REVIEW ARTICLE

CURRENT CONCEPTS

Memory Dysfunction

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Memory function is vulnerable to a variety of pathologic processes including neurodegenerative diseases, strokes, tumors, head trauma, hypoxia, cardiac surgery, malnutrition, attention-deficit disorder, depression, anxiety, the side effects of medication, and normal aging.[1,2] As such, memory impairment is commonly seen by physicians in multiple disciplines including neurology, psychiatry, medicine, and surgery. Memory loss is often the most disabling feature of many disorders, impairing the normal daily activities of the patients and profoundly affecting their families.

Some perceptions about memory, such as the concepts of "short-term" and "long-term," have given way to a more refined understanding and improved classification systems. These changes result from neuropsychological studies of patients with focal brain lesions, neuroanatomical studies in humans and animals, experiments in animals, positron-emission tomography, functional magnetic resonance imaging, and event-related potentials.

Memory is now understood to be a collection of mental abilities that depend on several systems within the brain. In this article, we will discuss the following four memory systems that are of clinical relevance: episodic memory, semantic memory, procedural memory, and working memory (Table 1). We will summarize the current understanding of memory from the point of view of functional neuroimaging and studies of patients with brain insults, which should aid clinicians in the diagnosis and treatment of the memory disorders of their patients. As therapeutic interventions for memory disorders become available, clinicians will increasingly need to be aware of the various memory systems in the brain.

A memory system is a way for the brain to process information that will be available for use at a later time.[3] Different memory systems depend on different neuroanatomical structures (Fig. 1 and 2). Some systems are associated with conscious awareness (explicit) and can be consciously recalled (declarative),[4] whereas others are expressed by a change in behavior (implicit) and are typically unconscious (nondeclarative). Memory can also be categorized in many other ways, such as by the nature of the material to be remembered (e.g., verbal[5,6] or visuospatial[5,7]).

Episodic Memory

Episodic memory refers to the explicit and declarative memory system used to recall personal experiences framed in our own context, such as a short story or what you had for dinner last night. Episodic memory has largely been defined according to the inability of people with amnesia due to lesions of the medial temporal lobe to remember experiences that healthy people can remember. Thus, this memory system depends on the medial temporal lobes (including the hippocampus and the entorhinal and perirhinal cortexes). Other critical structures in the episodic memory system (some of which are

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Table 1. Selected Memory Systems.

Memory System	Major Anatomical Structures Involved	Length of Storage of Memory	Type of Awareness	Examples
Episodic memory	Medial temporal lobes, anterior thalamic nucleus, mammillary body, fornix, prefrontal cortex	Minutes to years	Explicit, declarative	Remembering a short story, what you had for dinner last night, and what you did on your last birthday
Semantic memory	Inferolateral temporal lobes	Minutes to years	Explicit, declarative	Knowing who was the first president of the United States, the color of a lion, and how a fork differs from a comb
Procedural memory	Basal ganglia, cerebellum, supplementary motor area	Minutes to years	Explicit or implicit, nondeclarative	Driving a car with a standard transmission (explicit) and learning the sequence of numbers on a touch-tone phone without trying (implicit)
Working memory	Phonologic: prefrontal cortex, Broca's area, Wernicke's area Spatial: prefrontal cortex, visual-association areas	Seconds to minutes; information actively rehearsed or manipulated	Explicit, declarative	Phonologic: keeping a phone number "in your head" before dialing Spatial: mentally following a route or rotating an object in your mind

associated with a circuit described by Papez in 1937[8]) include the basal forebrain with the medial septum and diagonal band of Broca's area, the retrosplenial cortex, the presubiculum, the fornix, mammillary bodies, the mammillothalamic tract, and the anterior nucleus of the thalamus.[2] A lesion in any one of these structures may cause the impairment that is characteristic of dysfunction of the episodic memory system (Fig. 1).

Memory loss attributable to dysfunction of the episodic memory system follows a predictable pattern known as Ribot's law, which states that events just before an ictus are most vulnerable to dissolution, whereas remote memories are most resistant. Thus, in cases of dysfunction of the episodic memory system, the ability to learn new information is impaired (anterograde amnesia), recently learned information cannot be retrieved (retrograde amnesia), and remotely learned information is usually spared.[9]

Studies have shown that the episodic memory system includes the frontal lobes.[5,10] Rather than being responsible for the retention of information, the frontal lobes are involved in the registration, acquisition, or encoding of information[6]; the retrieval of information without contextual and other cues[11]; the recollection of the source of information[12]; and the assessment of the temporal sequence and recency of events.[13] Studies have also shown that the left medial temporal and left frontal lobes are most active when a person is learning words,[6] whereas the right medial temporal and right frontal lobes are most active when learning visual scenes.[7]

One reason that the frontal lobes are important for encoding is that they permit the person to focus on the information to be remembered and to engage the medial temporal lobes. Dysfunction of the frontal lobes may cause distortions of episodic memory as well as false memories, such as information that is associated with the wrong context[14] or with incorrect specific details.[15] Extreme examples of memory distortions include confabulation, which occurs when "memories" are created to be consistent with current information,[14] such as "remembering" that someone broke into the house and rearranged household items.

These differences between deficits in episodic memory that occur because of damage to the medial temporal lobes (and the Papez circuit) and those that occur because of damage to the frontal lobes can be conceptualized in an oversimplified but clinically useful analogy.[16] 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." Thus, if the frontal lobes are impaired, it is difficult — but not impossible — to get information in and out of storage. However, the information may be distorted owing to "improper filing" that leads to an inaccurate source, context, or sequence. If, however, the medial temporal lobes are rendered completely dysfunc-

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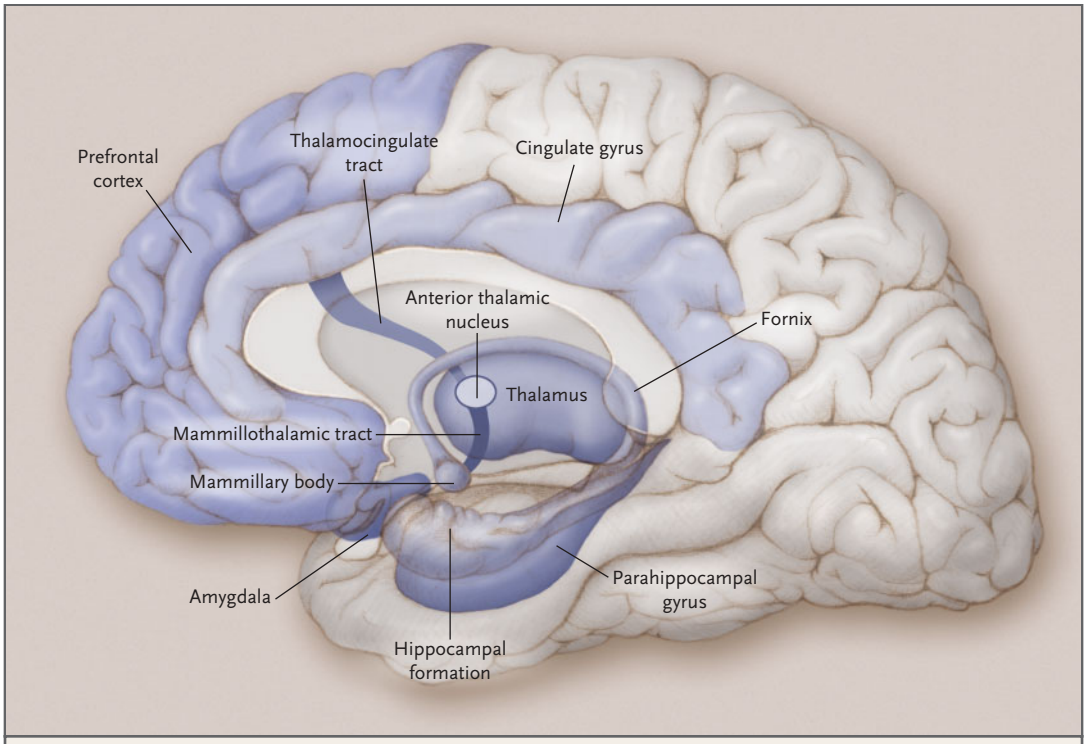

Figure 1. Episodic Memory.

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.

tional, it will be impossible for recent information to be retained. Older information that has been consolidated over a period of months or years is thought to be stored in other cortical regions and will therefore be available even when medial temporal lobes and the Papez circuit are damaged. For example, although patients with depression and those with Alzheimer's disease may exhibit episodic memory dysfunction, the former have a dysfunctional "file clerk" and the latter have a dysfunctional "recent memory file cabinet."

Disorders of episodic memory may be transient, such as those attributable to a concussion, a seizure, or transient global amnesia. Static disorders, such as traumatic brain injury, hypoxic or ischemic injury, single strokes, surgical lesions, and encephalitis, typically are maximal at onset (or for several days), improve (sometimes over periods of two years or more), and then are stable. Degenerative diseases, including Alzheimer's disease,[17] dementia with Lewy bodies, and frontotemporal dementia, begin insidiously and progress gradually. Disorders affecting multiple brain regions, such as vascular dementia and multiple sclerosis, progress in a stepwise manner. Other disorders of memory, such as those due to medications, hypoglycemia, tumors, and Korsakoff's syndrome, can have a more complicated and variable time course.

Once a disorder of episodic memory is suspected on the basis of a reported inability to remember recent information and experiences accurately, additional evaluation is warranted. A detailed history should be taken, with particular emphasis on the time course of the memory disorder. Interviewing a caregiver or other informant is usually critical for accuracy, since the patient will invariably not remember important aspects of the history. A history of other cognitive deficits (e.g., attention, language, visuospatial, and executive) should be elicited. A medical and neurologic examination should be performed, with a focus on searching for signs of systemic illness, focal neurologic injury, and neurodegenerative disorders.

Cursory cognitive testing may be performed by asking the patient to remember a short story or several words, or with the use of instruments such as

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the Mini–Mental State Examination,[18] the Blessed Dementia Scale,[19] the Three Words–Three Shapes memory test,[2] the word-list memory test of the Consortium to Establish a Registry for Alzheimer's Disease,[20] the Drilled Word Span Test,[2] and the Seven-Minute Screen.[21] In complex cases, a formal neuropsychological evaluation should be considered.

To aid in distinguishing disorders of episodic memory that are attributable to dysfunction of the frontal lobes from those attributable to dysfunction of the medial temporal lobes, difficulties in the encoding and retrieval of information should be contrasted with primary failure of storage. When information cannot be remembered even after encoding has been maximized by multiple rehearsals, and after retrieval demands have been minimized with the use of a multiple-choice recognition test, a primary failure of storage is present. (See the Supplementary Appendix, available with the full text of this article at www.nejm.org, for suggestions on how to use these tests in clinical practice.)

Laboratory and imaging studies will usually be indicated, according to the differential diagnosis. Treatment depends on the specific disorder. Cholinesterase inhibitors[22] and memantine[23] have been approved by the Food and Drug Administration (FDA) to treat Alzheimer's disease; the former have also been used to treat vascular dementia[24] and dementia with Lewy bodies.[25] Two recent reviews discuss the effectiveness of these treatments.[26,27]

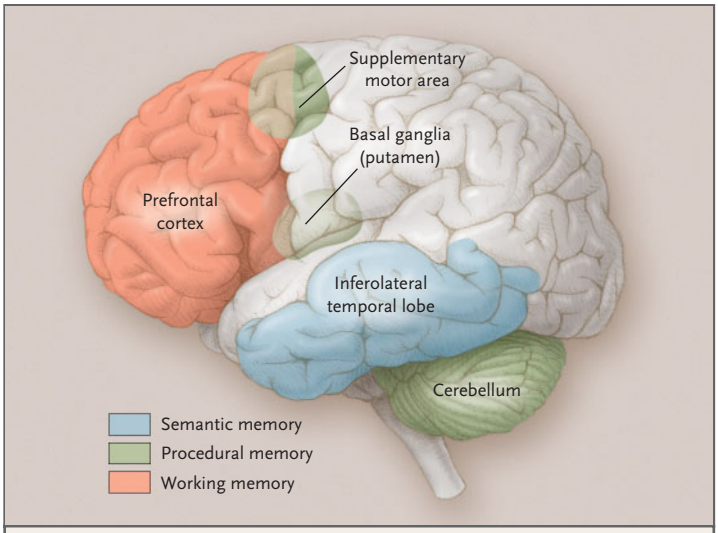

Figure 2. Semantic, Procedural, and Working Memories.

The 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.

SEMANTIC MEMORY

Semantic memory refers to our general store of conceptual and factual knowledge, such as the color of a lion or the first president of the United States, that is not related to any specific memory. Like episodic memory, semantic memory is a declarative and explicit memory system. Evidence that this memory system is different from episodic memory emerges from neuroimaging studies[28] 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 the Papez circuit (e.g., in Korsakoff's syndrome) or surgical removal of the medial temporal lobes.[29]

Since in its broadest sense semantic memory includes all our knowledge of the world not related to specific episodic memories, one could argue that it resides in multiple cortical areas. There is evidence, for example, that visual images are stored in nearby visual-association areas.[30] However, a more restrictive view of semantic memory, one that is justified in light of the naming and categorization tasks by which it is usually measured, localizes semantic memory to the inferolateral temporal lobes (Fig. 2).[31,32]

Alzheimer's disease is the most common clinical disorder disrupting semantic memory. This disruption may be attributable to pathology in the inferolateral temporal lobes[33] or to pathology in frontal cortexes,[34] leading to poor activation and retrieval of semantic information.[35] In Alzheimer's disease, episodic and semantic memory decline independently of each other, supporting the idea that two separate memory systems are impaired in this disorder.[36]

Other causes of the impairment of semantic memory include almost any disorder that may disrupt the inferolateral temporal lobes, such as traumatic brain injury, stroke, surgical lesions, encephalitis, and tumors (Table 2). Patients with the temporal variant of frontotemporal dementia, known as semantic dementia, also exhibit deficits in all functions of semantic memory, including

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Table 2. Four Memory Systems and Common Clinical Disorders That Disrupt Them.*

Episodic memory
Alzheimer's disease
Mild cognitive impairment, amnestic type
Dementia with Lewy bodies
Encephalitis (most commonly, herpes simplex encephalitis)
Frontal variant of frontotemporal dementia
Korsakoff's syndrome
Transient global amnesia
Concussion
Traumatic brain injury
Seizure
Hypoxic–ischemic injury
Cardiopulmonary bypass
Side effects of medication
Deficiency of vitamin B_{12}
Hypoglycemia
Anxiety
Temporal-lobe surgery
Vascular dementia
Multiple sclerosis
Semantic memory
Alzheimer's disease
Semantic dementia (temporal variant of frontotemporal dementia)
Traumatic brain injury
Encephalitis (most commonly, herpes simplex encephalitis)
Procedural memory
Parkinsons's disease
Huntington's disease
Progressive supranuclear palsy
Olivopontocerebellar degeneration
Depression
Obsessive–compulsive disorder
Working memory
Normal aging
Vascular dementia
Frontal variant of frontotemporal dementia
Alzheimer's disease
Dementia with Lewy bodies
Multiple sclerosis
Traumatic brain injury
Side effects of medication
Attention deficit–hyperactivity disorder
Obsessive–compulsive disorder
Schizophrenia
Parkinson's disease
Huntington's disease
Progressive supranuclear palsy
Cardiopulmonary bypass
Deficiency of vitamin B_{12}

* Tumors, strokes, hemorrhages, and other focal disease processes may affect these memory systems, depending on the neuroanatomical structures disrupted.

naming and single-word comprehension and impoverished general knowledge. They show relative preservation of other components of speech, perceptual and nonverbal problem-solving skills, and episodic memory.[37]

Disorders of semantic memory should be suspected when patients have difficulty naming items whose names they previously knew. The evaluation for disorders of semantic memory should include the same components as the evaluation used for disorders of episodic memory. The history and cognitive examination should ascertain whether the problem is solely attributable to a difficulty in recalling people's names and other proper nouns, which is common, particularly 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 for semantic categories (e.g., the number of names of animals that can be generated in one minute), whereas patients with a more severe impairment of semantic memory typically show a two-way naming deficit (i.e., they are unable to name an item when it is described and are also unable to describe an item when they are given its name). These more severely affected patients also show impoverished general knowledge. Treatment depends on the specific disorder.

PROCEDURAL MEMORY

Procedural memory refers to the ability to learn behavioral and cognitive skills and algorithms that are used at an automatic, unconscious level. Procedural memory is nondeclarative but during acquisition may be either explicit (such as learning to drive a car with a standard transmission) or implicit (such as learning the sequence of numbers on a touch-tone phone without conscious effort). That procedural memory can be spared in patients who have severe deficits of the episodic-memory system, such as patients with Korsakoff's syndrome or Alzheimer's disease or who have undergone surgical removal of the medial temporal lobes,[29,38] demonstrates that procedural memory depends on a memory system that is separate and distinct from the episodic memory and semantic memory systems.

Research with the use of functional imaging has shown that brain regions involved in procedural memory, including the supplementary motor area, basal ganglia, and cerebellum, become active as a new task is being learned (Fig. 2).[39] Corroborating evidence comes from studies of patients with le-

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sions in the basal ganglia or cerebellum who show impairment in learning procedural skills.[40] Because the disease process in early Alzheimer's disease affects cortical and limbic structures while sparing the basal ganglia and cerebellum, these patients show deficits in episodic memory but normal acquisition and maintenance of procedural skills.

Parkinson's disease is the most common disorder affecting procedural memory. Other neurodegenerative diseases that disrupt procedural memory include Huntington's disease and olivopontocerebellar degeneration. Patients in the early stages of these disorders perform nearly normally on episodic memory tests but show an impaired ability to learn skills.[38,41] Tumors, strokes, hemorrhages, and other causes of damage to the basal ganglia or cerebellum may also disrupt procedural memory. Patients with major depression have also been shown to have impairment in procedural memory, perhaps because depression may involve dysfunction of the basal ganglia (Table 2).[42]

Disruption of procedural memory should be suspected when patients show evidence of either the loss of previously learned skills or substantial impairment 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 golf club. Although they may be able to relearn the fundamentals of these skills, explicit thinking is often required for their performance. As a result, patients with damage to the procedural memory system may never achieve the automatic effortlessness of simple motor tasks that healthy people take for granted.

Evaluation of disorders of procedural memory is similar to that of disorders of episodic memory; treatment of the underlying cause depends on the specific disease process. It is worth noting that patients whose episodic memory has been devastated by encephalitis, for example, have had success in rehabilitation by using the procedural memory system to learn new skills.[43]

WORKING MEMORY

Working memory is a combination of the traditional fields of attention, concentration, and short-term memory. It refers to the ability to temporarily maintain and manipulate information that one needs to keep in mind. Because it requires active and conscious participation, working memory is an explicit and declarative memory system. Working memory has traditionally been divided into components that process phonologic information (e.g., keeping a phone number "in your head") or spatial information (e.g., mentally following a route) and an executive system that allocates attentional resources.[44]

Numerous studies have shown that working memory uses a network of cortical and subcortical areas, depending on the particular task.[45] However, virtually all tasks involving working memory require participation of the prefrontal cortex (Fig. 2).[5] Typically, the network of cortical and subcortical areas includes posterior brain regions (e.g., visual-association areas) that are linked with prefrontal regions to form a circuit. Studies have shown that phonologic working memory tends to involve more regions on the left side of the brain, whereas spatial working memory tends to involve more regions on the right side.[5] Studies have also shown that more difficult tasks involving working memory require bilateral brain activation, regardless of the nature of the material being manipulated.[46] Furthermore, there is an increase in the number of activated brain regions in the prefrontal cortex as the complexity of the task increases.[47]

Because working memory depends on a network of activity that includes subcortical structures as well as frontal and parietal cortical regions, many neurodegenerative diseases impair working-memory tasks. Studies have shown that patients with Alzheimer's, Parkinson's, or Huntington's disease or dementia with Lewy bodies, as well as less common disorders such as progressive supranuclear palsy, may show impaired working memory (Table 2).[48,49] In addition to 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 strokes, tumors, head injury, and multiple sclerosis, among others.[50,51] Because phonologic working memory involves the silent rehearsal of verbal information, almost any kind of aphasia can also impair it. Although the pathophysiology is not well understood, disorders that diminish attentional resources, such as attention deficit–hyperactivity disorder, obsessive–compulsive disorder, schizophrenia, and depression, can also impair working memory.[52-54]

A disorder of working memory can present in several ways. Most commonly, the patient will show an inability to concentrate or pay attention. Difficulty performing a new task involving multistep instructions may be seen. A disorder of working mem-

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ory may also present as a problem with episodic memory. In such cases, the evaluation will show a primary failure of encoding, because in order to transfer information into episodic memory, the information must first be "kept in mind" by working memory.[5]

Evaluation of working memory is similar to that of disorders of episodic memory. Treatment depends on the specific cause; for instance, stimulants have been approved by the FDA to treat attention deficit–hyperactivity disorder.[55,56]

CONCLUSION

Traditionally, memory has been viewed as a simple concept. In fact, the use of various methods has produced converging and complementary lines of evidence, suggesting that memory is composed of separate and distinct systems. A single disease process (such as Alzheimer's disease) may impair more than one memory system. Improved understanding of the types of memory will aid clinicians in the diagnosis and treatment of their patients' memory disorders. This knowledge will become increasingly important as more specific strategies emerge for the treatment of memory dysfunction.

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