HOW TO UNDERSTAND IT

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Memory dysfunction in neurological practice

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Complaints of impaired memory are among the most common symptoms reported to neurologists. Moreover, impairment of memory is one of the most disabling aspects of many neurological disorders, including neurodegenerative diseases, strokes, tumours, head trauma, hypoxia, cardiac surgery, malnutrition, attention deficit disorder, depression, anxiety, medication adverse effects, and just normal aging. This memory loss often impairs the patient's daily activities, profoundly affecting not just them but also their families.

Memory research that began with neuropsychological studies of patients with focal brain lesions now includes new methods such as positron emission tomography, functional MRI, and event-related potentials which have all provided a more refined and improved classification system. Instead of conceptualising memory as "short-term" versus "long-term", we now think of memory as a collection of mental abilities that use different systems within the brain. A memory system is a way that the brain processes information in order to make it available for use at a later time. Some systems are associated with conscious awareness (*explicit*) and can be consciously recalled (*declarative*), whereas others are typically unconscious (*non-declarative*) and are instead expressed by a change in behaviour (*implicit*).

Episodic memory is the explicit and declarative memory system that we all use to recall our personal experience

Here we will describe the four systems that are of clinical relevance: episodic memory, semantic memory, procedural memory, and working memory (table 1). Additional details may be found in Budson and Price[1] and the other references listed below.[2–6]

TABLE 1 Selected memory systems

Memory System	Examples	Awareness	Length of storage	Main anatomical structures
Episodic memory	Remembering a short story, what you had for dinner last night, and what you did on your last birthday	Explicit	Minutes to years	Medial temporal lobes, anterior thalamic nucleus, mamillary body, fornix, prefrontal cortex
Semantic memory	Knowing who was the first President of the US, the colour of a lion, and how a fork and comb are different	Declarative Explicit	Minutes to years	Inferior lateral temporal lobes
Procedural memory	Driving a standard transmission car (explicit), and learning the sequence of numbers on a touch-tone phone without trying (implicit)	Declarative Implicit	Minutes to years	Basal ganglia, cerebellum, supplementary motor area
Working memory	Phonological: keeping a phone number "in your head" before dialing Spatial: mentally following a route, or rotating an object in your mind	Non-declarative Explicit Declarative	Seconds to minutes; information actively rehearsed or manipulated	Phonological: prefrontal cortex, Broca's area, Wernike's area Spatial: prefrontal cortex, visual association areas

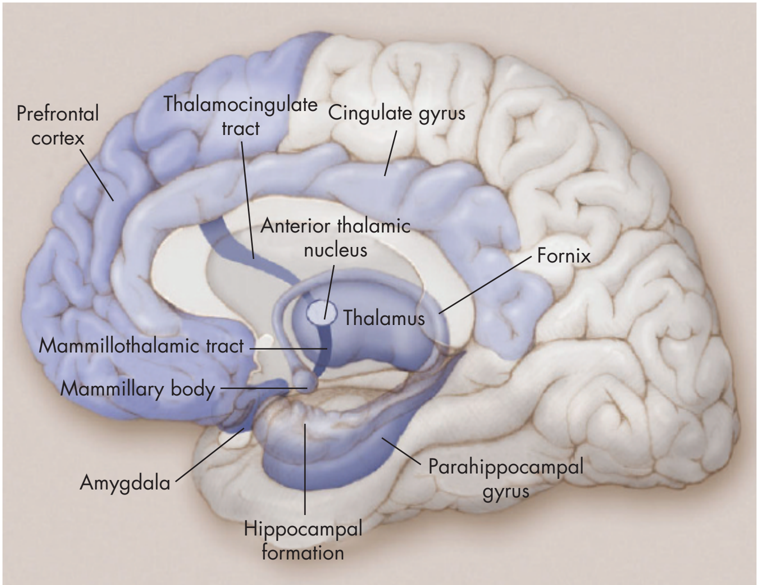

Figure 1
Episodic memory. The medial temporal lobes, including the hippocampus and parahippocampus, form the core of the episodic memory system. Other brain regions are also necessary for episodic memory to function correctly. (From Budson AE, Price BH. Memory dysfunction. *N Engl J Med* 2005;**352**:692–9. Copyright Massachusetts Medical Society. All rights reserved.)

EPISODIC MEMORY

Episodic memory is the explicit and declarative memory system that we all use to recall our personal experience, framed in our own context, such as remembering a short story or what we had for dinner last night. Episodic memory loss follows a predictable pattern known as Ribot's law: recently acquired memories are more vulnerable to loss than longer established ones. This memory system depends on the medial temporal lobes (including the hippocampus, entorhinal and perirhinal cortex). Other critical structures (some of which are associated with a circuit described by Papez in 1937) include the basal forebrain with the medial septum and the diagonal band of Broca's area, the retrosplenial cortex, the mammillothalamic tract, and the anterior nucleus of the thalamus. A lesion in any one of these structures may cause the impairment that is characteristic of dysfunction of the episodic memory system (fig 1).

The frontal lobes are also important for certain aspects of episodic memory, including the registration, acquisition, or encoding (learning) of information, retrieval of information without contextual and other cues, recalling the source of information, and assessing the temporal sequence and recency of events. The left medial temporal and frontal lobes are most involved when learning words, whereas the right medial temporal and frontal lobes are most involved when learning visual scenes. Distortions of memories, and false memories, may occur due to frontal lobe dysfunction, such as when information becomes associated with the wrong context, or specific details are incorrect.

One way to think about how the frontal and medial temporal lobes work together is by an oversimplified but useful analogy:

- the frontal lobes are the "file clerks" of the episodic memory system
- the medial temporal lobes are the "recent memory file cabinet"
- other cortical regions are the "remote memory file cabinet".

So if the frontal lobes are impaired, it is difficult, though not impossible, to get information in and out of storage. And the information may be distorted due to "improper filing" leading to inaccurate context or sequence. If the medial temporal lobes are damaged, it will be difficult or impossible for recent information to be retained. Older information that has been "consolidated" over months to years is thought to be stored in other cortical regions, and will therefore be available even when the medial temporal lobes are damaged.

Alzheimer's disease is the most common disorder that disrupts episodic memory. Recent research suggests that these patients suffer from memory distortions and false memories in addition to their failure to remember information. Other common disorders that disrupt episodic memory are listed in table 2.

If a patient presents with an inability to remember recent information and experiences, a disorder of episodic memory should be suspected. The evaluation should include a detailed history, with emphasis on the time course of the memory disorder. For example:

- degenerative diseases such as Alzheimer's start insidiously and progressively worsen
- vascular dementia and other multifocal disorders such as multiple sclerosis tend to start suddenly and progress in a stepwise manner
- static disorders such as strokes and traumatic brain injuries are typically maximal at onset, improve, and are then stable
- transient disorders of episodic memory include those attributable to a concussion, a seizure, and transient global amnesia.

Interviewing a family member or other informant is usually necessary because the patient will invariably not remember important aspects of their history. Any history of other cognitive deficits should also be elicited, such as attention, language, and visuospatial skills. Medical and neurological examination should be performed to look for signs of neurodegenerative disorders, focal neurological injury, and systemic illness.

There are many cognitive tests that can be used to assess a patient's episodic memory function. But the relationships between a patient's cognitive functions, test performance, and their "real life" activities are often complex. Test performance is rarely pathognomonic of a specific disorder. And no single test is capable of evaluating all aspects of memory. Factors confounding test interpretation include aphasia, dyslexia, low intellectual function, alterations in mood and motivation, confusion or delirium, psychosis, and medication adverse effects. Cognitive testing can be performed in the office by asking the patient to remember a short story or several words, or by using tests such as the Mini-Mental State Examination, Blessed Dementia Scale, and others.[1] The accompanying supplementary appendix available at http://www.nejm.org or http://www.thebrainlab.org provides additional guidance about how to use such tests in clinical practice. Formal neuropsychological testing is necessary in complex cases. Depending on the differential diagnosis, appropriate laboratory and imaging studies are then carried out.

TABLE 2 Four memory systems and the common clinical disorders which disrupt them

Disease	Episodic memory	Semantic memory	Procedural memory	Working memory
Alzheimer's disease	+++	++	–	++
Frontotemporal dementia	++	++	–	+++
Semantic dementia	+	+++	?	–
Lewy body dementia	++	?	?	++
Stroke and vascular dementia	+	+	+	++
Parkinson's disease	+	+	+++	++
Huntington's disease	+	+	+++	+++
Progressive supranuclear palsy	+	+	++	+++
Korsakoff syndrome	+++	–	–	±
Multiple sclerosis	+	±	?	++
Transient global amnesia	+++	±	–	–
Hypoxic–ischaemic injury	++	–	–	±
Head trauma	+	+	±	++
Tumours	±	±	±	±
Depression	+	±	++	±
Anxiety	+	–	–	±
Obsessive-compulsive disorder	+	–	++	++
Attention deficit hyperactivity disorder	–	–	?	+

+++, Early and severe impairment; ++, moderate impairment; +, mild impairment; ±, occasional impairment or impairment in some studies but not others; –, no significant impairment; ?, unknown.
Tumours, strokes and other focal disease processes may affect any of these memory systems depending on the neuroanatomical structures affected.

SEMANTIC MEMORY

Semantic memory is the explicit and declarative memory system that underpins our general store of conceptual and factual knowledge such as the colour of a lion, or the first President of the United States. It is not related to any "specific" memory. Indeed, in its broadest sense, semantic memory includes all our knowledge that is not related to a specific episodic memory, and thus can be kept in many cortical areas. Visual images, for example, are stored in or nearby visual association areas. A more restrictive view of semantic memory, justified in the light of the naming and categorisation tasks by which it is usually measured, suggests that it depends on the inferolateral temporal lobes (fig 2).

Alzheimer's disease is the most common disorder affecting semantic memory, as it is for episodic memory. This disruption may be attributable to pathology in the inferolateral temporal lobes or to pathology in frontal cortex, leading to poor activation and retrieval of semantic information. Supporting the idea that two separate memory systems are impaired in this disorder, episodic and semantic memory decline independently in Alzheimer's disease; one system may be affected first and decline faster than the

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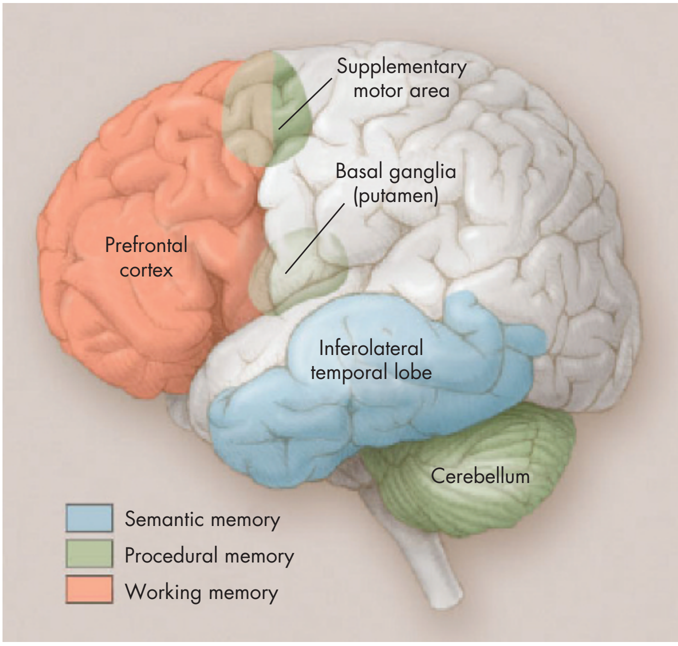

Figure 2
Semantic, procedural, and working memories. The inferolateral temporal lobes are important in the naming and categorisation tasks by which semantic memory is typically assessed. However, in the broadest sense, semantic memory may reside in multiple and diverse cortical areas that are related 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. (From Budson AE, Price BH. Memory dysfunction. *N Engl J Med* 2005;**352**:692–9. Copyright Massachusetts Medical Society. All rights reserved.)

other. Patients with the temporal variant of frontotemporal dementia (known as semantic dementia) have deficits in all aspects of semantic memory. Although articulation, non-verbal problem-solving skills, and episodic memory are relatively preserved, most aspects of language are impaired: semantic dementia patients have extreme difficulty naming, comprehending single words, and their general knowledge is impaired. Other common disorders that disrupt semantic memory include almost any pathology that affects the inferolateral temporal lobes, such as traumatic brain injury, stroke, surgical lesions, encephalitis, and tumours (table 2).

Although difficulty recalling people's names and other proper nouns is common (particularly for older people), impairment of semantic memory should be suspected when a patient also has difficulty recalling the names of common items. An evaluation for semantic memory impairment should include the same components as the evaluation of episodic memory disorders, as above. It is important to distinguish whether the problem is solely attributable to naming difficulties (anomia), or is attributable to a true loss of semantic information. For example, patients with mild dysfunction of semantic memory may only show reduced generation of words to semantic categories, such as the number of names of animals that can be generated in one minute. With severe impairment of semantic memory, however, patients have a "two-way" naming deficit: they are unable to name an item when it is described, and they are also unable to describe an item when given its name.

Procedural memory is the ability to learn behavioural and cognitive skills and algorithms that operate at an automatic, unconscious level

PROCEDURAL MEMORY

Procedural memory is the ability to learn behavioural and cognitive skills and algorithms that operate at an automatic, unconscious level. Procedural memory is non-declarative and generally implicit, such as learning to ride a bike or the sequence of numbers on a touch-tone phone without trying. Brain regions involved in procedural memory include the supplementary motor area, basal ganglia and cerebellum (fig 2).

Parkinson's disease is the most common disorder affecting procedural memory (table 2). Other neurological disorders that affect basal ganglia or cerebellar function also disrupt procedural memory, such as Huntington's disease and olivopontocerebellar atrophy, in addition to strokes and tumours affecting these brain structures. Patients with major depression also have impairment in procedural memory, perhaps because depression involves dysfunction of the basal ganglia. By contrast, because the disease process in early Alzheimer's disease affects cortical and limbic structures while sparing the basal ganglia and cerebellum, these patients show normal learning and maintenance of procedural skills.

Disruption of procedural memory should be suspected when there is either loss of previously learned skills or significant difficulty in learning new skills. Skills that are commonly affected include writing, playing a musical instrument, and swinging a tennis racket. Although these skills may be relearned, effortful explicit thinking is often required, such that patients with damage to the procedural memory system may never achieve the automatic effortlessness of simple motor tasks that healthy individuals take for granted. Evaluation is similar to that of episodic memory disorders. It is worth noting that the preserved procedural memory system has been used to rehabilitate patients whose episodic memory has been devastated by disease such as encephalitis.

WORKING MEMORY

Working memory is a combination of the traditional fields of attention, concentration and short-term memory. It is the explicit and declarative memory system that enables us to temporarily hold and manipulate information in our consciousness to assist in goal-oriented behaviour. Working memory is often divided into a central executive system that allocates attentional resources, and separate components that process phonological (such as keeping a phone number in mind) and spatial (such as mentally following a route) information. While the prefrontal cortex is the most invariant brain region involved (fig 2), working memory also uses a network of cortical and subcortical areas which differ depending upon the particular task. A typical network includes posterior brain regions (such as visual association areas) that are linked with prefrontal regions to form a circuit. Left-sided brain regions are more active during phonological working memory tasks, whereas right-sided brain regions are more active during spatial working memory tasks. However, regardless of the type of material being manipulated, as the complexity of the task increases there is an increase in the number of brain regions activated in the prefrontal cortex of both hemispheres.

Since working memory depends on a network of activity that includes subcortical structures as well as frontal and parietal cortical regions, it may be disrupted by many degenerative and other neurological disorders, including Alzheimer's disease, fronto-temporal dementia, vascular dementia, Parkinson's disease, multiple sclerosis, head injuries, tumours, and strokes (table 2).

Impairment of working memory most commonly presents as an inability to concentrate or pay attention. Trouble with working memory may also present as an apparent problem with episodic memory when information cannot be learned because it cannot be "kept in mind" by working memory. Continuing the filing analogy mentioned above, if poor working memory impairs the ability of the episodic memory file clerk to obtain new information, then it will be difficult or impossible to get that information into the episodic memory filing cabinet. Evaluation is similar to that for episodic memory disorders.

Working memory is the explicit and declarative memory system that enables us to temporarily hold and manipulate information in our consciousness

CONCLUDING COMMENTS

Although once considered a simple concept, converging and complementary lines of evidence suggest 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. Hopefully research leading to improved understanding of these memory systems will in turn lead to better treatments for memory disorders.

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