Clinical and Imaging Features of LATE: A Diagnostic Framework

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1

Disclosures

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

All relevant financial relationships with ineligible companies have been mitigated.

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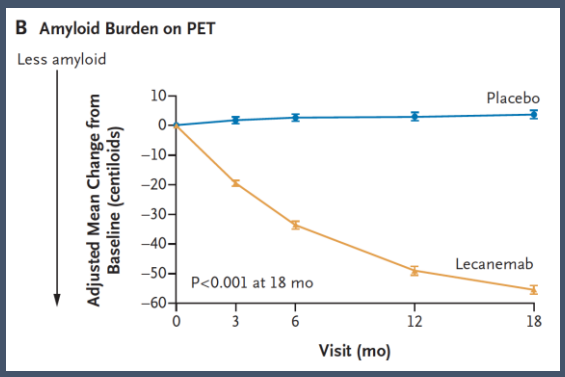
2

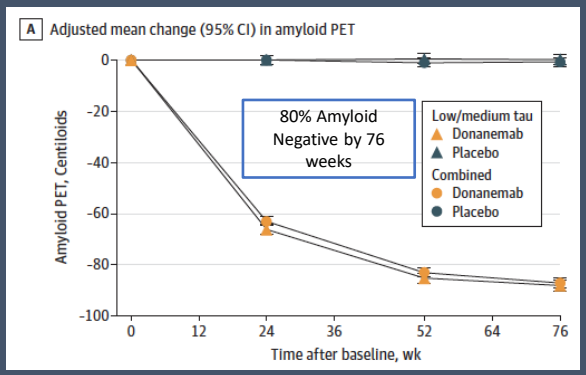
A new era of AD therapeutics: Anti-amyloid therapies

Lecanemab



Van Dyck et al., *NEJM*, 2022

Donanemab



Sims et al., *JAMA Neurology*, 2023

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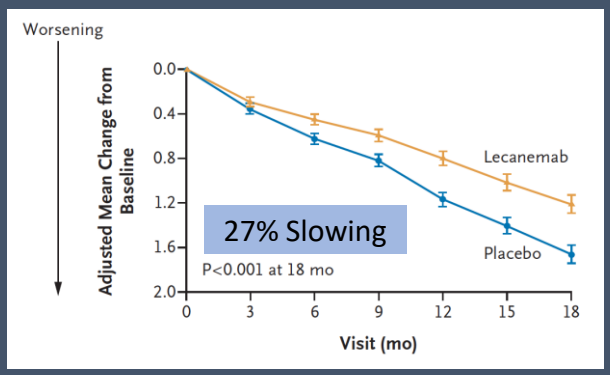
Modest clinical benefit despite robust amyloid clearance

Lecanemab (Leqembi)



Van Dyck et al., *NEJM*, 2022

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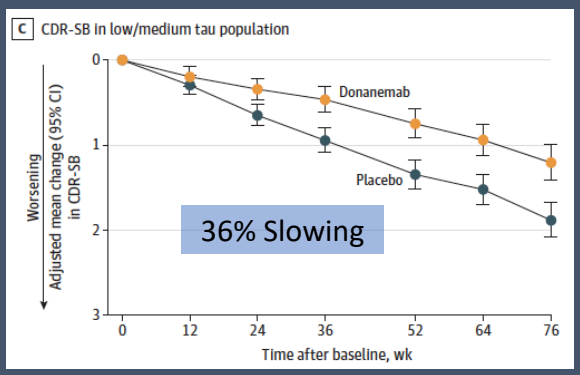

Sims et al., *JAMA Neurology*, 2023

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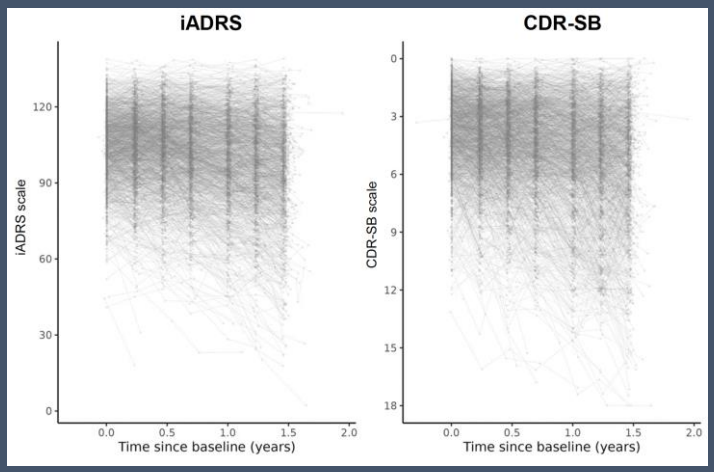
Cognitive course from TRAILBLAZER-ALZ 2



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University of Pennsylvania Health System

Mintun et al., *CTAD*, 2023

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Heterogeneity in Alzheimer's Disease

- Cognitive and behavioral symptoms
  - (e.g. memory, language, depression, anxiety)
- Pattern of AD-related pathology
- Age of onset
- Rate of progression
- Presence of co-pathologies (e.g. vascular disease, other proteinopathies)
- Presence of other medical conditions (e.g. diabetes, heart disease)
- Differences in resilience or vulnerability
- Social and structural determinants of health (e.g. education, stress, assess to healthcare)

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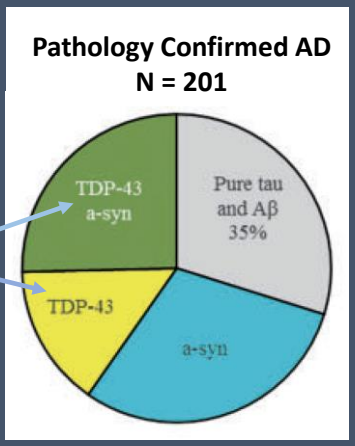
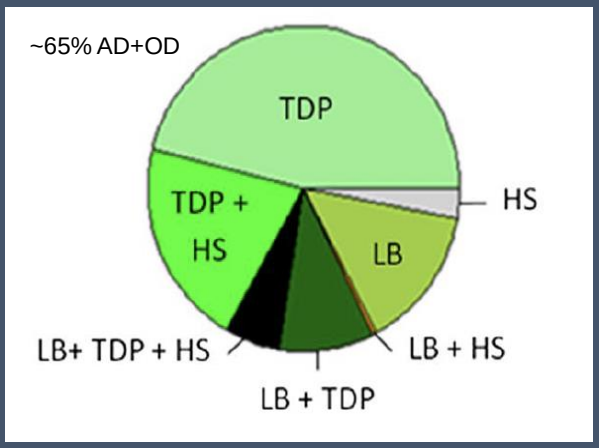
Mixed Pathologies is the Norm for AD

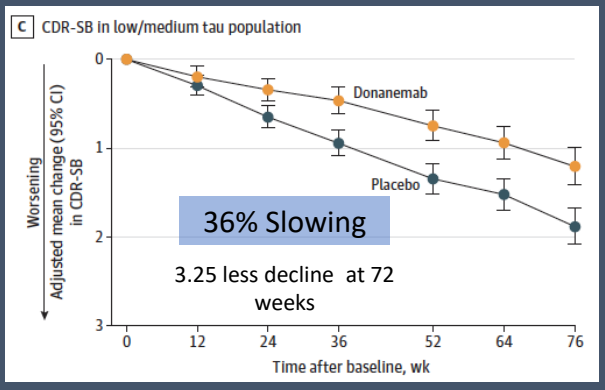


Robinson et al., *Brain*, 2018



Kapasi et al., *ACTA Neuropath*, 2017

Why not a bigger effect with anti-amyloid immune therapies?



Sims et al., *JAMA Neurology*, 2023

TABLE 3. Fractions of Alzheimer's Dementia Cases Attributable to Individual Neuropathological Indices

Neuropathological indices	N	N_est	Cases	Fraction % (95% CI)
NIA-Reagan pathological AD	512	302.22	209.78	40.97 (32.70–49.46)
Macroscopic infarcts	512	466.32	45.68	8.92 (4.40–13.67)
Lewy bodies	512	456.96	55.04	10.75 (7.34–14.22)
Hippocampal sclerosis	512	485.16	26.84	5.24 (3.12–7.43)
TDP-43 pathology	512	452.26	59.74	11.67 (6.99–16.46)
Cerebral amyloid angiopathy	512	470.51	41.49	8.10 (3.46–12.83)
Atherosclerosis	512	481.49	30.51	5.96 (1.76–10.24)
Arteriolosclerosis	512	485.57	26.43	5.16 (1.04–9.43)

Alzheimer's Disease pathology accounts for less than half the attributable risk of AD cases (30% not attributable to age-related pathologies)

Boyle et al., *Annals Neurology*, 2019

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?

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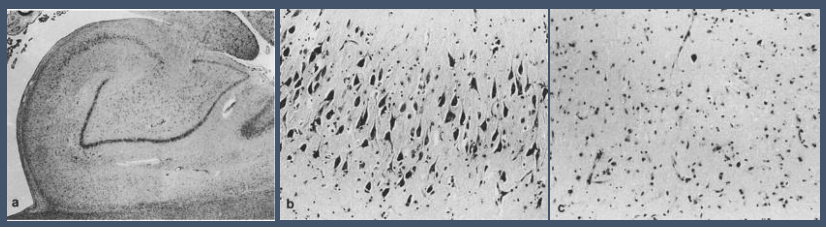
TDP-43 is common in older age and with AD – a long history

- 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

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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)

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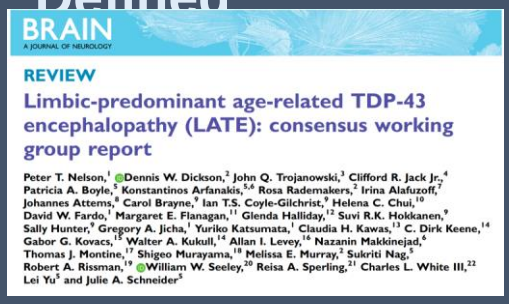
11

LATE Neuropathologic Change (LATE-NC) Defined


BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

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

Peter T. Nelson,[1] Dennis W. Dickson,[2] John Q. Trojanowski,[3] Clifford R. Jack Jr.,[4] Patricia A. Boyle,[5] Konstantinos Arfanakis,[5,6] Rosa Rademakers,[7] Irina Alafuzoff,[8] Johannes Attems,[8] Carol Brayne,[9] Ian T.S. Coyle-Gilchrist,[9] Helena C. Chui,[10] David W. Fardo,[1] Margaret E. Flanagan,[11] Glenda Halliday,[12] Suvi R.K. Hokkanen,[9] Sally Hunter,[9] Gregory A. Jicha,[1] Yuriko Katsumata,[1] Claudia H. Kawas,[13] C. Dirk Keene,[14] Gabor G. Kovacs,[15] Walter A. Kukull,[14] Allan I. Levey,[16] Nazanin Makkinejad,[6] Thomas J. Montine,[17] Shigeo Murayama,[18] Melissa E. Murray,[2] Sukriti Nag,[5] Robert A. Rissman,[19] William W. Seeley,[20] Reisa A. Sperling,[21] Charles L. White III,[22] Lei Yu[5] and Julie A. Schneider[5]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ORIGINAL PAPER

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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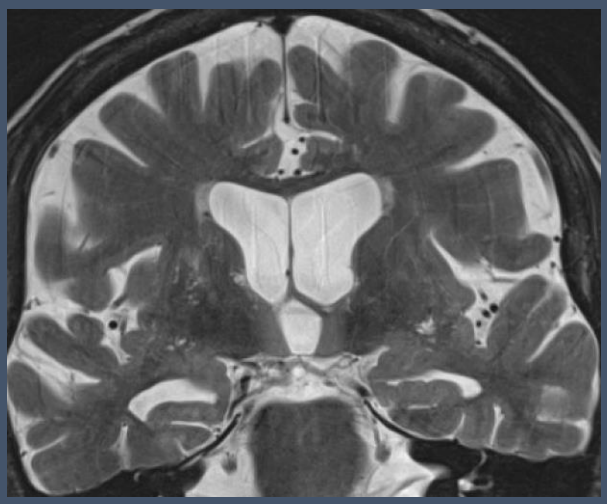
With definition, LATE begins to be considered in differential diagnosis in the clinic

- Retired engineer in early 80's with forgetfulness
  - Grand-son made high school hockey team; next day he forgot
  - Keeps more notes for reminders
  - Mild inefficiencies with finances, otherwise IADLs ok
  - No change in personality or language complaints
- Cognitive testing
  - MMSE 30/30
  - Borderline memory performance

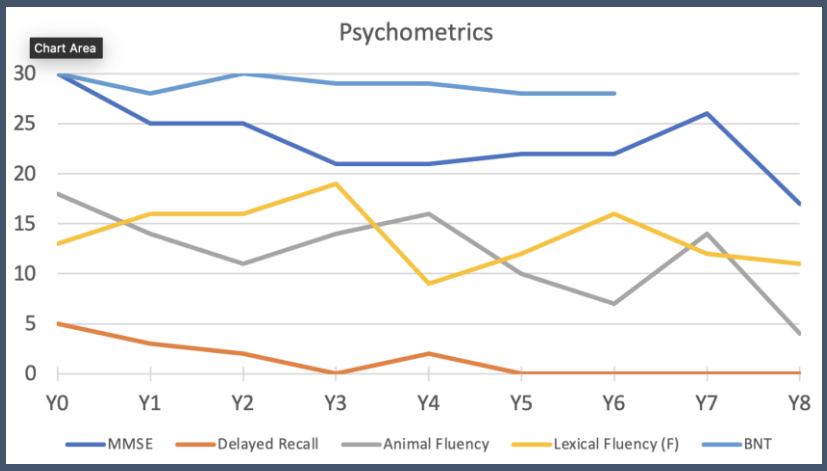
13

MRI



14

Slow progression



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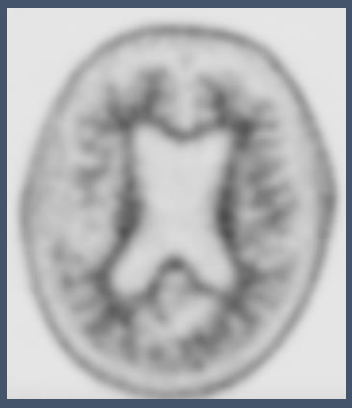
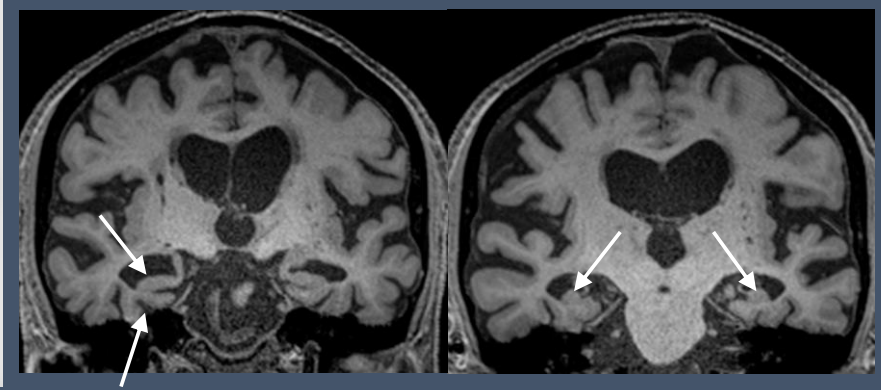
Diagnosed with AD Year 3; Amyloid PET Y5





Most likely etiology changed from AD to LATE

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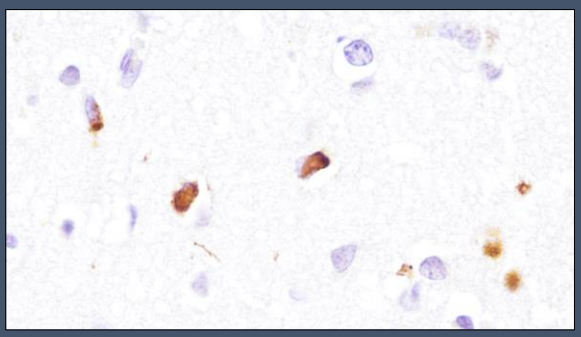
Autopsy (died 10 years after presentation)

- Limbic-predominant Age-related TDP-43 Encephalopathy (LATE-NC) Stage 3
- Hippocampal sclerosis
- Low level (barely) of Alzheimer's Disease Neuropathologic Change (ADNC; A1, B1, C0)



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Case

- 78 year old woman with arthritis, prior hysterectomy for uterine cancer, and depression
- Several years of memory loss
  - Misplacing things, forgetting where she parked, difficulty remembering events
- Increased difficulty using the computer
- Increased stress; struggles more with decisions

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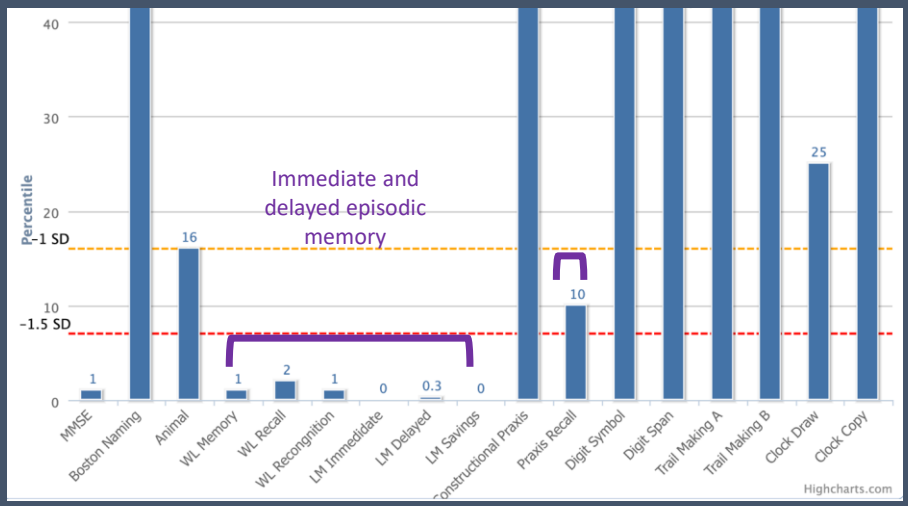
18

Amnestic syndrome



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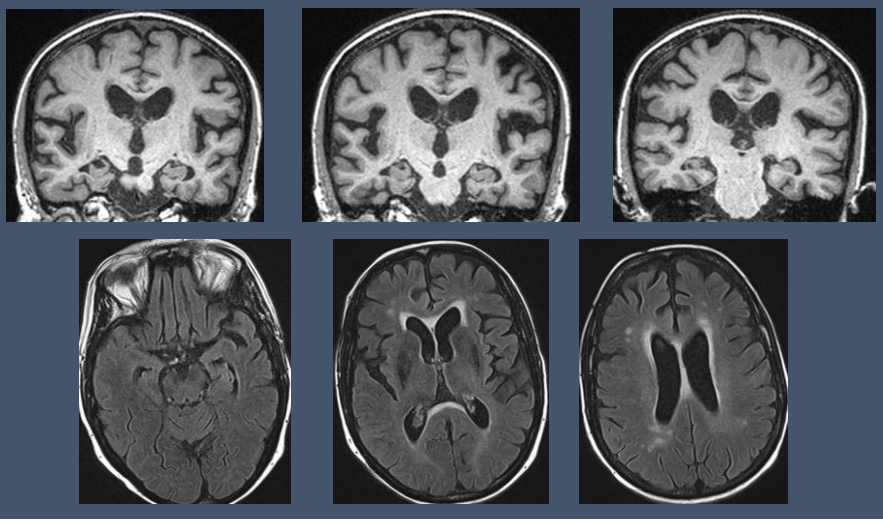
19

Initial MRI



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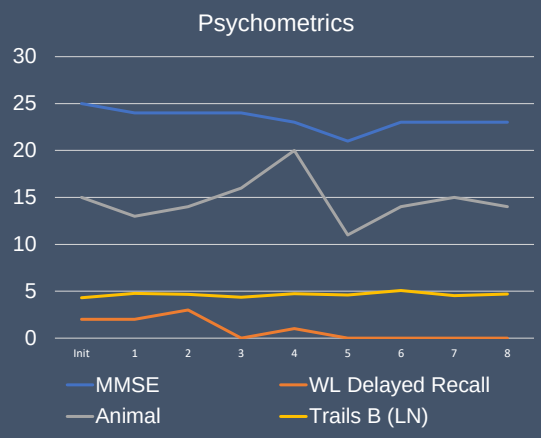
20

Very slow decline



9 Years Later

- Memory poor, but stable
- Some decrease in attention and motivation
- Disinhibition – says negative things about people while in the same room
- Diagnosis: **Alzheimer's Disease**

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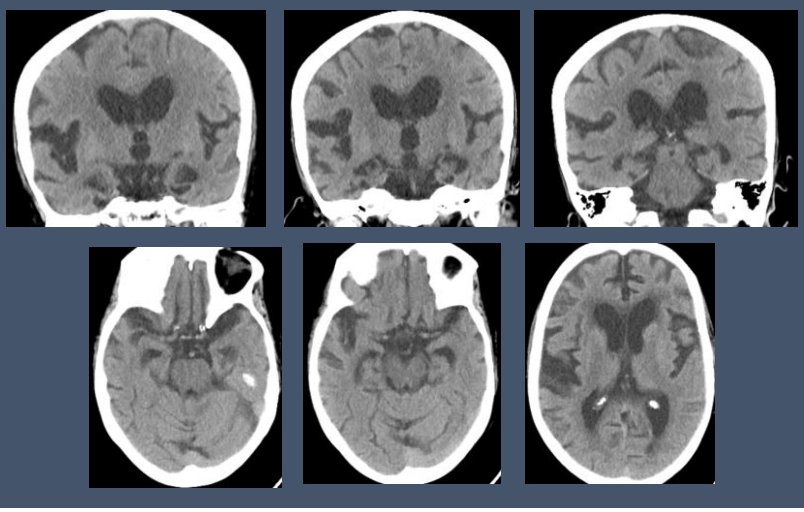
21

10 years after initial scan



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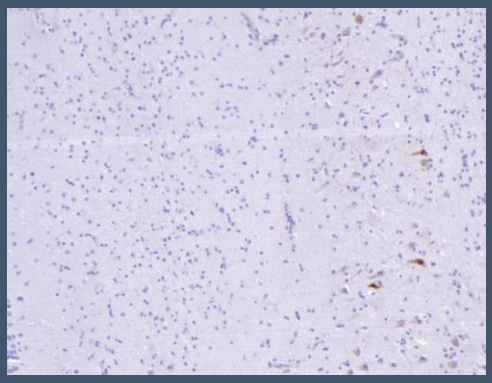
22

Autopsy



Hippocampus ~20x
1D3 antibody stains TDP-43

Not consistent with AD

Neuropath Diagnosis #1 = LATE-NC Stage 2

Neuropath Diagnosis #2 = Primary Age-related Tauopathy (PART)

Neuropath Diagnosis #3 = Lewy body disease, amygdala-predominant

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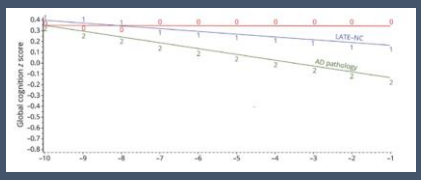
LATE produces a primarily amnestic syndrome

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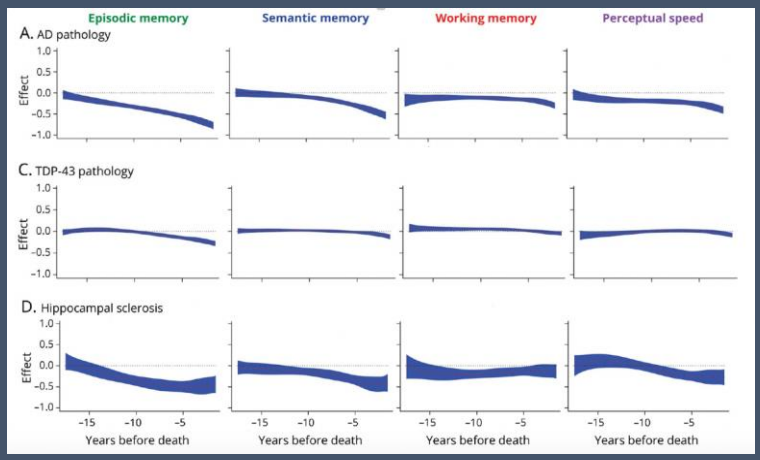
LATE-NC with versus without Hippocampal Sclerosis associated with more significant cognitive decline



Wilson et al, *Neurology*, 2019

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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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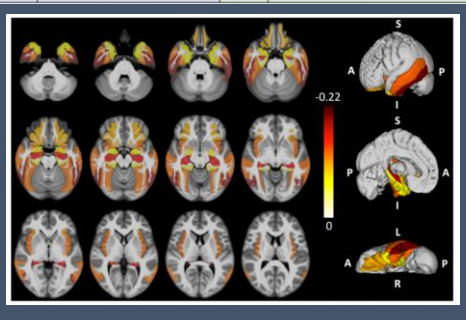
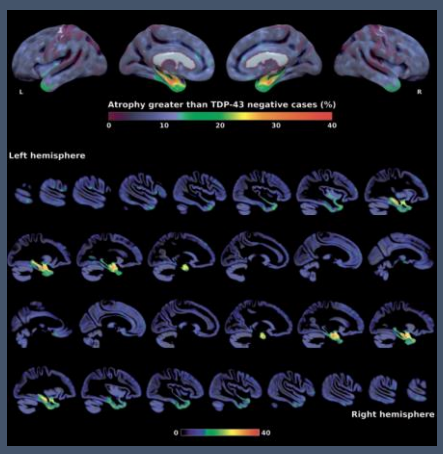
6	Basal ganglia, MFG	5	MFG





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

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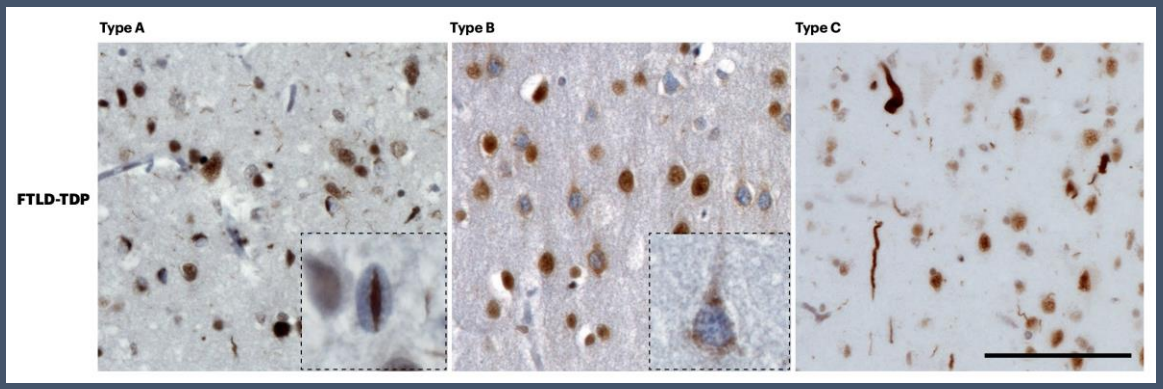
26

TDP-43 pathology of LATE resembles TDP-43 Type A



Grossman et al., *Nature Reviews Disease Primers*, 2023

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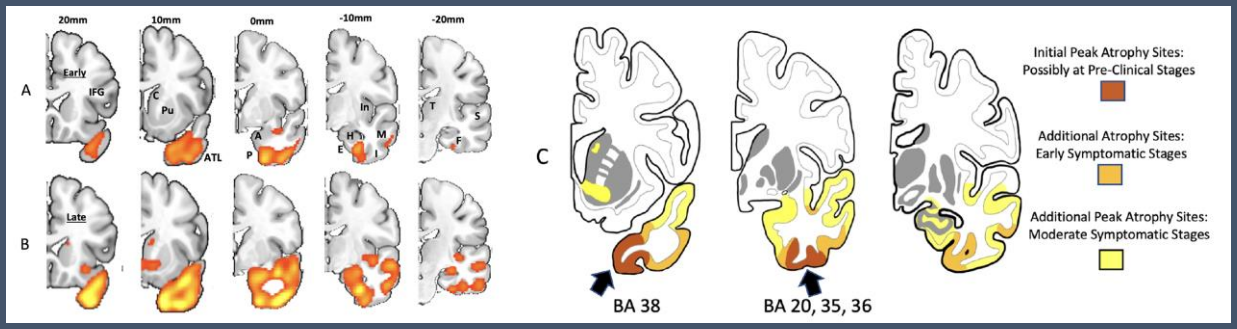
27

Anatomic topography overlaps significantly with TDP-43 Type C



Mesulam et al., *Annals Neurology*, 2023

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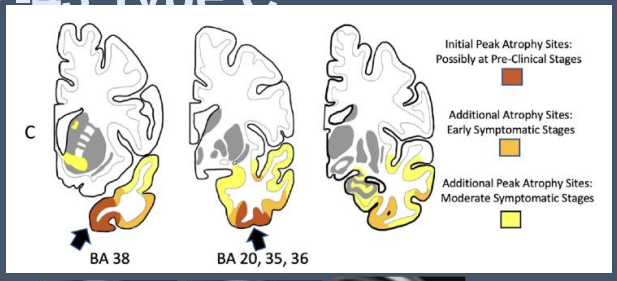
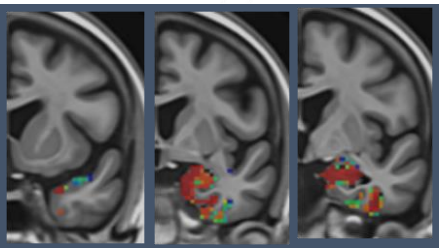
28

Anatomic topography overlaps significantly with TDP-43 Type C





Clinically defined LATE

Mesulam et al., *Annals Neurology*, 2023

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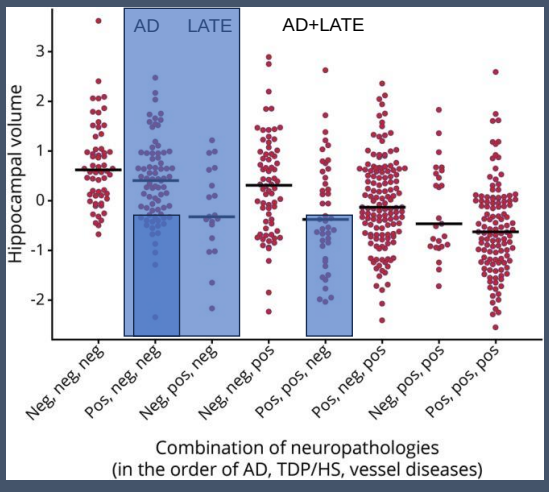
29

LATE-NC with or without ADNC is associated with smaller hippocampal volume than ADNC alone



Lower range of hippo volume in AD is enriched in AD+LATE

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

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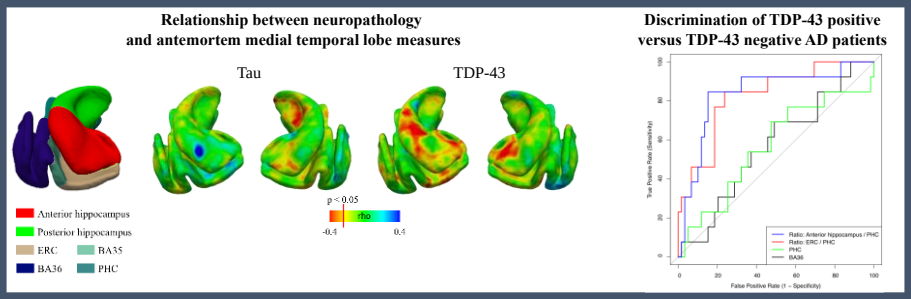
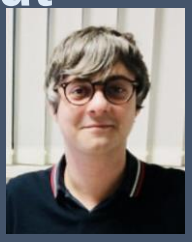
30

Pattern of MTL atrophy may differentiate AD with versus without TDP-43 pathology

- 89 individuals with Alzheimer's Disease pathology and antemortem T1-MRI
- TDP43 correlated most strongly with aHipp and ERC
- NFTs correlated most strongly with pHipp





Robin de Flores, PhD

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

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

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

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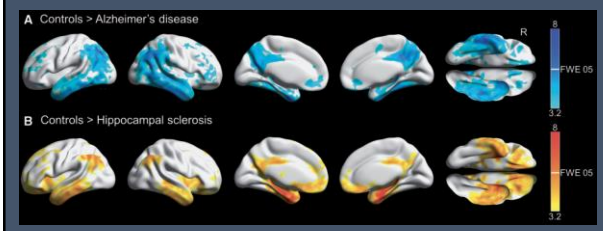
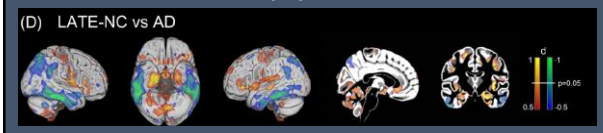
31

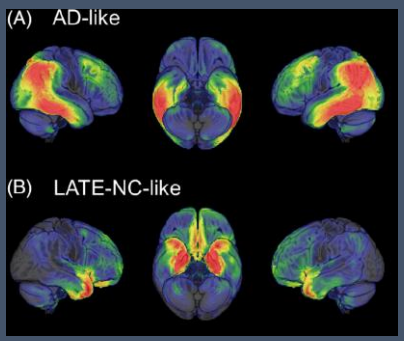
FDG PET signature of LATE-NC

Mayo Autopsy-confirmed



ADNI Autopsy-confirmed





Clinical AD patients with LATE-NC-like pattern

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

Inferior to Medial Temporal Ratio AUC ~0.85

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

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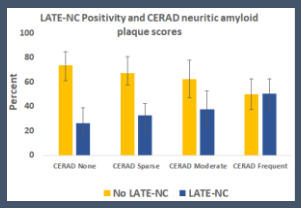
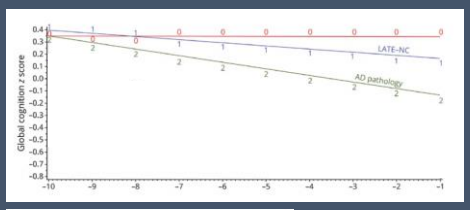
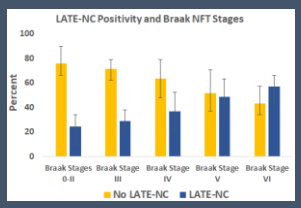
32

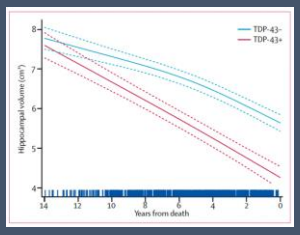
LATE-NC <u>most</u> commonly co-occurs with AD (>1/3) and is associated with an <u>accelerated</u> global cognitive decline

- 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; Josephs et al., *Lancet Neuro*, 2017

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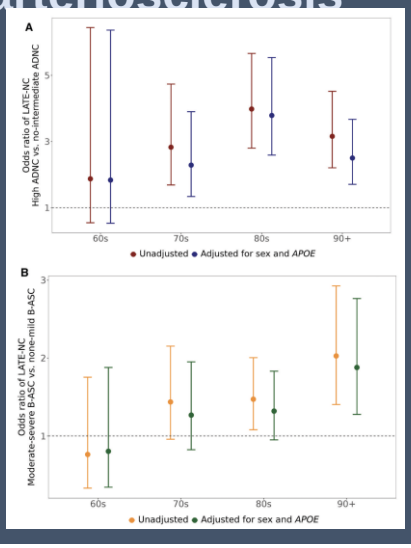
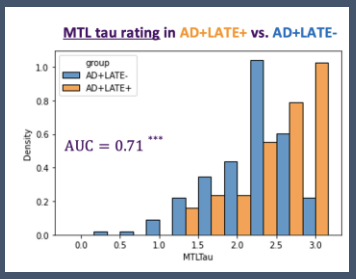
33

LATE-NC associated with AD severity and arteriosclerosis





Data from 202 autopsies at Penn ADRC with diagnosis of intermediate/high ADNC (excluding FTLD, non-AD tauopathies)

LATE+: LATE-NC stage 2 or 3 (n=38)
LATE-: LATE-NC stage 0 or 1 (n=168)

Nelson et al., *Journal of Neuropath and Exp Neuro*, 2024; Yushkevich et al., AAIC, 2024

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AD versus LATE?

- CSF
  - Low Abeta, normal t-tau/p-tau$_{181}$
- Dx: MCI due to AD and then dementia due to AD next year

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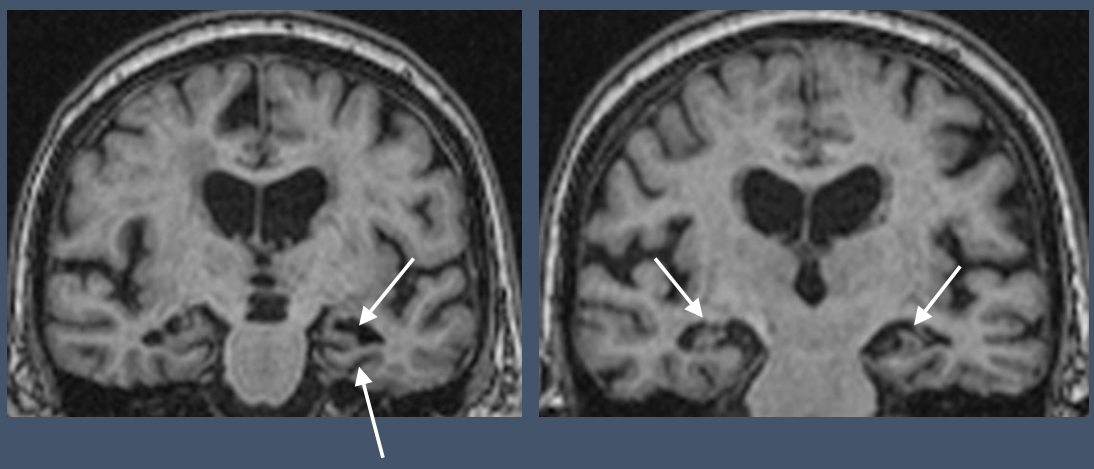
35

MRI



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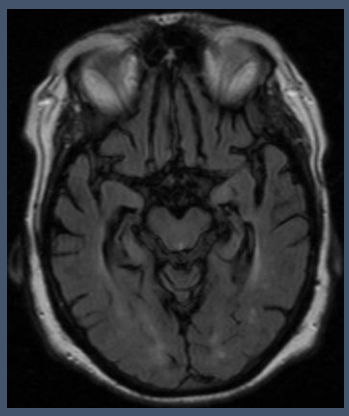
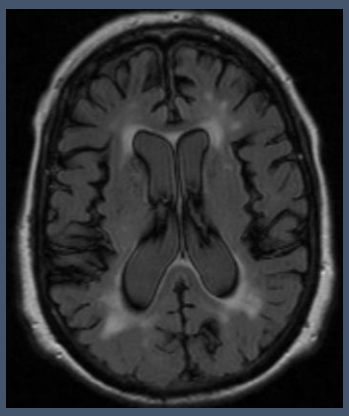
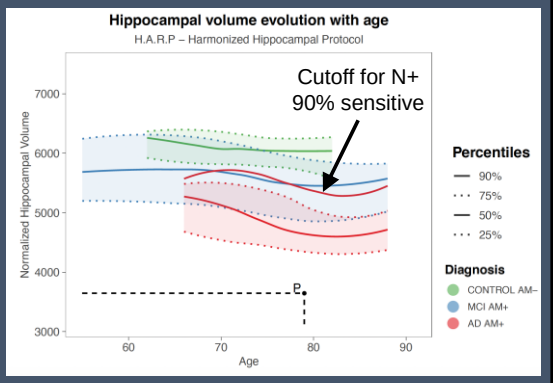
36

MRI







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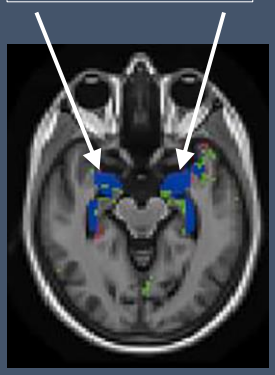
Autopsy >15 years after initial presentation

- Intermediate AD (A3, B2, C3)
- LATE Stage 3
- Amyloid Angiopathy

- Patient would have qualified for anti-amyloid therapies
  - At least at presentation, was LATE disease driving etiology?
  - Treatment appropriate?
  - ~25% of MCI A+ are T- in Braak I/II region (Tau PET)
  - ~1/3 of A+/N+ MCI are T- (CSF Tau; McCollum et al., *Neuroimage Clinical*, 2021)

Atrophy greatest is anterior MTL of A+T-N+ and A-T-N+



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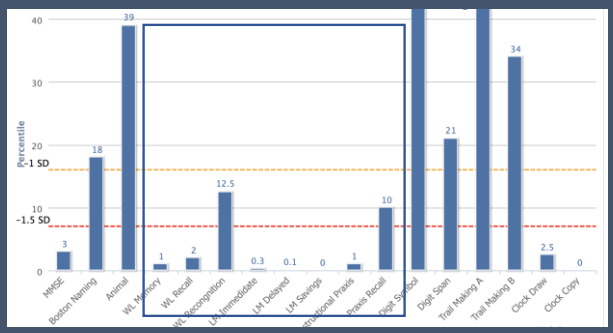
38

LATE as a co-pathology with AD

- Man in his early 70's with primarily forgetfulness
  - MMSE 26/30



CSF
$ptau_{181}$: 67 pg/ml (cutoff 22)
$Abeta_{42}$: 119 pg/ml (cutoff 191)

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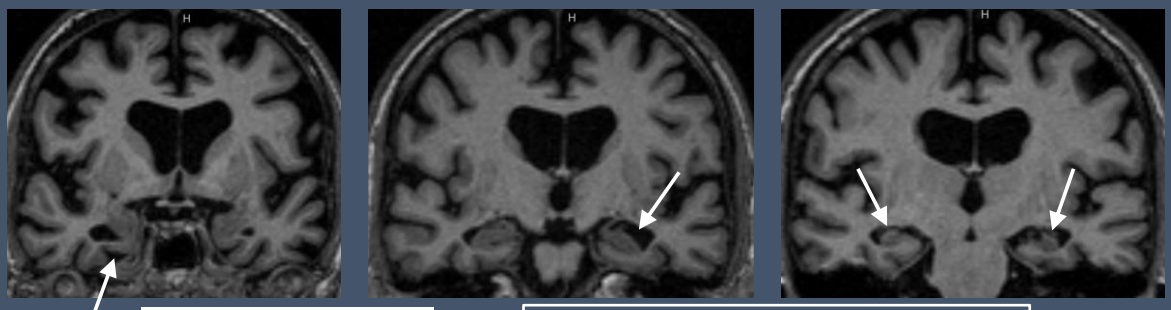
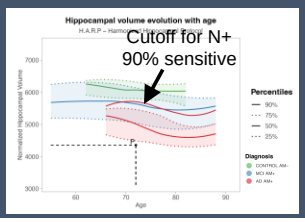
39

LATE as a co-pathology with AD





Autopsy
ADNC (A3, B3, C3)
LATE Stage 2
Low probability LB disease

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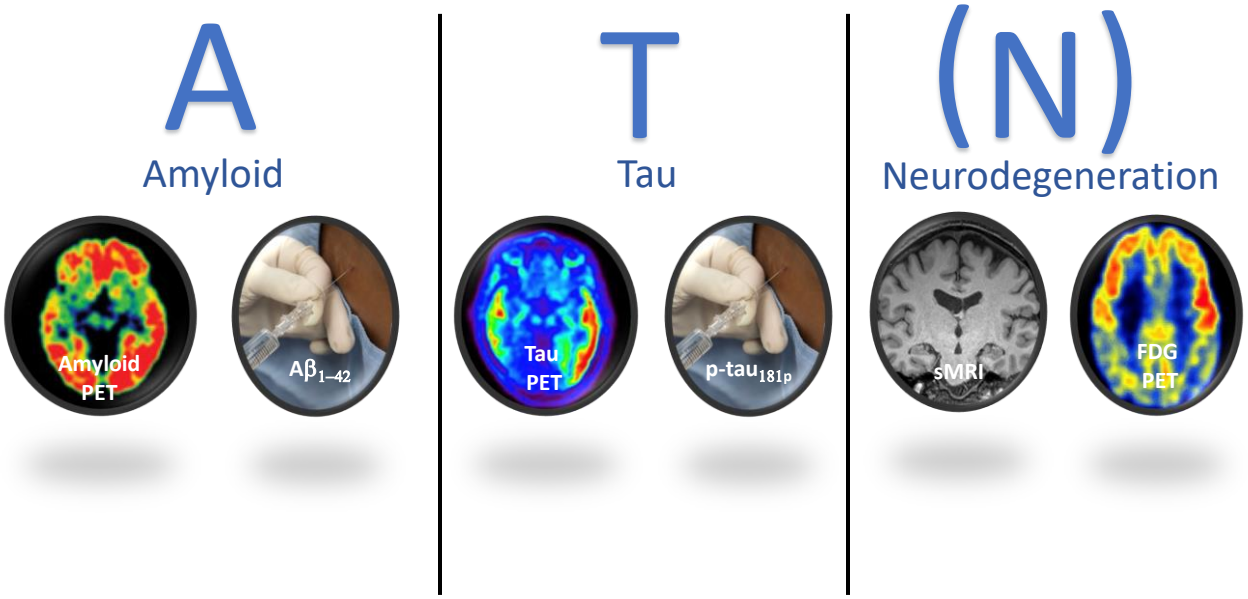
40



Jack et al., *Alzheimer's & Dementia*, 2018

41

41

Can we take advantage of N's nonspecificity

- Neurodegenerative measures are non-specific to AD
  - Non-AD pathologies
  - Vascular disease
  - Age-related changes
  - Development – interindividual differences
- In absence of biomarkers for non-AD proteinopathies (e.g. TDP-43), neurodegenerative measures may support presence of alternative pathologies
  - Patterns and severity of neurodegeneration may provide hints to co-pathology

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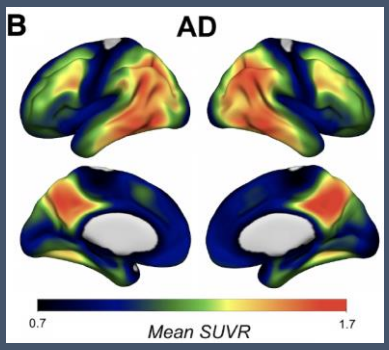
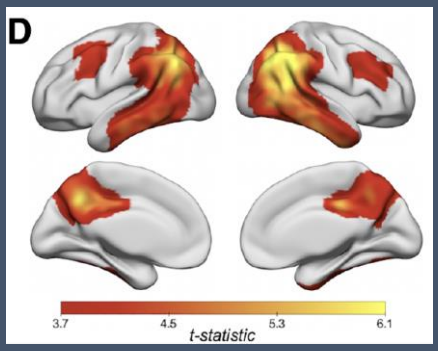
Tau PET pattern of uptake corresponds strongly with neurodegeneration

^{18}F-Flortaucipir Baseline



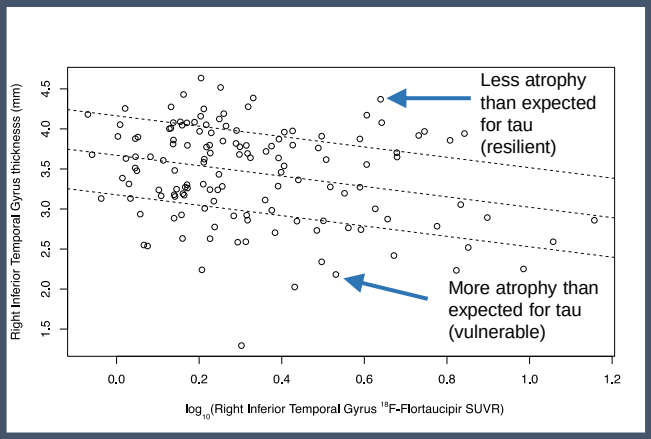
Longitudinal Atrophy



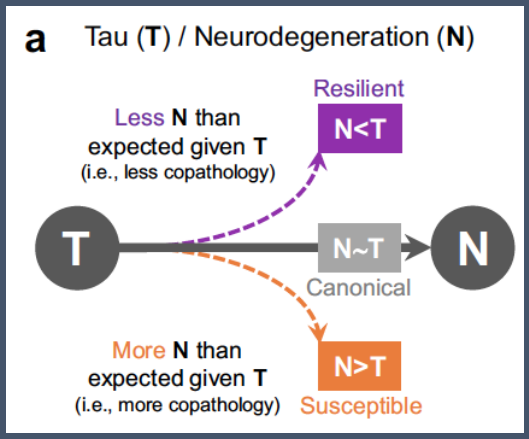
Harrison et al., Annals of Neurology, 2019

Tau distribution is the "Answer Sheet" for spatial pattern and degree of neurodegeneration due to AD pathology

Determining normative relationships of tau with neurodegeneration

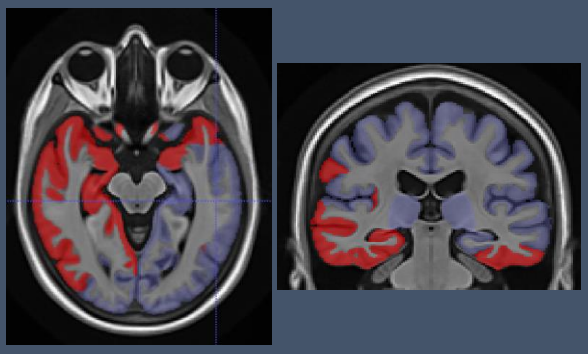


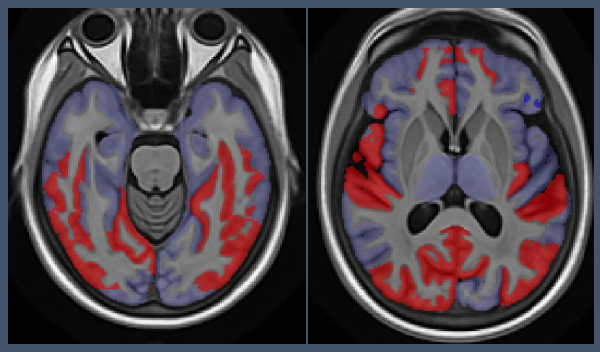
Das et al, *Annals of Neurology*, 2021



Duong et al, *Nature Communications*, 2022

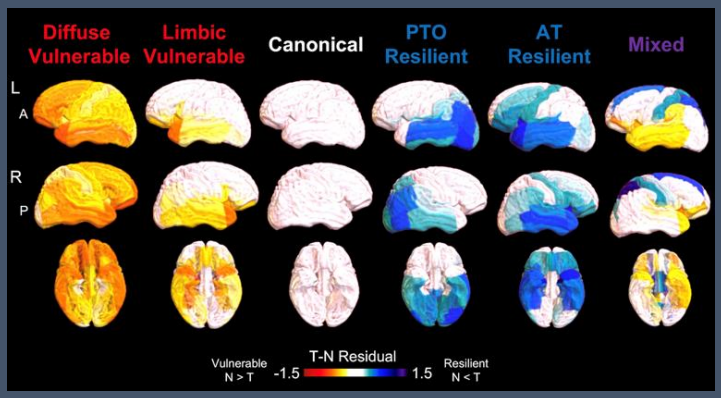
Spatial variability in mismatch regions

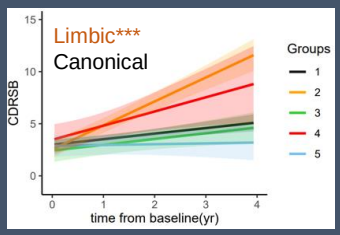




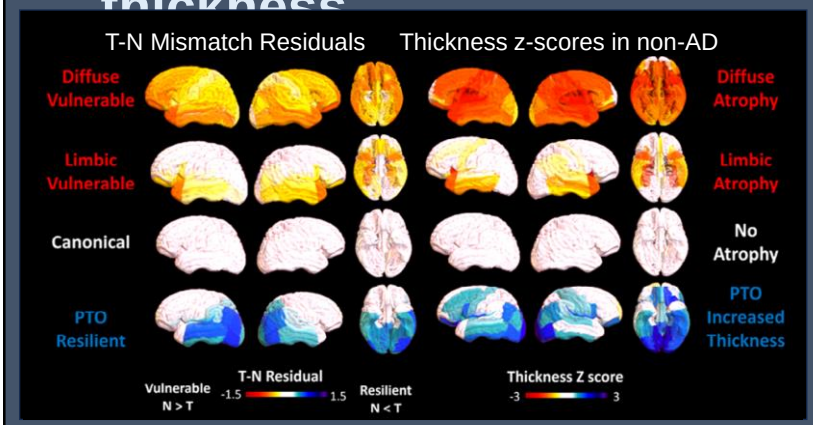
T-N Mismatch residual maps ADNI cohort (A+ MCI/AD)

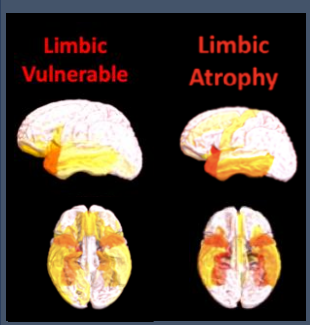
Xueying Lyu, BE Grad Student



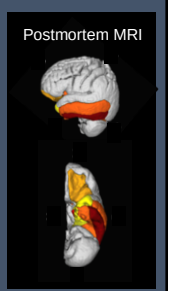


T-N mismatch patterns (AD effects removed) similar to patterns in non-AD symptomatic cases clustered by cortical thickness

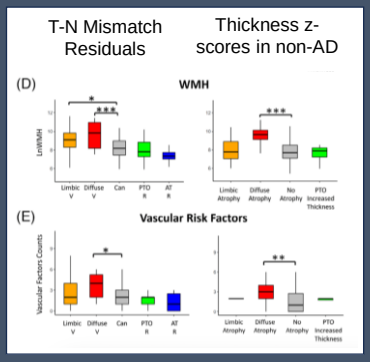




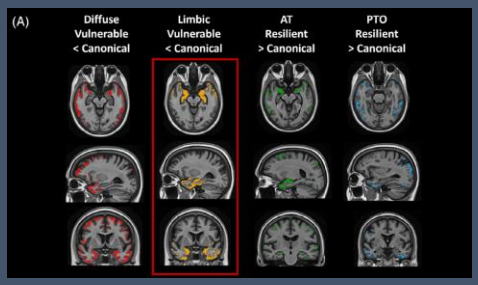
LATE-NC

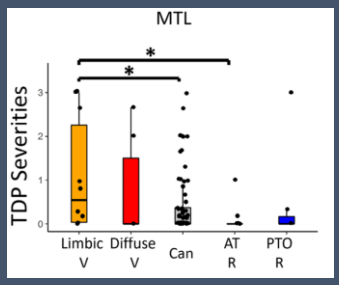


Associations with non-AD modulators



Antemortem MRI (N measure) with postmortem tau burden (T); 7 ROIs





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Lyu et al, *Alz & Dementia*, 2023

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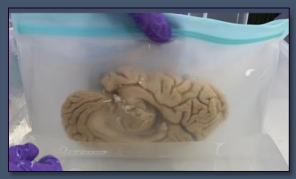
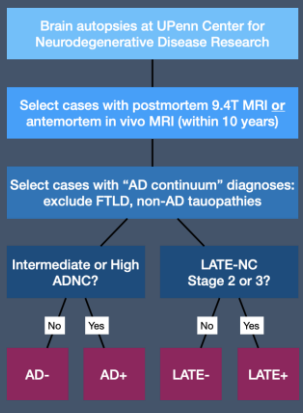
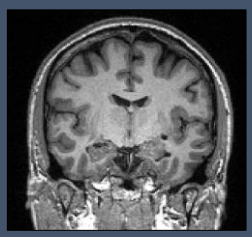
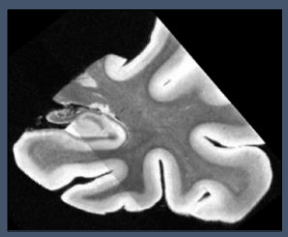
49

Post-mortem imaging









	Antemortem MRI dataset	Postmortem MRI dataset	Overlap
AD+LATE+	17	11	3
AD+LATE-	107	16	8
AD-LATE+	2	2	1
AD-LATE-	36	5	4
All	**162**	**34**	**16**

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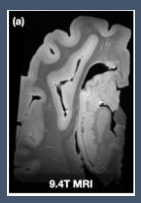
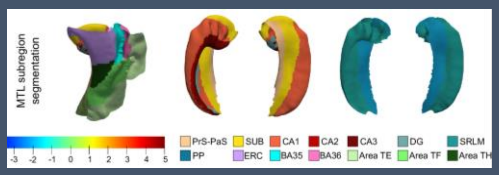
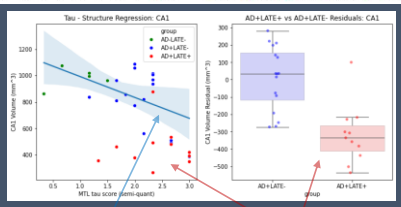
50

Postmortem validation of mismatch for AD/LATE-NC



Yushkevich et al., *Brain*, 2020

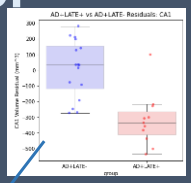


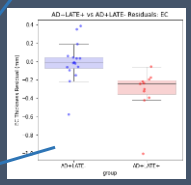


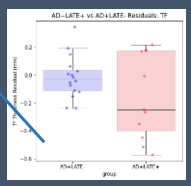
Regression between tau pathology and CA1 volume, fitted in the LATE- subgroup, represents expected relationship

AD+LATE+ subgroup is mostly below the regression line, residuals from the regression are significantly smaller compared to AD+LATE-

measure	T (Tau regression)	T (AD+LATE+ residuals)
PrS-PaS Thickness	3.074*	0.323
SUB Thickness	2.752*	2.784†
CA1 Volume	2.502*	4.665**
CA2 Volume	3.480**	2.328†
CA3 Volume	1.222	-0.705
DG Volume	0.852	2.121†
SRLM Thickness	1.275	2.371†
PP Thickness	1.991	-0.329
ERC Thickness	5.083**	3.495*
BA35 Thickness	1.864	1.733
BA36 Thickness	1.053	1.714
Area TE Thickness	3.765**	0.422
Area TF Thickness	3.648**	1.524
Area TH Thickness	3.691**	0.268







Yushkevich et al., *AAIC*, 2024

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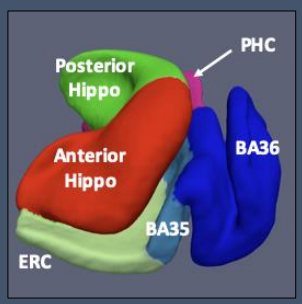
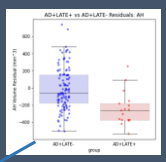
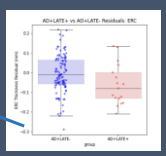
51

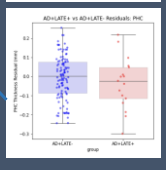
Antemortem imaging – quantitative histology



measure	T (Tau regression)	T (AD+LATE+ residuals)
Ant. Hipp. Volume	5.060***	4.362***
Post. Hipp. Volume	5.562***	4.654***
ERC Thickness	6.188***	2.914**
BA35 Thickness	5.199***	0.330
BA36 Thickness	3.078**	1.553
PHC Thickness	4.320***	1.318







Age, sex and antemortem interval (AMI) included as covariates in the linear model

MTL quantitative tau tangles burden rating and LATE status from ipsilateral hemisphere

Penn Memory Center
University of Pennsylvania Health System

Yushkevich et al., *AAIC*, 2024

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52

Proposal for clinical criteria for LATE

- 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

Wolk et al., *Alzheimer's & Dementia*, in press

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53

Core clinical syndrome

I. Core Clinical Syndrome* (1 and 2 required)
1. Primary amnestic syndrome with tempero-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
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

Wolk et al., *Alzheimer's & Dementia*, in press

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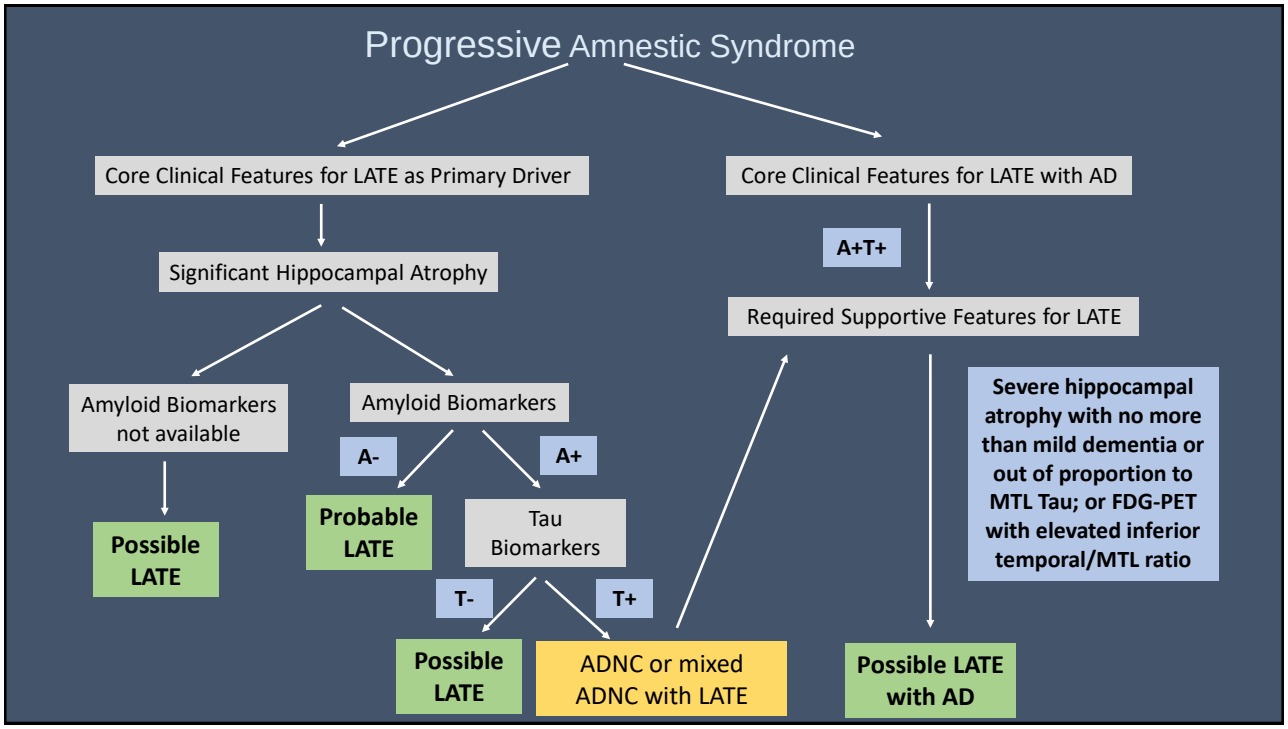
54



55

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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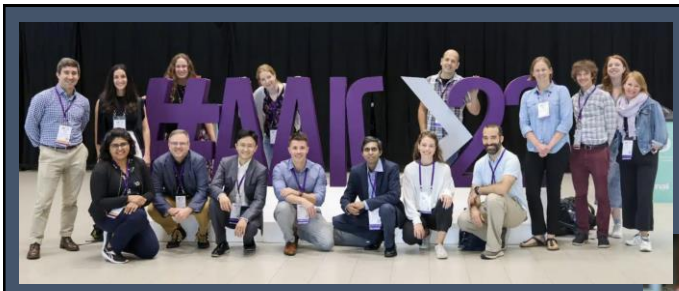
56



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MGH
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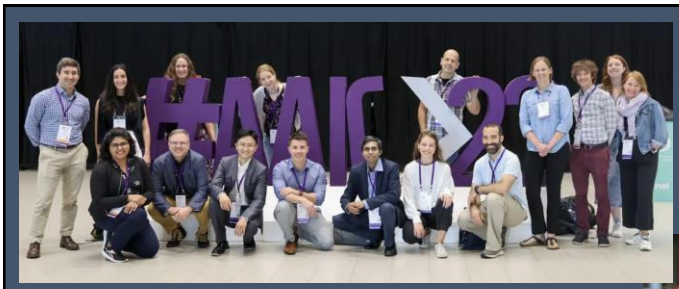
57



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58

Thank You

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59

60