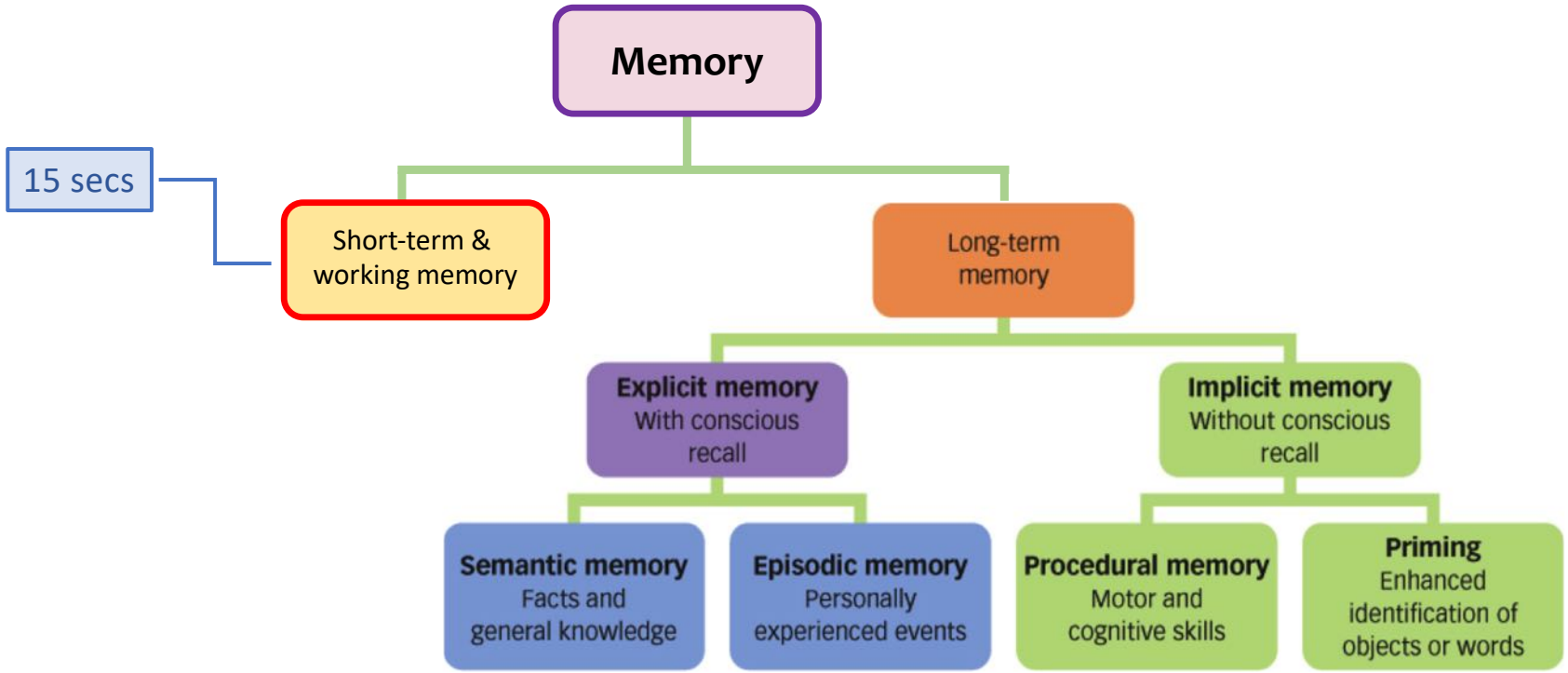
Disorders of memory

Masud Husain

Dept Experimental Psychology & Nuffield Dept Clinical Neurosciences, University of Oxford

Different types of memory

Fractionation of memory systems

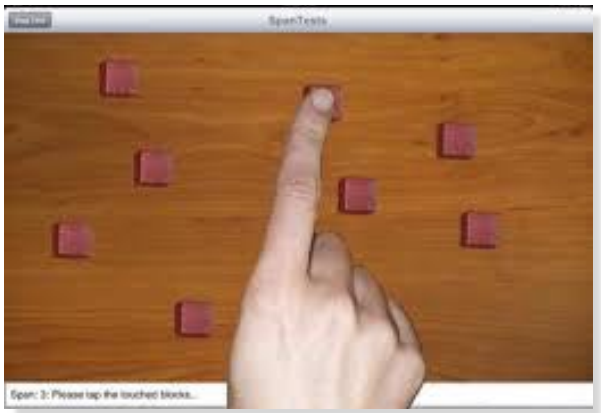


Clinical measures of STM

Forwards digit span (verbal) and spatial span (visuospatial) provide an index of STM capacity

9 1 5 2
7 3 6 1 4
8 5 2 7 6 3
5 9 6 1 4 8 3
6 8 2 5 9 4 1 7
1 6 3 8 7 4 9 5 2

Digit span test for verbal STM span

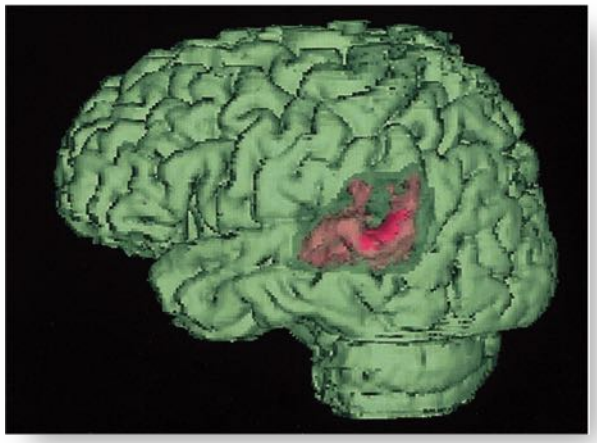


Corsi blocks test for visuospatial STM span – remember locations tapped in correct sequence

How many things (digits or spatial locations) can you remember?
At what sequence length ('span') of digits or tapped spatial locations does performance fail?

Patient studies reveal double dissociations

Between verbal deficits from left posterior lesions and visuospatial deficits from right hemisphere damage

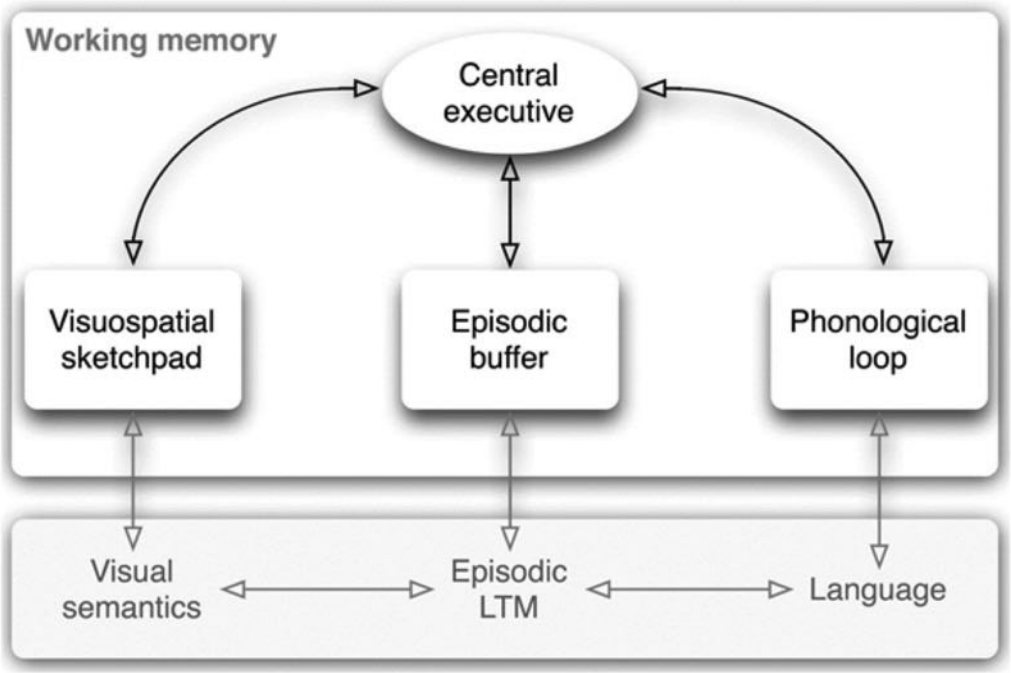


Patient KF (Shallice & Warrington, 1970) with a left parietal lesion had a digit span of only 2 but normal spatial span on Corsi blocks and normal long-term memory

By contrast, patient ELD (Hanley et al, 1991) with a right hemisphere lesion had an impaired spatial span but normal digit span and long-term memory

Working memory

Manipulation of STM contents



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

'Slave' storage systems

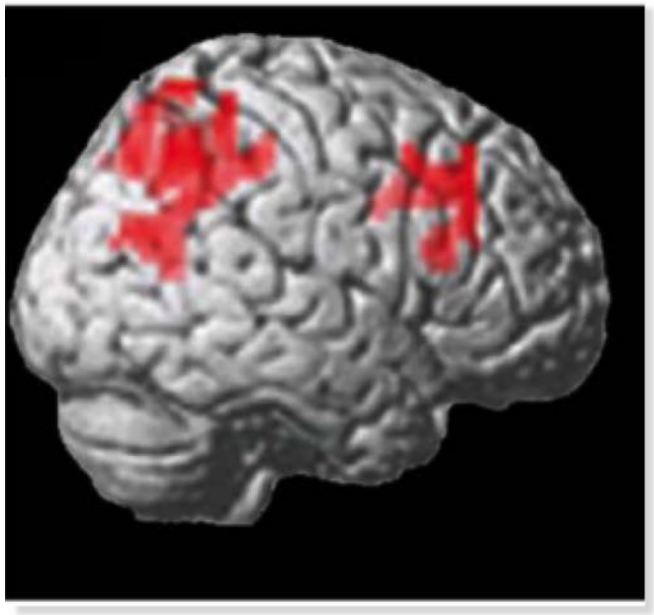
Crystallized LTM (long term memory) systems

Baddeley *Nature Rev Neurosci* 2003

Frontoparietal systems

Implicated in working memory tasks with one influential view being

Parietal cortex
maintenance / storage



Prefrontal cortex
manipulation & monitoring of information in STM

e.g. updating contents as in N-back tasks or reading them in reverse order as in reverse span tasks

BUT now clear that it is difficult to dissociate differences in function between parietal and prefrontal regions

Short-term and working memory

Summary 1

- **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.

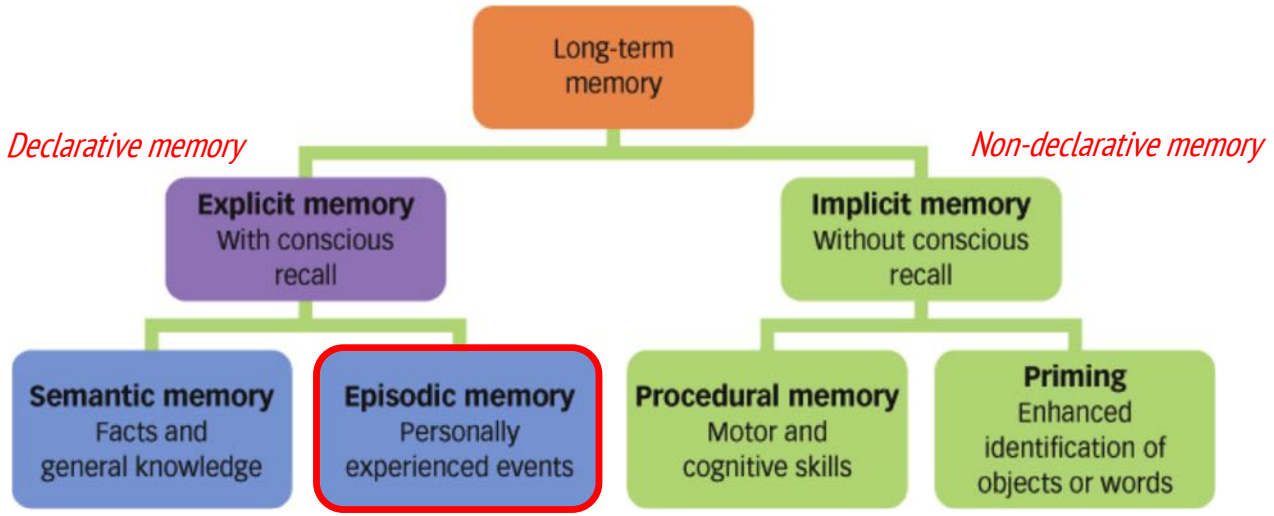
Short-term and working memory

Summary 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)

Fractionation of Long term memory

Into episodic and semantic memory



How do we test for episodic memory?

In the clinical assessment

Anterograde verbal memory

- Ask patient to recall details of very recent events, e.g. what happened to them in the last few days or how they got to the clinic
- You can tell them something about your own interests at the beginning of the interview and ask about these later
- Name and address recall (e.g. in Addenbrooke's Cognitive Examination – next slide)
- Formal tests: story recall or word list learning tests (e.g. Rey Auditory Verbal Learning Test (RAVLT) or California Verbal Learning Test (CVLT)).

Anterograde non-verbal memory

- Rey-Osterrieth Complex Figure recall from memory (after a delay)
- Recognition Memory Test (RMT) subset for faces: recall of a series of photographs of faces

Hodges (2007) *Cognitive Assessment for Clinicians* 2nd ed

Verbal episodic memory

For example by asking patient to remember a name and address

- Free recall is harder than recognition when people have to choose between alternative possibilities
- In the Addenbrooke's Cognitive Examination, participants learn a name and address over 3 trials (encoding) and are then asked to recall (retrieve) it at the end of the test. If they can't recall elements, they are given recognition test (choose between possible alternatives)

<table>
<tr><th colspan="4">M E M O R Y</th></tr>
<tr><td colspan="3">➢ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.</td><td>Memory
[Score 0 – 7]

☐</td></tr>
<tr><td></td><td>1st Trial</td><td>2nd Trial</td><td>3rd Trial</td></tr>
<tr><td>Harry Barnes
73 Orchard Close
Kingsbridge
Devon</td><td>_____ _____
____ _____ _____
_____
_____</td><td>_____ _____
____ _____ _____
_____
_____</td><td>_____ _____
____ _____ _____
_____
_____</td><td></td></tr>
</table>

Verbal episodic memory

For example by asking patient to remember a name and address

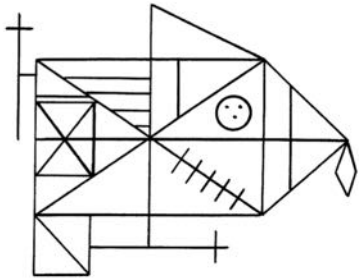
- In the Addenbrooke's Cognitive Examination, participants learn a name and address over 3 trials (encoding) and are then asked to recall (retrieve) it at the end of the test. If they can't recall elements, they are given recognition test (choose between possible alternatives)

MEMORY		
➢ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"		
Harry Barnes 73 Orchard Close Kingsbridge Devon	……. …… …… …… …… …… ……	**Memory** [Score 0-7] ☐
MEMORY		
➢ This test should be done if the subject failed to recall one or more items above. It all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.		**Memory** [Score 0-5] ☐

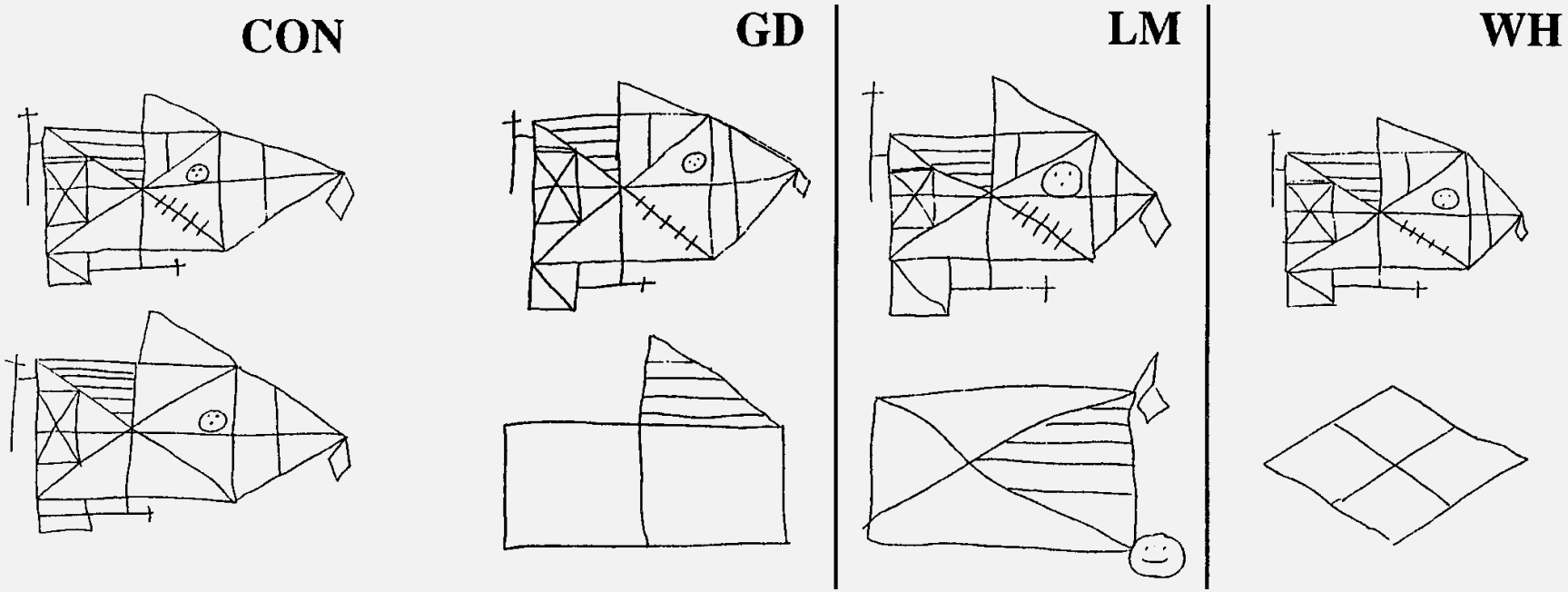
Jerry Barnes	☐	Harry Barnes	☐	Harry Bradford	☐	recalled	☐
37	☐	73	☐	76	☐	recalled	☐
Orchard Place	☐	Oak Close	☐	Orchard Close	☐	recalled	☐
Oakhampton	☐	Kingsbridge	☐	Dartington	☐	recalled	☐
Devon	☐	Dorset	☐	Somerset	☐	recalled	☐

Non-verbal episodic memory

For example by asking patient to remember a complex figure



- Rey-Osterrieth complex figure immediate copying and then 10-15 mins later



Rempel-Clower *et al* (1996) *J Neurosci* | *Squire's group*

How do we test for episodic memory?

In the clinical assessment

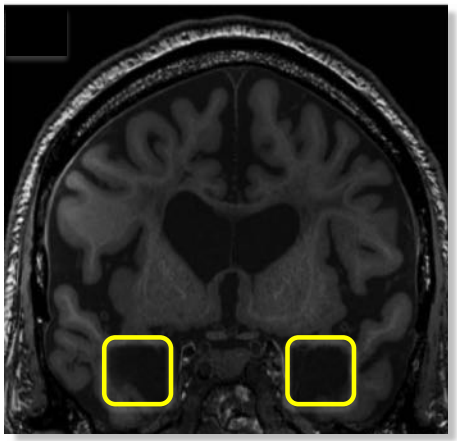
Retrograde memory

- Famous news or sports events from preceding months, years and decades: e.g., wars, scandals, political events, disasters
- Remote personal autobiographical memory
- Formal test: Autobiographical Memory Interview

Hodges (2007) *Cognitive Assessment for Clinicians* 2nd ed

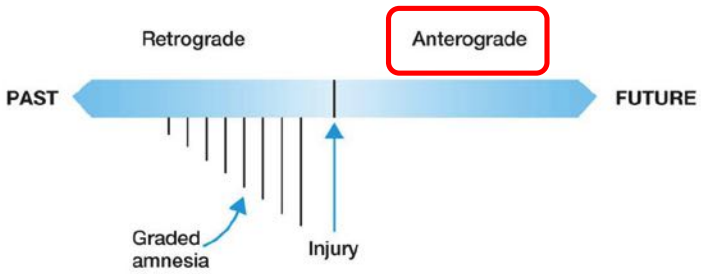
Patient HM

Had surgery for intractable epilepsy in 1953 and was left with a profound disorder of episodic memory



Patient HM with bilateral medial temporal lesions involving the hippocampus had severe deficits in long-term memory (LTM) but intact STM capacity

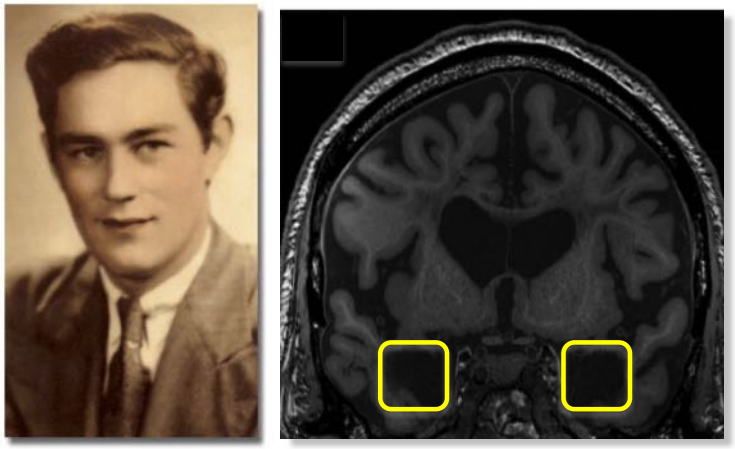
Severe anterograde amnesia



Couldn't learn new information such as events, names or even find his new home. Language 'frozen' in 1950s so new words introduced into the lexicon, e.g. jacuzzi, meant nothing to him.

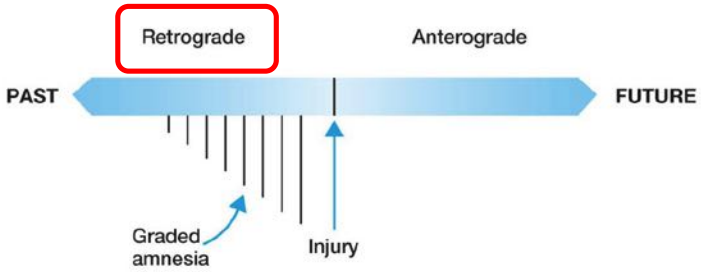
Patient HM

Had surgery for intractable epilepsy in 1953 and was left with a profound disorder of episodic memory



Patient HM with bilateral medial temporal lesions involving the hippocampus had severe deficits in long-term memory (LTM) but intact STM capacity

Severe but graded retrograde amnesia

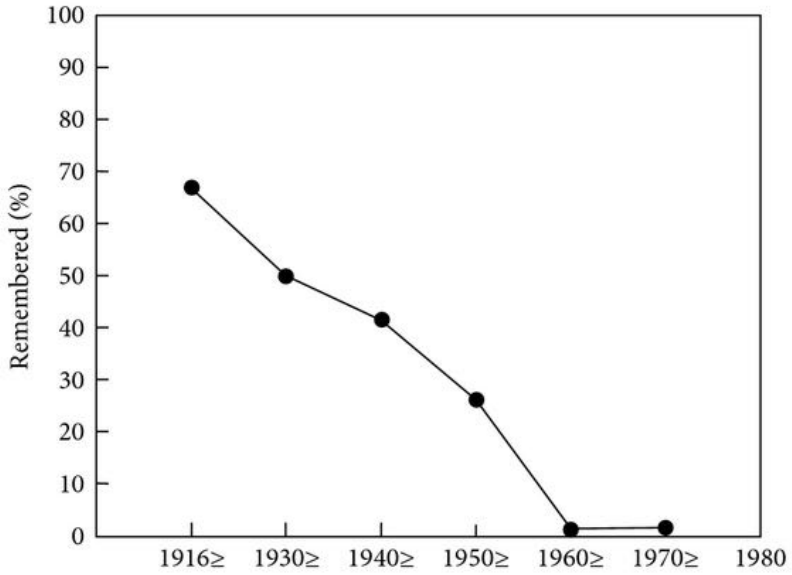


Could still recall childhood memories and jobs in teens and twenties, but difficulty remembering events that occurred in the years immediately preceding surgery.

Retrograde memory loss extended back 11yrs

Temporal gradient in retrograde amnesia (Ribot's law)

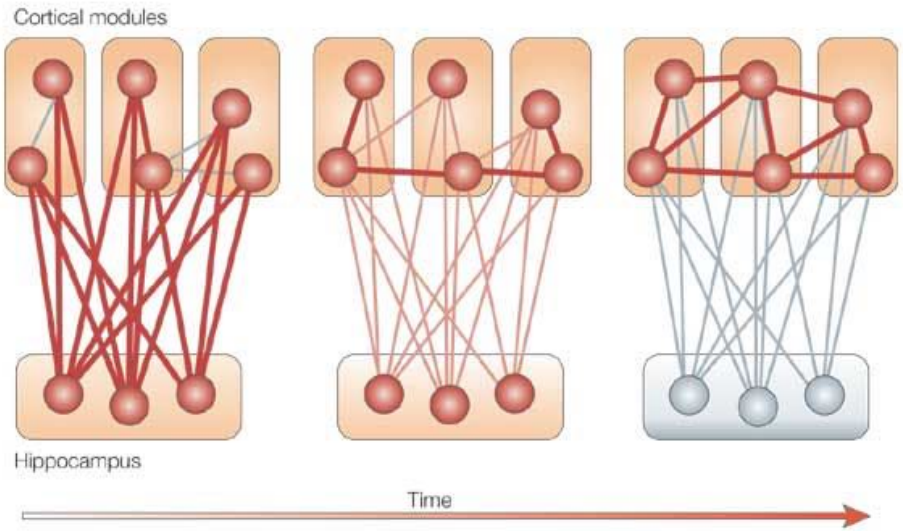
First in, last out | earliest memories survive best



Butters & Cermak 1986

Consolidation hypothesis of hippocampal role in memory

'Standard model' proposes initially hippocampal-cortical interactions are required but eventually transfers to cortex



'Standard model' of Larry Squire

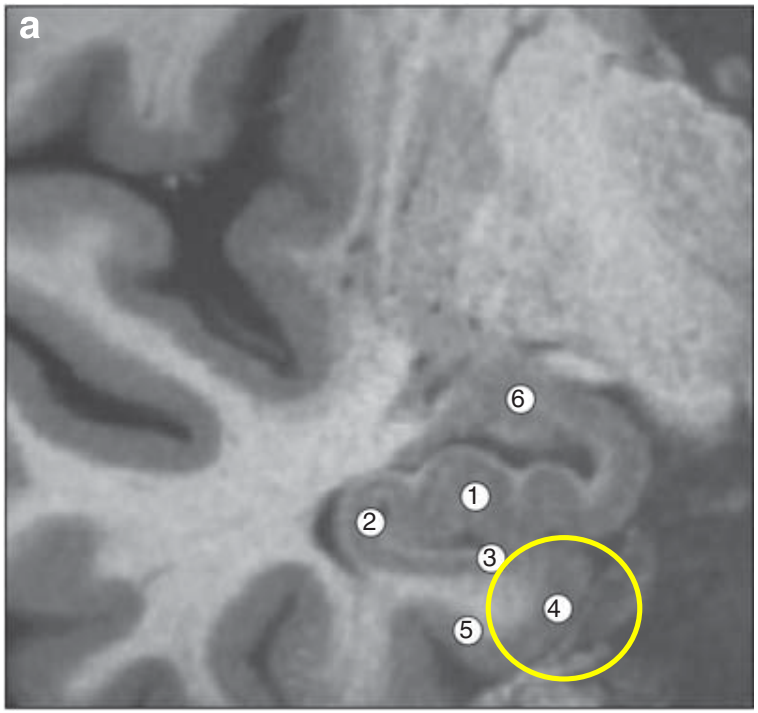
*So lesions of hippocampus won't erase old memories which are consolidated and robustly represented in the cortex. Hence **graded** retrograde amnesia after hippocampal lesions.*

But hippocampal lesions would prevent consolidation of new memories. Hence severe anterograde amnesia in HM.

Frankland & Bontempi (2005) *Nat Rev Neurosci*

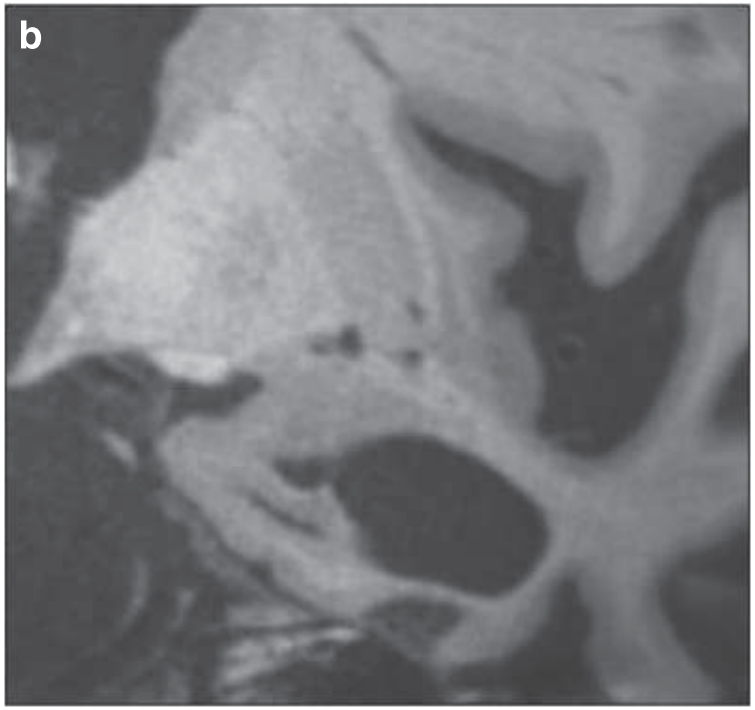
Medial temporal involvement in Alzheimer's disease

High resolution imaging at 7 Tesla



24 yr old healthy person

1 CA3 / dentate gyrus
2 CA1
3 Subiculum
4 Entorhinal cortex
5 Perirhinal cortex
6 Amygdala

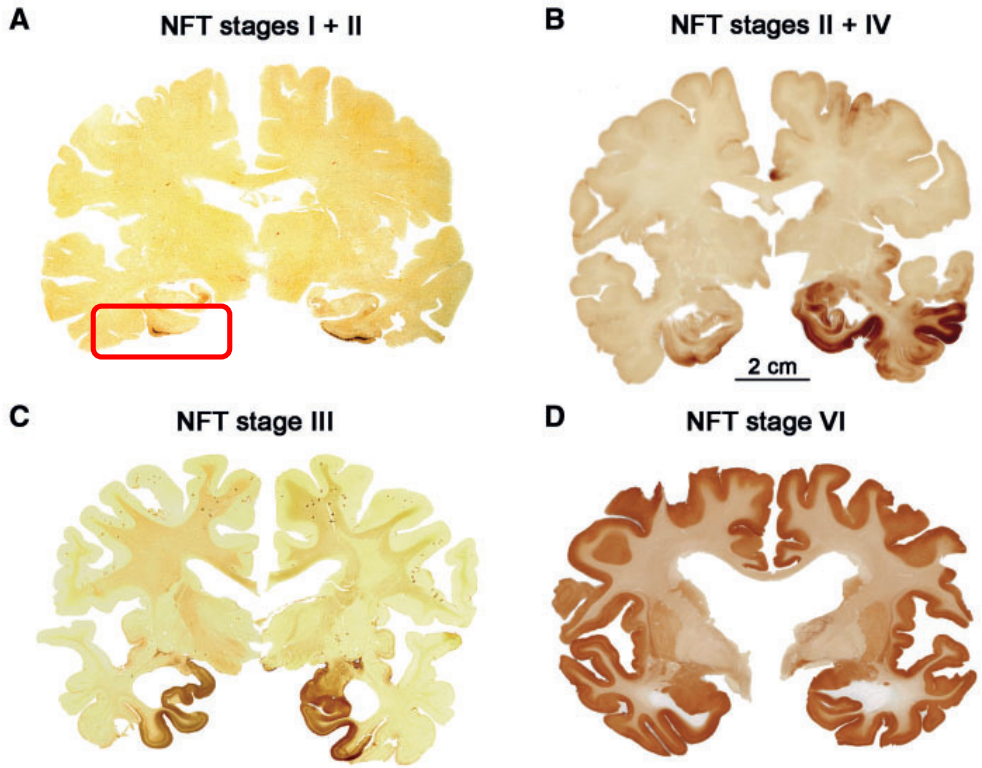


72 yr old with mild AD

Dickerson & Eichenbaum (2010) *Neuropsychopharm Rev*

Regional spread of Alzheimer pathology

Earliest regions to show tau pathology (neurofibrillary tangles) is entorhinal cortex | Braak staging



Mild cognitive impairment (MCI)

Prodromal Alzheimer's disease in many cases

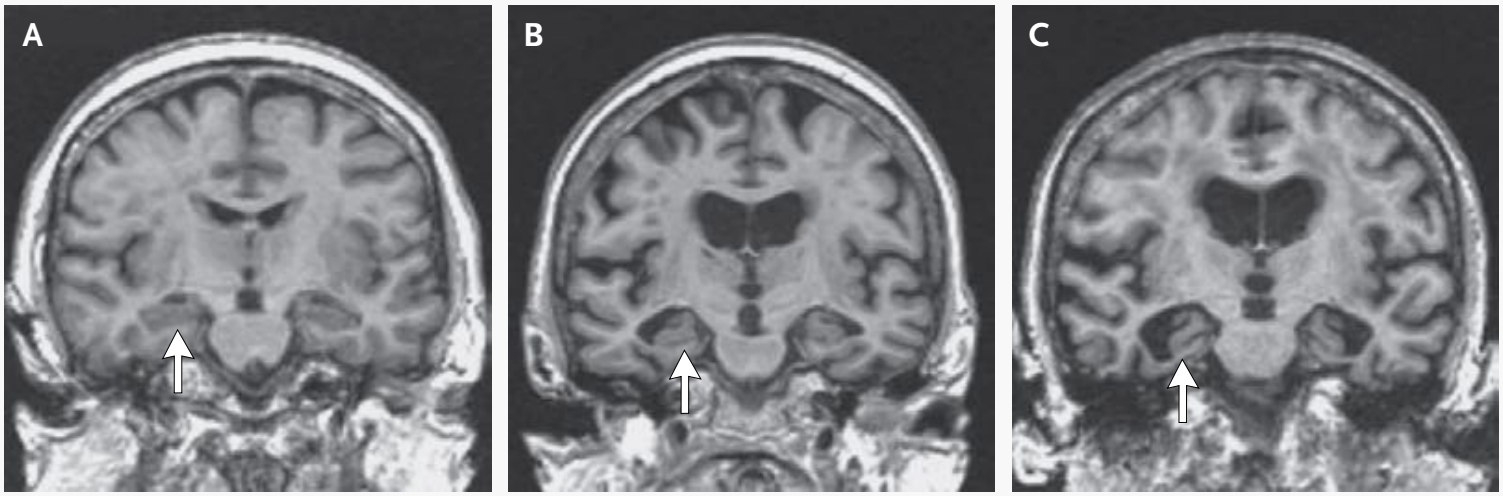


Figure 2. Coronal MRI Scans from Patients with Normal Cognition, Mild Cognitive Impairment, and Alzheimer's Disease.

The arrows depict the hippocampal formations and the progressive atrophy characterizing the progression from normal cognition (Panel A) to mild cognitive impairment (Panel B) to Alzheimer's disease (Panel C).

Petersen (2011) *New England J Med*

Mild cognitive impairment (MCI) and prodromal Alzheimer's

MCI Patients have an annual risk of ~10% conversion to diagnosis of Alzheimer's disease

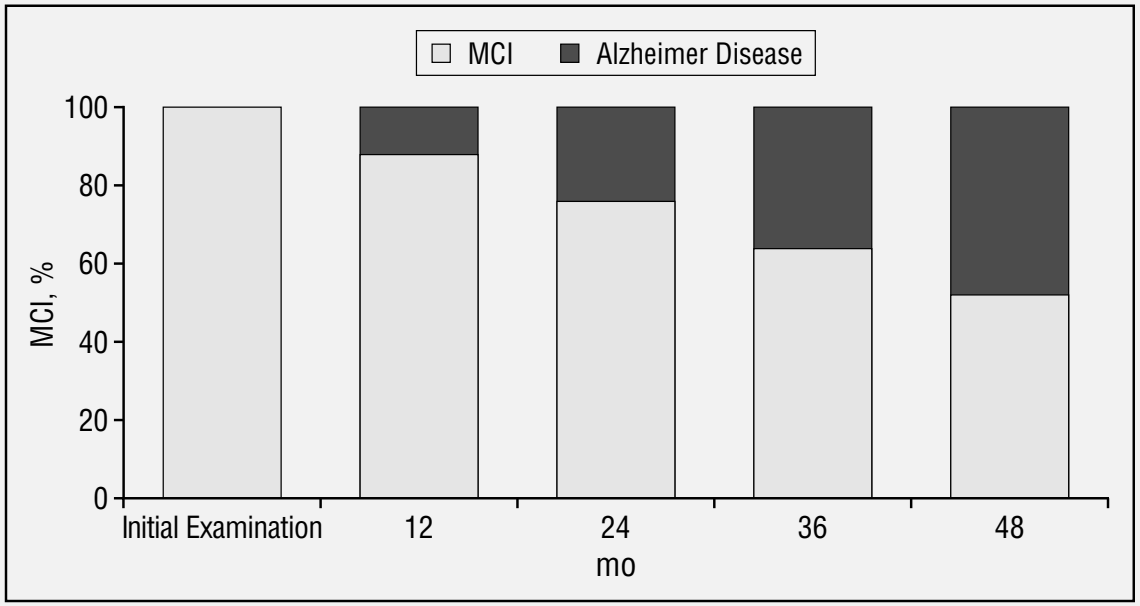


Figure 2. *Annual rates of conversion from mild cognitive impairment (MCI) to dementia over 48 months.*

Petersen *et al* (1999) *Arch Neurol*

DSM-5 criteria

For mild neurocognitive disorder

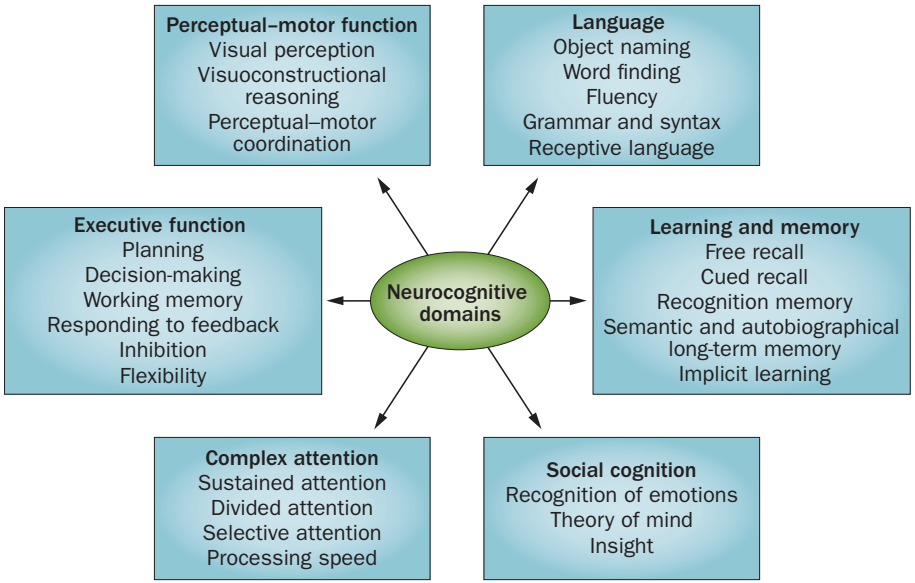
Box 2 | Diagnostic criteria for mild neurocognitive disorder

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual–motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia).

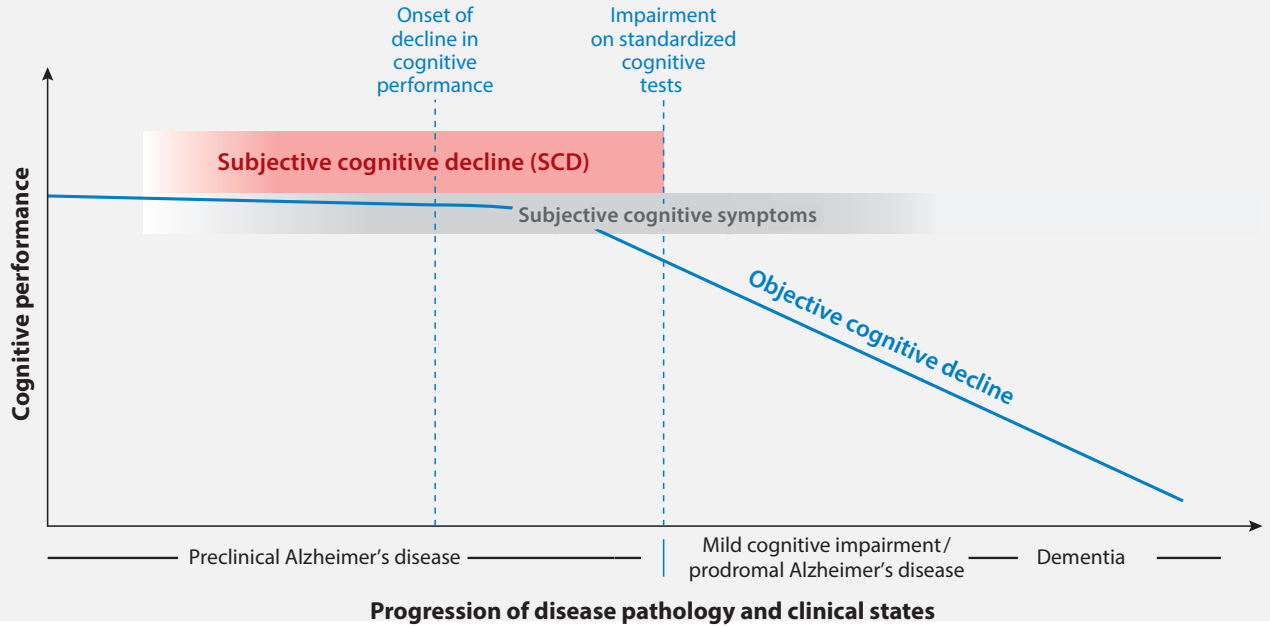


Neurocognitive domains

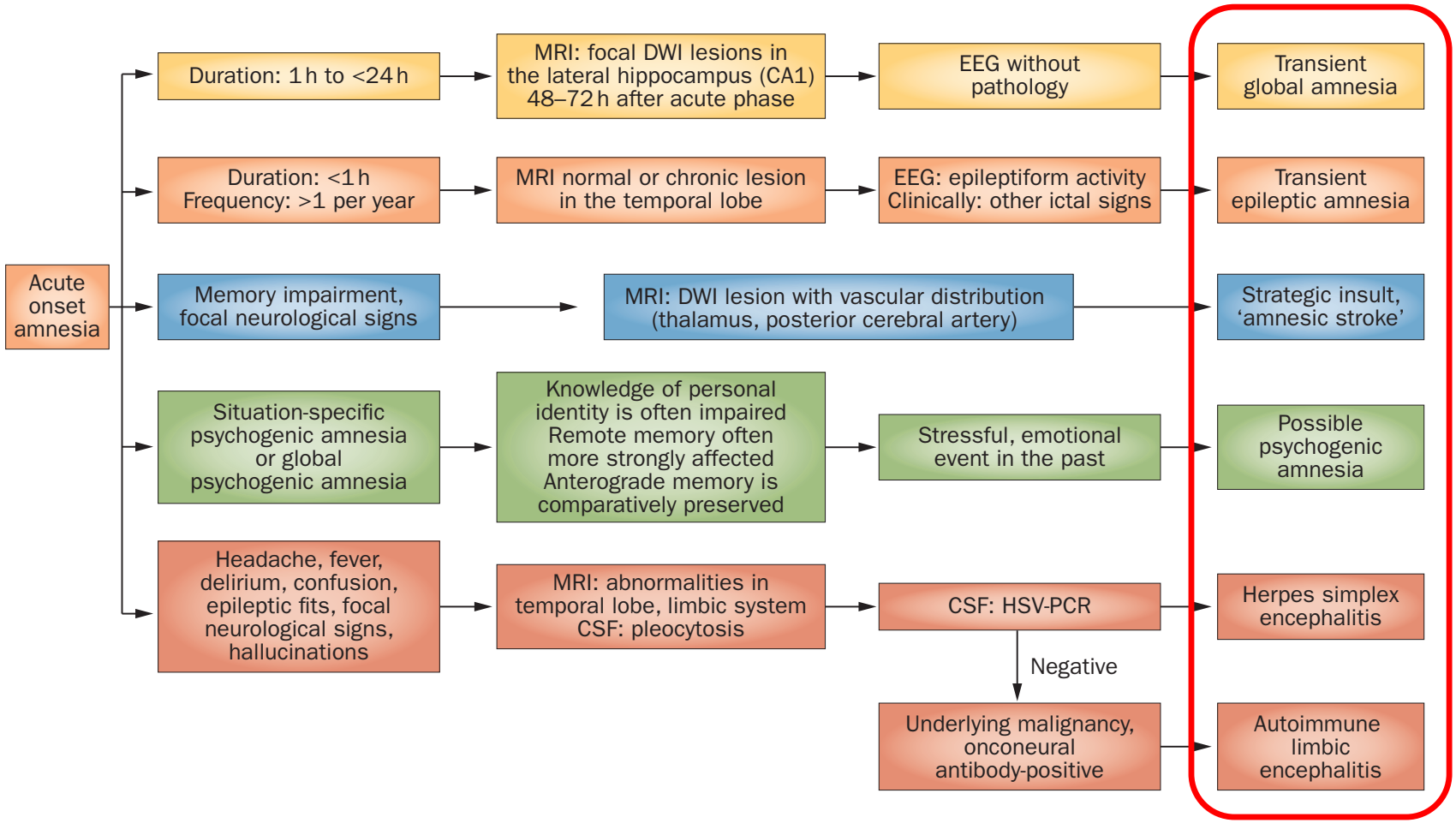
Subjective cognitive impairment (SCI) / decline (SCD)

Most cases are not prodromal Alzheimer's but nevertheless SCI is associated with increased risk of developing AD

- Individuals perceive decline in memory and/or other cognitive abilities relative to their previous level of performance, in the absence of objective neuropsychological deficits
- Increased risk of developing dementia, but exactly what is that risk?



Acute onset amnesia



Barsch & Butler (2013) *Nat Rev Neurol*

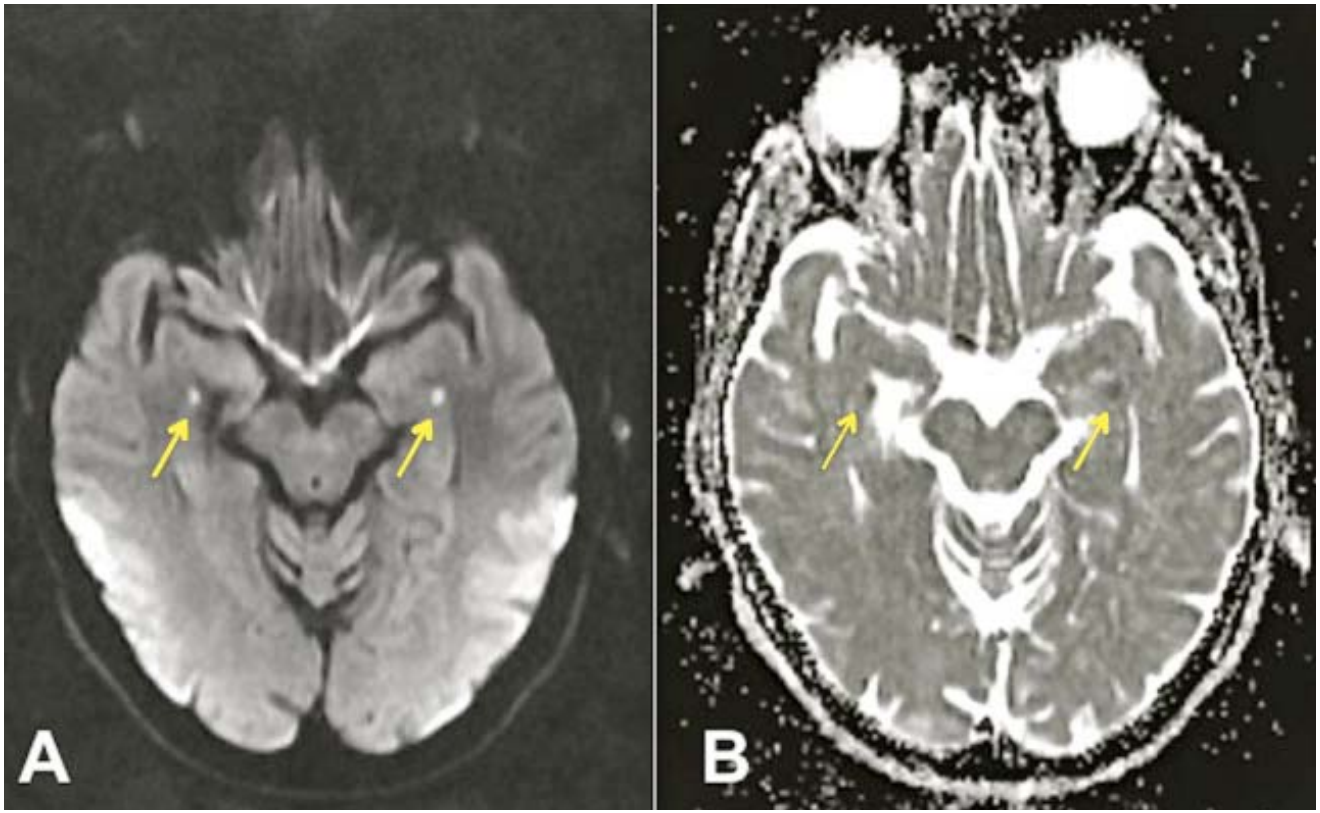
Transient global amnesia (TGA)

Episode of amnesia resolving within 24hrs

- Witnessed anterograde amnesia without clouding of consciousness or loss of personal identity
- Cognitive impairment limited to amnesia. No focal physical neurological signs or features of epilepsy. No recent head trauma or seizures.
- Resolution within 24hrs. Recurrence unusual but may occur in 6-10%
- Mild headache / nausea / dizziness might be present during attack
- **Memory during attack:** Episodic memory tested with recall of word list or complex figures shows dense anterograde amnesia. Performance on tests of retrograde amnesia variable but typically shows Ribot's gradient, particularly with respect to autobiographical details. Spatial memory deficits for learning and retrieval too. Semantic memory spared
- **Memory after attack:** Usually good but there is some debate on this. After recovery a dense amnesic gap for events that occurred during the attack itself often persists

Acute in MRI in TGA

Can sometimes detect punctate DWI change



MRI 48hrs after symptom onset

A) DWI
B) Restricted diffusion on ADC maps

Changes had resolved on repeat imaging 3 weeks later

Wilkinson et al (2013) *Practical Neurol*

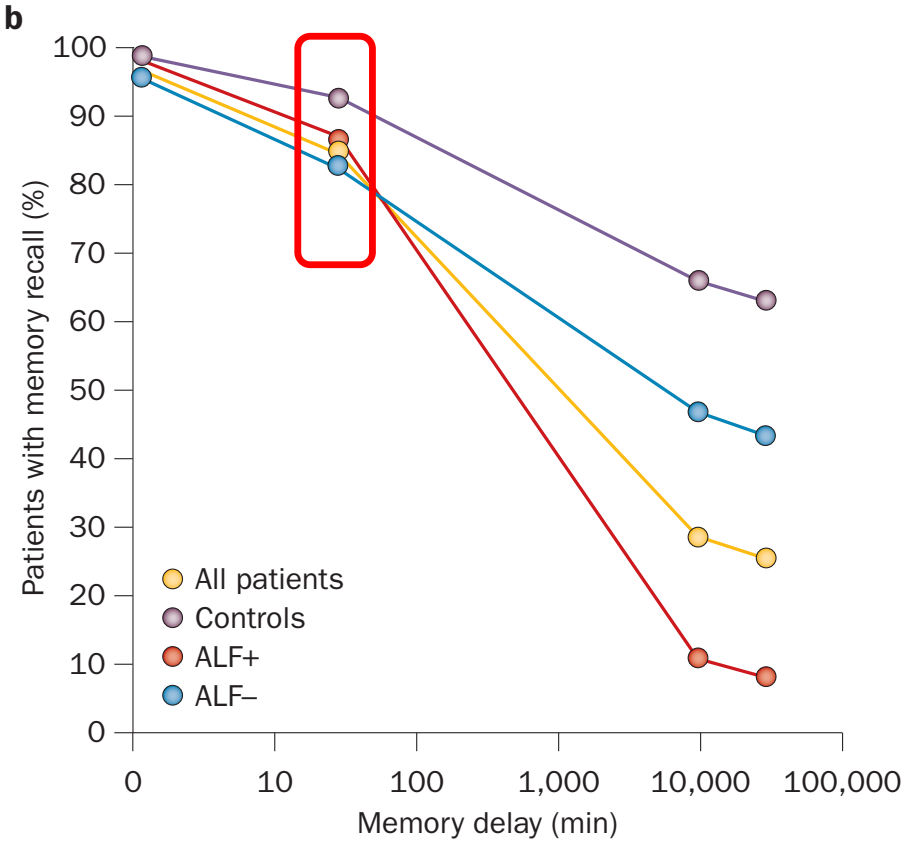
Transient epileptic amnesia (TEA)

Recurrent episodes associated with brief episodes of amnesia but with long term consequences

- Recurrent, witnessed episodes of transient amnesia (often during waking)
- Cognitive functions other than memory as judged by a reliable witness appear normal, e.g. speech, finding way around a house, even driving may be intact
- Evidence of epilepsy: concurrent suggestive clinical features (olfactory / gustatory hallucinations, automatisms such as lip smacking), abnormal EEG or clear-cut response to anticonvulsant therapy
- **Memory during attack:** Patients have difficulty laying down new memories (anterograde amnesia) and also retrieving past events (retrograde amnesia) BUT in contrast to TGA, anterograde deficit is often partial. >40% patients say they can recall "not being able to remember". They may repetitively ask questions but this is not as consistent as in TGA.
- **Memory after attack:** Most cases have significant ongoing difficulties with either remote autobiographical memory, accelerated long term forgetting (ALF) **after days**, spatial navigation / topographical amnesia.

Accelerated long-term forgetting in TEA

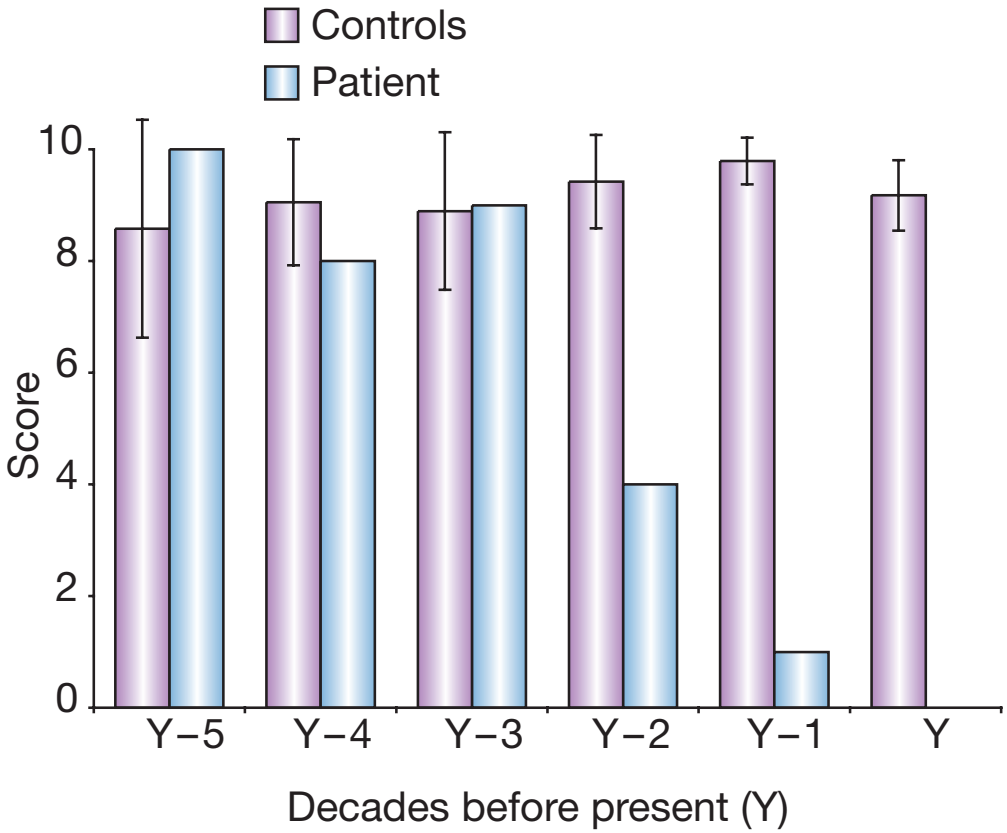
Standard neuropsychological testing of episodic memory might test recall after 15 or 30 minutes, not days



Barsch & Butler (2013) *Nat Rev Neurol*

Autobographical memory deficit in TEA

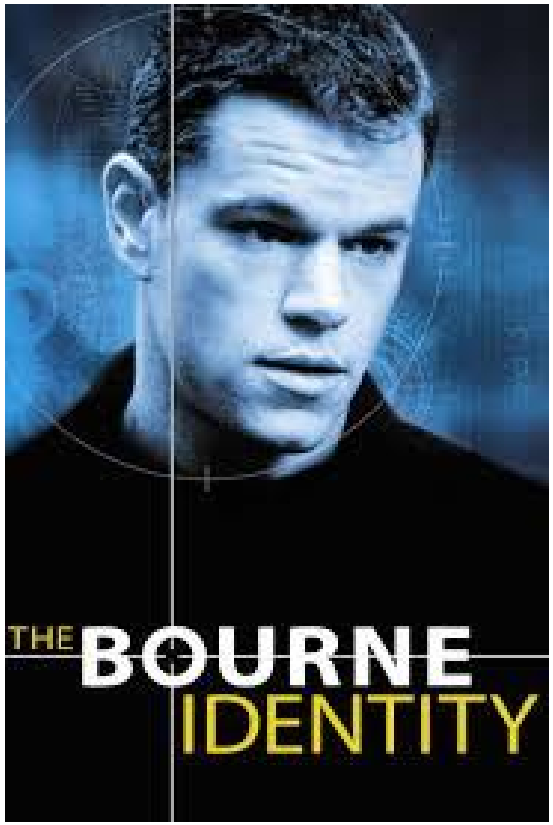
Gradient of deficit following Ribot's law



Butler & Zeman (1999) *Nat Rev Neurol*

Complete retrograde amnesia but intact anterograde memory

Jason Bourne in the 'Bourne Identity' has no idea who he is or what he did



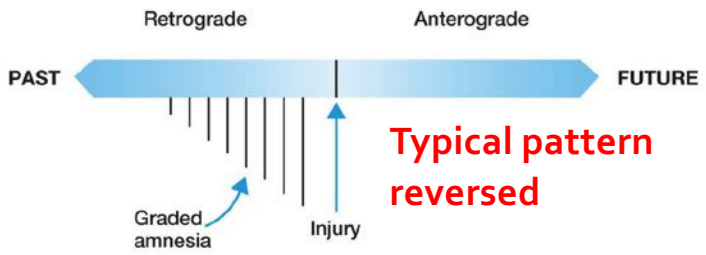
Psychogenic amnesia

Profound retrograde amnesia for personal events but often with intact anterograde memory

- Amnesia without any cause found on investigation
- Often associated with highly stressful life event as precipitant
- There may be a period of wandering or ‘psychogenic fugue’
- **Memory during attack:** Patient may not recall or their own name or be able to recognize family members. They may have no knowledge of who they are, where they live or what they do. They may have no knowledge of famous news events across their lifespan. But often have no difficulty remembering new information, e.g. from clinical staff. In fact they may be able to ‘relearn’ about themselves
- **Memory after attack:** Most cases have full recovery

Psychogenic amnesia vs TGA or TEA

Some important tell-tale differences



IN BOTH

Can be preceded by precipitating stress/significant life-event

Standard investigations (routine EEG, CT, MRI) can be normal

DIFFERENTIATION

Loss of personal identity in fugue, never in TGA

Repetitive questioning in TGA/TEA, seldom in fugue/psychogenic amnesia where there may be 'la belle indifference'

Other symptoms/signs, e.g. sensorimotor in TEA, wandering in fugue

'Temporal gradient' of retrograde amnesia in TGA/TEA vs. 'reversed gradient' in psychogenic amnesia

Kopelman (2003) *Practical Neurol*

Transient amnesia syndromes

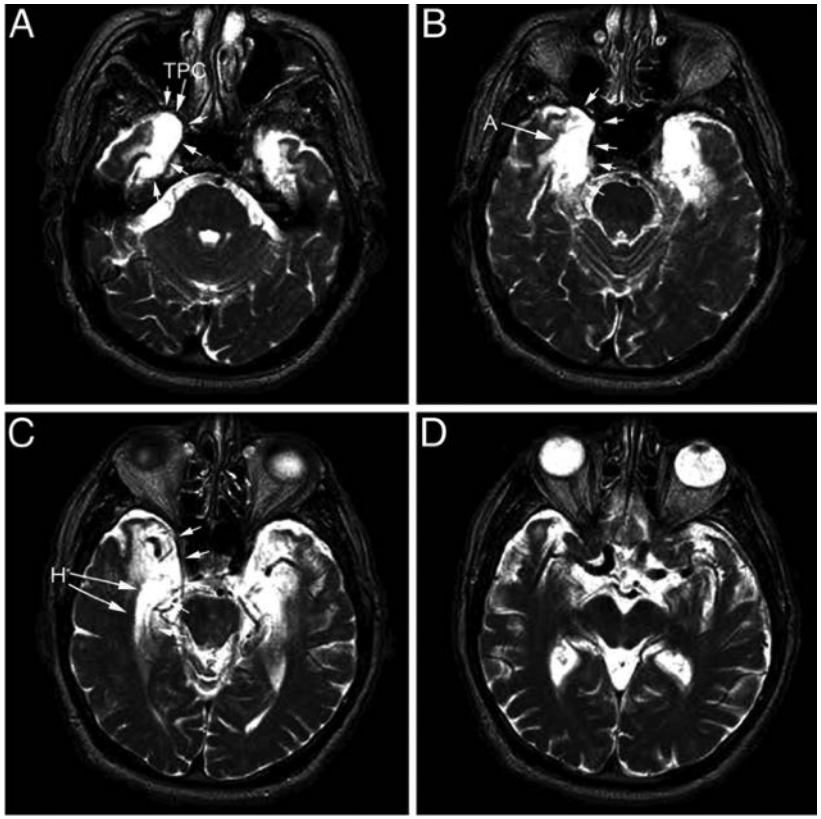
******

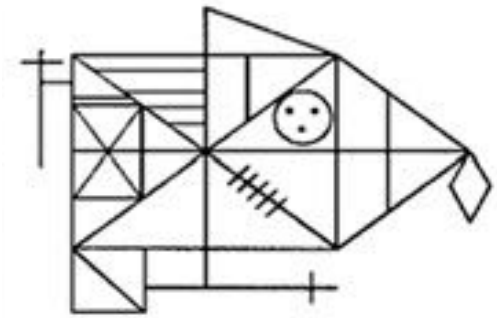
Table 1 Distinguishing clinical features of the transient amnesic syndromes.

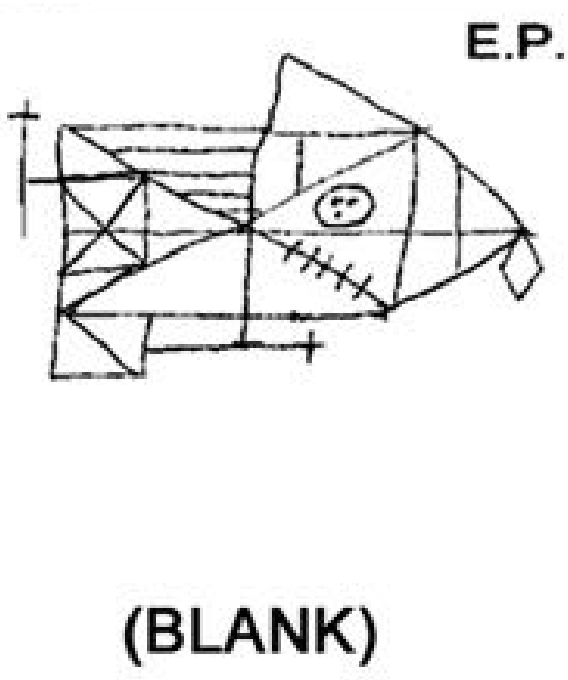
Feature	Transient epileptic amnesia	Transient global amnesia	Psychogenic amnesia
Typical age of onset	50–70 years	50–70 years	Any age
Past medical history	None	Migraine	'Organic' transient amnesia; substance abuse; psychiatric illness
Precipitants	Waking	Cold water; physical exertion; psychological stress	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

Amnesia with encephalitic syndromes

Viral encephalitis



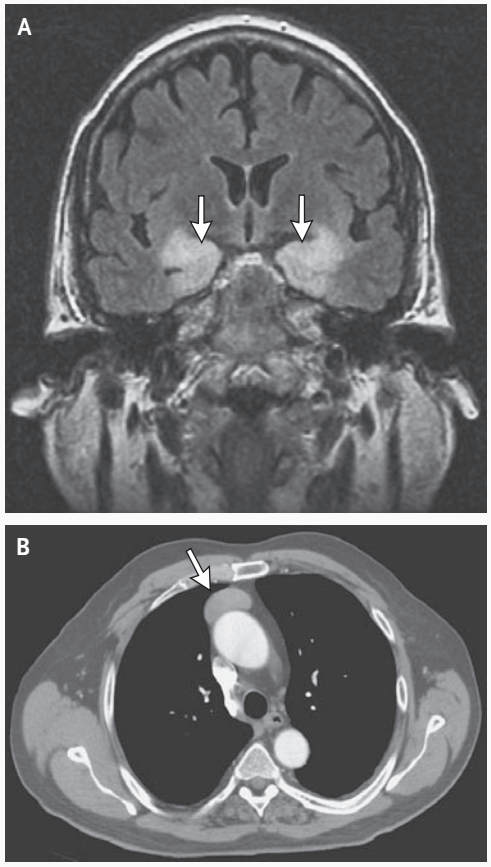




Insausti *et al* (2013) *PNAS* | *Squire's group*

Amnesia with encephalitic syndromes

Paraneoplastic limbic encephalitis



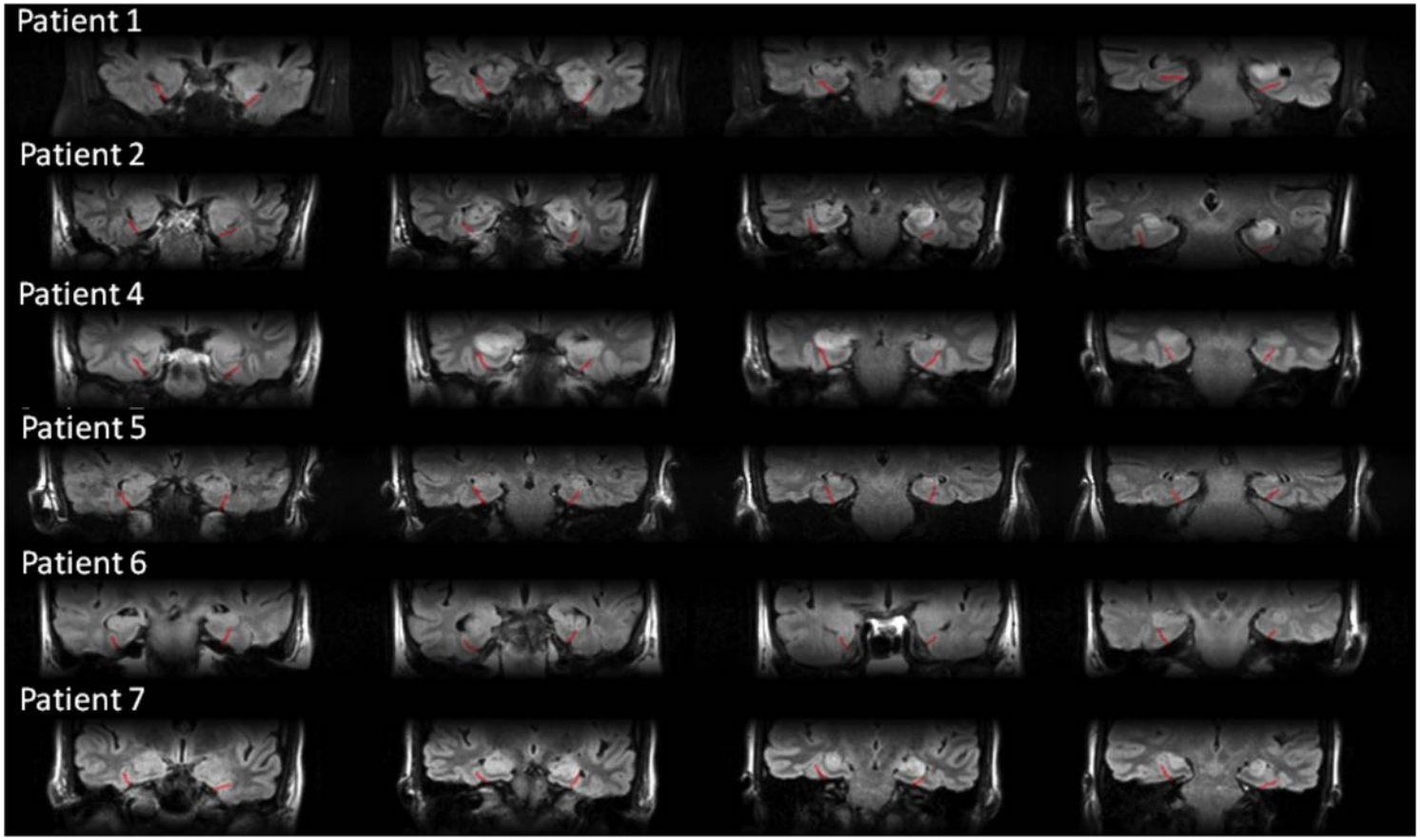
Antibody	Associated Cancers
Anti-Hu antibody (ANNA-1)	Small-cell lung cancer
Anti-CV 2 antibody (CRMP5)	Small-cell lung cancer, thymoma, testicular germ-cell tumor
Anti-Ma antibody (Ma 1, Ma 2)	Testicular cancer, lung cancer, breast cancer
Antiamphiphysis antibody	Small-cell lung cancer, breast cancer
ANNA-3	Small-cell lung cancer
PCA-2	Small-cell lung cancer

Associated here with carcinoid tumour involving thymus

Daffner *et al* (2008) *NEJM*

Focal MTL signal change with amnesia and seizures

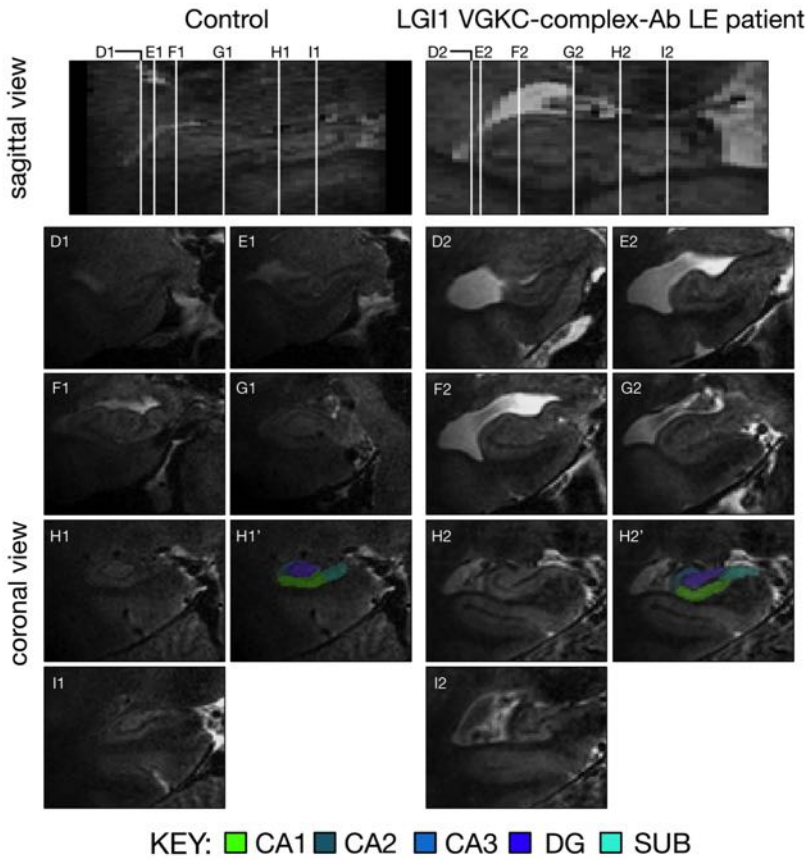
LGI1 antibody mediated limbic encephalitis

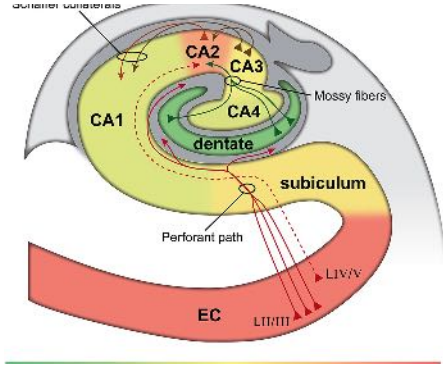


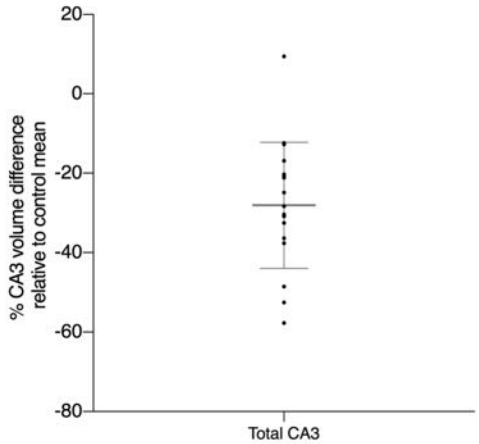
Pertzov *et al* (2013) *Brain*

Long-term hippocampal atrophy in LGI1 ab encephalitis

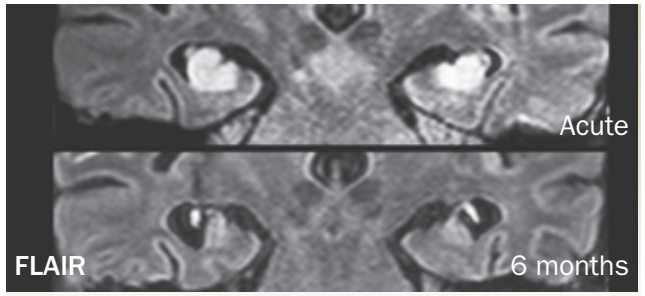
CA3 atrophy on 7T MRI



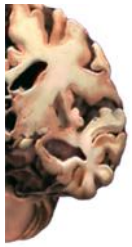




Miller *et al* (2017) *Brain*

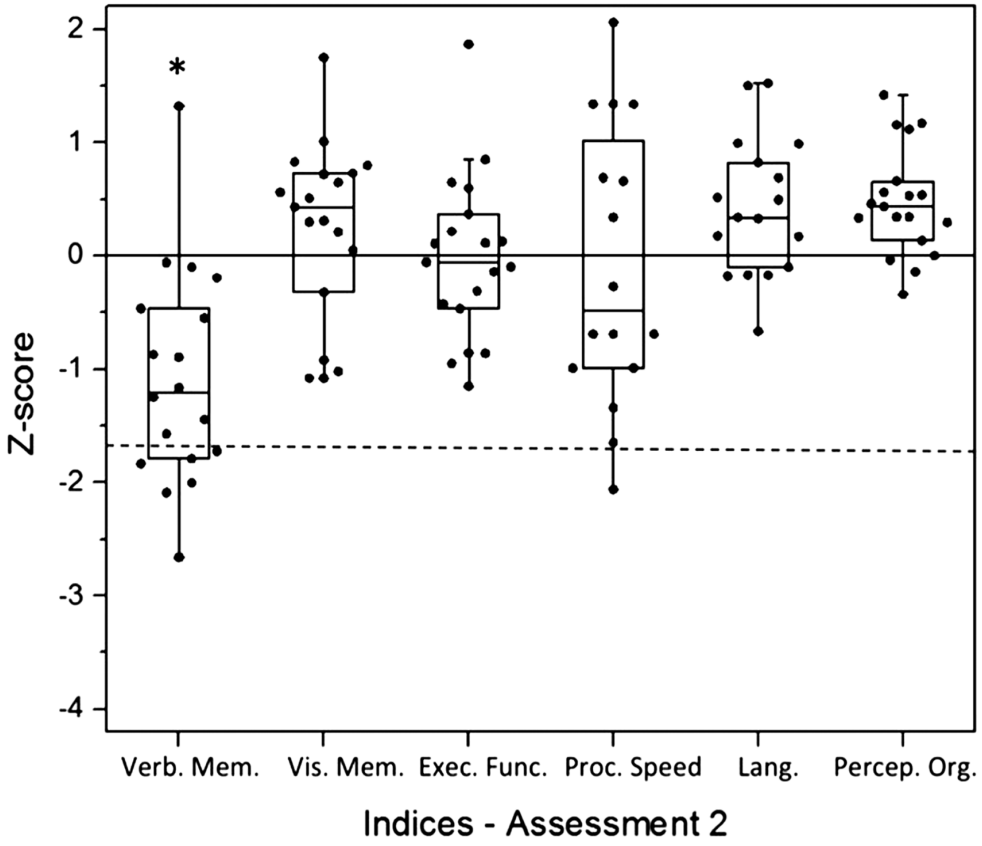


Barsch & Butler (2013) *Nat Rev Neurol*



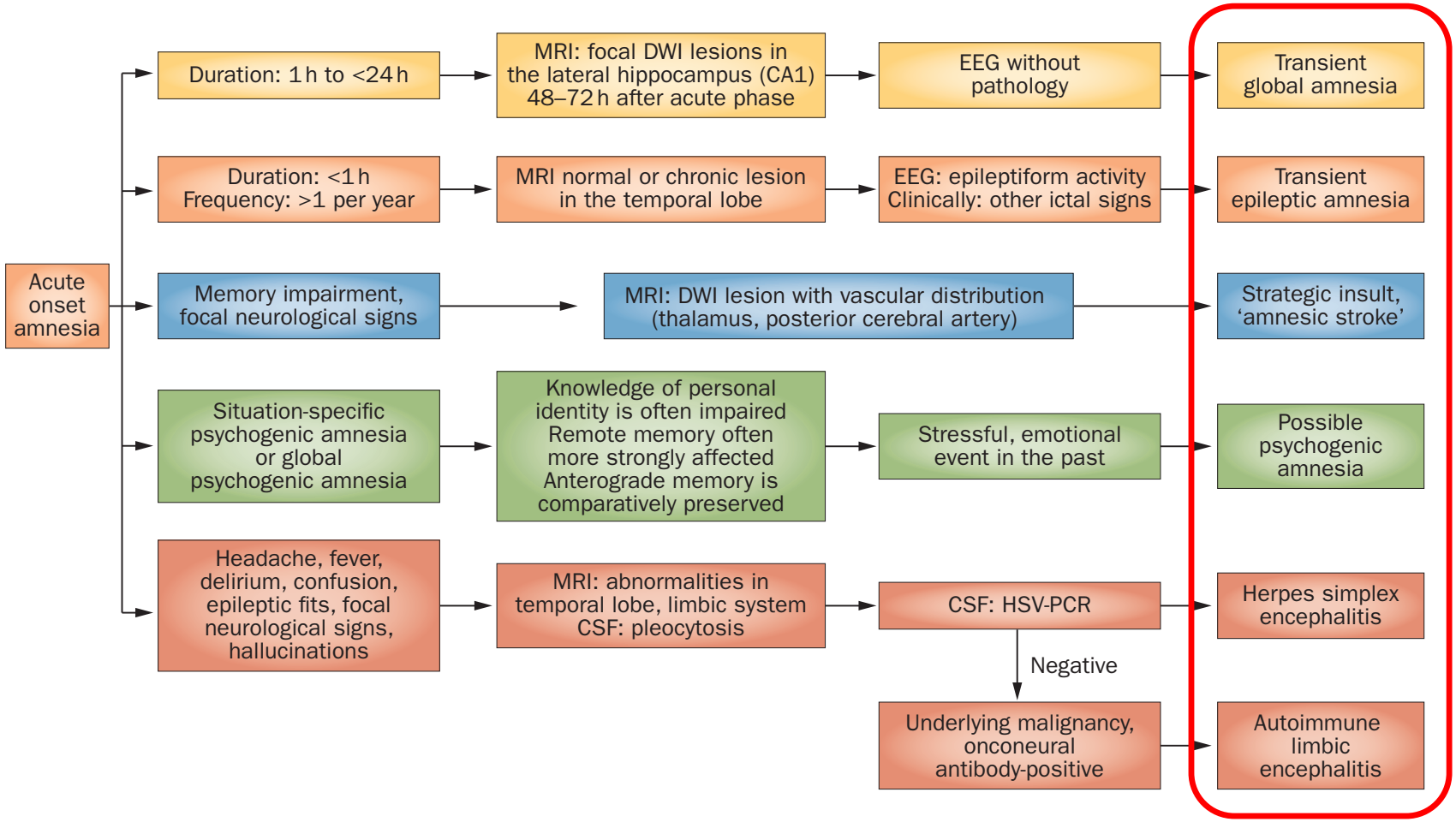
Long-term cognitive outcome in LGI1 ab encephalitis

Most prominent deficit is in episodic verbal memory



Butler *et al* (2017) *JNNP*

Acute onset amnesia

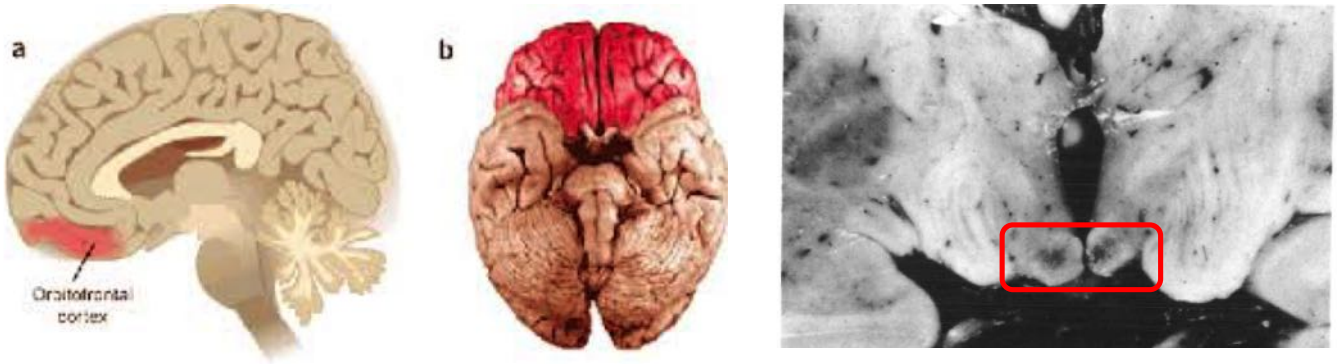


Barsch & Butler (2013) *Nat Rev Neurol*

Confabulation

False memories without conscious knowledge of their falsehood

Often a plausible, but imaginary, recollection of an event or sometimes a grand account of personal life



After orbitofrontal / ventromedial prefrontal cortex damage and in Korsakoff's syndrome

Wernicke-Korsakoff syndrome

Non-alcohol related causes

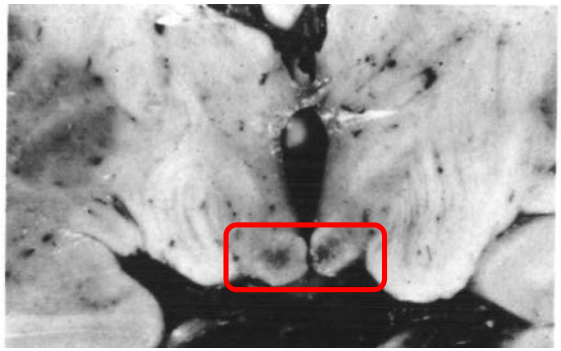
Table 2 Precipitating illness in cases of Wernicke-Korsakoff syndrome not related to alcohol

Precipitating illness	n (%)	Male	Female	Gender not reported
Gastrointestinal tract disease or surgery	213 (34)	78	135	0
(Bariatric surgery)	69 (11)	11	58	0
(Cancer)	54 (9)	29	25	0
(Obstruction)	25 (4)	12	13	0
(Pancreatitis)	11 (2)	6	5	0
(Crohn's disease)	6 (1)	0	6	0
(Other)	48 (8)	20	28	0
Hyperemesis gravidarum	115 (18)	0	115	0
Dietary insufficiency, starvation or vomiting	106 (17)	59	47	0
Leukaemia or cancer of lymphoid system	36 (6)	17	19	0
Intravenous feeding or hyperalimentation	29 (5)	10	11	8
Psychiatric disorders	13 (2)	4	9	0
(Schizophrenia spectrum)	7 (1)	4	3	0
(Anorexia nervosa)	6 (1)	0	6	0
Dialysis	11 (2)	7	4	0
HIV/AIDS	10 (2)	7	3	0
Other or unspecified	90 (14)	34	55	1

Scalzo *et al* (2015) *JNNP* 86: 1362

Korsakoff's syndrome

Amnesia due to thiamine deficiency



Haemorrhage then atrophy of mamillary bodies

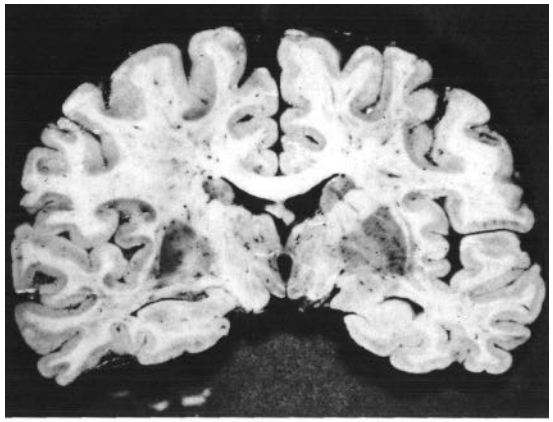
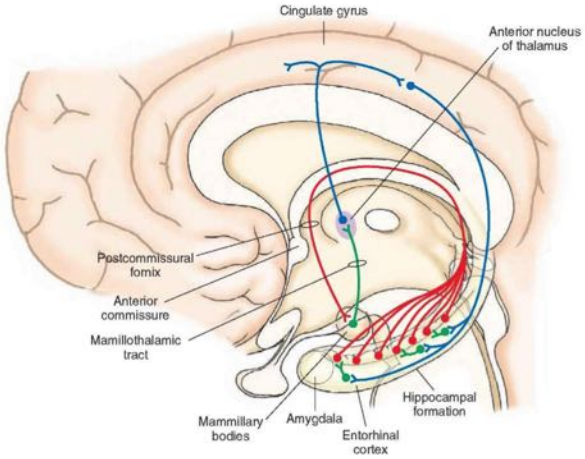
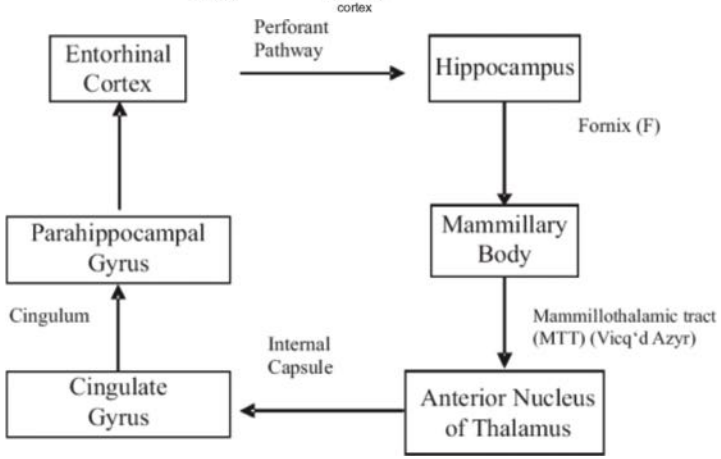


FIG. 4. *E.A.* The mammillary bodies are markedly shrunken.





Theories of confabulation

Propose a disorder of source monitoring or a deficit in strategic retrieval of memories

Temporality account

- Confusion over when they were exposed to information

Source monitoring account (not dissimilar to temporality accounts)

- Inability to distinguish the source of different memories

  e.g. "I went on a flight to New York by Concorde last week and then embarked on a cruise to the Caribbean, before dining with the King of Lesotho"

- The patient might have memories of seeing such events on television sometime in the past, even though he never did these himself

Strategic retrieval hypothesis

- Monitoring the quality of retrieved information fails in confabulators

Episodic memory

Summary 1

- **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

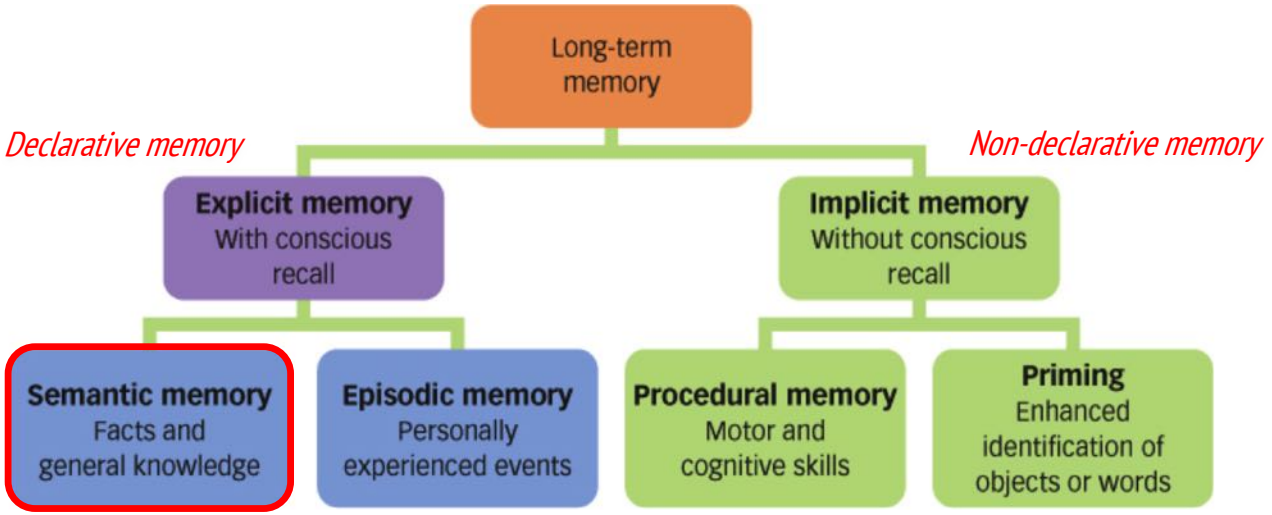
Episodic memory

Summary 2

- **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

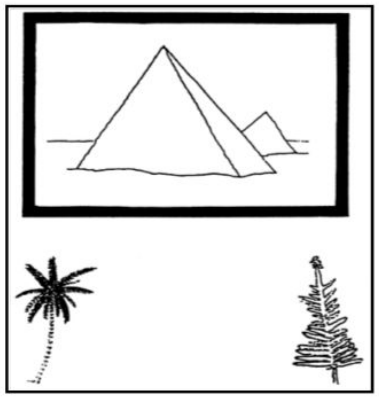
Fractionation of Long term memory

Into episodic and semantic memory



Testing semantic knowledge

Pyramid and Palm Tree Test



3 Picture Version

Pyramid

Palm Tree

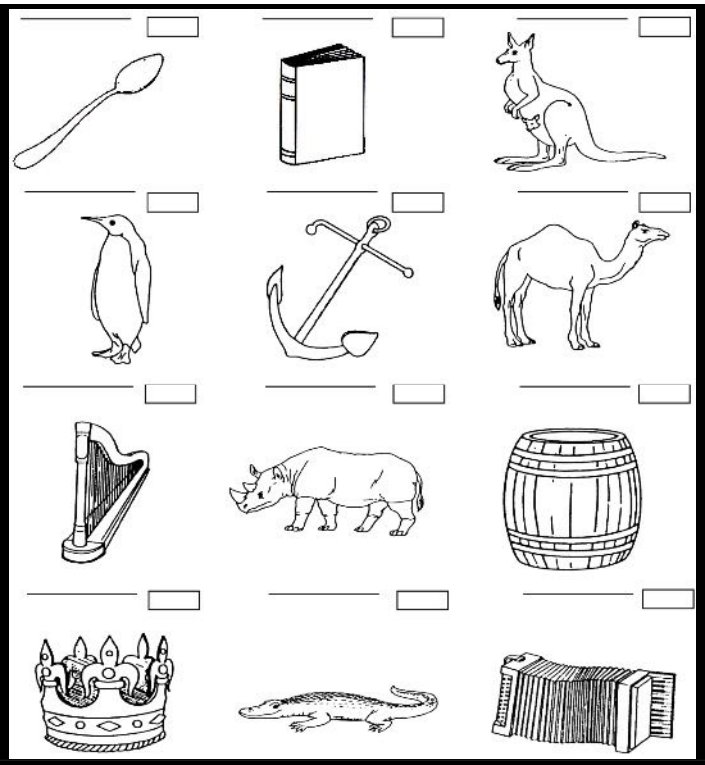
Fir Tree

3 Word Version

Pyramid and Palm Trees Test – which one of the two lower items goes with the upper item?

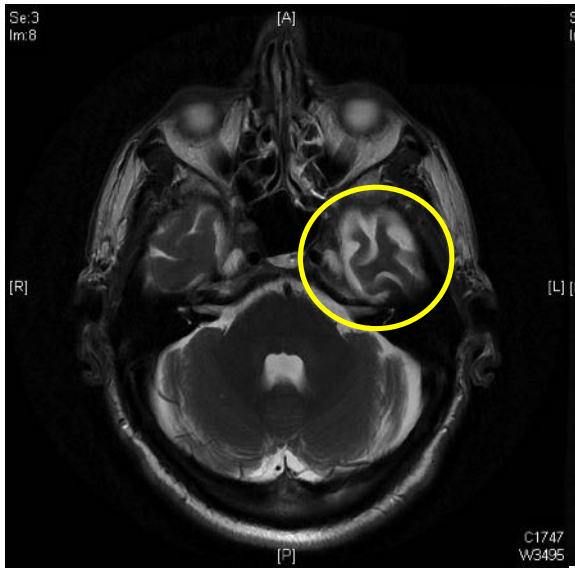
Testing semantic knowledge

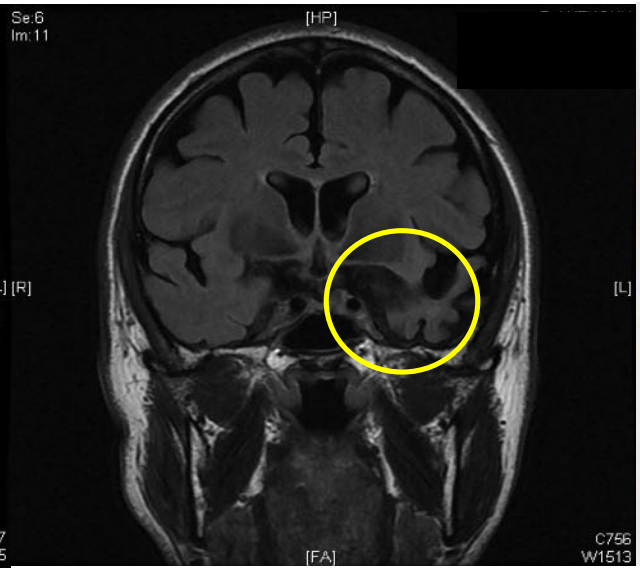
Naming and asking about the use of an object

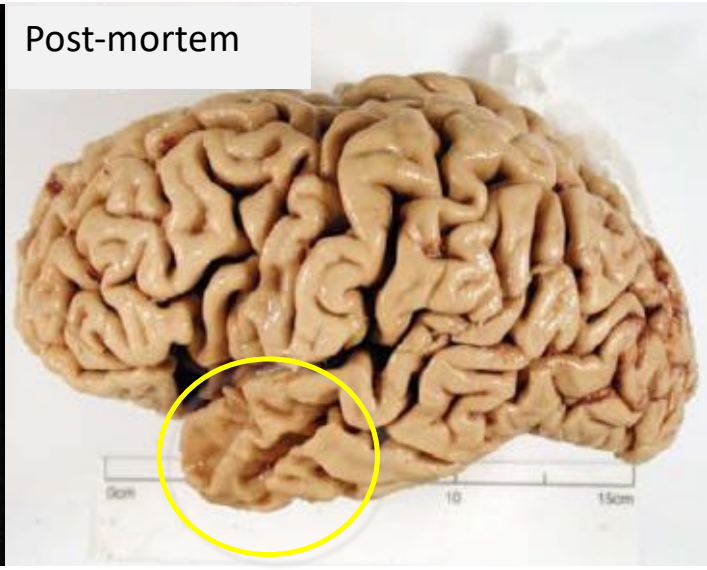


Semantic dementia

Atrophy of left temporal pole

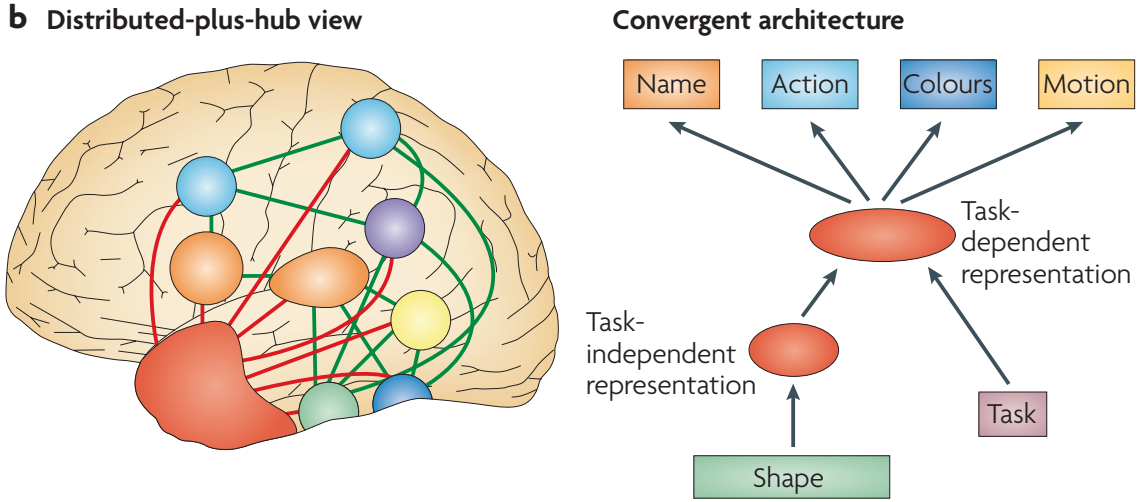


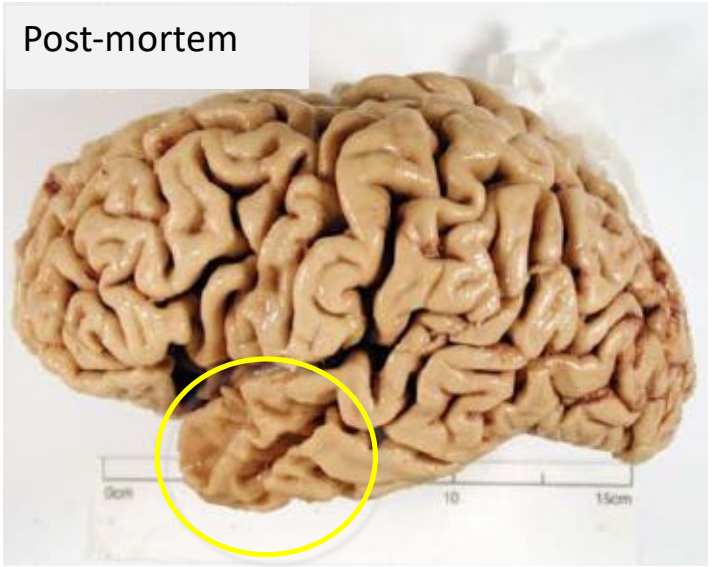




Semantic dementia

Semantic hub in left temporal pole?





Patterson *et al* (2007) *Nature Rev Neurosci*

Semantic memory

Summary 1

- **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

Semantic memory

Summary 2

- 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

Reading

General textbooks

- Hodges J (2017) Cognitive Assessment for Clinicians 3rd ed
- Husain M & Schott J (2016) Oxford Textbook of Cognitive Neurology & Dementia