169

PROGRESS IN BRAIN RESEARCH

Essence of Memory

EDITED BY
Wayne S. Sossin
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Preface

The following volume stems from a meeting of the same name ''The Essence of Memory'' held in Montreal from May 12 to 14, 2007 organized by the editors of this volume. The editors would like to acknowledge the support of the Groupe de Recherche sur le Système Nerveux Central, Université de Montréal, for the organization of the meeting. This meeting brought together an international group of investigators studying memory from the molecular, cellular, physiological and behavioral levels. The goal of the meeting was to see how these levels could talk to one another and to inform researchers in this field. In addition, for this book, we have recruited a number of additional leading investigators to fill in gaps necessitated by the limited time for presentations at the meeting. Several of these were from other attendees of the meeting, and several were by invitation. By trying to discuss the 'essence' of memory, we mean to distill the fundamental issues in the memory field that should transcend boundaries and hopefully eventually lead to an understanding of memory at the molecular level that will be able to be translated into pharmacological and behavioral treatments of memory disorders.

The volume begins with cellular and molecular approaches to understanding memory. There is an overview chapter by Dr. Sossin on molecular memory traces, discussing how our growing understanding of the molecular and cellular basis of the memory trace opens up opportunities and challenges for cellular and systems understanding of memory. In particular, an argument is made for multiple independent memory traces that are formed after an experience. This is followed by a series of chapters further elucidating these distinct molecular traces. Dr. Sacktor describes his research on PKMζ, which fulfills many of the requirements for a molecular memory trace. Another memory trace requires gene expression and local translation. Dr. DesGroseillers describes how mRNAs are transported in neurons and Dr. Klann then describes how the translation of these mRNAs is regulated, and how dysregulation of this pathway can disrupt memory. Dr. Sonenberg describes his recent findings that protein translation also regulates an important transcriptional switch that determines when long-term memory is induced. Drs. Abel and Nguyen describe the role of another critical signal transduction pathway, production of cyclic AMP, in multiple kinds of memory traces. Together these investigators highlight the recent advances in molecular cognition. After identifying important molecules involved in memory formation, mice are generated either lacking these molecules, or expressing blockers of this pathway, and then behavioral tests of memory are used to determine the importance of the molecular pathway.

The discussion of the molecular and cellular memory trace continues with a chapter from Dr. Frey, the discoverer of synaptic tagging. The memory trace is thought to be synapse-specific; however cellular processes such as translation and transcription may not be this local. Dr. Frey describes the mechanism of 'tagging' to allow for plasticity-related proteins to be restricted to activated synapses. Dr. Wang introduces another well-understood memory trace, the trafficking of ionotropic receptors, notably the glutamate sensing AMPA receptors, and describes how other systems like stress impact on the ability of this plasticity to occur. Dr. Bannerman examines memory in the absence of this pathway, suggesting interesting dissociations between different kinds of memory based on the trace that they use. Another type of memory trace is structural; both structural modification of synapses already present, and the generation of new synapses. Dr. Bailey and Kandel describe the evidence that structural modifications occur during memory

in invertebrates and then the question of whether similar changes occur in the rodent hippocampus are discussed by Dr. Muller.

An understanding of the 'essence' of memory must also elucidate memory at the systems level; understanding the anatomical constraints of the circuits underlying memory and identifying at which synapses the molecular and cellular events occur. Dr. Turrigiano discusses her work on how intrinsic properties are important during development to set up the system for efficient memory formation. Dr. McBain and Dr. Lacaille both discuss the importance of plasticity in inhibitory neurons both in controlling the memory systems, and perhaps in forming memories themselves. Dr. Lu describes his work on how molecules such as BDNF can impact the persistent activation of neurons seen during working memory.

The volume now moves into investigations of the 'essence' of memory at the whole animal level, where memory traces are examined during behavior. This problem is introduced by Dr. Castellucci in an introductory chapter. Dr. Glanzman describes the growing importance of post-synaptic changes in regulating the defensive reflex in *Aplysia* during associative conditioning; Dr. Davis describes how new molecular techniques in the fly allow monitoring of cellular memory traces during learning and the growing knowledge of the cellular organization of memory in the fruit fly. Dr. Suzuki describes her work on following memory formation using recordings in the monkey limbic area as they learn a new task.

The 'essence' of memory must reflect an understanding of our memory, human memory. In particular, a major justification for elucidating the molecular and cellular basis of memory traces is to help solve problems and pathologies of memory formation in humans. Over the last decade, studies of human memory have provided cognitive and neurobiological models of memory to explain, characterize and organize the act of memory within a coherent framework. This effort should lead to a better understanding of how events are typically encoded and retrieved by memory. It should also shed light on the memory changes that accompany human development and aging, the impact of memory-related disorders such as Alzheimer's disease or mild cognitive impairment, and the effect of stressful biological events such as anesthesia and surgery. This part of the volume starts with a chapter by Dr. Cowan who proposes a theoretical view regarding the distinction between important components of memory: short-term memory, working memory and long-term memory. He presents defining principles to dissociate those forms of memory and discusses why working memory tasks are such good predictors of high-level performance. In the following chapter, Dr. Rugg describes imaging studies to support a neurocognitive model of episodic memory. The proposed model addresses the correspondence between encoding and retrieval cues and the role of binding processes in episodic memory. Dr. Hasher describes her work on the role of distraction on memory processes and on complex cognitive tasks. She discusses that the age-related changes in attentional regulation can result in both costs and potential benefits on older persons' ability to complete memory and complex cognitive activities. Dr. Belleville introduces the notion of mild cognitive impairment, a potential precursor state of Alzheimer's disease. She discusses its impact on episodic memory and working memory and proposes that both components are impaired during the earliest phase of the disease. Dr. Isingrini presents a chapter where metamemory is conceived as a crucial component of memory performance. He discusses findings showing that this is a component critically modified by healthy aging and by Alzheimer's disease. Dr. Chertkow discusses the impact of Alzheimer's disease on memory by focusing on the notion of semantic memory, that is memory for words and concepts. In this chapter, Dr. Chertkow proposes a cognitive and a neurobiological model to account for the semantic memory breakdown characterizing Alzheimer's. Finally, Dr. Caza discusses a new area of research investigating the impact of anesthesia and surgery on memory processes. She introduces hypotheses regarding the underlying biological models for such an impact on memory and highlights areas for future investigation.

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Cellular and Molecular Approaches to the Essence of Memory

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CHAPTER 1

Molecular memory traces

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Abstract: To understand the essence of memory, one must examine the working of the brain on many levels. It is important to find the appropriate level to study the particular aspect of memory under investigation. In this review, I will focus on insights gained from examining memory at the molecular level. I will illustrate these insights with specific examples from examining the molecular and cellular mechanisms underlying long-term facilitation in the marine mollusk *Aplysia* and long-term potentiation, studied mainly in rodents. In particular, I will discuss how molecular memory traces are formed and focus in detail on what role increasing the level of proteins through protein synthesis and gene expression plays in memory formation. I will point out three important constraints from molecular work that should impact on cognitive modeling of the nervous system: (i) the induction of plasticity depends on the 'state' of the synapse; (ii) there are multiple independent molecular traces formed after experience with different half-lives; and (iii) the requirement for the conjunction of synaptic activation and new protein synthesis implies that new conjunctions are required to induce long-term memory formation.

Keywords: *Aplysia*; long-term facilitation; long-term potentiation; protein synthesis; gene expression

Introduction

Brains are not computers

Since our brain is made up of neurons, not silicon chips; and because the brain evolved, instead of being designed, there are molecular constraints on brain function. For an alternative example, let us examine the storage of memory on a computer. The fundamental mechanism of memory storage has changed multiple times (from electrostatic memories, to magnetic memories, to semiconductors, perhaps eventually to nanotubes), without the need for changes in higher-level computer languages or computer design. This is due to layers of engineering software between access and writing to memory and the actual mechanism involved in storing the memory. Being able to treat each module as a 'black box', without requiring knowledge of the underlying mechanism of action, is a strong engineering principle. The brain does not work this way, since it was created by evolution, not design. Thus, how memories are stored in the brain is constrained by the limitations of biology and could not be fundamentally changed as brains became more complex.

Most neuroscientists believe that memories are stored in the strengths of the synaptic connections between neurons. Consequently, the properties of neurons and the synapses that interconnect them are pivotal for understanding how our memory works. Nevertheless, just because molecules are

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important does not mean that one can understand complex mnemonic processes solely by understanding molecules or synapses; valuable insights are also needed from systems and cognitive level analysis. The key from molecular studies is to extract the rules from which these systems can be built up. For example, the most ambitious extraction from neurons to cognitive systems was the parallel distributed processing concept (PDP), where cognitive scientists attempted to extract the 'essence' of how neuronal systems work to generate interesting models for learning (McClelland and Rumelhart, 1985). A major rule that was extracted was that neurons connect to each other with a specific strength, this connection can be modified by some learning rule, and that each connection can be modified independently. Interestingly, to make these models work, they also required a new rule that the overall strength of connections to a neuron had to remain approximately the same so that as the strength of connections increased, other connections had to decrease. This kind of homeostatic rule is also present in neurons and our understanding of its importance for how the brain works is just beginning (Turrigiano and Nelson, 2000). This is an example of an engineering principle that is invariant, a system that works a certain way needs to encode it whether biological or silicon based. However, as discussed below, there are probably additional important constraints not captured by the PDP model that are required to understand how memories are encoded by the brain.

Model systems

Aplysia*, a cellular model for studying memory at the molecular level*

The reductionist approach is a powerful way to determine molecular mechanisms of memory. This approach assumes the mechanisms that underlie how memory works in simple systems will be conserved in higher systems due to conservation of molecular mechanisms affecting how synapses work. *Aplysia* is a marine mollusk with a simple nervous system. By a comprehensive examination of this system at the molecular, cellular and behavioral level, a number of important insights have been gained into the molecular mechanisms of memory formation (Kandel, 2001). The major memory examined in this system is changes in the defensive reflex of the animal, exemplified by the withdrawal of the gill or siphon, based on experience. At the simplest level, this reflex is mediated by a direct connection between sensory neurons that detect a touch and motor neurons that withdraw the gill or siphon. This reflex can be modulated by experience in a number of ways exemplifying many of the basic non-associative and associative learning paradigms (Hawkins et al., 2006). Habituation is the decrease in the reflex seen after multiple occurrences of a harmless touch. This can be explained at the cellular level by a decrease in the strength of the sensory–motor neuron connection, termed depression (Castellucci et al., 1970). Sensitization is the increase in the reflex after experiencing a noxious stimulus. This is a non-associative memory since the noxious stimulus does not have to be associated with the activation of the reflex. The noxious stimulus causes the release of serotonin (5-HT) (Marinesco and Carew, 2002), and 5-HT acts at multiple levels of the circuit to increase the defensive reflex (Frost et al., 1988), including increasing the strength of the sensory–motor neuron connection, a process known as facilitation (Castellucci and Kandel, 1976). Finally, if the animal is touched while it receives the noxious stimulus, an additional increase in the reflex occurs that reflects the associative change (Hawkins et al., 1983; Walters and Byrne, 1983). Here the coupling of 5-HT and firing of the sensory neuron leads to additional increases in the connection between the sensory and motor neurons.

One of the great strengths of this system is that a behavioral memory has been strongly associated with a specific change in synaptic strength between two identified neurons. Thus, one can study molecular mechanisms of memory at this specific synapse. Moreover, the sensory and motor neuron can be cultured from the animal and in culture they re-grow their synaptic connection and one can study depression and facilitation in a reduced system that mimics many of the mechanisms observed in the animal (Montarolo et al., 1986).

The CA3–CA1 synapse in vertebrates as a cellular model for associative learning

The hippocampus is the anatomical region required for many forms of associative learning in vertebrates. Also, due to its organized fiber tracts, it is a wonderful model for examining cellular plasticity, as it is simple to activate presynaptic fibers onto postsynaptic neurons and record the synaptic strength in a field recording. While long-term potentiation (LTP) was discovered in the fibers entering the hippocampus (the perforant pathway) (Bliss and Lomo, 1973), it has been studied most extensively in the connection between the CA3 neurons and the CA1 neurons. Unlike the non-associative facilitation induced by 5-HT in *Aplysia*, the increase in strength between CA3 neurons and CA1 neurons is associative, requiring both presynaptic firing in the CA3 neuron and postsynaptic depolarization in the CA1 neuron. This conjunction of inputs is required to open the *N*-methyl-D-aspartic acid (NMDA) receptor and calcium entry through this receptor induces LTP (Bliss and Collingridge, 1993). One major weakness of this system is the lack of knowledge of the specific function of the CA3–CA1 connection and how changes in the strength of these connections is related to the memories encoded in the hippocampus. Nevertheless, there is abundant evidence that this plasticity is important for memory and many of the fundamental molecular insights into memory have come from this system (Morris, 2003).

What types of cellular changes underlie memory formation?

Excitability changes

The major advantage of changing memories at synapses is the ability to strengthen specific inputs to a neuron based on those inputs coupling with the firing of the output neuron. This can lead to the forming of neuronal associations underlying associative memory as was famously outlined by Hebb (Cooper, 2005). However, while this review will focus on synaptic plasticity, not all memories need be encoded only by changes in synaptic strength. A neuron can also change the rate at which it fires action potentials to the same inputs, a change in excitability (Daoudal and Debanne, 2003; Schulz, 2006). In *Aplysia*, 5-HT increases the excitability of the sensory neuron through activation of a kinase, protein kinase A (PKA), and phosphorylation of potassium channels, S channels, that are open at rest (Siegelbaum et al., 1982). Closing these channels causes the neurons to depolarize and thus less input is required for them to reach the threshold for firing an action potential. It also closes channels that normally prevent the firing of multiple action potentials, a process known as anti-accommodation (Klein et al., 1986). In combination, these two molecular changes allow stimulation of the sensory neuron (a touch) to fire more action potentials, and thus lead to an increase in the defensive reflex. Excitability changes in *Aplysia* are both seen immediately after sensitization, or 5-HT addition in culture, and can last at least 24 h after training (Scholz and Byrne, 1987). The prolonged increase in sensitization is probably due to the persistent activation of PKA (see below).

Excitability changes have also been detected in vertebrate systems. During LTP there is an increase in excitability of the CA1 neurons as well as increases in synaptic strength (Xu and Kang, 2005). Moreover there are multiple examples of changes is ionic channels in dendrites affecting the propagation and integration of inputs and these changes can be local, either synapse or branch specific (Frick et al., 2004; Frick and Johnston, 2005). It will be interesting in the future to determine how important these changes are for memory. Clearly genetic changes that affect excitability do affect memory (Nolan et al., 2004; Hammond et al., 2006) but it is hard to determine if their effect is to change the state of the neuron to undergo plasticity, or is intrinsically involved in the plasticity itself. For example, a genetic change that reduces the ability of a dendritic region to depolarize will inhibit the ability of coincident inputs to activate NMDA channels and thus inhibit the ability to induce plasticity. In contrast, NMDA channel opening leading to calcium entry, activation of kinases and phosphorylation of an ion channel that leads to a long-term increase in the

ability of local excitatory postsynaptic potentials (EPSPs) to propagate down the dendritic branch would be an example where excitability changes are intrinsically involved in the memory trace.

Changes in synaptic strength

Synaptic strength is regulated by three parameters, the probability of release (p), the size of the response to a single vesicular release (q) and number of functional synapses (n). All are probably changed in distinct memory traces. There are also many different mechanisms to regulate each of these parameters. For example, the value of q is determined by: (i) the number and efficacy of postsynaptic receptors; (ii) the amount of transmitter/vesicle (which can be regulated by the number of vesicular transporters); (iii) the efficacy of neurotransmitter uptake; and (iv) the ionic concentrations that determine the driving force for the ionotropic receptors. All of these can be modulated by plasticity (Levenson et al., 2002; Malinow and Malenka, 2002; Woodin et al., 2003; Shen and Linden, 2005; Takamori, 2006).

Facilitation in Aplysia *sensory–motor neuron synapses is mainly determined by changes in the probability of release*

In *Aplysia*, depression, the cellular model for habituation, is due to a decrease in p and facilitation (Castellucci and Kandel, 1974), the cellular model for sensitization, is due to increases in p (Castellucci and Kandel, 1976). The decrease in p is not linked to a decrease in the frequency of spontaneous release (Eliot et al., 1994) and is mainly due to a decrease in calcium-secretion coupling (Zhao and Klein, 2002), the ability of calcium to induce release of vesicles. Facilitation is coupled with an increase in spontaneous release (Dale et al., 1988), however this increase is mediated by 5-HT activation of protein kinase C (PKC), but inhibitors of PKC do not block short-term facilitation (STF); thus this increase may not be related to facilitation (Ghirardi et al., 1992). Instead, facilitation is caused both by increased calcium entry due to action potential broadening, and additional PKA-dependent changes in the probability of release that have not yet been identified (Klein, 1994; Byrne and Kandel, 1996). At later points, 5-HT can increase n both due to the activation of silent synapses and the formation of new synapses (see Chapter 10 by Bailey and Kandel, this volume). Finally, 5-HT can also increase the number of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors as measured by the response to extracellular glutamate (Trudeau and Castellucci, 1995; Chitwood et al., 2001), however it has not yet been shown that these receptors are synaptic (and thus alter q) and the contribution of the increase in these receptors to sensitization is still under debate (see Chapter 17 by Glanzman, this volume).

Potentiation in CA3–CA1 synapses is mainly determined by changes in the reception of neurotransmitter

In CA3–CA1 neurons early LTP is due to increased levels of AMPA receptor activity. Thus, there is an increase in the reception of neurotransmitter or q, the size of the response to the release of a single vesicle. This is due to increased activity of AMPA receptors already present in the synaptic membrane, the insertion of more AMPA receptors into previously active synapses and the insertion of AMPA receptors into silent synapses (Liao et al., 1995). Changes in the probability of release have been inferred at later times after plasticity, due to a measured increase in the probability of release (Bolshakov et al., 1997; Zakharenko et al., 2001) and the requirement of presynaptic changes for prolonged potentiation after some stimulation paradigms (Huang et al., 2005). It is not clear if later stages of LTP at CA3–CA1 synapses are due to increased numbers of synaptic connections (see De Roo et al., Chapter 11).

The difference in the locus of the change in *Aplysia* sensory–motor neuron synapses and CA3–CA1 synapses does not reflect a fundamental difference between invertebrates and vertebrates, but is simply a function of the choice of model synapses. *Aplysia* still retains the mechanisms

required for insertion of AMPA receptors and this may play a role in associative sensitization at sensory–motor neuron synapses and probably at other synapses that have not been examined in detail (Roberts and Glanzman, 2003). Moreover, there are numerous examples of LTP in vertebrates that are mainly mediated by changes in p, notably the mossy fiber synapses connecting the dentate gyrus to CA3 (Zalutsky and Nicoll, 1990).

Molecular memory can be dissociated into temporal phases

Memory has been roughly divided into three temporal domains. Working memory refers to retention of events that can be represented by the continued firing of neurons that represent the stored information. Short-term memory refers to memories that are vulnerable to interference until they are consolidated; at the cellular and molecular level this is often associated with the lack of a requirement for protein synthesis. Finally long-term or consolidated memory represents a long-term store that is less vulnerable to interference and at the cellular and molecular level requires protein synthesis. This classification serves some purposes, but does not fully capture the cellular changes that underlie the memory trace. I would argue instead that there are multiple molecular traces that are induced by experience that last for various times and do or do not require new protein synthesis. These traces can be independent of each other.

If memories are stored in the strength of synapses, how are these changes stored. Is it in the state or level of a single molecule, or is it a more complex interaction between many molecules? One of the key problems to overcome is the long lifetime of a memory compared to the lifetime of an individual molecule. Moreover, unlike computer memories in neurons, there are distinct types of biological synaptic changes that last for different time periods. While memory in biological systems is vastly different than memory in computers, there is a useful analogy. In computers, memory storage devices are divided into volatile (such as dynamic random access memory where constant energy is required to maintain the memory) or static (such as memory encoded on a magnetic disc). In biological memory, this difference is not a dichotomy but a continuum where different types of memory storage require different amounts of energy to maintain. For example, if memory is encoded by changes in phosphorylation (i.e. due to production of a persistently active kinase), the memory is volatile and inhibiting the production of the kinase should eliminate the memory. In contrast, if memory is encoded by constructing new synapses, inhibiting production of new proteins should not immediately remove the synapse, and thus, the memory is more static.

Below, we will examine the molecular memory traces at the two model synapses under discussion and examine what traces underlie the different temporal domains in detail, concentrating on short- and long-term traces. For discussions of working memory, see Chapter 19 by Suzuki, this volume; Chapter 15 by Galloway et al., this volume.

Molecular traces of different volatility are induced by protein phosphorylation

Most short-term changes in synaptic strength are due to phosphorylation, either kinases adding phosphates, or phosphatases removing them. While the phosphorylation event itself is usually short lasting, depending on the consequence of phosphorylation the trace is graded in its volatility (Fig. 1). The half-life of messengers (calcium or second messengers (cyclic AMP, diacylglycerol, etc.), that activate the kinases/phosphatases ranges from seconds to minutes. Furthermore, the change can be easily reversed, i.e. a phosphate added by a kinase can be removed by a phosphatase. Thus in *Aplysia*, a single 5 min application of 5-HT leads to activation of PKA, phosphorylation of target molecules including ion channels and proteins involved in vesicular release and an increase in synaptic strength that lasts for about 20–30 min. Thus, this is a highly volatile memory trace. However, transient changes in phosphorylation sites can also lead to a longer-lasting change by inducing other events that may not reverse when the site is removed. For example, insertion and removal of AMPA receptors at CA3/CA1

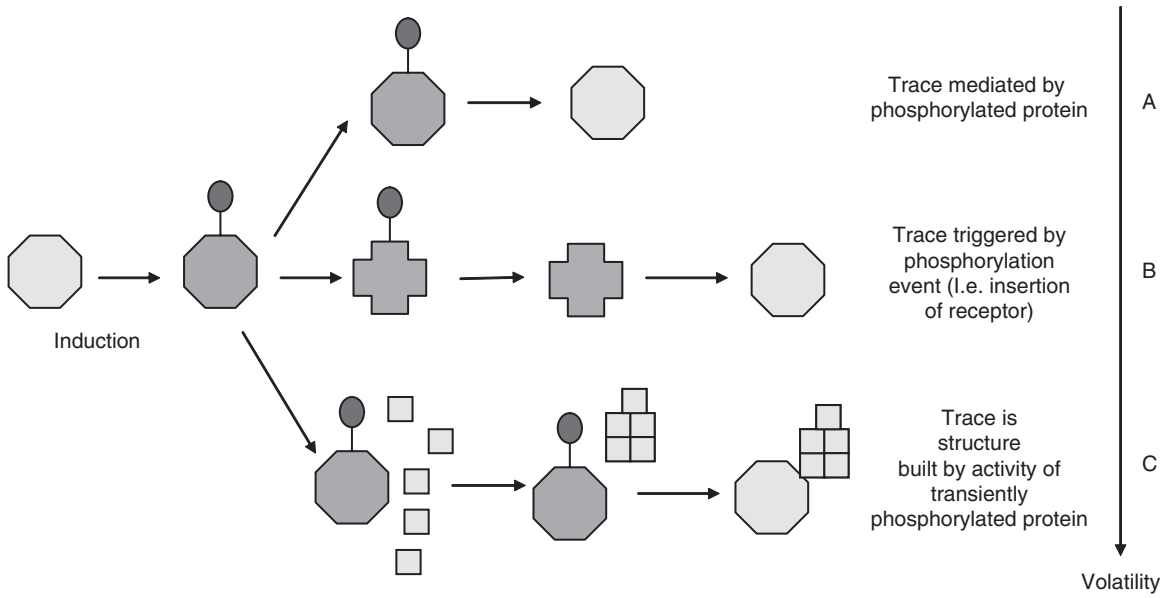

Fig. 1. Different molecular traces induced by phosphorylation have different volatility. (A) The simplest memory trace involves activation of kinase that phosphorylates a substrate. Phosphorylation of the substrate itself leads to an increase in synaptic strength through either increasing transmitter release (e.g. SNAP-25) or transmitter reception (e.g. CAMKII phosphorylation of AMPA receptors). Once the kinase is no longer active (degradation of second messengers), phosphatases remove the phosphate and the trace is erased. (B) Phosphorylation can induce a change in the protein (shift from hexagon to cross) that lasts longer than the phosphorylation itself. For example, phosphorylation of AMPA receptors may lead to insertion of the receptor that can persist after the phosphorylation has been removed. Some additional event then has to occur to erase the memory trace. (C) Phosphorylation can activate a protein (i.e. a regulator of actin polymerization, cofilin) that leads to a structural change (assembly of blocks into a house-like structure) that persists after the phosphorylation is removed and requires an active process to disassemble. The three changes are graded in their volatility. (See Color Plate 1.1 in color plate section.)

synapses requires several phosphorylation events, but the insertion or removal of the receptor may last longer than the change in phosphorylation. This would represent a less volatile trace, however, insertion of AMPA receptors can still be reversed by endocytosis of the receptors, and does not persist in the absence of additional events (i.e. the early form of LTP lasts only for a few hours). Thus this trace is less volatile than a simple phosphorylation event, but still is easily reversed (Fig. 1). Morphological changes that are induced by kinase activation are probably not reversed simply by removing the phosphate off the cytoskeletal regulators involved in inducing the change, and may persist in the absence of an active process that would lead to a reversal of the cytoskeletal change. Thus, morphological changes could represent a more 'static' change still induced by phosphorylation (Fig. 1). Thus, a common finding for most kinases involved in longer-lasting changes is that they are required to induce the change, but in many cases not for the maintenance of synaptic changes. An exception to this is when the molecular trace itself is a persistently active kinase (see below).

State-dependence of cellular memory traces

An important aspect of the memory trace is its induction; what is required to induce the memory trace. The state of the synapse is a critical regulator of the induction step, and thus depending on the state of the synapse, the identical stimulus can have different effects and induce different traces. The synapse regulates its own ability to be plastic, or metaplasticity (Abraham and Bear, 1996), at the molecular level by altering the rate-limiting steps in the induction of plasticity.