Chapter 7: Dementias

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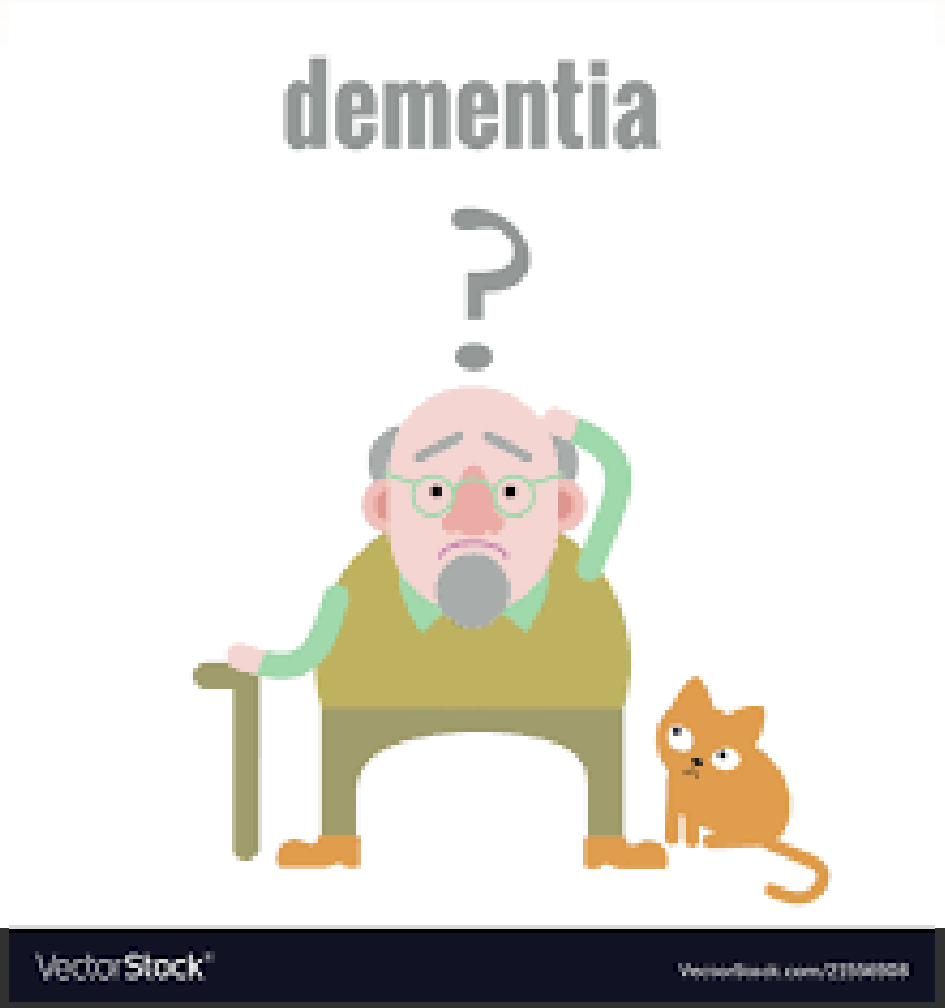

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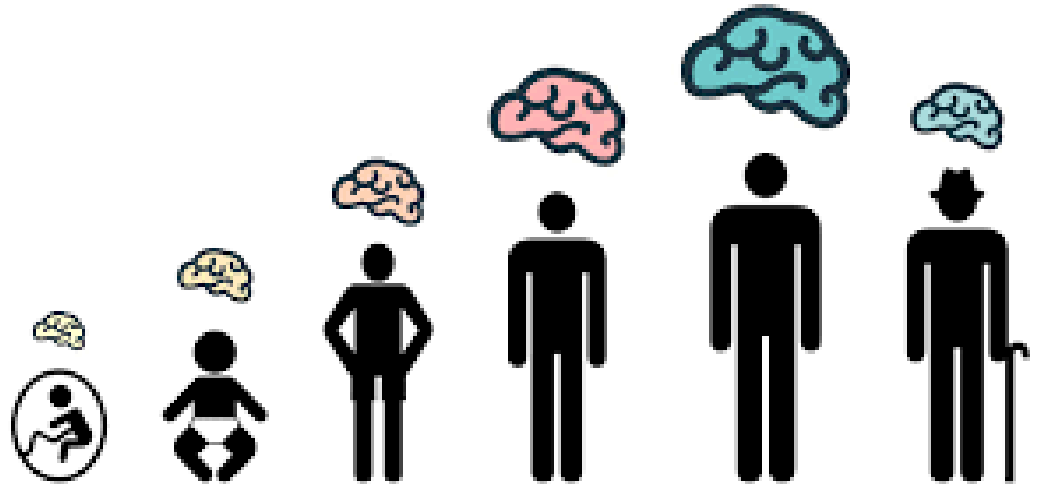
Dementias

1. Successful aging
1.1 Introduction
1.2 Associated neuroanatomical and neurophysiological changes
Neuroimaging findings
Neuropsychology of aging



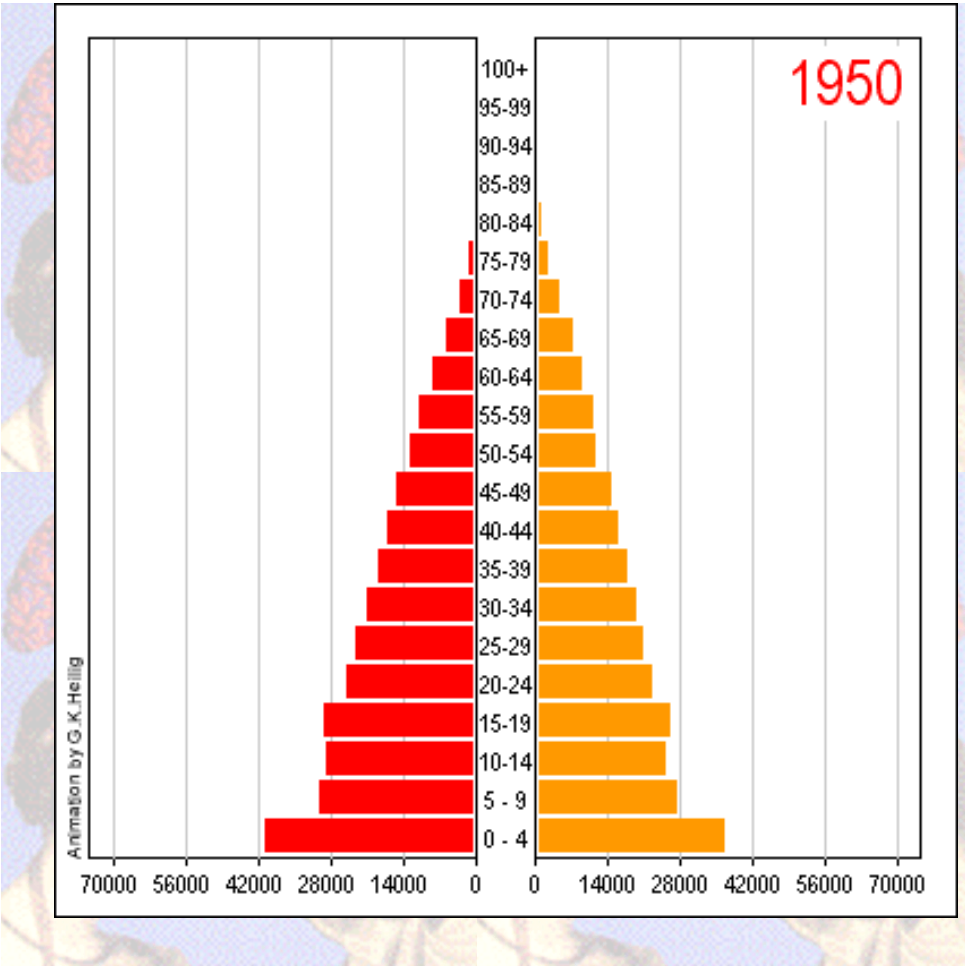
2. Dementias: general aspects
Definition of dementia
Types of dementia
Diagnostic tests
Differential diagnosis

3. Alzheimer's disease
AD: introduction and diagnostic criteria
Epidemiological data
Neuropathological characteristics and genetic factors
Structural and functional neuroimaging studies
Clinical (neuropsychology) and neurochemistry

1. Successful aging

1.1 Introduction

→ Approximately 10% of the global population is aged 65 or over, which amounts to roughly **800 million people** worldwide.



Asia
- **Population aged 65 or over: ~ 450 million.**
- **Percentage of total: ~ 55-60%** of the world's elderly popul

Europe
- **Population aged 65 or over: ~ 150 million.**
- **Percentage of total: ~ 18-20%**

North America
- **Population aged 65 or over: ~ 65-70 million.**
- **Percentage of total: ~ 8-10%.**

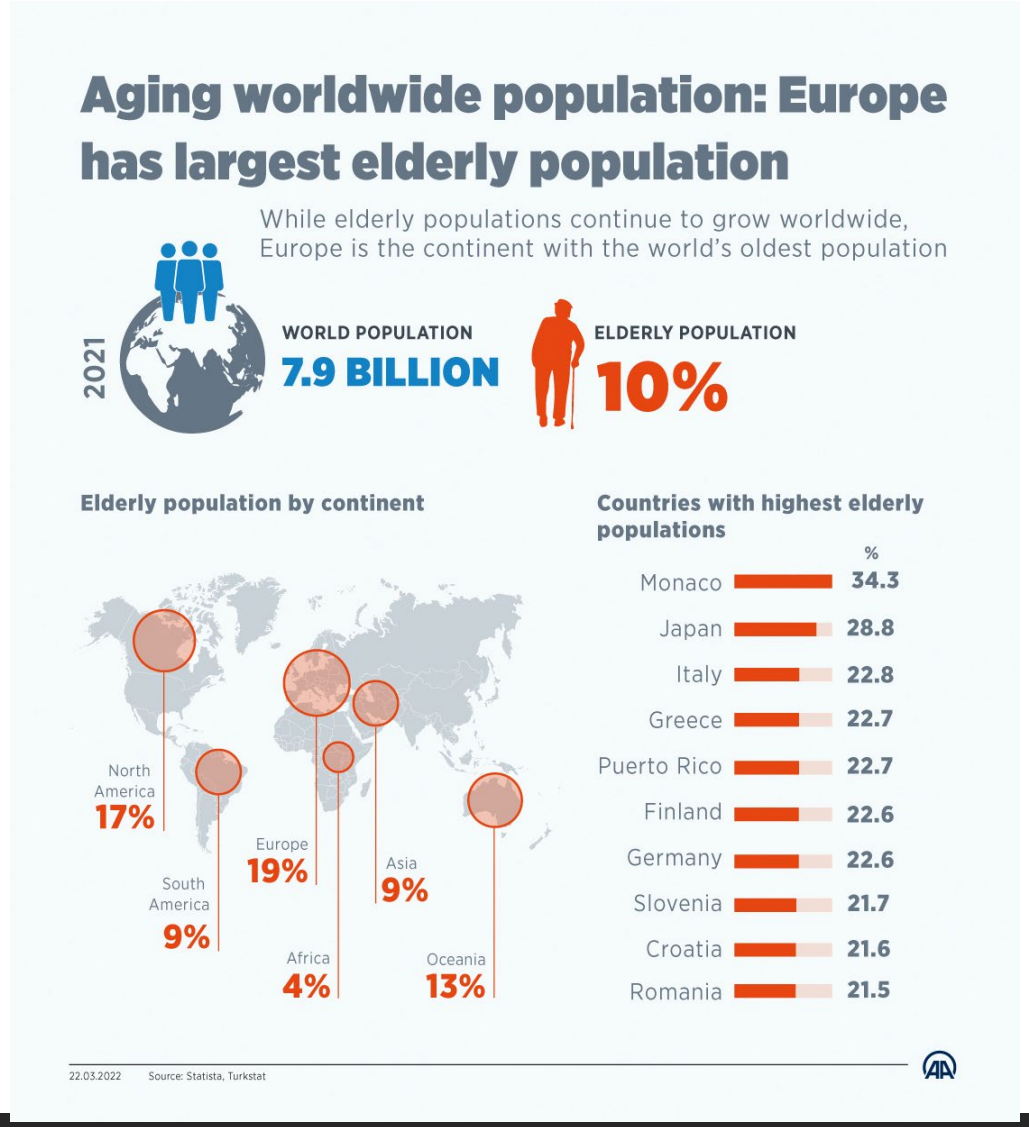
Latin America and the Caribbean
- **Population aged 65 or over: ~ 50 million.**
- **Percentage of total: ~ 6%**

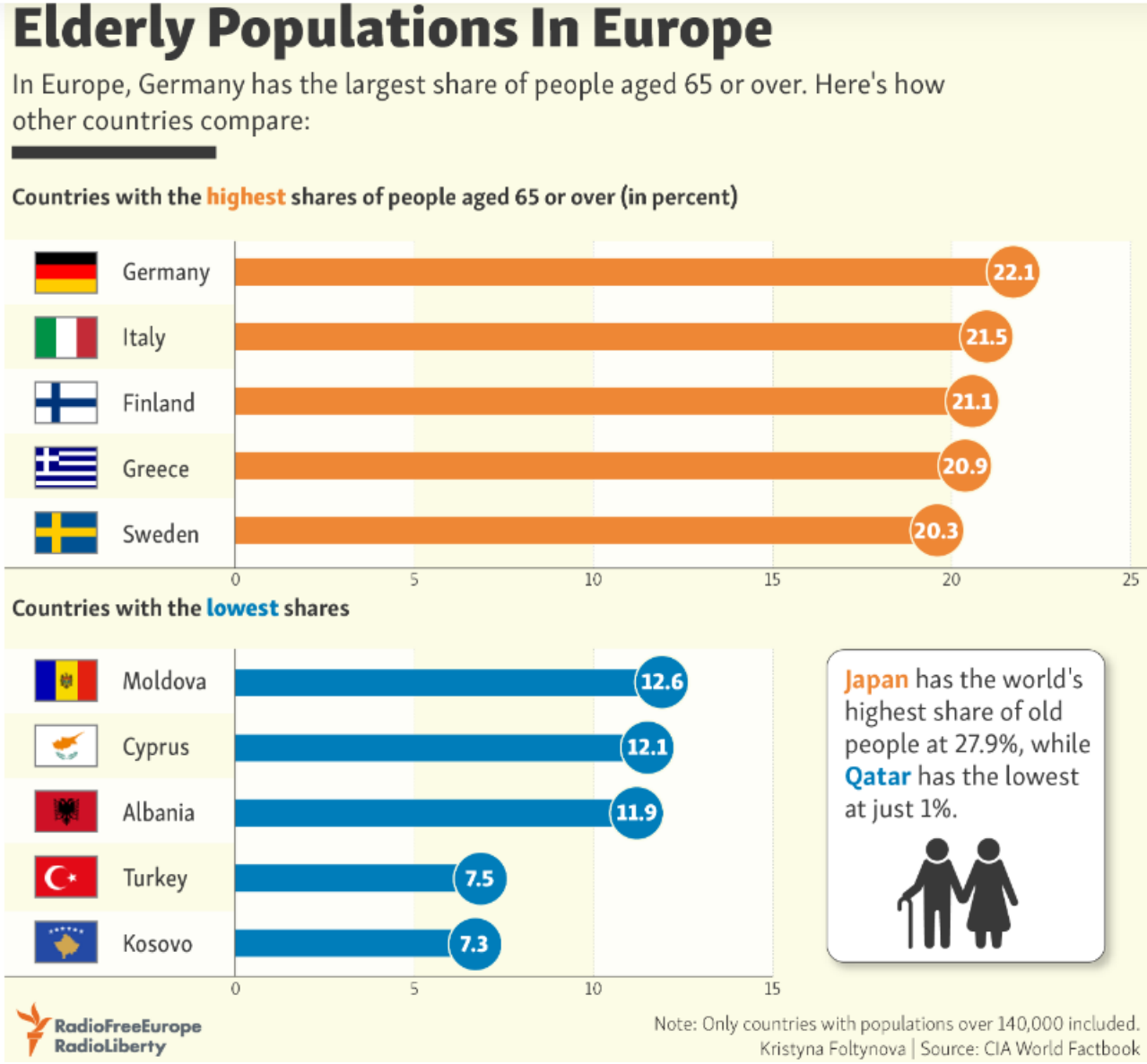
Africa
- **Population aged 65 or over: ~ 40 million.**
- **Percentage of total: ~ 5%**

Oceania
- **Population aged 65 or over: ~ 7-8 million.**
- **Percentage of total: ~ 1%.**

1. Successful aging

1.1 Introduction





1. Successful aging

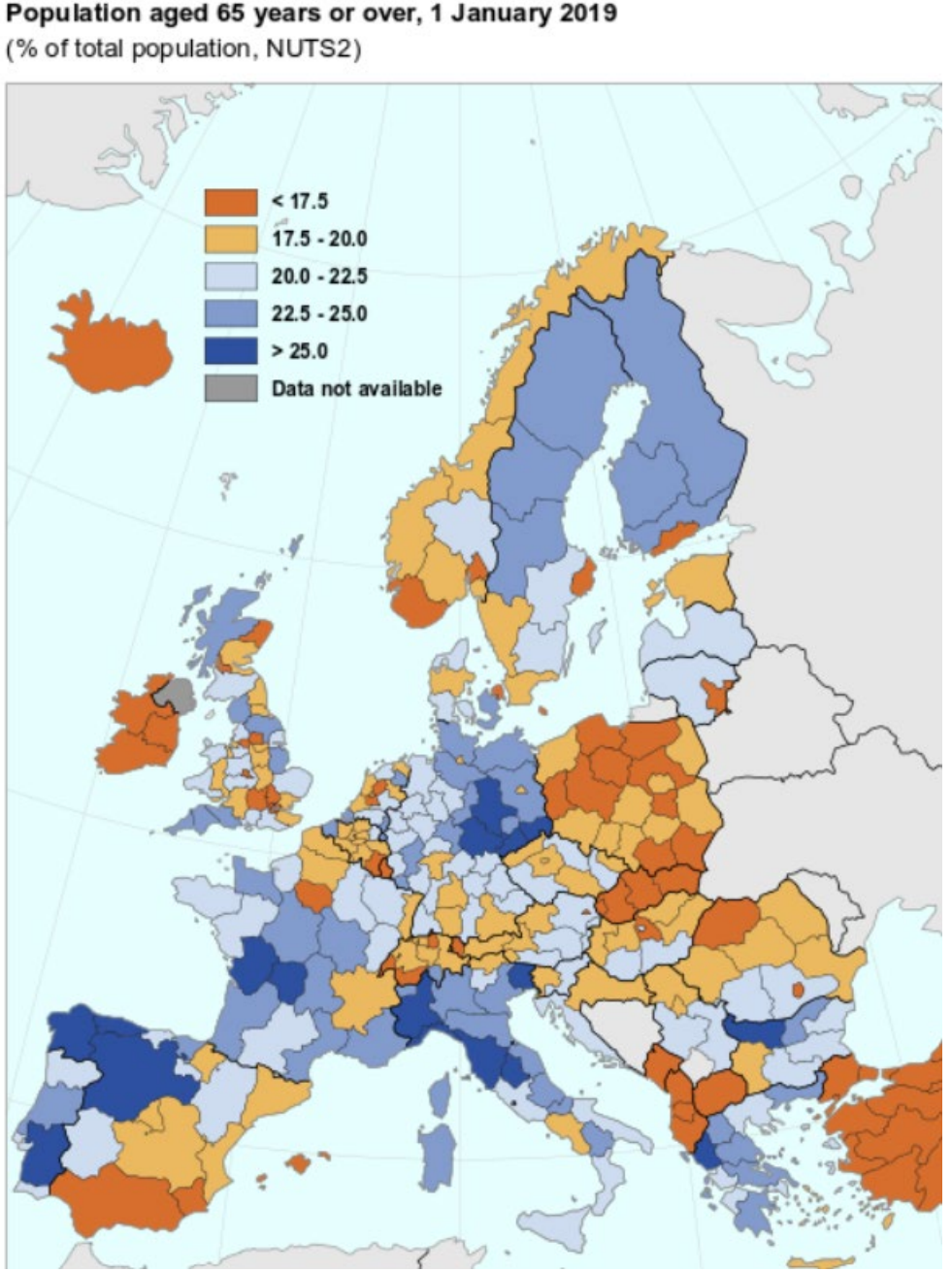
1.1 Introduction

Successful aging refers to the ability to maintain physical, cognitive and emotional well-being in older age.

→ It encompasses avoiding disease and disability, sustaining high cognitive and physical function, and engaging in life.

→ According to a Eurostat 2022 report, the population of people aged 65 or older in Europe is increasing, accounting for 20.8% of the total population, with life expectancy reaching 81 years in the EU.

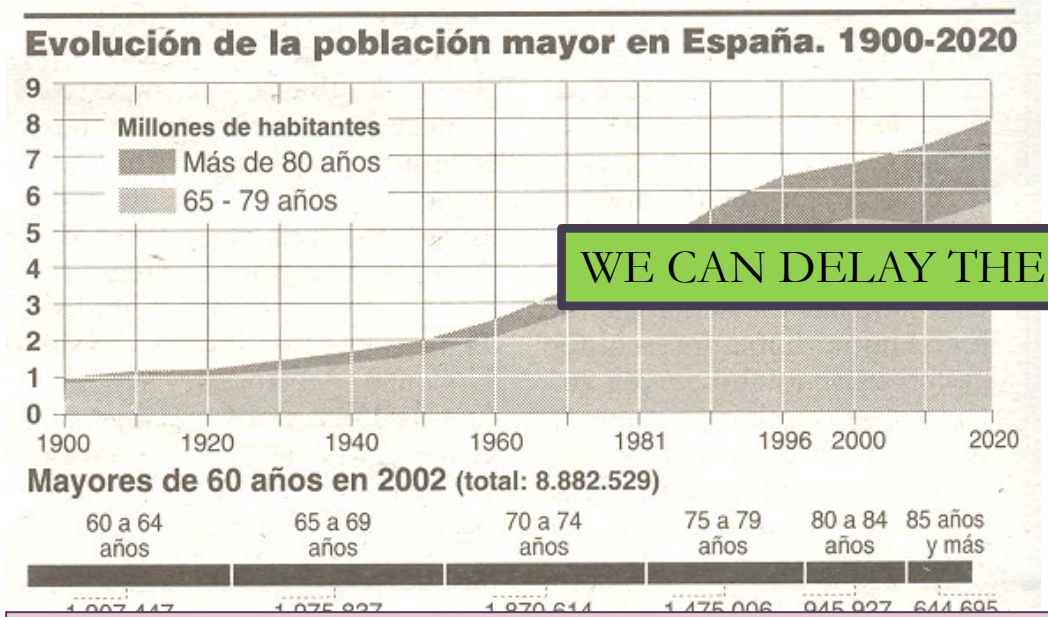
→ The World Health Organization (WHO) emphasizes successful aging to address the growing number of older adults in Europe and mitigate the impact of aging-related conditions such as dementia.



1. Successful aging

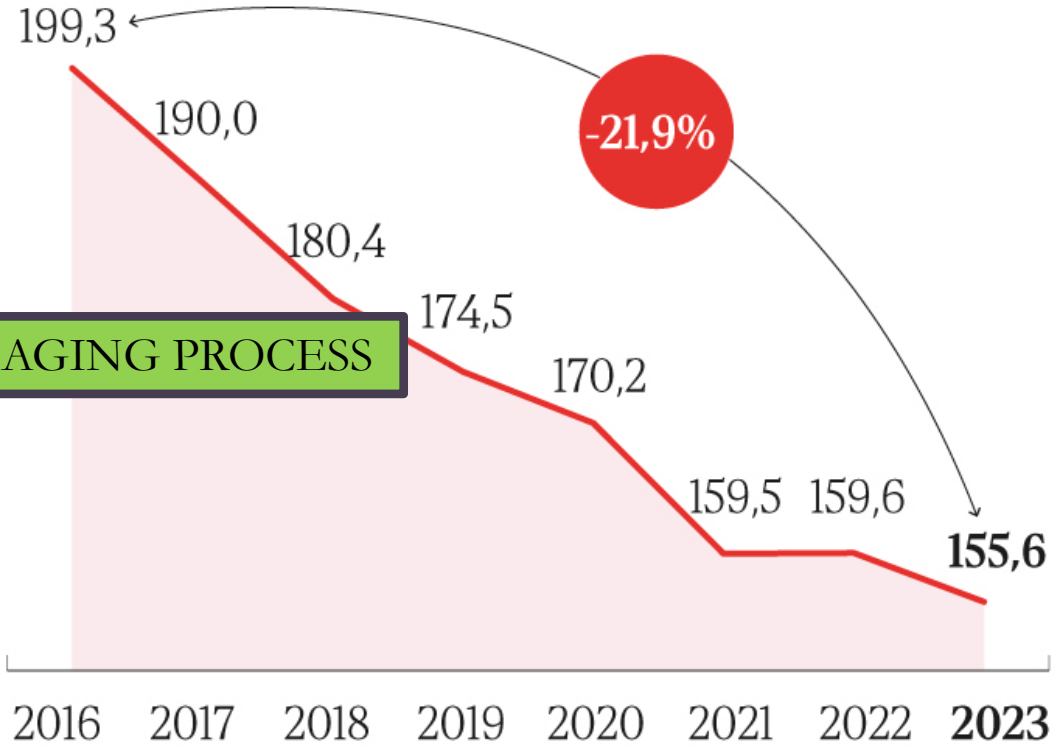
1.1 Introduction

Elderly population in SPAIN



Aging is associated **with gradual cognitive decline** (in memory, attention and executive functions), while domains such as crystallized intelligence may remain relatively stable.

Evolution of newborn babies in SPAIN



WE CAN DELAY THE NORMAL AGING PROCESS

Cognitive decline begins in middle age but significant decline typically occurs after 70.

The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are widely used to assess cognitive function.

1. Successful aging

1.1 Introduction

Cold Spring Harb Perspect Med. 2015 Dec; 5(12): a025965.
doi: 10.1101/cshperspect.a025965

Has the Rate of Human Aging Already Been Modified?

S. Jay Olshansky

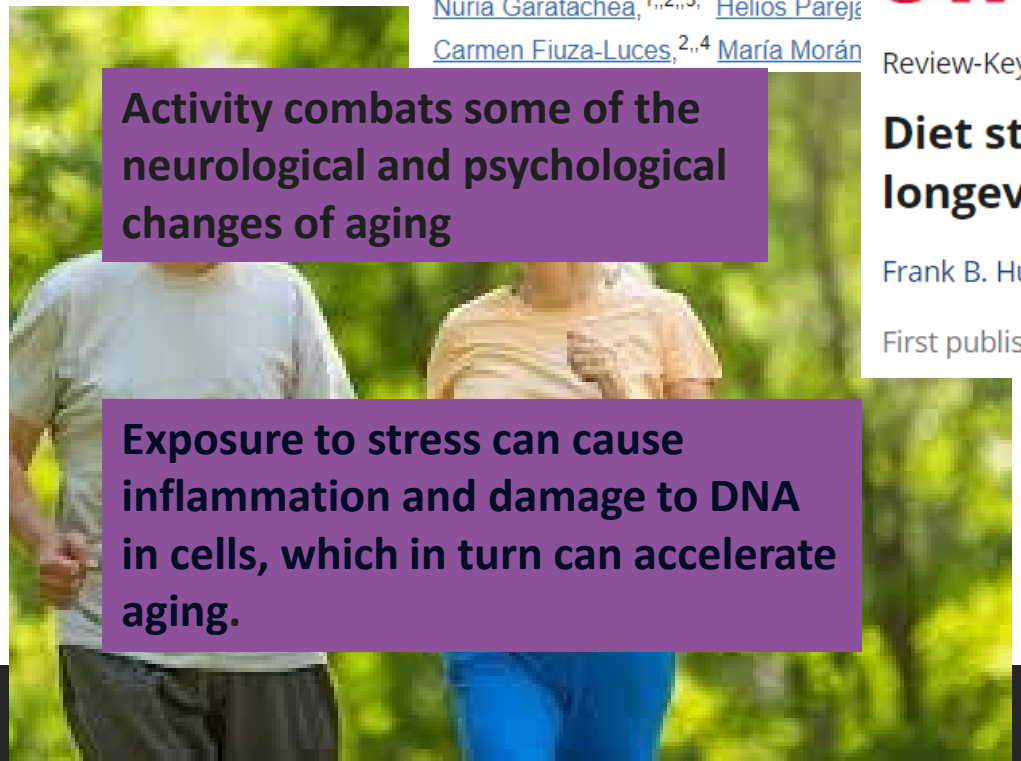
Rejuvenation Res. 2015 Feb 1; 18(1): 57–89.
doi: 10.1089/rej.2014.1623

Eating ultra-processed foods can speed up the aging of our cells.

PMCID: PMC4340807
PMID: 25431878

Exercise Attenuates the Ma

Nuria Garatachea,[1,2,3,*] Helios Pareja
Carmen Fiuza-Luces,[2,4] María Morán



Activity combats some of the neurological and psychological changes of aging

Exposure to stress can cause inflammation and damage to DNA in cells, which in turn can accelerate aging.

JIM Journal of Internal Medicine
Founded in 1863

Review-Key Symposium | Open Access

Diet strategies for promoting healthy aging and longevity: An epidemiological perspective

Frank B. Hu

First published: 23 C

Biomedicines. 2020 Jul; 8(7): 198.
Published online 2020 Jul 7. doi: 10.3390/biomedicines8070198

PMCID: PMC7400286
PMID: 32645916

The Link between Chronic Stress and Accelerated Aging

Yegor E. Yegorov,[1] Anastasia V. Poznyak,[2,*] Nikita G. Nikiforov,[3,4,5] Igor A.

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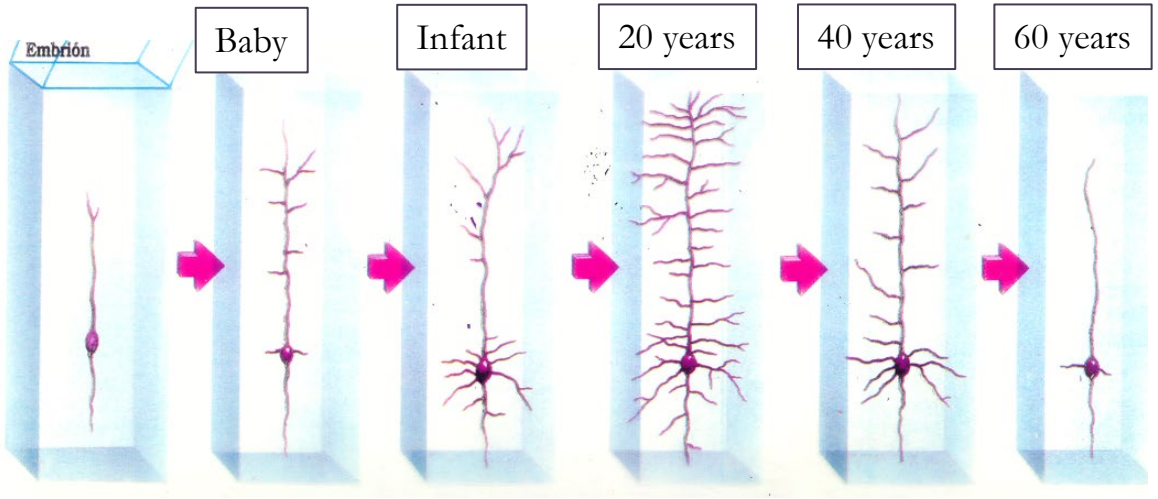
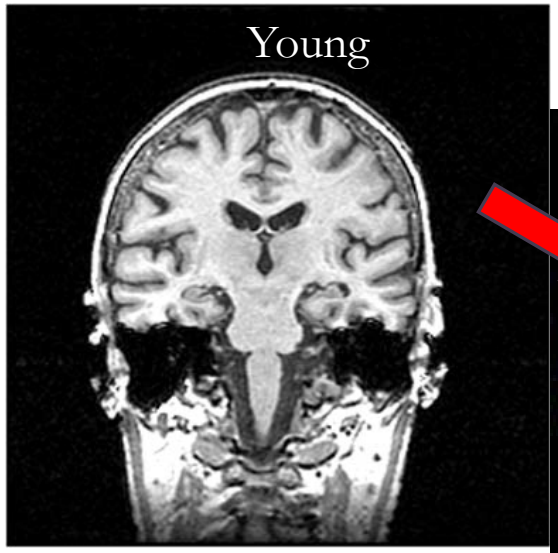
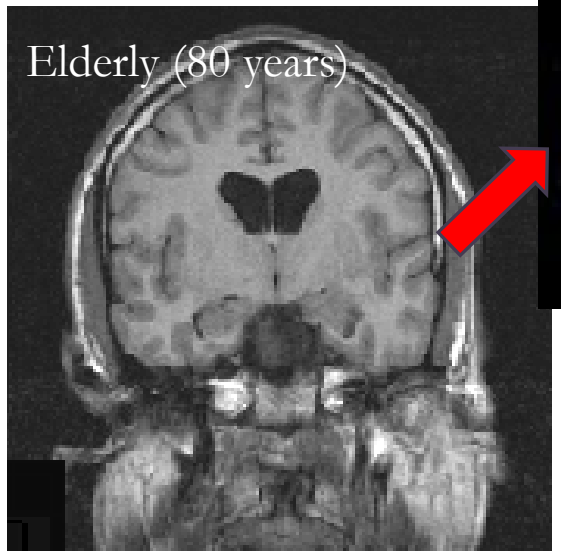
1. Successful aging

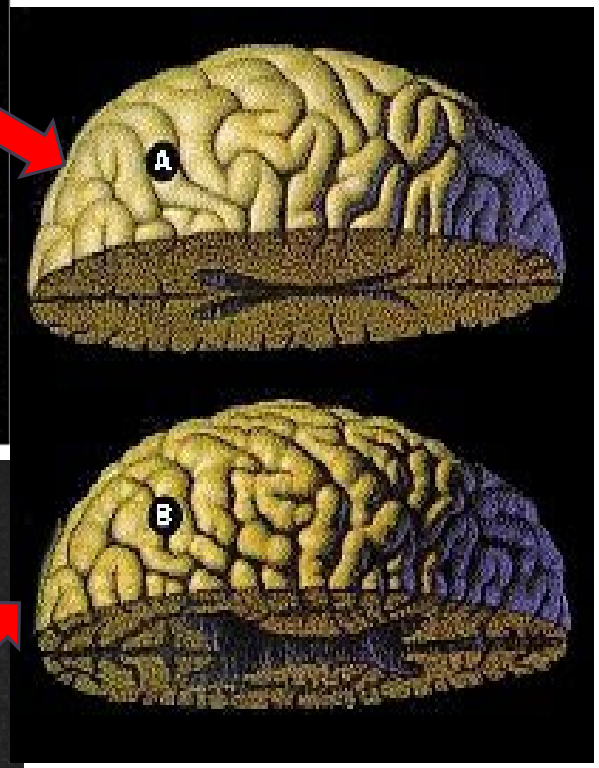
1.2 Associated neuroanatomical and neurophysiological changes

Cognitive decline parameter:
→ loss of brain weight and volume
→ decreased cortical thickness
→ global atrophy and increased size of sulci and fissures







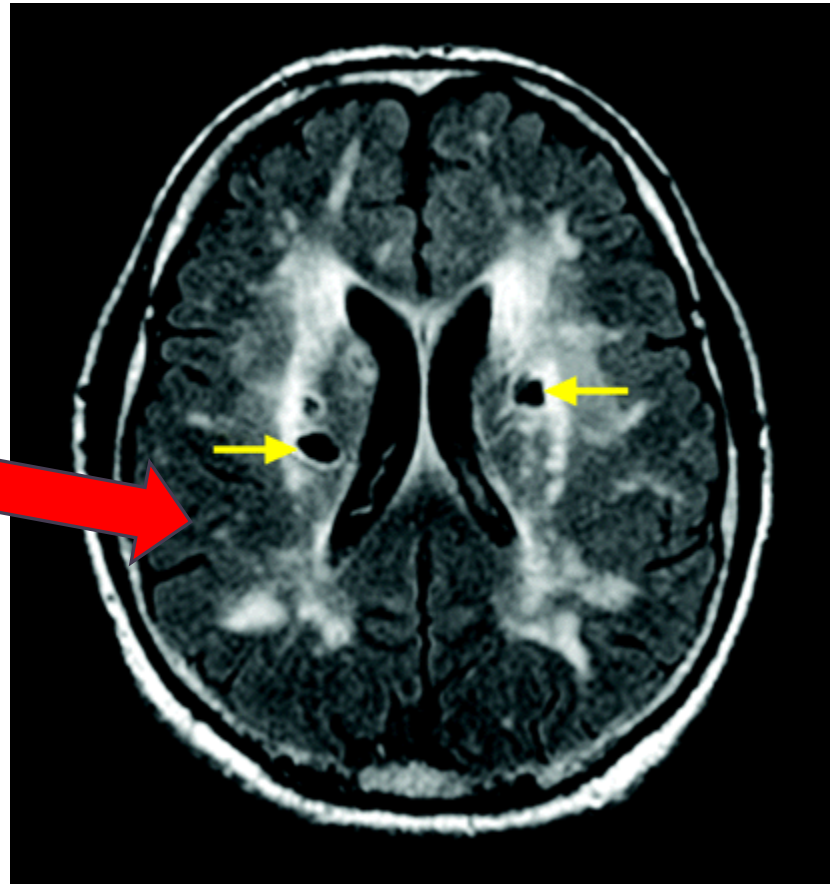


1. Successful aging

1.2 Associated neuroanatomical and neurophysiological changes

Leukoaraiosis is a radiological finding characterized by **white matter hyperintensities (**WMH) seen in neuroimaging, which indicates small vessel disease. It is linked with age-related cognitive decline and increased risk of dementia.

→Diffuse, **confluent white matter abnormality** (low density on CT, hyperintensity on T2-weighted or FLAIR MRI).



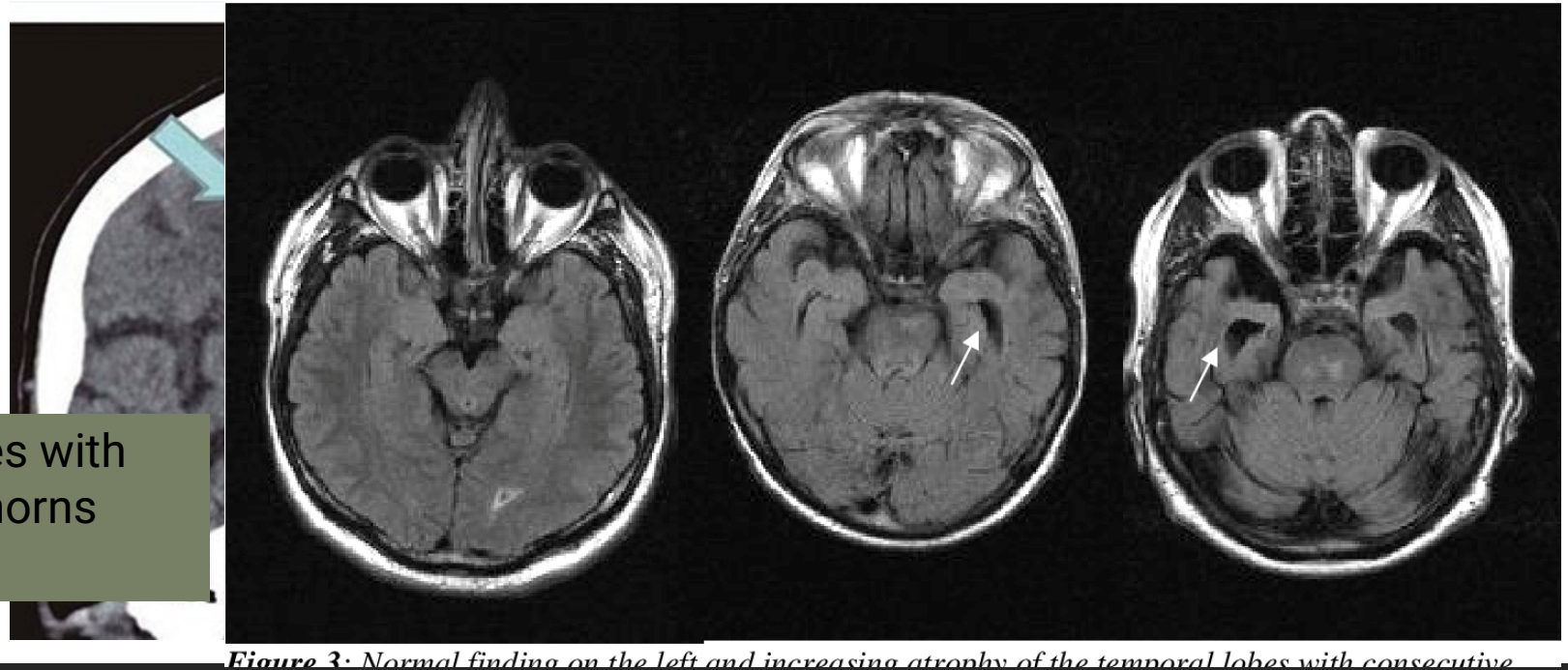
1. Successful aging

1.2 Associated neuroanatomical and neurophysiological changes

Neurodegeneration involves age-related brain changes that include loss of synaptic density, neuronal loss and the accumulation of proteins (e.g., amyloid-beta in Alzheimer's disease).

Neurodegenerative changes are more pronounced in those with dementia than in those with successful aging.

→ There is some atrophy on the frontal cortex and superior temporal.
→ There is less atrophy on the orbitofrontal, occipital and parietal cortices.



increasing atrophy of the temporal lobes with consecutive widening of the temporal horns (arrows) of the lateral ventricles.

Figure 3: Normal finding on the left and increasing atrophy of the temporal lobes with consecutive

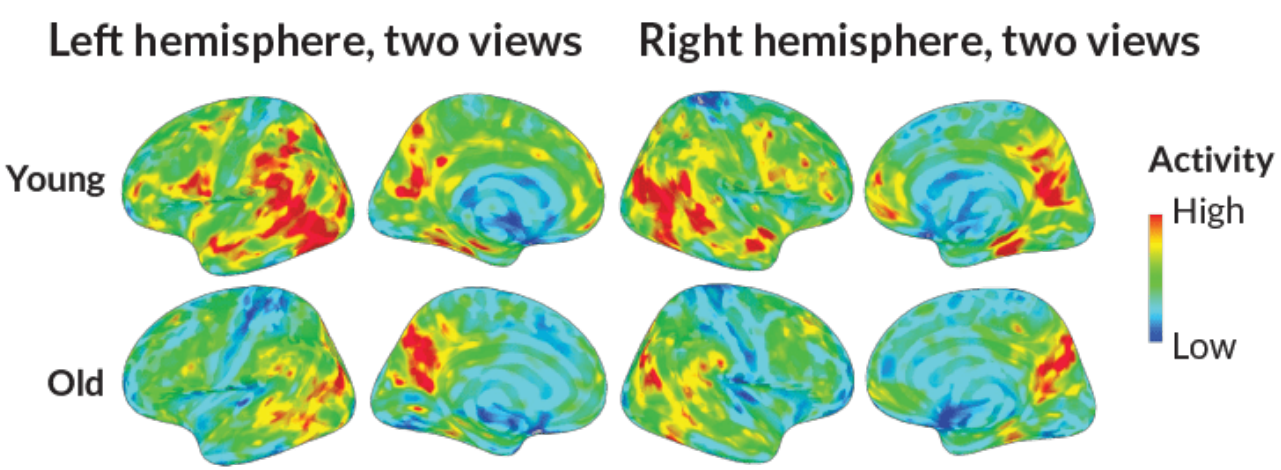
1. Successful aging

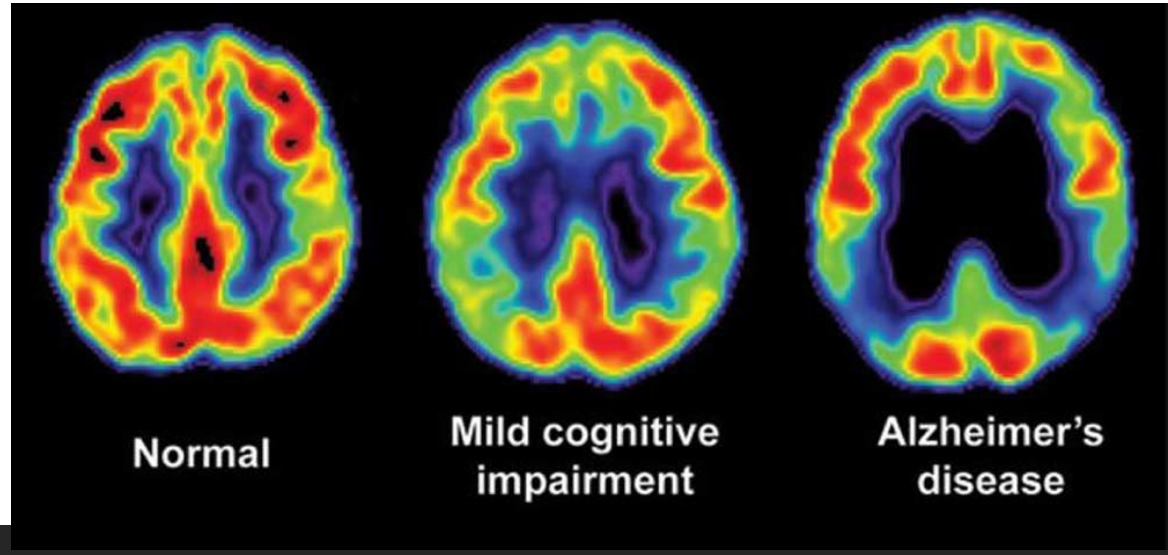
1.2 Associated neuroanatomical and neurophysiological changes: neuroimaging

•**MRI**: normal aging shows cortical thinning, especially in the prefrontal cortex, and ventricular enlargement.

•**fMRI**: reduced activity in key cognitive networks such as the default mode network (DMN).

•**PET**: age-related reductions in glucose metabolism and amyloid deposits (if present) even in healthy older adults.





1. Successful aging

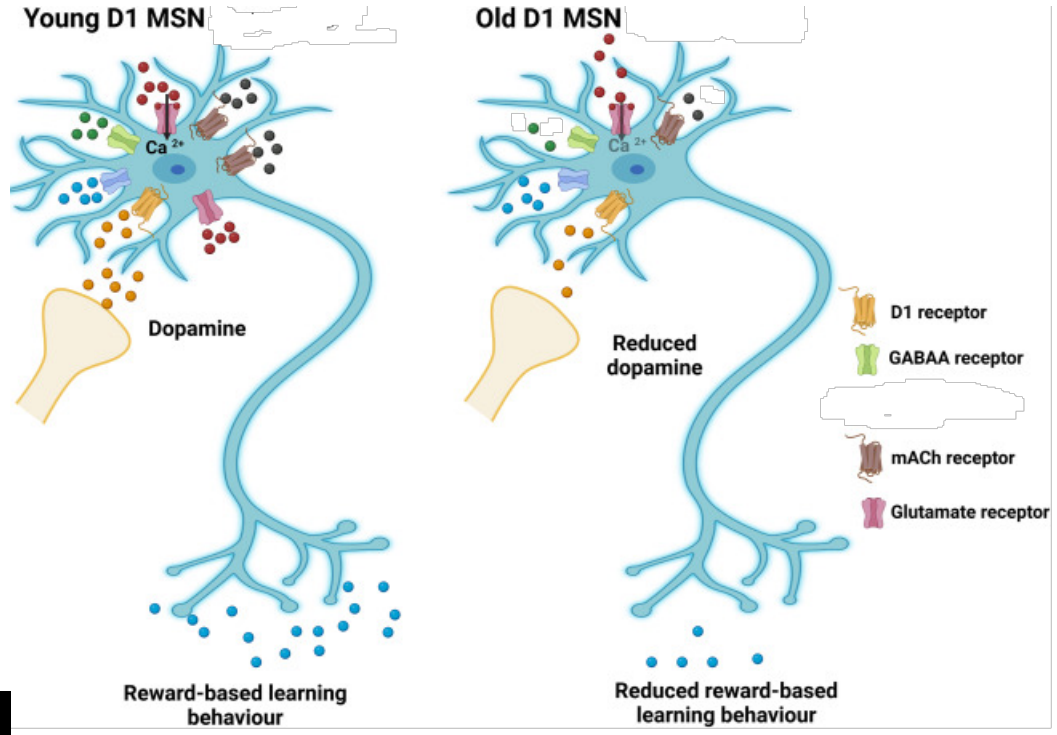
1.2 Associated neuroanatomical and neurophysiological changes

Neurochemical Changes

• **Dopamine**: aging is associated with reduced dopamine receptor density, especially in the striatum, affecting **motor control and executive function** as well as **motivation**.

• **Acetylcholine**: reduction in cholinergic activity, especially in the basal forebrain, is common with age, leading to declines in **attention and memory**.

• **GABA**: decreased GABAergic activity is linked to impaired inhibitory control and cognitive slowing in aging.



1. Successful aging

1.3 Neuropsychology of aging

- Intelligence tests (e.g. WAIS): Manipulative IQ decreases more than verbal IQ with aging (partial impairment of visuospatial functions)

Cognitive decline in aging is variable.

→ Processing speed and memory (especially episodic memory) decline.

Lower memory performance (lower amount of Ach): AMD (age-related memory impairment)

→ Executive functions decline.

Worse performance on frontal lobe tasks

→ Language skills and crystallized knowledge may remain intact.

Preservation or even improvement of linguistic functions (lexicon)

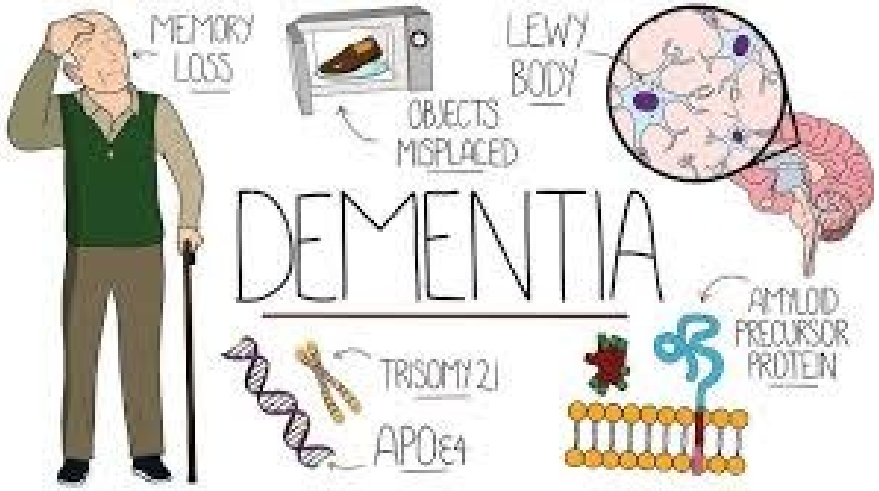
→ Cognitive reserve, or the brain's resilience to neuropathological damage, plays a role in maintaining function despite aging.

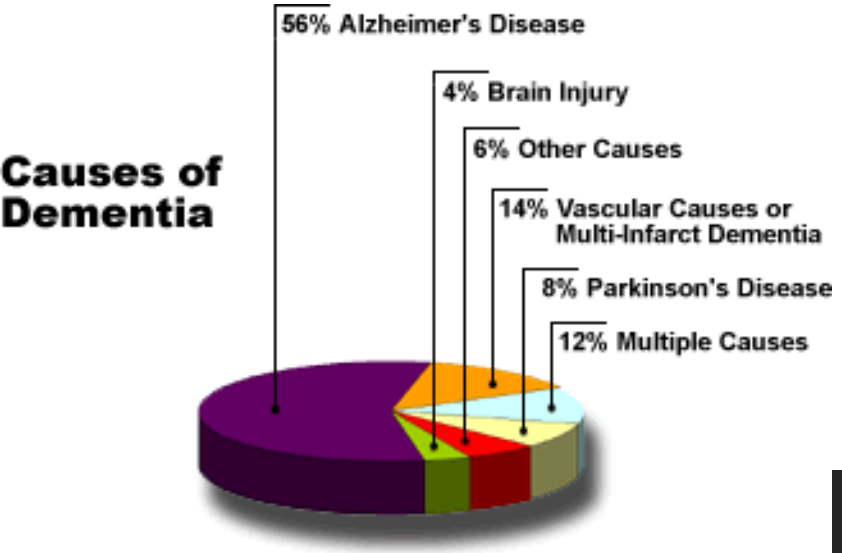
→ Cognitive slowing (leukoaraiosis) and parkinsonism (due to decreased dopamine) are observed.

2. Dementias: General aspects

2.1 Definition and diagnostic criteria

Dementia is a syndrome characterized by a decline in cognitive function severe enough to interfere with daily life and independence.





Diagnostic criteria for dementia (DSM-V)

Memory impairment: impaired ability to learn new information or recall old information.
One or more of the following: Aphasia (language disturbance). Apraxia (impaired ability to carry our motor activities despite intact motor function). Disturbance in executive functioning (e.g., planning and sequencing).
The cognitive deficits result in functional impairment (**social/ocupational**).
The cognitive deficits do not occur exclusively during a delirium.
It is NOT due to other medical or psychiatric conditions.

2. Dementias: General aspects

2.2 Types of Dementia

Type of Dementia	Characteristics
Alzheimer's Disease	Gradual memory loss, aphasia, apraxia, agnosia, amyl neurofibrillary tangles.
Vascular Dementia	Cognitive decline due to cerebrovascular events, often sudden onset witl stepwise progression.
Parkinson's Disease Dementia	Affects motor function first, followed by cognitive decline; related to dopamine depletion.
Huntington's Disease	Genetic disorder causing movement, cognitive, and psychiatric symptoms, typically starting in midlife.
Alcohol-Related Dementia	Cognitive decline related to chronic alcohol abuse; may include Wernicke-Korsakoff syndrome.
Chronic Pharmacological Intake	Cognitive decline due to long-term drug use (e.g., sedatives or anticholinergics).
Normal Pressure Hydrocephalus	Cognitive decline, gait disturbances, and urinary incontinence due to cerebrospinal fluid accumulation.
Encephalopathies	Brain dysfunction due to infections (e.g., prion diseases) or metabolic disturbances.
Miscellaneous Dementias	Includes dementia due to trauma, infections, and other less common etiologies.

Review > Nat Rev Neurol. 2017 Aug;13(8):457-476. doi: 10.1038/nrneurol.2017.96. Epub 2017 Jul 14.

A clinicopathological approach to the diagnosis of dementia

Fanny M Elahi [1], Bruce L Miller [1]

https://www.researchgate.net/publication/318434499_A_clinicopathological_approach_to_the_diagnosis_of_dementia

- Dementia classification
- AD as dual proteinopathy (AB fibrils)
- Risk factors
- Biomarkers
- Clinical syndromes
- Vascular dementia (clinical and biomarkers)
- Frontotemporal dementia (clinical and biomarkers)
- Lewy body dementia (a synucleinopathy) (clinical and biomarkers).
- Prion disease.

2. Dementias: General aspects

2.2 Types of Dementia

Frontotemporal Dementia

Frontotemporal Dementia

Behavioral and Emotional
- Difficulty planning and organizing
- Impulsive behaviors
- Emotional flatness or excessive emotions

Movement Problems
- Shaky hands
- Problems with balance and walking

Language Problems
- Difficulty making or understanding speech

There are several types of frontotemporal disorders, and symptoms can vary by type.

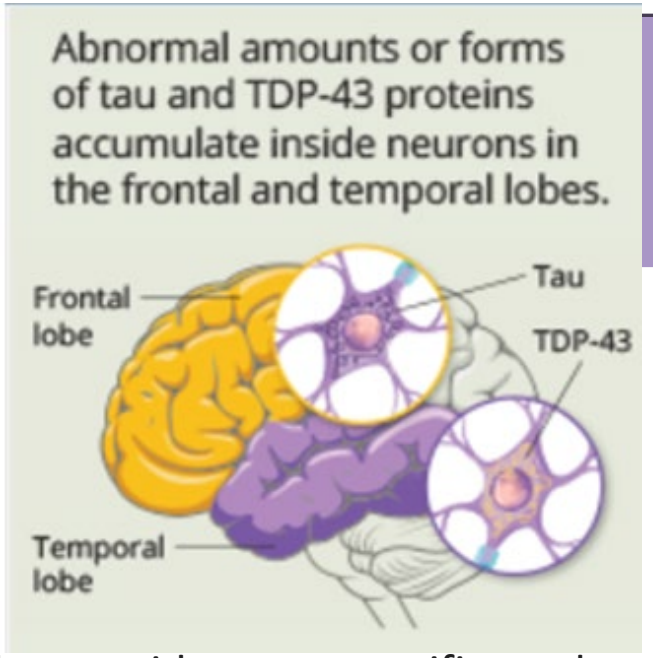
→ Frontotemporal dementia (FTD) is caused by a combination of genetic and environmental factors.

→ It is characterized by changes in behavior, personality and language skills.

→ Patients may may exhibit apathy or lack of motivation, inappropriate social behavior, impulsivity, repetitive behaviors, and difficulty with language comprehension or expression.

→ It typically affects individuals at a younger age.

→Specific markers that identify primary tauopathies or TDP-43 proteinopathies are still lacking.

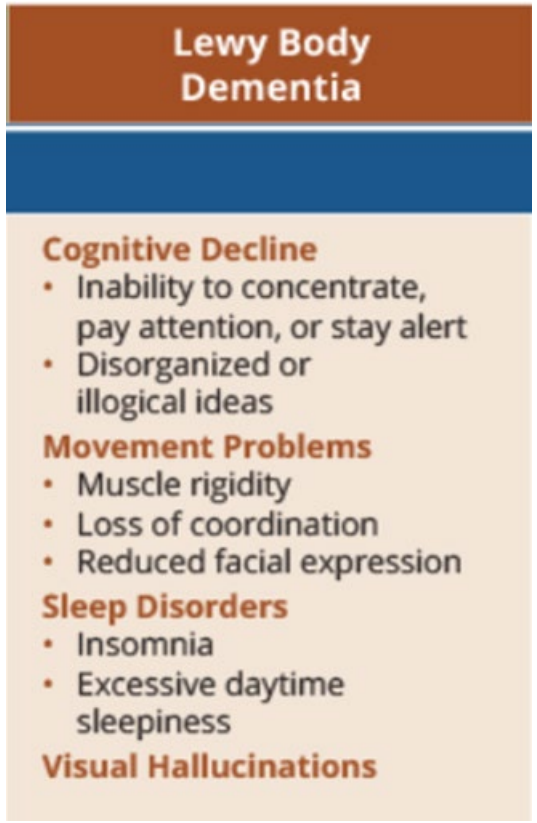


→ Greater attention has been paid to non-specific markers of neurodegeneration. In particular, multiple studies of neurofilament light chains have highlighted its importance as a diagnostic, prognostic and staging marker of FTD.

2. Dementias: General aspects

2.2 Types of Dementia

Lewy Body Dementia



→ Lewy body dementia is caused by clumps of proteins known as Lewy bodies, which appear in the nerve cells of the brain.

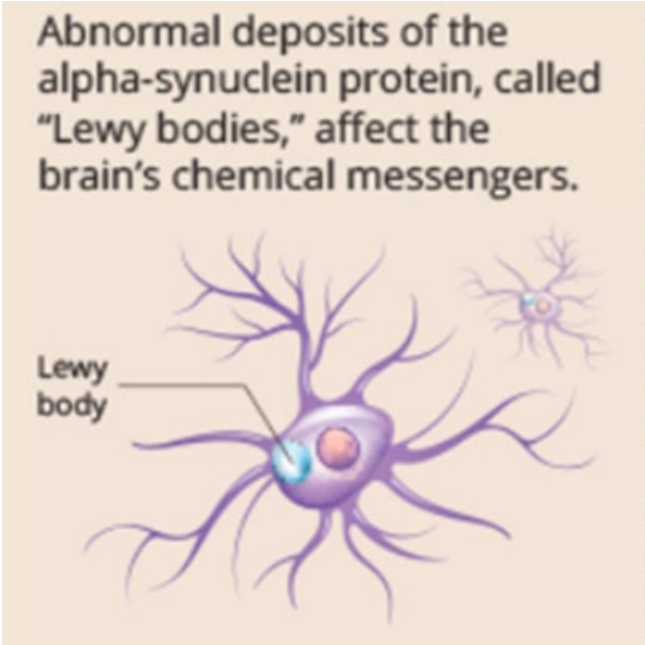
→ Lewy bodies are named after FH Lewy, the German doctor who first identified them.

→ Thinking problems similar to those of Alzheimer's disease occur.

→ These may include confusion, poor attention, visual-spatial problems, memory loss, and trouble sleeping.

→ People with Lewy body dementia can have rapid eye movement (REM) sleep behavior disorder.

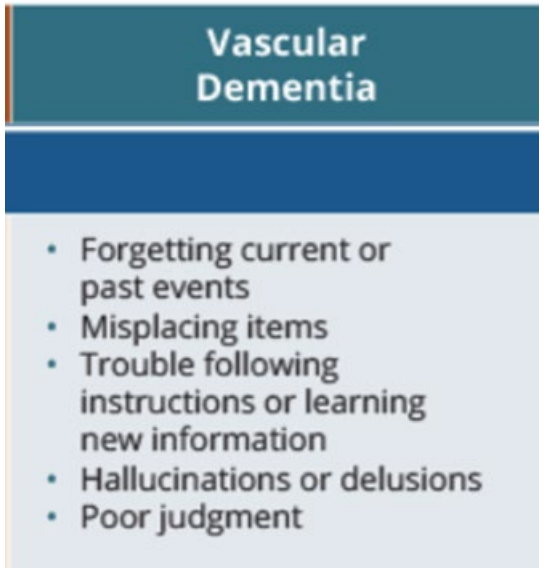
→ Typical age at diagnosis is 50 or older.



2. Dementias: General aspects

2.2 Types of Dementia

Vascular Dementia

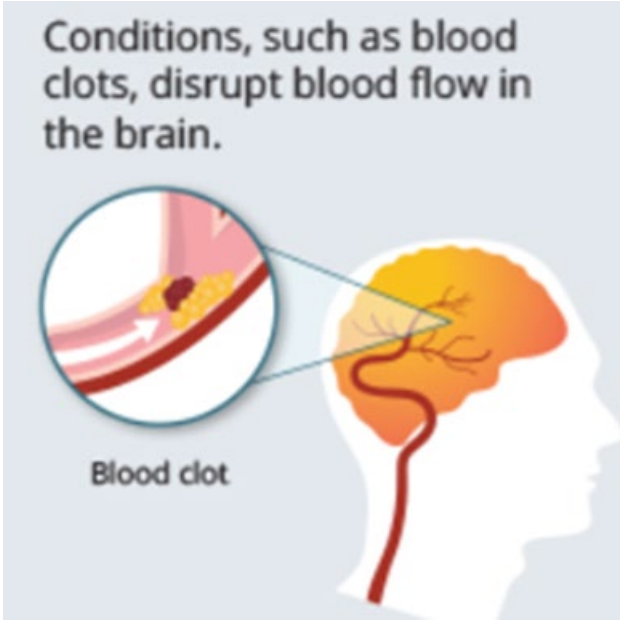


→ Vascular dementia is caused by a reduced flow of blood to the brain.
  → Reduced blood flow kill brain cells

→ Symptoms include problems with memory and focus, confusion, changes in personality and behavior, loss of speech and language skills, and sometimes physical symptoms such as weakness or tremors.

→ Vascular dementia tends to get worse over time.

→ The typical age of diagnosis is over 65 years.



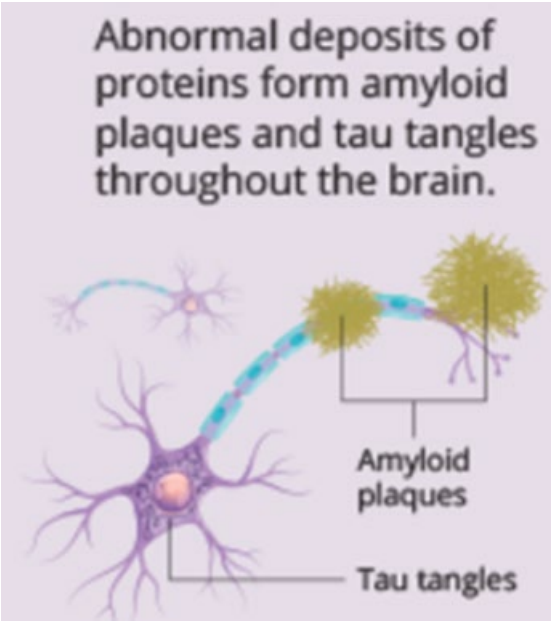
2. Dementias: General aspects

2.2 Types of Dementia

Alzheimer´s Disease

With Alzheimer's disease, the realization that something is wrong often comes gradually to the person and their family. Indicators include:

- Memory loss that disrupts daily life.
- Poor judgment leading to bad decisions.
- Loss of spontaneity and sense of initiative.
- Losing track of dates or not knowing current location.
- Taking longer to complete normal daily tasks.
- Repeating questions or forgetting recently learned information.
- Trouble handling money and paying bills.
- Challenges in planning or solving problems.
- Wandering and getting lost.
- Losing things or misplacing them in odd places.
- Difficulty completing tasks such as bathing.
- Mood and personality changes.
- Increased anxiety and/or aggression.



2. Dementias: General aspects

2.3 Diagnostic Tests

1.General Evaluation: initial assessments

- Clinical history
- General and neurological exploration
- Cognitive screening (Mini-Mental, IMC, MMSE, MoCA)

2. Paraclinical Testing

- Neuroimaging (MRI, CT)
- Blood and urine tests

3. Specific Testing (based on specific case information).

- Psychological testing
- Neurospychological tests (Wechsler Memory Scale for memory and Clock Drawing Test for visuospatial deficits
- Drug testing

2. Dementias: General aspects

2.4 Differential Diagnosis

• **Diffuse Brain Syndrome**, which is characterized **by global cognitive decline**, including attention, and is often seen in metabolic or toxic encephalopathies.
→ Confusion or delirium.

• **Focal Brain Syndrome**, which is characterized by cognitive impairments **restricted to specific areas** (e.g., Broca's aphasia in stroke).
→ Amnesia, dysphasia or aphasia.

• **Psychiatric Disorders (pseudodementia),** in which **cognitive impairment is reversible** via treatment of the mood disorder.
→ Depression, schizophrenia

• **Benign Memory Loss typical of Senescence**, which is **non-progressive memory loss associated with normal aging** that does not interfere significantly with daily function.

2. Dementias: General aspects

2.4 Differential Diagnosis

DEMENTIA	PSEUDODEMENTIA
Insidious onset	Sudden onset
Slow progression	Rapid progression
Lack of insight	Presence of insight
Confabulations	Memory disorders
Tendency to diminish disability	Tendency to emphasize disability
Behavior corresponding to the severity of illness	Behavior often not corresponding to the severity of illness
Lack of answers	General responses (i.e. "I do not know")
Worsening at night	No night changes
Incongruity of affect	Depressed mood
Few vegetative symptoms	Frequent vegetative symptoms
Infrequent psychiatric history	Frequent psychiatric history
Low suicide risk	High suicide risk

3. Alzheimer's Disease

3.1 Introduction and Diagnostic criteria

Alzheimer's disease (AD) is the most common form of dementia.

→ It is characterized by a progressive loss of memory, language and cognitive function.

→ It is also characterized by changes in behavior, personality, judgment and daily activities.

→ It is the most common cause of dementia in people over 65.

→ Risk factors include age, family history of dementia, and Down syndrome.

Diagnosis is based on clinical criteria (memory impairment plus at least one other cognitive domain) and confirmed through biomarkers (e.g., amyloid plaques on PET scans and cerebrospinal fluid analysis).

RESEARCH ARTICLE | Open Access

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr., J. Scott Andrews, Thomas G. Beach, Teresa Buracchio, Billy Dunn, Ana Graf, Oskar Hansson, Carole Ho, William Jagust, Eric McDade, Jose Luis Molinuevo ... See all authors

First published: 27 June 2024 | https://doi.org/10.1002/alz.13859 | Citations: 28

The 2024 revised criteria are founded on several core principles:

→ Alzheimer's disease is defined as a **biological process** that is first detectable by **abnormal biomarkers** of its defining **neuropathologic features (amyloid-β plaques and tau neurofibrillary tangles)** when an individual is asymptomatic.

→ The disease progresses biologically during the preclinical period; then, when a sufficient pathological burden is reached, symptoms appear and then progress.

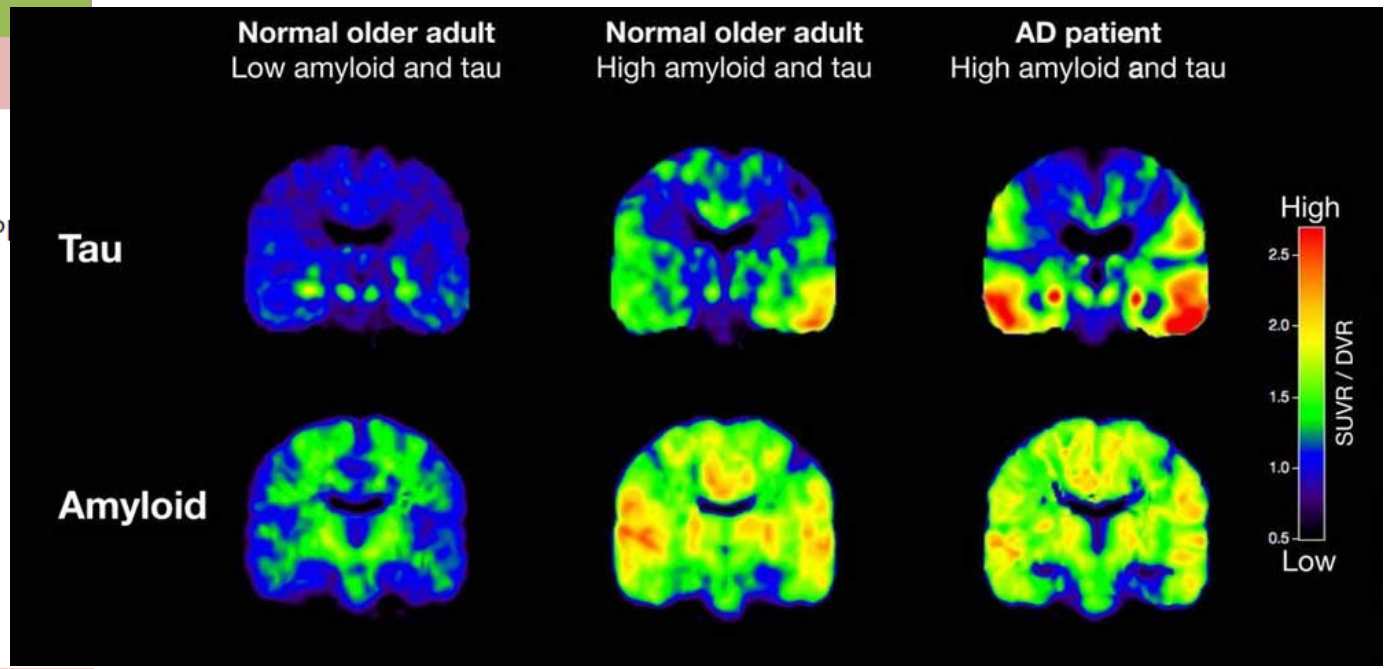
→ The entire course of disease may span up to 30 years.

3. Alzheimer's Disease

3.1 Introduction and Diagnostic Criteria

Abnormality on specific Core 1 biomarkers is sufficient to diagnose AD

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid P
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments [a]	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	



NfL = neurofilament light chain
MTBR = microtubule-binding region
FDG = fluorodeoxyglucose

3. Alzheimer's Disease

3.1 Introduction and Diagnostic Criteria

TABLE 2. Intended uses for imaging, CSF, and plasma biomarker assays.

Intended use	CSF	Plasma	Imaging
Diagnosis			
A: (Aβ proteinopathy)	—	—	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	—	p-tau217	—
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	—

3. Alzheimer's Disease

3.1 Introduction and Diagnostic Criteria

TABLE 2. Intended uses for imaging, CSF, and plasma biomarker assays.

Intended use	CSF	Plasma	Imaging
Staging, prognosis, as an indicator of biological treatment effect			
A: (Aβ proteinopathy)	—	—	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	—	p-tau217	—
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	—
T_2: (AD tau proteinopathy)	MTBR-tau243, other p-tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments	MTBR-tau243, other p-tau forms (e.g., p-tau205)	Tau PET
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	GFAP	—

3. Alzheimer's Disease

3.2 Epidemiological data

In Europe, Alzheimer's disease affects approximately 6-8% of people aged 65 and older, with prevalence rising to 30% in those over 85.

The European Alzheimer's Disease Consortium (EADC) estimates that 7.8 million Europeans were living with AD in 2022.

3. Alzheimer's Disease

3.2 Epidemiological data

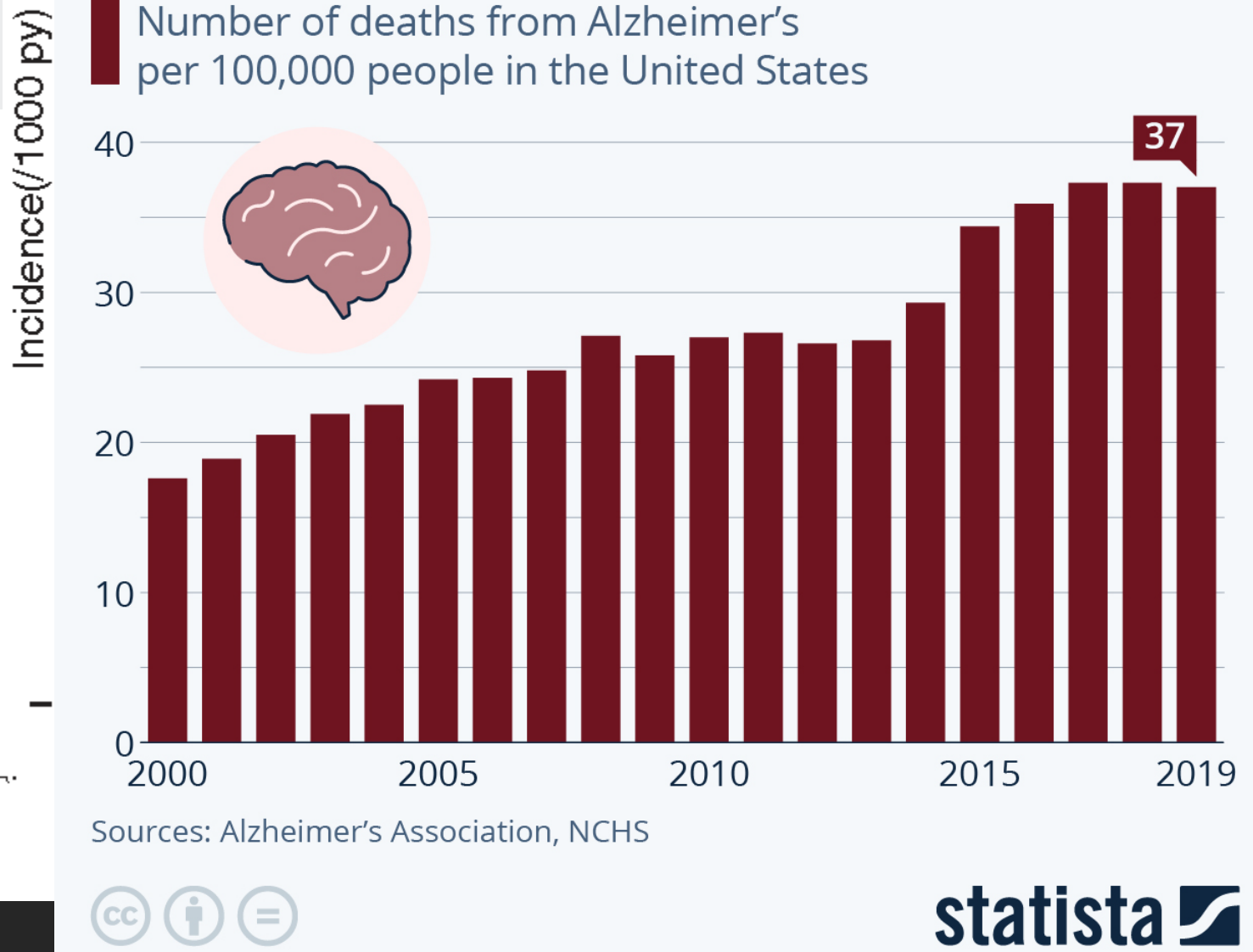
DOI: 10.1016/j.euroneuro.2005.04.003 • Corpus ID: 38526808

Prevalence of dementia in the elderly in Europe

C. Berr, J. Wancata, K. Ritchie • Published in European... 1 August 2005 • Medicine

Improvement in healthcare → longer life expectancy and better living conditions.

More elderly people= More dementia?



3. Alzheimer's Disease

3.2 Epidemiological data

Review > Biomolecules. 2022 Feb 3;12(2):249. doi: 10.3390/biom12020249.

Novel Nutraceutical Compounds in Alzheimer Prevention

Ricardo Benjamin Maccioni [1 2], Camila Calfío [1 2], Andrea González [1 2], Valentina Lüttges [1 2]

Affiliations + expand

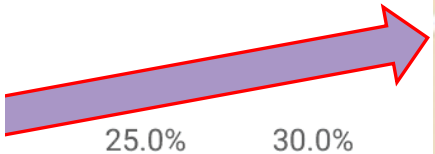
PMID: 35204750 PMCID: PMC8961630 DOI: 10.3390/biom12020249

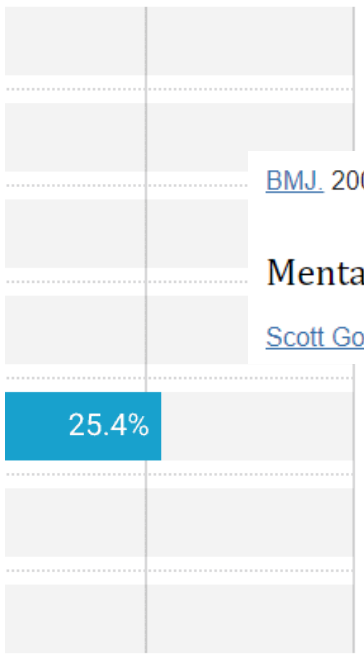
Full text links | Cite

Abstract

Alzheimer's disease (AD) incidence is increasing worldwide at an alarming rate. Considering this increase, prevention efforts, stemming from scientific research, health education, and public policies, are critical. Clinical studies evidenced that healthy lifestyles along with natural multitarget and disease-modifying agents have a preventative impact on AD or mitigate symptoms in diagnosed patients. The pathological alterations of AD start 30 years before symptoms, and it is essential to develop the capacity to detect those changes. In this regard, molecular biomarkers that detect early pathological manifestations are helpful. Based on markers data, early preventive interventions could reduce more than 40% of AD cases. Protective actions include exercise, shown to induce neurogenesis, cognitive stimulation, intellectual-social activity, and nutrition among others.

zheimer's diseas





BMJ. 2003 Jun 28; 326(7404): 1418.

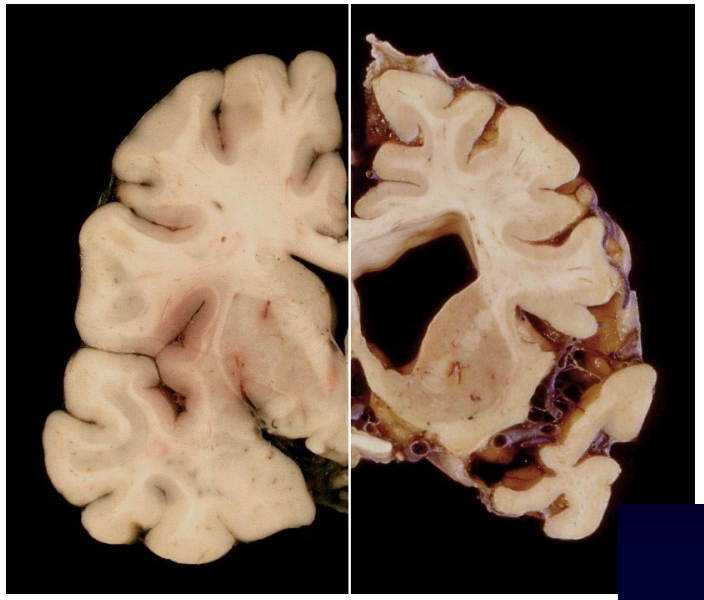
Mental activity may help prevent dementia

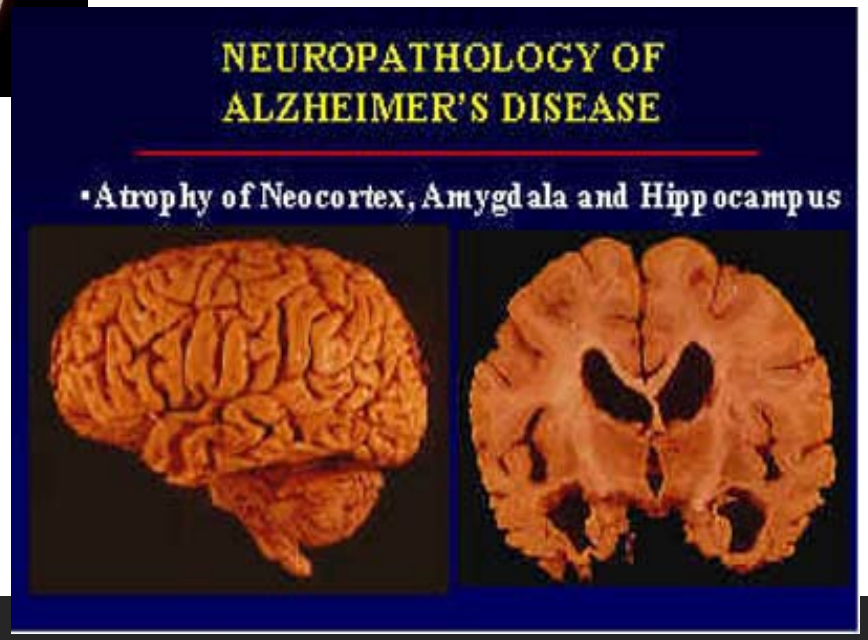
Scott Gottlieb

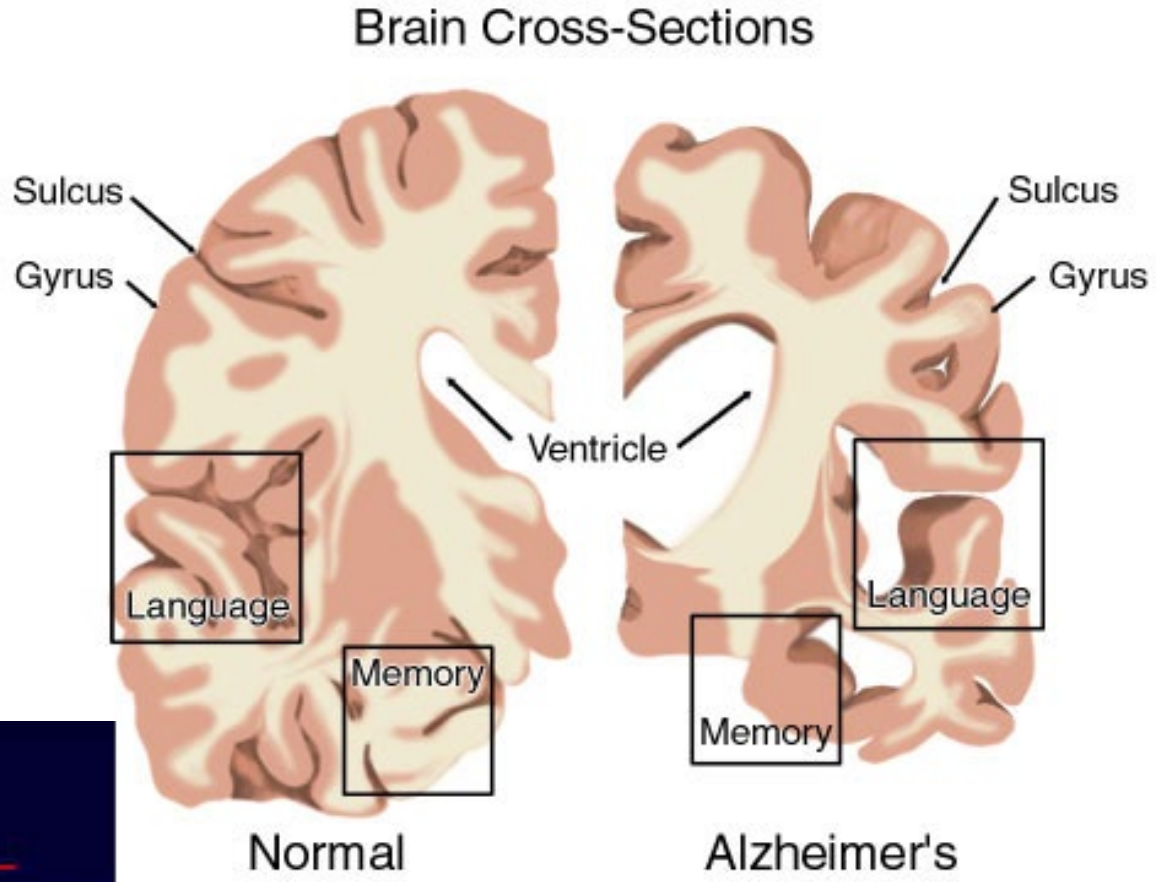
Source: Market.us Media

3. Alzheimer's Disease

3.3 Neuropathological characteristics: macroscopic







3. Alzheimer's Disease

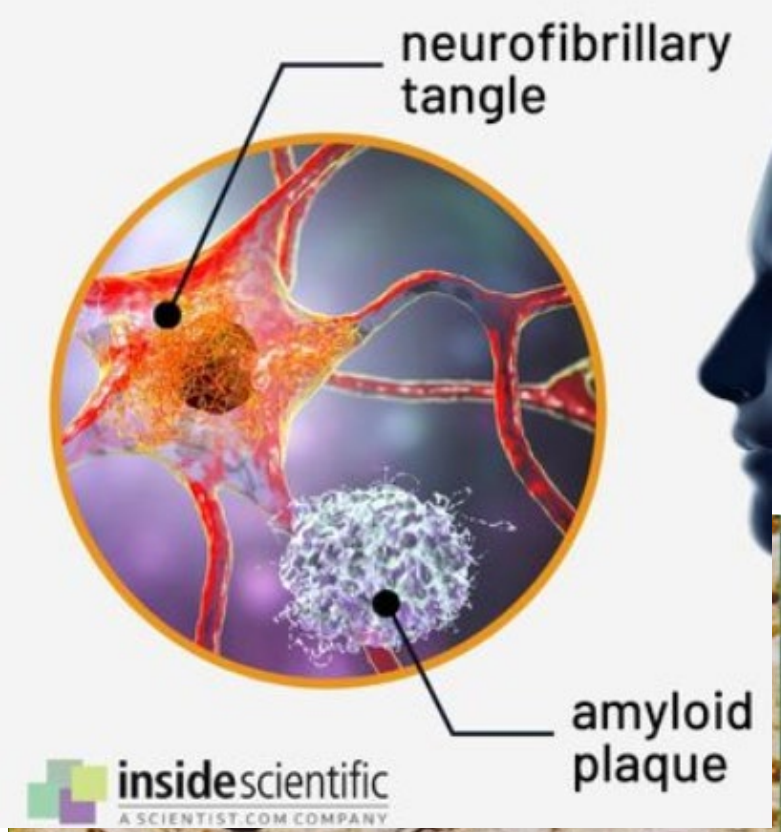
3.3 Neuropathological characteristics: microscopic

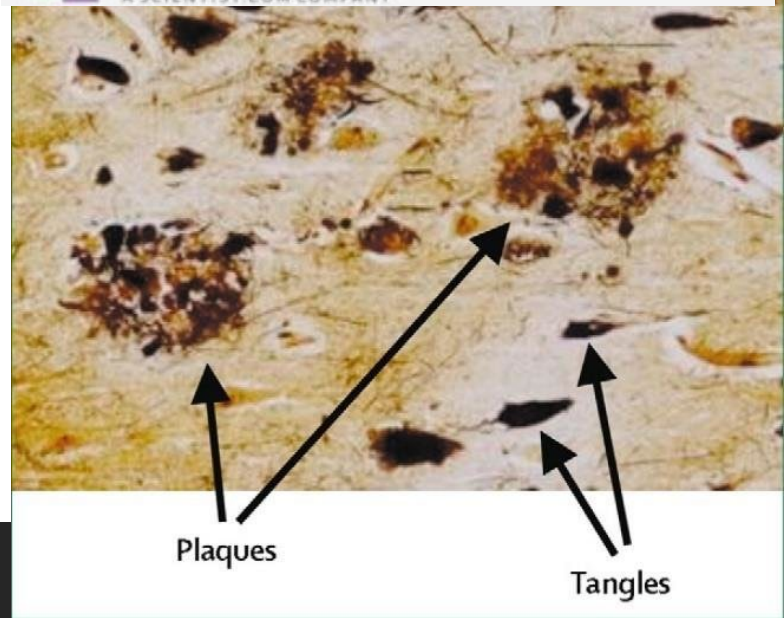
Inside Alzheimer's disease (4 min): AB amyloid and Tau

https://youtu.be/zTd0-A5yDZI?si=Ee_Kke6jNDyyziGr

• **Amyloid Plaques and Senile Plaques**: accumulation of beta-amyloid peptides in the brain forms plaques, thus contributing to neurotoxicity. Plaques are initially seen in the neocortex and hippocampus but spread to other areas as the disease progresses.

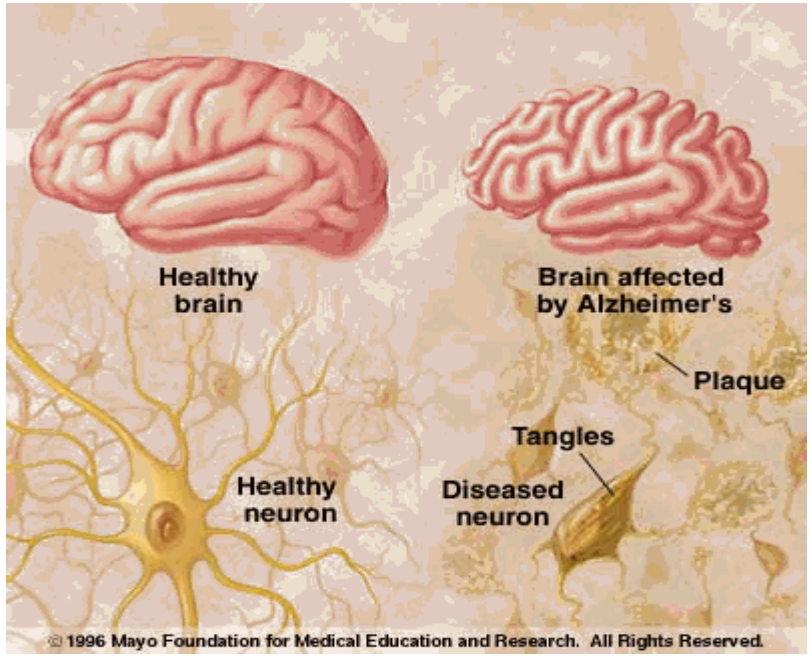
• **Neurofibrillary Tangles**: intracellular accumulations of hyperphosphorylated tau protein disrupt the cytoskeleton of neurons, causing cell death. Tangles spread from the entorhinal cortex to the neocortex as the disease advances.





3. Alzheimer's Disease

3.3 Neuropathological characteristics: microscopic



- → Plaque are insoluble deposits of a peptide called amyloid beta (Aβ amyloid).
- → It is formed when amyloid precursor protein is sequentially cleaved by 2 enzymes (beta and gamma secretase) to create other molecules that may play a role in the disease → Aβ is the main culprit.
- → Aβ clumps together and forms soluble oligomers.
- → Some oligomers aggregate into large insoluble fibrils that deposit in the brain as plaque.
- → These weaken communication and plasticity at synapses.
- → Aβ induces neuronal death and damage (also mediated by TAU, a component of tangles).
- → TAU stabilizes microtubules to carry molecules around the axon → in AD, TAU dissociates, becomes abnormal (TAU deposits) and kill the neurons.
- → Misfolded TAU proteins can spread into healthy neurons to spread the pathology.
- → Microglia take out Aβ but also become activated to induce inflammation
  - → Induce cytokine release
  - → Remove synapses by phagocytosis

3. Alzheimer's Disease

3.4 Genetic factors

Alzheimer's disease is associated with mutations on chromosomes 1, 14, 19 and 21 (familial AD).

→ Chromosomes 1,14,21 have been associated with early-onset AD.

→ The APOE ε4 allele on chromosome 19 increases vulnerability to sporadic AD (usually late-onset).

→ Those who inherit one copy of APOE-e4 from their mother or father have an increased risk of developing AD.

Genetic variants that cause Alzheimer's disease

Of the genetic variants so far associated with Alzheimer's, three rare single-gene variants are known to cause the disease:

- Amyloid precursor protein (*APP*) on chromosome 21
- Presenilin 1 (*PSEN1*) on chromosome 14
- Presenilin 2 (*PSEN2*) on chromosome 1

National Institute on Aging (.gov)
https://www.nia.nih.gov › health › alzheimers-disease-ge...
Alzheimer's Disease Genetics Fact Sheet

3. Alzheimer's Disease

3.4 Genetic factors

Category	Gene	Function/Role	Impact on Alzheimer's Disease
Early-Onset Alzheimer's	**APP** (Amyloid Precursor Protein)	Involved in the production of amyloid beta (Aβ) after cleavage by beta and gamma secretase.	Mutations lead to abnormal Aβ production and plaque formation.
	PSEN1 (Presenilin 1)	Part of the gamma secretase complex, involved in the cleavage of amyloid precursor protein.	Mutations cause abnormal processing of APP, increasing Aβ and plaque accumulation.
	PSEN2 (Presenilin 2)	Similar to PSEN1, involved in amyloid precursor protein cleavage via the gamma secretase complex.	Mutations contribute to abnormal Aβ production and plaque deposition.
Late-Onset Alzheimer's	**APOE** (Apolipoprotein E) - ε4 allele	Involved in cholesterol transport and Aβ metabolism.	APOE ε4 is the strongest genetic risk factor for late-onset Alzheimer's. It reduces Aβ clearance, increasing plaque risk.

circRNA from **APP Ge**

Urdánoz-Casado A, Sánchez-Luquin I, Mendioroz M.

Int J Mol Sci. 2023 Feb 21;24

› Acta Neuropathol Cor

Loss of prese phosphoryla

Carlos M Soto-Faguás [1]

Category	Gene	Function/Role	Impact on Alzheimer's Disease
Additional Risk Genes	**TREM2** (Triggering Receptor Expressed on Myeloid Cells 2)	Involved in microglial immune response and Aβ clearance.	Variants increase Alzheimer's risk by impairing microglial function and Aβ clearance.
	CLU (Clusterin)	Plays a role in amyloid beta clearance and cell survival.	Variants affect Aβ clearance and are associated with an increased Alzheimer's risk.
	ABCA7 (ATP-binding cassette sub-family A member 7)	Involved in lipid metabolism and amyloid processing.	Mutations impair the brain's ability to clear Aβ, raising the risk of Alzheimer's.
	CR1 (Complement Receptor 1)	Regulates the immune system and plays a role in clearing amyloid plaques.	Variants are linked to increased risk due to impaired plaque clearance.

APOE-4 genotype a

cognitive aging.

Bookheimer S, Burggren A.

Annu Rev Clin Psychol. 2009;5:343-62. doi: 10.1146/annurev.clinpsy.032408.153625.

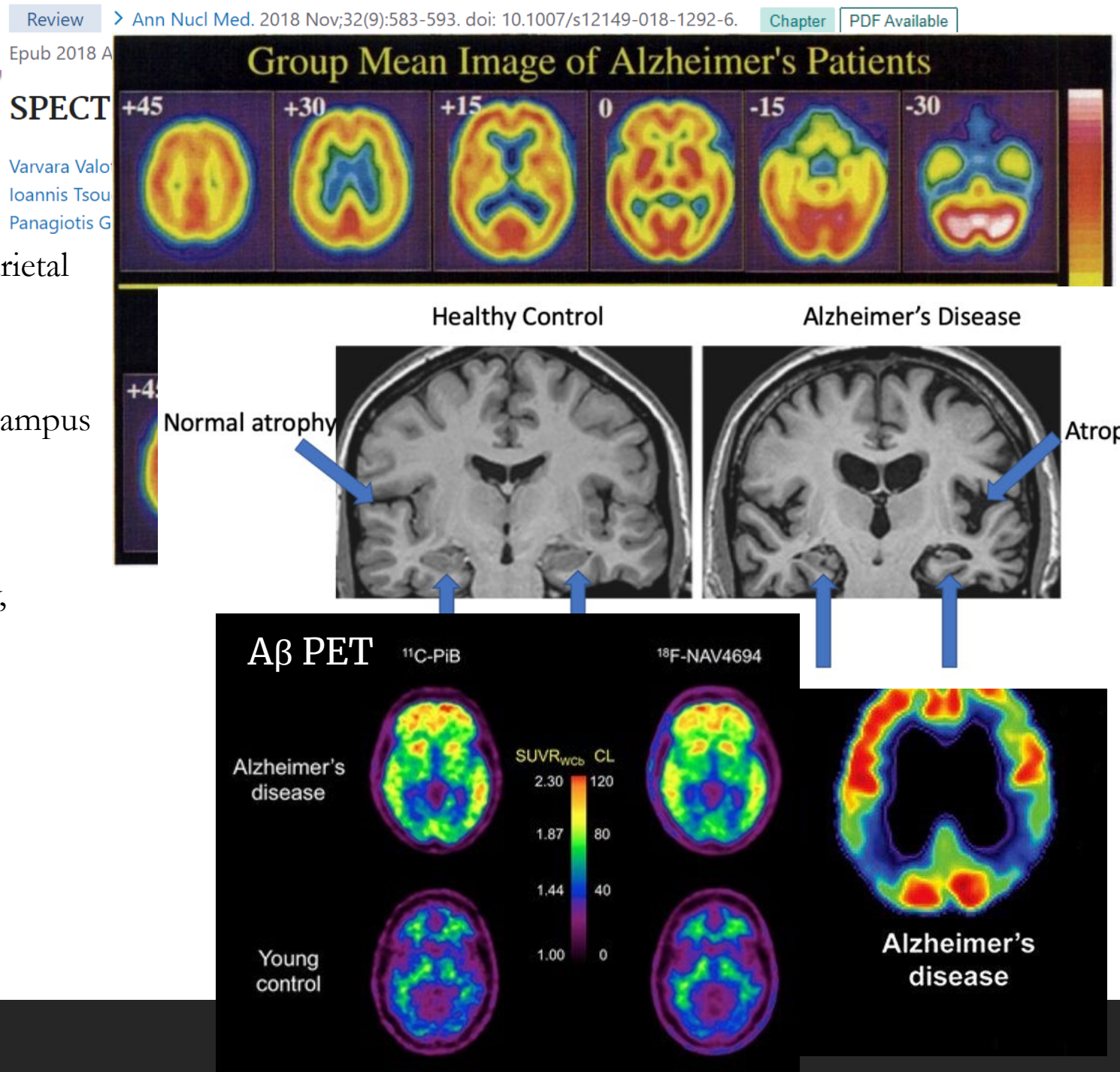
3. Alzheimer's Disease

3.5 Structural and functional neuroimaging studies

- **SPECT** shows reduced blood flow in the temporoparietal regions in AD patients.

- **MRI** reveals cortical atrophy, especially in the hippocampus and medial temporal lobe.

- **PET** detects amyloid-beta deposits and tau pathology, which indicates reduced glucose metabolism in AD-affected areas.

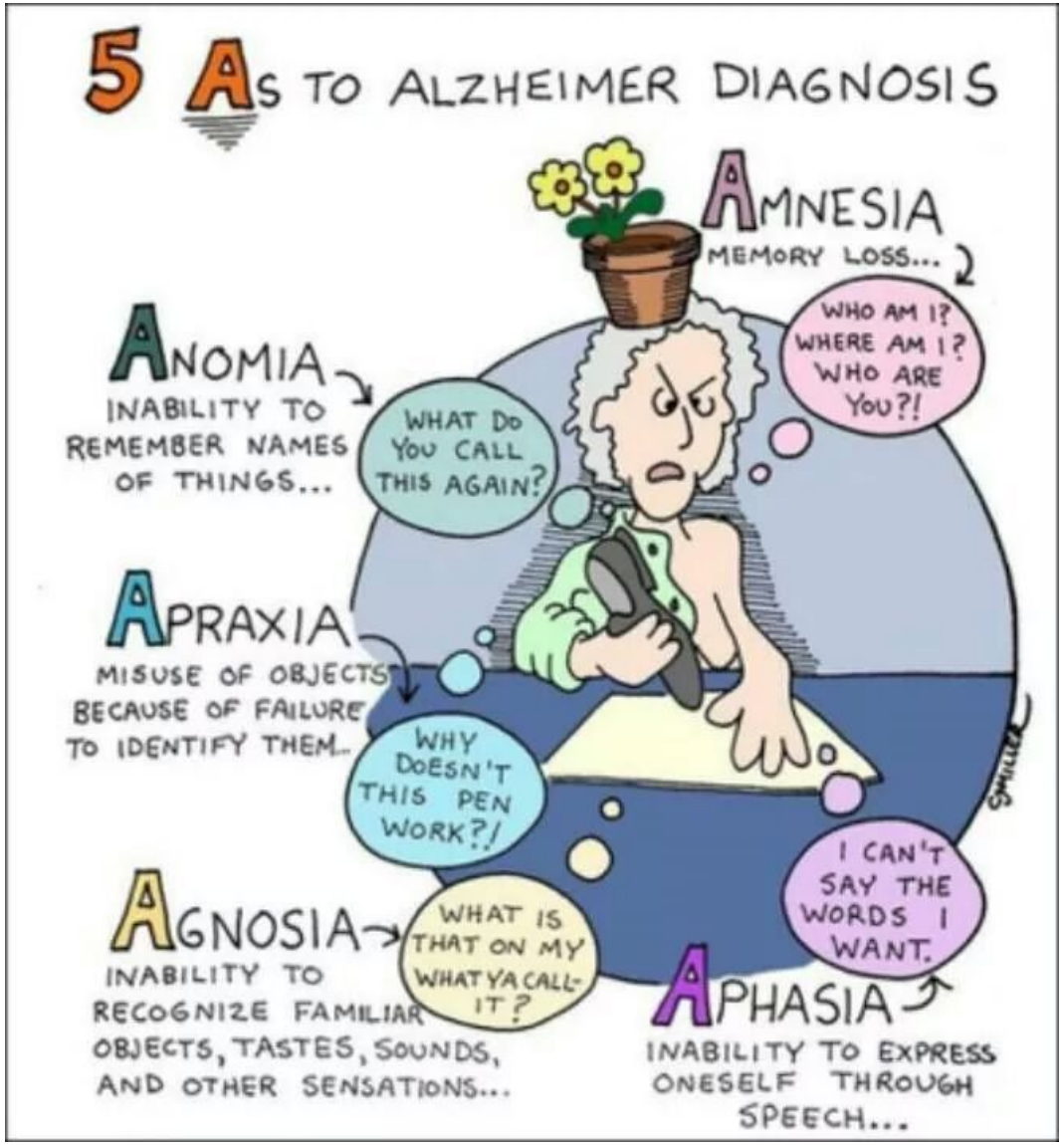


3. Alzheimer's Disease

3.6 Clinical and Neurochemical Aspects

Clinical (Neuropsychology):
→ AD presents as an amnestic, apractic, aphasic and agnosic syndrome.

→ Tests include the Boston Naming Test for language, the Rey Auditory Verbal Learning Test for memory, and the Trail Making Test for executive function.



3. Alzheimer's Disease

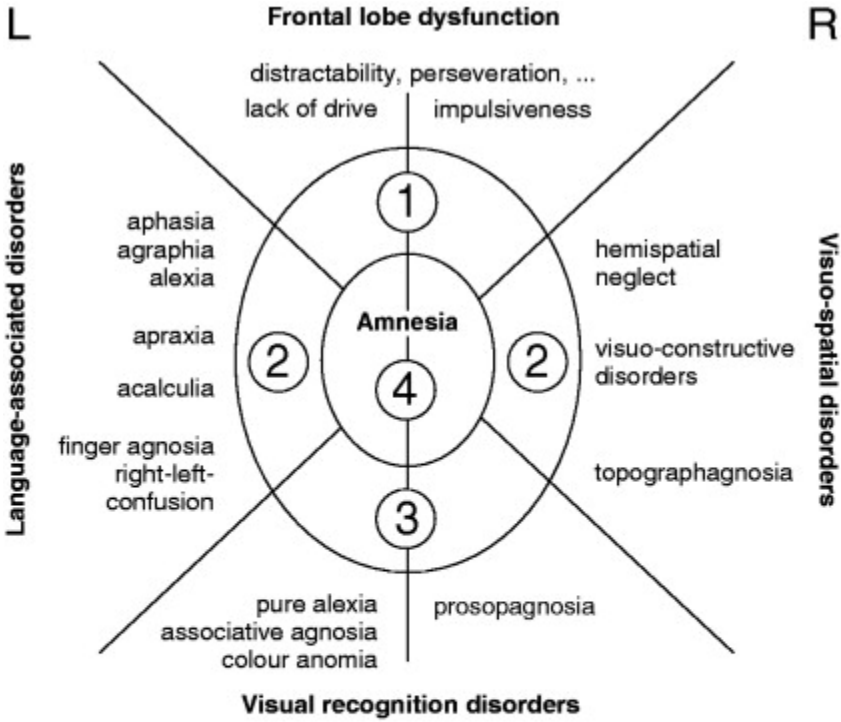
3.6 Clinical and Neurochemical Aspects

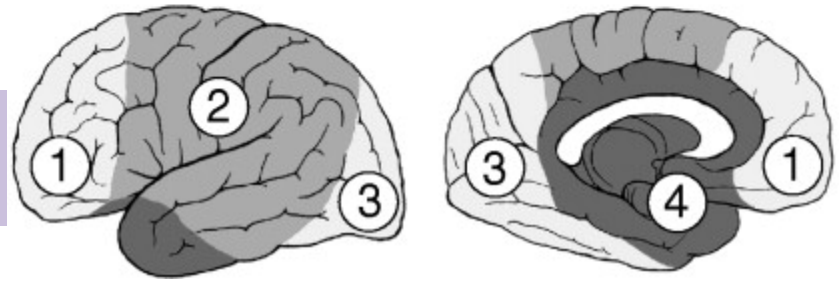
Handbook of Clinical Neurology
Volume 88, 2008, Pages 137-154

Chapter 6 Neuropsychological testing: bedside approaches

Armin Schnider

Characteristics	Testing
Initial screening for dementia	Folstein's Mini-Mental State Examination
Memory (amnesia)	Verbal memory, short-term memory, and long-term memory
Language (aphasia)	Verbal fluency, reading, writing and repetition, etc.
Movement following orders (apraxia)	Ideomotor praxias of imitation, symbolic, ideational and dressing
Perception difficulties (agnosia)	Masked figures, clock test, famous face recognition
Personality, behavior and routine changes	Sleeping, irritability, aggression, affective alterations, disorientation, social inhibition, hyperactivity, etc.



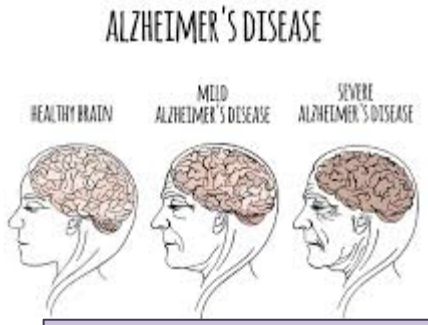


3. Alzheimer's Disease

3.6 Clinical and Neurochemical Aspects

Preclinical Alzheimer's Disease (Early Stage)
• **Symptoms**: no noticeable symptoms of memory loss or cognitive decline.
• **Neurological Changes**: the disease process begins years before symptoms appear and is characterized by the accumulation of amyloid beta (Aβ) plaques and tau tangles in the brain.
• **Detection**: abnormal biomarkers (e.g., imaging, cerebrospinal fluid analysis) can indicate Alzheimer's disease before symptoms become manifest.
• **Duration**: this stage can last for many years, and sometimes even decades.

Mild Cognitive Impairment (MCI) due to Alzheimer's Disease
• **Symptoms**: patients have mild memory problems and cognitive changes but can still carry out daily activities independently. They may experience occasional forgetfulness, difficulty in finding words, or trouble concentrating.
• **Cognitive Changes**: while some cognitive issues are observed, they do not yet interfere significantly with daily life. Not all people with MCI progress to Alzheimer's disease but this stage often precedes it.
• **Neurological Changes**: the buildup of plaque and tangles in the brain is more significant and begins to affect areas that control memory and learning.
• **Duration** varies but symptoms may persist for several years before progressing.



Mild (Early) Alzheimer's Disease
• **Symptoms**: clear memory problems, such as forgetting recent events, repeating questions, and misplacing items. Difficulty in managing finances, planning, or organizing becomes noticeable.
• **Cognitive and Behavioral Changes**: mild confusion, trouble with familiar tasks, changes in mood, and withdrawal from social activities may occur.
• **Neurological Changes**: damage spreads in areas of the brain involved in memory, thinking, and planning.
• **Duration**: this stage can last for 2 to 4 years, though it varies between individuals.

3. Alzheimer's Disease

3.6 Clinical and Neurochemical Aspects

Moderate (Middle) Alzheimer's Disease

- **Symptoms**: memory loss worsens, confusion increases, and difficulty in performing daily tasks becomes more pronounced. The patient may need assistance with complex tasks such as dressing, cooking or managing medications. Personality and behavioral changes (e.g., irritability, aggression, or depression) are more evident.
- **Cognitive Decline**: greater difficulty is observed with language, problem-solving and spatial awareness. The patient may struggle to remember their own personal history or get lost in familiar places.
- **Neurological Changes**: plaques and tangles spread to areas of the brain involved in sensory processing, reasoning and language.
- **Duration**: this stage typically lasts for 2 to 10 years, depending on individual factors.

Severe (Late) Alzheimer's Disease

- **Symptoms**: the patient loses the ability to communicate coherently, recognize loved ones, and to carry out any daily activities without assistance. They may require full-time care and experience significant physical deterioration, including difficulty swallowing, walking or controlling bodily functions.
- **Cognitive Decline**: the patient becomes completely dependent on others for care and experiences profound memory loss and confusion.
- **Neurological Changes**: damage affects almost the entire brain, leading to significant loss of brain tissue and severe cognitive and physical impairments.
- **Duration**: this stage can last for several months to years.

End Stage Alzheimer's Disease

- **Symptoms**: the patient is bedridden and completely dependent on caregivers for all aspects of daily life. They may lose the ability to speak and swallow and are highly vulnerable to infections such as pneumonia.
- **Cognitive Decline**: cognitive and physical decline are almost complete.
- **Neurological Changes**: extreme shrinkage of the brain is observed due to widespread neuron loss.
- **Duration**: this stage often lasts between a few months and several years. The disease is fatal, and death usually occurs due to complications.

3. Alzheimer's Disease

3.6 Clinical and Neurochemical Aspects

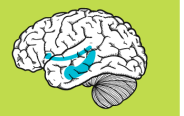
Stage	Symptoms	Neurological Changes	Duration
Preclinical Alzheimer's (Early)	No noticeable symptoms. Detected through biomarkers.	Accumulation of amyloid beta (Aβ) plaques and tau tangles begins.	Can last for years or decades.
Mild Cognitive Impairment (MCI)	Mild memory issues, forgetfulness, occasional word-finding problems.	Plaques and tangles spread to areas affecting memory and learning.	Varies; can persist for years.
Mild Alzheimer's (Early)	Clear memory loss, trouble managing daily tasks, confusion, mood changes, withdrawal.	Damage spreads to areas controlling memory, thinking, and planning.	2 to 4 years (varies by person).
Moderate Alzheimer's (Middle)	Increased memory loss, confusion, need assistance with daily tasks, personality changes.	Plaques and tangles spread to areas responsible for reasoning, language.	2 to 10 years.
Severe Alzheimer's (Late)	Loss of ability to communicate, complete dependence on others, loss of motor functions.	Damage affects nearly the entire brain, severe loss of brain tissue.	Several months to years.
End Stage Alzheimer's	Bedridden, unable to speak, loss of all bodily functions, highly vulnerable to infections.	Extreme brain shrinkage due to widespread neuron death.	A few months to several years.

Stages of Alzheimer

1. Mild cognitive impairment

Duration: 7 Years

Disease begins in Medical Temporal Lobe

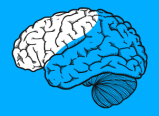


Symtoms: Short term Memory loss

2. Mild Alzheimer's

Duration: 2 Years

Disease spreads to lateral temporal and pariel lobes

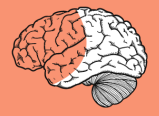


Symptoms: Reading Problem, Poor object recognition, Poor direct sense

3. Moderate Alzheimer's

Duration: 2 Years

Disease spreads to frontal lobe



Symptoms: Reading Problem, Poor object recognition, Poor direct sense

4. Severe impairment

Duration: 2 Years

Disease spreads to Occipital Lobe

Symptoms: Visual problems

The Seven Stages of Alzheimer's

1

No cognitive impairment

Symptoms: appears normal

2

Very mild cognitive decline

Symptoms: basic forgetfulness

3

Mild Cognitive Decline

Symptoms: struggle with social tasks, trouble thinking of the right word, misplacing objects

4

Moderate cognitive decline

Symptoms: struggle with complex tasks, personality changes (i.e. moodiness, etc), changes in sleep

5

Moderately Severe Decline

Symptoms: trouble with recalling personal details, emotional changes (i.e paranoia), cognitive issues

Caretaker now required.

6

Severe Decline

Symptoms: problems getting dressed, sleep issues, bladder and bowel control, major behavioral changes (i.e. getting lost)

Extensive assistance.

7

Very Severe Cognitive Decline

Symptoms: conversation not possible, abnormal reflexes, physical impairment

Extensive care required.

3. Alzheimer's Disease

3.6 Clinical and Neurochemical Aspects

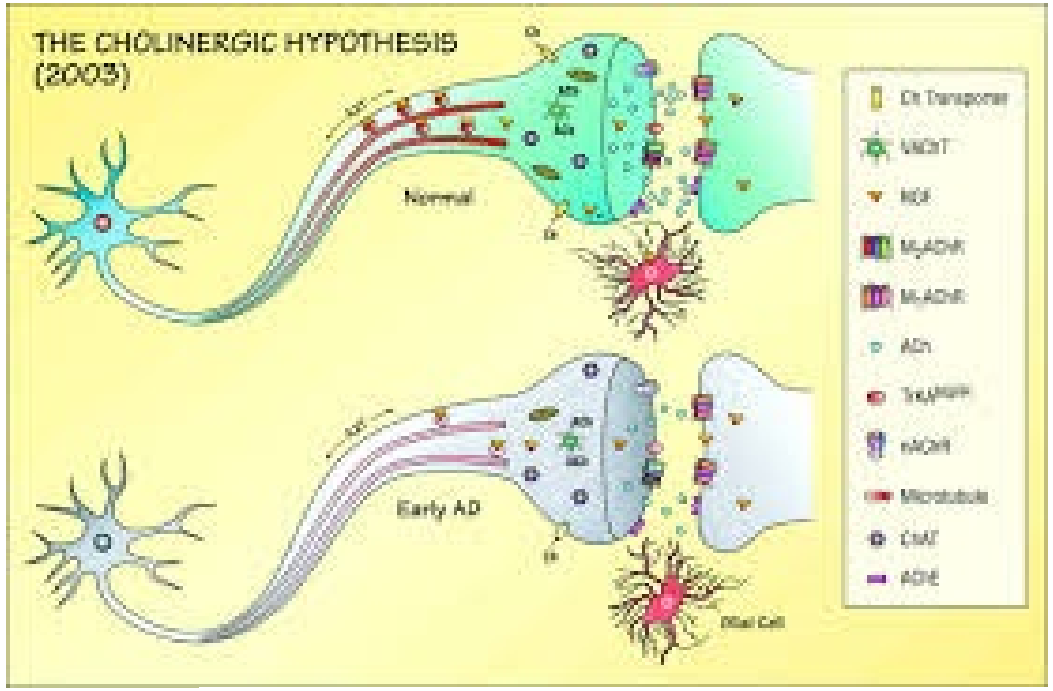
Neurochemistry:

→ The cholinergic hypothesis is the earliest theory about the pathogenesis of AD.

→ Acetylcholine (ACh) is an important excitatory neurotransmitter involved in learning, memory and other higher behaviors.

→ The cholinergic hypothesis suggests that reduced acetylcholine activity leads to cognitive decline.

→ There is significant cholinergic loss, particularly from the basal nucleus of Meynert, with projections to the hippocampus and cortical areas.



Molecules. 2022 Mar; 27(6): 1816.
Published online 2022 Mar 10. doi: 10.3390/molecules27061816

Role of Cholinergic Signaling in Alzheimer's Disease

Zhi-Ru Chen,[1,2,†] Jia-Bao Huang,[1,2,†] Shu-Long Yang,[3,4,*] and Fen-Fang Hong[1,*]

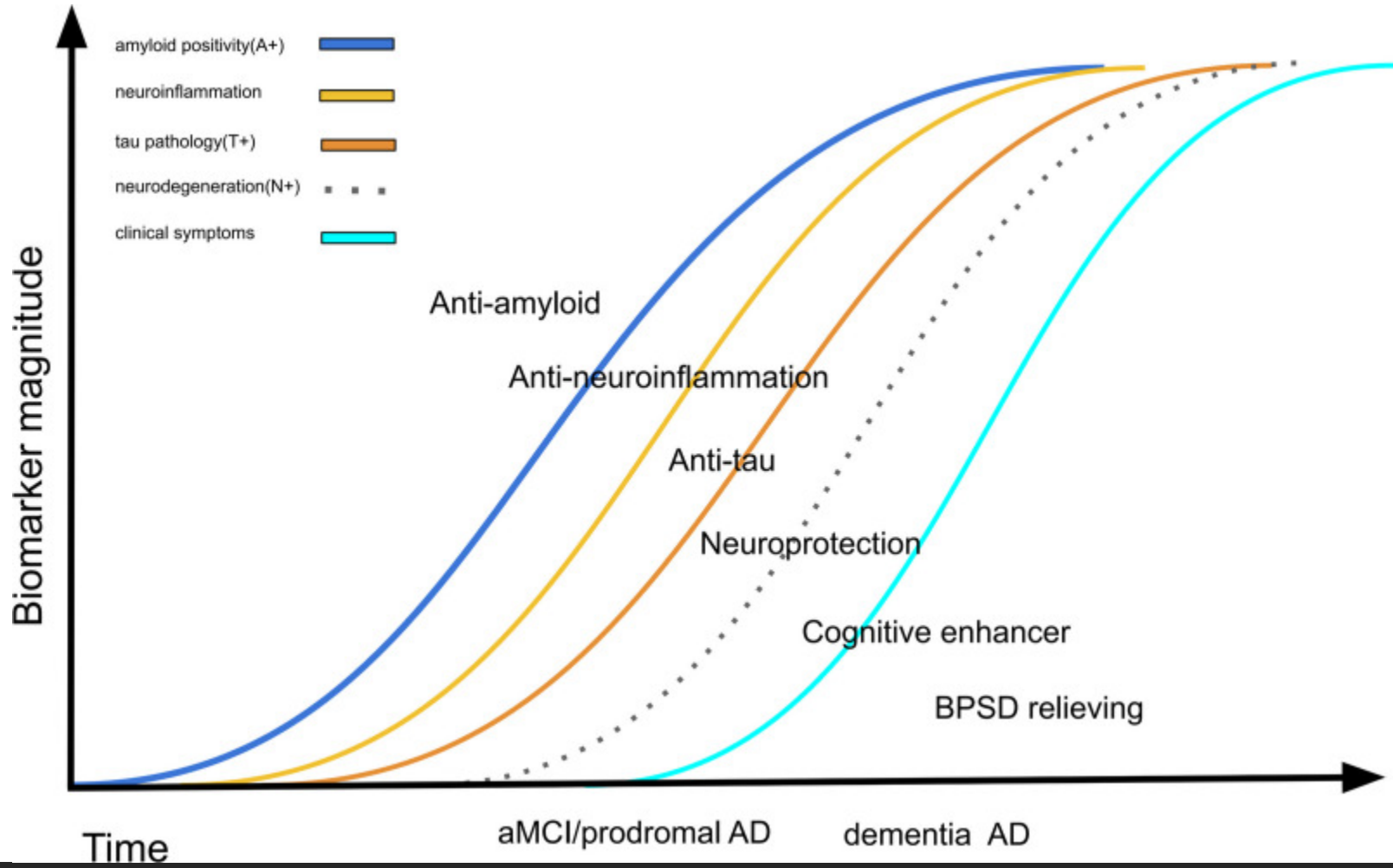
3. Alzheimer's Disease

3.6 Clinical and Neurochemical Aspects

Neurochemistry:

→ The amyloid hypothesis states that the pathophysiology and clinical course of Alzheimer's disease progresses as follows:

1. amyloid accumulation
2. neuroinflammation
3. tau accumulation
4. brain metabolism dysfunction
5. brain atrophy
6. cognitive decline (from mild cognitive impairment to dementia)



3. Alzheimer's Disease

3.7 Treatment

- **Pharmacological Treatments**:
    - **Cholinesterase Inhibitors** (donepezil, rivastigmine, galantamine) aim to boost acetylcholine levels in the brain.
    - **NMDA Receptor Antagonists** (memantine) mitigate glutamatergic excitotoxicity.

- **New Compounds Under Investigation**:
    - **Anti-Amyloid Drugs**: monoclonal antibodies such as aducanumab target amyloid plaques.
    - **Tau-Targeting Therapies** aim to reduce the formation of neurofibrillary tangles.

3. Alzheimer's Disease

3.7 Treatment

Vaccines to specifically target the prevention and treatment of Alzheimer's are still in development. If you have Alzheimer's disease, you'll probably have a buildup of tau proteins, beta-amyloid plaques, and inflammation in your brain and spinal cord. 20 ene 2024

WebMD
https://www.webmd.com › alzheimers › alzheimers-disea...

Is an Alzheimer's Disease Vaccine Possible? - WebMD

J Biomed Sci. 2023; 30: 83.
Published online 2023 Oct 2. doi: 10.1186/s12929-023-00976-6
PMCID: PMC10544555
PMID: 37784171

Clinical trials of new drugs for Alzheimer disease: a 2020–2023 update

Li-Kai Huang,[#1,2,3] Yi-Chun Kuan,[#2,3,4,5] Ho-Wei Lin,[6] and Chaur-Jong Hu[✉1,2,3,4]

Clinical treatment

Combination of:

- neuropsychological intervention (cognitive stimulation)
- pharmacological treatment to stimulate cognitive function
- pharmacological treatment to target behavioral symptomatology
- Support for family or caregivers

Are there any other treatments to target amyloid and tau plaques?

3. Alzheimer's Disease

3.7 Treatment

Medications are approved by:

→ **The European Medicines Agency (EMA)**

→ **The U.S. Food and Drug Administration (FDA)**

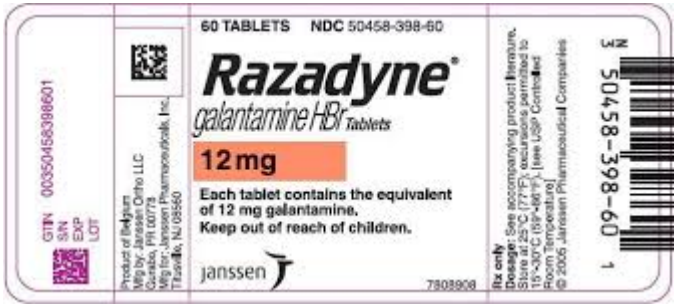
Cholinesterase inhibitors (Aricept®, Exelon®, Razadyne®)

** Donepezil (Aricept®) has been approved to treat all stages of Alzheimer's disease.

→ This drug selectively and reversibly inhibits the acetylcholinesterase enzyme, which normally breaks down acetylcholine. The main pharmacological actions of the drug are believed to occur as the result of this enzyme inhibition, which enhances cholinergic transmission, which in turn relieves the symptoms of Alzheimer's Disease.

**Galantamine (Razadyne®) has been approved for mild-to-moderate stages of Alzheimer's disease.

→ This drug is a cholinesterase inhibitor with a dual mechanism of action. It is a reversible inhibitor of acetylcholine esterase that enhances the intrinsic action of acetylcholine on nicotinic receptors, leading to increased cholinergic neurotransmission in the CNS.



Donepezil and galantamine were approved through European mutual recognition procedures in 1997 (2011 in the Netherlands) and 2000, respectively; rivastigmine and memantine were approved through the centralized procedures of the European Medicines Agency (EMA) in 1998 and 2002, respectively..

3. Alzheimer's Disease

3.7 Treatment

On 22 August 2024 the UK's Medicines and Healthcare products Regulatory Agency (MHRA) announced the approval of lecanemab (monoclonal antibody) for the treatment of early Alzheimer's disease (mild cognitive impairment and mild dementia).

→ This drug selectively binds to the highly neurotoxic **Aβ protofibrils** and is thought to reduce Aβ protofibrils and amyloid plaques (Aβ plaques) in the brain.

On 3 July 2024 the U.S. FDA approved the use of donanemab (similar to lecanemab), a ground-breaking new treatment for early Alzheimer's disease.

On 25 July 2024 Leqembi (lecanemab) was not approved for use by EMA → this decision is currently being reevaluated.

Alzheimer's drug from Eisai and Biogen rejected in Europe

26 jul 2024 — Lilly's amyloid-lowering **drug** Kisunla, also known as donanemab, gained U.S. **approval** this year and is being reviewed by **European** regulators.

What can we do as psychologists? → Neuropsychobiology

Hat's story: living with Alzheimer's disease (3:30 min) → research?

https://youtu.be/8MhAn54w6t8?si=WXIM1FAwzZMp50RK

5:03 / 6:07

Susan's Story | Alzheimer's Disease (6 min) → Neuropsychology support/ Emotional support

https://youtu.be/L_DQJH8EJ4Q?si=5UOiD45Gmuz4D1EV

Innovation→ Magnetoelectric nanoparticles (MENPs)