

# Limbic-predominant age-related TDP-43 Encephalopathy (LATE)

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# Disclosures

- I am on the Speakers Bureau of MedBridge.
- CME policy: Within the past 24 months, I have not had any relevant financial relationships with any commercial interest relevant to the content I am presenting for this activity.

# Learning Objectives

- Identify clinical features of limbic predominant age-related TDP-43 “encephalopathy” (LATE)
- Recognize imaging features of LATE
- Consider clinical implications of a diagnosis of LATE
- Distinguish LATE from other dementia-related TDP-43 diseases
- Compare prognostic implications of “pure” LATE neuropathologic change (LATE-NC) versus co-morbid Alzheimer’s disease neuropathologic change (AD-NC)

# Historical perspective: identification of TDP-43

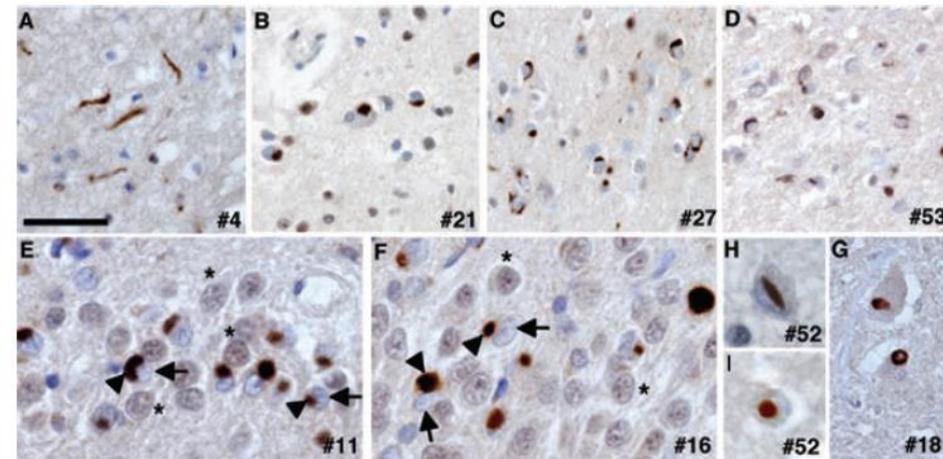
- Transactive response DNA-binding protein of 43 kDa
- 1995: identified as suppressor of HIV-1 gene expression
- 2006: hyperphosphorylated, ubiquitinated cytoplasmic inclusions (“UBIs”) identified as pathologic feature of *ALS and FTLD*

REPORTS

## Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,<sup>1,11\*</sup> Deepak M. Sampathu,<sup>1\*</sup> Linda K. Kwong,<sup>1\*</sup> Adam C. Truax,<sup>1</sup> Matthew C. Micsenyi,<sup>1</sup> Thomas T. Chou,<sup>2</sup> Jennifer Bruce,<sup>1</sup> Theresa Schuck,<sup>1</sup> Murray Grossman,<sup>3,4</sup> Christopher M. Clark,<sup>3,4</sup> Leo F. McCluskey,<sup>3</sup> Bruce L. Miller,<sup>6</sup> Eliezer Masliah,<sup>7</sup> Ian R. Mackenzie,<sup>8</sup> Howard Feldman,<sup>9</sup> Wolfgang Feiden,<sup>10</sup> Hans A. Kretzschmar,<sup>11</sup> John Q. Trojanowski,<sup>1,4,5</sup> Virginia M.-Y. Lee<sup>1,4,5</sup>†

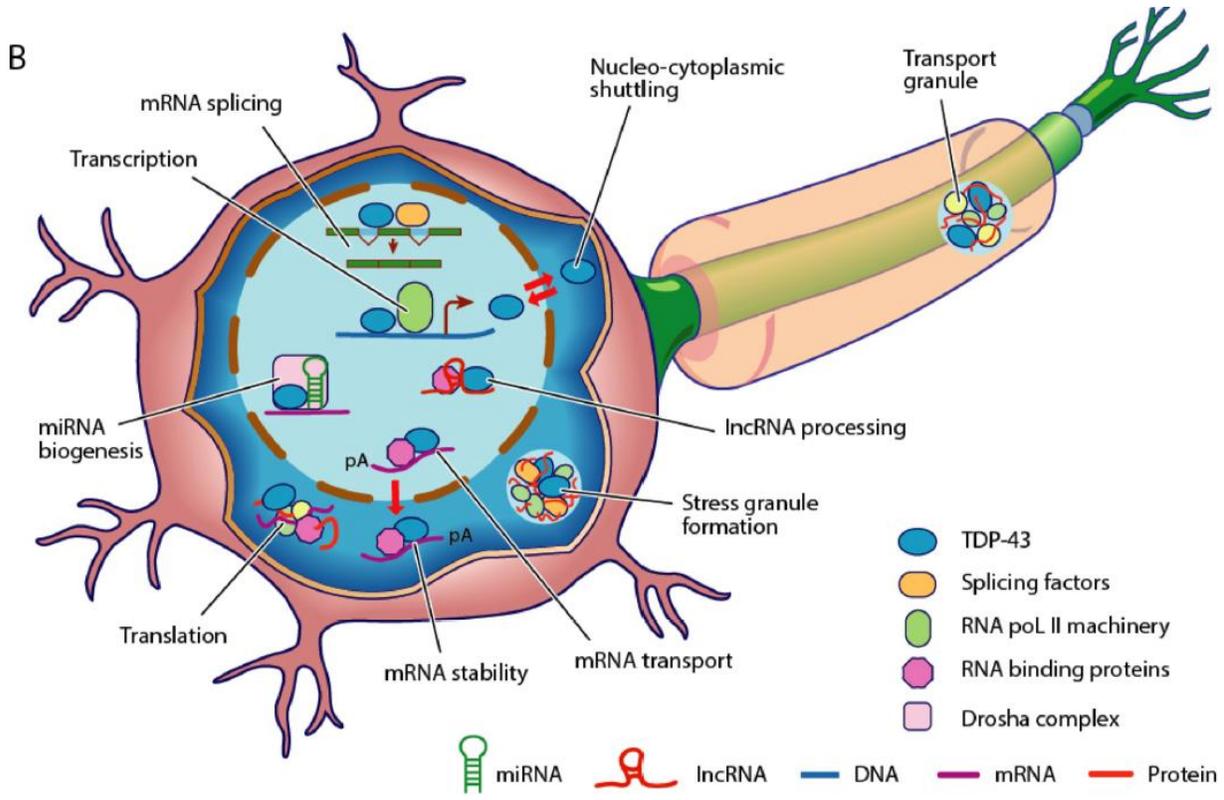
Ubiquitin-positive, tau- and  $\alpha$ -synuclein-negative inclusions are hallmarks of frontotemporal lobar degeneration with ubiquitin-positive inclusions and amyotrophic lateral sclerosis. **Although the identity of the ubiquitinated protein specific to either disorder was unknown, we showed that TDP-43 is the major disease protein in both disorders.** Pathologic TDP-43 was hyperphosphorylated, ubiquitinated, and cleaved to generate C-terminal fragments and was recovered only from affected central nervous system regions, including hippocampus, neocortex, and spinal cord. TDP-43 represents the common pathologic substrate linking these neurodegenerative disorders.



**Fig. 2.** Spectrum of FTLD-U neuropathology detected by anti-TDP-43. Immunohistochemistry of FTLD-U frontal cortex with anti-TDP-43 reveals robust staining of UBIs in FTLD-U (A) type 1, (B) type 2, (C) type 3, and (D) H4DD2. (E and F) Strong staining of UBIs (arrowheads) in hippocampal dentate granule neurons. Note clearing of nuclear TDP-43 (arrows) in UBI-bearing neurons compared that of with normal neurons (\*). TDP-43-positive lentiform (H) and round (G) intranuclear UBIs in H4DD2 and Lewy body-like round inclusions in motor neurons of spinal cord (I). Scale bar in (A) corresponds to 50  $\mu$ m [(A) to (D) and (G)], 25  $\mu$ m [(E) and (F)] and 20  $\mu$ m [(H) and (I)].

# TDP-43 is involved in multiple cellular functions

- Nucleus: mRNA transcription, splicing, transport
- Cytoplasm: formation of stress and ribonucleoprotein (RNP) transport granules



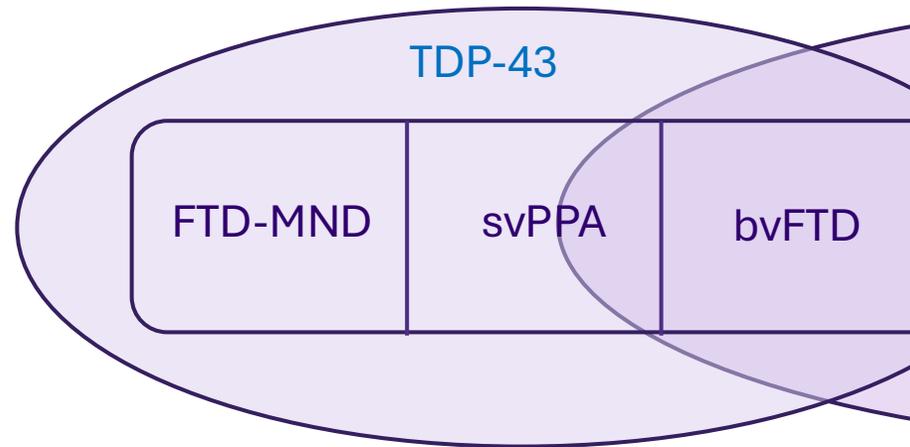
- Shuttles between nucleus and cytoplasm
  - Under normal physiologic conditions, primarily localized in the nucleus
- Also localizes to mitochondria
- Critical for normal development of central nervous system in early embryogenesis

De Boer et al *JNNP* 2020

# Dementia-related TDP-43 clinical spectrum (broadly)

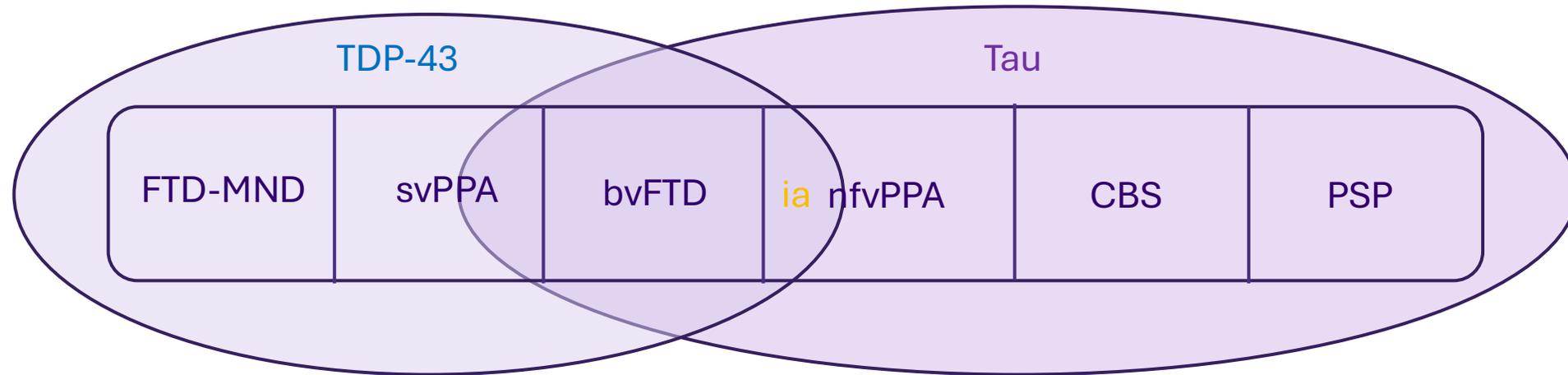
- Motor neuron disease (MND)
- Frontotemporal dementia (FTD)
  - behavioral variant frontotemporal dementia
  - semantic variant primary progressive aphasia
- FTD-MND

# FTD Clinical Syndromes and Pathology



- Frontotemporal dementia – motor neuron disease
- Semantic variant Primary Progressive Aphasia
- Behavioral variant frontotemporal dementia

# FTD Clinical Syndromes and Pathology 2



- Frontotemporal dementia – motor neuron disease
- Semantic variant Primary Progressive Aphasia
- Behavioral variant frontotemporal dementia
- Nonfluent variant Primary Progressive Aphasia
- Corticobasal syndrome
- Progressive supranuclear palsy

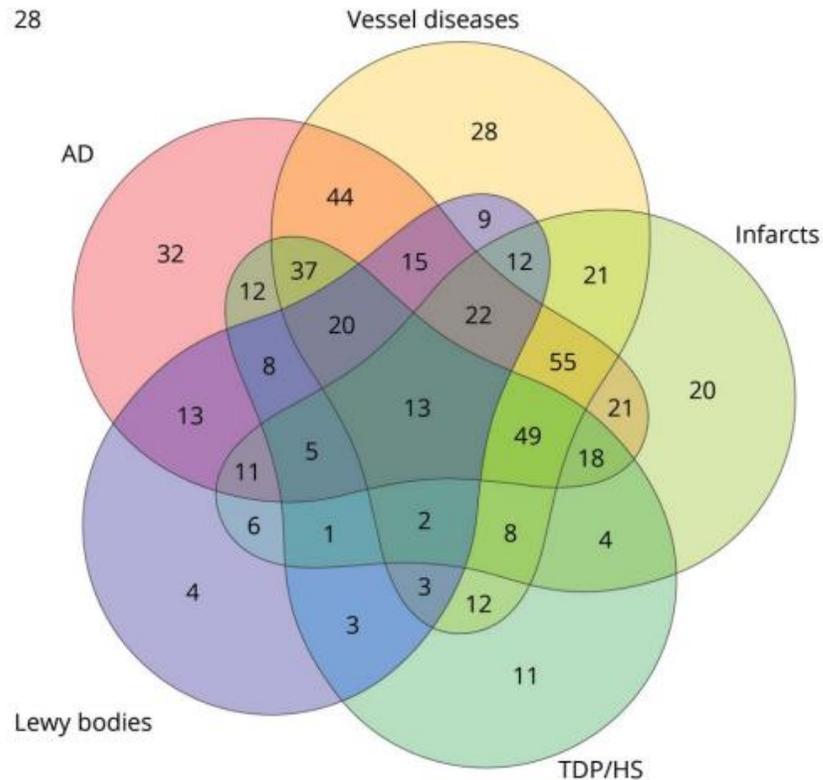
# Dementia-related TDP-43 clinical spectrum (broadly 2<sup>nd</sup> slide)

- Motor neuron disease (MND)
- Frontotemporal dementia
  - behavioral variant frontotemporal dementia
  - semantic variant primary progressive aphasia
- FTD-MND
- Limbic predominant age-related TDP-43 “encephalopathy” (LATE)

Newer TDP-43 disease entity:  
Limbic Predominant Age-Related TDP-43  
Encephalopathy (“LATE”)

# Limbic Predominant Age-Related TDP-43 Encephalopathy (“LATE”)

Figure 2 Pattern of mixed pathologies in older persons



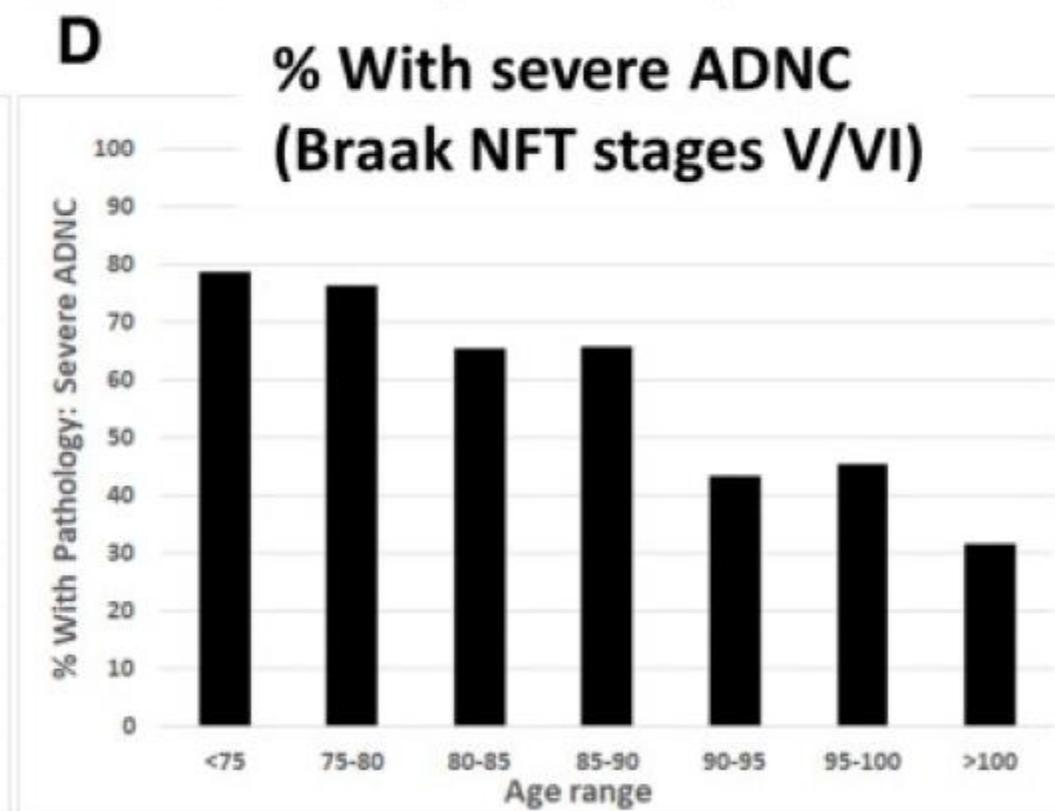
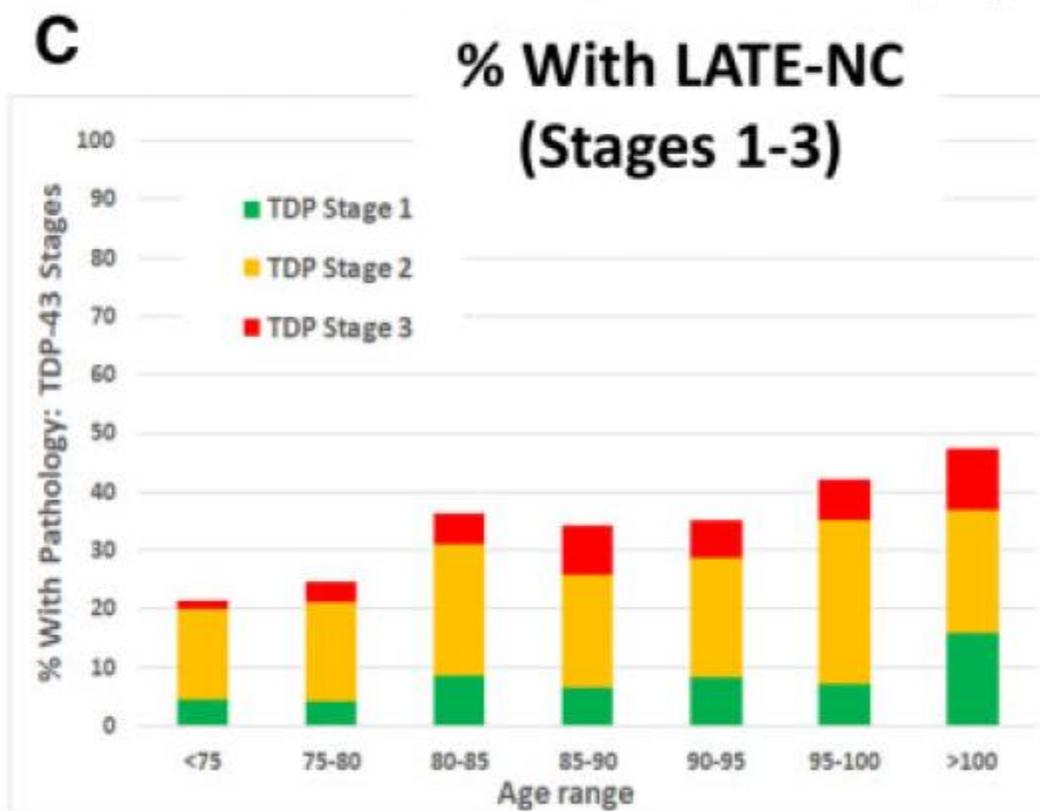
LATE-NC present in ~30% of human brains  $\geq 85$ yo  
(NC = neuropathologic change)

547 autopsies in older cohort

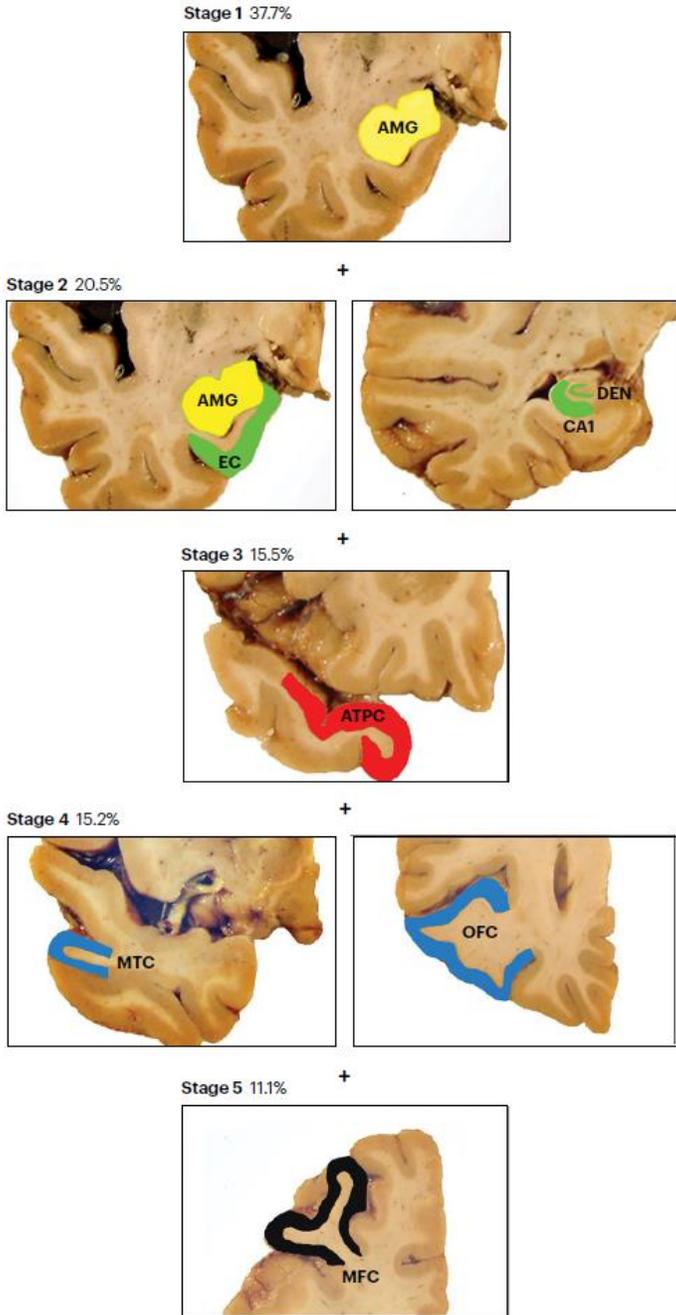
- Ave 90.4yo at death
- 42.4% Alzheimer’s disease (AD) dementia
- 68.6% AD-NC; only 8.5% “pure” AD-NC
- 80% multiple neuropathologies

# With advancing age, LATE-NC increases & AD-NC decreases

NACC multicentre autopsy cohort data ( $n = 806$ )



# LATE-NC pathologic staging



- **Stage 1:** amygdala
  - → typically no cognitive impairment
- **Stage 2:** entorhinal cortex, dentate, CA1
- **Stage 3:** anterior temporal pole cortex
  - → Stage 3 and beyond more likely to have dementia
- **Stage 4:** middle temporal cortex, orbitofrontal cortex
- **Stage 5:** middle frontal cortex

# LATE-NC staging systems

## LATE-NC related stages based on anatomic distribution of TDP-43 pathology

Simplified staging of TDP-43 proteinopathy* for routine LATE-NC diagnosis (consensus recommendation)		Josephs TDP-43 proteinopathy staging (KA Josephs et al, 2013)		Rush University TDP-43 proteinopathy staging (S Nag et al, 2017)	
0	None	0	None	0	None
1	Amygdala	1	Amygdala	1	Amygdala
2	Hippocampus	2	Entorhinal cortex, subiculum	2	Entorhinal cortex, CA1
		3	Dentate, Occipitotemporal cortex	3	Anterior temporal cortex
		4	Insula, Inf temporal cortex	4	Midtemporal and orbitofrontal cortex
		5	Inf olive, midbrain		
3	Middle frontal gyrus (MFG)	6	Basal ganglia, MFG	5	MFG

\*-Any TDP-43 proteinopathy is seen in that anatomic region

- Initial pathology confined to the amygdala, and without clinical symptoms
- Hippocampal region with mild cognitive symptoms

# LATE: clinical features

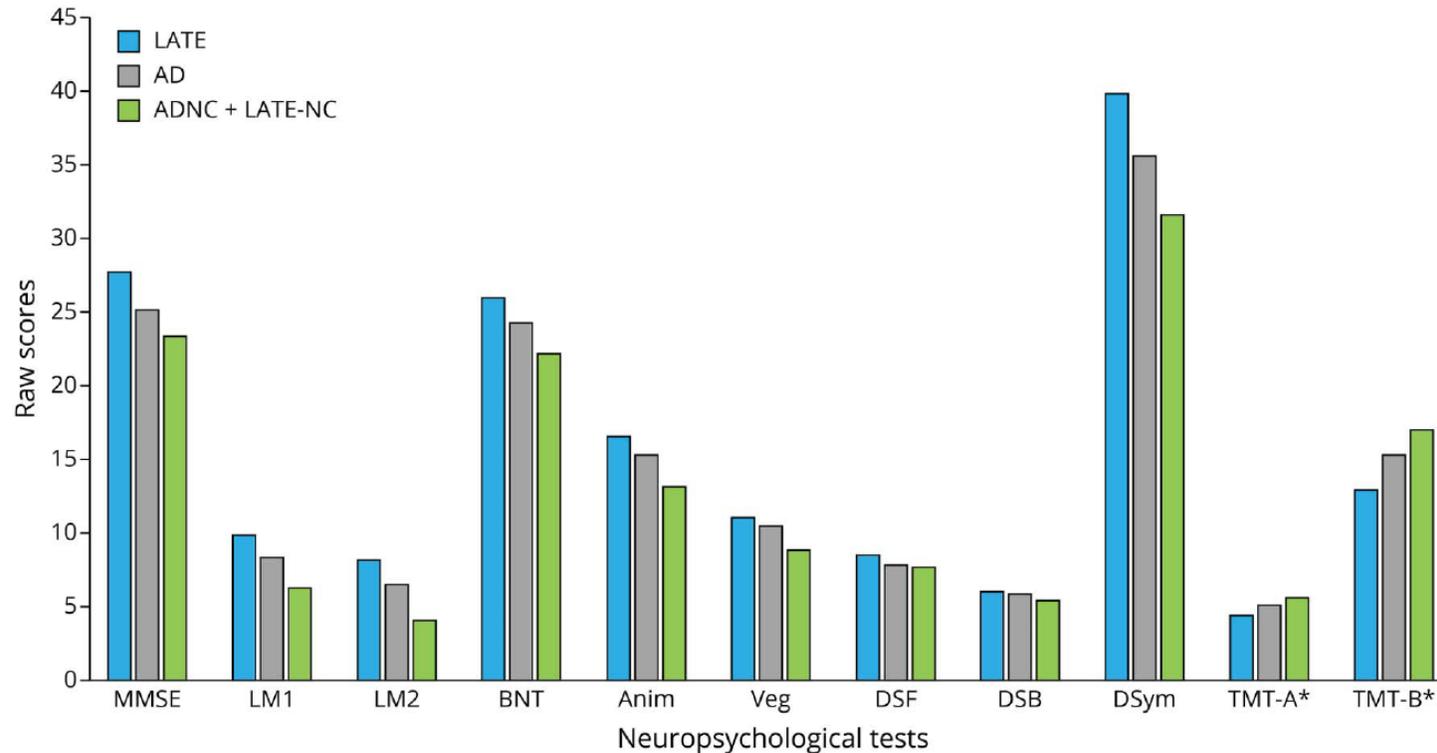
- Older person with progressive memory loss and progressive hippocampal atrophy → *sounds like Alzheimer's disease!*
- Demographic features
  - No sex difference
  - Pure LATE-NC more common > 90yo (“oldest old”)

# LATE: cognitive profile

- Clinical mimic of cognitive impairment due to Alzheimer's disease, with some distinguishing features
- Cognitive profile
  - Relatively isolated episodic memory impairment for more than 2 years
    - Able to encode, but impaired recall after a delay even with cues
    - May have mild semantic memory deficits
      - Naming, knowledge of famous people / events
  - Other cognitive domains relatively spared until later in disease course
    - Versus multidomain decline in typical Alzheimer's disease

# LATE: Cognitive Profile

**Figure** Neuropsychological Test Performance by Pathology Group

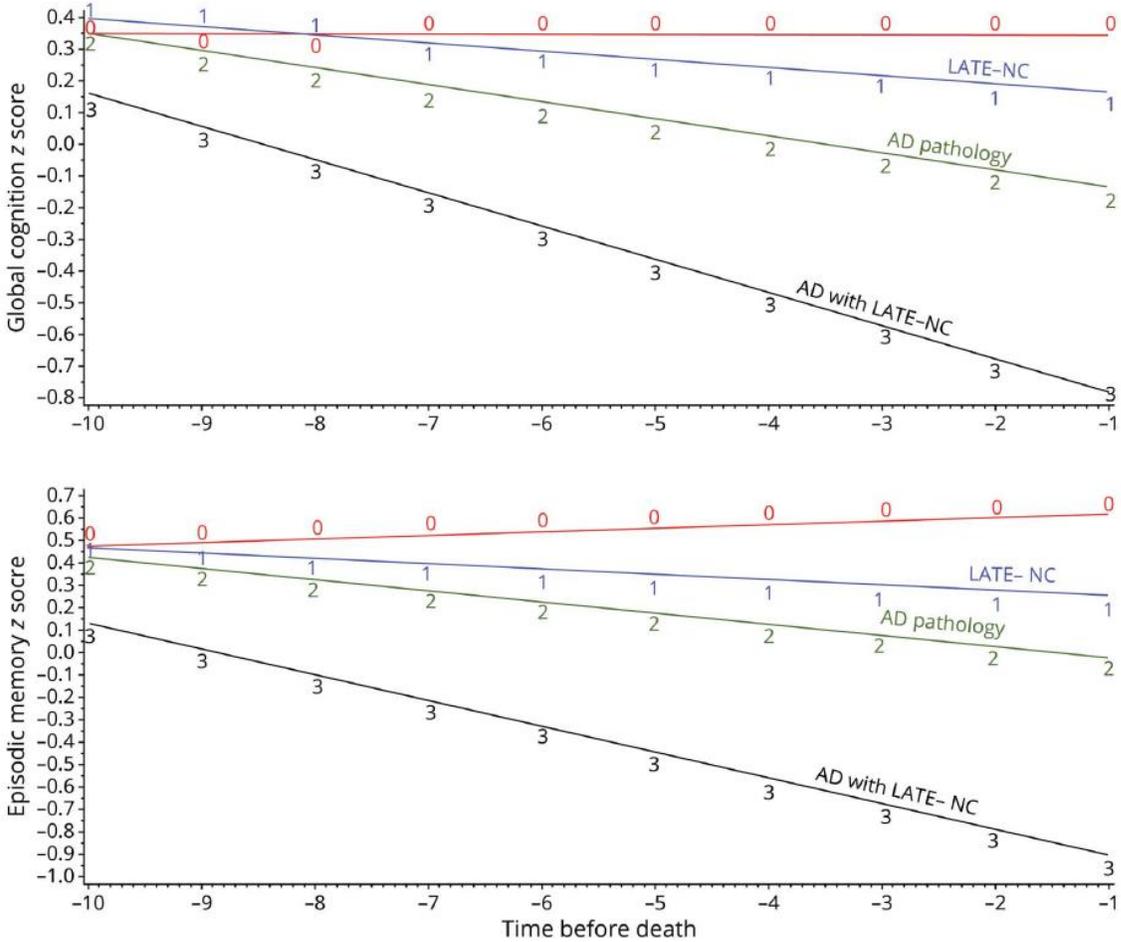


Individuals with pure LATE-NC demonstrate better test performance than those with AD-NC

Anim = Animal Naming; BNT = Boston Naming Test-Short Form; DSB = Digit Span Backward; DSF = Digit Span Forward; DSym = Digit Symbol Substitution; LM1 = Logical Memory I; LM2 = Logical Memory 2; MMSE = Mini-Mental State Examination; TMT-A = Trail Making Test, A; TMT-B = Trail Making Test, B; Veg = Vegetable Naming. All values represent raw, unadjusted performance. Values denoted with \* have been divided by 10 for ease of visualization.

# LATE: cognitive profile 2

**Figure 2** Cognitive trajectories for those with LATE-NC, AD pathology, and mixed AD with LATE-NC pathology



Individuals with pure LATE-NC experience slow cognitive decline, especially episodic memory loss

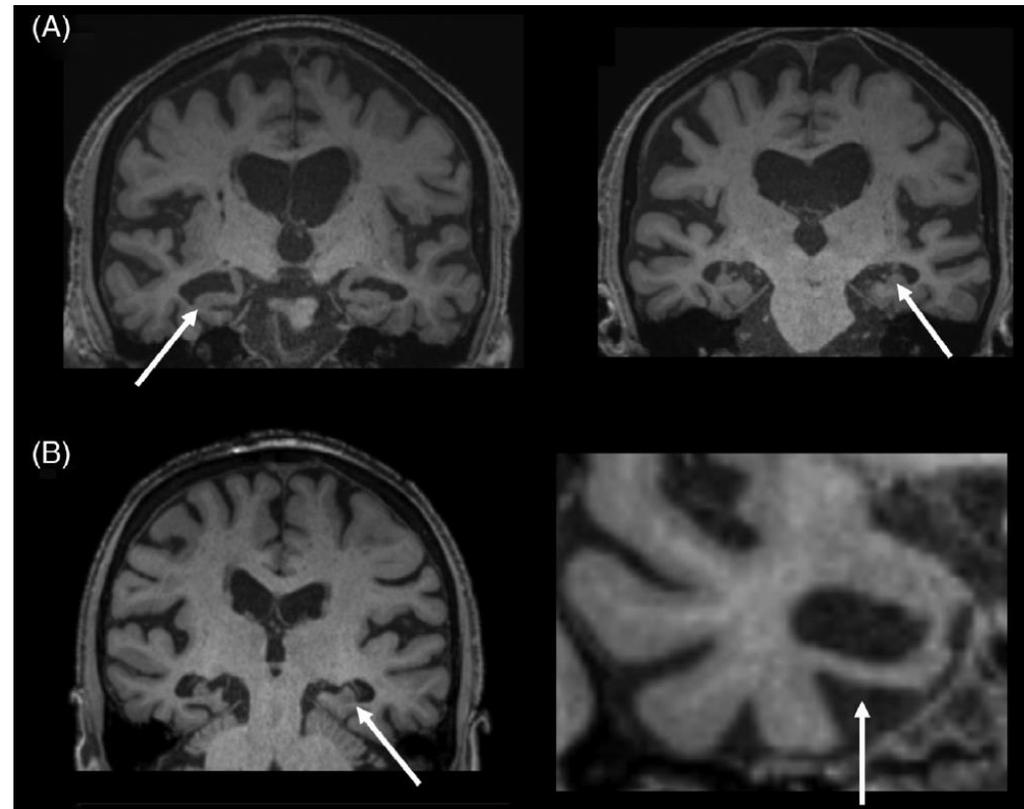
Individuals with AD-NC and LATE-NC experience more rapid cognitive decline

Derived from mixed-effect models adjusted for age, sex, education, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, any Lewy body pathology, and APOE ε4. AD = Alzheimer disease; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change.

# LATE: structural imaging findings

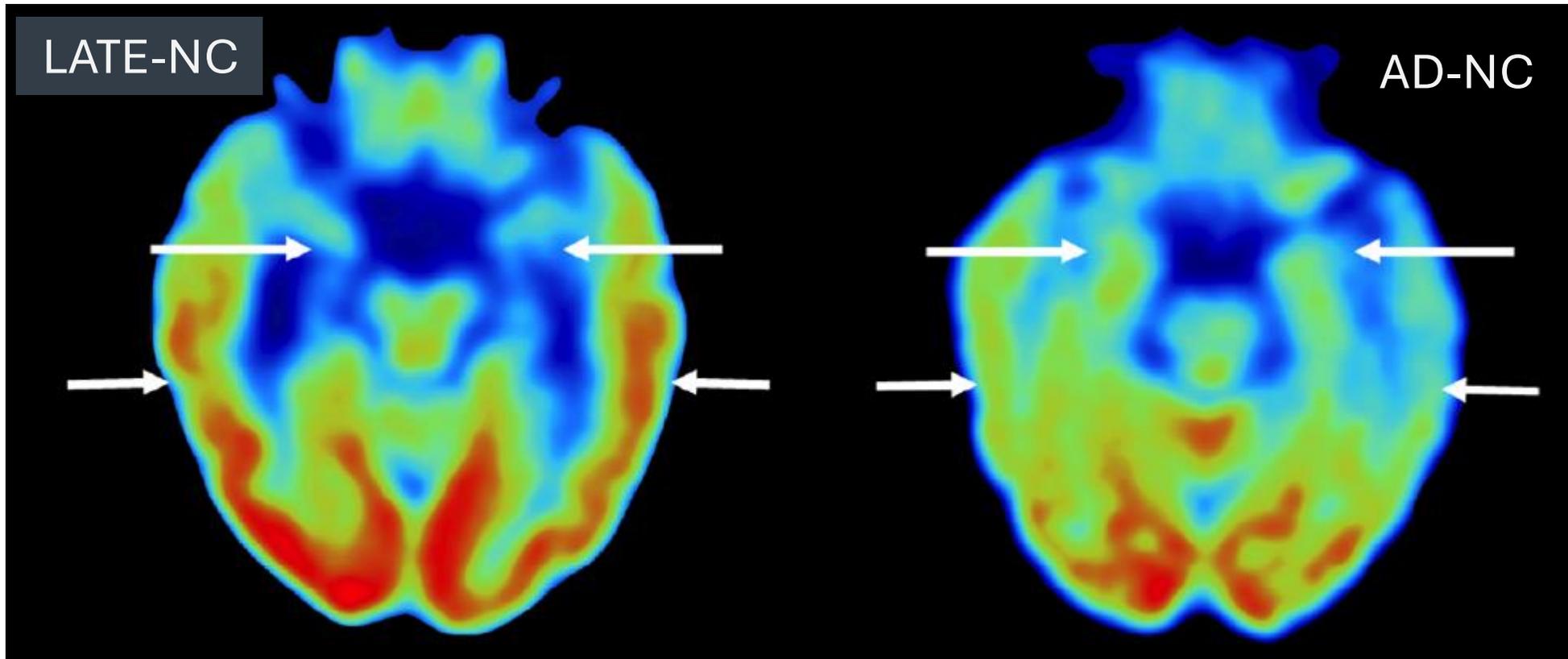
- Hippocampal atrophy out of proportion to global brain atrophy

- Widening of collateral sulcus and thinning of adjacent cortical structures (not typically seen in “pure” AD-NC)

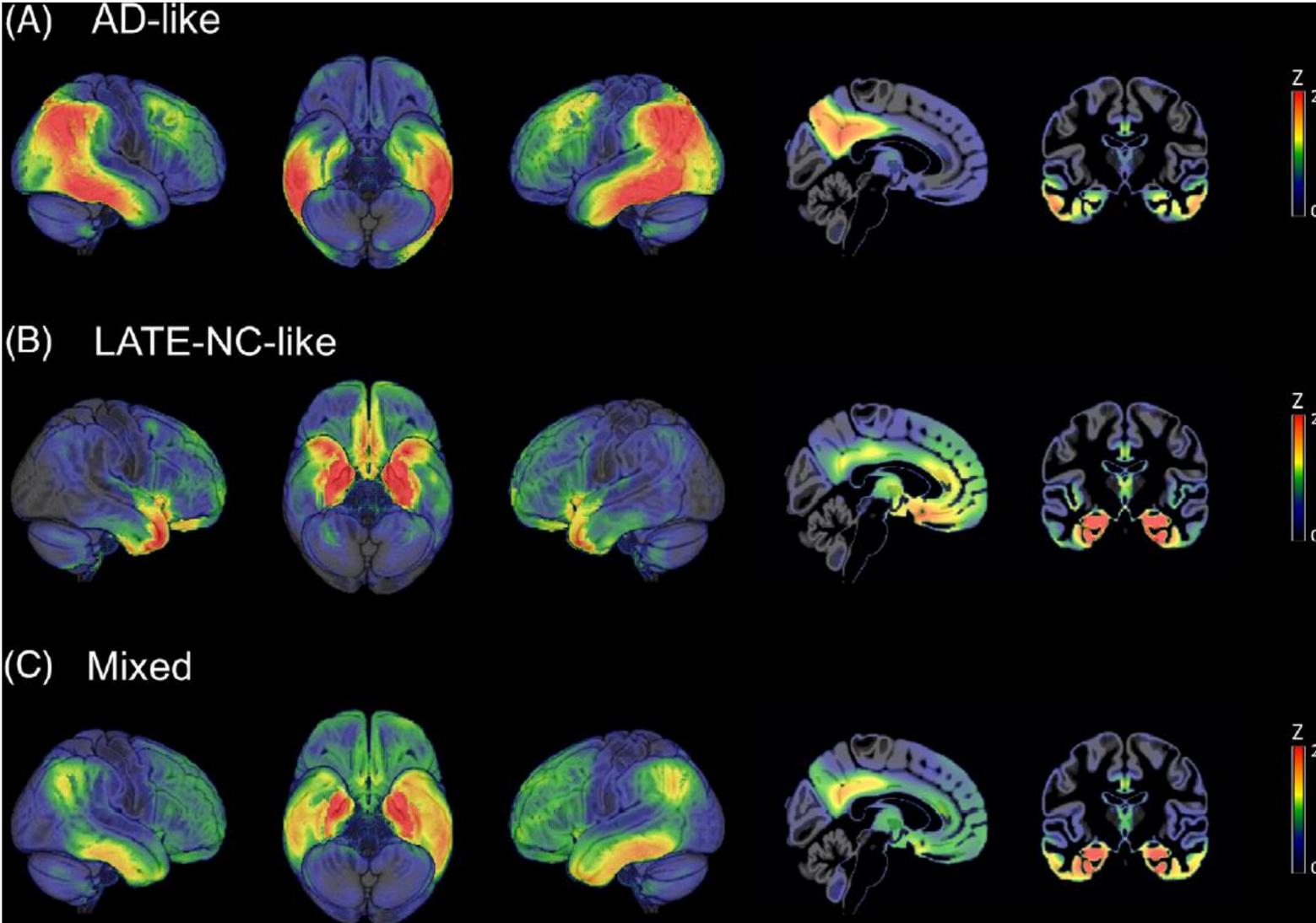


# LATE: FDG-PET imaging findings

- Hypometabolism in medial temporal lobe and orbitofrontal cortex, with relative preservation of inferior temporal cortex



# LATE: FDG-PET imaging findings



# LATE-NC clinical take home points

*What we (think we) know so far*

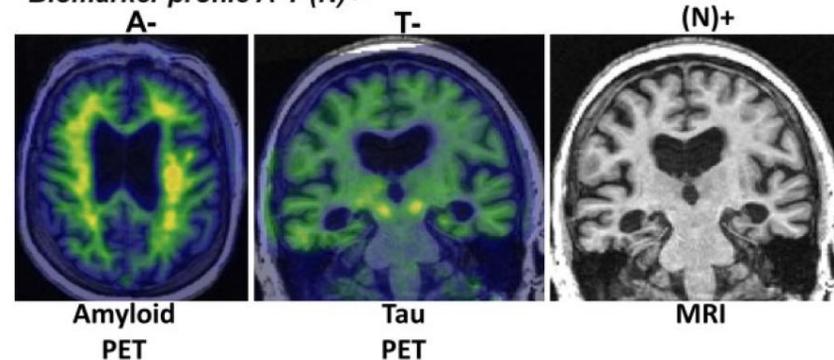
- Pure LATE-NC
  - 90+ (uncommon < 75yo)
  - Relatively pure amnesic syndrome
  - Slow progression
  - Significant hippocampal atrophy out of proportion to global brain atrophy
- LATE-NC + AD-NC
  - Faster progression than either in isolation

# Why does LATE-NC matter clinically?

- Increasing availability of molecular diagnostics and disease modifying therapies which target AD-specific pathophysiology
  - AD-specific work up for progressive memory loss may be non-revealing
  - AD neuropathology may only be part of the underlying etiology
- Need for improved diagnostic accuracy to inform prognostication and treatment options
  - What is the primary “driver” of current symptoms?
  - Should anti-amyloid therapy be pursued in the setting of poly-proteinopathy?

**A** 86 yo F, progressive amnesic dementia

Biomarker profile A-T-(N)+



# Stay tuned: LATE “Trial Ready Cohort”

- 5 west coast sites: University of California - Irvine, University of California - San Diego, University of Southern California, Oregon Health Sciences University, University of Washington
- Inclusion of multiple pathologies
- Trial readiness: >85yo often excluded from trials
- Exploration of digital health assessments

# Multi-site study design (“Trial Ready Cohort”)

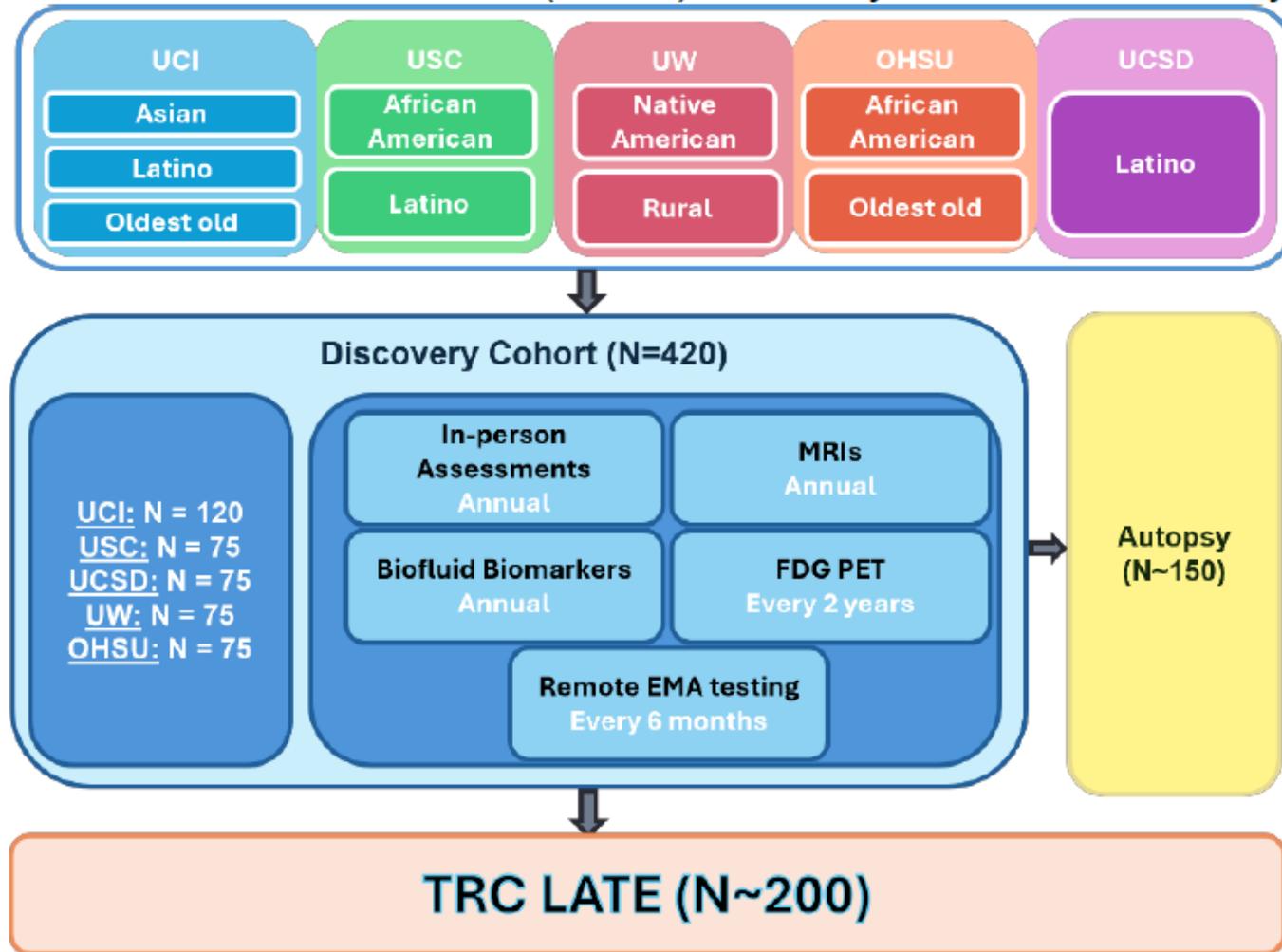


Table 1. Enrollment Criteria
<b>Inclusion Criteria for <i>Discovery Cohort</i> N=420</b>
Age ≥85 years
For cognitively unimpaired individuals: subjective memory impairment OR Hippocampal atrophy on existing MRIs
For cognitively impaired individuals: clinical diagnosis of amnesic MCI OR AD dementia
CDR < 2

Additional requirements for <i>TRC-LATE</i> N~200
Amnesic MCI or AD dementia
Disproportionate (to AD biomarker) medial temporal hypometabolism/atrophy
Willingness to participate in clinical trials

[late.mind.uci.edu](http://late.mind.uci.edu)

Thank You!  
QUESTIONS?

