e6 Memory Loss

Thomas D. Bird, Bruce L. Miller

Memory allows us to store, retain, and retrieve information. These three processes influence and are modified by the type of information that is to be remembered, the duration of time over which it must be retained, and the way in which the brain will use the information in the future. The neural circuits underlying these processes are dynamic, reflecting the flexibility of memory itself. To delineate the neural circuitry underlying it, it is helpful to break down memory into simpler components. This categorization, however, need not lead to the assumption that memory is not a unitary phenomenon.

LONG-TERM MEMORY

In an effort to explain why focal brain damage affects some aspects of memory but not others, a fundamental distinction has been made between *declarative memory*, which refers to the conscious memory for facts and events, and *nondeclarative memory*, which refers to memory for skills, habits, or other manifestations of learning that can be expressed without awareness of what was learned (Fig. e6-1). Patients with bilateral medial temporal lobe (MTL) damage show declarative memory deficits in the face of intact nondeclarative memory. For example, such a patient may learn to play the piano, over time, without remembering a single practice session or even recognizing the teacher who patiently works with him everyday.

DECLARATIVE MEMORY

Within the declarative memory system, *episodic* and *semantic* memory can be distinguished. *Episodic memory* allows the recollection of unique personal experiences. With episodic memory, the person reexperiences the sights, sounds, smells, and other details of a specific event. Many episodic memories are kept for minutes and hours but soon discarded. Others remain for the course of a lifetime. This temporal difference in storage probably reflects different physiologic processes at work (see below). *Semantic memory*, in contrast, refers to knowledge about the world; generic information that is acquired across many different contexts and accessed without accompanying details of the time when the words or facts were remembered. One's vocabulary and knowledge of the associations between verbal concepts make up the bulk of semantic memory. This fractionation of declarative memory is supported by evidence that episodic and semantic memory have distinctive anatomic substrates.

Episodic Memory In the MTL, the hippocampal formation receives processed sensory information from association areas in the frontal, parietal, and occipital lobes via the parahippocampal cortex. Given these multiple cortical neuroanatomical connections, the hippocampus is well placed to create associations between simultaneously occurring stimuli in our sensory world. Key structures involved with episodic memory include the hippocampus, entorhinal cortex, mammillary bodies, and thalamus. Alterations of episodic memory can be devastating. Overly intense or painful episodic memories can result in posttraumatic stress disorder, a devastating illness in which patients repeatedly reexperience unpleasant episodes from their lives. By contrast, loss of episodic memories, as in Alzheimer's disease (AD), will prevent the individual from learning new things about the world and will eventually strip away the old memories that constitute a life biography.

Given its anatomic placement and architecture, the hippocampus has the unique ability to bind together "what happened," "when it happened," and "where it happened." The architecture of the hippocampus includes a circular pathway of neurons from the entorhinal cortex to the dentate gyrus and CA3 and CA1 neurons of the hippocampus to the subiculum and back to the entorhinal cortex. This pathway is heavily damaged in AD. Individual elements of episodic memories are permanently stored within the same neocortical regions that are involved in initial processing and analyzing of sensory information (neocortex). Each different cortical region makes a unique contribution to the storage of a given memory, and all regions participate together in the creation of a complete memory representation. The hippocampal formation, then, is saddled with the task of binding together these different regional contributions into a coherent memory trace. The connections within the hippocampal formation and between the MTL and neocortical regions are formed more rapidly than are the connections between disparate cortical regions. Therefore, when a particular cue in the environment or the mental state of the person activates cells in the cortical regions, the MTL network that is associated with that cue is reactivated and the entire neocortical representation is strengthened. As multiple reactivations occur, the connections between the relevant neocortical regions are slowly strengthened until the memory trace no longer depends on the MTL's activity but is instead entirely represented in the cortex.

While the MTL learns quickly and has a limited capacity for storage, the neocortex learns slowly and has a very large storage capacity. In both regions, learning occurs via Hebbian synapses, whereby "cells that fire together, wire together." With repeated activations, memories become "consolidated" in the neocortex and, therefore, independent of the MTL. This process, by which the burden of long-term (permanent) memory storage is gradually assumed by the neocortex, ensures that the MTL system is constantly available for the acquisition of new information. Recent evidence, however, points to the hippocampus as serving a critical function in the retrieval of detailed episodic memories, regardless of the age of the memory.

Injury anywhere along this septohippocampal pathway can lead to severe loss of episodic memory. Patients with injury to this system will exhibit anterograde amnesia, an inability to commit new information to memory. Memories that were established before the injury (remote memories) tend to be relatively preserved, although a retrograde amnesia, going back anywhere from minutes to years, is usually evident. Larger lesions cause a more extensive retrograde memory deficit. Also, as brain injury improves over time, the retrograde memory impairment tends to diminish, and the temporal gradient for memory loss shrinks.

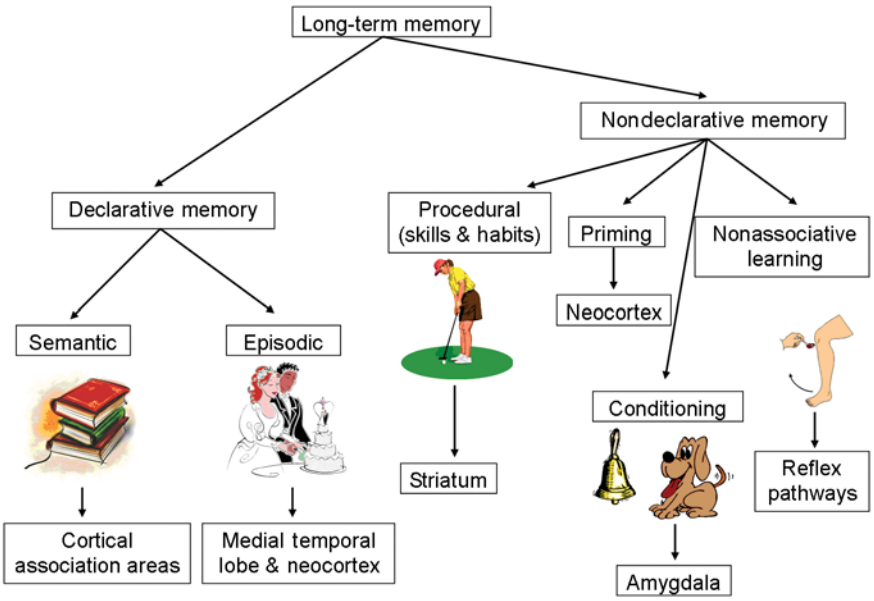

FIGURE e6-1 Fractionation of long-term memory. *(Adapted from LR Squire, SM Zola: Proc Natl Acad Sci U S A, 24: 13515, 1996.)*

The most common cause for entorhinal dysfunction is AD, which begins in the entorhinal cortex and then spreads to the hippocampus. A common mechanism for hippocampal dysfunction is traumatic injury because the hippocampi sit adjacent to, and are easily pushed against, bone in the middle cranial fossa. The hippocampus, particularly the CA1 and subicular region, is very sensitive to metabolic insults, including hypoxia, hypoglycemia, and prolonged seizures. Vascular infarction can occur with occlusion of the hippocampal branches off the posterior cerebral arteries. Infections, in particular herpes simplex encephalitis, can selectively attack the medial temporal regions, leading to severe and permanent deficits in episodic memory.

Additionally, severe loss of episodic memory can also be due to dysfunction in the mammillothalamic memory system. The amnesia of Korsakoff's syndrome is due to injury from hemorrhage into the mammillary bodies and dorsomedial nuclei of the thalamus. Furthermore, recent studies of patients with stroke in the left dorsomedial nucleus of the thalamus suggest that injury here alone will precipitate a severe amnesia. Finally, tumors can injure the septum, fornix, or medial temporal lobes, leading to amnesia.

Emotion plays a key role in enhancing the ability to remember personal episodes and other information encoded in a particular affective state. Emotionally charged events are more easily remembered than emotionally neutral episodes, and highly vivid "flashbulb" memories are often laid down during traumatic or emotional events; sometimes during positive but often during negative events. In humans, the amygdala modulates memory processes during emotional experiences.

One simple way to test episodic memory is to ask the patient to recall recent events such as what he did on the last big holiday, what is going on in the news, or what she had for breakfast. With regard to personal episodic memories, it is always necessary to have a historian who can verify that the recent memories are correct (not confabulated).

Semantic Memory Unlike episodic memory, the recall of semantic memory does not lead to the retrieval of details of when, or where, the information was acquired. For example, we remember that a fork is a utensil that is used for eating food without remembering when we learned the word *fork* or when we discovered its use. Semantic memory is composed of a complex hierarchy of knowledge about the world. Knowing that a fork is generally used for eating depends on understanding that in certain social situations, eating with only our hands is inappropriate, and that some foods are more easily eaten with a fork than another available utensil, such as a spoon. While a fork may be useful in many different situations, our semantic hierarchy reminds us that its main function is to facilitate eating. These ideas are held together in the semantic memory system, which spans across the association areas of the neocortex. Therefore, if we are in a situation that requires using a fork as a tool in a novel manner, we can still call upon our semantic memory system to aid us in solving the problem.

Evidence that semantic memories are independent of the septohippocampal and mamillothalamic memory systems comes from humans with injury to these systems who maintain access to semantic knowledge despite profound deficits in episodic memory. In contrast, patients with primarily anterior and lateral temporal lobe damage show intact episodic memory but impaired semantic memory. The finding that children born with hippocampal sclerosis and lifelong episodic memory impairments can still function fairly well in school suggests that semantic memories are not wholly dependent upon intact episodic memory.

In semantic dementia, a syndrome associated with neurodegenerative disease that begins in the anterior temporal lobes, both the simple labeling process (naming) and knowledge about the identity of people and objects are lost. Patients with semantic dementia classify objects into increasingly superordinate categories, having lost access to specific exemplars. Hence, a hawk becomes a "hunting bird," then a "bird," then an "animal," and then a "thing" as the disease worsens. Eventually all objects are classified with a series of simple stereotyped phrases. Bilateral anterior temporal dysfunction is the anatomic substrate of semantic dementia, a subtype of the frontotemporal lobar degenerations. Aside from semantic dementia, the other disorders that lead to this syndrome include limbic encephalitis, associated with viral or paraneoplastic processes, and herpes simplex encephalitis.

Bedside assessment of semantic memory is difficult, but the gravest deficits may be seen if the patient is unable to name common objects such as a pen or watch or less common objects such as a stethoscope or a fluorescent bulb.

NONDECLARATIVE MEMORY

Nondeclarative memory is an umbrella term for a heterogeneous collection of nonconscious memory abilities that involve multiple distinct neural regions, including the amygdala, basal ganglia, cerebellum, and sensory cortex (Fig. e6-1). *Procedural memory* is one type of nondeclarative memory. The difference between declarative memory and procedural memory is the difference between "knowing that" and "knowing how." *Procedural learning* describes the formation of skills and habits. Because it requires extensive practice, it is a slow and inflexible learning system that eventually takes on an automatic or reflexive quality. It is, however, long-lasting and reliable: even after years of absence from a bicycle, a bike rider does not lose the skill entirely.

Procedural memory involves motor, perceptual, and cognitive processes. For example, flipping pancakes is a motor skill, a parent's attentiveness to his or her baby's cry in a distant room involves perceptual learning, and increasing alacrity in solving Sudoku puzzles with practice requires cognitive skills. While declarative memory can, in some cases, enhance or hasten the acquisition of skills and habits, conscious awareness of learning is not necessary; once the information is acquired, it often becomes difficult to verbalize how it was learned. Cognitive psychologists have shown that in some cases, declarative memory processes can hinder nondeclarative learning, suggesting that there are times when the two memory "systems" may compete for cognitive resources.

The forms of perceptual and motor learning that can occur without conscious recollections are mediated in part by contractions and expansions of representations in the sensory and motor cortex. One study, for example, has shown that the cortical representation of the fingers of the left hand of musical string players is larger than that in nonmusicians, suggesting that the representation of different parts of the body in the primary somatosensory cortex of humans depends on use and changes to conform to the current needs and experiences of the individual. Discrete cortical regions exist in the anterior temporal lobes in which object knowledge (such as words related to color, animals, tools, or action) is organized as a distributed system. Here the attributes of an object are stored close to the regions of the cortex that mediate perception of those attributes.

Recent research now points to the basal ganglia as fundamental in motor skill learning, while the cerebellum is involved in the association of a visual cue with a motor action. Parkinson's disease (PD) causes damage to the basal ganglia and is associated with impairments in habit learning but spares declarative memory. The basal ganglia project to and receive projections from the frontal cortex, and this corticostriatal loop has been implicated in the learning of skills and habits. Furthermore, recent functional MRI work suggests that the MTL-based declarative memory and the corticostriatal procedural memory systems operate independently from each other and may in fact compete for cognitive resources. That is, basal ganglia activity is negatively correlated with MTL activity when both systems are engaged by a particular task.

Bedside testing of nondeclarative memory is outside the realm of the generalist, but deficits may be reported by patients or their families.

MOLECULAR AND NEUROCHEMICAL BASIS OF LONG-TERM MEMORY

Long-term potentiation (LTP), which refers to a long-lasting enhancement of synaptic transmission resulting from repetitive stimulation of excitatory synapses, is presumed to be involved in episodic memory acquisition and storage. LTP occurs in the hippocampus and is mediated by *N*-methyl-D-aspartate (NMDA) receptors as well as the cyclic AMP–responsive element-binding (CREB) protein. Animal experiments have

shown that the formation of new episodic memories leads to physiologic changes in the synapse, while longer-term memory requires new protein synthesis and leads to physical changes at neuronal synapses.

The cholinergic system also plays an important role in memory, and anticholinergic agents such as atropine and scopolamine interfere with memory. Choline acetyltransferase (the enzyme catalyzing the formation of acetylcholine) is known to be deficient in the cortex of patients with AD. The brains of AD patients show severe neuronal loss in the nucleus basalis of Meynert, the major source of cholinergic input to the cerebral cortex. These findings form the basis for the use of cholinesterase inhibitors in the treatment of AD, with benefits thought to arise from increased levels of available acetylcholine. Behavior and mood are modulated by noradrenergic, serotonergic, and dopaminergic pathways, and norepinephrine has been shown to be reduced in the brainstem locus coeruleus in AD. Also, neurotrophins are postulated to play a role in memory in part by preserving cholinergic neurons. GABA agonists including the benzodiazepines are associated with reversible but sometimes severe episodes of amnesia. Working memory (see below) is strongly modulated by dopamine.

SHORT-TERM MEMORY

WORKING MEMORY

While the fractionation of memory into declarative and nondeclarative systems has provided a reasonable framework for understanding many aspects of memory's neurologic underpinnings, another major division of memory has used time as the distinguishing characteristic. While some information is retained for only a few seconds—enough time to hear, remember and dial a phone number—other memories are seemingly remembered throughout a life span. This brief type of memory differs from long-term memory, not only in terms of duration of retention but also with regard to its function and neuroanatomy.

Working memory stores items only as long as the information is in consciousness and is either being rehearsed (subvocally) or manipulated in some other fashion (i.e., rotated or integrated with existing information in semantic memory). The capacity of working memory is limited by attention. Normal individuals can hold about seven (plus or minus two) "bits" of information in working memory; these bits can be manipulated and either discarded or associated and transferred into long-term memory. Working memory is highly vulnerable to distraction and sometimes is even called *working attention* to emphasize the conscious and effortful processes that it entails. In the most widely accepted conceptualization of working memory, there are four main components: (1) a central executive that keeps track of and gathers information; (2) a visual system called the *visuospatial scratchpad*, which holds visual representations of objects; (3) a phonologic "system" that holds verbal information; and (4) an episodic buffer that is capable of binding together information from different modalities into a coherent trace.

Lesions that disrupt the structure or function of the dorsolateral frontal or posterior parietal regions decimate working memory. These deficits in working memory have a profound effect on the organism by disrupting the learning process downstream to working memory, or by affecting activities that directly depend on an intact working memory. In the classic amnesic syndrome, patients have intact working memory but cannot transfer information from working memory into long-term store.

Single-cell recordings have uncovered a network of neurons in the posterior parietal and dorsolateral frontal lobes where activity is high only during periods when information is being held in memory for use over just a few seconds. These neurons appear to provide an important functional basis for working memory. Similarly, functional imaging studies from humans show that the dorsolateral frontal lobes, particularly Brodmann area 46, are critical for working memory.

TESTING MEMORY AT THE BEDSIDE

Testing of memory should be performed in anyone in whom memory deficits are a concern, whether these concerns are raised by the patient, family, or health care workers. If the deficits are subtle, the testing may require a comprehensive consultation with a neuropsychologist, neuropsychiatrist, or behavioral neurologist. However, memory testing can be an extremely valuable component of the neurologic examination and performed effectively at the bedside. There are a wide variety of brief standardized screens of cognition, but the most commonly used test is the Mini Mental Status Examination (Table 365-5), a 30-point test that is strongly dependent on working (spell "world" backwards) and episodic memory (orientation and three-word recall). Testing semantic and procedural memory is usually outside the realm of the generalist, but if deficits in these systems are suspected, further tests are warranted.

Of all the memory processes, working memory is perhaps the easiest to assess at the bedside. The most common bedside test of working memory involves asking patients to repeat a series of digits orally, with the clinician gradually increasing the number of to-be-retained digits. There are two ways of administering the test. Asking the patient to repeat the digits in the same order as they were delivered is called *digit span forward*. In contrast, the clinician may also ask the patient to repeat the digits in reverse order, called *digit span backward*. Digit span forward is a test of attention, while digit span backward is a simple probe of working memory. The capacity for digit span forward is typically six numbers, while normal adults can generally repeat five digits backward.

FURTHER READINGS

BADDELEY A: Working memory: Looking back and looking forward. Nat Rev Neurosci 4:829, 2003

EICHENBAUM H et al: The medial temporal lobe and recognition memory. Ann Rev Neurosci 30:123, 2007

GILBOA A et al: Retrieval of autobiographical memory in Alzheimer's disease: Relation to volumes of medial temporal lobe and other structures. Hippocampus 15:535, 2005

NADEL L, MOSCOVITCH M: Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 7:217, 1997

PACKARD MG, KNOWLTON BJ: Learning and memory functions of the basal ganglia. Annu Rev Neursci 25:563, 2002

PERRY RJ, HODGES JR: Spectrum of memory dysfunction in degenerative disease. Curr Opin Neurol 9:281, 1996

POLDRACK RA et al: Interactive memory systems in the human brain. Nature 414:546, 2001

SQUIRE LR, ZOLA-MORGAN S: The medial temporal lobe memory system. Science 253:1380, 1991

——— et al: The medial temporal lobe. Annu Rev Neurosci 27:279, 2004