Memory Maintenance
The Changing Nature of Neural Mechanisms
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ABSTRACT—Change in the synaptic communication between neurons—known as synaptic plasticity—plays a key role in learning and memory. It is not yet clear, however, whether the properties of synaptic plasticity are sufficient to account for long-term-memory maintenance. Recent studies have revealed that synaptic plasticity can indeed persist for weeks or months, as might be expected of a long-term-memory mechanism. However, memories encoded by neural systems are not static; they continue to evolve as new learning occurs. Furthermore, neural-network modeling has shown that synapses must be able to reconfigure their connection strengths during new learning if old information is to be preserved. Recent tests confirm that synapses, once modified, retain their capacity for further modification, indicating that they can indeed operate in the manner predicted to be necessary for memory maintenance in a dynamic learning network.

KEYWORDS—synaptic plasticity; memory maintenance; neural networks; long-term potentiation

How is information learned, stored, and maintained in the brain? Historically, it has been supposed that these processes involve changes in the structure or function of neurons, particularly at the synaptic junctions through which they communicate. Thus, most theories postulate that synapses are likely sites of activity-induced change—known as plasticity—that could be responsible for reordering the communication between neurons during learning. By such restructuring, those same networks active during learning could then be readily re-engaged during memory retrieval. In Hebb's (1949) theory, synapses are strengthened as a function of neuronal co-activity, a principle now codified by the mnemonic “cells that fire together, wire together.” In addition, more recent theories and empirical evidence suggest that a weakening of synaptic communication is also a memory mechanism. In this article, I will consider the properties and mechanisms of the synaptic plasticity that may underlie the maintenance of long-term memory, in light of recent advances in this area.

LONG-TERM POTENTIATION

In a landmark discovery, Bliss and Lom (1973) reported that electrically induced neural activity can cause a persistent increase in the strength of transmission at the activated synapses (Fig. 1), a phenomenon termed long-term potentiation (LTP). There now exists a wealth of evidence supporting the working hypothesis that the molecular mechanisms underpinning LTP and its opposite synaptic change, long-term depression (LTD), are also engaged by the naturally occurring synaptic plasticity generated during learning (Martin, Grimwood, & Morris, 2000). However, it is important to keep in mind that LTP and LTD are phenomena that are studied in the laboratory, using electrical stimulation to generate neural activity that is only a simulation of the neural activity that occurs during learning. Thus, while one approach to testing this hypothesis is to compare the relevant properties of LTP and memory, as I do below, it is necessary to be cautious in expecting too close a correspondence between the properties of plasticity at single synaptic junctions and the properties of memories that are distributed over networks of neurons and synapses.

A key question regarding any neural mechanism of memory has been whether it can last long enough to account for the longevity of long-term memory. Most studies of LTP persistence in animals typically have reported LTP to last from hours to weeks but ultimately decaying to baseline. However, LTP lasting stably for many months has now been reported (Abraham, Greenwood, Logan, Mason-Parker, & Dragunow, 2002). This is not to say that the potentiated synapses remain continuously active over this time, but that there is an enduring enhancement of their ability to communicate with the neurons to which they connect. Thus, it has been frequently hypothesized that if synaptic plasticity contributes to initial learning, its enduring persistence could underpin the memory retention for that learned event (Abraham, 2003). However, I will present recent findings that challenge this conventional wisdom and that point
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There is considerable evidence from both animal and human studies that, after learning, memory undergoes a time-dependent consolidation process such that it becomes resistant to treatments given post-training that can otherwise cause amnesia for the learned event. Many theorists now distinguish two forms of consolidation: cellular consolidation and systems consolidation.

The concept of cellular consolidation arose from animal studies showing that newly formed memories require the triggering of protein synthesis in order to survive longer than a few hours (Squire, 1986). Administration of a protein-synthesis inhibitor during or just after training impairs long-term retention of that memory without affecting initial learning or retention over the first few hours. This implies that, at a cellular level, neurons are triggered during training to make additional proteins that in some way help preserve the newly changed synaptic connection strengths. In a remarkable correspondence, LTP also shows a fundamental dependence on new protein synthesis in order to last longer than a few hours. The identity and function of the key proteins have yet to be fully characterized, but it is likely that the newly synthesized proteins contribute to changes in the fine structure of synapses, thereby locking in the functional changes that occur more immediately during learning. In another point of correspondence, the long-term persistence of LTP is best achieved by multiple episodes of synaptic activity spaced over time; likewise, memory retention is far superior after spaced training than after the same number of training trials occurring in rapid succession (DeZazzo & Tully, 1995).

Systems consolidation refers to a change in the way memories are stored, such that, with time, they lose reliance on the brain structures that were essential for successful retention early after learning. Systems consolidation studies have focused on structures in the brain’s medial temporal lobe, such as the hippocampus. Many episodic- and spatial-memory tasks are dependent on the integrity of the hippocampus and related structures early after training, but eventually the information is consolidated in other brain regions, such that memory retention is unimpaired even if the hippocampus is completely removed (Wiltgen, Brown, Talton, & Silva et al., 2004). In contrast to cellular consolidation, however, systems consolidation can take days, weeks, or even years to be accomplished. It has been hypothesized that this lengthy consolidation period permits repeated cycling of activity between the hippocampus and neocortex, a major area for very-long-term memory storage, so that new information initially stored in the hippocampus can slowly be integrated into cortical networks without disrupting the information already stored there (McClelland, McNaughton, & O’Reilly, 1995).

**MEMORY REACTIVATION, RECONSOLIDATION**

The fact that consolidated memories are resistant to the disruptive effects of amnestic treatments has been construed as reflecting a permanent change in the function of the relevant synapses. It is a curious fact, therefore, that reactivation of consolidated memories—for example, by presentation of cues associated with the original learning—renders those memories susceptible once again to disruption by amnestic treatments such as protein-synthesis inhibitors or electroconvulsive shock (Misanin, Miller, & Lewis, 1968). This implies that a new wave of cellular-consolidation processes takes place following reactivation. Further, a new wave of systems consolidation may also take place, in some cases involving brain regions different from those critical for initial consolidation (Dudai & Eisenberg, 2004). Such reactivation effects may appear to be maladaptive, insofar as they put information at risk of being degraded after having initially been consolidated. However, this may be a necessary risk if new information from additional experiences or training trials is to be melded with the information already resident in the brain (see below). Taken together, the evidence for both consolidation and reconsolidation of memory suggests that the strength and identity of the synapses storing memories in the brain are likely to be continually undergoing change.

**MAINTENANCE OF LTP VERSUS MAINTENANCE OF MEMORY**

The capacity of LTP in the hippocampus and cortex of rodents to persist across months has been offered as strong support for its

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**Fig. 1.** Induction of long-term potentiation (LTP) in the rat hippocampus. Plotted are mean field excitatory postsynaptic potentials (fEPSPs) generated by low-frequency electrical stimulation of an excitatory pathway in the hippocampus of 5 animals; fEPSPs are expressed as a percent change from the average baseline value (0–30 min). Brief high-frequency (400 Hz) stimulation (arrow) produced an increased synaptic potential, which remained potentiated for the duration of the experiment. Waveforms at top are average fEPSPs recorded from a single animal before and after high-frequency stimulation, at the times indicated by the numbers. (Calibration bars: 3 mV, 5 ms.)
candidacy as a long-term-memory mechanism (Abraham et al., 2002). But is the capacity for long-term persistence a necessary prerequisite for a memory mechanism? The evidence for memory consolidation and reconsolidation suggests that memory maintenance is a dynamic process that may require more flexibility in synaptic efficacy than could be produced by a single bout of plasticity at the time of learning that is then stably preserved.

These considerations led us to address the question of why LTP can appear to persist so stably, particularly in the hippocampus, which is probably not a long-term information store. We hypothesized that this apparent stability may be a result of conducting our experiments in laboratory animals, typically housed in isolation from other animals and having limited learning opportunities. Indeed, we have recently shown that otherwise stably potentiated synapses are capable of further change, even long after the induction of LTP, if hippocampal neurons are activated in a significant way. In one set of experiments we used high-frequency stimulation (HFS) to establish saturated and persistent LTP in the synapses of the lateral perforant pathway, which connects the medial temporal cortex with the hippocampus. At either 21 or 100 days following LTP induction, HFS was delivered to a neighboring pathway. At either time point this procedure rapidly and completely reversed LTP in the lateral perforant path synapses (Abraham, 2003).

In a second set of experiments, stable LTP was induced in perforant path synapses, and then 2 weeks later animals were given periodic exposure to an enriched environment consisting of a large chamber with novel objects (changed daily), a novel food, and other animals. Exposure to the new environment for only 1 hour per day was sufficient to partially reverse the previously established LTP. Repeated overnight exposure led to a larger and more rapid reversal (Abraham et al., 2002). Interestingly, the LTP was harder to reverse if the environment treatment occurred 3 months rather than 2 weeks following LTP induction, implying that there had been a lengthy cellular consolidation process during that period. Taken together, our data indicate that LTP does not reflect a permanent change in synaptic strength, but rather that synapses operate as “sample and hold” devices such that plasticity, once induced, will be maintained until further relevant neural activity generates additional change. Importantly, the LTP-reversal effects bear formal similarity to the effects that interfering behavioral events have on the retention of long-term memory (Wixted, 2004).

The fact that both memory and synaptic plasticity remain changeable, even once apparently consolidated, casts serious doubt on the idea that memory retention requires preservation of a specific set of synaptic connection strengths. Instead, continued bouts of neural activity and synaptic plasticity long after learning may be necessary to maintain information in dynamic networks. Transgenic mice (i.e., mice genetically modified using molecular cloning technology) have been used to elegantly demonstrate that ongoing synaptic plasticity is very likely necessary for memory retention. For example, transgenic animals were created whereby it was possible to prevent LTP from occurring by stopping production of a critical protein (the NR1 subunit of the N-methyl-D-aspartate receptor). Inhibiting the synthesis of NR1 proteins for the first 1 to 2 weeks after training on a variety of hippocampus-dependent tasks impaired retention of those tasks (Shimizu, Tang, Rampon, & Tsien, 2000). Remarkably, when memories were allowed to consolidate for 6 months prior to inhibiting production of NR1, memory retention could still be impaired, but only when NR1 production was inhibited over a 4-week period (Cui et al., 2004). These findings imply that ongoing synaptic plasticity is necessary for even very-long-term retention of information, and again point to a prolonged consolidation process (Wixted, 2004). The results could imply that plasticity is necessary for restoring the synaptic strength changes that had occurred during learning but had passively or actively degraded over time. Alternatively, the ongoing plasticity may be needed to accommodate new information as it is acquired during daily life in the posttraining period. The latter possibility is supported by the network modeling I now describe.

**NEURAL-NETWORK MODELING**

Despite the rapidly growing advances in neuroscience, there is no technique that can directly assess whether learning-related changes in synaptic strengths are exactly preserved during memory retention. What is needed is an ability to repeatedly read out the strengths of the specific synapses involved in learning a task and to correlate those strengths with the ability to remember that information after various retention intervals or interfering events. Such a capacity is available, however, in computer-generated neural-network models.

The stability of connection strengths during repeated learning was tested in a standard artificial neural network using a learning algorithm known as back propagation (see Abraham & Robins, 2005, for details). The network was initially trained on 10 input–output pairings, equivalent to paired-associate learning, after which the strength of each connection in the network was noted. The network was then trained sequentially on 40 new input–output pairings, and after each new pairing the network was probed for its retention of the old information as well as for the degree of change in the connection strengths. As seen previously in the first generation of back-propagation models, learning new items caused “catastrophic interference” on the old items—that is, poor retention. Remarkably, however, this interference occurred with little change in the connection strengths. In contrast, under conditions whereby old information was preserved during new learning by being periodically rehearsed, connection strengths changed dramatically during new learning (Abraham & Robins, 2005). These findings strongly support the contention above that preservation of synaptic strength change is not a useful strategy for preserving information in networks that continue to learn.
that networks can generate many synaptic-strength solutions to solve a given input–output pairing and that during new learning a network must search to find a new solution that can accommodate both the new and the old information. Thus, in models at least, a memory is defined by the functional ability to generate the correct output pattern for a given input pattern, and not by a specific pattern of synaptic strengths within the network.

**FINAL REMARKS**

LTP and LTD are candidate mechanisms for memory, not least because of their capacity to stably persist over time. It is now apparent, however, that in networks that continue to learn, it is counterproductive for synaptic strengths to be permanently fixed after one learning episode. We propose a modified view, namely that synapses have a sample-and-hold capacity, such that strength changes that are induced during learning are stably maintained until such time as they must be modified to accommodate new information. This viewpoint suggests that a neural mechanism of memory should not be defined by its ability to persist for as long as the memory, not only because the synaptic loci and strengths may keep changing but also because the memory itself can keep changing, as psychologists have amply shown. Nonetheless, it remains important for psychologists and neuroscientists to continue refining their understanding of the synaptic basis of memory maintenance. For example, under what circumstances does learning-related synaptic plasticity overwrite old information, causing memory loss, and when does it participate in rewiring networks to preserve both types of information? Are there brain areas more suited to one of these processes than to the other, and if so, do the properties of synaptic plasticity differ between them? Such advances are necessary for informing the search for the molecular mechanisms underlying synaptic plasticity, a search that is critical for identifying the molecules to be targeted by therapeutic interventions to protect against the loss of memory abilities.

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**REFERENCES**


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**Recommended Reading**

Abraham, W.C. (2003). (See References)


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