Advances in Clinical Definitions and Biomarker Development for LATE

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Disclosures

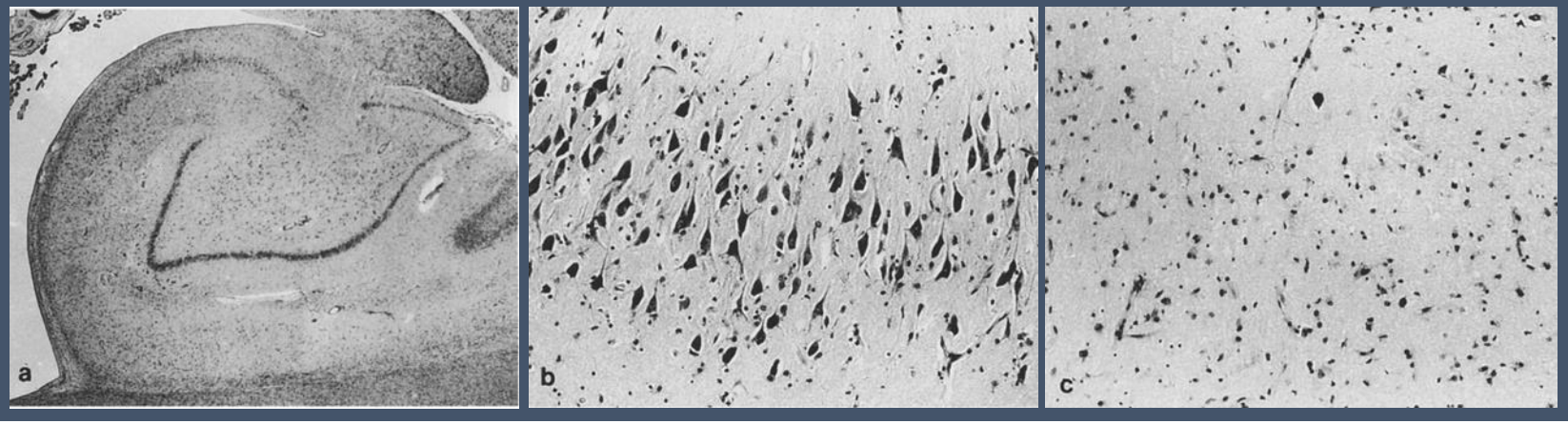
- David Wolk has served as a paid consultant to Eli Lilly, GE Healthcare, and Qynapse. He serves on a DSMB for Functional Neuromodulation and GSK. He is a site investigator for a clinical trial sponsored by Biogen.

Why should we care about detecting LATE-NC clinically?

- Growing awareness that TDP-43 is an important modulator of late-life cognitive decline
  - Recognition accelerated by reification of Limbic-Predominant Age-Related TDP-43 Encephalopathy (LATE) consensus workgroup report (Nelson et al., Brain 2019)
- With increased awareness, comes increased recognition of patients with clinical syndromes suggestive of LATE
- Importance amplified by emergence of disease-modifying medicines targeting AD biology heralding precision medicine era
  - LATE and AD have similar clinical features; in those without AD (amyloid PET negative), many will have LATE
  - LATE frequently co-occurs with AD; impact on outcomes with these therapies?

TDP-43 is common in older age and with AD – a long history

- Dennis Dickson and colleagues reported in 1994 that hippocampal sclerosis (HS) is common in absence of AD in those over 80 (26%)
  - Noted that “in some patients memory disturbance was disproportionate to deficits in other cognitive areas”
- TDP-43 defined as major component of inclusions in FTLD-ALS (Neuman, …Trojanowski, Lee, *Science*, 2006; Arai et al., *Biochem Biophys Research Comm*, 2006)
- TDP-43 found to be common in hippocampal sclerosis of aging and AD (Amador-Ortiz, …Dickson, *Annals of Neurology*, 2007)



Dickson et al., ACTA Neuropathologica, 1994

TDP-43 is common in older age and with AD – a long history

- TDP-43 and AD independently associated with hippocampal structure and memory decline (Josephs et al., *ACTA Neuropathologica*, 2014)
- Common in absence of AD in older individuals (>80 yo; ~1/3rd) and associated with memory deficits (Nag et al., *Neurology*, 2017)
- Associated with limbic structures
  - Staging schemes developed (Josephs et al., ACTA Neuropathologica, 2016; Nag et al., *ACTA Neuropathologica Communications*, 2018)

LATE Neuropathologic Change (LATE-NC) Defined

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

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ORIGINAL PAPER

Check for updates

LATE-NC staging in routine neuropathologic diagnosis: an update

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B 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

Staging and localization of TDP-43 provide clues of expected associated symptoms

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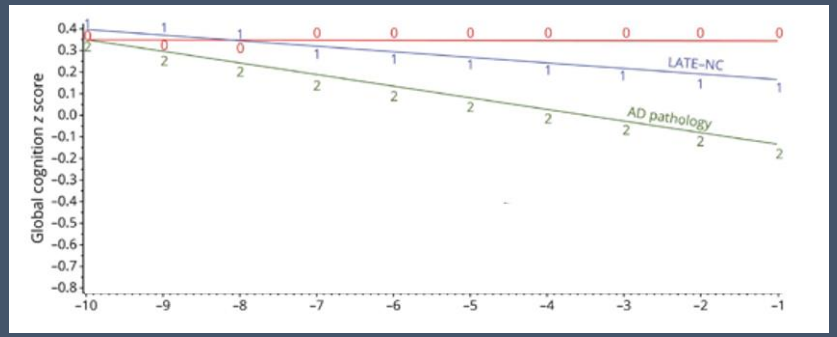
LATE produces a primarily amnestic syndrome

	LATE-NC
Global cognition	
Reference (no AD, TDP-43, or HS)	0.025
LATE-NC	
ADNC	
Episodic memory	
Reference (no AD, TDP-43, or HS)	0.002
LATE-NC	
ADNC	
Semantic memory	
Reference (no AD, TDP-43, or HS)	0.258
LATE-NC	
ADNC	
Working memory	
Reference (no AD, TDP-43, or HS)	0.159
LATE-NC	
ADNC	
Perceptual speed	
Reference (no AD, TDP-43, or HS)	0.239
LATE-NC	
ADNC	
Visuospatial ability	
Reference (no AD, TDP-43, or HS)	0.672
LATE -NC	
ADNC	



- LATE-NC is primary pathology
  - Slower course than Alzheimer's Disease
  - Relatively isolated episodic memory decline (as opposed to typical AD which is often more multi-domain)
  - Involvement of semantic memory variable, but often mildly involved (Nag et al. ACTA Neuropath Comm, 2018)
  - ? Neurobehavioral associations (Liu et al, *Brain*, 2020), but clearly less so than FTD-spectrum

Kapasi et al., *Neurology*, 2020

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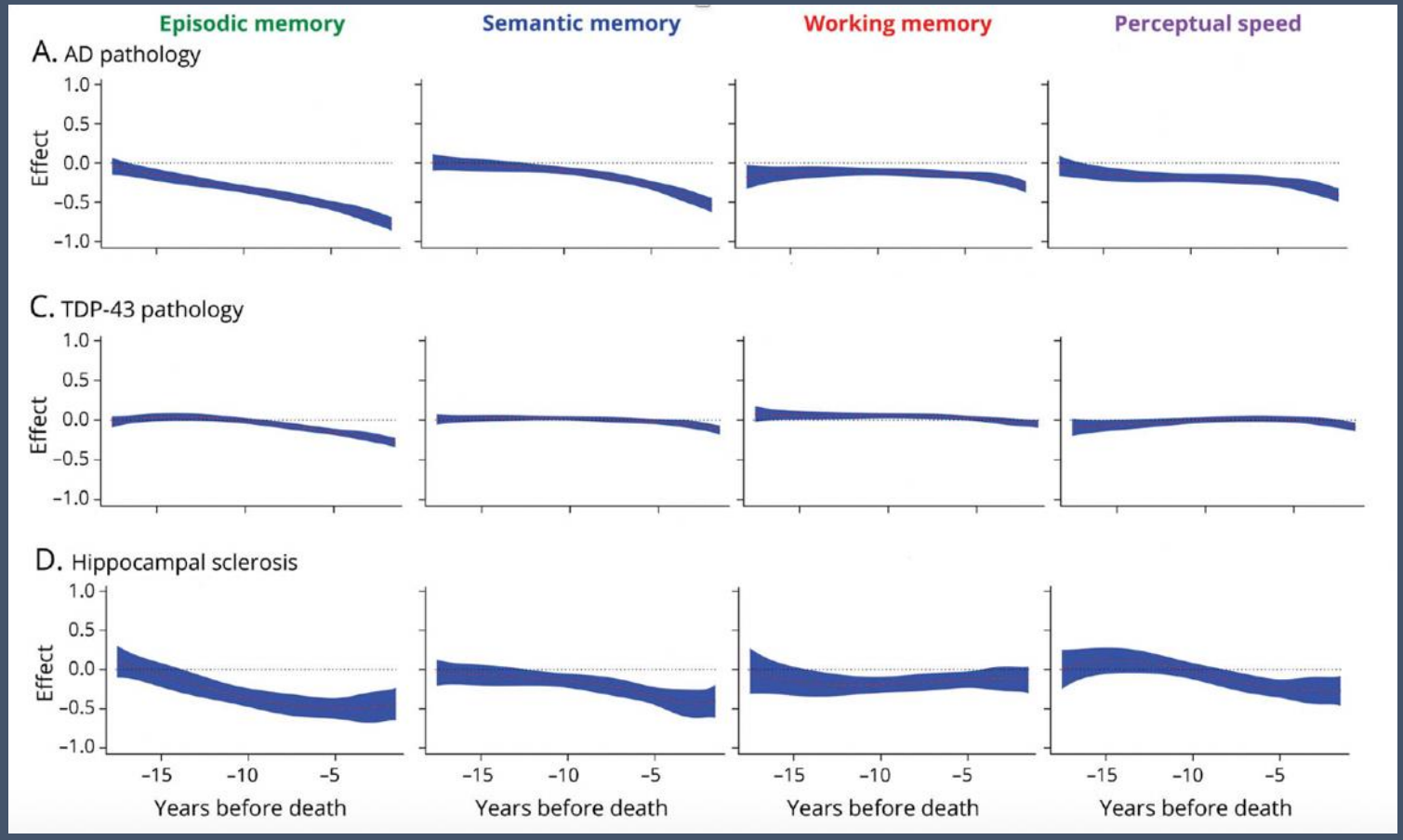
LATE-NC with versus without Hippocampal Sclerosis associated with more significant cognitive decline



Wilson et al, *Neurology*, 2019

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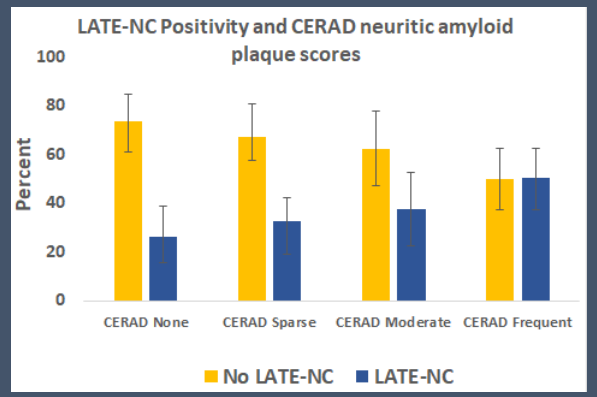
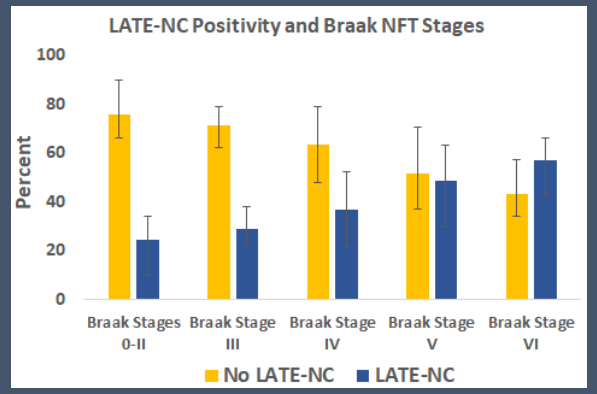
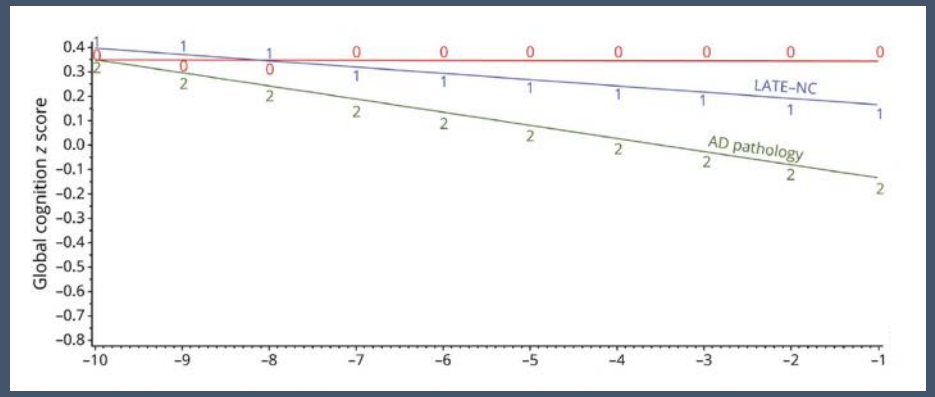
LATE-NC most commonly co-occurs with AD (>1/3) and is associated with an accelerated global cognitive decline

- 13 community- or population-based autopsy cohorts
  - N=6,251
  - Avg age of death = 88.0 yrs
- ~1/2 with severe AD pathology also have LATE-NC!

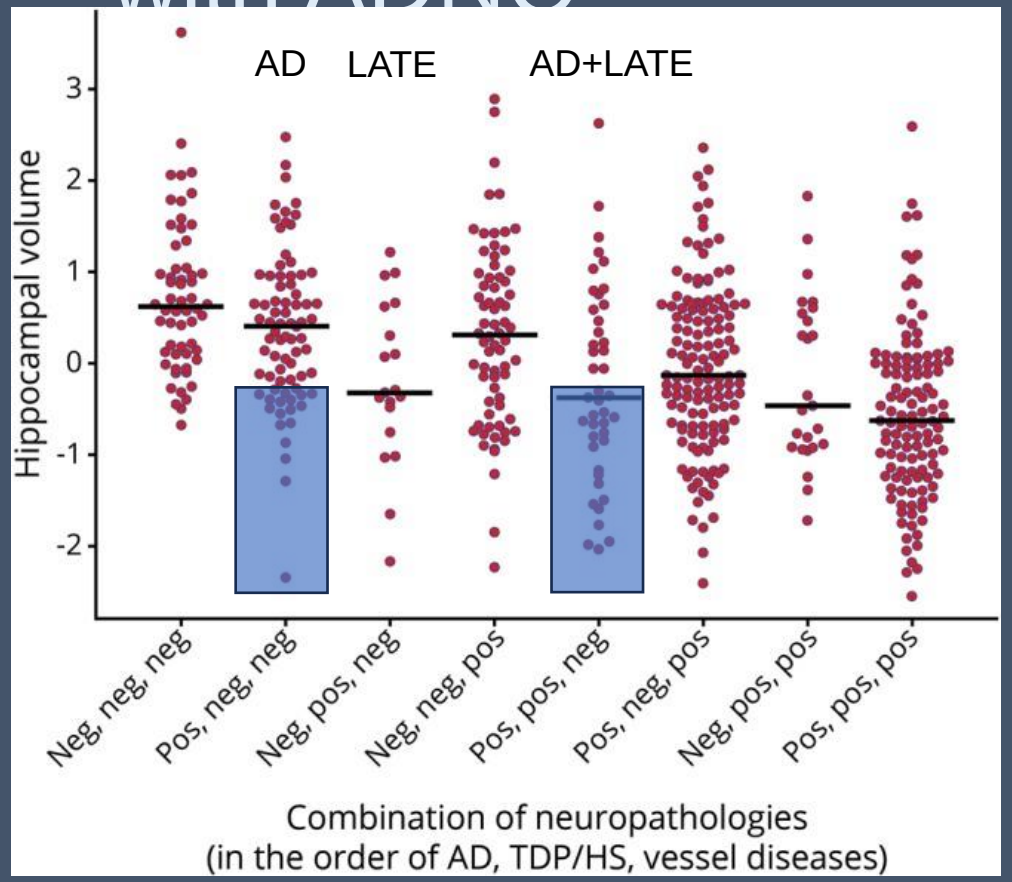




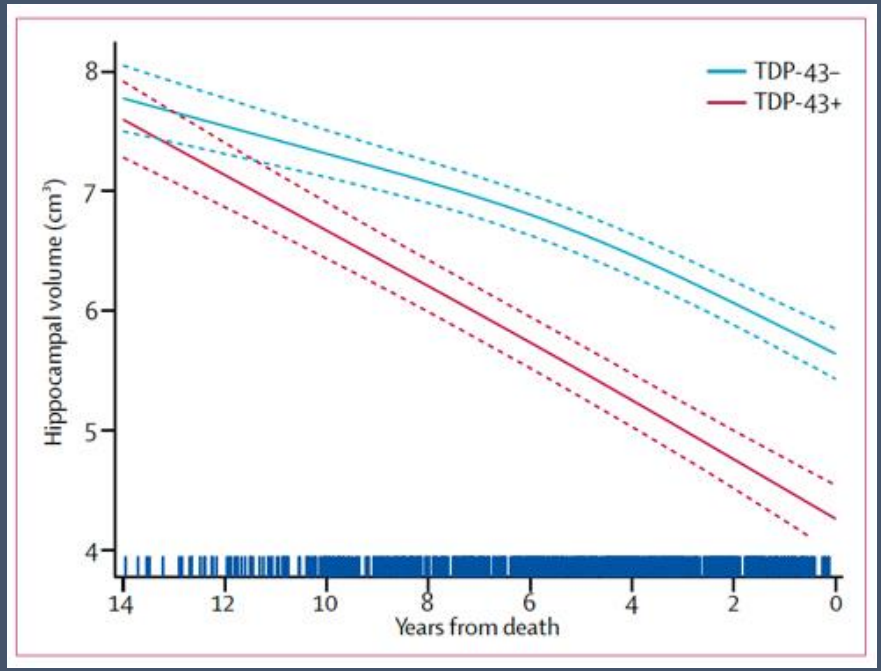


Nelson et al, *ACTA Neuropath,* 2022; Kapasi et al., *Neurology*, 2020; Gauthreaux et al., *J Neuropathol Exp Neurol,* 2022

LATE-NC is associated with lower hippocampal volume and accelerated atrophy when concomitant with ADNC



Lower range of hippo volume in AD is dominated by AD+LATE



Yu et al., Neurology, 2020; Josephs et al., *Lancet Neuro*, 2017

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Cortical pattern of atrophy matches distribution of TDP-43

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
1	Amygdala	1	Amygdala
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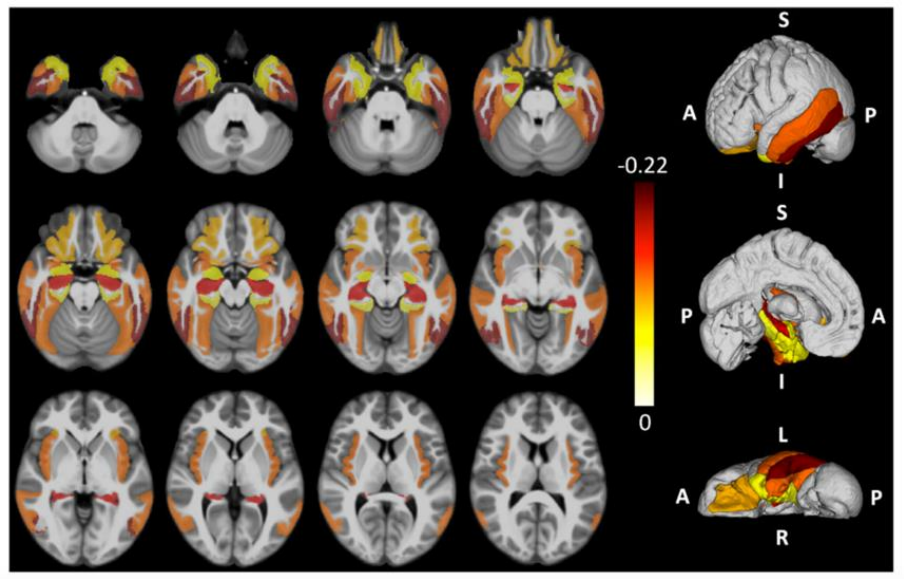

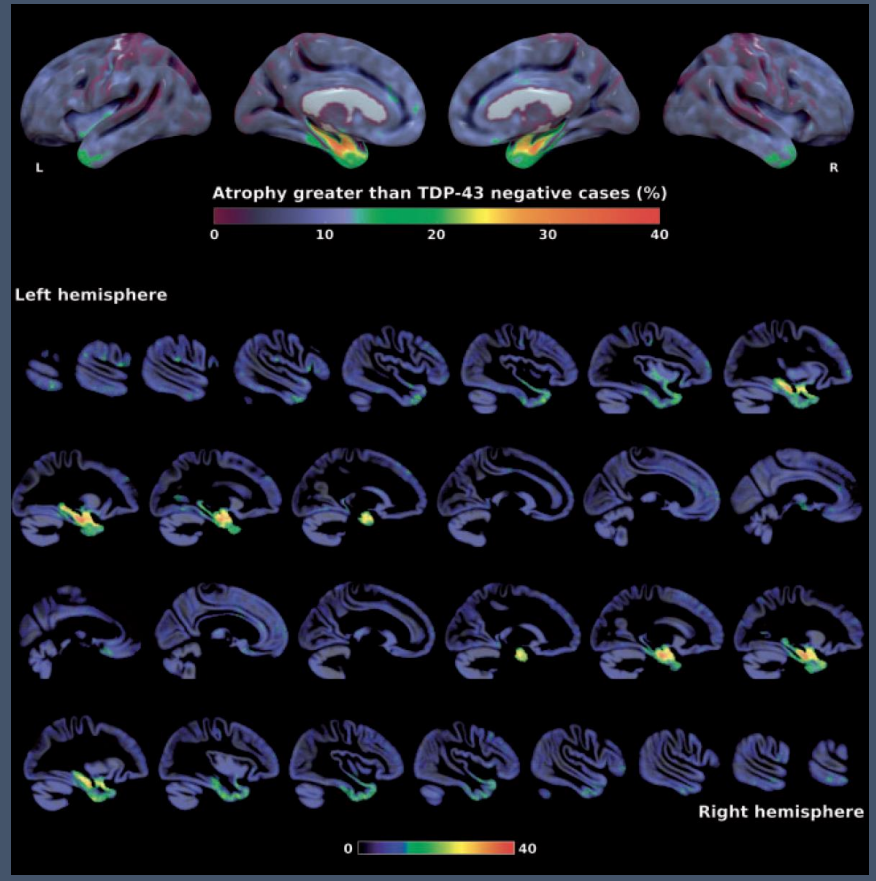

Nelson et al., *Brain*, 2019; Benjanin et al., *Brain*, 2019

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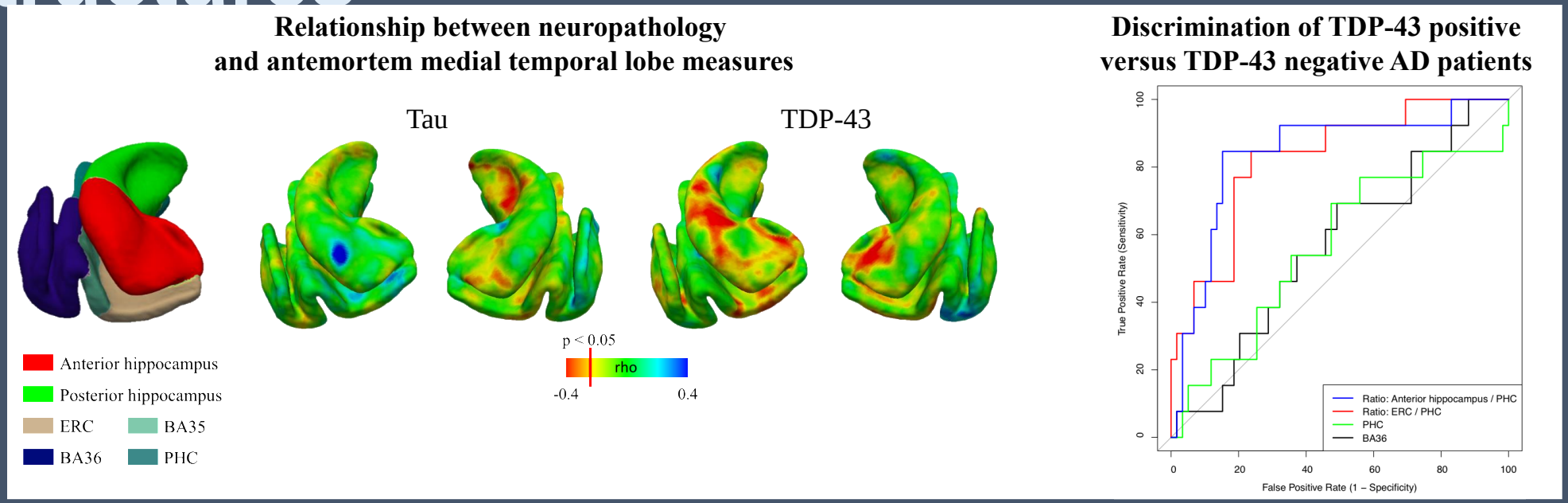
MTL atrophy tends to affect more anterior structures



aHipp/PHC: AUC = 0.84
(95% CI: 0.72 – 0.97)

ERC/PHC: AUC = 0.82
(95% CI: 0.70 – 0.93)

De Flores et al., *Alz & Dementia,* 2020

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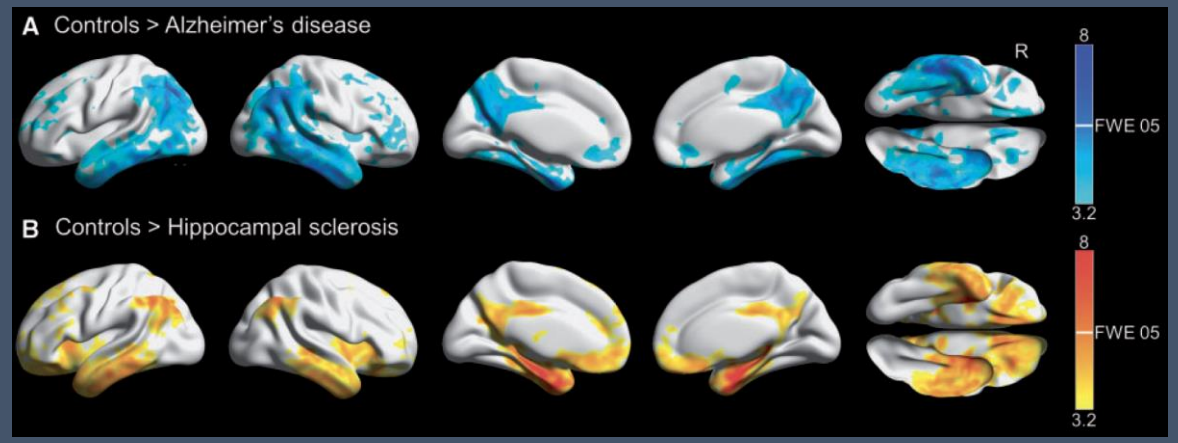
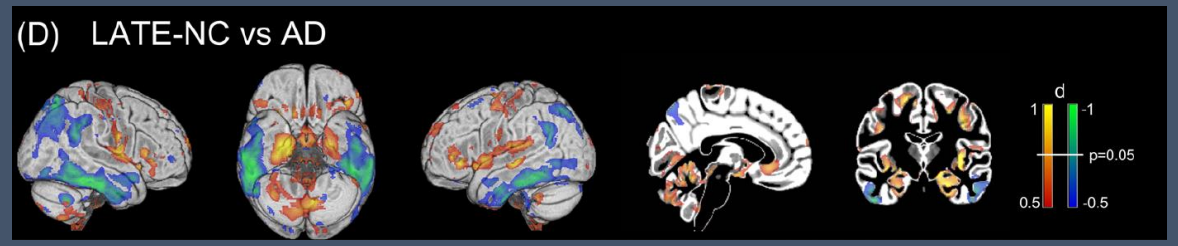
FDG PET signature of LATE-NC

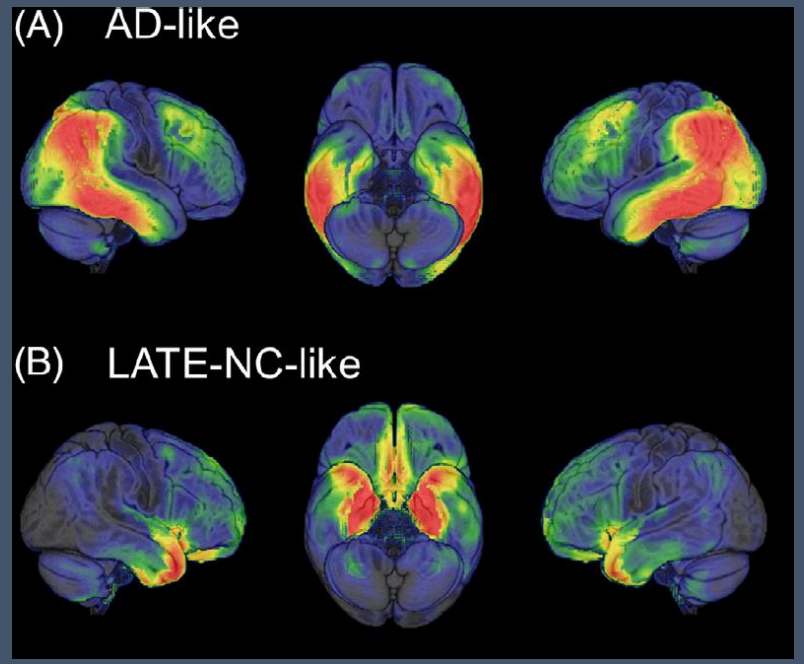
Mayo Autopsy-confirmed



ADNI Autopsy-confirmed



Inferior to Medial Temporal Ratio AUC ~0.85



Clinical AD patients with LATE-NC-like pattern

- Less abnormal AD molecular biomarkers
- Less ApoE4
- Higher rate of TMEM106B risk allele

Botha et al., *Brain*, 2018; Grothe et al., *Alz & Dementia*, 2023

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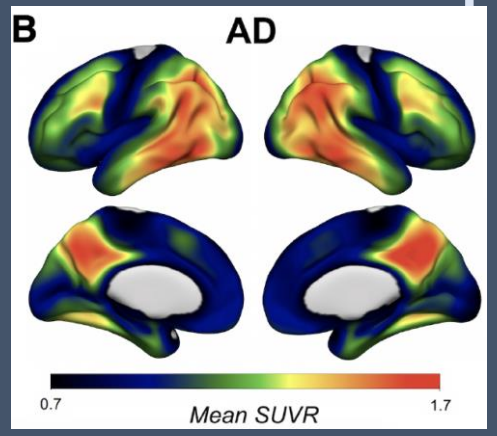
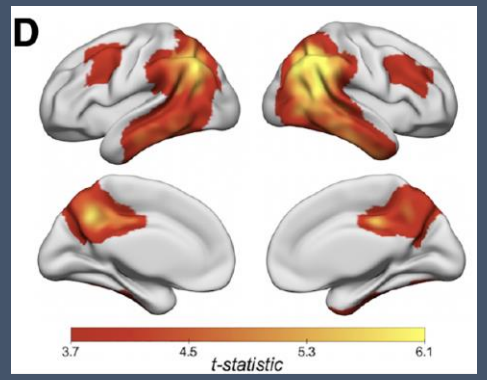
Can we detect patterns of mixed LATE-NC and ADNC?

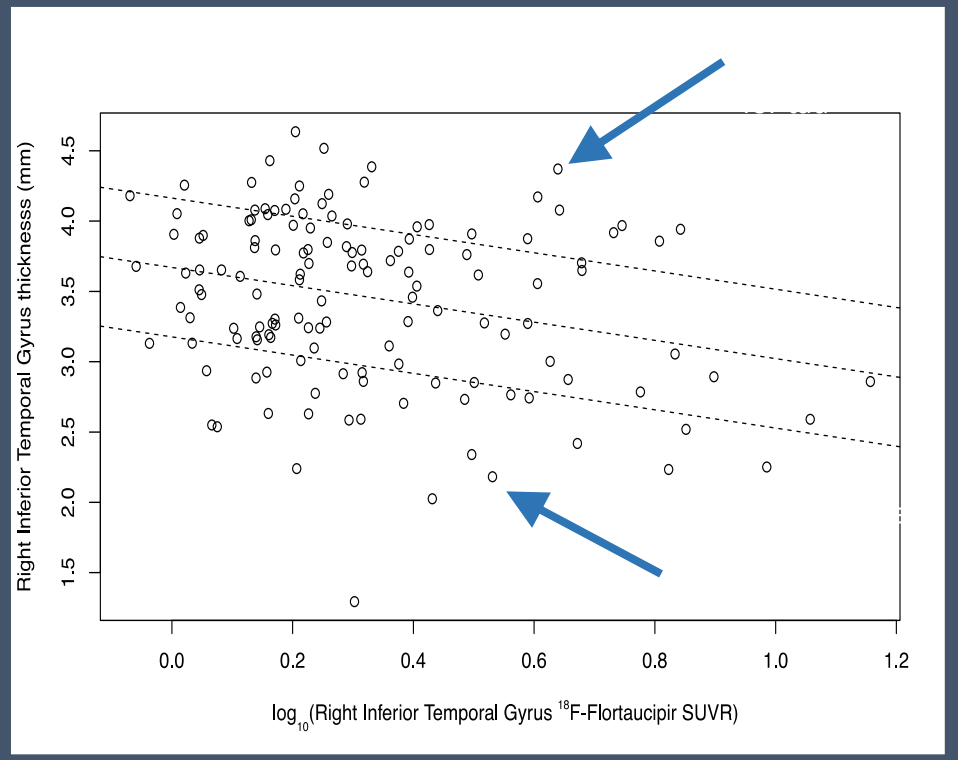
Residual atrophy beyond expected for Tau may reflect co-pathologies

Baseline Tau PET

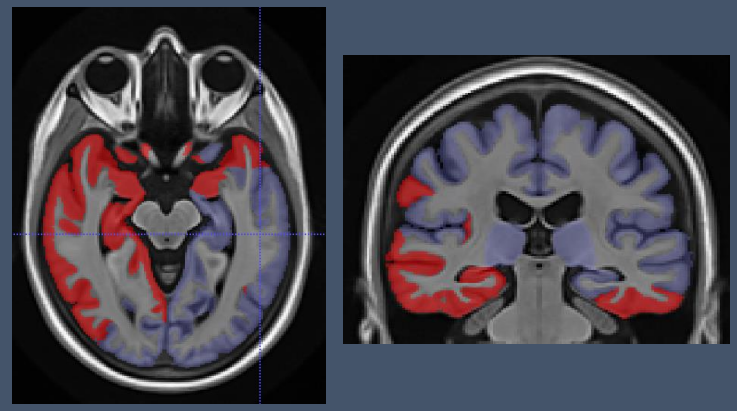


Longitudinal Atrophy





Limbic “vulnerable”; more atrophy than expected for tau



Harrison et al., *Annals of Neurology*, 2019

Das et al., *Annals of Neurology*, 2021

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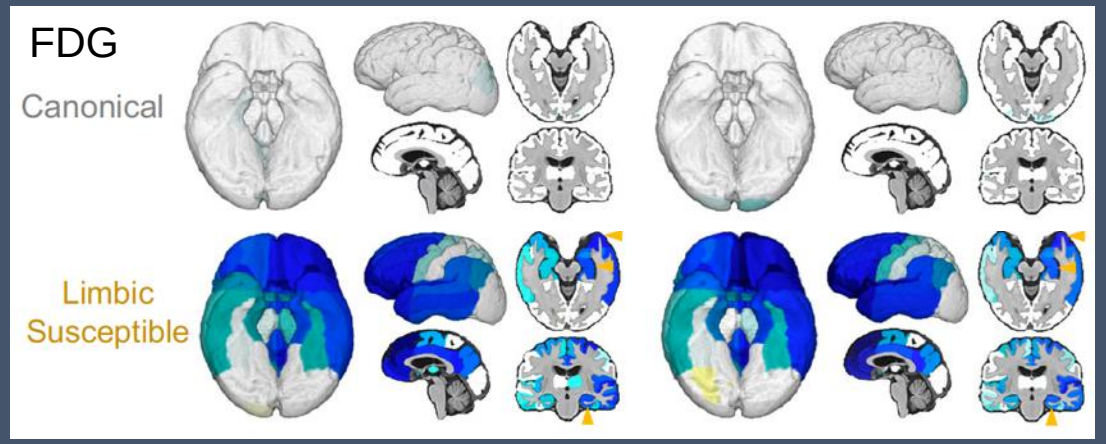
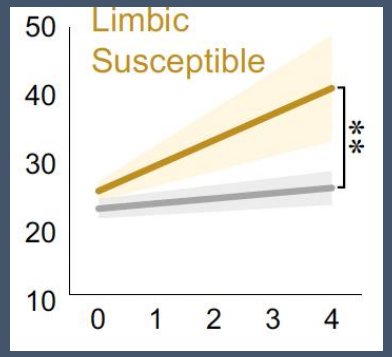
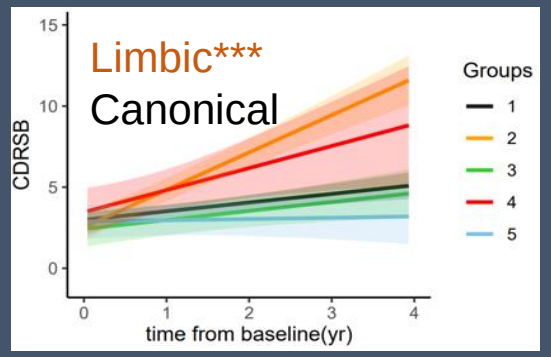
Detecting LATE-NC with ADNC

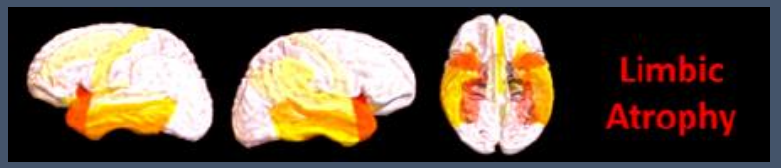
- Cluster of limbic vulnerable with FDG PET and MRI
- Pattern of residual (regressed out AD) similar to LATE-NC alone

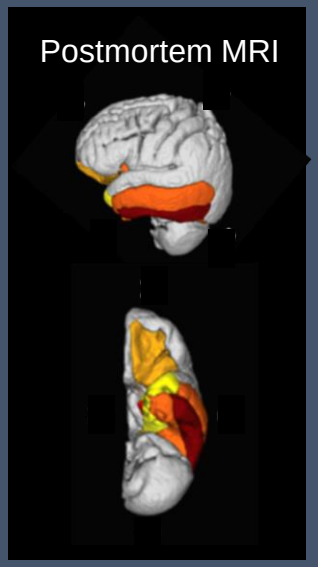


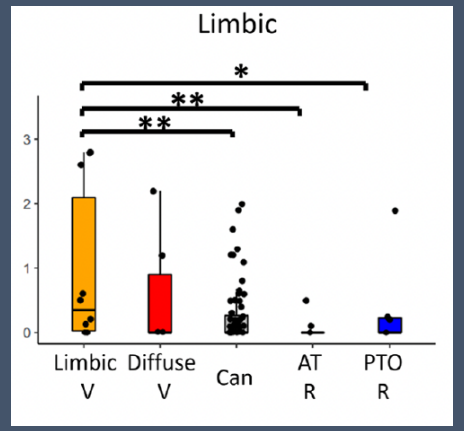




Amyloid Negative Limbic Cluster







Das et al., *Annals of Neurology*, 2021; Doung et al., *Nature Communications*, 2022; Lyu et al., *Alz & Dementia*, 2024

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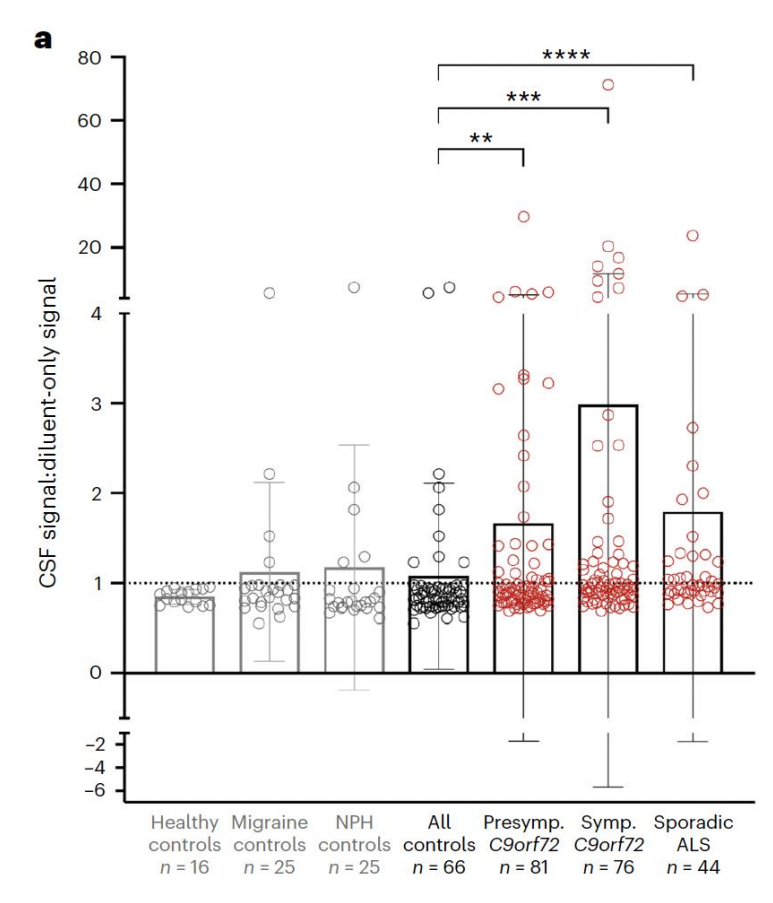
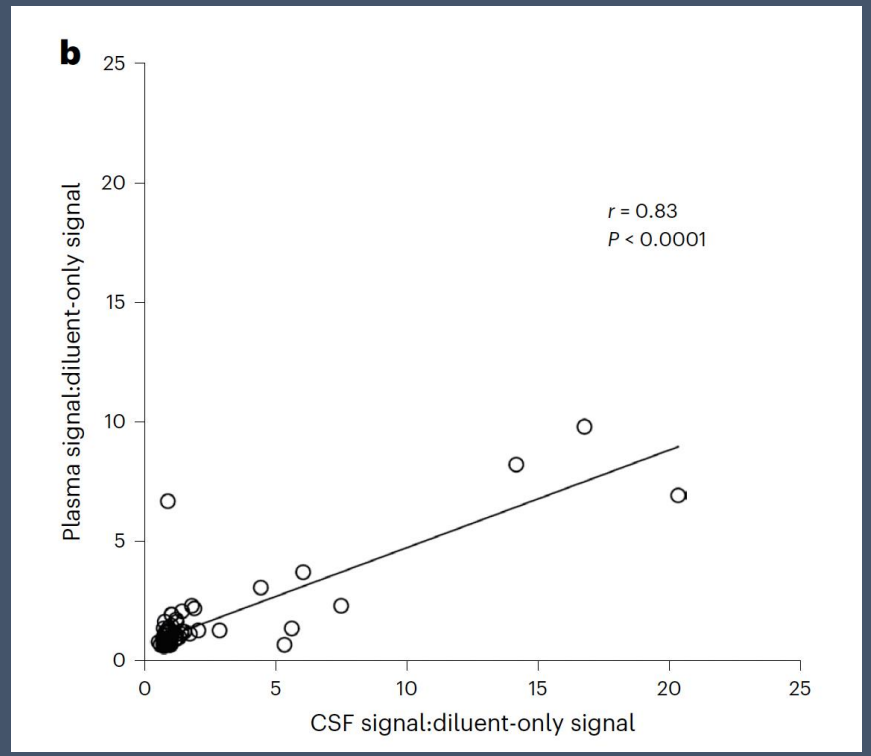
Biofluid biomarkers of TDP-43 – Cryptic peptides (Irwin et al., *Nature Medicine*, 2024; Seddighi et al., *Science Translational Medicine*, 2024)

- TDP-43 is a DNA/RNA binding protein
- Loss of nuclear TDP-43 and cytoplasmic aggregation leads to splicing errors and cryptic exons
- Small percentage of mis-spliced produce cryptic peptides
- Hepatoma-derived growth factor-like protein 2 (HDGFL2) highly expressed in CNS with cryptic exon that produces immunogenic epitope

Biofluid biomarkers of TDP-43





Irwin et al., *Nature Medicine*, 2024

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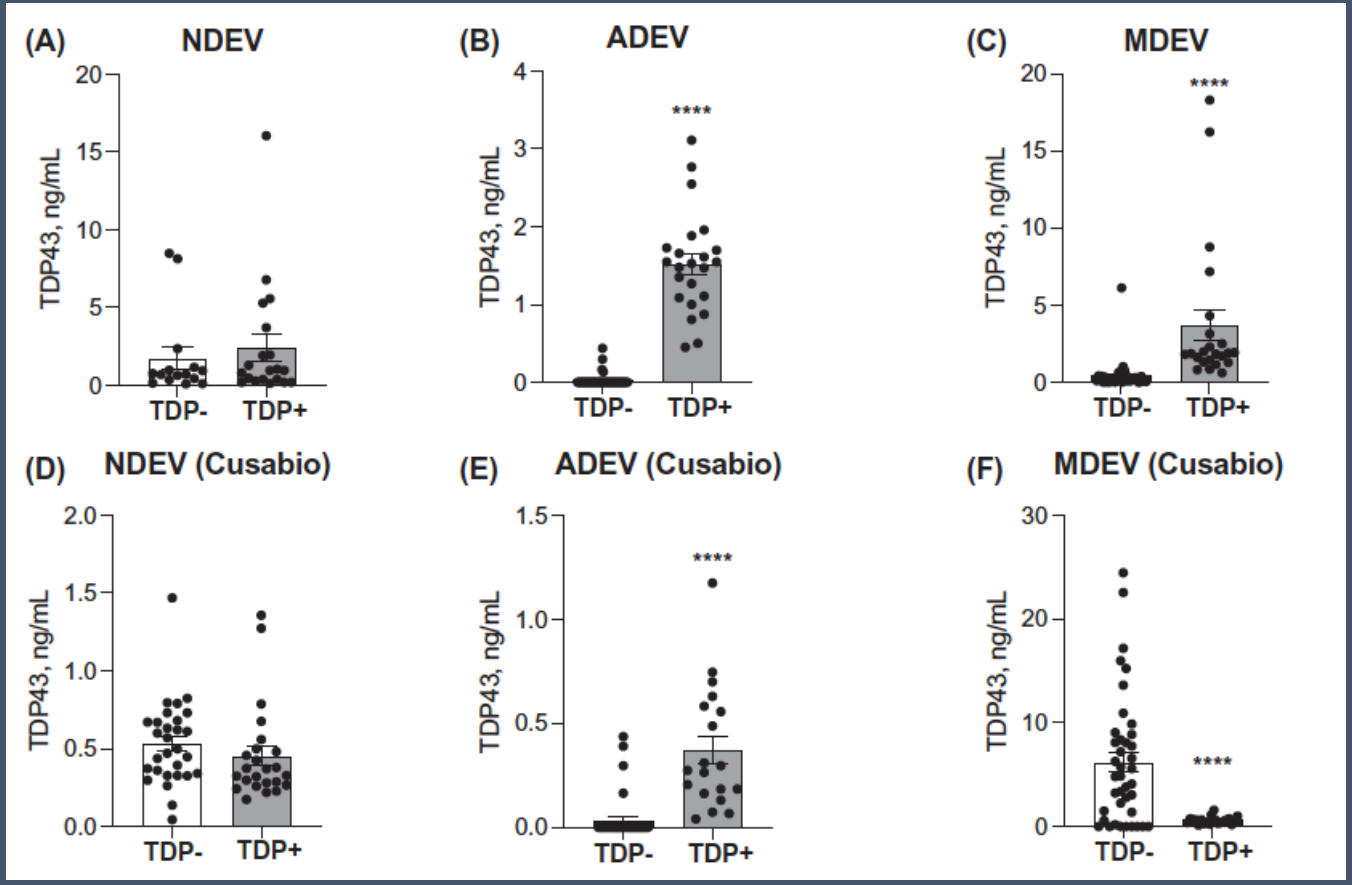
TDP-43 measured in extracellular vesicles



Winston et al., *Alz & Dementia: DADM*, 2021

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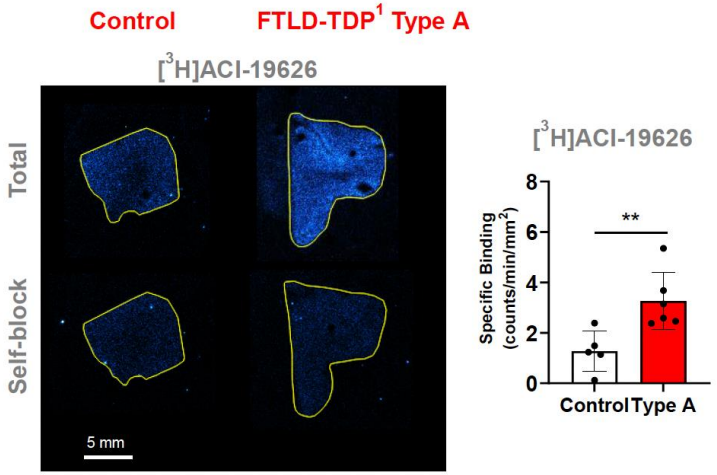
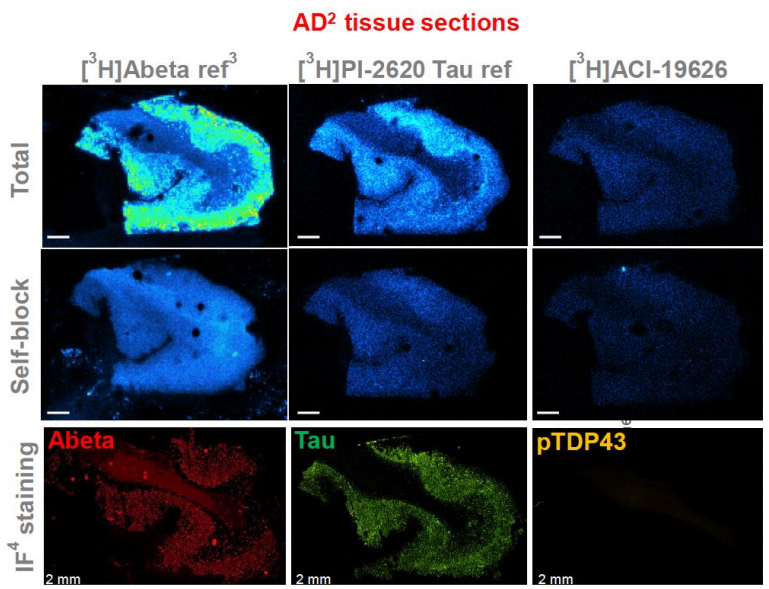
PET TDP-43 tracer

ACI-19626, first in class TDP-43 PET ligand

Target engagement and selectivity using autoradiography on patient brain sections





Seredenina et al., ADPD 2024

- ACI-19626 shows target engagement on brain samples with FTLD-TDP type A pathology which is commonly found in brains of FTLD-TDP GRN[5], LATE[6] and AD
- ACI-19626 displays excellent selectivity to TDP-43 over Abeta and Tau in AD brain sections

(1) Frontotemporal lobar degeneration with TDP-43 pathology; (2) Alzheimer's disease; (3) reference; (4) immunofluorescence; (5) mutation in progranulin gene; (6) limbic-predominant age-related TDP-43 encephalopathy

Seredenina et al., *ADPD*, 2024

Proposal for clinical criteria

- Why now, especially without a TDP-43 specific molecular biomarker?
  - Some are already making this diagnosis in specialty centers
  - Absence of LATE clinical diagnostic criteria impedes clinical and basic research into the pathogenesis and treatment
  - LATE has different prognostic implications than AD for patients and families
  - With FDA-approval of anti-amyloid therapies, many ineligible for treatment based on the absence of “positive” AD biomarkers may instead have LATE-NC
  - It is unclear the degree to which those with AD + LATE will respond to anti-amyloid therapies; a means to identify an enriched population with co-pathology will advance research for determining the modulating effect of LATE co-pathology

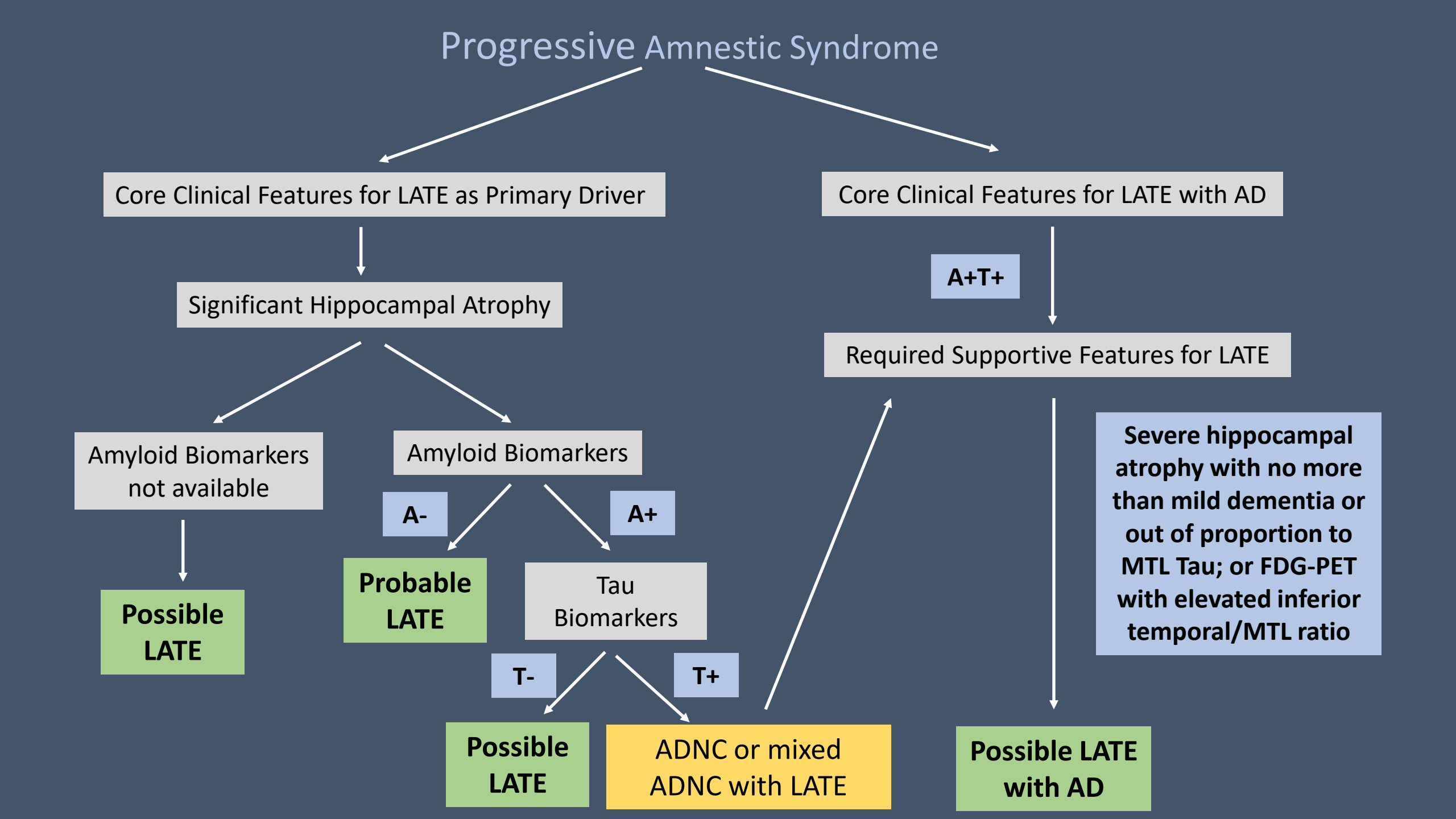
Proposal for clinical criteria

- Committee of 36 expert clinicians, trialists, pathologists, neuroimagers, neurochemists, basic scientists, and community researchers
  - Initially met as part of a workshop May, 2023 to discuss gaps and opportunities
  - Developed framework for diagnostic criteria
- In absence of a specific TDP-43 biomarker, diagnosis is at best probabilistic
- Define two contexts for clinical diagnosis
  - LATE-NC as primary driver of symptoms with non-significant ADNC
    - Possible or probable LATE
  - LATE-NC mixed with ADNC
    - Possible LATE

Core clinical syndrome

I. Core Clinical Syndrome* (1 and 2 required)
* 1. Primary amnestic syndrome with temporo-limbic memory loss * 2. Other cognitive domains largely spared until much later in the course 3. May have mild semantic memory impairment 4. Indolent course with predominant amnestic syndrome present for at least 2 years 5. Age generally > 75 years old

Core Clinical Syndrome: AD+LATE
1. Progressive amnestic, multi-domain syndrome; memory loss may be particularly severe relative to other cognitive domains 2. Generally, more rapid course than typical AD alone


Progressive Amnestic Syndrome
Core Clinical Features for LATE as Primary Driver
Core Clinical Features for LATE with AD
Significant Hippocampal Atrophy
A+T+
Required Supportive Features for LATE
Amyloid Biomarkers not available
Amyloid Biomarkers
A-
A+
Possible LATE
Probable LATE
Tau Biomarkers
T-
T+
Possible LATE
ADNC or mixed ADNC with LATE
Possible LATE with AD
Severe hippocampal atrophy with no more than mild dementia or out of proportion to MTL Tau; or FDG-PET with elevated inferior temporal/MTL ratio

Conclusions

- **LATE-NC is common and important driver of late life cognitive symptoms**
- **Common co-pathology with ADNC**
- **Imaging and cognitive features reflect the distribution of TDP-43 pathology**
- **Probabilistic designation of LATE-NC can be determined based on clinical and imaging features (higher confidence when can rule out AD)**
- Clinical criteria require validation in large in vivo studies

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Thank You