

Multicohort characterization of brain volume and cognitive decline in Alzheimer's disease cases with and without LATE-NC

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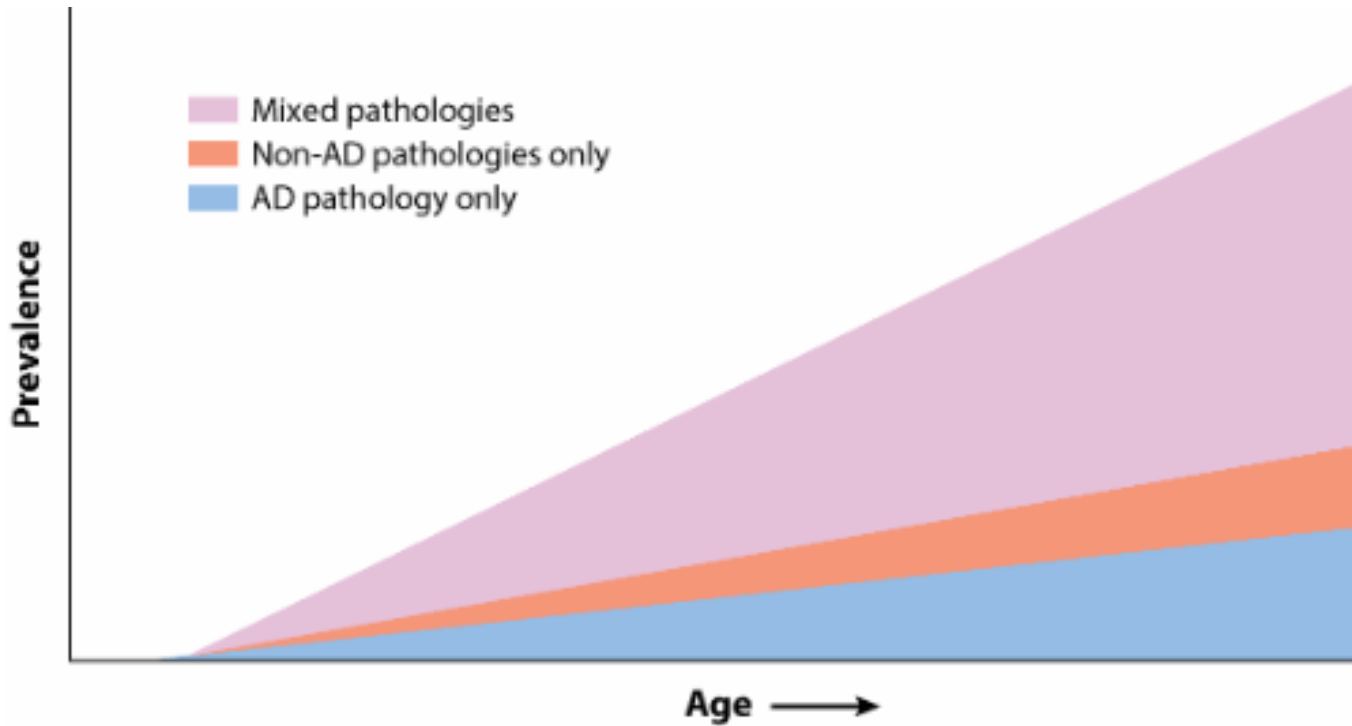
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Presentation Objectives

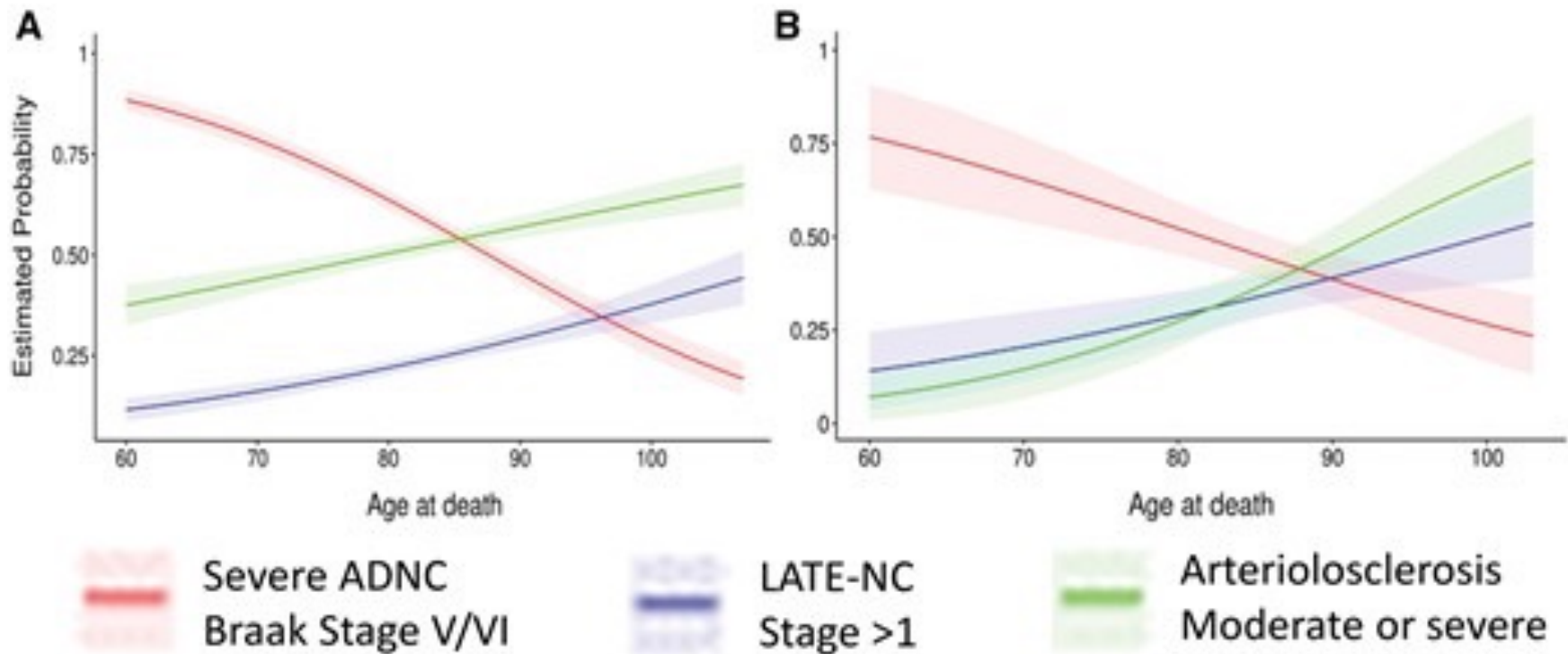
- Review clinical dementia in the oldest-old
- Outline recently proposed clinical criteria for LATE in cases with confirmed Alzheimer's disease pathology
- Describe study sample and design
- Review study results
- Discuss implications of study for identifying comorbid LATE-NC clinically

Dementia is more commonly due to mixed neuropathologies the oldest-old



AR James BD, Bennett DA. 2019.
Annu. Rev. Public Health 40:65–84

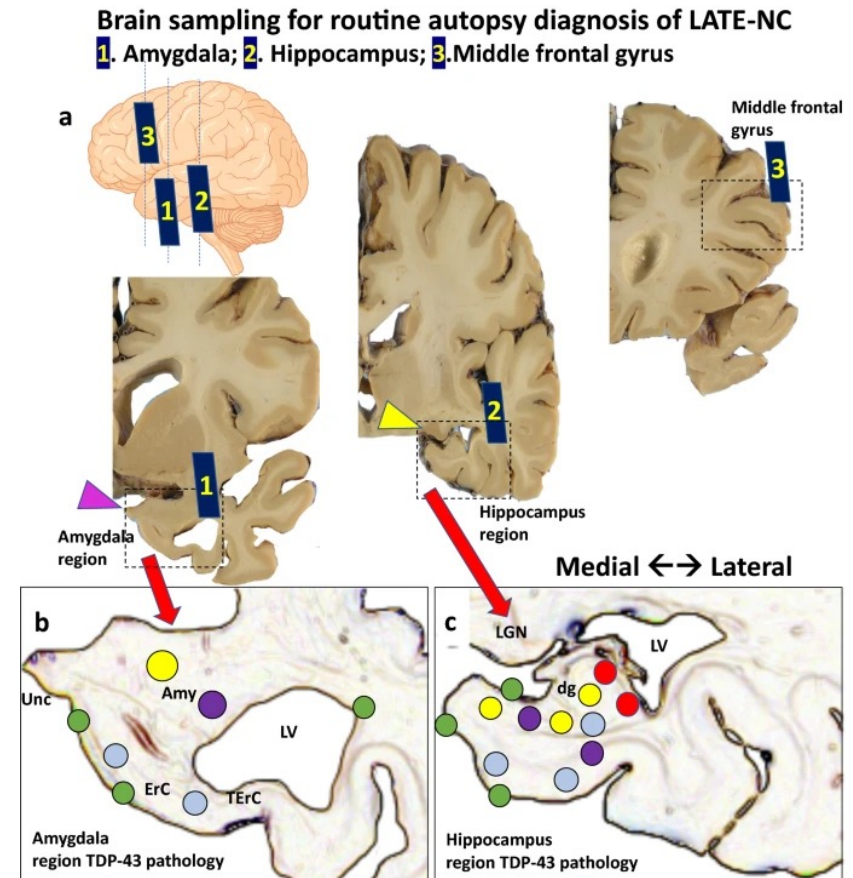
While the prevalence of severe AD pathology decreases in oldest-old age, the prevalence of arteriolosclerosis and LATE-NC increases with age



**Select neuropathologies, estimated probabilities stratified by age:
NACC cohort (n=1964; A) and in the UK-ADRC community-based cohort (n=276; B)**

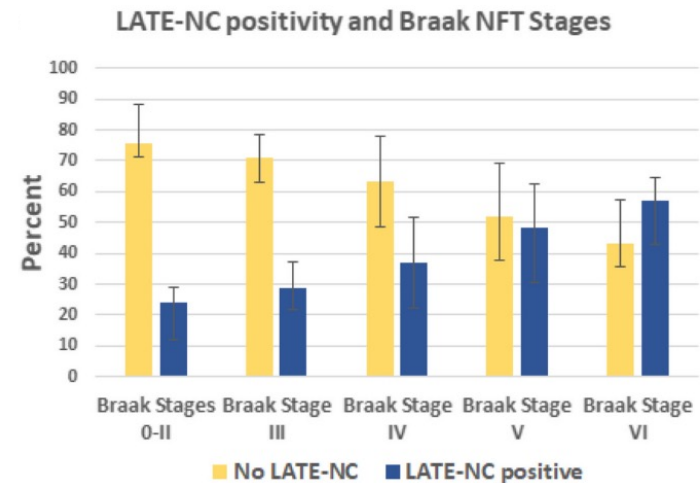
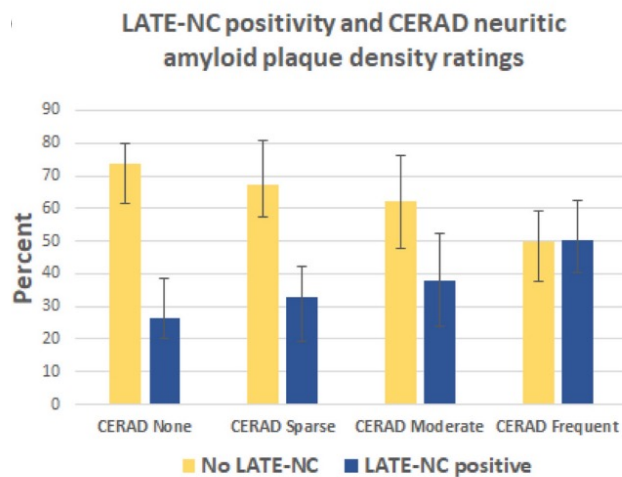
Limbic predominant Age-related TDP-43 Encephalopathy Neuropathologic Change (LATE-NC)

- LATE-NC is a common cause of dementia, particularly in the oldest-old
 - LATE-NC (pathological) versus LATE (clinical)
- Relates to significant hippocampal/medial temporal lobe atrophy, episodic memory decline
- No currently approved molecular biomarker for TDP-43

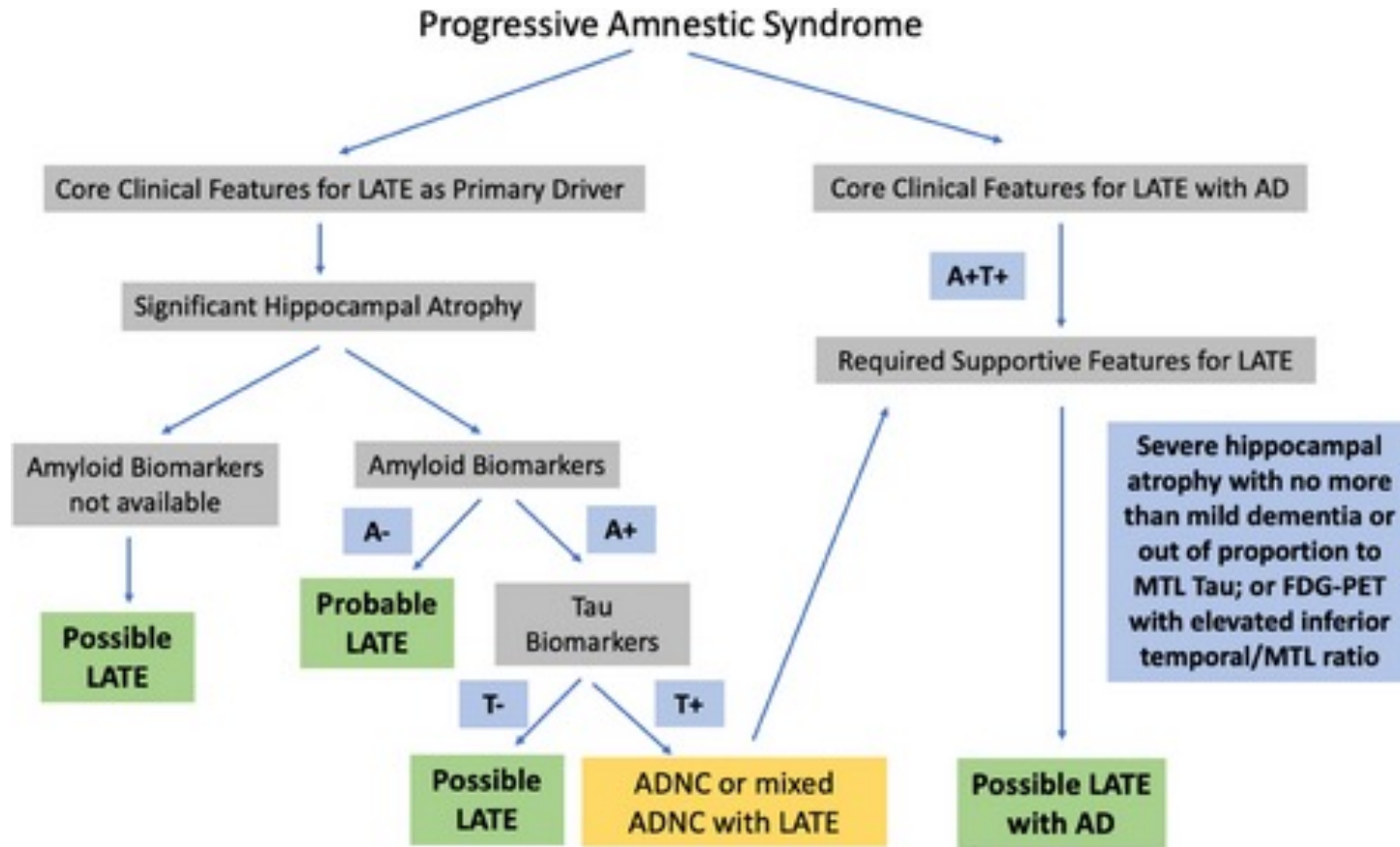


LATE-NC is a common AD co-pathology

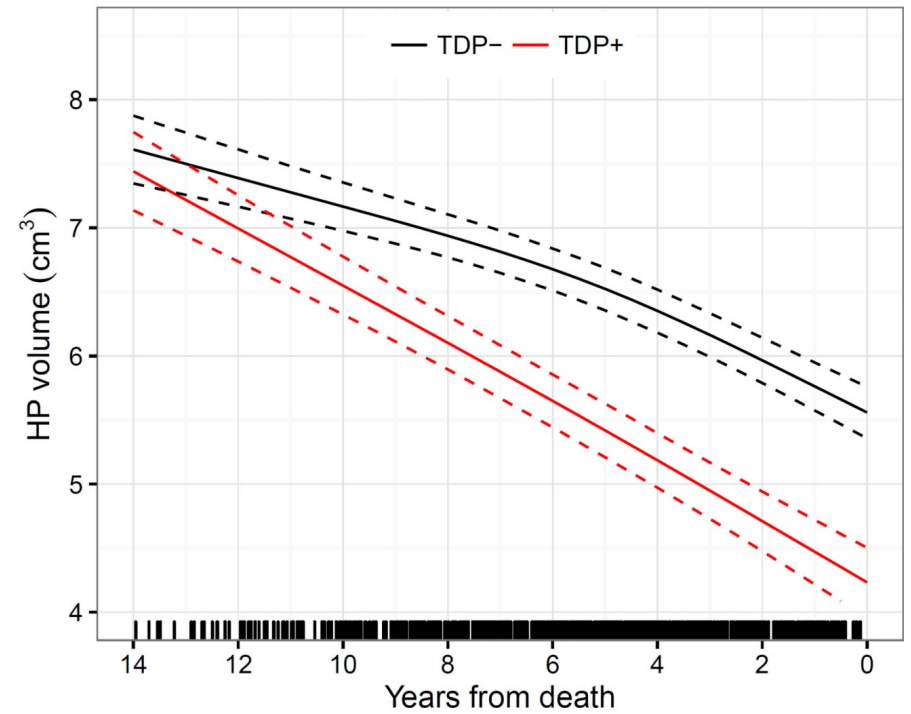
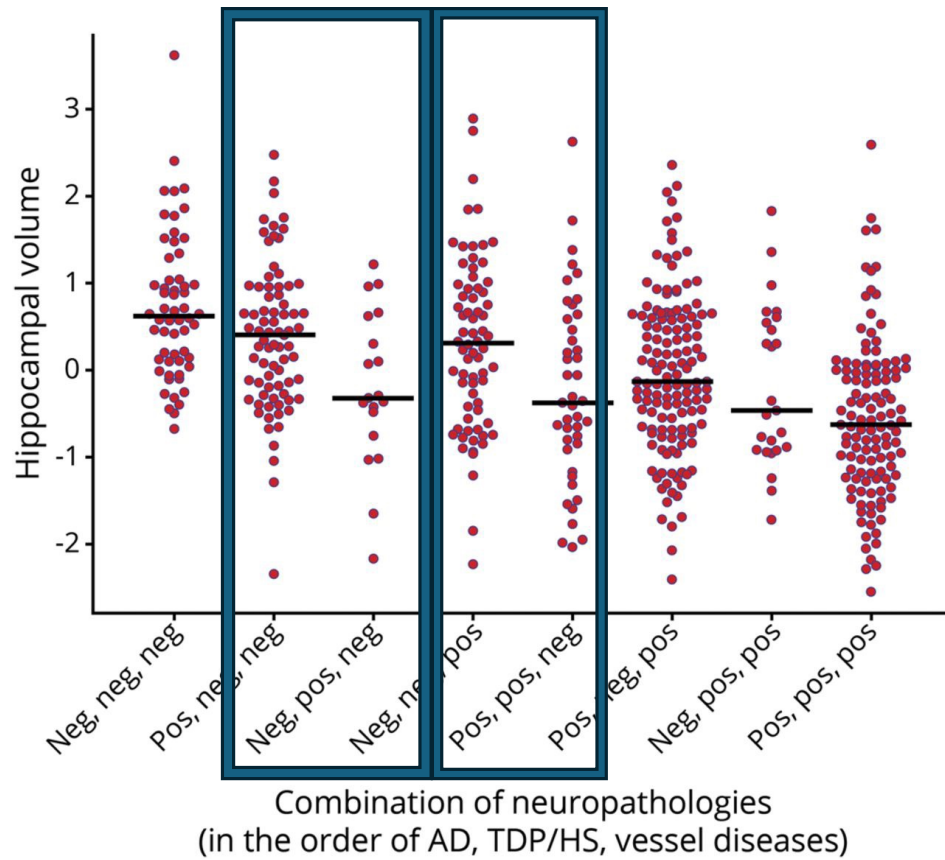
- LATE-NC frequency increases with greater amyloid and neurofibrillary tangle pathology
 - LATE-NC is present in **50%** of cases with severe AD pathology
- Important to understand the impact of LATE-NC on outcomes of disease-modifying therapies for AD



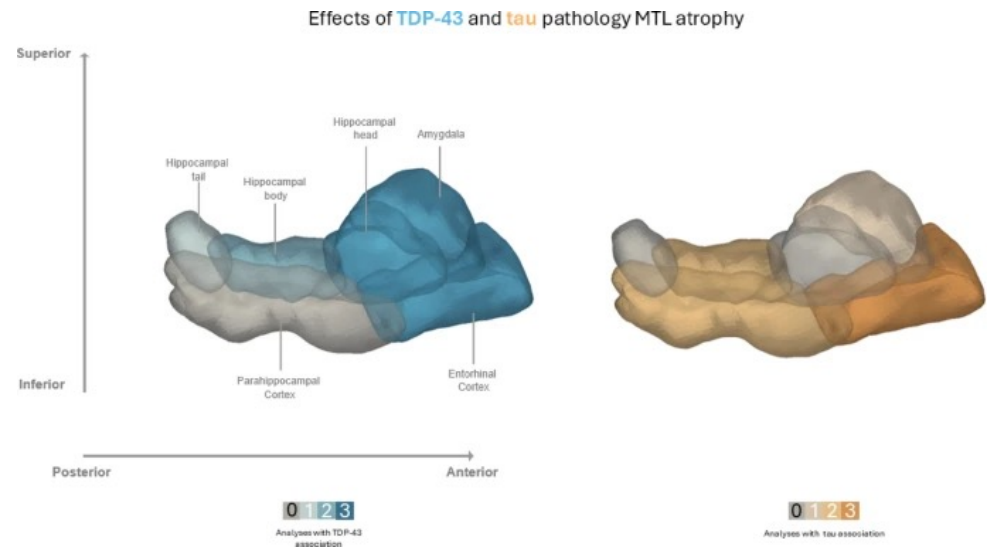
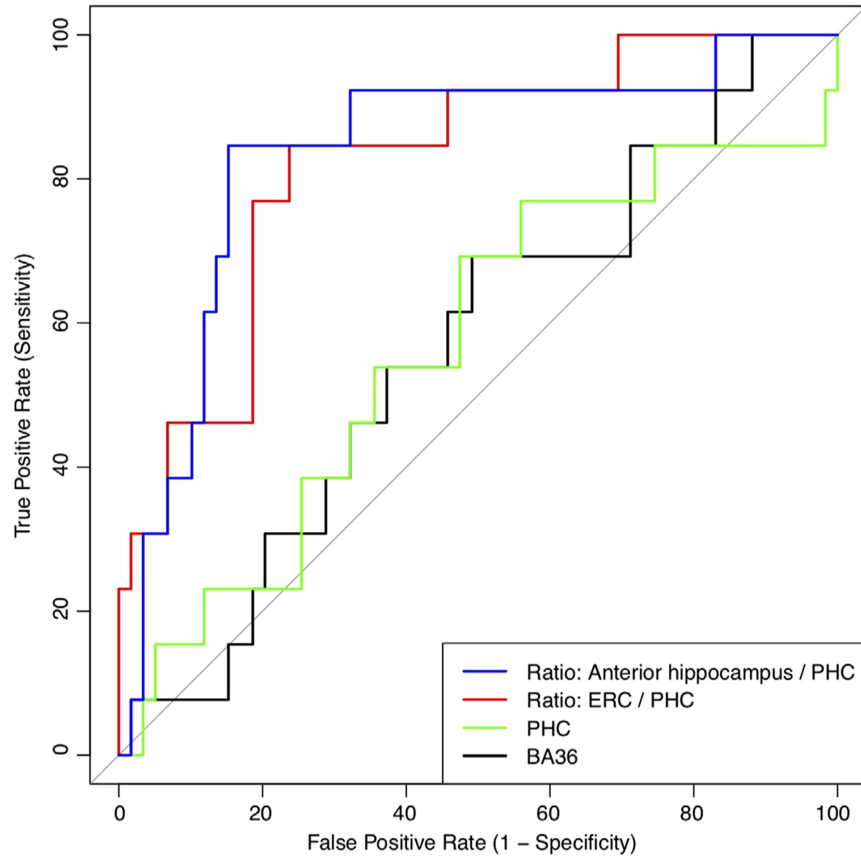
LATE-NC/AD Clinical Criteria



LATE-NC relates to significantly smaller hippocampal volume than AD pathology alone



LATE-NC relates to an anterior-to-posterior gradient of MTL atrophy



LATE-NC/AD relates to a faster rate of memory and language decline

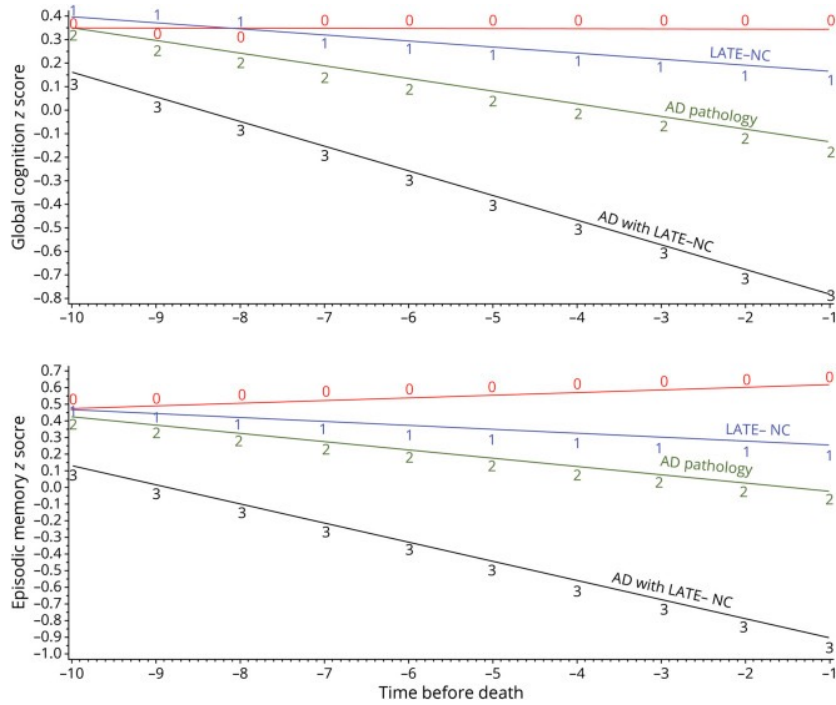


Table 3 Relation of TDP-43 and age-related pathologies to cognitive outcomes

Model terms	Estimate (standard error), p value					
	Global cognitive function	Episodic memory	Semantic memory	Working memory	Perceptual speed	Visuospatial abilities
Model 1						
TDP-43 pathology	-0.23 (0.08), 0.006	-0.40 (0.10), <0.001	-0.32 (0.11), 0.003	-0.11 (0.09), 0.246	-0.06 (0.10), 0.594	0.02 (0.10), 0.831
AD pathology	0.03 (0.21), 0.878	0.14 (0.25), 0.568	0.08 (0.27), 0.768	-0.17 (0.23), 0.480	0.03 (0.26), 0.922	-0.13 (0.24), 0.831
Macroinfarcts	-0.57 (0.10), <0.001	-0.59 (0.12), <0.001	-0.73 (0.13), <0.001	-0.48 (0.11), <0.001	-0.51 (0.13), <0.001	-0.35 (0.12), 0.003
Levy bodies	-0.58 (0.11), <0.001	-0.64 (0.13), <0.001	-0.61 (0.14), <0.001	-0.36 (0.12), 0.003	-0.33 (0.14), 0.018	-0.27 (0.13), 0.036
Hippocampal sclerosis	-0.07 (0.25), 0.780	-0.10 (0.29), 0.737	-0.02 (0.31), 0.944	0.13 (0.27), 0.643	-0.35 (0.31), 0.258	-0.001 (0.28), 0.997
Model 2 (excluding participants with hippocampal sclerosis)						
TDP-43 pathology	-0.08 (0.10), 0.454	-0.28 (0.12), 0.018	-0.06 (0.12), 0.617	0.03 (0.11), 0.787	0.19 (0.12), 0.125	0.25 (0.11), 0.029
AD pathology	-0.03 (0.21), 0.881	0.12 (0.25), 0.620	-0.05 (0.26), 0.851	-0.23 (0.24), 0.325	-0.06 (0.26), 0.818	-0.29 (0.24), 0.233
Macroinfarcts	-0.61 (0.10), <0.001	-0.65 (0.12), <0.001	0.71 (0.13), <0.001	-0.53 (0.11), <0.001	-0.53 (0.13), <0.001	-0.35 (0.12), 0.029
Levy bodies	-0.54 (0.11), <0.001	-0.59 (0.13), <0.001	-0.54 (0.14), <0.001	-0.34 (0.13), 0.008	-0.33 (0.14), 0.019	-0.26 (0.13), 0.041

Abbreviations: AD = Alzheimer disease; TDP-43 = TAR DNA-binding protein 43. Cognitive outcomes are estimated from separate linear regressions, all adjusted for age at death, sex, and education.

Problem and Study Aim

In this study, we aimed to evaluate the relationship of autopsy-confirmed AD cases with and without LATE-NC with longitudinal cognitive decline and medial temporal lobe volume in a large, multicohort clinicopathologic sample.

We hypothesized that comorbid LATE-NC pathology would relate to (1) memory and language decline, and (2) both hippocampal and extrahippocampal medial temporal lobe volume

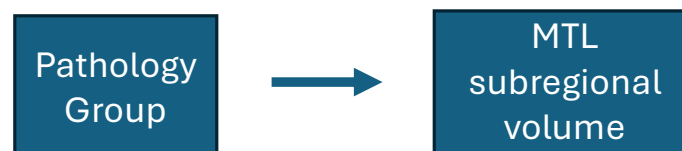
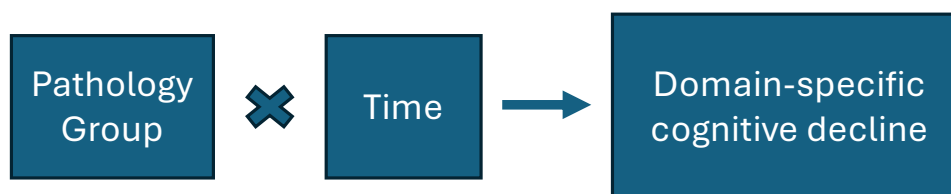
Methods

- Harmonized data was acquired from the **AD Sequencing Project Phenotype Harmonization Consortium**
- Participants ages 65+ at death with post-mortem characterization of AD and LATE-NC
 - AD+ = Moderate/Severe pathology
 - LATE-NC+ = Stage 1+
- Sample with harmonized longitudinal memory, language, and executive function domain scores derived from neuropsychological assessments
- Subsample with T1 brain magnetic resonance imaging (MRI) used to quantify MTL volume



Statistical Analyses

- 4 groups:
 - No pathology
 - AD only
 - LATE-NC only
 - AD and LATE-NC
- Linear mixed effects regression models assessed the effect of *group x time* on cognitive decline
- Linear regression models assessed the effect of *group* on MTL subregional volume



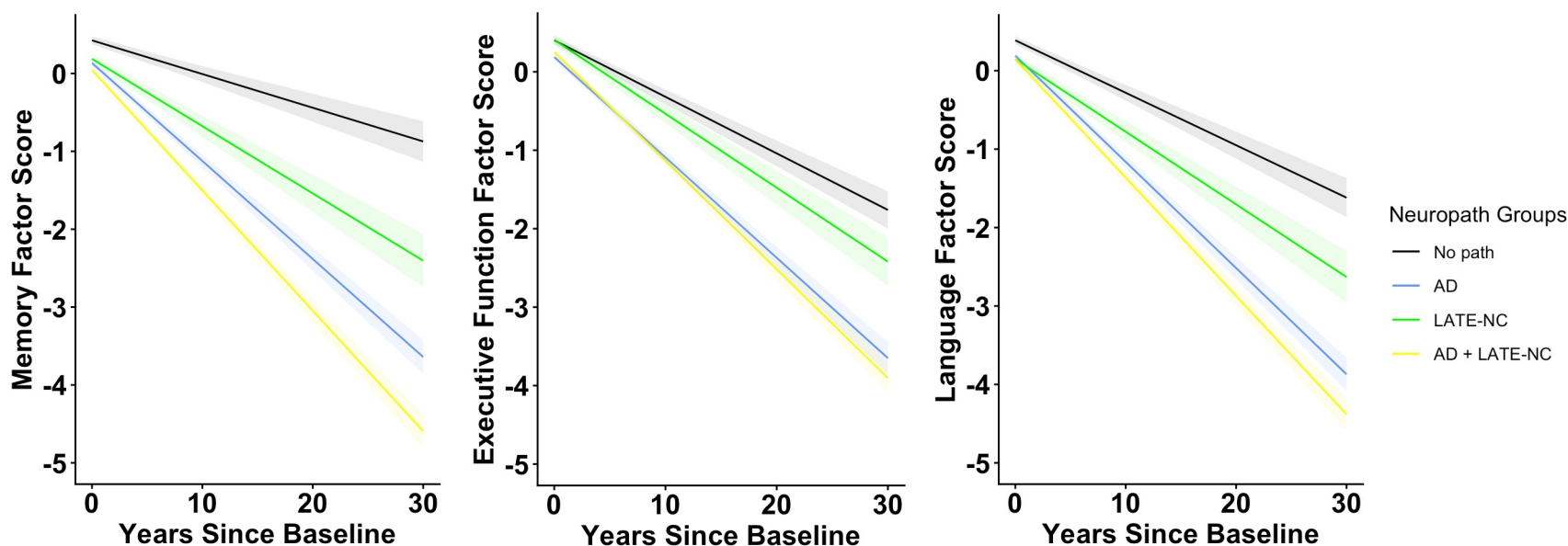
Results

Participant Characteristics

	ALL n=5,947	No pathology n=1,340	AD n=1,924	LATE-NC n=728	AD + LATE-NC n=1,955	p-value
Age at last visit, years	83.6±9.4	82.1±9.0	82.4±9.4	83.9±10.6*°	85.6±8.7*° †	<0.001
Sex, % female	58	53	57	55	63	<0.001
Education, years	15.8±3.2	16±3.2	15.8±3.3	15.9±3.0	15.7±3.2	0.14
Time between MRI and autopsy, years	2.3±2.6	1.8±2.2	2.3±2.6*	2.1±2.4*°	2.7±2.8*° †	<0.001
Diagnosis at last visit (frequency, %)	CN=26 MCI=15 Dem=59	CN=50 MCI=17 Dem=33	CN=20 MCI=16 Dem=64	CN=31 MCI=18 Dem=50	CN=12 MCI=12 Dem=75	<0.001
Race, % NHW	93	93	94	93	93	0.18
APOE-ε4, % positivity	42	15	45	17	47	<0.001
Atherosclerosis, %	42	39	40	39	47	<0.001
Arteriolosclerosis, %	48	41	54	46	55	<0.001
Memory	-0.6±1.0	0.1±0.9	-0.7±1.0*	-0.4±1.0*°	-1.1±0.9*° †	<0.001
Executive Function	-0.5±0.9	-0.1±0.8	-0.7±1.0*	-0.3±0.9*°	-0.7±0.9*° †	<0.001
Language	-0.6±1.0	-0.1±0.9	-0.6±0.9*	-0.5±0.9*°	-0.9±1.0*° †	<0.001

*= different from no pathology group; °= different from AD pathology group, †= different from LATE-NC pathology group

While LATE-NC relates to a *slower* rate of cognitive decline compared to AD alone, comorbid AD and LATE-NC relates to a *faster* rate of cognitive decline compared to AD alone



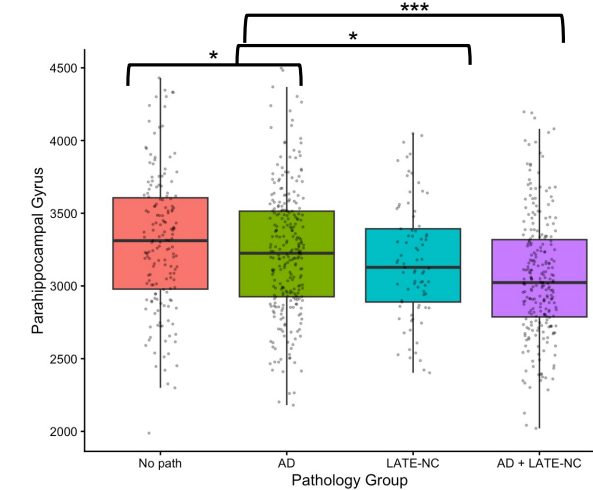
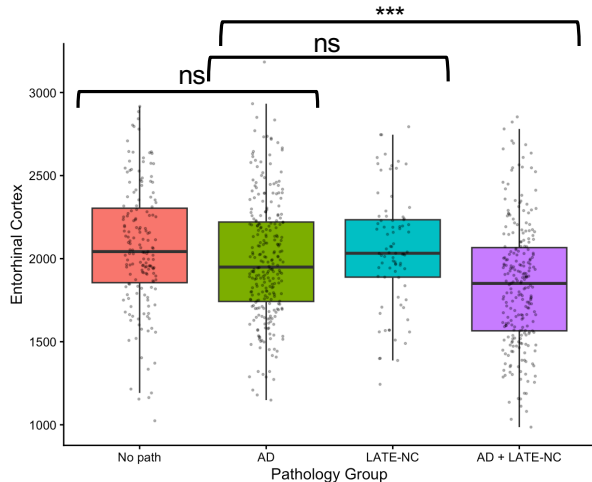
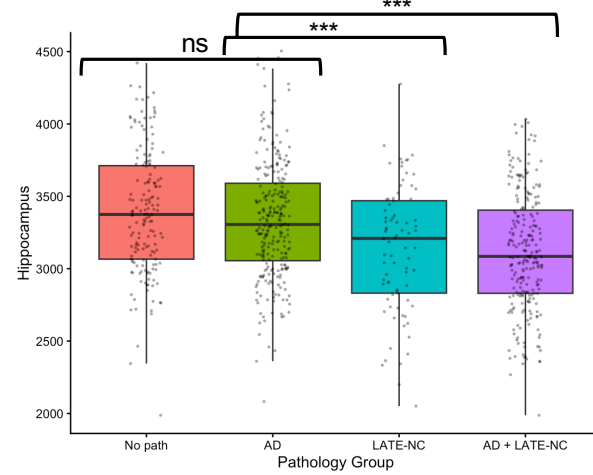
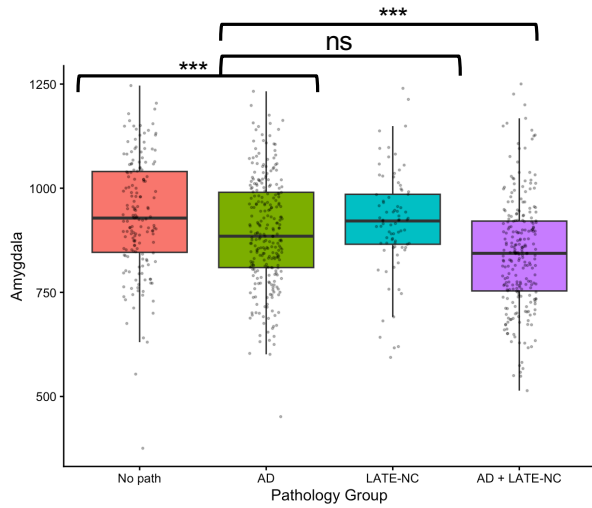
	β [95% CI]	p-value	β [95% CI]	p-value	β [95% CI]	p-value
No pathology	0.39 [0.34, 0.44]	<0.001	0.31 [0.25, 0.36]	<0.001	0.36 [0.31, 0.42]	<0.001
LATE-NC	0.19 [0.13, 0.25]	<0.001	0.19 [0.12, 0.25]	<0.001	0.23 [0.16, 0.29]	<0.001
AD + LATE-NC	-0.14 [-0.18, -0.09]	<0.001	-0.37 [-0.42, -0.31]	0.02	-0.08 [-0.13, -0.03]	<0.001

Participant Characteristics – MRI Subsample

	ALL n=751	No pathology n=163	AD n=264	LATE-NC n=81	AD + LATE-NC n=243	p-value
Age at last scan, years	82.1±8.5	81.8±8.2	79.9±9.1*	83.7±7.4°	84.1±7.9°	<0.001
Sex, % female	61	61	59	60	63	0.85
Education, years	15.6±3.3	15.1±3.5	15.8±3.4	15.7±3.2	15.6±2.9	0.19
Time between MRI and autopsy, years	5.1±3.1	4.4±3.1	5.0±3.1	5.8±3.5*	5.3±2.8*	0.004
Diagnosis at last visit (frequency, %)	CN=44 MCI=25 Dem=31	CN=74 MCI=16 Dem=10	CN=35 MCI=26 Dem=39	CN=55 MCI=26 Dem=19	CN=31 MCI=30 Dem=38	<0.001
Race, % NHW	92	87	93	90	95	0.02
APOE-ε4, % positivity	35	13	43	11	48	<0.001
Atherosclerosis, %	31	29	30	35	31	0.86
Arteriolosclerosis, %	45	31	48	41	53	<0.001
Memory	-0.1±0.8	0.4±0.7	-0.2±0.9*	0.1±0.8*°	-0.4±0.8*° †	<0.001
Executive Function	0.03±0.8	0.3±0.7	-0.1±0.8*	0.3±0.7°	-0.1±0.7*†	<0.001
Language	0±0.7	0.3±0.6	-0.1±0.7*	0.1±0.6	-0.1±0.7*†	<0.001

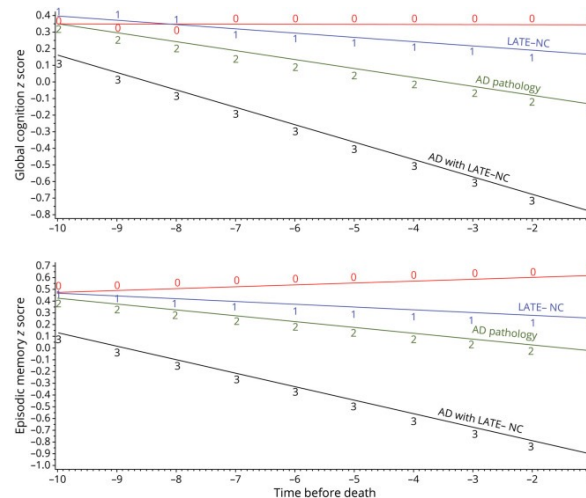
*= different from no pathology group; °= different from AD pathology group, †= different from LATE-NC pathology group

MTL volume differs by post-mortem pathology



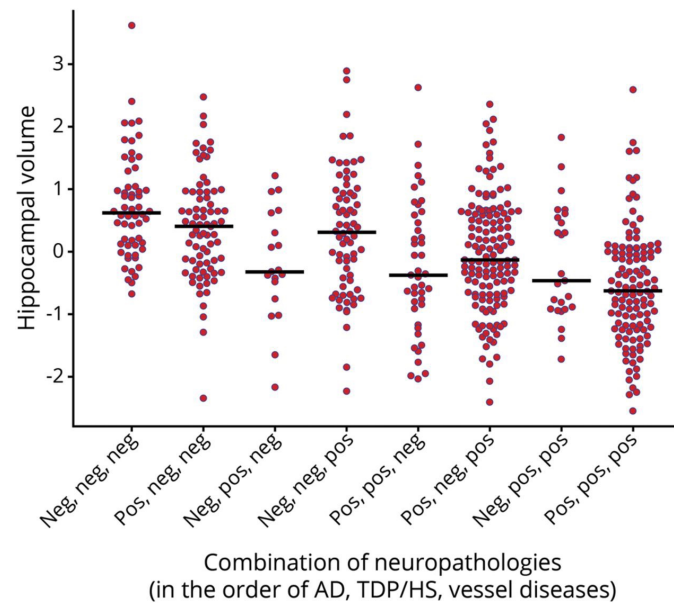
Conclusions

- LATE-NC is associated with multimodal cognitive decline
 - AD, LATE-NC, and comorbid AD and LATE-NC relates to a *faster* rate of cognitive decline compared to no pathology
 - While LATE-NC relates to a *slower* rate of cognitive decline compared to AD alone, comorbid AD and LATE-NC relates to a *faster* rate of cognitive decline compared to AD alone



Conclusions

- Comorbid AD and LATE-NC is associated with greater hippocampal and extrahippocampal medial temporal lobe atrophy than AD alone
 - LATE-NC alone relate to greater hippocampal atrophy than AD alone



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