LEARNING, MEMORY, AND LANGUAGE

LEARNING AND MEMORY. A major breakthrough in understanding how the brain accomplishes learning and memory began with the study of a person known by his initials, H.M. As a child, H.M. developed a severe and intractable epilepsy, and an experimental surgical treatment involving removal of the medial regions of his temporal lobes greatly alleviated the seizures. However, the surgery left H.M. with severe amnesia. He can remember recent events for only a few minutes and is unable to form explicit memories of new experiences. Talk with him awhile, and then leave the room. When you return, he has no recollection of ever having seen you.

Despite his inability to remember new information, H.M. remembers his childhood very well. From these observations, researchers concluded that the parts of H.M.'s medial temporal lobe that were removed, including the hippocampus and *parahippocampal region*, play critical roles in converting memories of experiences from short-term memories to long-term, permanent memories. The fact that H.M. retains some memories for events that occurred long before his surgery indicates that the medial temporal region is not the site of permanent storage but instead plays a role in the organization and permanent storage of memories elsewhere in the brain.

The medial temporal region is richly connected to widespread areas of the cerebral cortex, including the regions responsible for thinking and language. Whereas the medial temporal region is important for forming, organizing, consolidating, and retrieving memory, cortical areas are important for the long-term storage of knowledge about facts and events and for how this knowledge is used in everyday situations.

Our ability to learn and consciously remember everyday facts and events is called *declarative memory*. Studies using functional brain imaging have identified a large network of areas in the cerebral cortex that work together to support declarative memory. These cortical areas play a distinct role in complex aspects of perception, movement, emotion, and cognition.

When we have new experiences, information initially enters *working memory*, a transient form of declarative memory. Working memory depends on the prefrontal cortex as well as other cerebral cortical areas. Studies on animals have shown that neurons in the *prefrontal cortex* maintain relevant information during working memory and can combine different kinds of sensory information when required. In humans, the prefrontal cortex is highly activated when people maintain and manipulate memories.

Distinct areas within the prefrontal cortex support *executive functions*, such as selection, rehearsal, and monitoring of information being retrieved from long-term memory. To serve these functions, the prefrontal cortex also interacts with a large network of posterior cortical areas that encode, maintain, and retrieve specific types of information, such as visual images, sounds, and words, as well as where important events occurred and much more.

Semantic memory is a form of declarative knowledge that includes general facts and data. Although scientists are just beginning to understand the nature and organization of cortical areas involved in semantic memory, it appears that different cortical networks are specialized for processing particular kinds of information, such as faces, houses, tools, actions, language, and many other categories of knowledge. Studies using functional imaging of normal humans have revealed zones within a large cortical expanse that selectively process different categories of information, such as animals, faces, or words.

Our memories of specific personal experiences that happened at a particular place and time are called *episodic memories*. It is generally believed that the medial temporal lobe areas serve a critical role in the initial processing and storage of these memories. Studies have shown that different parts of the parahippocampal region play distinct roles in processing "what," "where," and "when" information about specific events. The hippocampus links these elements of an episodic memory. The linkages are then integrated back into the various cortical areas that represent the details of each type of information.

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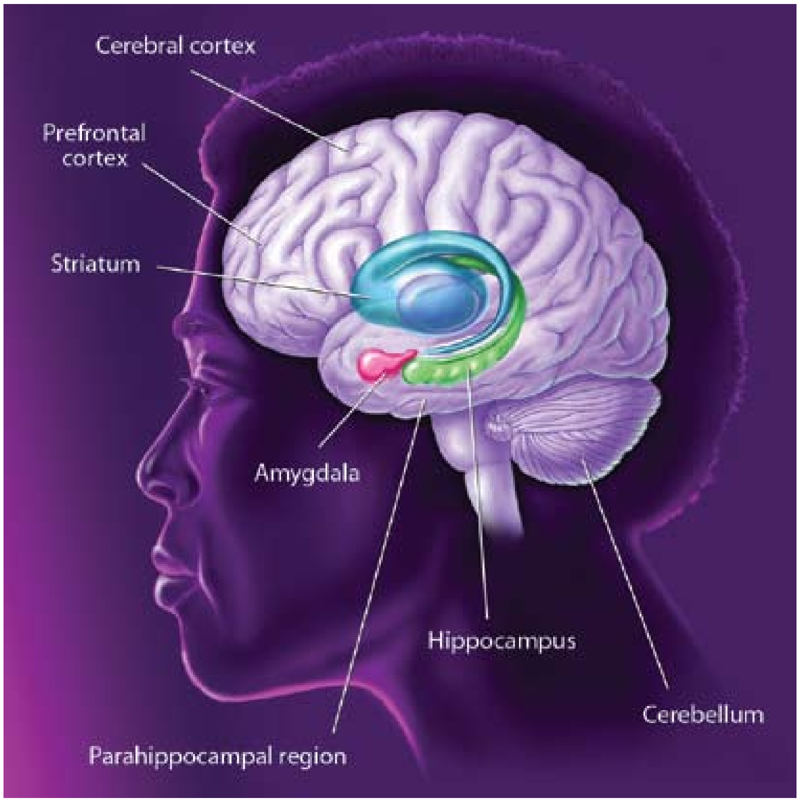

LEARNING AND MEMORY. Different brain areas and systems mediate distinct forms of memory. The hippocampus, parahippocampal region, and areas of the cerebral cortex (including prefrontal cortex) compose a system that supports declarative, or cognitive, memory. Different forms of nondeclarative, or behavioral, memory are supported by the amygdala, striatum, and cerebellum.

The fact that H.M. and other people with amnesia show deficits in some types of memories and not others indicates that the brain has multiple memory systems supported by distinct brain regions. *Nondeclarative knowledge*, the knowledge of how to do something, is expressed in skilled behavior and learned habits and requires processing by the basal ganglia and cerebellum. The cerebellum is specifically involved in motor tasks that are time-dependent. The amygdala appears to play an important role in emotional aspects of memory attaching emotional significance to otherwise neutral stimuli and events. The expression of emotional memories involves the hypothalamus and sympathetic nervous system, which support emotional reactions and feelings. Thus, the brain appears to process different kinds of information in separate ways.

How exactly are memories stored in brain cells? After years of study, much evidence supports the idea that memory involves a persistent change in synapses, the connections between neurons. In animal studies, researchers found that this occurs in the short term through biochemical events that affect the strength of the relevant synapses. Turning on certain genes may lead to modifications within neurons that change the strength and number of synapses, stabilizing new memories. Researchers studying the sea slug *Aplysia californica*, for example, can correlate specific chemical and structural changes in relevant cells with several simple forms of memory that the animal shows.

Another important model for the study of memory is the phenomenon of *long-term potentiation* (LTP), a long-lasting increase in the strength of a synaptic response following stimulation. LTP occurs prominently in the hippocampus, as well as in the cerebral cortex and other brain areas involved in various forms of memory. LTP occurs through changes in the strength of synapses at contacts involving N-methyl-d-aspartate (NMDA) receptors.

Subsequently, a series of molecular reactions plays a vital role in stabilizing the changes in synaptic function that occur in LTP. These molecular events begin with the entry of calcium ions into the synapse, which activates the cyclic adenosine monophosphate (cAMP) molecule. This molecule activates several kinds of enzymes, some of which increase the number of synaptic receptors, making the synapse more sensitive to neurotransmitters. In addition, cAMP activates another molecule, called cAMP-response element binding protein (CREB). CREB operates within the nucleus of the neuron to activate a series of genes, many of which direct protein synthesis. Among the proteins produced are neurotrophins, which activate growth of the synapse and increase the neuron’s responsiveness to stimulation.

Many studies have shown that the molecular cascade leading to protein synthesis is not essential to initial learning or to maintaining short-term memory; however, this cascade is essential for long-term memory. In addition, studies using genetically modified mice have shown that alterations in specific genes for NMDA receptors or CREB can dramatically affect the capacity for LTP in particular brain areas, and the same studies have shown that these molecules are critical to memory.

The many kinds of studies of human and animal memory have led scientists to conclude that no single brain center stores memory. It most likely is stored in distributed collections of cortical processing systems that are also involved in the perception, processing, and analysis of the material being learned. In short, each part of the brain most likely contributes differently to permanent memory storage.

Language

One of the most prominent human abilities is language, a complex system involving many components, including sensory-motor functions and memory systems. Although the neural basis of language is not fully understood, scientists have learned a great deal about this function of the brain from studies of patients who have lost speech and language abilities owing to stroke, and from brain imaging studies of normal people.

It has long been known that damage to different regions within the left hemisphere produce different kinds of language disorders, or aphasias. Damage to the left frontal lobe can produce nonfluent aphasias, such as *Broca's aphasia*, a syndrome in which speech production abilities are impaired. Speech output is slow and halting, requires effort, and often lacks complexity in word or sentence structure. By comparison, comprehension of heard speech is spared, although structurally complex sentences may be poorly understood.

Damage to the left temporal lobe can produce fluent aphasia, such as *Wernicke's aphasia*, in which comprehension of heard speech is impaired. Speech output, although of normal fluency and speed, is often riddled with errors in sound and word selection and tends to be unintelligible gibberish.

Damage to the superior temporal lobes in both hemispheres can produce *word deafness*, a profound inability to comprehend auditory speech on any level. Whereas Wernicke's aphasics can often comprehend bits and pieces of a spoken utterance and can comprehend isolated words, patients with word deafness are functionally deaf for speech, lacking the ability to comprehend even single words, despite being able to hear sound and even identify the emotional quality of speech or the gender of the speaker.

Research on aphasia has led to several conclusions regarding the neural basis of language. Researchers once believed that all aspects of language ability were governed only by the left hemisphere. Recognition of speech sounds and words, however, involves both left and right temporal lobes. In contrast, speech production is a strongly left-dominant function that relies on frontal lobe areas but also involves posterior brain regions in the left temporal lobe. These appear to be important for accessing appropriate words and speech sounds.

Recently, functional imaging methods have identified new structures involved in language. For example, systems involved in accessing the meaning of words appear to be located (in part) in the middle and inferior portions of the temporal lobe. In addition, the anterior temporal lobe is under intense investigation as a site that may participate in some aspect of sentence-level comprehension.

Recent work has also identified a sensory-motor circuit for speech in the left posterior temporal lobe, which is thought to translate between speech recognition and speech production systems. This circuit is involved in speech development and is thought to support verbal short-term memory.

Although the understanding of how language is implemented in the brain is far from complete, there are now several techniques that may be used to gain important insights into this critical aspect of brain function.