Neuroimaging/neuropathology correlates: a study in the "older old"

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Overview

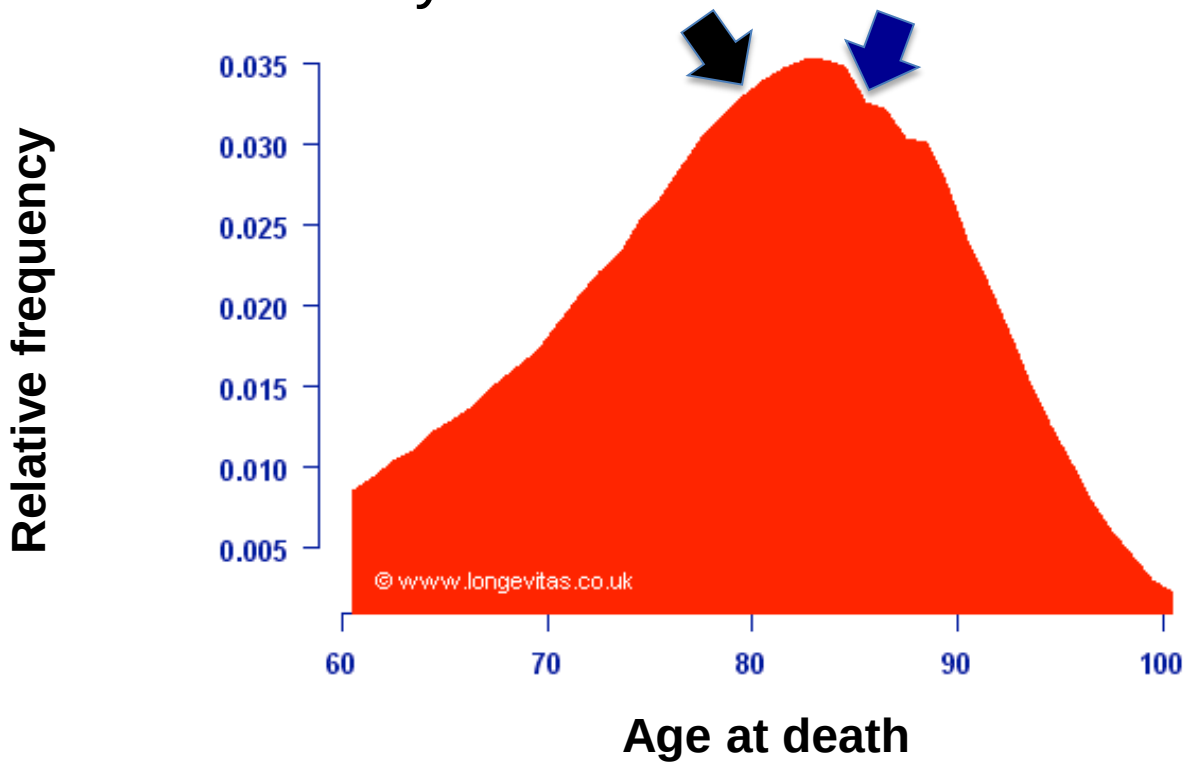
1. The population of particular interest at the Oregon ADC
2. The dementia phenotype associated with white matter hyperintensities (WMHs)
3. A “twin” study: pathologic structural correlates of WMHs
4. A serendipitous “discovery”
5. Implications for how we think about dementia in older patients

The Oregon ADC

- Focus on healthy aging
- The Oregon Brain Aging Study:
  - Initiated 1989
  - Community-dwelling, >65, free of known risk factors for cognitive decline (vascular disease, hypertension, diabetes)
  - Annual neurological/neuropsych/mental functioning/balance tests, MRIs
- 74% convert to MCI at average 89.9 years
- 43% of MCI convert to dementia

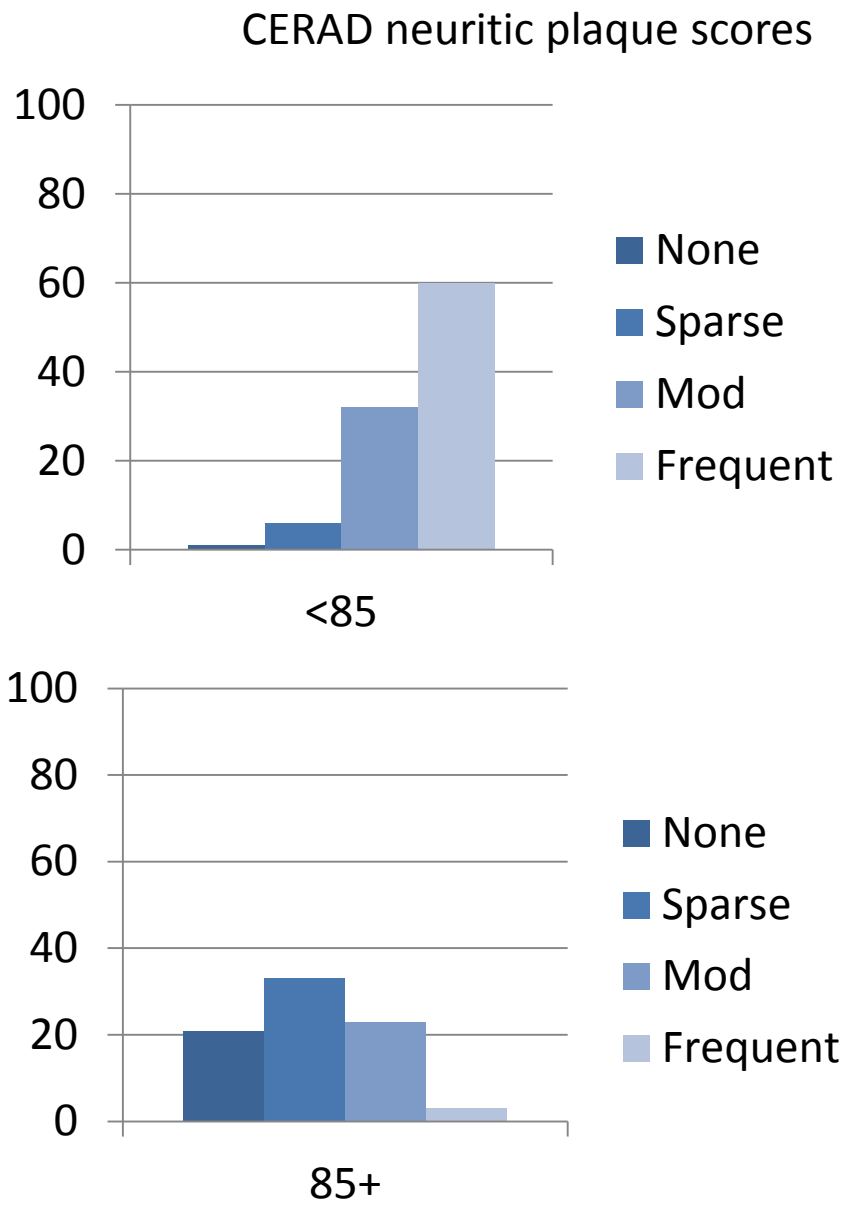
Overall US life expectancy is now 79 years

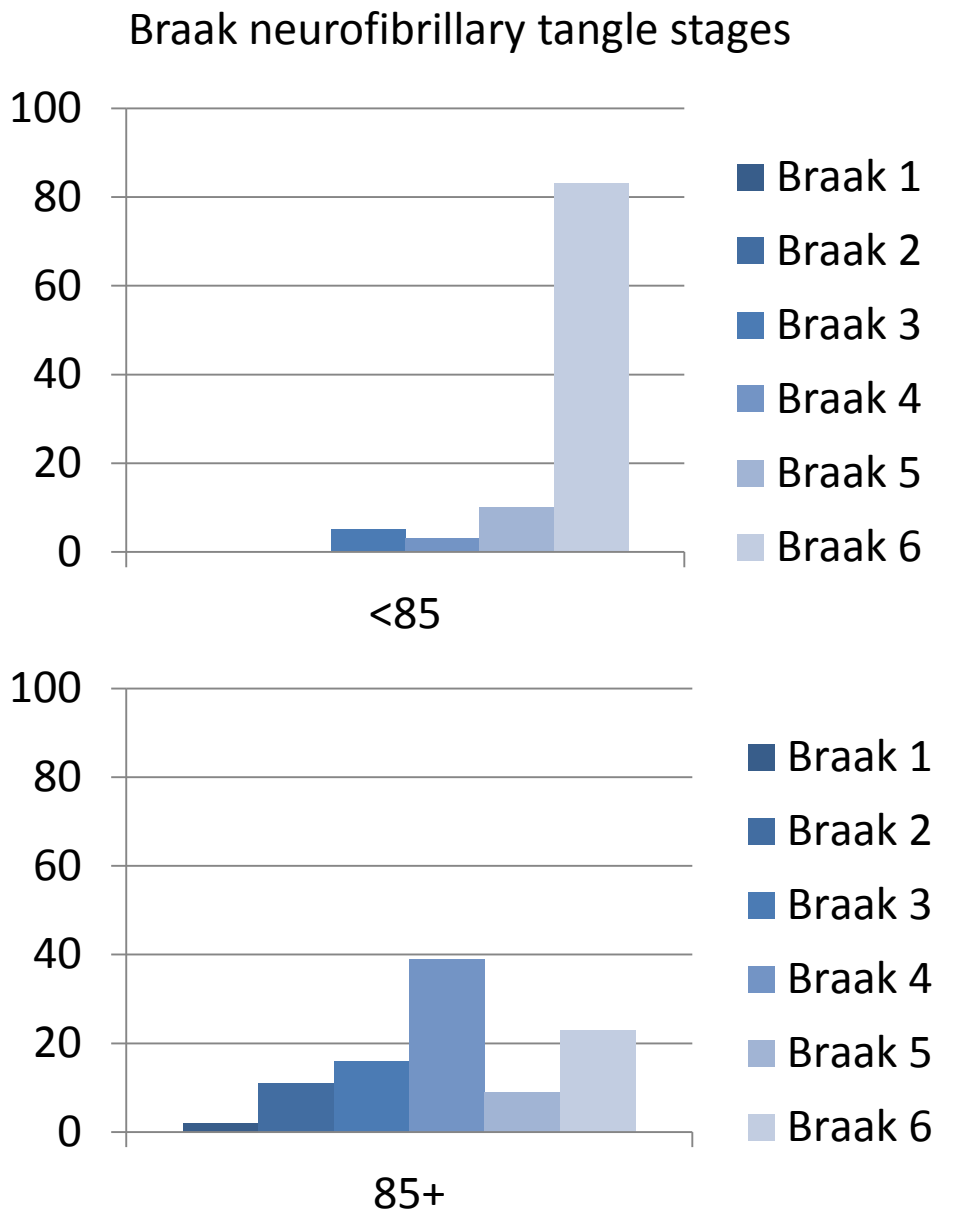
US life expectancy for 40M+ >65 is now 84 years



- The “older old” are relatively unique as a study population, but are the dominant population that is susceptible to dementia in western societies

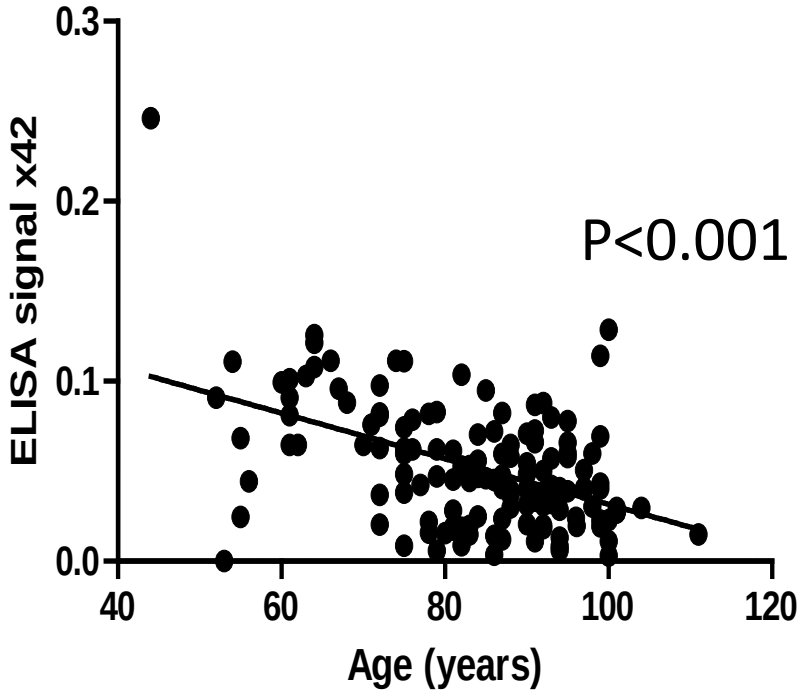
NP and NFT scores in younger and older demented, all OADC subjects (without synucleinopathy, FTLD, non-AD tauopathy), past 10 years (%)



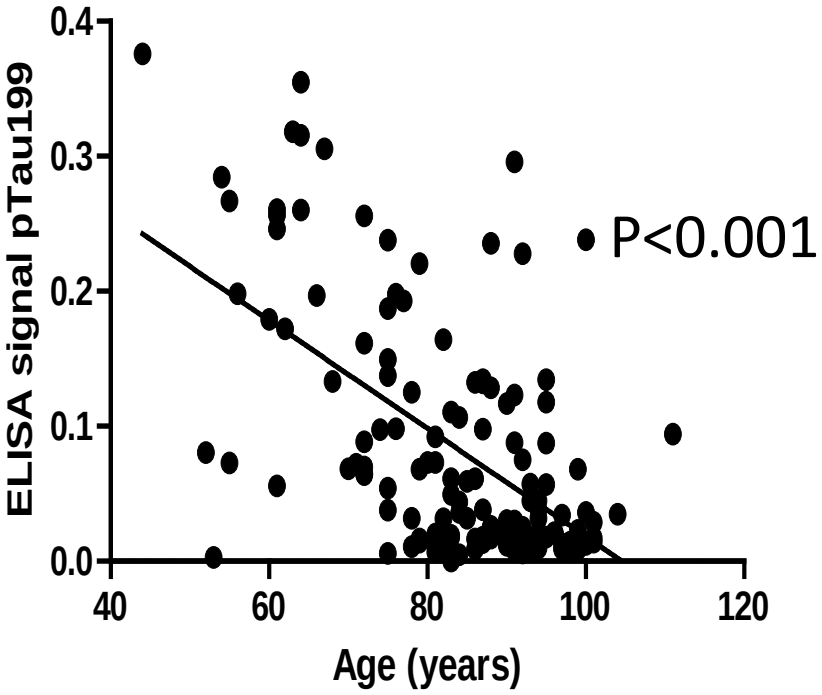


Biochemical hallmarks of AD decrease with age

Insoluble Aβ42

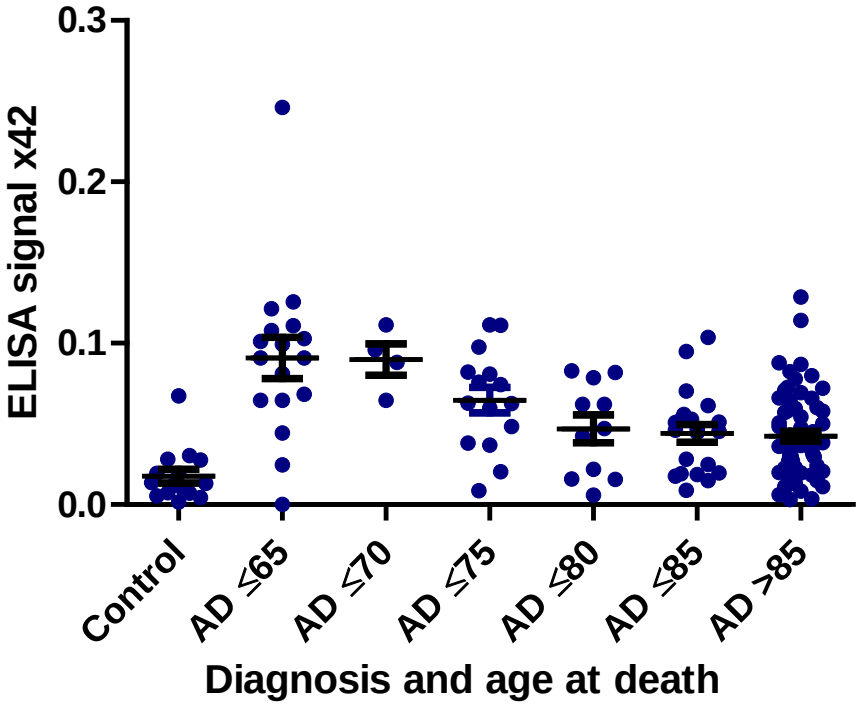


Insoluble phosphotau

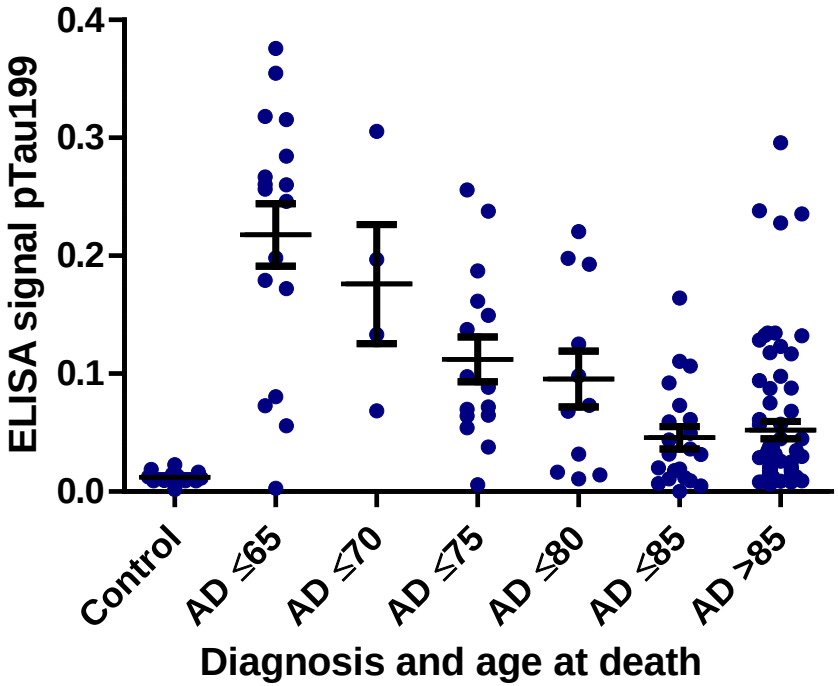


A plateau occurs at around age 80-85

Insoluble Aβ42



Insoluble phosphotau

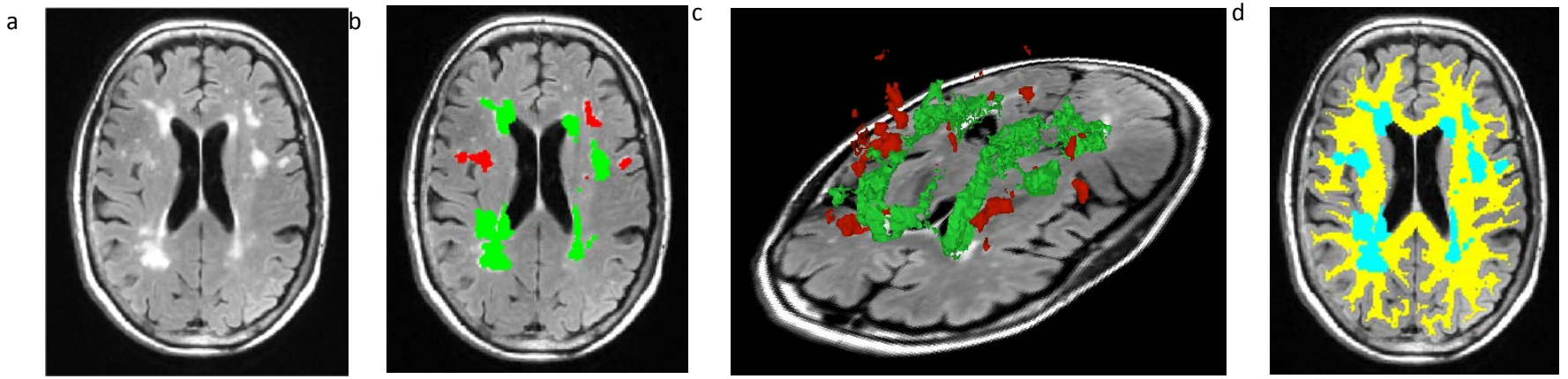


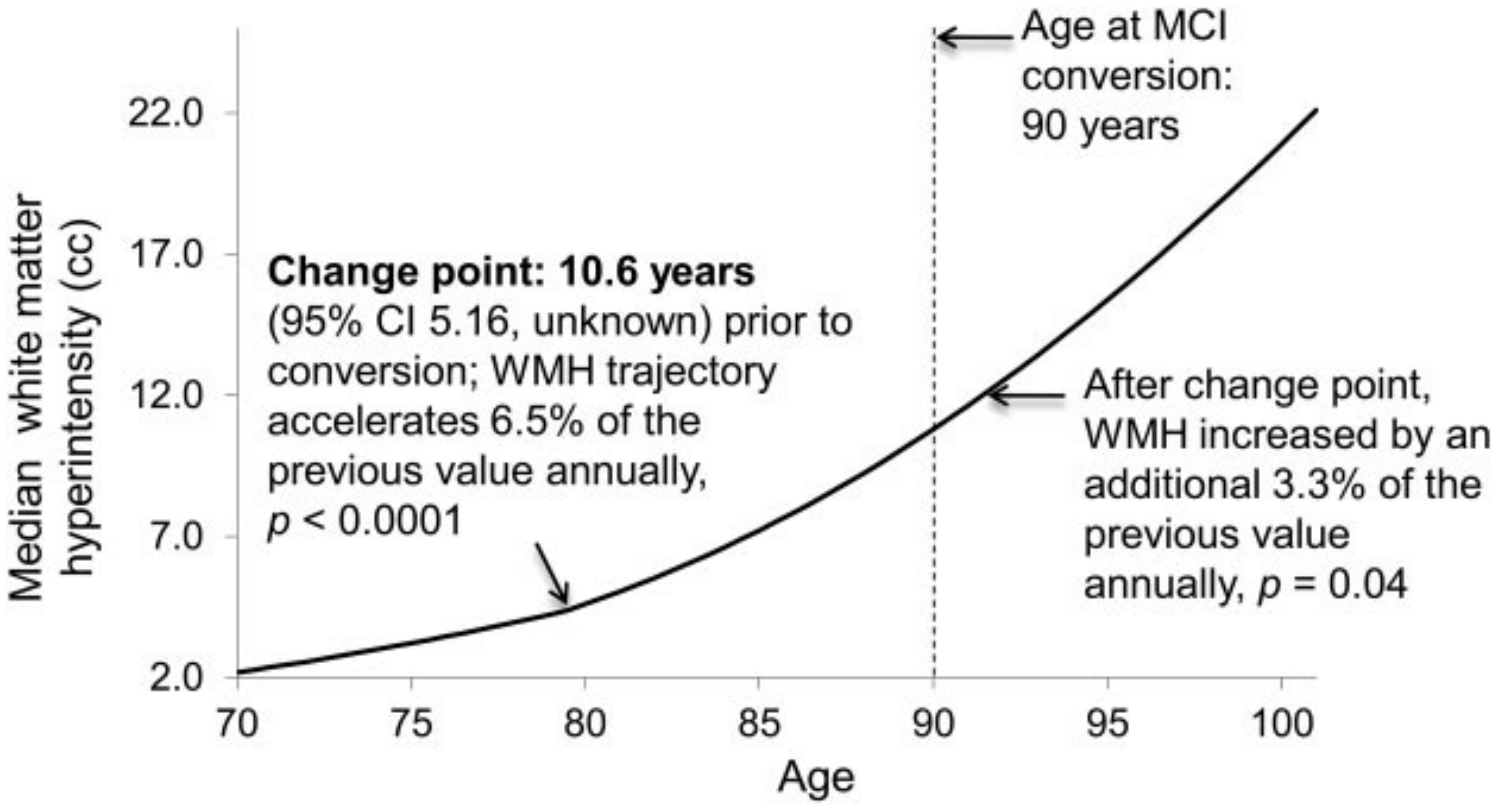
Phenotypes of cognitive impairment at age >85

- "Pure AD": relatively rare
- Hippocampal sclerosis: more common
- "Mixed dementia": very common
  - Sparse neuritic plaques
  - Braak stage 4 NFTs
  - Variable microvasculature-based tissue injury
  - "Dementia of the oldest (older?) old" ("DOOO")

White matter hyperintensities

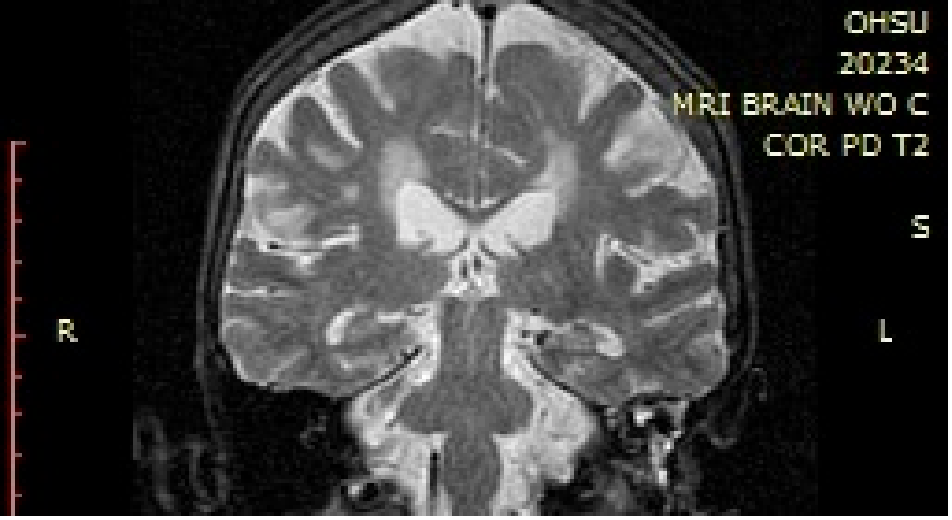
- A possible marker of non-cortical based contribution to dementia in older subjects
- Observed on T2-weighted MRI scans
- Age and vascular risk factors are main clinical associations
- Associated with cognitive impairment
- Accelerated WMH volume change point 10 years before MCI [Silbert et al., 2012]
- Neuropathologic correlates described previously: “incomplete ischemic destruction” with myelin pallor proceeding to tissue infarction

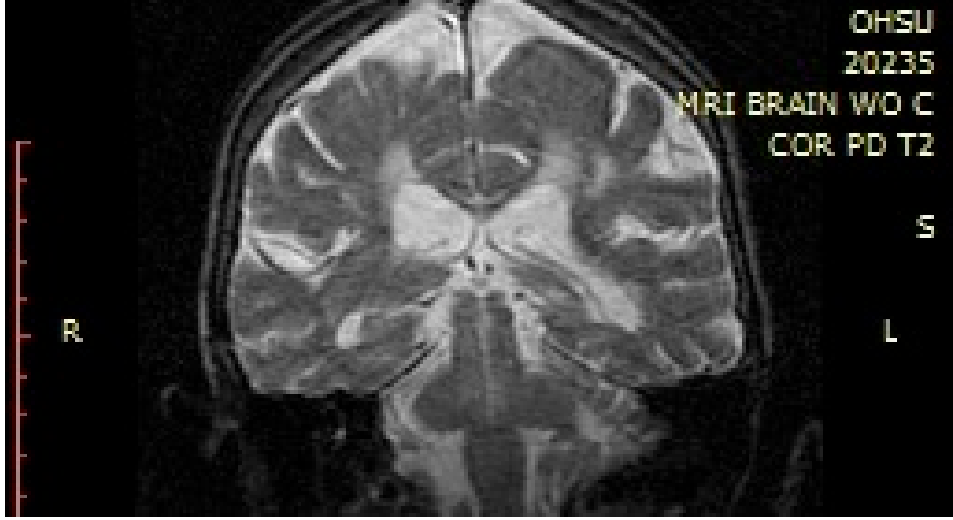




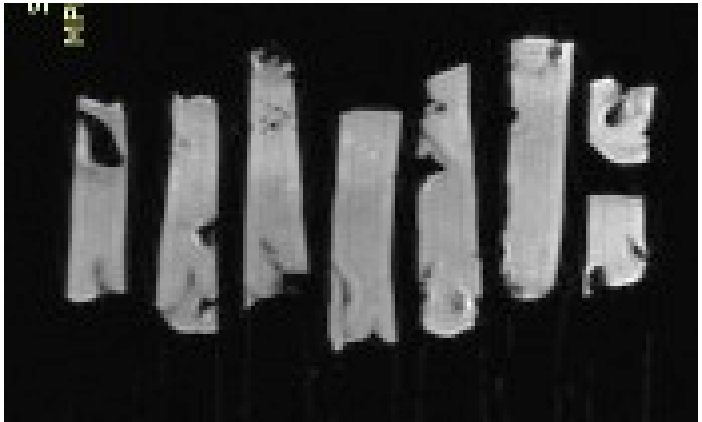
Silbert, et al. Neurology, 2012

Enter the twins (stage left and right)

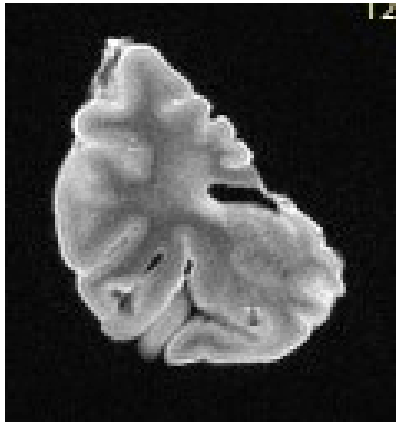


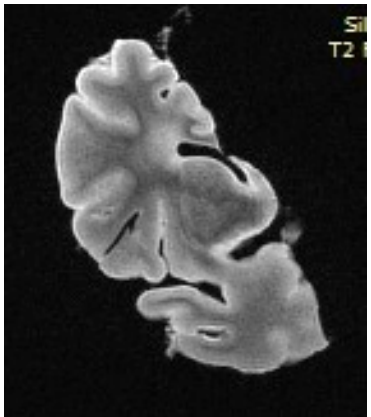


- Mild cognitive impairment, MRI showed moderate to high WMH burden; the twins died within days of each other
- Neuropathology: sparse neuritic plaques, Braak 4 NFTs, high microvascular lesion burden
- Prototypical “mixed” or “DOOO” pathologic findings investigated by postmortem MRI followed by histopathologic correlation



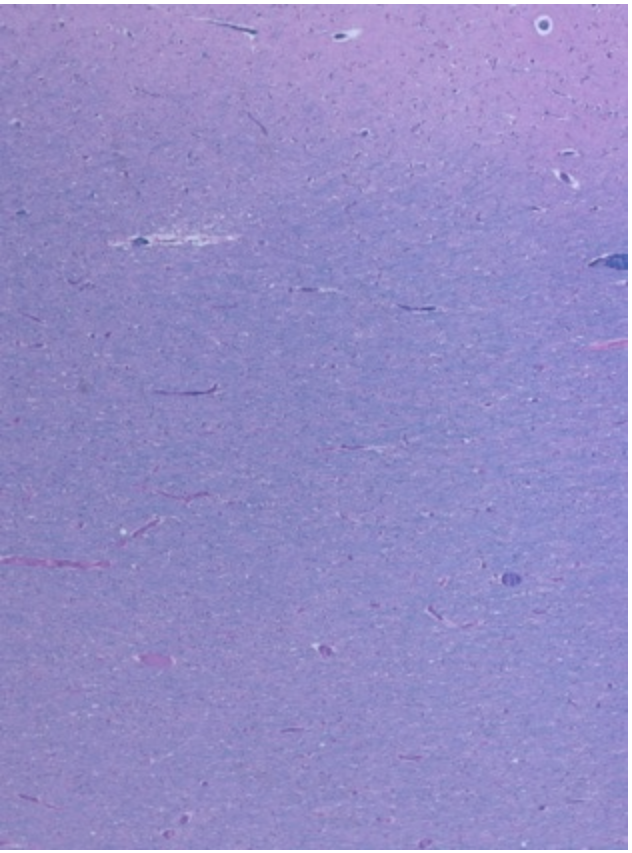
12 paired WM areas each brain



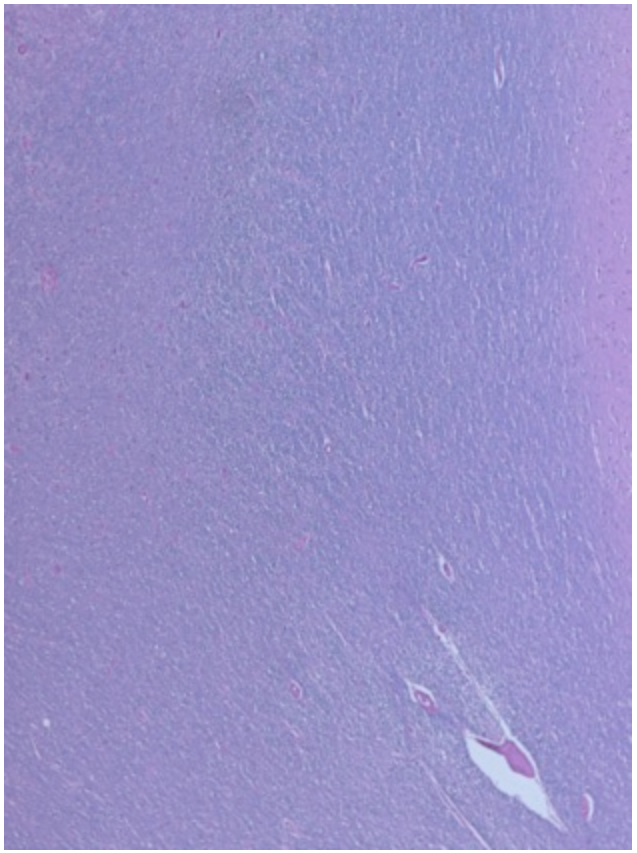


Myelin pallor correlates with WMH abnormality

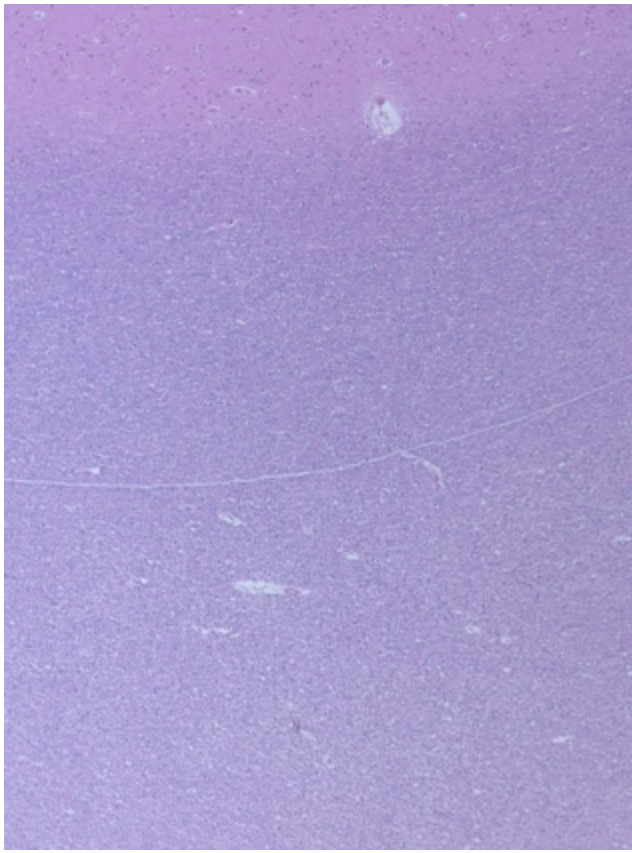
Nonimpaired control



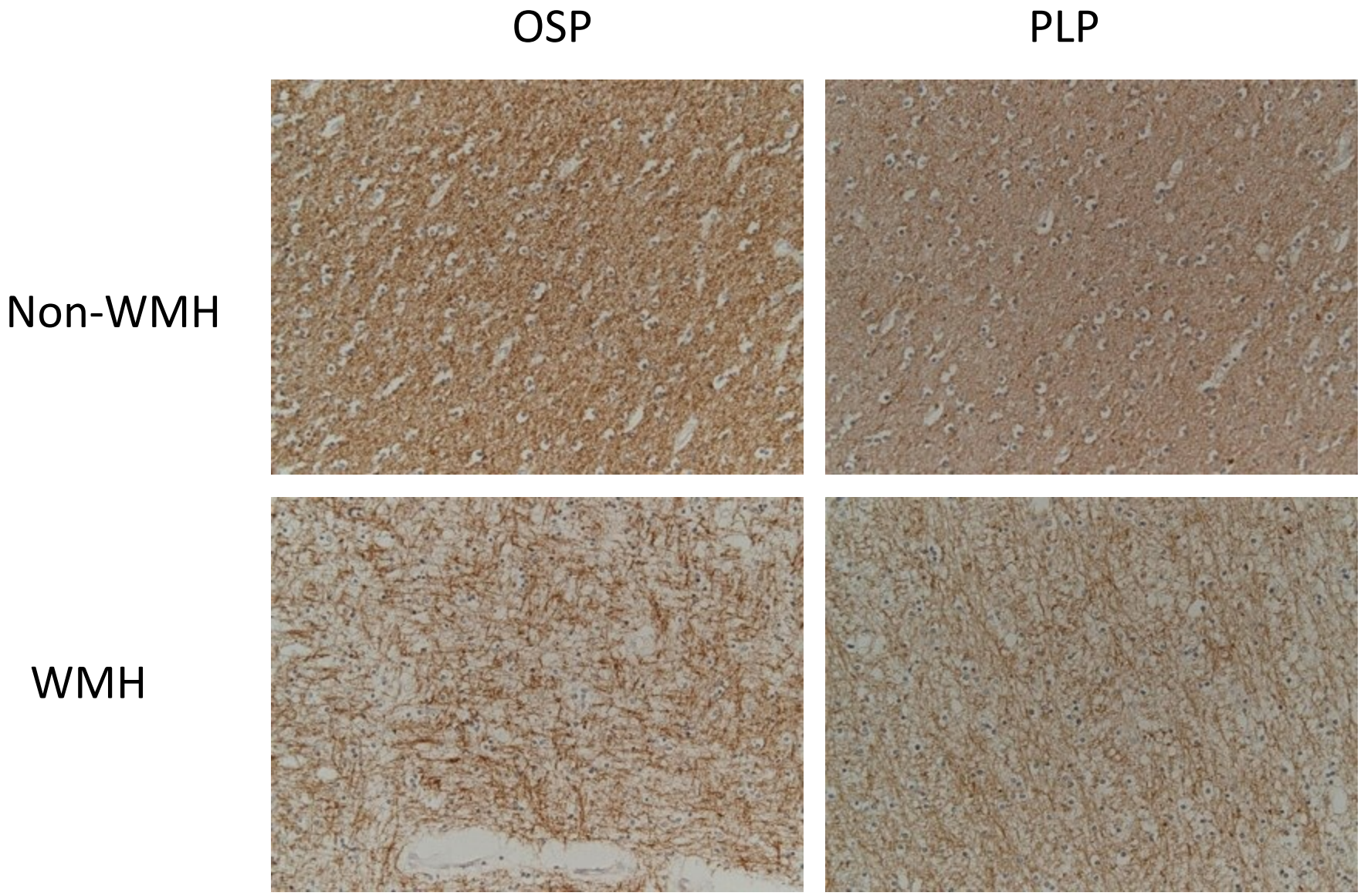
Twin non-WMH



Twin WMH



Many myelin proteins affected in areas of myelin pallor

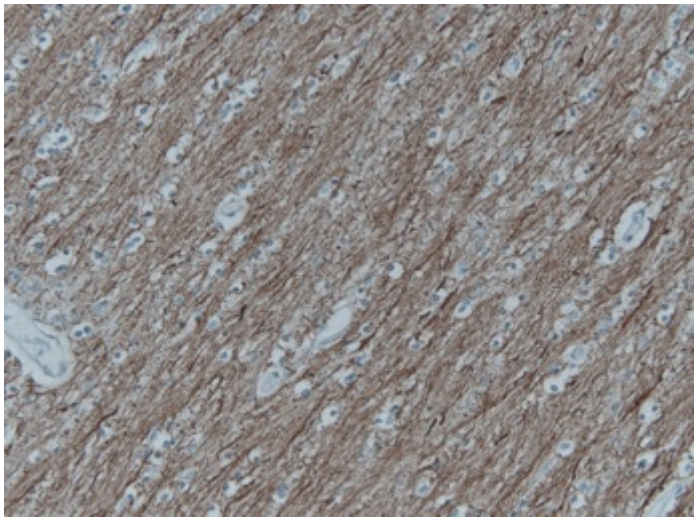


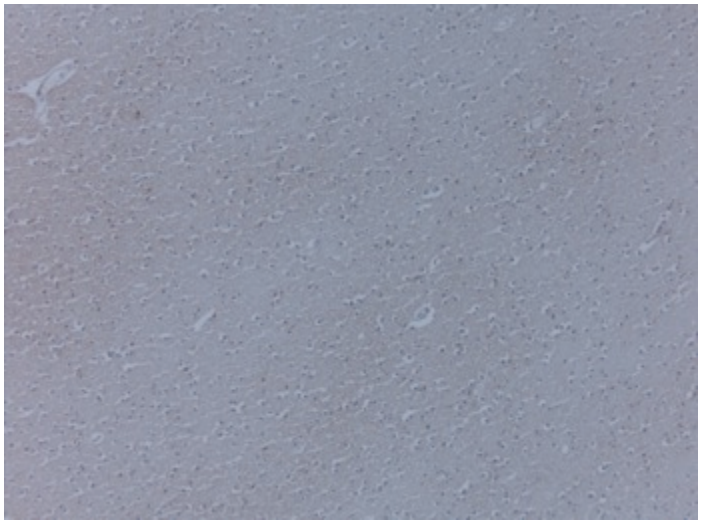
Axons affected in areas of most marked myelin pallor

NFL

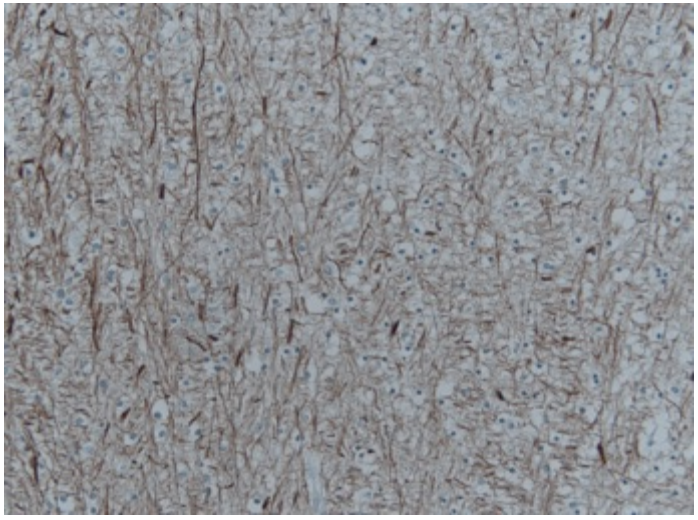
APP

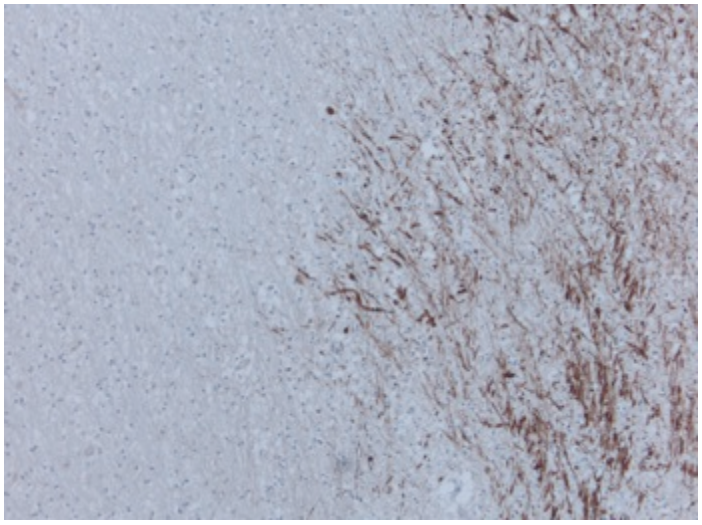
Non-WMH



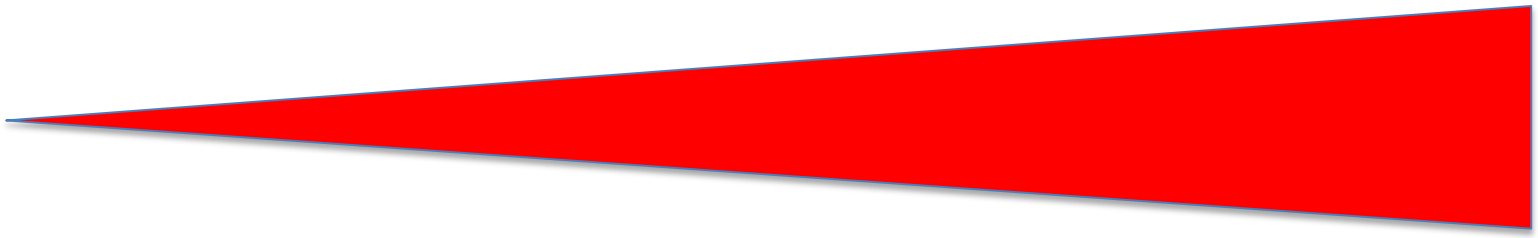


WMH





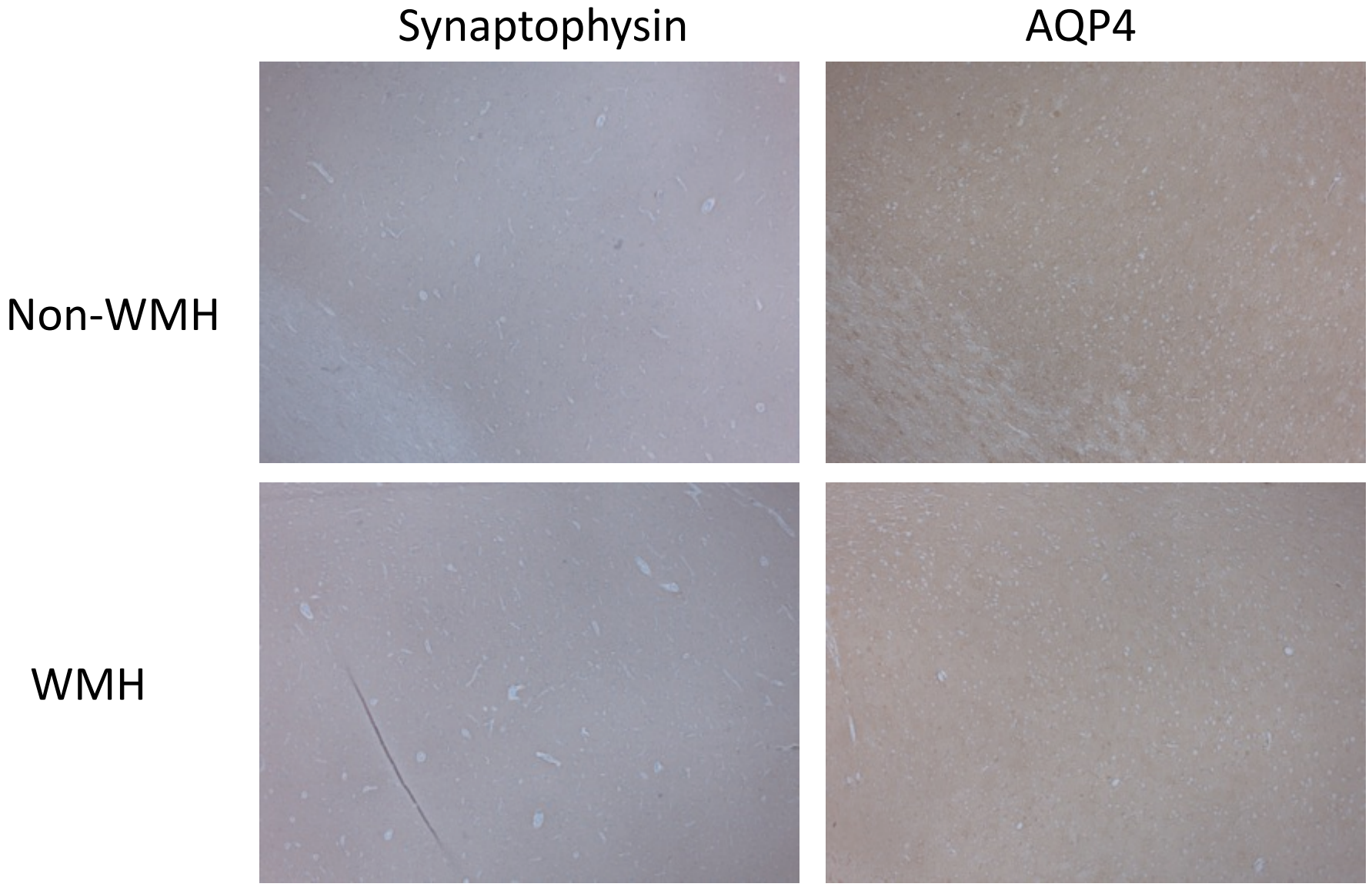
Progressive WM injury in WMHs



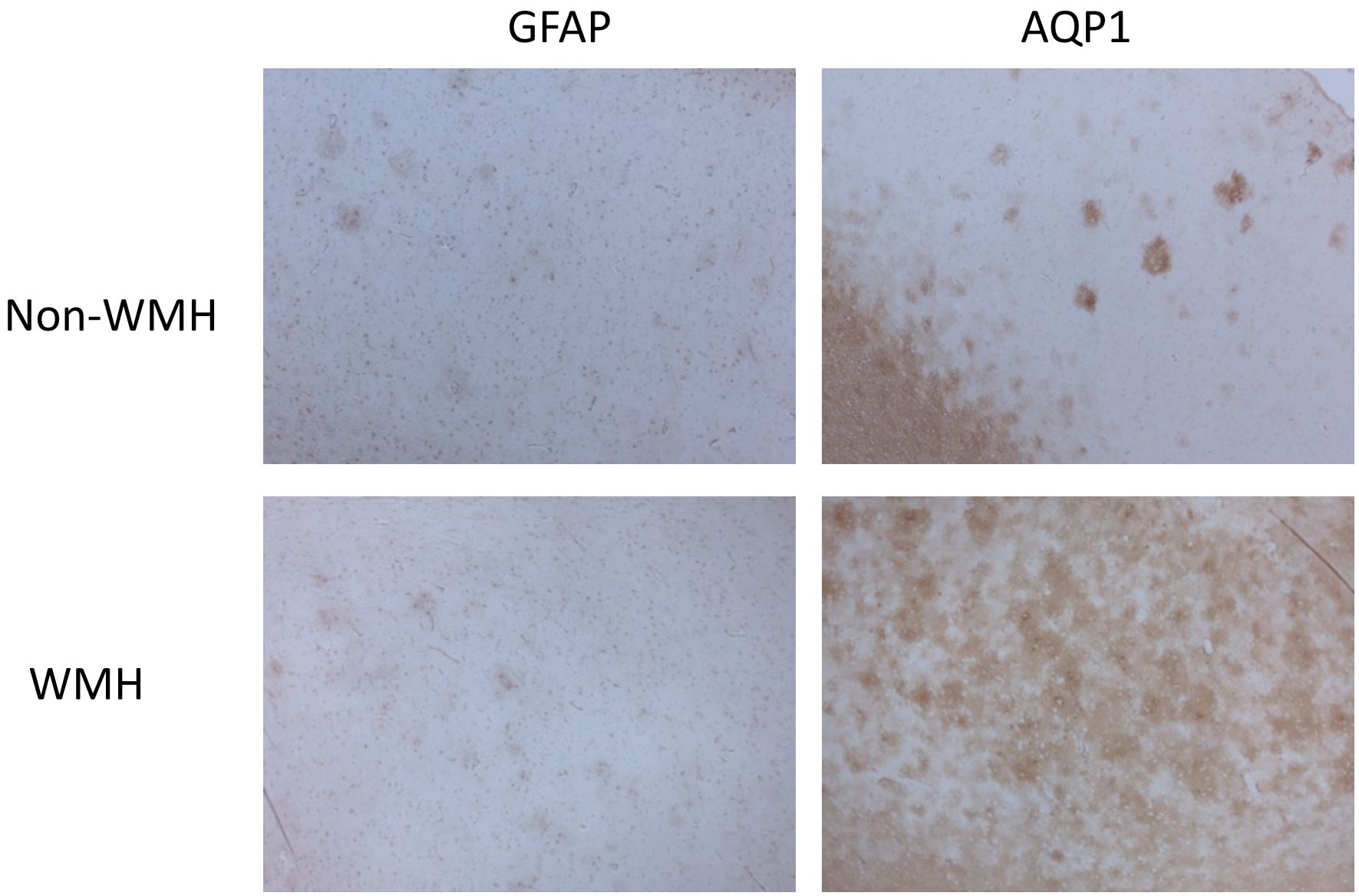
Normal Myelin damage Axonal damage

- Ongoing work: what imaging findings correlate with clinical and histologic features of these types of tissue injury?

Changes in cortex overlying WMHs



Other astrocyte changes in cortex overlying WMHs



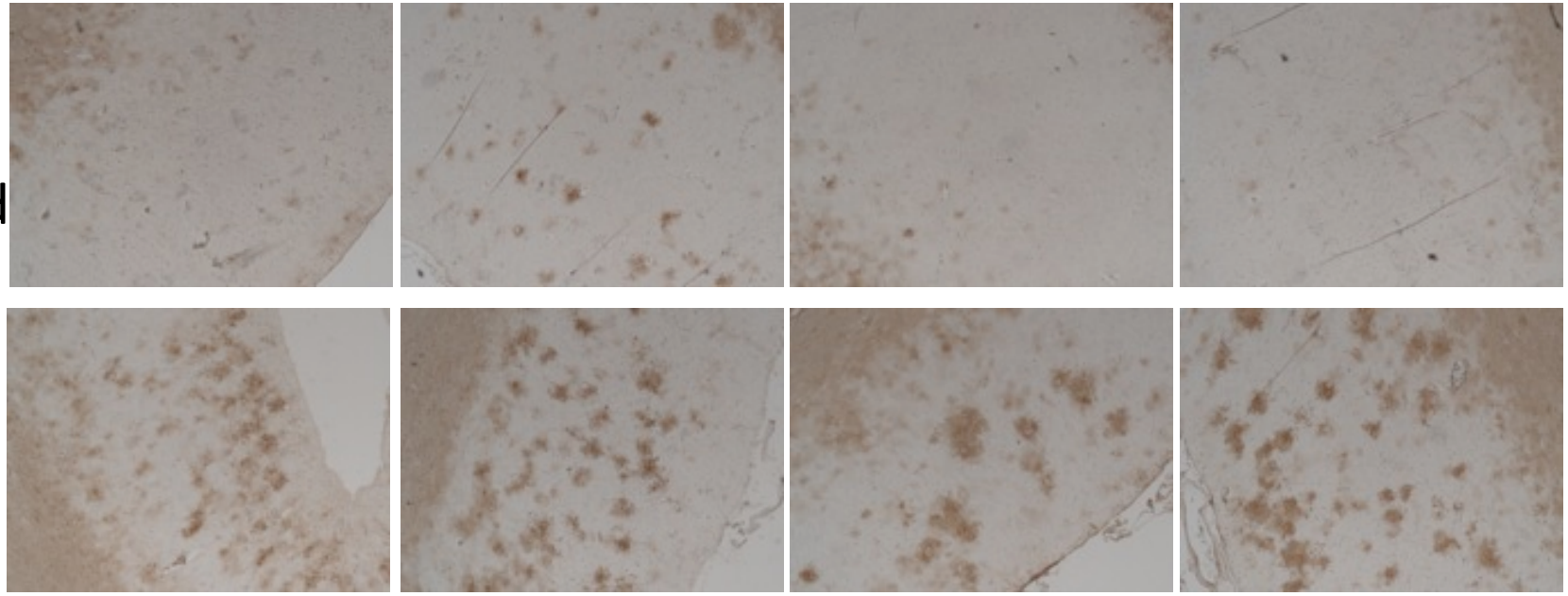
Aquaporin 1

- Normally expressed in choroid plexis; water-selective (non-ionic) channel for CSF production
- Not detected in astrocytes in normal brain
- Increased in reactive astrocytes in a host of injuries including trauma, AD (plaque-associated), MS, CJD, epilepsy
- A sensitive marker of altered vascular permeability associated with brain responses to disease?

Frontal cortex in impaired (CDR=1 or greater) vs. non-impaired (CDR=0) patients >85 years (none with high-burden AD)

Non-impaired

DOOO



Open questions

- Is AQP1 merely a supersensitive GFAP surrogate (“pathology integrator”), or does it inform us of the presence and nature of a clinically relevant disease process in older patients?
- Is AQP1 expression a purely reactive phenomenon to injury, or do changes in astrocyte function (“astrocytopathy”) contribute to brain dysfunction in this population?
- Is astrocytopathy a viable therapeutic target?

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