Gazzaniga, M. S., Ivry, R. B., & Magnum, G. R. (1998). Cellular Basis of Memory. *Cognitive Neuroscience: The Biology of the Mind* (pp 283, 285-288). New York: Norton.

to ones used for new semantic learning in patient K.C.; however, normal subjects can readily remember the episode of learning new definitions, whereas K.C. learned them without any episodic memory of the learning experience.

On the day of study, 120 of the definitions were presented to the normal volunteer subjects. Then on the next day, when scanning was performed, these 120 plus a novel 120 definitions were included. During some scanning sessions, new and old definitions were given in such a way that mostly old definitions were presented; during others, mostly new ones were presented. Blood flow was compared for when subjects heard mostly new versus mostly old definitions. The subjects' performance was better than 95% in identifying old versus new items; they correctly recognized the definitions they had heard before. In conjunction with this, cerebral blood flow rose in the right dorsolateral prefrontal cortex. Some activation occurred in the left dorsolateral prefrontal cortex, but not in areas symmetrical to those in the right, and to a lesser degree. In addition, activation was found in the parietal lobe (Figure 7.34).

Encoding and retrieval processes were lateralized in the left and right hemispheres, respectively, giving rise to a model with the acronym of HERA, which stands for hemispheric encoding retrieval asymmetry. It represents the idea that encoding is more in the left hemisphere and retrieval is more in the right. Both processes occur predominantly in the dorsolateral prefrontal cortex. In encoding and retrieving information from long-term memory, cortical areas, not the hippocampus, are most active. Indeed, the medial temporal lobe is not activated, as we find for encoding faces or explicit retrieval. Despite the lack of consistency in hippocampal activations, the activations of the frontal cortex during encoding and retrieval are supported by data from PET experiments. Any model of brain and long-term memory must consider how the medial temporal and frontal cortex interact during encoding and retrieval.

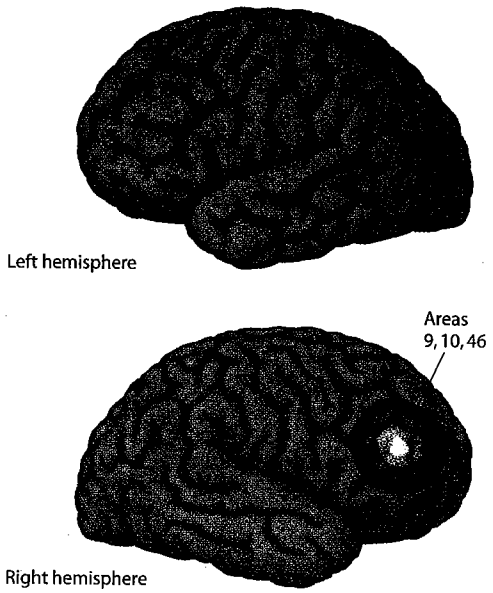


Figure 7.34 Activations of right inferior frontal regions involved in memory retrieval. Adapted from Kapur et al. (1994).

In summary, neuroimaging studies demonstrated patterns of neuronal activation that are consistent with memory systems derived from cognitive research, studies in human amnesics, and animal models. Neuroimaging also provided some notable findings in the cognitive neuroscience of memory, including, for example, the hemispheric asymmetries in encoding and retrieval. Functional neuroimaging clearly will continue to provide invaluable information about human memory and its neural substrates in the healthy human.

CELLULAR BASIS OF MEMORY

In dwelling on the big picture of memory research, we may have lost sight of the fact that memory entails changes in neurons that facilitate storage of new information. Memory is the result of changes in the strength of synaptic influences among neurons in neuronal networks that process and store information.

Long-Term Potentiation and the Hippocampus

Because of the hippocampal formation's role in memory, it has long been hypothesized that neurons in the hippocampus must be plastic, that is, able to change their synaptic interactions. Since the late 1960s researchers have sought the mechanisms behind this type of plasticity in learning and memory storage. Although it is now clear that storage itself is not in the hippocampus, this was not understood when work on hippocampal cell physiology first began. This fact does not invalidate the hippocampal models we examine, because the same cellular mechanisms can operate in various cortical and subcortical areas.

First, let us quickly review the three major excitatory

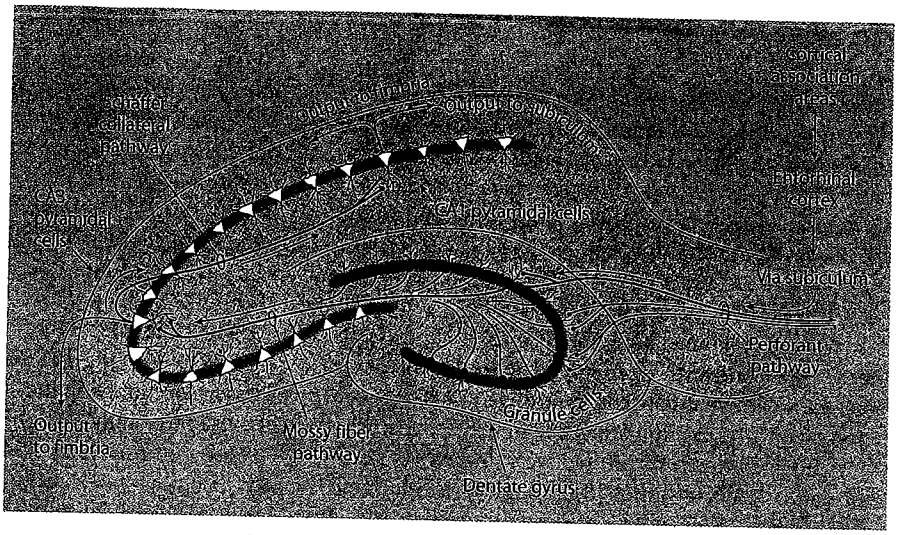


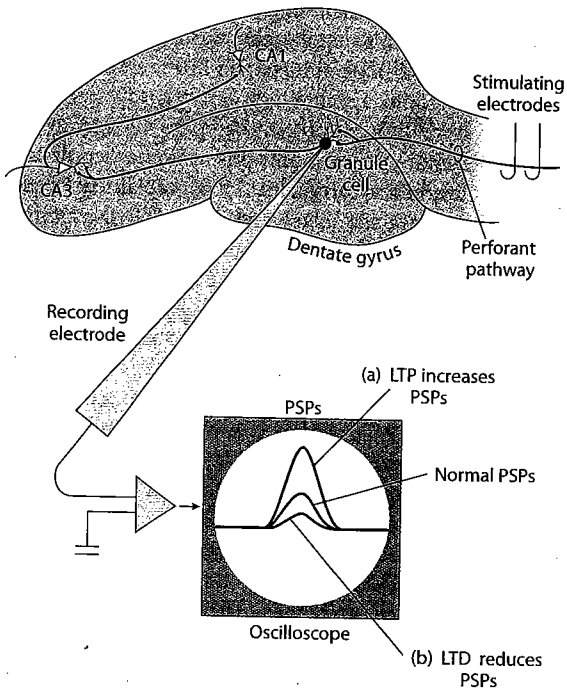
Figure 7.35 Diagram of the synaptic organization of the rat hippocampus.

synaptic pathways in the hippocampus (Figure 7.35): (1) the perforant pathway that forms excitatory connections between the parahippocampal cortex and the granule cells of the dentate gyrus, (2) the mossy fibers that connect the granule cells of the dentate gyrus to the CA3 pyramidal cells (on dendritic spines), and (3) the Schaffer collaterals that connect the CA3 pyramidal cells to the CA1 pyramidal cells. This system provides an opportunity for researchers to examine synaptic plasticity as the mechanism of learning at the cellular level.

In studies by Bliss and Lømo (1973) stimulation of axons of the perforant pathway of the rabbit resulted in a long-term increase in the magnitude of excitatory postsynaptic potentials (EPSPs). That is, the stimulation led to greater synaptic strength in the perforant pathway such that later stimulation created larger postsynaptic responses in the granule cells of the dentate gyrus. This phenomenon, named *long-term potentiation* (LTP) (*potentiate* means "to strengthen or make more potent"), was later extended to the other two excitatory pathways of the hippocampus. The changes could last for hours in isolated slices of hippocampal tissue placed in dishes, where recording was easier. LTPs can even last for days or weeks in living animals. It has since been found that the LTPs in the three pathways vary; nonetheless, Hebb's (1949) law is confirmed physiologically by the discovery of LTP: The law states that if a synapse is active when a postsynaptic neuron is active, the synapse will be strengthened.

One way that LTPs can be recorded is by placing a stimulating electrode on the perforant pathway and a recording electrode in a granule cell of the dentate gyrus (Figure 7.36). First, a single pulse is presented, and the resulting EPSP is measured. The size of this first recording is the strength of the connection before the LTP is induced. Then the perforant pathway is stimulated with a burst of pulses; early studies used approximately 100 pulses per sec but more recent ones use as few as five pulses per sec. After LTP is induced, a single pulse is sent again, and the magnitude of the EPSP in

Figure 7.36 Stimulus and recording setup for the study of long-term potentiation (LTP) in perforant pathways. **(a)** The pattern of responses before and after inducing LTP is shown (microvolts). **(b)** The pattern of response in long-term depression (LTD) is shown.



the postsynaptic cell is measured. The magnitude of the EPSP grows after LTP is induced, signaling the greater strength of the synaptic effect (Figure 7.36a). A fascinating finding is that when the pulses are presented at a slow rate, the opposite effect, long-term depression (LTD), develops (Figure 7.36b).

HEBBIAN LEARNING

Associative LTP is an extension of Hebb's law and asserts that if a weak and a strong input act on a cell at the same time, the weak synapse becomes stronger. This has been tested directly by manipulating LTP in the CA1 neurons of the hippocampus. When two weak inputs (W1 and W2) and one strong input (S1) are given to the same cell, and when W1 and S1 are active together, W1 is strengthened whereas W2 is not. Subsequently, if W2 and S1 are active together, W1 is not affected by the LTP induced from W2 and S1. From this finding, three rules for associative LTP can be stated: More than one input must be active at the same time (cooperativity), weak inputs are potentiated when co-occurring with stronger inputs (associativity), and only the stimulated synapse shows potentiation (specificity).

For LTP to be produced, the postsynaptic cells must be depolarized in addition to receiving excitatory inputs; in fact, LTP is reduced by inhibitory inputs to postsynaptic cells. As well, when postsynaptic cells are hyperpolarized, LTP is prevented. Conversely, when postsynaptic inhibition is prevented, LTP is facilitated. If an input that is normally not strong enough to induce LTP is paired with a depolarizing current to the postsynaptic cell, LTP can be induced.

THE NMDA RECEPTOR

That an excitatory input and postsynaptic depolarization are needed to produce LTP is explained by the properties of the doubly gated *N*-methyl-*D*-aspartate (NMDA) receptor located on the dendritic spines of postsynaptic neurons that show LTP. Glutamate is the major excitatory transmitter in the hippocampus, and it can bind with NMDA and non-NMDA receptors. When 2-amino-5-phosphonopentanoate (AP5) is introduced to CA1 neurons, NMDA receptors are chemically blocked and LTP induction is prevented. But the AP5 treatment does not produce any effect on previously established LTP in these cells. Therefore, NMDA receptors are central to producing LTP but not maintaining it. It turns out that maintenance of LTP may depend on the non-NMDA receptors.

What is the cellular mechanism that permits LTP to develop via the NMDA receptors, and why does blocking them with AP5 prevent LTP? NMDA receptors are normally blocked by magnesium ions (Mg^{2+}). The Mg^{2+} ions can be ejected from the NMDA receptors only when the neurotransmitter glutamate binds to the receptors and when the membrane is depolarized; that is, the NMDA receptors are transmitter and voltage dependent (gated). When these two conditions are met, Mg^{2+} is ejected and calcium (Ca^{2+}) can enter the cell (Figure 7.37).

The effect of Ca^{2+} influx via the NMDA receptor is critical in forming LTP. Ca^{2+} acts as an intracellular messenger conveying the signal which changes enzyme activities that influence synaptic strength. Despite rapid advances in understanding the mechanisms of LTP at physiological and biochemical levels, the molecular mechanisms of synaptic strengthening in LTP are still subject to extensive debate.

The synaptic changes that create a stronger synapse after LTP induction likely include presynaptic and postsynaptic mechanisms. One hypothesis is that LTP raises the sensitivity of postsynaptic non-NMDA glutamate receptors and prompts more glutamate to be released presynaptically. Or perhaps changes in the physical characteristics of the dendritic spines transmit EPSPs more effectively to the dendrites. Finally, via a postsynaptic to presynaptic cell message, the efficiency of presynaptic neurotransmitter release is increased.

LONG-TERM POTENTIATION AND MEMORY PERFORMANCE

Having identified a candidate cellular mechanism for long-term plastic changes in synaptic strength, it should be possible to produce deficits in learning and memory by eliminating LTP. Chemically blocking LTP in the hippocampus of normal mice impairs their ability to demonstrate normal place learning; thus, blocking LTP prevents normal spatial memory. In a similar way, genetic manipulations that block the cascade of molecular triggers for LTP also impair spatial learning. These experiments provided strong evidence of impairing spatial memory by blocking NMDA receptors and preventing LTP.

Studies with different results cast doubt on the role of LTP in learning and memory, however (Bannerman et al., 1995) (Saucier and Cain, 1995). Both experiments found that pharmacological NMDA receptor blockers did not stop rodents from learning how to navigate in a water maze; the animals were able to develop a new spatial map even when LTP was prevented. Unlike previous studies, these studies pretrained the rodents to swim to a platform, which prevented the impairment of new spatial learning when the NMDA receptors were blocked. When mice were pretrained by either a water maze task or a nonspatial task, the introduction of AP5 (the NMDA receptor blocker) in the hippocampus pre-

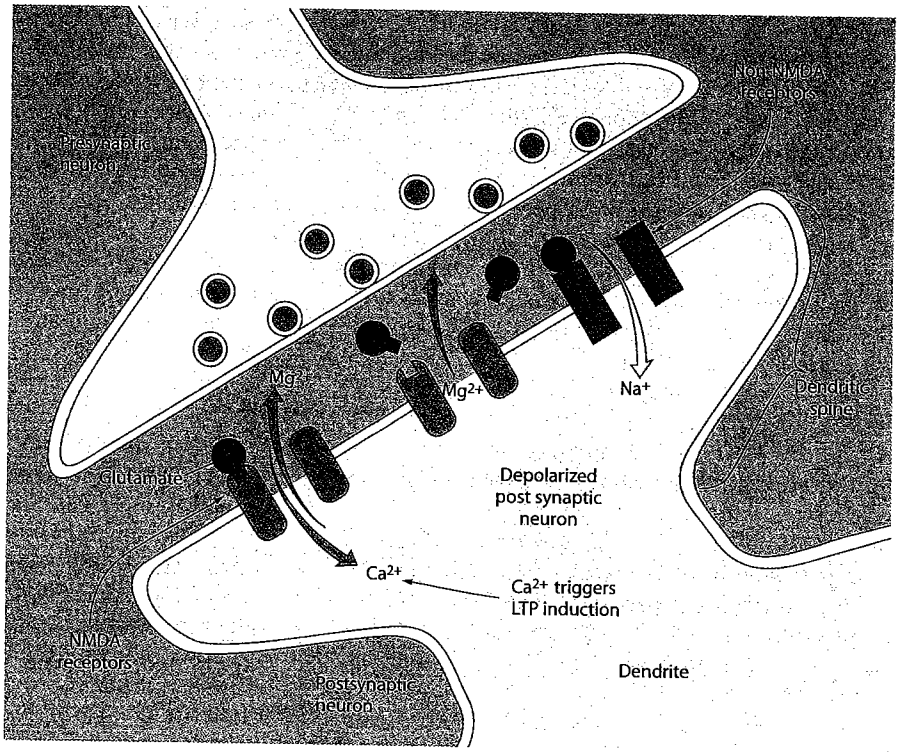


Figure 7.37 The role of Mg^{2+} and Ca^{2+} in the functioning of the NMDA receptor.

vented new learning in mice pretrained for the nonspatial task, but it did not affect mice pretrained for the spatial task. The conclusion is that NMDA receptors may be needed to learn a spatial strategy but not to encode a new map. Another experiment also reported that blocking LTP did not affect behavior, but the pattern was slightly different. When mice were pretrained with a nonspatial task, spatial memory was not interrupted by introducing an NMDA antagonist. The conclusion is that the pretraining merely allowed the motor-related side effects of NMDA receptor blockage to be avoided. Although these two studies did not exclude the possibility that new spatial learning involves NMDA receptors, they do point to the possibility that at least two memory systems could utilize NMDA receptors. These systems participate in the water maze task but could possibly be consolidated by pretraining.

The role of LTP in memory on the cellular and behavioral levels is still being unraveled. There is great debate over whether the maintenance of LTP is located presynaptically or postsynaptically and even whether LTP is necessary for spatial memory. Two points of agreement are that LTP does exist at the cellular level and that NMDA receptors play a crucial role in LTP induction in many pathways of the brain. Because LTP is also in brain areas outside the hippocampal system, the possibility that LTP forms the basis for long-term modification within synaptic networks remains promising.

SUMMARY

The ability to acquire new information and retain it over time defines learning and memory. Cognitive theory and neuroscientific evidence argue that memory is supported by multiple cognitive and neural systems. These systems support different aspects of memory, and their distinctions in quality can be identified. Sensory registration, perceptual presentation, working memory, semantic memory, and episodic memory, as well as memory for skills and procedures, all represent systems or subsystems for learning and memory. The brain structures that support various memory processes differ depending on the type of information to be retained.

The biological memory system includes the medial

temporal lobe, which forms and consolidates new episodic and perhaps semantic memories; the prefrontal cortex, which encodes and retrieves information; the temporal cortex, which stores episodic and semantic knowledge; and the association and sensory cortices for aspects of implicit perceptual memory. Other cortical and subcortical structures participate in learning skills and habits, especially those with implicit motor learning.

The brain is not equipotential in the storage of information, and although widespread brain areas cooperate in learning and memory, the individual structures form systems that support and enable rather specific memory processes. At the cellular level, changes in the synaptic strengths between neurons in neural networks in the medial temporal lobe, neocortex, and elsewhere are the most likely mechanisms for learning and memory, including LTP and LTD. We are rapidly developing a very clear understanding of molecular processes that support synaptic plasticity, and thus learning and memory in the brain.

SUGGESTED READINGS

BADDELEY, A. (1986). *Working Memory.* Oxford, UK: Clarendon Press/Oxford University Press.

BADDELEY, A. (1995). Working Memory. In *The Cognitive Neurosciences* M.S. Gazzaniga (Ed.), (pp. 755–764). Cambridge, MA: MIT Press.

COHEN, N.J., and EICHENBAUM, H. (1993). *Memory, Amnesia and the Hippocampal System.* Cambridge, MA: MIT Press.

COLLINGRIDGE, G.L., and BLISS, T.V.P. (1995). Memories of NMDA receptors and LTP. *Trends Neurosci.* 18:54–56.

ERICSSON, K., and CHASE, W. (1982). Exceptional memory. *Am. Sci.* 70:607–615.

GABRIELI, J., FLEISCHMAN, D., KEANE, M., REMINGER, S., and MORELL, F. (1995). Double dissociation between memory systems underlying explicit and implicit memory in the human brain. *Psychol. Sci.* 6:76–82.

HILTS, P.J. (1995). Memories ghost: the strange tale of Mr. M. and the nature of memory. New York: Simon and Schuster.

LARKMAN, A.U., and JACK, J.B. (1995). Synaptic plasticity: Hippocampal LTP. *Curr. Opin. Neurobiol.* 5:324–334.

MCCLOSKEY, M., WIBLE, C., and COHEN, N. (1988). Is there a special flashbulb-memory mechanism? *J. Exp. Psychol. Gen.* 117:171–181.

MILLER, G. (1994). The magical number seven, plus or minus two: Some limits on our capacity for processing information. *Psychol. Rev.* 101:343–352.

PALLER, K., KUTAS, M., and MCISAAC, H. (1995). Monitoring conscious recollection via the electrical activity of the brain. *Psychol. Sci.* 6:107–111.

SCHACTER, D., ALPERT, N., SAVAGE, C., RAUCH, S., et al. (1996). Conscious recollection and the human hippocampal formation—Evidence from positron emission tomography. *Proc. Nat. Acad. Sci. U.S.A.* 93:321–325.

SQUIRE, L.R., and ZOLA-MORGAN, S. (1991). The medial temporal lobe memory system. *Science* 253:1380–1386.

THOMPSON, C., COWAN, T., and FRIEMAN, J. (1993). *Memory Search by a Memorist.* Hillsdale, NJ: Lawrence Erlbaum Associates.

TULVING, E., and SHACTER, D.L. (1990). Priming and human memory systems. *Science* 247:301–306