

# **Dementia and ‘Healthy Ageing’: is the pathology any different?**

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# DEMENTIA

Loss of connectivity within association neocortex  
and hippocampus

Multiple causes,

Mostly neurodegenerative

Some vascular/infective/toxic/traumatic/tumour

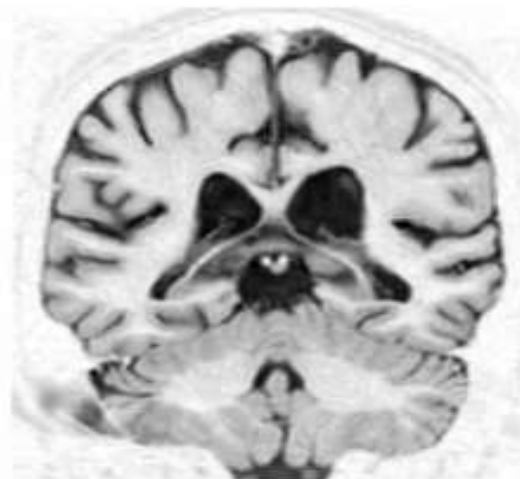
# MAJOR CAUSES OF DEMENTIA

- **Alzheimer's disease**
- **Parkinson's disease dementia and Lewy body dementia**
- **Cerebrovascular disease and 'multi-infarct dementia**
  
- Frontotemporal dementia and related disorders
- Corticobasal Degeneration and Progressive Supranuclear Palsy
- Creutzfeldt-Jakob disease and related disorders
- Huntington's disease
- Motor Neurone Disease dementia

# ALZHEIMER'S DISEASE

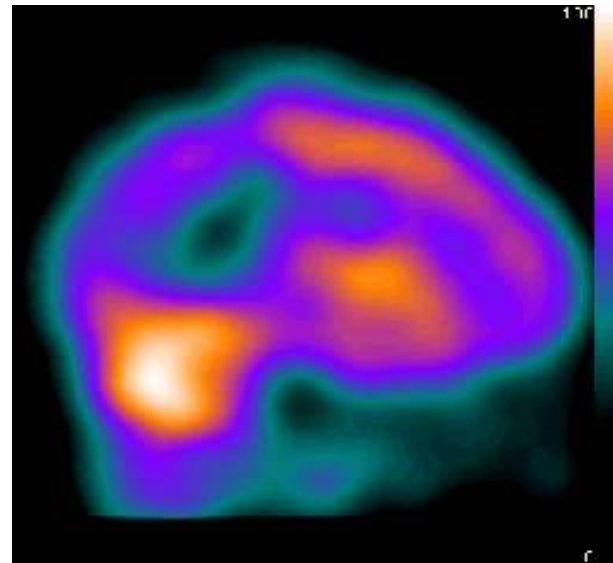
## CLINICAL

- Amnesia
- Aphasia
- Visuospatial disorder
- Apraxia



## RADIOLOGICAL

- Cerebral atrophy
- Ventricular dilatation
- Reduced tracer uptake in posterior parietal cortex



# GROSS PATHOLOGY OF ALZHEIMER'S DISEASE



**NORMAL**

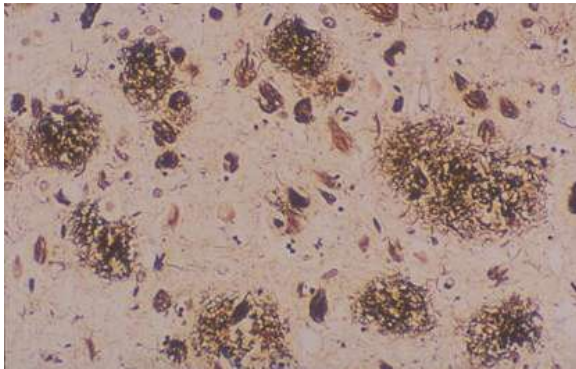


**AD**

- **CEREBRAL ATROPHY**
- **VENTRICULAR DILATATION**
- **DECREASED BRAIN WEIGHT**

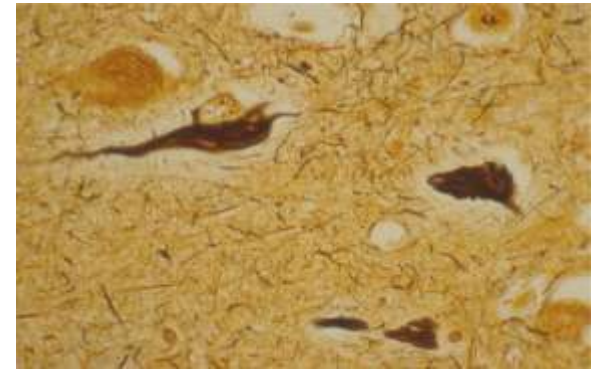
# HISTOPATHOLOGY

## “classic lesions”

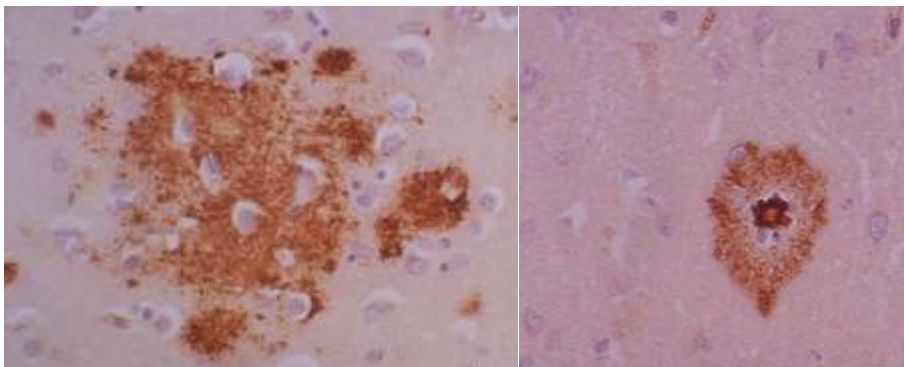


**Senile Plaque**

**Silver**

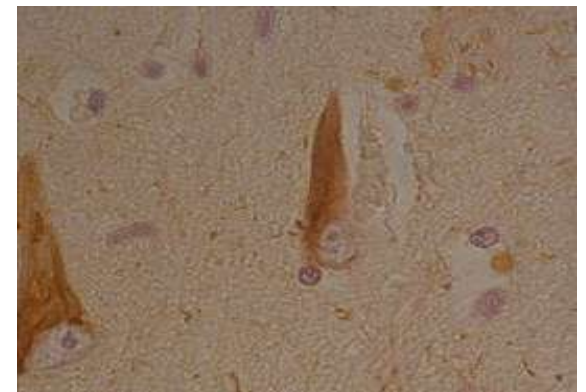


**Neurofibrillary Tangle**



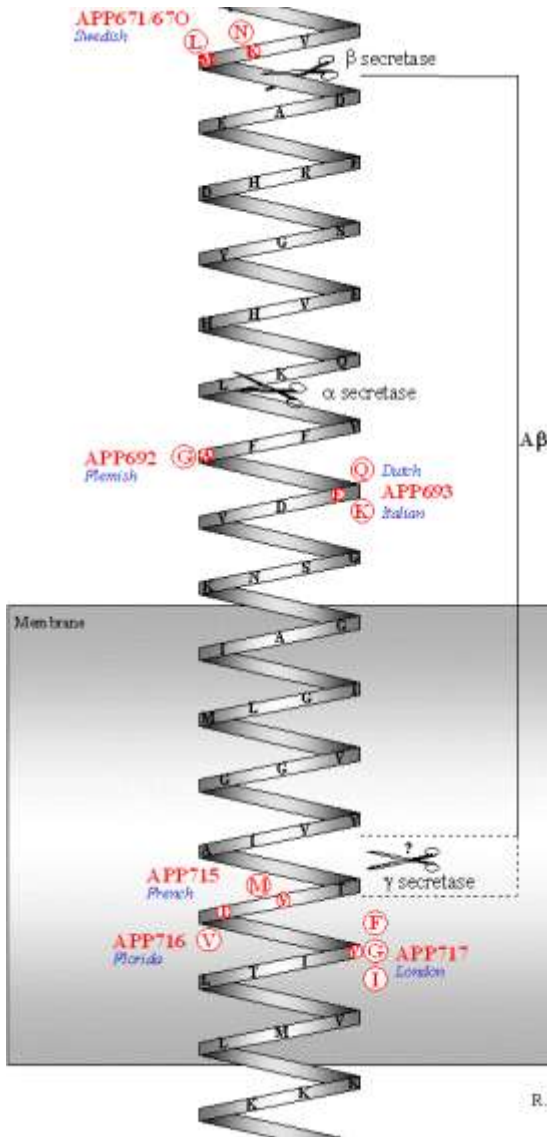
**$\beta$ -amyloid**

**IHC**

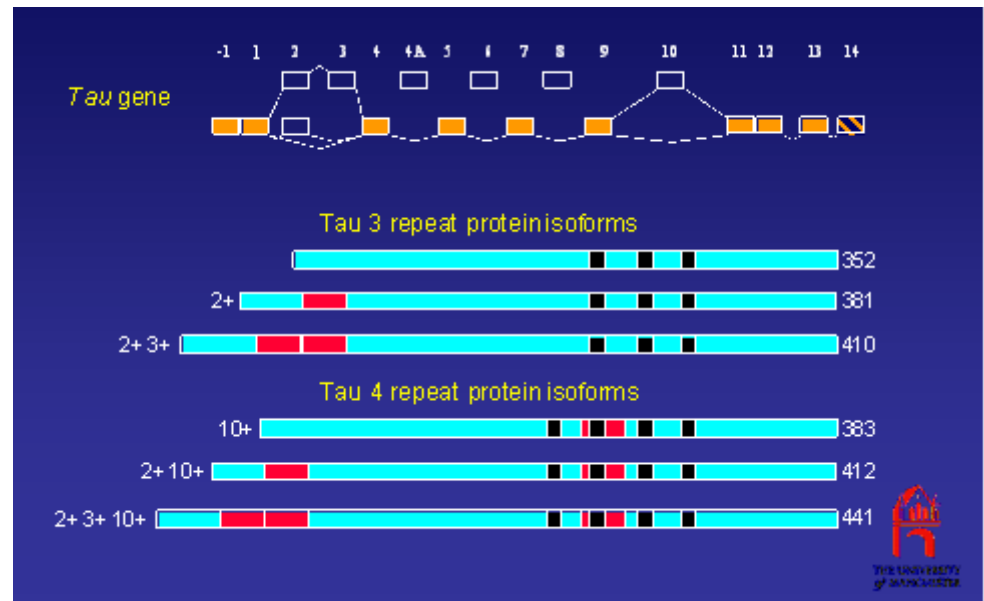


**tau**

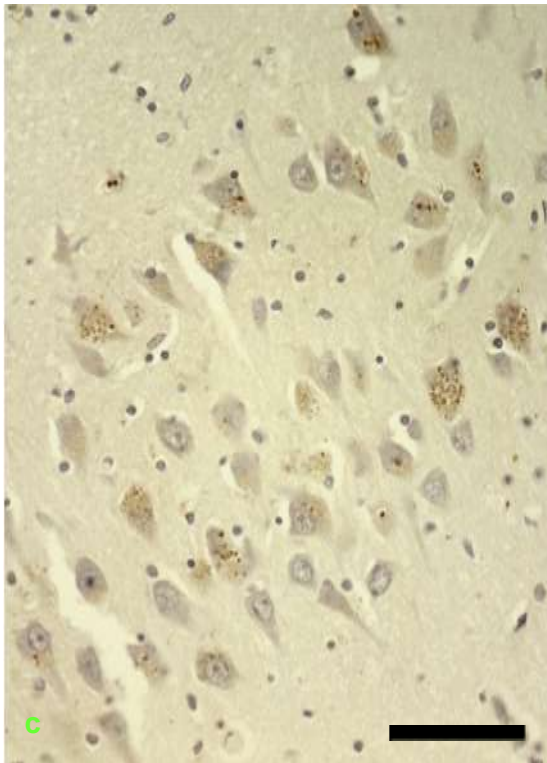
# β-amyloid and tau



R. Crook & J. Hardy



# **PIN1 CHANGES (Granulovacuolar Degeneration)**



**Hippocampus**

**Mostly CA2 and CA1  
Pyramidal cells**



# **PARKINSON'S DISEASE**

## **(Parkinson's disease dementia Lewy body dementia)**

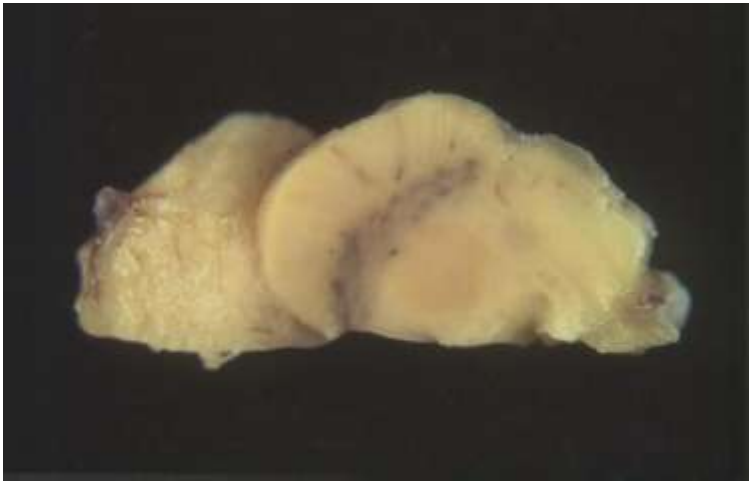
### **Clinical**

Fluctuating cognitive decline  
Delusions, hallucinations  
Parkinsonism

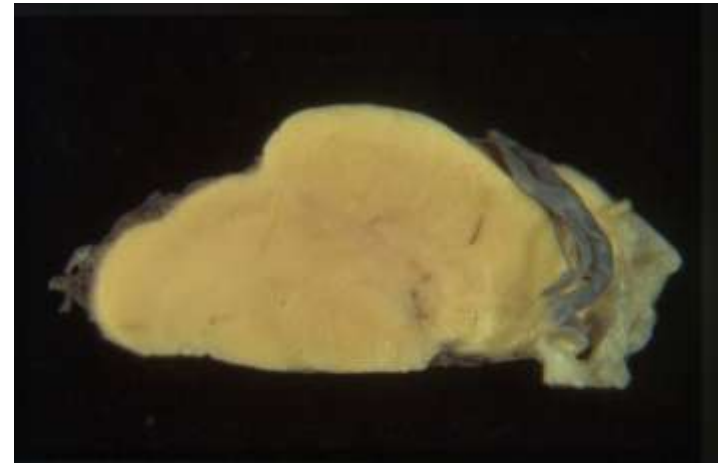
### **Radiological**

Cerebral atrophy  
Bilateral loss of tracer  
uptake from posterior  
cerebral cortex

# GROSS PATHOLOGY



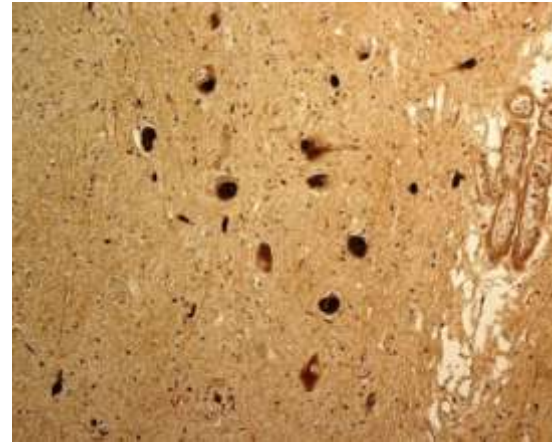
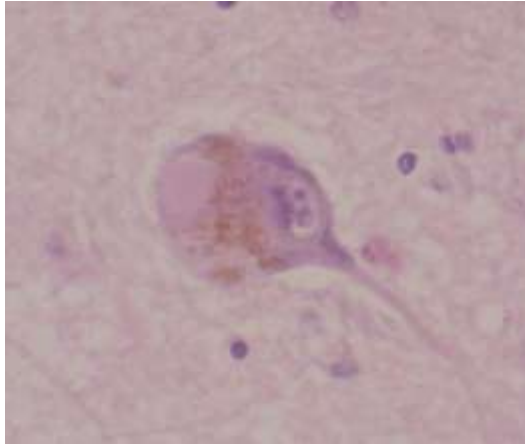
**NORMAL**



**PD/LBD**

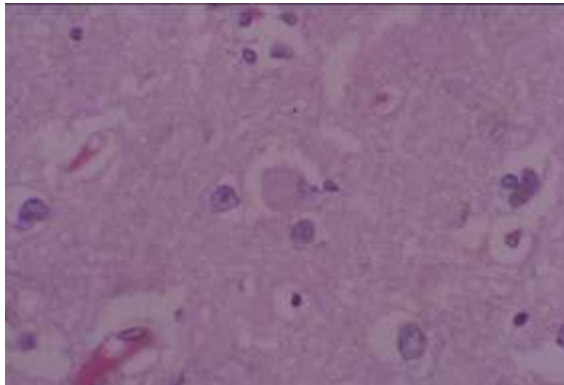
**Loss of cells from substantia nigra**

# LEWY BODY DEMENTIA



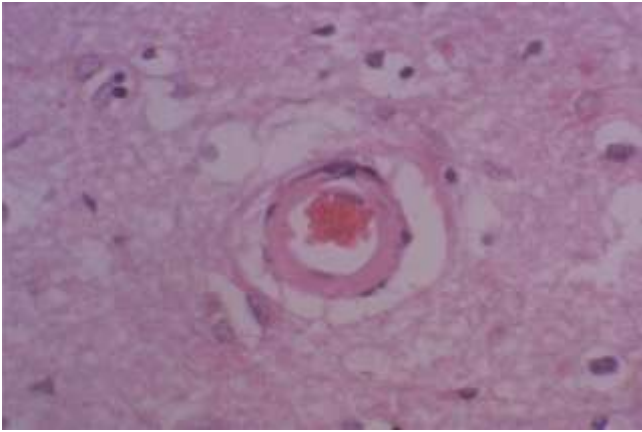
**H&E**

**Lewy bodies in substantia nigra  $\alpha$ -syn**

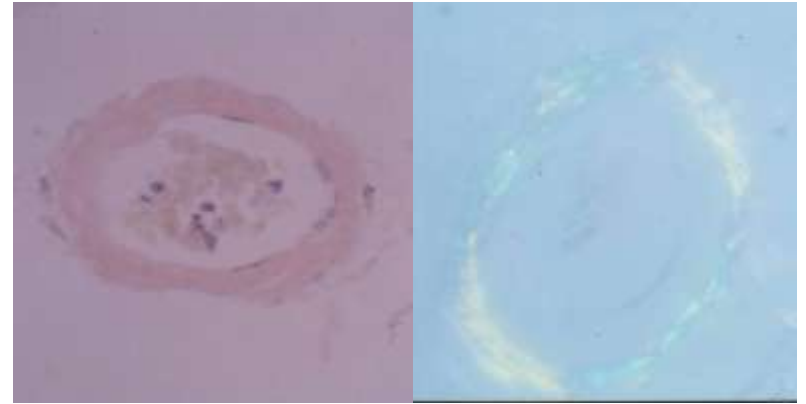


**Lewy bodies in cerebral cortex**

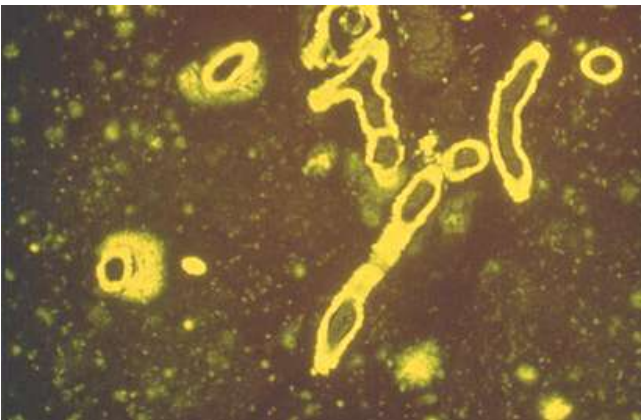
# CEREBROVASCULAR DISEASE (Cerebral Amyloid Angiopathy)



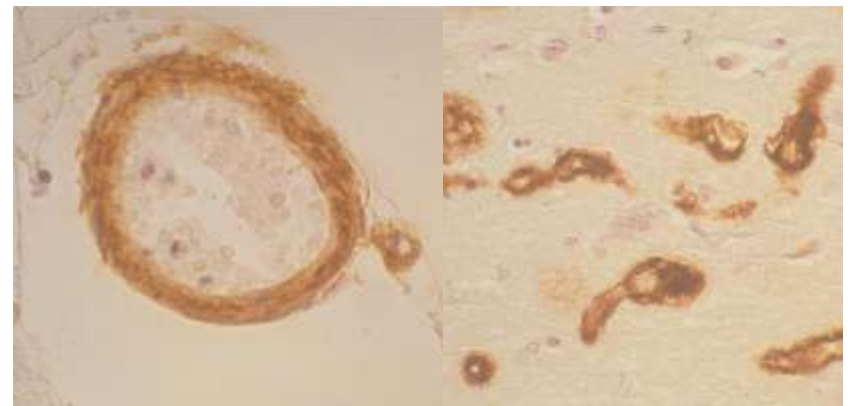
**H&E**



**Congo red**

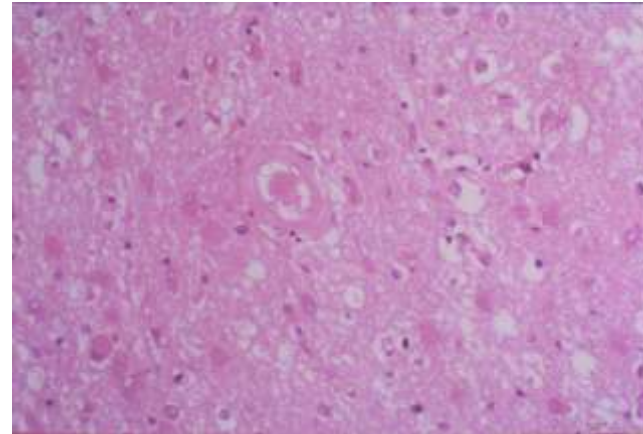
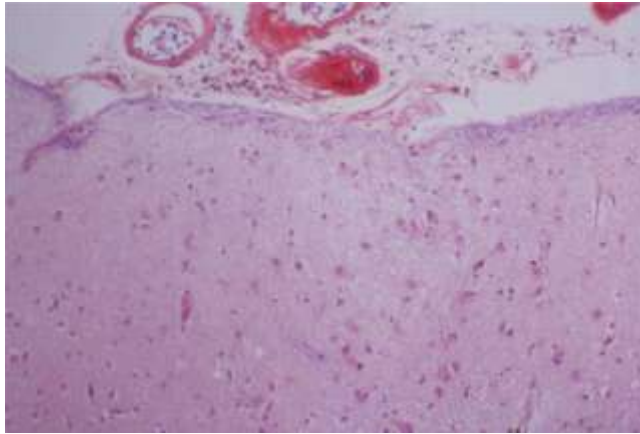


**Thioflavin S**

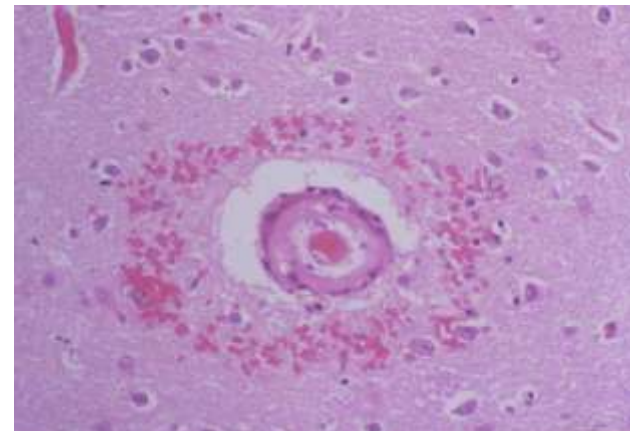
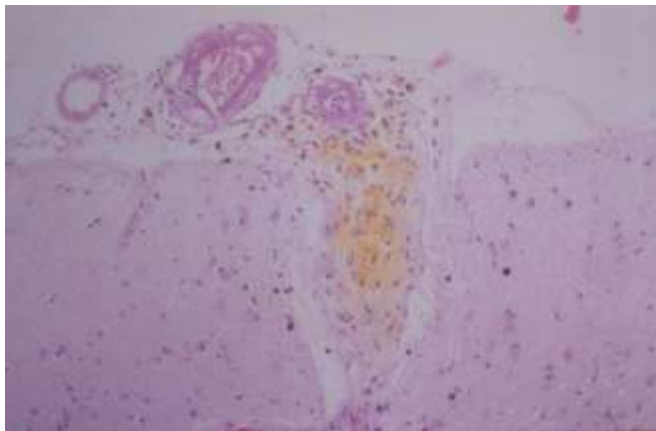


**A $\beta$  immunostain**

# AFFECTS OF CAA

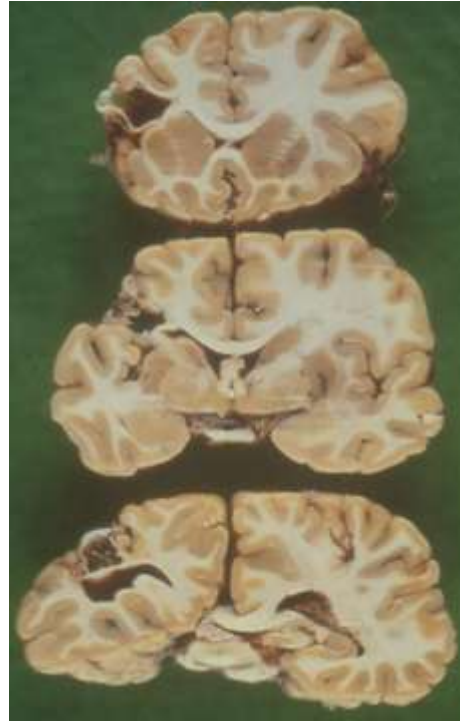
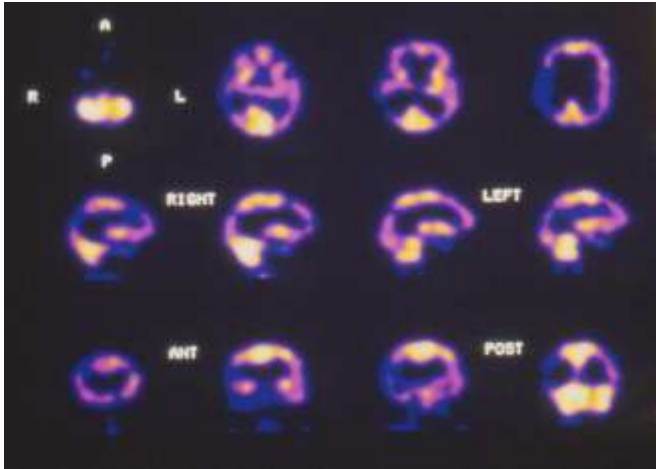


**Increased risk of cerebral infarction**



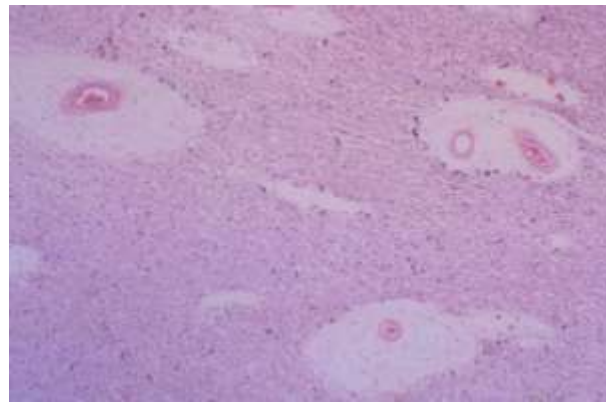
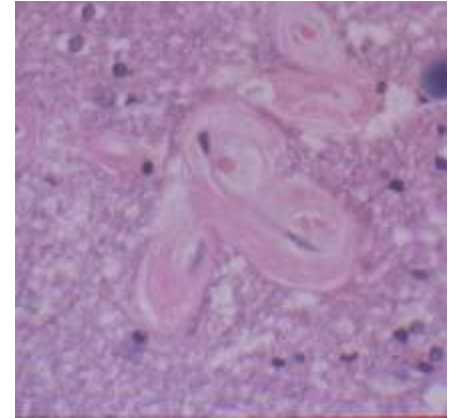
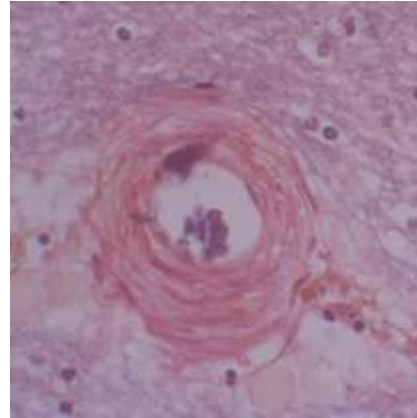
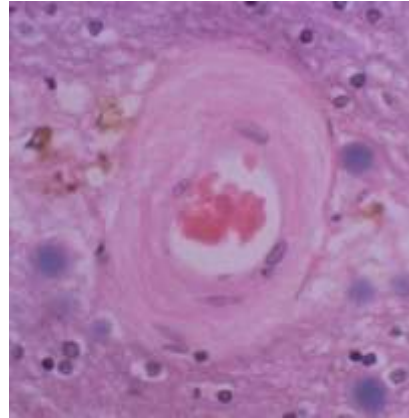
**Increased risk of cerebral haemorrhage**

# ATHEROSCLEROSIS



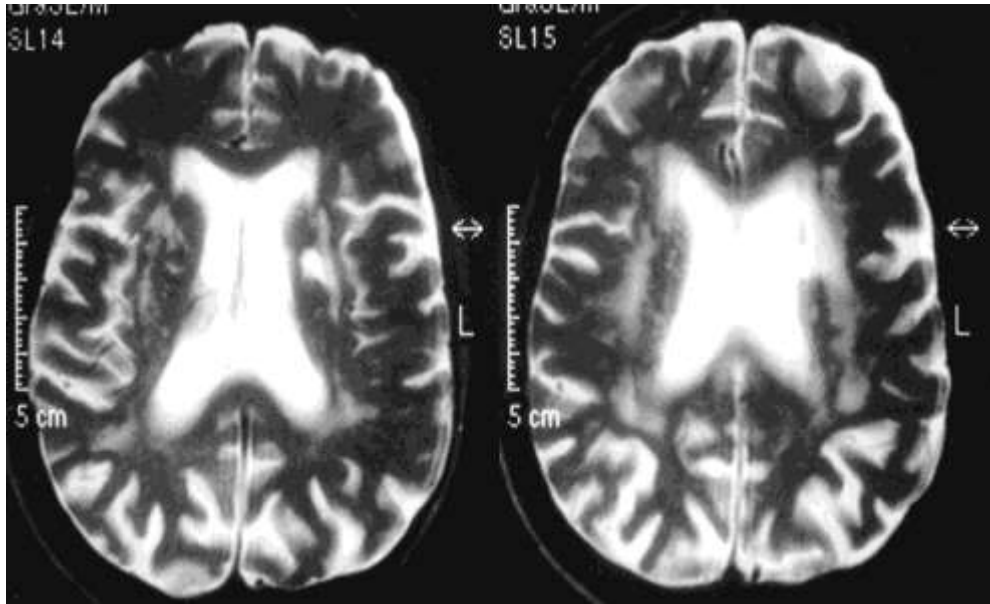
**Infarctions due to large vessel disease (atherosclerosis) are coincidental in Alzheimer's disease**  
**In absence of Alzheimer's disease may be sufficient to cause multi-infarct dementia**

# ARTERIOSCLEROSIS

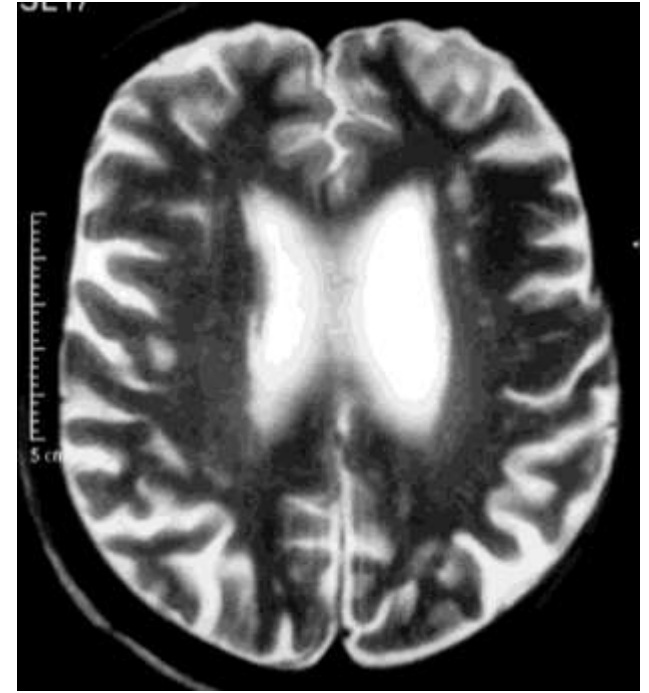


- Thickening of vessel wall
- Dilatation of perivascular spaces
- Common cause of “multi-infarct” (vascular) dementia

# WHITE MATTER LESIONS



**Vascular dementia**

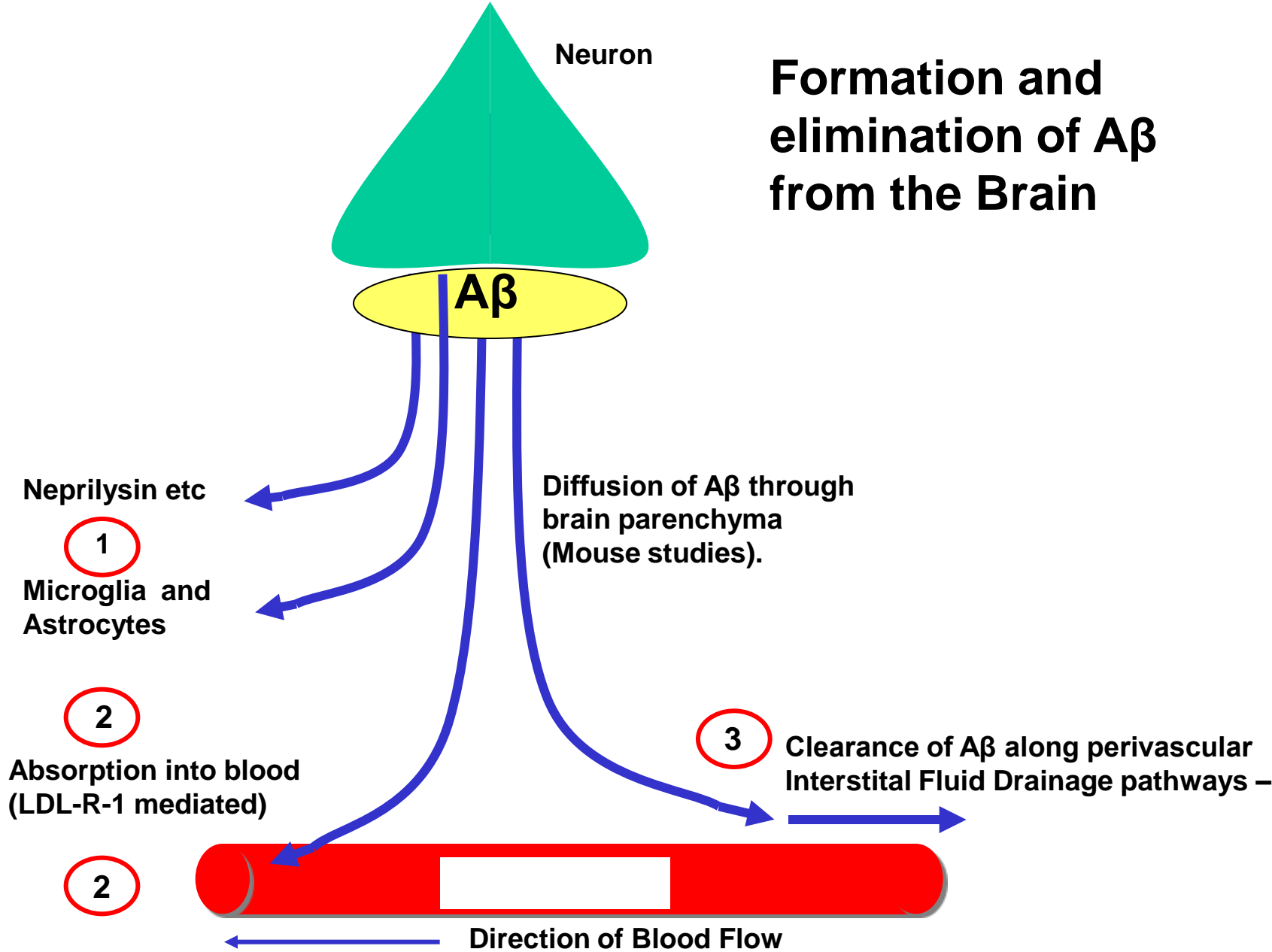


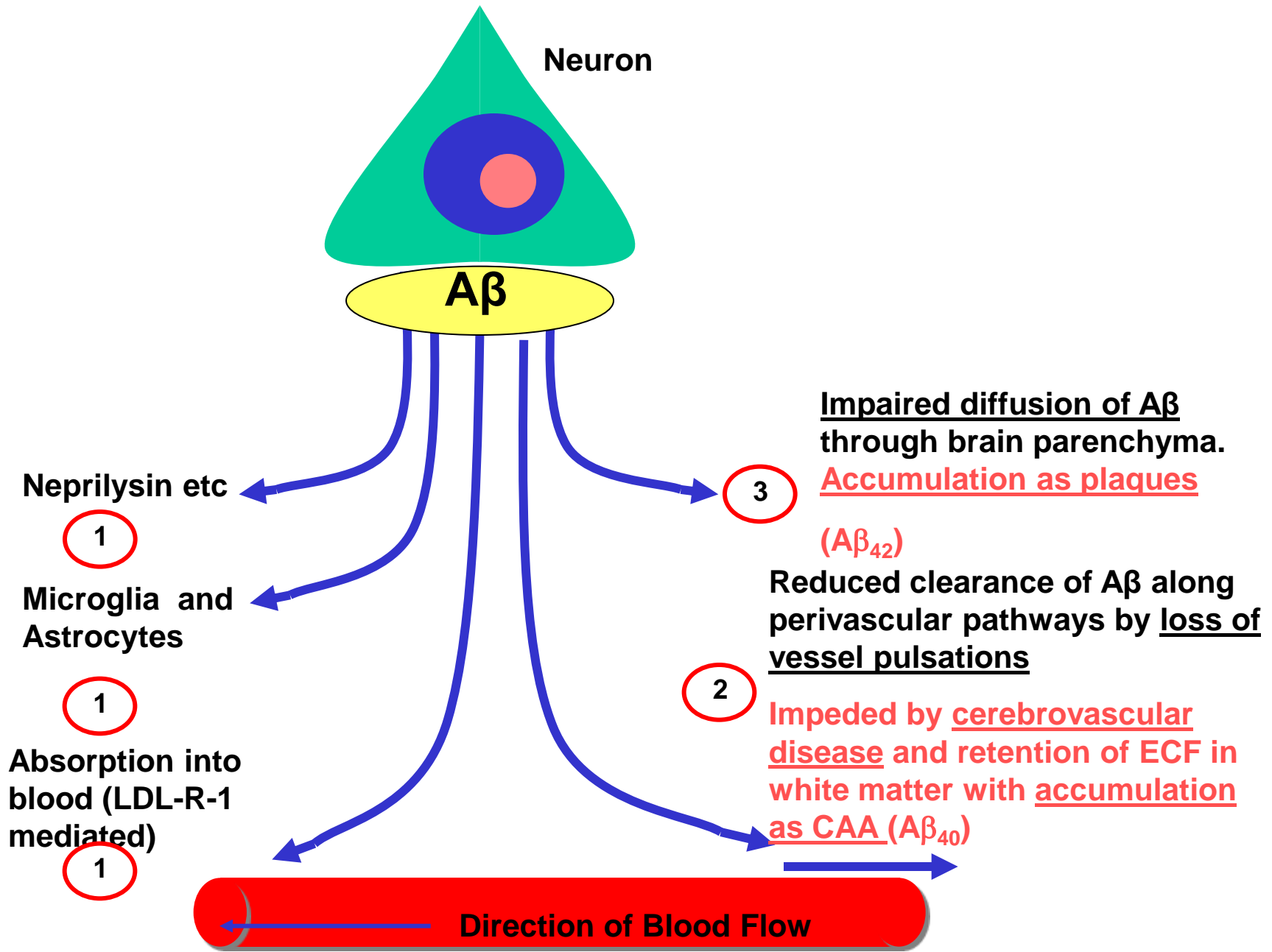
**AD**

**White matter lesions are radiologically present in 50-70% cases of AD**



# Formation and elimination of A $\beta$ from the Brain





# Longitudinal Ageing Study

34 cases (14M, 20F) come to post mortem

Mean age 83.8 years, range 72-94 years

30 cases, so far, assessed for:-

A $\beta$  (CERAD – Mirra et al 1990),

Tau (Braak stage, Braak and Braak 1991)

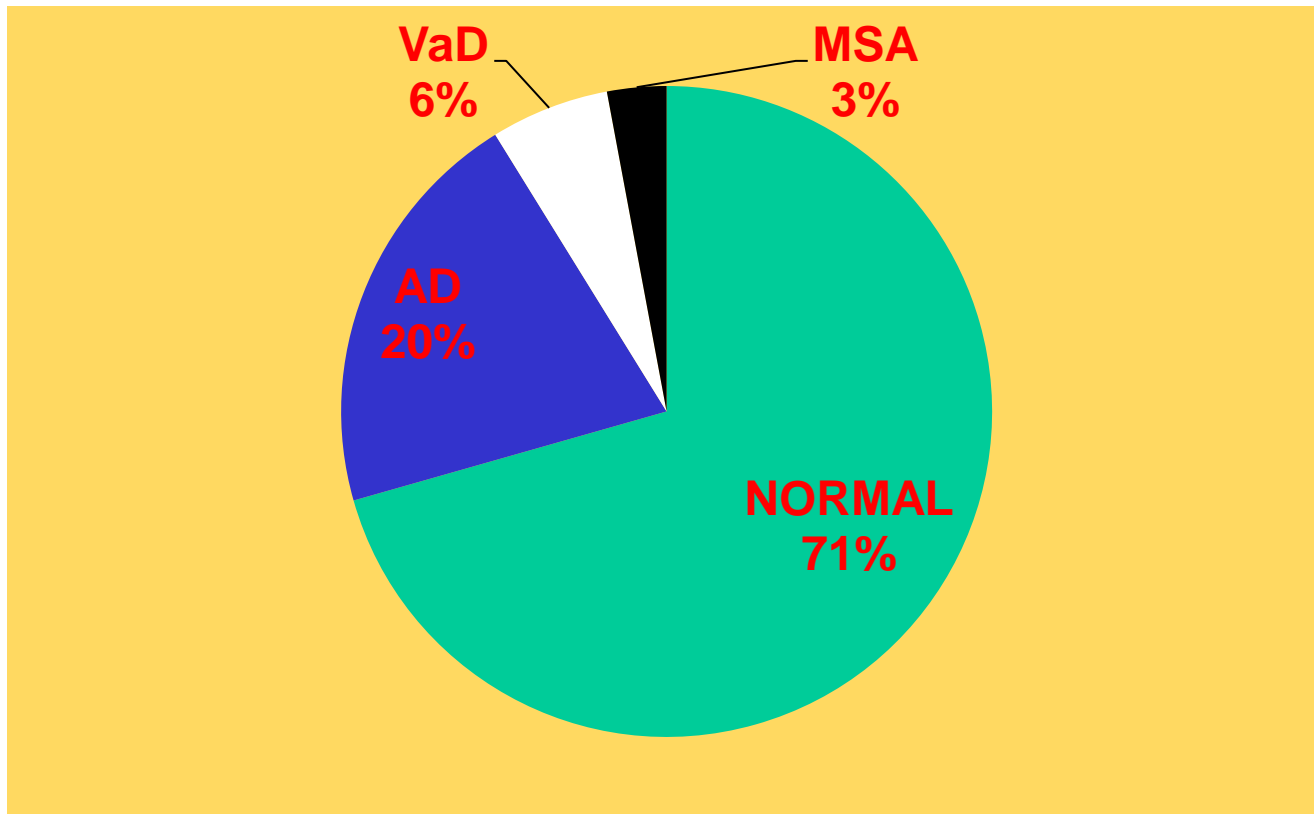
PIN1/GVD (Dakson et al 2010)

$\alpha$  -synuclein (Foulds et al 2010)

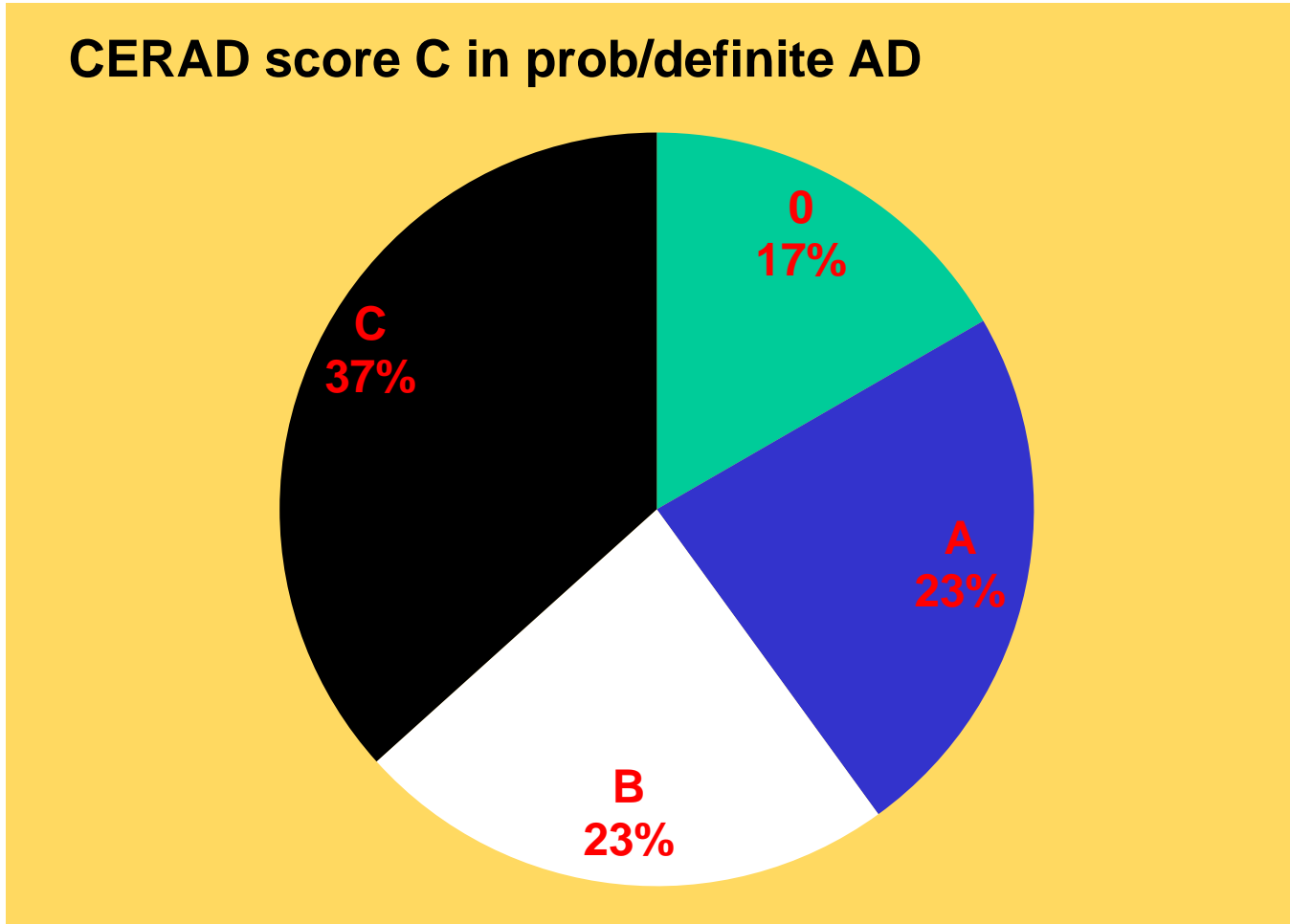
Cerebrovascular disease (BDR 2010)

*APOE* genotype (Wenham et al 1990)

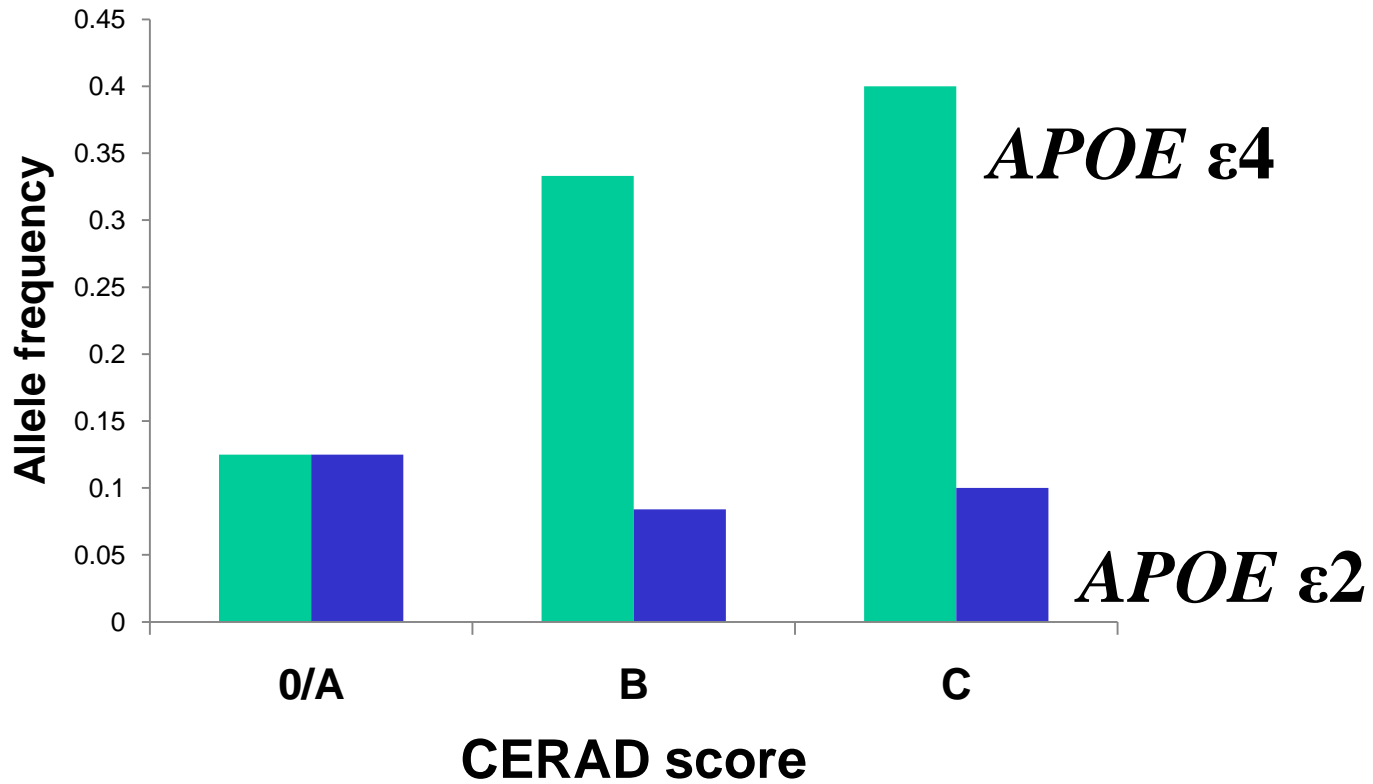
# CLINICAL DIAGNOSIS



# PLAQUE (CERAD) SCORE



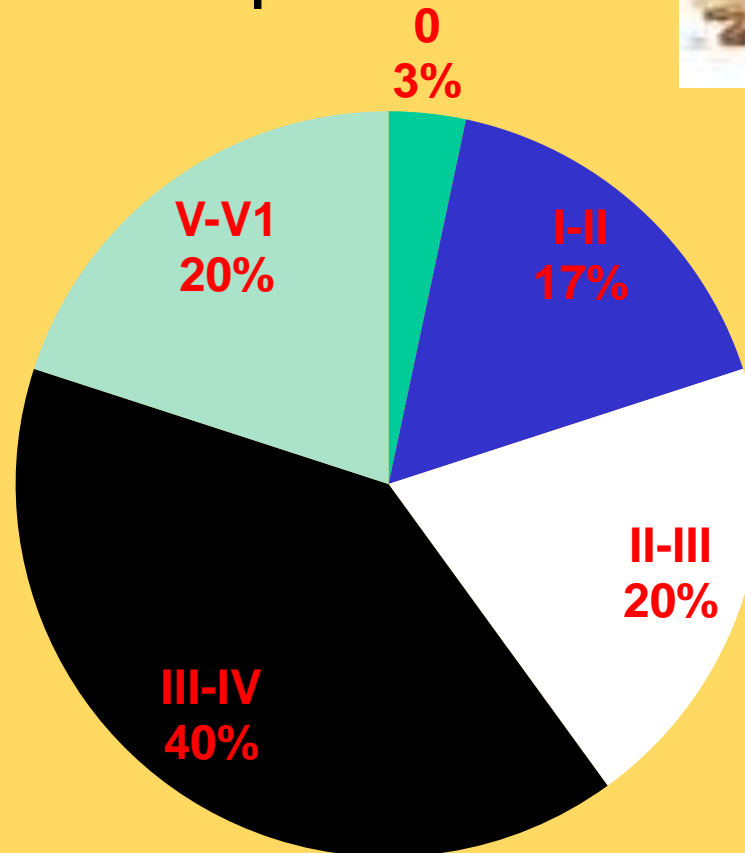
# *APOE* ALLELE AND PLAQUE SCORE



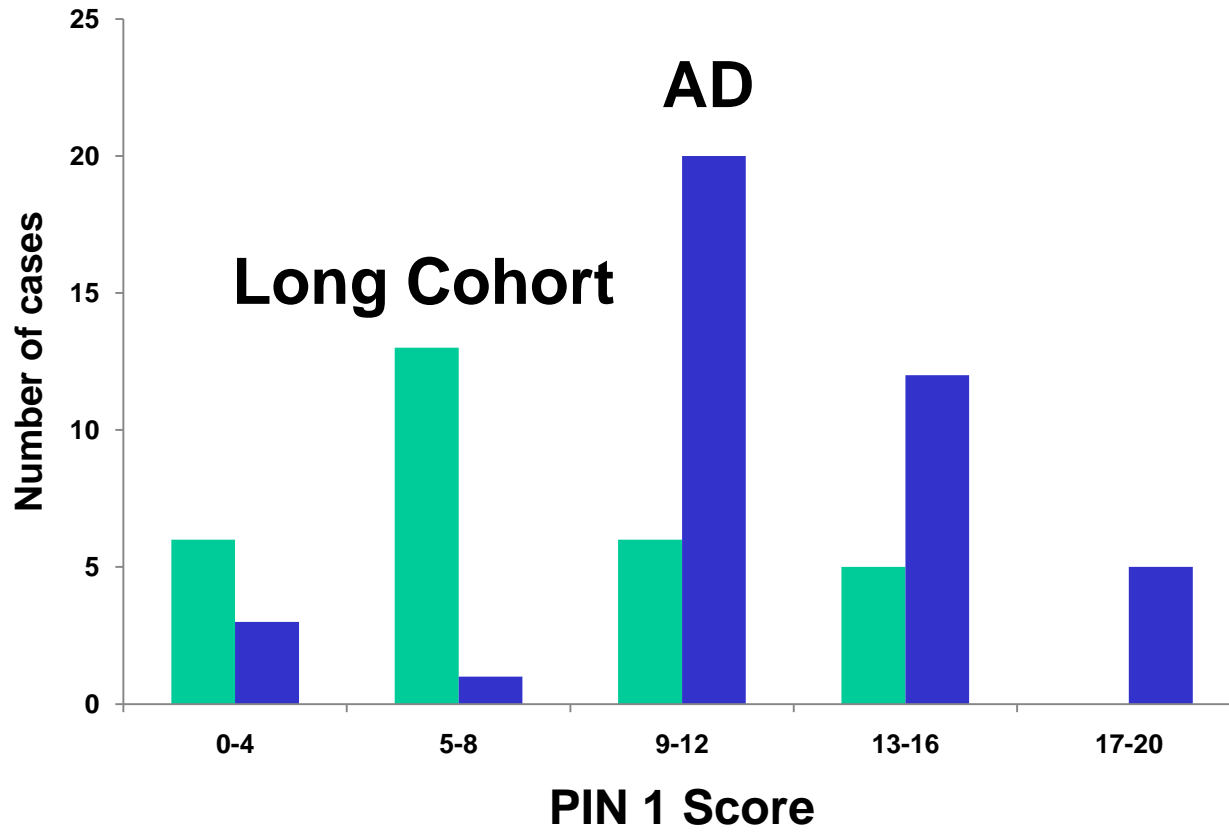
# BRAAK STAGEING



Braak stages 5 and 6 are prob/definite AD

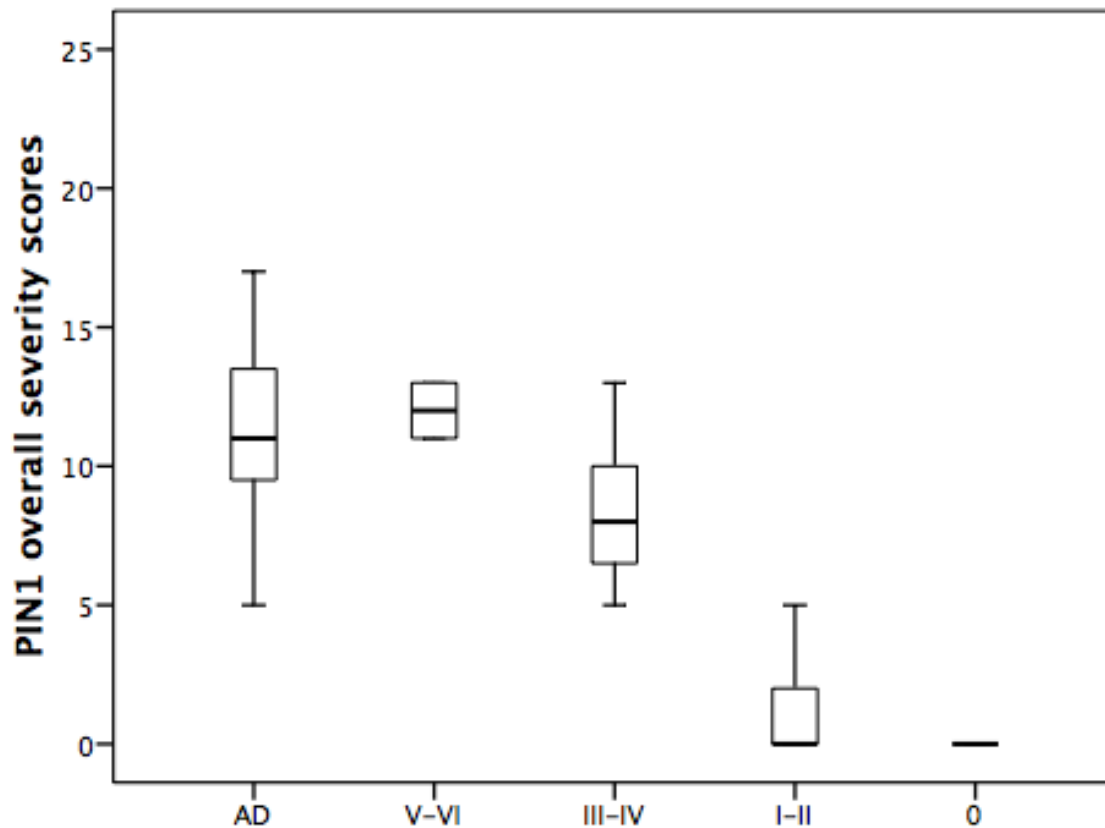


# PIN1 (GVD) PATHOLOGY

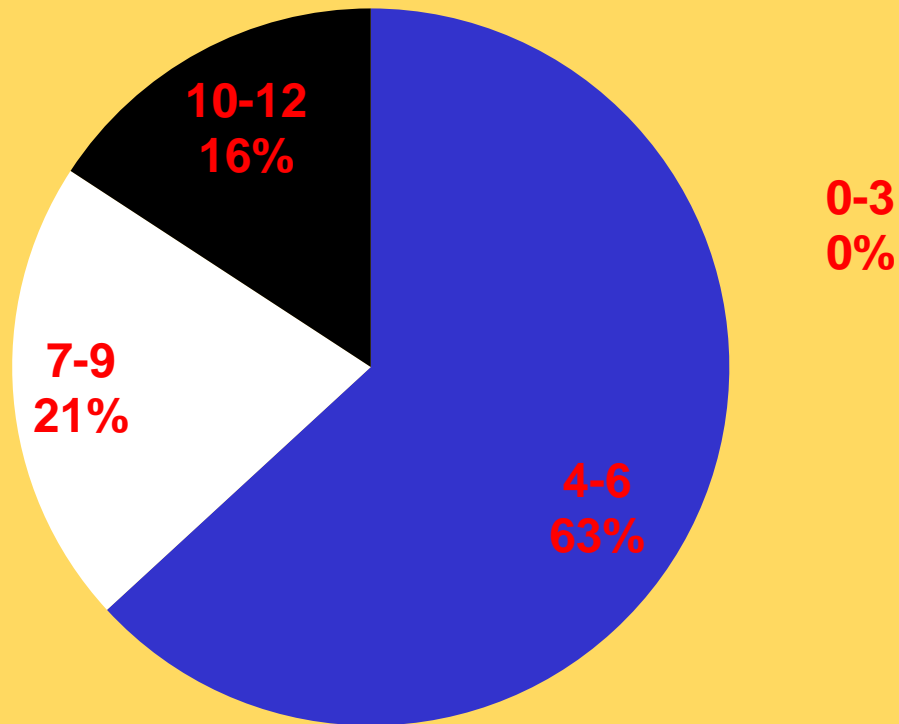




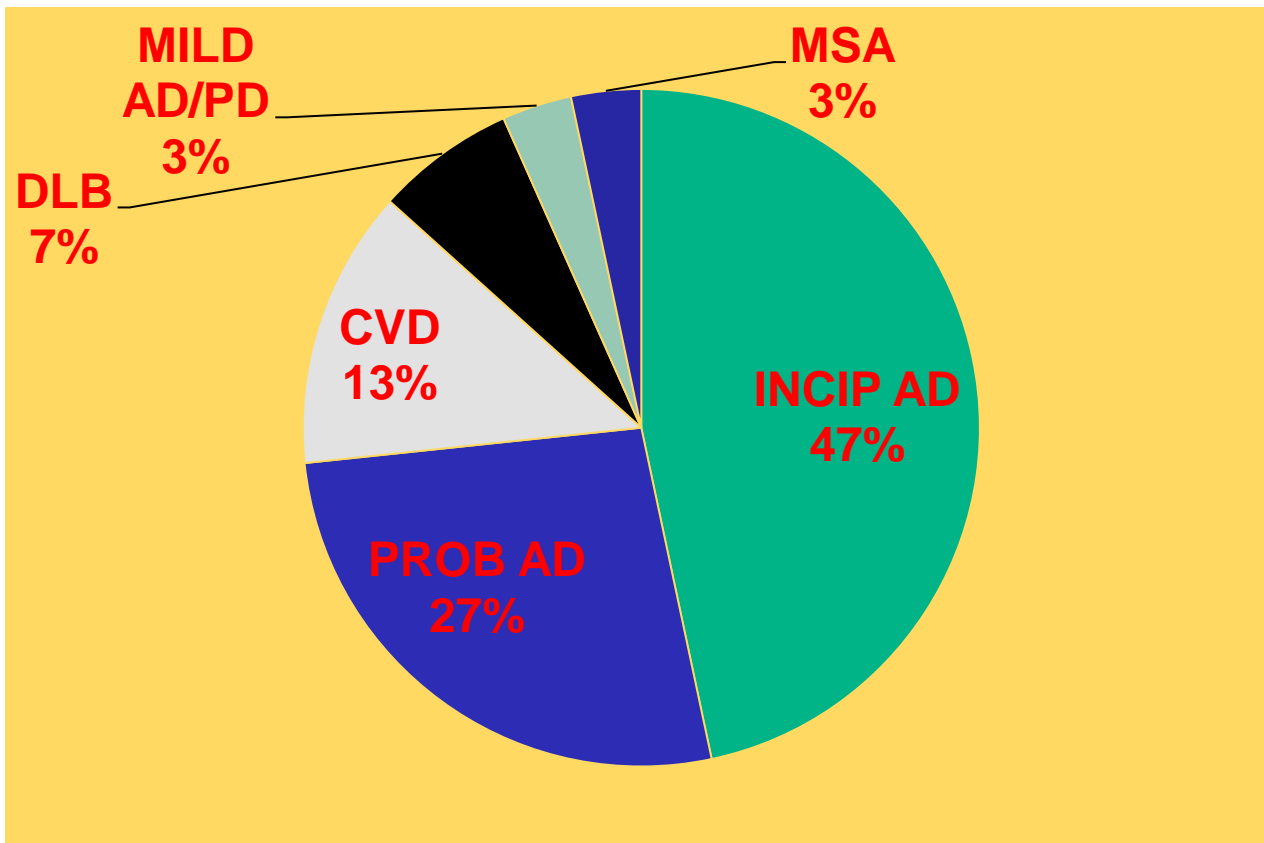
# PIN1 (GVD) PATHOLOGY and BRAAK STAGE



# CEREBROVASCULAR CHANGES

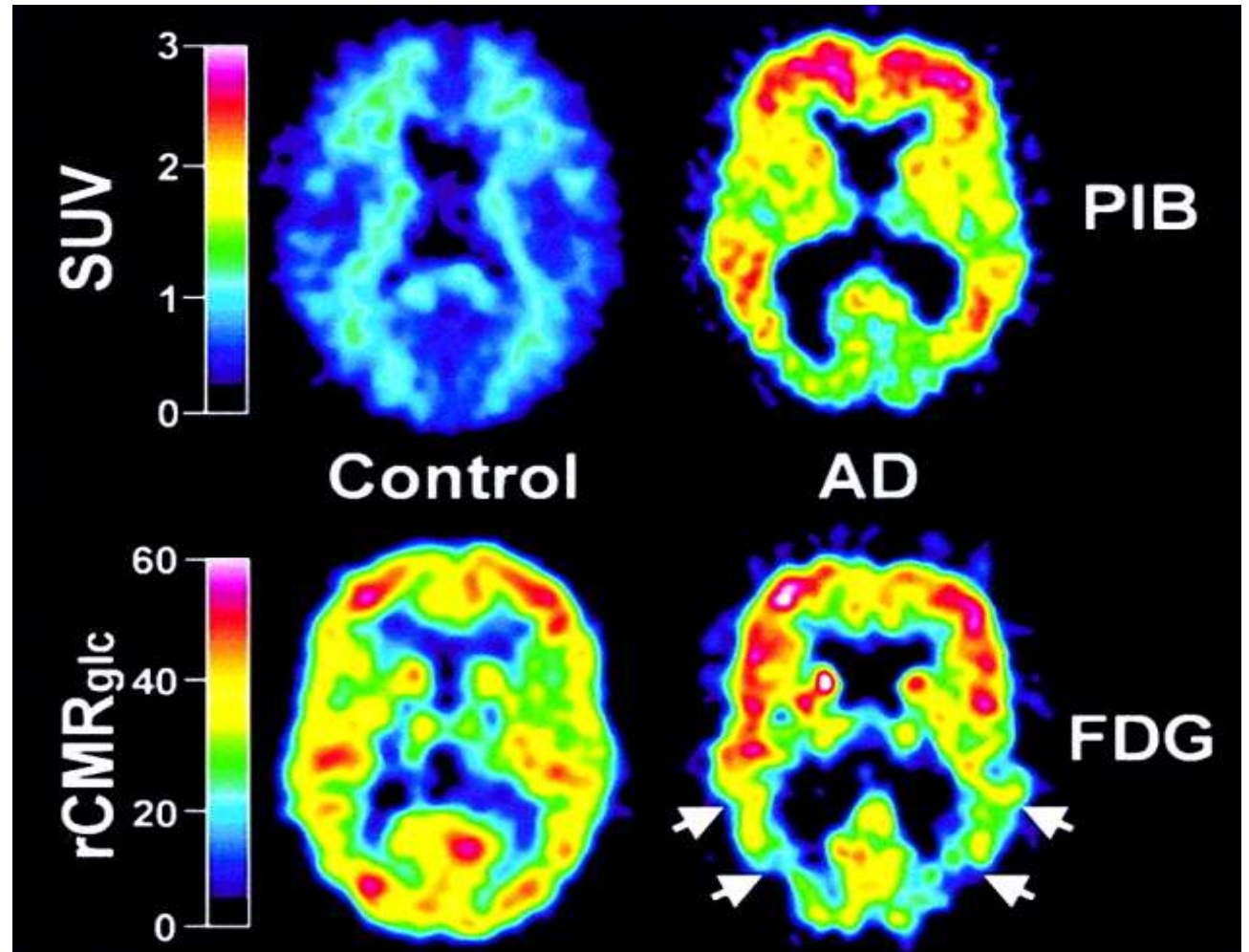
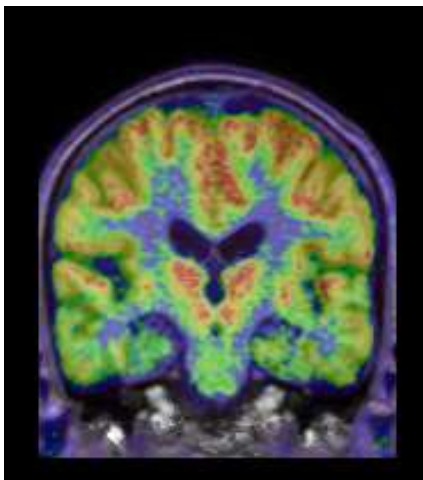
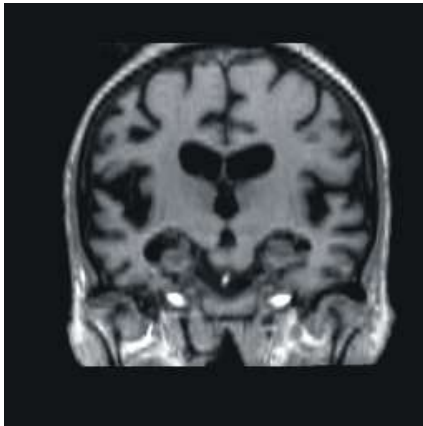


# NEUROPATHOLOGY



# BIOMARKERS (1)

Imaging – MRI/PET (FDG or amyloid)



# BIOMARKERS (1)

Disadvantages:

1. MRI/FDG - Non-specific, surrogate marker (cerebral atrophy, blood flow, glucose uptake)
2. Amyloid - Non-selective - amyloid in virtually all older subjects. Does not predict conversion normal/MCI/AD

# BIOMARKERS (2)

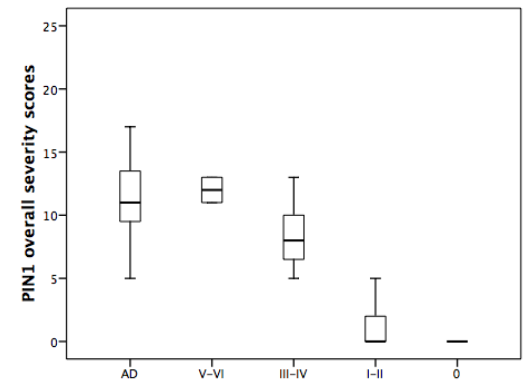
## Cerebrospinal fluid or serum/plasma

AD – CSF:  $A\beta_{42}$  and/or Ptau196 increased in AD vs controls

BUT CSF:  $A\beta_{42}$  does not predict conversion ND/MCI/AD and Ptau raised in other tauopathies.

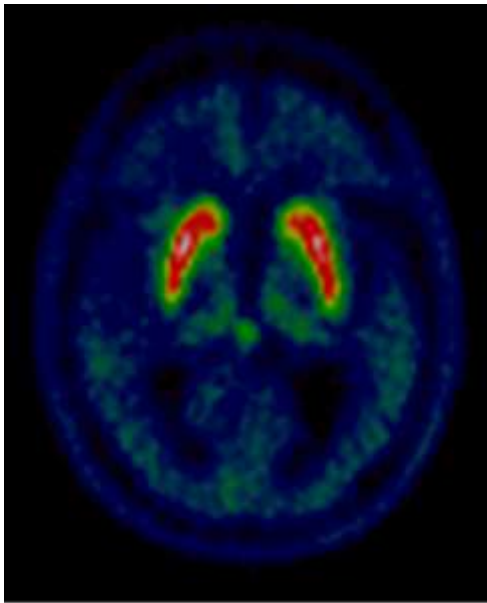
## PIN1 as possible biomarker

**Blood marker preferable**

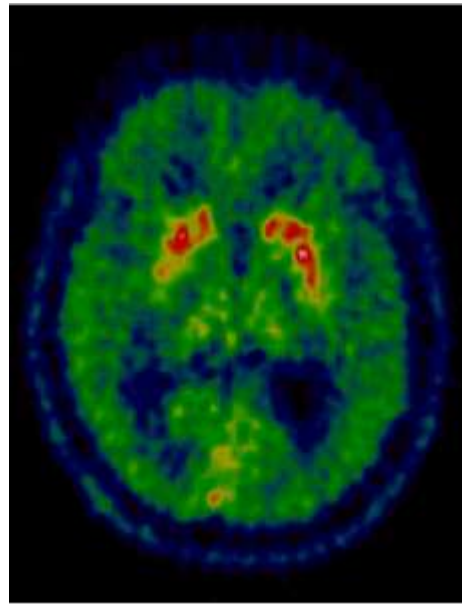


# BIOMARKERS (3)

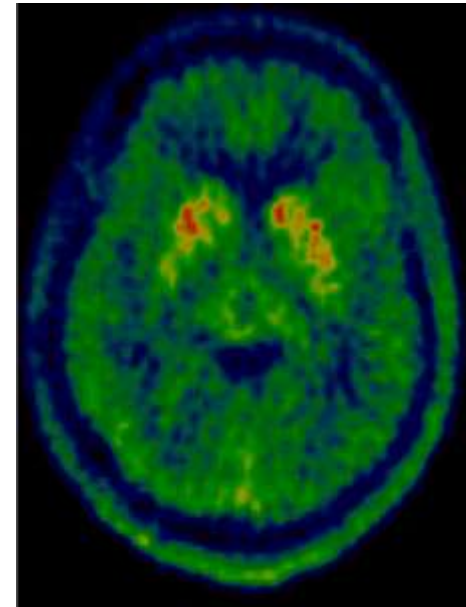
## PET Imaging in Parkinson's Disease Diagnosis



Normal Subject



Early Parkinson's  
Disease

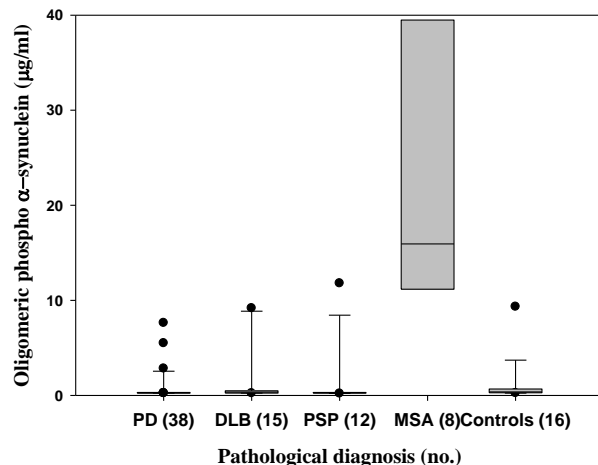


Advanced Parkinson's  
Disease

# BIOMARKERS (4)

**Differentiation of PD/DLB from other parkinsonian disorders (eg PSP/CBD (tauopathy) and MSA ( $\alpha$ -synuclein)).**

**Increased CSF  $\alpha$ -synuclein (total or oligomeric forms) in PD vs controls.**



**Oligomeric, phosphorylated  $\alpha$ -synuclein increased in MSA**



# CONCLUSIONS

## **In an elderly cohort:**

83% show  $\beta$ -amyloid deposition

97% have tau pathology (60% AD/incipient AD).

90% have PIN1 changes (33% in AD range).

100 % show cerebrovascular disease

Cognitively normal and AD cases lie on a continuum of pathological ( $\beta$ -amyloid, tau and PIN1) change

**AD is 'ultimate expression of biological ageing'?**

# Acknowledgements



**BRAINS FOR DEMENTIA RESEARCH**

Increasing knowledge - Finding a cure

A partnership between the Alzheimer's Research Trust and Alzheimer's Society

Leading the fight  
against dementia

**Alzheimer's  
Society**

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**wellcome**trust

