Memory | Normal brain systems and disorders of memory

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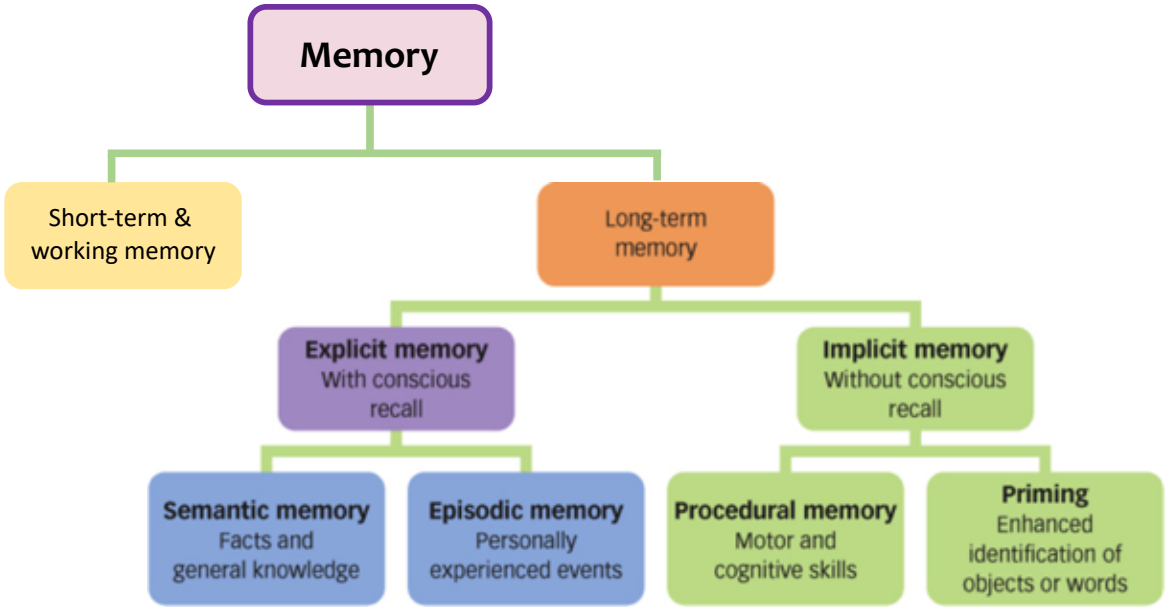
Normal brain memory systems[1]

- Memory has traditionally been fractionated into several different domains. The first dissociation is between **short-term memory (STM)** and **long-term memory (LTM)**
- Within STM, **working memory** refers to brain systems and processes required for the active manipulation or protection of STM contents
- LTM is divided into **explicit (declarative) memory** versus **implicit (non-declarative) memory** systems
- Explicit memory is itself further fractionated into **episodic memory** and **semantic memory**

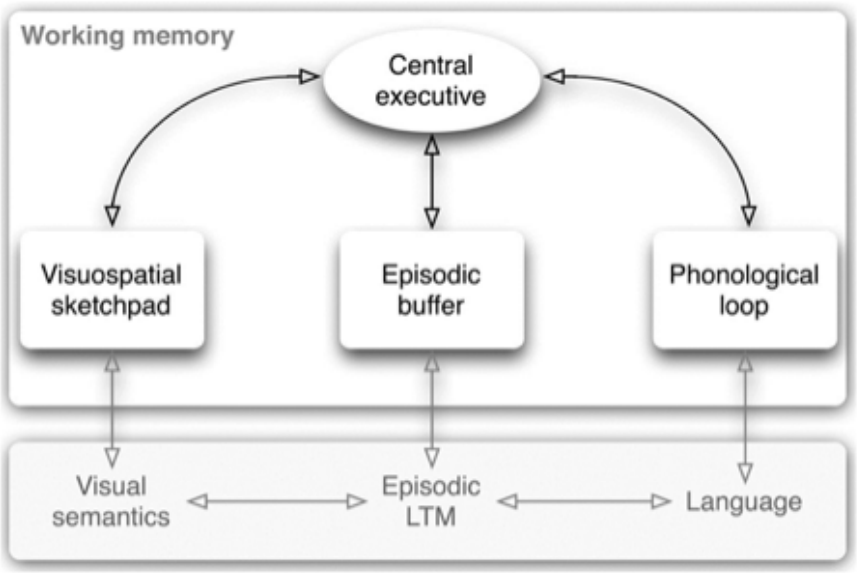


Memory is fractionated into different systems

The traditional view is that these different types of memory are dissociable and served by different brain regions.

Short-term memory (STM) and working memory[2]

- **STM** is often used to refer to **passive storage** over **seconds**
- **Working memory** refers to **executive control** over material stored in STM
- STM stores are 'modality specific', e.g. visuospatial material may be held in a separate store **(visuospatial sketchpad)** to verbal material **(phonological loop)**
- Early focal lesion and functional imaging studies suggested that STM stores reside in **posterior parietal cortex** (visuospatial material in the right parietal cortex and verbal material in the left) whereas executive control systems reside in **dorsolateral prefrontal cortex**. This division may be an over-simplification but can be helpful.



Executive control mechanisms manipulate contents of STM, e.g., *reverse or backward digit span test* where people are required to recall a sequenc of numbers in reverse

'Slave'storage systems

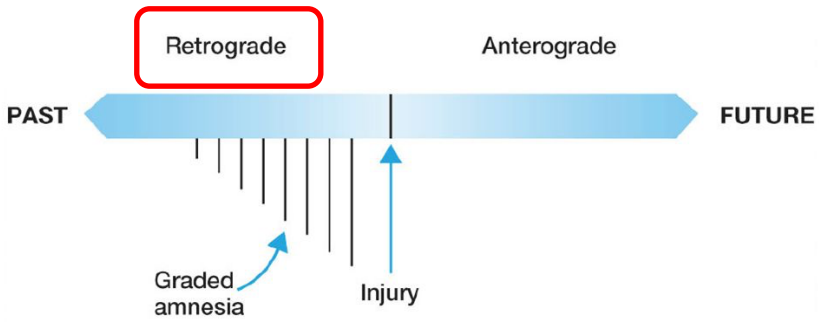
Crystallized LTM (long term memory) systems

Working memory refers to STM *plus* Executive control over the contents of STM
Executive control has been attributed to prefrontal brain regions whereas passive stores are considered to reside in posterior parietal cortex. STM stores may interact with LTM systems.[2]

- Verbal STM **storage capacity** is measured at the bedside using **digit span** (how many numbers in a sequence can be recalled)
- Visuospatial STM **storage capacity** is measured using the **Corsi blocks** (how many spatial locations in a sequence can be recalled)
- **Verbal working memory** (storage plus executive control) is measured by using **reverse digit span** (how many numbers in a sequence can be recalled in reverse order)
- **Visuospatial working memory** is measured by using **reverse Corsi blocks** (how many location in a sequence can be recalled in reverse order)

Episodic memory[3]

- **Episodic memory** refers to consciously recalled personal experiences and specific events that happened in the past
- **Retrograde memory** is memory for distant events in the past while a**nterograde memory** is memory for newly learnt material
- The **hippocampus** and associated medial temporal lobe structures play a key role in episodic memory
- **Confabulation** refers to false memories without conscious knowledge of their falsehood



Hippocampal damage is associated with severe deficits in episodic memory

Classically, complete lesions of the hippocampus lead to severe anterograde amnesia and a graded retrograde amnesia, such that more recent events are recalled very poorly but remote events, from many years ago, are remembered much better[4,5].

- **Anterograde memory** is often tested by getting the patient to learn a name and address, and asking them to recall it minutes later
- Alternatively, you can tell them something about your own interests at the beginning of the consultation and ask them to recall these at the end
- Neuropsychologists test **verbal** anterograde memory with story recall or word list learning. **Visual** anterograde memory is often tested with recall of a complex figure
- **Retrograde memory** is assessed by asking the patient to recall past personal, news or sport events. It might be necessary to corroborate some of the information
- More formally, retrograde memory can be tested using the Autobiographical Memory Interview

Free recall is harder than recognition tests of memory where people have to choose between alternative possible answers. Some patients might not freely recall a name and address they had been asked to learn minutes before, but if they are given choices of which elements were in the name and address, they can perform better than chance.

Episodic memory deficits can arise in progressive neurodegenerative conditions such as **Alzheimer's disease** or its prodromal condition, **mild cognitive impairment (MCI)**; occur transiently, in conditions such as **transient global amnesia (TGA)** or **transient epileptic amnesia (TEA)**[6]; or can be of sudden-onset and leave a permanent deficit as in **limbic encephalitis**[7] or **herpes simplex encephalitis**.

Table 1 Distinguishing clinical features of the transient amnesic syndromes.

Feature	Transient epileptic amnesia	Transient global amnesia	Psychogenic amnesia
Typical age of onset	50–70 years	50–70 years	Any age
Past medical history	None	Migraine	'Organic' transient amnesia; substance abuse; psychiatric illness
Precipitants	Waking	Cold water; physical exertion; psychological stress	Minor head injury; stress; depression
Ictal memory profile	Anterograde and retrograde amnesia showing within-patient variation; patient might later partially recall attack); retrograde procedural memory intact	Profound anterograde amnesia including repetitive questioning; variable retrograde amnesia; intact nondeclarative memory	Highly variable: often profound retrograde amnesia with loss of personal identity; relatively preserved anterograde memory; variable procedural memory
Duration of amnestic episode	Usually <1 h but can last much longer (days)	Typically 4–10 h	Days or months
Recurrence	Mean frequency 13 attacks per year	Rare	Rare
Postictal and interictal memory	Accelerated forgetting; remote autobiographical memory loss; topographical amnesia	Grossly intact, but subtle deficits might persist for several months	Variable: patient might be able to 'relearn' the past
Other features	Olfactory hallucinations; oroalimentary automatisms; brief loss of responsiveness	Headache and/or nausea	Focal 'neurological' symptoms or signs, such as hemiparesis

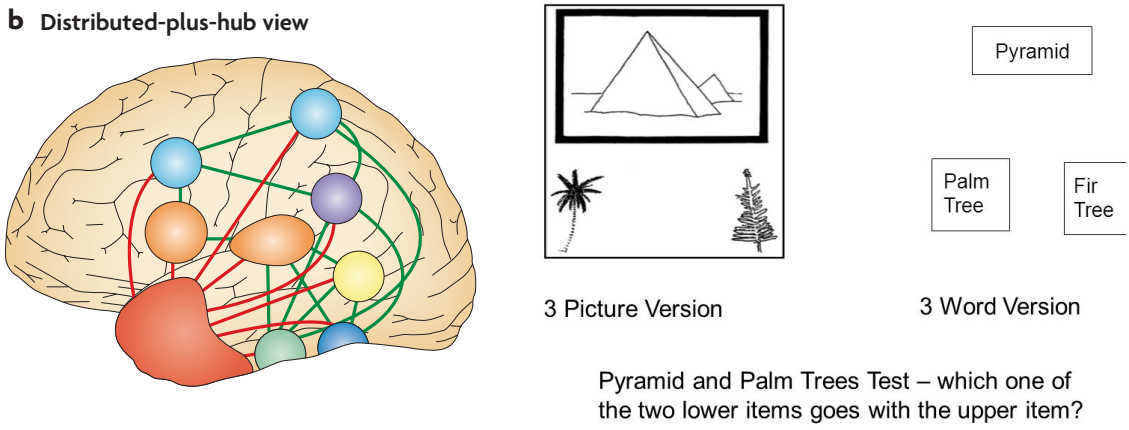
TGA versus TEA[13] from Butler & Zeman *Nat. Clin. Pract. Neurol.* **4,** 516–521 (2008)

Episodic memory deficits associated with confabulation[8] have been associated particularly with **Korsakoff's syndrome**[9] or damage to **orbitofrontal cortex**[8].

Remember also that depression, anxiety, stress and poor sleep can also lead to deficits on episodic memory tests. **Subjective cognitive impairment** or **subjective cognitive decline** can be related to these symptoms[10].

Semantic memory[11]

- **Semantic memory** refers to recollection of facts, concepts and general knowledge about the world
- The **left temporal pole** is considered to be a critical brain region for semantic memory



Left temporal lobe is crucial for semantic memory

This can be tested in patients by assessing semantic knowledge, for example with the Pyramid and Palm Trees test.

- At the bedside semantic memory can be assessed by asking the patient to name objects or line drawings of objects, and then asking them to explain what they are or what they are used for. For example, you might point to a telephone or a watch, or a stethoscope
- Alternatively, give the name of an object and ask them to explain its use.
- Neuropsychologists test semantic memory more formally using tasks that probe semantic knowledge
- For example, in the Pyramid and Palm Trees Test patients have to say which of the two choices are closer semantically to the target object

Case histories

Case 1[1] **|** Ch 33 Husain M & Schott J *Oxford Textbook of Cognitive Neurology & Dementia*

A 76 year old right-handed man presented with a two year history of memory loss characterized by misplacing personal belongings, forgetting appointments and repeating himself during conversations. He retired from teaching at the University where he was a professor because of cognitive difficulties. He acknowledged forgetting recent conversations and his wife reported that he forgot entirely about plans that have been discussed several times previously. He had become more anxious and dependent on his wife.

- MMSE score: 24/30.
- Neuropsychology: Severely impaired delayed recall plus deficits on visuoperceptual skills
- MRI brain: Generalized volume loss

Notes

Case 2[12] **|** *New England Journal of Medicine* (2011) 364:2227

A 70 year old woman has been noticing increasing forgetfulness over the past 6 to 12 months. Although she has always had some difficulty recalling the names of acquaintances, she is now finding it difficult to keep track of appointments and recent telephone calls. She drives a car, pays the bills and lives independently without difficulty.

- Slight difficulty on delayed recall but otherwise normal
- MRI brain: Normal

Notes

Case 3[13] **|** *Nature Clinical Practice Neurol,* now *Nat Rev Neurol* (2008) 4:516

A 54 year-old right-handed academic presented the four year history of recurrent episodes of transient amnesia and a progressive decline in memory. His first episode began abruptly as he emerged from the shower one morning. He could not recall events. Alone in the house and curious as to why he should be showering so late in the day he went out of his car and felt that the bonnet was warm, implying that he had already been out. After about an hour the patient's memories from earlier in the day gradually returned. Over the next three years the patient experienced six further amnestic attacks. They all occurred on waking and were characterized by retrograde amnesia for events of the past few days or weeks. Between attacks, the patient began to notice persistent memory deficits. His recollection of many salient, personal events, such as family holidays and weddings from the past 30 years became sketchy or completely absent.

- MMSE: 27/30, consistently failing to recall three words after a brief delay
- CT brain: Unremarkable

Notes

Case 4[6] **|** *Nat Rev Neurol* (2013) 9:86

A 65-year-old woman experienced an episode of amnesia after working hard in the garden for some hours. She began asking repeatedly "Where am I?", "What time is it?" and "Why are all these branches lying around?" She appeared perplexed and irritated. She was profoundly amnestic, with a retention span of three minutes and retrograde amnesia extending 20–30 years in the past. The amnesia resolved over about seven hours, although the patient continued to feel irritable and anxious for some days.

- MRI brain: Focal diffusion weighted signal changes in the hippocampus

Notes

Case 5[1] **| Ch 11** Husain M & Schott J *Oxford Textbook of Cognitive Neurology & Dementia*

NA was a 71-year-old right-handed professional woman who presented with a four year history of progressive difficulty thinking of words, especially nouns. She reported difficulty reading or following what she was watching on the television. She had forgotten how to cook.

- Spontaneous speech was characterized by word finding difficulty and insertion of general substitutions (e.g. 'thingy') or replacement of words with related ones (e.g. 'knife' for 'scissors')
- Object naming profoundly impaired
- MRI brain: Severe left temporal lobe atrophy

Notes

Case 6[14] **|** *JAMA Neurol* (2016) 73:1248

A man in his 70s with a history of chronic cognitive decline attributed to hepatic encephalopathy presented with one week of confusion, worse than his baseline state. He had a history of alcoholic cirrhosis. Examination revealed anterograde worse than retrograde memory deficits. There was no evidence of asterixis, nystagmus, ophthalmoplegia ataxia.

- MRI brain: Hyperintensity in the periaqueductal grey matter, mamillary bodies and medial thalamic nuclei, together with volume loss in the corpus callosum and generalised cortical atrophy.

Notes

Case 7[15] **|** *New England Journal of Medicine* (2011) 365:1825

A 75-year-old physician was seen because of memory loss and episodes of near-syncope. The patient had been generally well, except for mild and gradual memory loss, until 7 months earlier, when episodes of diffuse tingling and a sensation of flushing began to occur intermittently, lasting about a minute. Light-headedness and difficulties with word finding developed 4 months before presentation in association with the episodes and progressed to near-syncope 4 weeks before presentation. The patient reported an intermittently irregular pulse but no other speech, vision, other sensory, or motor symptoms.

Twelve days after his initial visit, the patient saw a neurologist. He reported that he had spells that lasted up to 1 minute that were preceded or followed by olfactory hallucinations of food and occasionally abnormal tastes. During the spells, he noted abnormal movements of the right arm, with tightening of the right shoulder and elbow, involuntary supination of the right hand, flexion of the right fingers, and jerking of the right hand when writing, in addition to slowed speech and word-finding difficulties, facial paraesthesiae (greater on the right side), and facial twitching on the right side. There was no impairment of consciousness or disturbance of speech, but he described feeling faint, light-headed, generally weak, and sometimes diaphoretic

- MRI brain: Left medial temporal lobe, including the amygdala and the anterior hippocampus, showed slightly greater T2 -weighted signal than contralateral structures, plus mild expansion of the left amygdala.

Notes

Case 8 | *Unpublished*

A 66 year-old man presented with memory complaints. Six years previously he had been diagnosed with simple partial sensory seizures associated with an olfactory aura preceding each episode. MRI brain and EEG were normal; detailed neuropsychological assessment was also in the normal range across all cognitive domains. His seizures initially responded to lamotrigine 150 mg twice daily but he complained that his memory was progressively deteriorating. He became depressed and was started on citalopram by his GP.

Subsequently, he was unable to continue working, encountering difficulty remembering names of clients and getting lost driving in familiar locations. On the Addenbrooke's Cognitive Examination-III (ACE-III) screening test he scored 85/100 with the most notable deficiencies in memory (18/26) and verbal fluency (10/14). Detailed neuropsychological assessment now revealed a global decline in performance from two years earlier, including in memory (both immediate and delayed verbal and visual recall) but also in attention, executive function and processing speed. Thus cognitive impairment affected several domains and extended beyond deficits in episodic memory. Ambulatory EEG demonstrated abnormal focal sharp and slow wave discharges involving both right and left temporal lobes.

- MRI brain: Slight atrophy of the body and tail of the hippocampus on the right

He continued to experience partial sensory seizures as well as brief periods of disorientation which were considered to be complex partial seizures. His cognitive impairment continued to have a major impact on everyday life. A further clinical diagnosis was made. He was started on a new treatment and the dose of lamotrigine was increased further to 200 twice daily. Despite this, both types of seizure continued. Therefore levetiracetam was added.

With levetiracetam 250 mg twice daily there were no further overt seizures. On the ACE -III his performance initially improved to 96/100, which was attributed to better control of seizures. Repeat EEG performed two years later showed no evidence of epileptiform activity but the ACE-III score declined to 87/100.

- Repeat MRI brain: MRI showed further slight atrophy of the medial temporal lobe, most prominently on the right.

Notes

Recommended general reading

1. Hodges J (2017) *Cognitive Assessment for Clinicians* 3nd ed
2. Husain M & Schott J (2016) *Oxford Textbook of Cognitive Neurology & Dementia*

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