Clinicopathologic complexities – the multi-proteinopathy problem

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The Diagnostic Process

1. Detailed history including family history, neuro exam, cognitive screen
2. Laboratory assessments
3. Structural imaging (MRI preferred)
4. Detailed neuropsychology testing if needed
5. Additional work-up if indicated (CSF, PET, etc.)

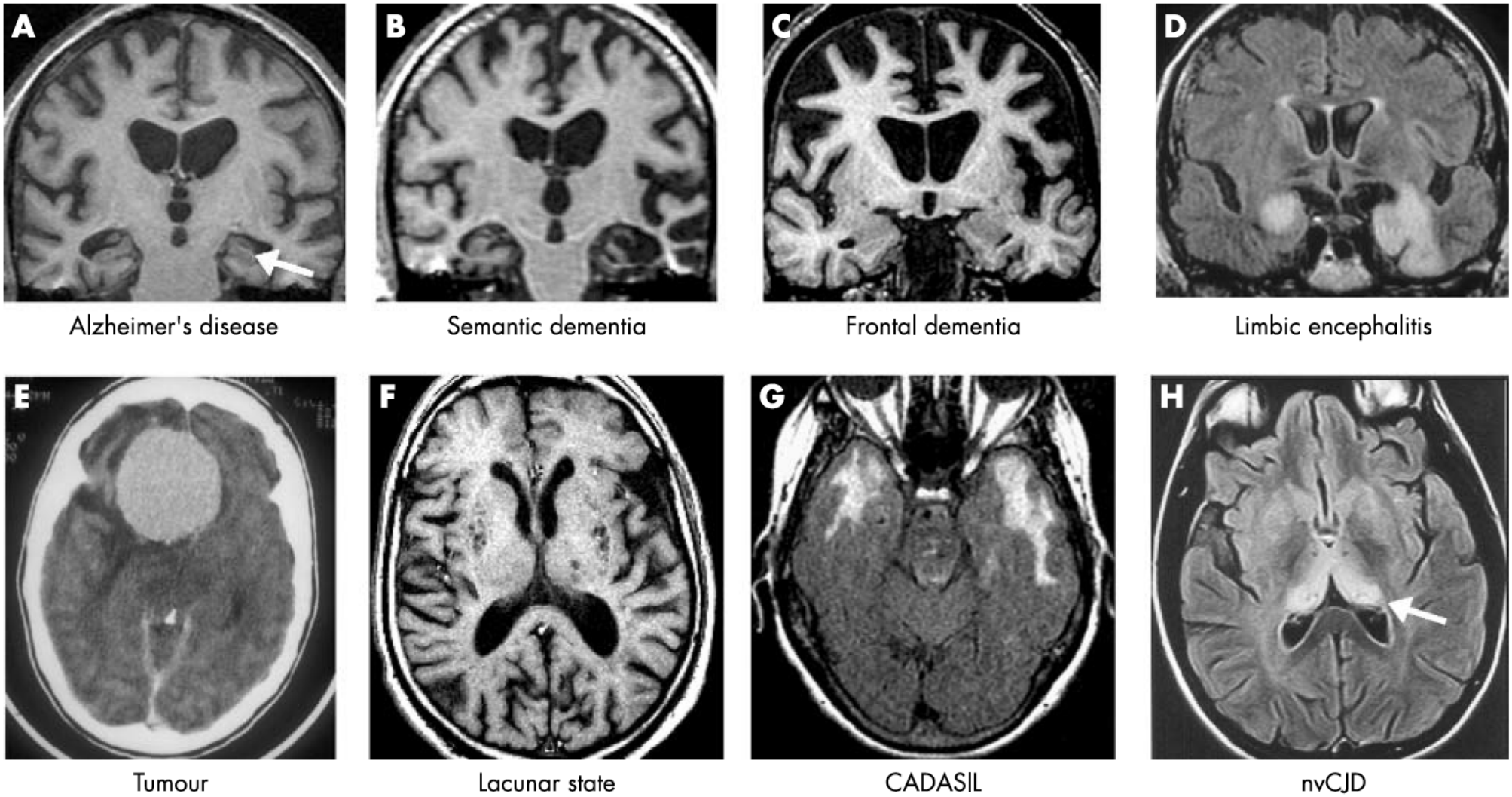
HPI + Cognitive Data + Neurologic Exam

- Formulate the differential diagnosis on the basis of published criteria
  - NIA-AA criteria for MCI and dementia / Dubois criteria
  - AD variants – Crutch criteria for PCA; Gorno -Tempini lvPPA criteria
  - FTD – Lund-Manchester or Neary criteria
  - McKeith DLB criteria
  - Etc.

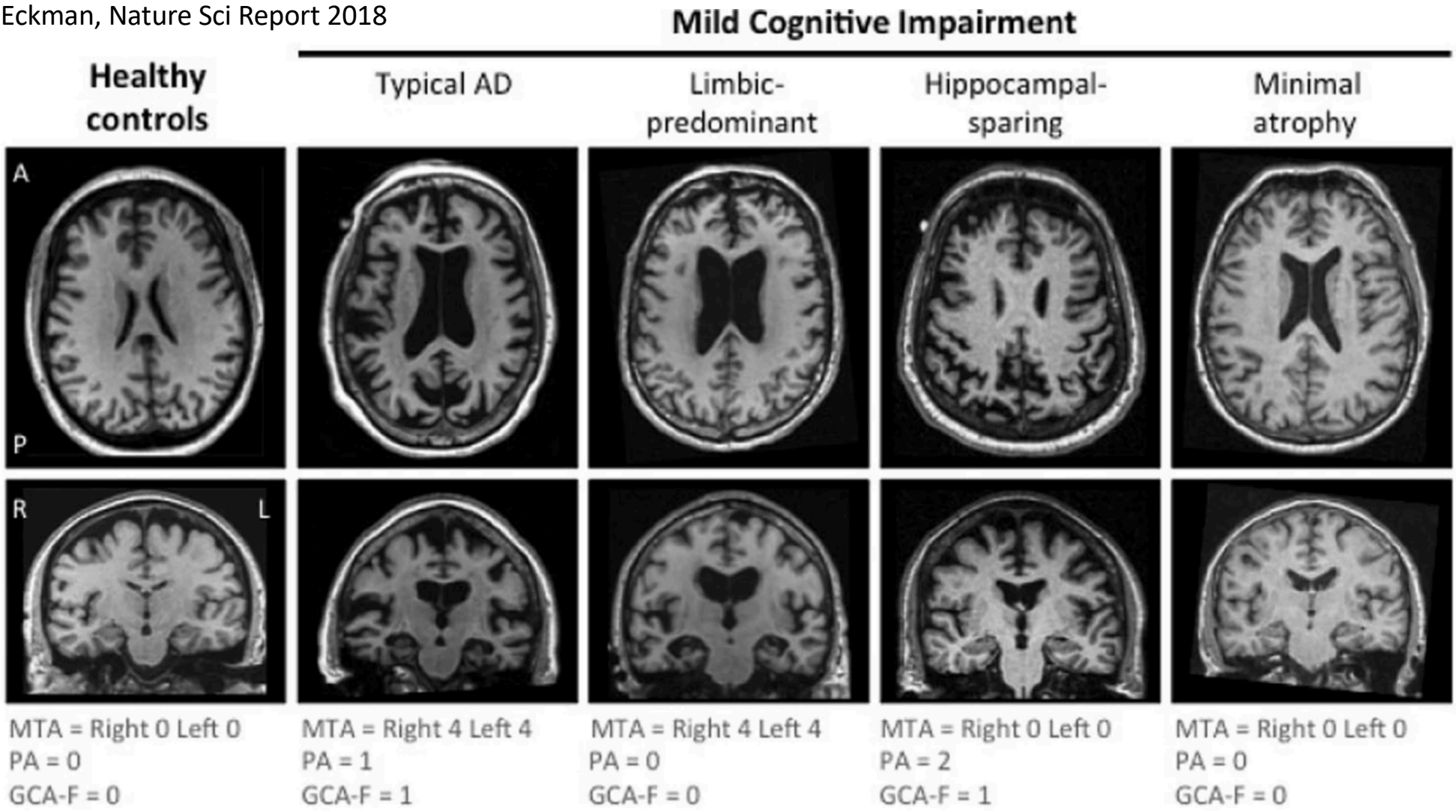
Rule Out Etiologies

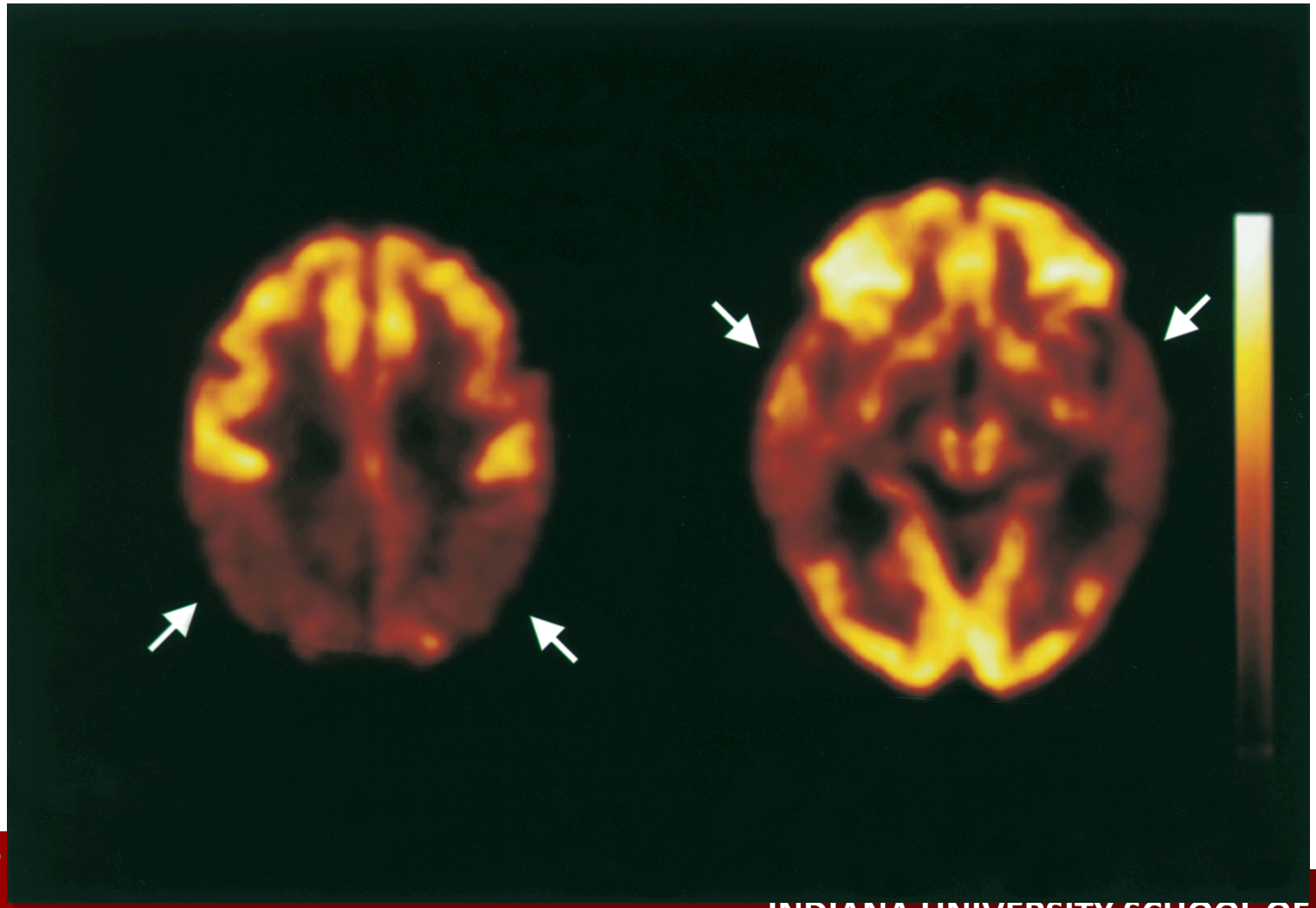
- Depression
- Hypothyroidism
- Vit. B12 deficiency
- End organ failure
- NPH
- Subdural hematoma
- Toxic encephalopathy
- HIV/Syphilis as appropriate

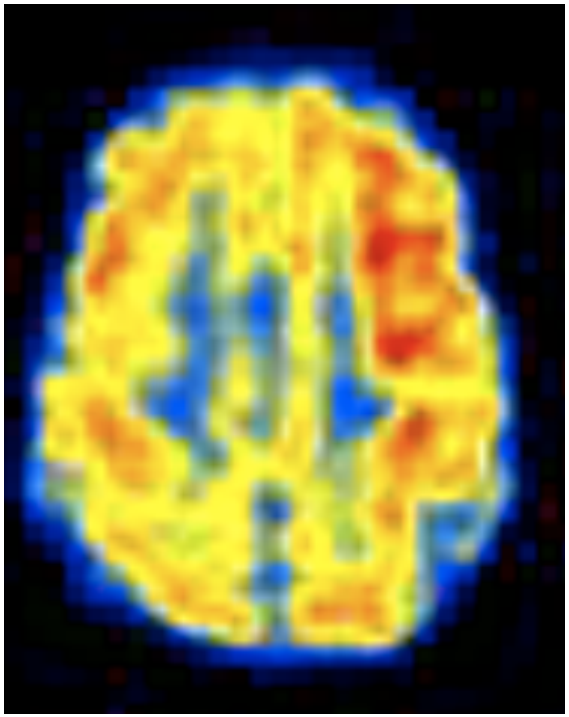
Sampson et al., Postgrad medicine 2004



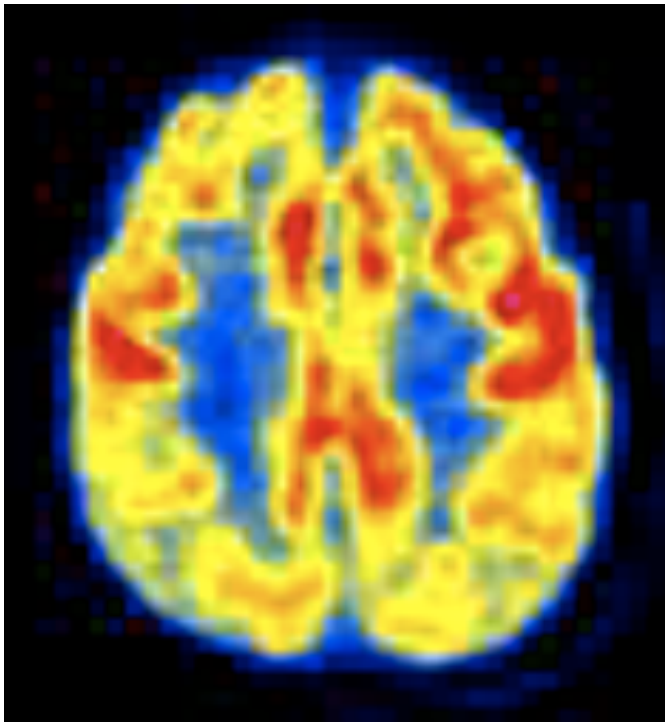
Eckman, Nature Sci Report 2018



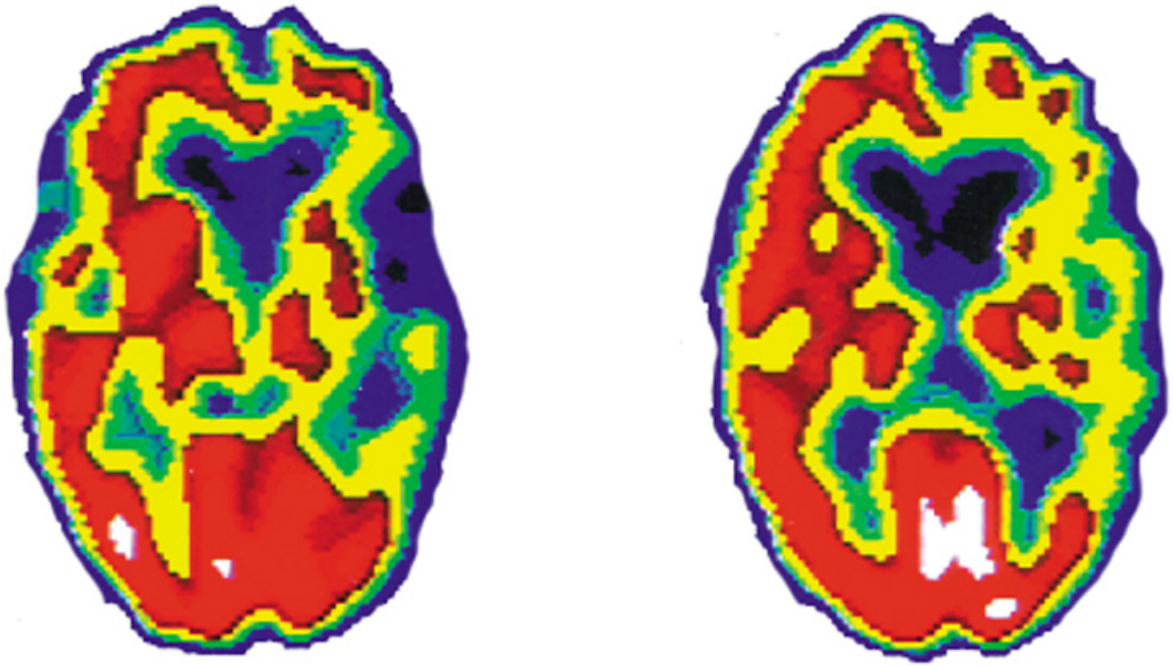




CBD

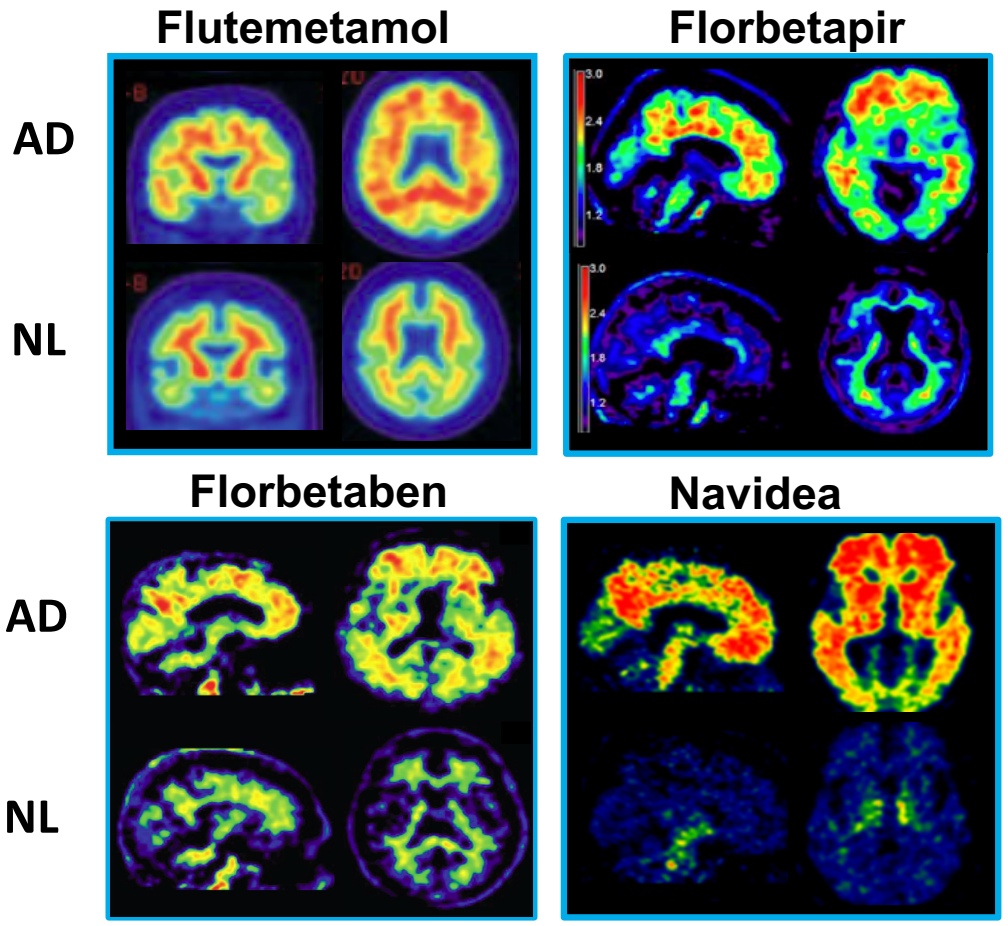


DLB

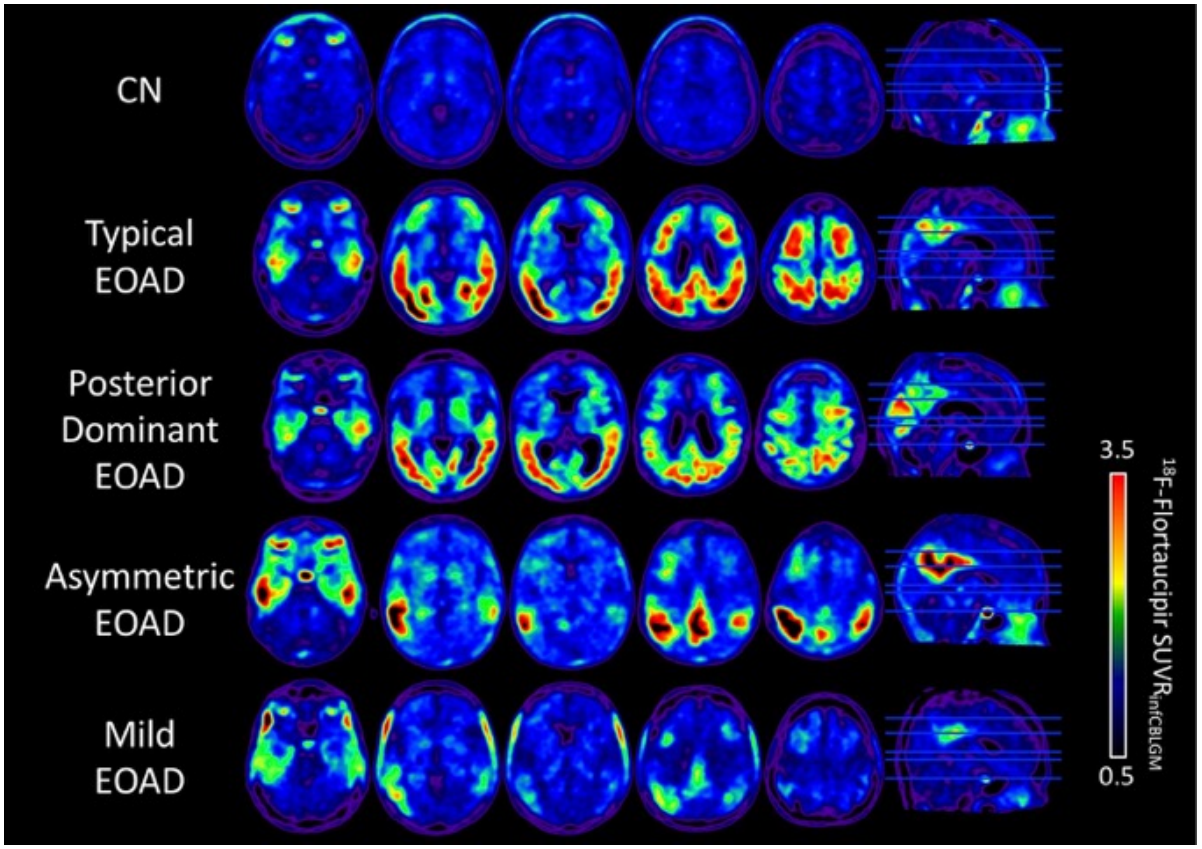


PNFA

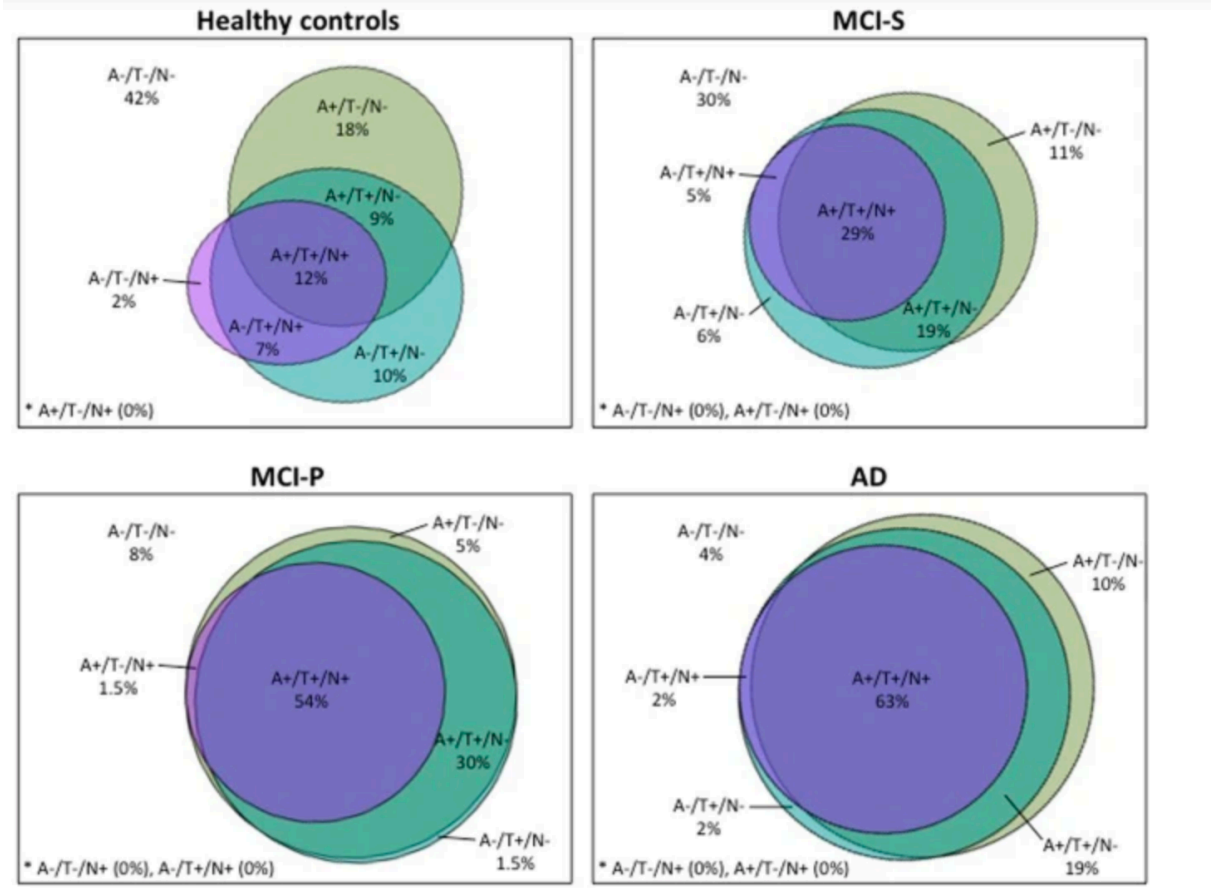
Amyloid PET



Tau PET – LEADS data



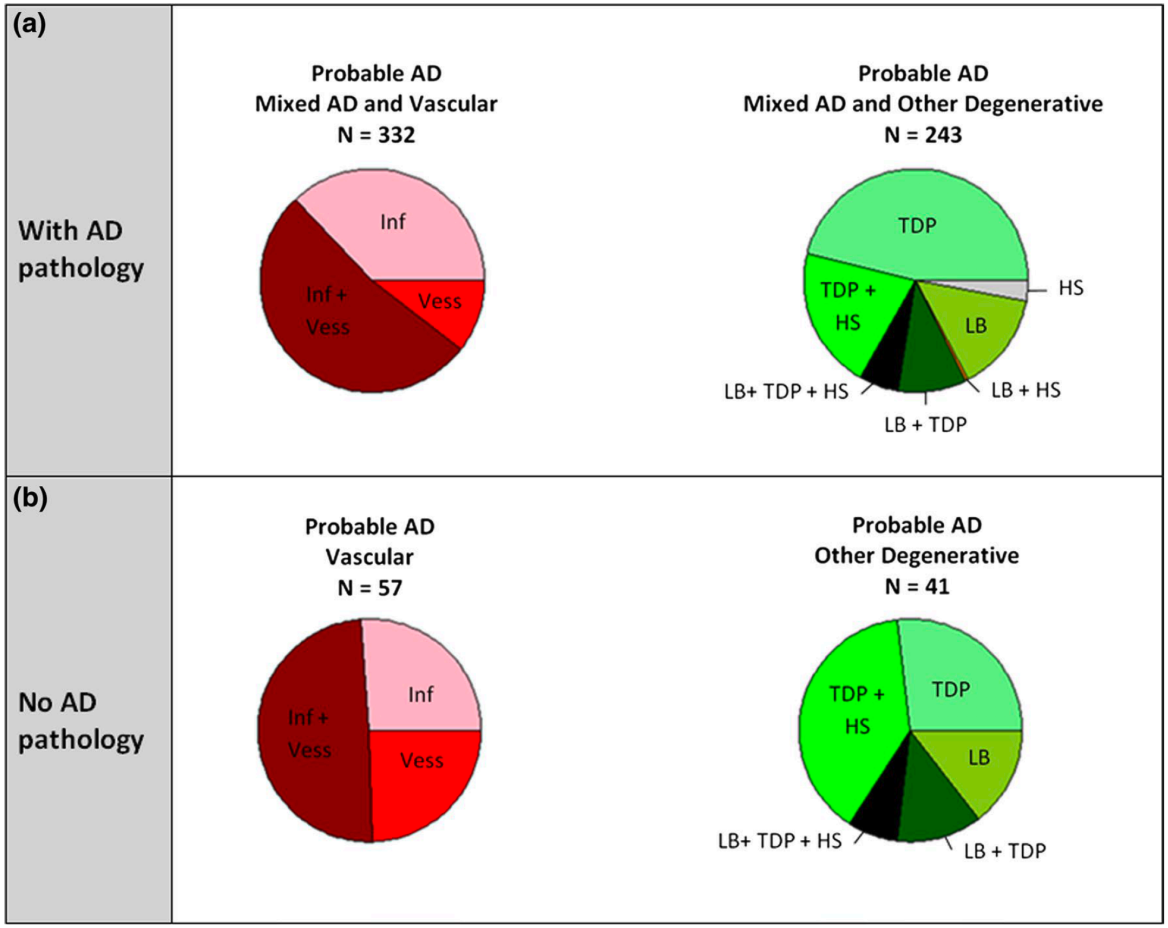
ROS MAP



Prevalence of each A/T/N group Percentages of participants in each ATN group for healthy controls, MCI-S, MCI-P, and AD. HC = healthy controls. MCI-S = MCI participants that are clinically stable across time. MCI-P = MCI participants that progress to AD. AD = Alzheimer's disease. MCI = mild cognitive impairment. CSF = cerebrospinal fluid. A – = CSF Aβ normal. A + = CSF Aβ abnormal. T – = CSF p-tau normal. T + = CSF p-tau abnormal. N– = CSF t-tau normal. N + = t-tau abnormal.

Kapasi et al, Acta Neuropathol 2017

And it is getting more complicated…



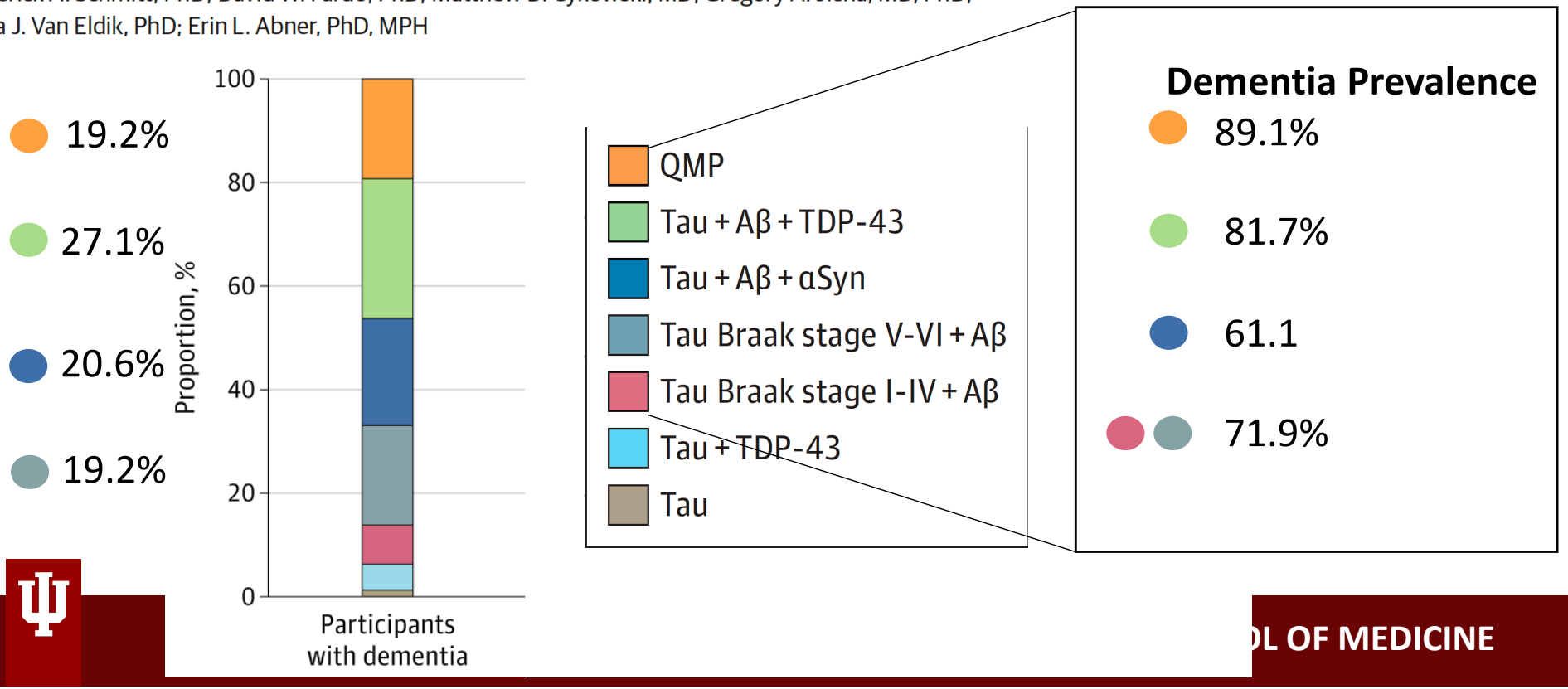
ROS MAP

Kapasi, Acta Neuropath 2017

JAMA Neurology | Original Investigation

Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults

Shama Karanth, MDS; Peter T. Nelson, MD, PhD; Yuriko Katsumata, PhD; Richard J. Kryscio, PhD; Frederick A. Schmitt, PhD; David W. Fardo, PhD; Matthew D. Cykowski, MD; Gregory A. Jicha, MD, PhD; Linda J. Van Eldik, PhD; Erin L. Abner, PhD, MPH



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- 14/83 (16.9%) of cognitively normal participants had quadruple proteinopathy
- MCI with quadruple proteinopathy showed faster conversion to dementia (more aggressive disease)
- PURE AD was rare (19.2%)

LATE (Nelson, Brain 2019)

- LATE is 100x more common that FTD due to TDP-43
- Clinically: older patients (LATE-20% in 80+ years old), more gradual cognitive decline and more agitation than pure AD but the combination – accelerated cognitive decline > pure AD
- Imaging: asymmetric, more severe hippocampal atrophy (anterior hippocampus), hypometabolism/atrophy in the medial temporal lobe and inferior frontal gyrus

ARTAG (Nolan et al. J Neuropathol Exp Neurol 2019)

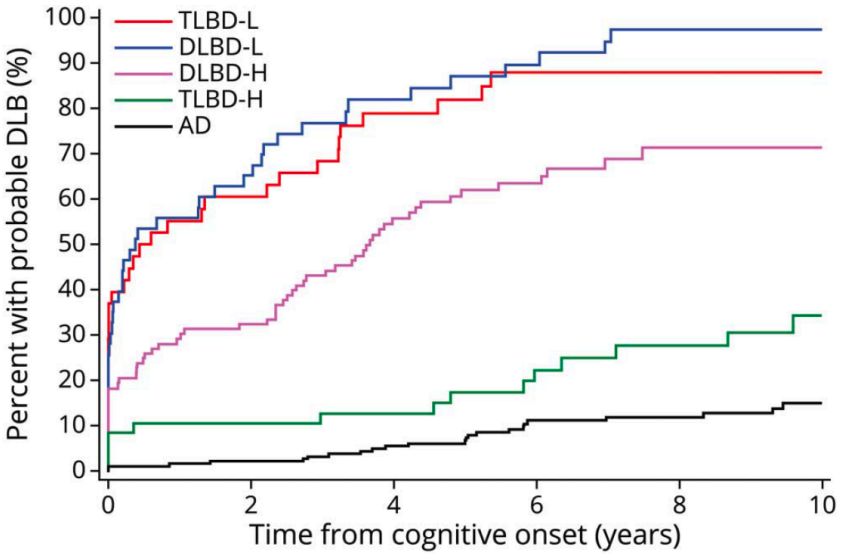
- 64% of autopsy cases (N=83) showed ARTAG
  - 67% of amnestic predominant
  - 43% of CBD
  - 57% of lvPPA
  - 57% of very mild dementia
  - 50% of PCA
  - All CN (N=3)

LBD spectrum (Ferman et al, Neurology 2020)

- In the presence of **tau NFTs** the diagnostic accuracy of clinical Dx of probable DLB (2+ of VH, fluctuations, parkinsonism, RBD) and DLB syndrome (1 sx) declined
  - w/o NFT - 96% sensitivity for prob DLB with diffuse LB
  - w NFT – 70% sensitivity for prob DLB with diffuse LB (+ onset of DLB clin syndrome later in the disease course)
- Among those with pure AD pathology 16% had 2+ and 22% 1 feature c/w clinical Dx of probable DLB or DLB syndrome

LBD + NFT affect both the clinical presentation and prognosis

Figure 1 Cumulative incidence model for the latency of probable dementia with Lewy bodies (DLB) across pathologic subgroups



L - NFT-
H – NFT+

Causative Pathology

- Can clinicians accurately predict all concomitant proteinopathies in the absence of biomarkers?

WE CAN'T

- **In cases with multiple proteinopathies, a formal clinicopathologic consensus conference might be warranted** to determine the primary etiology via interpretation of the pathology data in the context of the observed clinical syndrome