Memory Dysfunction

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **This article reviews the current understanding of memory system anatomy and physiology, as well as relevant evaluation methods and pathologic processes.**

RECENT FINDINGS: **Our understanding of memory formation advances each year. Successful episodic memory formation depends not only on intact medial temporal lobe structures but also on well-orchestrated interactions with other large-scale brain networks that support executive and semantic processing functions. Recent discoveries of cognitive control networks have helped in understanding the interaction between memory systems and executive systems. These interactions allow access to past experiences and enable comparisons between past experiences and external and internal information. The semantic memory system is less clearly defined anatomically. Anterior, lateral, and inferior temporal lobe regions appear to play a crucial role in the function of the semantic processing system. Different but tightly interconnected cortical regions, such as the prefrontal region, may play a controlling role in this system. The presentation of clinical disease affecting memory is the result of the selective vulnerability of the memory system. An understanding of current concepts of memory anatomy, physiology, and evaluation plays a central role in establishing an accurate diagnosis.**

SUMMARY: **Different memory systems rely on separate but overlapping distributed brain networks. Certain pathologic processes preferentially affect memory systems. An understanding of memory formation stages will enable more accurate diagnosis.**

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INTRODUCTION

Memory is the ability to capture externally or internally presented information, store it, and reconstruct it later. We are consistently presented with a flow of new information, which needs to be processed and sometimes acted upon. For us to adapt and survive, our brain, through the evolutionary process, developed a well-calibrated mechanism to capture our experiences, which then shape our actions. This mechanism enables the species to adapt more quickly to a changing environment and to respond to a stimulus by comparing it with past experiences. Memory also plays a crucial role in human advancement; without it, we would be in a perpetual cycle of reinvention.

Forgetfulness is one of the most frequent symptoms in patients presenting to cognitive disorders clinics. This article approaches memory function and dysfunction from a clinical perspective.

MEMORY CLASSIFICATION

Several memory classifications exist. One widely used classification is based on the involvement of consciousness in memory use. Consciously evoked memories are declarative (explicit), while memories that do not need conscious involvement are nondeclarative (implicit).[1] Declarative memory can be further classified into episodic and semantic memory. Episodic memory is the ability to store and retrieve past episodes and experiences, while semantic memory refers to general knowledge of people, objects, words, and concepts without reference to a specific autobiographical episode. Nondeclarative memory is frequently acquired with practice and can be used without conscious involvement. Procedural memory is a memory for motor skills and belongs to the nondeclarative memory group. Priming (an attribute of memory in which prior exposure to a stimulus may influence later response) and classical conditioning are other examples of this group of memories.

Working memory refers to the ability to keep the information trace active in the brain for a short period of time after the initial stimulus is no longer available in the environment. Working memory function is typically considered a part of the executive system, although the importance of this process in establishing a more permanent trace in the brain demonstrates the blurred lines between various cognitive functions.

It is important to stress that the temporal lobes play an important role in declarative memory function (the medial regions for episodic memory and anterior, lateral, and inferior regions for semantic memory). In clinical practice, physicians most frequently evaluate declarative memory function, which is the focus of this article.

NEUROANATOMY OF MEMORY

The following section reviews anatomic structures involved in the function of different types of memory.

Working Memory

The working memory system supports actively holding on to information after it is no longer present in the environment. This buffer system is supported by the networks connecting the prefrontal cortex with association temporoparietal cortical regions.[2] The prefrontal cortex plays an executive role in relation to association temporoparietal regions, where the actual information is represented. This system is further subdivided into specialized networks to actively maintain verbal, spatial, and object information.[3,4] While this function is an important step in memory formation, it does not mean that people who have working memory deficits are unable to form long-term memories.

Episodic Memory

Memory formation and retrieval is a fluid process, although to simplify the clinical approach, this process can be divided into three stages: encoding, storage, and retrieval. Accumulating scientific data indicate that memory function is not localized to one brain region but rather is distributed through interconnected brain networks. One of the most crucial memory formation steps is the ability to create a trace of the event or fact in the brain that, in many cases, will be transferred from immediate to long-term storage. Multiple behavioral, electrophysiologic, and neuroimaging studies have demonstrated that medial temporal lobe structures (the entorhinal cortex and hippocampus) play a critical

role in linking information from different cortical regions. This allows the integration of information and the ability to store it for a long period of time. Association and limbic cortical regions connect to the hippocampal formation through several synaptic relays via entorhinal, perirhinal, and parahippocampal cortices.[5] The efferent projections from hippocampal formations reach association cortices through projections from parahippocampal regions.

Damage to medial temporal lobe structures produces significant impairment in the formation of new memories as well as in the storage and retrieval of recently acquired information. Damage to medial temporal lobe structures frequently leaves the retrieval of memories formed a long time ago intact. This supports the hypothesis that memories become less dependent on medial temporal lobe structures over time. This process is known as *consolidation*.[6]

Medial temporal lobe structures play a central role in information transfer from short-term to long-term storage, ie, in episodic memory retention. Current functional imaging data demonstrate that, in addition to medial temporal lobe structures, other large-scale networks support successful encoding and retrieval processes: executive control and semantic processing networks are activated during new information encoding, while the retrieval process is associated with increased activity in regions associated with executive control and default mode networks.[7–10] This should not be surprising as these steps require attention allocation, guided control, organization, and monitoring of information along with its semantic processing (**FIGURE 3-1**).

The activation of the dorsolateral prefrontal cortex along with medial temporal lobe structures during the encoding process increases the chances of information being encoded.[11] In addition to executive network activation, the semantic network regions (primarily involving temporal poles and the lateral temporal cortex) are also activated during encoding, presumably for semantic information processing.[8]

Along with the medial temporal lobe structures, frontal lobe regions associated with executive control and medial parietal regions are also activated during the retrieval process.[7,10,12] This possibly facilitates and monitors the appropriateness of the information to be retrieved for the current situation. Memory retrieval errors occur because of impaired monitoring by the executive control system or impaired interactions between large-scale networks. The posterior cingulate cortex and precuneus (regions overlapping with default mode network areas) are also activated during information retrieval, although their exact roles are yet to be established. Some studies did not demonstrate impaired retrieval with damage in these areas.

It is important to understand that the actual information (separate features of memory) is represented in association cortical regions. Medial temporal lobes bind these separate features through several cortical connections into one cohesive memory. Scientific data also suggest that hemispheric specialization exists for information encoding (eg, verbally based memories appear to lateralize more to the left hemisphere and visuospatially based memories appear to lateralize to the right hemisphere).[13,14]

The external information relayed through the association cortex reaches the hippocampus through the entorhinal cortex. Hippocampal cells project to mammillary bodies, which, in turn, project to the anterior thalamic nuclei and the cingulate gyrus and then back to the hippocampus. The cingulate gyrus also has extensive cortical connections. This is known as the Papez circuit, and

KEY POINTS

- Memory is classified into declarative and nondeclarative forms. Declarative memory is further classified into episodic and semantic. Nondeclarative memory is classified into procedural memory, priming, and classical conditioning.
- Working memory is the brain's ability to keep information active after it is no longer available in the environment.
- Working memory function is supported by brain networks connecting frontal, parietal, and temporal lobes and has specialized parts for holding verbal, object, and spatial information.
- The episodic memory formation process can be divided into encoding, storage, and retrieval stages.
- Medial temporal lobe structures (entorhinal cortex and hippocampus) play a critical role in linking information represented in different cortical regions and its transfer from short-term to long-term storage.
- Executive control networks are active along medial temporal lobe structures during memory encoding and retrieval. Semantic processing networks are also activated during information encoding.
- An anatomically and functionally intact Papez circuit is important in information transfer from short-term to long-term storage.

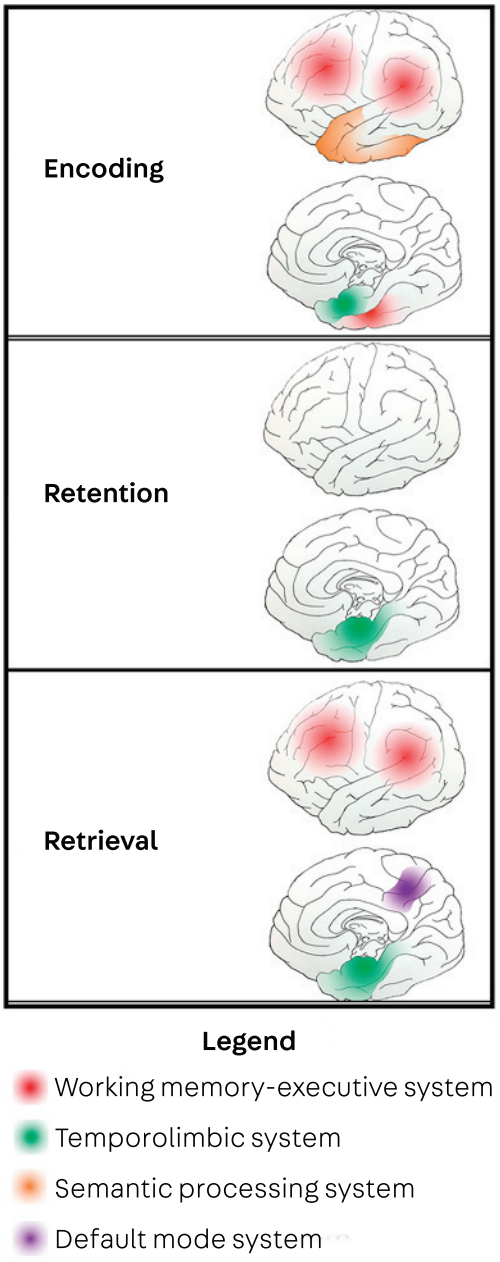

FIGURE 3-1
Systems involved in episodic memory formation.
Original drawing by Jennifer Ann Ross.

interactions between these structures are important in long-term memory formation (FIGURE 3-2).[15]

Human cognitive control depends on well-calibrated interactions between the lateral frontoparietal central executive network, the medial frontoparietal default mode network, and the medial frontoinsular salience network. The central executive network is active during many cognitive tasks requiring information processing and decision making, especially regarding externally presented information. In contrast, the default mode network is active during internal mentation, autobiographical memory retrieval, and social cognition. Data also demonstrate that the frontoparietal control network can be coupled with the default mode network during self-referential goal-directed activity.[16] The salience network is important in identifying behaviorally important stimuli and redirecting the action of other executive networks toward those stimuli. To successfully guide our decisions and behaviors, these networks have to be (and are) well connected with the memory system. Because memories also undergo semantic processing, the memory system is also well connected with the semantic system. The amygdaloid complex, orbitofrontal cortex, and insula play a role in the emotional enhancement of memories,[17] increasing the probability that information will be encoded.

Semantic Memory

Semantic memory neuroanatomy and functional organization are less defined. Semantic memory relates to general knowledge rather than specific episodes; thus, it is not surprising that networks supporting this system are widely distributed throughout the brain. Studies have demonstrated that anterior,

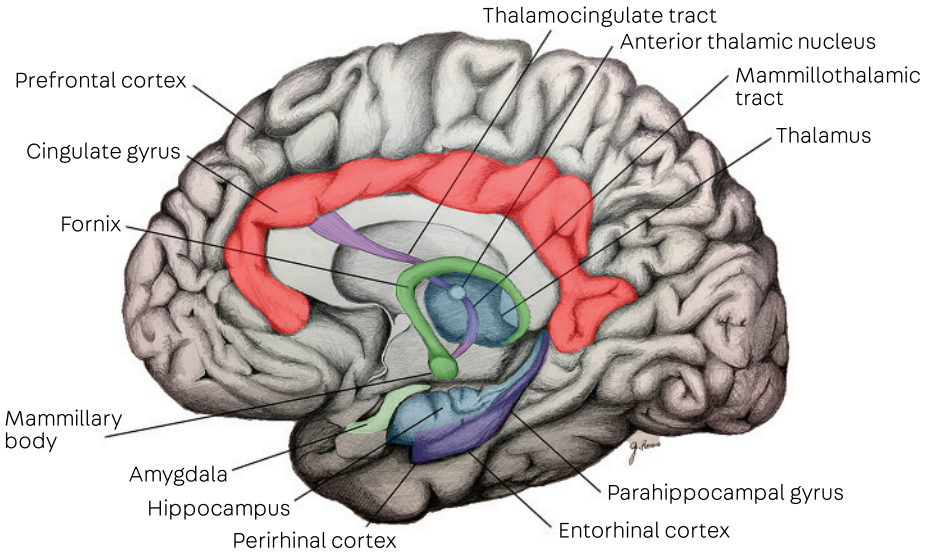

FIGURE 3-2
Papez circuit.
Original drawing by Jennifer Ann Ross.

KEY POINTS

- **The amygdaloid complex plays a role in the emotional enhancement of memories, increasing the probability that information will be encoded.**
- **The semantic network consists of interconnected anterior, lateral, and inferior temporal; dorsolateral prefrontal; and lateral parietal regions.**
- **Procedural memory is a memory system for motor skills. The structures that are involved in procedural memory include the supplementary motor cortex, superior parietal lobule, basal ganglia, and cerebellum.**

inferior, and lateral temporal cortical regions are important in supporting the semantic system. The anterior portions of the temporal lobes have been suggested to act as an important "amodal" hub for binding distinct association modality-specific regions that are involved in information representation.[18] Recent discoveries also demonstrated that the lateral temporal, inferior parietal, and prefrontal regions are involved in semantic information processing at one stage or another. More specific functions for these regions are yet to be determined, although it is possible that the prefrontal cortex plays a role in organizing and retrieving specific semantic information.[19]

The described episodic and semantic memory systems rely on distinct brain networks. The boundaries between these networks overlap anatomically and functionally.

Procedural Memory

Memory for motor skills is called procedural memory. Acquired motor skills usually operate automatically without substantial involvement of consciousness, as with the skills needed to drive a car or ride a bicycle. As the operation of this system is not associated with conscious awareness, it belongs to a group of nondeclarative (or implicit) memories. The anatomic procedural memory system relies on interconnected regions of supplementary motor areas as well as the superior parietal lobule, basal ganglia, and cerebellum.[20]

MEMORY EVALUATION

The following section provides a general overview of the office-based evaluation of memory.

Screening Evaluation

It is important to evaluate level of consciousness, alertness, attention, and language function before assessing memory, because abnormalities in these

cognitive domains may affect the results on tests of memory. An adequately functioning neurovisual system is also necessary for visual memory function.

Working memory can be evaluated in the office by giving the patient a series of numbers to repeat and increasing the number of digits with each trial until the patient fails (digit span). On average, people with normal working memory should be able to recite seven digits (plus or minus two). The test can be made more complex by asking the patient to recite numbers in reverse sequence; backward span is normally not less than the same forward span minus two. The Serial 7s test can also be used for working memory evaluation; this test also involves mental calculations and is thus a measure of working memory only if the patient is able to carry out the required mental arithmetic. The subject is asked to subtract 7 from 100 and to keep subtracting 7 from each consecutive number. Serial 3s can be used as a simpler version of the same test. Reciting months of the year in reverse order is an alternate test of working memory that does not involve mental calculations.

Various memory tests evaluate different aspects of episodic memory. General episodic memory screening consists of inquiring about recent autobiographical and current news events. This general screening can help establish if the amnesia is anterograde or retrograde. The most commonly used and easy-to-perform memory tests often provide the patient with a number of words (commonly 3 to 10) for verbal-based memory or geometric shapes for visual-based memory. The patient is asked to reproduce the words or shapes after sufficient time has passed (usually 10 minutes or more). More complex testing determines if the patient remembers specific items placed in specific locations in the testing area. As a substitution to learning random words or shapes, the examiner can read a story to the patient and later ask the patient to repeat it. This test also involves logical organization of the information. Retrograde amnesia can be detected by testing the knowledge for events that occurred before the onset of illness.

The Three Words-Three Shapes Test is an easy test to assess verbal and nonverbal memory.[21] The patient is initially provided with three words and three shapes, then asked to write them on a sheet of paper without further instructions. FIGURE 3-3 demonstrates three words and three shapes, which are taken from the original test. The six items are then taken away, and the patient is asked to write the words and draw the items from memory. This step tests the patient's incidental recall ability.

FIGURE 3-3
Three Words-Three Shapes Test.
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The same items are presented to the patient up to 3 more times until the patient correctly registers at least five items. This is called effortful encoding. If memory is more strongly affected, the patient may not be able to register several items even after three extra trials. The patient is then asked to reproduce the six items from memory after 10 to 15 minutes. This portion evaluates delayed recall. If some of the items are missing or incorrect, the patient is presented with lists of multiple words and shapes that include the original items and asked to identify the original three words and three shapes. This step evaluates recognition.

The Three Words-Three Shapes Test evaluates several aspects of memory. The inclusion of verbal and nonverbal items evaluates both verbal and nonverbal memory. Immediate (working memory) recall is tested when the patient is asked to present the items immediately following exposure to them. The patient's ability to encode information is evaluated according to the number of times he or she must be exposed to the items before registering them. The ability to store and retrieve the information is tested when the patient is asked to actively recall the items, while the storage (retention) function is tested by evaluating recognition ability.

Semantic memory could be tested by asking the patient to name pictures, match pictures with words, or recognize objects and their parts, or by evaluating semantic fluency (eg, by asking the patient to name as many animals as possible in 1 minute).

KEY POINTS

- A suboptimal level of consciousness, alertness, attention, language, or neurovisual function can affect memory performance.
- Neuropsychological testing objectively evaluates the performance of different cognitive domains (including memory).

Neuropsychological Testing

Neuropsychological evaluation was designed to objectively evaluate different aspects of cognition and is more comprehensive than screening tests used in a typical medical office setting. An in-depth discussion of different neuropsychological tests is beyond the scope of this article; only general principles are discussed.

Working memory can be evaluated during neuropsychological testing using digit span or visual span tests from the Wechsler Adult Intelligence Scale–Fourth Edition[22] and Wechsler Memory Scale–Fourth Edition,[23] among others. The neuropsychological memory evaluation addresses several aspects of memory, including immediate and delayed recall, verbal and nonverbal memory, and recognition. The tests most commonly used in a neuropsychological assessment typically include both word list learning tasks (eg, California Verbal Learning Test–Second Edition,[24] Rey Auditory Verbal Learning Test[25]) and memory tasks involving narratives/stories (eg, Wechsler Memory Scale–Fourth Edition Logical Memory Test[23]).

Nonverbal memory can be evaluated with the Rey-Osterrieth Complex Figure Test[26] and the Visual Reproduction Test from the Wechsler Memory Scale. This test indicates memory impairment only when other neurovisual functions (eg, construction, spatial functions) are preserved.

For practical reasons, the clinician should determine in a neuropsychological evaluation what stages of episodic memory are affected, because this may guide localizing the process that will help in establishing the diagnosis. If memory storage/retention is demonstrated to be affected the most, then the pathology should localize to the medial temporal lobe structures or other structures that are part of the Papez circuit (such as the mammillary bodies, anterior thalamic nuclei, or fornix). If encoding, retrieval, or both are significantly affected, then the pathology usually localizes in more distributed networks (refer to the discussion on memory neuroanatomy).

Semantic knowledge is also evaluated during neuropsychological testing. Examples of tests used include a category fluency test, the Boston Naming Test,[27] vocabulary testing, and certain parts of the Wechsler Adult Intelligence Scale–Fourth Edition and Northwestern University Famous Faces Test.[28]

MEMORY DYSFUNCTION CLASSIFICATION

The following section reviews different types of memory impairment.

Classification of Amnesias

Memory impairment, or amnesia (from the Greek word *amneesya*, meaning "without memory"), is frequently divided into anterograde (impaired ability to form new memories) and retrograde (impaired recall of events occurring before the pathologic insult). Retrograde amnesia frequently has a temporal gradient: memories that were formed closer to an insult are more likely to be forgotten than memories formed further from the insult. This is a possible reflection of a consolidation process.

The etiology of amnesia can be suspected based on the timeline of disease development. In this regard, amnesias can be classified into acute and nonacute. Acute amnesias can be further divided into persistent and transient. Persistent acute amnesias are usually due to a cerebrovascular event or traumatic brain injury. Transient acute amnesias may be caused by transient ischemic event, transient global amnesia syndrome, or epileptic events. Nonacute amnesias may be caused by metabolic factors (such as thiamine deficiency), neurodegenerative conditions, space-occupying lesions, demyelinating disorders, or other etiologies.

For practical reasons, episodic memory impairment can be classified in a simplified way into two groups: (1) amnesias primarily presenting with impaired retention due to dysfunction of the medial temporal lobes and connected limbic structures (temporolimbic system) and (2) amnesias that result from inadequate memory encoding, retrieval, or both, involving the medial temporal lobes and executive networks. This is an artificial classification; it is rarely absolute and should only be used as a guideline.

Impaired Working Memory

Working memory can be affected by many neurologic and psychiatric disorders. This may not be surprising because of the wide distribution of the working memory system through the brain. Examples of conditions that may affect working memory include delirium from any cause, cerebrovascular disease (ischemic and hemorrhagic); traumatic brain injury; and neurodegenerative, demyelinating, and psychiatric conditions.

Impaired Retention of Episodic Memory

Effective information retention is primarily dependent on an intact medial temporolimbic system. The structures that are important in information retention include the hippocampi with surrounding parahippocampal cortical regions as well as the fornix, mammillary bodies, anterior and mediodorsal thalamic nuclei, and cingulate cortex.

Impaired retention can be recognized in testing by the rapid decay of new information after ensuring that the information was (at least partially) encoded. Patients with impaired retention demonstrate an inability to hold information for a longer period of time; during testing, this presents with a loss of information

with a time delay. This manifests with an inability to retrieve information as well as an inability to recognize previously presented information (CASE 3-1). Retention deficits have multiple etiologies. These etiologies vary from focal lesions affecting the brain regions previously discussed to progressive pathologies that tend to affect these regions.

ALZHEIMER DISEASE. Alzheimer disease (AD) is the most common age-related progressive neurodegenerative disorder. In most cases, it presents with an impaired ability to retain new memories, and this feature remains the most salient as the disease progresses. Histopathologically, AD is characterized by extracellular fibrillary amyloid deposition and intracellular neurofibrillary tangle aggregation. These two pathologic changes initially occur in distinctive brain regions: fibrillary amyloid begins accumulating in certain cortical regions (posterior cingulate cortex, precuneus, and prefrontal regions), while neurofibrillary tangles begin forming in neurons of the medial temporal lobe structures.[29,30]

OTHER PROGRESSIVE AMNESTIC DISORDERS. Progressive amnestic disorders due to suspected non-Alzheimer pathophysiology are conditions that present with clinical characteristics that are similar to AD but do not demonstrate amyloid deposition with in vivo amyloid imaging.[31] These conditions include medial temporal tauopathy without amyloidosis,[32] late-onset hippocampal sclerosis,[33] and (yet to be further characterized) argyrophilic grain disease.[34] These conditions are diagnosed during histologic evaluation and cannot reliably be distinguished from AD in the clinic.

OTHER NEURODEGENERATIVE DISEASES. Other neurodegenerative diseases can also involve an amnestic component, although this frequently occurs later in disease progression. These diseases include frontotemporal dementia, Creutzfeldt-Jakob disease, and more advanced cases of Lewy body spectrum disorders.

SPECIFIC CEREBROVASCULAR SYNDROMES. An amnestic syndrome with severe retention deficits can be observed after ischemic or hemorrhagic damage to specific structures involved in memory formation. Cerebrovascular events in one or both hippocampi due to occlusion in the posterior cerebral artery hippocampal branches can manifest with amnesia. Bilateral hippocampal strokes are more likely to produce overt amnesia than unilateral strokes, although amnesia can frequently be detected during neuropsychological evaluation even with unilateral damage.[35] Similar amnestic syndromes can be observed with diencephalic vascular insults occurring in thalamic arterial branch territories.[36] Amnestic syndromes are also associated with anterior communicating artery cerebrovascular events involving basal forebrain structures, although the clinical symptoms are usually less severe.

THIAMINE DEFICIENCY (KORSAKOFF SYNDROME). Korsakoff syndrome is usually preceded by Wernicke encephalopathy, which presents with abrupt-onset confusion that is associated with cerebellar dysfunction and oculomotor impairment. If this condition is not treated promptly with thiamine supplementation, patients are usually left with a significant amnestic disorder.

KEY POINTS

- Amnesias are divided into anterograde and retrograde. Retrograde amnesias frequently have a temporal gradient; memories that were formed closer to an insult are more likely to be forgotten than memories formed further from the insult.
- Amnesias can be also divided into acute and nonacute. Acute amnesias can be further divided into persistent and transient.
- Working memory dysfunction can be seen in many neurologic and psychiatric conditions.
- Impaired retention of episodic memory can be seen when pathologic processes affect the medial temporal lobe and related limbic structures. Clinically, it presents with a rapid decay of newly learned information.

Classic symptoms of Korsakoff syndrome include disorientation, confabulation, and anterograde and retrograde amnesia. Patients with Korsakoff syndrome show difficulties with episodic memory and the temporal order of events. The regions implicated in Korsakoff syndrome include the mediodorsal thalamic nuclei and mammillary bodies.[37]

TRAUMATIC BRAIN INJURY. Traumatic brain injury is a mechanical brain injury caused by acceleration and deceleration forces. These forces cause distinct microstructural and biochemical changes at the microscopic level, disrupting axonal and synaptic functions. Posttraumatic amnesia can occur due to injury to distinct medial temporal lobe structures, although a significant proportion of patients do not demonstrate any specific lesions when using conventional structural brain imaging techniques. More advanced structural and functional imaging studies demonstrate that patients in this category have widespread network disruptions. In particular, it was demonstrated that posttraumatic amnesia is associated with damage in the parahippocampal subdivision of the

CASE 3-1

A 75-year-old woman was brought to the clinic by her daughter for forgetfulness. The daughter had noticed some "benign" memory slips starting about 2 years ago but initially did not think much of it. More recently, her mother had started asking the same questions fairly frequently and was sometimes retelling the same stories within a short time frame. While the patient still lived alone and managed her household, she had recently been asking for help organizing her bills. She sometimes realized that she was becoming more forgetful. No geographical disorientation, difficulty in expressing herself or understanding what other people were saying, or recognition deficits were reported. She did not report any symptoms of anxiety, mood, or psychotic disorders. No other neurologic symptoms were reported, including changes in motor function or occurrence of tremor. The patient reported restful sleep. As she lived alone, it was not known if she had any sleep-related nocturnal behaviors. The patient's appetite was good, and her weight was stable. Past medical history was significant for hypertension and a mildly elevated low-density lipoprotein cholesterol level. Her family history was unremarkable.

The patient was awake, alert, and fully oriented. Attention was preserved, as was demonstrated by normal performance on the Serial 7s test. The patient made two mistakes but was able to self-correct during a Trail Making Test Part B. The patient was given the Three Words-Three Shapes Test and was able to recall two words and two shapes on the incidental part. She needed two extra trials to register all six items, was able to recall one word and one shape in 10 minutes, and correctly recognized one word and two shapes. Language examination demonstrated mild anomia but was otherwise normal. Visuospatial testing was normal. General neurologic examination was unremarkable.

cingulum bundle and reduced connectivity between the parahippocampus and posterior cingulate cortex.[38]

HYPOXIC-ISCHEMIC BRAIN INJURY. Hypoxic-ischemic brain injury occurs when the oxygen supply or blood flow falls below the threshold needed to support normal neuronal metabolism. Hippocampal pyramidal CA1 cells are among the most sensitive to a lack of oxygen and can be irreversibly damaged after ischemia lasting 3 to 5 minutes.[39] Amnesia with significant retention deficit can be the only residual symptom even if ischemia is promptly reversed.

INFECTIOUS AND INFLAMMATORY ENCEPHALITIDES AFFECTING LIMBIC AND ASSOCIATED STRUCTURES. Certain infectious and inflammatory encephalitides affect limbic and associated structures. Limbic encephalitis can be caused by a virus, such as herpes simplex 1, or by an immune system–mediated mechanism, either idiopathic or cancer-related (paraneoplastic).[40] These diseases frequently have a pronounced amnestic-retentive syndrome.

Routine blood work was performed, which included vitamin B_{12} and thyroid-stimulating hormone (TSH) levels, with normal results. MRI of the brain was performed and demonstrated mild generalized brain atrophy that was possibly more pronounced in posterior regions and also involved medial temporal lobe structures (FIGURE 3-4).

The patient was referred for a detailed neuropsychological examination. The results demonstrated episodic memory impairment primarily affecting the memory retention stage. Mild impairments in executive and language functions were also present.

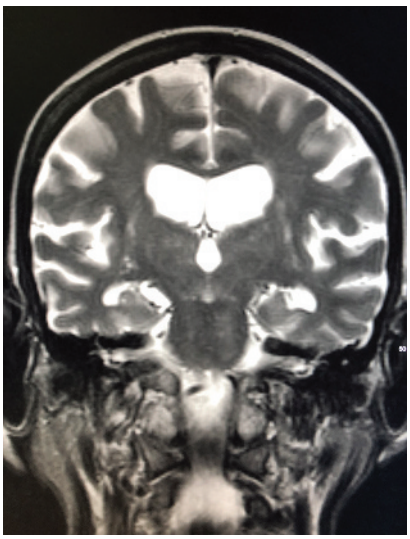

FIGURE 3-4
Coronal T2-weighted brain MRI of the patient in CASE 3-1 demonstrating generalized brain atrophy, particularly involving bilateral medial temporal lobe regions.

COMMENT

Evaluation in the office and neuropsychological testing results demonstrated that the patient's forgetfulness was primarily based on impaired memory retention. Combining this impression with a normal general workup and abnormal structural imaging findings, the patient was suspected to have a cognitive disorder primarily affecting medial temporal lobe structures. Epidemiologically, the highest suspicion would be for an underlying Alzheimer-type pathology.

SPACE-OCCUPYING LESIONS. Memory retention can be affected if a space-occupying lesion (eg, infectious, inflammatory, or tumor) is located in the temporolimbic region.

TRANSIENT GLOBAL AMNESIA. Transient global amnesia is a syndrome that presents with a transient (typically several hours but less than 24 hours in duration) inability to form new memories (anterograde amnesia), associated with repetitive comments and questions and some retrograde amnesia during the attack.[41] This condition usually develops in patients who are in their fifties to seventies and may recur in some patients. When a careful history is taken, it is commonly noted that the patient was involved in a characteristic precipitating activity at the onset of the attack, such as extreme physical exertion, acute immersion in cold water, sexual intercourse, or severe pain or emotional distress.[42] MRI studies using diffusion-weighted imaging (DWI) in patients with transient global amnesia have shown unilateral or bilateral punctate hippocampal lesions in some patients, peaking in detection rate on the third day after the event.[43] The etiology of this syndrome remains controversial.[41,44,45]

AMNESTIC SYNDROME RELATED TO MEDIAL TEMPORAL LOBE EPILEPSY. An amnestic syndrome related to medial temporal lobe epilepsy may occur if epilepsy is accompanied by hippocampal sclerosis.[46] The syndrome of transient epileptic amnesia is a unique mesial temporal lobe epilepsy syndrome that presents as recurrent transient amnestic attacks that should be clinically distinguished from transient global amnesia. As noted by Butler and colleagues,[47] characteristic features of transient epileptic amnesia include episodes that are frequent (median of 12 per year) and brief (median 30 to 60 minutes) and often occur on awakening. Patients with transient epileptic amnesia typically have the onset of their condition later in life (mean onset 62 years of age), and their attacks typically cease with administration of an antiepileptic agent. Patients with transient epileptic amnesia may or may not have evidence for other findings or symptoms of temporal lobe epilepsy, such as epileptiform EEG abnormalities or other clinical features such as lip smacking or olfactory hallucinations associated with the attacks.[47] Although attacks typically are well controlled with antiepileptic agents, Butler and colleagues[48] have also noted that transient epileptic amnesia is associated with a unique interictal amnestic syndrome including accelerated long-term forgetting and autobiographical amnesia.

Impaired Encoding and Retrieval of Episodic Memory

The memory formation step of the incorporation of information traces within neuronal networks in the brain is called encoding. In contrast, retrieval is the allocation and reconstruction of information that was previously encoded. As a general rule, executive frontoparietal networks act together with the medial temporolimbic system during information encoding and retrieval. The broader anatomic distribution of systems involved during these steps explains why encoding and retrieval can be affected by pathologic processes located in multiple brain regions.

Upon examination, impaired encoding can be demonstrated by a patient's inability to register new information. Impaired retrieval manifests with diminished recall of encoded information; however, the patient demonstrates at least a partially preserved recognition of originally presented stimuli, thereby demonstrating at least a partially functioning retention mechanism (CASE 3-2).

Any pathology affecting the limbic system and its associated structures can affect encoding, retrieval, and retention. The pathologic processes that can affect encoding and retrieval include the following:

- Alzheimer disease
- Non-Alzheimer neurodegenerative conditions, such as Lewy body spectrum disorders or frontotemporal dementia
- Traumatic brain injury
- Space-occupying lesions
- Hydrocephalus
- Demyelinating disorders
- Vascular cognitive impairment

As already noted, vascular insults located in the limbic and associated regions can present with episodic memory retention impairment; however, vascular insults can also affect encoding and retrieval of memories. Clinicians frequently encounter brain scans of the patients that demonstrate more diffusely distributed presumed ischemic changes based on microvascular changes that are located in hemispheric white matter. These changes affect the tracts connecting the various brain regions necessary for optimal information encoding and retrieval. Some of these patients present with stepwise deterioration, although a significant proportion presents with slowly deteriorating cognitive function.[49]

It is important to stress that anxiety, mood, and psychotic disorders can also affect memory formation at any stage.

Impaired Semantic Memory

Semantic knowledge impairment can be seen acutely with stroke involving dominant temporal and parietal cortices, traumatic brain injury, and infectious (particularly herpes encephalitis) and inflammatory conditions. The prototypical disorder initially targeting the semantic system is the semantic variant of primary progressive aphasia. For more information on aphasia, refer to the article "Primary Progressive Aphasia and Stroke Aphasia" by Murray Grossman, MDCM, FAAN, and David J. Irwin, MD,[50] in this issue of *Continuum*. Other neurodegenerative disorders, such as AD, can also present with the progressive loss of semantic knowledge.[51] Focal lesions involving anterior, lateral, and inferior temporal lobes can also present with impaired semantic knowledge. Clinically, these patients demonstrate impaired knowledge of objects, words, and concepts. Language is affected and becomes empty of meaning. Patients also frequently demonstrate two-way naming deficits: they are unable to either name the object or point to the correct object when prompted. The patient begins to use superordinate category names for specific objects (eg, referring to a dog as an animal) or to use semantic paraphasias as a substitution for an actual name.[52]

Impaired Procedural Memory

Procedural memory is tested less frequently in the clinical setting. As noted previously, anatomic regions involved in procedural memory impairment include the supplementary motor cortex, superior parietal lobule, basal ganglia, and cerebellum. Focal lesions in these regions, such as stroke or tumor,

KEY POINTS

- Impaired encoding or retrieval of episodic memory or both can be observed when pathologic processes affect the medial temporal lobe, executive networks, or both. Clinically, impaired encoding presents with a diminished ability to register new information. Impaired retrieval presents with the impaired active recall of encoded information, with at least partially preserved recognition of the information that was originally presented.
- Impaired semantic memory can present when the pathologic process affects the main hubs of the semantic network. Clinically, it presents with the loss of word, object, and concept meaning.

can produce procedural memory deficits. Progressive neurodegenerative conditions, such as corticobasal syndrome and Parkinson disease, can also affect this system.

MEMORY DISTORTIONS

While memory loss is one of the most frequently encountered symptoms in memory clinics, clinicians may also see patients with memory distortions. Memory distortions can affect the content or temporal relations of events. While benign memory distortions can be seen in healthy people, significant distortions usually signify brain dysfunction and result in confabulations. Confabulations do not have to be logical or even consistent, and the patient may say two things that contradict each other. Patients are usually not concerned about the errors if they are pointed out to them. As confabulations are deficits of retrieval, it is not surprising that frontally based executive control network dysfunction plays a role in their development.[53] Confabulations have been described in patients with the involvement of various frontal lobe regions, although the inferior medial prefrontal system may play a crucial role.[54] As one can expect, confabulations are associated with diseases that affect these brain regions, rather than the disease process itself. Confabulations more frequently involve episodic memories,

CASE 3-2

An 80-year-old woman presented to the clinic with her son for evaluation of forgetfulness that became apparent several years ago. The forgetfulness had slowly worsened over time. The son described his mother as being easily distracted and repeating the same questions within a short time frame. The patient lived alone and managed her household seemingly without any difficulties, although her son had started questioning her ability to drive safely after she recently missed several stop signs. The patient had never become lost in a familiar area. Her son did not notice any changes in her language or behavior. She did not report any symptoms of anxiety, mood, or psychotic disorders. No other neurologic symptoms were reported, including changes in motor function, occurrence of tremor, or balance deficits. Her past medical history was significant for hypertension and treated hypothyroidism. Her father suffered a stroke at age 85, and her mother died from ovarian cancer.

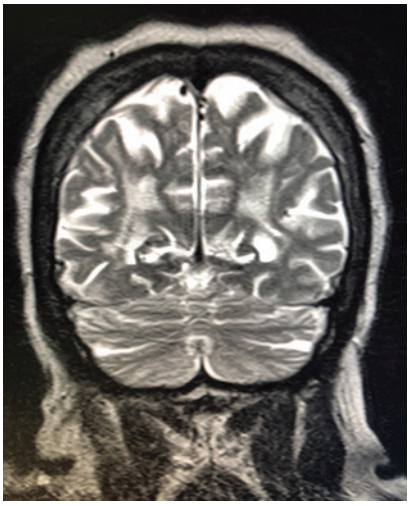

FIGURE 3-5
Coronal T2-weighted brain MRI of the patient in CASE 3-2 demonstrates significant periventricular and subcortical white matter changes and generalized brain atrophy.

The patient was awake, alert, and fully oriented. Attention testing revealed difficulties performing the

although semantic memories could be affected as well. Confabulations are observed not only in patients with memory disorders but also in patients with deficits in other domains (anosognosias), such as confabulations in patients with cortical blindness (Anton syndrome).

CONCLUSION

The human brain has a finely tuned mechanism to form and store memories. Memory formation is a fluid process involving memory encoding, which provides the ability to store and retrieve memories. The boundaries between different stages of memory formation are not as clear. As this process involves many interconnected and widely distributed brain regions, it is not surprising that encoding can be affected by various pathologic processes. It is important to understand that memory impairment is a result of the disruption of these mechanisms and that certain pathologic processes tend to affect one or another stage of memory formation. The first step in evaluating forgetfulness is to clarify what type of memory is impaired at what formation stage. This will become a guiding step to identify the underlying pathologic process that causes this impairment.

Serial 7s test and difficulties switching between the letters and numbers during the Trail Making Test Part B. The patient was able to recall one word and one shape on the incidental part of the Three Words-Three Shapes Test. She needed four extra trials to register all six items but was able to recall one correct word, one false word and two shapes after 10 minutes. She was able to recognize all six items correctly. Language and visuospatial testing were unremarkable.

The patient had routine blood work performed, including vitamin B_{12} and thyroid-stimulating hormone (TSH) levels, with normal results. MRI of the brain was performed and demonstrated at least moderate periventricular and subcortical white matter changes and mild generalized brain volume loss (FIGURE 3-5). She was referred for a detailed neuropsychological examination. The results demonstrated episodic memory impairment primarily affecting memory retrieval and, to a lesser extent, encoding stages. There was also a fairly pronounced impairment in executive functions. Other cognitive domains were spared.

COMMENT

Based on evaluation in the office and neuropsychological testing results, this patient's forgetfulness was suspected to be due to the dysfunction of frontal executive networks rather than medial temporal lobe and related structures. Combining testing results with findings from structural imaging, the most likely etiology for this patient's symptoms would be vascular cognitive impairment. Without further evaluation with biomarkers, dual pathology of this syndrome cannot be excluded.

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REFERENCES

1 Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A 1996;93(24):13515–13522. doi:10.1073/pnas.93.24.13515.

2 Nee DE, D'Esposito M. The representational basis of working memory [published online ahead of print September 28, 2016]. Curr Top Behav Neurosci. doi:10.1007/7854_2016_456.

3 Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. Cereb Cortex 1996;6(1):11–20. doi:10.1093/cercor/6.1.11.

4 Courtney SM, Ungerleider LG, Keil K, Haxby JV. Object and spatial visual working memory activate separate neural systems in human cortex. Cereb Cortex 1996;6(1):39–49. doi:10.1093/cercor/6.1.39.

5 Lavenex P, Amaral DG. Hippocampal-neocortical interaction: a hierarchy of associativity. Hippocampus 2000;10(4):420–430. doi:10.1002/1098-1063(2000)10:4<420::AID-HIPO8>3.0.CO;2-5.

6 Frankland PW, Bontempi B. The organization of recent and remote memories. Nat Rev Neurosci 2005;6(2):119–130. doi:10.1038/nrn1607.

7 Huijbers W, Schultz AP, Vannini P, et al. The encoding/retrieval flip: interactions between memory performance and memory stage and relationship to intrinsic cortical networks. J Cogn Neurosci 2013;25(7):1163–1179. doi:10.1162/jocn_a_00366.

8 Wolk DA, Dickerson BC; Alzheimer's Disease Neuroimaging Initiative. Fractionating verbal episodic memory in Alzheimer's disease. Neuroimage 2011;54(2):1530–1539. doi:10.1016/j.neuroimage.2010.09.005.

9 Spaniol J, Davidson PS, Kim AS, et al. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. Neuropsychologia 2009;47(8–9):1765–1779. doi:10.1016/j.neuropsychologia.2009.02.028.

10 Huijbers W, Pennartz CM, Cabeza R, Daselaar SM. The hippocampus is coupled with the default network during memory retrieval but not during memory encoding. PLoS One 2011;6(4):e17463. doi:10.1371/journal.pone.0017463.

11 Reber PJ, Siwiec RM, Gitelman DR, et al. Neural correlates of successful encoding identified using functional magnetic resonance imaging. J Neurosci 2002;22(21):9541–9548.

12 Buckner RL. Functional-anatomic correlates of control processes in memory. J Neurosci 2003;23(10):3999–4004.

13 Bohbot VD, Kalina M, Stepankova K, et al. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 1998;36(11):1217–1238. doi:10.1016/S0028-3932(97)00161-9.

14 Chen KH, Chuah LY, Sim SK, Chee MW. Hippocampal region-specific contributions to memory performance in normal elderly. Brain Cogn 2010;72(3):400–407. doi:10.1016/j.bandc.2009.11.007.

15 Papez JW. A proposed mechanism of emotion. Arch Neur Psych 1937;38(4):725–743. doi:10.1001/archneurpsyc.1937.02260220069003.

16 Spreng RN, Steven WD, Chamberlain JP, et al. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. Neuroimage 2010;53(1):303–317. doi:10.1016/j.neuroimage.2010.06.016.

17 Kumfor F, Irish M, Hodges JR, Piguet O. Frontal and temporal lobe contributions to emotional enhancement of memory in behavioral-variant frontotemporal dementia and Alzheimer's disease. Front Behav Neurosci 2014;8:225. doi:10.3389/fnbeh.2014.00225.

18 Guo CC, Gorno-Tempini ML, Gesierich B, et al. Anterior temporal lobe degeneration produces widespread network-driven dysfunction. Brain 2013;136(pt 10):2979–2991. doi:10.1093/brain/awt222.

19 Wagner AD, Paré-Blagoev EJ, Clark J, Poldrack RA. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. Neuron 2001;31(2):329–338. doi:10.1016/S0896-6273(01)00359-2.

20 Daselaar SM, Rombouts SA, Veltman DJ, et al. Similar network activated by young and old adults during the acquisition of a motor sequence. Neurobiol Aging 2003;24(27):1013–1019. doi:10.1016/S0197-4580(03)00030-7.

21 Weintraub S, Mesulam MM. Mental state assessment of young and elderly adults in behavioral neurology. In: Principles of behavioral neurology. Philadelphia, PA: FA Davis, 1985.

22 Wechsler D. Wechsler adult intelligence scale–fourth edition. San Antonio, TX: Pearson, 2008.

23 Wechsler D. Wechsler memory scale–fourth edition. San Antonio, TX: Pearson, 2009.

24 Delis DC, Kramer JH, Kaplan E, Ober BA. California verbal learning test. 2nd edition. San Antonio, TX: Psychological Corporation, 2000.

25 Schmidt M. Rey auditory and verbal learning test. A handbook. Los Angeles, CA: Western Psychological Services, 1996.

26 Osterrieth PA. Le test de copie d'une figure complexe: contribution à l'étude de la perception et de la mémoire. Arch Psychol 1944;30:286–356.

27 Kaplan E, Goodglass H, Weintraub S. Boston naming test. Baltimore, MD: Lippincott Williams & Wilkins, 2001.

28 Gefen T, Wieneke C, Martersteck A, et al. Naming vs knowing faces in primary progressive aphasia: a tale of 2 hemispheres. Neurology 2013;81(7): 658–664. doi:10.1212/WNL.0b013e3182a08f83.

29 Sperling RA, Laviolette PS, O'Keefe K, et al. Amyloid deposition is associated with impaired default network function in older persons without dementia. Neuron 2009;63(2):178–188. doi:10.1016/j.neuron.2009.07.003.

30 Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995;16(3):271–278. doi:10.1016/0197-4580(95)00021-6.

31 Jack CR Jr, Wiste HJ, Knopman DS, et al. Rates of β-amyloid accumulation are independent of hippocampal neurodegeneration. Neurology 2014;82(18):1605–1612. doi:10.1212/WNL.0000000000000386.

32 Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 2014;128(6):755–766. doi:10.1007/s00401-014-1349-0.

33 Leverenz JB, Agustin CM, Tsuang D, et al. Clinical and neuropathological characteristics of hippocampal sclerosis: a community-based study. Arch Neurol 2002;59(7):1099–1106. doi:10.1001/archneur.59.7.1099.

34 Ferrer I, Santpere G, van Leeuwen FW. Argyrophilic grain disease. Brain 2008;131(pt 6): 1416–1432. doi:10.1093/brain/awm305.

35 Szabo K. Hippocampal stroke. Front Neurol Neurosci 2014;34:150–156. doi:10.1159/000356438.

36 Graff-Radford NR, Damasio H, Yamada T, et al. Nonhaemorrhagic thalamic infarction. Clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by computerized tomography. Brain 1985;108(pt 2): 485–516. doi:10.1093/brain/108.2.485.

37 Nardone R, Höller Y, Storti M, et al. Thiamine deficiency induced neurochemical, neuroanatomical, and neuropsychological alterations: a reappraisal. ScientificWorldJournal 2013;2013:309143. doi:10.1155/2013/309143.

38 De Simoni S, Grover PJ, Jenkins PO, et al. Disconnection between the default mode network and medial temporal lobes in post-traumatic amnesia. Brain 2016;139(pt 12): 3137–3150. doi:10.1093/brain/aww241.

39 Gee CE, Benquet P, Raineteau O, et al. NMDA receptors and the differential ischemic vulnerability of hippocampal neurons. Eur J Neurosci 2006;23(10):2595–2603. doi:10.1111/j.1460-9568.2006.04786.x.

40 Rosenfeld MR, Dalmau JO. Paraneoplastic disorders of the CNS and autoimmune synaptic encephalitis. Continuum (Minneap Minn) 2012; 18(2):366–383. doi:10.1212/01.CON.0000413664.42798.aa.

41 Arena JE, Rabinstein AA. Transient global amnesia. Mayo Clin Proc 2015;90(2):264–272. doi:10.1016/j.mayocp.2014.12.001.

42 Fisher CM. Transient global amnesia. Precipitating activities and other observations. Arch Neurol 1982;39(10):605–608.

43 Ryoo I, Kim JH, Choi BS, et al. Lesion detectability on diffusion-weighted imaging in transient global amnesia: the influence of imaging timing and magnetic field strength. Neuroradiology 2012;54(4):329–334. doi:10.1007/s00234-011-0889-4.

44 Lewis SL. Aetiology of transient global amnesia. Lancet 1998;352(9125):397–399.

45 Gonzalez-Martinez V, Comte F, de Verbizier D, Carlander B. Transient global amnesia: concordant hippocampal abnormalities on positron emission tomography and magnetic resonance imaging. Arch Neurol 2010;67(4):510. doi:10.1001/archneurol.2010.50.

46 Miller LA, Muñoz DG, Finmore M. Hippocampal sclerosis and human memory. Arch Neurol 1993; 50(4):391–394. doi:10.1001/archneur.1993.00540040051014.

47 Butler CR, Graham KS, Hodges JR, et al. The syndrome of transient epileptic amnesia. Ann Neurol 2007;61(6):587–598. doi:10.1002/ana.21111.

48 Butler C, van Erp W, Bhaduri A, et al. Magnetic resonance volumetry reveals focal brain atrophy in transient epileptic amnesia. Epilepsy Behav 2013;28(3):363–369. doi:10.1016/j.yebeh.2013.05.018.

49 Price CC, Jefferson AL, Merino JG, et al. Subcortical vascular dementia: integrating neuropsychological and neuroradiologic data. Neurology 2005;65(3):376–382. doi:10.1212/01.WNL.0000168877.06011.15.

50 Grossman M, Irwin DJ. Primary progressive aphasia and stroke aphasia. Continuum (Minneap Minn) 2018;24(3 Behavioral Neurology and Psychology):745–767.

51 Rogers TT, Ivanoiu A, Patterson K, Hodges JR. Semantic memory in Alzheimer's disease and the frontotemporal dementias: a longitudinal study of 236 patients. Neuropsychology 2006;20(3):319–335. doi:10.1037/0894-4105.20.3.319.

52 Rogers TT, Lambon Ralph MA, Garrard P, et al. Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol Rev 2004:111(1):205–235. doi:10.1037/0033-295X.111.1.205.

53 Gilboa A, Alain C, Stuss DT, et al. Mechanisms of spontaneous confabulations: a strategic retrieval account. Brain 2006;129(pt 6):1399–1414. doi:10.1093/brain/awl093.

54 Turner MS, Cipolotti L, Yousry TA, Shallice T. Confabulation: damage to a specific inferior medial prefrontal system. Cortex 2008;44(6):637–648. doi:10.1016/j.cortex.2007.01.002.