NORMAL BRAIN

AGING BRAIN,

MILD COGNITIVE IMPAIRMENT

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- MEMORY is ability to store and retrieve information when people need it.
- The four general types of memories are **sensory memory, short-term memory, working memory, and long-term memory**.
- Long-term memory can be further categorized as **explicit (conscious) and implicit (unconscious)**

Sensory memory

- Allows to remember sensory information after the stimulation has ended
- There are three types of sensory memory: ***iconic*** which is obtained through sight; ***echoic*** which is auditory; and ***haptic*** which is through touch
- Typically sensory memory only holds onto information for brief periods.
- When a sensory experience keeps recurring ,it might move to your short-term memory or more permanently to long-term memory.

Short-term Memory

- Allows to recall specific information about anything for a brief period usually last for less than a minute
- Can sometimes become long-term memories with some effort

Working Memory

- Involves the immediate and small amount of information that a person actively uses as they perform cognitive tasks.

Long-term Memory

- These memories can last for days to years.
- Range in significance from recalling the name of a friendly face at coffee shop to important bits of information like a close friend's birthday or home address
- No limit to how much our long-term memory can hold and for how long

➢ Two main categories: explicit and implicit long-term memory.

Explicit Long-term Memory

- Memories consciously and deliberately took time to form and recall.
- Explicit memory holds information such as best friend's birthday or phone number.
- It often includes major milestones in life, such as childhood events, graduation dates, or academic work learned in school.

Explicit memories can be episodic or semantic.

Episodic memory - formed from particular episodes in life

eg .the first time rode a bike or first day at school.

Semantic memory - general facts and bits of information absorbed over the years.

eg. recall a random fact while filling in a crossword puzzle

Implicit long-term Memory

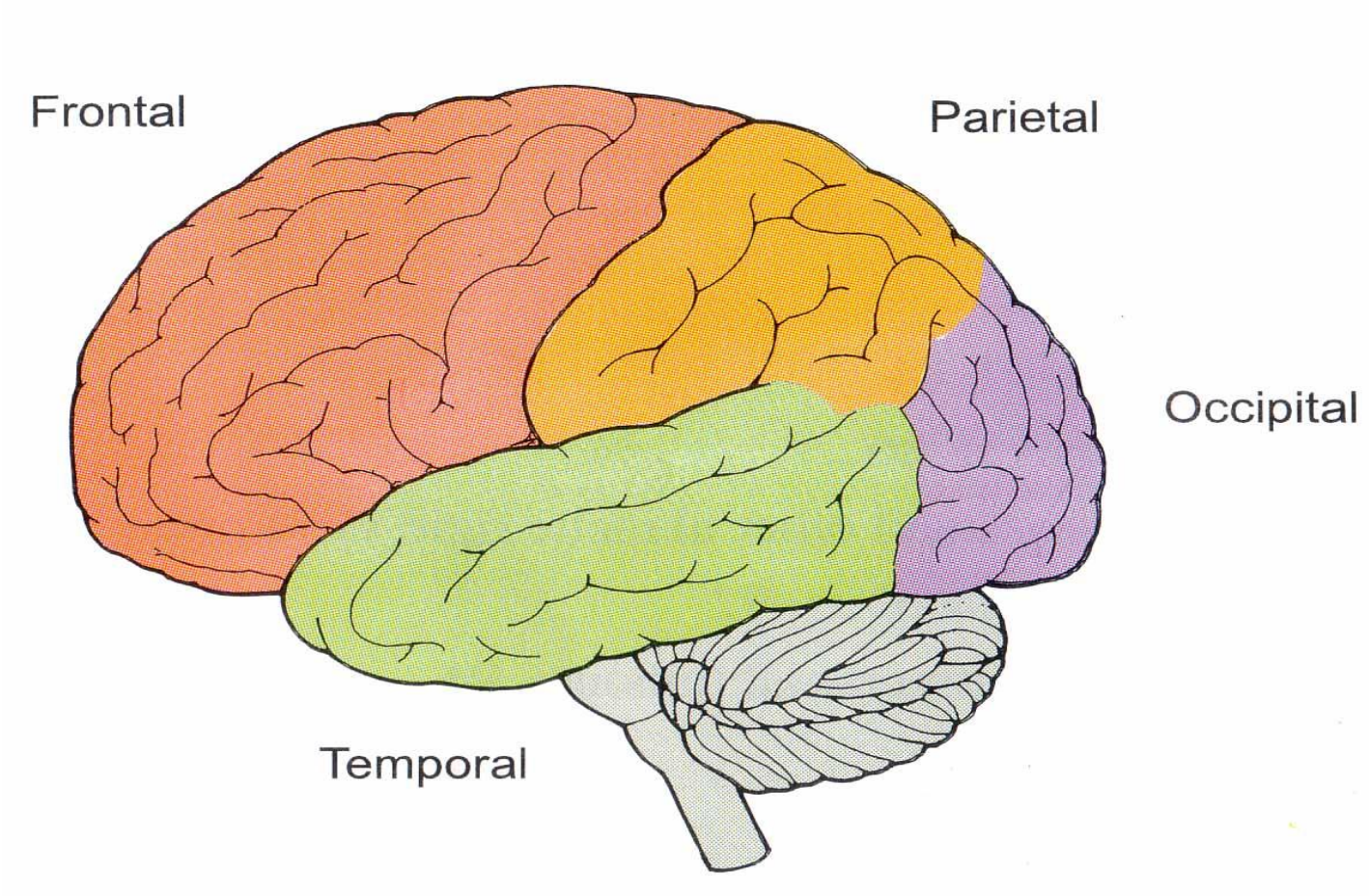
- Does not require any conscious retrieval.
- Types of implicit memories :

Procedural memory- the memory of how to do certain things

Priming memory-the phenomenon whereby exposure to a stimulus influences a response to a later stimulus

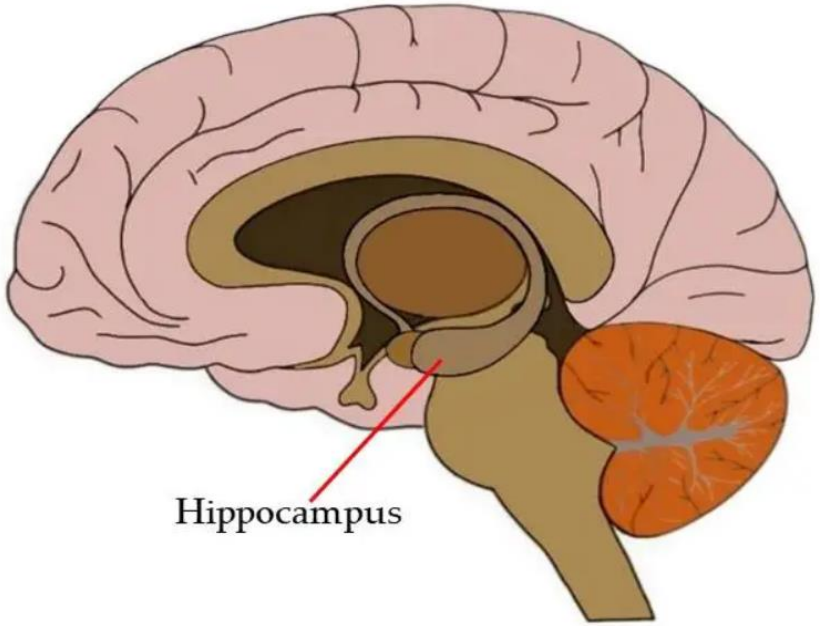
Conditioning memory –the process of learning associations between a stimulus and a response

Normal brain



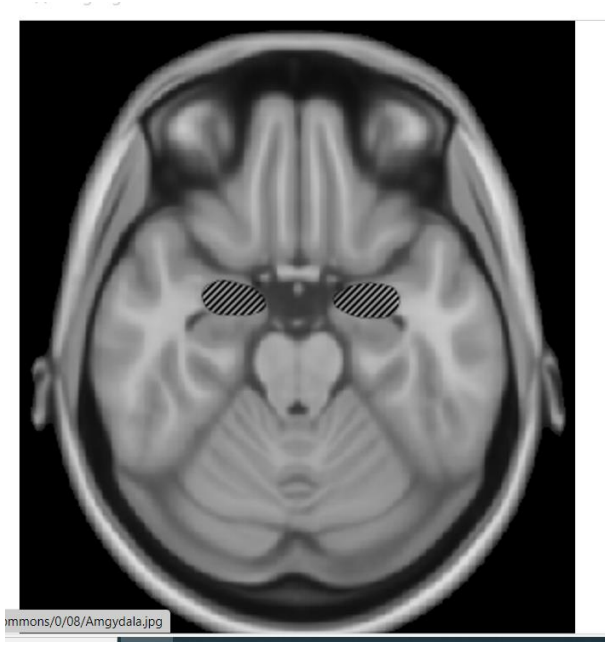
Hippocampus

- Contains cognitive maps in humans, responsible for
  - New memories formation (damage → anterograde amnesia)
  - Memory consolidation (conversion of short term memory to long term memory)
  - Episodic memories



Amygdala

- Associated with both emotional learning and memory, as it responds strongly to emotional stimuli, especially fear.
- Lesions in the amygdalae - impair motivation, as well as the processing of emotions

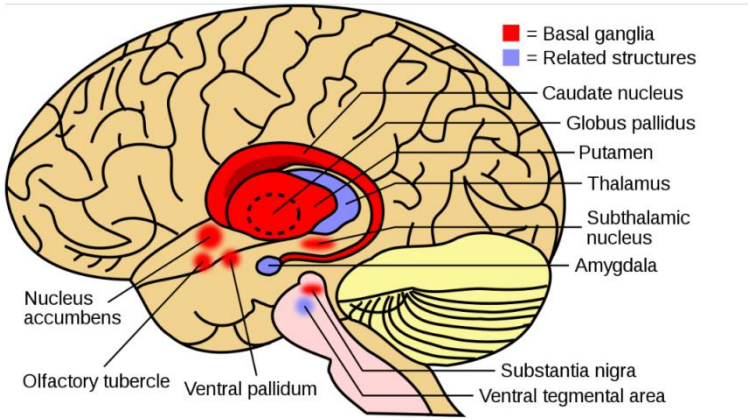


Cerebellum

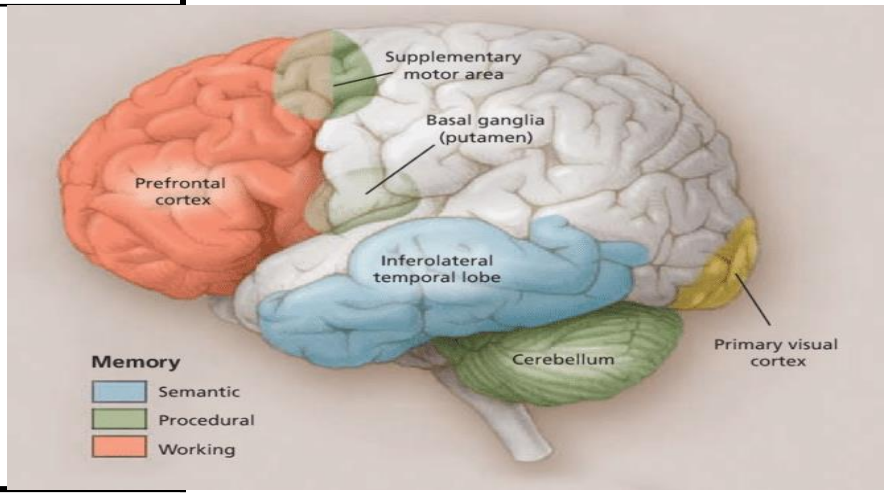
- Involved in the encoding of complex memories, plays a role in the learning of **procedural memory**, and motor learning
- Damage can result in problems with movement, specifically coordinate timing and accuracy of movements, and to make long-term changes (learning) to improve these skills

Basal Ganglion

- Associated with learning, memory, and unconscious memory processes, such as motor skills and **implicit memory**.



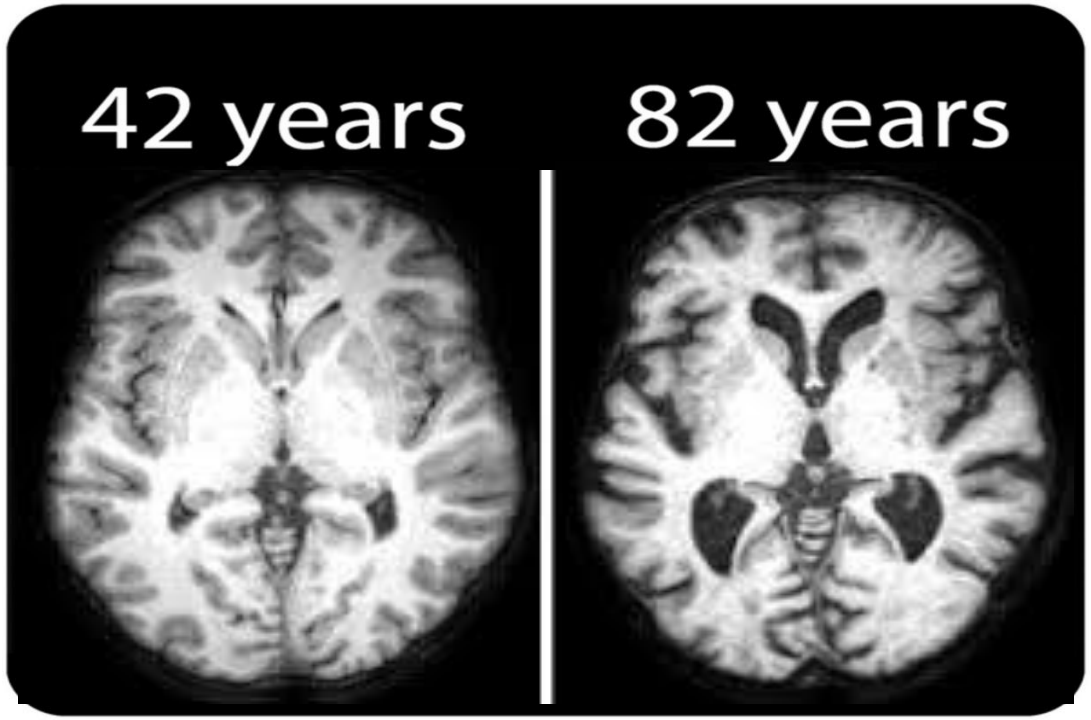
Lobe	Function	Effects of damage Cognitive / Bahavioural
Frontal	Personality Emotional control Social behavior Language Micturition Contralateral motor control	Disinhibition Lack of initiation Anti-social behavior Impaired memory, Expressive dysphasia Incontinence Contralateral Hemiplegia
Parietal: dominant	Language Reading Writing Calculation Skill	Dysphasia Dysiexia Dysgraphia Dyscalculia Apraxia Agnosia



Parietal: non-dominant	Spatial orientation Constructional skills	Spatial disorientation Neglect of non-dominant side Constructional apraxia Dressing apraxia
Temporal: dominant	Auditory perception Language Verbal memory Smell Balance	Receptive aphasia Dyslexia Impaired Complex hallucinations (smells, sound, vision, memory)
Temporal: non-dominant	Auditory perception Melody / pitch perception Non-verbal memory Smell Balance	Impaired musical skills (tone perception) Impaired non-verbal memory Complex hallucinations (smells, sound, vision, memory)
Occipital	Visual processing	Visual inattention Visual loss Visual agnosia

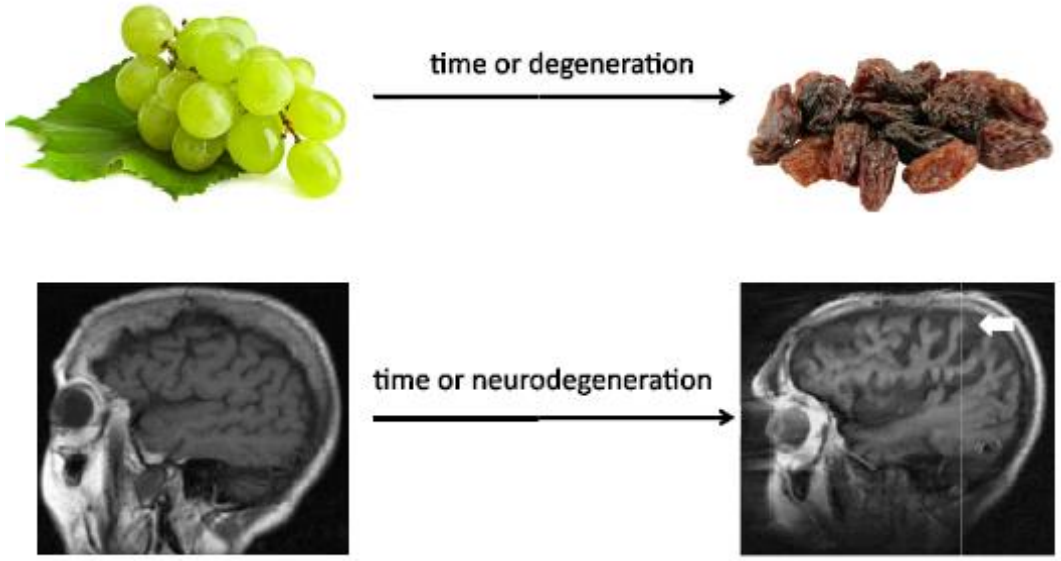
Aging Brain

- Aging of the brain is a process of transformation - physical, biological, chemical, and psychological changes in older age



Aging Brain

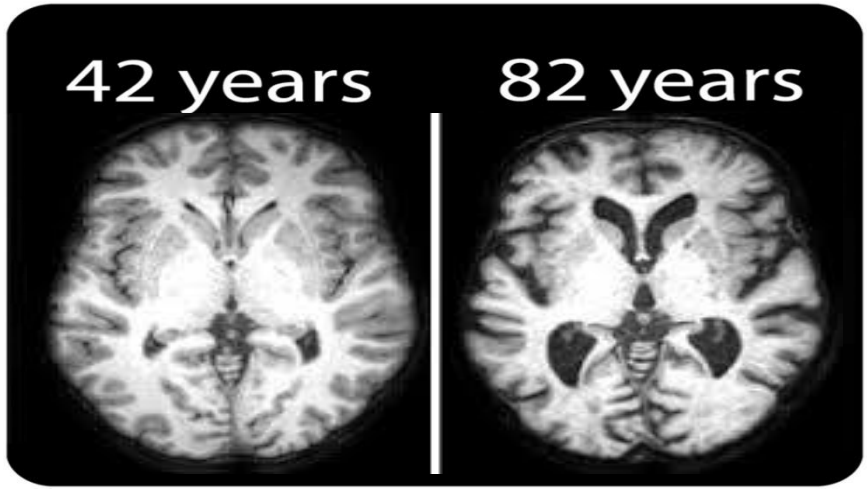
- Cerebral ageing is a complex and heterogeneous process associated with a high degree of inter-individual variability and characterized by a pattern of **selective loss and preservation**.



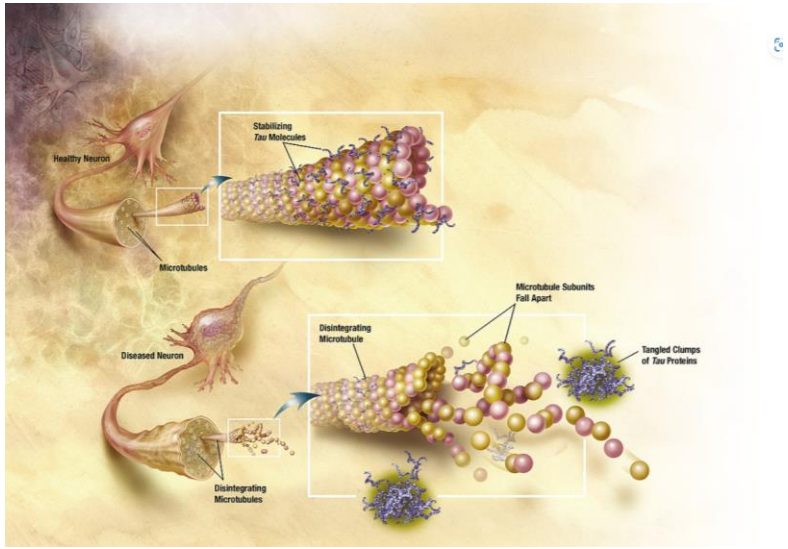
Changes associated with healthy aging of brain - structural, biological, chemical, and psychological changes

A. StructuralChanges

- Shrink at a rate of **1% per year** especially gray matter volume
- Frontal lobe followed by the temporal lobes (Insula and superior parietal gyri are also especially vulnerable to gray matter losses)



Neurofibrillary tangles



- One of the important differences between normal ageing and pathological ageing is the **location of neurofibrillary tangles**.
- In non demented person ages, the density of tangles are generally increased but number of tangles in each affected cell body is relatively low & restricted to olfactory nucleus, parahippocampal gyrus, amygdala & entorhinal cortex.
- Unlike tangles, amyloid plaque, main neurodegenerative contributor commonly found in the brain of patients with Alzheimer's disease is not consistent feature of normal aging.

B. Chemical changes

- Age-related changes in dopamine synthesis, binding sites, and number of receptors
- Decreasing levels of different serotonin receptors and the serotonin transporter
- Glutamate tends to decrease with age

C. Neuropsychological changes

- Changes in orientation
- Changes in attention
- Changes in memory
- Changes in language
- Brain activation patterns
- Changes in learning and behavioral flexibility

Case study

- Mrs. A, 81 years, with hypertension and hyperlipidemia, stating that **“I am forgetting things I just heard.”**
- Mrs. A and her husband began noticing mild memory problems **1.5 years** earlier, and report slow progression .
- Her husband noticed changes in **problem solving and time management.**

- Mrs. A was easily distracted and had difficulty remembering recent conversations.
- She misplaced objects and spent time looking for them.
- She read and wrote less than before.
- She repeatedly asked how to do things on her computer and cell phone.
- Her husband reported that she exhibited no initiative, and that their home seemed more disorganized.

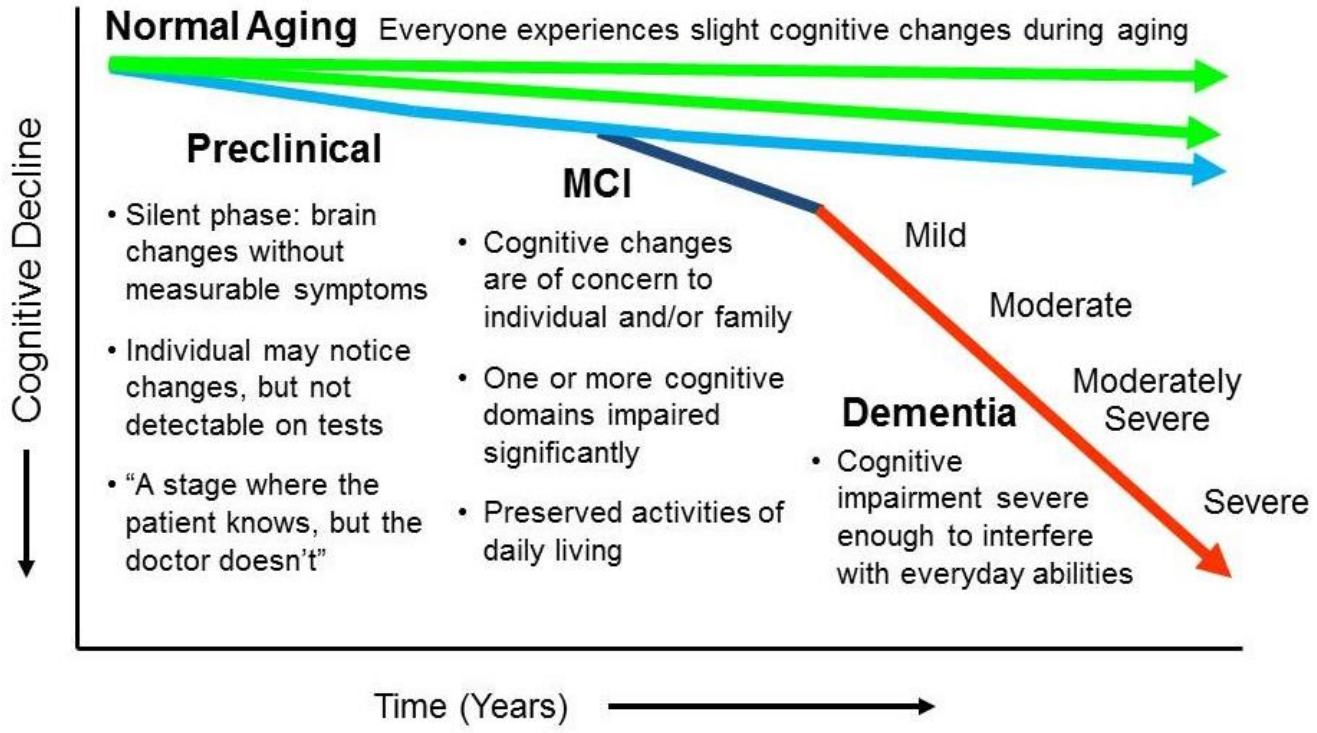
- She had difficulty planning dinner and her cooking was simpler.
- Both denied changes in language or speech.
- She continued to drive locally without accidents but had difficulty remembering directions to familiar places.
- Mrs A had no hallucinations or delusions.
- She slept well, her mood was fine, and she exhibited no behavioral problems or personality changes.

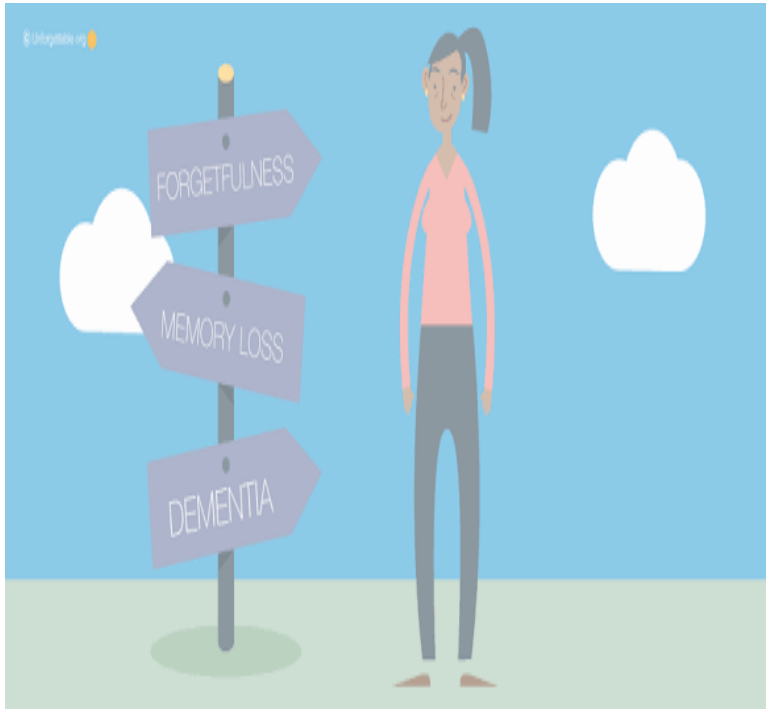
- Functionally, she remained independent in all activities of daily living (ADLs).
- She had urinary frequency and over the past couple of months she had a few incidents of incontinence, especially when awakening from a nap.
- In **instrumental activities of daily living (IADLs),** Mr A had recently taken over paying bills.
- Finally, even with a compartmentalized pill-box, she occasionally forgot to take her medications (amlodipine 5 mg daily; losartan 50 mg twice daily; and ergocalciferol 1,000 units daily.)

WHAT'S Dx OF THE PATIENT?

- MILD COGNITIVE IMPAIRMENT (MCI)

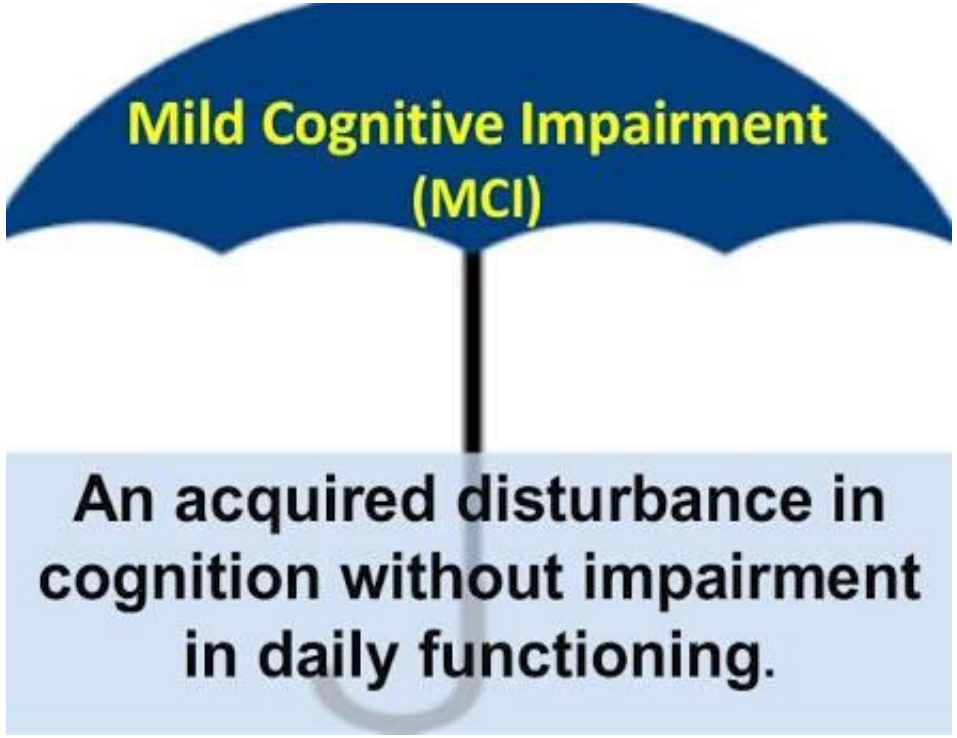
Normal Aging vs Mild Cognitive impairment vs Dementia





Mild cognitive Impairment(MCI)

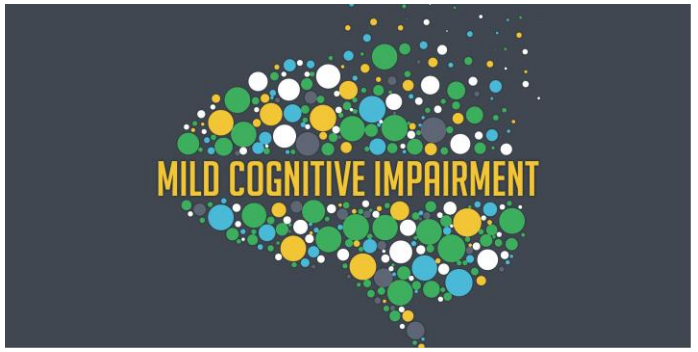
- Clinical syndrome defined as cognitive decline greater than that expected for a person's age and education level but does not affect notably with activities of daily life .



Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

- **Mild cognitive impairment (MCI)** is a state intermediate between normal cognition and dementia, with essentially preserved functional abilities.

Core features of MCI …….



- Memory complaints (preferably corroborated by an informant);
- objective memory impairment (for age and education);
- normal or preserved general cognitive function;
- intact activities of daily living; and
- no presence of dementia.

Epidemiology

- MCI is most commonly seen in the older adult population. The prevalence increases with advanced age.

- Estimated prevalence by age is as follows:

➢ age 65 to 69 years: 6.4%;

➢ age 70 to 74 years: 10.1%;

➢ age 75 to 79 years: 14.8%; and

➢ age 80 to 84 years: 25.2%

Neurology. 2018;90:126-135.

Risk factors for MCI

Older age
Apoplipoprotein ε4 allele
Sex: Higher in men,[10, 36, 41, 43, 46, 47] higher in women,[45] and no sex difference.[48]
Low number of years of education
Vascular risk factors: Type 2 diabetes, hypertension, obesity, dyslipidemia, smoking
Cardiovascular disease outcomes: coronary artery disease, atrial fibrillation, congestive heart failure, cerebrovascular disease
Systemic inflammation: C-reactive protein.
Neuropsychiatric conditions: depression, anxiety, apathy.
Protective factors
Higher education
Cognitively stimulating activities
Physical exercise/activities
Dietary factors: mono and polyunsaturated fatty acids
Mediterranean diet

Dement Geriatr Cogn Disord. 2007; 24:307–316. [PubMed: 17848793]
Neurology. 2004; 63:115–121. [PubMed: 15249620]

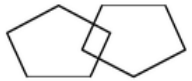
SCREENING AND DIAGNOSIS

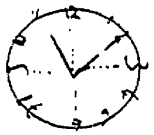
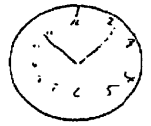
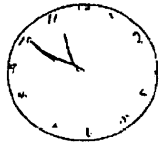
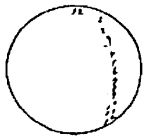
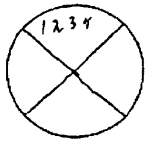
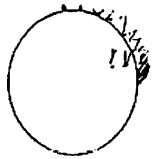
- A widely recognized instrument for detection of cognitive impairment is **Mini-Mental State Examination (MMSE).**
- Sensitivity was 49% with an acceptable specificity of 92% in detecting dementia with a CDR of 0.5 (questionable dementia). (Mary Ganguli et al., 1993)
- MMSE predicted future cognitive decline with good accuracy (79.9%) and specificity (86.4%), and moderate sensitivity (67.2%). (Haiqun Xie et al., 2011)

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

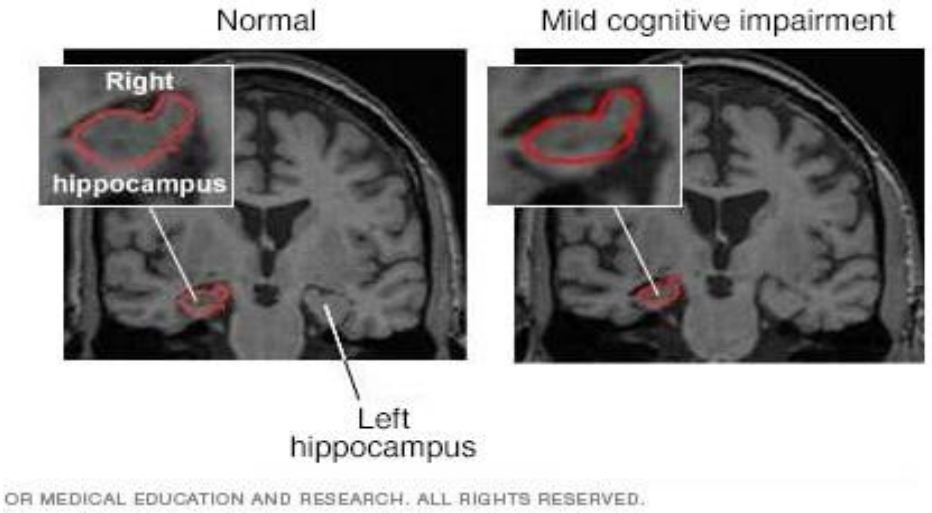
Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

1. Perfect	 
2. Minor visuospatial errors *Examples* - Mildly impaired spacing of times - Draws times outside circle - Turns page while writing numbers so that some numbers appear upside down - Draws in lines (spokes) to orient spacing	 
3. Inaccurate representation of 10 after 11 when visuospatial organization is perfect or shows only minor deviations. *Examples* - Minute hand points to 10 - Writes '10 after 11' - Unable to make any denotation of time	 
4. Moderate visuospatial disorganization of times such that accurate denotation of 10 after 11 is impossible. *Example* - Moderately poor spacing - Omits numbers - Perseveration – repeats circle or continues on past 12 to 13, 14, 15 etc. - Right-left reversal – numbers drawn counter clockwise - Dysgraphia – unable to write numbers accurately	 
5. Severe level of disorganization as described in 4.	 
6. No reasonable representation of a clock Exclude severe depression or other psychotic states. *Examples* - No attempt at all - No semblance of a clock at all - Writes a word or name	 

NEUROIMAGING AS IT STANDS NOW: WHAT SCANS ARE CLINICALLY USEFUL IN THE WORK-UP OF AN MCI PATIENT?

- To rule out non-neurodegenerative conditions that may **mimic** MCI
  - brain neoplasm
  - subdural hematoma
  - vascular dementia
  - normal pressure hydrocephalus.

STRUCTURAL NEUROIMAGING

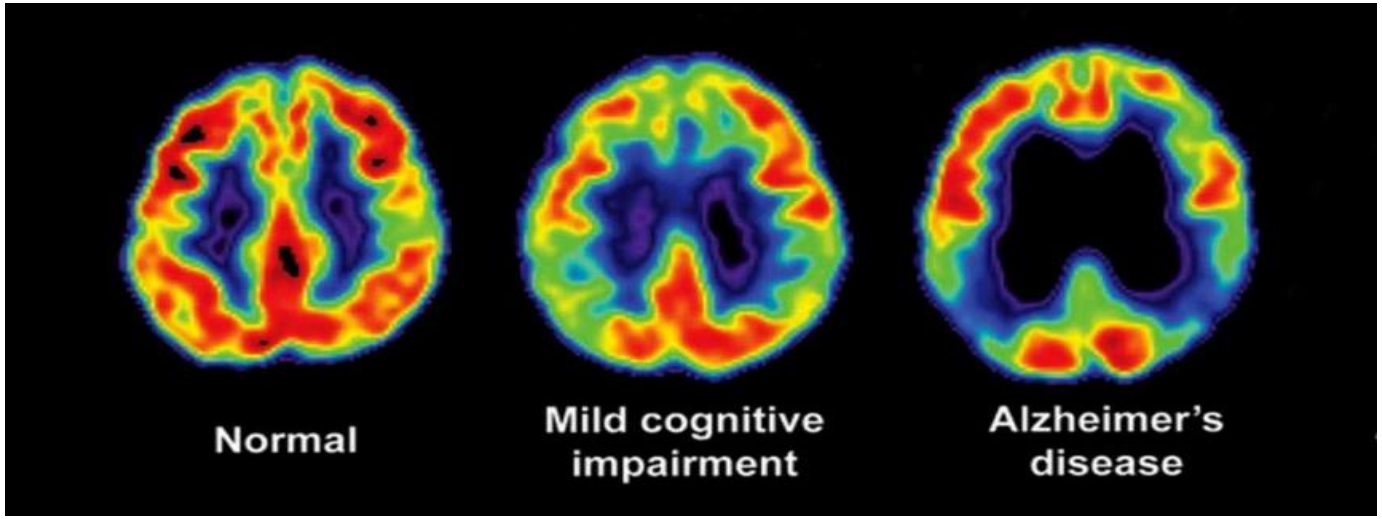


Brain shrinkage

These **MRIs** reveal shrinkage of the hippocampus, a part of the brain associated with memory, during the transition from normal cognitive function to mild cognitive impairment.

FUNCTIONAL AND AMYLOID IMAGING NEUROIMAGING

- Fluorodeoxyglucose positron emission tomography **(FDG-PET)** can detect regions of hypo metabolism in the brain(demonstrate reduced glucose metabolism in the parietal and superior /posterior temporal regions) which may be characteristic of MCI due to AD, AD dementia, or other causes for cognitive impairment.



LABORATORY TESTING

- Laboratory testing of complete blood count, electrolytes, glucose, calcium, thyroid function, vitamin B12, and folate is recommended to identify potentially reversible forms of MCI including infection, renal failure, hypo- hyperglycemia, hypo- or hypercalcemia, hypo- or hyperthyroidism, and B12 / folate deficiency.

- Laboratory testing for liver function, syphilis, Lyme titers (Borrelia), and HIV may reveal rarer causes for cognitive impairment.

GENETIC BIOMARKERS

- ***APOE ε4*** is also associated with more rapid cognitive decline in older persons, especially in episodic memory, during the follow-up period.
- However, *APOE* genotyping is not currently recommended for regular predictive and diagnostic testing in general populations because of low sensitivity and specificity.

Arch Neurol, 2002. **59**(7): p. 1154-60.

CSF BIOMARKERS

1. **CSF amyloid beta 1-42 (Aβ1-42)** concentrations are consistently and significantly reduced in patients with AD by approximately 50% when compared with healthy control subjects.

- Also, MCI subjects with later conversion to AD have lower CSF Aβ1-42 concentrations at baseline when compared with non-converters.

NeuroRx, 2004. **1**(2): p. 213-25.

CSF BIOMARKERS

2. Tau protein in CSF

- P-tau may also be used to identify AD before the onset of dementia, i.e. at the stage of MCI.
- In MCI subjects, high p-tau concentrations correlated with a decline in cognitive performance and conversion to AD.
- p-tau proved to be a powerful predictor of AD in MCI subjects, even in with a short mean observation interval (1 to 2 years).

Neurology, 2007. **69**(24): p. 2205-12.

MANAGEMENT

- Currently, no drug has proven effective in treatment of MCI.
- Cholinesterase inhibitors and memantine have not been shown to decrease risk of progression from MCI to dementia
- Ginkgo biloba , testosterone supplementation in older men showed no benefit for cognitive function in a randomized controlled trial.

Neurology. 2018;90:126-135.

AMERICAN ACADEMY OF NEUROLOGY®

NONPHARMACOLOGIC TREATMENTS

Counseling on behaviors

Various behavioral interventions, particularly aerobic exercise and mental activity, may have beneficial effects on cognitive function in older adults with MCI.

Neurology. 2001;56(9):1133-1142
BMC Neurol. 2012;12:128.

- Observational studies suggest that the Mediterranean diet also may reduce the risk of converting from MCI to dementia.

- Psychotherapy may modestly increase patients' acceptance of an MCI diagnosis and also provide knowledge, insight, acceptance, and coping skills for significant others

DRIVING

- Testing for deficits in visuospatial and executive function (Clock Drawing Task and Trail making tests),cognitive domains thought to be important for driving safely, or formal driving evaluation may provide useful information.

PROGNOSIS

Patients can be counselled that

- A minority will progress to dementia annually
- (40-70%) may not progress to dementia even after 10 years
- (15-20%) will have improved cognition 1-2 years later.

“A forgetful person, in no real distress who can no longer do their job, can no longer be independent and

who cannot really sustain any

ordinary sensible conversation.”


Thank You For Your Attention