TDP-43 pathology and memory impairment in elders without pathologic diagnoses of AD or FTLN

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ABSTRACT

Objective: To investigate the association of TAR DNA-binding protein 43 (TDP-43) pathology with memory, other cognitive domains, and dementia in community-dwelling elders without pathologic diagnoses of Alzheimer disease (AD) or frontotemporal lobar degeneration (FTLD).

Methods: Of 1,058 autopsied participants, 343 (32.4%) did not have pathologic diagnoses of AD or FTLD. Diagnosis of dementia was based on clinical evaluation and cognitive performance tests, which were used to create summary measures of global cognition and of 5 cognitive domains. TDP-43 pathology evaluated in 6 brain regions by immunohistochemistry was converted into a summary measure of TDP-43 severity.

Results: Of 343 participants, 135 (39.4%) had TDP-43 pathology with a mean TDP-43 severity score of 0.394 (SD 0.490). TDP-43 inclusions were confined to the amygdala (stage 1) in 43.7% of participants, 40% showed additional involvement of the hippocampus or entorhinal cortex (stages 2), while fewer (16.3%) showed additional TDP-43 pathology in the temporal and frontal cortices (stage 3). Severity of TDP-43 pathology was independently related to lower function in global cognition and episodic and semantic memory while increased odds of dementia was only a trend. When participants with hippocampal sclerosis (HS) were excluded from the models, TDP-43 pathology remained associated with lower episodic memory but relationships with global cognition, semantic memory, and dementia were attenuated.

Conclusions: TDP-43 pathology in elders, without pathologic diagnoses of AD or FTLD, is common and independently associated with lower function in episodic memory, while its associations with global cognitive impairment and dementia are difficult to separate from HS. *Neurology*® 2017;88:653-660

GLOSSARY

AD = Alzheimer disease; **CAA** = cerebral amyloid angiopathy; **FTLD** = frontotemporal lobar degeneration; **HS** = hippocampal sclerosis; **LB** = Lewy bodies; **MARS** = Minority Aging Research Project; **MAP** = Rush Memory and Aging Project; **MMSE** = Mini-Mental State Examination; **ROS** = Religious Orders Study; **TDP-43** = TAR DNA-binding protein 43.

The initial report that a 43-kD protein (TAR DNA-binding protein 43 [TDP-43]) binds to the transactivating responsive DNA sequence of HIV type I¹ was followed by the original observation of cytoplasmic TDP-43 protein aggregates in neurons and glia in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis.^{2,3} Subsequent to this, TDP-43 deposition was reported in other neurodegenerative diseases such as Alzheimer disease (AD),⁴⁻⁶ in which the reported frequency of TDP-43 inclusions was as high as 57%⁷ and 72%.⁸ TDP-43 pathology was also reported in persons with age-related hippocampal sclerosis (HS),^{4,9,10} Lewy body-related diseases,¹¹ and even in chronic traumatic encephalopathy.¹² Widespread TDP-43 protein deposition in brain in these diseases resulted in inclusion of these diseases in a novel group termed TDP-43 proteinopathies.¹³

TDP-43 pathology in cases with a pathologic diagnosis of AD was associated with lower cognitive function,⁷ and in our previous study of 130 older community-dwelling Religious Orders Study participants with a full spectrum of AD pathology, TDP-43 was independently related to the trajectory of cognitive decline, most notably episodic memory decline, and dementia.¹⁴ The

Supplemental data
at Neurology.org

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focus of the current study is on the role of TDP-43 in aging, memory loss, and dementia in an important subgroup of elders without a pathologic diagnosis of AD or FTLN. In this study, the hypothesis that TDP-43 pathology is related to impaired episodic memory and dementia independent of subthreshold levels of AD and other age-related pathologies was tested in over 340 older persons without pathologic diagnoses of AD or FTLN from 3 longitudinal studies of aging and dementia: the Rush Memory and Aging Project (MAP), the Religious Orders Study (ROS), and the Minority Aging Research Project (MARS).

METHODS Participants. Exclusion criteria were a pathologic diagnosis of AD based on the National Institute on Aging–Reagan criteria,¹⁵ moderate or frequent Consortium to Establish a Registry for Alzheimer’s Disease neuritic plaque scores, and III/IV or V/VI Braak stages and those with a pathologic diagnosis of FTLN. These criteria resulted in inclusion of 343 of 1,058 autopsied participants from 3 longitudinal clinical–pathologic cohort studies of aging and dementia—Rush MAP (n = 186), ROS (n = 152), and MARS (n = 5)—each approved by the institutional review board of Rush University Medical Center. All data collections (antemortem and postmortem) were similar in these studies, allowing combined analyses of the cohorts. A signed informed consent was obtained from each participant for annual examination and for brain donation at the time of death.

Clinical evaluation. Each participant had uniform clinical evaluation at baseline and annually thereafter, which included a standardized battery of 19 cognitive performance tests as described previously.^{16,17} The Mini-Mental State Examination (MMSE) and Complex Ideational Material were used for descriptive purposes or diagnostic classification, respectively. The remaining 17 tests assessed function of 5 cognitive domains including episodic, semantic, and working memory, perceptual speed, and visuospatial ability. The raw scores of the individual tests were standardized by conversion to z scores using the baseline mean and SD of all participants and averaged to yield summary measures of each area of cognitive function.¹⁶ The z scores of all 17 tests were averaged to compute the global cognitive function score (table 1). Since ceiling and floor artifacts as well as random variability were minimized by using composite measures, all values were included in the analyses.

Criteria of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association¹⁸ were used for diagnoses of dementia and probable AD. A history of cognitive decline, evidence of impairment in episodic memory, and at least one other cognitive domain was required for diagnosis of AD. Possible AD included participants who fulfilled criteria for AD but also were diagnosed with another brain condition contributing to cognitive impairment.¹⁹ Functional impairment was not a requirement for diagnosis of dementia and dementia status proximate to death was assigned by a board-certified neurologist after review of all clinical information. Stroke and Parkinson disease were diagnosed based on history and clinical examination as described previously.¹⁷

Pathologic analyses. The average postmortem interval was 9.3 hours (SD 9.8). Macroscopic brain examination included

documentation of the age, volume, and anatomic location of all macroscopic infarcts, while microscopic examination performed of hematoxylin & eosin–stained sections from a minimum of 9 blocks including 5 cortical areas (midfrontal, midtemporal, parietal, cingulate, and entorhinal), mid-hippocampus (CA1 and dentate), basal ganglia, thalamus, and midbrain documented the location and age of all microscopic infarcts. Only chronic macroinfarcts and microinfarcts were included in the analyses as dichotomous variables. A semiquantitative grading system from 0 (none) to 6 (severe) was used to assess atherosclerosis in arteries at the base of the brain and arteriolosclerosis in basal ganglia arterioles as described previously.²⁰ A unilateral coronal section of the midhippocampus at the level of the lateral geniculate body was used for diagnosis of HS, which was graded as absent or present as described previously.⁹

Modified Bielschowsky silver stain was used to quantitate neuritic and diffuse plaques and neurofibrillary tangles in 5 brain regions, having the highest density of these structures, as described previously.²¹ The raw count for each of the 3 pathologies was divided by the group SD of each marker and values were averaged across the regions to develop a summary score for each participant. The summary scores of the 3 AD markers were averaged to yield the global measure of AD pathology for each participant.

Immunohistochemical analyses. Sections of 6 brain regions (amygdala with entorhinal cortex, CA1, and dentate of the hippocampus, midfrontal, and midtemporal cortices) were used to detect TDP-43 protein using a phosphorylated monoclonal TARSP-1D3 (pS409/410; 1:100, Ascension, Munich, Germany) anti-TDP-43 antibody.²² A semiquantitative estimate of TDP-43 cytoplasmic inclusions in neurons and glia was obtained using a 6-point scale as described previously¹⁴ (table e-1 and figure e-1 at Neurology.org). A summary level of severity was used for analyses based on the mean of the semiquantitative scores from each of the 6 regions. To increase the validity of study findings, and because TDP-43 pathology appears to start and then spread from the amygdala,^{9,23,24} only participants having TDP-43 pathology data available from the amygdala and any of the 3 regions listed above were included in the analyses. In addition, for descriptive purposes only, TDP-43 distribution was grouped into 3 stages (stage 1, localized to amygdala; stage 2, extension to hippocampus or entorhinal cortex; stage 3, extension to the neocortex).⁹

Lewy bodies (LB) were assessed in 6 regions as described previously,¹⁴ and recorded and analyzed as a dichotomous variable. Cerebral amyloid angiopathy (CAA) was evaluated in meningeal and intracortical vessels in 4 cortical sections (midfrontal, midtemporal, inferior parietal, and occipital) immunostained for β -amyloid as described previously.²⁵

Statistical analyses. Demographics, clinical characteristics, and age-related pathologies including macroinfarcts and microinfarcts, AD, LB, HS, and vascular pathologies such as arteriolosclerosis, atherosclerosis, and CAA in participants without and with TDP-43 pathology were compared using χ^2 or *t* statistics.

Linear regression analyses were used to determine the association of TDP-43 pathology with global cognitive function and separately the outcome measures of episodic, semantic, and working memory, perceptual speed, and visuospatial skills, while multiple logistic regression analyses evaluated the association of TDP-43 pathology with dementia as a binary outcome. In both analyses, models controlled for the age-related pathologies listed above, then in another set of analyses the models controlled additionally for HS, and finally, associations were tested in models from which participants with HS were excluded. To test whether HS modified the association of TDP-43 pathology with cognition or dementia, an

Table 1 Clinicopathologic characteristics of 343 participants by TAR DNA-binding protein 43 (TDP-43) pathology

Characteristic	TDP-43 pathology		p Value
	Not present (n = 208)	Present (n = 135)	
Age at death, y, mean (SD)	85.7 (7.2)	89.1 (6.7)	<0.001
Female, n (%)	122 (58.7)	94 (69.6)	0.040
Education, y, mean (SD)	16.2 (3.8)	15.9 (3.1)	0.381
Clinical characteristics			
No cognitive impairment	112 (54.6)	60 (45.8)	0.023
Mild cognitive impairment	63 (30.7)	36 (27.5)	
Dementia	30 (14.6)	35 (26.7)	
Cognitive function tests proximate to death, mean (SD)			
MMSE score	25.6 (5.7)	23.8 (7.3)	0.017
Global cognition	−0.24 (0.8)	−0.48 (1.1)	0.028
Episodic memory	−0.03 (1.0)	−0.41 (1.2)	0.003
Semantic memory	−0.37 (1.1)	−0.63 (1.2)	0.042
Working memory	−0.31 (0.9)	−0.40 (1.0)	0.441
Perceptual speed	−0.69 (1.1)	−0.86 (1.1)	0.185
Visuospatial ability	−0.24 (1.0)	−0.19 (1.1)	0.655
Pathologic characteristics, n (%)			
Macroinfarcts	68 (33.1)	44 (34.1)	0.860
Microinfarcts	54 (26.3)	35 (27.1)	0.874
Arteriolosclerosis	139 (67.1)	109 (81.3)	0.004
Atherosclerosis	158 (77.1)	113 (83.7)	0.137
Cerebral amyloid angiopathy	119 (58.0)	83 (61.9)	0.475
Lewy bodies	43 (20.8)	31 (23.0)	0.631
Hippocampal sclerosis	4 (1.9)	13 (9.7)	<0.001
AD pathology summary measure, mean (SD)	0.20 (0.2)	0.17 (0.2)	0.248
Tangles, mean (SD)	2.32 (2.4)	2.72 (2.7)	0.138
Amyloid, mean (SD)	0.96 (1.9)	0.99 (1.7)	0.855
TDP-43 pathology, n (%)			
Stage 0	208 (60.6)		
Stage 1		59 (43.7)	
Stage 2		54 (40.0)	
Stage 3		22 (16.3)	

Abbreviations: AD = Alzheimer disease; MMSE = Mini-Mental State Examination. Values are χ^2 or t test as appropriate.

interaction term for TDP-43 pathology by HS was added to the analyses. All models controlled for age, sex, and education.

SAS software (version 9.3) of the SAS system for Linux was used for all analyses. Models were validated with graphic and analytic techniques to check for possible nonlinearity and interactions. A p value of less than 0.05 was considered statistically significant.

RESULTS Of the 343 participants without pathologic diagnoses of AD or FTL, TDP-43 pathology was present in 135 participants (39.4%), of whom almost three-quarters were without dementia; specifically, 45.8% had no cognitive impairment, 27.5% had mild

cognitive impairment, and 26.7% had dementia (table 1). Female participants were more likely to have TDP-43 pathology than male participants, while there was no difference in education between participants without and with TDP-43 pathology. Participants with TDP-43 pathology were older at the time of death and the frequency and mean severity score of TDP-43 pathology was greater in those 90 years of age or greater as compared to those aged <90 years (table 2).

Both the TDP-43 severity score and the TDP-43 stage were strongly related (figure 1). Most TDP-43

Table 2 Clinicopathologic characteristics of 343 participants by age

	<90 y (n = 214)	≥90 y (n = 129)	p Value
Clinical characteristics			
Female, n (%)	149 (60.8)	92 (66.7)	0.255
Education, y, mean (SD)	16.1 (3.8)	16.0 (3.4)	0.669
MMSE score, mean (SD)	25.5 (6.1)	23.8 (6.9)	0.013
Global cognition, mean (SD)	−0.25 (0.9)	−0.51 (1.0)	0.009
Pathologic characteristics, n (%)			
Macroinfarcts	69 (28.2)	55 (39.9)	0.019
Microinfarcts	58 (23.7)	44 (1.9)	0.083
Arteriolosclerosis	77 (31.7)	53 (38.7)	0.167
Atherosclerosis	85 (35.1)	56 (40.9)	0.266
Cerebral amyloid angiopathy	41 (17.0)	31 (22.6)	0.181
Lewy bodies	48 (19.6)	35 (25.4)	0.176
Hippocampal sclerosis	9 (3.7)	8 (5.8)	0.342
TDP-43 pathology	69 (31.9)	58 (48.7)	0.002
AD pathology summary measure, mean (SD)	0.17 (0.2)	0.21 (0.2)	0.116
TDP-43 pathology severity score, mean (SD)	0.26 (0.6)	0.49 (0.8)	0.004

Abbreviations: AD = Alzheimer disease; MMSE = Mini-Mental State Examination; TDP-43 = TAR DNA-binding protein 43. Values are χ^2 or t test as appropriate.

scores were in the range of 1–3 with fewer scores in the 4–5 range. The mean TDP-43 severity score for all regions was 0.394 (SD 0.49), being maximal in the amygdala (mean 0.91, SD 1.4) and least in the mid-frontal cortex (mean 0.05, SD 0.32). TDP-43 inclusions were confined to the amygdala (stage 1) in 43.7% of participants, 40% showed additional involvement of the hippocampus or entorhinal cortex (stages 2), while fewer (16.3%) showed additional TDP-43 protein localization in the temporal and frontal cortices (stage 3).

TDP-43 and other age-related pathologies. The frequency of HS was almost 5-fold greater in participants having

TDP-43 pathology; however, fewer than 10% of those with TDP-43 pathology had HS (table 1). On the other hand, almost all participants with HS had TDP-43 pathology, making it difficult to comment on HS in the absence of TDP-43 pathology, which was only present in 4 participants. In contrast to HS, the subthreshold burden of AD pathology was similar in those with and without TDP-43 pathology. Finally, participants with TDP-43 pathology were also more likely to have arteriolosclerosis. The frequency of other age-related pathologies including macroinfarcts, microinfarcts, atherosclerosis, CAA, and LBs did not statistically differ in persons without and with TDP-43 pathology.

TDP-43 pathology, cognition, and cognitive domains. Data on the cognitive profiles associated with TDP-43 pathology in elders without pathologic diagnoses of AD or FTLN are not known. There was no statistical difference ($p = 0.350$) in the average clinical interval between the last assessment for cognitive function and death in those without (9.5 months) and with (10.6 months) TDP-43 pathology. The mean scores for global cognition and episodic and semantic memory were lower in participants with as compared to those without TDP-43 pathology (table 1). Using linear regression models, TDP-43 pathology was independently associated with a lower level of global cognitive function and episodic and semantic memory ($p < 0.001$) and these associations remained when the model controlled for HS (table 3, model 1). HS was not associated with lower function in global cognition

Figure 1 Boxplots of the TAR DNA-binding protein 43 (TDP-43) pathology burden in the 6 regions in stages 0–3 show that severity is highest in stage 3

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

Model terms	Estimate (standard error), <i>p</i> 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
Lewy 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
Lewy 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.

or any of the cognitive domains. When HS cases were excluded from the model (table 3, model 2), TDP-43 pathology remained associated with episodic memory ($p = 0.018$) but associations with global cognition and semantic memory were attenuated and no longer significant.

To further evaluate the role of HS with TDP-43 pathology, in additional analyses, a term for an interaction between TDP-43 pathology and HS was added to each of the linear regression models with global cognitive function and 5 separate cognitive domains as outcomes. In these models, the interaction term for TDP-43 and HS pathologies did not reach statistical significance ($p = 0.091$), whereas TDP-43 pathology remained associated with episodic memory ($p = 0.016$).

TDP-43 pathology and dementia. Dementia was more frequent and the mean MMSE score was lower in elders having TDP-43 pathology (table 1), especially in those 90 years of age or older, who had an MMSE score of 23.8 (SD 6.9) as compared to the MMSE score of 25.5 (SD 6.1) in those <90 years (table 2). Of the participants with dementia, 67.7% had a clinical diagnosis of probable AD, 23.1% had a diagnosis of possible AD, while 9.2% were diagnosed with other dementias (table 4). Pathologic examination of those with dementia showed that half (50.8%) of the participants had TDP-43 pathology (table 4). In both groups with and without TDP-43 pathology, other pathologies were present to account for dementia, such as LB disease, numerous macroscopic and microscopic infarcts, and HS.

In logistic regression analyses, controlling for demographics and other age-related pathologies, TDP-43 pathology was associated with higher odds of dementia (odds ratio 1.81, 95% confidence interval 1.17–2.81, $p = 0.008$), which was reduced to a trend ($p = 0.065$) when the model controlled for HS pathology. Also, the association of TDP-43 pathology with dementia was attenuated when HS cases were excluded from the model. Additional analyses, which included a term for an interaction between TDP-43 pathology by HS, failed to show interaction between these 2 pathologies ($p = 0.128$).

DISCUSSION This study extends current knowledge on the relation of TDP-43 pathology and cognition to the subgroup of older persons without a pathologic diagnosis of AD or FTLT. Taking advantage of 3 community-based studies, this study demonstrates that TDP-43 pathology is common in persons without pathologic diagnoses of AD or FTLT and is independently associated with impairment in episodic memory. The association of TDP-43 pathology with global cognition and dementia varies depending on whether models include or exclude HS.

Table 4 Frequency of clinical and pathologic findings in 65 participants with dementia and absence of pathologic Alzheimer disease (AD) by TAR DNA-binding protein 43 (TDP-43) pathology

	Probable AD (n = 44)		Possible AD (n = 15)		Other dementias (n = 6)	
	TDP-43 pathology					
	Present (n = 25)	Absent (n = 19)	Present (n = 7)	Absent (n = 8)	Present (n = 1)	Absent (n = 5)
Clinical findings						
Stroke	7	7	7	8	0	2
Parkinson disease	1	0	0	0	0	0
Pathologic findings						
Hippocampal sclerosis	8	1	0	0	0	0
Lewy bodies	14	7	1	1	1	2
Arteriolosclerosis	8	11	5	5	4	0
Atherosclerosis	9	14	7	7	0	5
Cerebral amyloid angiopathy	8	8	1	3	0	1
Macroscopic infarcts	13	12	6	9	0	4
Microscopic infarcts	10	9	0	0	0	1
Multisystem atrophy	1	0	0	0	0	0
Primary age-related ^a tauopathy	1	0	0	0	0	0

^aFrequent tangles in the medial temporal lobe and absence of β -amyloid plaques.

Impaired episodic memory is a hallmark of AD, but molecular imaging is leading to increased recognition of misdiagnosis in spite of typical clinical features.²⁶ In the current study, though participants with a pathologic diagnosis of AD were excluded and models controlled for subthreshold levels of AD pathology, TDP-43 pathology was specifically related to episodic memory. One other study that investigated TDP-43 pathology and cognition in persons with minimal AD pathology found no association of TDP-43 with cognition but there was not a focus on neuropsychological testing.⁸ Meanwhile, the association of TDP-43 pathology with memory loss in cohorts that included those with a pathologic diagnosis of AD has been reported.^{7,14} The current findings suggest that TDP-43 pathology needs to be considered when evaluating memory loss in older persons without biomarker evidence of AD pathology.

The association between TDP-43 pathology and episodic memory in this study appears not to be driven by HS, since the association was maintained after exclusion of HS cases. However, the association between TDP-43 and dementia in those without a pathologic diagnosis of AD is less certain. Indeed, data from the full cohort (with and without a pathologic diagnosis of AD) suggest that the association of TDP-43 pathology with more global dysfunction is driven by HS.⁹ As noted previously,⁹ the frequency of HS is greater in participants having TDP-43 pathology. In the current study, this relationship extends to persons without a pathologic diagnosis of

AD. The frequency of HS in this cohort is low; however, most had TDP-43 pathology (76%). The number of HS cases is likely an underestimate given that HS may be missed when assessed in only one section of hippocampus unilaterally. Better understanding of the public health effect of TDP-43 pathology will require further study of both TDP-43 and HS pathologies and their separate and combined roles in memory loss and dementia.

The frequency of TDP-43 pathology in this study, in the absence of pathologic diagnoses of AD or FTLT, was 39.4%. In the study of elderly participants with minimal senile neuropathologic changes, TDP-43 pathology was observed in 40%,⁸ although TDP-43 localization was mainly in neurites with rare neuronal cytoplasmic inclusions, whereas cytoplasmic inclusions were specifically investigated in the current study. Other studies have reported TDP-43 pathology in 27%–36.4% of cognitively normal persons but a pathologic diagnosis of AD was not excluded and the brain regions examined differed across studies.^{27,28}

In the present study, TDP-43 pathology was more common in those over 90 years of age. An association with age has been noted previously, including a study of controls with minimal AD pathology,⁸ in older adults with and without mental illness having TDP-43 pathology,²⁹ and in a population-based study that included AD cases.²⁸ Given a growing oldest-old population where the pathologic diagnosis of AD is still common but arguably declining in frequency,³⁰ it is important to recognize the role of TDP-43 pathology in memory loss in aging.

In pathologic AD, the amygdala and entorhinal cortex were most frequently sampled for detection of TDP-43 pathology, which was positive in 57%–72% of cases.^{7,8} Further analysis of these cases suggested that TDP-43 pathology affected structures in the medial temporal lobe first followed by higher order association cortices.^{23,24,31} This pattern of TDP-43 deposition was also observed in the present study, with 83.7% showing amygdala, hippocampus, or entorhinal cortex positivity (stages 1 and 2) and only 16.3% showing positivity in the temporal or frontal cortices (stage 3). This pattern is similar to our previous study of participants including those with a pathologic diagnosis of AD.⁹

Strengths of this study include detailed data on diagnosis and neuropsychological test performance proximate to death and detailed data on multiple neuropathologies on a large number of participants, blinded to clinical data. The cohort studies also have high follow-up and autopsy rates that provide internal validity of findings.

This study also has limitations. Although this is the largest study of TDP-43 pathology in patients without a pathologic diagnosis of AD in the literature, the total number is still relatively small. The ROS participants likely have better dietary intake, access to health care, and levels of education, which may affect cognitive risk. The number of minorities is small and further study will be needed in minority cohorts. Finally, as previously noted, this study may underestimate the frequency of HS, leading to an underappreciation of the effect of HS as a synergistic pathology.

AUTHOR CONTRIBUTIONS

S.N., L.Y., R.S.W., D.A.B., and J.A.S. contributed to study concept and design. S.N. and J.A.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. E.-Y.C., S.N., and J.A.S. were responsible for acquisition, analysis, or interpretation of data. S.N. drafted the manuscript and all authors critically revised the manuscript for intellectual content and interpreted the statistical analyses. D.A.B. and J.A.S. obtained funding and provided administrative, technical, and material support.

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DISCLOSURE

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