

MEMORY SYSTEMS

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ABSTRACT

Converging evidence from patient and neuroimaging studies suggests that memory is a collection of abilities that use different neuroanatomic systems. Neurologic injury may impair one or more of these memory systems. Episodic memory allows us to mentally travel back in time and relive an episode of our life. Episodic memory depends on the hippocampus, other medial temporal lobe structures, the limbic system, and the frontal lobes, as well as several other brain regions. Semantic memory provides our general knowledge about the world and is unconnected to any specific episode of our life. Although semantic memory likely involves much of the neocortex, the inferolateral temporal lobes (particularly the left) are most important. Procedural memory enables us to learn cognitive and behavioral skills and algorithms that operate at an automatic, unconscious level. Damage to the basal ganglia, cerebellum, and supplementary motor area often impair procedural memory.

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INTRODUCTION

The ability to remember one's personal past is a fundamental feature that defines the human conscious experience. Disorders of memory can have devastating consequences for patients and families. Although numerous medical conditions may precipitate memory loss, the aging of our population, with its attendant increased prevalence of Alzheimer disease (AD) and other neurodegenerative conditions, has accentuated the need for the clinician to have a general understanding of normal memory functioning and the differential diagnosis associated with its disruption.

Critical to any discussion of memory is the concept of a memory system, which can be loosely defined as a brain system that supports the maintenance of information that impacts behavior after passage of time from initial acquisition.¹ Although one of the earliest

assertions that human memory is subserved by several different memory systems was by the 18th century French philosopher Maine de Biran, the characterization of the famous patient Henry Molaison ("HM"; 1926–2008) provided the experimental support to popularize this conception. HM underwent bilateral medial temporal lobe (MTL) resections for intractable epilepsy in 1953. Unfortunately, the procedure resulted in the unintended consequence of profound amnesia in which he was unable to acquire new memories of experiences or events following the surgery. The description of this outcome firmly established the MTL system as essential to episodic memory and was disseminated to the scientific community in the highly influential 1957 manuscript by Milner and Scoville entitled "Loss of Recent Memory after Bilateral Hippocampal Lesions."²

KEY POINT

- When medial temporal lobe structures are damaged and episodic memory is impaired, learning can still occur through other memory systems such as procedural memory.

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KEY POINT

- Memory impairment may be seen even if the medial temporal lobes are spared. Frontal lobes, inferolateral temporal lobes, basal ganglia, and cerebellum may all cause certain kinds of memory impairment.

It was the sparing of other aspects of HM’s learning and memory, however, that provided the foundation for the notion of separable memory systems. For example, his ability to learn new motor skills, demonstrate the effects of perceptual priming, and retrieve remote pieces of semantic memory suggested that these processes were not entirely dependent on MTL function. Additional dissociations revealed in HM and other patients provide evidence that there are separable memory systems.

Although there is not complete agreement on the best way to categorize these systems, almost all accounts involve separation into declarative and nondeclarative forms of memory. Declarative memories can be put into words and generally

involve explicit access or conscious awareness of information, whereas nondeclarative memories cannot be verbalized and are instead manifested by changes in behavior. In the current review, we will discuss two forms of declarative memory—episodic and semantic—and one form of nondeclarative memory—procedural. Working memory, another form of declarative memory, is covered elsewhere in this issue, although we have included it in selected tables and figures for comparison (**Table 1-1**). As outlined below, one of the major values of considering memory in this manner is that these systems rely on a dissociable neuroanatomy, which has variable sensitivity to different disease processes and, thus, has localizing and diagnostic implications in the context of impairment.

TABLE 1-1 Comparison of Clinically Relevant Memory Systems

| Memory System | Examples | Awareness | Length of Storage | Major Anatomic 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, mamillary body, fornix, prefrontal cortex |
| Semantic memory | Knowing who was the first US president, the color of a lion, and how a fork and comb are different | Explicit Declarative | Minutes to years | Inferior lateral temporal lobes |
| 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 |
| Working memory | Phonologic: 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 | Phonologic: prefrontal cortex, Broca area, Wernike area Spatial: prefrontal cortex, visual association areas |

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EPISODIC MEMORY

Definitions

The patient in **Case 1-1** had a relatively selective impairment of episodic memory.

Episodic memory is the memory system that allows us to remember past experiences and episodes in our life, or as Endel Tulving put it, the kind of memory that allows us to “mentally travel” in time.³ Two features differentiate episodic memory from other memory systems. (1) Episodic memory involves a form of consciousness in which the *self* is central—autonoetic or self-knowing consciousness according to Tulving. In other words, it involves remembering one’s

own experience of an event. (2) Only episodic memory is tightly linked to a sense of time. Indeed, time forms part of the context by which these events are represented, allowing for differentiation of events in the recent past from more remote events.

Episodic memories may be fractionated in a number of different ways, which often have implications for the nature of an impairment of memory and the underlying neural substrate involved. One such division is the difference between *item* and *associative memory*. Whereas item memories are for individual items without context, associative memories involve the linking of multiple aspects of an event. For

KEY POINTS

- Episodic memory impairments are common and often disrupt the lives of patients and their families.
- Episodic memory is the type of memory we usually mean when we talk about memory. It is memory for an episode of one’s life.

Case 1-1

A 75-year-old man had decline in his memory over about 1 year. Per his wife, this was manifested by his repeating questions and forgetting their daily plans. She noted little change in his ability to perform instrumental activities of daily living, such as driving or handling the finances, but he did have greater difficulty with remembering details of books or shows that they had watched together. He admitted that his memory was poorer and felt a sense of foreboding about the future. On examination, he showed very poor verbal and visual memory, and limited knowledge of current events despite avidly watching the news. Although he recalled 6/10 words on the third immediate recall trial of a verbal memory task, his delayed recall was 0/10, and he only recognized 4/10 items and made one false alarm. His retention of a story based on initial encoding was very poor. Nonetheless, he performed in the normal range on almost all tests of language, executive functioning, attention, and visuospatial ability. He was given a diagnosis of amnesic mild cognitive impairment. Note the diminutive hippocampi on his MRI (**Figure 1-1**).

Comment. This patient has an impairment of episodic memory. A relatively isolated impairment of episodic memory is a common feature of early AD given the early neuropathology in the MTLs with this condition. This patient has a high likelihood of progressing from amnesic mild cognitive impairment to clinical AD.

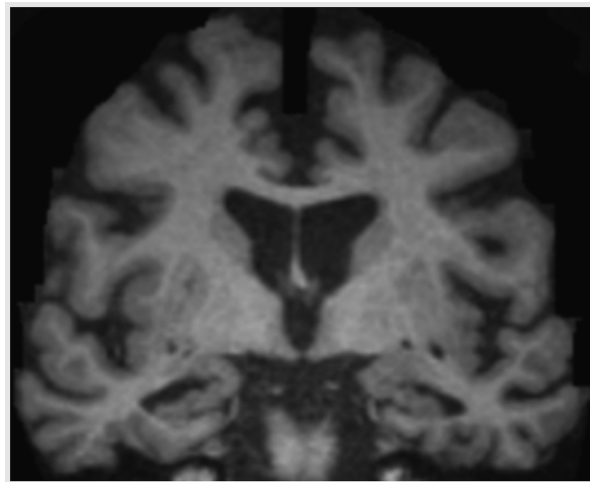


FIGURE 1-1

MRI coronal T1-weighted image. Note the relatively disproportionate atrophy of the bilateral hippocampi consistent with the temporolimbic memory impairment of this patient.

KEY POINT

- The hippocampus and other medial temporal lobe structures are critical for normal episodic memory function.

example, one may remember having seen a friend earlier in the day and also the color of the friend's shirt and the location of the meeting. A common test of associative memory is to have subjects study word pairs. At testing, the subject is shown one word in the pair and is asked to recall the second, associated word. A related concept is *source* memory, which is the ability to remember the specific context from which a memory came. A common memory error is related to this notion, sometimes referred to as *reality monitoring*. An example is when you are unable to remember whether you actually turned off the stove or just thought about turning it off. Source memory is frequently tested in the laboratory by having subjects study two lists. At testing, they need to decide not only whether a particular item was studied, but remember from which list it came.

A related formulation to the item versus associative or source memory distinctions is the difference between familiarity and recollection,⁴ a difference that may reflect dissociable underlying medial temporal and neocortical structures. Familiarity is conceptualized as an acontextual sense of prior encounter. An example of an experience of familiarity is when people see someone that they are sure they have previously met but cannot recall how it is that they know that person ("That person is so familiar to me! Where do I know him from?"). In contrast, recollection is the more detailed retrieval of information ("Oh, that's Bob. I met him at my sister's birthday party last week"). Although sometimes recollection occurs spontaneously, at other times additional conscious, effortful searching of one's memory stores is needed.

A final important distinction is between retrograde and anterograde amnesia. Relative to the time of the brain injury, anterograde amnesia is the in-

ability to form new memories, whereas retrograde amnesia is the loss of previously acquired memories.

Functional Neuroanatomy of Episodic Memory

The MTL—and particularly the hippocampus—is traditionally thought to be the anatomic seat of episodic memory, as exemplified by the severe amnesia of HM; however, a number of other neural systems appear to be involved. The processes that support episodic memory occur from the time the to-be-remembered event is encountered (*encoding*) to the act of remembering (*retrieval*). In between are processes involved in the maintenance of these memories. If the memory is to last for an extended period of time, an additional process known as *consolidation* occurs. Given the disparate nature of these operations, it is perhaps not surprising that episodic memory requires diverse neural systems for its proper function and, thus, a variety of brain injuries can result in impaired memory. Historically, it has been difficult to gain traction on the nature of neural activity associated with these different stages of memory. The advent of functional neuroimaging techniques has allowed for assessment of neural activity during memory encoding and retrieval, which has added greatly to our understanding of these processes (**Figure 1-2**). We will outline a number of critical brain regions associated with episodic memory function.

Medial temporal lobe. Much of what we know about normal episodic memory function comes from studying patients with amnesia resulting from MTL lesions. The MTL is a complex structure frequently divided into hippocampal and extrahippocampal regions.⁵ The hippocampal structures include the dentate gyrus, cornus ammonis subfields (CA 1, CA2, and CA3), and the postsubiculum. Extrahippocampal structures

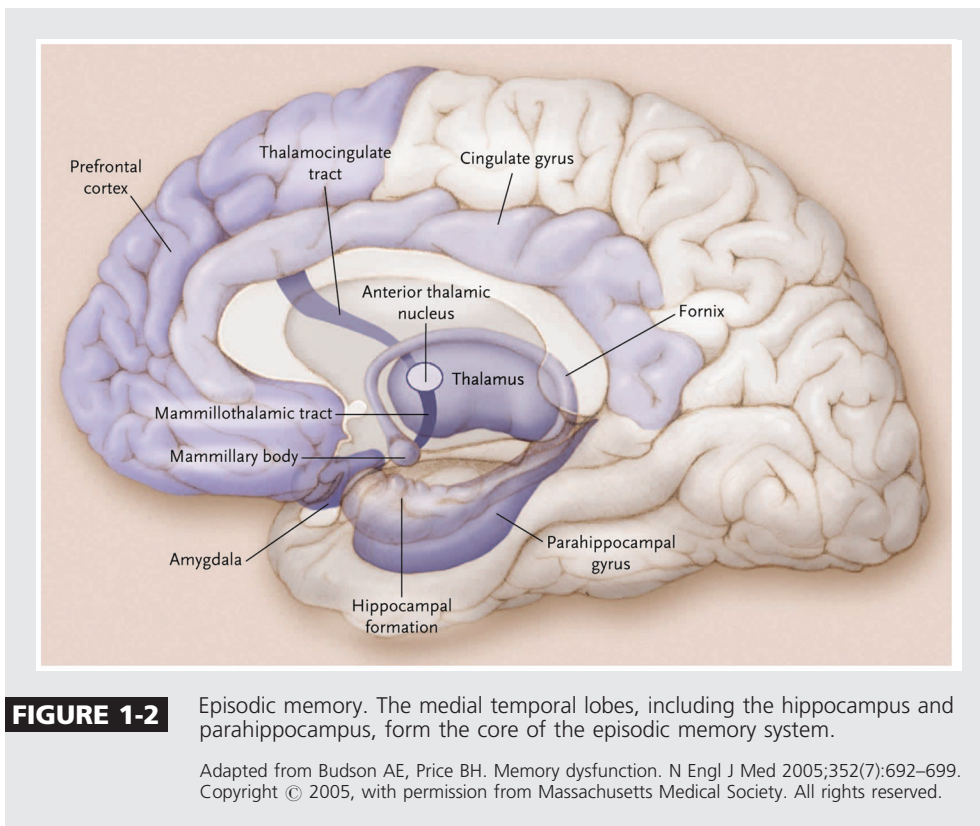


FIGURE 1-2

Episodic memory. The medial temporal lobes, including the hippocampus and parahippocampus, form the core of the episodic memory system.

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KEY POINT

■ An injury to episodic memory typically causes (1) anterograde amnesia: an inability to form new memories, and (2) retrograde amnesia: a loss of previous memories. There are, however, always (3) some preserved remote memories.

include the entorhinal, perirhinal, and parahippocampal cortices.

Whereas isolated hippocampal lesions produce significant amnesia, inclusion of surrounding extrahippocampal MTL structures tends to produce even more profound memory loss.⁶ Some work has suggested that there may be a division of labor within the MTLs with regard to the nature of their memory stores.^{6–8} Hippocampal lesions tend to produce impairment on tasks of associative memory, source memory, and recollection, with relative sparing of item memory and familiarity. However, the additional involvement of extrahippocampal MTL regions impairs item memory as well. These and other findings suggest that the hippocampus is involved in the binding of different elements of a prior study episode. By contrast, the perirhinal cortex and parahippocampus appear critical for the storage of these individual elements. An influential model is that the perirhinal cortex and para-

hippocampus differentially encode object and spatial elements of an episode, respectively, which are then bound by the hippocampus (**Figure 1-3**).⁸

In addition to significant anterograde amnesia, patients with MTL injury frequently experience retrograde amnesia. Often times, the retrograde amnesia is greatest for events learned nearest the time of MTL injury but is spared for more remote episodes. This somewhat paradoxical pattern of memory loss has been labeled as Ribot law⁹ and may reflect the changing representation of memories over time. One popular account to explain this phenomenon is the “standard consolidation” model.^{10,11} This model argues that when memories are initially formed, the MTL—likely, the hippocampus—binds neocortically represented features of an event. Partial cues that reactivate elements of the episode will also activate related features mediated by connections with the hippocampus. However, over time, these

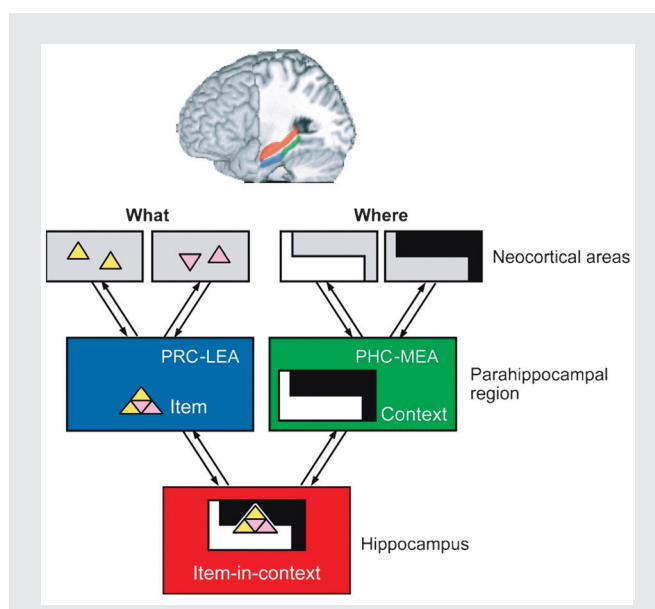


FIGURE 1-3 Functional organization of the medial temporal lobe system. Neocortical input regarding the object features (*what*) converges in the perirhinal cortex (PRC) and lateral entorhinal area (LEA), whereas details about the location (*where*) of objects converge in the parahippocampal cortex (PHC) and medial entorhinal area (MEA). These streams converge in the hippocampus, which represents items in the context in which they were experienced. Reverse projections follow the same pathways back to the parahippocampal and neocortical regions. Back projections to the PHC-MEA may support recall or context, whereas back projections to the PRC-LEA may support recall of item associations.

Adapted with permission from Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 2007;30:123–152.

form the perforant pathway (the main input to the hippocampus). Such pathology appears to result in a cortico-hippocampal disconnection,¹² perhaps preventing the binding of different neocortical elements necessary for effective encoding. Thus, it is not surprising that memory loss is an early feature of this condition (**Case 1-1**). As AD progresses, all regions of the MTL become significantly involved, further devastating the episodic memory system. Other factors that likely contribute to the memory loss include reduced cholinergic input due to basal forebrain pathology and involvement of frontal-subcortical networks. It has also recently become apparent that β -amyloid ($A\beta$), the protein fragment that forms the hallmark amyloid plaques of AD, in its soluble form may inhibit long-term potentiation, a critical cellular mechanism for learning and memory.¹³

Extended medial temporal memory system. Several structures with significant connectivity to the MTL proper are critical to episodic memory, as evidenced by the amnesia associated with their injury. Many of these regions were previously described by Papez in the circuit that bears his name.¹⁴ Lesions to the mamillary bodies, bilateral fornices (an efferent pathway from the hippocampus to the mamillary bodies), and the anterior thalamic nucleus (which receives inputs via the mamillothalamic track from the mamillary bodies) all produce episodic memory impairment that is difficult to distinguish from hippocampally based amnesia (**Figure 1-2**).⁶ Additionally, the posterior cingulate and retrosplenial cortex also have dense connections with the hippocampus and anterior thalamic nucleus, and amnesia associated with retrosplenial lesions have been described.¹⁵ Although isolated lesions in these related structures are uncommon, Korsakoff syndrome represents a classic form of amnesia associated with pathology in the anterior

neocortical representations form their own associations and the critical role of the MTL in retrieval may become diminished or absent, and, thus, an older memory may not be affected by MTL pathology.

A number of conditions produce memory impairment through MTL injury. These conditions include AD, dementia with Lewy bodies, hippocampal sclerosis, posterior cerebral artery stroke, hypoxic-ischemic injury, and viral and limbic encephalitis. By far the most common cause of memory loss in older adults is AD, which is associated with extensive neuropathology in the MTL. In particular, early neurofibrillary tangle pathology is found in the entorhinal cortex layer II neurons, which

thalamic nucleus and the mamillary bodies.¹⁶

Frontal lobes. While their deficit is generally more subtle than that seen with medial temporal lesions, patients with frontal lobe damage frequently exhibit episodic memory impairment. These patients tend to have relatively selective impairment on memory tasks that require the linking of different features of a prior episode. As such, patients with frontal lobe damage tend to have difficulty on tests of associative or source memory,¹⁷ memory for temporal order of presentation,¹⁸ and recollection.⁴ However, performance is often normal on tests of item memory or familiarity. Patients with frontal lobe damage also tend to have more difficulty on memory tasks that require spontaneously generated encoding or retrieval strategies, but show improvement in the context of “environmental support.” For example, patients with frontal lobe lesions tend to perform more poorly on a memory test if told to simply study a list of words rather than when instructed to perform a specific encoding operation, such as to form a mental image of each study item. This notion also applies to different test formats, as an unconstrained free recall task is much more difficult for patients with frontal lobe lesions than cued recall or recognition memory.¹⁹ On these latter tasks, these patients may show little or no deficit at all. Thus, as a general principle, prefrontal regions appear to be involved in different aspects of cognitive control mechanisms that enhance memory encoding and retrieval²⁰ rather than supporting the retention of information (likely a medial temporal function).

In addition to failure to retrieve information from prior events, patients with frontal lobe lesions are particularly susceptible to memory distortions and false memories. This is likely related to their poor memory for contextual or associative details of a prior episode.²¹

These patients may conflate details of various events and are susceptible to errors of reality monitoring reflective of source memory confusions. In more extreme cases, patients may exhibit spontaneous and sometimes elaborative confabulations. Potential contributors to the tendency to confabulate include combined MTL and frontal lobe dysfunction (such as is seen in AD, frontotemporal degeneration, and Korsakoff amnesia), poor selection or focus of the to-be-retrieved memories, impaired monitoring and editing of retrieved information, and impaired source monitoring and retrieval of temporal contextual details.²²

Differences in memory performance between conditions that affect the MTL and those that affect the frontal lobes can be conceptualized by analogy. The episodic memory system can be thought of as a filing system. The frontal lobes are analogous to the “file clerk” of the episodic memory system, the MTL (and Papez circuit) to the “recent memory file cabinet,” and other cortical regions to the “remote memory file cabinet.” Thus, if the frontal lobes are damaged, it is difficult—but not impossible—to get information in and out of storage. Additionally, when the frontal lobes are damaged, 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 MTLs are impaired, it may be impossible for recent information to be stored. 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 MTL or Papez circuit is damaged. See **Table 1-2** for characteristics of memory impairment due to frontal versus medial temporal injuries.

A number of conditions produce memory impairment that is due, at least in part, to frontal lobe dysfunction. In addition to frontal strokes and mass lesions, other conditions

KEY POINTS

- Alzheimer disease is by far the most common cause of episodic memory impairment.
- Memory distortions, false memories, and confabulation may occur with damage to frontal cortex.
- Think of episodic memory as a filing system: The frontal lobes are the filing clerk, the medial temporal lobes are the recent memory file cabinet, and other cortical regions are the older memory file cabinet.

TABLE 1-2 Memory Deficits With Medial Temporal Lobe Versus Frontal Lobe Lesions

| Characteristic | Medial Temporal Lobe Lesion | Frontal Lobe Lesion |
|---|---|---|
| Immediate memory | Normal to mildly impaired | Impaired |
| Free recall | Impaired | Impaired |
| Recognition memory or cued recall | Impaired | Often normal |
| Source or associative memory (ie, recollection) | Impaired | Impaired |
| Item memory (ie, familiarity) | Impaired | Normal |
| Effects of environment support | Minimal enhancement of memory performance | Significant enhancement of memory performance |
| Tendency for false memory or confabulation | Variable | High |

associated with a frontally based episodic memory impairment include frontotemporal degeneration, vascular dementia (particularly when associated with subcortical white matter disease), dementia with Lewy bodies, multiple sclerosis, depression, and head trauma. Distinguishing between memory impairment due to medial temporal injury and that associated with frontal lobe dysfunction has potential diagnostic value. For example, while measures of free recall and associative memory do not differentiate patients with AD from those with subcortical vascular dementia, measures of recognition memory (with patients with AD performing more poorly) appear to have better specificity.²³ Although generally more subtle, “healthy” age-associated memory loss tends to be qualitatively similar to memory loss due to frontal lobe injury. This phenomenology is consistent with data supporting the relatively selective vulnerability of frontal lobe function in aging as a result of cortical volume loss, anterior white matter disruption, and dopaminergic depletion.²⁴

Other regions. Several other regions appear to be important substrates for episodic memory function. Lesions of the basal forebrain, often due to anterior communicating artery aneurysm rupture, produce memory impairment. This region is the main source of cholinergic input to the MTLs and neocortex. Blockade of acetylcholine with the muscarinic antagonist scopolamine produces amnesia in healthy individuals.²⁵ The relative decline in acetylcholine associated with basal forebrain pathology in AD is the rationale for the use of cholinesterase inhibitors in this condition. Given a general decline in cholinergic function with aging, it is not surprising that cholinergic blockers, such as scopolamine, have greater effects on memory and cognition in older than young adults, which is why anticholinergic medicines should be avoided in older individuals.

Recent work, driven largely by the functional imaging literature, has suggested that the parietal lobes also participate in episodic memory retrieval. Studies have consistently revealed

midline and lateral parietal activations associated with successful retrieval of memories.²⁶ While midline structures, including retrosplenial cortex, have been implicated in episodic memory, prior work had not suggested a role for the lateral parietal cortex. A recent focus on episodic memory in patients with lateral parietal lesions has revealed, perhaps, subtle deficits in this population. While these patients appear to retrieve contextual details of prior episodes to a similar extent as controls, they seem to have greater difficulty doing so spontaneously and their memories may be associated with less confidence or vivid-

ness.^{27,28} A number of potential hypotheses have been postulated as to the function of the parietal cortex in episodic memory and are just now beginning to be tested experimentally.²⁶

SEMANTIC MEMORY

Definitions

The patient in **Case 1-2** had a relatively selective impairment of semantic memory. Semantic memory defines our knowledge of the world, including general information about objects, people, historical events, and word meaning.³ Examples of semantic knowledge

KEY POINT

- Semantic memory is memory for knowledge of the world when it is unconnected with a specific episode of one's life.

Case 1-2

A 73-year-old man had several years of cognitive decline. Most salient to him was difficulty naming and even recognizing a variety of items that used to be familiar to him. For example, his wife bought a bag of microwave popcorn that he examined at great length, eventually asking his wife what it was used for. On the way to one of his clinic visits he saw a cement truck and commented that he had never seen such an unusual truck before. He described marked difficulty in being able to name or even recognize close friends—they did not look familiar to him. Despite these issues, he had minimal functional decline and scored 24/30 on the Mini-Mental State Examination. His wife described his day-to-day memory as essentially unchanged. He spoke fluently on examination and had reasonable comprehension of simple words. He had marked naming impairment on the Boston Naming Test (14/30 correct), and he could name only three vegetables in 1 minute. He performed average to above average on tests of executive function, attention, and visuospatial memory. An MRI scan revealed severe bilateral anterior and inferior-lateral temporal lobe atrophy. This patient was felt to have the early stages of semantic variant of primary progressive aphasia. Note the significant atrophy in the anterior, inferior, and lateral temporal lobe on an MRI scan (**Figure 1-4**).

Comment. This patient had a relatively selective deficit of semantic memory, but essentially spared episodic memory function. This case further illustrates the dissociation of these two memory systems.

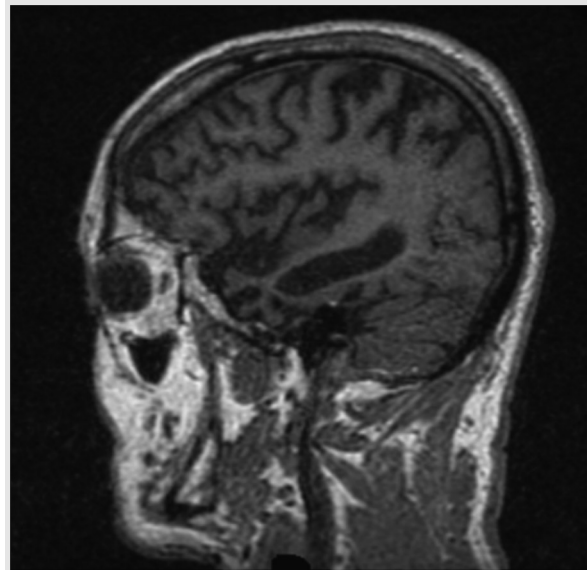


FIGURE 1-4 MRI sagittal T1-weighted image. Note the severe temporal lobe atrophy, which includes anterior, inferior, and lateral regions, relative to the rest of the brain.

KEY POINTS

- Previously learned semantic information will be intact when a patient experiences an isolated loss of episodic memory.
- The inferolateral temporal lobes (particularly the left) are critical for semantic memory.

are tigers have stripes and *Philadelphia is the largest city in Pennsylvania*. This form of declarative memory can be differentiated from episodic memory because its retrieval is not associated with a sense of self-experience or linked to a particular spatial and temporal context. For example, remembering watching President Barack Obama’s inauguration speech on television with one’s wife is an example of an episodic memory while knowing that he is president is a semantic one. That episodic and semantic memory represent different memory systems is supported by the dissociations in impairment associated with different brain lesions. For example, the patient HM, who had bilateral MTL resections, displayed profound amnesia with relative sparing of previously learned semantic information.

Semantic memory impairment is most frequently manifested by naming deficits. This impaired naming is not mitigated by the use of phonemic cues, and often naming errors reflect semantically related word choices (eg, *dog* for *lion*). Different from a pure anomia, however, these patients will also display evidence of nonverbal impairment, such as matching pictures of items into different semantic categories, and difficulty in providing definitions or descriptions of items when provided with their names. Category fluency, in which patients are asked to name as many items as they can think of in a particular semantic category (eg, animals), is another bedside test that is often impaired in those with semantic memory dysfunction.

Functional Neuroanatomy of Semantic Memory

While semantic memory is likely represented in a distributed fashion throughout much of the neocortex, the inferolateral temporal lobes (particularly the left) are the brain regions whose injury is most associated with disruption of semantic knowledge. Indeed, semantic variant of primary progressive aphasia, the archetypal disease producing a relative pure semantic knowledge impairment, is associated with relatively focal neurodegeneration in this region (**Figure 1-5**).

Rare instances of category-specific semantic deficits have provided additional insight into the neural organization of semantic memory. The literature describes a number of patients with relatively selective impairment of knowledge of living things (eg, animals and vegetables) but preserved knowledge of artifacts, such as tools.²⁹ The opposite dissociation has also been described, strengthening the functional segregation of these forms of semantic memory. Work has suggested that these dissociated representations may be a reflection of the nature by which

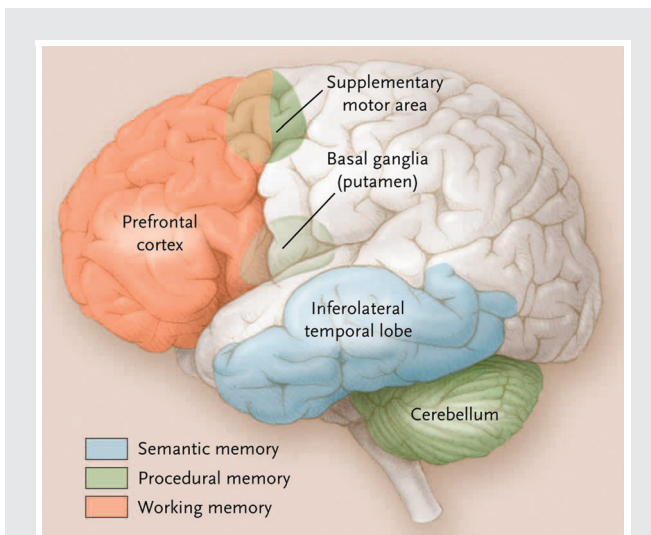


FIGURE 1-5 Semantic, procedural, and working memory. The anterior and inferolateral temporal lobes are important in the naming and categorization tasks by which semantic memory is typically assessed. However, in the broadest sense, semantic memory may reside in multiple and diverse cortical areas that 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.

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one experiences these different categories.³⁰ For example, our knowledge of animals usually is largely related to the visual modality, while our experience with tools is more related to motor representations.

Semantic memory deficits are most commonly seen in patients with AD and are likely a reflection of the pathology in inferolateral temporal neocortex. Of course, AD is also associated with significant episodic memory impairment, which often dominates the initial clinical picture. Other conditions associated with semantic memory impairment include semantic variant of primary progressive aphasia, herpes encephalitis, trauma, and occasionally stroke.

Overlap Between Semantic and Episodic Memory

Despite being considered separate memory systems, semantic and episodic memory interact in important ways. For example, work from the cognitive psychology and functional imaging literature supports the benefit of semantic encoding on subsequent episodic memory of studied items.^{31,32} Further, semantic deficits themselves sometimes correlate with performance on episodic memory tasks, presumably by reducing the effectiveness of the encoding process.³³

The episodic memory system is also critical for the formation of new semantic memories, as evidenced by the profound impact of MTL lesions on such new semantic memory formation. While factlike learning in patients with severe bilateral medial temporal injury has been reported, this appears largely relegated to fragmented information likely supported by perceptual learning rather than true pieces of new semantic information.³⁴ Even relatively limited hippocampal lesions can seriously degrade the acquisition of new semantic knowledge.

Autobiographic memories are another area in which episodic and seman-

tic memories overlap. These memories of our own personal experiences are generally conceived as a type of episodic memory. More remote autobiographic memories, however, often become qualitatively more akin to semantic knowledge and are likely supported, in part, by the semantic memory system. One simple test is that if, when recalling a memory, you can see yourself in it, the memory is likely semantic rather than episodic, since you would not ordinarily see yourself in a memory.

PROCEDURAL MEMORY

Definitions

Procedural memory is the nondeclarative memory system that refers to the ability to learn cognitive and behavioral skills and algorithms that operate at an automatic, unconscious level. Examples include learning to ride a bicycle or play the piano. 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 MTLs), it is clear that the procedural memory system is separate and distinct from the episodic memory system.³⁵

Functional Neuroanatomy of Procedural Memory

Patients with damage to the basal ganglia or cerebellum show impairment in learning procedural skills.³⁶ Functional neuroimaging has found that these regions—and the supplementary motor area—become active as a new procedural memory task is being learned³⁷ (**Figure 1-5**). Because the basal ganglia, cerebellum, and supplementary motor area are relatively spared in early AD, these patients show normal acquisition and maintenance of their procedural memory skills, despite their episodic and semantic memory deficits.³⁸

Patients in the early stages of Parkinson disease show impaired procedural

KEY POINTS

- Because Alzheimer disease affects the inferolateral temporal lobes, it is the most common cause of semantic memory impairment. Semantic variant of primary progressive aphasia, encephalitis, trauma, and stroke are other causes of semantic memory impairment.
- Procedural memory is memory for cognitive and behavioral skills and algorithms that are typically operating unconsciously—such as riding a bicycle.
- Critical brain regions for procedural memory are the basal ganglia, cerebellum, and supplementary motor area.

KEY POINT

- Parkinson disease is the most common disorder disrupting procedural memory. Huntington disease, tumors, strokes, and hemorrhages may also disrupt procedural memory.

memory while performing nearly normally on episodic memory tests.³⁸ Procedural memory is also disrupted by other causes of damage to the basal ganglia or cerebellum, including Huntington disease, olivopontocerebellar degeneration, tumors, strokes, and hemorrhages. Patients with major depression may also show impairment in procedural memory tasks, perhaps because depression involves dysfunction of the basal ganglia.³⁹

Disruption of procedural memory should be suspected when patients show evidence of either the loss of previously learned skills (compared with their baseline) or substantial difficulties in learning new skills. For example, patients may lose the ability to perform automatic, skilled movements, such as writing, playing a musical instrument, or swinging a tennis racket. 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. 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.⁴⁰

CONCLUSIONS

Evidence from patient studies and more recent neuroimaging research suggest that memory is composed of separate and distinct systems. An understanding of these different memory systems will aid the clinician in the diagnosis and treatment of the memory disorders of their patients.

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