Dementia

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Dementia

- An *acquired syndrome* consisting of a decline

  in memory and other cognitive functions

- Impairment in social or occupational functioning

Classification of Dementias

- **Primary versus secondary** *based on the pathophysiology* leading to damaged brain tissue
- **Cortical versus sub-cortical** *depending on the cerebral location* of the primary deficits
- **Reversible versus irreversible** *depending on optimal treatment* expectations
- **Early** (before age 65) **versus late onset**

Dementias

Most Common Dementias

1-Alzheimer Disease

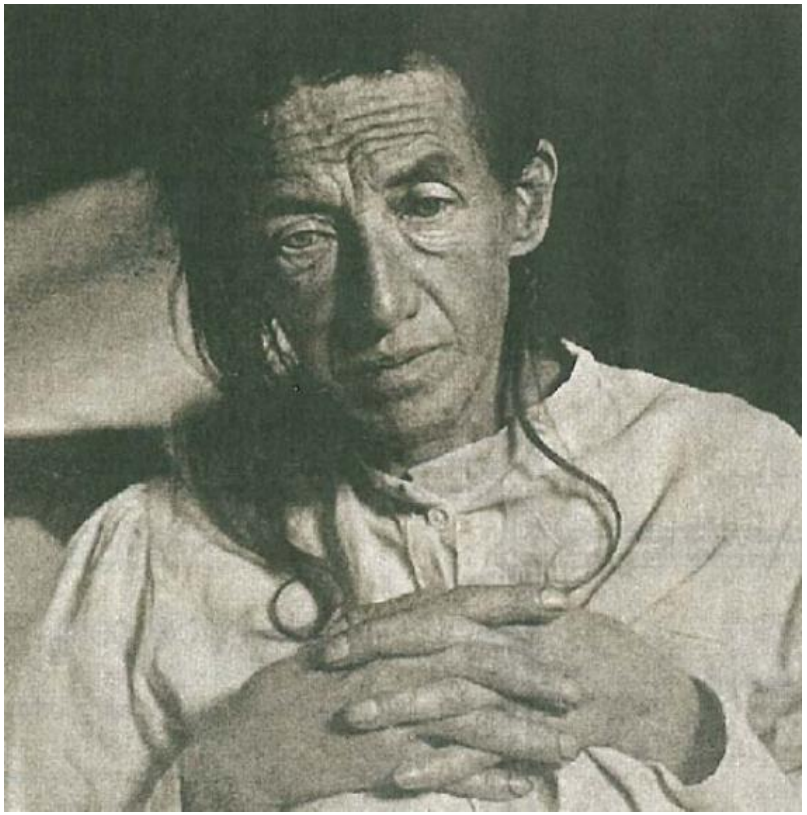
2-Lewy Body Dementia

3- Vaskular Dementia

Degenerative Dementias

- Alzheimer Disease
- Lewy Body Dementia
- Frontal Lobe Dementia
- Parkinsonism and Dementia

Alzheimer



Alzheimer's Disease

- In 1901, a German psychiatrist named Alois Alzheimer observed a patient named Mrs. Auguste D.
- This 51-year-old woman suffered from a loss of short-term memory and some behavioral symptoms
- in 1906, the patient died, and Dr. Alzheimer sent her brain to a laboratory. Pathologic evaluation identify amyloid plaques and neurofibrillary tangles.
- Dr. Alzheimer discribed was the first time the pathology and the clinical symptoms of the disorder in 1906 and published his findings in 1907

Alzheimer's Disease

- The most common form of dementia
- AD affects about 20-25 million people in the world, and that number is projected to reach 80 million by the year 2050
- Prevalance >65 ;%5-10 , >85 %25-50
- '*Oldest old* ' / 'Graying population'/ 'Modern epidemia'

Demografics of Aging

- >85 is fastest growing demographic group
- 20% of population by 2030 will be over 65
- There will be more

  women than men
- Life expectancy: (F > M)
  - 1950 50 yrs
  - 2012 79 yrs

Alzheimer's Disease

- Short-term memory impairment AND
- At least one of the following:
  - Aphasia - language impairments
  - Apraxia - motor memory impairments
  - Agnosia - sensory memory impairments
  - Abstract thinking / Exec. function impairments
- Impairment in social and/or occupational functions

Aphasia

- Characterized initially by a fluent aphasia
  - Able to initiate and maintain a conversation
  - Impaired comprehension
  - Intact grammar but paraphasias
  - circumlocutions, tangential and often using nonspecific phrases (“the thing”)
- Later language can be severely impaired with mutism, echolalia.

Apraxia

- Inability to carry out motor activities despite intact motor function

Agnosia

- The inability to recognize or identify objects despite intact sensory function
- Can be visual or tactile

Impaired Executive Function

- Difficulty with planning, initiating, sequencing, monitoring or stopping complex behaviors.

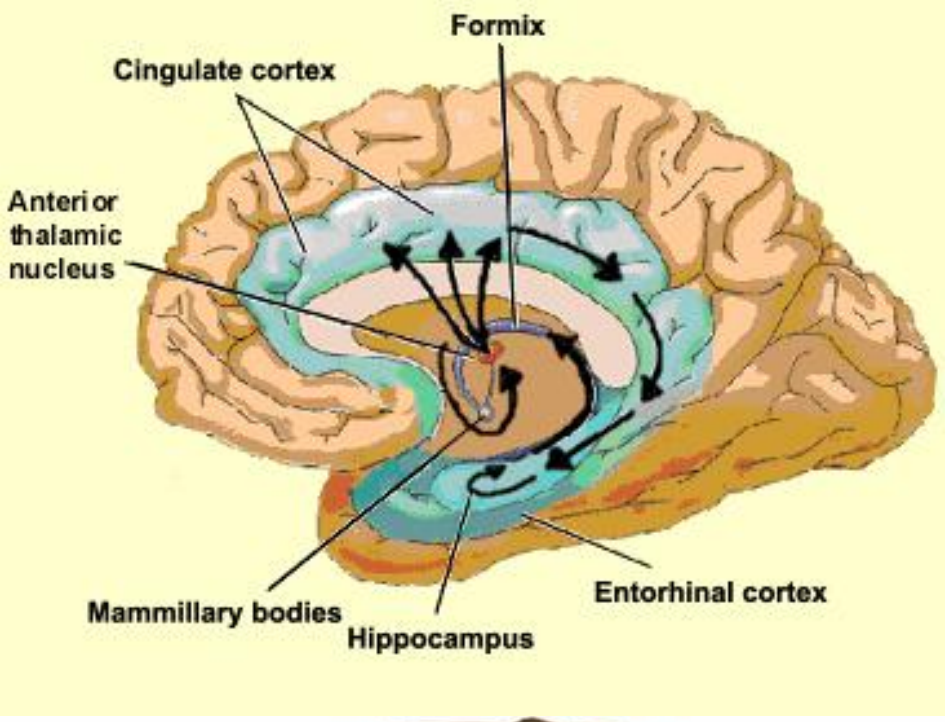
- Contributes to loss of intrumental activities such as shopping, meal preparation, driving and managing finances.

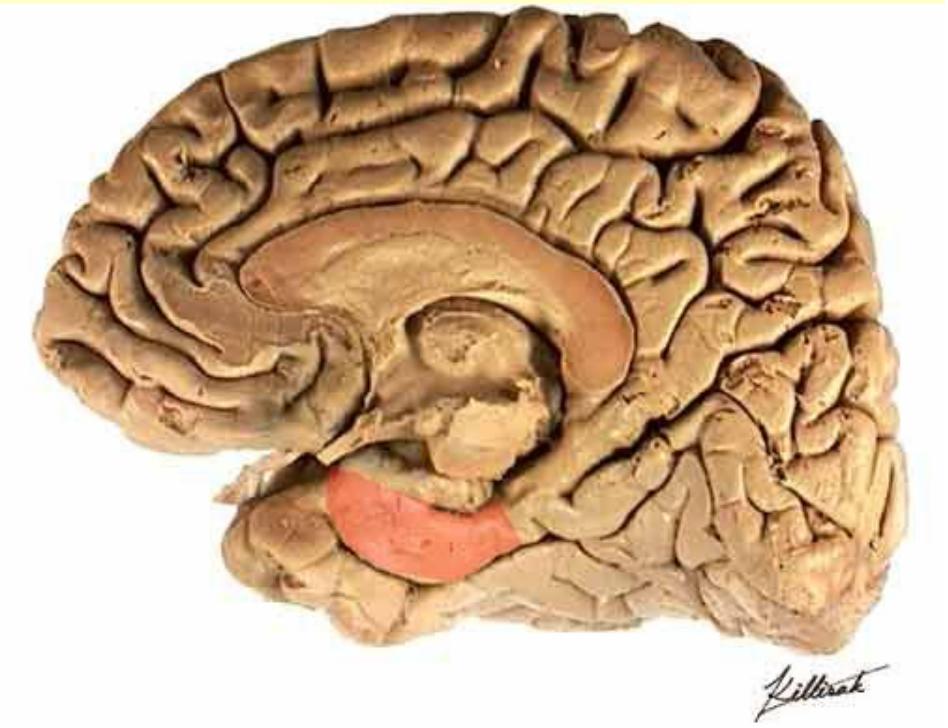
Pathology

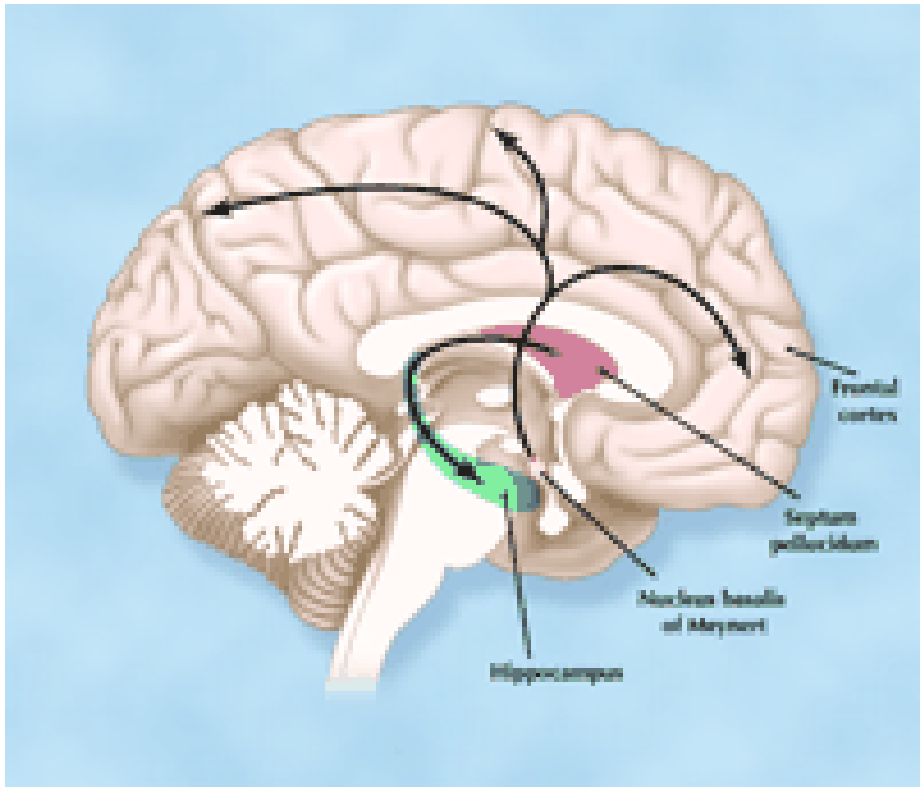
- Neuropathological hallmarks:
  - **Amyloid-rich neuritic plaques** -*extracellular* - abnormal insoluble amyloid (beta) protein fragments
  - **Neurofibrillary tangles** - *intracellular* - disturbed tau-microtubule complexes (hyperphosphorylated tau)

- Cholinergic system degeneration with significant loss of neurons in certain areas (such as Nucleus Basalis of Meynert)

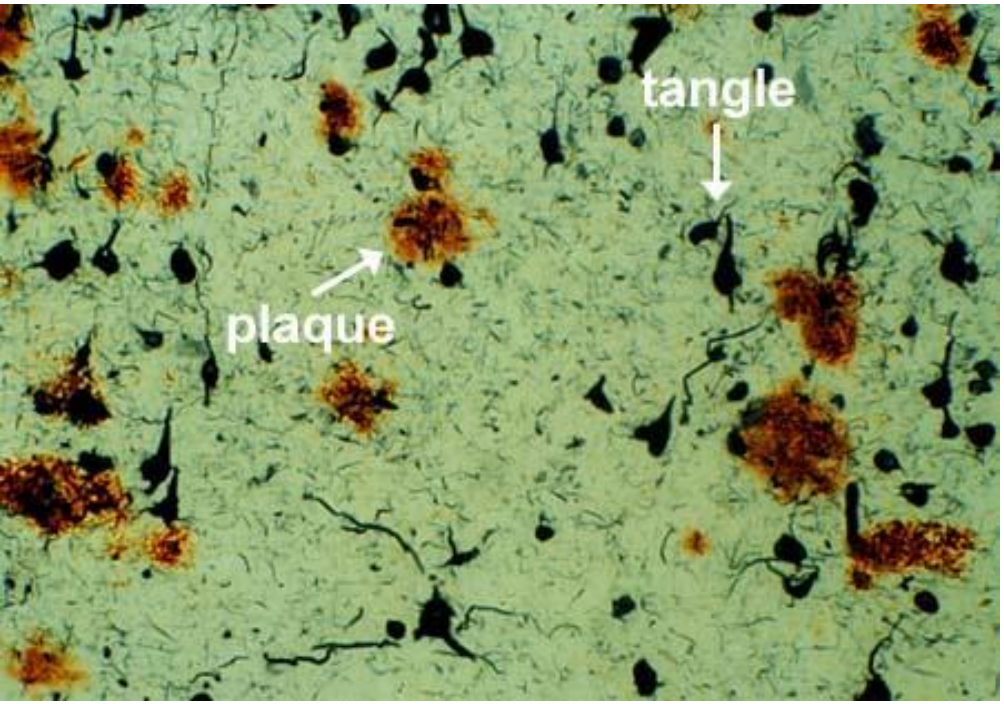
- Degeneration often begins in **entorhinal cortex** and progresses to other limbic structures

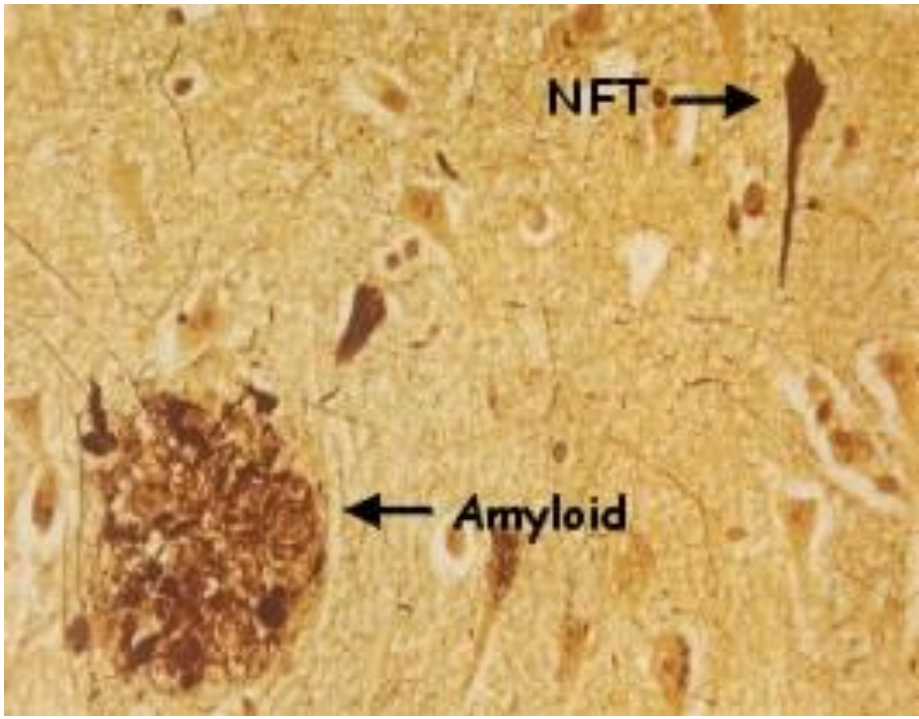

Formix
Cingulate cortex
Anterior thalamic nucleus
Mammillary bodies
Hippocampus
Entorhinal cortex

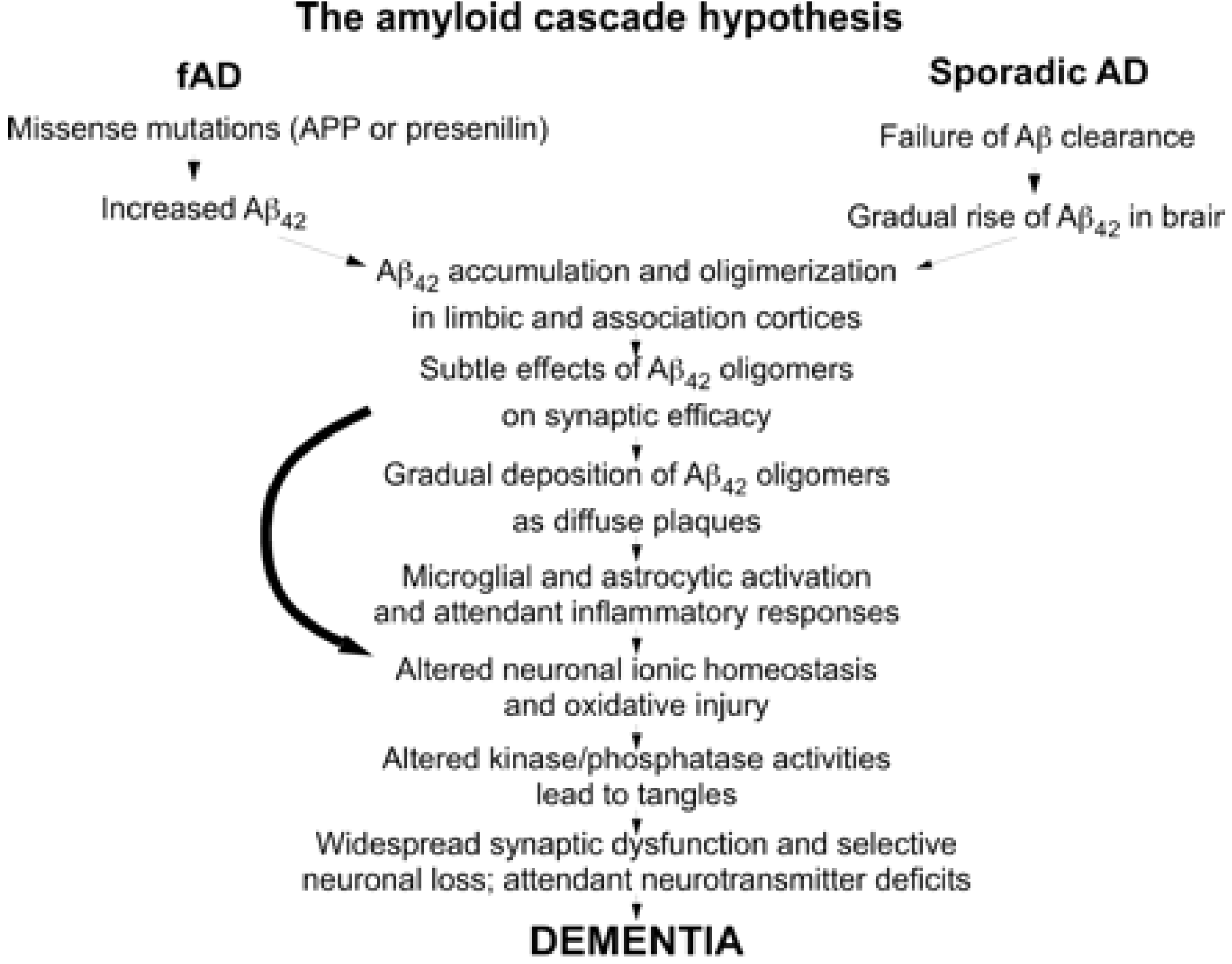


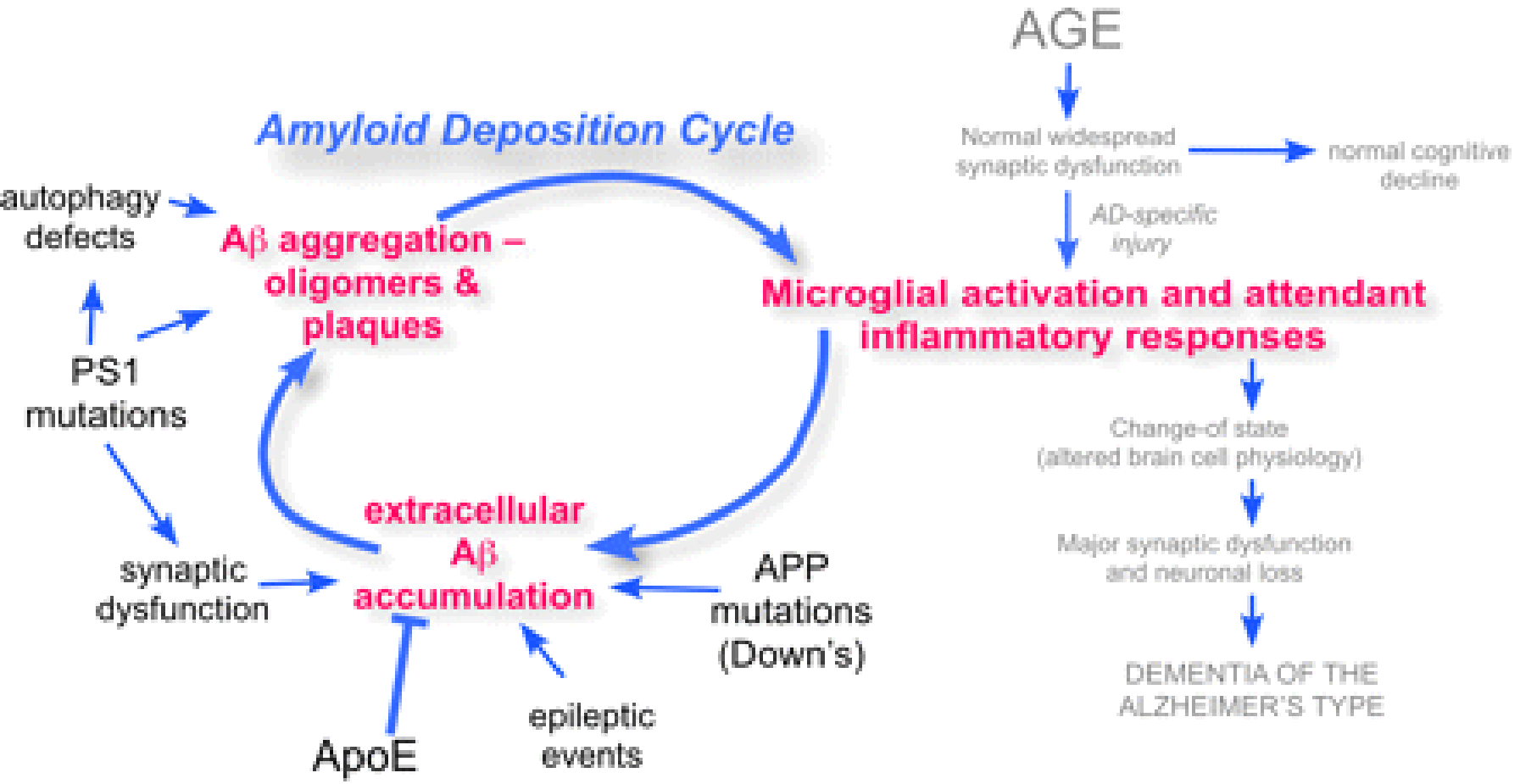

Frontal cortex
Septum pellucidum
Nucleus basalis of Meynert
Hippocampus

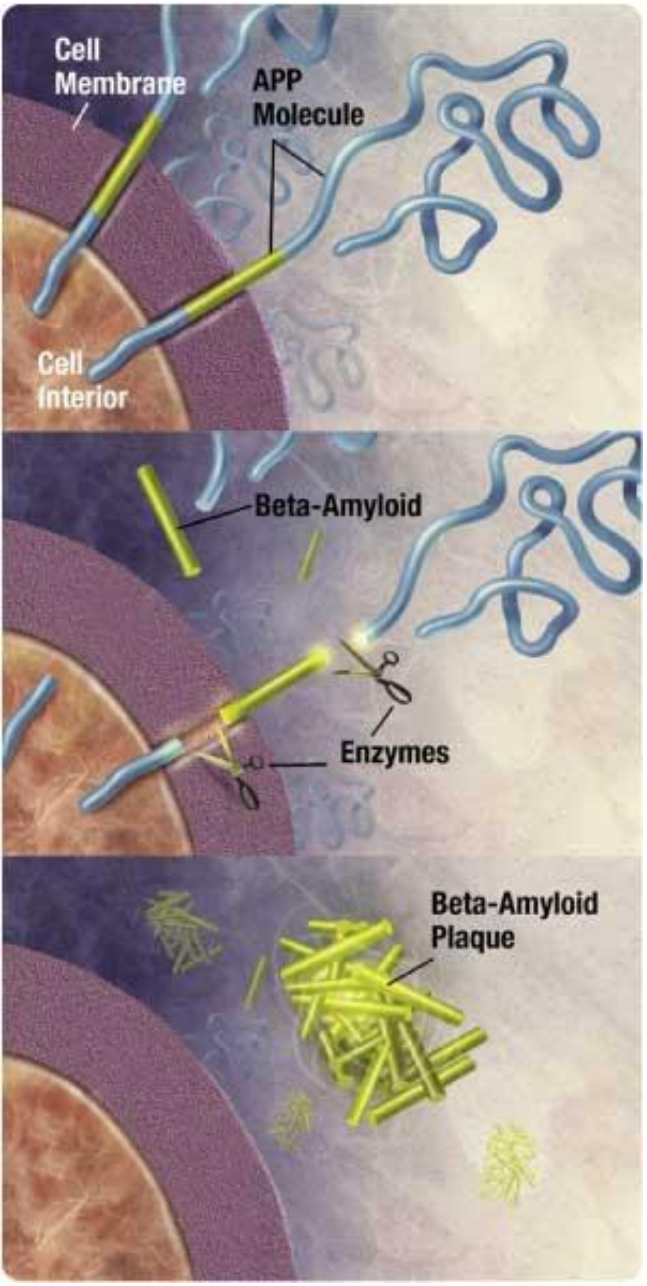
Pathology

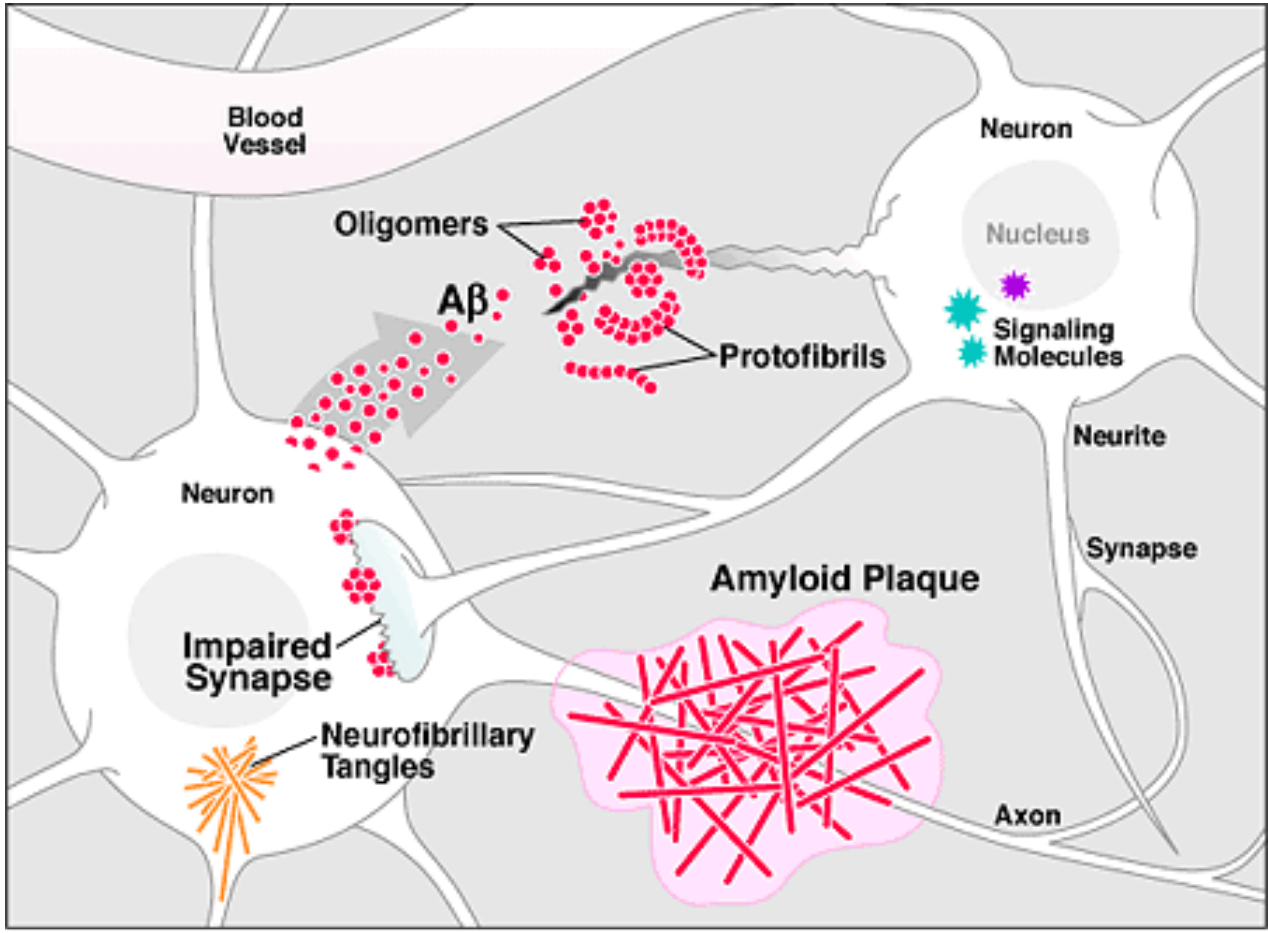





The amyloid cascade hypothesis
fAD
Sporadic AD
Missense mutations (APP or presenilin)
Failure of Aβ clearance
Increased Aβ42
Gradual rise of Aβ42 in brair
Aβ42 accumulation and oligimerization
in limbic and association cortices
Subtle effects of Aβ42 oligomers
on synaptic efficacy
Gradual deposition of Aβ42 oligomers
as diffuse plaques
Microglial and astrocytic activation
and attendant inflammatory responses
Altered neuronal ionic homeostasis
and oxidative injury
Altered kinase/phosphatase activities
lead to tangles
Widespread synaptic dysfunction and selective
neuronal loss; attendant neurotransmitter deficits
DEMENTIA


AGE
Amyloid Deposition Cycle
Normal widespread synaptic dysfunction
normal cognitive decline
AD-specific injury
autophagy defects
Aβ aggregation – oligomers & plaques
Microglial activation and attendant inflammatory responses
PS1 mutations
Change-of state (altered brain cell physiology)
extracellular Aβ accumulation
synaptic dysfunction
APP mutations (Down's)
Major synaptic dysfunction and neuronal loss
DEMENTIA OF THE ALZHEIMER'S TYPE
ApoE
epileptic events


Cell Membrane
APP Molecule
Cell Interior
Beta-Amyloid
Enzymes
Beta-Amyloid Plaque


Blood Vessel
Neuron
Oligomers
Nucleus
Aβ
Signaling Molecules
Protofibrils
Neurite
Neuron
Synapse
Amyloid Plaque
Impaired Synapse
Neurofibrillary Tangles
Axon

Pathophysiology

- Altered amyloid and tau protein metabolism
- Inflammation
- Oxidative stress
- Hormonal changes (Estrogen loss)

Risk Factors for AD

- Age
- Family history
- APOE 4 genotype
- Vascular risk factors
- Down's syndrome (trisomy 21)
- Head Trauma (esp. late in life)
- Late-onset depression (after age 65)
- Mild Cognitive Impairment (MCI)

Alzheimer Disease

- Most cases of AD are sporadic

- Familial forms of AD: Autosomal dominant AD, less than 5%

Genetic risk factors

- **Chromosome 19** - autosomal recessive - Apolipoprotein E-4 allele - associated with late-onset disease
- **Chromosome 1, 14, 21** - autosomal dominant mutations - associated with early-onset/familial cases. Amyloid processing genes.
  - The amyloid precursor protein (*APP*) gene on chromosome 21
  - The presenilin-1 (*PS1*) gene on chromosome 14
  - The presenilin-2 (*PS2*) gene on chromosome 1

Protective Factors in AD

- Education
- APO E 2

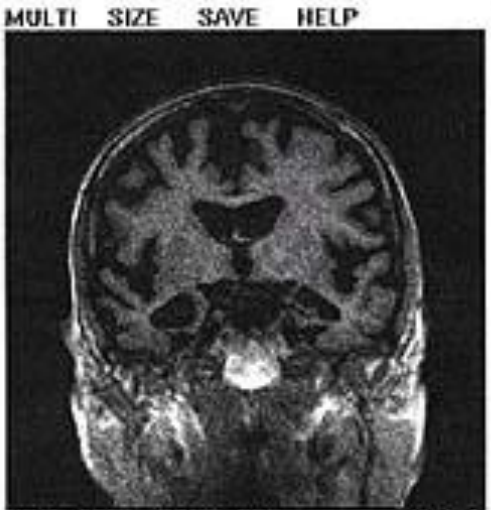
- Statin use?
- Anti-inflammatory agents ?
- Estrogen replacement therapy ??

Diagnosis

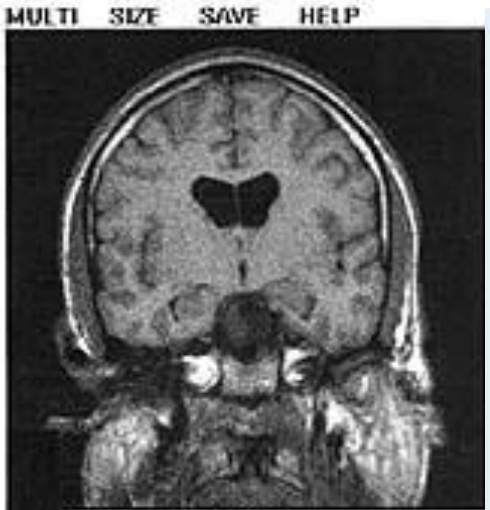
- Definitive diagnosis of AD : an autopsy or brain biopsy
- In clinical practice, the diagnosis is usually made on the basis of the history and findings on Mental Status Examination and radiologic evaluation ; Probable or possible AD

Alzheimer's Disease

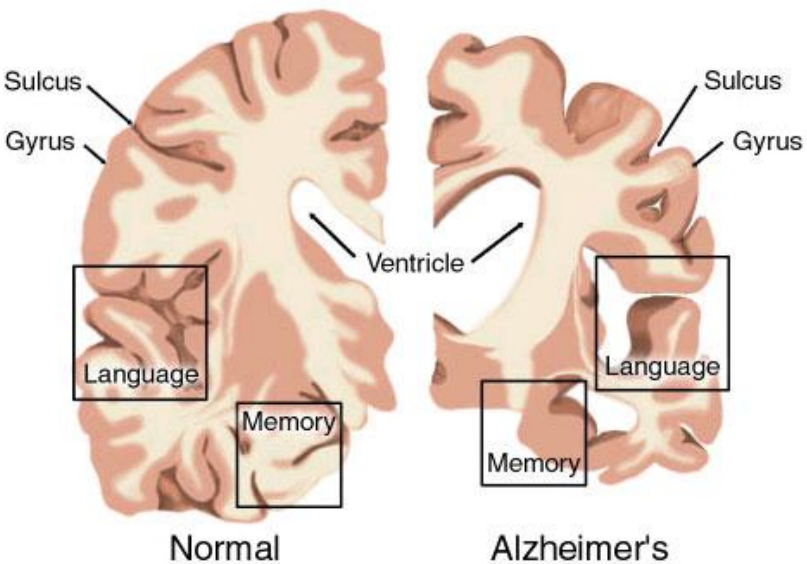
- Short-term memory impairment AND
- At least one of the following:
  - Aphasia - language impairments
  - Apraxia - motor memory impairments
  - Agnosia - sensory memory impairments
  - Abstract thinking / Exec. function impairments
- Impairment in social and/or occupational functions
- *At least one supportive test*
    - *CSF* Amyloid *β, total tau, fosfo tau levels*
    - *Retention in* Amyloid *PET*
    - *Medial temporal lobe atrophy in MRI*
    - *Temporoparietal hypometabolism in FDG PET*
- Not explainable by another disorder

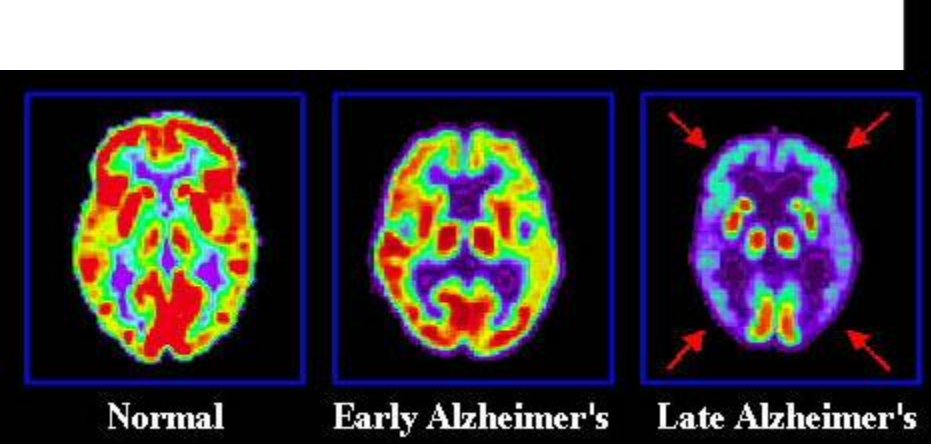


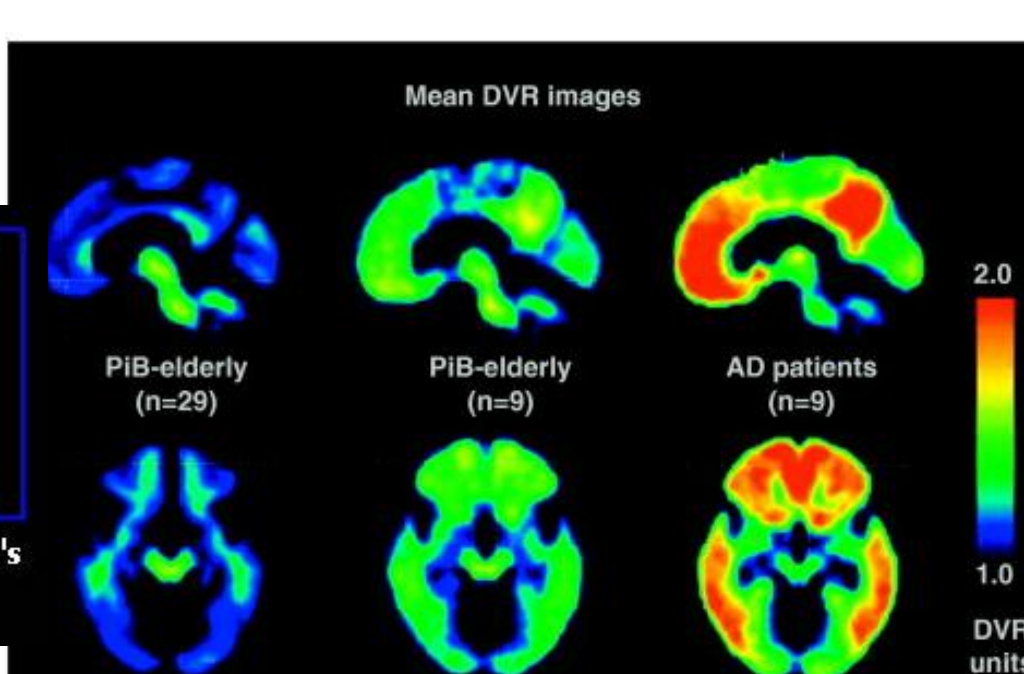
Brain with A.D



Normally Aged Brain







Treatment

- Symptomatic therapies
  - Cholinesterase inhibitors

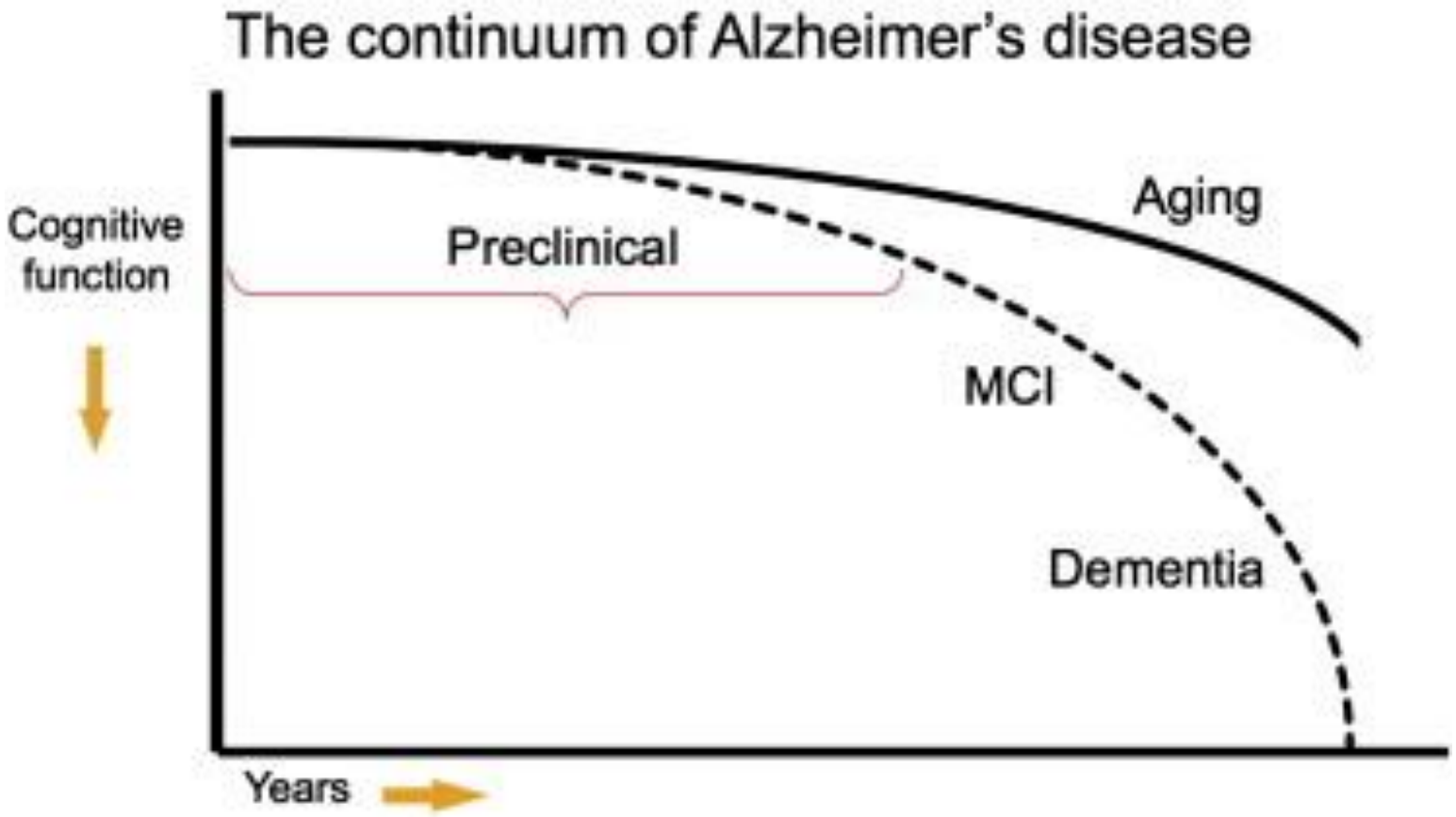
    These drugs block the esterase-mediated metabolism of acetylcholine to choline and acetate.

    This results in: Increased acetylcholine in the synaptic cleft

  - Partial *N* -methyl-D-aspartate (NMDA) antagonist

Treatment

- Treatment of secondary symptoms of AD (depression, agitation, psychosis and sleep disorders)


The continuum of Alzheimer's disease
Cognitive function
Aging
Preclinical
MCI
Dementia
Years

MCI

- Some congnitive dysfunctions
- Functional activities are largely preserved
- MCI does not meet the criteria for dementia

Dementia with Lewy Bodies (DLB)

1. The central feature : Progressive cognitive decline with social or occupational dysfunction
2. Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for possible DLB.

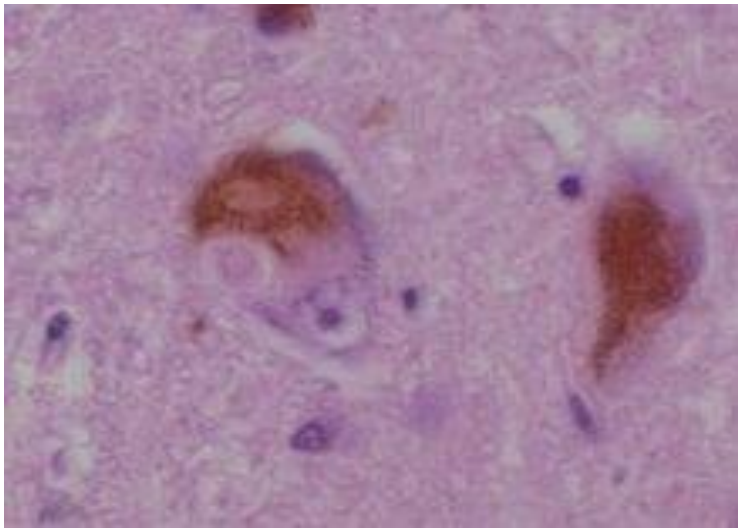
- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous motor features of parkinsonism

3. Features supportive of the diagnosis are

- repeated falls
- syncope
- transient loss of consciousness
- neuroleptic sensitivity
- systematized delusions
- hallucinations in other modalities.

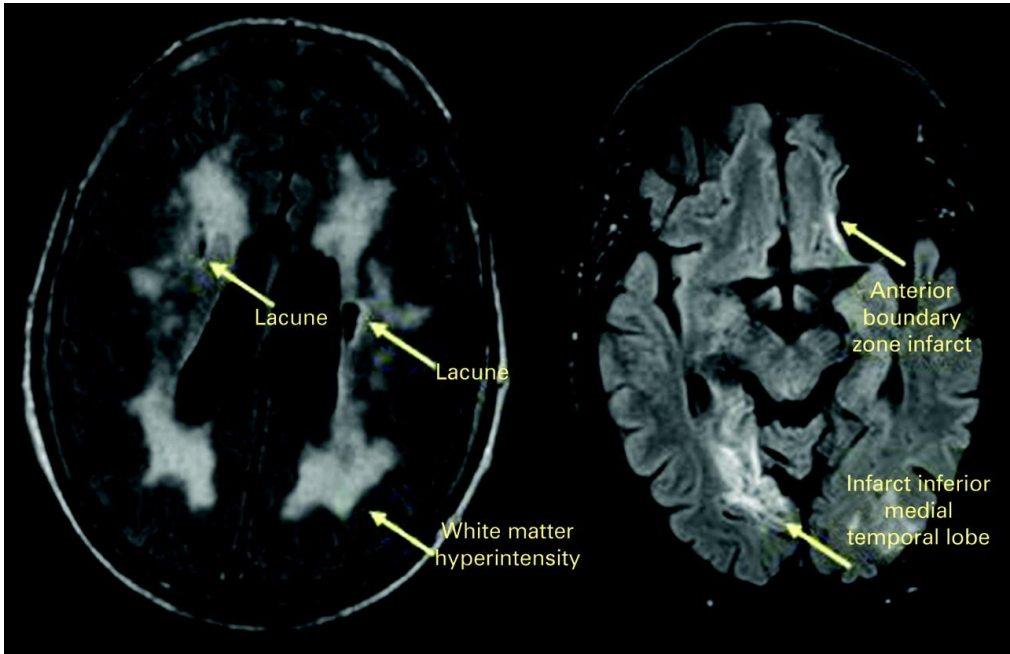
Lewy Body Pathology

- Concentric spheres found within vacuoles (eosinophilic cytoplasmic inclusions)
- Seen in *cortex, midbrain and brainstem neurons* in patients especially with Lewy Body dementias (also idiopathic parkinsonism)
- The main structural component is alpha-synuclein, a presynaptic protein, the function of which is unknown
- Neurofilament proteins and ubiquitin are other important constituents of LBs



Vascular Dementia

- The onset of cognitive deficits associated with a stroke
- Abrupt onset of symptoms followed by stepwise deterioration
- Findings on neurologic examination consistent with prior stroke(s)
- Infarcts on cerebral imaging



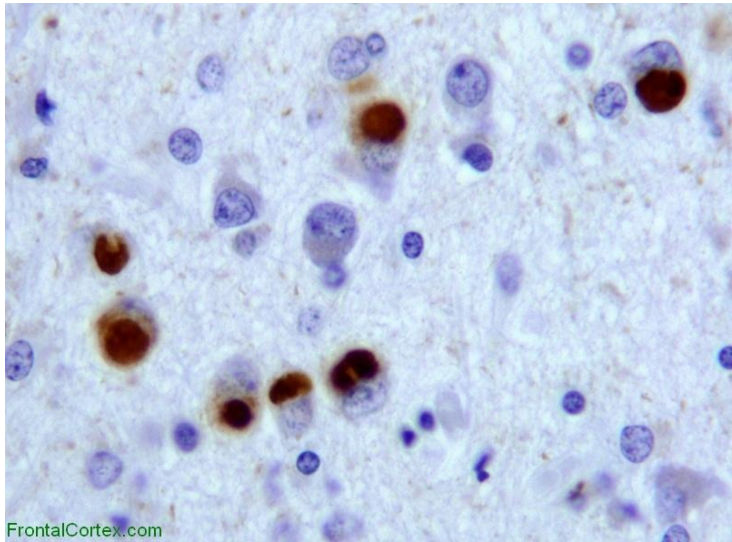
Frontotemporal Dementia

- Characterized by focal atrophy of the frontal and temporal lobes
- Clinically, presents with language abnormalities and behavioral disturbances.
- Pick's disease was the first recognized subtype of FTD, one that is characterized pathologically by the presence of Pick bodies

(silver staining intracytoplasmic inclusions)

in the neocortex and

hippocampus.



Frontotemporal Dementia

- Occurs between the ages of 35 and 75 years, and only rarely after age 75; the mean age of onset is the sixth decade
- Both sexes are equally affected.
- Familial occurrence occurs in 20 to 40 percent of cases and may be associated with a variety of identified mutations in the tau gene on chromosome 17
- Tau gene mutation also have seen in progressive supranuclear palsy (PSP),[13] corticobasal degeneration, and the amyotrophic lateral sclerosis (ALS)

Frontotemporal Lobe Dementia

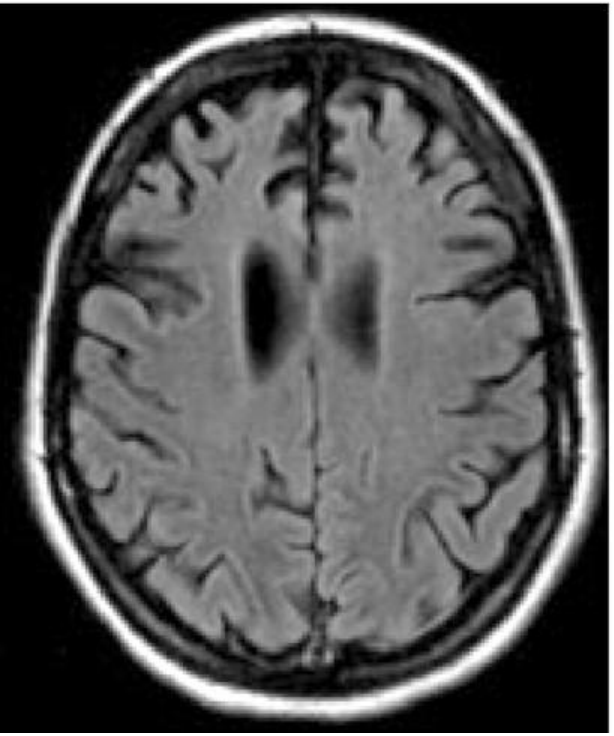
Core Features

- Insidious onset and gradual progression
- Early decline in social/interpersonal conduct
- Early impairment in personal conduct
- Early loss of insight
- Early emotional blunting

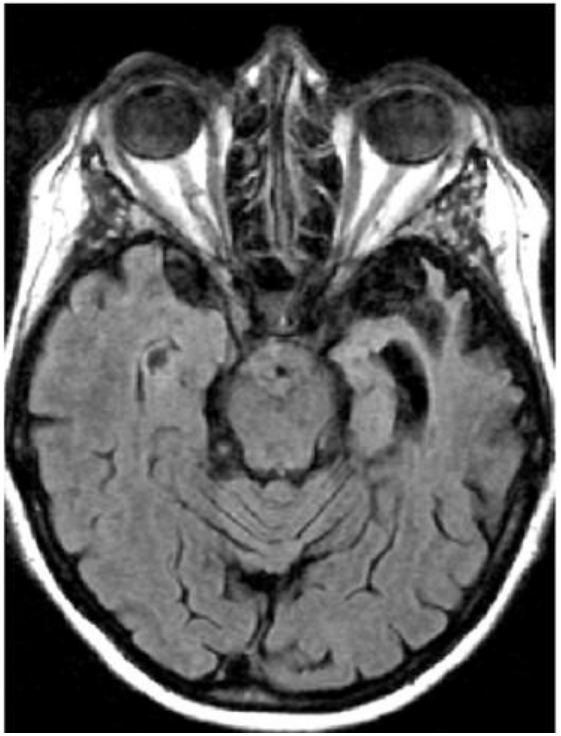
Supportive Features

- Behavior disorder – hygiene, grooming, mental rigidity, dietary changes, perseverative behavior
- Speech and language – perseveration, mutism, economy of speech
- Physical signs – akinesis, rigidity, tremor, labile BP

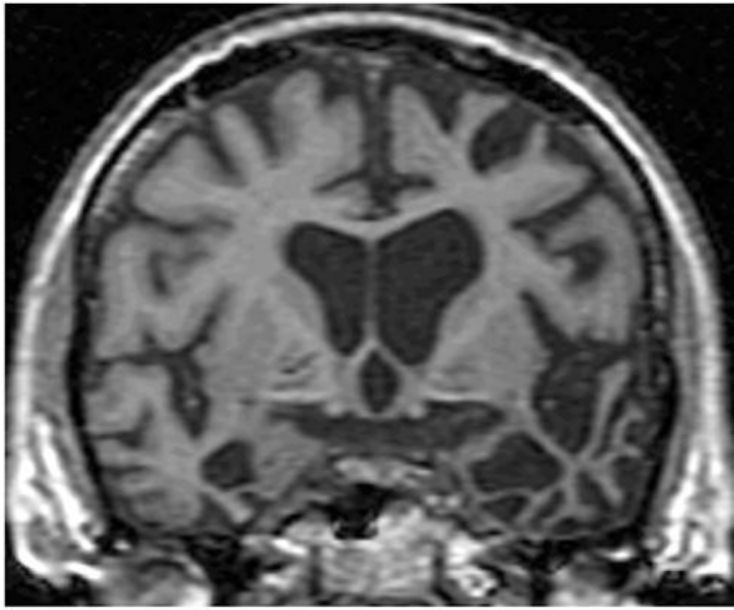
Frontotemporal dementia



Progressive non-fluent aphasia



Semantic dementia



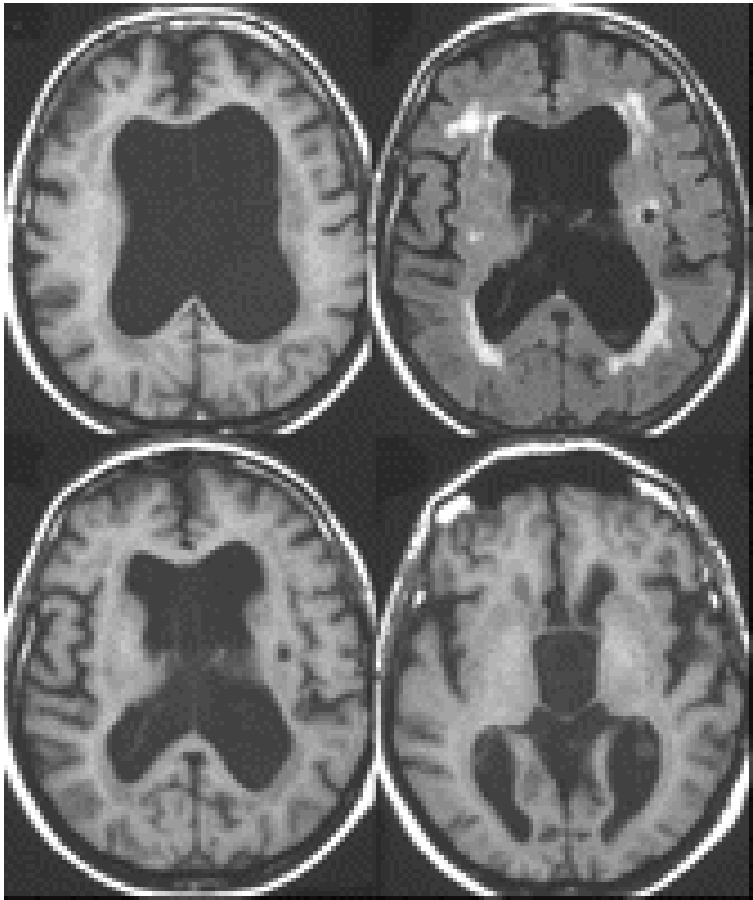
Parkinsonism and Dementia

- Parkinson Disease Dementia (PDD)

- Dementia with CBD, MSA, PSP

Normal-Pressure Hydrocephalus

- A condition of pathologically enlarged ventricular size with normal opening pressures on lumbar puncture
- Triad;
  - dementia
  - gait disturbance
  - urinary incontinence
- Reversible by the placement of a ventriculoperitoneal shunt



Dementia associated with infectious diseases

- HIV
- Prion diseases
- Neurosyphilis
- PML
- Encephalitis (Toxo, *Criptococus*, CMV, Herpes, Tbc, Lyme, Wipple, Brucella)
- SSPE

Metabolic Toxic Dementias

- Endocrinopathies: Hypotiroidism. Hypoparatiroidism, Cushing disease,
- Liver dysfunction
- Uremia
- Vitamine deficiencies (B12, Tiamin)
- Drugs; Anticholinergic , antihystaminic
- Alcohol abuse
- Heavy metals (arsenic, lead, mercury)
- Organic toxins (i insecticides, spreys)

Other Etiologies for Dementia

- Posttraumatic
- Slowly progressive intracranial mass
- Paraneoplastic

Reversible Reasons

- B12 deficiency
- Hypotiroidsm
- Other metabolic reasons
- NPH
- Some brain tumors
- Subdural hematoma

Pseudodementia

- Depression
- Schizophrenia

- Mental Reterdation is not dementia

Steps to take in Dementia Evaluation

- History
- Physical and Neurological Exam
- Cognitive Screening Test
- Rule out Reversible Causes
- Neuroimaging
- Consider the Etiology
- Treatment

History Taking and Examinations

- Get history also from caregiver or spouse
- Ask activities of daily living (Telephone, travel, shopping, meals, housework, medicine, money, bathing, dressing, grooming, toileting)

- Importance of Cognitive Screening
  - Establish a baseline level of functioning
  - Allows for objective documentation of cognition

Labwork

- Electrolytes
- BUN
- CBC
- Liver Enzymes
- TSH
- B12 Level
- Syphilis?
- Others only if clinical suspicion high

Neuroimaging

- CT, MRI
- Functional Imaging--not in initial workup