither, though, should this interpretation of synapse specificity be used as evidence to support LTP's role in learning.

The second and more common use of the term "synapse specificity" is in reference to potentiation that is limited to synapses active during stimulation (as opposed to inactive synapses). Under these conditions, potentiated synapses are proposed to reflect an independent memory store, and those synapses would be preferentially activated during retrieval, a seemingly critical feature of memory. In our opinion, and probably that of many others, this is one of the more compelling aspects of the hypothesis that hippocampal LTP is involved in memory formation. Unlike the prior description of the term "specificity," this usage does not necessarily require that potentiation be restricted to a modification of the synapse. Rather, specificity here suggests that changes will be restricted to those synapses (and possibly other compartments) that are active during the induction of LTP.

At this point, it should be noted that the plastic changes associated with learning are often *not* limited to the synapses active during the learning event. In fact, many models of complex memory processing explicitly require that memory become distributed among different locations in the nervous system following its initial induction (see, e.g., Atkinson & Shiffrin 1968; Eisenstein & Reep 1985), and several lines of empirical evidence support such a view. For instance, in the chick nervous system, the necessary circuitry for the expression of conditioned taste aversion (a form of associative memory) shifts to several anatomically distinct brain areas within days after initial learning, such that a lesion that disrupts recall at one retention interval may not affect retention at another (Rose 1992; 1995). In the isolated ganglion of the cockroach, an operant leg position response expressed in the prothoracic ganglion of the roach will later be expressed in an untrained, mesothoracic leg, suggesting transfer of information between ganglia (Hoyle 1980; for review, see Eisenstein & Reep, 1985). Evidence for the transfer of "stored" information out of the hippocampus has also been found. The noted patient H.M. (Scoville & Milner 1957), who underwent bilateral excision of the medial temporal region (including parahippocampal gyrus, amygdala, and anterior portions of the hippocampus), cannot transfer short-term memories into long-term storage, though very short-term memories and many memories established prior to surgery are spared. This, as well as corroborative work with animals (e.g., Kim & Fanselow 1992), indicates that the hippocampus is not in fact a memory "store" but rather a temporary holding site critical to the integration and consolidation of memories that presumably occur in higher cortical areas or elsewhere (see Squire et al.; Zola-Morgan & Squire 1991). Thus, in general, it does not appear that the brain structure used for acquiring memories is necessarily the site for storage.

Nonetheless, if one accepts the premise that synapse specificity is a defining feature of memory induction, then evidence that LTP is not specific to the synapses that were active during stimulation suggests that LTP fails to meet the requirements for a memory mechanism. Recently, several researchers have reported that the potentiation is not specific to the synapses that were active during afferent stimulation. Boenhoffer et al. (1989) recorded simultaneously from neighboring CA1 pyramidal cells while stimulating the afferent Schaffer collateral fibers at a low frequency, which in itself will not induce LTP. When stimulation was paired with depolarization of one of the pyramidal cells, potentiation was observed not only in that cell but in a neighboring cell as well. This result was elaborated by Schuman and Madison (1994), who reported that a spread of potentiation could be detected 250 μm (but not 500 μm) away from the site of induction and that inhibition of the diffusible gas nitric oxide blocked the spread. These results suggested that the conditions that induce LTP at one synapse could spread over potentially thousands of adjacent synapses, thus abrogating the possibility that tetanized synapses serve as individual memory

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storage units. It should be noted, however, that such a dissipating spread of potentiation might well contribute to the generalization gradient, which is a ubiquitous feature of most instances of learning (Mackintosh 1975). (This discussion is subject to two caveats. First, the influence of nitric oxide on the maintenance of LTP has been studied most intensively in the hippocampus slice preparation, in which the effects have been equivocal [Cummings et al. 1994]. Second, the gas might not play a critical role in memory induction under physiological conditions in vivo. For instance, Bannerman et al. [1994] reported that a 90% inhibition of nitric oxide synthesis in the brain had no effect on acquisition in the water maze, although nonspecific behavioral impairments were apparent.)

In addition to the spread of overt potentiation to nearby synapses, changes also accompany the induction of LTP that are not limited to active synapses or even nearby synapses. For example, unilateral tetanization of the perforant pathway induces LTP in the dentate gyrus and an increase in messenger RNA (mRNA) for a presynaptic glutamate receptor on the stimulated (ipsilateral) side 2 hours later (Smirnova et al. 1993). Within 5 hours of the induction of LTP, however, levels of mRNA are also increased on the contralateral side, in areas that presumably are not exhibiting LTP. Thus, mRNA levels are increased in response to the induction of LTP in regions that do not exhibit enhanced synaptic efficacy and presumably were not active during tetanization. Smirnova et al. (1993) concluded that "the induction of LTP at one stage in a neural network may lead to modification in synaptic function at the next stage of the network." In a related example, LTP was again induced in the dentate gyrus following unilateral tetanization of the perforant pathway. One hour later and in the presence of potentiation in the dentate gyrus, there was a bilateral increase in the binding affinity of the AMPA type of glutamate receptor (Tocco et al. 1992). This increase was not confined to the dentate gyrus but occurred in regions throughout both hippocampi. Although not synapse-specific, the increase was "specific" in the sense that it was prevented by NMDA antagonists and did not occur in response to stimulation at frequencies too low to elicit LTP. As a third example, unilateral tetanization of the perforant pathway caused a bilateral increase in mRNA for two neurotrophins; brain-derived neurotrophic factor and nerve growth factor (Castren et al. 1993). These three examples are considered "nonspecific" responses to LTP and, therefore, might be of minimal interest to those concerned with understanding the mechanism of LTP induction. Nonetheless, it is clear that several changes in neuronal function are occurring in response to the typical induction protocols for LTP and that those changes are not limited to the synapses active during LTP induction.

Although these data indicate that the effects of LTP are not confined to the synapses active during the induction protocol, when viewed from an integrated brain systems approach these transynaptic and "nonspecific" effects may provide some of the most convincing evidence that LTP does have physiological relevance. Were one to assume that information transfer in the nervous system occurs during memory storage, as a number of studies suggest, then the transynaptic modifications may provide clues about the mechanism of that transfer and, therefore, memory formation itself. For example, the fact that tetanization of the perforant pathway in the hippocampus can increase AMPA binding as remotely as in the neocortex (Tocco et al. 1991) suggests that the conditions that induce LTP in the hippocampus also affect structures involved in perception and presumably memory storage. We believe that these nonspecific responses should not be dismissed but, rather, should be appreciated as providing potential clues about the neural mechanisms of information processing.

In summary, the assertion that hippocampal LTP is a memory device because of its limitation to synapses themselves or to synapses active during tetanization reflects a preconception about the nature of memory, rather than an empirically derived observation about memory. For two decades, the presumed "synapse-specific" nature of LTP was cited as support for the argument that hippocampal LTP is a viable substrate of memory. Since it has been shown that LTP is not necessarily confined to the active synapse, it has been suggested that LTP is a viable substrate of memory because memories are "distributed" (see Barinaga 1994, for commentary). Obviously, these two lines of reasoning are incompatible and reflect our tendency to validate the theory that LTP is a mechanism of learning and memory by invoking the theory itself.

2.5. Long-lasting, but decremental. One of the most perplexing issues regarding memory storage in the brain is *how* a biological representation of a memory can be sustained for such lengthy periods of time. The mechanism suited for such a task must be capable not only of acquiring and encoding the perceived information but also of storing it long after the proteins involved in the initial storage have been degraded and replaced (hours to days; for a discussion of mechanisms that might underlie long-term modifications of synaptic efficacy, see Lisman 1994; Miller & Kennedy 1986; Schwartz & Greenberg 1987). Indeed, relative to most forms of neuronal plasticity, LTP is long-lasting. Other forms of potentiation in the mammalian nervous system persist for seconds, usually not hours, and certainly not weeks. In contrast, LTP can persist for weeks in area CA1 in vivo (a median of 10.5 days in CA1; Staubli et al. 1987) and for approximately 8 hours in vitro (Reymann et al. 1985).

There is no doubt that LTP is long-lasting, but is it long-lasting enough? Memories can persist intact throughout the life span of the animal (Spear 1978), whereas LTP decays (cf. Staubli & Lynch 1987). To retard the rate of decay, many investigators who have observed the effects of LTP on behavior deliver multiple tetani, sometimes exceeding 100 high-frequency trains over days or weeks (e.g., Castro et al. 1989). However, even with this extended "training" regimen, potentiation almost always decays to baseline levels within one week. These results suggest that, although LTP is long-lasting, its time course does not correspond to that of a typical long-term memory. It is obvious that many memories do not last a lifetime, but, taking this point into consideration, we would then have to propose that LTP is involved in the storage of only short-term to intermediate-term memories. Again, we would be at a loss for a brain mechanism for the storage of a long-term memory.

To account for the decremental nature of LTP, some have suggested that a process opposing LTP, such as LTD, can supplant previously potentiated synapses (Pavlides et al. 1988; Sejnowski 1990). Thus, LTP would decay because

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of the natural occurrence of LTD in subsets of the potentiated synapses. Similarly, it has been shown that potentiation of one subset of synapses can cause depression of surrounding, nonpotentiated synapses ("heterosynaptic depression"; Lynch et al. 1977). Although these observations can explain the decremental nature of LTP in vivo, they do not necessarily address the hypothesis that LTP underlies long-term (days to years) memory storage; the loss of LTP would degrade the memory regardless of whether the loss was due to inherent decay or it was due to supplantation by LTD. It should be noted that decremental LTP in the hippocampus is fatal only to the hypothesis that LTP is responsible for storage of long-term memories in the hippocampus; it is not necessary for the hypothesis that LTP in the hippocampus serves a temporary role in the acquisition of sensory information, with the memory trace eventually being distributed in other brain locations. With respect to LTP in the hippocampus, this latter hypothesis is consistent with the empirical evidence suggesting that the hippocampus is preferentially involved in the acquisition of specific types of short-term memory. It must be noted nonetheless that nondecremental LTP has not been observed in any brain structure.

2.6. Strengthening through repetition and facilitated reacquisition. Another potential link between LTP and memory is "strengthening through repetition." Although memory induction can certainly be complete within a single trial (Estes 1970; Rock 1956), there are numerous instances in which memory is strengthened by repeated exposure to the learning event. Thus, if LTP is involved in memory formation, it too should be strengthened through repetition. Indeed, synaptic efficacy can be strengthened through repeated exposure to the tetanizing stimulus, provided that the additional tetani are delivered before the potentiation decays back to baseline levels. If the response is allowed to decay to baseline, however, LTP is neither more easily induced nor more persistent than after the initial induction (de Jonge & Racine 1985). Therefore, hippocampal LTP does exhibit aspects of "strengthening through repetition" but does not exhibit "facilitated reacquisition," which is a defining feature of most memory processes (see, e.g., Matzel et al. 1992; Miller et al. 1986; Spear & Riccio 1993).

2.7. Associativity and cooperativity. Two additional features of hippocampal LTP, associativity and cooperativity, are often cited as evidence that LTP is involved in the learning process. The terms "associativity" and "cooperativity" derive from the procedures used in Pavlovian conditioning, in which two stimuli or events presented in a temporally contiguous manner tend to become associated with one another. [This is an oversimplification of the characteristics of Pavlovian learning; for further discussion of the subject, see Rescorla (1988)]. With regard to LTP, "cooperativity" refers to the observation that an intensity threshold must be met for successful induction (Bliss & Gardener-Medwin 1973). This threshold can be reached through intense stimulation of a single afferent fiber or a few afferent fibers or cooperatively through a lower intensity stimulation of many fibers (McNaughton et al. 1978). Similarly, "associativity" refers to the observation that roughly contiguous, low-intensity stimulation of two pathways, or higher intensity stimulation of weak inputs, converging on the same cell, is sufficient for the induction of LTP when stimulation of neither pathway alone is sufficient (Barrionuevo & Brown 1983; Levy & Steward 1979; 1983). Associativity probably represents the same underlying mechanism as cooperativity, but it differs somewhat operationally in that associative interactions can occur across spatially distal regions of a dendrite and may reflect the contiguous pre- and postsynaptic activity implied by Hebb's Rule. Typically, both associativity and cooperativity are explained by the necessity for a sufficient level of postsynaptic activity (McNaughton et al. 1978) and are presumed to reflect the summation of multiple postsynaptic calcium signals. The existence of associativity and cooperativity in LTP is important for several reasons. First, their existence indicates that physiologically relevant levels of stimulation can induce LTP. Second, the phenomena suggest that LTP is unlikely to result from normal activity but, rather, might be reserved for detection of spatially and temporally contiguous events. This latter point will be recognized as analogous to a defining feature of classical conditioning, and thus has been cited as support for the role of LTP in associative learning (e.g., Brown et al. 1990).

Although the associative and cooperative properties of LTP lend support to its relevance to Pavlovian conditioning, aspects of the two phenomena raise questions about this presumed connection. For example, the stimulation of two converging inputs is most effective in inducing LTP when those two inputs are stimulated in a temporally contiguous or near-contiguous (100 msec) manner. In contrast, the optimal ISI (interstimulus interval) between the conditioned stimulus and unconditioned stimuli in classical conditioning varies from several hundred milliseconds in the rabbit eye blink preparation, to several seconds in rabbit conditioned bradycardia, to tens of seconds for many conditioned emotional responses, to hours for conditioned taste aversions (for review, see Mackintosh 1974). Moreover, a constant ISI can produce inhibitory or excitatory learning depending on the interval between successive trials (Kaplan & Hearst 1985), and the systematic relationship between the onset of stimuli is entirely absent in the case of context learning. Consequently, the observation that the induction of LTP is most effective at relatively short ISIs (0–200 msec) should not be taken as evidence for its relevance to Pavlovian conditioning, both because there is no universally optimal ISI and because the interval used to induce associative LTP is shorter than is optimal for any behavioral conditioning procedure of which we are aware. It should be noted, though, that near-simultaneity of stimuli has been suggested to support efficient *learning* in Pavlovian paradigms, whereas the expression of that learning depends on the response system under study (Matzel et al. 1988; Rescorla 1980; 1988). These issues reflect the danger of oversimplifying Pavlovian phenomena in order to force a comparison to a biological system.

A second issue with associativity and cooperativity concerns the neural mechanism that underlies the induction of hippocampal LTP. As was described above, associativity and cooperativity are thought to arise from a sufficient level of postsynaptic activity and, hence, an accumulation of postsynaptic calcium. In essence, the associative feature of LTP is simply the successful expression of what might occur "nonassociatively," that is, with sufficient stimulation of a single afferent fiber. This raises questions regarding its general relevance to Pavlovian conditioning, or even to

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associative learning in general. In summary, the associative and cooperative features of LTP suggest certain similarities to basic associative learning, but a direct link between the associative features of LTP and associative memory has not been made (for further discussion, see Diamond & Rose, 1994).

3. LTP and behavioral indices of memory

To this point, we have reviewed a number of the cellular properties of hippocampal LTP that many consider to be indicative of, or at least compatible with, its role in learning and memory processes. Many of the these correlations were based on preconceptions about what the critical features of memory formation should be, and some were indeed *consistent* with those necessary for memory formation. Others, such as the spread of certain "nonsynaptic" correlates of hippocampal LTP to nonstimulated pathways, are inconsistent with certain preconceptions about memory processes but might provide important clues regarding the role that the induction of LTP in vivo plays in behavior. We shall now review a series of experiments that are often cited as evidence in support of a link between hippocampal LTP and memory storage.

Among the more than 1,000 articles published between 1990 and 1997 that refer specifically to LTP in the title, the vast majority either imply or explicitly state in the abstract or introduction that LTP is a memory storage device. The statements range from speculation that LTP "may underlie learning" to definitive statements that it "underlies learning and memory," "is associated with the formation of memory," and "contributes to memory encoding." It was thus surprising to discover that, among more than 1,000+ articles, fewer than 60 described a behavioral manipulation of memory itself. When the search was extended back to 1974, fewer than 80 among over 1,300+ articles with LTP in the title described any behavioral manipulation relevant to the assessment of memory. Given these statistics, one might assume that it had been demonstrated that LTP was "the memory mechanism" and that further studies were unnecessary. In fact, many articles with a behavioral manipulation provide evidence to the contrary (see *Hippocampus*, 1993, No. 2; Bannerman et al. 1995; Saucier & Cain 1995).

3.1. Pharmacological and genetic manipulations of LTP.

Three lines of evidence supported the premise that hippocampal LTP is involved in acquisition and/or storage of memories. The first involved the pharmacological blockade of LTP induction, followed by learning trials and ultimately a test of memory. In response to a competitive NMDA antagonist that prevents the induction of *some* forms of LTP, rats were impaired in their ability to perform the Morris water maze, a spatial memory task that requires the hippocampus for successful completion (Morris et al. 1986). This experiment and a multitude of similar ones encountered interpretive difficulties, owing to the effects of NMDA receptor antagonists on sensory/motor performance; most of these drugs are chemically related to the street drug PCP, "angel dust," which can cause profound perceptual distortion, even hallucinations (Julien 1992). Concerns about performance were expressed in a series of comments and rebuttals published in the journal *Psychobiology* (Keith & Rudy 1990), and we will not thoroughly review them here. However, the debates were based on experiments that remain the most often cited evidence for a link between hippocampal LTP and behavioral learning, so a brief overview is required.

In the critique by Keith and Rudy (1990), it was noted that, in tasks requiring the hippocampal formation for acquisition (e.g., the water maze and olfactory discrimination learning), NMDA receptor antagonists in concentrations that do not induce obvious behavioral impairments only mildly disrupt acquisition, and only under a narrow range of conditions. Moreover, drug-treated animals ultimately attain levels of performance equivalent to those of untreated control animals. Keith and Rudy interpreted these results as evidence that activation of the NMDA receptor (and hence NMDA-dependent LTP) is not necessary and certainly not sufficient for learning these tasks. The authors suggested further that the mild "learning" deficit induced by the NMDA antagonist reflects no more than a subtle sensory or motor impairment and/or an anxiolytic effect (Bennet & Amrich 1986; Clineschmidt et al. 1982). Staubli (1990) and Lynch and Staubli (1990) interpret these results somewhat differently, suggesting that under normal conditions NMDA receptor-dependent LTP is the primary mechanism underlying learning but that, in its absence, a secondary and slower learning mechanism is used. Hence, the animals learn, but at a reduced rate. Because biological systems are often redundant, this latter interpretation is certainly plausible, even though it is not an obvious a priori prediction. Moreover, olfactory discrimination learning is possible in neonatal and prenatal rats (Johanson & Hall 1979; Smotherman 1982; Smotherman & Robinson 1991) prior to the expression of NMDA receptors (Baudry et al. 1981; Duffy & Teyler 1978; Harris & Teyler 1984; Wilson 1984). Although it is not known whether these forms of learning require a hippocampus during early development, the observations suggest that NMDA-dependent forms of plasticity are not the "primary" mechanism of memory during that time, yet learning does occur.

In response to concerns about performance deficits resulting from peripheral injection of NMDA antagonists, Morris et al. (1986) injected the antagonist directly into the ventricle surrounding the hippocampus and found that rats were still impaired in their acquisition of the maze. On the first three-trial block (before any substantial learning would normally occur), animals treated with the antagonist exhibited an increase in escape latency relative to that of the untreated group or a group treated with an inactive isomer of the drug. These results suggested that the antagonist did have an effect on processes other than memory formation itself. Indeed, intraventricular administration reduces, but does not necessarily eliminate, the possibility that sensory, motor, or motivational processes have been disrupted. It has been reported that the ventricular administration of the NMDA receptor antagonist AP5 evokes subtle anxiolytic and analgesic effects, impairs motor control, and induces muscle flaccidity (Dale 1989; Dale & Roberts 1985; Turski et al. 1985). One study reported that, after administration of the highest dose of antagonist, during the first 9 trials rats "occasionally fell off the escape platform" (Morris et al. 1986). Recent work by Cain et al. (1996) and Caramanos and Shapiro (1994) provides more evidence of behavioral abnormalities following intraventricular administration of

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NMDA receptor antagonists. Using concentrations comparable to those reported by Morris et al. (1991) and Davis et al. (1992), Cain et al. report that the rats display behavioral hyperactivity and ataxia, a decrease in the rate of swimming, thigmotaxis, and a variety of indirect swim patterns. These behavioral disturbances accounted for over 70% of the variance in acquisition of the water maze task.

To reduce the influence of motor deficits following the administration of NMDA receptor antagonists, Morris trained his rats to use the escape platform in a water maze prior to actual spatial navigation training in the maze (e.g., Davis et al. 1992; Morris et al. 1991). With this pretraining, the antagonist impaired spatial learning but did not elicit an obvious motor impairment and did not impair performance on the first trial. In addition, the antagonist did not affect performance on the visual version of the task, in which a platform is randomly located in each trial and the rat must find it and escape. Importantly, in companion histological and electrophysiological studies, Morris et al. (1989) demonstrated that the radiolabeled NMDA antagonists did not diffuse out of the hippocampus and that only concentrations of the antagonist that impaired LTP impaired spatial learning. This comprehensive series of experiments led Morris to conclude that "these data provide strong support for the now widely accepted view that the neural mechanisms underlying NMDA-dependent hippocampal LTP play a role in spatial and perhaps other kinds of learning" (Morris et al. 1991; see also Davis et al. 1992).

Several comments should be made regarding this conclusion. First, the antagonist only "slows the rate of learning rather than blocking learning completely," so the findings do not support the idea that NMDA receptor-dependent LTP is a singular neural mechanism for the establishment of a neural memory trace. Second, it appears that the procedures used by Morris et al. (1991) and Davis et al. (1992) might not have been adequate to control for the antagonist's effects on motor performance. Very recently, it was reported by Saucier and Cain (1995) and Morris and colleagues (Bannerman et al. 1995) that prior training with a spatial or nonspatial version of the water maze attenuated deficits in subsequent maze learning conducted under the influence of NMDA receptor antagonists. Two different interpretations of these results were offered, one suggesting that NMDA receptor activation (and by association, LTP) is still involved in learning the spatial maze, but not in the learning of spatial location per se (i.e., nonspatial aspects of the task). The other interpretation, preferred by Saucier and Cain, is that the prior training on a maze precludes the sensory and motor deficits typically encountered during the initial acquisition of spatial learning, so NMDA receptor activation (and LTP) is not necessary for hippocampal learning. In summary, NMDA receptor antagonists can impair performance (and perhaps procedural memory formation) in spatial learning tasks, but it is not clear that the effect is specific to learning or to a disruption of hippocampal LTP.

By way of contrast with the impaired performance observed in the water maze, others have reported that NMDA antagonists can actually facilitate learning. Mondadori and colleagues (e.g., 1989) have reported an *enhancement* in passive avoidance learning following peripheral administration of NMDA antagonists that prevent LTP. Consistently with the discussion of the antagonist and spatial learning, it could be argued that the enhancement is due to effects on motor performance. For example, the antagonist could impair performance on the spatial navigation task and facilitate performance in the passive avoidance task simply because the first task requires active and coordinated movement, whereas the second task requires passivity. Mondadori et al. (1989) performed a range of control procedures to rule out such an interpretation. For example, rats that received the drug did not exhibit an increase in their latency to initiate normal exploratory behavior. Consequently, we are left to conclude either that the results of these various studies can be explained by motor impairments or that they directly reflect the effect of NMDA antagonists on memory formation. If the latter is true, then NMDA antagonists can either retard or facilitate, or have no effect on, learning.

Adding to the complexity of this issue, it is also the case that NMDA antagonists have effects on tasks that have no obvious dependence on the hippocampus. Robinson (1993) and Servatius and Shors (1996) reported that NMDA antagonists retard classical conditioning of the eye blink response, a task that is not dependent on an intact hippocampus. Thus, one can obtain decrements in learning with NMDA antagonists even when there is no reason, a priori, to believe that hippocampal LTP is essential to the process. It is interesting to note that the noncompetitive NMDA antagonist MK-801 did not prevent the "LTP-like" increases in synaptic efficacy in the hippocampus that parallel this form of learning (Weisz et al. 1984), further supporting our contention that all forms of synaptic potentiation should not be classified as LTP.

At the behavioral level, attempts to clarify the biological basis of learning through pharmacological manipulation are certain to be plagued by issues of "nonspecific" effects on performance. At the cellular level, these problems are no less intractable. Consider, for example, studies aimed at establishing a connection between protein kinases in hippocampal LTP and learning (Malenka et al. 1989; Malinow et al. 1989; O'Dell et al. 1991b; Zhuo et al. 1994). Two factors (somewhat related) have made it especially difficult to deduce the contribution of these enzymes to LTP. First, kinase inhibitors are relatively nonspecific, owing to their effects on enzymes or cascades other than those that were intended. Second, the kinases that are targeted are often involved in a multitude of cellular processes which are unrelated to plasticity. The first factor has been, at least in part, addressed with the relatively new technique of gene deletion, in which a gene for a specific protein is ablated in the embryonic mouse. This strategy has been used to assess the role of CaM kinase (Silva et al. 1992a; 1992b) and a subtype of tyrosine kinase (O'Dell et al. 1992) in hippocampal LTP and learning. Both mutations resulted in partial impairments of LTP and corresponding impairments of spatial performance in the Morris water maze. Although these techniques may increase specificity for a targeted protein, interpretation is complicated by the fact that the animal has gone through development without the gene, and many of the targeted proteins are critical for normal cellular and behavioral development. For example, deletion of the *fyn* gene used in one gene knockout study (Grant et al. 1992) was later reported to retard the development of myelination in the nervous system (Umemori et al. 1994) and to disrupt normal suckling in neonates (sometimes

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resulting in death), as well as to cause gross abnormalities in the hippocampal formation (Yagi et al. 1993). In addition, the location of the deficit caused by the knockout is not specific to a particular brain region, and the knockouts may cause gross anatomic abnormalities. For example, the *fyn* gene knockout results in an irregular and undersized olfactory bulb (Yagi et al. 1993). There are also numerous dissociations between the effects of the gene lesions and learning. For example, deletion of the *pcd* gene caused degeneration of Purkinje cells in the cerebellum but had no apparent effect on the gross morphology of the hippocampus. Interestingly, the *pcd* deletion impaired performance in the Morris water maze (Goodlett et al. 1992).

Gene mutations can introduce gross behavioral abnormalities that, as with NMDA antagonists, can have profound effects on performance irrespective of learning. In one study (Silva et al. 1992a), mice lacking the gene for CaM kinase were slow to learn the location of the hidden platform in a Morris water maze, suggesting a role for the kinase in spatial learning. However, the deficient animals were slow to swim to the platform on the first training trial, before any learning could have occurred. The poor performance was attributed to "fatigue" in the mutant mice that was suggested to result from abnormal "jumpiness," a descriptor that has now found its way into several of the reports concerned with the learning capacity of mutant mice (Sakimura et al. 1995). The *fyn* knockout mutants (Grant et al. 1992) displayed a similar performance deficit on the first trial, again prior to the point at which learning could have occurred. Further, the mutants learned at a *rate* similar to that of wild-type controls and, by the sixth trial, the two groups were performing at identical levels. In fact, because some mutant mice reached a preimposed 60-second cutoff on the first trial, the rate of learning for the group might have been underestimated; it might have *exceeded* that of the wild-type controls. A more detailed account of the interpretative difficulties in these particular studies has been presented by Deutsch (1993). Given the evidence published to date, we are inclined to accept his conclusion that there is "no evidence that the mutant mice in [these] studies suffered from a specific impairment of memory."

3.2. Deficient LTP is not necessarily accompanied by deficient memory. Despite the interpretive difficulties in the studies discussed above, one might still consider the overall data set as at least consistent with the supposition that hippocampal LTP is involved in the learning process. However, the convergence of evidence on a single viable hypothesis requires not only that a given data set be consistent with that hypothesis but also that potentially disconfirming experiments be conducted (studies that could, in principle, either prove or disprove *alternative* hypotheses). For example, one might ask whether there are chemicals known to either block or enhance LTP that do not affect learning. Among the dozens of compounds shown to retard the induction of LTP in the hippocampus, only a few directly influence learning, and many others have no effect on learning. For example, saccharin is reported to block the induction of LTP in area CA1 of the hippocampus (Morishita et al. 1992), but chronic and acute administration induces no obvious memory deficits, and in some cases *enhances* retention (Stefurak & van der Kooy 1992). Another study suggesting a dissociation between LTP and learning involved the gene deletion technique. Abeliovich et al. (1993a) generated mice deficient in the gene for a subtype of the enzyme PKC (protein kinase C). At the synaptic level, the mice displayed normal synaptic transmission, but most failed to develop hippocampal LTP. At the behavioral level, despite mild ataxia, the mice exhibited normal learning in the Morris water maze. That is, in the near absence of measurable LTP, learning and memory were not affected. In a subsequent article, some of the same authors (Abeliovich et al. 1993b) presented evidence that LTP was not impaired when the synapses were first depressed by a low-frequency stimulus train. This set of data did not measure behavior, so the evidence that deficient LTP was accompanied by normal learning was not addressed.

As with the studies using NMDA antagonists, either we can assume that perceptual and motor deficits in response to genetic manipulations were not adequately controlled and that they account for the observed effects on learning, or we can be satisfied that these sometimes obvious, and at other times subtle, deficits were not responsible for the learning deficits and that learning itself was affected. Once again, if we accept the latter position, then it is clear that blocking hippocampal LTP can impair, enhance, or have no effect on learning.

3.3. Saturation of the capacity for plasticity. Another line of evidence linking hippocampal LTP to behavioral learning was correlational and followed logically from the NMDA blockade studies. The rationale for these studies was based on the premise that, if synaptic potentiation was necessary for the formation of new memories, then artificially inducing hippocampal LTP at as many synapses as possible should affect subsequent acquisition of new memories. By 1989, this rationale had been systematically applied to two different learning tasks, classical conditioning and spatial maze learning. The effects of prior LTP induction were initially reported to be bidirectional and thus were reminiscent of the NMDA antagonist studies just discussed. In the first study, Berger (1984) reported that the repeated induction of unilateral LTP in the dentate gyrus over a 5-day period facilitated acquisition of a classically conditioned nictitating membrane response 24 hours later. Based on these results, Berger concluded that "the cellular mechanisms underlying LTP may be the basis for learning-induced changes in hippocampal unit activity during nictitating membrane conditioning." Insofar as the hippocampus is not necessary for normal acquisition of the nictitating membrane response (Berger & Orr 1983; McCormick et al. 1982; Thompson 1990), it is clear that, if LTP is affecting learning at all, it is doing so indirectly and is not the sole or even the primary mechanism underlying the storage of the learned response. These results are consistent with the finding that NMDA antagonists that block LTP can impair nonhippocampal-dependent learning (Robinson 1993; Shors & Servatius 1995). They are also consistent with the idea, explored below (sect. 4), that LTP is not a memory storage mechanism, but one that can modify effective acquisition of a learned response.

Instead of a *facilitation* in learning, however, one might have predicted that the induction of hippocampal LTP would saturate those synapses that are normally recruited during learning and thus would *impair* acquisition. This prediction was initially tested by McNaughton et al. (1986)

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and by Castro et al. (1989), using an experimental design conceptually similar to that used by Berger (1984). Animals were chronically implanted bilaterally with electrodes in the perforant pathway and the dentate gyrus. The perforant pathway was repeatedly tetanized over a 34-day period, inducing persistent LTP in the dentate gyrus. The rats were then trained on the circular platform task, which requires the animal to use spatial cues to find an escape hole in a circular board (McNaughton et al. 1986). They were also trained in the Morris water maze (Castro et al. 1989), the task used to demonstrate that the pharmacological blockade of hippocampal LTP blocks learning. In both tasks, and in contrast to classical conditioning (Berger 1984), these animals were impaired in their ability to learn the spatial task. Despite the inconsistency, these results were interpreted as indicative of a critical role for hippocampal LTP in memory formation. (It should be noted that LTP induction was more widespread [bilateral as opposed to unilateral] and extensive [34 days as opposed to 5 days] in the study by Castro et al. than in that of Berger.)

These apparently contradictory results have been interpreted to reflect the two tasks' differential dependence on the hippocampus (see, e.g., Shors & Dryver 1992). For example, if hippocampal LTP is necessary for learning, as in the spatial task, then inducing it would impair learning; if the hippocampus is not necessary for the task, as in classical conditioning, then learning could be enhanced via some excitatory stimulation of the hippocampus. This idea had some plausibility; memory systems that are dependent on different neuroanatomical substrates can compete for behavioral control (see, e.g., McDonald & White 1993; 1995), suggesting the possibility that the induction of LTP might impair spatial learning (hippocampal dependent) while facilitating eye blink conditioning (cerebellar dependent). However, the same logic could be used to suggest that hippocampal lesions (a more invasive analog of LTP-induced saturation) would also facilitate eye blink conditioning, an effect that has not been observed (see, e.g., Solomon & Moore 1975). In any case, an explanation based on certain types of learning being dependent on different brain structures has some appeal, even though it is decidedly post hoc, and again raises the question of whether any experimental result could disprove the hypothesis that LTP is a memory mechanism.

Any concerns about inconsistencies between studies may have been unwarranted. Since the initial report of Castro et al. (1989), workers in a number of laboratories, including the one in which the observation of Castro et al. originated, have reported that tetanization of the perforant pathway *does not* impair spatial learning (Robinson 1992; Sutherland et al. 1993; see Bliss & Richter-Levin, 1993, for review). In retrospect, it is perhaps not surprising that one cannot easily "saturate" the capacity for potentiation in the hippocampus; otherwise, one would have to question its adaptability. Taken to the extreme, this would suggest an easily attainable upper limit on memory capacity, something that has not been demonstrated experimentally (see Spear, 1978, for discussion). Having acknowledged that saturation may be functionally difficult (Korol et al. 1993), Barnes et al. (1994) used stimulation parameters designed to saturate more completely the capacity for potentiation in the dentate gyrus. With these conditions, there was no impairment of spatial learning in either the water maze or the circular platform task, although there was a "deficit" on the fourth of five trial blocks during reversal training on the circular platform. However, even regarding a minor impairment, there was no correlation between the magnitude of induced LTP and the behavioral deficit in that trial. If the potential for further LTP was indeed occluded, as suggested, these data provide strong evidence that hippocampal LTP is not necessary for spatial learning.

3.4. Correlations between modulators of LTP and behavior. Correlational evidence can be powerful when an array of correlations lends support to a given hypothesis, rules out alternative hypotheses, and converges on a single viable conclusion (see Garner et al. 1956). In the context of hippocampal LTP and memory formation, one could reasonably ask about the correlations between known modulators of LTP and the capacity to store new memories. For example, it is well established that chronic lead or alcohol consumption is detrimental to memory storage, and both impair the induction of LTP (see, e.g., Altmann et al. 1993; Morrisett & Swartzwelder 1993). To speculate that these compounds retard learning as a result of their effect on hippocampal LTP is misleading, given that there are other established mechanisms by which these substances could affect memory storage. For instance, alcohol, which after consumption has a wide distribution in brain tissue (as well as in the periphery), causes membrane fluidization, depresses both inhibitory and excitatory synaptic activity, and ultimately depresses activity in the cerebral cortex (for review, see Julien 1992). All of these effects disrupt normal CNS function and thus could disrupt the processing of information necessary for memory formation. Specifically, depression of activity in the cerebral cortex retards memory retrieval and storage (see, e.g., Horel 1993; Martin-Elkins et al. 1989), and thus a disruption of LTP by alcohol could be superfluous relative to a more gross deficit in cerebral activity. Until it is demonstrated that the alcohol-induced disruption of LTP impedes memory formation independent of alcohol's known effects on other processes, there is no reason to conclude that alcohol affects learning through its disruption of LTP. Correlations between manipulations that affect both hippocampal LTP and learning (e.g., anxiolytics, del Cerro et al. 1992; stress, Shors et al. 1990; antidepressants, Watanabe et al. 1993) have begun to pervade the literature and might erroneously reinforce the presumed link between hippocampal LTP and learning.

3.5. Natural stimulation patterns that induce LTP. In an effort to approximate endogenous conditions more closely, many researchers study the relationship between hippocampal LTP and learning under more "natural" conditions, such as olfactory discrimination. Olfaction is a primary sensory modality in the rat, and olfactory information is processed, in part, by the hippocampal formation. Sensory input is relayed from the olfactory bulb to the piriform cortex and separately to the hippocampus via the entorhinal cortex. Lynch and his colleagues have found substantial correlations between hippocampal LTP in this system and olfactory learning. For example, when tetanic stimulation of the lateral olfactory tract was used as a discriminative cue, evoked responses in the piriform cortex were potentiated in the animals that learned the discrimination (Roman et al. 1987). In addition, the unit cellular activity recorded in the piriform cortex during learning was similar in pattern to the tetanic stimulation used for discrimination (McCollum et al. 1991). Animals exposed to the stimulation in a

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behaviorally irrelevant manner did not learn and did not exhibit LTP. These findings appear to be unique to the olfactory system; such stimulation would typically induce LTP in the hippocampus, regardless of whether the animals learned.

Others have established connections between LTP and learning by using tetanic stimulation as a sensory cue. In one study, stimulation of the perforant pathway (sufficient to induce LTP) was used as a CS to predict the occurrence of a footshock US (LaRoche et al. 1989). Learning was measured as a suppression of lever pressing for food during the fear-evoking CS. Rats that learned the task exhibited a higher level of LTP after training than those who did not learn as well, leading to the interpretation that learning is accompanied by an increase in LTP (or at least that animals that learn most rapidly exhibit an increased capacity for LTP). This facilitation of learning was specific to LTP; it did not occur (1) when LTP was blocked by administration of an NMDA antagonist, (2) when the stimulation was below the threshold for LTP induction, or (3) when the induction of LTP was inhibited by concomitant activation of commissural inputs. Using a similar procedure, Bergis et al. (1990) reported that the decay rate of LTP correlated with the amount of forgetting and that associative training resulted in an increased capacity for LTP 48 hours later.

Although these results suggest a link between hippocampal LTP and learning, they are perhaps not surprising. There is a vast literature on brain stimulation and its use as a substitute for sensory stimuli. In particular, it has been repeatedly demonstrated that high-frequency electrical stimulation can be used as a discernible "cue" for the establishment of Pavlovian and other types of conditioning. The stimulation patterns typically used in these studies are very similar to those patterns initially described by Bliss and Lomo to induce LTP: 100-Hz stimulation for 1 second. The effectiveness of high-frequency stimulation is not limited to its use as a CS. It can also be used as a US; Vandercar et al. (1970) reported that 100-Hz, 1-second stimulation delivered to the septum and the hypothalamus was an effective US in heart rate conditioning and that the CR was indistinguishable from that obtained with a US of peripheral shock (see also Salafia et al. 1979; Prokasy et al. 1983). It is difficult to evaluate the many studies using brain stimulation and the potential contribution of LTP to any effects on learning. This is true, in part, because most studies using brain stimulation do not record electrical activity (much less LTP). However, given the numerous studies, brain sites, and experimental paradigms, it seems likely that there are many instances in which brain stimulation mediates behavior (Salafia et al. 1977) without necessarily inducing hippocampal LTP. In summary, one explanation for the enhanced learning observed after the induction of LTP is that brain stimulation serves as an effective and salient sensory cue.

One of the more convincing links between learning and hippocampal LTP involves the use of theta-frequency stimulation. As was mentioned above, when LTP was first described, the inducing stimulus consisted of a 100-Hz train of stimulation for 1 second (100 pulses in total). The relevance of this type of stimulation to learning was questioned, because this amount or frequency of activity rarely occurs in the brain. In the 1980s, a connection between a known brain rhythm and LTP was established by Larson et al. (1986) and Larson and Lynch (1988; 1989) and in a related manner by Buzsaki et al. (1987), Rose and Dunwiddie (1986), and Greenstein et al. (1988). Using a paradigm patterned after the endogenous "theta" rhythm, one could effectively induce LTP extracellularly with short 100-Hz bursts delivered at five to eight cycles per second (about 50 pulses total). These rhythms are naturally prominent in the hippocampus and fall into two types (Bland 1986; Bland et al. 1984; Kramis et al. 1975; Sainsbury et al. 1987). The first is dependent on motor activity and falls within a range of 8–11.9 Hz. The second type is not dependent on movement and consists of a slightly lower frequency (Kramis et al. 1975). Furthermore, the second type is dependent on the release of acetylcholine into the hippocampus from the septum (Bland et al. 1984).

Theta rhythms were once considered to be indicative of the learning process, but the consensus view today is that the first type of theta activity occurs in close correlation with concurrent voluntary motor activity, such as head turning, walking, running, forelimb movements, or changes in posture (Fox et al. 1986; Vanderwolf 1969; see Vanderwolf, 1988, and Vanderwolf & Cain, 1994, for reviews). The second type can be induced without movement during exposure to arousing and stressful stimuli, such as predators (Sainsbury et al. 1987), tail pinch (Stewart & Vanderwolf 1987), water deprivation (Berry & Swain 1989; Maren et al. 1994), and brief tail shocks (Shors et al., in press). Neither type appears to be directly involved in memory formation.

With regard to how these rhythms become incorporated into the animals' perception of its environment, rats apparently sniff at a frequency comparable to theta rhythm, and the sniffs are time locked to hippocampal theta activity (Maorides 1975). Even though theta activity is not observed during sniffing episodes when the animal is motionless (indicating that the rhythm is related to head movement; Vanderwolf 1988), some have suggested that animals process information at a rhythm very similar to the most effective stimulus for inducing LTP. This correlation provides some behavioral relevance to hippocampal LTP and its induction parameters. Consistent with this view, theta activity in CA1 pyramidal cells occurs during a rat's sampling of a discriminative stimulus in an odor task (Otto et al. 1991). These general connections between theta activity and the induction of hippocampal LTP reinforce the presumed relevance of hippocampal LTP to behavior. Nonetheless, since theta activity occurs in many brain regions and diffusely across synapses in those regions, and is similarly associated with a broad range of behaviors, it is unclear how it could contribute to the specificity of synaptic changes presumed to underlie memory formation or storage.

In addition to concerns about nonspecificity, there are also dissociations between theta activity and learning. Black (1975) trained dogs to press a lever in the presence of one stimulus, but to refrain from responding in the presence of a second stimulus, to avoid the onset of a shock. The animals successfully learned both responses, but theta activity was observed only during the active response. Moreover, dogs can be trained to elicit theta activity to terminate one auditory stimulus that signals an impending shock and to refrain from displaying theta activity in response to a second stimulus that signals shock (Black et al. 1970). These experiments suggest that theta activity is not a prerequisite for the establishment of learning but may

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correlate highly with the expression of some motor responses. In summary, the connection between theta activity and LTP is promising with regard to LTP's functional relevance but does not distinguish between an effect on motor performance and one on memory storage.

Finally, we return to the observation that potentiation of an evoked response in the dentate gyrus accompanied acquisition of a classically conditioned eye blink response (Weisz et al. 1984). We suggested above that there was no evidence that this type of potentiation is related to the phenomenon of LTP (or at least LTP induced by high-frequency stimulation of the perforant pathway). Others apparently share this concern, and refer to these forms of potentiation as "postconditioning potentiation" (Weisz 1984) and "behavioral LTP" (Hargreaves et al. 1990). However, given the proposed link between theta activity and hippocampal LTP induction just discussed, these examples of behavioral LTP deserve further attention. At issue is whether the increase in the evoked response following learning is a form of LTP. While no direct evidence is forthcoming, several pieces of evidence suggest that it is not. As mentioned, Robinson (1993) reported that NMDA antagonists that block LTP do not block the increase in the evoked response that accompanied learning. In addition, Krug et al. (1990) compared hippocampal LTP induced by high-frequency stimulation to the potentiation induced by avoidance learning. The potentiation induced by tetanic stimulation caused a decrease in the spike latency, whereas behavioral learning resulted in an increase in spike latency. Analogously, Hargreaves et al. (1990) found no evidence of potentiation in the dentate gyrus despite learning in a radial arm maze or a one-way avoidance task. Moreover, hippocampal LTP could be induced using traditional tetanization techniques following learning in each of these tasks. The results of both Krug et al. and Hargreaves et al. strongly suggest that the learning-induced increase in the evoked response and hippocampal LTP need not share common mechanisms and that LTP is not the mechanism underlying learning-induced potentiation.

3.6. Summary of behavioral evidence. Based on a review of the current behavioral literature, a number of general conclusions can be drawn. In summary, drugs or genetic manipulations that block hippocampal LTP impair performance in some tasks and facilitate performance in other tasks. The interpretation of these effects is confounded by the variability in brain structures necessary for successful completion of the task, the potential effects of the manipulations on sensory and motor performance, and the neuroanatomical deformities induced by the genetic manipulation. In addition, whereas a number of studies have found evidence that "LTP-like" increases in synaptic efficacy occur in the hippocampus during learning of tasks as diverse as spatial learning, associative eye blink conditioning, conditioned suppression of activity, and olfactory discriminations, other studies show no evidence of potentiation despite robust learning. Still others show evidence of a form of potentiation qualitatively different from that following the induction of LTP, and artificial induction of LTP (i.e., saturation) has no clear effect on subsequent learning. Finally, although it is intriguing that tetanic stimulation mimicking an endogenous brain rhythm can induce hippocampal LTP, the rhythm is more generally associated with voluntary motor activity and arousal, rather than memory storage per se, and is clearly not necessary for memory induction. Based on the data reviewed here, it does not appear that the induction of LTP is a necessary or sufficient condition for the storage of new memories.

4. A new and nonspecific hypothesis

In questioning the role of LTP in learning, it is often said that LTP should be considered a memory mechanism until a mechanism is elucidated that is more consistent with our understanding of memory processes. Other candidate forms of plasticity have been described that, though differing in mechanistic detail, maintain a functional similarly; that is, each would result in an increase in synaptic efficacy (see Hawkins et al. 1993). Whether these mechanisms should be considered unique categories of plasticity or simply subcategories under the larger classification of LTP is debatable (see sect. 2.2). As was discussed above, we must be careful about the way in which we apply the term "LTP" to increases in synaptic efficacy. Most would agree, however, that memory formation involves the modification of synaptic transmission. To the extent that "LTP" is used to refer only to an enhancement of synaptic efficacy, *some* form of LTP somewhere in the nervous system is likely to contribute to memory formation. In this regard, we are unable to offer a "better" hypothesis. We have, however, generated several alternative hypotheses for how a mechanism like LTP could be used by the brain to accomplish behavioral objectives other than the storage of memory.

First, we must consider the most extreme alternative; that is, LTP serves no functional role and is an artificially induced form of synaptic plasticity with no endogenous counterpart in the human brain. Although it is certainly possible, this alternative seems improbable owing to the fact that LTP-like increases in synaptic efficacy do occur naturally within the brain, as do patterns of activity similar to those used to induce LTP. Instead, we propose here an interpretation of the role of LTP that we believe is consistent with a majority of the data reviewed so far. Specifically, we propose that LTP is the neural equivalent of an arousal or attention device and that it acts by increasing the gain of neural representations of environmental stimuli. If one assumes that an environmental cue is represented in the brain as a synaptic response or pattern of responses, then the induction of an LTP-like phenomenon would magnify that response(s), allowing for more efficacious detection of stimuli in general. Such an increase in gain (and consequent perceptual awareness) could then modify learning by increasing the likelihood that contingent relationships between stimuli are recognized. Thus, we are proposing that LTP is not a mechanism for memory storage and retrieval but that it does play an *incidental* role in memory formation.

As in the discussion of LTP and memory, one must consider the functional relevance of such an arousal mechanism and whether it is consistent with what we know about how animals respond and survive in their natural environment. A time when such a mechanism would be particularly useful is during and after potentially life-threatening events, for example, encounters with predators. Immediately after an encounter with a predator, the likelihood of another encounter is relatively high (the predator is in the vicinity and knows the prey's location). During this period of time, vigilance (alert watchfulness) should likewise be

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high in order to process environmental information in a timely and efficient manner. Presumably, a mechanism that is rapidly induced and heightens attentional processes could be critical for survival and would be highly selected for. There are a number of indications that the process we commonly describe as "attention" is accompanied by a neural phenomenon that could either induce LTP or enhance the degree of potentiation. For instance, one of the few times when theta activity is observed during immobility is upon presentation of novel sensory stimuli (Kramis et al. 1975), such as a predator (cat or ferret, Sainsbury et al. 1987) or an acute and uncontrollable stressor (Shors et al. 1997). We have thus postulated that exposure to an aversive and frightening event enhances endogenous theta activity and rapidly induces an LTP-like phenomenon, which then increases attention to environmental stimuli. Once the neural representation of the relevant stimuli is potentiated, responses and/or learning *may* be facilitated, but, again, any facilitation is only incidental to the increase in stimulus processing. Depending on the aversiveness and potential threat of the experience, the potentiation and consequent attention to the environmental cues are maintained from hours to days, and this represents a typical time course for the decay of LTP. When the chance of another attack or aversive event is once again low, synaptic efficacy returns to baseline levels, in preparation for subsequent events and perhaps to conserve resources.

Before describing our hypothesis in more detail, we should define our use of the terms "attention," "arousal," and "vigilance." First, it should be recalled that attention is usually treated as a system that is external to and independent of memory but one that can strongly influence the memory induction process (Norman & Shallice 1986; Posner & Petersen 1990). As a process, attention is divisible into several components (Posner & Pedersen 1990), a primary one being analogous to *arousal.* Arousal is an overall receptivity to stimuli and is considered the most general and nonspecific form of attention. It prepares the organism to deal with sensory information from multiple modalities and locations. Typically, however, the capacity to process multiple events simultaneously is limited. Thus, we also need a mechanism that allows us to shift attention as a function of what is novel and significant. This process is often referred to as *selective attention,* which focuses resources on the most critical information for further processing. Such selection can be based on general stimulus properties, such as its familiarity, or particular properties, such as its modality, intensity, or spatial location. When selective attention is maintained over time (hours to days), this constitutes a state of alert watchfulness, or *vigilance.* Here we hypothesize that exposure to novel and/or fear-provoking events induces a form of plasticity similar in mechanism and function to LTP. Such a mechanism could potentially strengthen the neural representation of sensory stimuli, effectively increasing the attention devoted to them (i.e., induction of a state of arousal). Once the relevant stimuli are identified and selected (selective attention), a more sustained state of vigilance may develop, allowing attention to be maintained for an extended period of time.

At least since the empirical demonstrations of Pavlov, it has been known that increasing the intensity of a cue will enhance learning when the cue is relevant. What we are proposing here is that events that arouse an animal's attention do so by inducing a potentiation of neuronal responses, which has the functional effect of increasing the intensity of impinging stimuli. Accordingly, manipulations that increase arousal or attention should incidentally facilitate learning when it is dependent on the processing of particular environmental cues. Indeed, Spitzer et al. (1988) reported that increased attention enhances a monkey's neuronal responses to the discriminated stimulus and enhances the monkey's discriminative ability. Also, in response to an aversive (and presumably arousing) experience of inescapable tail shocks, rats become sensitized to discrete sensory cues and independently learn an associative eye blink response at a facilitated rate (Servatius & Shors 1994; Shors et al. 1992). As with LTP, the effects of the arousing experience on learning can be long-lasting, sometimes persisting for 48 hours after the event has terminated.

LTP has a number of properties considered desirable in a memory storage device, and we have reviewed a number of them. For instance, a memory mechanism should reflect properties central to the formation and storage of memories, that is, should be rapidly induced, long-lasting, and inducible through natural stimulation patterns. If LTP is not a memory storage mechanism, but rather an attentional device, then its properties should be likewise consistent with those of attention. Therefore, we will now review the various characteristics of LTP that are (or are not) consistent with its proposed role as an attention device in the mammalian brain.

4.1. Long-lasting but decremental and facilitated reacquisition. The temporal characteristics of LTP appear to be more consistent with the typical time course of fluctuations in attention than that of memory storage per se. In terms of induction, both attention and memory must be rapidly induced. However, in terms of maintenance, LTP decays more rapidly than does memory, a relatively stable process. The time course of LTP does coincide with that of an attentional process, which should persist from hours to days but eventually return to baseline.

It was noted above that, unlike the case with memories, LTP does not exhibit facilitated reacquisition; following decay, a second induction of LTP is not more easily accomplished than the initial induction. The presence of facilitated acquisition, however, is not a necessary component for the increase in attention or vigilance that occurs in response to an arousing event. To be most effective, it should activate and subsequently inactivate. Facilitated reactivation would serve no obvious functional value in an attentional device.

4.2. Deficient LTP is not necessarily accompanied by deficient memory. In every instance of which we are aware, pharmacological, genetic, and neurophysiological manipulations that eliminate the capacity for LTP induction affect only the *rate* at which some tasks are learned and do not block learning entirely. Such results, though inconsistent with LTP's role as a memory storage device, are consistent with its role in attentional processes associated with effective memory formation. If indeed LTP serves to enhance the effective processing of sensory stimuli, one would expect that the administration of NMDA antagonists that prevent LTP would cause a greater learning deficit when the cues are of low salience. Indeed, Staubli et al. (1989)

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reported that NMDA antagonists impaired olfactory learning only when the olfactory cues were delivered at low intensities and did not impair learning when more intense stimuli were used. Also, with the Morris water maze, rats injected with the antagonist are not impaired (or are minimally impaired) in their ability to find the platform either when they can visualize the platform or when they have previously learned the procedures of the task (Bannerman et al. 1995; Saucier & Cain 1995). Thus, it appears that the more subtle aspects of sensory processing are impaired by blocking LTP, not the ability to form new memories. (It should be noted that this effect is not universal among tasks: in eye blink conditioning, NMDA antagonists impaired learning whether the stimuli were delivered at a normal or a high intensity; Servatius & Shors 1996).

4.3. Dependence on NMDA receptor activation. If one of the factors that can induce LTP is exposure to an aversive and arousing experience, then the persistent behavioral consequences should be prevented by blocking LTP induction during the experience. In a procedural conditioning task, injection of an NMDA antagonist just prior to exposure to an aversive and arousing experience prevented the sensitization to explicit sensory cues and the facilitated learning that normally occurs 24 hours later. However, the antagonist had no effect on normal learning (Shors & Servatius 1995). (As was discussed above, a similar antagonist with a longer half-life and delivered at a higher dose does impair learning; Servatius & Shors 1996). In another task that requires a high degree of vigilance and attention for its completion, differential reinforcement of a low response rate (DRL), performance was severely impaired by NMDA receptor antagonists (Tonkiss et al. 1988). Importantly, the decrease in DRL performance occurred even after the task was well learned, mitigating the possibility that the NMDA antagonist was interfering with memory storage. These results distinguish between LTP as a mechanism underlying the induction of the neural memory trace and as a modifier of another, distinct process that may accompany and influence memory formation. Consequently, we would suggest that the induction of LTP prior to or during early training might be pivotal in determining how quickly and to what degree a particular event is stored in memory.

4.4. Correlations between modulators of hippocampal LTP and behavior. If LTP is a neural mechanism of arousal or attention rather than of memory formation, manipulations intended to increase arousal and vigilance should have effects similar to those of LTP induction. Indeed, exposure to an aversive and stressful event produces biochemical, electrophysiological, and molecular effects that are similar, and in some cases identical, to those following high-frequency stimulation. For example, an increase in binding affinity of the AMPA type of glutamate receptor occurs in the hippocampus in response to the induction of LTP. The increase in binding is virtually indistinguishable from that induced in response to the acute inescapable stressor of restraint and intermittent tail shocks (Tocco et al. 1991; 1992). In addition, a previous induction of LTP and exposure to an aversive and arousing event both impair subsequent LTP induction (Foy et al. 1987; Shors & Dryver 1994; Shors & Thompson 1992; Shors et al. 1989) and enhance the subsequent extracellular response to theta burst stimulation (Shors & Dryver 1994; Shors et al., in press). As was discussed above, exposure to a stressful and arousing event facilitates acquisition of the classically conditioned eye blink response (Servatius & Shors 1994; Shors et al. 1992), as does the induction of LTP in the dentate gyrus (Berger 1984; see Rioux & Robinson, in press, for an exception). Other examples of common targets for LTP induction and the arousing experience include the immediate early genes *zif*-268 and c-*fos* in the hippocampus (Abraham et al. 1993; Cole et al. 1989; Kaczmarek 1992; for exceptions, see Schreiber et al. 1991) and nitric oxide activity (Sadile & Papa 1993; Schuman & Madison 1991).

When an animal can attain control or perceived control over an aversive experience, the degree of arousal is substantially decreased (Overmier & Seligman 1967; Seligman & Maier 1967; see Seligman & Johnston, 1973, for a review). If LTP is involved in arousal and attentional processes, then manipulating the degree of arousal should, in turn, alter the amount of potentiation that is induced. Allowing an animal to acquire control over the fearful experience partially ameliorates the impairment of LTP induction in area CA1 of the hippocampus (Shors et al. 1989). Furthermore, a suboptimal induction of LTP can be optimized by exposing the rat to an aversive and uncontrollable stressor such as foot shock during exposure to the tetanus (Seidenbecher et al. 1995). Overall, the number of similarities between the effects of an arousing experience and the induction of LTP suggests, at the very least, a convergence on similar neuronal mechanisms.

4.5. Saturation of the capacity for plasticity. In the absence of preconceptions regarding the role of LTP in memory storage, other potential roles for LTP become evident, including the role in attention that we propose. In fact, the evidence in support of LTP's role in attention may be as strong as that for its role in memory storage. For example, artificial induction of LTP had no effect on subsequent acquisition of water maze learning, but there was a strong positive correlation between the rat's capacity for LTP and the speed with which it escaped the aversive environment (Jeffery & Morris 1993; but see Cain et al. 1993). Moreover, rats that were most susceptible to LTP induction spent more time, when the platform had been removed, in the quadrant of the maze that previously contained the platform, a common measure of retention. One interpretation of this latter effect is that LTP induction alters performance variables such as perseveration, rather than impinging directly on memory formation. The induction of perseverative behavior is common when an animal is in a fearful and attentive state. Following exposure to a fear-provoking event, acquisition of a spatial maze task is impeded by the rat's tendency to perseverate prior to the initiation of a response (Shors & Dryver 1992). At first approximation, these findings appear to be inconsistent with our contention that an arousing experience induces LTP and directs attention to sensory stimuli during learning. However, they are not necessarily inconsistent if one recognizes that perseveration (focused attention) might degrade performance (but not necessarily learning) in a task requiring complex, diverse motor responses in an environment containing both relevant and irrelevant cues (e.g., the radial arm maze) but might facilitate acquisition of simple reflex behavior in a task in which irrelevant cues are minimized (e.g., eye blink

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conditioning). As was discussed above, Berger (1984) reported that the previous induction of LTP in the hippocampus facilitated eye blink conditioning to a discrete CS. The task was a standard delay task, which is not dependent on the hippocampus for acquisition (Weisz et al. 1984), so LTP could not be forming the memories themselves. It could, however, enhance the general salience and perceived intensity of the limited cues presented in the environment, an effect known to facilitate acquisition of the CR (Scavio & Gormezano 1974).

4.6. Natural stimulation patterns that induce LTP. The possibility that hippocampal LTP is a mechanism for the neural induction of attention or arousal is further supported by the observation that afferent stimulation that mimics the endogenous theta rhythm is an extremely effective stimulation pattern for inducing LTP (Greenstein et al. 1988; Larson et al. 1986). As we noted above, endogenous theta rhythms are associated with voluntary motor activity but can be induced by exposure to aversive events, even in the absence of an overt motor response. This is not simply an effect of subthreshold (i.e., undetected) muscular exertion, because muscular effort alone is not sufficient to induce theta activity; for example, hanging by the forepaws or balancing motionless on the hindlimbs does not induce theta rhythm in the rat (Vanderwolf 1988). Because theta activity correlates highly with (and may actually precede) motor behaviors associated with exploration as well as exposure to aversive stimuli (for exceptions, see Balleine & Curthoys 1991), it seems parsimonious to suggest that it might be an index of arousal. Consistent with such a view, it has been reported that the amount of theta rhythm can predict the rate of acquisition in a simple associative task (Berry & Thompson 1978). Using a natural inducer of theta activity, water deprivation, Berry and Swain (1989) found that the rate of learning was accelerated. In addition, water deprivation was reported to enhance the induction of LTP and, concurrently, fear conditioning to context (Maren et al. 1994).

A prevalent form of theta activity is generated via a cholinergic output from the septum, which projects to the hippocampus and elsewhere (Bland 1986; Bland et al. 1984). The mechanism whereby fear-provoking experiences enhance attention could be initiated by acetylcholine released into the hippocampus during the experience (Mark et al. 1996). Furthermore, the sensitization to discrete sensory cues produced by an aversive experience is prevented by blocking cholinergic receptors during the aversive experience (Shors et al. 1995). Importantly, if we accept the proposal that theta stimulation induces an LTP-like phenomenon endogenously, then such an induction protocol would most likely have widespread effects. Such widespread effects might be necessary, at least initially, in order to enhance processing of all stimuli. Perhaps these effects are reflected in the nonspecific responses to LTP induction described above, that is, the increase in mRNA for the glutamate receptor and neurotrophins. Some of these effects might likewise coincide with the widespread increase in neuronal activity that occurs in many brain regions during learning.

4.7. Synaptic efficacy and specificity. The notion that LTP is a substrate of learning and memory arose, in part, from the proposition that enhancing synaptic transmission would be an effective way to "construct" and retrieve specific memories in a neuronal network (see, e.g., Hebb 1949; James 1892; Spencer 1870; Tanzi 1893). If this idea is valid, one would expect that enhancing synaptic transmission would enhance memory formation. Recently, this hypothesis was tested with a class of drugs known as ampakines, which enhance synaptic transmission by increasing the mean open time of the AMPA type of glutamate receptor. As predicted, the drugs facilitated learning in a number of tasks, from olfactory discrimination to maze learning (Staubli et al. 1994; in press). One of the questions that arises is whether the drugs facilitate memory formation itself or the processing of sensory information prior to memory storage. We tested one of these questions in a classical conditioning task and found that rats treated with the drug displayed an enhanced responsiveness to discrete sensory cues. Even when the sensitization to cues was reduced (by lowering the intensity of the CS), facilitated acquisition of conditioned eye blink response occurred (Shors et al. 1995). It is noted that the drug was injected peripherally, so the increase in synaptic transmission occurred throughout the brain (Staubli et al. 1994). Thus, the drug could not by itself form the "memory," because it would not affect specific synapses; it could nonetheless prime the network such that subsequent memories are more easily induced. These results are parsimoniously in keeping with the idea that enhancing synaptic neurotransmission (inducing LTP-like phenomenon) enhances the neural representation of cues in the brain (even if below threshold for a sensitized behavioral response), which incidentally enhances learning when the cues are relevant. In accordance with the more general assumption that the efficacy of synaptic transmission should directly influence the rate of learning, Matzel et al. (1996) have reported a strong correlation between the strength of the synaptic integration between two sensory systems and the capacity to form an association between stimuli presented in those sensory modalities. Moreover, Matzel et al. reported that poor learning (which correlated with weak synaptic transmission) could be facilitated simply by increasing the intensity of the sensory stimuli (and thus the amplitude of synaptic potentials).

As was noted above, LTP is often described as "synapse specific," but in actuality it is not confined to synapses and spreads to neighboring synapses. The hypothesis proposed here is not dependent on the limitation of LTP to specific synapses. Many responses to fearful stimuli are nonspecific in the sense that they are not confined to one synapse or a set of synapses (Schreiber et al. 1991). At a functional level, fear responses are typically induced by a single stressful event (or series of events) but generalize to subsequent events (Maise & Jackson 1979; Overmier & Seligman 1967; Shors et al. 1992). As one might expect, changes in brain activity associated with attention are initially broad, but they narrow considerably as attention becomes focused on the relevant cues. Therefore, as attention is maintained, there is a shift in brain activity from the regions of irrelevance to those necessary for processing specific stimuli. For example, there is an increase in activity in visual areas when processing a visual cue in a task and a corresponding decrease in areas such as the auditory cortex that are not involved in the task (Haxby et al. 1994; for reviews, see Haxby et al. 1991 and Greenwood et al., 1993). One could

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imagine that a brain-ubiquitous mechanism such as LTP could be quite useful as an attention device by initially enhancing the general salience of cues, followed by a more focused attention on relevant stimuli and their associations.

4.8. Distribution throughout the nervous system. A presumed role for LTP in attention might even explain its existence in such a diverse set of brain regions. For example, LTP in the superior colliculus could be involved in directing spatial attention through its involvement with saccadic eye movements (Sheliga et al. 1995). A role for LTP in attention is also consistent with its prominence in the hippocampus, which some consider an online processor for regulating attention to incoming sensory information (Grossberg 1975; Mackintosh 1975; Moore & Stickney 1980; Schmajuk 1990; Schmajuk & DiCarlo 1991) and/or exploration (Buzsaki & Czeh 1992). LTP would be particularly effective in this context when a high state of vigilance has been induced but the relevance of the information has yet to be established. The hypothesis is also consistent with the relatively nonspecific increase in cell excitability observed in the hippocampus during acquisition in a variety of tasks, some of which clearly are not dependent on the hippocampus for memory storage (Berger et al. 1976; McCormick & Thompson 1984). In fact, LTP's wide distribution throughout the nervous system is perhaps one of the most convincing aspects of its proposed role in attention.

The hypothesis presented here is less "specific" than the prevailing alternative. First, it is not constrained by the preconception that LTP serves as a mechanism for synapse-specific modifications underlying memory. The hypothesis does, however, predict that there should be enhanced synaptic efficacy following exposure to aversive and arousing stimuli. In the only direct test of this hypothesis to date, synaptic responses in area CA1 of the hippocampus were not potentiated in response to the aversive event of acute inescapable tailshocks, in apparent disagreement with our predictions (Shors et al., in press). However, in another study, synaptic responses elicited by a discrete auditory stimulus were increased following exposure to tetanic stimulation. This synaptic potentiation was observed in a pathway from the thalamus to the amygdala, one that is thought to be involved in fear conditioning (Rogan & LeDoux 1995). These results suggest that tetanic stimulation can increase the neural representation of sensory stimuli. Perhaps a similar effect can be induced by previous exposure to fear-provoking experience. In this hypothesis, the increase in synaptic efficacy would initially facilitate sensory processing and might incidentally have an impact on future learning. (It is recognized that these data reflect phenomena occurring in brain structures other than the hippocampus, so it could be the case that LTP is used for different purposes in different brain structures. This is a difficult position to refute, but there is no a priori reason to accept it without evidence to substantiate LTP's role in memory or any other cognitive process.)

In summary, we have proposed that, when a stressful and arousing stimulus is encountered, a phenomenon mechanistically similar to LTP is induced, functionally increasing the neuronal representation of environmental stimuli. To the extent that those stimuli require storage in memory, that storage may be incidentally facilitated. Such a transition from nonspecificity to specificity is, in our view, a necessary criterion for a system that must be constantly prepared to respond to environmental change without prior knowledge of its significance.

5. Concluding remarks

In the vast spectrum of experimental results, support can be found for virtually any hypothesis regarding the role of LTP in memory. This may not be surprising, given the prominent role that LTP plays in the hippocampal plasticity and the debate that has raged for five decades concerning the role of the hippocampus in learning and memory storage (see, e.g., Bunsey & Eichenbaum 1996; Cho & Kesner 1995; McClelland et al. 1995; Nadel 1994). We have suggested in this target article that much of the support for the connection between LTP and memory arose from a preconception that LTP *is* a learning mechanism. Consequently, the hypothesis that LTP plays a critical role in memory storage has gained a conceptual hold on the field, which limits our capacity both to evaluate data critically and to recognize alternative hypotheses as the data suggest them. The task is further complicated by the fact that many forms of plasticity fall under the category of "LTP," yet "LTP" is treated as a unitary phenomenon with respect to its role in behavior.

We recognize that the alternative hypothesis we have proposed is subject to many of the same criticisms as the prevailing hypothesis we have criticized, and that it will ultimately prove as difficult to test. However, it does, at the very least, suggest "how" a mechanism such as LTP might be useful to an awake, behaving animal under native circumstances. Moreover, it leads to the obvious conclusion that experiments purported to establish a link between LTP and memory are subject to multiple, and even equally viable, interpretations.

In closing, we again wish to list the various roles that LTP might play in the awake behaving animal. The most extreme possibility is that LTP is neither an information-processing device nor a memory mechanism. A less extreme alternative is that LTP plays a critical role in the processing of sensory information necessary for the establishment of stable memories and that it is induced in response to environmental stimuli. Information processing has costs in addition to its obvious adaptive benefits, and an efficient brain should use mechanisms that allocate and reallocate resources depending on current demands, past experiences, and anticipated events. Owing to its pervasive and ubiquitous nature, this may be a role particularly suited for LTP. With respect to learning, the lack of conclusive evidence indicating a necessary contribution of LTP to memory induction per se, as well as recent evidence to the contrary, should be a sufficient reason for our pausing to reevaluate the conceptual hold that this hypothesis has on current thinking.

ACKNOWLEDGMENTS

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Keeping faith with the properties of LTP

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Abstract: Despite close scrutiny in recent years, the traditional properties of LTP are holding up remarkably well, and they remain a credible influence on the belief that LTP has something to do with learning and information storage.

The late Graham Goddard once wrote, "Physiological psychology is an act of faith; it is the illogical assertion that to proceed with faulty assumptions is better than to do nothing at all and that, as knowledge is acquired, the imponderable problems will disappear" (Goddard 1980, p. 240). Certainly one of the greater articles of faith in neuroscience over the past 20 years has been that LTP serves as a memory storage mechanism. Unfortunately, it is equally clear that convincing data to substantiate this belief have been slow in coming, as the Shors & Matzel (S&M) target article emphasizes. But is it time for a mass conversion? For the time being, I remain a believer, in part because the arguments put forward by S&M do not make a strong case against the traditional, if faulty, assumptions. My discussion will focus on the properties of LTP which, though perhaps not central pieces of evidence, lend credibility to the concept of LTP as an information storage mechanism.

Input and synapse specificity. (1) LTP is input specific, according to dozens of published papers (sect. 2.4). The two contraindicative papers cited by S&M in fact do not conflict with the principle of input specificity (Bonhoffer et al. 1989; Schuman & Madison 1994). Only active synapses were modified in these two studies; these studies did show an intriguing departure from traditional "Hebbian" LTP, however, in that an intercellular messenger substituted for postsynaptic activity for some synapses. (2) E-S potentiation can be largely accounted for by synaptic changes (e.g., changes in the excitation/inhibition ratio; Abraham et al. 1987). Indeed, E-S potentiation is also input specific and is not accompanied by changes in the passive properties of the postsynaptic neurons, as demonstrated by the two papers cited by S&M to support their claim that LTP, in this case E-S potentiation, is not "synapse" specific (Andersen et al. 1980; Chavez-Noriega et al. 1990). Finally, the possibility that memory storage locations (and biochemical correlates of LTP) may move across brain regions over time is not a strong argument against synapse specificity. It is entirely possible that those later changes occur through an LTP-like process generated by circuit reverberation subsequent to the initial training or stimulation episode. A further caveat is that there are as yet no specific biochemical markers that can be used to track the location of LTP induction.

LTP persistence. LTP in the hippocampus is typically decremental (sect. 2.5), but it is worth noting that in some cases it may not be, such as after seizures in the dentate gyrus (Barnes et al. 1994), after theta-burst stimulation in area CA1 (Staubli & Lynch 1987), or after repeated stimulus episodes in the neocortex (Racine et al. 1995). Decremental LTP could represent the natural and expected active loss of the artificial and uninformative synaptic changes induced experimentally. Alternatively, it may be that memories are also always decremental, but are periodically restrengthened by conscious or unconscious rehearsal or reactivation from events that have associations with the prior learned event. This condition has yet to be modelled experimentally for the LTP paradigm. In any event, there is a great need to study LTP persistence much further in those areas (e.g., neocortex) where long-term memories are probably stored. Finally, the S&M argument that memory shows facilitated reacquisition but LTP does not is unconvincing (sect. 2.6). There is a very real chance that the threshold for the behavioural expression of a learned response is well above that for LTP expression at selected sites in a network, and that facilitated reacquisition occurs because some synapses remain partially potentiated.

Cooperativity/associativity. This important aspect of LTP is dismissed lightly by S&M (sect. 2.7), but their two main arguments are worth debating. First, the value of contrasting the optimal timing of environmental stimuli for classical conditioning with that for electrical stimuli for LTP is questionable because one does not know when the critical neural activity for LTP occurs following the delivery of the environmental stimuli. Second, while S&M suggest that LTP can in principle be produced by activity in a single fiber, negating the need for associativity, recent evidence suggests that this is not the case (Debanne et al. 1996).

In conclusion, my belief is that the traditionally viewed properties of LTP are still accurate, and they continue to support the view of LTP as a selective storage mechanism, rather than as a global arousal mechanism. I have, in addition to these comments on the properties of LTP, one further observation regarding the behavioral importance of LTP; neurally encoded information might need to be shifted and stored for shorter or longer periods in multiple anatomical locations during various kinds of cognitive activity, independently of whether learning as typically studied in animal experiments is occurring. LTP could serve these processes as well, and to cover these wider possibilities I believe it makes more sense to refer to LTP as an *information* storage mechanism. Furthermore, even learning itself is likely to involve distributed storage at many nodes in a network. It should come as no surprise, therefore, if LTP in a single synaptic pathway does not correlate particularly well with learning or memory performance, particularly when the contribution to information processing by that pathway is poorly understood anyway. Thus, understanding the function of LTP within a particular structure or set of synaptic connections must start with an understanding of the function of that structure. With all due respect for the labors across decades by hippocampal researchers, we remain far from that critical information. The neocortex may yet prove to be a better model system in this regard.

State-dependent suppression of LTP induction after learning: Relation to phasic hippocampal network events

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Abstract: This commentary argues that (1) arousal is not sufficient to induce LTP in the hippocampus, (2) learning can profoundly modulate synaptic plasticity in a state-dependent manner without affecting baseline synaptic efficacy, and (3) unilateral, synapse-specific LTP induction triggers an interhippocampal communication manifested as bilateral increases in gene expression at multiple sites in the hippocampal network.

There is a great need to understand activity-dependent synaptic plasticity at the systems level, and to identify the full range of

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functions subserved by various types of LTP and LTD in hippocampal pathways. Shors & Matzel (S&M) provide a timely and welcome challenge to preconceptions of LTP as a memory storage mechanism.

Arousal is not enough. S&M's hypothesis is: that (1) arousal or vigilance results in LTP-like increases in synaptic efficacy in the hippocampus, and (2) LTP is a mechanism for enhancing sensory processing (with only an incidental role in learning and memory). In apparent contradiction to this hypothesis, a variety of conditions resulting in behavioral arousal fail to induce changes in synaptic efficacy. For example, active avoidance (shuttle box) conditioning or pseudoconditioning employing electrical footshock as the aversive UCS has no effect on synaptic efficacy in the medial perforant path input to dentate gyrus, yet such training is both arousing and demanding in terms of sensory vigilance. Furthermore, acute cold exposure associated with high stress levels of serum corticosterone has no effect on synaptic efficacy in the dentate gyrus of freely moving rats (Bramham et al., submitted). As pointed out in the target article (sect. 4.8, para. 2), acute inescapable footshock also fails to alter synaptic efficacy in field CA1 (Shors et al., in press). Thus, arousal or stress does not appear to be sufficient to induce LTP, at least not as detected by evoked field potential recording. The behavioral settings in which arousal-induced LTP would occur need to be more clearly defined. Although the hippocampus is not required to learn the CS–UCS association in rabbit eyeblink conditioning, it may allow context-specific, behaviorally appropriate expression of learning. Perhaps arousal contributes to the induction of LTP-like changes associated with context-specific expression of the conditioned response.

Learning and state-dependent modulation of LTP. A variety of learning paradigms are followed by a critical period of prolonged REM sleep that is necessary for memory formation. We have found that LTP induction is modulated in a state-dependent manner during the critical period after avoidance learning; tetanus applied during REM sleep induces normal LTP, whereas LTP induction is suppressed during still-alert wakefulness (Bramham et al. 1994). Failure to induce LTP is consistent with prior induction and saturation of LTP during arousal, as suggested by Shors and Dryver (1994; and sect. 4.4, para. 1). This interpretation does not hold for avoidance learning, however, because LTP is reliably induced during REM sleep and because learning does not affect synaptic efficacy. Thus, learning can suppress LTP induction in a state-dependent manner without influencing baseline synaptic efficacy.

One surprising feature of the learning-induced suppression is its all-or-none nature; in most cases tetanus evokes either full LTP or no LTP. In naive rats, the same all-or-none pattern of suppression occurs during slow-wave sleep (Bramham & Srebro 1989). Thus, LTP is phasically modulated during alert wakefulness after learning and during slow-wave sleep in naive rats. Suppression of LTP induction may be related to the timing of tetanus delivery relative to spontaneous population events in the hippocampal network. Hippocampal sharp waves and dentate spikes are particularly interesting in this regard; in naive rats they occur most frequently during slow-wave sleep and to a lesser extent in alert wakefulness (Bragin et al. 1995; Buzsaki 1989). We have speculated that LTP suppression is linked to an increase in the frequency of network events in alert wakefulness after learning. It is conceivable that arousal contributes to such a mechanism but, again, as with eye-blink conditioning, the effect would have to be learning-specific.

Focal LTP triggers an interhemispheric communication manifested as enhanced gene expression in the hippocampal network. S&M have emphasized trans-synaptic effects of tetanus-evoked LTP in the hippocampus, including a bilateral enhancement in the binding affinity of AMPA receptors (sect. 2.4, para. 6–8). We have studied the effect of inducing LTP in the dentate gyrus of freely moving rats on neurotrophin and tyrosine kinase receptor gene expression (Bramham et al. 1996). Depending on the mRNA species, LTP induction led to unilateral (granule cells) or bilateral (granule and pyramidal cells) increases in gene expression. Both unilateral and bilateral effects were NMDA receptor-dependent, LTP-specific, and occurred in the absence of seizure activity. Furthermore, bilateral electrophysiological recordings showed that LTP did not occur in the contralateral dentate gyrus, and this was corroborated by a unilateral increase in the expression of the immediate early gene *zif*/268. Bilateral changes in gene expression are thereby linked to focal, synapse-specific LTP induction. The mechanism for the bilateral effects is unknown, although bilaterally synchronized sharp waves and dentate spikes are plausible mediators. Whatever the mechanism, the available evidence suggests that widespread, persistent changes in hippocampal neuronal function after arousal (enhanced AMPA binding) or learning (enhanced neuronal excitability) may be a secondary network effect of focal, synapse-specific LTP.

Importance of behaviour in LTP research

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Abstract: Shors and Matzel's evaluation of approaches to the behavioural function of LTP is welcome, and should encourage a widening of conceptual approaches to this problem. In addition to their call for increased sophistication in thinking about LTP, there needs to be a parallel increase in sophistication in the study of behaviour. Changes in emotional state or tone may be a better function for LTP than attention mechanisms.

Shors & Matzel's (S&M's) thoughtful evaluation of the assumption that LTP underlies learning reminds us that convincing empirical demonstrations of fundamental phenomena are the foundation of any science. Their comments on multiple definitions of LTP (sect. 2.2) and the difficulty of functionally linking potentiation phenomena to behavioural learning (sect. 3) are especially lucid and useful. Care must be taken with what we call LTP in a given experiment. This is especially true if one agrees with Morris and Davis that "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, p. 368).

Care must also be taken with what we call learning – or more to the point, learning impairments – in LTP research. This can be as difficult as defining and studying LTP, but it is not clear that all neuroscientists appreciate this point. Too often learning is equated with hidden platform search time in a water maze, for example, and the subtleties of behaviour in this complex task go unnoticed. To pursue this example, hidden platform search time is a poor measure of spatial localization capacity (Shenck & Morris 1985) since a rat that merely swims away from the maze wall will have much shorter search times than a rat that swims thigmotaxically (Whishaw & Jarrard 1995). A rat that achieves short search times by swimming away from the wall need not know anything about the exact location of the platform.

This example is only one of many that could be given, particularly where studies with neurotransmitter antagonists or lesions are concerned. Detailed analyses of behaviour in the water maze have shown that NMDA and muscarinic antagonists cause various sensorimotor disturbances (thigmotaxic swimming, etc.), which are strongly correlated with poor maze acquisition measures (Cain et al. 1996; 1997; Saucier et al. 1996). In contrast, rats that are first familiarized with the general requirements of the task by nonspatial pretraining (NSP; Morris 1989) learn the exact location of the platform as quickly and effectively as controls under a dose of NMDA or muscarinic antagonist that severely impairs naive rats and blocks dentate LTP (Bannerman et al. 1995; Saucier & Cain 1995). This suggests that (1) the water maze task is more complex than is commonly thought; (2) NSP separates learning the general

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task requirements from learning the location of the hidden platform (Morris 1989); (3) approaches involving NSP or other novel training methods, together with detailed behavioural analyses, allow informative tests of whether the hippocampus or NMDA-dependent LTP are crucial for spatial learning (Bannerman et al. 1995; Cain & Saucier 1996; Saucier & Cain 1995; Schallert et al. 1996; Whishaw et al. 1995); (4) making inferences from behaviour to unseen phenomena such as neural mechanisms of learning requires caution (Vanderwolf & Cain 1994).

Although I applaud the suggestion that LTP might serve a novel function such as an attention mechanism (sect. 4), I am not sure that attention is the best candidate. The time course of LTP seems too long and apparently rigid for the rapid shifts in attention that can occur when an animal ceases to pay attention to food and immediately shifts its attention to an approaching predator. Many examples in human behaviour could be given. One of the most important properties of LTP as a learning mechanism, its persistence, makes it less suited for an attention mechanism. Depotentiation would be required to remove no-longer-relevant LTP, but then another mechanism would be needed to "decide" what is behaviourally relevant and to selectively depotentiate the recently-potentiated synapses. Another problem is the fact that attention is difficult to define and study since it derives from the vague language of everyday experience. Experiments on attention involving shock could involve stress and emotional responses. In fact, changes in emotional state (another vague and difficult topic) might be a better candidate function for LTP because they are probably longer lasting than attentional shifts, and better fit the time course of LTP and some of the anatomical facts (LTP occurs in autonomic ganglia).

It may be easy to criticise S&M's proposal, but that is not the intent. Rather, it is to call for as much sophistication in behavioural analysis, whether of learning, attention, or emotional changes, as has been applied to analysis of the cellular mechanisms of LTP. Any widening of conceptual approaches to the functions of LTP is to be welcomed. I hope Shors & Matzel's effort is rewarded by a widening of behavioural research approaches to LTP.

Without LTP the learning circuit is broken

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Abstract: Since learning emerges from a circuit mediating behavior it is unrealistic to require LTP to be a *sufficient* explanation of it; however, LTP is a *necessary* component of some learning circuits. The properties of that component bear a closer formal relationship to the acquisition of associative strength than to the modulation of attention.

I chose to paraphrase Ms. Turner's lyrics to illustrate where Shors & Matzel (S&M) have gone astray. Learning is a change in an organism's reactions to stimuli because of experience. It is a behavioral phenomenon depending on a circuit mediating between sensation and action, not just a property of activity at a single synapse. LTP is a change in activity across a single synapse. Since learning is a property of an entire functional circuit, any single synaptic change cannot be a sufficient explanation of learning. A better question is whether LTP plays a necessary role in the functioning of the circuit mediating a particular learned behavior? Current evidence suggests that it does; without LTP some learning circuits, at least, are broken. If LTP is necessary for learning, one must ask what role it plays in the circuit. The preponderance of the evidence is more consistent with LTP's role in acquiring associative strength rather than the attentional role the target article attributes to it. LTP is a learning mechanism.

The target article often confuses synaptic and circuit levels of analysis. The synaptic properties that make LTP a plausible mechanism for association formation need not have a one-to-one isomorphism with the properties of the entire behavioral system. For example, S&M worry that the optimal timing of stimuli at the to-be-potentiated synapse appear different from the optimal timing of stimuli for learning. In fear conditioning, a CS may be presented for several minutes before the US is presented, whereas in LTP the weak stimulus and tetanus must occur within a narrow window. However, as long as the CS generates a unique pattern of activity at the to-be-potentiated synapses at the time that US information arrives, a coincidence detection mechanism such as LTP would support association formation. The many synapses through which that information passes could optimize the efficiency of LTP and learning theory has provided several error correction algorithms that should refine that associative learning, even though those functions are executed at synapses other than the ones that are strengthened (Young & Fanselow 1992).

Another example of confusing synapse and system levels of analysis appears when S&M dismiss LTP as a learning mechanism because the effects of saccharin on a hippocampal slice (Morishita et al. 1992) differ from the effects of oral ingestion of saccharin by an intact animal on a task that does not require the hippocampus (Stefurak & van der Kooy 1992).

Section 3.4 begins with the statement, "Correlational evidence can be powerful when an array of correlations lends support to a given hypothesis" and ends by saying, "correlations between manipulations that affect both hippocampal LTP and learning have begun to pervade the literature." The intervening sentences dismiss this pervasive evidence because any single correlation may arise from something other than a cause and effect relationship. However, when the correlational matrix is substantial enough, a cause and effect relationship becomes the most parsimonious account. Let me add a few cells to the matrix relating contextual fear conditioning to hippocampal LTP. Water deprivation enhances hippocampal LTP and contextual fear conditioning but does not affect auditory fear conditioning (Maren et al. 1994a; 1994c). Males show more hippocampal LTP and contextual fear conditioning than females but there is no gender difference in auditory conditioning (Maren et al. 1994b). The NMDA antagonist AP5 blocks acquisition but not the expression of contextual fear conditioning (Kim et al. 1991) just as it does hippocampal LTP (Collingridge et al. 1983). The AP5 experiments ruled out anxiolytic, analgesic, sensory, and motor effects (Kim et al. 1991). In addition, AP5-treated rats reacted normally to the shock US and a previously conditioned contextual CS.

As an alternative to the view that LTP mediates acquisition, S&M argue that LTP enhances attention. Learning theory provides a rigorous framework for testing such a view (e.g., Mackintosh 1975). First, a manipulation of attention should affect what happens *after* attention is altered not what happened before. For example, enhancing attention with a post-trial surprising event influences the learning that occurs on the trial after the surprising event not what happens on the trial preceding the surprise (Mackintosh 1975). This provides an easy test of the authors' hypothesis. If LTP is blocked, then only the learning that occurs subsequent to the event that established LTP should be affected.

Thus the target model predicts that NMDA antagonists should not block the learning that occurs on the first training trial. However, contextual fear caused by a single trial is eliminated by AP5 pretreatment (Kim et al. 1992). Second, formal models of learning suggest that manipulations that affect attention should affect the rate of learning but not the asymptote of learning (e.g., Mackintosh 1975; Rescorla & Wagner 1972). An ideal test of this prediction would use a procedure where an NMDA antagonist partially interfered with acquisition and the levels of performance were not obscured by performance floors or ceilings, so that learning rate and asymptote can be cleanly assessed. Such data are available and the results are unambiguous (Maren et al. 1996). AP5 did not affect the rate of acquisition but lowered the asymptote to one-third of normal. This result is more in line with an occlusion of association formation than a change in attention.

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A causal relationship between LTP and learning? Has the question been answered by genetic approaches?

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Abstract: Gene targeting has generated a great deal of data on the molecular mechanisms of long-term potentiation and its potential role in learning and memory. However, the interpretation of some results has been questioned. Compensatory mechanisms and the contribution of genetic background may make it difficult to unequivocally prove the existence of a causal (genetic) link between LTP and learning.

Perhaps the most compelling evidence for the association between LTP and learning has come from molecular genetic studies using gene targeting in embryonic stem (ES) cells (Silva et al. 1992). Geneticists argued that they "can obviate the lack of highly specific pharmacological tools to study various enzymes" and can investigate the consequences of the introduced mutation for behavior and LTP (Tonegawa et al. 1995). Although these approaches are undoubtedly elegant and do provide crucial insight regarding the role that certain genes may play in synaptic plasticity and learning, they suffer from problems not principally different from previous techniques they have criticized (Crusio 1996). Briefly, the concerns are the following:

Is gene targeting a specific manipulation from a physiological and behavioral view point? The problem of compensatory mechanisms. Although one may be able to target a single gene, such a manipulation may not be as specific as previously hoped. As a result of the introduced mutation, gene expression may be absent in several brain areas, thus the locale of the disruption may be fairly nonspecific, leading to performance deficits unrelated to learning, a point made in the target article. Furthermore, the mutation may trigger compensatory mechanisms that may mask certain phenotypical changes or *introduce* some (Gerlai 1996b). Certain genes in the biochemical pathway of the targeted gene may become over- or underexpressed, leading to secondary developmental or physiological alterations. However, compensatory processes may occur at any level of the biological organization. Even behavioral compensation is possible. Imagine a mouse with genetically disrupted olfaction. This alteration may force the mouse to prefer visual stimuli to olfactory, which may in turn lead to multiple changes in neural processes and brain areas involved in processing visual stimuli. An investigator may then conclude that the targeted gene plays a crucial role in vision. Gene targeting studies trying to link LTP to learning may face similar enigmas. Teasing out the direct and indirect effects of the mutation is certainly not trivial and will undoubtedly require coordinated efforts among scientists from several fields of biology.

Is the targeted gene responsible for the observed correlated changes in LTP and behavior? The problem of genetic background. An investigator of the above imaginary mouse may still argue that the definition of "gene function" is a highly philosophical one, and despite all concerns, the targeted gene *is* responsible, at least in some indirect way, for the phenotypical alterations observed in mutants. Unfortunately, however, this may not be so. Most gene targeting studies suffer from a common problem that makes the interpretation of their results questionable (Gerlai 1996a). The mutant mice used were hybrids between strain 129 (the genotype of the embryonic stem cell used for gene targeting) and another strain (usually C57BL/6) with which the chimeric mouse carrying the 129 type sperm with the mutation was crossed (Gerlai 1996a). This hybrid origin led to a situation in which the phenotypical alterations might not have been due to the mutation introduced but to an undefined number of background genes linked to the targeted locus (see Fig. 1). It has hence proved uncertain whether the observed impairments in LTP and learning are due to the same or different genes.

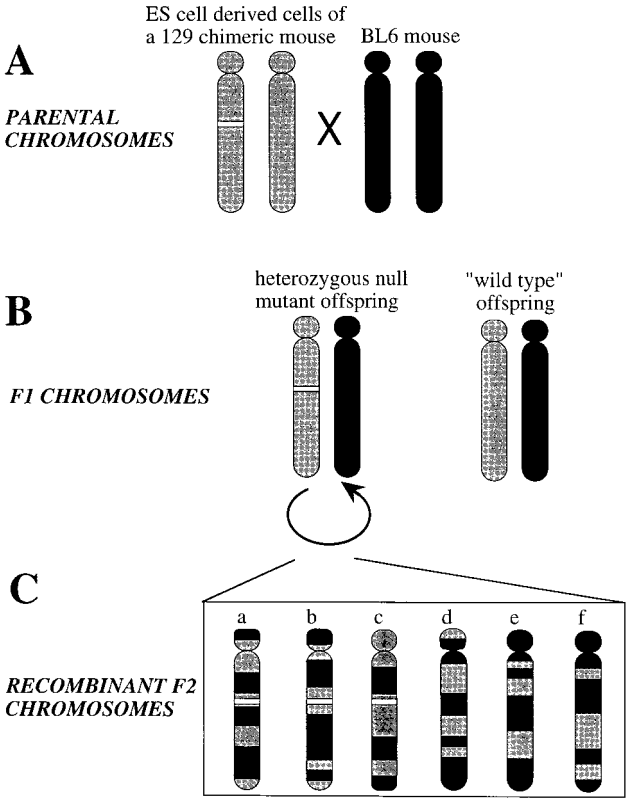


Figure 1 (Gerlai). *Chromosomal constitution of mice generated by gene targeting.* ES cells originating from mouse 129 carry one chromosome (grey) with the disrupted allele (white lesion) of the targeted gene. If these ES cells populate the germ-line in the chimeric mice, the mutation will be transmitted when the chimera is mated. A cross between a germline transmitting chimera and a C57BL/6 mouse (BL6, black chromosomes: panel A) will produce an F1 population (panel B) in which 50% of the animals will have one copy of the mutant allele (heterozygous mutants) and 50% of them will have no mutant allele (wild type animals) at the targeted locus. Using Southern blotting or PCR (polymerase chain reaction) one can detect the presence of the mutant allele and identify the heterozygous mutant animals. If these animals are mated with each other, according to Mendel's law, homozygous mutant (two mutant alleles), heterozygous mutant (one mutant and one wild type allele) and wild type (two wild type alleles) animals will be obtained. It is also important to remember, however, how genes at loci other than the targeted one will be inherited. Cross-over events during the meiotic process of gametogenesis will "shuffle" the alleles of these background genes and will create recombinant chromosomes (panel C) which will characterize the genotype of the sperm and the egg of the F1 mice. The genotype of an F2 individual, therefore, will be represented by a pair of such recombinant chromosomes. For example, a homozygous null mutant mouse may have chromosomes a and b, a and c, or b and c; a heterozygous mouse may have one of the recombinant chromosomes with the lesion (a, b, or c) and another without the lesion (d, e, or f); whereas a wild type control mouse may have chromosomes d and e, d and f, or e and f. Panel C shows that the null mutant allele of the targeted gene will be surrounded by 129-type genes, however, the wild type allele of the gene will be surrounded by BL6 type genes. This linkage disequilibrium is simply due to the fact that the null mutant allele came from a strain 129 genetic background. In an F2 animal of the above origin, the null mutant allele could be surrounded by BL6 genes only if, during the meiotic processes of gametogenesis, cross-overs occured precisely flanking both sides of the targeted gene, events whose combined probability is infinitesimally small.

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The problem is exemplified by the marked genetic differences between inbred mouse strains. For example, the 129 genome contains several mutations and the 129 phenotype is characterized by unique behavioral, neurophysiological, and neuroanatomical abnormalities (see Abel et al. 1996; Gerlai 1996a; Lathe 1996), including severely impaired spatial learning performance and hippocampal LTP. The latter "correlation" may be due to a common mechanism, as suggested by Abel et al. (1996), but it may also be due to a fortuitous gene association (or linkage disequilibrium). Other strains (e.g., DBA/2) do not exhibit such a correlation (compare Abel et al. 1996 and Paylor et al. 1994). Since no quantitative genetic analysis has been carried out to estimate genetic correlations (see e.g., Crusio et al. 1989), and cosegregation of LTP and learning abilities has not been demonstrated, one may not be able to conclude that the traits are causally linked. At this point, therefore, one has to concede and prudently accept the fact that the "genetic evidence" obtained so far may have to be viewed with caution. Perhaps inducible and region specific gene expression (Mayford et al. 1996) and knockout (Tsien et al. 1996) systems or a thorough quantitative genetic analysis will be more elucidating.

Beyond attention: The role of amygdala NMDA receptors in fear conditioning

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Abstract: Several types of amygdala-dependent learning can be blocked by local infusion of NMDA antagonists into the amygdala. This blockade shows anatomical, pharmacological, temporal, and behavioral specificity, providing a pattern of data more consistent with a role for NMDA receptors in learning than in arousal or attention, and supporting the contention that an "LTP-like" process is a neural substrate for memory formation.

In focusing almost exclusively on the hippocampal literature, Shors & Matzel (S&M) overlook amygdala-dependent learning, which provides some of the more compelling evidence in favor of the LTP-memory hypothesis. Whatever may be true of the hippocampal literature, interpretation of the behavioral effects of pharmacological manipulations of the amygdala does not appear to be confounded by "the variability in brain structures necessary for successful completion of the task," or by "the potential effects of the manipulations on sensory or motor performance" (sect. 3.6).

The neural substrates of fear conditioning are well characterized, and in particular, the amygdala is invariably necessary for the acquisition of fear conditioning. Furthermore, pathways by which the amygdala activates target areas involved in producing specific behavioral components of conditioned fear have been identified (Davis 1992; Kapp et al. 1992; LeDoux et al. 1988). Hence, fear conditioning is well suited for investigating the pharmacological basis of learning and memory.

Local infusion of NMDA receptor antagonists into the amygdala blocks acquisition of fear-potentiated startle and conditioned freezing (Campeau et al. 1992; Fanselow & Kim 1994; Miserendino et al. 1990), inhibitory avoidance learning (Izquierdo et al. 1992; Jerusalinsky et al. 1992; Kim & McGaugh 1992; Liang et al. 1994), odor aversion learning (Hatfield & Gallagher 1995; Staubli et al. 1989), and appetitive conditioning (Burns et al. 1994). This blockade shows anatomical, pharmacological, temporal, and behavioral specificity, and thus does not seem simply to be a by-product of a more generalized drug-induced deficit.

Anatomical specificity. The basolateral amygdala (BLA) has a high density of NMDA receptors and is a probable site of convergence of CS and US information (Romanski et al. 1993). The central nucleus of the amygdala, adjacent to the BLA, is also critical for fear conditioning, but has a much lower concentration of NMDA receptors (Monaghan & Cotman 1985). It is interesting therefore, that a blockade of the acquisition of conditioned freezing occurs when the NMDA antagonist, DL-2-amino-5-phosphonovalerate (AP5), is infused into the BLA, but not when it is infused into the central nucleus (Fanselow & Kim 1994). In addition, infusion of AP5 into the striatum, which is dorsal to the amygdala and has a high concentration of NMDA receptors, does not block retention of inhibitory avoidance (Kim & McGaugh 1992).

Pharmacological specificity. Fear-potentiated startle is not attenuated by local infusion of the β-adrenergic antagonist, propranolol (Miserendino et al. 1990). Furthermore, taste-potentiated odor conditioning is blocked by the NMDA antagonist, d-AP5, but not by the 1-AP5 enantiomer, which has a much lower affinity for the NMDA receptor (Hatfield & Gallagher 1995). The deficit in inhibitory avoidance induced by AP5 is reversed by immediate post-training infusion of the agonist, NMDA (Liang et al. 1994), further suggesting that the learning impairments induced by AP5 result from a specific, competitive antagonism of NMDA receptors.

Temporal specificity. Doses of NMDA antagonists that block learning do not block the expression of Pavlovian conditioned fear in response to explicit cues (Campeau et al. 1992; Gewirtz & Davis, in press; Miserendino et al. 1990; but see also Maren et al. 1996), inhibitory avoidance (Kim & McGaugh 1992; Liang et al. 1994), odor aversion learning (Hatfield & Gallagher 1995; Staubli et al. 1989), or appetitive conditioning (Burns et al. 1994) when infused immediately prior to test. Furthermore, Pavlovian fear conditioning (Miserendino et al. 1990) and inhibitory avoidance (Jerusalinsky et al. 1992; Liang et al. 1994) are blocked when AP5 is infused very close to the time of training, but not thereafter. In addition, intra-amygdala AP5 blocks long-term conditioned fear (i.e., assessed at least 24 hours after training) but not short-term conditioned fear (i.e., assessed during training, Kim & McGaugh 1992; Kim et al. 1992). In contrast, infusion of AP5 into the dorsal striatum impairs short-term, but not long-term inhibitory avoidance (Kim & McGaugh 1992). The fact that intra-amygdala NMDA antagonists applied more than one hour after training do not impair learning argues against the possibility that the selective impairment of long-term (and not short-term) memory is caused by a lesion that develops over several days.

Behavioral specificity. The same dose of AP5 in the amygdala that blocks acquisition of inhibitory avoidance learning does not block water maze learning (Liang et al. 1994), suggesting that NMDA antagonist-induced deficits in fear conditioning are not attributable to the same gross impairments that may account for deficits in water maze learning (Cain et al. 1996; Saucier et al. 1996).

S&M suggest that LTP plays a role in a cognitive function that is a prerequisite for learning, rather than in learning itself. According to this account, intra-amygdala NMDA antagonists could impair fear conditioning by interfering with sensory processing (i.e., transmission of CS information, US information, or both) or arousal. The sparing of short-term memory and the expression of long-term memory indicates that intra-amygdala NMDA antagonists do not block CS processing in the amygdala. However, simple Pavlovian conditioning does not allow as easy a determination of whether NMDA antagonists interfere with the ability of the reinforcer (i.e., the US, typically footshock) to activate the amygdala. For example, the fact that intra-amygdala AP5 does not produce analgesia during fear conditioning (Kim & McGaugh 1992; Liang et al. 1994; Miserendino et al. 1990) does not rule out the possibility that it interferes with US processing in the amygdala itself. This can be evaluated directly through second-order conditioning, however, where the CS is paired with another CS (the first-order CS that had previously been paired with the US), rather than with the US itself. In second-order conditioning, the

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first-order CS is the reinforcer and the degree to which the first-order CS elicits conditioned fear is a measure of the ability of the reinforcer to activate the amygdala. In fact, even though the expression of first-order conditioning is actually enhanced by applying intra-amygdala AP5, the acquisition of second-order conditioning is blocked (Gewirtz & Davis, in press). Hence, AP5 does not block activation of the amygdala by either the CS or the reinforcer.

Intra-amygdala AP5 also does not appear to produce deficits in arousal. Behavioral indices of conditioned fear and heightened arousal are identical (Davis 1992; Kapp et al. 1992). Hence, the sparing, or even enhancement of the expression of conditioned fear resulting from intra-amygdala AP5 application indicates that there is no impairment of arousal. In addition, an arousal deficit would not be expected to produce a selective impairment of long-term, and not short-term memory, but rather an impairment of both.

Of course, NMDA receptor antagonism may block learning by interfering with cellular processes unrelated to LTP. Nevertheless, the involvement of an "LTP-like" mechanism in the amygdala (Chapman et al. 1990) in fear conditioning appears a distinct possibility. Recently, LTP In the BLA has been successfully induced by high frequency electrical stimulation of specific pathways likely to carry CS information to the BLA (Maren & Fanselow 1995; Rogan & LeDoux 1995). Moreover, stimulation of the same pathway enhances evoked synaptic potentials produced by an auditory stimulus that can act as a CS in fear conditioning (Rogan & LeDoux 1995).

Given the evidence described above, it would surely be premature for us to embrace an alternative to the LTP-memory hypothesis, particularly one that had less, rather than more explanatory power than the hypothesis we would be abandoning.

Adaptive timing, attention, and movement control

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Abstract: Examples of how LTP and LTD can control adaptively-timed learning that modulates attention and motor control are given. It is also suggested that LTP/LTD can play a role in storing memories. The distinction between match-based and mismatch-based learning may help to clarify the difference.

Our neural modeling work has also led us to conclude that "all forms of synaptic modifications related to learning and memory are not equivalent." Calling the study of these changes "the search for the engram" does create a strong impression to the contrary. I will first review results relevant to Shors & Matzel's (S&M's) claim "that LTP is the neural equivalent of an arousal or attention device."

For definiteness, I will initially consider the learning of the rabbit nictitating response, although the mechanisms are of broader significance. Both the hippocampal dentate-CA3 circuit and the cerebellar Purkinje cell-subcerebellar nucleus circuits are implicated in this process. We have proposed that both circuits carry out adaptively timed learning. Neither learned change "stores an engram," however.

It is proposed that the hippocampal circuit maintains attention on salient cortical representations for a task-relevant duration while also inhibiting orienting responses that could otherwise reset attention and trigger exploratory behaviors (Grossberg & Merrill 1992; 1996; Grossberg & Schmajuk 1989). This process enables a learning subject to cope with the fact that many associations, notably with rewarding and punishing events, are made over variable time delays. Without an adaptive timing process, an animal could not learn to wait for delayed consequences, and would instead relentlessly explore the world searching for immediate gratification. The adaptive timing process influences other learning processes as well, including the encoding of declarative memories, by holding in short-term memory cortical representations that could not otherwise be associated with delayed environmental contingencies. We have shown how paradoxical data about declarative and procedural memories, including hippocampal amnesias, may be clarified by such an adaptive timing process. (I hasten to add that it is not proposed that this is the only type of LTP/LTD the hippocampal system supports.)

The hippocampal dentate-CA3 circuit enables an animal to focus attention quickly upon behaviorally salient cues, both positive and negative, yet also maintain attention on such cues for task-determined durations. Drawing attention rapidly to salient cues can be a matter of life or death, as when a predator is rapidly approaching. On the other hand, fast attention could also prematurely release motor responses in a task-inappropriate way. We have proposed that cerebellar learning enables conditioned motor responses to be released with an appropriate delay even if attention is quickly deployed. In particular, we have modeled LTD of Purkinje cells as an adaptively timed gate. When this gate opens throughout a learned interval, it enables conditioned motor gains to be released via a subcortical pathway (Fiala et al. 1996; Grossberg & Merrill 1996). We have developed a detailed biochemical model of how the metabotropic glutamate receptor (mGluR) system may mediate the slow adaptive timing process. We have also summarized data showing that this system may be phylogenetically old and may have evolved to deal with a general problem of maintaining cell sensitivity to variable intensities and durations of stimulation.

Using these distinct hippocampal and cerebellar models, we have suggested how the three properties of fast attention, task-appropriate attentional maintenance, and properly delayed release of motor behaviors are all achieved, even though neither of the LTD/LTP adaptively timed processes encodes declarative memories. In both cases, the slower learning processes modulate faster learning processes that may encode cognitive, emotional, or motor memories.

Another distinction that is useful to keep in mind is the difference between mismatch-based learning and match-based learning. Mismatch-based learning is often used to learn spatial and motor skills, whereas match-based learning is used to learn sensory and cognitive representations. The former is easily extinguished. In particular, our biochemical cerebellar model suggests how LTD can be extinguished due to the presentation of a conditioned stimulus without an unconditioned stimulus. This is adaptive because there is no reason to remember the spatial and motor maps, delays, and gains that are appropriate to our smaller bodies and childhood muscles as we grow up. Match-based learning can persist for many years, as we accumulate more knowledge about the world (Carpenter & Grossberg 1993; Grossberg 1976). I believe that the evidence does support a role for LTP in this sort of learning as well. In particular, our models anticipated the type of Hebbian and anti-Hebbian mixture of effects that has been used to model recent data about NMDA receptors (Artola & Singer 1993). It remains to be seen how match-based and mismatch-based learning mechanisms compare on the biochemical level.

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LTP plays a distinct role in various brain structures

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Abstract: LTP is thought to be an experimental model for studying the cellular mechanism of learning and memory. Shors & Matzel review some contradictory data concerning the linkage between LTP and memory and suggest that LTP does not underlie learning and memory. LTP is a cellular and synaptic process and cannot be a memory mechanism. In fact, it is a cellular information storage mechanism.

LTP was first described in the hippocampal formation and has subsequently been observed in the central and peripheral nervous systems. Activity-dependent long-term changes of synaptic efficacy have long been thought to form a basis for learning and memory. A large body of physiological and biochemical data exists. Numerous excellent reviews of LTP have accordingly appeared (e.g., Bliss & Collingridge 1993) in recent years and have provided an up-dated summary of cellular and molecular mechanisms for LTP and/or LTD. A majority of experimental evidence has supported the link between LTP and memory. Some contradictory data, however, have appeared. In the target article, Shors & Matzel (S&M) review a range of cellular and behavioral characteristics of LTP and evaluate whether they are consistent with the notion that LTP underlies learning and memory. They go on to suggest that "much of the present focus on LTP reflects a preconception that LTP is a learning mechanism, although the empirical evidence often suggests that LTP is unsuitable for such a role" (Abstract). The target article deserves attention because it reflects on whether hippocampal LTP plays a role in learning and memory.

A number of experiments support a link between synaptic enhancement and behavior. For example, intrahippocampal infusions of nanomolar quantities of AP5 are sufficient to impair spatial learning in a water maze (Morris et al. 1989). Several studies have established that post hippocampus-dependent tasks are also impaired by NMDA antagonists (Shapiro & O'Connor 1992; Willner et al. 1992). These studies suggest that blocking NMDA receptors is sufficient to impair several types of learning thought to involve hippocampal processing (Morris 1994). Furthermore, several studies have reported a correlation between molecular and cellular facts for LTP and learning. For example, an auto-associative learning task is correlated with an increase in glutamate release and with phosphoinositide turnover in the dentate gyrus (Laroche et al. 1991).

Recently, LTP has been observed in various cortical areas. The LTP in these areas differs in several aspects from hippocampal LTP (Teyler 1989). In recent experiments, a direct projection from CA1 and the subiculum to the prefrontal cortex supported LTP (Laroche et al. 1990), which could go on for several days (Otto et al. 1991). To investigate the role of LTP in this pathway in learning, the field potential in the prefrontal cortex induced by CA1-subicular stimulation was observed in a tone-shock classical conditioning paradigm. Conditioning resulted in a delayed increase in the field potential (Doyère et al. 1993). Physiological data suggest an important role for this pathway in hippocampo-cortical communication in learning and memory. Recent approaches have made a basic distinction between the operations of the hippocampal system and the neocortex (Alvarez & Squire 1994): the hippocampal system is able to change quickly. On the other hand, neocortical synapses change slowly. Consolidation occurs when the hippocampal system repeatedly reactivates representation in the neocortex; this eventually leads to strong interconnections among cortical sites, which can support memory independently of the hippocampal system.

According to Dudai's (1989) definition, memories are experience-dependent interval representations, that is, neuronally encoded versions of the world capable of guiding behavior. It is the circuit level that is expected to encode specific representations and perform molar computations on these representations. LTP is a cellular and synaptic process. Consequently, it follows that LTP cannot be a memory mechanism; it is a candidate cellular information storage mechanism.

The nature of a representation in the circuit and the effect of LTP on this representation must be addressed. Thus, a biologically realistic dynamic model of LTP has to be developed. Recently, an integrated model of LTP-like and LTD-like synaptic modifications has been proposed (Kitajima & Hara 1997). These modifications include two forms of homosynaptic modification, two forms of associative modification and one form of heterosynaptic modification. The model is constructed by making certain assumptions and by referring to the physiological and biochemical data likely to underlie the induction and expression of long-term potentiation and long-term depression. Computer simulations have been performed, and the simulation results proved to be in good agreement with relevant experimental results. Thus, the model may produce realistically different forms of synaptic modification.

Various studies suggest that hippocampal LTP accompanies and may be a functional substrate of certain forms of memory: these relationships between hippocampal LTP and hippocampus-dependent memory strongly suggest that the integrative functions of the hippocampal system include a capacity to store intermediate-term information (Eichenbaum & Otto 1992). However, the details of hippocampal information processing and hippocampus-dependent memory representation remain to be clarified.

Active resetting of potentiated synapses prevents saturation of LTP and makes the synapses more responsive than does passive decay (Linden 1994). Hippocampus-dependent memory (declarative memory) is identified by its essentially relational representation and its representational flexibility (Eichenbaum et al. 1991). Furthermore, synaptic modification is regulated by various spatial and temporal interactions. A full understanding of the functional role of the hippocampus and the brain in which the mechanisms of LTP and LTD are embedded requires physiologically realistic computer simulations. Thus, this model for LTP-like and LTD-like synaptic modifications can be applied to neural networks of the hippocampus and to various other regions of the brain.

LTP and learning: Let's stay together

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Abstract: The hypothesis that there is a 1:1 correspondence between LTP and learning is simplistic, and the correlation approach to testing it is therefore too limited. The alternative hypothesis that LTP plays a role in arousal is consistent with activity-dependent neuromodulation, but ignores the Hebbian properties of LTP. LTP may involve both types of mechanisms, suggesting a possible synthesis of the two hypotheses.

Shors & Matzel (S&M) perform a valuable service by reviewing the literature on the relationship between long-term potentiation (LTP) and learning and pointing out that the evidence that the two are connected is surprisingly weak considering how popular the idea is. Acceptance of a connection between LTP and learning has been largely based on uncritical acceptance of supporting evidence, weak logic, and faith. Unfortunately, in attempting to reject this connection S&M make some of the same mistakes.

The null hypothesis that many in the field started with is that there is a 1:1 correspondence between LTP and learning. One popular approach to testing that hypothesis has been to alter the neural substrates of LTP through lesions, drugs, or genetic modifications, and to see whether LTP and learning are affected in parallel – that is, whether they are correlated. Usually LTP and

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learning are both judged on a binary scale (present or absent, normal or abnormal), so there are four possible outcomes. Initial studies demonstrated a number of correlations between LTP and learning (either both present or both absent), supporting a connection but clearly not demonstrating it. The hope was that as the number of such correlations increased, the case for a connection would become increasingly strong.

Subsequent studies, however, have also revealed a number of dissociations between LTP and learning (one present and the other absent). These contradict the null hypothesis stated above, and S&M take them as evidence that LTP is not involved in learning. These dissociations, however, might also be taken as reminders that neither LTP nor learning are unitary entities, so the null hypothesis is too simplistic. Psychologists have distinguished many different types and aspects of learning (explicit and implicit; short- and long-term; acquisition, retention, and retrieval, etc.). A single learning task generally involves many, but not all of these. Similarly, biologists have now distinguished several different types and sites of LTP (NMDA-dependent and independent; early and late-phase; CA1, CA3, dentate gyrus, amygdala, and many cortical locations, etc.). As a consequence, a given type of LTP at a given site might not be involved in a given learning task, and hence would not be expected to correlate with it.

This argument suggests that the null hypothesis we started with must at least be made somewhat more sophisticated. For example, a new null hypothesis might be that there is a 1:1 correspondence between a particular type and site of LTP and a particular type and aspect of learning. However, because biological and psychological processes are often distributed, redundant, and nonlinear, one might still observe dissociations. For example, an animal might be able to learn the same task different ways, so that one type of learning (and LTP) could compensate for the loss of another. Conversely, two different types of learning might be required to master the task, so that behavioral performance could be poor even if one type of learning (and LTP) is normal. Thus, even if a given type and site of LTP is normally involved in a given learning task, it may be neither necessary nor sufficient for it. Unfortunately, with the current methods it would be difficult to distinguish between that possibility and the alternative possibility that LTP is really not involved in learning.

These arguments illustrate some of the limitations of the correlational method of testing a connection between LTP and learning and suggest that the approach must either be improved or extended. Since the target article was submitted, several papers have been published describing improvements to this approach. For example, genetic modifications can now be targeted more or less specifically to different brain structures (Mayford et al. 1995; Tsien et al. 1996) and they can be turned on and off in adult animals (Mayford et al. 1996), removing the most serious limitations of the genetic methodology. In addition, several researchers have begun to extend the correlational approach by attempting to relate both LTP and learning to the activity of individual neurons recorded in freely behaving animals (McHugh et al. 1996; Rotenberg et al. 1996). Doing so adds an intermediate or circuit level of analysis between the cellular and behavioral level, and may make it possible to bridge the gap experimentally. Initial results with each of these new techniques have supported the hypothesis that LTP and learning are connected (Bach et al. 1995; Mayford et al. 1996; McHugh et al. 1996; Rotenberg et al. 1996; Tsien et al. 1996). This is obviously just a beginning, but these new methodologies should permit more powerful tests of that hypothesis.

S&M propose as an alternative the "new and nonspecific hypothesis" that LTP is involved in arousal and attention, rather than learning. More specifically, they propose that during arousal cholinergic inputs to the hippocampus induce theta rhythm, which facilitates LTP and causes a strengthening of the neural representations of environmental stimuli. This mechanism is functionally equivalent to activity-dependent neuromodulation induced by coincident firing of a presynaptic neuron and a modulatory neuron ("Pre-Mod" coincidence), and is well suited for learning stimuli that occur at the same time as an arousing event (Hawkins et al. 1993). However, S&M's hypothesis ignores a key feature of NMDA-dependent LTP: that it is Hebbian in the sense that it is induced by coincident firing of a presynaptic neuron and a postsynaptic neuron ("Pre-Post" coincidence – Hawkins et al. 1993). Hebbian plasticity has been a popular learning rule in artificial neural networks because it leads to strengthening of synapses that are active together, rather than at the same time as an arousing event. In LTP this is referred to as cooperativity and associativity, and it is a natural mechanism for learning configurations of stimuli that occur together in the environment. As much as anything else, this property has encouraged the hypothesis that LTP is involved in explicit forms of learning. However, the two hypotheses are not mutually exclusive. Recent evidence suggests that LTP may involve "Pre-Mod" as well "Pre-Post" coincidence mechanisms (Arancio et al. 1996; Hawkins et al. 1993). If so, LTP could be involved both in arousal aspects of learning, as suggested by Shors & Matzel, and in explicit forms of learning, as is commonly supposed.

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LTP is neither a memory trace nor an ultimate mechanism for its formation: The beginning of the end of the synaptic theory of neural memory

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Abstract: The problem of neural memory storage is discussed, based on the results of studies of memory impairment after hippocampal lesions, motor learning, and electrophysiological research on "spinal memory." I support Shors & Matzel's major statements. The absence of reliable evidence on the LTP memory storage function and other data cast doubt on the synaptic theory of memory.

(1) The aim of the target article is to analyze soberly the boom in studies of the LTP as the only neuronal phenomenon directly related to brain memory mechanisms. This is a timely, important contribution. The main statements concerning the absence of reliable evidence in favor of LTP as a direct manifestation of memory storage and the authors' alternative interpretation are rather close to my own views (Latash 1997). Shors & Matzel (S&M) base their arguments mainly on the results of biochemical, biophysical, and molecular biological studies whereas I will focus on neurophysiological, neurological, and psychological aspects of the problem.

(2) The identification of LTP with the formation and storage of brain memories has never been based on direct evidence for memory in the neuronal system studied. Indirect evidence is based on two major preconceptions: (a) locating memory traces (at least of short-term memory, STM) in the hippocampus, and (b) increased synaptic conductivity as a substrate of memory storage (STM and long-term memory, LTM).

The first preconception is based on clinical evidence of Korsakoff's amnesia after bilateral destruction of the hippocampal system and on the discovery of hippocampal LTP. A careful analysis of memory function in patients and experimental animals with hippocampal lesions, however, has failed to reveal any deficits in either STM or LTM storage. The main symptom is a deterioration of the transition of new memories to LTM, but its manifestations "shrink" when the significance of new messages increases or retrieval testing becomes more sophisticated (Knowlton & Squire 1993; Warrington & Weiskrantz 1978). Hippocampal lesions lead

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to deficits in explicit memory, which normally involves consciousness or some aspects of arousal. Close relations of the hippocampal complex to arousal mechanisms, especially to motivational and emotional aspects that determine initiative, suggest that they too may malfunction in hippocampal lesions. Explicit LTM recording could utilize, at least partially, mechanisms of implicit memory that may create serious problems with addressing and consciously retrieving new memories, despite the proper functioning of brain retrieval mechanisms. Thus, to agree with S&M, hippocampal LTP appears to be a manifestation of arousal specifically related to the formation of new explicit memories.

(3) If LTP is not related to memory storage, the hypothesis about the synaptic nature of memory (the second precondition) loses its basic, decisive support. The hypothesis is founded on the old view of learning as a creation of connections among "neural centers" ("beating a trail"), with increased conductivity along appropriate neuronal chains. This assumption, even in its modern forms (based on the idea of synaptic "use and disuse" [Eccles] or post-presynaptic interaction [Hebbian synapses]), has basic weaknesses because of the strict, unanimous, and permanent character of single synapse memory load. Identical memories occupy all synapses of a single axon for a lifetime, functionally blocking them against new messages that emerge during repetitions of a memorized performance, providing reliable action in unpredictably changing conditions. This is true even for automated actions (Bernstein 1967).

All this demands a huge redundancy of synapses, thus raising the question of whether it is quantitatively possible to store all memories accumulated during an entire life's experiences. Moreover, not all neurons have the ability to memorize. If each synaptic memory is involved in many semantic memories, an enormous control system would be needed to realize the combinatorics of these rigid elements. Presumably, a functional element of memory is a neuronal network, with the neuron being a structural element. Then a neuron should memorize various codes that determine its involvement in different nets through a special organization of its output. The code variation can be created through different input interactions that are only possible in the postsynaptic (intraneuronal) substrate.

These speculations are supported by electrophysiological studies reproducing the DiGiorgio-Gerard "spinal memory" phenomenon in decerebrate and nondecerebrate animals (cats, rats) in the form of a stable amplitude asymmetry of ventral root monosynaptic reflex responses (VR MSRR) emerging after hemicerebelloectomy (Latash 1979; 1997). Thus, memory was directly tested in a very simple neuronal formation: a two-neuron arc with the following results: (a) The VR MSRR amplitude asymmetry in L-S spinal segments occurs and acquires features of LTM after a "fixation time." It endures after an upper spinal transsection, throughout the duration of the experiment (several hours). Local cooling, which arrests neurodynamics, does not prevent a restoration of memorized asymmetries after subsequent rewarming; a similar restoration happens after brief pharmacological suppression of the asymmetry. (b) In spinal animals, unilateral segmental input through muscle afferents cannot produce memorized VR MSRR asymmetries, but it does elicit them in decerebrate animals; the asymmetry can be produced in spinal animals by unilateral stimulation of flexor reflex afferents. (c) A "spinal memory" cannot be created by direct synaptic interactions in the monosynaptic reflex arc. The memory effect is suppressed by selective pharmacological blockade of interneurons controlling the two-neuron arc. The control manifests itself postsynaptically and can be retrieved through synapses unable to record the memory. Although "spinal memory" seems to be related to implicit memory, it is doubtful that the neuronal mechanisms of LTM storage are qualitatively different from those of explicit memory. So, the synaptic theory of neural memory is facing hard times.

Arousing the LTP and learning debate

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Abstract: Shors & Matzel provide compelling arguments against a role for hippocampal long-term potentiation (LTP) in mammalian learning and memory. As an alternative, they suggest that LTP is an arousal mechanism. I will argue that this view is not a satisfactory alternative to current conceptions of LTP function.

Does hippocampal long-term potentiation (LTP) mediate mammalian learning and memory? While many of us hope (in our true-to-Kuhn ways) that the answer is a resounding "Yes!", Shors & Matzel (S&M) remind us of the many reasons why LTP may not be a learning and memory mechanism. To quell our distress after having dismissed LTP as a cellular mechanism for learning and memory, S&M kindly provide an alternative "new and nonspecific" hypothesis that LTP in the brain is an "attentional or arousal device." In this commentary, I will not dispute the many arguments against a role for LTP in learning and memory. Rather, I will argue against S&M's alternative proposal that LTP is an arousal or attentional mechanism. I will conclude that, in the absence of a viable alternative hypothesis, LTP must remain a candidate cellular mechanism for mammalian learning and memory.

As discussed by S&M, LTP is an enduring enhancement of synaptic efficacy that can be induced in several regions of the mammalian brain. Although many investigators have advocated a role for LTP in learning and memory, S&M carefully illustrate the problems with this hypothesis and offer an alternative. Conceding that "LTP-like increases in synaptic efficacy do occur naturally within the brain," S&M propose that LTP is not a learning and memory mechanism, but rather an arousal mechanism for "increasing the gain of neural representations of environmental stimuli." I will refer to this as the "arousal hypothesis." The essence of S&M's arousal hypothesis is that increases in synaptic efficacy (presumably in the form of hippocampal LTP) accompany aversive or "frightening" events, and this functions to increase attention and enhance processing of environmental stimuli. Increased attention and enhanced processing of environmental stimuli may lead to facilitated learning, yielding an apparent correlation between LTP and learning. It is important to note that according to S&M's arousal hypothesis, LTP only *modulates* stimulus representation; it does not serve as the neural substrate for representing stimuli. Thus, LTP is viewed as a process that precedes and modulates memory formation but is not a memory mechanism itself.

Although consistent with some empirical evidence (e.g., Shors & Servatius 1995), the arousal hypothesis runs into trouble upon closer examination. First, it has difficulty handling data indicating that one-trial learning tasks, such as one-trial contextual fear conditioning, which require LTP induction. In this task rats are placed in a novel chamber and given a single footshock. Because the arousal hypothesis holds that arousing events (e.g., footshock) only "influence future learning," (sect. 4.8) it is not evident why manipulations that affect hippocampal LTP induction should influence one-trial learning.

According to the arousal hypothesis, at least one footshock trial is needed to induce arousal-related LTP, and this arousal-related LTP would then modulate conditioning on subsequent conditioning trials. On this view, manipulations that affect LTP induction should influence only learning that occurs *after* the first footshock trial. However, intracerebroventricular infusion of APV (an NMDA receptor antagonist) prevents the acquisition of one-trial contextual fear conditioning (Kim et al. 1992), and a manipulation that facilitates LTP induction (i.e., water deprivation) enhances this form of learning (Maren et al. 1994a; 1994c). It is interesting

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that water deprivation does not affect the magnitude of fear conditioning produced by three conditioning trials (Maren et al. 1994a; 1994c). S&M could of course argue that water deprivation is sufficient to induce arousal-mediated LTP prior to training, and thereby enhances conditioning. However, we have found no evidence that water deprivation induces LTP; instead our results suggest that water deprivation augments the capacity for LTP induction during conditioning.

Hence, the modulation of one-trial contextual fear conditioning by manipulations that affect LTP induction suggests that LTP is required for forming either context representations or context-shock associations (several reports are consistent with the former), because any post-shock influence of LTP on sensory processing would be irrelevant to this form of learning. Indeed, post-shock administration of NMDA receptor antagonists does not affect the strength of context conditioning (Kim et al. 1992; Maren et al. 1996). Collectively, these results are more consistent with a role for hippocampal LTP in encoding contextual representations during training rather than in enhancing stimulus processing after shock has occurred.

Second, the arousal hypothesis attributes the effects on learning of manipulations that induce arousal (like foot shock) to enhanced sensory processing, whereas these effects may be attributable to other processes such as generalization of contextual fear. For example, Shors and Servatius (1995) have reported that NMDA receptor antagonists prevent inescapable shocks from facilitating subsequent eyeblink conditioning. Based on this, S&M suggest that tail shock induces a form of NMDA receptor-dependent hippocampal LTP that enhances sensory processing and enables eyeblink conditioning to be acquired at a rapid rate. It is equally possible, however, that inescapable tail shock generates context-shock associations (see Minor et al. 1984) that generalize to the eyeblink conditioning session, thereby sensitizing eyelid responses and apparently facilitating learning (Servatius & Shors 1994). Thus, the generalization of contextual fear from the tail shock phase to the conditioning phase, not shock-enhanced sensory processing, may account for facilitated eyeblink conditioning in previously shocked rats. Contextual fear established during the tail shock phase may be represented in the form of hippocampal LTP, thereby accounting for its sensitivity to NMDA receptor blockade.

In view of these examples, I conclude that the arousal hypothesis does not fair well in handling data sets that are easily accommodated by hypotheses that posit a role for LTP in encoding information during learning.

Repetition priming: Memory or attention?

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Abstract: There is no general agreement as to the meaning of long-term potentiation, but this cannot be resolved by using it to explain additional phenomena. Increased attention to recently experienced stimuli is a form of learning known to neuropsychologists as repetition priming. As more is learned about the neurochemistry of synaptic change, the term LTP will wither.

It is difficult to criticise the thesis, promulgated (and exhibited) in the target article, that much confusion surrounds the role of LTP in learning. I believe the confusion is largely terminological; some people use LTP to refer to any stimulation-induced change in synaptic effectiveness; others would confine its use to the change produced by tetanizing NMDA synapses; and LTP is sometimes used as a hypothetical process that is responsible for memory at synapses whose physiological responses have never been measured.

Unfortunately, although the target article raises this problem, it does not tackle it very seriously, and in places it perpetuates it. It assumes, for example, that if memory is not impaired by NMDA receptor blockers then LTP is not a memory mechanism. Instead of trying to clarify the meaning of LTP, and of memory, Shors & Matzel (S&M) try to involve LTP in an area that is even more confused than memory, namely attention. The authors' suggestion that the time course of LTP is more in keeping with attention than memory is surely incorrect, even for the extreme example of predator shock they present. Under normal circumstances, as I examine a drawing, or as a rat explores a new environment, selective attention shifts every few seconds. Long-term depression would seem to be the operative process as each item is examined and then forsaken.

S&M's new hypothesis that LTP acts by increasing the gain of neural representations of stimuli (sect. 4, para. 2) bears a strong resemblance to a form of memory neuropsychologists refer to as "repetition priming" (Tulving & Schacter 1990). Subjects respond more promptly to the second presentation of a target word, for example, though they may not consciously remember the first presentation. Would it not be simpler to acknowledge that memory may take many forms, including implicit memories that influence behavior but are not consciously accessible, than to muddy the waters further by calling some types of memory attention?

The evidence that events influence future behavior by changing the effectiveness of synapses is by now overwhelming. It is also clear that there is more than one neurochemical mechanism for producing changes in synaptic effectiveness; in fact, long-term memories appear to require a number of steps (Bear 1997). These may include (1) immediate changes in the structure of the receptor protein and probably of active afferent terminals, serving, among other things, as markers for future reactions; (2) the production of one or more second messengers that can bind to the internal parts of membrane spanning proteins to change membrane conductivity, as well as activating enzymes that synthesize highly mobile products like nitric oxide, and others that invade the cell nucleus and turn on immediate early genes; (3) marked terminals and receptors may then be modified more permanently by the diffusing products of these reactions. It may be necessary for two or more different pathways to be active at about the same time for all these reactions to take place.

Which, if any, of the many neural storage mechanisms we continue to call LTP will cease to be important as we learn more about their detailed neurochemistry, but it seems very likely that all of them, including the ones we now refer to as LTP, will be thought of as related in various ways to learning and memory.

Cortical plasticity and LTP

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Abstract: In the developing and adult cortex, just as in the adult hippocampus, LTP is unable to account for a variety of types of functional plasticity.

The target article by Shors & Matzel (S&M) points out some of the difficulties in relating long-term potentiation (LTP) in the mammalian hippocampus to learning and memory formation. LTP has also been proposed as the basis for plasticity in the developing and adult cerebral cortex.

Changes in the response properties of neurons in adult neocortex occur on a variety of time scales. The most rapid time scale we will refer to as "cortical dynamics." This category includes rapid alterations in receptive field structure by stimuli outside the classical receptive field, a context dependent effect that is present

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even in primary sensory cortex (Sillito et al. 1995; Toth et al. 1996; Zipser et al. 1996). Changes on this time scale occur instantaneously and persist only during the presence of the modifying sensory stimulus. They are hypothesized to reflect the convergence of synaptic inputs, including subthreshold inputs, which have recently been shown to be extensive in primary sensory cortices (Moore & Nelson 1994; Toth et al. 1996).

A second time scale for changes in neuronal responses is short-term plasticity. This class of changes includes longer-lasting changes in the weights of already existing connections, not simply the recruitment of a different pattern of existing connections. Pettit and Gilbert (1992) have shown that in primary visual cortex, neurons can increase the size of their receptive field when the classical (action-potential inducing) receptive field is masked and stimuli are presented to the surround. This change takes minutes to occur and persists after the cessation of the stimulus. Similarly, in the primate auditory cortex, inducing two neurons to fire in temporal synchrony in response to an auditory stimulus increases the strength of their cross-correlograms (Ahissar et al. 1992), a modification which takes between 70–850 seconds. Phenomena such as working memory, perceptual priming and focal attention may be supported by mechanisms on this time scale. Recent results demonstrating rapid changes in synaptic efficacy in cortical transmission (Abbott et al. 1997; Markram et al. 1997) provide attractive candidate mechanisms for short-term plasticity.

A third time scale is long-term plasticity. On this time scale, we include modifications in receptive field structure that persist from minutes to hours, and include permanent changes in cortical organization. These types of changes may underlie long-term memory storage in the cortex (Buzsaki 1989). This time scale of change probably also underlies the cortical response to long-lasting changes in peripheral input. A recent example of this kind of plasticity is the demonstration that temporally correlated input across the distal finger pads in monkeys causes a reorganization of the cortical map, so that these finger pads become spatially contiguous in the somatosensory cortex (Wang et al. 1995; see also Diamond et al. 1994).

What does cortical LTP, a phenomenon lasting between tens of minutes and hours, have to do with these three types of cortical plasticity? All three phenomena share a dependence on temporal convergence of inputs to support their mechanisms, a requirement for LTP as well. However, by definition, rapid modifications in receptive field structure (cortical dynamics and short-term plasticity) do not use LTP. Hence, two classes of important receptive field modifications (relating to perception) cannot be understood by the study of LTP. Long-term plasticity includes a variety of phenomena, including persistent changes in synaptic transmission and anatomical changes in the cortex (Darian-Smith & Gilbert 1995). While some of these phenomena may be supported by LTP-like mechanisms (see Dinse et al. 1993 for evidence that LTP-like stimuli can shift the location of receptive field maps in primary sensory cortex), other changes cannot be accounted for by cortical LTP as currently defined. We conclude with S&M that the emphasis placed on LTP as a catch-all for neuronal plasticity, in this case in the cortex, is inappropriate. The phenomenology of relevant plasticity is far more varied and complex than LTP as we currently understand it.

At the core of the question of how LTP relates to these different time scales of cortical plasticity is the question of why the cortex should modify its organization. We describe above a variety of answers to this question, including context-dependent binding of features, working memory, perceptual priming, and long-term memory. While a detailed discussion of these phenomena is beyond the scope of this commentary, we do point out that, whatever the time scale and purpose of plasticity in the cortex, the cortex must show plasticity for features that it encodes.[1] Furthermore, plasticity for emergent cortical features (e.g., orientation tuning) can only be modified at the level of the cortex. Mechanisms underlying such changes are likely to hold the key to understanding cortical plasticity across time scales of expression (e.g., Fregnac et al. 1988).

NOTE

1. We make this point in the context of several studies that have reported cortical plasticity as the result of temporary or permanent lesions to the spatial topography of sensory input. There is extensive plasticity in topographic maps at peripheral stages in the input pathway (e.g., Devor & Wall, 1981 [rat dorsal horn]) which can occur rapidly (within minutes) and with relatively small perturbations of the peripheral input pattern (i.e., anesthesia of a local region; Pettit & Schwark 1993 [cat dorsal column nuclei]; Nicolelis et al. 1993 [rat thalamus]). While we agree that some modification of the spatial sensory map (e.g., retinotopy) may occur in the cortex, this plasticity is clearly not unique to the cortex, and many of the results showing "cortical plasticity" can be readily explained by subcortical changes (Merzenich et al. 1983). Furthermore, because of the spread in afferent projections as information rises in sensory systems, plasticity in peripheral nuclei can have a greater effect than cortical plasticity, and can perhaps better explain more radical forms of map alteration (Pons et al. 1991).

Preconceptions and prerequisites: Understanding the function of synaptic plasticity will also depend on a better systems-level understanding of the multiple types of memory

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Abstract: Although it is not their fault, Shors & Matzel's attempt to review the LTP and learning hypothesis suffers from there being no clear published statement of the idea. Their summary of relevant evidence is not without error, however, and it oversimplifies fundamental issues relating to NMDA receptor function. Their attentional hypothesis is intriguing but requires a better systems-level understanding of how attention contributes to cognitive function.

Shors & Matzel's (S&M's) cautionary tale provides useful insight into the minds of critics. Their somewhat over-literal interpretation of the "LTP and learning" (LL) hypothesis characterises it as riddled with terminological ambiguities and held together more by preconception than by evidence. To them, it has for too long been "the only show in town." Their idea is that synaptic plasticity alters attention to sensory stimuli. In my view, part of S&M's apparent confusion surrounding the LL hypothesis is of their own making, and the evidence supporting a role for LTP in certain types of learning is stronger than they surmise. Moreover, a weakness of their new hypothesis is that our systems-level understanding of "attention" is arguably as limited as that of the multiple types of "learning." A prerequisite for progress is better systems-level understanding of both processes.

A difficulty with the LL hypothesis has always been that, despite being widely discussed, there is no one clear statement of the idea to which neuroscientists can turn. Rather, it has evolved from the baroquely worded question with which Bliss and Lomo (1973) concluded their pioneering paper, through a number of statements implicating changes in synaptic efficacy in information storage (e.g., Bliss & Collingridge 1993; Goelet et al. 1986; McNaughton 1983; McNaughton & Morris 1987; Morris et al. 1991; Teyler & Discenna 1987). The simplest statement of the hypothesis, and one without any preconception about LTP and memory storage, is that "the neural mechanisms of activity-dependent hippocampal synaptic plasticity are activated during and necessary for certain kinds of learning and memory." I see this as a kind of "foundation stone" for a subsequent and more specific hypothesis.

This simplest version of LL is supported by the finding of correlations between the persistence of synaptic enhancement

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and the retention of hippocampus-dependent memory, and by the deleterious effects upon memory of physiological saturation and pharmacological blockade of LTP (Barnes 1988). My reading of the relevant literature is more positive than S&M's, primarily with respect to pharmacological studies of NMDA receptor-dependent LTP. S&M's account is not without error:

(1) The competitive antagonist AP5 that I and others have used is not "chemically related to angel-dust."

(2) Morris et al. (1986) did not "inject the antagonist directly into the ventricle." We used chronic intraventricular infusions via minipumps. These infuse continuously at the rate of 0.5 ul/hr for up to 14 days, an infusion regime that rarely results in the sensorimotor disturbances that follow acute injections and is, incidentally, approximately 420 times slower a rate of infusion than that used by Cain et al. (1996).

(3) Although it is true that AP5 only "slows the rate of learning" of a spatial reference memory task, this is also true of ibotenate hippocampal lesions (Morris et al. 1990). It is surely unreasonable to expect the subtle effects of an NMDA receptor antagonist on glutamatergic neurotransmission to be functionally more deleterious than those of a lesion.

(4) S&M also miss the point of the Bannerman et al. (1995) study. What we claimed evidence for was an NMDA antagonist-induced dissociation between different components of spatial learning, not between spatial and procedural components of the task (see Experiment 4 of that paper). To this list I would add:

(5) Using the watermaze, Robert Steele, Stephen Martin and I have recently obtained a highly significant AP5-induced, delay-dependent deficit in a delayed-matching-to-place (DMP) task that is also exquisitely sensitive to hippocampal lesions. AP5 treated rats perform normally at short memory delays but are severely impaired at longer delays. Such findings cannot be accommodated in terms of drug-induced sensorimotor disturbances (which were in any case not observed).

Nonetheless, we should always recognise the logical weakness of interpreting the effects of AP5 on behaviour as being necessarily arising from blocking NMDA receptor-dependent LTP. There may be other physiological effects of blocking slow but long-lasting NMDA currents. In lamprey spinal cord, for example, NMDA receptor activation turns on a calcium-dependent potassium current that repolarises the neuron and participates in the rhythmic control of swimming (Grillner et al. 1987). By analogy, antagonising hippocampal NMDA receptors may disrupt the dynamic systems properties of the hippocampal formation and this, rather than LTP blockade, could be responsible for impairments of hippocampus-dependent learning. More specific types of intervention are needed, such as drugs acting on the biochemical pathways responsible for LTP induction, but downstream of the NMDA receptor. Gene-targeting techniques, although not without drawbacks, constitute an alternative approach, particularly as the discovery of regionally specific genes (e.g., Tsien et al. 1996a) and the use of inducible promoters are collectively leading to new avenues of investigation (Mayford et al. 1996). The path of true science ne'er runs straight.

What about S&M's "new and nonspecific hypothesis"? On my reading, S&M implicitly adopt a "reflex" model of brain function in which circuits in the brain mediate links between stimulus and response. In such a framework, attention serves to enhance stimulus salience and can powerfully affect learning. However, S&M's identification of LTP with attention strikes me as "overliteral" in the sense that their mind's eye may be seeking an unnecessary isomorphism between the augmentation of stimulus salience characteristic of "attention" and the augmentation of neural responsiveness achieved by increased "synaptic efficacy."

I hold to a more eclectic view of the computational capacities of brain circuitry and the algorithms that different circuits compute. These include implementing multiple types of learning and memory beyond simple conditioning, and include memory for events (episodic memory) and the acquisition of knowledge (semantic memory). Attention influences the acquisition of these also, but there is no sense in which they represent a direct link between stimulus and response. They are behaviourally "silent" (although the knowledge acquired can be reflected in behaviour with appropriate tasks). Intact hippocampal function appears to be necessary for our capacity to record events on-line and to remember where they have occurred. A neural mechanism that can alter synaptic efficacy rapidly using a correlational type of synaptic learning rule with some measure of input-specificity and variable temporal persistence (Frey & Morris 1997) is ideal for linking events to spatial context. I refer to this aspect of episodic memory as the "automatic recording of attended experience" (Morris 1996) and see no sound reason to reject the hypothesis that hippocampal synaptic plasticity plays a critical role in the neural mechanisms of its implementation.

Long-term potentiation: Does it deserve attention?

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Abstract: Shors & Matzel's target article is a thought-provoking attempt to reconceptualise long-term potentiation as an attentional or arousal mechanism rather than a memory storage mechanism. This is incompatible with the facts of the neurobiology of attention and of the behavioural neurophysiological properties of hippocampal neurons.

Shors & Matzel (S&M) have provided an interesting and comprehensive review of the LTP literature, raising many interesting points about the field, in particular concerning the conceptual hold that seeing LTP as the biological basis of memory may have in limiting our capacity to recognize alternative hypotheses about its other possible functions. In this commentary we focus on the major and minor problems in S&M's review of the field generally and the attentional LTP hypothesis specifically. We suggest that the known facts of attentional function and of hippocampal function are incompatible with the attentional interpretation of LTP.

Minor issues. LTP, memory, and the hippocampus: S&M argue that memory necessary involves the strengthening of synapses, but logically memory could be also stored by a use-dependent weakening of synapses. Providing a long list of agents and asking whether they all affect similar mechanisms is plainly unreasonable as these agents have been used to differentiate different components of LTP itself (e.g., PTP, STP, early and late phases of LTP, etc.). This list of agents has also been used to investigate memory without any claims for memory having a unitary mechanism.

S&M, in their review of LTP and behavioural indices of memory, conclude that there is no convincing, unproblematic link between the two, and that the gene mutation studies have inevitably confounded studies because of the gross behavioural abnormalities they have introduced. Tsien et al. (1996b), however, have produced a mouse strain in which the deletion of the NMDA R1 gene is restricted to CA1 and the mutant mice grew to adulthood without obvious abnormalities. These mice lacked both LTP and NMDA receptor-mediated epsc (excitatory postsynaptic current) and, more important, they were impaired in the hidden platform spatial memory component of the Morris water maze task, but not in the nonspatial visually cued platform test. This strongly supports the idea that LTP in CA1 is crucial in the formation of at least certain types of memory. In a related experiment using the same mice, McHugh et al. (1996) found a significant decrease in the spatial selectivity of individual place fields and deficits in the coordinated firing of pairs of neurons tuned to similar locations.

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Again, this supports the idea that NMDAR-mediated plasticity is required for the proper representation of space in CA1.

S&M claim that the hippocampus is not a memory store but a temporary holding site. It is logically possible that the hippocampus holds memories also; there is no necessary requirement for a mechanism to erase memories after they've been consolidated in cortex. Moreover, the apparently long gradient of retrograde amnesia (in patient H.M., of the order of two to five years) stretches the concept of "temporary storage" by the hippocampus to the breaking point (Corkin 1984).

It is further claimed that there is a problem regarding the decremental nature of LTP. On a different view there is no problem at all: synaptic weight changes induced by LTP in the artificial state (whether *in vivo* or *in vitro*) are meaningless to the brain because they do not reflect the storage of a memory that will ever be accessed. This weight change does not reflect any information storage and is not tagged in any way which says these synapses cannot be overwritten. A poor analogy might be the perturbing of local storage sites on a floppy disk because of contact with, say, a small magnet. This will cause a local change in "storage" on the floppy disk, but the hard drive will subsequently be able to overwrite this local area because the storage change there is not tagged to prevent it being overwritten.

Major issues. The conceptual core of the target article relies on a reinterpretation of LTP as an arousal or attentional device, acting to enhance the gain of neural representations of environmental stimuli. How these neural representations become established is completely unspecified, but presumably it has something to do with the use-dependent change in synaptic weights or some other unspecified mechanism. A reply about the alternative to use-dependent changes which give rise to neural representations (memories) would be most valuable. Another major point that has been ignored throughout the target article is how LTP occurs naturally rather than artificially and a reply about how LTP occurs naturally and how it might be measured online would be extremely useful.

There are a number of more serious difficulties for this hypothesis, however. LTP has been most typically examined in the hippocampus, but there has been no comment on the functions of hippocampal neurons beyond the indirect implication that they have some function in spatial information processing. Many studies (O'Keefe 1979; O'Mara 1995) indicate that individual hippocampal neurons represent the position in space of the freely moving animal – "place cells." These neurons are often described as being behaviour-independent and location-specific in their activity – place cells fire independently of ongoing behaviour such as feeding, grooming, locomotion, rearing, or sniffing. Place cells also participate in memory (O'Keefe & Speakman 1987). S&M's hypothesis would seem to require that such cells be "attentional," given their role in LTP and spatial representation. This cannot be the case, given that place cells are behaviour-independent.

Studies of the neural bases of attention also seem incompatible with S&M's hypothesis. "Inhibition of return" is the well-known phenomenon whereby attending to a previously attended location is actually inhibited compared to attending other locations. How can LTP as an enhancement of neuronal response be involved with this attentional inhibition? Furthermore, there is no evidence that the hippocampal formation is involved in attentional processes at all. Instead, a network of nonhippocampal systems subserving different forms of attention appears to exist. In Posner and Dehaene's scheme (1994), where selective attention is concerned, the posterior parietal cortex releases attention from a current focus, the midbrain (superior colliculus) moves attention to a cued area, and the lateral pulvinar nucleus of the posterolateral thalamus selects the contents of the attended area and enhances them for more anterior areas to process and decide behaviour. The latter "executive" system is mediated primarily by the anterior cingulate cortex. A further network of attention has been identified as one used for vigilance and arousal, involving frontal and parietal areas of the nondominant hemisphere. S&M would therefore need to show that the hippocampal formation is activated during attentional tasks in order to support their theory. The known connectivity of the hippocampus alone is incompatible with this idea.

In summary, therefore, we believe there are a large number of major and minor conceptual problems with the hypothesis as presented which render it untenable. However, it is now time to think of both alternative interpretations of LTP and alternative mechanisms of memory storage, and we applaud Shors & Matzel for launching this debate.

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Stress, LTP, and depressive disorder

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Abstract: Preoccupation with LTP as a putative memory mechanism may have retarded the consideration of pathological modulation of synaptic plasticity in clinical disorders where memory dysfunction is not a primary feature. Encouraged by Shors & Matzel's review, we consider the relationship between stress, synaptic plasticity, and depressive disorder.

Shors & Matzel (S&M) provide a welcome re-appraisal of the role of long term potentiation (LTP). The biochemical machinery which is proposed to support LTP – glutamatergic neurotransmission and the NMDA receptor – has long been implicated in a variety of clinical disorders, ranging from the excitotoxic damage that occurs after stroke, through epilepsy and the modulation of pain, to the neurobiology of psychotic states. Preoccupation with LTP as purely a memory mechanism, however, may have delayed considering disrupted synaptic plasticity as an important pathological consequence of putative excitatory amino acid system dysfunction in neuropsychiatric disorder.

Our work centres on the neurobiology of depressive disorder. Earlier work conducted by Shors and her colleagues (Shors et al. 1989) has been of special interest. The key finding is the alteration in rodent hippocampal LTP following exposure to stress, with most marked disruption observed following the induction of "learned helplessness." The phenomenon of learned helplessness and its physiological and biochemical correlates have attracted considerable interest over the years in the modelling of human depressive disorder. Though Kim et al. (1996) have drawn attention to this in discussing stress induced modulation of LTP, they restricted their analysis to purely cognitive aspects of depressive disorder, just as S&M focus on attentional mechanisms. Stress induced alterations in LTP may, however, play a more central role in pathological mood states.

A number of independent studies have implicated NMDA receptor function in the pathophysiology of depressive disorder. Drugs active at the NMDA receptor have antidepressant properties in pre-clinical drug screening procedures (Trullas & Skolnick 1990). Moreover, a number of different, established antidepressant agents cause adaptation of the NMDA receptor complex (Paul et al. 1994), and abnormalities in NMDA receptor characteristics have been described post-mortem in the brains of suicide victims (Nowak et al. 1995). However, the consequences of these diverse findings for functional correlates, such as modulation of LTP, have been little explored.

We have reported that repeated electroconvulsive stimulation (ECS), a potent antidepressant treatment, enhances synaptic connectivity in the dentate gyrus of the hippocampus and reduces the degree to which LTP can be induced in rats (Stewart & Reid 1993). The effect gradually regresses over a period of about 40 days (Stewart et al. 1994), is associated with the induction of

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GluR1mRNA in the hippocampus (Naylor et al. 1996) and can be blocked by prior administration of ketamine (Stewart & Reid 1994). Though mindful that our findings may have some bearing on the well known amnesic effects of electroconvulsive therapy (ECT), we also considered the possibility that our observations might be relevant to the therapeutic, antidepressant effects of ECT. Our most recent work (Stewart et al. 1996) indicates that chronic administration of fluoxetine, a chemical antidepressant without effect on memory, has quantitatively similar effects to ECS on LTP induction. We propose that this common property of very different antidepressant agents in enhancing synaptic connectivity represents the mechanism for their clinical efficacy.

Given that Shors and colleagues indicate that inescapable stress, like ECS, enhances synaptic connectivity, this proposal may appear paradoxical. However, S&M clearly imply that they consider stress induced enhancement of synaptic efficacy to be adaptive in the face of threatening events. Henke (1990) has shown that dentate field potentials may, in fact, be enhanced or reduced following restraint stress. Individual rats varied in their response, and those animals who displayed a reduction in synaptic transmission after stress were more likely to suffer stress-related gastric ulceration. Henke concluded that reduction of synaptic efficacy following stress was associated with impaired coping ability. He has also shown that artificial enhancement of synaptic efficacy via the induction of LTP in the dentate gyrus using high frequency stimulation reduces gastric ulcer formation in stressed rats (Henke 1989). This stress protective alteration in plasticity is equivalent to the antidepressant induced changes we have observed. The apparent paradox is thus resolved: we hypothesise that a stress induced increase in synaptic efficacy is indeed adaptive, as Shors & Matzel suggest, and that those animals that fail to mount such a response may be converted to responders ("treated") by direct high frequency stimulation of the dentate gyrus, by electroconvulsive stimulation, or by the administration of chemical antidepressants. This in turn provides a novel perspective in which to conceptualise the pathophysiology of depressive disorder.

As in long-term memory, LTP is consolidated by reinforcers

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Abstract: Recent evidence from our lab indicates that LTP shares an important property with memory consolidation: it is consolidated by natural reinforcement. Nevertheless, the hypothesis, that LTP-like mechanisms or other forms of enhanced synaptic efficacy are basic elements in learning is not unequivocally supported. Skepticism aside, LTP is an accessible experimental model that is optimally equipped for the investigation of the cellular and molecular machinery involved in synaptic weight changes.

1. Inadmissable levels of comparison. LTP is certainly not the only form of activity-dependent synaptic plasticity in a continuum of changes from adaptation to pathology, as stated earlier by McEachern and Shaw (1996). Despite the lack of conclusive evidence that LTP is an elementary memory storage device, it is still a viable candidate for such a function. The contribution of other, nonsynaptic, changes should of course not be ruled out. The many inconsistencies in relationship between LTP and memory storage, reviewed in the target article by Shors & Matzel (S&M) may arise from the fact that the question itself is flawed. Might it be wrong to presuppose that such different levels of analysis can be compared? LTP is a property of a single synapse that adjusts synaptic efficacy, whereas memory formation is a property of the whole brain that enables an individual organism to adapt to changes in its environment. Behavioral learning and memory are the result of network operations which cannot be explained by the simple sum of single synapse action. The network clearly uses a distributed storage system involving different levels of interaction, many individual synapses, and very different molecular machinery for the regulation of efficacy. Many years ago Hansjürgen Matthies emphasized this general idea with the following remark: "A transistor or microcircuit alone can never explain the function of television or a personal computer, although it is a necessary element!"

Today we know that just as there are many types of learning, there are many types of LTP. To find a simple correlation among these complex phenomena seems impossible. Lack of correlation could occur if inappropriate types and structures were compared or if compensation by other mechanisms can take place. Why should NMDA receptor antagonists block all types of learning (cf. sect. 3.1.)? Another subset of network elements that do not depend on NMDA receptor dependent plasticity might be involved, or the same network may use additional types as VDCC- or mGluR-dependent LTP. Several investigators have reported that even in neurons known to exhibit NMDA receptor dependent LTP, other forms of NMDA receptor-independent LTP can occur (Grover & Teyler 1995; Manahan-Vaughan & Reymann 1996). Thus, the individual players in the cascades underlying potentiation, depotentiation, and depression might vary across neurons of different phenotypes, or even within neurons, as a function of the eliciting stimulus, the contribution of modulators, and so forth. Such a spectrum of different types and mechanisms of potentiation gives the system a high degree of freedom, although it uses the basic governing principle of synaptic efficacy change.

Other inconsistencies described by S&M can easily be rebutted as failures to perform the appropriate experiments. Changes in nondirectly activated synapses or structures do not necessarily mean that LTP is not specific (cf. sect. 2.4.) if remote changes are not physiologically controlled. The failure to demonstrate nondecremental LTP (cf. sect. 2.5) can be due to methodological limitations such as recording stability or the minor nature of changes in cortex. S&M's discussion of discrepancies in optimal interstimulus intervals in associative LTP versus conditioning (cf. sect. 2.7) fails to consider that more delayed associations between converging inputs may depend on newly synthesized proteins as described recently by Frey and Morris (1997) or in our LTP-reinforcement studies mentioned below.

2. Levels of arousal or reinforcement qualities? Our lab recently evaluated the effect of behavioral and motivational states, which are known to affect learning, on LTP induced by strong or weak tetanic stimulation in the dentate gyrus of freely moving rats (Seidenbecher et al. 1997). The strong tetanization produced a "saturated" LTP which lasted more than 24 hours, and did not differ significantly between behavioral states. LTP induced by weak tetanization, however, did differ across behavioral states. LTP which normally lasted only 5–7 hours was clearly prolonged to more than 24 hours if the water-deprived rats were allowed to drink during or up to 30 min after the tetanus. Similar results were obtained using footshock instead of water.

We concluded that both appetitive and aversive stimuli act within a certain time window as reinforcers to consolidate LTP much as in memory formation. It seems plausible that during our strong and perhaps less physiological stimulation, the transmitter systems (such as norepinephrine and dopamine) involved in the reinforcement already seem to be activated by the electrical stimulation. At first glance these findings support S&M's idea that LTP is a neural equivalent to an arousal or attention device in the brain (cf. sect. 4). In our experiments, however, motivation alone (e.g., thirst) does not influence LTP. Furthermore, the behavioral triggers of our changes were very specific, as was the association with weak tetanus-treated synapses.

That these mechanisms converge on similar neuronal mechanisms (norepinephrine and similar forms of LTP) in some structures is not sufficient argument for reducing the function of LTP to a merely amplifying mechanism for neuronal representation of sensory stimuli. Our behaviorally induced late LTP instead reflects

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the association of an external signal with a relevant reinforcement situation. In conclusion, LTP seems to need a mechanism similar to that underlying motivation, arousal, and reinforcement in memory storage.

Learning and synaptic plasticity

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Abstract: Controversy surrounds several experiments that have addressed whether selective synaptic strengthening occurs during learning. To date, the evidence suggests that widespread alterations in synaptic strength, through either kindling or electroconvulsive shock, can disrupt this hypothetical process. The lack of evidence for selective modification of learning through LTP stimulation, however, provides difficulties for both the prevailing hypothesis and the hypothesis advanced by Shors & Matzel. Subsequent experiments may indicate a role for LTP in both learning and arousal.

One intriguing and difficult problem in the behavioural neurosciences is to determine the neural mechanism(s) of learning and memory. An approach adopted by behavioural neuroscientists to simplify the problem is the model-phenomena approach in which investigators attempt to correlate similarities between the characteristics and mechanisms of LTP and learning or to demonstrate that experimentally induced LTP alters subsequent learning ability. Although this approach has merit, it may also oversimplify a complex problem.

Shors & Matzel's (S&M's) target article is a comprehensive critique of the major lines of experimental evidence that have raised the possibility that hippocampal LTP is a neural mechanism of mammalian learning and memory. S&M do not discount this hypothesis completely, but they argue that most experimental results are more consistent with the hypothesis that LTP indirectly modulates learning and memory by facilitating attention/arousal. A role of LTP in arousal would better explain some experimental data. For example, NMDA antagonists, which block the induction of NMDA-dependent LTP, reduce the rate at which animals acquire some tasks but do not eliminate learning. However, S&M's hypothesis is subject to many of the same criticisms as the original hypothesis, a fact recognized by S&M.

One line of evidence (see sect. 3.3, saturation of the capacity for plasticity) does not appear to support either hypothesis. A fairly direct test of the prevailing hypothesis involves experimentally increasing synaptic strength (i.e., LTP induction) and observing the effects of that manipulation on subsequent learning. Two studies (Berger 1984; McNaughton et al. 1986) with apparently contradictory results pioneered this approach and their results dominated the literature for nearly a decade (also see Castro et al. 1989). As noted by S&M, subsequent tests of the hypothesis have yielded negative results, with one exception. Barnes et al. (1994) reported a small but significant effect of LTP on a rat's ability later to acquire the Barnes circular maze task. LTP, however, did not disrupt subsequent acquisition of the Morris water maze task. In contrast to the ineffectiveness of LTP, intense electroconvulsive shock disrupted acquisition of the Morris water maze task. The explanation of previous failures of LTP to disrupt spatial learning was that those studies failed to potentiate a sufficient number of synapses. This is reasonable, but a "theoretical saturation point," and the "probable nonlinear relationship between memory disruption and saturation of the synaptic weight distribution" (Barnes et al. 1994, p. 5805) were the basis for this explanation. Furthermore, the widespread neural changes produced by electroconvulsive shock are probably more similar to those produced by kindling stimulation than by normal LTP-inducing stimulation. Kindling, under certain conditions, also disrupts spatial learning (Robinson et al. 1993). Despite producing a potentiation effect, the mechanisms of kindling differ, in many respects, from the mechanisms of LTP (Cain 1989). Thus, convincing evidence that LTP disrupts spatial learning is still lacking.

In contrast to the results of the second major study (Berger 1984), we demonstrated that experimentally induced hippocampal LTP did not facilitate discrimination learning (Rioux & Robinson 1995). Furthermore, during subsequent reversal learning, a hippocampus-dependent task, hippocampal LTP was ineffective in altering the acquisition of the discriminative response. Thus, it appears LTP is ineffective in modulating learning (or attention/arousal) whether or not the task is hippocampus-dependent. Our finding that hippocampal LTP does not alter classical conditioning of the rabbit nictitating membrane response could have arisen because the task (discrimination between stimuli in two different modalities) required less attention than the task (discrimination between two auditory signals) utilized by Berger (1984). Thus, LTP may exert less of an effect on the rate of conditioning under conditions when the task requires less attention. Although it is not directly suggested by S&M, this explanation fits the framework of their hypothesis.

Kindling, however, facilitates the learning of the initial discrimination but retards the rate of reversal learning (Robinson et al. 1989). This is similar to the disruptive effect of electroconvulsive shock on spatial learning. Hence experimental results previously viewed as contradictory may be fairly similar. In particular, widespread neural changes, whether induced by kindling or by electroconvulsive shock, appear to disrupt certain types of learning, whereas LTP-inducing stimulation, which is more limited in terms of the number of altered synapses, does not appear to alter learning. The effects of both kindling stimulation and intense electroconvulsive shock on learning suggest that there may be some merit in Barnes et al.'s (1994) "theoretical saturation point." However, the extent of the neural changes produced by both stimulation techniques is unknown. The resultant behavioural change could accordingly be attributed to any number of neural sites and mechanisms.

The failure of experimentally induced LTP to alter subsequent learning, either directly or indirectly, does not justify accepting the extreme alternative: "LTP is neither an information-processing device nor a memory mechanism" (see sect. 5, concluding remarks). The acquisition, storage, and recall of information are likely accomplished by numerous brain regions, utilizing a variety of mechanisms and subject to many modulatory influences. Recent experiments demonstrate that (1) LTP can be induced in many brain regions, (2) involves a number of different mechanisms, and (3) is subject to numerous modulatory influences. Behavioral neuroscientists, however, are attempting to correlate a neural event induced at a single site, and influenced by a multitude of known and unknown factors, with the expression of complicated behaviours. Given the complexity, it is possible that both the LTP = learning and LTP = arousal hypotheses are correct. For example, naturally occurring LTP of brain stem inputs to the hippocampal formation and various cortical regions may increase attention/arousal and thereby facilitate the rate of learning, whereas naturally occurring LTP of sensory inputs may facilitate the formation of associations through selective synaptic strengthening. In sum, both hypotheses have merit, but lack experimental support. The prevailing hypothesis has generated many studies that have increased our understanding of brain plasticity and its relation to behaviour, whereas Shors & Matzel suggest alternative approaches in the search for the engram.

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LTP and memory: Déjà vu

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Abstract: Shors & Matzel's conclusion that LTP is not related to learning is similar to one we reached several years ago. We discuss some methodological advances that have relevance to the issue and applaud the authors for challenging existing dogma.

In 1986, Morris et al. introduced a strategy to link LTP to learning. They reasoned that if NMDA-dependent LTP in the hippocampus was a neural mechanism necessary for learning, then blocking the induction of LTP by an NMDA antagonist could prevent animals from learning behaviors such as place learning in the Morris water maze, which depend on the hippocampus. This work was followed shortly by another paper by Staubli et al. (1989), who used the same logic but applied it to another behavioral task, learning a set of odor discriminations. In both cases, the authors concluded that the behavioral results supported the notion that LTP was a learning mechanism because rats treated with the NMDA antagonists were impaired compared to controls. These papers gave considerable momentum to the LTP-learning hypothesis.

However, in a paper that generated a lively discussion, we (Keith & Rudy 1990) offered a critique of that work and concluded that the results provided grounds for rejecting the hypothesis because (a) although somewhat impaired, the rats in these experiments did solve the problems, and (b) the residual impairment could be a "performance effect" of the drug.

Shors & Matzel's (S&M's) review indicates that the situation has further deteriorated for the LTP-learning hypothesis. Indeed, the recent literature confirms our conclusion that NMDA-dependent LTP is not required for learning the place task. The most convincing evidence comes from studies where normal rats are trained to solve the place task in one room and then taken to a *new room* where they learn to find the hidden platform under the influence of an NMDA antagonist (e.g., Cain & Saucier 1996). Pretrained drug-treated rats learned the second task just as placebo-treated rats do. Thus, the impairment displayed by drug-treated task-naive rats was due to properties of the drug that interfered with performance, not with learning and memory for spatial cue configurations needed to localize the hidden platform.

This finding should be of great concern to researchers using *instrumental learning tasks* to relate brain processing to learning processes. The Morris task is particularly limited as a tool for assessing drug and lesion effects on learning because once the rat is placed in the swimming pool, the experimenter has lost complete control of the experiment because it is the rat's behavior which determines the quality and quantity of the information it receives. Drug administration, gene manipulations, or brain lesions could all alter the manner in which the rat contacts the relevant features of the environment rather than the neural mechanisms involved in learning.

The pretraining experiment illustrates that the learning/performance distinction is not just an abstraction put forth by hypercritical psychologists; when properly addressed it can provide grounds for rejecting a hypothesis. Researchers using the Morris task to claim that a particular drug, gene, lesion or the like influences the fundamental learning and memory processes underlying the task should be required to determine whether the pretraining manipulation eliminates the impairment before the work can be published.

When animal learning theory experienced a resurgence in the 1960s it was in part because the experimenters used Pavlovian conditioning procedures which permitted the control of the relevant parameters of the experiment (e.g., stimulus intensity, intertrial interval, and interstimulus interval). Given the advantages of Pavlovian procedures and the problems with the Morris task, it is hard to understand why researchers continue to use it to relate brain processes to learning and memory.

As Shors and Matzel's (S&M's) target article illustrates, it is tough to convince a critical reader that NMDA-dependent LTP, induced by delivering electric shock to neural pathways, is a memory storage device for a particular learned behavior. Perhaps a better question is which of the many pharmacological and molecular mechanisms revealed by LTP studies offer testable hypotheses about neural processes that may participate in learning and memory? One need not get caught up in trying to defend LTP per se as a mechanism of learning.

S&M propose a new role for LTP. According to them, LTP provides a neural mechanism for arousal or for increasing the salience of environmental stimulation. We raise two questions about this hypothesis. First, does the hypothesis suggest new experiments? Is it testable? Unfortunately, S&M suggest no new experiments to test the hypothesis. Second, after considering S&M's argument for the parallels between behavioral arousal and LTP, we wonder why LTP shouldn't be considered a byproduct of arousal and not a mediator of its effects? Another alternative is that LTP may have no functional significance.

On balance, we applaud the authors for bringing this diverse literature together and challenging existing dogma. Right or wrong, the new hypothesis about the functional significance of LTP should be welcomed as a signal that the field is ready to acknowledge more openly the empirical anomalies that undermine the LTP = learning hypothesis and to consider new hypotheses. The first idea is rarely the correct one.

Stimulus configuration, long-term potentiation, and the hippocampus

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Abstract: Shors & Matzel propose that hippocampal LTP increases the effective salience of discrete external stimuli and thereby facilitates the induction of memories at distant places. In line with this suggestion, a neural network model of associative learning and hippocampal function assumes that LTP increases hippocampal error signals to the cortex, thereby facilitating stimulus configuration in association cortex. Computer simulations show that under these assumptions the model correctly describes the effect of LTP induction and blockade in classical discriminations and place learning.

Schmajuk and DiCarlo (1992) described a neural network model of classical conditioning (see Fig. 1) that comprises one input layer, one hidden layer, and two output layers. The output activities of the input layer, as_1, as_2, and as_X, code simple stimuli CS_1 and CS_2, and the context, CX. Input units form direct associations, VS_1, VS_2, VS_X, with the first output layer. In addition, input units form associations, VH_{ij}, with the hidden-unit layer. The output activities of the hidden-unit layer, an_1, an_2, and an_3, are assumed to code configural stimuli denoted by CN_1, CN_2, and CN_3. In turn, hidden units form associations, VN_1, VN_2, VN_3 with the first output layer.

The associations between simple and configural stimuli and the unconditioned stimulus (US), VS_i and VN_j, are controlled by a simple delta rule that minimizes the output error, $EO = US - B$, between the actual value of the US and its aggregate prediction, B. B and the conditioned response are proportional to the sum of the activation of simple and configural associations with the US ($\Sigma_i as_i VS_i + \Sigma_j an_j VN_j$). The associations between simple stimuli and the hidden units, VH_{ij}, are regulated by hidden-unit error, EH_j, proportional to $an_j VN_j EO$.

Schmajuk and DiCarlo (1992; Schmajuk & Blair 1993) suggested how different blocks in the model could be mapped onto different brain regions. Whereas hidden units are assumed to represent neural populations in association cortex, output units can represent either cerebellar circuits controlling the nictitating

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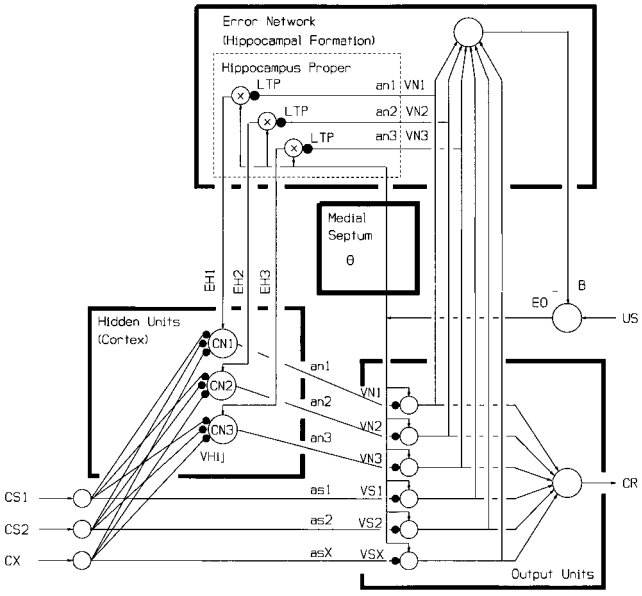


Figure 1 (Schmajuk). Diagram of the Schmajuk and DiCarlo model (adapted from Schmajuk & DiCarlo 1992). CS: conditioned stimulus, CN_j: configural stimulus, VS_i: CS-US association, VN_j: CN_j-US associations, VH_{ij}: CS_i-CN_j; association, US: unconditioned stimulus, B: aggregate prediction, EH_j: error signal for hidden units, EO: error signal for output units, θ: theta rhythm. The hippocampus block includes the hippocampus proper (CA1 and CA3 regions). The hippocampal formation block includes the hippocampus proper, dentate gyrus, subiculum, presubiculum, and the entorhinal cortex. Arrows represent fixed synapses. Solid circles represent variable synapses.

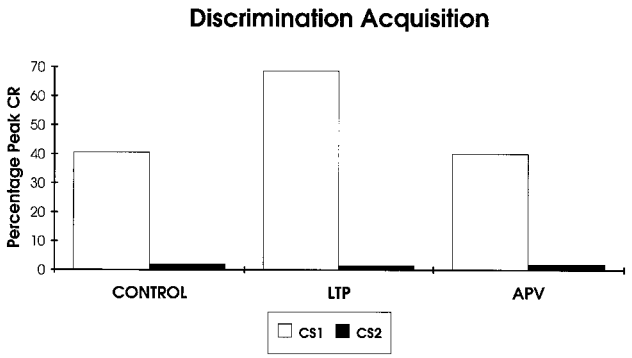


Figure 2 (Schmajuk). Computer simulations of discrimination acquisition after LTP induction and blockade. Percentage peak CR amplitude for normal animals evoked by CS_1 and CS_2 after 5 nonreinforced CS_1 trials alternated with 5 reinforced CS_2 trials (discrimination acquisition). Induction of LTP was simulated by a twenty-fold increase in error signal for the hidden units. D-amino-phosphovalerate (APV) blockade of endogenous LTP was simulated by making the error signal for the hidden units equal to zero. Simulation details and parameter values are those used in Schmajuk and DiCarlo (1992). CS duration is 200 msec, CS intensity is .5, Context intensity is .5, and US intensity is 1. Twenty hidden units were used.

membrane response, or caudate circuits controlling spatial behavior. Units computing the hidden-unit error signals, EH_j, represent pyramidal cells in the hippocampus proper, and units computing the aggregate prediction, B, represent neurons in the entorhinal cortex.

Output error, EO, coded as theta rhythm (θ) and assumed to reach the hippocampus from the medial septum, modulates the responsiveness of pyramidal cells in CA1 and CA3 regions to perforant path inputs (an_j VN_j) thereby yielding the error signal for the association cortex, EH_j.

Schmajuk and Blair (1993) proposed that the effect of lesions to the hippocampus proper (regions CA3 and CA1) could be described by assuming $EH_j = 0$, and lesions of the hippocampal formation (hippocampus proper, dentate gyrus, subiculum, presubiculum, and entorhinal cortex) by assuming $EH_j = 0$ and $B = 0$. Under these hypotheses, the SD model correctly describes the effects of selective and nonselective lesions in a large number of classical conditioning paradigms and spatial learning.

Although the original SD model does not assume information storage in the hippocampus, Schmajuk and DiCarlo (unpublished results; Buhusi & Schmajuk 1996) studied the consequences of assuming that perforant path connections to granule dentate cells and CA3 pyramidal cells store associations between an_j VN_j and θ (Robinson 1986). Whereas LTP-induced increments in these connections would increase the cortical error signal EH_j, blockade of endogenous LTP would decrease EH_j.

Berger (1984) found that entorhinal cortex stimulation that produced LTP increased the rate of acquisition of a two-tone classical discrimination of the rabbit NM response. Morris et al. (1986) showed that application of D-amino-phosphovalerate (APV), an antagonist of the NMDA class of glutamate receptor, does not impair a visual discrimination task.

Figure 2 shows that according to the SD model, and in agreement with Berger (1984), LTP facilitates discrimination acquisition by increasing EH_j, thereby fostering cortical learning. It is interesting to note that an alternative "memory" assumption – CS-CS associations are stored in the hippocampus – incorrectly predicts that the discrimination should be impaired because CS+ and CS− become associated when LTP is induced. Figure 2 also shows that, in agreement with Morris et al. (1986), APV blockade of endogenous LTP does not impair the acquisition of a visual discrimination because a simple discrimination can be learned even in the absence of cortical units.

Using the SD model, Schmajuk and Blair (1993) simulated place learning in the Morris water maze by exposing the network to different points in the tank and consistently rewarding it at the location where the platform is located. At each location, the network's inputs are the visual angles to four visual landmarks. After training, the system becomes maximally active at the spatial location where the hidden platform is encountered and displays decremental generalization at other locations. Schmajuk (1990) suggested that animals might navigate to the location of the platform by following the gradient of the network's output from any novel start point in the periphery of the tank.

Figure 3 shows that, in agreement with Barnes et al. (1994), whereas normal animals show maximal activity at the location of the hidden platform, LTP induced by maximal electroconvulsive shock (which produces a thorough saturation of hippocampal synapses), impairs the prediction of the precise location of the platform. Similarly, in agreement with Morris et al. (1986), APV treated animals are also impaired at the prediction of the location of the platform.

According to the SD model, LTP induction facilitates classical discriminations by facilitating CN-US associations but impairs spatial navigation by excessively increasing the gain for cortical learning, thereby hindering stable learning of the visual angles to distal landmarks. Similarly, LTP blockade spares classical discriminations because CN–US associations are not necessary to respond preferentially to the reinforced CS, but it impairs spatial navigation because cortical learning (reflected in the formation of CNs) is needed to learn about the visual angles to distal landmarks.

Shors & Matzel propose that hippocampal LTP, instead of being the substrate for memory storage, increases the effective salience of discrete external stimuli and thereby facilitates the induction of memories at distant places. In a similar vein, the SD model assumes that hippocampal LTP stores cortical–septal associations, thereby increasing hippocampal error signals which facilitate

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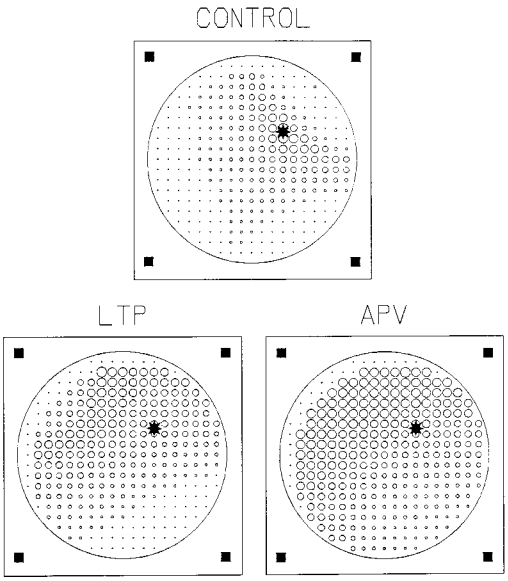


Figure 3 (Schmajuk). Computer simulations of spatial learning after LTP induction and blockade. Simulated prediction of the location of the hidden platform at different points in the Morris water maze after 100 trials, equivalent to 10 experimental trials, for Control, LTP, and APV cases. The large circle represents the boundary of the Morris tank; four spatial landmarks are represented by solid boxes, and the arrow indicates the location of the hidden platform. The squares represent four visible distal landmarks outside of the pool with visual angles Ω_i, which are the input to the system. The magnitude of the network's prediction of the location of the platform at each point in the pool is represented by the sizes of the small circles. Induction of LTP was simulated by a 20-fold increase in error signal for the hidden units. D-aminophosphovalerate (APV) blockade of endogenous LTP was simulated by making the error signal for the hidden units equal to zero. Simulation details and parameter values are described in Schmajuk and Blair (1993). Twenty hidden units were used.

stimulus configuration in the cortex. Computer simulations show that under these assumptions the model correctly describes the effect of LTP induction and blockade in classical discriminations and spatial learning.

Long term potentiation: Attending to levels of organization of learning and memory mechanisms

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Abstract: Shors & Matzel set up a straw man, that LTP is a memory storage mechanism, and knock him down without due consideration of the important relations among different levels of organization and analysis regarding LTP, learning, and memory. Assessing these relationships requires analysis and hypotheses linking specific brain regions, neural circuits, plasticity mechanisms, and task demands. The issue addressed by the authors is important, but their analysis is off target.

Shors and Matzel (S&M) address important questions about the relationships between memory and LTP. They argue that the evidence does not support the claim that LTP is a memory mechanism. We agree. As S&M indicate, LTP is one of several physiological phenomena that reflect a variety of synaptic plasticity mechanisms operating in different neural circuits which may or may not be required for learning different kinds of information. Assessing the relationship between mechanisms of LTP and learning requires focused analysis and precisely linked and limited hypotheses about specific brain regions, neural circuits, plasticity mechanisms, and task demands. Unfortunately, S&M do not provide these. Rather, they set up a straw man: that LTP is a memory storage mechanism. S&M do not consider seriously the widely recognized fact that different learning tasks require different neural circuits and perhaps different plasticity mechanisms; they either overlook or do not analyze sufficiently the cognitive requirements for different learning and memory tasks, and they ignore the computational mechanisms that are required to account for different aspects of learning.

The relations between LTP and memory pose a complex problem. The Venn diagram in Figure 1 illustrates a subset of the problem (computation and neural representation issues are ignored). Each circle represents a subset of behaviors or neural mechanisms. Learning and memory processes, NMDA-receptor dependent mechanisms, synaptic plasticity mechanisms, LTP requirements, and hippocampus-dependent functions each comprise logically separable domains. The intersection X represents hippocampus-dependent learning requiring the NMDA receptor-dependent synaptic plasticity as revealed by LTP experiments. If X does indeed exist, then the mechanisms underlying LTP have a lot to do with learning in an important but restricted domain. Unfortunately, several of S&M's arguments focus outside this crucial intersection.

S&M cite experiments revealing transynaptic and spreading effects of LTP induction treatments. However, a universally recognized caveat about electrical stimulation of neural circuits is that it can produce transynaptic effects far from the stimulation site.

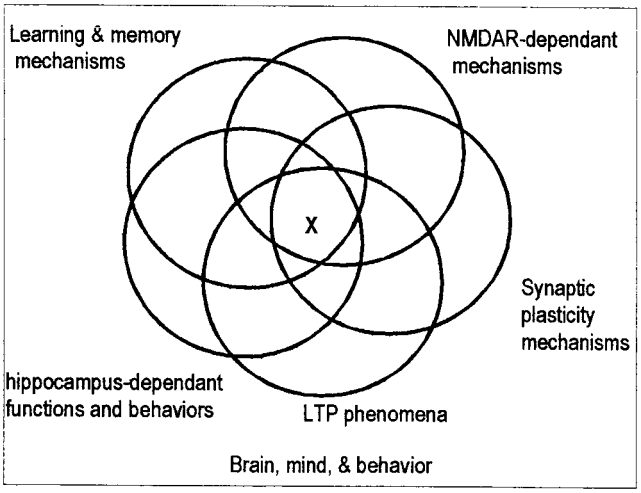


Figure 1 (Shapiro & Hargreaves). The Venn diagram describes some of the logical relationships that must be made clear in order to test links between LTP and memory. The rectangle defines the set of phenomena of interest to *BBS* readers: brain, mind, and behavior. Each labelled circle defines a subset of that domain. Regions of overlap denote logical intersections, or conjunctions of phenomena included within more than one subset. Thus, the intersection of LTP phenomena and NMDA receptor-dependent mechanisms includes LTP in CA1 and in the dentate gyrus; mossy fiber potentiation is not NMDA receptor dependant, and is therefore within the domain of LTP phenomena but outside the intersection. X marks the hypothetical 5-way conjunction that is crucial here: a type of learning that requires NMDA-receptor dependent synaptic plasticity in the hippocampus and is revealed by LTP experiments. If X is not empty, then mechanisms of LTP are important for learning.

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S&M argue that because LTP induction procedures alter physiology and neurochemistry beyond the monosynaptic pathway of interest, LTP is not synapse specific. The result is correct, but the interpretation is not relevant for understanding the initial steps of information storage. A key issue is whether (for example) NMDA-receptor-dependent synaptic plasticity in the hippocampus is controlled by local conditions of depolarization and transmitter release. None of the experiments cited refute this hypothesis, which may be tested by simultaneous patch recording of dendritic regions of depolarized and "distant" cells. Only if distant cells' dendritic regions potentiate without localized depolarization, will S&M be shown to be right in their claim that LTP is irrelevant to information storage mechanisms.

Further confusion among levels of analysis appears in the "strengthening through repetition and facilitated reacquisition" argument. S&M attempt to equate changes in synaptic activation shown in repeated LTP experiments with changes in whole animal behavior after repeated learning trials. Computational analysis distinguishes between learning rules, on the one hand, and neural representations on the other. Neural circuits comprised of cells interconnected by plastic synapses have network properties; these include facilitated reacquisition as well as pattern completion, resistance to degradation, and so on (Hinton et al. 1986). These networks require synaptic plasticity for learning, but plasticity alone is insufficient for the network level properties. Thus, the argument that LTP does not demonstrate facilitated reacquisition is irrelevant to whether or not LTP reflects a biological learning rule.

Hippocampal cell activity demonstrates rapid encoding that does depend on local NMDA-receptors (McHugh et al. 1996) and synaptic plasticity (Rotenberg et al. 1996); it also shows pattern completion (Hetherington et al. 1997; 1993). Facilitated reacquisition by hippocampal circuits alone has not been demonstrated, but such a finding is not necessary or relevant to the argument that some mechanisms of LTP are shared by mechanisms of learning at a synaptic level. Higher level learning and memory functions may depend upon these mechanisms, but require a higher (local circuit or network) level of organization for their explanation.

We also agree with S&M that experiments using NMDA receptor antagonists provide ambiguous evidence about the role of such receptors in learning. The most important caveat is that, of necessity, drugs are given during learning and performance, increasing the likelihood that non-mnemonic sensorimotor side effects influence behavior. Drug administration during learning is necessary because NMDA-receptor dependent plasticity should be most important during that time. In a series of experiments, we have found that several NMDA receptor antagonists impair spatial learning, but not spatial working memory performance in familiar environments (Caramanos et al. 1994; Shapiro et al. 1990; 1992). Specifically, rats given NMDA receptor antagonists could not learn the standard Olton radial maze task, but given the same dose of drug could perform the task after they were trained. Unlike Cain's and Morris's results in the water maze (Bannerman et al. 1995; Saucier et al. 1995), training only ameliorated the effects of the drugs in the training environment. Rats trained in one room, and unaffected by the drug in that room, performed poorly and did not learn the task when given the same dose of drug and tested in another, unfamiliar room (Caramanos et al. 1994; Shapiro et al. 1990; 1992). The sensory, attentional, motivational, motor, and other requirements for the task were identical in the familiar and unfamiliar rooms. Rather, the rooms differed only in stimulus content, and task performance depended on the extent to which the rats had encoded that content in memory. The same dose of NMDA receptor antagonists that disrupts synaptic plasticity in the hippocampus (Hargreaves et al. 1997) has no effects on hippocampal place fields in familiar environments but prevents normal stabilization of hippocampal place fields in unfamiliar environments across sessions (Austin et al. 1990; 1993; Hargreaves et al. 1997). Thus, NMDA receptor antagonists do impair the acquisition of spatial representations required for radial maze behavior and reflected in stable hippocampal place fields.

After setting up and knocking down the straw man that LTP is a memory mechanism, S&M propose that LTP reflects an attentional or arousal mechanism, but admitting that many of the same arguments against a memory role for LTP also argue against their own proposal. The problem with this argument is not that LTP and arousal or attention are in principle incompatible, but that the details of specific circuits, synapses, and plasticity and computational mechanisms are again ignored. The proposal that LTP serves as an attentional or arousal mechanism is as misguided as the argument that LTP should serve as a memory mechanism.

In summary, the important question is not whether LTP is a memory mechanism but whether synaptic plasticity mechanisms that underlie LTP in specific neural circuits are crucial for learning in tasks that require these circuits. New and powerful evidence suggests that some mechanisms subserving NMDA-receptor dependent LTP in CA1 pyramidal cells of the hippocampus are also necessary for learning the standard water maze task. Molecular genetic experiments have demonstrated that time- and region-selective impairment in NMDA-dependent synaptic plasticity selectively impairs hippocampal LTP and spatial memory (Mayford et al. 1996; Mchugh et al. 1996; Rotenberg et al. 1996; Tsien et al. 1996a; 1996b). In one of these experiments, NMDA receptors were eliminated only in CA1 and this was sufficient to impair CA1 LTP, spatial learning, and informational place fields. Dentate gyrus LTP was intact in these mice. A complementary study shows that knocking out LTP in the dentate gyrus does not impair spatial learning in the water maze (Nosten-Bertrand et al. 1996). A third shows that an inducible mutant CaMKII blocks CA1 LTP and spatial learning, and that preventing the expression of the mutant enzyme reverses both the learning impairment and the LTP blockade. Together, these results show that NMDA-receptor dependent mechanisms in CA1 are required for both the observation of LTP and for spatial learning. Further analysis of specific synaptic plasticity mechanisms in specific neural circuits will help determine how the brain learns, represents, and remembers specific types of information.

Classical conditioning has much to do with LTP

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Abstract: Shors & Matzel somewhat lightly dismiss the evidence that a process like LTP may underlie the learning-induced increase in neuronal activity in the hippocampus in eyeblink conditioning. I provide some 12 lines of evidence supporting this hypothesis and the further hypothesis that this learning-induced LTP-like hippocampal plasticity can play a critical role in certain aspects of learned behavior.

Shors & Matzel (S&M) are to be commended for questioning the received wisdom that LTP is the mechanism of memory storage in the hippocampus. There is certainly no strong and detailed causal chain from hippocampal LTP to learned performance for any aspect of learning. Indeed, it is astonishing that so little effort has been expended on the LTP-memory hypothesis, given that the neural substrate of memory is arguably the most important unsolved problem in neuroscience and psychology. Instead, enormous amounts of money and effort have been devoted to the analysis of the mechanisms of LTP, yet another example of the triumph of technology over purpose.

I will comment briefly and only to S&M's discussion of work on classical conditioning of the eyeblink response. As they almost correctly state (in sect. 2.2), the necessary and sufficient circuitry

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for the acquisition of the classically conditioned eyeblink response resides in the cerebellum. They leave out the qualifier that this is true for delay but not trace conditioning. The cerebellar circuit is also necessary but not sufficient for trace learning. Solomon et al. (1986) showed that hippocampal lesions markedly impair subsequent learning of the trace eyeblink conditioned response, a result replicated more recently by Moyer et al. (1990). Kim et al. (1995) showed that the hippocampus was necessary for immediate (days) but not long-term (weeks) retention of the trace eyeblink CR.

Under all normal conditions, including delay training, the learning-induced increase in neuronal activity in the hippocampus resulting from eyeblink conditioning is an invariable concomitant of learning that precedes the occurrence and form of the behavioral CR, both within trials and across the trials of training, and it predicts the occurrence and form of the learned behavioral response (Berger et al. 1986). The properties of this learning-induced increase in hippocampal neuronal activity closely parallel the properties of hippocampal LTP in at least 10 ways:

1. Both are expressed by pyramidal (and granule) neurons.
2. Both result in pronounced and long-lasting increases in neuronal excitability.
3. Both decay with a very slow time course (days to weeks).
4. Only a small number of stimulations are needed for each.
5. Both show a similar rapid time-course of development.
6. The magnitude of increase in neuronal response (excitability) is similar in both.
7. Very specific patterns of stimulation are needed for each.
8. Both exhibit "associativity."
9. The theta frequency is critical for both (stimulation; spontaneous activity).
10. Marked and virtually identical patterns of increased AMPA receptor binding in the hippocampus occur in both.

Particularly striking is the time-limited duration of this learning-induced neural activity in the hippocampus, closely paralleling the period of time when the hippocampus is necessary for retention of trace conditioning (Katz & Steinmetz 1994; Kim et al. 1995; L. Thompson et al. 1996) and the time period of duration of LTD induced in the hippocampus *in vivo* (Shors & Matzel, sects. 2.5 through 4.3 and Staubli & Lynch 1987).

In addition to these correspondences, there are at least two intervention studies. Berger (1984) showed that induction of LTP by perforant path stimulation markedly facilitated subsequent discrimination learning in rabbits. L. Thompson et al. (1992) showed that administering an agonist to the glycine site on the NMDA receptor in rabbits markedly facilitated subsequent learning of the trace eyeblink CR. Perhaps the most direct evidence is provided by Weisz et al. (1984). They stimulated the perforant path (test pulses) during eyeblink conditioning and showed that behavioral learning was accompanied by a marked and closely corresponding increase in the monosynaptic field potential in the dentate gyrus. S&M discount this finding on two grounds. First, they state that the learning-induced increase in the monosynaptic response in the dentate gyrus is not LTP because the pattern of activation of the dentate is not the same as when LTP is induced. This is of course a specious argument. It is also false. Weisz et al. (1982) showed that as eyeblink conditioning is learned, there is a dramatic increase in theta frequency driving of the dentate gyrus, the ideal condition for the induction of LTP.

S&M's second objection concerns the study by Robinson (1993), who reported that MK801 impaired acquisition of the delay eyeblink CR without altering the learning-induced increase in the perforant path–granule cell response. The Robinson study is fatally flawed on several grounds. Most critical is the fact that he did not run the control group absolutely essential to determining whether MK801 at the doses and conditions he used would actually impair the induction of dentate LTP with tetanic stimulation of the perforant path. He used subcutaneous administration of MK 801 and found only a partial effect on the acquisition of the eyeblink CR and no effect on performance of the CR. In a much more careful study, Cox et al. (1994) administered the same dose of MK 801 intravenously, found almost complete prevention of the acquisition of the eyeblink CR and virtually complete abolition of CR performance. It seems likely that the MK 801 effect is due to actions on the cerebellar circuit, a testable and intriguing possibility. The Robinson study is therefore a non sequitur.

On balance, the evidence would seem very strong that a process like LTP underlies the learning-induced increase in hippocampal neuronal activity in classical conditioning, a process that has all the properties of a time-limited memory that does determine learned performance under some conditions. Shors & Matzel appear to require an isomorphic relationship between hippocampal functions and learned behaviors, an unreasonable demand, given the multiple determinants of behavior. In eyeblink conditioning the hippocampus appears to be forming a "declarative" memory about the situation; this memory is not needed to perform the basic delay CR but is needed for more complex task demands like trace CR acquisition.

Hippocampus and LTP: Here we go around again

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Abstract: A fundamental assumption in Shors & Matzel's target article is that brain activity can be related to the traditional categories of mentalistic psychology. This has led them to make numerous further assumptions that are contradicted by the available evidence.

Shors & Matzel's (S&M's) target article is very timely. Now that the hypothesis that hippocampal LTP is essential for much of learning and memory lies in rubble, the time is ripe for the suggestion that LTP is involved in attention. After all, virtually every major structure, neurotransmitter, and pattern of electrical activity in the forebrain has been related to memory and attention at some point in the past 40 years. Why should LTP not share the same fate?

Much of what is laughingly called "behavioral" neuroscience resembles a vast merry-go-round, full of frenzied activity and noise, with regular appearances and disappearances of the same characters, and making no progress whatsoever. The fundamental problem, it seems to me, lies in attempting to relate neurobiological measures to traditional psychological concepts. There is good reason for the belief that the major function of the central nervous system is the control of behavior. However, what we see in contemporary "behavioral" neuroscience is an absurd attempt to relate an enormously rich and detailed knowledge of neuroanatomy, neurochemistry, neuropharmacology, and electrophysiology to a simple set of mentalistic concepts that has not changed fundamentally since the days of Plato and Aristotle.

Attempts to shoehorn the wealth of existing data into this archaic conceptual scheme inevitably means that many facts are left out. For example, in section 4.6, S&M suggest that hippocampal theta waves are related to "arousal" and in section 4, paragraph 4, "arousal" is defined in terms of "overall receptivity to stimuli." Facts that directly contradict this simple hypothesis have been known for several decades. Anaesthetized animals (low arousal level, one presumes) continue to display one form of theta activity but an unanaesthetized rat that is displaying piloerection, exophthalmos, and freezing behavior (high arousal level, one presumes) shortly after receiving a painful electric shock, does not display theta activity at all. Similarly, the experiments by A. H. Black (Black 1975; Black et al. 1970; cited by S&M) demonstrate clearly that theta activity is not related to "attention."

As another example, S&M accept without comment the proposition that the hippocampus is "critical to the formation of certain types of memories" even though a fair evaluation of the available evidence does not support it (Horel 1994; Vanderwolf & Cain 1994).

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As yet another example, the persistent belief that hippocampal theta *must* have something to do with such supposed processes as attention, memory, or fear appears to have led S&M to assume that "exposure to an aversive and frightening event enhances endogenous theta activity" and further to imply that naturally occurring theta may produce LTP. Neither of these assumptions is in agreement with the facts. It has been known for nearly 30 years that hippocampal theta occurs primarily in close association with certain patterns of motor activity, regardless of whether aversive or frightening events have occurred. A rat walking quietly across its home cage displays better developed and higher frequency theta activity than an immobile rat exposed to the sight or smell of a predator. Moreover, there is no good evidence that endogenous theta waves can induce LTP and strong evidence against it. Training rats on a one-way avoidance task or a maze (both associated with prominent theta activity) does not produce hippocampal LTP (Hargreaves et al. 1990).

The current preoccupation with mentalistic concepts hinders progress in neuroscience. A recent attempt to summarize what is actually known about the mind has concluded that traditional mentalistic concepts lie outside the province of natural science (Vanderwolf, in press). Behavior, however, is quite amenable to scientific investigation. It is high time that we begin to take it seriously.

NMDA receptors: Substrates or modulators of memory formation

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Abstract: We agree with Shors & Matzel's general hypothesis that the proposed link between NMDA-dependent LTP and memory is weak. They suggest that NMDA-dependent LTP is important to arousal or attentional processes which influence learning in an anterograde manner. However, current evidence is also consistent with the view that NMDA receptors modulate memory consolidation retroactively, as occurs in several other receptor classes.

We applaud Shors & Matzel's (S&M's) attempt to broaden the scope of LTP-learning discussions and their critical reevaluation of data most often cited as evidence in favor of the LTP-learning hypothesis. We wish to draw attention to additional evidence that seems inconsistent with the LTP-learning hypothesis, but which may be consistent with a role for NMDA receptors in memory modulation.

Because NMDA antagonists disrupt LTP without disrupting postsynaptic responses, it is reasonable to attribute the disruption of LTP to direct effects on plasticity. It is often assumed, therefore, that effects of these drugs on learning must also be due to direct effects on plasticity. However, findings with intact preparations indicate that NMDA antagonists can indeed disrupt baseline neurophysiological measures. In the hippocampus, where much of the early and still influential work relating LTP to memory was first done (e.g., Morris et al. 1986), NMDA antagonists disrupt the atropine-sensitive component of theta (Leung & Desborough 1988), decrease the power across all frequency bands of hippocampal EEG (Boddeke et al. 1992), and significantly reduce the occurrence of complex spike discharges (Abraham & Kairiss 1988). In addition, intrahippocampal infusions of D,L-AP5, at a dose which impairs memory, including memory in the water task (Morris et al. 1986), dramatically reduce the EPSP slope and population spike amplitude, and increase spike latency of perforant-path dentate gyrus evoked responses (Walker & Gold 1994). These effects on both behavior and physiology can not even be attributed with confidence to NMDA blockade insofar as similar results were obtained with the presumably inactive isomer, L-AP5, at doses near those effective for D- and D,L-AP5.

Arguing by analogy, most versions of the LTP-learning hypothesis include findings to the effect that NMDA antagonist effects are restricted to learning, as they clearly are to LTP induction (i.e., NMDA antagonists do not disrupt the expression or maintenance of pre-established LTP). However, accumulating evidence that NMDA antagonists can disrupt retention when administered soon after training (Flood et al. 1990; Izquierdo & Medina 1993) seem inconsistent with at least a simple version of that hypothesis, though such data may be perfectly compatible with a role for NMDA receptors in memory consolidation.

Also consistent with an involvement of NMDA receptors in consolidation is evidence that, when learning is assessed at both brief and long train-test intervals, the memory impairments that ultimately emerge do so despite initially intact learning (Kim & McGaugh 1992; Ungerer et al. 1991). Thus, NMDA receptors may be less necessary for learning than is generally thought, with functions perhaps more akin to memory modulation than to memory formation.

That NMDA receptors are not necessary for learning is also supported by evidence from several spatial tasks, in which the deficits normally produced by NMDA blockade are prevented either by non-NMDA drugs which enhance memory, e.g., glucose, physostigmine, naloxone (Walker & Gold 1992), and oxiracetam (Belfiore et al. 1992), by preexposure to the test environment (Shapiro & Caramanos 1990), or by spatial or even nonspatial pretraining (Bannerman et al. 1996; Saucier & Cain 1995). Again, findings such as these may be more consistent with an involvement of NMDA receptors in memory modulation rather than memory formation and indicate, at a minimum, that an intact population of NMDA receptors is not necessary for all forms of learning.

As also seen with many other memory modulators, NMDA antagonists disrupt paradoxical sleep for several hours after drug injection (Stone et al. 1992). Given the important role of paradoxical sleep in memory consolidation (Smith 1995), it seems likely that this consequence of NMDA blockade might contribute, in at least some instances, to effects on retention.

We hope our comments highlight the fact that NMDA receptors are involved in multiple processes which include but are not limited to LTP. Other processes include memory consolidation, paradoxical sleep, various measures of neurophysiological function, and probably attention or arousal. It is important to note that disruption of each is likely to impair learning and memory and it is therefore important that these alternatives be considered carefully and addressed experimentally before attributing the amnestic effects of NMDA antagonists to effects on endogenous LTP.

Authors' Response

LTP: Memory, arousal, neither, both

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Abstract: The neurophysiological phenomenon of LTP (long term potentiation) is considered by many to represent an adequate mechanism for acquiring or storing memories in the mammalian brain. In our target article, we reviewed the various arguments put forth in support of the LTP/memory hypothesis. We concluded that these arguments were inconsistent with the purported data base and proposed an alternative interpretation that we suggested was at least as compatible with the available data as the more widely held view. In doing so, we attempted to illustrate that the

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inadequacy of present experimental designs did not permit us to distinguish between equally viable hypotheses. In the four years since we wrote the first draft of our target article, hundreds of additional studies on LTP have been published and their results have been incorporated into current theories about memory. A diverse group of commentators responded to our target article with their own theories of how memories might be stored in the brain, some of which rely on LTP. Some commentators doubted whether memories can be stored through modifications of synaptic strength. Some assert that it will never be possible to understand the neural mechanisms of memory; still others remain hopeful that we will accomplish some semblance of a resolution, provided we appreciate LTP's role in a subset of seemingly amorphous memory systems. In summary, although it is commonly written that "LTP is a memory storage device," the divergence of views among the commentators suggests, at least as strongly as our target article, that such conviction is unwarranted and fails to acknowledge both the lack of consensus regarding the role of LTP in memory and the complexity of the phenomenon of memory itself.

Introduction

Near the conclusion of our target article, we proposed an alternative to the widely-held hypothesis that LTP (long term potentiation) is a memory storage device. With this "new and nonspecific" hypothesis, we suggested that exposure to aversive events might induce LTP in vivo. It was proposed that such a nonspecific potentiation of synaptic efficacy persistently enhances the neural representation of environmental stimuli and thereby the perception of, or attention to, those stimuli. Thus our hypothesis is consistent with the view that LTP participates in memory formation, but is incompatible with the hypothesis that it is a substrate of memory storage. In our target article, we stated explicitly that our alternative view of the role of LTP in memory was only one of several possible alternative hypotheses that could be constructed based on available evidence. Our failure to find conclusive support for any single interpretation arose in part from what we perceived as the inadequacy of experiments related to the subject, that is, the same data set could be interpreted as consistent with at least two hypotheses. Although we considered our alternative hypothesis to be secondary to our more general critique of the evidence in support of LTP as a storage device, the majority of commentators addressed our alternative hypothesis rather than the larger topic. We might suggest (but do not necessarily believe) that this reflects a growing consensus that the mechanism of LTP is inconsistent with its purported role in the storage of memories.

At first we were somewhat surprised by the focus of the commentaries, because the purpose of the target article was not to debate the merits of a relatively new and untested hypothesis, but rather to appraise critically the primary hypothesis as it has existed for the past 20 years. Yet the focus on our alternative hypothesis was beneficial in several respects; it placed the phenomenology of LTP in a different context, an exercise that should in principle illuminate the strong versus the weak points of any position. It generated other alternative hypotheses such as the one discussed by **Moore & Sur,** who suggest that LTP might participate in neural development through the strengthening of relevant circuits, and one proposed by **Reid & Stewart,** who suggest that LTP-like processes participate in depressive illness. In addition, the debate raised a number of new issues about the characteristics of memory formation and storage itself, whether the properties of LTP are consistent with those characteristics, and whether neurophysiological phenomenon (like LTP) can ever be unambiguously related to complex emergent processes like memory or arousal. Whether the connection between LTP and memory is strengthened or weakened will remain largely a matter of opinion until the appropriate and conclusive experiments are conducted. To that end, we hope this has been a productive exercise.

We have organized our response to the commentators into three general categories. First we address the commentaries in which it is argued that LTP *is* sufficient to serve as a memory storage device. Second, we address the commentaries that discuss whether or not a general mechanism like LTP could serve to modulate arousal, sensory, or attentional processes. Third, we review empirical and conceptual evidence that support an even more radical departure from conventional wisdom (alluded to by **Latash** and by **Moore & Sur**), which is that a change in synaptic weights, induced through LTP or any other process, may not serve any direct function in memory storage.

R1. Is LTP a memory storage device?

Many commentators focused exclusively on the observed correlation between the modulation of NMDA receptors and memory, and by inference, the role of NMDA receptor-dependent LTP in memory. There are several interpretative difficulties that arise when making such an inference. First, the NMDA receptor contributes to normal synaptic transmission and cellular transduction processes; it does not exist for the sole purpose of inducing LTP. Second, NMDA receptor activation or inhibition can affect perception, affect, or motor performance in ways that can confound the interpretation of its specific effects on memory. Last, many instances of NMDA receptor-induced plasticity that are related to learning appear to be neither necessary nor sufficient for the storage or expression of memory.

The majority of studies relating LTP to learning and memory are based on the effects of administering NMDA receptor antagonists prior to training. As noted by **Walker & Gold,** NMDA receptor blockade has many effects on the organism that can indirectly influence learning and memory. As they note, NMDA antagonists inhibit paradoxical sleep, and interestingly, LTP is optimally induced during the rapid eye movement (REM) stage of sleep, as noted by **Bramham.** Some of the consequences of NMDA receptor activation that could be disrupted by their inhibition include the dephosphorylation of major cytoskeletal proteins such as MAP-2 in the hippocampus (Halpain & Greengard 1990), estrogen-induced increases in spine density in the hippocampus of females (Wooley & McEwen 1994), modulation of hyperventilation (Graham et al. 1996; Soto et al. 1995), regulation of cell body and dendritic outgrowth during development (Kalb 1994), up regulation of platelet-activating factor in acquired immune deficiency syndrome (Nishida et al. 1996), inhibition of thermal hyperalgesia (Eisenberg et al. 1995; Mao et al. 1992), regulation of inflammatory pain (Chapman et al. 1995) and oxidative stress (Bondy & Guo 1996), secretion of gonadotropin-releasing hormone (Bourguignon et al. 1992), regulation of circadian rhythms (Ding et al. 1994), and neuronal volume after swelling (Churchwell et al. 1996). As added complications, administration of NMDA receptor antagonists can

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also radically increase the release of acetylcholine into the hippocampus (Giovannini et al. 1994), and acute (<2 hr) administration induces major cell proliferation in the dentate gyrus of the hippocampus (Cameron et al. 1995). All of these effects are in addition to potential sedative and anxiolytic effects of NMDA receptor antagonists, and again, *their role in normal synaptic transmission.* Of course, any reduction in synaptic efficacy could itself act to retard learning simply via a resultant decrease in the capacity to process stimuli efficiently (e.g., Matzel et al. 1996). It is therefore hard to ascribe a definitive role of the NMDA receptor-dependent LTP in memory storage, a conclusion echoed by **Cain** and **Walker & Gold.** These commentators, as well as **Shapiro & Hargreaves,** describe evidence that indicates that the effects of NMDA receptor antagonists on learning can often be accounted for by their effects on performance or perception. And although **Morris** should be credited with conducting the most carefully conceived and controlled experiments employing this strategy, his experiments are also subject to other interpretations as described in the following paragraphs.

Many commentators suggest that we ignored the obvious resolution to the sometimes enigmatic role of LTP in memory storage, which is that NMDA-dependent LTP is necessary only for a subset of memory systems or learning tasks (e.g., **Fanselow, Hara & Kitajima, Maren, Morris, Shapiro & Hargreaves**). If in fact the evidence indicated that NMDA receptor-dependent LTP was a substrate mechanism for *any* form of memory storage, we would have been amiss. In our target article, we focused on published reports in which a particular learning paradigm was specifically related to NMDA receptor-dependent forms of LTP, and most of these observations were based on learning paradigms that are hippocampal-dependent. Some examples, though previously suggested to be reflective of a role of LTP in learning, are more ambiguous because of a lack of knowledge regarding their neuroanatomical substrates. The fact that the substrates of *some* tasks are unknown has seemingly led some commentators to dismiss the preponderance of examples that are not subject to the same criticism. Although it is easy to dismiss the contradictory evidence we presented by alluding to LTP's presumed role in different "memory systems," such an argument is valid only if there is one clear instance in which LTP in one brain region is necessary for one type of memory.

To ensure that the preceding argument is not overlooked, we will address it empirically with a single, circumscribed set of observations. It is the consensus view among many who study memory processes that the hippocampus (or at least the dorsal hippocampus; Moser et al. 1993) is critically involved in the short-term storage of spatial memories. Moreover, at least two of the major synaptic connections in that structure display LTP that is dependent on activation of the NMDA type of glutamate receptor: the perforant path/dentate gyrus granule cells and the Schaffer collateral/CA1 pyramidal cells. Thus, with spatial learning, we have a perfect system to assess the role of the NMDA receptor-dependent LTP in one brain area on one form of learning (or "memory system"). How does the evidence stack up? As described in our target article, a blockade of NMDA receptors in the hippocampus often impairs spatial performance in ways unrelated to memory (e.g., as reflected in performance on the first training trial, before learning has occurred). In some published reports, these performance deficits are overcome with extended training and the drug-treated animals reach a level of responding comparable to untreated animals. In some instances, however, the performance of drug-treated animals is not impaired on the first trial, allowing the conclusion that the deficit on later trial is a reflection of a learning failure (e.g., Davis et al. 1992). Despite the sometimes conflicting results and multiple interpretations of this data, observations such as these are the core of evidence that NMDA receptor-dependent LTP is necessary for learning.

Apparently even the least ambiguous of these observations can be accounted for by other than a learning failure. For instance, Saucier and **Cain** (1995; also see Cain et al. 1996) as well as Bannerman et al. (1995), demonstrated that if animals are trained without the antagonist on a spatial or nonspatial version of a maze and later trained with the antagonist on a spatial version of the task with a new set of spatial cues, their performances on the second spatial task are unaffected or minimally affected by the antagonist. Thus, without the benefit of hippocampal LTP, the animals are perfectly capable of forming hippocampal-dependent spatial memories. One interpretation of these results is that the pretraining without the antagonist allows the animals to overcome sensorimotor, emotional, or motivational effects of NMDA receptor antagonists that could otherwise impair the learning and/or performance of the treated animals (Saucier & **Cain** 1995). Another interpretation – and the one preferred by Bannerman et al. (1995) – is that NMDA receptor-dependent LTP must be necessary for learning some "nonspatial" component of spatial memory. But this prediction was clearly not generated a priori, and to our knowledge, has no independent empirical support. To reiterate a point made in our target article, we must ask what evidence would ever be sufficient to disprove the LTP-memory hypothesis among its supporters?

As a second example of the presumed relationship between spatial memory and LTP in the hippocampus, we recall the studies that evaluated whether the saturation of the capacity for hippocampal LTP impairs learning. As discussed in our target article, repeated tetanization of the perforant pathway and the presumed saturation of the capacity for LTP induction does not impair performance on several spatial memory tasks, that is, the animals are perfectly capable of forming hippocampal-dependent spatial memories. Of course one could argue that the saturation was less than complete (e.g., **Robinson**). Even if we accept this argument, we might expect that there would be some saturation of some of the available synapses and thus there would be some impairment of memory. This was the a priori hypothesis for which no support was found. One could also argue that the critical region for spatial learning was not tetanized (Barnes et al. 1994). For example, the dorsal hippocampus was primarily affected in the initial studies. Subsequent studies have determined, however, that the dorsal hippocampus does seem to be a critical region for spatial learning; lesions to the dorsal part of the hippocampus had a much larger impact on spatial learning than did lesions to the ventral part (Moser et al. 1993). Moreover, nearly all of the studies that have directly tested the effects of LTP induction on behavior have used the perforant path-dentate gyrus synapse. This is primarily because stimulation of the perforant path will tetanize a large number of granule cell synapses. However, a recent study reported that genetically manipulated animals without LTP

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in the dentate gyrus could still learn the spatial maze task (Nosten-Bertrand et al. 1996). It therefore appears that LTP in the dentate gyrus is not necessary for spatial learning, and any effects of dentate LTP on spatial learning, if they were to occur, would not be necessary for memory. As a final example, we ask whether there are instances in which the hippocampus is required for normal spatial memories but NMDA receptor activation is not required by the LTP in that structure. Indeed pigeons, a preeminent example of an efficient spatial learner, exhibit impaired spatial learning following hippocampal ablation (Good & Macphail 1994), but LTP in that structure is induced without NMDA receptor activation (Wierazco & Ball 1993). That is, the animal is perfectly capable (actually quite expert) at making hippocampal-dependent spatial memories without any contribution of NMDA receptor-dependent hippocampal LTP. Thus with regard to the "multiple memory systems" argument posed by some commentators, it seems that even the most preeminent type of memory associated with LTP and the hippocampus, that is, spatial memory, does not fare well with respect to its dependence on NMDA receptor-dependent LTP.

The idea that LTP's role in memory will be resolved by an allusion to its role in a specific memory system assumes that our field has established an accepted framework for categorizing memory systems and their neuroanatomical substrates. This assumption is not supported by the views of various commentators. In fact, the asserted roles of the hippocampus in memory span from statements that all memories are stored in the hippocampus to another assertion that "a fair evaluation of the available evidence" supports no role for the hippocampus in memory storage whatsoever (**Vanderwolf;** also see **Latash**). Still others suggest that the hippocampus may serve a function in timing rather than memory (**Grossberg**). Even if a consensus were forthcoming, there is no inherent characteristic of LTP expression (i.e., enhanced synaptic efficacy) that renders it uniquely suitable as a substrate mechanism for any of the more than 26 different memory systems that have been proposed (see Eichenbaum et al. 1991). Somewhat ironically, the often cited "associative" nature of hippocampal LTP (which we suggest is not well suited for storing associative relations) should suggest that it is a poor candidate device for storing spatial memories, because spatial memory tasks are specifically intended to minimize the contribution of associative learning (e.g., **Morris** 1981). Based on issues such as these, it is difficult to imagine that any clear resolution of the role of LTP in memory will be forthcoming based on nonspecific allusions to multiple memory systems.

As with spatial learning, the temporal requirements for the induction of associative LTP (optimally induced with a 100–200 msec interstimulus interval) would suggest a priori that it is unsuited for learning about temporally diffuse cues such as those represented by a context (i.e., location). Nevertheless, a number of commentators refer to context as the critical issue with respect to LTP's role in memory. For example, **Maren** and **Fanselow** suggest that hippocampal LTP may play a unique role in coding contextual memories based on reports that ventricular infusion of NMDA receptor antagonists impairs the formation of a context-shock association (i.e., contextual fear) as measured by context-induced freezing. These results are suggestive and are not confounded by some of the interpretive difficulties described for spatial learning experiments, for example, motivation to respond or impaired motor behavior. Indeed, Maren and Fanselow argue that the effects of the antagonist on memory formation are not caused by nonspecific effects on arousal or sensory processing. This argument is most persuasive with respect to one-trial contextual fear conditioning, in which the animal's arousal and sensory processing capacity should be at basal levels prior to the first trial. This argument assumes that we expect NMDA receptors to play a role in *nothing* but the modulation of arousal or sensory processing, an assumption that is clearly incorrect as noted above and by a number of commentators. To reiterate, NMDA receptors participate in normal synaptic transmission (i.e., processing of stimuli), the regulation of stress hormones, enzymes, and neurotransmitters, as well as anxiety, analgesia, and sedation. Any or all of these effects could (or should) impede one-trial learning of any type.

The focus of many responses on contextual learning stems from reports that the hippocampus is necessary for learning about contextual cues. It should be noted, however, that there is recent evidence to suggest that the hippocampus does not store (even for the short term) contextual memories (also see **Vanderwolf** and **Cain** 1994). For instance, Hall et al. (1996) reported that hippocampus lesions have no effect on contextual cueing (better responding to a stimulus in the context in which it was trained versus a nontraining context) or on an animal's capacity to learn a discrimination based on contextual stimuli (also see Good & Honey 1991). Given these examples, it appears that the hippocampus may not be necessary for "remembering" or coding contextual information, per se. It is therefore difficult to conclude what role, if any, hippocampal LTP might serve in storing contextual memories.

In our target article, we intended to focus on the hippocampus. This was not meant to confine the argument unnecessarily or to limit the responses to those having to do with the structure. Indeed, we noted in our target article that the most persuasive evidence that LTP does play a role in memory formation (perhaps not storage) comes from its potential role in fear conditioning, which is dependent on the amygdala. In several paradigms of conditioned fear, NMDA receptor antagonists in the amygdala prevent acquisition. In addition, NMDA receptor-dependent LTP can be induced in the amygdala by stimulation of the hippocampal formation (**Maren** and **Fanselow** 1995). It is in this vein that both Fanselow and **Gewirtz & Davis** support LTP's role in memory. Again though, this conclusion is based largely on the observation that local administration of NMDA receptor antagonists impairs or prevents amygdala-dependent forms of fear conditioning. Whether those effects are the result of an inhibition of LTP induction remains to be seen. And again, blocking NMDA receptors can induce anxiolytic effects. This is particularly relevant in the present case, because local administration of anxiolytics to the amygdala dose dependently interfere with the acquisition of fear conditioning. For instance, both anxiolytics and analgesics are reported to impair the acquisition of fear conditioning (e.g., Beck & Fibiger 1995; Harris & Westbrook 1995; Inoue et al. 1996; Westbrook et al. 1991). One argument against this interpretation is a study from Fanselow's lab in which NMDA receptor antagonists administered to the amygdala prevent long-term, but not short-term, fear conditioning (Kim et al. 1992). These data

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provide an argument against the anxiolytic properties of NMDA receptor antagonists as mediators of this memory failure, because NMDA receptor antagonism did not interfere with the encoding process but did interfere with long-term storage or retrieval. These data provide little support for a role of LTP in memory storage, however. Activation of NMDA receptors is necessary for the *induction* of LTP, but not its expression. In the study of Kim et al. (1992), short-term memory was not impaired, suggesting that NMDA receptor-dependent LTP was not necessary for memory induction.

Another demonstration of LTP's potential role in amygdala-dependent memory is described in the commentary by **Gewirtz & Davis.** In contrast to Kim et al. (1992), they reported that NMDA antagonists prevent the acquisition of fear-potentiated startle (and presumably the induction of LTP; Campeau et al. 1992), and expression of the intact memory in control animals was dependent on synaptic transmission through the AMPA receptor, which is necessary for the expression of LTP (Kim et al. 1993). Despite the fact that >90% of synaptic transmission in the brain is dependent on current through this receptor, at least these data are consistent with the induction (acquisition) and expression (storage and retrieval) aspects of LTP. Unfortunately, the use of receptor antagonists, whether focally of systemically administered, to establish the role of LTP in memory will lead to results that have multiple interpretations. As noted by **Hawkins,** if we ever hope to resolve these issues, we will all need to be "somewhat more sophisticated" in our construction and tests of the null hypothesis (also see **Morris**).

In restating some of the issues raised by **Rudy & Keith** (1990) regarding the sensory/motor effects of NMDA receptor antagonists, we did not intend to imply that all of the effects of the antagonists on acquisition were the result of performance deficits. As correctly suggested by **Morris,** the effects of targeted and dose-dependent effects of antagonism of hippocampal NMDA receptors on both LTP and spatial learning suggest that the effects of NMDA receptor antagonism are not simply the result of sensorimotor disturbances. First of all, we should state that we recognize that not all NMDA receptor antagonists are equally "clean." For instance, the street drug referred to as "angel dust" (the dissociative anesthetic phencyclidine) does block NMDA receptors and is closely related to ketamine, an NMDA receptor antagonist used in several early studies of LTP. But as implied by Morris, phencyclidine and ketamine have effects on other transmitter systems and more "side-effects" than the competitive antagonists commonly used in his experiments. Likewise, route of administration is an important determinant of the specificity of a drug's action; a slow, chronic, intraventricular infusion of the competitive NMDA antagonist AP5, a technique commonly employed by Morris, appears to have far fewer detrimental effects on sensorimotor function than even a single acute intraventricular dose of the same drug (note however, that Morris acknowledges that AP5 administration may modulate current flow through K^+ channels, and thereby may disrupt hippocampal system properties). Using such a technique, Morris and his colleagues have reported that AP5 administration prior to spatial training prevented acquisition in the Morris water maze (but see caveats above). Similar results were found in the Olton radial maze, as discussed by **Shapiro & Hargreaves** who note that such antagonists impaired acquisition but not performance in retention tests. Although suggestive, such studies do not allow us to conclude that an animal's perception or affective state was altered in a way that selectively impairs the memory storage mechanism. As noted in the prior paragraphs, inhibition of the NMDA receptor is correlated not only with a disruption of LTP induction, but also a disruption of calcium-dependent processes from synaptic growth to cell proliferation to acetylcholine release, all of which confound the interpretation of LTP's role in memory. Therefore, in the end, we must ask whether the hypothesis that NMDA receptor-dependent hippocampal LTP underlies hippocampal-dependent memory formation is the best interpretation of these results? Based on the discussion of the role of hippocampal LTP in hippocampal-dependent memory, we would answer with a resounding "not really."

We must disagree with **Fanselow**'s comment that "learning is a change in an organism's reactions to stimuli because of experience. It is a behavioral phenomenon. . ." Contemporary theories of learning would suggest that learning is not about reactions to stimuli (though it can be expressed as such), nor is it necessarily reflected in behavior. To suggest that learning is a "reaction" and is necessarily accompanied by a behavioral change does not address the essence of learning, which might be better described as an animal's representation of its environment. Rescorla (1988) has noted that viewing learning simply as a reaction will surely confound our understanding of the phenomenon and will lead to experimental results that we cannot interpret. But in all fairness, Fanselow's intent was not to define learning, but to address a second issue in which we are in complete agreement. It is unreasonable to expect that all aspects of learning would be accounted for by properties inherent to a single synapse. He notes that we have created an indefensible "straw horse" in suggesting such a relationship. Similarly, **Shapiro & Hargreaves** suggest that our criticisms of the LTP-memory hypothesis are akin to an attack on a "straw man." Likewise, **Hawkins** and **Reymann** argue that we are unreasonable in expecting a 1:1 relationship between memory processes and LTP mechanisms. They are all correct, but we were not wrong. In fact, we never suggested that LTP could be a memory mechanism only if its properties were like those of memory (e.g., it's associative, long-lasting, and strengthened with repetition). Rather, we were responding to the common assertion in the literature that LTP is a memory device because it has properties that are superficially similar to memory. The presumed commonality of these properties is often offered as evidence that LTP is a memory mechanism. As described in our target article, on close inspection the properties of LTP are either incompatible with, or dissimilar to, features of memory. For instance, the decay rate of LTP is too rapid for the long-term storage of memories (a concern not specifically addressed by any of the commentators). But to a reasonable person, these apparent inconsistencies should be of little concern because we should not expect a single synapse to reflect properties of a complex, integrative *process* such as memory. Our only concern is that these "similar features" are in fact incompatible with memory processes and thus provide no support for the role of LTP in memory storage. It is interesting that when noting the discordance between mechanisms of LTP and memory, we

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are accused of creating a "straw horse." Contrast this rebuttal with the hundreds of articles that go unchallenged that suggest a link between the two phenomena based on the same superficial similarities.

Although we may seem disgruntled with the present state of knowledge, we are optimistic nonetheless that in time empirically-based descriptions of memory storage and expression will begin to emerge. Others are less optimistic. **Vanderwolf** states that the hypothesis that LTP is essential for memory "lies in rubble," but nevertheless regards us as riding a merry-go-round, repeating the mistakes of the past. One of these mistakes is apparently to attempt to relate neurophysiological responses to any psychological phenomenon, which Vanderwolf argues is "outside the province of natural science." As an alternative approach, Vanderwolf suggests that we limit our investigations to more tractable phenomenon, such as behavior. However, we would be negligent (or at least unimaginative) were we to ignore difficult questions just because prior attempts at answering them have made little progress (although we are not even in agreement with this latter assumption). To investigate "psychological" phenomenon that were not directly observable, Garner et al. introduced the concept of converging operations in 1956, a concept that was an impetus for the success of modern cognitive science, and an aid to understanding mechanisms of memory. Rather than ignore difficult questions, our efforts might be better spent designing experiments that provide unambiguous convergent support for one hypothesis while disproving another. Although such experiments may not yet be technically feasible or even comprehensible, to suggest that memory cannot (or should not) be studied at the neurophysiological level is inconsistent with the physical reality of the brain. Nevertheless, we agree in principle with Vanderwolf's general exhort. Complex memory is surely an emergent property of the nervous system, and cannot be sensibly reduced to properties of a single synapse or even a synaptic phenomenon such as LTP. But as we note above, to do so was not our intent.

In contrast to the views of **Vanderwolf, Thompson** is much more optimistic about the possibility of finding substrates of memory in the mammalian brain and is surprisingly optimistic about LTP's role in memory formation. In particular, Thompson discusses the training-induced increase in hippocampal unit activity that occurs in response to a conditioned stimulus (CS) and develops during the acquisition of a conditioned eyeblink response (Berger et al. 1983a; 1983b). In his commentary, he lists features of the increase in unit activity that are nominally similar to characteristics of hippocampal LTP, and we acknowledge an impressive homology between them (but hope others will not accuse him of creating a "straw horse"). In fact, the concordance between the increased unit activity and LTP may provide some of the best evidence that LTP can be induced during learning. If we accept as a given that increased unit activity in response to the CS is a type of LTP (and as noted in our target article and in section R3 below, to do so might be in error), we can then ask what role this form of LTP has in memory or its expression. As Thompson describes, the increase in unit activity can be observed during rapidly acquired short-delay conditioning as well as during acquisition of trace conditioning (where the offset of the CS precedes the onset of the US). Whereas delay conditioning is hippocampal-independent, trace conditioning is severely retarded by hippocampal lesions (Solomon et al. 1986). This raises an interesting paradox that is not easily resolved. What is the role of the hippocampus and hippocampal "LTP" during eyeblink conditioning, given that it is not necessary for the acquisition of normal responses? One possibility is that hippocampal activity is correlated with another learned response altogether, that is, while we experimenters monitor the eye for signs of learning, the animal is learning many things, and is making conditioned heart-rate and fear responses, learning about the experimental context, and so forth, and the development of all of these conditioned responses may recruit unique or overlapping brain areas, including the hippocampus. This is a less than satisfactory resolution to our paradox though, because the increase in hippocampal activity is so well correlated with the development of the conditioned eye blink response per se. A worse resolution, but more frank reply, is that we simply do not know what the hippocampus is doing during this type of learning, much less what LTP might be contributing to its function. To add to the confusion, consider the data of Neuenshwander-El Massiouri et al. (1991), who trained rats in a "blocking" procedure in which a CS does not come to evoke a conditioned response if trained in the presence of a second CS that is already a good predictor of the unconditioned stimulus (US). Although the blocked stimulus did not evoke a behavioral response, it did induce an increase in multiunit activity in area CA3 of the hippocampus comparable to that seen in unblocked animals that learned normally. Together, the studies of Berger et al. (1986a; 1983b) and Neuenshwander-El Massiouri et al. (1991) indicate that unit activity in the hippocampus increases in response to a CS that still elicits a conditioned response after hippocampal lesions, and similarly increases in response to a CS that evokes no behavioral response. A student of logic would observe that this LTP-like increase in hippocampal activity is neither necessary nor sufficient for the generation of conditioned responses indicative of memory. As delineated by a wealth of data from **Thompson**'s laboratory, the cerebellar circuit is necessary for the generation of conditioned eyeblink responses, suggesting the possibility that hippocampal activity might modulate either acquisition or expression of these responses, and that this modulation may only be necessary for the more difficult task of trace conditioning.

One potential role for the hippocampus during trace eyeblink conditioning might be to keep the neural representation of the CS "active" until the US occurs. This type of sustained response would be particularly beneficial in the case of trace conditioning, and would be necessary early in training when the animal does not know what the biological significance of a stimulus is or will be. Once the significance of a stimulus is established, it need not be processed in this manner and would no longer require this "attention" (a central assumption of contemporary theories of associative learning as represented by Pearce & Hall 1980). Such a role is consistent with the relatively fast decay rate of both LTP and the increased hippocampal unit responses after conditioning (although the eyeblink response itself remains intact). **Grossberg** proposes a more elaborate but compatible role for the hippocampal circuit. He suggests that it maintains a cortical representation for a period of time while also inhibiting orienting responses that might other-

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wise distract the animal from the immediately relevant stimulus. He further notes that such a system would allow an animal to cope or adapt to variable time delays. These hypotheses are consistent with a role for LTP in memory modulation as opposed to memory storage.

Even within the realms of the classical eyeblink conditioning paradigm, with its fine stimulus control and extensive data base, there are inconsistencies with respect to the role that LTP and NMDA-receptor activation play in the acquisition of the conditioned response. With respect to NMDA receptor activation, we reported that NMDA receptor antagonism prevents early acquisition but not retention of the conditioned eyeblink response in the rat (Servatius & Shors 1996), whereas Cox et al. (1994) reported that NMDA antagonists prevent both acquisition and retention. **Robinson** reported an effect of NMDA antagonists on acquisition of conditioned responding although the LTP-like increase in hippocampal unit activity was not affected. With respect to the induction of LTP prior to training, Berger (1984) found that LTP induction could enhance acquisition of a discrimination whereas Robinson found no effect. In his commentary, Robinson suggests that the difference between these studies may be the result of his use of different modalities of CSs, as opposed to Berger's use of the same modality. Although admittedly post-hoc, the difference in these results would suggest that LTP induction must be having its effect on stimulus properties (such as cue salience or even modality) rather than memory storage or association formation. And once again, because the hippocampus is not necessary for learning such a discrimination, it must be the case that the stimulation is having effects on aspects of the task that do not require the structure for memory storage. It is noteworthy that the hippocampus is necessary for the acquisition of a post-discrimination reversal in the same task (Berger & Orr 1983). Such an effect is consistent with the idea that the hippocampus (and perhaps LTP) acts to enhance and sustain the stimuli encountered in the environment without a prior knowledge of whether or how they will be associated or dissociated in the future.

On a somewhat different topic, **Abraham** and **Shapiro & Hargreaves** take issue with our questioning whether LTP is synapse-specific. Abraham notes that the spread of LTP to inactive synapses is really just another form of activity mediated by an intercellular messenger. This is a novel use of the standard meaning of "activity," and does not address the incompatibility of this observation with the synapse-specific role that LTP has been presumed to play in modifying the flow of information through neural networks (i.e., how unstimulated synapses become potentiated is not relevant to this issue). Likewise, he notes that the diffusion of biochemical correlates of LTP induction across brain regions is not a reason to question the dogma of synapse-specificity because "it is entirely possible that those later changes occur through circuit reverberation, an LTP-like process subsequent to the initial training or stimulation episode." Although we cannot reject Abraham's hypothesis (anything is possible), he does not cite relevant data and we are aware of none that would suggest its validity (see **Bramham** for relevant discussion). Likewise, there are little data to suggest that the increase in somatic excitation that accompanies LTP can be accounted for by synaptic modifications (quite the contrary). Whether or not memory is synapse-specific is a conceptual concern that we do not have the necessary data (or maybe even the technology) to address. As suggested by Shapiro & Hargreaves, it would be instructive to have data from simultaneous patch recordings of dendritic regions of depolarized and distant cells. But even if the dendrites of distant cells were potentiated without localized depolarization, it would still not address whether LTP (synapse-specific or not) was relevant for information storage, unless one could measure these responses in all cells of a behaving animal during "information storage." In the end, the common view that LTP is synapse-specific is not informative with respect to assessing the role of LTP in memory.

Regarding bilateral changes in gene expression and receptor affinity following unilateral LTP induction, **Bramham** notes that bilateral changes in gene expression are linked to focal, synapse-specific LTP induction. We are in complete agreement on this point and have published data to that effect (Tocco et al. 1992). The point that we had tried to convey is that there are a number of transynaptic effects that are a consequence of tetanic stimulation in vivo. They are robust and not limited to superfluous molecules. At issue was the fact that one cannot necessarily attribute the in vivo effects of tetanic stimulation to the synapses that were potentiated.

Several of the commentators addressed the value of neural networks and computer simulations in our understanding of memory processes in the brain. Although we believe that computer simulations and models such as those proposed by **Schmajuk** and **Grossberg** are valuable as explanatory and heuristic tools, it is only half true that "a full understanding of the functional role of the hippocampus and the brain in which the mechanism of LTP and LTD are embedded requires physiologically realistic computer simulations" as argued by **Hara & Kitajima.** It would be impossible to develop a "realistic simulation" without phenomena to simulate, or when the phenomena have been inaccurately described. We return therefore to a point made in our target article, in which we suggested that an incorrect theory (much as a "correct" one) will accrue its own momentum and so will proliferate a tainted view of reality. In this regard, computer models are not likely to provide conclusive evidence for or against a role for LTP in learning. (It is noted, that Watson & Crick, 1953, elucidated a reasonable model of the DNA molecule that has had a degree of heuristic impact, but did so with the aid of conclusive empirical data from Franklin [Franklin & Gosling 1953] and Wilkins [Wilkins et al. 1953] as well as a rudimentary appreciation of the constraints imposed by biochemistry and biophysics.)

One of the greatest impediments to uncovering the neurobiological substrates of memory is the difficulty in distinguishing the effects of a manipulation on learning from those on performance (either during training or at the time of testing). This is also a principal impediment to understanding the role of LTP in memory or even determining if it has any role at all. These issues are discussed in the commentary by **Keith & Rudy,** which suggests that researchers who use instrumental learning tasks such as the Morris water maze should routinely pretrain animals in a similar task before any drug or neurophysiological manipulation to minimize performance deficits. The basis for such a concern is illustrated by the studies described above by Bannerman et al. (1995) and Saucier and Cain (1995) in which it was demonstrated that pretraining eliminates the

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deficits in spatial maze learning that follow administration of NMDA receptor antagonists. We agree that strategies such as these should be implemented as a matter of course, at least for those studies in which it is technically feasible. There are some paradigms for which such control procedures would be difficult. For example, pretraining is impossible in gene deletion studies, in which the gene is absent throughout development.

Some of the interpretive difficulties of gene knockout studies are lessened by more recent experiments that employ the technology of transient and localized knockouts. In these studies, a gene is manipulated in a specific brain region during adulthood (e.g., Mayford et al. 1996; Rotenberg et al. 1996). In a recent set of studies, Tsien et al. (1996) reported that a localized knockout of the NMDA receptor subunit prevented the induction of LTP, as would be expected. The rats also displayed impaired learning in a spatial water maze task. Of course, there are still some technical limitations and no pretraining on the nonspatial or other spatial task was conducted. Although in principle a gene deletion should be more specific to a particular receptor than is a pharmacological manipulation, gene deletion studies are subject to the same caveats as studies based on pharmacological manipulations. (The more general problem of divergent genetic backgrounds in mutant versus wild-type mice also arises, as described by **Gerlai.**) Not to beat a straw horse, but **Rudy & Keith** note that "drug administration, gene manipulations or brain lesions could all alter the manner in which the rat contacts the relevant features in the environment rather than the neural mechanisms involved in learning," an opinion echoed by **Cain.** The question of LTP's role in memory will be plagued by issues of performance versus memory as long as we fail to acknowledge that the problem exists.

R2. Does LTP modulate sensory processing and thereby modulate memory?

Many of the responses were directed at our "new and nonspecific hypothesis," the title of which was adapted from Baudry and Lynch's (1984) "new and specific hypothesis." There, they proposed a specific role for postsynaptic glutamatergic receptors in the expression of LTP and, by inference, in memory. In our hypothesis, it was proposed that a naturally-occurring induction of LTP in the awake behaving animal would nonspecifically enhance the amplitude of neural representations of environmental stimuli. This generalized enhancement of cue salience could in turn enhance learning about relevant cues. **Shapiro & Hargreaves** (also see **Hawkins, Milner, Morris, O'Mara et al., Vanderwolf**) state that the hypothesis relating LTP to attention or arousal suffers from the same interpretative difficulties as the more common assertion that LTP is a memory storage device. The prevalence of this sentiment was in some respects encouraging, because it suggests that even among its proponents, there is some skepticism regarding the idea that LTP is a substrate mechanism of memory storage. What we tried to convey in the article and in particular in the section titled a "new and nonspecific hypothesis" (sect. 4) was that a mechanism such as LTP could indeed have effects on memory that were incidental to any role of LTP in the actual storage of memories. We also tried to convey the difficulty caused by trying to distinguish between alternative possibilities based on available data. Many of the relevant issues regarding this point have been addressed in the previous section. In the present section, we will respond to several comments that reflect specifically on the role of LTP in arousal and attention.

A number of commentators agreed with our premise that under some conditions LTP may subserve arousal. For instance, **Hawkins** notes that nonassociative forms of LTP may underlie arousal, whereas associative forms may underline learning. This is based on the idea that in the latter case, the modification of synapses that are active together is particularly well suited for learning about configurations of stimuli, but would not serve any function as a gain control mechanism as we suggested. We appreciate the potential explanatory value of this distinction as well as the difficulty for our alternative hypothesis posed by "associative" forms of LTP. Nevertheless, we are concerned that there is no real distinction between the two forms of LTP, because the difference between associative and nonassociative LTP may be one of degree (as discussed in the target article). This will remain a concern until an associative form of LTP is shown to contribute to the formation of an associative memory, which to date it has not. Nevertheless, the supposition of Hawkins has important implications as well as heuristic value.

From a somewhat different perspective, but still related to arousal, **Reymann** supports a role for LTP in memory processes through its role in motivational systems. He elaborates on his data that we mentioned in the target article. In these studies, he demonstrated that the longevity of LTP was enhanced by giving a foot-shock or providing water to water-deprived rats after exposure or in combination with the tetanization and the subsequent induction of LTP. Of course, we would interpret these finding as evidence that arousal associated with foot-shock and water deprivation enhances the induction of LTP, but as **Reymann** notes, there are alternative explanations that are equally congruent with a role of LTP in memory consolidation. Perhaps we cannot adequately evaluate memory consolidation independent of arousal, as has been suggested by Spear (1976). Experimental designs described by Reymann will certainly aid in the elucidation of this issue, but at present we remain uncertain as to whether arousal and consolidation are independent, overlapping, or codependent processes.

At this time, it seems appropriate once again to discuss the role of NMDA receptors in LTP versus their critical role in other phenomena such as stress, arousal, pain, and cell proliferation, and even suicide in humans (Nowak et al. 1995; see **Reid & Stewart**). First of all, it should be noted that a number of studies have reported that the effects of NMDA receptor antagonists on learning (often spatial learning) can be prevented by the coadministration of other agents. For example, Spruijt et al. (1994) reported that an ACTH fragment enhances attention to cues and overcomes the deficits in spatial learning induced by NMDA receptor antagonists. In addition, **Walker & Gold** discuss their studies in which glucose administration overcomes the performance deficits associated with NMDA receptor antagonism. Note that neither glucose administration nor an ACTH analog should affect current flow through the a pharmacologically-blocked NMDA receptor channel, though each could increase general levels of arousal (reversing the effects of NMDA receptor blockade) and could thus improve memory (e.g., Benton et al. 1994).

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Other commentators were less favorably disposed toward our suggestion that LTP may contribute to arousal. Unfortunately, our alternative hypothesis was misrepresented by some commentators. For example, **Morris** noted that we suggested that "attention serves to enhance stimulus salience." We did not propose that the induction of LTP induced attention directly. Rather, we proposed that exposure to a stressful (i.e., arousing) event induced LTP-like phenomenon (via NMDA receptor activation) that in turn enhanced the neural representation of cues in the environment. It is the enhanced representation of cues that directs attention to the stimuli. It is this increase in perceived salience that in turn impinges on learning. Thus, our hypothesis is that LTP induction affects attention indirectly, not that LTP induces attention itself. In fact, a literal reading of Morris' statement that LTP plays a role in the "automatic recording of attended experience" is not so different from our perspective, at least if an exaggerated perception of stimuli *prior* to "learning" about their significance constitutes the "recording of attended experience."

In the target article, we stated that the decay rate of LTP was more consistent with the time course of attention and arousal than memory storage. Although none of the commentators suggested how a decremental mechanism like LTP could subserve a long-lasting or permanent process like memory, proponents of the LTP-memory theory nevertheless attacked our alternative based on their perception of incongruent time courses of LTP and behavioral arousal. **Milner** states that a role for LTP in attention was "surely incorrect" and stated that selective attention "shifts every few seconds." First, it is well established that many types of attention (and/or arousal) persist beyond seconds, so it is unclear why Milner focuses on only one example. Selective attention, a process that shares many features of working memory, is a form of attention for which it is beneficial to engage in rapid transitions in focus while a general state of "attentiveness" can be sustained. Milner uses the examples of himself examining a drawing or a rat exploring a novel environment, examples that are clearly not relevant to the process to which we specifically referred – exposure to a frightening or life-threatening event. In addition, it is well established that human subjects can be in a chronic state of arousal while engaging in transitions of selective attention, suggesting a clear distinction between two states. Moreover, subjects in a state of high arousal learn better (as indexed in retention) than subjects trained under conditions of low arousal (see Levonian, 1972, for an extensive review), and learning is enhanced even under conditions in which the subjects are required to engage in transitions of selective attention. Finally, drugs that induce a condition referred to as "high arousal" (a chronic condition) uniformly enhance learning (for reviews, see Martinez 1992; McGaugh & Dawson 1972). Thus, our contention that the decay rate of LTP was consistent with a role in arousal (but not long-term memory) is consistent with available data. Curiously, Milner suggests that replacing LTP with LTD as a mechanism for selective attention would make sense out of nonsense.

Cain also noted that attention is too transient a state to be subserved by LTP, and suggested a role for LTP in an emotional state rather than in attention. We are in partial agreement with Cain, and erred in using the terms "attention" and "arousal" synonymously. Although poorly defined, we attempted to convey the view that exposure to a frightening and aversive event might induce a phenomenon analogous to LTP, thereby inducing a perceived increase in cue salience. Thus the concept of arousal is more analogous to a "state" than is attention. It is important, though, that we did not propose that LTP induces attention, rather we proposed that an LTP-like mechanism enhances the neural representation of cues. This enhancement in turn increases attention to those cues and could thereby influence learning. In our view, therefore, LTP might be better described as contributing to a state of arousal that in turn may increase attention.

Our suggestion that LTP could indirectly subserve attention or arousal led **Vanderwolf** to conclude that we are guilty of making the same logical leap that has afflicted LTP-memory advocates. Having contributed much to our understanding of theta activity and its role in behavior, Vanderwolf is particularly concerned about our allusion to a role for theta activity in attention. Although it is certainly not a counterargument, in deference to Vanderwolf's concern we are compelled to state again that in our view, LTP's proposed role in attention is supported by much of the same data that points to its role in memory storage. This concordance illustrates the point that the function of LTP is far from unequivocal and that convergent evidence cannot distinguish between these two viable hypotheses. But more specifically, Vanderwolf suggests that theta activity does not correlate well with the states of arousal that we suggest, and that there is no evidence that natural theta rhythms induce LTP. Regarding this latter point, it must be noted that nearly every review of LTP's role in memory states that it can be induced naturally by endogenous theta rhythms. Although a consensus view is by no means necessarily a correct one, we simply intended to imply that LTP could occur under natural conditions. (Prior to the demonstration that a theta-patterned stimulus could induce hippocampal LTP, most induction protocols used physiologically untenable stimulation patterns.) We were careful not to imply that theta activity was directly related to learning or memory, and stated so explicitly. However, with respect to arousal, data gathered by one of the coauthors does suggest that theta is enhanced after an arousing stimulus such as during exposure to restraint and intermittent tail shocks (Shors et al. 1997). In any case, we did not state that any arousing event would enhance theta, only that it has been associated with arousing stimuli under conditions of restraint and no overt movement. The point was simply that theta activity is induced in response to a stimulus that can either impede (Shors & Dryver 1992) or facilitate hippocampal-dependent memory (Beylin & Shors, submitted). In addition, it is noted that the relationship between theta activity and future rate of learning is not limited to shock-induced theta activity. Berry and Swain (1989) reported that water deprivation enhanced theta activity and the degree activity was strongly correlated with the animal's capacity for classical eyeblink conditioning with an auditory CS and contextual fear conditioning (Maren et al. 1994; contrast these observations to a critical assertion of **Fanselow** who argues that water deprivation does not enhance associative learning). Again, though, we do not claim that theta is necessary for memory; rather, we note that exposure to a threatening or arousing event can enhance theta activity under certain conditions (Shors et al. 1997b) and this particular pattern of stimulation is effective for activating NMDA receptor channels in a manner that efficiently

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induces LTP (Larson et al. 1986). In our opinion and as explicitly stated, the connection between theta activity and LTP simply advances us toward the threshold for accepting the proposition that LTP occurs in the behaving animal and may therefore have behavioral relevance. What of the sometimes poor correlation between theta activity and states of arousal or active learning suggested by Vanderwolf? It appears that theta activity may contribute to one or both of these processes under some conditions, but it is certainly not required.

In the four years since our target article was written, a number of the behavioral and biological characteristics of the effects of stress on associative learning have been elucidated. Most important for this discussion, we have determined that the stress-induced facilitation of associative learning that was posed as a model for our new hypothesis is dependent on NMDA receptor activation in the amygdala (Shors et al. 1997b; 1997d). It appears therefore that NMDA receptor activation is also necessary for "learning" to make new associations at a facilitated rate. **Maren** suggests that the animal was associating the context with the stressful experience, which then facilitated conditioning at the time of training. He may have misinterpreted these studies because the stressful event occurs in a completely different context than does the subsequent conditioning. This is not to say that contextual cues do not contribute to the facilitation even in ostensibly different contexts. For example, there are some contextual cues that are similar between the two environments such as being taken out of the cage, potential smells in the lab, the experimenter, and so forth. And certainly, contextual cues do contribute if manipulated directly; rats that are trained in the same context in which they are stressed learn faster still (Shors & Servatius 1997c) and a number of the biological correlates of the facilitated learning are reactivated by reexposure to the context. For example, exposure to a stressor enhanced [3H]PDBU (a marker for protein kinase C) binding in the basolateral nucleus of the amygdala. This effect was prevented by NMDA receptor blockade and reactivated by reexposure to the stressful context days later (Shors et al. 1997). Similarly, exposure to the stressful event persistently suppressed spontaneous unit activity in the basolateral nucleus. This effect, too, was prevented by NMDA receptor blockade during the stressful event and reactivated days later by reexposure to the context (Chachich et al. 1997). Therefore, although context conditioning can contribute to the effects of stress and potentially LTP on associative learning, it is not the determinant of it.

R3. Are changes in synaptic strength necessary for memory storage?

Milner states that "evidence that events influence future behavior by changing the effectiveness of synapses is by now overwhelming." If, as implied, Milner is referring to some well-established fact about the role of synaptic change in memory, then we are astounded. The less than overwhelming consensus for this assertion is apparent in comments by **Vanderwolf,** who suggests that the study of memory "lie outside the province of natural science." What, then, is the evidence that synaptic modifications contribute to memory storage? We address this issue somewhat reluctantly because of a concern raised in our target article, namely, that an increase in synaptic efficacy is not synonymous with the induction of LTP. In fact, we noted that if the term "LTP" was simply used as a synonym for an increase in synaptic efficacy, then the term becomes meaningless. Nonetheless, we will turn briefly to the more general topic of whether modifications of synaptic conductance have been demonstrated to contribute to memory storage.

Contrary to popular belief, no direct evidence has ever been presented to indicate that synapse-specific modifications contribute to the expression or storage of memories. A number of studies have indicated that an increase in unit responses can accompany learning, such as during classical eyeblink conditioning, as was discussed in comments by **Thompson.** Likewise, increases in unit or multiunit activity, as well as synaptic transmission, have been demonstrated to occur following fear conditioning (Neuenschwander-El Massioui et al. 1991; Quirk et al. 1995) and avoidance learning (Kubota & Gabriel 1995; Urban et al. 1995). Of course, this type of observation is limited by the fact that it is not possible to determine whether these changes in activity are (1) storing the memory, (2) representing the expression of the memory, or (3) simply a byproduct of behavioral responses induced by the memory (see Hargreaves et al. 1990, for a detailed discussion). Moreover, the fact that the increases in activity are often observed in brain areas not necessary for learning or memory expression suggest that they do not necessarily "store" the memory.

Although these issues are often overlooked, observations of increased unit activity, even synaptic efficacy, following learning raise a much more fundamental question: Are these changes limited to synapses or are they a reflection of an increase in somatic excitability? As discussed in the target article, LTP itself is not limited to an increase in synaptic efficacy, but rather, is a combined effect that reflects an increase in synaptic efficacy and a general increase in postsynaptic excitability. There is little, if any, data from vertebrate animals that distinguishes between the presumed effect of memory induction on synapses and other cellular compartments, such as the soma. A hint at the answer does come from examinations of invertebrate learning and memory in which the nervous systems contain identifiable cell bodies and tractable pathways of synaptic integration. In both aplysia and hermissenda, learning-induced modifications of synaptic efficacy have been reported (Frysztak & Crow 1994; **Hawkins** et al. 1983), and these synaptic modifications are essential to the expression of learned behavioral changes indicative of memory. In each case, however, the increases in synaptic efficacy are well established to arise at least in part from a decrease in potassium current(s) across the cell soma (see Matzel et al. 1997, for review). As a result, it is more likely that the cell will fire an action potential given a constant level of stimulation, fire an increased number of action potentials for a given level of depolarization, and that the duration of each individual action potential will be prolonged. Each of these biophysical modifications (originating not at the synapse but at the cell body) has the net effect of enhancing synaptic transmission onto postsynaptic targets. Thus although synaptic transmission is "potentiated," the modification is actually afferent to the synapse itself. It must be noted that although these modifications in somatic properties are sufficient to account for a modification of current flow through the neural network of these animals, it is possible

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that other synapse-specific modifications are also occurring. In hermissenda, no relevant data is available, although in aplysia, differential conditioning of multiple inputs onto a common target suggests that a synapse-specific modification may also be induced during learning (Clark & Kandel 1993).

Communal support is strong, but the evidence is weak, that memories are stored as modifications of synaptic strength. Therefore we must ask whether such changes would be suitable for storing memories. The simplest way to answer such a question would be to ask whether synaptic "weights" are sufficiently stable to store long-term memories. In the case of LTP, the decay rate is clearly too fast to be of use in this regard. Additional data suggest a similar conclusion. For instance, during metamorphosis, both vertebrate and invertebrate brains undergo a virtually complete synaptic reorganization, including the loss and regrowth of virtually every synapse as well as a restructuring of the synaptic network. At the same time, cell bodies remain intact. An obvious prediction of a synaptic theory of memory storage would be that the memories coded prior to metamorphosis would be lost because the fine network of synaptic weights has been entirely disrupted. On the contrary, memories are retained across metamorphosis in both vertebrate (Miller 1977) and invertebrate (Tully et al. 1994) species. As a second piece of evidence, it has recently been reported that female rats lose and regrow 35% of hippocampal synaptic spines – but not cell bodies – during each 5-day estrous cycle (Woolley & McEwen 1992). Because dendritic spines represent 90% of the excitatory synapses of pyramidal cells, these changes are not trivial. It is not known whether other brain areas undergo a similar loss and regrowth of synapses, or whether the same subset of synapses are lost during each cycle (although this latter possibilty seems unlikely). But if a fine network of synaptic weight changes were necessary for the storage and expression of memories, then females should exhibit severe memory impairments during each cycle of estrus, and the constant loss and regrowth of synapses should result in a virtual loss of all memories of durations greater than several weeks (assuming a random 35% loss during each cycle). It is certainly true that females have differential learning rates on some tasks. Relative to males, they are reported to be deficient in contextual fear conditioning (Maren et al. 1994), but proficient in classical eyeblink conditioning (Wood & Shors 1996). They do not, however, exhibit dramatic changes in hippocampal-dependent spatial learning across the estrous cycle (Berry et al. 1997; Warren & Juraska 1997), despite significant variation in synaptic density (Woolley & McEwen 1992) and hippocampal LTP across the same time period (Warren et al. 1995). As another example, we direct the reader to our target article where we describe the repeated failures of many laboratories to observe any detrimental effect of nonspecific saturation of synaptic transmission on subsequent learning. Similarly, electroconvulsive shock tetanizes virtually all synapses in the brain (surely disrupting the information flow through a network of synapses), but disrupts only those memories acquired within a very narrow time window immediately prior to administration of the shock (see Miller & Marlin, 1984, for review), that is, long-term memories are unaffected by a complete reorganization of synaptic weights. Although it was our intent in the target article, these data and the inability to connect synaptic LTP with memory storage may lead one to agree with recent reviews (Smythies 1997) and **Latash,** who notes that "the synaptic theory of neural memory is facing hard times."

What do synapses do if they do not store memories? For years, students of psychophysics, perception, and neurophysiology have held to the belief that the vast number of contact points contained in a synaptic arbor are used to instill fine gradations of resolution to signals that would otherwise be more akin to a digital event – all or none. Similarly, synapses integrate signals from many different sources, providing a situation in which no single input is solely responsible for the postsynaptic action potential (again as a means for increasing resolution). Can the conclusion that synaptic weights do not store memories be incorporated by network modelers of memory? A cursory inspection of commonly cited network models suggests that this assumption is already accommodated by these models. Although modelers often speak of synapses, their models most typically incorporate a 1:1 correspondence between the synapse and the cell body, rendering the synapse functionally superfluous. Likewise, many models that are closely tied to actual neurophysiological evidence explicitly disregard the role of synapses when describing phenomenon such as pattern recognition or memory (e.g., Hopfield 1995; Tesauro 1988).

If synapses do not store memories but synaptic transmission is necessary for memory induction, then we would predict that any manipulation that disrupts synaptic transmission should have a similar effect on memory. In our target article and our responses above, we voice this concern with regard to the disruptive effect of NMDA receptor antagonists on memory formation. The converse is also true. Any manipulation that facilitates synaptic transmission should be beneficial to memory formation. Indeed, a number of stimulants (e.g., nicotine, cocaine, amphetamine) increase transmission in subpopulations of neurons and enhance various forms of memory. Likewise, drugs that enhance synaptic transmission through the AMPA subtype glutamate receptor also enhance various forms of memory (e.g., Shors et al. 1995; Staubli et al. 1994). The enhancing effect of an increase in synaptic transmission can be interpreted at least two ways. One is that "LTP" has been induced, which in turn promotes memory formation. This should be recognized as antithetical to the assumptions of researchers who predict that LTP induction should retard subsequent learning. Another possibility is that the enhancement of transmission simply facilitates the induction of LTP, which it does (Staubli et al. 1994) One interpretation is that the enhanced neurotransmission enhances stimulus processing, which can influence the storage of memories. In support of this final point, the drugs that enhance synaptic transmission through the AMPA receptor not only enhance classical conditioning, but also induce pseudoconditioning and sensitized responses to cues in the environment (Shors et al. 1995). Similarly, Matzel et al. (1996) reported that the basal level of synaptic efficacy between relevant sensory systems correlated highly with an animal's capacity to learn a Pavlovian association. Likewise, Jeffery and **Morris** (1993) report that synaptic efficacy within the hippocampus (as indexed by the capacity for LTP induction) was well correlated with the induction of spatial memories in the rat. In summary, synaptic transmission clearly modulates memory formation, but it is less clear that synaptic transmission is a substrate for memory storage.

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R4. Conclusion

The goal of the target article was to create a debate about the role of LTP in learning and memory processes. We likewise hoped to generate ideas about how memories are stored in the brain. Momentarily ignoring the warning that memory is an emergent process of the nervous system, we can offer two extreme possibilities as potential memory storage mechanisms. One is that a single general mechanism pervades numerous brain structures and is used to encode all types of memories. If we are open to the possibility that NMDA receptor-dependent LTP is not a memory mechanism, then this possibility cannot be abandoned. The other possibility is that there are different storage mechanisms for different types of memory in different brain structures that store memories for different periods of time. This hypothesis was foreshadowed by **Hawkins** who states that "processes are often distributed, redundant, and nonlinear." And of course, there could be some combination of these two extremes, as was also suggested and favored by Hawkins. At present we are not sure which of the three possibilities is most correct, although recent reviews of the literature point to the latter (e.g., Hawkins et al. 1993; Matzel et al. 1997) and suggest common themes as well as dissimilarities among superficially disparate systems.

It would certainly simplify our lives if there were a single mechanism expressed ubiquitously throughout the nervous system(s) for all types of memory. Such an outcome would not be unprecedented. Prior to its elucidation, it was less than obvious that the structure of DNA and the mechanism for creating genes and gene products would be so simple (conceptually, if not in practice) and at the same time so widely conserved. Although such a possibility for a memory mechanism is appealing, it finds little current empirical support (as suggested by the popular response among commentators that NMDA receptor-dependent LTP could only subserve a subset of memory systems). Although we maintain that LTP, in and of itself, is insufficient to store memories, we believe that it is unreasonable to abandon the *possibility* that it does, just as it is unreasonable to focus exclusively on the *assumption* that it does.

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