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Understanding Memory Dysfunction

Andrew E. Budson, MD

^{*}Center for Translational Cognitive Neuroscience, Geriatric Research Education Clinical Center, Bedford VA Hospital, Bedford, MA; Boston University Alzheimer's Disease Center, Department of Neurology, Boston University School of Medicine, Boston, MA.

Abstract

Background: Although traditionally memory has been viewed as a simple concept, converging and complementary evidence from patient studies and more recent neuroimaging research suggest that memory is a collection of mental abilities that use different neuroanatomical systems within the brain. Neurologic injury may cause damage to one or more of these memory systems.

Review Summary: In this review a number of different memory systems are discussed, including their function, neuroanatomy, and the different disorders that disrupt them. Episodic memory, the most clinically relevant memory system, depends upon the hippocampus and other medial temporal lobe structures, the limbic system, and the frontal lobes. Several other kinds of memory are contrasted with episodic memory, including semantic memory, simple classic conditioning, procedural memory, priming, and working memory.

Conclusion: Improved understanding of these different types of memory will aid the clinician in the diagnosis and treatment of the memory disorders of their patients. As more specific therapeutic strategies are developed for the treatment of diseases which cause memory dysfunction, this knowledge will become increasingly important.

Keywords

memory; Alzheimer disease; frontal lobes; false memory; memory distortions

Neurologists are increasingly referred patients with complaints of impaired memory. Memory dysfunction can be caused by a diverse group of neurologic disorders, including neurodegenerative diseases, strokes, tumors, head trauma, hypoxia, cardiac surgery, malnutrition, attention deficit hyperactivity disorder, depression, anxiety, and medication effects.^{1,2} Memory function can also be altered by normal aging.³ Although once thought to be a simple concept, we now consider memory to be a collection of mental abilities that use different systems and components within the brain. Memory research that began with neuropsychological studies of patients with focal brain lesions and now includes newer methods such as positron emission tomography, functional MRI, and event-related potentials has provided the rationale for a more refined and improved classification system.⁴ In this article, a number of different forms of memory will be reviewed, including the important anatomic structures for each, and the major neurologic disorders that disrupt them (Tables 1

and 2). A greater understanding of these memory systems will aid neurologists in their diagnosis and treatment of the memory disorders of their patients. This improved understanding will become increasingly important as new therapeutic interventions for memory disorders are developed.

A memory system is a way for the brain to process information that will be available for use at a later time.⁵ Some systems are associated with conscious awareness (explicit) and can be consciously recalled (declarative), whereas others are typically unconscious (nondeclarative) and are instead expressed by a change in behavior (implicit).⁶ Memory can also be categorized in other ways, such as the nature of the material to be remembered, verbal⁷ versus visual.⁸

Episodic Memory

Episodic memory refers to the explicit and declarative memory system used to remember a particular episode of your life.

Episodic memory refers to the explicit and declarative memory system used to remember a particular episode of your life, such as sharing a meal with a friend. This memory system is dependent upon the medial temporal lobes (including the hippocampus), as episodic memory has been largely defined by what patients with medial temporal lobe lesions cannot remember relative to healthy individuals. Other critical structures in the episodic memory system (some of which are associated with a circuit described by Papez in 1937⁹) include the basal forebrain with the medial septum and diagonal band of Broca, the retrosplenial cortex, the presubiculum, the fornix, mammillary bodies, the mammillothalamic tract, and the anterior nucleus of the thalamus (Fig. 1).² A lesion in any one of these structures may cause the impairment that is characteristic of dysfunction of the episodic memory system.

Memory loss due to dysfunction of the episodic memory system generally follows a pattern known as Ribot's law, which states that events just prior to an ictus are most vulnerable to decay, whereas remote memories are more resistant. Thus, dysfunction of the episodic memory system typically causes greatest disruption in the ability to learn new information (anterograde amnesia) and moderate disruption in the ability to recall recently learned information (retrograde amnesia), whereas the ability to recall remotely learned information is generally intact (Fig. 2).¹⁰

The core of the episodic memory system is the medial temporal lobe and hippocampus.

The core of the episodic memory system is the medial temporal lobe and hippocampus. It is worth examining these structures more closely. The medial temporal lobes may seem simple but they are actually neuroanatomically complex structures with multiple regions and subregions. In Figure 3 you can see the medial temporal lobe structures, including the parahippocampal gyrus, presubiculum, subiculum, and hippocampus proper, including its subregions.

Although we do not completely understand how the medial temporal lobes store and retrieve memories, our current understanding from cognitive neuroscience is as follows. An individual experiences an episode of their life, such as having breakfast that morning. The

cortically distributed patterns of neural activity representing the sights, sounds, smells, tastes, emotions, and thoughts during that episode are transferred first to the parahippocampal region and then to the hippocampus proper (Fig. 4). After being transferred to the entorhinal cortex, the information is processed in the dentate gyrus, and then transferred to the CA3 region where it is further processed (Fig. 5). It is in this CA3 region where the critically important hippocampal index is assigned, allowing the memory to be stored in a unique way so that it can later be recalled.

Typically memories are retrieved when a cue from the environment matches a part of the stored memory. Continuing our breakfast example, years later the individual might now bite into a little cake that tastes remarkably like the one that he had previously at breakfast. This sensory cue is transferred from the cortex to the parahippocampal region and to the hippocampus (Fig. 4). After the cue is transferred from the entorhinal cortex it now goes directly to the CA3 region where the original hippocampal index is retrieved (Fig. 6). When found, the hippocampal index may be used to retrieve much of the original pattern of the neural activity representing the original episode stored in memory. This retrieved pattern of activity may then be transferred to the CA1 region, the subiculum, the entorhinal cortex, and then back to the cortex—recreating all sights, sounds, smells, tastes, emotions, and thoughts of the original memory episode (Fig. 4).

The hippocampus remains critical for memory retrieval until a process known as consolidation occurs.

The hippocampus remains critical for memory retrieval until a process known as consolidation occurs. Much research still needs to be done to better understand consolidation, but one thought is that once a memory is consolidated the distributed pattern of cortical neural activity is directly linked together, such that when a cue is encountered, the memory may be retrieved directly from cortical-cortical connections, without the need for the hippocampus. And, although there are many details that need to be learned, there is much data suggesting that sleep is critical for consolidation to occur.^{11,12}

In looking at the cognitive neuroscience model just presented of how memories are stored and retrieved, it is the CA3 region of the hippocampus that seems most critical—it is this region in which the hippocampal index is formed, and in which pattern matching of cues and memories occurs. Although we do not exactly know how the CA3 region is involved in these activities, a number of models using neural networks have been proposed. A simplified example of such a model is as follows. In this example, we will show how an individual can find their car when they park in a parking garage over 3 successive days—and also why it is sometimes difficult for an individual to find their car. In this mythical parking garage, there are 2 areas, Red and Blue, and 2 levels, 1st and 2nd. Two affective states, happy and sad, are also shown to represent not only emotions but other contextual details that may differ between one day and the next. On the first day, the car is parked in the Red area, on the 1st floor, and it was a good day. From this distributed pattern of neural activity a hippocampal index can be formed that helps one remember that the car was parked in the Red area, on the 1st floor, and half-way down the aisle on the left (Fig. 7a). On the second day, the car is parked in the Blue area, on the 2nd floor, and it was not such a good day. Nonetheless, this

distinct pattern of neural activity allows a unique hippocampal index to form that enables one to remember that the car was parked in the Blue area, on the 2nd floor, and half-way down the aisle on the right (Fig. 7b). On the third day, the car is also parked in the Blue area, on the 2nd floor, and it again was not such a good day (Fig. 7c). Although one might wish that a hippocampal index will form to enable one to remember that the car was parked in the Blue area, on the 2nd floor, and all the way down the aisle on the left—there is a problem. When there are completely overlapping patterns of neural activity, a separate hippocampal index cannot form. Instead, there is a single hippocampal index that forms for both days 2 and 3 (Fig. 7d). This hippocampal index is strengthened for the common aspects of the 2 memories: parking in the Blue area, on the 2nd floor. But, this index will also contain divergent aspects of the memory: half-way down the aisle on the right and all the way down the aisle on the left. Thus, on day 3, it will be easy to remember that the car is parked in the Blue area on the 2nd floor, but it will be difficult to remember if it is parked half-way down the aisle on the right or all the way down the aisle on the left.

Over the last 10 years, it has become increasingly clear that in addition to the medial temporal lobes and Papez’s circuit, the frontal lobes are also important for episodic memory.

Over the last 10 years, it has become increasingly clear that in addition to the medial temporal lobes and Papez’s circuit, the frontal lobes are also important for episodic memory.^{13,14} Whereas the medial temporal lobes are critical for the retention of information, the frontal lobes are important for the acquisition, registration, or encoding of information⁷; retrieval of information without contextual and other cues¹⁵; recollection of the source of information¹⁶; and assessment of the temporal sequence and recency of events.¹⁷ Also, notable is that the left medial temporal and left frontal lobes are most active when a person is learning words,⁷ and that the right medial temporal and right frontal lobes are most active when learning visual scenes.⁸

One important reason why the frontal lobes are highly involved in episodic memory is that they enable the individual to focus their attention on the information to be remembered and to engage the medial temporal lobes. Dysfunction of the frontal lobes may cause a variety of memory problems, including distortions of episodic memory and false memories, such as when information becomes associated with the wrong context¹⁸ or incorrect specific details.¹⁹ Extreme memory distortions are often synonymous with confabulations, which occur when “memories” are created to be consistent with current information,¹⁸ such as “remembering” that someone broke into the house and rearranged household items.

A clinically useful analogy can be used to help conceptualize the dysfunction in episodic memory that occurs due to damage to the medial temporal lobes (and Papez’s circuit) versus damage to the frontal lobes.^{20,21} The frontal lobes are analogous to the “file clerk” of the episodic memory system, the medial temporal lobes to the “recent memory file cabinet,” and other cortical regions to the “remote memory file cabinet” (Table 3). Thus, if the frontal lobes are impaired, it is difficult—but not impossible—to get information in and out of storage. For example, getting information into storage may require stronger encoding, and getting information out of storage may require stronger cues from the environment.

Additionally, when the frontal lobes are impaired the information stored in memory may be distorted due to “improper filing” that leads to an inaccurate source, context, or sequence. If, on the other hand, the medial temporal lobes are impaired, it may be impossible for recent information to be stored. This will often lead the patient to ask for the same information again and again—perhaps 20 times in an hour. Older information that has been consolidated over months to years is likely stored in other cortical regions and will therefore be available for retrieval even when the medial temporal lobes or Papez’s circuit are damaged. To illustrate this analogy we can compare the episodic memory dysfunction attributable to Alzheimer disease versus depression. Patients with Alzheimer disease have a dysfunctional “recent memory file cabinet,” whereas patients with depression have a dysfunctional “file clerk.”

The time course of the patient’s episodic memory deficit is often extremely helpful in distinguishing different disorders. Disorders of episodic memory may be transient, such as those due to concussion, seizure, or transient global amnesia. Static disorders, including traumatic brain injury, hypoxic or ischemic injury, single strokes, surgical lesions, and encephalitis, are typically maximal at onset, improve, and then become stable. (Note that in static disorders the onset may last several days, and the period of improvement may last 2 years or more.) Degenerative diseases, such as Alzheimer disease,²² dementia with Lewy bodies, and frontotemporal dementia, begin insidiously and progress gradually. Disorders that affect multiple brain regions, such as multiple sclerosis and vascular dementia, generally progress in a stepwise manner. Some disorders of memory can have a more complicated and variable time course, including memory dysfunction attributable to tumors, hypoglycemia, medications, and Korsakoff syndrome.

When a disorder of episodic memory is suspected due to inability to remember recent information and experiences accurately, further evaluation is warranted. A detailed history of the memory dysfunction should be taken, with particular emphasis on the time course of the memory disorder. Speaking with a caregiver or other informant is usually critical, since the patient with memory dysfunction will invariably not remember important aspects of the history. A history of other cognitive deficits (such as deficits in attention, language, visuospatial, and executive function) should be obtained. Medical and neurologic examinations should be performed, searching for signs of systemic illness, focal neurologic injury, and neurodegenerative disorders.

Brief cognitive testing may be performed by asking the patient to remember several words or a short story, or by using tools such as Mini-Mental State Examination,²³ the Blessed Dementia Scale,²⁴ the Three Words-Three Shapes memory test,² the word list memory test of the Consortium to Establish a Registry for Alzheimer disease,²⁵ the Drilled Word Span Test,² and the Seven-Minute Screen.²⁶ To help distinguish episodic memory dysfunction attributable to impairment of the frontal lobes versus impairment of the medial temporal lobes, difficulties in the encoding and retrieval of information should be contrasted with a primary failure of storage. When information cannot be remembered even when multiple rehearsals have maximized encoding, and retrieval demands have been minimized with the use of a multiple-choice recognition test, a primary failure of storage is present. In complex cases, a formal neuropsychological evaluation should be obtained.

The history, examination, and cognitive testing will suggest a differential diagnosis, which in turn will determine which laboratory and imaging studies are indicated. Treatment depends upon the specific disorder identified. Cholinesterase inhibitors have been approved by the Food and Drug Administration (FDA) to treat Alzheimer disease²⁷ and Parkinson disease dementia²⁸; these medications have also been used to treat vascular dementia²⁹ and dementia with Lewy bodies.³⁰ Memantine has been approved to treat Alzheimer disease, with or without concomitant treatment with cholinesterase inhibitors.³¹

Semantic Memory

Semantic memory refers to our store of conceptual and factual knowledge that is not related to any specific memory.

Semantic memory refers to our store of conceptual and factual knowledge that is not related to any specific memory, such as the color of broccoli or what a fork is used for. Like episodic memory, semantic memory, is an explicit and declarative memory. Evidence that semantic memory and episodic memory are separate memory systems has come from both neuroimaging studies⁴ and the fact that previously acquired semantic memory is spared in patients who have severe impairment of the episodic memory system, such as with disruption of Papez's circuit or surgical removal of the medial temporal lobes.³²

In its broadest sense, semantic memory includes all our knowledge of the world not related to any specific episodic memory. It could therefore be argued that semantic memory resides in multiple cortical areas throughout the brain. For example, there is evidence that visual images are stored in nearby visual association areas.³³ A more restrictive view of semantic memory justified in light of the naming and categorization tasks by which it is usually tested, however, localizes semantic memory to the anterior and inferolateral temporal lobes (Fig. 8).^{34,35}

The most common clinical disorder disrupting semantic memory is Alzheimer disease. This disruption may be due to pathology in the anterior and inferolateral temporal lobes³⁶ or to pathology in the frontal cortex,³⁷ leading to poor activation and retrieval of semantic information.³⁸ Supporting the idea that 2 separate memory systems are impaired in Alzheimer disease, episodic and semantic memory decline independently of each other in this disorder.³⁹

Almost any disorder that can disrupt the anterior and inferolateral temporal lobes may cause impairment of semantic memory.

Almost any disorder that can disrupt the anterior and inferolateral temporal lobes may cause impairment of semantic memory, including traumatic brain injury, stroke, surgical lesions, encephalitis, and tumors (Table 2). Patients with semantic dementia (the temporal variant of frontotemporal dementia) exhibit deficits in all functions of semantic memory, such as naming, single-word comprehension, and impaired general knowledge (such as the color of common items). Other aspects of cognition, however, are relatively preserved, including components of speech, perceptual and nonverbal problem-solving skills, and episodic memory.⁴⁰

Although naming difficulties (particularly with proper nouns) are common in healthy older adults, naming difficulties may also be a sign of a disorder of semantic memory. When a disorder of semantic memory is suspected, the evaluation should include the same components as the evaluation for episodic memory disorders. One of the first aspects of the history and cognitive examination that should be ascertained is whether the problem is solely one of difficulty in recalling people's names and other proper nouns (common in healthy older adults) or to a true loss of semantic information. Patients with mild dysfunction of semantic memory may show only reduced generation of words in a semantic category (for example, the number of grocery items that can be generated in 1 minute), whereas patients with a more severe impairment of semantic memory usually show a 2-way naming deficit: they are unable to name an item when it is described, and they are also unable to describe an item when it is named. General knowledge is also impoverished in these more severely affected patients. Treatment will depend upon the specific disorder identified.

Simple Classic Conditioning

Simple classic conditioning involves the pairing of 2 stimuli—an unconditioned stimulus and a conditioned stimulus. When paired together repeatedly, the response can then be elicited by the conditioned stimulus alone (Table 1). Think of the famous case of Pavlov's dog: the meat (the unconditioned stimulus) is paired with the bell (the conditioned stimulus). After a number of pairings, the response—salivation—is elicited by the bell (the conditioned stimulus) alone.⁴¹ This form of memory is nondeclarative and implicit because conscious awareness (although often present) is not necessary for the learning to take place. Two types of conditioning are that of an autonomic conditioned response (such as a fear response), and a motoric conditioned response (such as an eyeblink). The amygdala, related structures, and connections in the basolateral limbic system (including the dorsomedial thalamic nuclei, subcallosal area, and the stria terminalis) are important for autonomic conditioning (Fig. 1).⁴² In motoric conditioning, the cerebellum appears to play the most important role (Fig. 8).^{43,44}

Although disruption of this form of memory rarely comes to clinical attention, patients have been described with selective impairment of simple classic conditioning. In one study, 3 patients are reported. The first, who had selective bilateral amygdala damage, had no difficulty with episodic memory (remembering a new list of items) but could not acquire a classic conditioning autonomic response. The second patient, who had selective bilateral hippocampal damage, showed episodic memory dysfunction (being unable to remember the list of items) but did acquire the classic conditioning. The third, who had bilateral damage to both amygdala and hippocampi, showed impairment in episodic memory and also did not acquire the classic conditioning.⁴⁵ Other patients who have disruption in the amygdala, thalamus, or cerebellum may also show impairments of one or more types of simple classic conditioning, including those with Alzheimer disease (impaired autonomic conditioning due primarily to pathology in amygdala⁴⁶) and those with damage to the cerebellum or its connections (impaired motor conditioning⁴⁷).

Procedural Memory

Procedural memory refers to the ability to learn cognitive and behavioral skills and algorithms that operate at an automatic, unconscious level.

Procedural memory refers to the ability to learn cognitive and behavioral skills and algorithms that operate at an automatic, unconscious level. Procedural memory is nondeclarative and implicit. Examples include learning to ride a bike or play the piano (Table 1). Because procedural memory is spared in patients who have severe deficits of the episodic memory system (such as those who have undergone surgical removal of the medial temporal lobes), it is clear that the procedural memory system is separate and distinct from the episodic memory system.^{32,47}

Functional imaging research has shown that a number of brain regions involved in procedural memory become active as a new task is learned, including the supplementary motor area, basal ganglia, and cerebellum (Fig. 8).⁴⁸ Convergent evidence comes from studies of patients with damage to the basal ganglia or cerebellum who show impairment in learning procedural skills.⁴⁹ Because the basal ganglia and cerebellum are relatively spared in early Alzheimer disease, despite their episodic memory deficit these patients show normal acquisition and maintenance of their procedural memory skills.

Parkinson disease is the most common disorder disrupting procedural memory. Patients in the early stages of Huntington chorea and olivopontocerebellar degeneration also show impaired procedural memory while performing nearly normally on episodic memory tests.^{47,50} Other causes of damage to the basal ganglia or cerebellum including tumors, strokes, and hemorrhages may also disrupt procedural memory. Patients with major depression also show impairment in procedural memory tasks, perhaps because depression involves dysfunction of the basal ganglia.⁵¹

Disruption of procedural memory should be suspected when patients show evidence of either substantial difficulties in learning new skills (compared with their baseline) or the loss of previously learned skills. For example, patients may lose the ability to perform automatic, skilled movements, such as writing, swinging a tennis racket, or playing a musical instrument. Although these patients may be able to relearn the fundamentals of these skills, explicit thinking becomes required for their performance. As a result, patients with damage to the procedural memory system lose the automatic effortlessness of simple motor tasks that healthy individuals take for granted. The evaluation of disorders of procedural memory is similar to that of disorders of episodic memory; treatment depends upon the specific disease process. Lastly, it is worth noting that patients whose episodic memory has been devastated by a static disorder, such as encephalitis, have had successful rehabilitation by using procedural memory (and other nondeclarative forms of memory) to learn new skills.⁵²

Priming

Priming occurs when a prior encounter with a particular item changes the response to the current item (Table 1). Because this phenomenon occurs even if the individual does not consciously remember encountering the prior item, priming is another example of an

implicit and nondeclarative form of memory. Priming is often divided into perceptual priming, which is modality specific (eg, auditory, visual) and does not benefit from elaborate encoding when materials are being learned, versus conceptual priming, which is not modality specific and shows enhancement with increased encoding.

Perceptual priming depends upon a perceptual representation system, involved in processing information regarding the form and structure of items but not their meanings.⁵³ Converging evidence suggests that posterior cortical regions involved in processing of sensory information are important for perceptual priming. A patient with bilateral occipital lobe lesions demonstrated normal episodic memory and conceptual priming while failing to show perceptual priming.⁵⁴ Neuroimaging studies of visual perceptual priming using PET and fMRI show changes in activation of visual peristriate cortex.⁵⁵ By contrast, neuroimaging studies of conceptual priming typically show changes in left prefrontal regions.⁵⁵ Most studies have shown that patients with early degenerative diseases that do not affect the sensory association cortices, such as Alzheimer, Parkinson, and Huntington diseases, demonstrate normal perceptual priming.⁵⁶ For conceptual priming, however, many studies have found these groups to be impaired.⁴⁷

Working Memory

Working memory refers to the ability to temporarily maintain and manipulate information that one needs to keep in mind.

Bringing together the traditional fields of attention, concentration, and short-term memory, working memory refers to the ability to temporarily maintain and manipulate information that one needs to keep in mind. Requiring active and conscious participation, working memory is an explicit and declarative memory system. Working memory has traditionally been divided into 3 components: one that processes phonologic information (eg, keeping a phone number “in your head”), one that processes spatial information (eg, mentally following a route), and an executive system that allocates attentional resources.⁵⁷

Studies have demonstrated that working memory involves a network of cortical and subcortical areas, which differ depending on the particular task.⁵⁸ Participation of the prefrontal cortex, however, is involved in virtually all working memory tasks (Fig. 8).¹³ The network of cortical and subcortical areas typically includes posterior brain regions (eg, visual association areas) that are linked with prefrontal regions to form a circuit. Research suggests that spatial working memory tends to involve more regions on the right side, and phonologic working memory tends to involve more regions on the left side of the brain. Bilateral brain activation is observed, however, in more difficult working memory tasks, regardless of the nature of the material being processed.¹ Additionally, an increase in the number of brain regions activated in prefrontal cortex is observed as the complexity of the task increases.⁵⁹

Because working memory depends upon networks that include frontal and parietal cortical regions as well as subcortical structures, most neurodegenerative diseases impair working memory. Studies have demonstrated that working memory may be impaired in patients with Alzheimer disease, Parkinson disease, Huntington chorea, and dementia with Lewy bodies,

as well as less common disorders such as progressive supranuclear palsy (Table 2).^{60,61} In addition to these neurodegenerative diseases, almost any disease process that disrupts the frontal lobes or their connections to posterior cortical regions and subcortical structures can interfere with working memory. Such processes include tumors, strokes, multiple sclerosis, head injury, and others.^{62,63} Because it involves the silent rehearsal of verbal information, almost any type of aphasia may impair phonologic working memory. Disorders that diminish attentional resources, including attention deficit hyperactivity disorder, obsessive compulsive disorder, depression, and schizophrenia, can also impair working memory.⁶⁴⁻⁶⁶

Disorders of working memory may present in several different ways. Often the patient will exhibit an inability to concentrate or pay attention. Impairment in performing a new task with multistep instructions is frequently seen. Interestingly, a disorder of working memory may also present as a problem with episodic memory, because information must first be “kept in mind” by working memory in order for episodic memory to encode it.¹³ Such cases will therefore show a primary impairment in encoding.

The evaluation of disorders of working memory is similar to that of disorders of episodic memory. Treatment depends upon the underlying cause. Stimulants, approved by the FDA for the treatment of attention deficit hyperactivity disorder,^{67,68} will often be helpful in disorders of working memory.

CONCLUSION

Although traditionally, memory has been viewed as a simple concept, converging and complementary evidence from patient studies and more recent neuroimaging research suggest that memory is composed of separate and distinct systems. Improved understanding of these different types of memory will aid the clinician in the diagnosis and treatment of the memory disorders of their patients. As more specific therapeutic strategies are developed for the treatment of diseases that cause memory dysfunction, this knowledge will become increasingly important.

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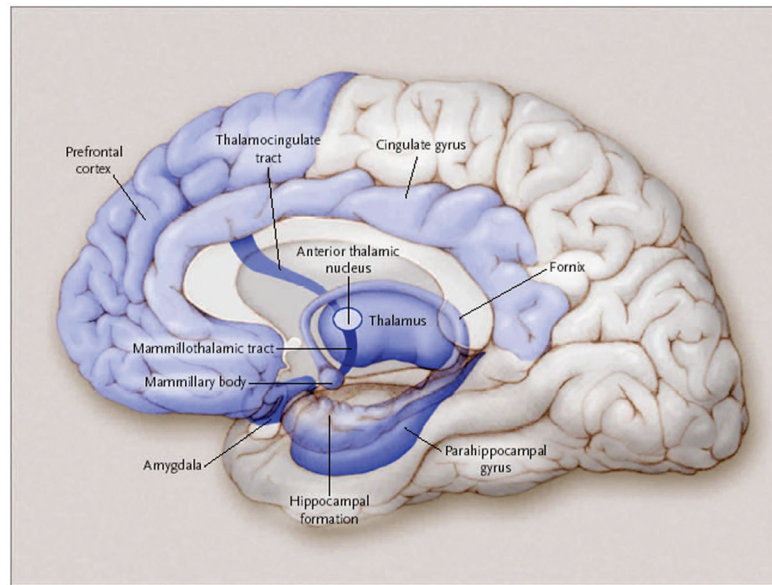


FIGURE 1. Episodic memory. The medial temporal lobes, including the hippocampus and parahippocampus, form the core of the episodic memory system. Other brain regions are also necessary for episodic memory to function correctly. In addition to being involved in episodic memory, the amygdala is also important for the autonomic conditioning. (Adapted with permission from Budson and Price, *New England Journal of Medicine*, 2005).

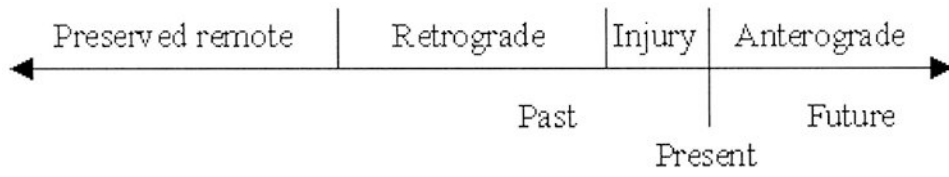


FIGURE 2.
Ribot's law.

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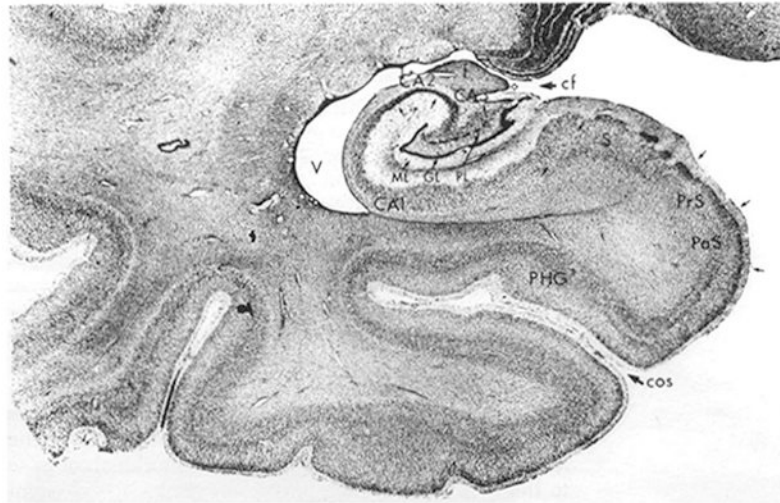


FIGURE 3.

Detailed anatomy of the medial temporal lobe. PHG, indicates parahippocampal gyrus; Pr, presubiculum; v, ventricle; S, subiculum. CA1, CA2, and CA3 are subregions of the hippocampus, and ML, GL, and PL are different regions of the dentate gyrus of the hippocampus. (Adapted with permission from Martin JH. *Neuroanatomy: Text and Atlas*. New York, NY: Elsevier, 1989, p. 391; permission granted by Elsevier).

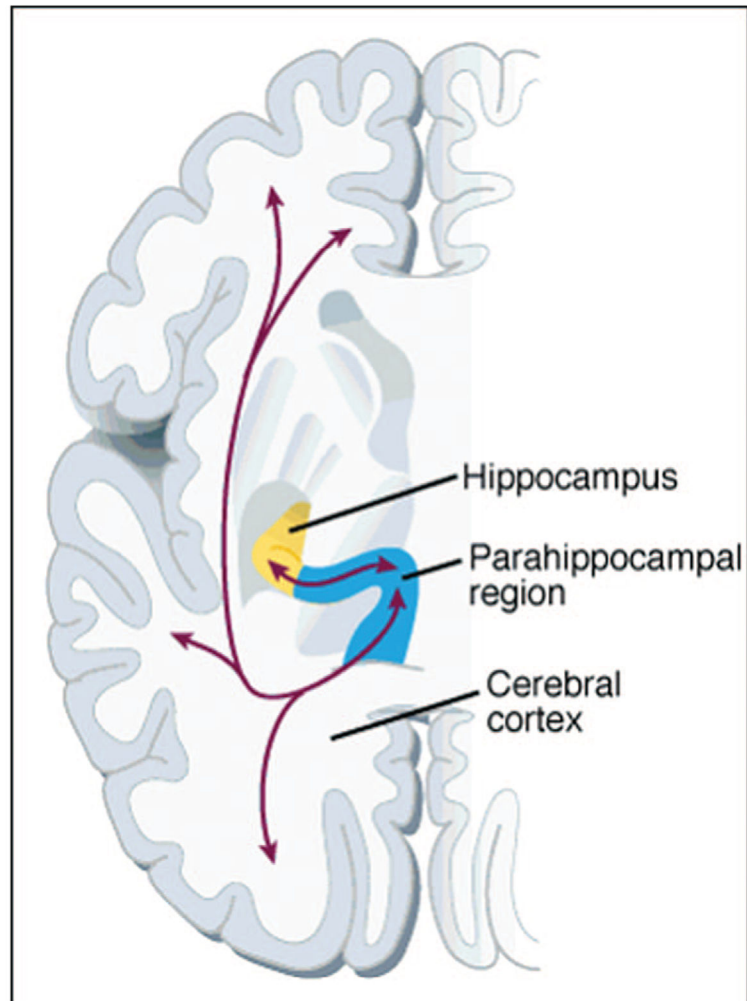


FIGURE 4. Areas of the cerebral cortex, including sensory areas, are connected bidirectionally to the parahippocampal region, which is in turn bidirectionally connected to the hippocampus. (Adapted with permission from Eichenbaum, 1997; permission granted by Science Magazine).

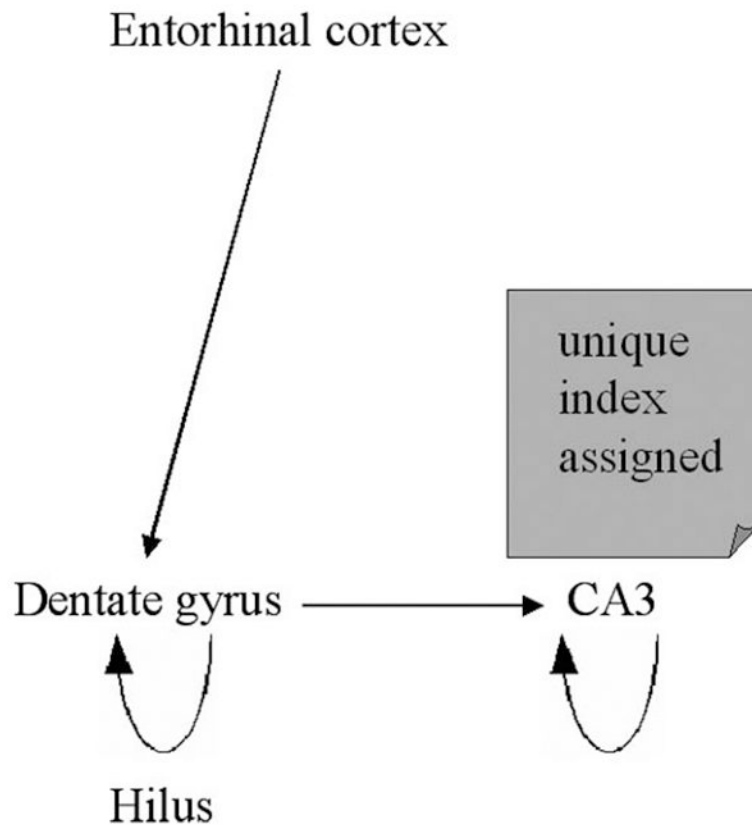


FIGURE 5. Schematic representation of encoding in the medial temporal lobe.

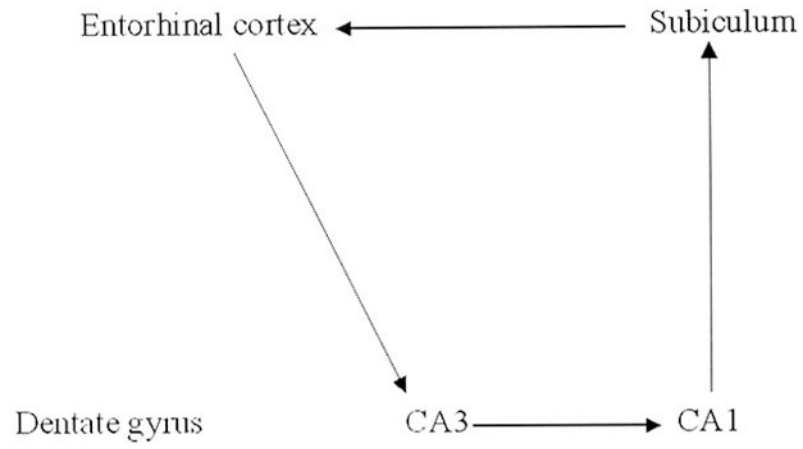


FIGURE 6.
Schematic representation of retrieval in the medial temporal lobe.

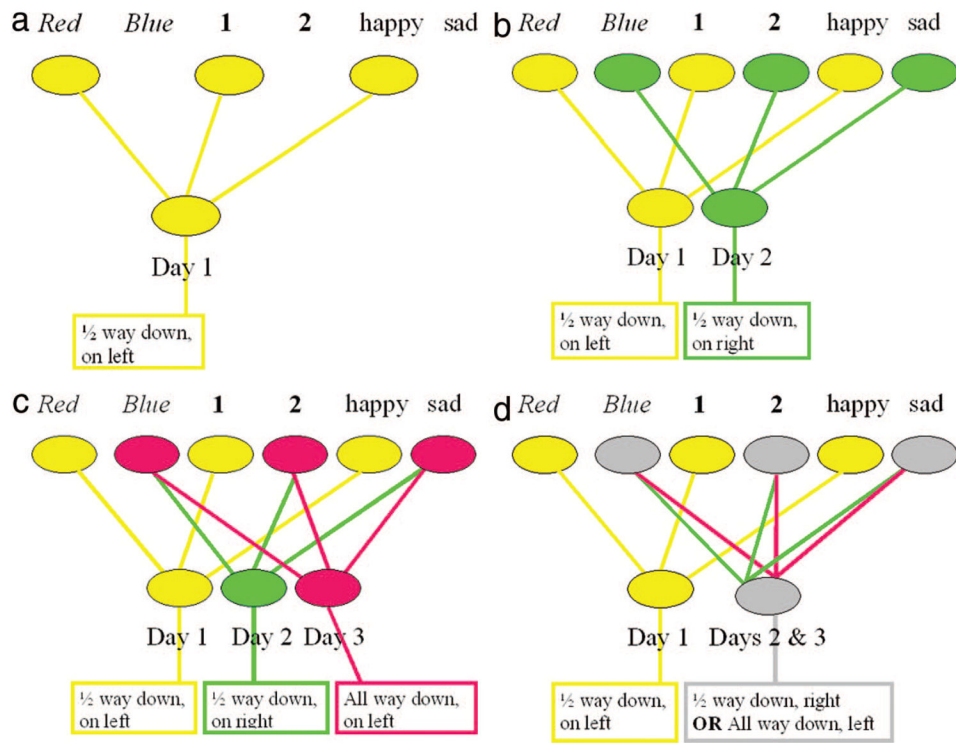


FIGURE 7.
 A neural network model. See text for details.

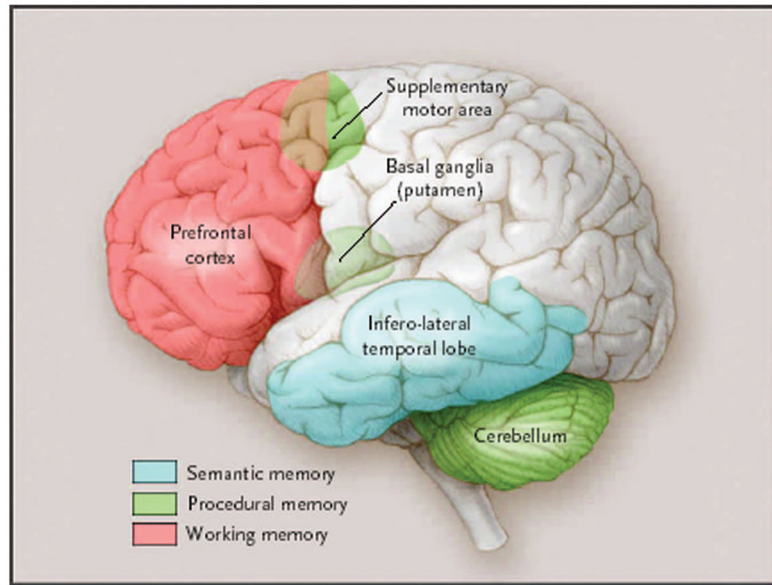


FIGURE 8.

Semantic, procedural, and working memory. The anterior and inferolateral temporal lobes are important in the naming and categorization tasks by which semantic memory is typically assessed. However, in the broadest sense, semantic memory may reside in multiple and diverse cortical areas that are related to various types of knowledge. The basal ganglia, cerebellum, and supplementary motor area are critical for procedural memory. The prefrontal cortex is active in virtually all working memory tasks; other cortical and subcortical brain regions will also be active, depending on the type and complexity of the working memory task. In addition to being involved in procedural memory, the cerebellum is also important for the motoric conditioning. (Adapted with permission from Budson and Price, *New England Journal of Medicine*, 2005).

Selected Memory Systems

TABLE 1.

Memory System	Examples	Awareness	Length of Storage	Major Anatomical Structures
Episodic memory	Remembering a short story, what you had for dinner last night, and what you did on your last birthday	Explicit declarative	Minutes to years	Medial temporal lobe, anterior thalamic nucleus, mammillary body, fornix, prefrontal cortex
Semantic memory	Knowing who was the first President of the US, the color of a lion, and how a fork and comb are different	Explicit declarative	Minutes to years	Inferior lateral temporal lobes
Autonomic simple	Pavlov's dog: a fear response conditioning	Implicit nondeclarative	Minutes to years	Amygdala and basolateral limbic system
Motonic simple classical conditioning	Eye-blink conditioning	Implicit nondeclarative	Minutes to months	Cerebellum
Procedural memory	Driving a standard transmission car, and learning the sequence of numbers on a touch-tone phone without trying	Implicit nondeclarative	Minutes to years	Basal ganglia, cerebellum, supplementary motor area
Perceptual priming	Word-stem completion: octopus → oct_____	Implicit nondeclarative	Minutes to days	Cortical sensory association areas (eg, extrastriate visual cortex for visual perceptual priming)
Conceptual priming	Word-stem completion: sea creatures → oct_____	Implicit nondeclarative	Minutes to days	Inferior prefrontal cortex
Working memory	Phonological: keeping a phone number "in your head" before dialing Spatial: mentally following a route, or rotating an object in your mind	Explicit declarative	Seconds to minutes; information actively rehearsed or manipulated	Phonological: prefrontal cortex, Broca's area, Wernicke's area Spatial: prefrontal cortex, visual association areas

TABLE 2.

Selective Memory System Disruptions in Common Clinical Disorders

Disease	Episodic Memory	Semantic Memory	Simple Classical Conditioning	Procedural Memory	Priming	Working Memory
Alzheimer disease	+++	++	+	-	- perceptual + conceptual	++
Frontotemporal dementia	++	++	?	-	?	+++
Semantic dementia	+	+++	?	?	?	-
Lewy body dementia	++	?	?	?	?	++
Stroke and vascular dementia	+	+	+	+	+	++
Parkinson disease	+	+	-	+++	-	++
Huntington disease	+	+	-	+++	-	+++
Progressive supranuclear palsy	+	+	?	++	?	+++
Korsakoff syndrome	+++	-	+	-	+	++
Multiple sclerosis	+		+	?	-	++
Transient global amnesia	+++		?	-	-	-
Hypoxic-ischemic injury	++	-	-	-	+	++
Head trauma	+	+			?	±
Tumors	±	±	±	±	±	±
Depression	+	±	?	++	?	±
Anxiety	+	-	±	-	±	±
Obsessive compulsive disorder	+	-	±	++	±	++
Attention deficit hyperactivity disorder	-	-	-	?	±	+

+++ indicates early and severe impairment; ++, moderate impairment; +, mild impairment; ±, occasional impairment or impairment in some studies, but not others; -, no significant impairment; ?, unknown.

TABLE 3.

A Filing Analogy of Episodic Memory

Brain Structure	Analogy
Frontal lobes	File clerk
Medial temporal lobes	Recent memory files
Other cortical regions	Remote memory files

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