Limbic-predominant age-related TDP-43 encephalopathy, ADNC pathology, and cognitive decline in aging

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Abstract

Objective

To examine the impact of 3 pathologic groups, pure limbic-predominant age-related transactive response DNA-binding protein 43 encephalopathy (LATE) neuropathologic changes (NC), pure Alzheimer disease neuropathologic change (ADNC), and mixed ADNC with LATE-NC, on late-life cognitive decline.

Methods

Data came from 1,356 community-based older persons who completed detailed annual cognitive testing and systematic neuropathologic examination at autopsy to identify LATE-NC, ADNC, and other age-related pathologies. Persons were categorized into (0) a group without a pathologic diagnosis of LATE or ADNC ($n = 378$), (1) LATE-NC without ADNC ($n = 91$), (2) ADNC without LATE-NC ($n = 535$), and (3) mixed ADNC with LATE-NC ($n = 352$). We used mixed-effect models to examine the group associations with rate of decline in global cognition and 5 cognitive domains and then examined whether age modified associations.

Results

Compared to those without LATE-NC or ADNC, those with pure LATE-NC had a faster decline in global cognition ($p = 0.025$) and episodic memory ($p = 0.002$); however, compared to persons with pure ADNC, those with pure LATE-NC showed a slower decline. Those with mixed ADNC with LATE-NC showed the fastest decline compared to those with either pathology alone. Persons ≥ 90 years of age with mixed ADNC with LATE-NC had slower cognitive decline compared to those ≤ 89 years of age.

Conclusion

Persons with pure LATE-NC follow a slower trajectory compared to those with pure ADNC. Those with mixed LATE/ADNC have a steeper decline than individuals with either pathology alone. In addition, age may modify the effect of pathology on cognitive decline. These findings have important implications for the development of biomarkers and prognosis for late-life cognitive decline.

Classification of evidence

This study provides Class I evidence that LATE-NC and Alzheimer disease pathologic changes are associated with different trajectories of late-life cognitive decline.

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→ Class of Evidence

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Glossary

AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; FTLN = frontotemporal lobar degeneration; HS = hippocampal sclerosis; LATE = limbic-predominant age-related TDP-43 encephalopathy; MAP = Rush Memory and Aging Project; MARS = Minority Aging Research Study; NC = neuropathologic changes; NIA = National Institute on Aging; ROS = Religious Orders Study; TDP-43 = transactive response DNA-binding protein 43.

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It is well recognized that brains of older persons harbor multiple pathologies and that determinants of late-life cognitive decline extend beyond Alzheimer disease (AD) neuropathologic changes (ADNC).¹⁻³ There has been an increasing awareness that transactive response DNA-binding protein 43 (TDP-43) proteinopathy contributes to cognitive decline and Alzheimer dementia.⁴⁻⁶ Misfolded TDP-43 protein aggregates, originally recognized in amyotrophic lateral sclerosis and frontotemporal lobar degeneration (FTLD), have been shown to be present in nearly 50% of brains of persons >80 years of age and in higher stages are commonly associated with comorbid hippocampal sclerosis (HS).^{7,8} Most important, the clinical manifestation of TDP-43 pathologic lesions can recapitulate the clinical and neuroimaging picture of Alzheimer dementia, including episodic memory impairment⁹ and progressive hippocampal atrophy,¹⁰ thus presenting a challenge for clinical diagnosis. TDP-43 associated with HS most commonly occurs with comorbid ADNC⁴ and, to a lesser extent, with Lewy body pathology, argyrophilic grain disease,¹¹ and chronic traumatic encephalopathy.¹²

Progression of TDP-43 lesions in aging initially occurs in the amygdala, extending to limbic and neocortical brain regions, a pattern different from that seen in amyotrophic lateral sclerosis or FTLN.^{13,14} The amygdala is the most commonly involved region; however, the association with cognitive impairment and dementia is observed when TDP-43 pathology progresses from the amygdala to the hippocampus/entorhinal cortex.⁴ To increase awareness of this important disease in advanced age, a consensus group proposed the term limbic-predominant age-related TDP-43 encephalopathy (LATE), which is defined by the presence of TDP-43 pathology in limbic brain regions and beyond, with or without the presence of HS.¹⁵ Here, we continue to use the term LATE neuropathologic changes (LATE-NC).

Understanding disease progression and clinical heterogeneity is important for prognosis and for the development of biomarkers. We previously reported that LATE-NC advanced beyond the amygdala is related to cognitive decline.⁹ In the current study, we extend prior findings in a larger sample to

examine cognitive trajectories over the course of time among specific pathologic disease groups to determine whether the rate of cognitive decline differs between groups. Data came from 1,356 participants enrolled in 1 of 3 longitudinal clinical pathologic cohort studies of aging. Pathologic disease groups were categorized according to no ADNC or LATE-NC, those with pure LATE-NC, those with pure ADNC, and those with mixed ADNC with LATE-NC. We used mixed-effect models to examine the group associations with rate of decline in global cognition and 5 cognitive domains, and then we examined whether age modified the associations.

Methods

Standard protocol approvals, registrations, and patient consents

Each study was approved by the Rush University Medical Center institutional review board. Written informed consent was obtained from all study participants as was an Anatomical Gift Act for organ donation.

Study objective

The goal of this study was to examine the impact of 3 pathologic groups, pure LATE-NC, pure ADNC, and mixed ADNC with LATE-NC, on late-life cognitive decline, a Class I criteria for rating diagnostic accuracy studies.

Participants

Participants enrolled in 1 of 3 ongoing epidemiologic longitudinal clinical-pathologic studies of aging, the Rush Memory and Aging Project (MAP), the Religious Orders Study (ROS), and Minority Aging Research Study (MARS).^{16,17} All 3 studies share nearly identical study designs, operations, and protocols, with the only exception that brain donation is required in ROS/MAP but optional in MARS. Rush MAP began in 1997 and recruits older adults from across the Chicagoland metropolitan area. ROS started in 1994 and recruits older priests, nuns, and brothers from 45 sites across the United States. Eligibility in both ROS and MAP requires enrollment without known dementia, agreement to undergo annual clinical evaluation and interview, including detailed neuropsychological testing, and consent to organ donation at the time of death. MARS started in 2004 and enrolls older Blacks free of dementia. Participants undergo the same clinical and neuropsychological testing as in ROS and MAP, with brain donation being optional. Follow-up across all studies exceeds 85%, with autopsy rates exceeding 80% for ROS and MAP and 67% for MARS.

At the time of the analyses, 4,353 older persons were recruited, of whom 4,229 (97%) completed baseline cognitive assessments. Of 4,229 persons, 3,732 had longitudinal cognition with at least 2 follow-up visits for cognitive evaluations, 1,826 participants died, 1,590 were autopsied, and 1,556 had ADNC neuropathologic workup. To exclude potential sources of bias, we excluded those who had missing LATE-NC 2/3

Figure 1 Sample size

Flowchart shows composition of final sample size. ADNC = Alzheimer disease neuropathologic change; AGA = Anatomical Gift Act; DLB = dementia with Lewy body disease; FTLD = frontotemporal lobar degeneration; HS = hippocampal sclerosis; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change.

diagnosis ($n = 163$), those who had missing HS diagnosis ($n = 5$), and those with a pathologic diagnosis of FTLT ($n = 14$), including FTLT-TDP ($n = 4$) and other FTLT tauopathies ($n = 10$). We further excluded persons who did not fit the pathologic criteria for our groups ($n = 4$ for persons with only HS diagnosis, no ADNC/TDP-43, and $n = 14$ for persons with ADNC with HS, no TDP-43). Complete neuropathologic data to meet the pathologic criteria for the current study were available on 1,356 persons (MAP $n = 737$, ROS $n = 594$, MARS $n = 25$) (figure 1). Mean age at death was 89.4 years (SD 6.6); mean education was 16.1 years (SD 3.6); and 932 (68.7%) were women.

Assessment of longitudinal cognition

To exclude any potential sources of bias, all final clinical data summaries were determined by investigators blinded to neuropathology. A standard uniform annual cognitive assessment was administered to each participant at baseline and at each follow-up evaluation (mean follow-up 9.0 years, SD 5.3 years, range 1–24) with a harmonized battery of 18 neuropsychological tests. Assessment covers a broad range of cognitive abilities, including memory, attention, language, perception, and orientation. The Mini-Mental State Examination and Complex Ideation Material (2 tests) are used only for clinical descriptive purposes. Seven tests of episodic memory, 2 of semantic memory, 3 of working memory, 2 of perceptual speed, and 2 of visuospatial ability were administered as previously described.^{16,17} Performance on 16 tests was used to compute a measure of global cognition, with higher scores indicating better cognitive performance. For computation of the composite measure of global cognition, scores on individual tests were converted to z scores with the baseline mean and SD and averaged together. Composite measures of global cognition were calculated if more than half the z scores were nonmissing. Summary scores for each cognitive domain were derived by averaging the z scores of the neuropsychological tests specific to that particular cognitive domain, as previously described.^{18,19}

Assessment of neuropathology

The average postmortem interval was 9.5 hours (SD 8.65 hours), and brain autopsy follows standard procedure, as previously described.²⁰ After a gross examination, 1 hemisphere was fixed for at least 48 to 72 hours in 4% paraformaldehyde in 0.1 mol/L phosphate buffer. Paraformaldehyde-fixed cerebral hemispheres were cut into 1-cm coronal slabs, and a minimum standard set of 11 regions were blocked, including middle frontal gyrus, middle temporal, entorhinal, inferior parietal, calcarine, and anterior cingulate cortices, basal ganglia, thalamus, hippocampus, midbrain, and cerebellum. In addition, blocks were taken from both hemispheres for any macroscopic infarcts observed during gross examination. All blocks were dehydrated and embedded in paraffin wax, and sections (6/20 μm) were stained.

Alzheimer disease neuropathologic changes

Manual counts of neuritic and diffuse plaques and neurofibrillary tangles in an area of greatest density from each region

were used to determine Braak staging and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score. A pathologic diagnosis of AD was determined by intermediate or high likelihood with modified National Institute on Aging (NIA)–Reagan criteria. ADNC was evaluated with a modified Bielschowski stain from 5 brain regions: midfrontal, middle temporal, entorhinal, and parietal cortices and hippocampus, as previously described.²⁰ β -Amyloid deposition to determine Thal phase is detected with immunohistochemistry and performed on 7 brain regions, including 3 neocortical regions, hippocampus, basal ganglia, midbrain, and cerebellum. Use of the new NIA–Alzheimer's Association criteria²¹ incorporating Braak, CERAD, and Thal to determine pathologic diagnosis of AD is ongoing in ROS, MAP, and MARS, and the criteria show high concordance with our modified NIA–Reagan diagnosis (κ coefficient = 0.96). In addition, paired helical filament tau was identified by an antibody specific to phosphorylated tau, AT8 (1:2,000; Thermo Fisher Scientific, Waltham, MA) on 20- μm sections. Quantification of neuronal neurofibrillary tangle density per 1 mm was performed using systematic sampling on 8 brain regions, and an average composite density value across all brain regions was used. Composite measures were computed only if ≥ 4 regions were nonmissing.²²

TDP-43 pathology and HS

Phosphorylated TDP-43 pathology was assessed by immunohistochemistry using a monoclonal antibody to phosphorylated TDP-43 (pS409/410; 1:100). TDP-43 was performed on 6 brain regions; amygdala, hippocampus, dentate gyrus, entorhinal cortex, and midfrontal and middle temporal cortices. Semiquantitative measures of pathogenic TDP-43 cytoplasmic inclusions (both neuronal and glial) were determined from the number of inclusions in a 0.25- mm^2 area of greatest density, as previously described.⁹ Four distinct stages based on pathologic distribution of TDP-43 lesions were created; stage 0 (no presence of TDP-43), stage 1 (TDP-43 localized to the amygdala), stage 2 (extension of TDP-43 to the hippocampus or entorhinal cortex), and stage 3 (extension into the neocortex).^{7,9}

HS was evaluated unilaterally in the midhippocampus at the level of the lateral geniculate nucleus.⁷ On the basis of the presence of severe neuronal loss and gliosis in the CA1/subiculum subregion of the hippocampus, HS was treated as present or absent for analyses.

Other age-related pathologies

Chronic gross infarcts were identified visually on gross examination and confirmed by histology. Chronic microinfarcts, not visible to the naked eye, were identified under the microscope with hematoxylin & eosin stain in a minimum set of brain regions: 7 cortical regions, 2 subcortical regions, midbrain, and cerebellum.²⁰ Infarcts (both gross and microscopic) were categorized dichotomously as present or absent for analyses.

Meningeal and parenchymal vessels from 4 neocortical regions were evaluated on sections immunostained with 3

monoclonal antibodies against β -amyloid, 4G8 (1:9,000; Covance Labs, Madison, WI), 6F/3D (1:50; Dako North America, Inc, Carpinteria, CA), and 10D5 (1:600; Elan Pharmaceuticals, San Francisco, CA).²³ According to the burden of amyloid deposition in the vessels, cerebral amyloid angiopathy (CAA) was scored as 0 = no deposition, 1 = scant amyloid deposition, 2 = circumferential deposition in up to a total of 10 vessels, 3 = circumferential deposition in up to 75% of vessels, and 4 = circumferential deposition in >75% of vessels. A score for each region was created from the maximum of the meningeal and parenchymal scores. A continuous summary score was created by averaging scores across regions. For analyses, CAA was graded as none vs mild/moderate/severe.

For arteriolosclerosis, vessels in the basal ganglia were evaluated on hematoxylin & eosin–stained sections. Grading used a semiquantitative 4-level rating system (none, mild, moderate, and severe) based on the histologic changes of the small arterioles.²⁴ For analyses, arteriolosclerosis was graded as none vs mild/moderate/severe. The circle of Willis at the base of the brain was evaluated for large vessel cerebral atherosclerosis, including evaluation of the vertebral, basilar, posterior, middle, and anterior cerebral arteries and their proximal branches.²⁴ Visual inspection used a semiquantitative 4-level grading system, and atherosclerosis was graded as none vs mild/moderate/severe for analyses.

Lewy body pathology was assessed with antibodies to phosphorylated α -synuclein (1:100; Zymed Labs, South San Francisco, CA) in 7 regions, including substantia nigra, limbic, and neocortex, as described previously,²⁵ and treated as none vs the presence of any Lewy body pathology in analyses.

Statistical analyses

The definition of LATE-NC was dichotomized to include those with limbic or neocortical TDP-43 pathology (i.e., stage 2 or 3) with or without the presence of HS. The definition of ADNC was dichotomized to include those with intermediate or high likelihood of AD by NIA-Reagan criteria. Persons were categorized into 4 groups: (0) a reference group without ADNC or LATE-NC ($n = 378$), (1) LATE-NC with no ADNC ($n = 91$), (2) ADNC without LATE-NC ($n = 535$), and (3) ADNC with LATE-NC ($n = 352$) (figure 1). We used χ^2 and analysis of variance tests to compare differences between pathologic groups. We used linear mixed-effect models with random intercept and slope. The longitudinal outcomes of interest were annual scores for global cognition and 5 separate cognitive domains. The predictors of interest were the 3 pathologic groups; LATE-NC, ADNC alone, and mixed ADNC with LATE-NC, with the reference group being those without LATE-NC or ADNC (group 0). Models were adjusted for potential confounders: demographics (age, sex, and education), other common age-related pathologies (macroinfarcts and microinfarcts, CAA, arteriolosclerosis, and Lewy body pathology), and *APOE* $\epsilon 4$. The interaction term between time in years to death with each pathologic group

estimates the difference in cognitive slopes relative to the reference group. Estimates were compared with Bonferroni-adjusted post hoc tests to identify group differences in rate of decline. Due to the possibility of mesial temporal tangle burden influencing cognitive impairment,²⁴ sensitivity analyses were adjusted for global neurofibrillary tangle burden to examine the pathologic effect of LATE-NC across global cognition and episodic memory. Subsequent analyses further classified persons in group 3 (ADNC with LATE-NC) into (1) those with ADNC + TDP-43 (stage 2/3) with no HS and (2) those with ADNC + TDP-43 (stage 2/3) + HS (figure 1). Mixed-effect models, adjusted for demographics and age-related pathologies, were used to assess whether there were differences between those with ADNC + TDP-43 and those with ADNC + TDP-43 + HS.

To uncover potential differences by age, we created a binary variable for age at death >90 or <90 years, with age ≤ 89 years as the reference group. In our second set of models, we used mixed-effect models and included 3-way interaction terms for pathologic groups $\times$ binary age $\times$ time, adjusting for sex, education, other age-related pathologies, and *APOE* $\epsilon 4$ with longitudinal cognition as the outcome. We compared estimates of cognitive slopes across the same pathologic group in both age categories. Statistical significance for all analyses was determined at an α level of 0.05. Analyses were performed with SAS/STAT software, version 9.4 for Linux (SAS Institute Inc, Cary, NC).

Data availability

Raw data are available by request through the Rush Alzheimer's Disease Center Research Resource Sharing Hub (radc.rush.edu/).

Results

Among 1,356 participants, 91 (6.7%) participants met the criteria for pure LATE-NC, 535 (39.5%) for isolated ADNC, and 352 (26.0%) for mixed ADNC with LATE-NC. Demographic, clinical, and pathologic data for all participants and each group are presented in table 1. The reference group (those with no ADNC/LATE-NC) were younger, were less likely to be >90 years of age, and had lower *APOE* $\epsilon 4$ positivity. Both the LATE-NC and mixed ADNC with LATE-NC groups were ≈ 2 years older than those with isolated ADNC and more likely to be ≥ 90 years of age. Comorbid pathology was common across all groups. Those in the reference group or pure LATE-NC group were less likely to have moderate to severe CAA and Lewy body pathology. Other cerebrovascular pathology was present in $\approx 30\%$ of persons across all pathologic groups.

Rate of cognitive decline among pathologic groups

We used mixed-effect models to determine the rate of cognitive decline across pathologic groups adjusted for demographics, other age-related pathologies, and *APOE* $\epsilon 4$ and examined whether the rate of decline differed between groups

Table 1 Demographics and characteristics of participants with LATE-NC and/or ADNC diagnosis

	All (n = 1,356)	No AD or LATE-NC (n = 378)	Pure LATE-NC (n = 91)	Pure ADNC (n = 535)	Mixed ADNC with LATE (n = 352)	p Value
Demographics						
Age at death, mean (SD), y	89.4 (6.64)	86.29 (7.06)	91.6 (5.79)	89.7 (6.24)	91.9 (5.56)	<0.001
Age ≥90 y, % (n)	56.6 (767)	40.2 (152)	65.9 (60)	57.4 (307)	70.5 (248)	<0.001
Female, % (n)	68.7 (932)	60.3 (228)	72.5 (66)	70.3 (376)	74.4 (262)	<0.001
Education, mean (SD), y	16.1 (3.61)	16.3 (3.60)	16.4 (3.41)	16.2 (3.72)	15.73 (3.46)	0.12
APOE ε4, % (n)	25.2 (337)	10.6 (40) ^a	18.9 (17) ^a	27.3 (144) ^b	39.2 (347) ^a	<0.001
Clinical, mean (SD)						
MMSE score, lv	21.42 (6.62)	25.5 (5.80)	22.5 (7.35)	20.4 (9.02)	14.8 (10.16)	<0.001
Global cognition score, bl	-0.11 (0.69)	0.06 (0.58)	0.03 (0.68)	-0.08 (0.66)	-0.36 (0.78)	<0.001
Global cognition score, lv	-0.96 (1.23)	-0.25 (0.87)	-0.71 (1.09)	-1.03 (1.18)	-1.75 (1.18)	<0.001
Episodic memory score, bl	-0.15 (0.86)	0.11 (0.65)	0.003 (0.85)	-0.12 (0.81)	-0.50 (1.02)	<0.001
Episodic memory score, lv	-0.95 (1.41)	-0.07 (1.02)	-0.72 (1.33)	-0.99 (1.36)	-1.91 (1.28)	<0.001
Semantic memory score, bl	-0.14 (0.91)	0.05 (0.75)	-0.01 (1.02)	-0.12 (0.82)	-0.42 (1.08)	<0.001
Semantic memory score, lv	-1.29 (1.70)	-0.44 (1.10)	-0.94 (1.39)	-1.33 (1.61)	-2.25 (1.91)	<0.001
Working memory score, bl	0.02 (0.79)	0.06 (0.78)	0.11 (0.82)	0.03 (0.78)	-0.07 (0.78)	0.07
Working memory score, lv	-0.70 (1.11)	-0.26 (0.90)	-0.51 (1.00)	-0.77 (1.13)	-1.12 (1.14)	<0.001
Perceptual speed score, bl	-0.15 (0.91)	-0.06 (0.92)	0.03 (0.86)	-0.11 (0.90)	-0.35 (0.91)	<0.001
Perceptual speed score, lv	-1.22 (1.20)	-0.68 (1.10)	-0.95 (1.10)	-1.26 (1.17)	-1.79 (1.10)	<0.001
Visuospatial ability score, bl	-0.03 (0.83)	0.05 (0.85)	0.13 (0.84)	0.001 (0.82)	-0.19 (0.82)	<0.001
Visuospatial ability score, lv	-0.57 (1.08)	-0.25 (0.97)	-0.30 (0.92)	-0.59 (1.09)	-0.96 (1.10)	<0.001
Neuropathologic, % (n)						
Any macroscopic infarcts	35.8 (486)	32.8 (124)	38.5 (35)	36.5 (195)	37.5 (132)	0.51
Any microscopic infarcts	28.9 (392)	26.2 (99)	30.8 (28)	27.7 (148)	33.2 (117)	0.16
CAA (moderate-severe)	35.6 (482) ^b	17.3 (64) ^b	23.1 (21)	40.9 (218) ^a	50.1 (179) ^a	<0.001
Arteriolosclerosis (moderate-severe)	32.5 (439) ^a	30.0 (113) ^a	34.4 (31)	32.1 (171) ^a	35.2 (124)	0.59
Atherosclerosis (moderate-severe)	32.5 (440) ^a	33.7 (127) ^a	33.0 (30)	30.7 (164) ^a	33.8 (119)	0.38
Any Lewy body pathology	26.7 (362)	21.8 (82)	23.1 (21)	27.1 (145)	32.5 (114)	0.01

Abbreviations: AD = Alzheimer disease; ADNC = AD neuropathologic changes; bl = baseline; CAA = cerebral amyloid angiopathy; LATE = limbic-predominant age-related TDP-43 encephalopathy; lv = last evaluation; MMSE = Mini-Mental State Examination; NC = neuropathologic changes.

^a Data missing for ≤5 participants.

^b Data missing for 6 to 12 participants.

(tables 2 and 3). Compared to those with no ADNC or LATE-NC pathology, persons with pure LATE-NC pathology showed an additional decline of 0.025 unit per year in global cognition and 0.04 unit per year in episodic memory, while those with pure ADNC pathology or mixed ADNC with LATE-NC pathology showed faster decline in global cognition and all cognitive domains. Compared to those with pure ADNC pathology, those with pure LATE-NC pathology showed half the rate of decline in

both global cognition and episodic memory, while those with mixed ADNC with LATE-NC showed a 2-fold faster rate of decline in global cognition and all domains (figure 2).

Due to the possibility of mesial temporal tangle burden influencing cognitive impairment²⁶ in persons with pure LATE-NC, we conducted sensitivity analyses adjusting for demographics, vascular pathologies, Lewy bodies, and

Table 2 Effect of pathology on the rate of decline in global cognition and 5 cognitive domains

Cognitive domain	Pathologic group	Slope estimate (95% CI)	p Value
Global cognition	No pathology (referent)	−0.001 (−0.024 to 0.008)	0.931
	LATE-NC	−0.025 (−0.036 to −0.014)	0.025
	ADNC	−0.053 (−0.067 to −0.039)	<0.001
	ADNC with LATE-NC	−0.104 (−0.308 to 0.010)	<0.001
Episodic memory	No pathology (referent)	0.016 (−0.002 to 0.034)	0.066
	LATE-NC	−0.040 (−0.065 to −0.015)	0.002
	ADNC	−0.066 (−0.082 to −0.050)	<0.001
	ADNC with LATE-NC	−0.132 (−0.152 to −0.112)	<0.001
Semantic memory	No pathology (referent)	−0.004 (−0.026 to 0.018)	0.720
	LATE-NC	−0.018 (−0.049 to 0.013)	0.258
	ADNC	−0.058 (−0.078 to −0.038)	<0.001
	ADNC with LATE-NC	−0.125 (−0.148 to −0.102)	<0.001
Working memory	No pathology (referent)	−0.016 (−0.030 to −0.002)	0.029
	LATE-NC	−0.015 (0.035 to 0.005)	0.159
	ADNC	−0.030 (−0.043 to −0.017)	<0.001
	ADNC with LATE-NC	−0.055 (−0.070 to −0.040)	<0.001
Perceptual speed	No pathology (referent)	−0.031 (−0.048 to −0.014)	<0.001
	LATE-NC	−0.015 (−0.039 to 0.009)	0.239
	ADNC	−0.045 (−0.061 to −0.029)	<0.001
	ADNC with LATE-NC	−0.077 (−0.095 to −0.059)	<0.001
Visuospatial ability	No pathology (referent)	−0.019 (−0.033 to −0.005)	0.010
	LATE-NC	−0.004 (−0.024 to 0.016)	0.672
	ADNC	−0.023 (−0.036 to −0.010)	<0.001
	ADNC with LATE-NC	−0.039 (−0.054 to −0.024)	<0.001

Abbreviations: ADNC = Alzheimer disease neuropathologic changes; CI = confidence interval; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes.

Linear regression models with interaction of each pathologic group × time, adjusted for age, sex, education, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, any Lewy body pathology, and *APOE* ε4.

neurofibrillary tangle burden in additional models. After adjustment for global tangle burden, persons with pure LATE-NC pathology showed additional decline in global cognition (estimate −0.024, 95% confidence interval [CI] −0.046 to −0.002) and episodic memory (estimate −0.037, 95% CI −0.057 to −0.017) compared to reference group.

Because LATE-NC is defined by having TDP-43 pathology (stage 2/3) with or without HS, we divided the mixed ADNC with LATE group into those with (1) AD + TDP-43, no HS (*n* = 264) and (2) AD + TDP-43 + HS (*n* = 88) to assess differences in the rate of cognitive decline. After adjustment for demographics and age-related pathologies, both groups showed significant decline in global cognition and all domains

(data not shown). Compared to those with AD + TDP-43 and no HS pathology, those with AD + TDP-43 + HS showed a faster decline in global cognition (estimate −0.029, 95% CI −0.049 to −0.009), specifically episodic memory on average by 0.03 units per year (95% CI: −0.050 to −0.010) and semantic memory on average by 0.06 units per year (95% CI −0.100 to −0.021). No significant differences were observed between these 2 groups across working memory, perceptual speed, or visuospatial ability (data not shown).

Age, pathology, and cognitive decline

Prior studies show that with increasing age, ADNC burden starts to plateau, while non-ADNC occur more frequently in those >90 years of age.²⁷ We next examined whether the effect

Table 3 Comparisons of slope estimates between each pathologic group across global cognition and 5 cognitive domains

	LATE-NC	ADNC	ADNC with LATE-NC
Global cognition			
Reference (no AD, TDP-43, or HS)	0.025	<0.001	<0.001
LATE-NC		0.010	<0.001
ADNC			<0.001
Episodic memory			
Reference (no AD, TDP-43, or HS)	0.002	<0.001	<0.001
LATE-NC		0.038	<0.001
ADNC			<0.001
Semantic memory			
Reference (no AD, TDP-43, or HS)	0.258	<0.001	<0.001
LATE-NC		0.006	<0.001
ADNC			<0.001
Working memory			
Reference (no AD, TDP-43, or HS)	0.159	<0.001	<0.001
LATE-NC		0.118	<0.001
ADNC			<0.001
Perceptual speed			
Reference (no AD, TDP-43, or HS)	0.239	<0.001	<0.001
LATE-NC		0.010	<0.001
ADNC			<0.001
Visuospatial ability			
Reference (no AD, TDP-43, or HS)	0.672	<0.001	<0.001
LATE-NC		0.055	<0.001
ADNC			0.010

Abbreviations: AD = Alzheimer disease; ADNC = AD neuropathologic changes; HS = hippocampal sclerosis; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes; TDP-43 = transactive response DNA-binding protein 43. Slope estimates were compared with Bonferroni-adjusted post hoc tests.

of pathology on global cognitive decline differed between the old (≤ 89 years of age) and the oldest old (≥ 90 years) (table 4), adjusting for demographics, age-related pathologies, and *APOE* $\epsilon 4$. Compared to those persons < 90 years of age with no pathology, those with pure LATE-NC in the same age group showed 0.04-unit additional decline per year in global cognition, those with pure AD had a 0.06-unit per year additional decline, and those with mixed AD with LATE-NC pathology showed a 0.13-unit decline. In contrast, among persons ≥ 90 years of age, the effect of having pure AD or mixed AD with LATE-NC was attenuated. Specifically, compared with persons < 90 years of age, the strength of association of AD with annual global cognitive decline was $\approx 20\%$ weaker in persons ≥ 90 years of age (estimate 0.02, 95% CI 0.003–0.037). Separately, the strength of association of

mixed AD and LATE-NC with global cognitive decline was $\approx 40\%$ weaker in the oldest old (estimate 0.04, 95% CI 0.064–0.016) and displayed on average a 0.09-unit decline per year. Similar attenuation was also observed for pure LATE-NC, but it did not reach statistical significance between those < 90 and > 90 years of age ($p = 0.130$).

Discussion

In this study, we leverage data from $> 1,300$ community-based older persons to extend our current knowledge of specific single and mixed pathology groups and their relationship with late-life cognitive decline. Persons with pure LATE-NC demonstrated additional decline in global cognition and episodic

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

Derived from mixed-effect models adjusted for age, sex, education, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, any Lewy body pathology, and *APOE* ϵ 4. AD = Alzheimer disease; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change.

memory compared to the reference group; however, the rate of decline was slower compared to those with pure ADNC or mixed ADNC with LATE. Those with mixed ADNC and LATE-NC showed the greatest decline across global cognition and all domains. In persons with pure LATE-NC, we observed no age difference in the rate of decline. However, persons ≤ 89 years of age with either pure ADNC or mixed ADNC with LATE demonstrated a stronger magnitude of effect on global cognition compared to those ≥ 90 years of age.

The term LATE-NC was coined by a working consensus group in an effort to raise awareness of TDP-43 proteinopathy in advanced age, specifically in older persons >80 years of age.¹⁵ We and others have shown that LATE-NC, independently of ADNC, is associated with clinical and imaging features that mimic Alzheimer dementia, specifically episodic memory decline and hippocampal atrophy.^{4,10,28,29} The current study extends our previous findings with a larger sample size to demonstrate that persons with pure LATE-NC show decline in global cognition and episodic memory but follows a slower trajectory compared to those with pure ADNC. These

findings are consistent with prior studies reporting that those with HS without ADNC show slower cognitive decline compared to those with AD alone.³⁰ We find that LATE-NC most commonly coexists with ADNC (25%) compared to pure LATE (6%). Prior studies from our group reported that comorbid ADNC and TDP-43 pathology can be found in $>50\%$ of brains from older persons.⁴ In the current study, we report a lower frequency, a consequence of our LATE definition. We and others have shown that the presence of amygdala-only inclusions is not related to appreciable cognitive impairment during life,¹⁵ and therefore, we did not include persons with amygdala-only TDP-43 inclusions in current study. However, further work is needed to determine clinical/behavioral manifestations of amygdala-only TDP-43 pathology. There is a gap in knowledge regarding whether FTLTDP and LATE-NC represent 2 separate pathologic diseases or lie on the same continuum. In this study, to exclude a potential source of bias, we excluded cases with a pathologic diagnosis of FTLTDP and found that those with pure LATE-NC showed decline in episodic memory. However, future work to examine whether persons with LATE-NC without ADNC exhibit aspects of a frontotemporal dementia clinical syndrome, including relationships with social and behavioral cognition, would

Table 4 Effect of pathology on global cognitive decline >90 and <90 years of age

	Age at death			
	≤89 y		≥90 y	
	Slope estimate (95% CI)	p Value	Slope estimate (95% CI)	p Value
No pathology (referent)	−0.003 (−0.020 to 0.015)	0.740	−0.002 (−0.022 to 0.018)	0.857
LATE-NC	−0.042 (−0.079 to −0.004)	0.030	−0.007 (−0.0267 to 0.013)	0.615
ADNC	−0.061 (−0.081 to −0.041)	<0.001	−0.040 (−0.060 to −0.020)	<0.001
ADNC with LATE-NC	−0.127 (−0.147 to 0.107)	<0.001	−0.084 (−0.103 to −0.064)	<0.001

Abbreviations: ADNC = Alzheimer disease neuropathologic changes; CI = confidence interval; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes. Linear regression models including 3-way interactions between each pathologic group × binary age × time. Models adjusted for sex, education, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, any Lewy body pathology, and *APOE* ε4.

be of importance and may offer new insights that could bridge the gap between FTLT-TDP and LATE-NC.

Previous reports show that comorbid TDP-43 pathology exacerbates the clinical phenotype of ADNC, with mixed ADNC with TDP-43 being associated with more severe cognitive impairment^{7,28,31} and increased odds for Alzheimer dementia.⁴ The current study extends these findings on mixed pathologies, showing that mixed ADNC with LATE-NC exerts an additive effect on the trajectory of decline in global cognition and all cognitive domains. Furthermore, we present data to suggest that in the absence of HS pathology, the effect of ADNC with TDP-43 is deleterious for decline across all cognitive domains, while the effect of comorbid HS pathology is specifically worse for decline in episodic and semantic memory. HS is intricately intertwined with TDP-43 pathology, and having both pathologies has previously been reported to be related to greater cognitive impairment.⁷ Multiple studies aim to understand independent effects of neurodegenerative pathologies in aging. While these studies have been valuable, it is possible that comorbid neurodegenerative pathologies may interact,³² and further work is needed to understand whether the presence of 1 neurodegenerative pathology contributes to the aggregation or accumulation of another.

While an ADNC diagnosis is common in older age groups, it rarely occurs in isolation and commonly occurs in the form of mixed pathologies, especially in persons with cognitive impairment.³³ In addition, LATE-NC can be identified in 1 of 5 postmortem brains from those >80 years of age.¹⁵ There are limited data on the clinical impact of mixed pathologies in the oldest old, and even more so on the role of single vs mixed pathologies on cognitive decline. In previous studies, we have shown that TDP and ADNC are independently related to cognitive decline.^{9,34} In the present study, we specifically investigate isolated forms of LATE-NC and ADNC vs mixed ADNC/LATE-NC and find that the effect for all 3 pathologic groups in the oldest old group (≥90 years of age) with global cognitive decline is attenuated, especially in those with mixed ADNC/LATE-NC. This finding suggests that clinical

manifestation of neuropathologic features may differ across younger vs older age groups and that other additional factors that promote resilience may be involved in the oldest old. However, it is also plausible that those with more severe cognitive decline may have an earlier mortality, leading to a potential survival bias. Further phenotyping of these groups will be important in extending our knowledge of resilience or longevity in the oldest old. A prior study showed that the deleterious impact of pathology does not vary across age.³⁵ A possible explanation for the discrepancy between the latter study and our study could be the analytic approach. In the prior study, individual pathologies, including amyloid, tangles, TDP-43, and HS, were examined with cognitive decline using age as a continuous variable in mixed effect change point models. In the the current study, we categorized persons in defined pathology groups, and had cutoff points at >90 and <90 years. This discrepancy in findings emphasizes the importance of and ongoing need to study pathologies as both single and mixed pathology groups.

Overall, these data advance our understanding of relationships of 3 pathologic groups, pure LATE-NC, pure ADNC, and mixed ADNC with LATE, with cognitive decline, adding to the existing literature on the neuropathologic footprint contributing to late-life cognitive decline in older persons. We show that persons with pure LATE-NC pathology follow a different cognitive trajectory compared to those with pure ADNC and that age may modify the risk for cognitive decline, especially in those who harbor mixed pathologies. Furthermore, we begin to understand clinical manifestations of LATE-NC in isolated forms of the disease and in mixed forms of the disease with which patients may present in a real-world setting. These data provide important insights into the pathologic basis contributing to disease processes and clinical heterogeneity. A major strength of this study is that persons underwent detailed longitudinal cognitive evaluations and systematic neuropathologic assessments for both ADNC and LATE-NC in postmortem brains from 3 well-established cohort studies. Individuals with LATE-NC but lacking substantial ADNC are generally underrecognized,

especially in a dementia clinic setting. Thus, our sample size of LATE-NC without ADNC from a community-based cohort provides an additional strength to this study. Limitations of the present study are that the study sample was largely non-Latinx white and relatively highly educated; thus, these data may not generalize to diverse populations. Unilateral pathologies, specifically the presence of unilateral HS,³⁶ were not accounted for because autopsy pathology data were collected from 1 hemisphere. Although we did assess multiple cognitive domains in this study, we did not have information to assess behavioral/social cognitive domains, which would provide important information to the field. Future work examining genetic risk factors and structural changes in the brain across different pathology groups will be imperative in understanding the full picture of disease heterogeneity and will be necessary in aiding the development of biomarkers for Alzheimer dementia.

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Disclosure

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