Dementia Classification

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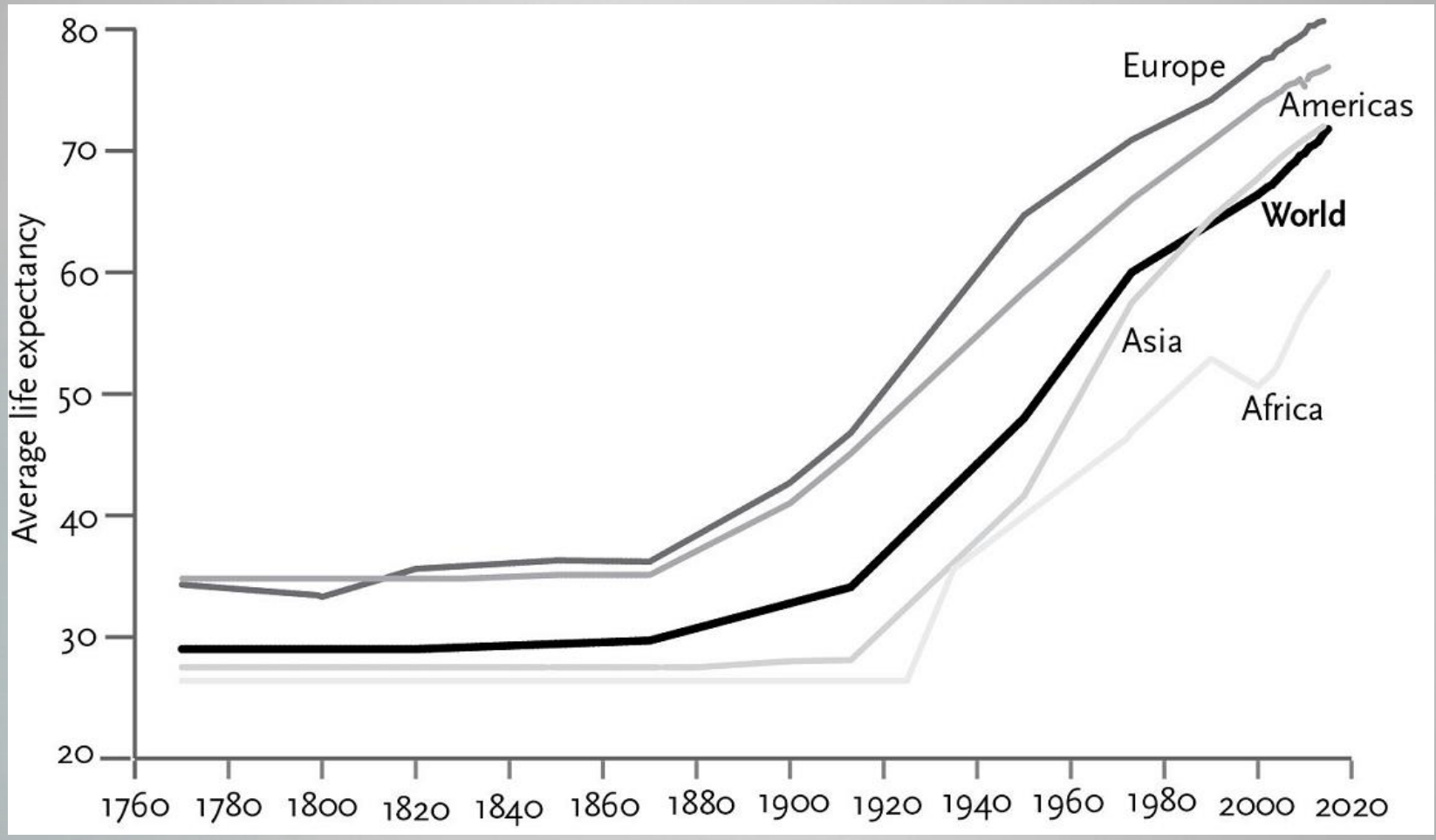
Ph.D Neuroscience

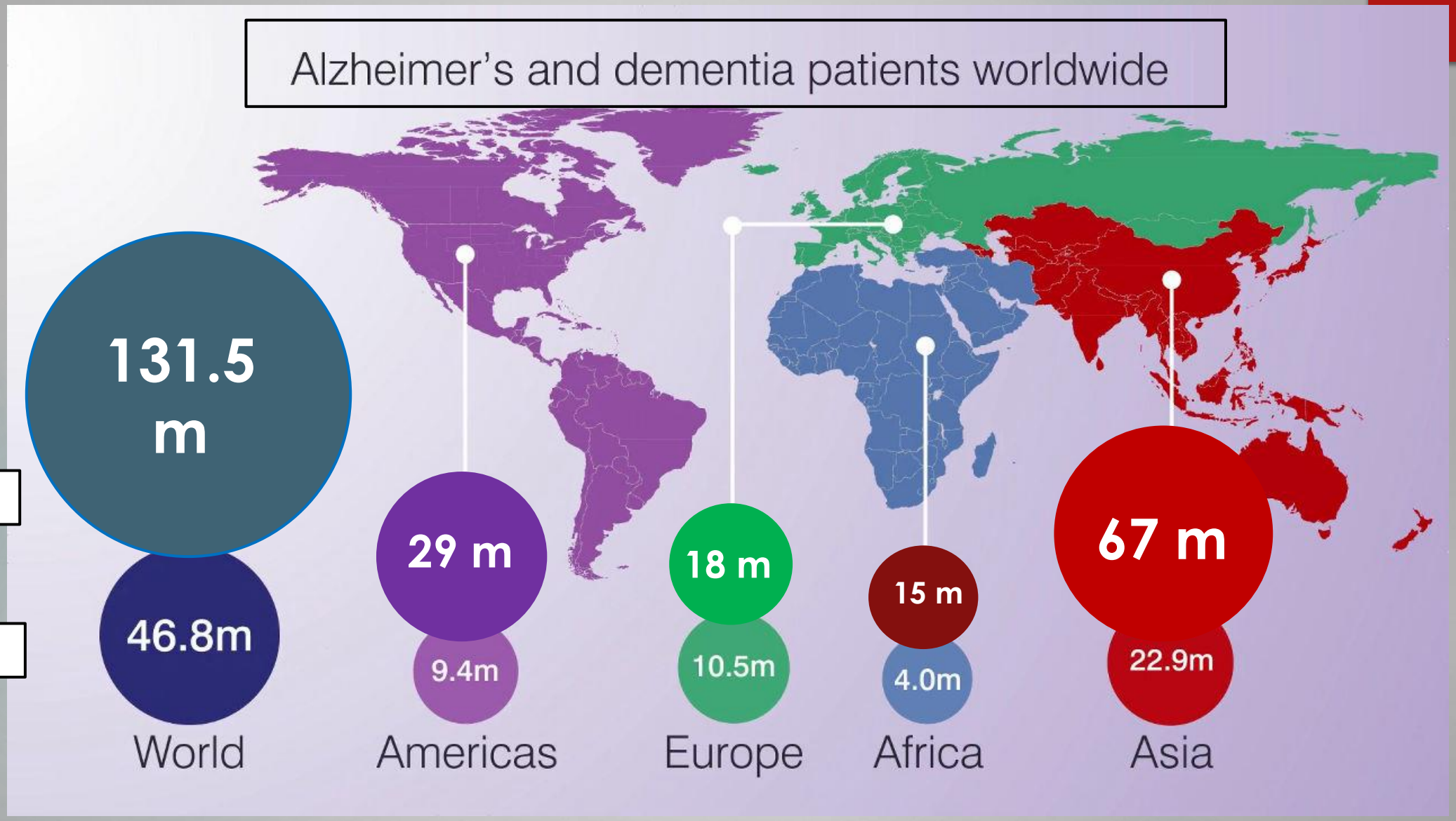
خوش بینی به آینده بشر

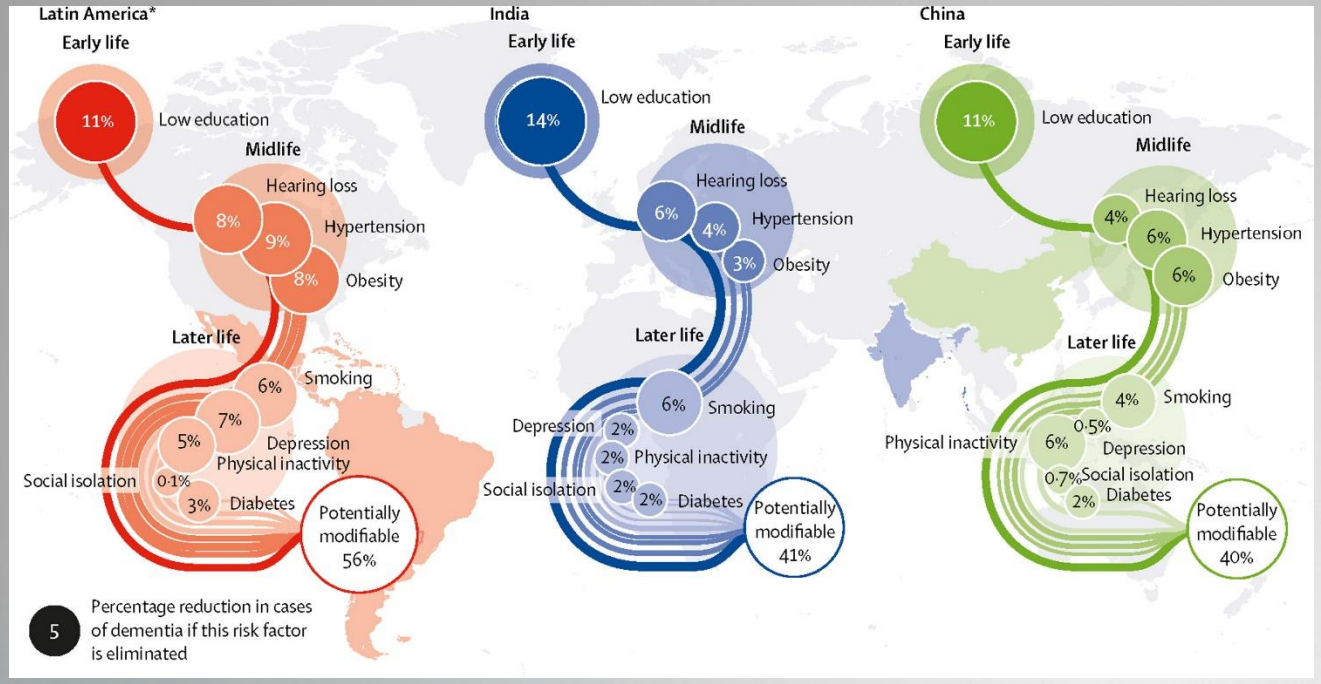


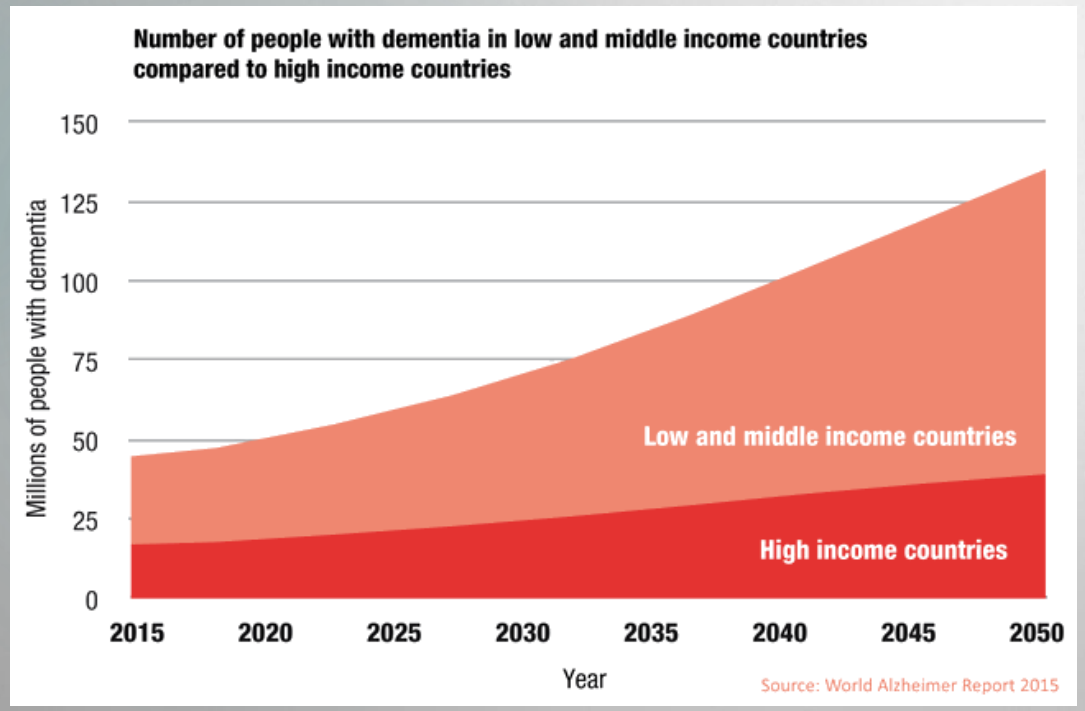
Dementia

- Dementia is defined as an acquired progressive reduction in cognitive abilities that impairs the successful performance of activities of daily living.

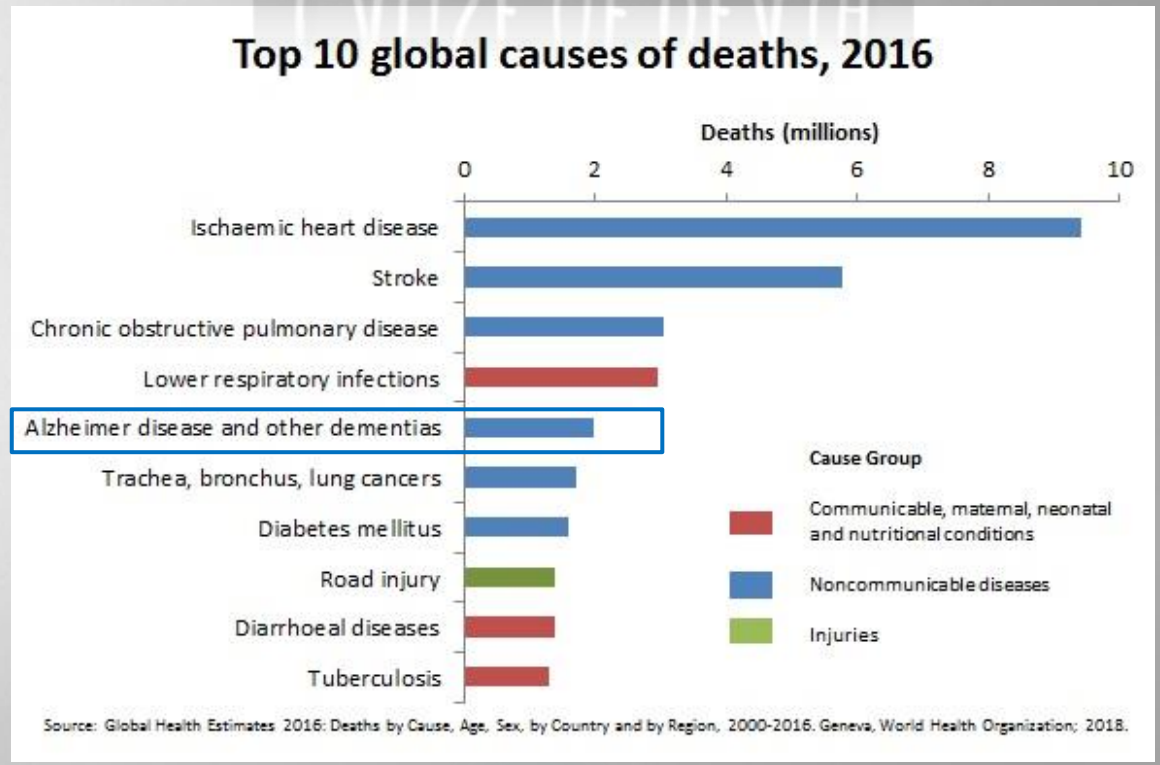
- In addition to memory, dementia may erode other mental faculties, including language, visuospatial, executive, calculation, judgment, and problem-solving abilities


Alzheimer's and dementia patients worldwide
2050
2015
131.5 m
46.8m
World
29 m
9.4m
Americas
18 m
10.5m
Europe
15 m
4.0m
Africa
67 m
22.9m
Asia





ALZHEIMER'S IS THE 5TH LEADING CAUSE OF DEATH



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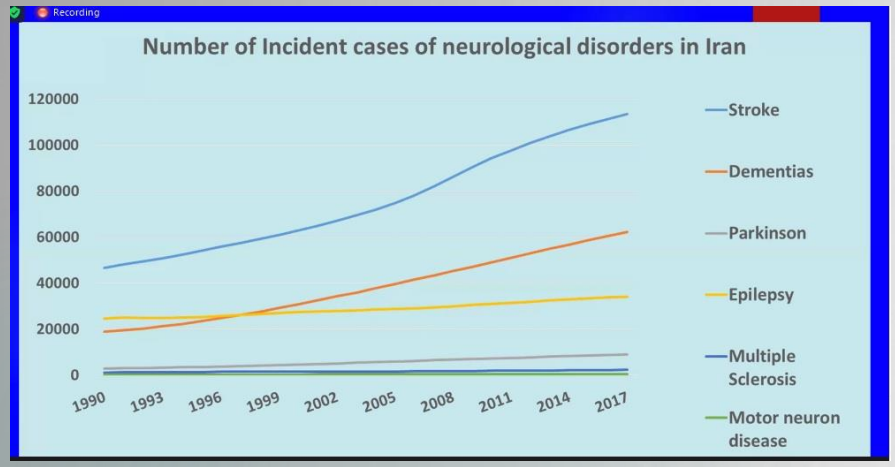
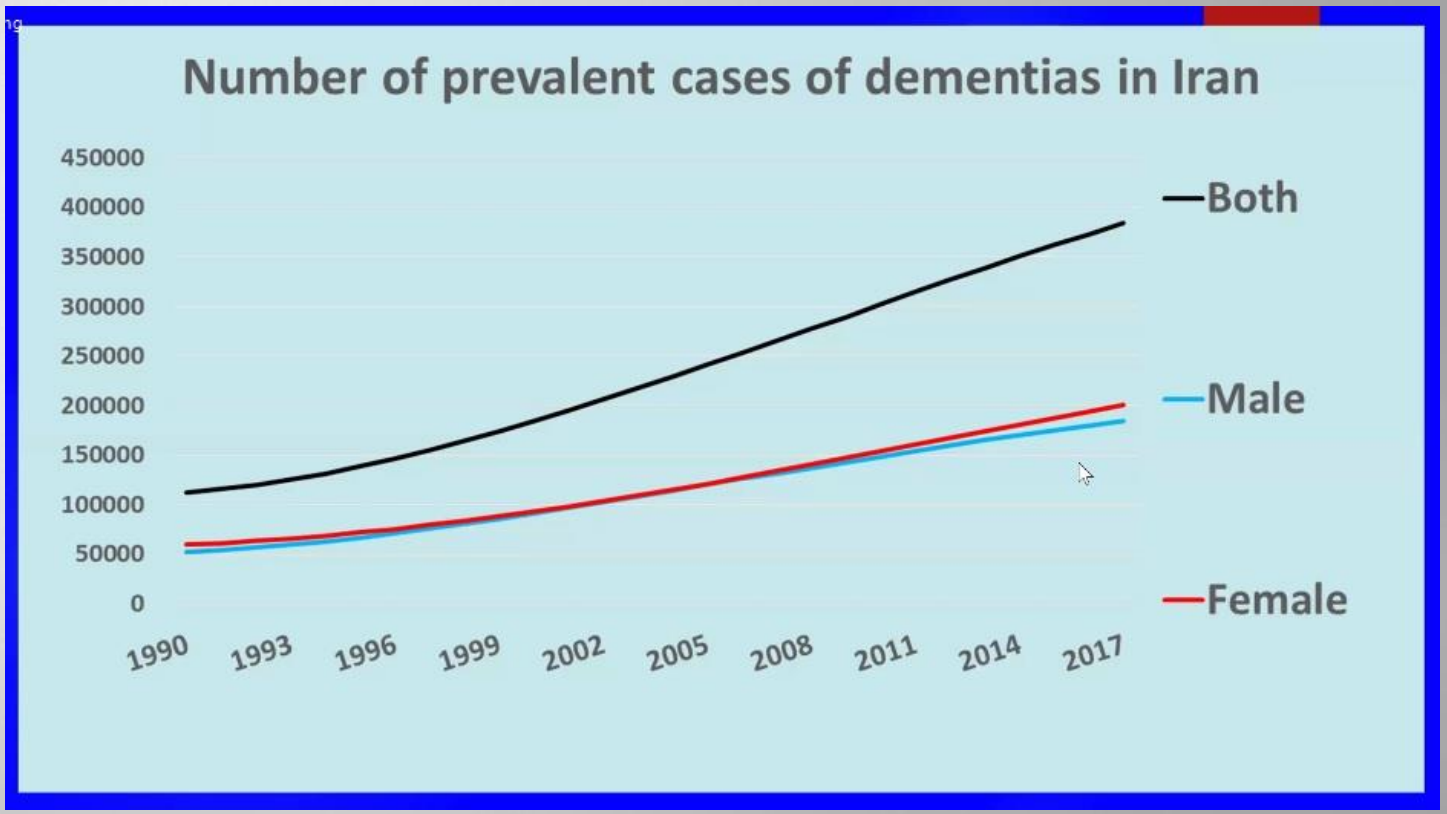
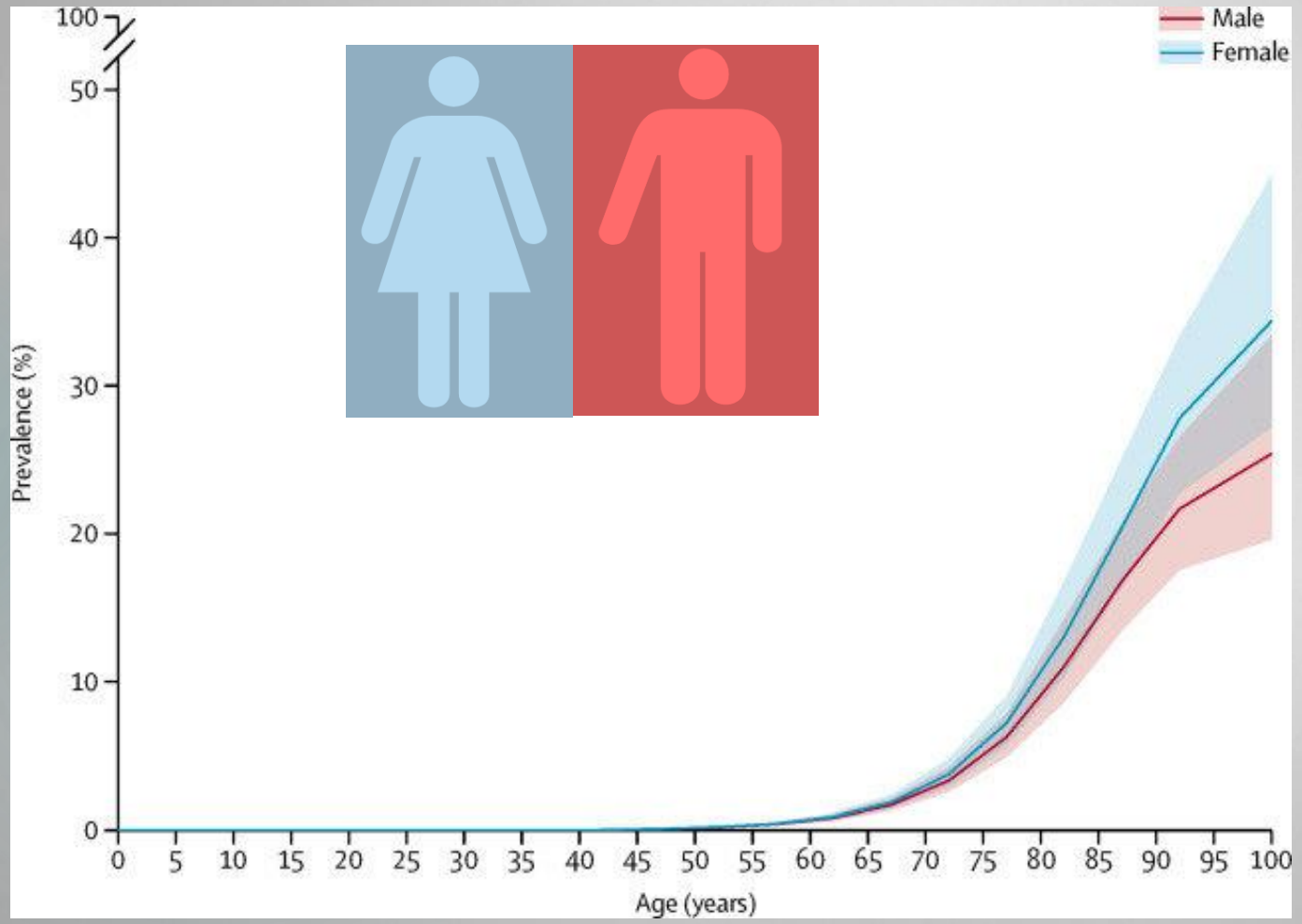


Number of deaths, incident and prevalent cases due to neurological diseases in Iran in 2017

	Deaths	Incident cases	Prevalent cases
Stroke	36,360	113,460	974,150
Dementias	21,450	62,300	385,000
Parkinson's disease	2,670	9,060	77,600
Epilepsy	660	34,100	328,600
Multiple Sclerosis	290	2,270	62,400
Motor Neuron Disease	100	430	1,650
Headache	-	12,040,000	41,260,000



Male & Female



10% of persons aged >70 years and 20–40% of individuals aged >85 years have clinically identifiable memory loss

THE CAUSES OF DEMENTIA

Table 5-1. Neurologic Changes in Normal Aging.

Cognitive
Slowed information processing
Impaired learning and recall of new information
Reduced spontaneous word finding and verbal fluency
Increased reaction time
Neuro-ophthalmologic
Small, sluggishly reactive pupils
Impaired upgaze
Impaired convergence
Motor
Atrophy of intrinsic hand and foot muscles
Increased muscle tone
Flexion (stooped) posture
Small-stepped or broad-based gait
Sensory
Reduced visual acuity
Reduced auditory acuity
Reduced gustatory acuity
Reduced olfactory acuity
Reduced vibration sense
Reflexes
Primitive reflexes
Absent abdominal reflexes
Absent ankle reflexes

- The single strongest risk factor for dementia is increasing age. The prevalence of disabling memory loss increases with each decade for those aged >50 and is usually associated with the microscopic changes of AD at autopsy.

Most Common Casuses

1. Alzheimer's disease
2. Vascular Dementia
3. PDD/LBD spectrum
4. Alcoholism

Less Common Casuses

1. Vitamin deficiencies
2. Endocrine and other organ failure
3. Chronic infections
4. Head trauma and diffuse brain damage
5. Neoplastic
6. Toxic disorders
7. Degenerative disorders
8. Psychiatric
9. Metabolic disorders

Classification

REVERSIBLE

- Depression, delirium
- Emotional disorders
- Metabolic disorders (e.g., hypothyroidism
- Eye and ear impairments
- Nutritional (e.g., B12 deficiency)
- Tumors
- Infections
- Alcohol, drugs, medication interactions

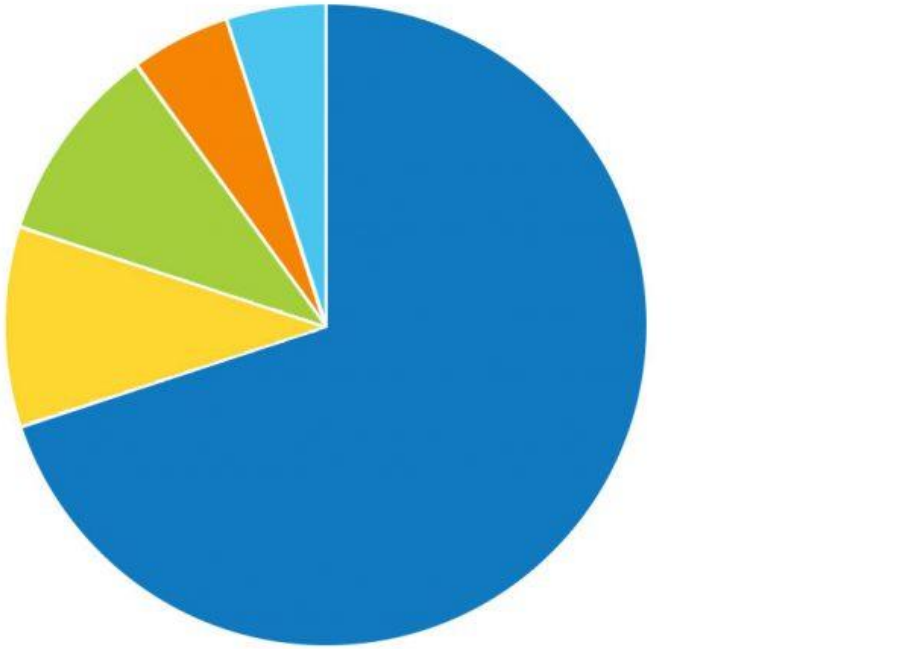
IRREVERSIBLE

- Dementia of the Alzheimer's type
- Dementia of the Parkinson's type
- Huntington's disease
- Frontotemporal dementia
- Vascular Dementia

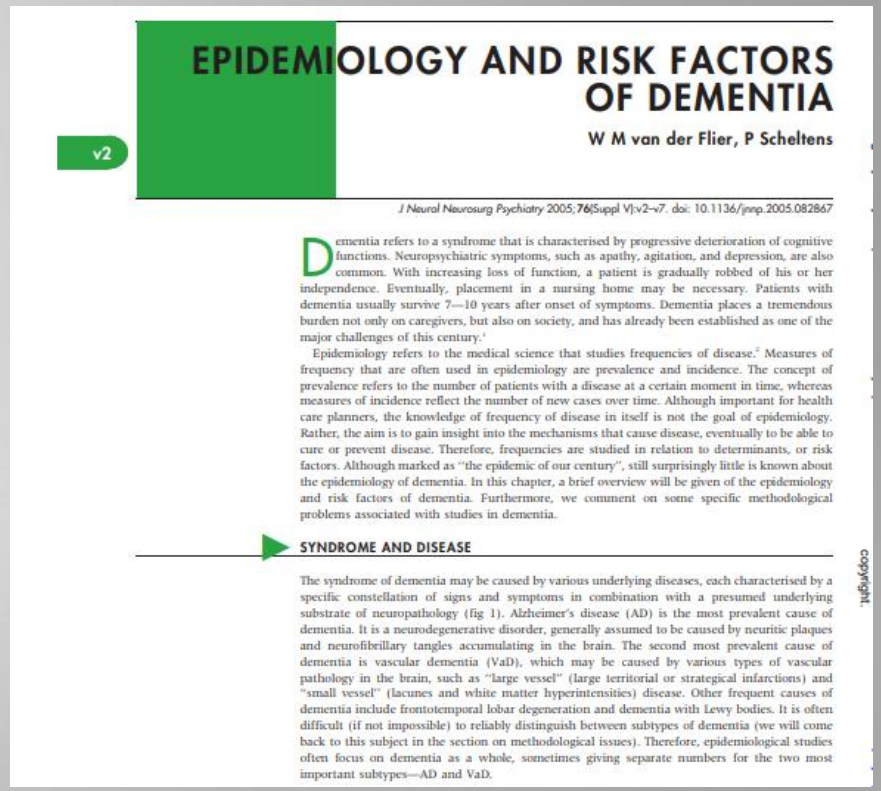
Types of Dementia	
Cortical Dementia	Dementia where the brain damage primarily affects the brain's cortex, or outer layer. Cortical dementias tend to cause problems with memory, language, thinking, and social behavior.
Subcortical Dementia	Dementia that affects parts of the brain below the cortex. Subcortical dementia tends to cause changes in emotions and movement in addition to problems with memory.
Progressive Dementia	Dementia that gets worse over time, gradually interfering with more and more cognitive abilities.
Primary Dementia	Dementia such as Alzheimer's disease that does not result from any other disease.
Secondary Dementia	Dementia that occurs as a result of a physical disease or injury.

The clinical course may be slowly progressive, as in Alzheimer's disease (AD); static, as in anoxic encephalopathy; or may fluctuate from day to day or minute to minute, as in dementia with Lewy bodies (DLB).

Different Types of Dementia (by %)



Alzheimer's Disease (60-80%)
Vascular Dementia (10%)
Lewy Body Dementia (5-15%)
Frontotemporal Dementia (2-5%)
Other Types of Dementia



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EPIDEMIOLOGY AND RISK FACTORS OF DEMENTIA

W M van der Flier, P Scheltens

J Neurol Neurosurg Psychiatry 2005;76(Suppl V):v2–v7. doi: 10.1136/jnnp.2005.082867

Dementia refers to a syndrome that is characterised by progressive deterioration of cognitive functions. Neuropsychiatric symptoms, such as apathy, agitation, and depression, are also common. With increasing loss of function, a patient is gradually robbed of his or her independence. Eventually, placement in a nursing home may be necessary. Patients with dementia usually survive 7—10 years after onset of symptoms. Dementia places a tremendous burden not only on caregivers, but also on society, and has already been established as one of the major challenges of this century.[1]

Epidemiology refers to the medical science that studies frequencies of disease.[2] Measures of frequency that are often used in epidemiology are prevalence and incidence. The concept of prevalence refers to the number of patients with a disease at a certain moment in time, whereas measures of incidence reflect the number of new cases over time. Although important for health care planners, the knowledge of frequency of disease in itself is not the goal of epidemiology. Rather, the aim is to gain insight into the mechanisms that cause disease, eventually to be able to cure or prevent disease. Therefore, frequencies are studied in relation to determinants, or risk factors. Although marked as "the epidemic of our century", still surprisingly little is known about the epidemiology of dementia. In this chapter, a brief overview will be given of the epidemiology and risk factors of dementia. Furthermore, we comment on some specific methodological problems associated with studies in dementia.

SYNDROME AND DISEASE

The syndrome of dementia may be caused by various underlying diseases, each characterised by a specific constellation of signs and symptoms in combination with a presumed underlying substrate of neuropathology (fig 1). Alzheimer's disease (AD) is the most prevalent cause of dementia. It is a neurodegenerative disorder, generally assumed to be caused by neuritic plaques and neurofibrillary tangles accumulating in the brain. The second most prevalent cause of dementia is vascular dementia (VaD), which may be caused by various types of vascular pathology in the brain, such as "large vessel" (large territorial or strategical infarctions) and "small vessel" (lacunes and white matter hyperintensities) disease. Other frequent causes of dementia include frontotemporal lobar degeneration and dementia with Lewy bodies. It is often difficult (if not impossible) to reliably distinguish between subtypes of dementia (we will come back to this subject in the section on methodological issues). Therefore, epidemiological studies often focus on dementia as a whole, sometimes giving separate numbers for the two most important subtypes—AD and VaD.

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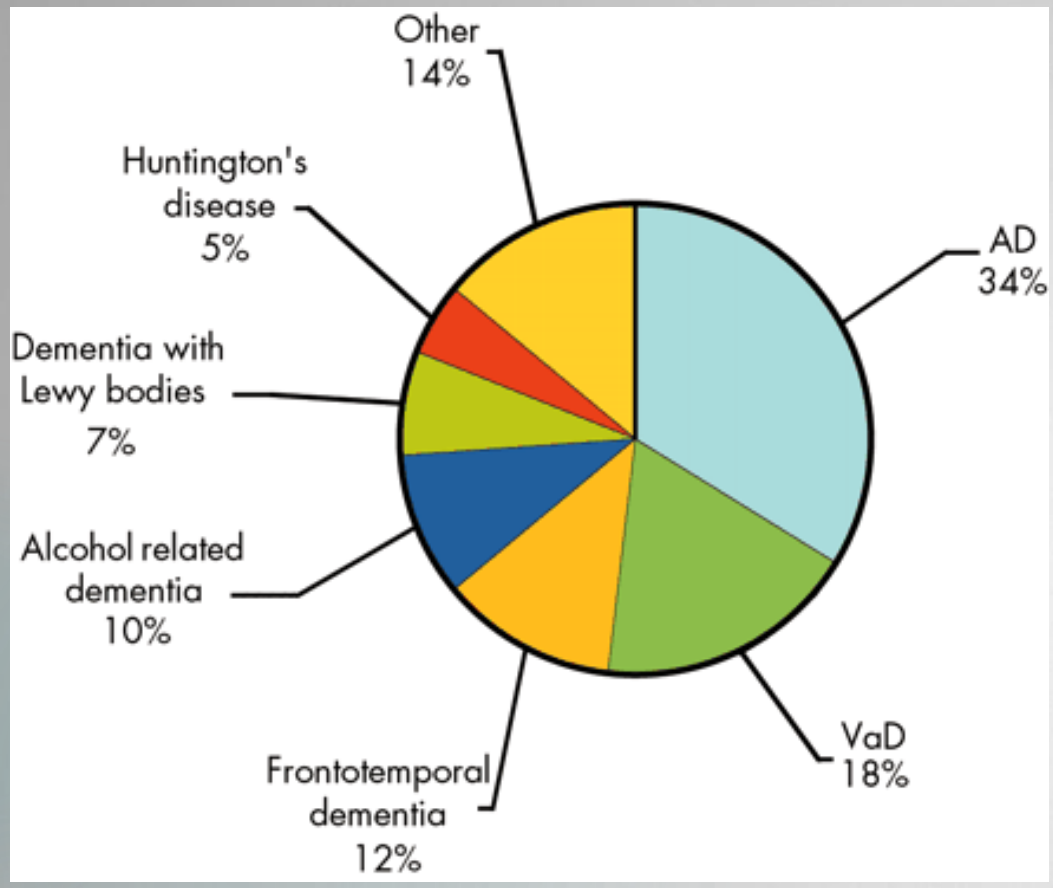
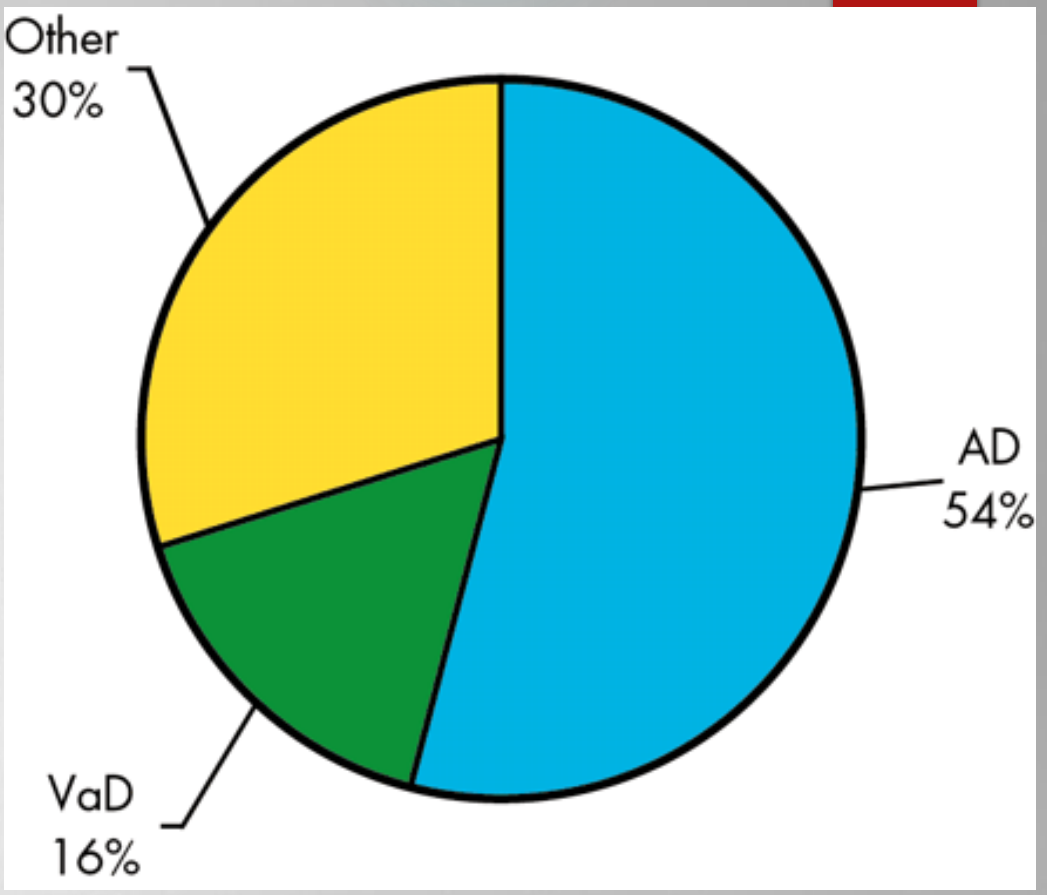


Causes of dementia with young onset (< 65 years).

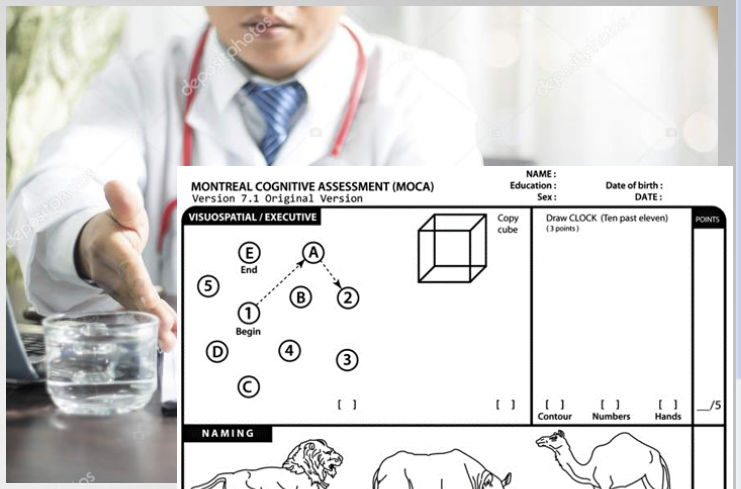


Causes of dementia with late onset (⩾ 65 years).

https://jnnp.bmj.com/content/76/suppl_5/v2

APPROACH TO THE PATIENT

- History
- Psychiatric Assessment
- LABORATORY TESTS

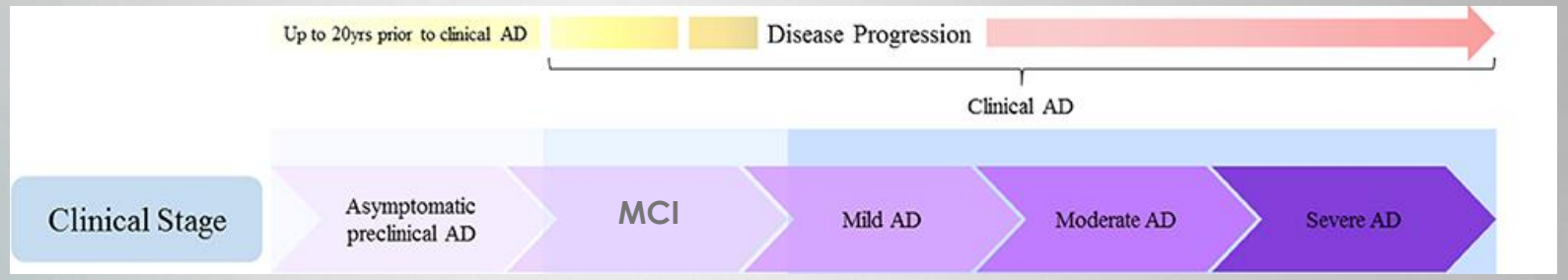


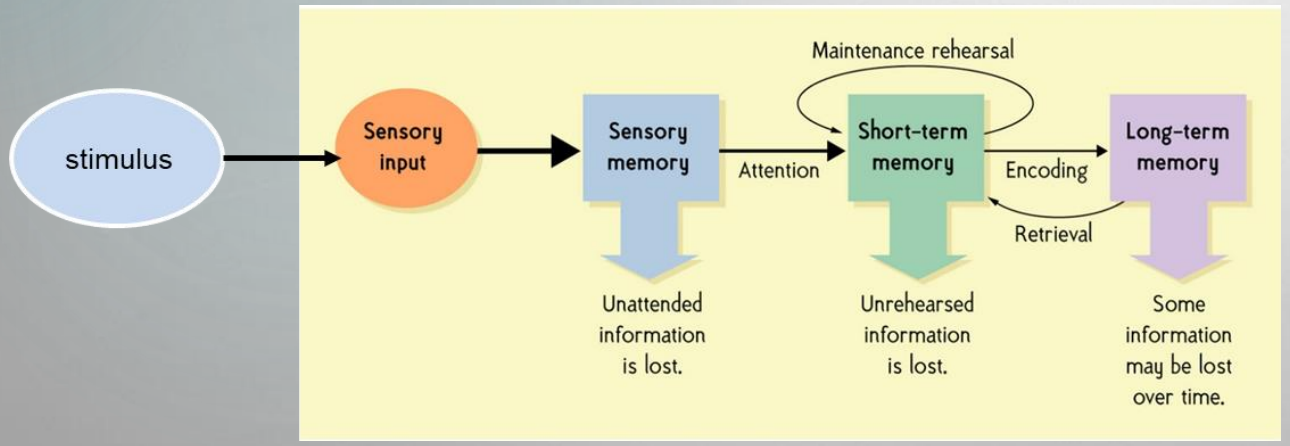
Test
Blood
Hematocrit, mean corpuscular volume (MCV), peripheral blood smear, vitamin B_{12} level
Thyroid function tests
Liver function tests
Ceruloplasmin, copper
FTA or MHA-TP
Cerebrospinal fluid
VDRL
Cytology
14-3-3 protein
Aβ42, tau, phospho-tau
HIV mRNA
CT scan or MRI
PET Scan
EEG

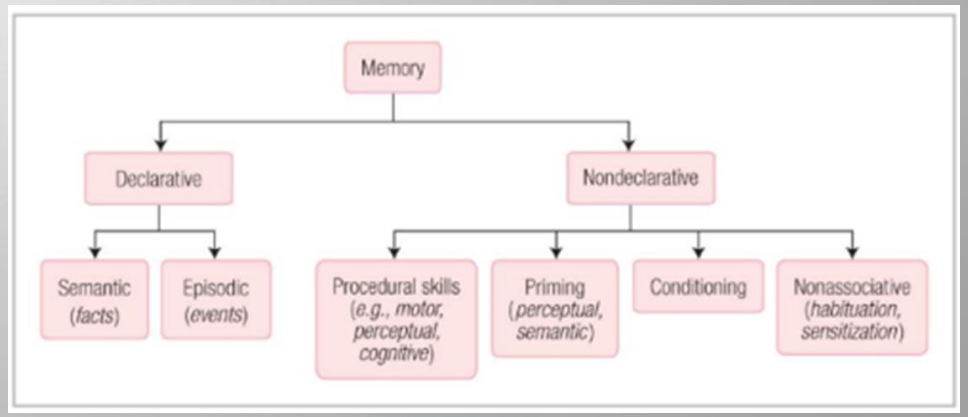
Alzheimer's

Alzheimer's

- Slowly progressive episodic or periodic memory loss over several years (75%)

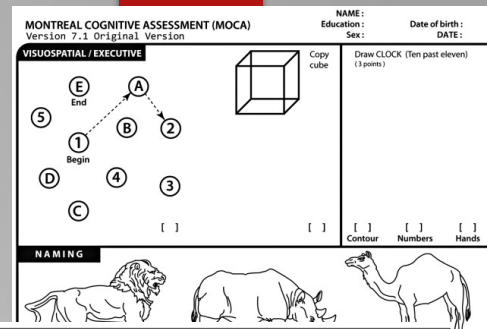


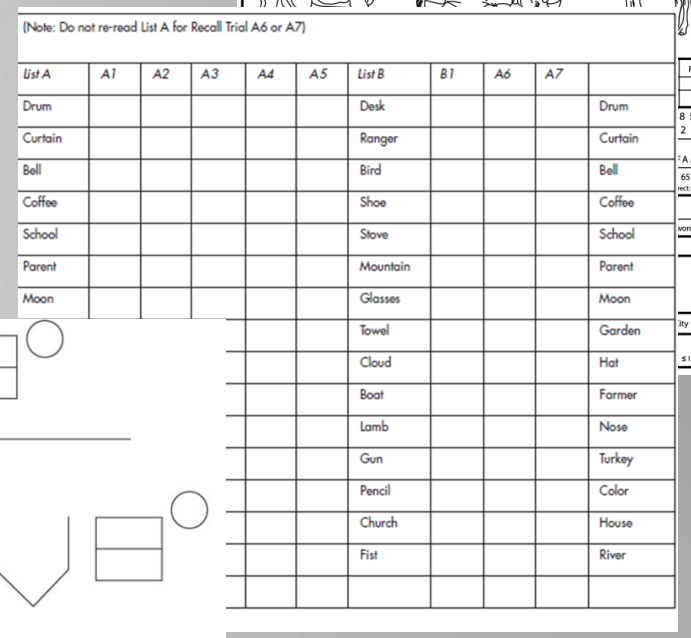




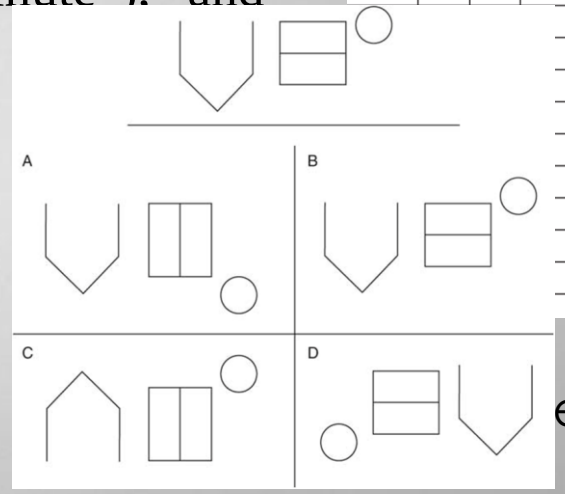
- Other symptoms :
- Difficulty with managing money, driving, shopping, following instructions, finding words, or navigating, depressive features, social withdrawal, and irritability or anxiety .

- Test :
- involve episodic memory(verbal or visual episodic memory) , category generation (“name as many animals as you can in 1 minute”), and visuoconstructive ability.

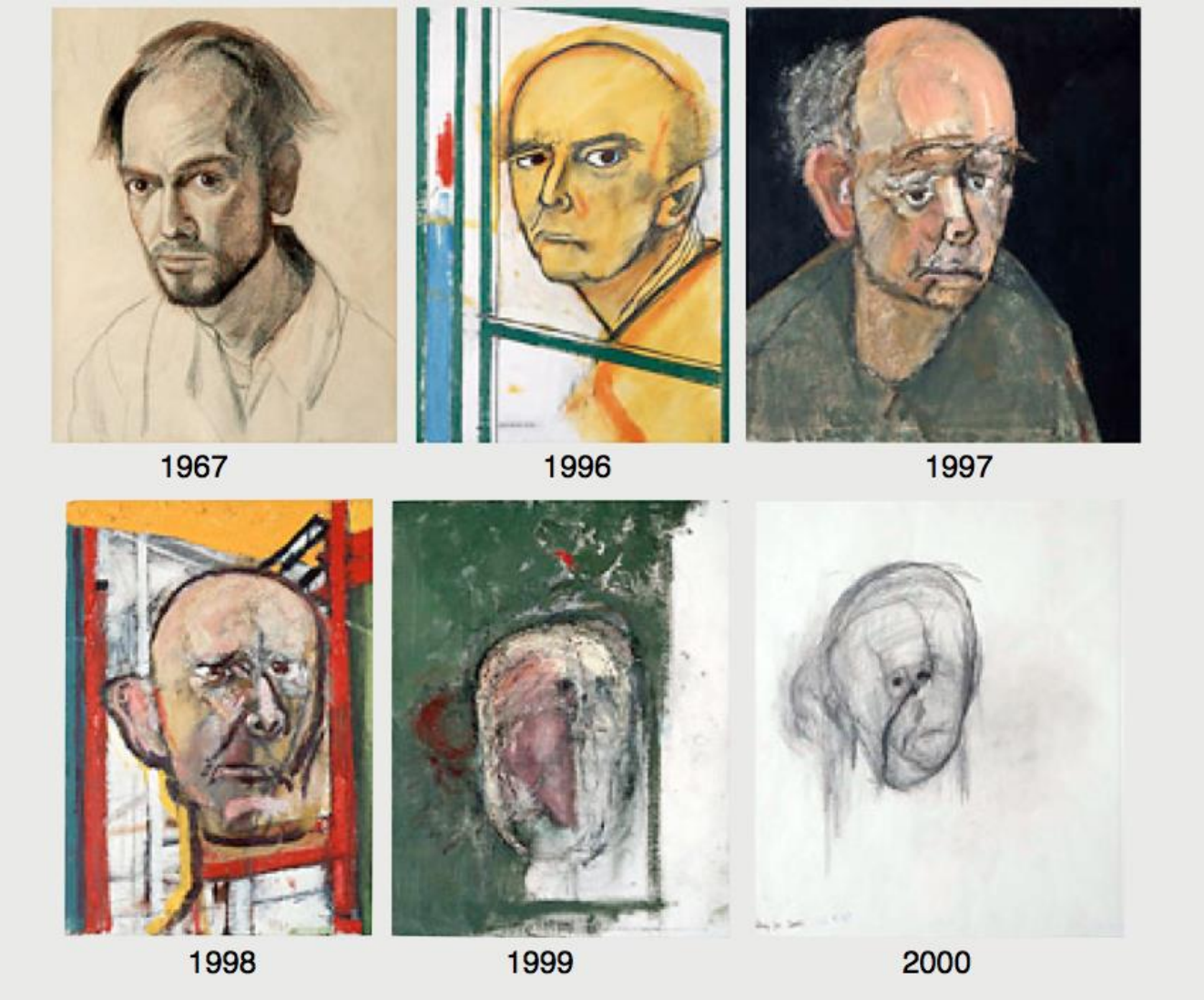




erbal Learning Test



Benton Visual Retention Test



William Utermolen (1914-2009)

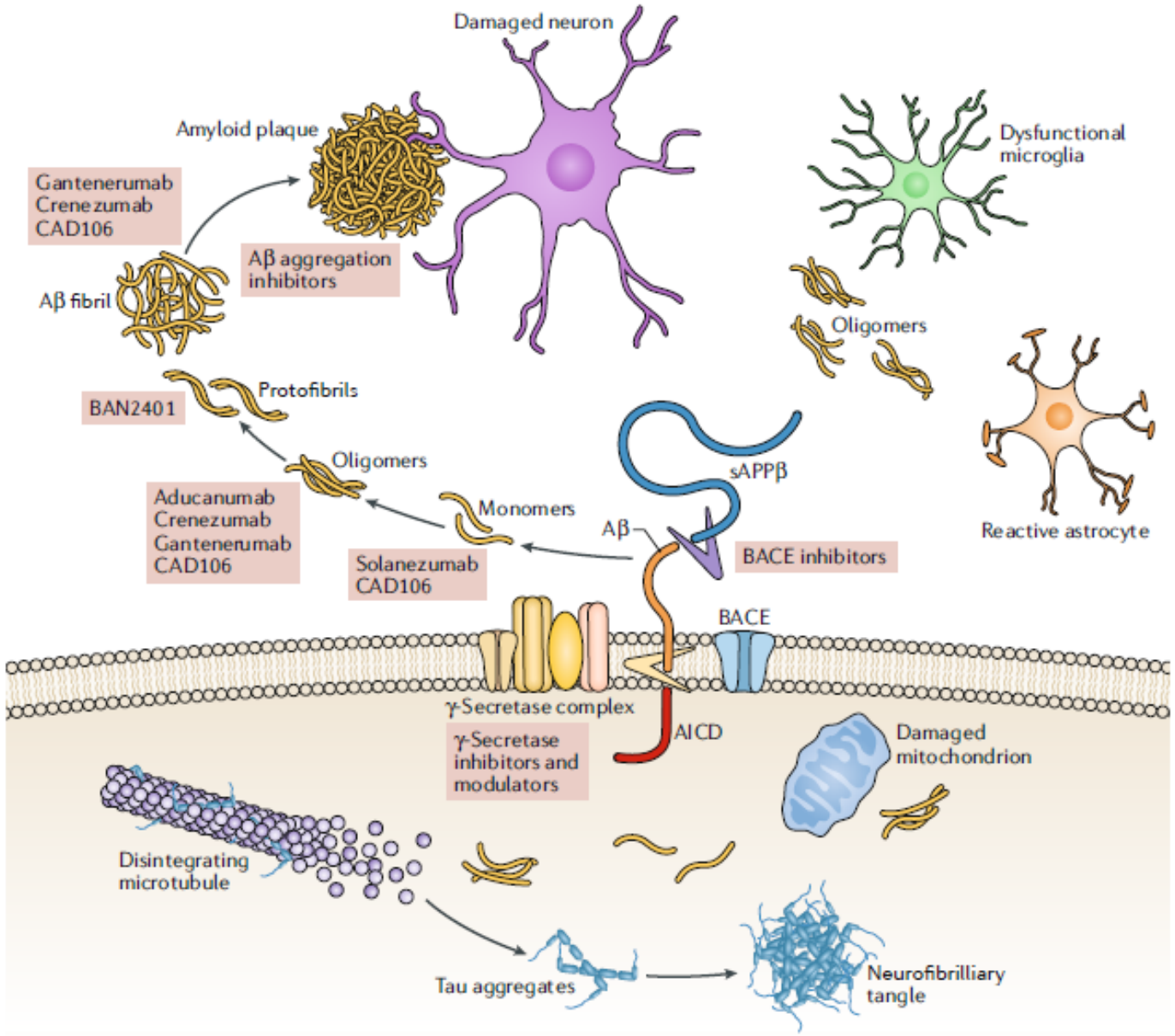
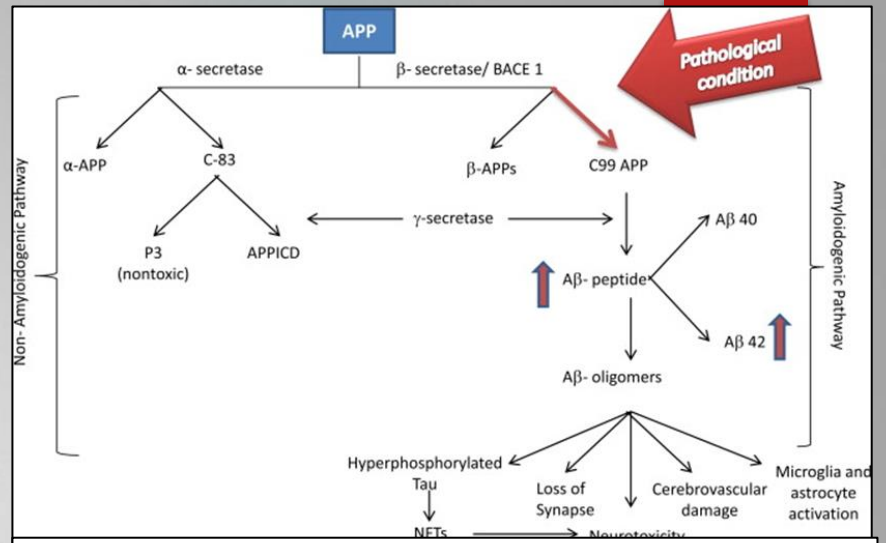
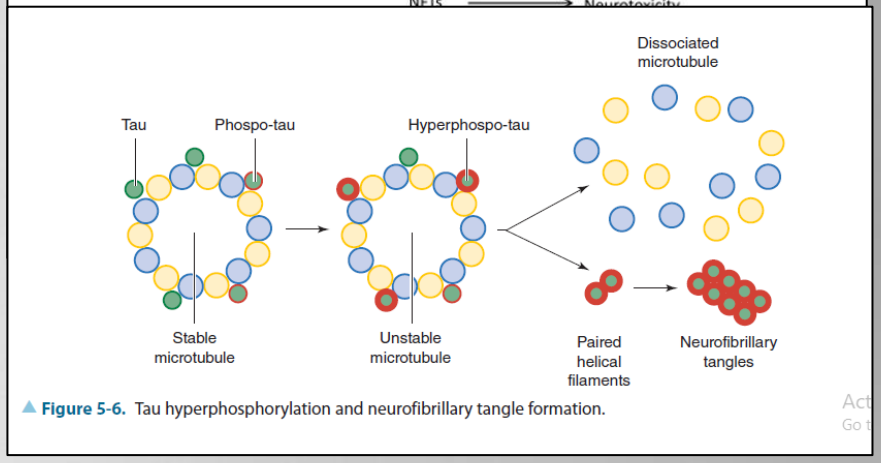
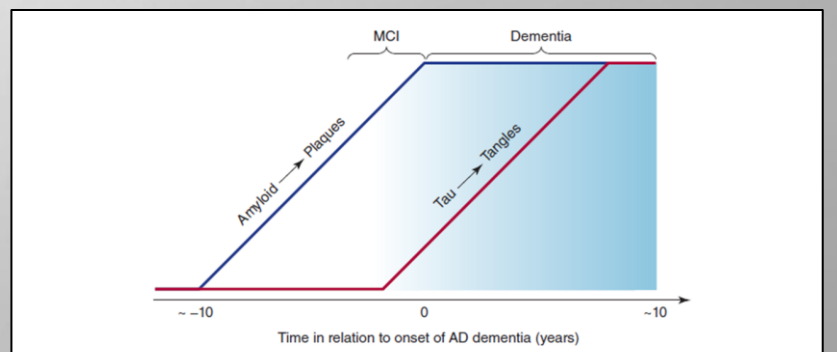


Fig. 1 | **Targets of anti-Aβ drugs.** Mechanisms of action of the main anti-amyloid-β (Aβ) drugs that are currently in phase III clinical development for the treatment of Alzheimer disease. AICD, amyloid precursor protein intracellular domain; BACE, β-secretase; sAPPβ, soluble amyloid precursor protein-β.

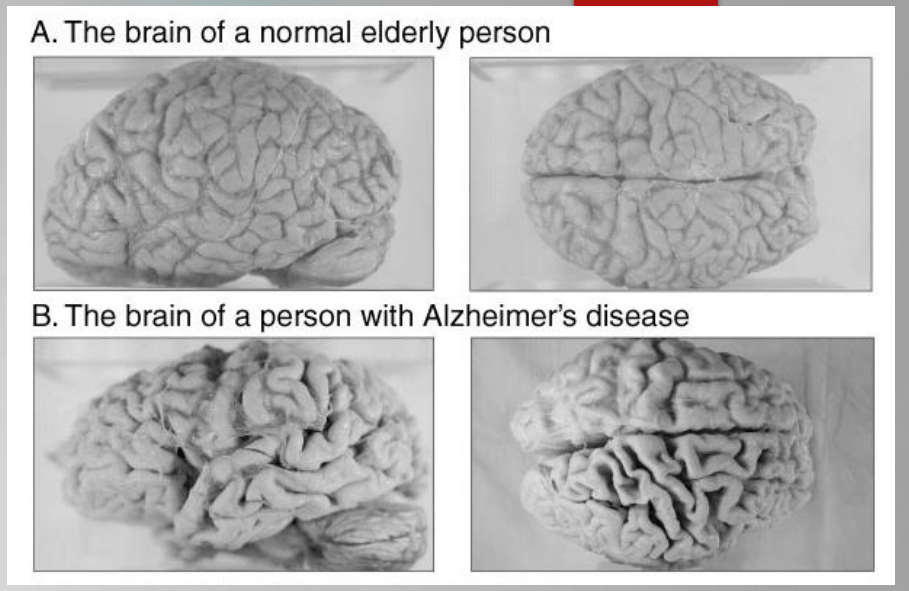




▲ **Figure 5-6.** Tau hyperphosphorylation and neurofibrillary tangle formation.

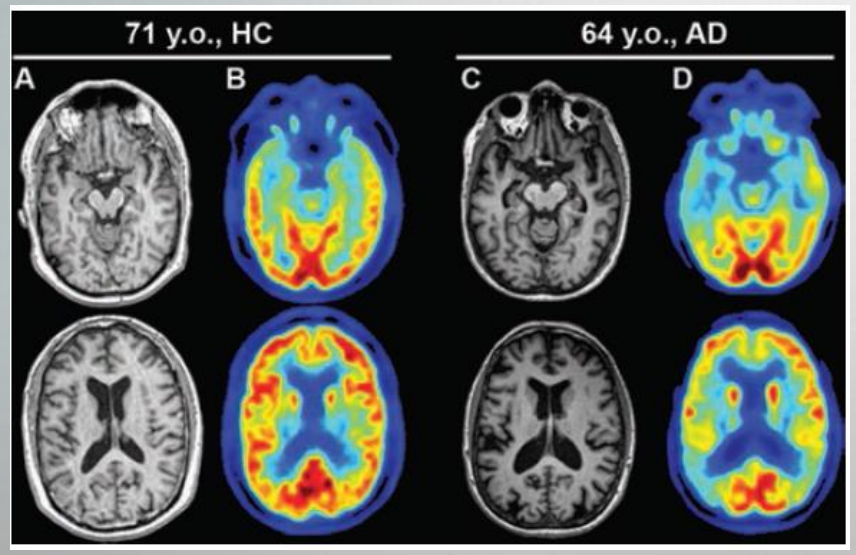


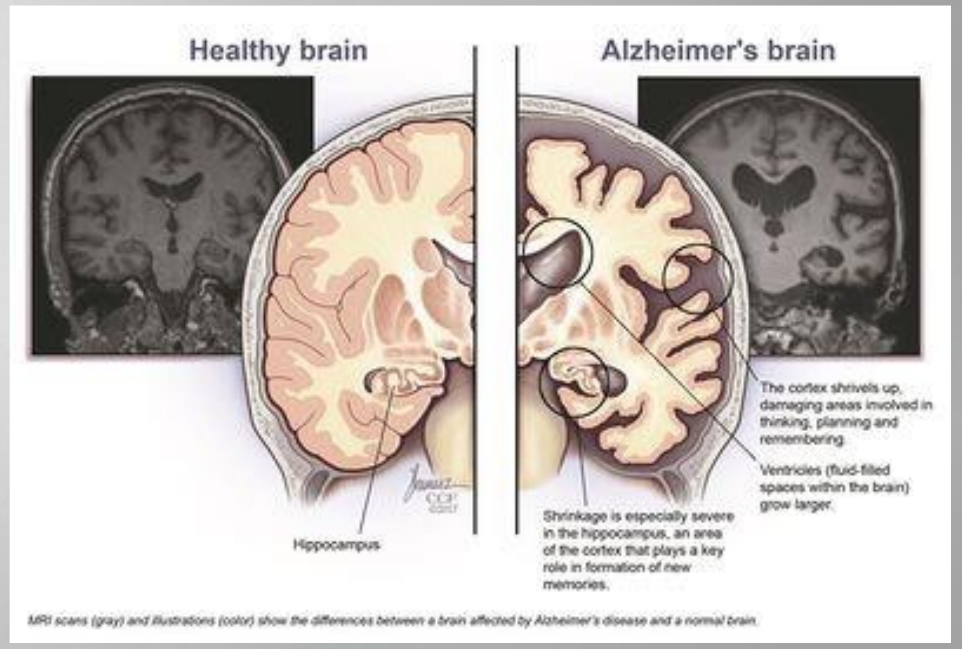
▲ **Figure 5-7.** Relationship between plaques, tangles, and clinical progression of Alzheimer disease (AD). MCI, mild cognitive impairment.



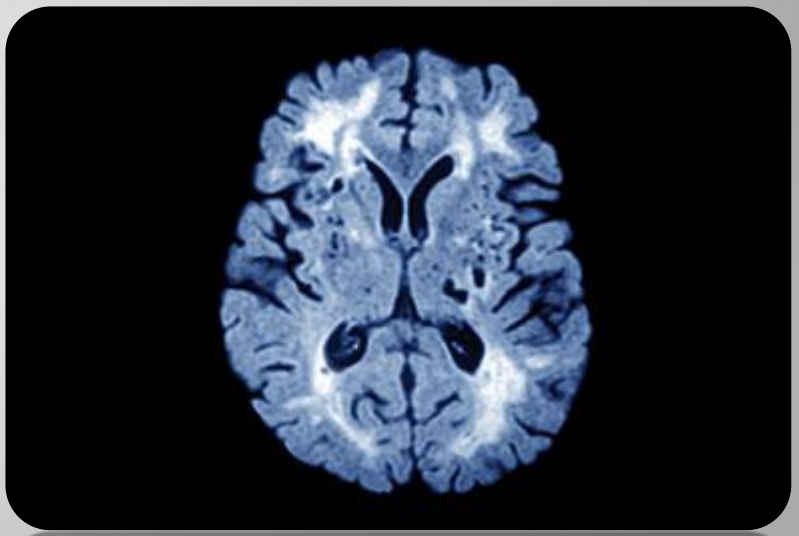
- In typical amnestic AD, brain atrophy begins in the medial temporal lobes (Hippocampal atrophy) and spreading to parietal and temporal lobes and frontal cortex.

- SPECT and PET show temporal- parietal hypoperfusion or hypometabolism in AD.





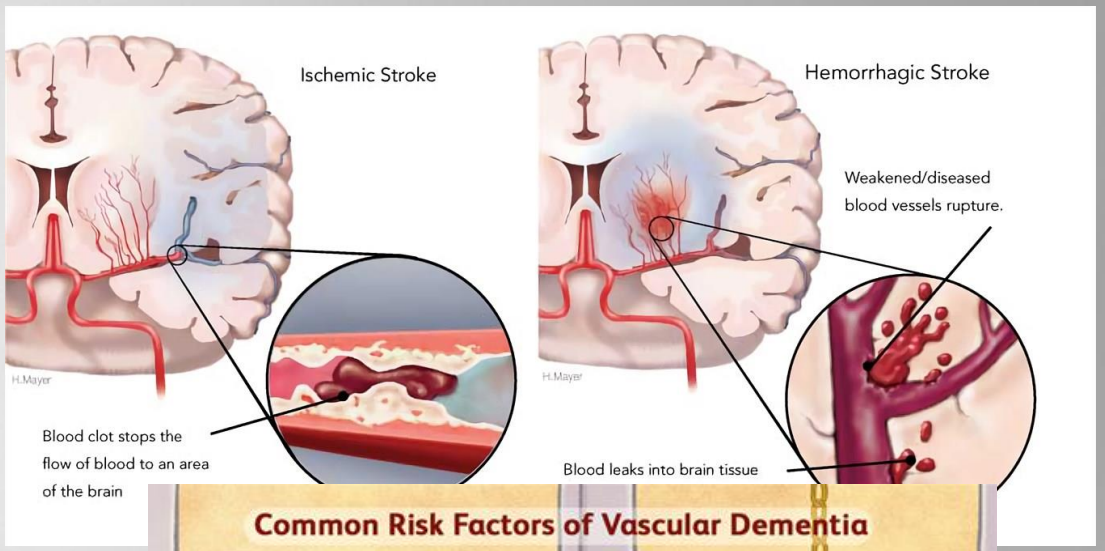
Vascular Dementia

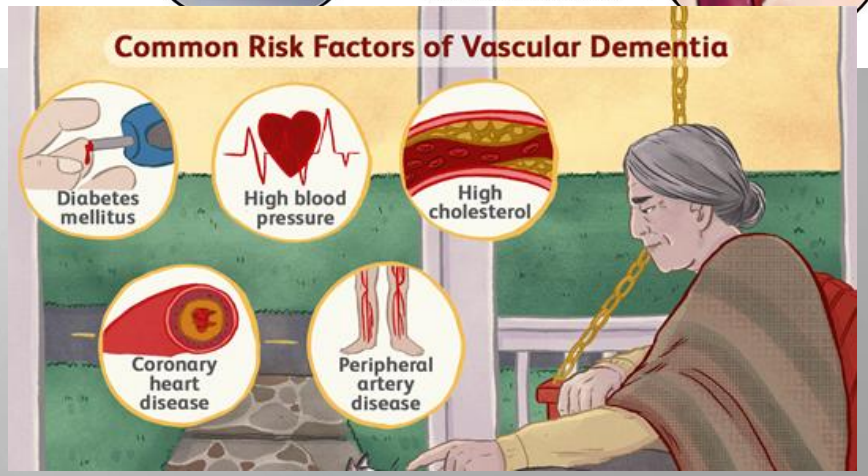


Vascular Dementia (VaD)
Vascular Cognitive Impairment (VCI)

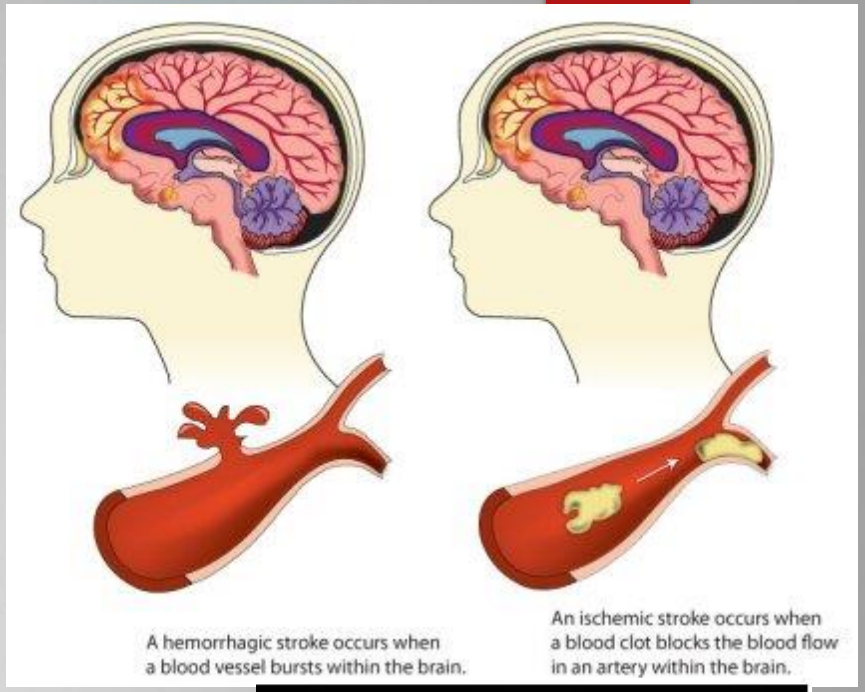
- Vascular disease can disrupt structural cognitive networks with lesions such as microinfarcts, microbleeds, macroinfarcts, large hemorrhages, and progressive white matter degeneration

- Vascular dementia is related to vascular problems (AGE) like high cholesterol and high blood pressure, heart attack, diabetes, and heart disease, peripheral vascular disease.

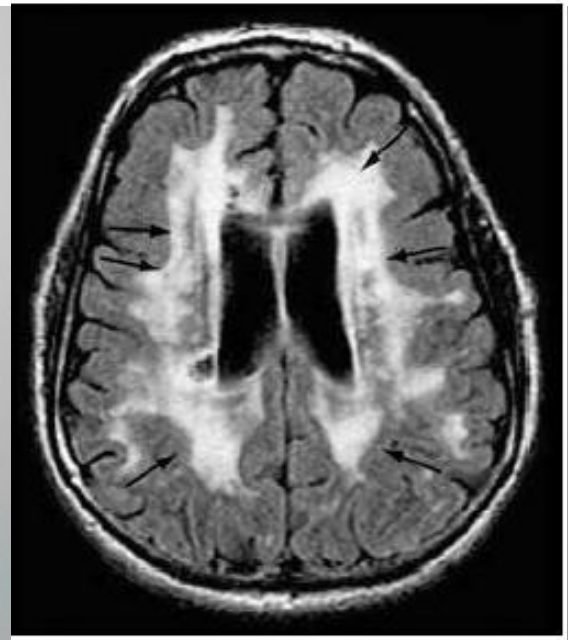




- The two most common being Multi-infarct dementia and Diffuse white matter dementia.
- progresses gradually ,large or small, brain volume damage

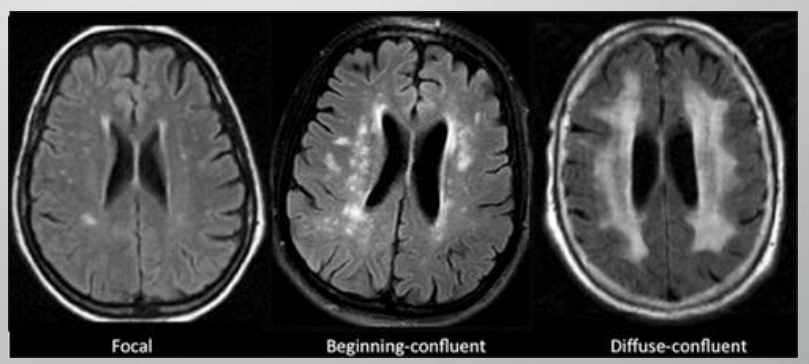


- Diffuse white matter disease (Binswanger's disease or subcortical vascular dementia) is associated with damage to the brain's white matter, or nerve fibres.
- It is caused by high blood pressure, thickening of the arteries and inadequate blood flow.

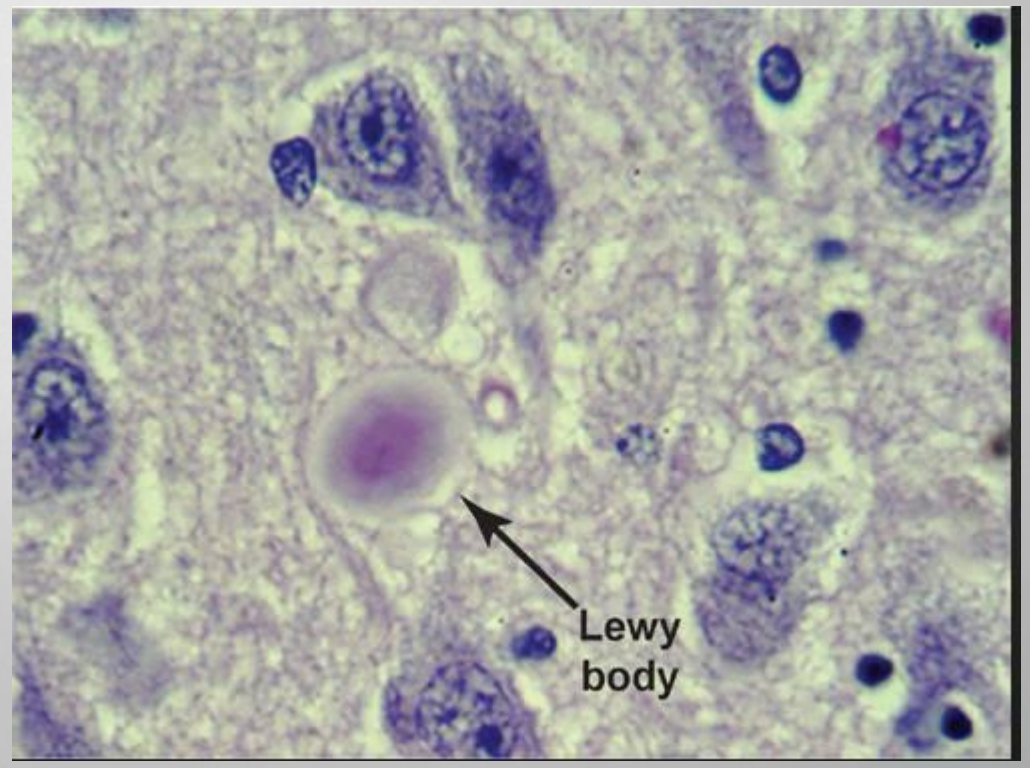


- Vascular dementia causes a decline in cognitive function. It Is associated with focal damage in a variable network of cortical and subcortical regions or white matter tracts that disconnect nodes within distributed networks

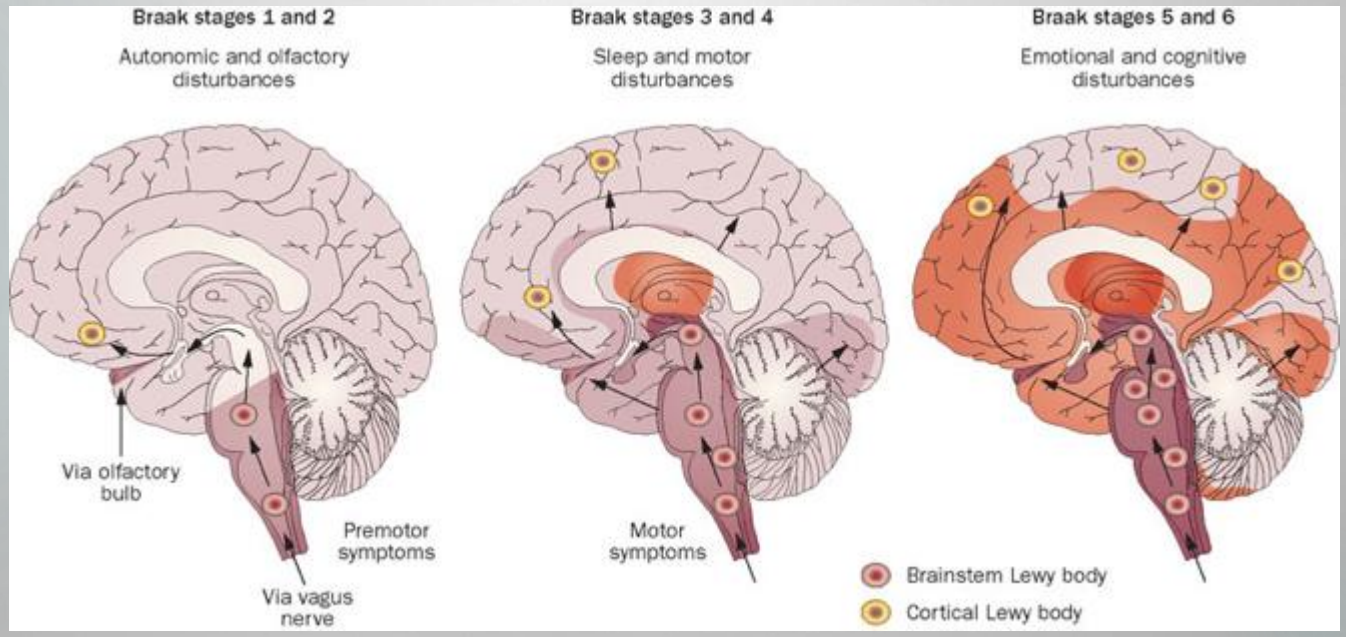
- Patients demonstrate a mixture of executive control and visuospatial deficits, with judgment, reasoning, and memory. Gait disturbance (prominent psychomotor slowing).



Dementia with Lewy Bodies



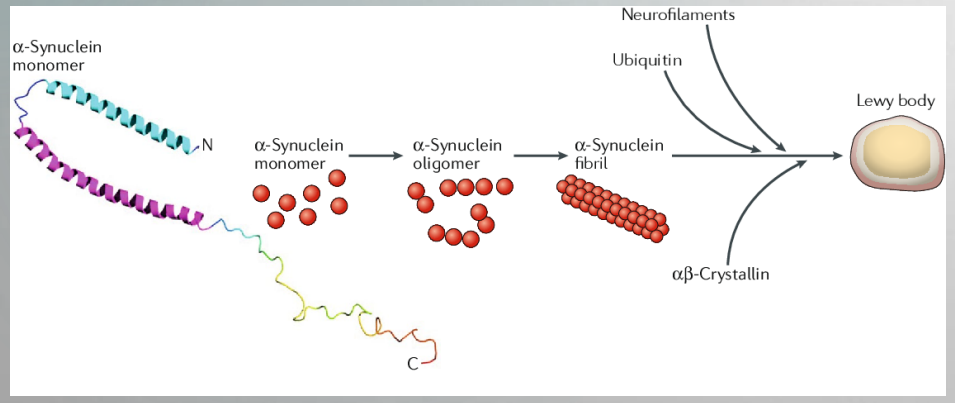
- Lewy body disease once conceptualized as a disease of the substantia nigra,
- Lewy pathology most often begins in the enteric and autonomic nervous systems before ascending through the brainstem to the substantia nigra, limbic system, and ultimately the cerebral cortex.
- In other individuals, disease may begin in the olfactory bulb and spread inward through olfactory system connections.

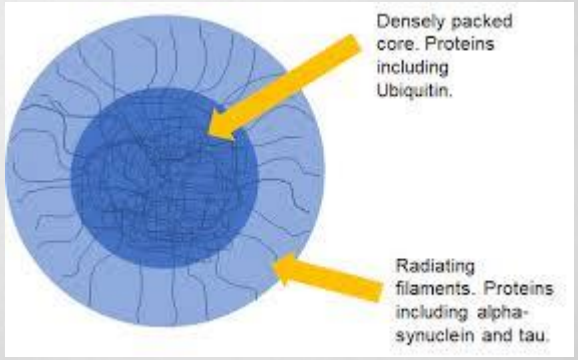


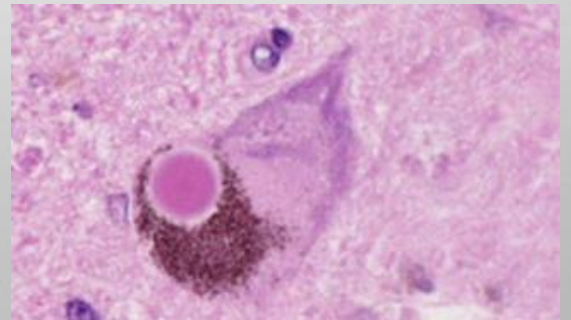
- Some patients, dementia and a neuropsychiatric syndrome precede or co-emerge with the parkinsonism, and the patient is diagnosed with dementia with Lewy bodies (DLB).
- In other patients with long-standing Parkinson's disease (PD) without cognitive impairment slowly develop a dementia that is associated with visual hallucinations and fluctuating alertness. In this scenario, the term Parkinson's disease dementia (PDD) is often used.

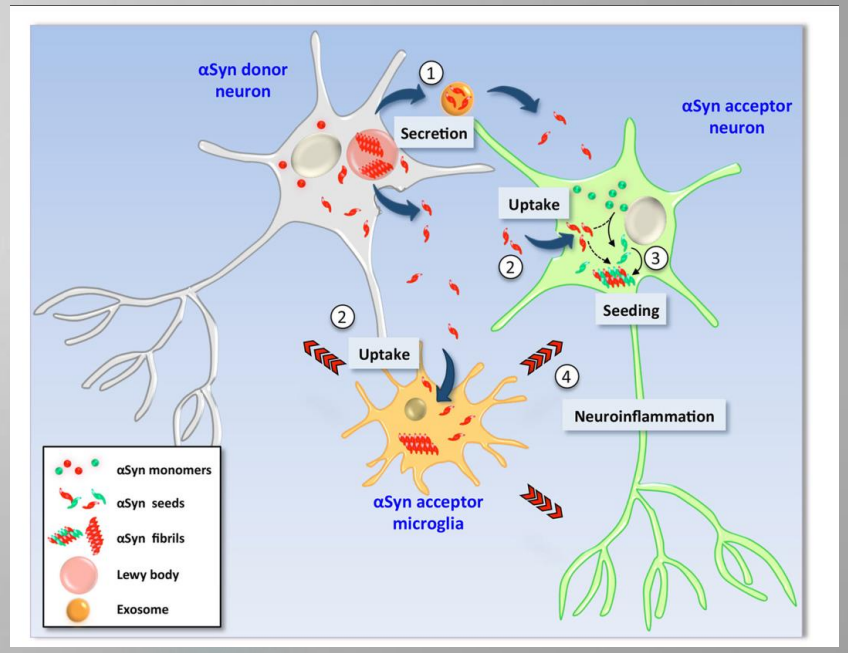
- The key neuropathological feature in LBD is the presence of Lewy bodies .
- Inclusion bodies are aggregates of misfolded proteins (alpha-synuclein protein: Synapse) which are hallmarks of many neurodegenerative diseases and accumulated in the brain cells either in the cytoplasm or cell nucleus.

Frederic Henry Lewy





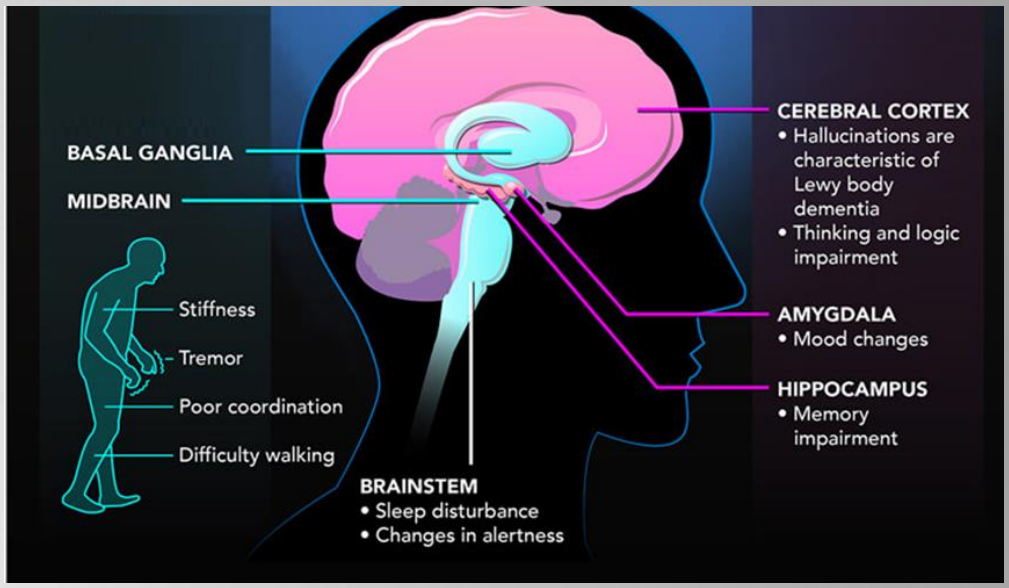




Dementia with Lewy Bodies

- Fluctuating alertness, excessive daytime sleepiness Loss of skeletal muscle paralysis during dreaming

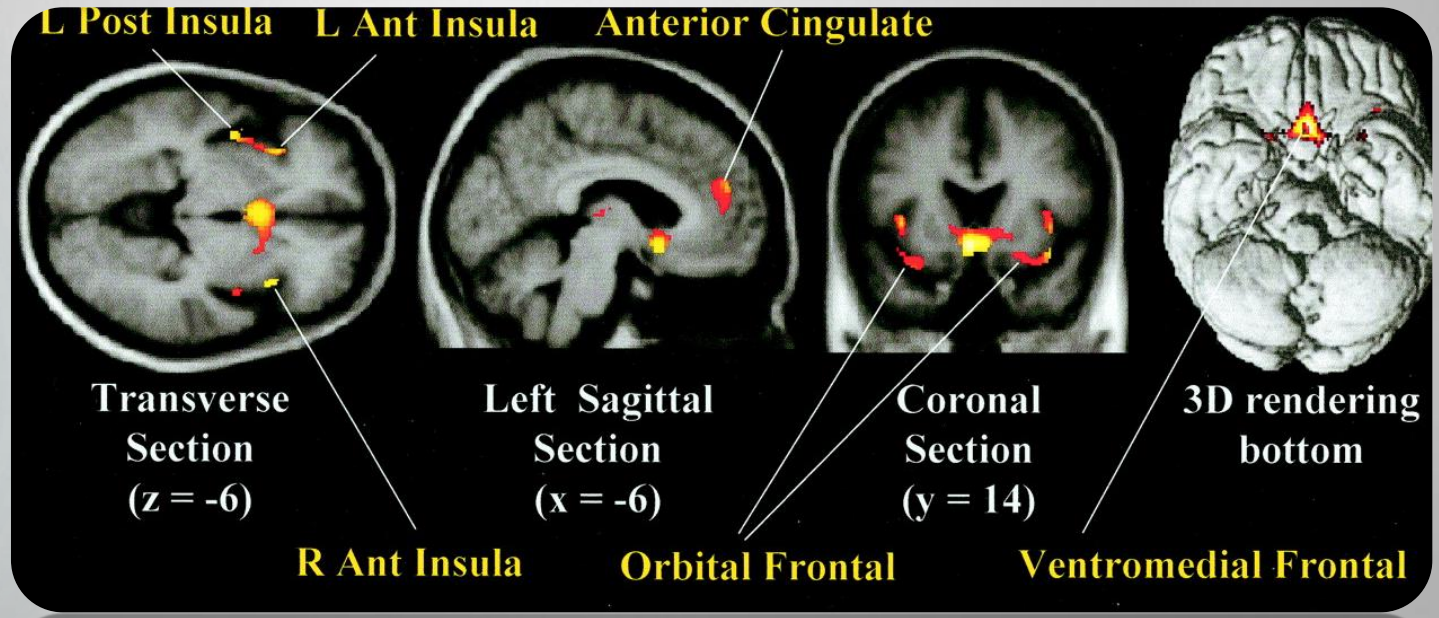
- Parkinsonism syndrome (resting tremor, cogwheel rigidity, bradykinesia)
- Rapid eye movement (REM) behavior disorder (RBD) cholinergic deficit, owing to basal forebrain and pedunculopontine nucleus;
- Visual hallucinations (tmeporal lobe)



Gastrointestinal problems

- Cognitively, DLB features relative preservation of episodic memory but , logic and thinking impairment .
- Often more severe visuospatial and executive deficits than seen in patients with early stages of Alzheimer’s disease.

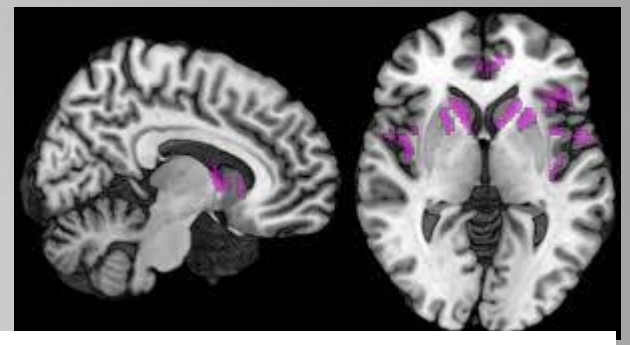
Frontotemporal Dementia

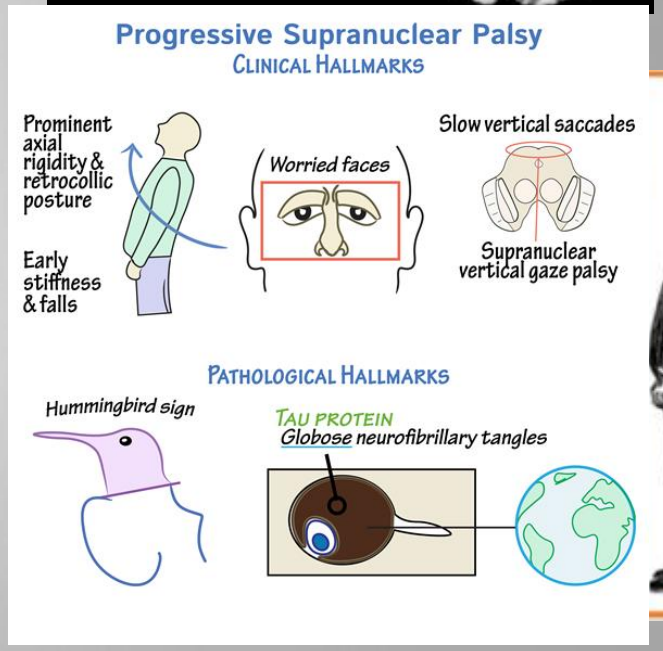


Frontotemporal dementia (FTD)

- ٧٠-٥٠ age
- In FTD, dramatic personality change with apathy, overeating, compulsions, disinhibition, euphoria, and loss of empathy are early and common

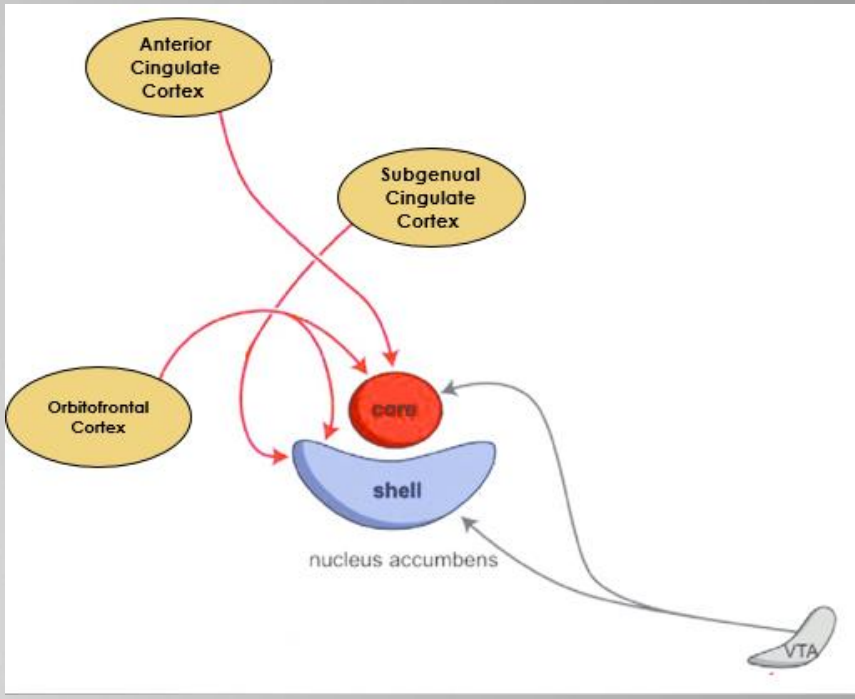
- Progressive supranuclear palsy syndrome (PSP-S)
- Corticobasal syndrome (CBS)
- A relative sparing of memory and visuospatial abilities.





Frontotemporal dementia (FTD)

- Lesions of frontal-striatal pathways produce specific and predictable effects on behavior.
- The dorsolateral prefrontal cortex –to-the caudate nucleus
- The lateral orbital frontal cortex-to-ventromedial caudate
- The anterior cingulate cortex and adjacent medial prefrontal cortex project to the nucleus accumbens



FTD

Insidious onset
Gradual progression
Exclusion criteria:
- Deficits better explained by other medical disorders
- Deficits better explained by a psychiatric disorder
- Biomarkers strongly suggest other neurodegenerative process

BV-FTD

At least three:
- Behavioural disinhibition
- Apathy or inertia
- Loss of sympathy or empathy
- Stereotypical, compulsive, or perseverative behaviour
- Hyperorality or dietary changes
- Executive deficits with relative sparing of visuospatial skills and memory

PPA

Prominent language impairment
Language deficits impair daily functioning
Aphasia is the most prominent initial-phase deficit
Exclusion criteria:
- Prominent early deficits in episodic memory, visual memory, or visuoperceptual skills
- Prominent early behaviour disturbances

SV-PPA

Impaired confrontation naming
Impaired single-word comprehension
At least three:
- Impaired object knowledge
- Surface dyslexia or dysgraphia
- Spared repetition
- Spared speech production

NFV-PPA

At least one:
- Agrammatism in production
- Apraxia of speech

At least two:
- Impaired comprehension of complex sentences
- Spared single-word comprehension
- Spared object knowledge

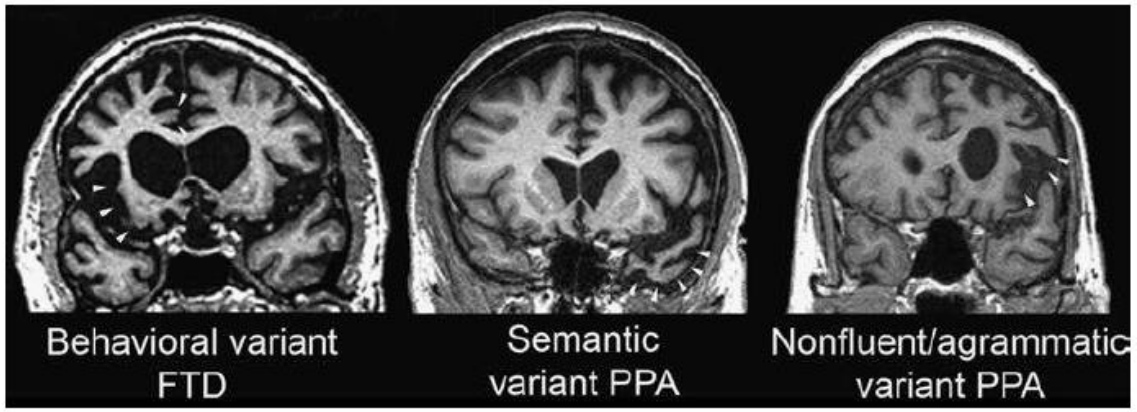


FIGURE 424-1 Three major frontotemporal dementia (FTD) clinical syndromes. Coronal magnetic resonance imaging sections from representative patients with behavioral variant FTD (*left*) and the semantic (*center*) and nonfluent/agrammatic (*right*) variants of primary progressive aphasia (PPA). Areas of early and severe atrophy in each syndrome are highlighted (*white arrowheads*). The behavioral variant features anterior cingulate and frontoinsular atrophy, spreading to orbital and dorsolateral prefrontal cortex. Semantic variant PPA shows prominent temporopolar atrophy, more often on the left. Nonfluent/agrammatic variant PPA is associated with dominant frontal opercular and dorsal insula degeneration.

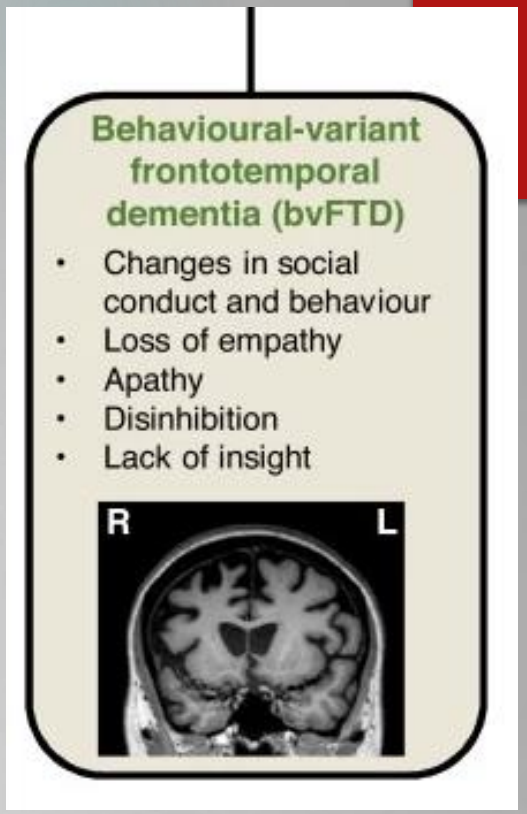
Medial and orbital frontal spreading to dorsolateral prefrontal cortex degeneration

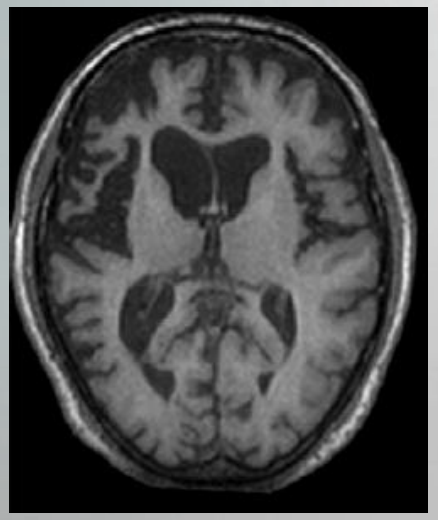
Anterior cingulate degeneration

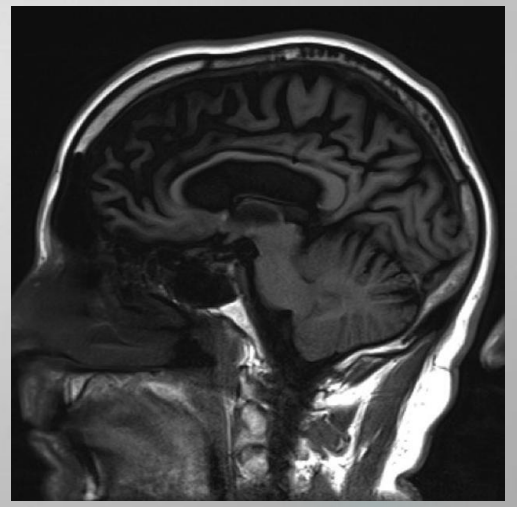
Anterior insula degeneration

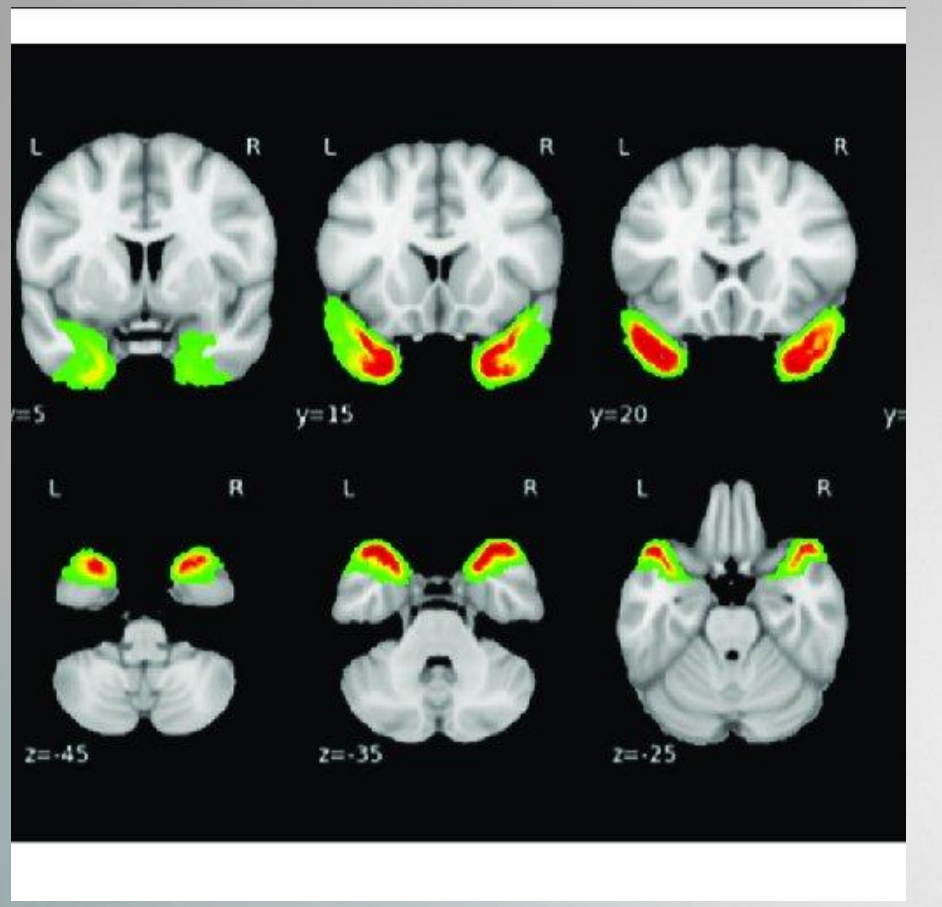
Basal ganglia Degeneration

Predicts bvFTD.









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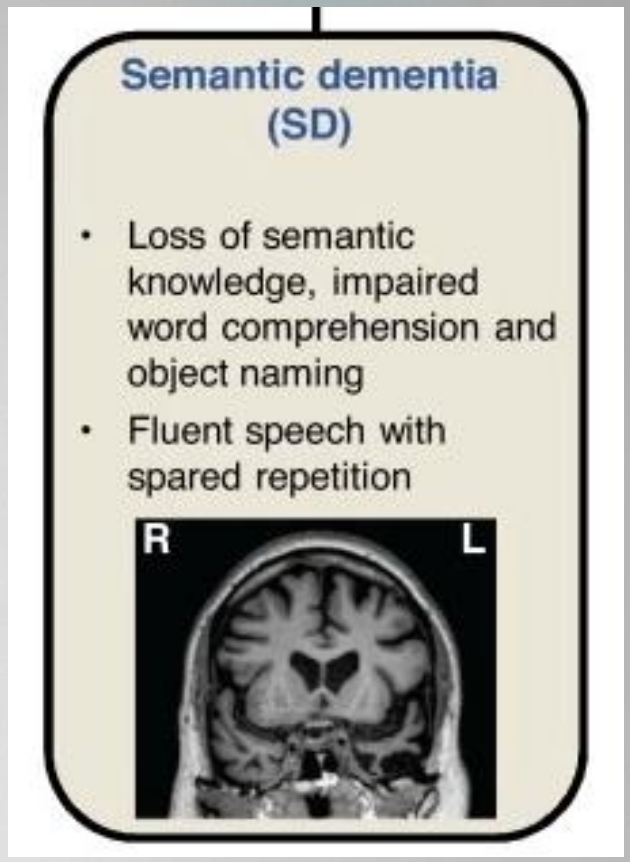
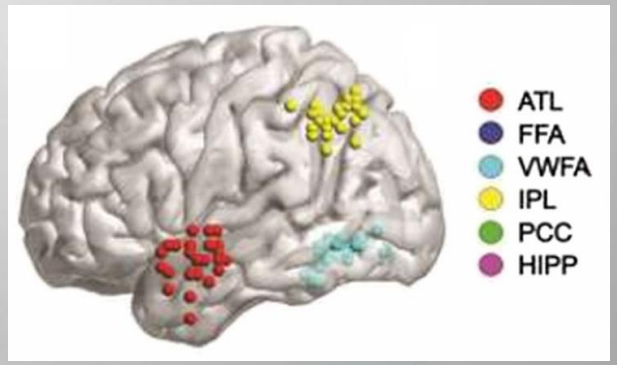
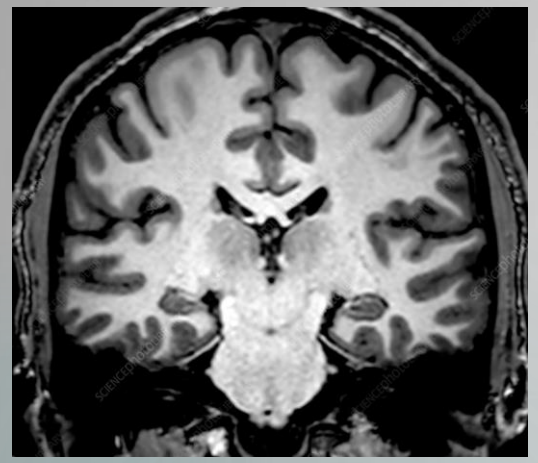


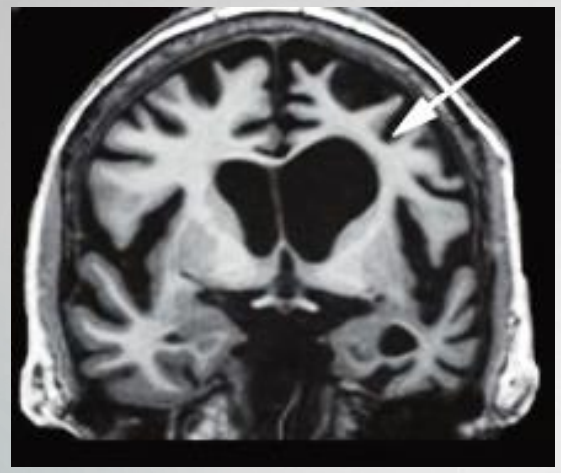


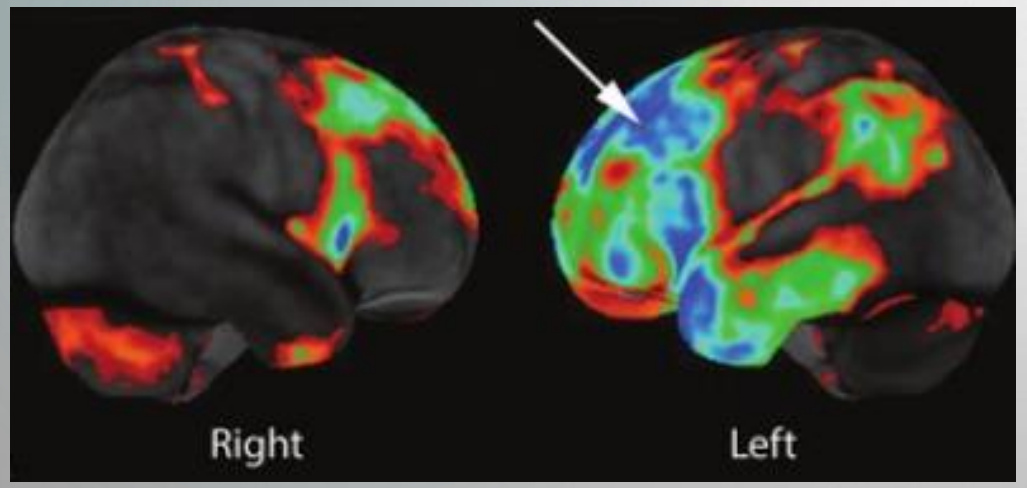
Temporopolar *degeneration presents with semantic variant PPA*

Nonfluent/agrammatic variant PPA

Frontal opercular ,dorsal insula, precentral gyrus atrophy.







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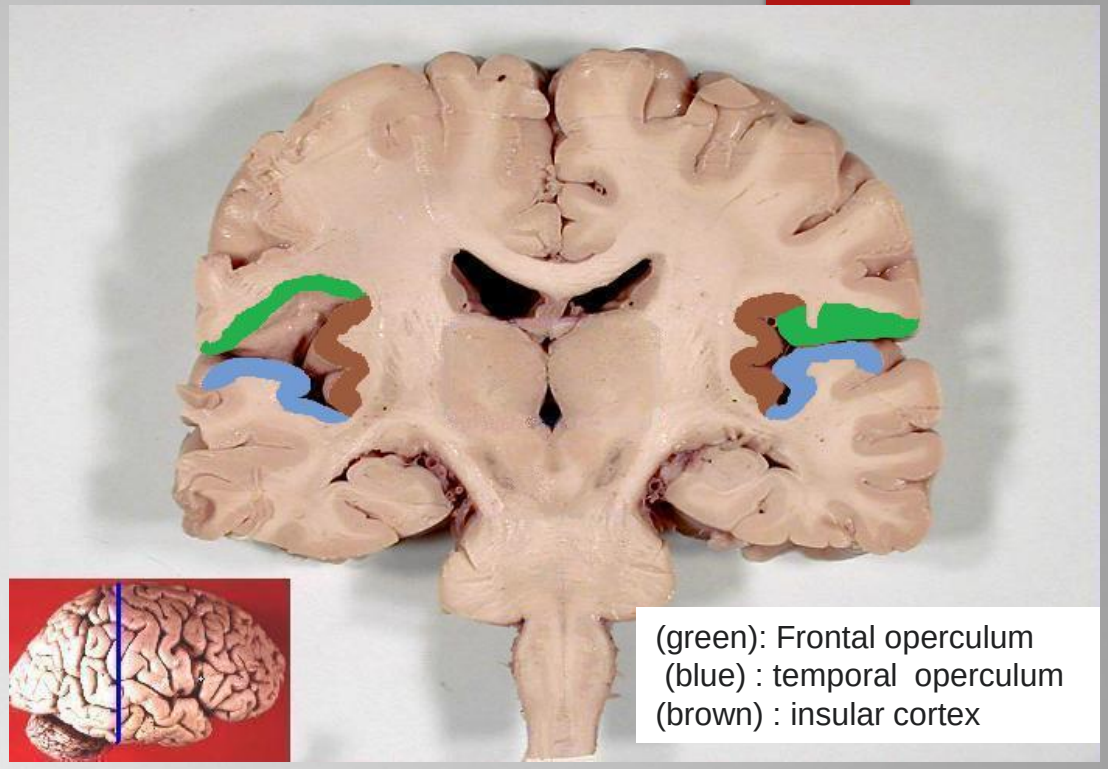
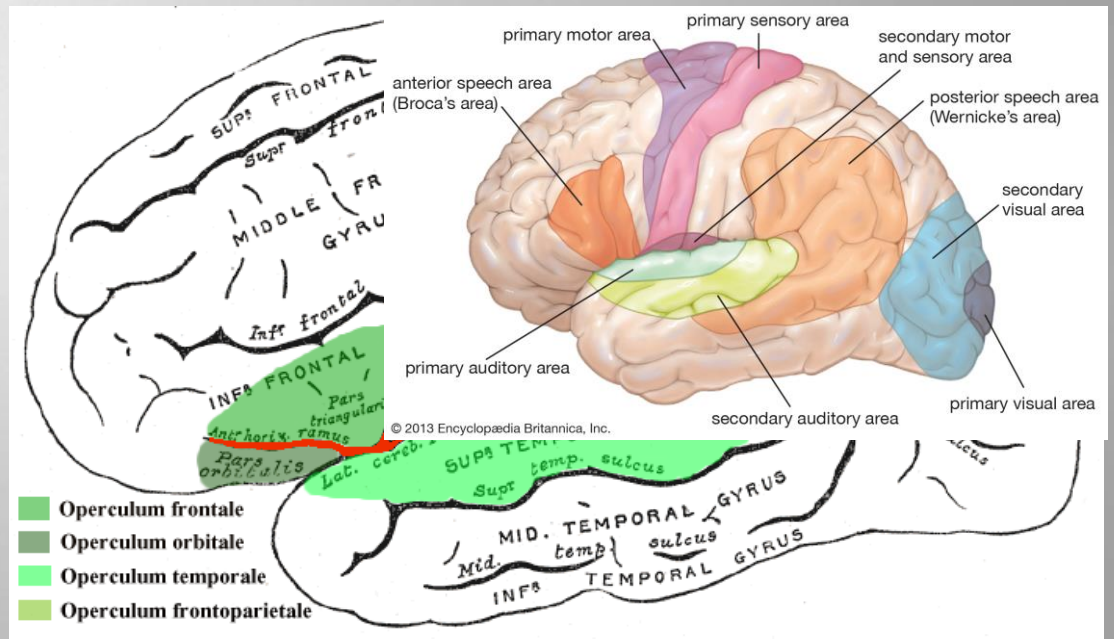
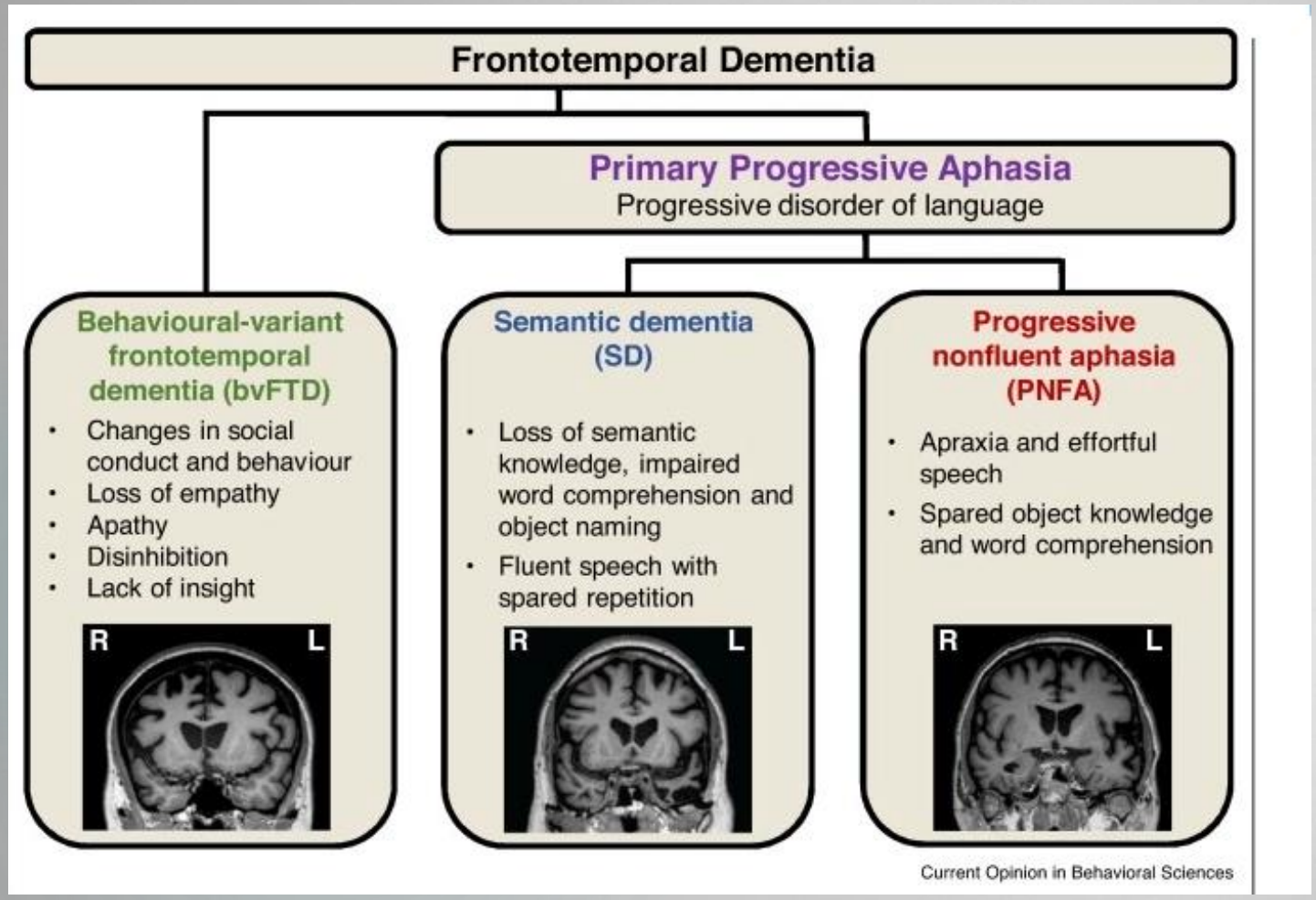
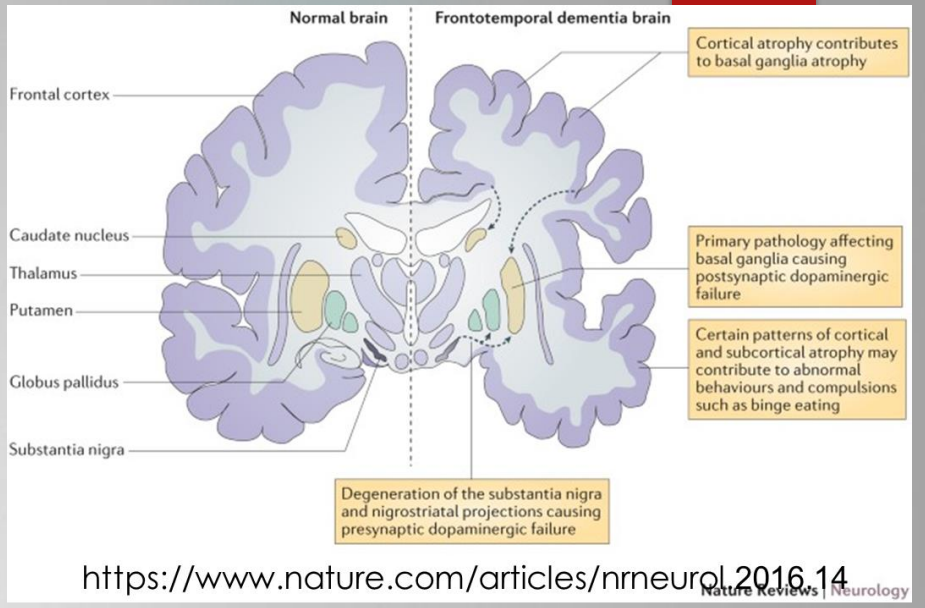


(green): Frontal operculum
(blue) : temporal operculum
(brown) : insular cortex







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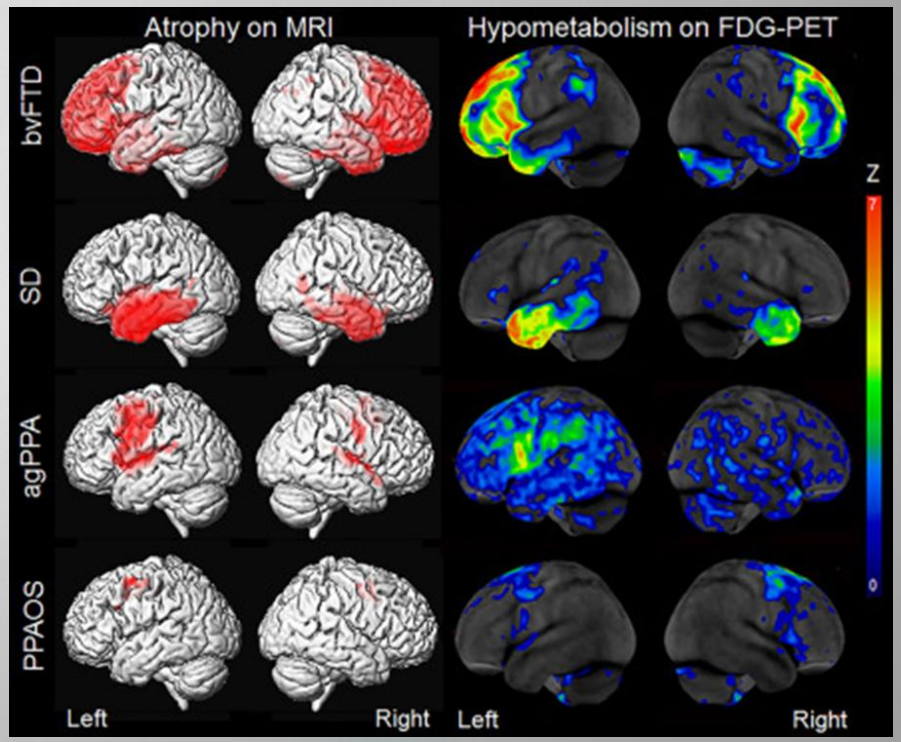


Less Common Casuses

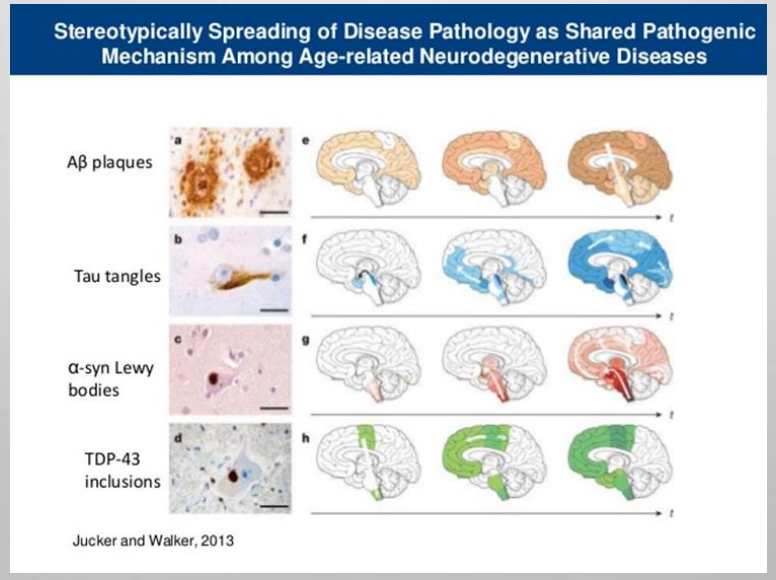
1. Vitamin deficiencies
2. Endocrine and other organ failure
3. Chronic infections
4. Head trauma and diffuse brain damage
5. Neoplastic
6. Toxic disorders
7. Degenerative disorders
8. Psychiatric
9. Metabolic disorders
10. Prion :CJD

Biomarker

TABLE 25-2 The Molecular Basis for Degenerative Dementia

DEMENTIA	MOLECULAR BASIS	CAUSAL GENES (CHROMOSOME)	SUSCEPTIBILITY GENES	PATHOLOGIC FINDINGS
AD	Aβ/tau	*APP* (21), *PS-1* (14), *PS-2* (1) (<2% carry these mutations, most often in *PS-1*)	*Apo ε4* (19)	Amyloid plaques, neurofibrillary tangles, and neuropil threads
FTD	Tau	*MAPT* exon and intron mutations (17) (about 10% of familial cases)	H1 *MAPT* haplotype	Tau neuronal and glial inclusions varying in morphology and distribution
	TDP-43	*GRN* (10% of familial cases), *C9ORF72* (20–30% of familial cases), rare *VCP*, very rare *TARDBP, TBK1, TIA1*		TDP-43 neuronal and glial inclusions varying in morphology and distribution
	FUS	Very rare *FUS*		FUS neuronal and glial inclusions varying in morphology and distribution
DLB	α-Synuclein	Very rare *SNCA* (4)	Unknown	α-Synuclein neuronal inclusions (Lewy bodies)
CJD	PrP^{SC}	*PRNP* (20) (up to 15% of patients carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	PrP^{SC} deposition, panlaminar spongiosis

Abbreviations: AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.



Thanks for your attention