

# Overview of neurological changes in Alzheimer's disease

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# Alzheimer's disease



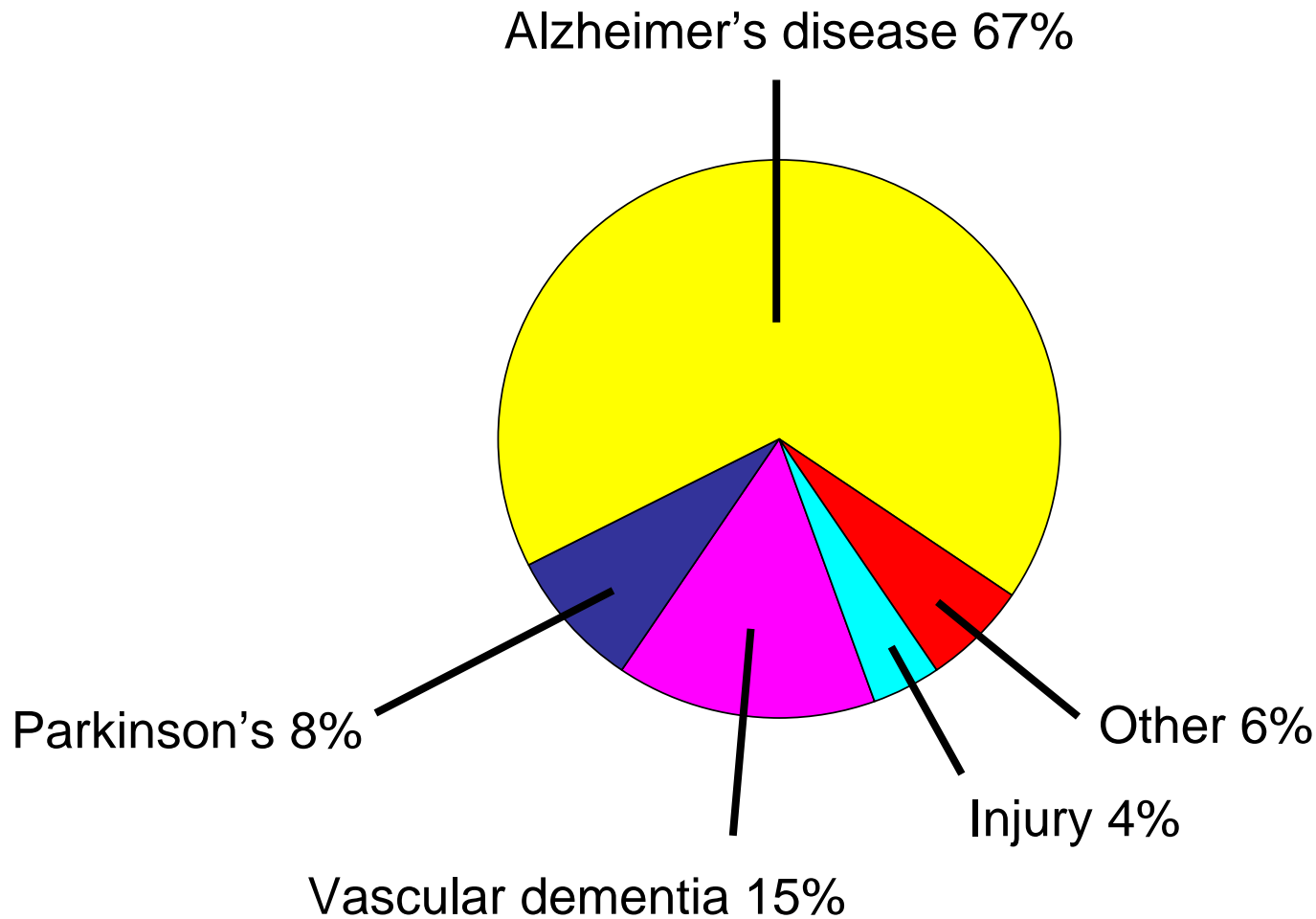
Alois Alzheimer  
1864-1915



Auguste D.  
1850-1906

Case presented November 26<sup>th</sup> 1906

# Alzheimer's disease –major cause of dementia



# AD – clinical features

AD is the most common cause of **dementia**:

*Evidence of a decline in memory and thinking which is of a degree sufficient to impair functioning in daily living, present for six months or more.*

**According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), dementia is defined as memory impairment (amnesia) plus one or more of the following:**

- **aphasia - difficulty with language**
- **apraxia - problems with complex movements**
- **agnosia - difficulty with identifying objects**
- **impaired executive functioning - making everyday decisions**

**Additional symptoms:**

- **Psychosis and agitation**
- **Mood change and apathy**

**Diagnosis:**

- **Possible** – atypical clinical features but no alternative diagnosis without histologic confirmation
- **Probable** – typical clinical diagnosis without histologic confirmation
- **Definite** – clinical diagnosis plus histologic confirmation

# Mini-Mental State Exam

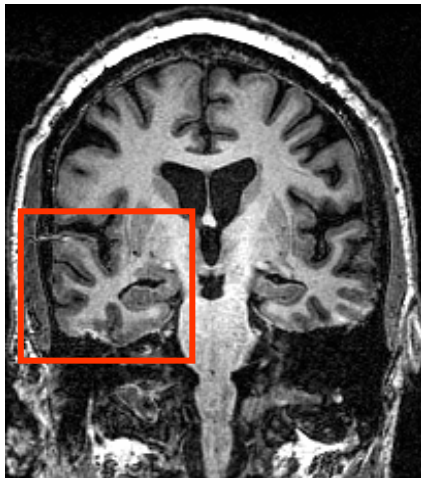
<b>Orientation</b> What is the (year) (season) (date) (day) (month)? Where are we: (country) (city) (part of city) (number of flat/house) (name of street)?	5 5
<b>Registration</b> Name three objects: one second to say each. Then ask the patient to name all three after you have said them. Give 1 for each correct answer. Then repeat them until he learns all three. Count trials and record.	3
<b>Attention and calculation</b> Serial 7s: 1 for each correct answer, stop after five answers. Alternatively spell 'world' backwards.	5
<b>Recall</b> Ask for the three objects repeated above. Give 1 for each correct answer.	3
<b>Language</b> Name a pencil and watch (2). Repeat the following: 'No ifs, ands or buts' (1). Follow a three-stage command: 'Take a paper in your right hand, fold it in half and put it on the floor' (3). Read and obey the following: Close your eyes (1). Write a sentence (1). Copy a design (1).	9

Total = 30

# AD - pathology

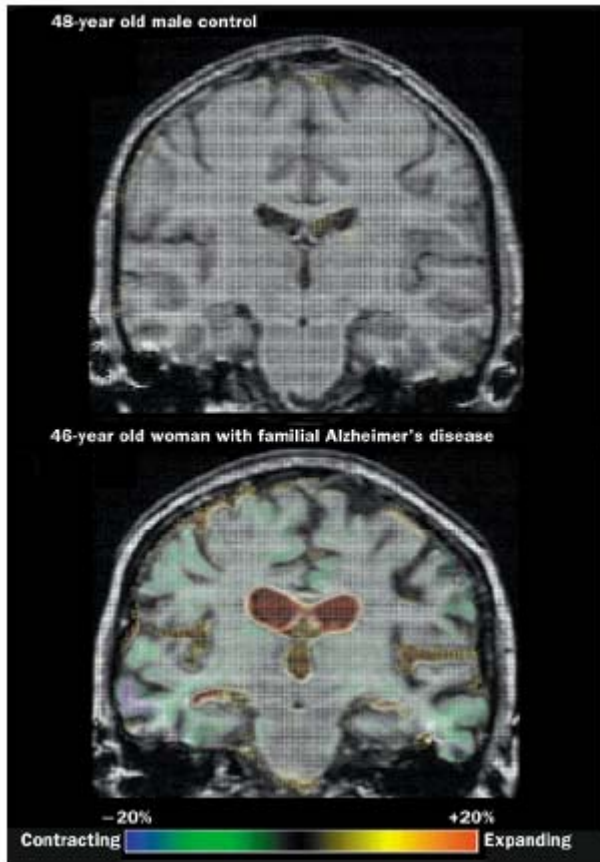
Normal

AD



# AD - pathology

## 'Subtractive' MRI



48 year old control over 11 months

46 year old AD patient over 14 months

### Global loss of brain matter/year

Controls = 0.24%

At risk individuals = 1.0%

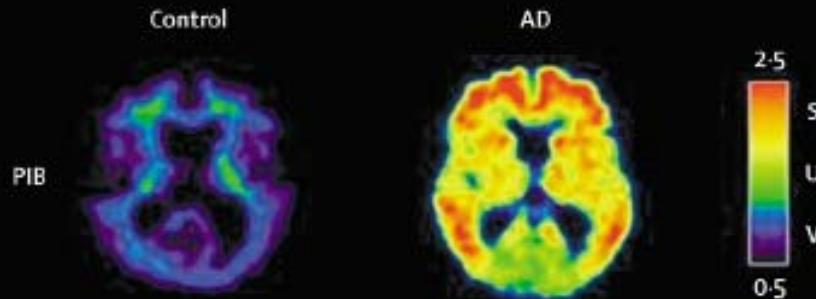
Mild to moderate AD = 2.20%

# Imaging pathology in the AD brain

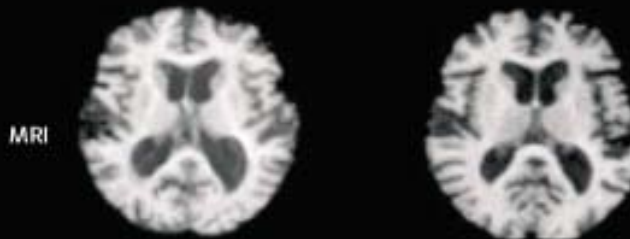
71 years  
MMSE 30

69 years  
MMSE 21

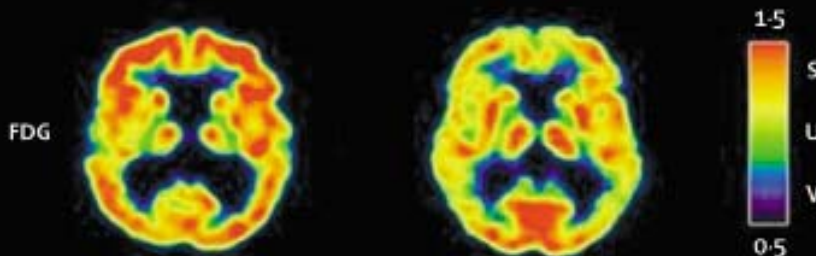
Amyloid  
plaques



Brain  
tissue

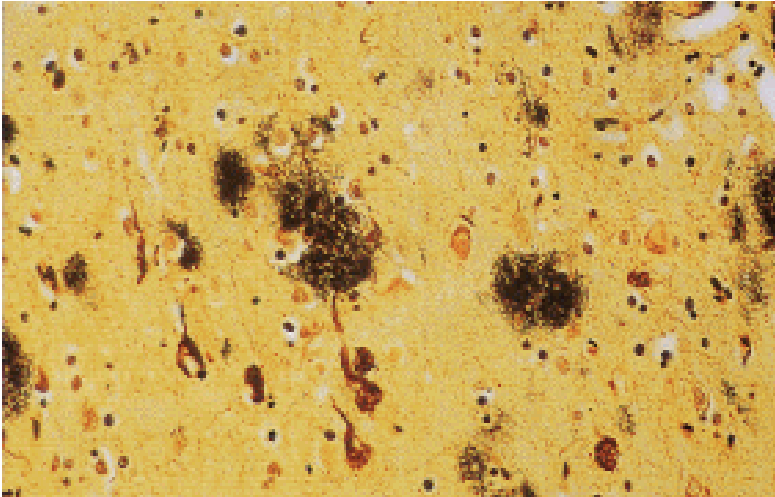


Oxygen  
use



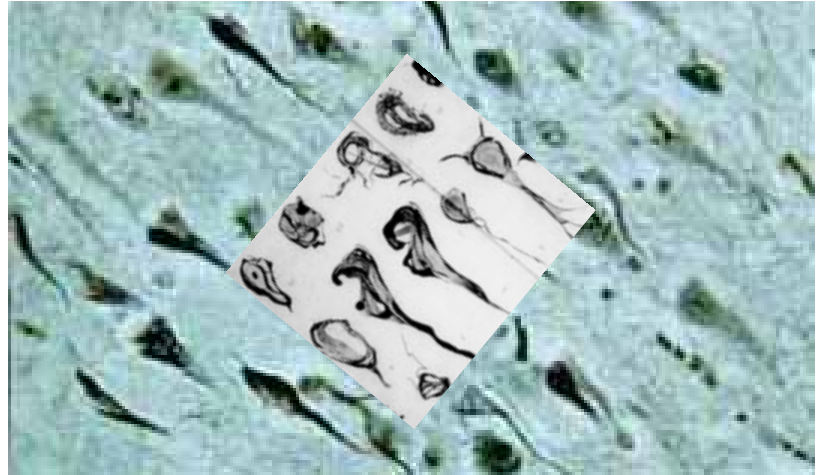
# AD- Pathophysiology

Plaques



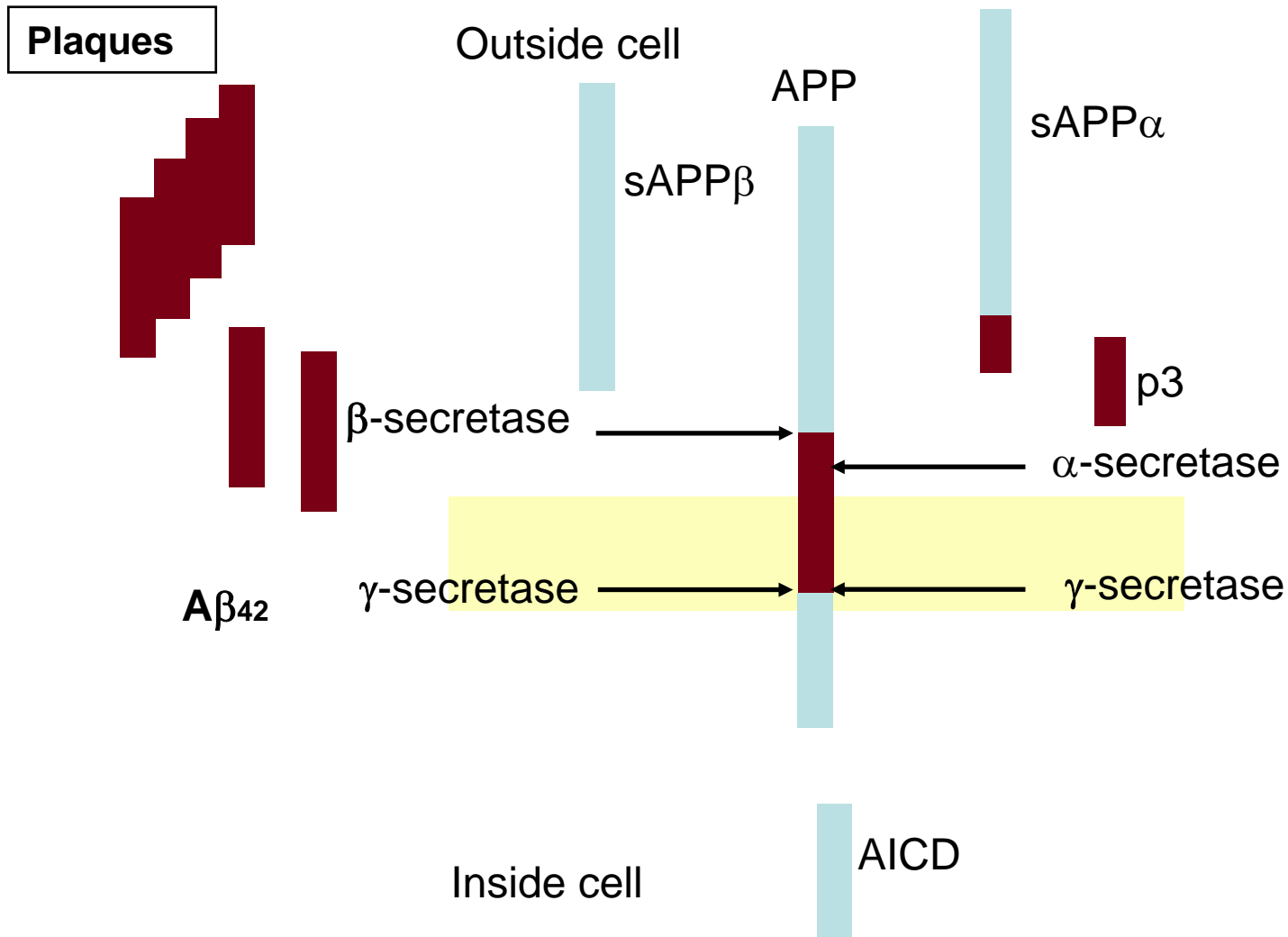
Largely A $\beta$  peptide

Tangles

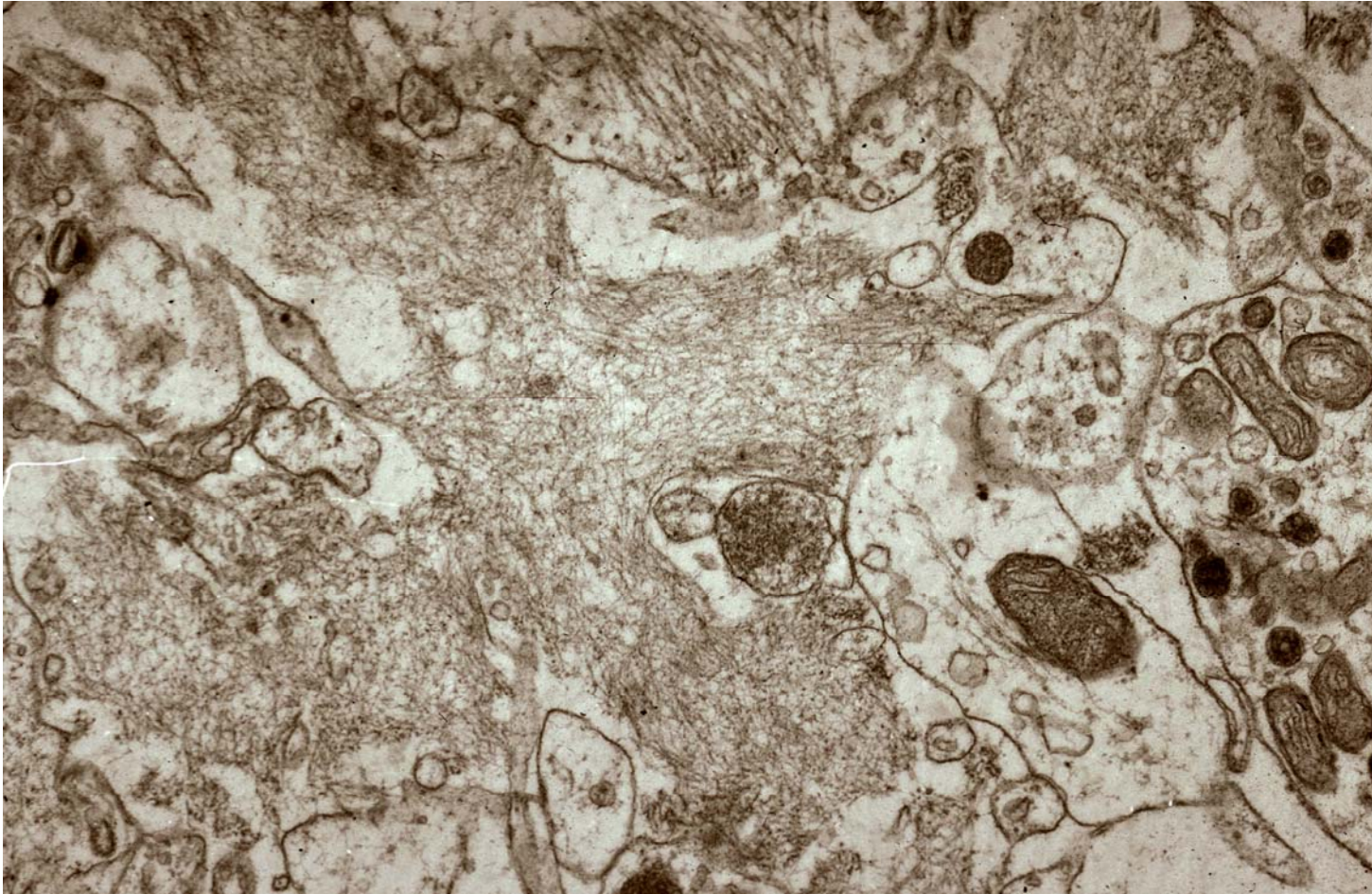


Hyperphosphorylated  
tau filaments

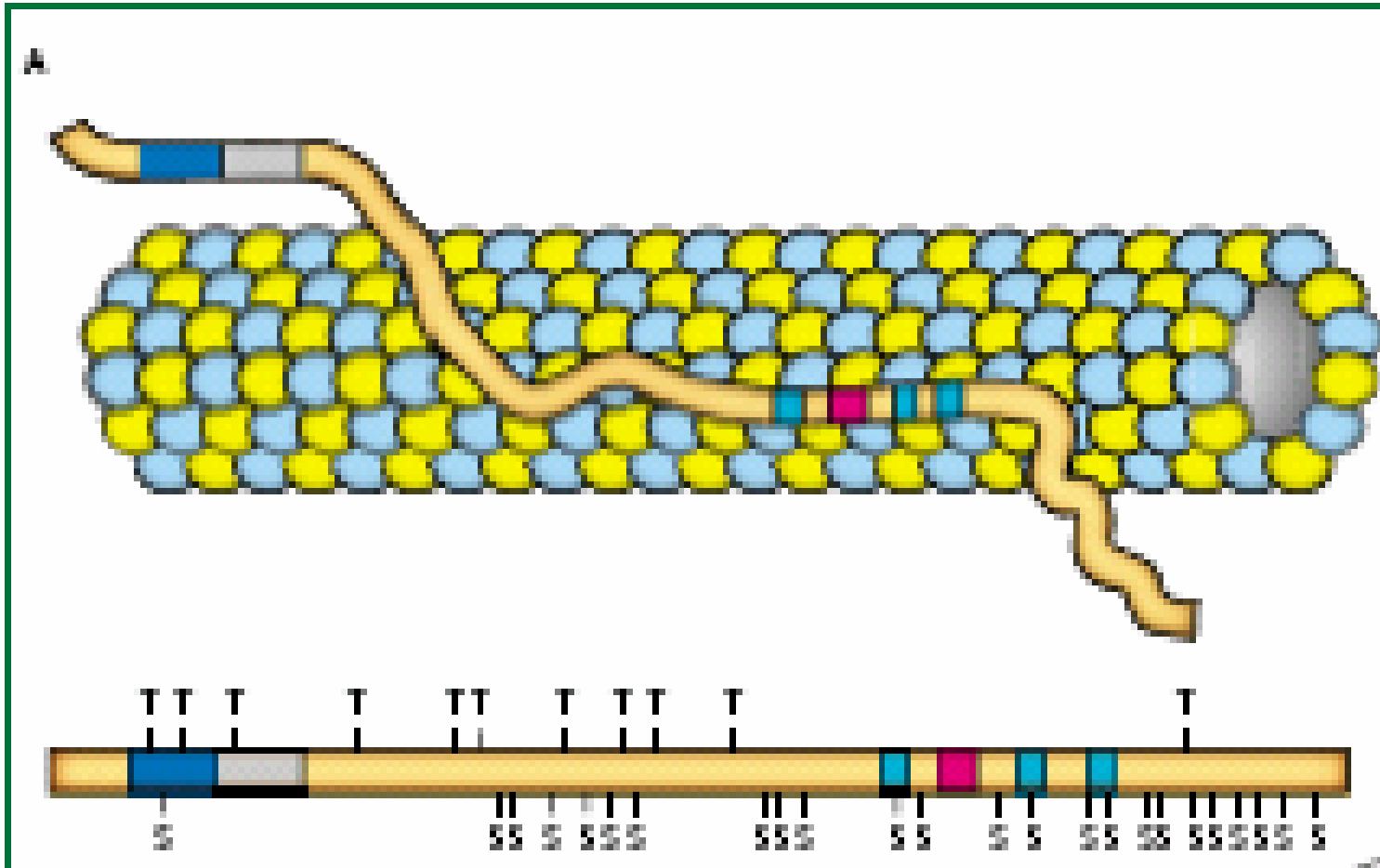
# APP metabolism – 2 pathways



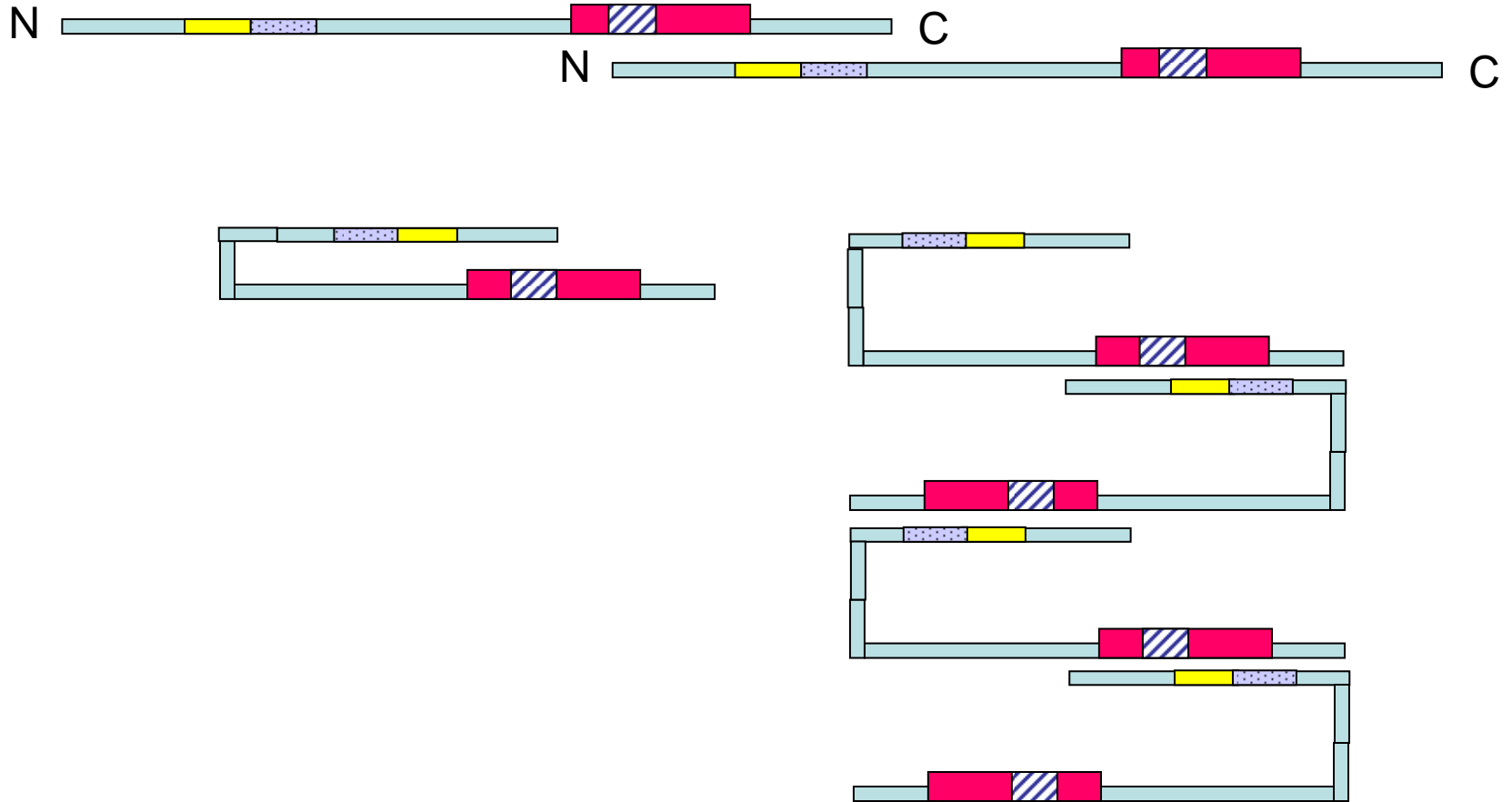
**Amyloid plaque is fibrillar and extracellular.**



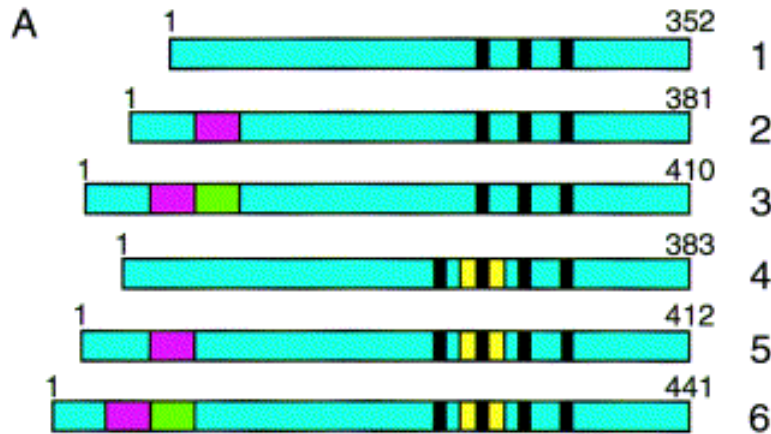
# Tau protein: intracellular role in stabilizing microtubules



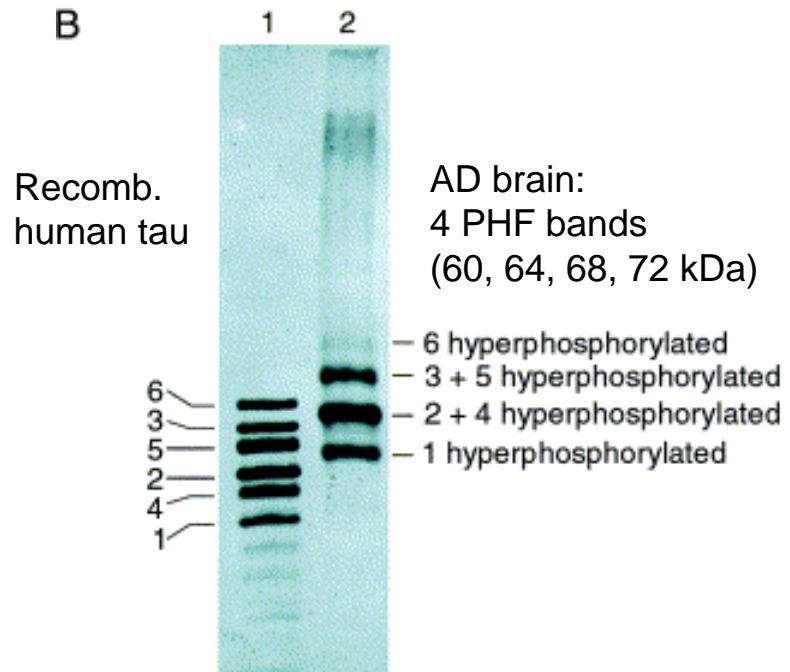
# Tau – can form aggregates in AD



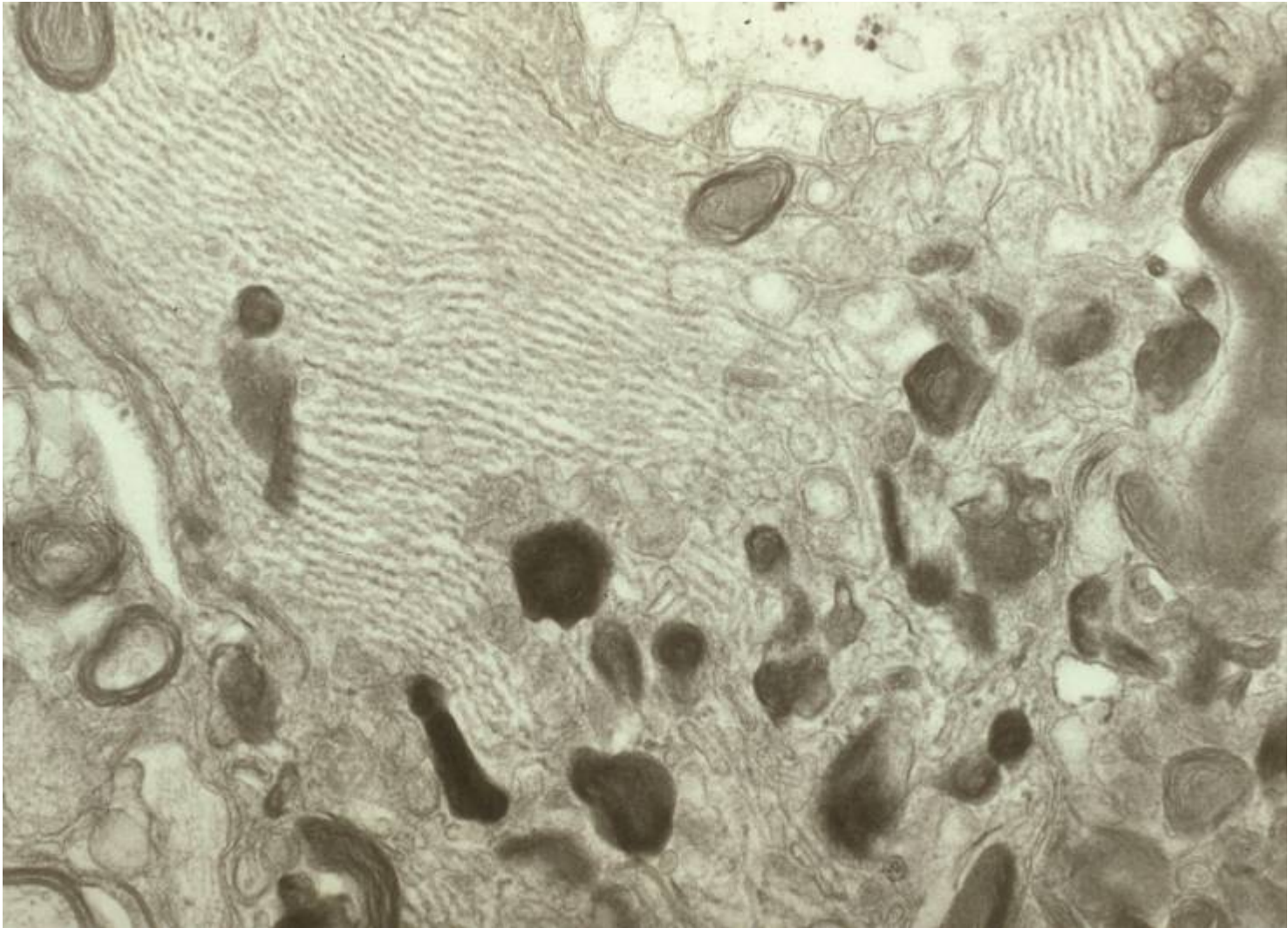
# Tau – multiple forms of the protein and multiple phosphorylations



Hyperphosphorylation reduces ability of tau to bind to microtubules



Spillantini & Goedert (1998)



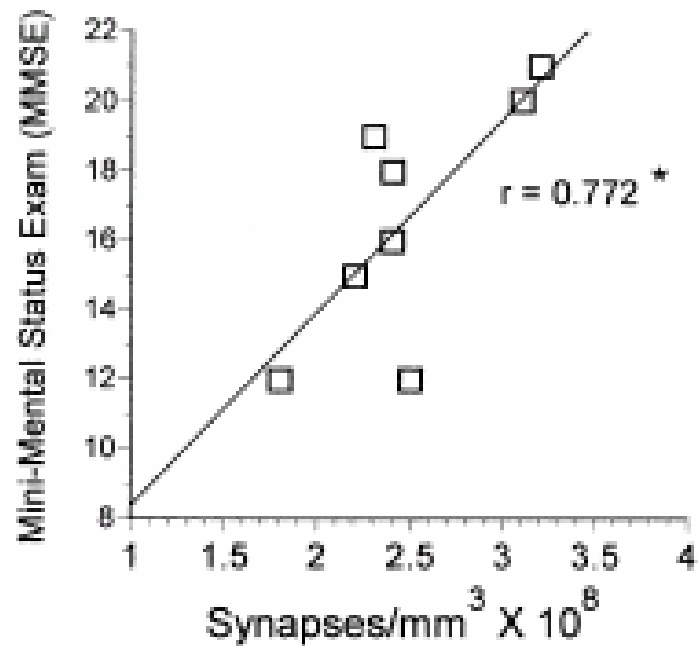
**Axon in plaque with PHF and dense bodies near the synapse.**



**The tangle is made up of paired helical filaments (PHF) composed of hyperphosphorylated Tau.**

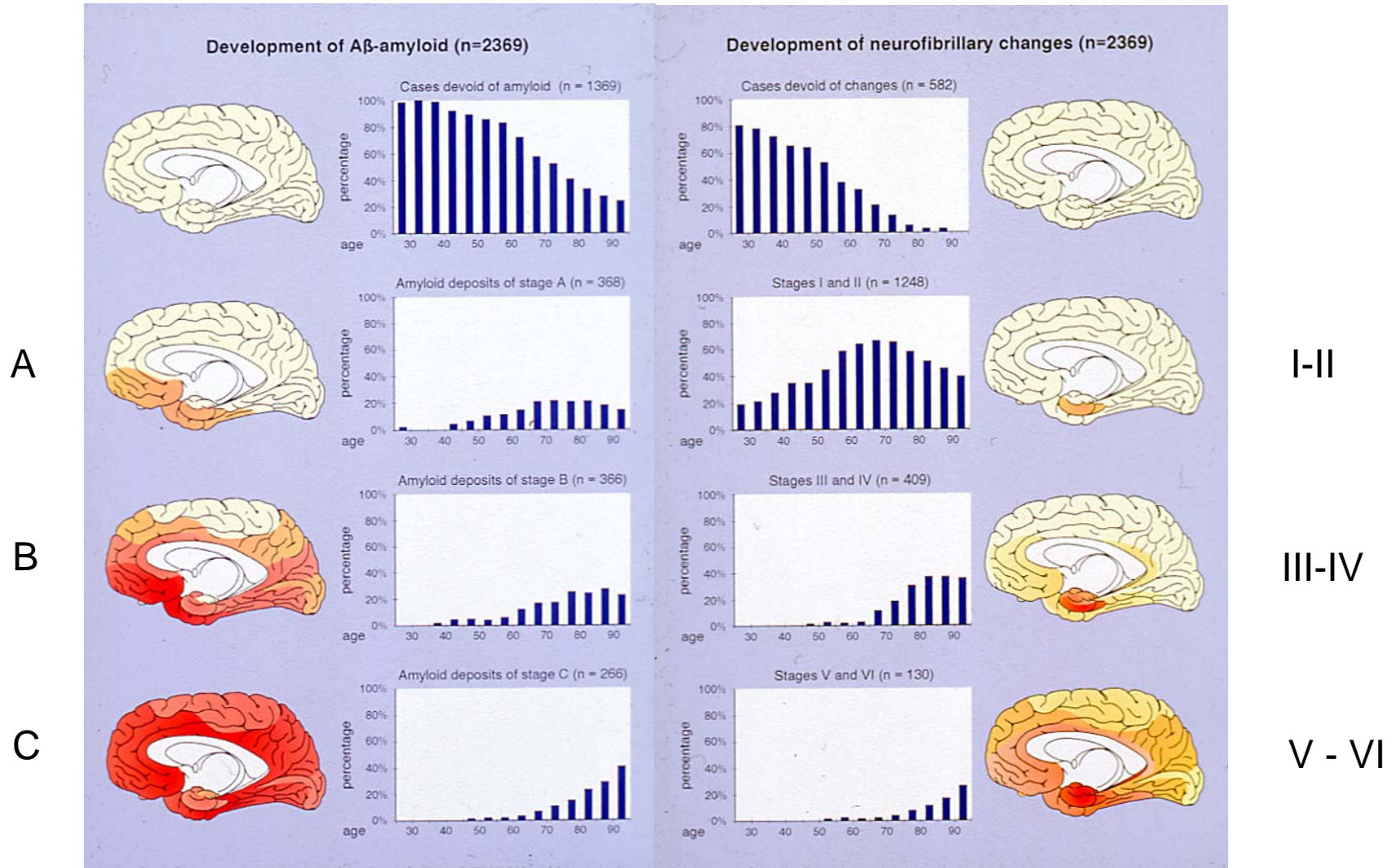
# What causes dementia in AD?

- Loss of synapses
- Loss of neurons

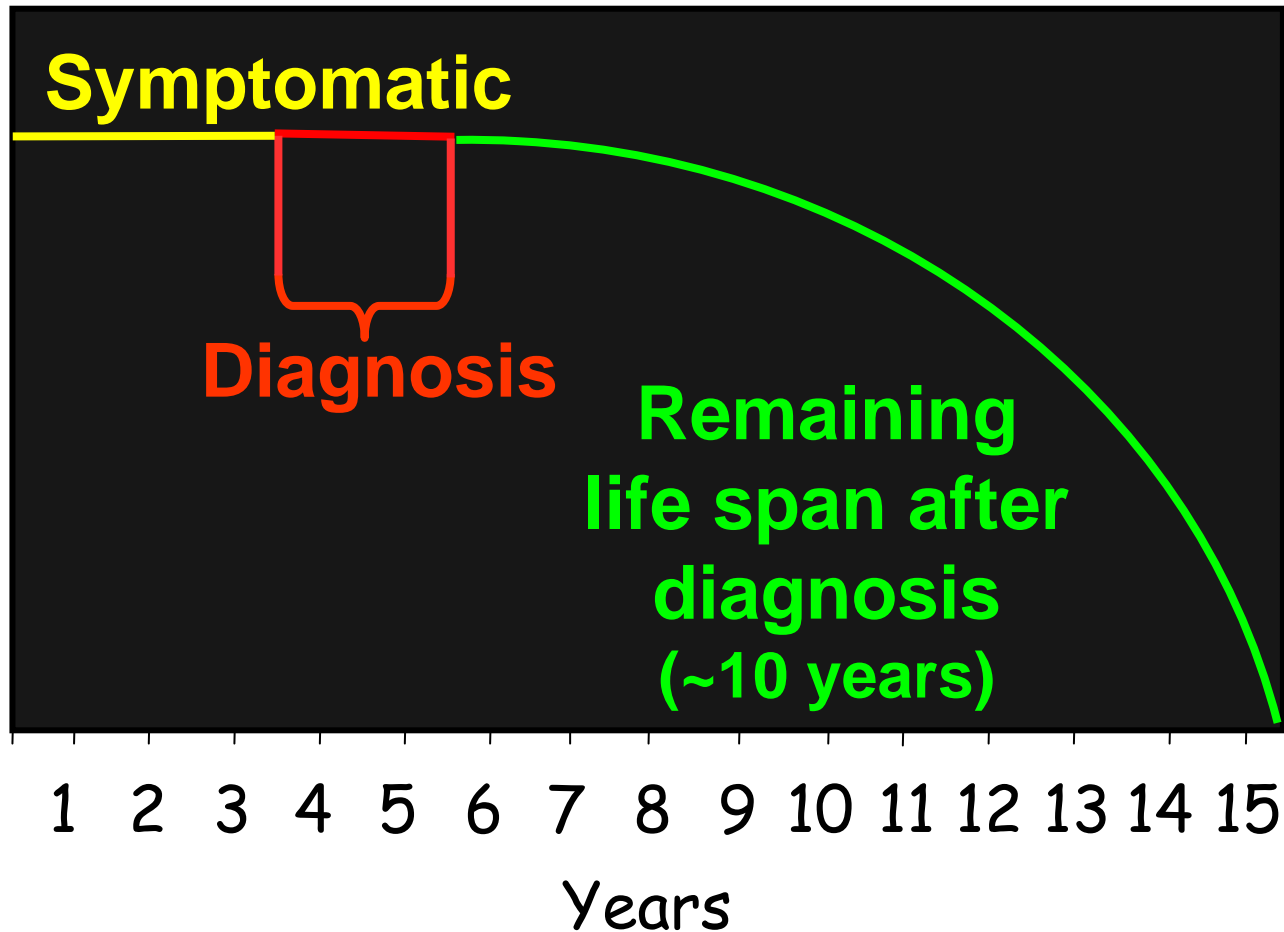


Frontal cortex – Price 2003

# The progression of AD



# Disease progression



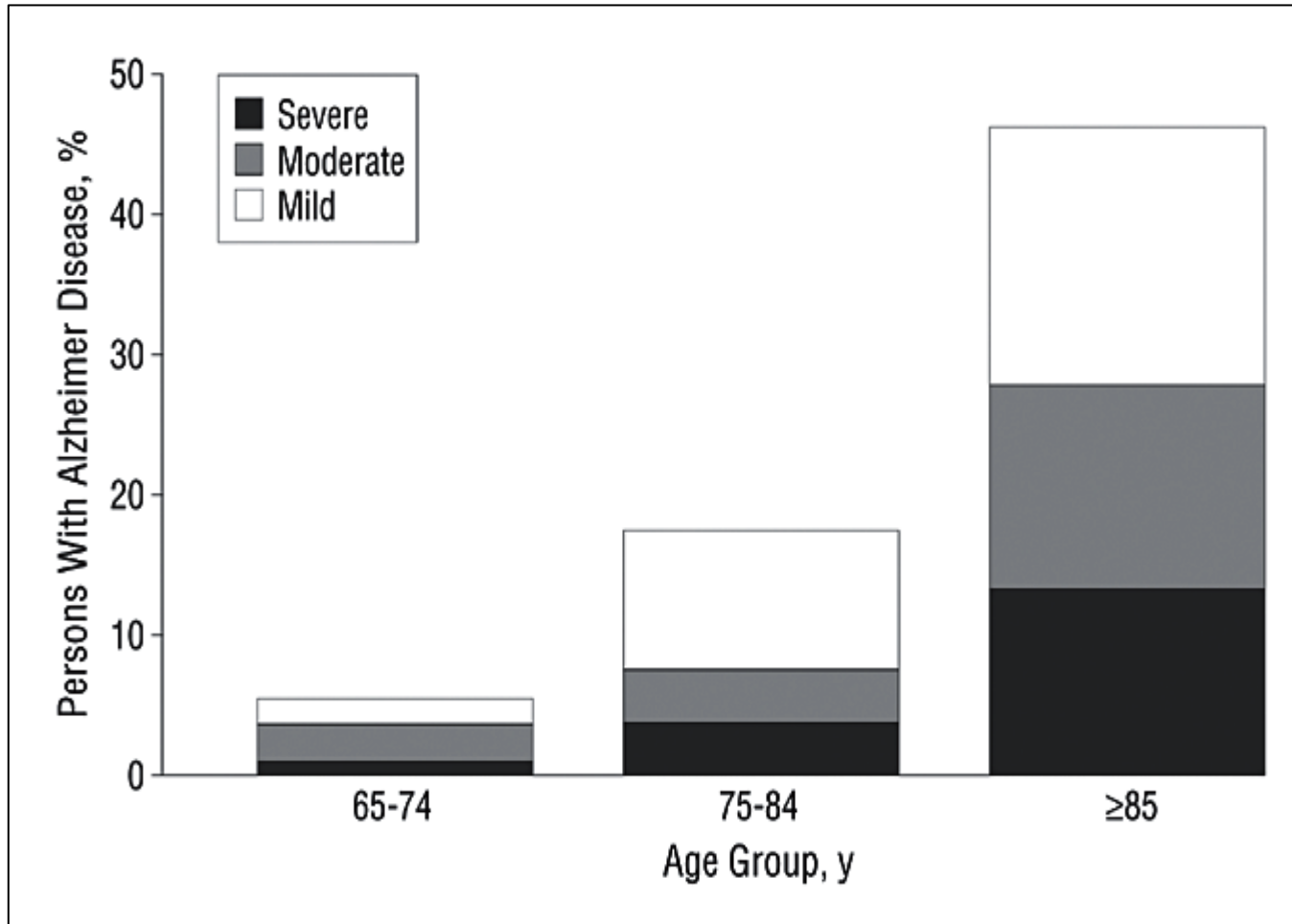
# AD Staging and cognitive decline

<b><i>Stage</i></b>	<b><i>Pathology</i></b>	<b><i>Cognitive domain</i></b>
I – II 'transentorhinal'	Entorhinal Cortex Mild involvement of HPC (CA1)	Episodic memory
III – IV 'limbic'	EC / HPC subiculum (mild), Basal forebrain, Some cortical (frontal / temporal)	Executive function  Working memory
V – VI 'isocortical'	Severe cortical association areas, amygdala, thalamic, striatal, SN	Extensive deficits not restricted to cognition

# AD, PD, MS comparison

	<b>Alzheimer's disease</b>	<b>Parkinson's disease</b>	<b>Multiple sclerosis</b>
<b>Age of onset</b>	increases with age, most >60	increases with age, mean 62	20 – 35
<b>Gender distribution</b>	slight increase F	slight increase M	F>>M
<b>Patients in U.S.</b>	4.3 million	~ 500,000	~ 300,000
<b>Initial clinical course</b>	insidious, gradually progressive	insidious, gradually progressive	relapsing/remitting
<b>Cognitive/behavioral change</b>	Early; most prominent	Normal early; change with advanced disease	May occur, especially with progression.
<b>Motor system change</b>	Mild parkinsonism in ~20%	Early change; bradykinesia, rigidity, resting tremor	Yes, many manifestations

# Prevalence of AD - USA



# Summary

- The pathology of AD has been rigorously documented: plaques and tangles are the hallmarks of the disease
- The actual mechanism(s) by which neurons are killed in the disease remain(s) obscure
- There are no therapies currently available that prevent or slow the progression of the disease
- Current symptomatic therapies offer only modest improvements in cognitive performance for a limited period of time.