Current understanding of Alzheimer's disease diagnosis and treatment

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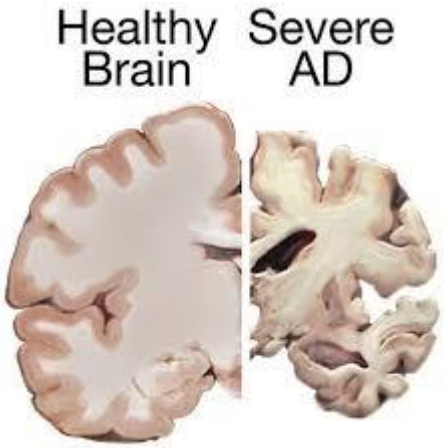
Origin of Alzheimer's Disease

The disease was first described by Dr. Alois Alzheimer, a German physician, in 1906. Alzheimer had a patient named Auguste D, in her fifties who suffered from what seemed to be a mental illness. But when she died in 1906, an autopsy revealed dense deposits, now called neuritic plaques, outside and around the nerve cells in her brain. Inside the cells were twisted strands of fiber, or neurofibrillary tangles. Since Dr. Alois Alzheimer's was the first person who discovered the disease, AD was named after him.

Auguste D

Dementia



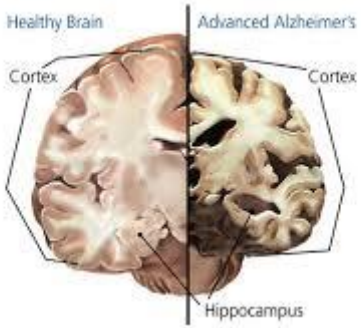
Dementia is a clinical syndrome characterized by progressive decline in two or more cognitive domains, including memory, language, executive and visuospatial function, personality, and behavior, which causes loss of abilities to perform instrumental and/or basic activities of daily living.

MCI AND DEMENTIA

MCI: when cognitive decline does not interfere with daily function, are considered to have

Dementia: When cognitive decline interferes with independent function,

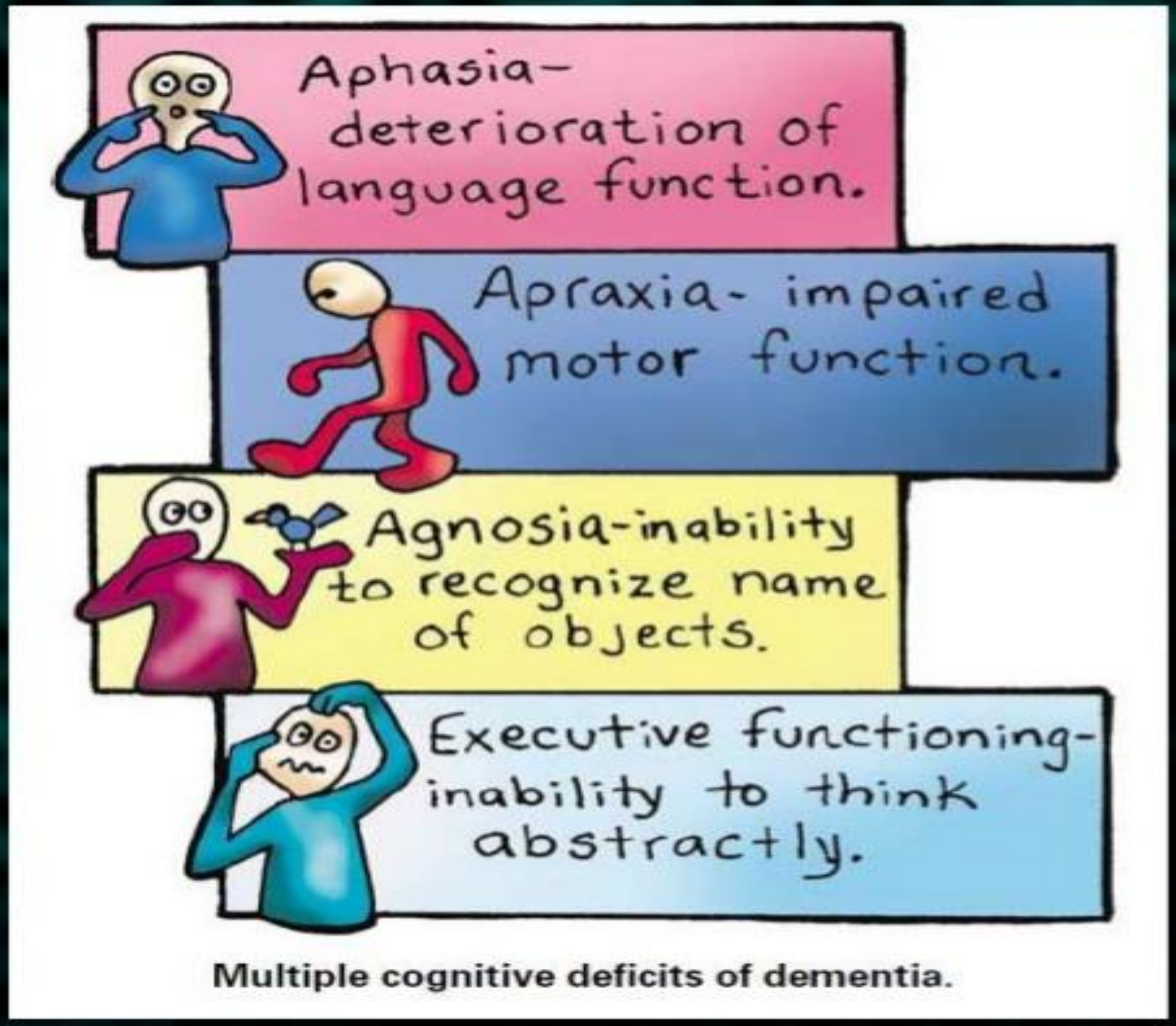
Alzheimer’s disease



(AD) is the most common cause of dementia and accounts for up to 80% of all dementia diagnoses:

1- early onset: before 65y –relatively rapid course

2- late onset: after 65y



Multiple cognitive deficits of dementia.

EPIDEMIOLOGY

The incidence and prevalence of AD increase dramatically with age.

Approximately 80% of patients with AD are older than age 75, with disease incidence increasing from

2 per 1000 at ages 65 – 74

37 per 1000 at age 85 and older

Nearly two-thirds of patients with AD are women, likely reflecting both increased life duration and biological factors

overall lifetime risk for AD: At age 65 is 21.1% for women and 11.6% for men

Risk Factors

- Advancing Age
- Female sex
- Family history
- Education
- Environmental factors: Aluminum- Mercury - viruses
- vascular risk factors,
- Common sleep disturbances such as insomnia and obstructive sleep apnea
- Traumatic brain injury
- Late-life depression

GENETIC RISK FACTORS

Late-onset AD is a complex genetic disorder, with an estimated heritability of 60% to 80%.

The strongest genetic risk factor for late-onset AD is: (APOE)

apolipoprotein E genotype has three common alleles:

ε2 (8.4% estimated allele frequency in the population),

ε3 (77.9%)

ε4 (13.7%)

- **APOE ε4** :3 in heterozygotes and 8 to 12 in hemozygots
- Each APOE ε4 allele reduces the average age of symptom onset by about a decade.
- Female carriers of APOE ε4 are at increased risk compared to male carriers, particularly between the ages of 65 and 75

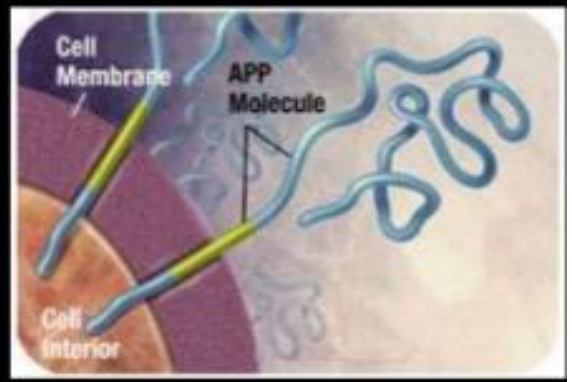
- the ε2/ε2 and ε2/ε3 genotypes are protective

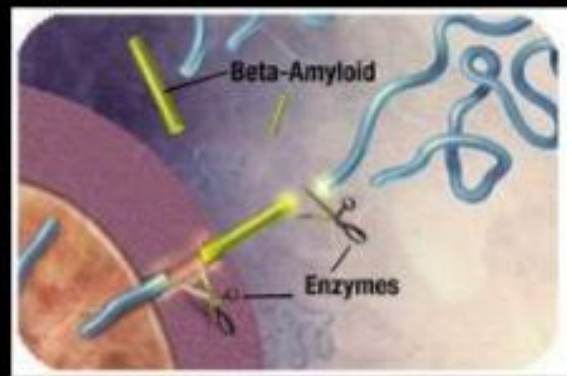
APOE ε4 mechanisms to AD risk

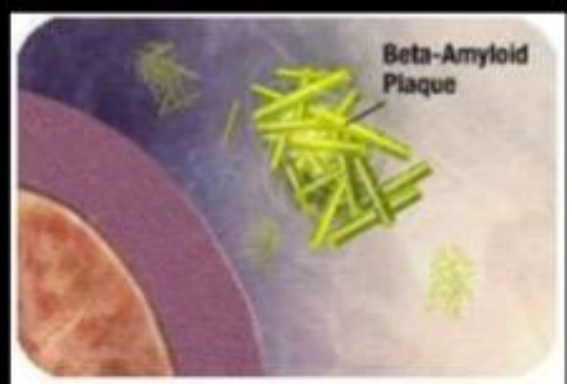
- enhanced aggregation and decreased clearance of the amyloid-β (Aβ) polypeptide
- increased tau phosphorylation
- reduced glucose metabolism
- vascular, and mitochondrial function
- network hyperexcitability
- And neurodevelopmental differences.

Pathogenesis of Alzheimers

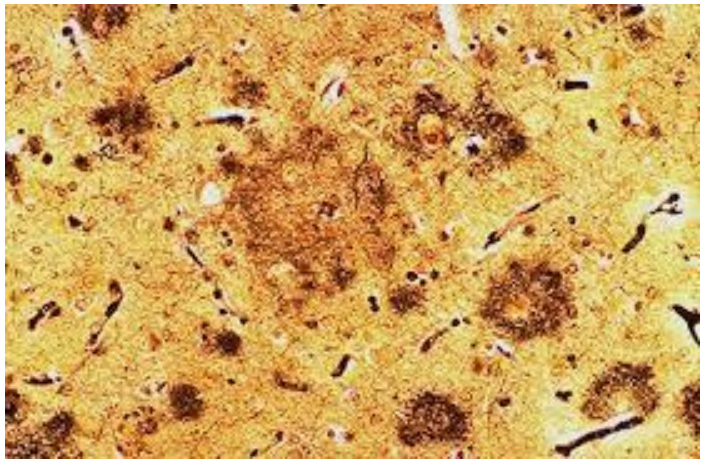
- Two microscopic features are characteristic of Alzheimers`s disease
  - Extracellular amyloid plaques
    - Consisting of amorphous extra cellular deposits of Aβ protein
  - Neurofibrillary tangles
    - Comprising of filaments of phosphorylated Tau protein

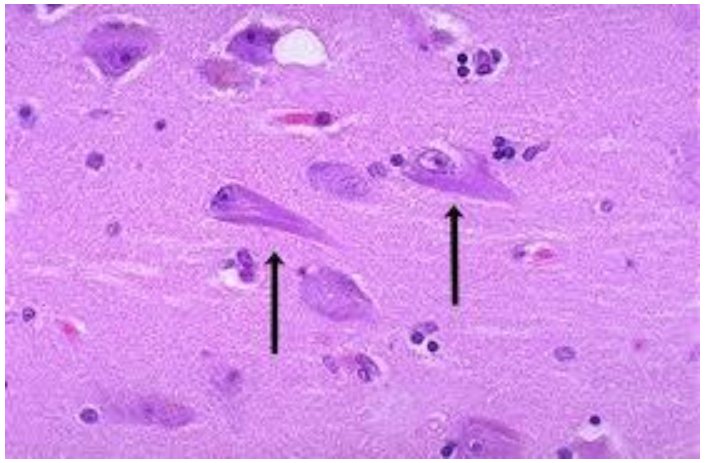






NEUROPATHOLOGY



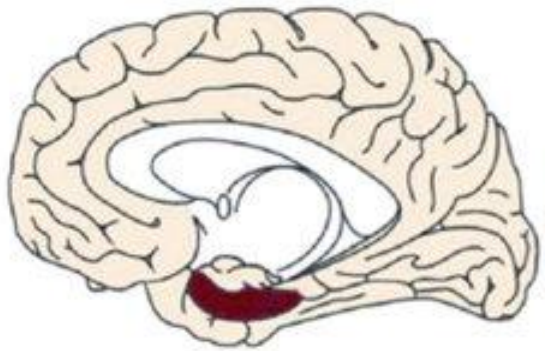


Aβ plaques first appear in the neocortex, then spread successively into the hippocampus and limbic structures, striatum and diencephalon, brainstem, and cerebellum

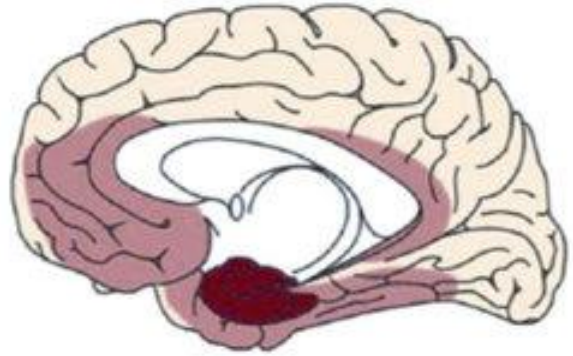
The distribution of tangles typically follows a hierarchical pattern described by Braak stages:

1. first in the transentorhinal and entorhinal cortex (Braak stages I and II)
2- limbic (Braak stages III and IV)
3-Neocortical (Braak stages V and VI) regions.

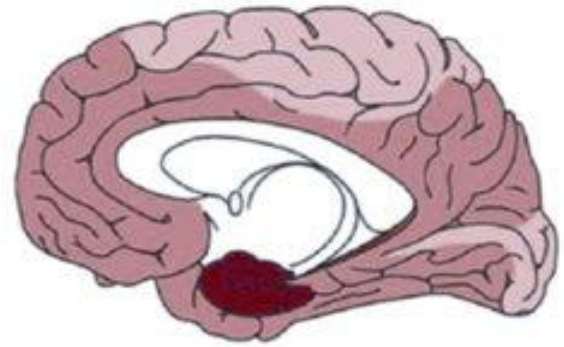
A. Braak stages (post mortem)



Transentorhinal (I/II)

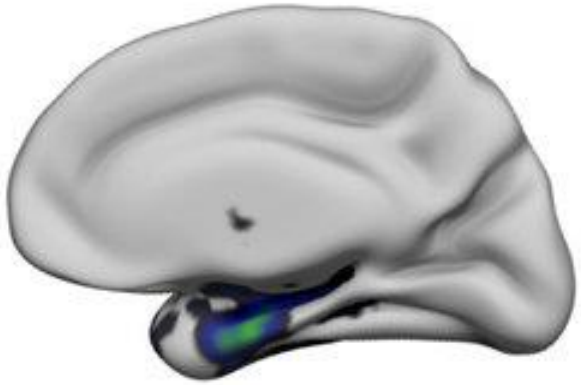


Limbic (III/IV)

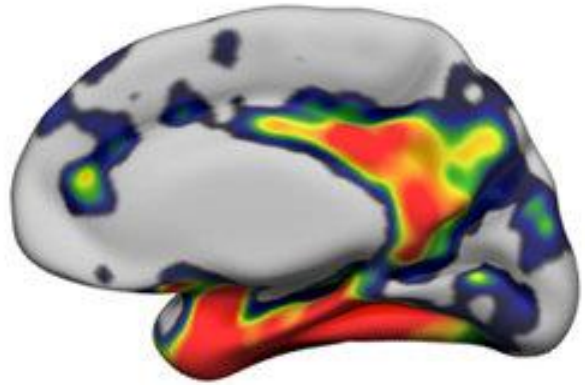


Neocortical (V/VI)

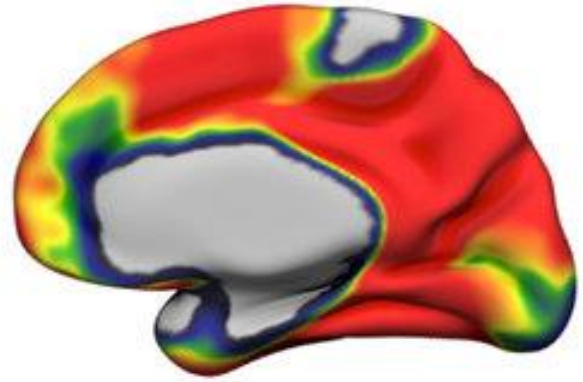
B. Tau tracer uptake (PET)



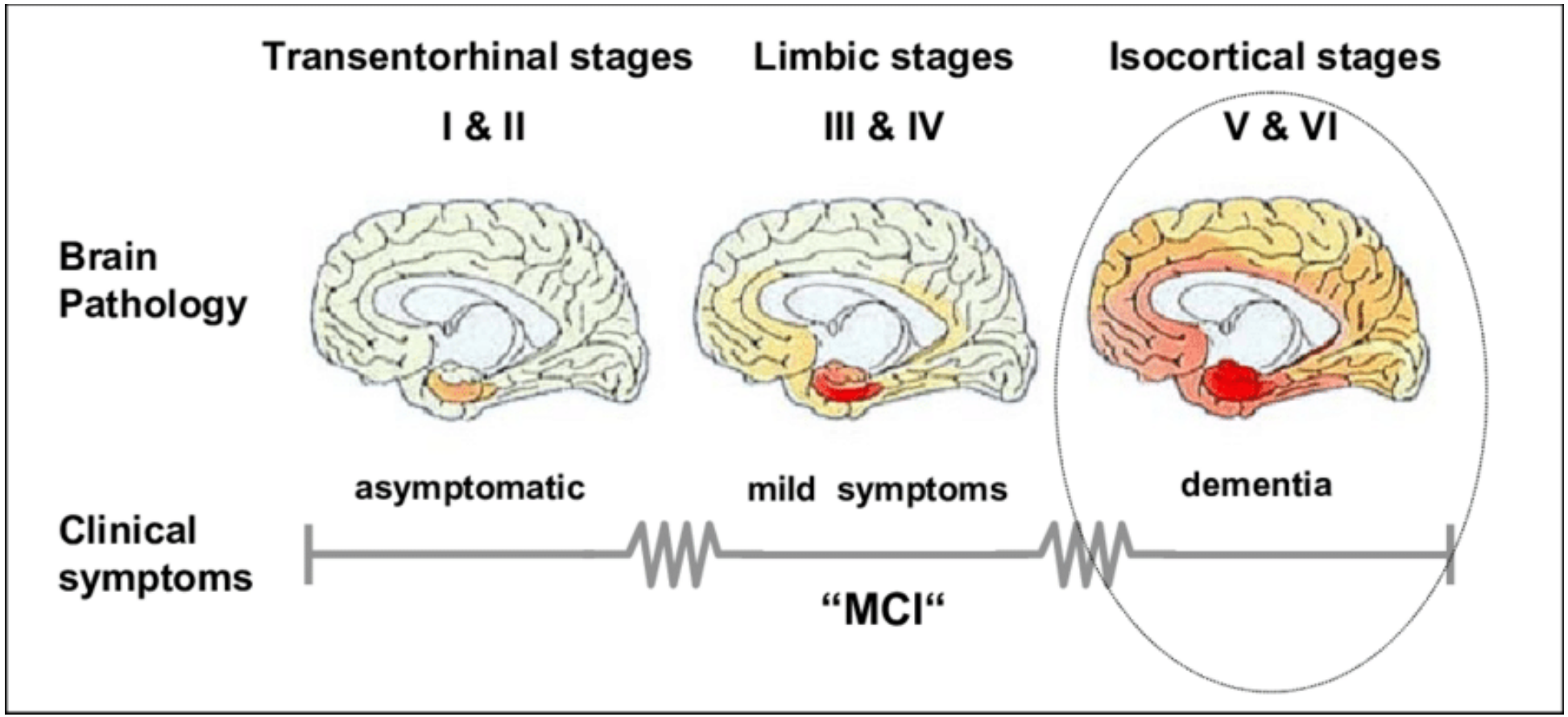
$Stage_{I/II} > Stage_{0}$



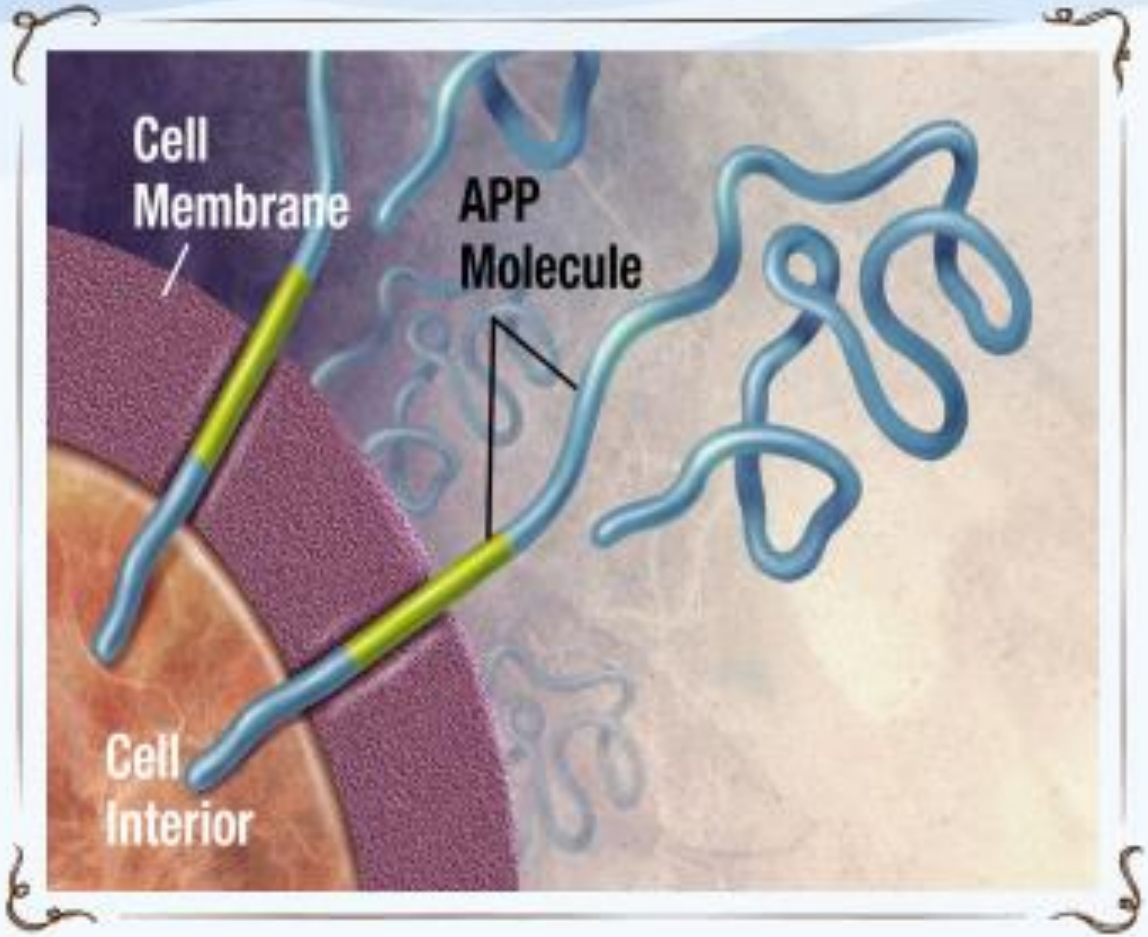
$Stage_{III/IV} > Stage_{I/II}$



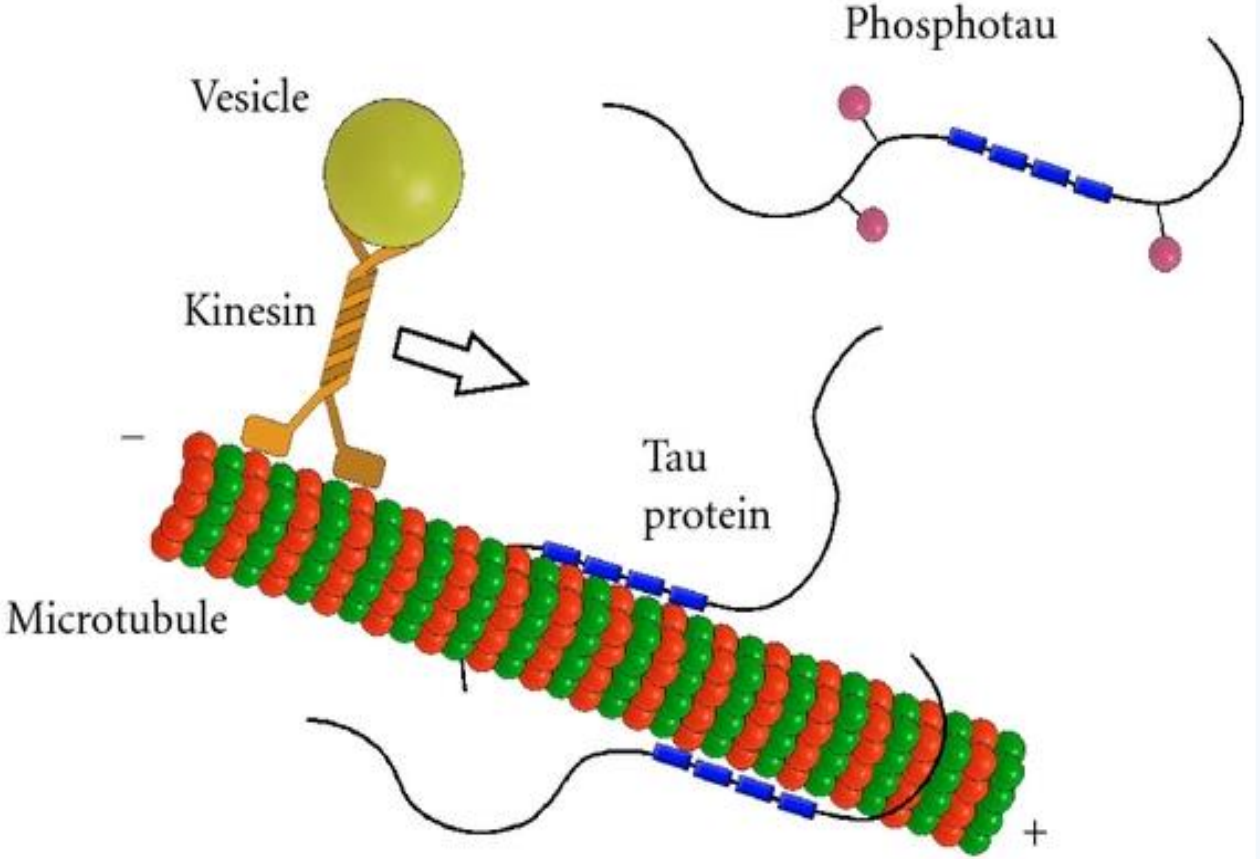
$Stage_{V/VI} > Stage_{III/IV}$


Transentorhinal stages
I & II
Limbic stages
III & IV
Isocortical stages
V & VI
Brain Pathology
Clinical symptoms
asymptomatic
mild symptoms
dementia
"MCI"

Cognitive symptoms correlate more strongly with the burden and distribution of neurofibrillary pathology than with Aβ pathology

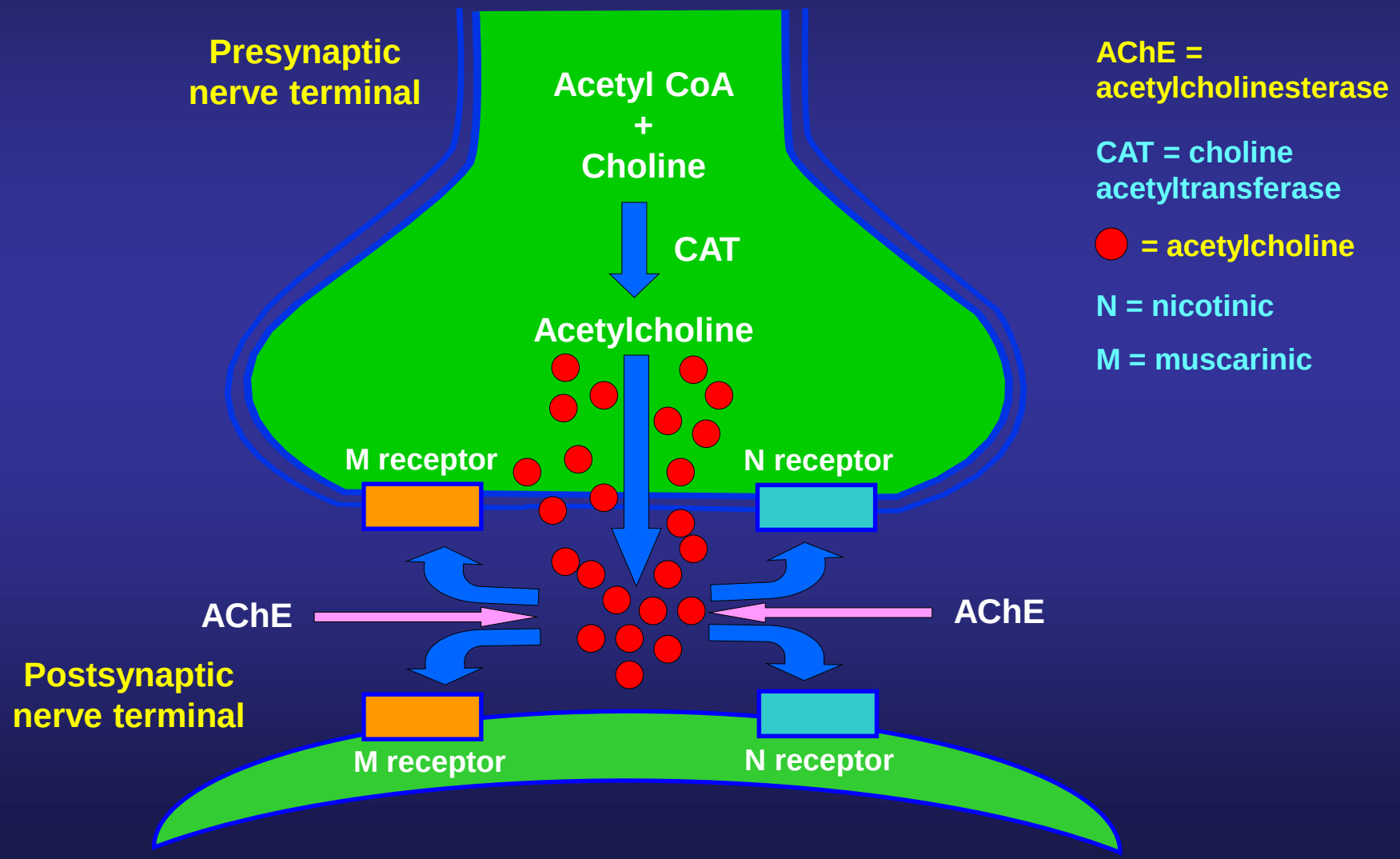


- **Amyloid precursor protein (APP)** is membrane protein
- Sits in the membrane and extends outward.
- It is thought to be important for neuronal growth, survival, and repair



‘Tau’ Hypothesis

Action of ACh at pre- and postsynaptic nerve terminals and its removal by AChE



neuronal loss and brain atrophy

Glutamatergic neurons in the entorhinal cortex and the CA1 sector of hippocampus

Cholinergic neurons in the basal forebrain

Diagnosis

Diagnosis

- patient history
- Neuropsychological evaluation (MMSE, MOCA)
- Noncontrast CT-scan and MRI
- Biomarkers
- SPECT (single photon emission computed tomography)
- PET

Per American Academy of Neurology (AAN) guidelines, the following laboratory tests should be ordered in the routine evaluation of patients with cognitive decline:

- complete blood cell count, ESR
- serum electrolytes
- liver and renal function tests
- thyroid function tests
- serum vitamin B12, folate

Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date:_____

Instructions: Ask the questions in the order listed.
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 of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then 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. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79,72, 65, …) Stop after five answers. 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**

AMYLOID-β AND TAU BIOMARKERS

- **CSF** :reductions in levels of Aβ1-42 and increases in total tau (t-tau) and phosphorylated tau (p-tau)
- **CSF** biomarkers are also helpful in predicting clinical progression in MCI

- amyloid deposition is not specific to AD clinical phenotypes and can be also seen in dementia with Lewy bodies, CAA, and in a proportion of cognitively healthy older individuals

- t-tau are a nonspecific marker of neurodegeneration and can be seen in other conditions associated with rapid neuronal death (eg, Creutzfeldt-Jakob disease, acute ischemia, and traumatic brain injury).

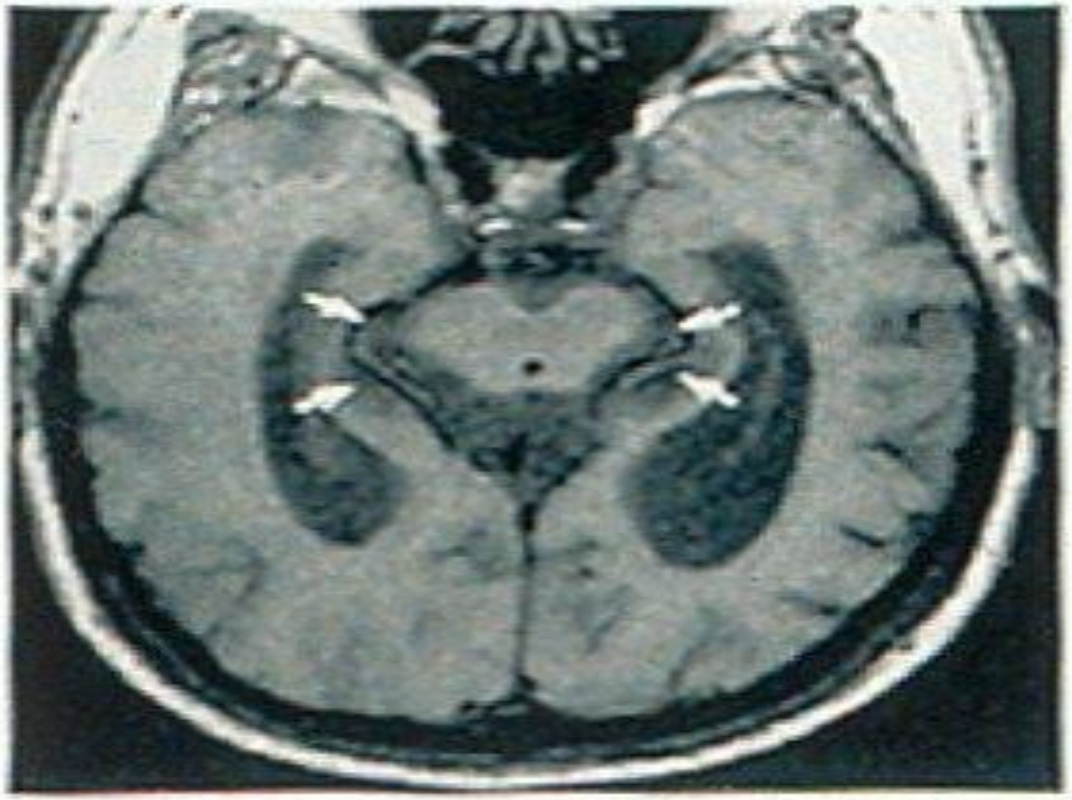
MRI

The hallmark MRI changes of late-onset AD include:

atrophy of the hippocampus and medial temporal lobes,

cortical atrophy (primarily involving temporoparietal cortex), and ventricular enlargement

Alzheimer's Disease: CT Scan



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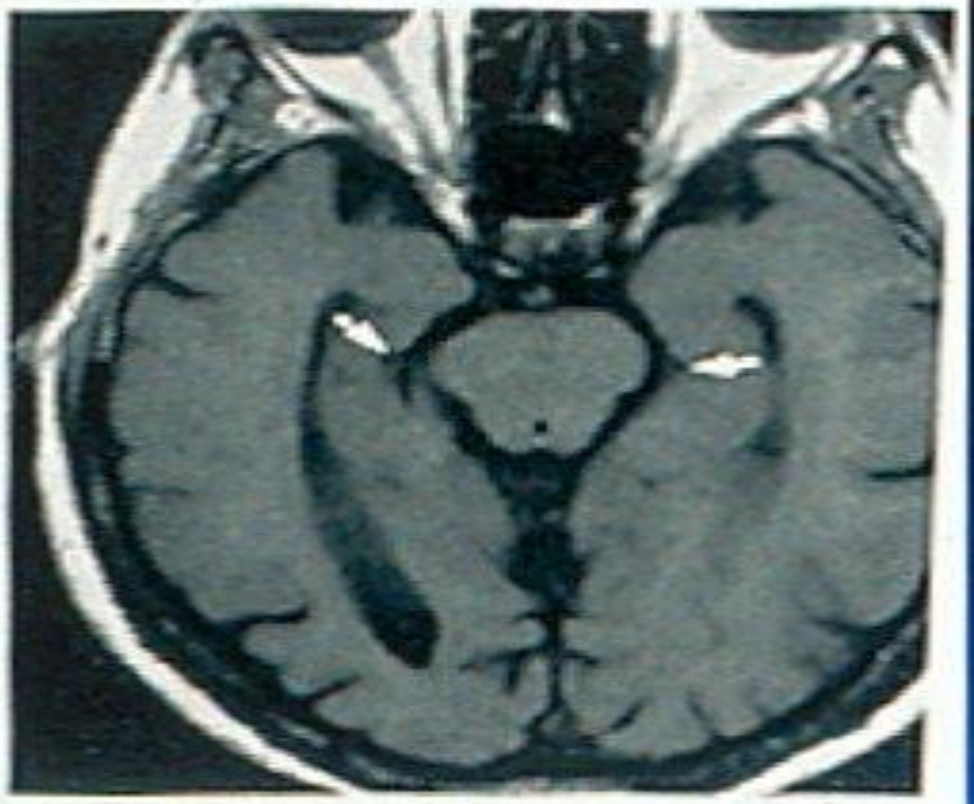
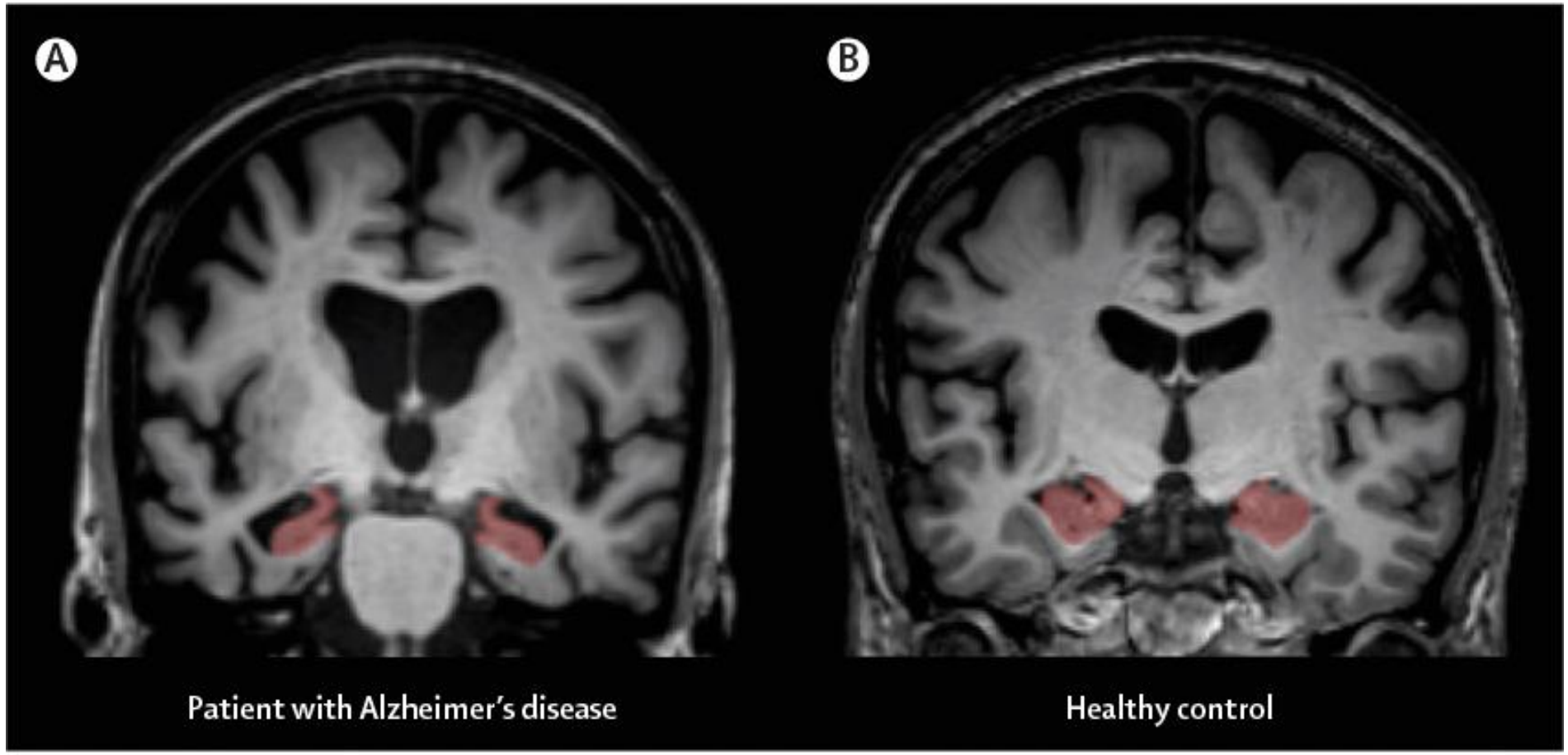


3

Hippocampal volume loss
Enlargement of choroid -
hippocampal fissure

Normal
86 year old


A
B
Patient with Alzheimer's disease
Healthy control

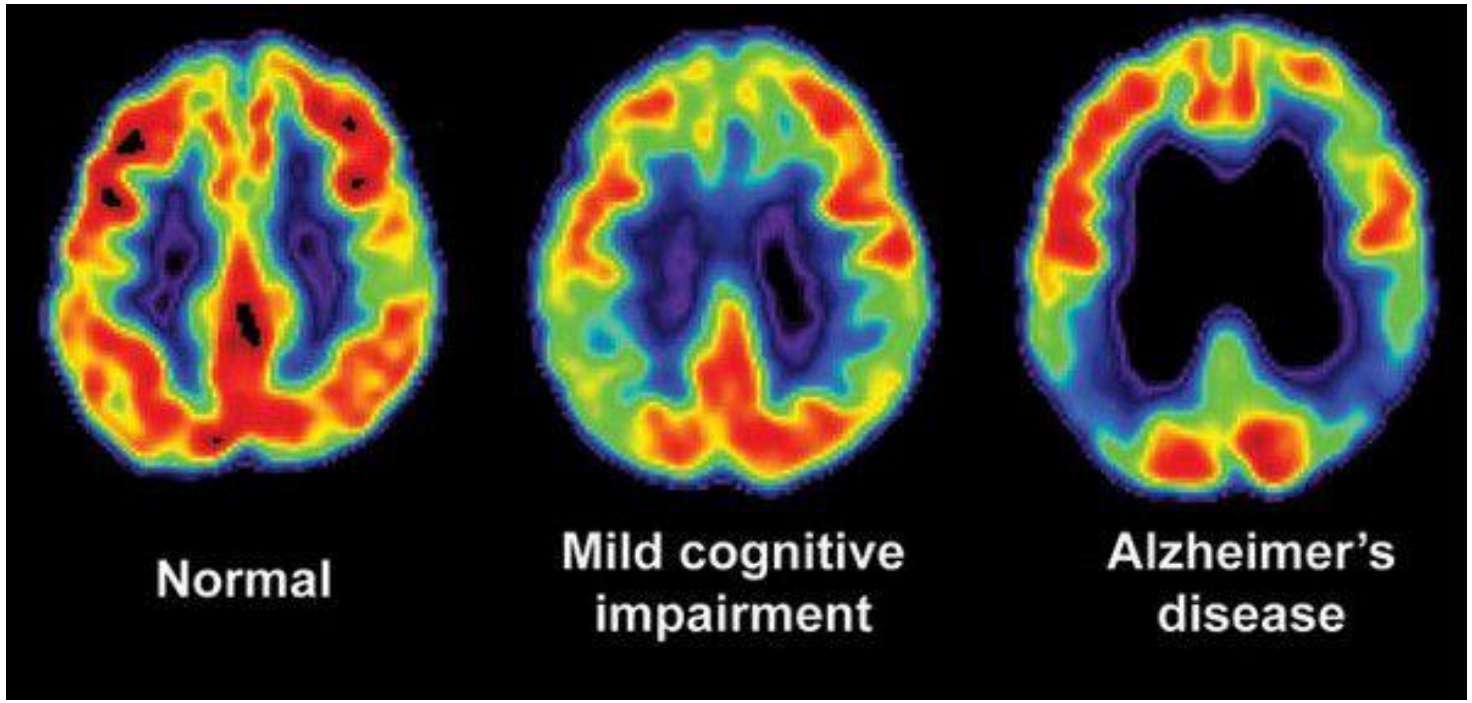
PET- SPECT

- **(FDG-PET)** Functional brain imaging with fludeoxyglucose positron emission tomography
- **(SPECT)** single-photon emission computed tomography

perfusion scans

. The classic pattern of hypometabolism (FDG-PET) or hypoperfusion (SPECT) associated with AD involves reduced activity in the temporoparietal cortex and posterior cingulate/precuneus. As with MRI, cortical changes are more prominent in early-onset than late-onset AD.

SPECT



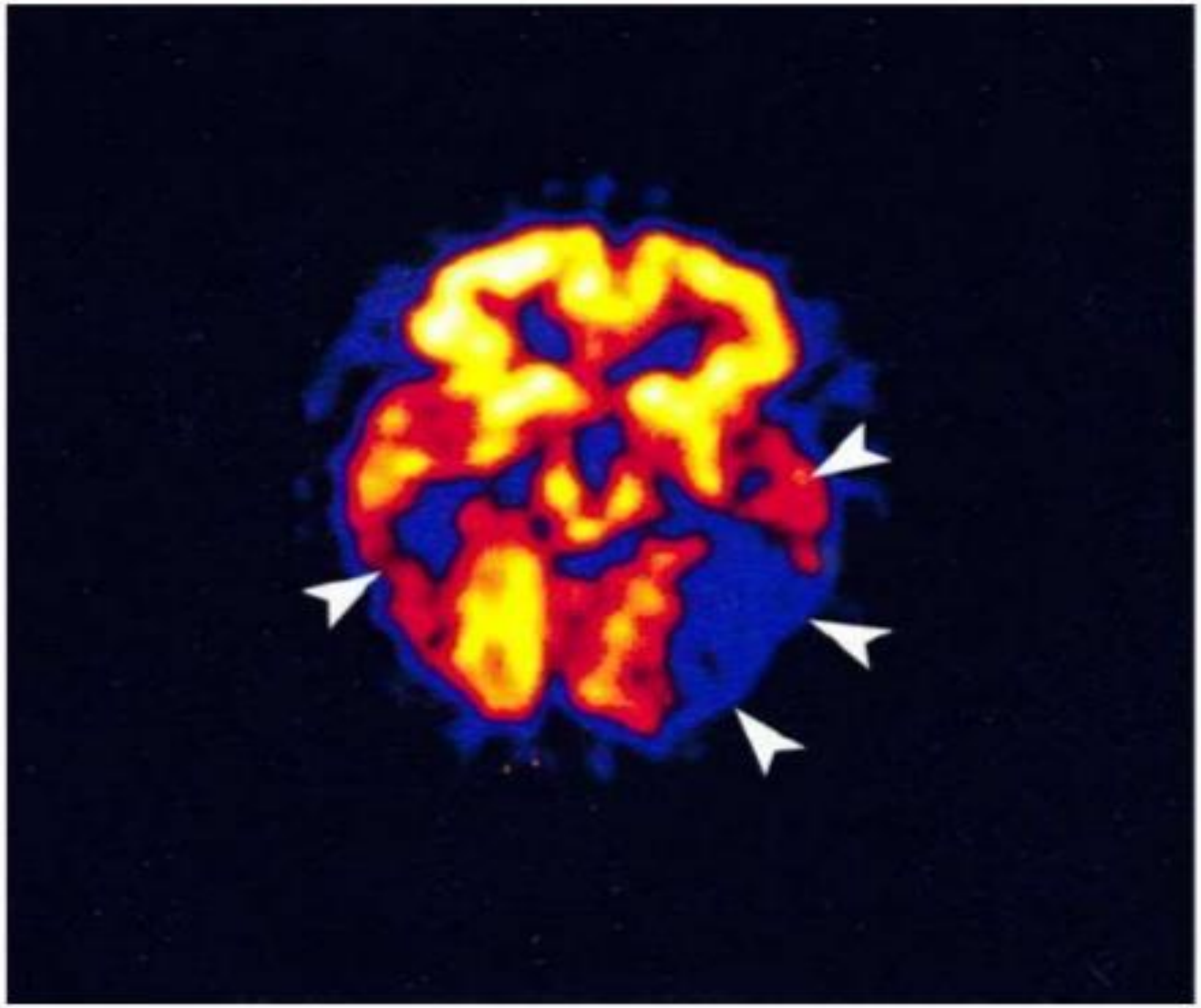
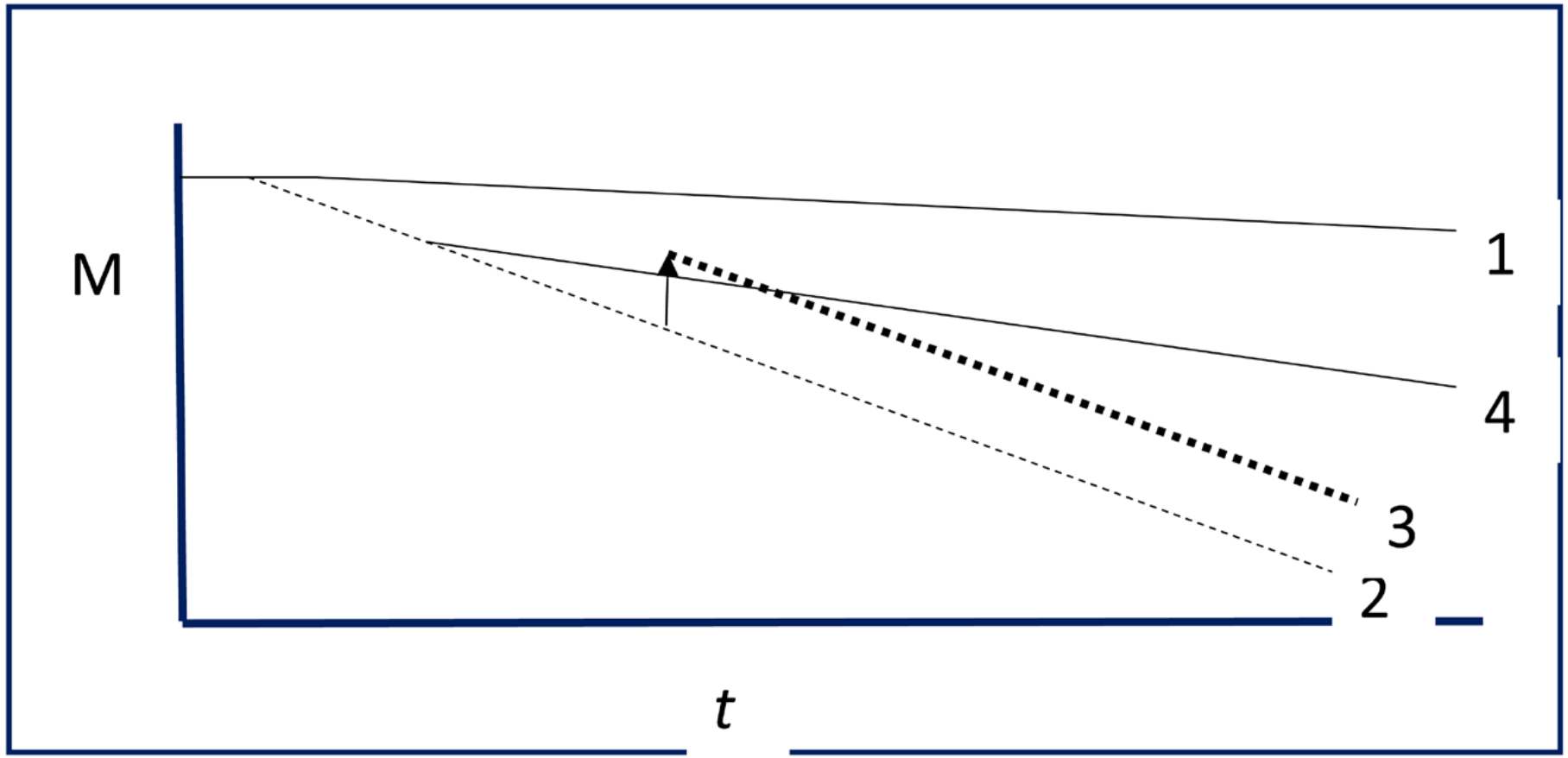
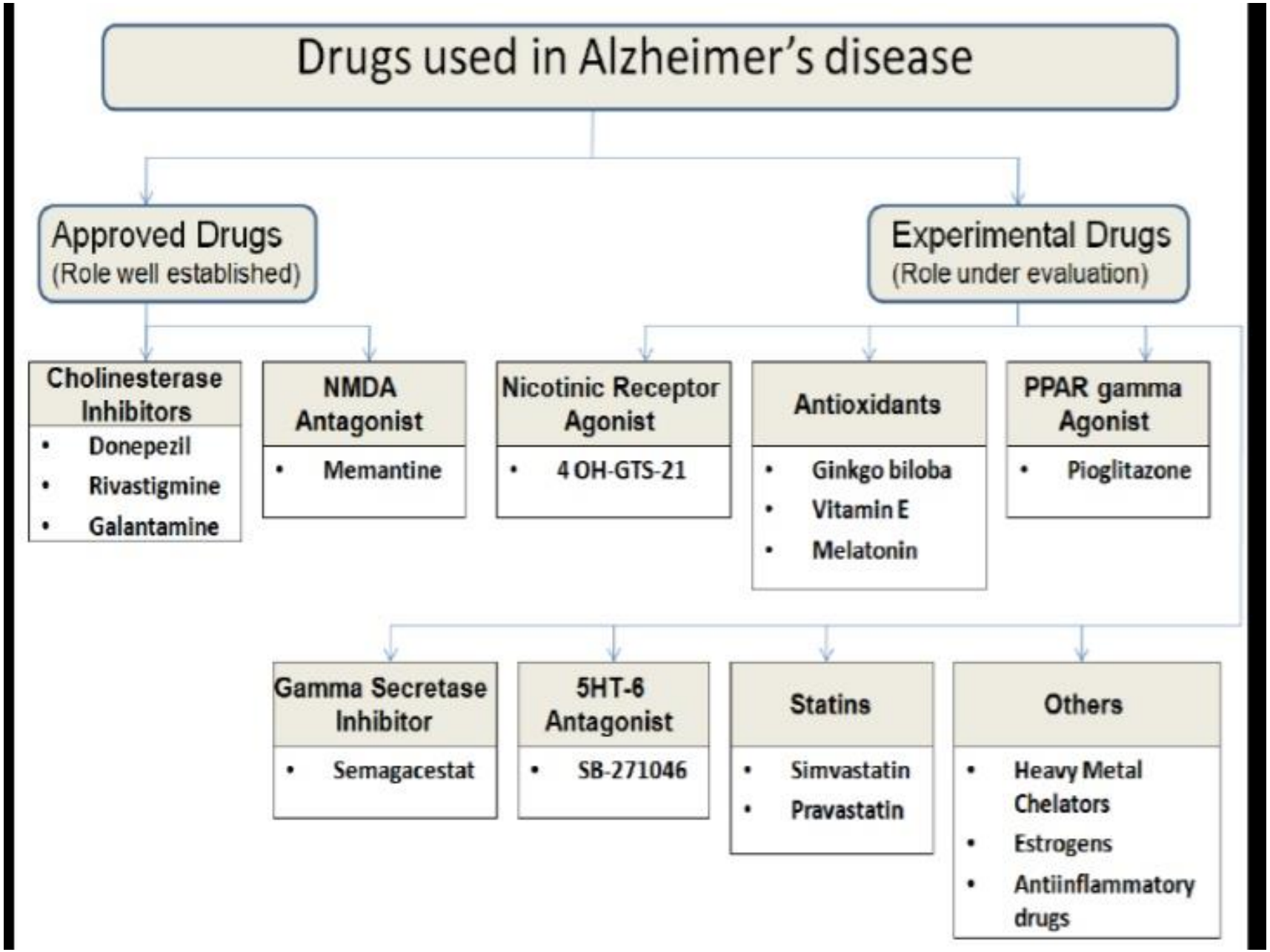


Figure 2-6. Example of axial (horizontal) PET scan of male patient with Alzheimer's disease, showing defects (arrowheads) in metabolism in the regions of cerebral cortex of brain.

MANAGEMENT

Memory and Alzheimer's disease. Rate of decline of memory (M) over time (t, months to years).
Memory declines slowly in normal aging (1). Alzheimer's disease is marked by more rapid cognitive decline often starting earlier in life (2). Current therapies enhance cognition without changing the rate of decline in AD (3). The anticipated effect of novel therapies is reduction in the rate of decline (4).




Drugs used in Alzheimer's disease
Approved Drugs
(Role well established)
Experimental Drugs
(Role under evaluation)
Cholinesterase Inhibitors
• Donepezil
• Rivastigmine
• Galantamine
NMDA Antagonist
• Memantine
Nicotinic Receptor Agonist
• 4 OH-GTS-21
Antioxidants
• Ginkgo biloba
• Vitamin E
• Melatonin
PPAR gamma Agonist
• Pioglitazone
Gamma Secretase Inhibitor
• Semagacestat
5HT-6 Antagonist
• SB-271046
Statins
• Simvastatin
• Pravastatin
Others
• Heavy Metal Chelators
• Estrogens
• Antiinflammatory drugs

(AChEIs)

- First approved in 1993
- Ach is an important neurotransmitter in brain regions involved in memory
- Also may affect behavior and daily functioning
- AD is associated with loss of cholinergic neurons in the basal forebrain. AChEIs enhance cholinergic transmission by inhibiting the hydrolysis of acetylcholine in the synaptic cleft.

Three AChEIs are used in clinical practice:

donepezil, galantamine, rivastigmine

adverse effects

- gastrointestinal upset and loss of appetite
- urinary frequency,
- muscle cramps,
- vivid dreams
- Slowing of cardiac conduction can occur, and AChEIs should be used with caution in patients at risk for bradycardia.
- Additional rare, but potentially serious, adverse effects reported for rivastigmine include increased pulmonary and gastric secretions,

warranting caution in patients with uncontrolled obstructive airway disease, gastrointestinal bleeding, and gastric ulcer disease.

Frontotemporal Dementia (FTD)

لوب فرونتال و تمپورال درگیر است (رفتار و تکلم درگیر است)

آلزایمر ابتدا تمپورال و پاریتال را درگیر میکند(حافظه)

در هر دو پروتئین تائودیده میشود ولی آمیلوئید غیرطبیعی منحصر آلزایمر است

سومین علت شایع دمانس است (بعد از آلزایمر و دمانس واسکولر)

وجود هر سه پروتئین :

Tau – TDP43 – Fused in-sarcoma

سن شروع ۶۰- ۵۰

Frontotemporal Dementia (FTD)

Lewy body disease

هیستوپاتولوژی : اجسام اینتراسیتوپلاسمی ائوزینوفیلی(لوی بادی)در ساقه مغز و کورتکس.

این انکلوزیون ها شامل پروتئینSynuclein

که در پارکینسون بدون دمانس نیز دیده می شود

synucleinopathiesبنابراین بیماری پارکینسون و بیماری لوی بادی تحت عنوان :

بیماری لوی بادی عمدتا باعث اختلال شناخت می شود تا حافظه

علایم : اختلال شناخت نوسان دار – هالوسیناسیون بینایی – علایم پارکینسونیسم خصوصا رژیدیته و برادی کینزی

درمان:داروهای آنتی پارکینسون برای علایم حرکتی

ممانتین و داروهای آنتی کولین استراز ممکنست موثر باشد

Thanks for your attention