Effect Modifiers of TDP-43-Associated Hippocampal Atrophy Rates in Patients with Alzheimer's Disease Neuropathological Changes

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Abstract.

Background: Transactive response DNA-binding protein of 43 kDa (TDP-43) is associated with hippocampal atrophy in Alzheimer's disease (AD), but whether the association is modified by other factors is unknown.

Objective: To evaluate whether the associations between TDP-43 and hippocampal volume and atrophy rate are affected by age, gender, apolipoprotein E (*APOE*) ϵ 4, Lewy bodies (LBs), amyloid- β ($A\beta$), or Braak neurofibrillary tangle (NFT) stage.

Methods: In this longitudinal neuroimaging-clinicopathological study of 468 cases with AD neuropathological changes ($A\beta$ -positive) that had completed antemortem head MRI, we investigated how age, gender, *APOE* ϵ 4, presence of LBs, $A\beta$, TDP-43, and Braak NFT stages are associated with hippocampal volumes and rates of atrophy over time. We included field strength in the models since our cohort included 1.5T and 3T scans. We then determined whether the associations between hippocampal atrophy and TDP-43 are modified by these factors using mixed effects models.

Results: Older age, female gender, *APOE* ϵ 4, higher field strength, higher TDP-43, and Braak NFT stages were associated with smaller hippocampi. Rate of atrophy was greater with higher TDP-43 and Braak NFT stage, but lower in older patients. The association of TDP-43 with greater rate of atrophy was enhanced in *APOE* ϵ 4 carriers ($p = 0.04$).

Conclusion: Neurodegenerative effects of TDP-43 seem to be independent of most factors except perhaps *APOE* in cases with AD neuropathological changes. TDP-43 and tau appear to behave independently of one another.

Keywords: Alzheimer's disease, apolipoprotein E4, atrophy, dementia, hippocampus, MRI, pathology, TDP-43

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INTRODUCTION

Hippocampal atrophy (HA) is a prominent feature of Alzheimer's disease (AD) and, even though not specific to it [1, 2], it is often used as a preclinical and disease progression biomarker of AD [3–5] and is sometimes used as a secondary outcome for clinical trials [6]. Hippocampal volume declines with age [7, 8]; however, the rate of atrophy is greater in patients with AD compared to individuals with typical aging with different studies reporting the percentages of annual hippocampal volume loss varying between 1.4% and 15% among AD patients [7, 9, 10]. A recent report modeling brain volumes loss over the adult lifespan in a clinical cohort concluded that the hippocampi were affected in AD patients in their 40 s, followed by the amygdala and lateral ventricles [11]. Greater degree and faster rate of HA are associated with greater cognitive decline, more severe memory impairment, and overall graver clinical prognosis [5, 12, 13]. Therefore, understanding the pathogenesis and risk factors of HA rates are important and carry clinical value in disease management.

Previous studies have shown that gender [14, 15] and apolipoprotein E (*APOE*) ϵ 4 [16, 17] might have an effect on degree and rate of HA. Great effort was placed into determining the drivers of hippocampal neurodegeneration with the principal candidates being amyloid- β ($A\beta$) and tau due to their direct association with AD [18] as well as transactive response DNA-binding protein of 43 kDa (TDP-43), often detected in brains concurrently with AD pathology, which has been proven to play a critical role in HA in patients with comorbid AD [19]. While smaller hippocampal volumes have been associated with higher burden of neurofibrillary tangles (NFT) [20] and senile plaques [21], TDP-43 has also been found to be associated with decreased hippocampal volumes in cross-sectional studies [19]. Furthermore, TDP-43 has been shown to be associated with faster rates of HA over time in individuals with intermediate-high likelihood AD [22], an association that was magnified in cases with higher Braak NFT stage [22]. Therefore, TDP-43 and tau are both implicated in increased degree and rate of HA in cases with comorbid AD, although it is unclear whether these proteins are acting independently or synergistically. Unlike tau and TDP-43, accumulation of $A\beta$, on the other hand [23], appears to not be associated with hippocampal volume or faster rates of HA [24, 25]. Other frequent pathologies such as Lewy body disease (LBD) has also been studied for a possible additive effect on

HA in cases of mixed AD/LBD with results demonstrating no significant contribution of Lewy bodies (LBs) to the degree of hippocampal neurodegeneration [26–32].

Given that a number of demographic, genetic, and pathological factors that have been found to be associated with the degree and rate of HA in AD, pathogenesis in cases with Alzheimer's disease neuropathological changes (ADNC) appears to be more complex than just the aggregation of tau and $A\beta$. Little is known about how these demographic, genetic, and pathological factors interact with each other and contribute to neurodegeneration in AD. Understanding the interplay among these drivers of HA can shed light on the neurobiology of neurodegeneration in AD, as well as aid in prediction of clinical prognosis of patients with AD and prompt to early interventions [13]. In this study we investigated whether the associations of TDP-43, a key player of AD neurodegeneration [22], with rate of HA is modified by age, gender, *APOE* ϵ 4 carrier status, presence of LBs, $A\beta$, and/or Braak NFT stage.

MATERIALS AND METHODS

Study design and participants

We conducted a longitudinal neuroimaging-clinicopathological study using an autopsy cohort of participants who were enrolled in the Mayo Clinic Alzheimer's Disease Research Center (ADRC), the Mayo Clinic Alzheimer's Disease Patient registry (ADPR), or the Mayo Clinic Study of Aging (MCSA) [33], and were prospectively followed to the time of their death and had a brain autopsy available. The patients died between May 12, 1999 and December 31, 2015. From this cohort we identified all participants who met the following inclusion criteria: the participants had at least one antemortem structural MRI performed; the participants had received an AD spectrum pathological diagnosis in accordance with the National Institute on Aging–Alzheimer Association (NIA-AA) neuropathologic diagnostic criteria [34] (i.e., participants had to have $A\beta$ deposition present in the brain); and participants had their TDP-43 status determined as described below. Cases with a pathological diagnosis of frontotemporal lobar degeneration, progressive supranuclear palsy, or corticobasal degeneration were excluded. The total of 468 of participants met our inclusion criteria.

At the time of enrollment participants' demographics (age, gender, etc.) were collected and *APOE*

genotyping was performed on all participants, as previously described [35, 36].

Standard protocol approvals, registrations, and patient consents

This study has been approved by the Mayo Clinic institutional review board, and all subjects and/or their proxies signed a written informed consent form before taking part in any research activities in accordance with the Declaration of Helsinki.

Pathological analysis

All cases underwent pathological examination according to the recommendations of the NIA-AA [34]. Each individual was assigned a Braak NFT stage 0–VI [18] and neocortical neuritic plaque density score 0–3 according to the Consortium to Establish a Registry for AD (CERAD) [37]. Presence of LBs in the brainstem, limbic system or amygdala, or neocortex was documented and staged according to National Alzheimer's Coordinating Center (NACC-LEWY) [38].

Cases were designated as TDP-43-positive (TDP-43(+)) if TDP-43 immunoreactive neuronal cytoplasmic inclusions, dystrophic neurites, or neuronal intranuclear inclusions were identified in the amygdala which has been shown and validated to be the earliest region involved in AD [39–44]. For all cases in which TDP-43 was observed in the amygdala, we subsequently assessed for the presence of TDP-43 in the hippocampus (subiculum, CA1, and dentate fascia) and beyond [39, 40]. The cases were considered TDP-43 negative if no TDP-43 immunoreactive inclusions were detected in the amygdala; no additional regions were screened. All cases were then classified as: TDP-43 stage 0 = those without any TDP-43 immunoreactivity; TDP-43 stage 1 = those with TDP-43 restricted to the amygdala; and TDP-43 stage ≥ 2 = those with TDP-43 in hippocampus with or without lesions beyond the hippocampus. This categorization was used to allow the TDP-43 effect to vary by stage 0 versus stage 1 versus stage ≥ 2 [39, 40]. The grouping of those in stages 2 and above was based on the commonality of hippocampal TDP-43 and to keep the analyses tractable [22].

MRI analysis

All MRI were performed using a standardized protocol that included a T1-weighted 3-dimensional

volumetric sequence. While some subjects had been scanned at 1.5T and some at 3T, longitudinal analyses were always run using sets of serial scans performed at the same field strength. MRI protocol parameters were stable within the field strength and did not require to be adjusted for in the further analyses. All images underwent pre-processing that included corrections for gradient non-linearity and intensity inhomogeneity [45]. Serial hippocampal volumes were calculated using FreeSurfer software version 5.3.0 (<http://surfer.nmr.mgh.harvard.edu/>) [46]. All scans were first run through the FreeSurfer cross-sectional pipeline, followed by the longitudinal pipeline. The total of 354/468 (76%) participants had serial MRI (>1 scan) (Table 1) which were used for calculation of the rate of HA over time. For subjects with only one MRI, hippocampal volumes were calculated from the cross-sectional FreeSurfer pipeline. Cross-sectional and longitudinal hippocampal volumes calculated by the FreeSurfer were interchangeable ($r=0.99$).

Statistical analysis

We used mixed effects models to examine whether rates of HA differed by patient characteristics. We fit linear mixed effects models using log-transformed hippocampal volume as the outcome and using non-transformed volume as the outcome. The log-transformed models have the primary advantage of admitting an interpretation in terms of percentage differences but we report both models as they have complimentary interpretations.

A mixed model for longitudinal data can be thought of as simultaneously modeling cross-sectional effects, i.e., factors associated with higher versus lower volume, and longitudinal within-subject effects, i.e., factors associated with faster versus slower within-person change. All models included cross-sectional and longitudinal fixed effects for the following variables: age at death, gender, *APOE* $\epsilon 4$, Braak NFT stage (numeric score 1–6), TDP-43 stage (numeric score with 3 levels), LBs (present versus absent), $A\beta$ (numeric score with 3 levels), field strength (two categories), and total intracranial volume (TIV [numeric]). In our models $A\beta$ neuritic plaque density, Braak NFT stage, and TDP-43 stage were treated as linear terms; age was modeled to be interpreted by decade and time was modeled relative to death. Models included subject-specific intercepts and slopes which allow for correlation among observations within individuals and allow for individuals

Table 1
Characteristics and MRI scan distribution of study participants

Characteristic	All (n = 468)	TDP-43(-)* (n = 248)	TDP-43(+) [†] (n = 220)	p
Female, n (%)	242 (52%)	113 (46%)	129 (59%)	0.005
APOE carrier, n (%)	250 (54%)	114 (46%)	136 (62%)	<0.001
Education, y	14 (6, 20)	14 (6, 20)	14 (8, 20)	0.62
Age at first MRI scan, years	78 (45, 100)	77 (45, 100)	79 (53, 99)	0.002
Age at last MRI scan, years	81 (49, 100)	80 (49, 100)	82 (53, 99)	0.003
Age at death, years	85 (51, 104)	84 (51, 103)	87 (56, 104)	<0.001
Pathological characteristics				
Presence of Lewy bodies, n (%)	157 (34%)	71 (29%)	86 (39%)	0.02
Tau, Braak NFT stage I-VI, n (%)				<0.001
Braak I	7 (1%)	5 (2%)	2 (1%)	
Braak II	36 (8%)	28 (11%)	8 (4%)	
Braak III	29 (6%)	24 (10%)	5 (2%)	
Braak IV	72 (15%)	48 (19%)	24 (11%)	
Braak V	117 (25%)	51 (21%)	66 (30%)	
Braak VI	207 (44%)	92 (37%)	115 (52%)	
Amyloid- β , CERAD A1-3, n (%)				0.003
A1	74 (16%)	52 (21%)	22 (10%)	
A2	127 (27%)	68 (27%)	59 (27%)	
A3	267 (57%)	128 (52%)	139 (63%)	
MRI distribution, n (%)				
Field strength				<0.001
1.5T only	296 (63%)	130 (52%)	166 (75%)	
3T only	93 (20%)	70 (28%)	23 (10%)	
Mixed	79 (17%)	48 (19%)	31 (14%)	
Number of MRI scans	3.0 (1.0, 9.0)	3.0 (1.0, 9.0)	3.0 (1.0, 9.0)	0.53
Serial MRI, n (%)				0.52
> 1 Scan	354 (76%)	191 (77%)	163 (74%)	

Data shown are n (%) or median (range). For categorical variables, *p*-values are from Fisher's Exact Test. For continuous variables, *p*-values are from Wilcoxon rank sum test. *TDP-43-negative; [†]TDP-43-positive.

to have higher or lower volumes and faster or slower atrophy due to unmeasured, person-specific factors.

To evaluate the evidence as to whether age, gender, APOE, LBs, A β , or Braak NFT stage acted as TDP-43 effect modifiers we used likelihood ratio tests by testing one three-way interaction at a time (e.g., "age $\times$ TDP-43 $\times$ time"). We also performed a sensitivity analysis by fitting a simplified model omitting gender and LBs separately by last clinical diagnosis prior to death. All statistical analysis was done in R (Version 3.4.2).

RESULTS

Demographic, genetic, pathological, and neuroimaging characteristics of the study participants are summarized in Table 1. Based on last diagnosis prior to death 71 (15%) patients were cognitively unimpaired, 47 (10%) had mild cognitive impairment (MCI), 254 (54%) had a clinical diagnosis of Alzheimer's dementia, and 96 (21%) had other diagnoses (e.g., vascular dementia, dementia with Lewy bodies, etc.). Of the 468 cases included in this study,

220 (47%) were TDP-43(+). When comparing TDP-43(+) to TDP-43(-) cases, female gender, APOE carrier status, older age at death and last MRI scan, higher Braak NFT and neuritic plaque stages, as well as higher prevalence of LBD were more common among TDP-43(+) cases, (*p* < 0.05).

Older age, female gender, APOE ϵ 4 carrier status, 3T field strength, increase of Braak NFT, and higher TDP-43 stage were associated with reduced hippocampal volume cross-sectionally (Fig. 1A, C; Table 2).

In terms of longitudinal effects, the rate of HA was clearly associated with age, Braak NFT stage, and TDP-43 stage in both percentage change and volume change models. Whereas accumulation of tau and TDP-43 were associated with greater rates of HA, the rate of HA was lower in patients who died at older ages (Fig. 1B, D; Table 2). There was some indication in the log-transformed model that APOE ϵ 4, 3T field strength, and A β were associated with increased HA in percentage terms, however these factors did not appear to be associated with greater loss in absolute volume terms.

Fig. 1. Estimates and 95% confidence intervals for the main models. The time estimates for panels B and D do not correspond to a constant, but instead an estimate of the atrophy rate for an 85-year-old male two years prior to death with amyloid level A2, Braak NFT stage 5, no Lewy bodies, a 1.5L TIV, who was scanned at 1.5T. The age effect shown is for a 10-year older age at death. The effects for amyloid stage, Braak NFT stage, and TDP-43 stage are for a one-level higher stage. The effect for total intracranial volume (TIV) is for a 200 cm³ greater volume.

When we analyzed our data by clinical diagnosis we found that higher TDP-43 stage was associated with reduced hippocampal volumes cross-sectionally in clinical Alzheimer's dementia patients when compared to cognitively unimpaired patients and other dementia. Reduced hippocampal volumes on cross-sectional analysis were also found in clinical Alzheimer's dementia (cAD) patients with increasing neuritic A β stage when compared to cognitively

unimpaired patients (Fig. 2A, C; Table 3). No cross-sectional differences associated with Braak NFT stage were found, as well as no differences in longitudinal effects of the three proteins on hippocampal volumes among the clinical groups (Fig. 2B, D; Table 3).

When we allowed for age, gender, *APOE*, LBs, A β , and Braak NFT stage to modify the association of TDP-43 with HA rates (Fig. 3), only *APOE* $\epsilon 4$ had a

Table 2
Estimates and 95% confidence intervals from log-volume and volume models

Cross sectional effects	Log-volume model*	<i>p</i>	Volume model†	<i>p</i>
	Estimate (95% CI)		Estimate (95% CI)	
Age at death (10 y older)	-7 (-9, -6)	<0.001	-438 (-541, -335)	<0.001
Female versus male	-8 (-12, -4)	<0.001	-466 (-678, -254)	<0.001
<i>APOE</i> ε4+ versus ε4-	-7 (-11, -3)	<0.001	-367 (-561, -174)	<0.001
Amyloid (1 level higher)‡	-3 (-6, 1)	0.11	-124 (-292, 44)	0.15
Braak NFT stage (1 level higher)	-4 (-6, -2)	<0.001	-262 (-358, -167)	<0.001
LBs (present versus absent)	-1 (-5, 3)	0.67	-36 (-233, 161)	0.72
TDP-43 stage (1 level higher)	-8 (-10, -6)	<0.001	-412 (-519, -304)	<0.001
3T scan versus 1.5T	-7 (-9, -6)	<0.001	-433 (-497, -369)	<0.001
TIV (200 cm ³)	2 (0, 3)	0.02	81 (-4, 165)	0.06
Longitudinal rate effects				
Time (1y)	-2.1 (-2.5, -1.6)	<0.001	-145 (-169, -121)	<0.001
Age at death (10 y older)	0.2 (0.0, 0.4)	0.06	23 (12, 34)	<0.001
Female versus male	0.0 (-0.4, 0.4)	0.93	6 (-17, 29)	0.61
<i>APOE</i> ε4+ versus ε4-	-0.3 (-0.7, 0.0)	0.08	-2 (-21, 18)	0.88
Amyloid (1 level higher)	-0.3 (-0.6, 0.0)	0.07	-11 (-28, 7)	0.24
Braak NFT stage (1 level higher)	-0.4 (-0.6, -0.2)	<0.001	-21 (-31, -11)	<0.001
LBs (present versus absent)	0.0 (-0.4, 0.3)	0.93	-4 (-23, 16)	0.71
TDP-43 stage (1 level higher)	-0.7 (-0.9, -0.5)	<0.001	-23 (-34, -12)	<0.001
3T scan versus 1.5T	-0.5 (-0.8, -0.2)	0.003	-6 (-25, 12)	0.50
TIV (200 cm ³)	0.1 (-0.1, 0.3)	0.25	2 (-10, 13)	0.78

The age effect shown is for a 10-year older age at death. The effects for amyloid stage, Braak NFT stage, and TDP-43 stage are for a one-level higher stage. The effect for total intracranial volume (TIV) is for a 200 cm³ greater volume. *Estimates are expressed in terms of percentages.

†Estimates are expressed in terms of mm³. ‡Amyloid-β neuritic plaque stage, CERAD A1-3.

significant effect (likelihood ratio $p = 0.04$ in the log-transformed model, Table 4) on TDP-43-associated HA rates; the effect of a 1-unit increase in TDP-43 stage was slightly greater (by $\sim 0.3\%$ /year, Table 5) in *APOE* ε4 carriers compared to non-carriers.

DISCUSSION

In this neuroimaging-clinicopathological study of 468 older adults with an ADNC, we found that older age, female gender, the *APOE* ε4 allele, Braak NFT stage, and TDP-43 stage were cross-sectionally associated with smaller hippocampal volumes. Longitudinally, older age at death was associated with slower rate of HA, whereas advanced TDP-43 stage and Braak NFT stage were associated with greater rates of HA. Given the association between TDP-43 and both degree and rate of HA, we assessed whether these effects are modified by age, gender, *APOE* ε4 carrier status, LBs, Aβ, and/or Braak NFT stage. We found the effect of greater TDP-43 stage to be somewhat greater in *APOE* ε4 carriers compared to non-carriers, but otherwise behaved similarly and independently across all the other subgroups.

We found that an increase by one point in the TDP-43 stage and one point in the Braak NFT stage

were both associated with greater rates of HA, which is consistent with our earlier findings [22]. It is important to emphasize that our findings show that not only hippocampal TDP-43 (TDP-43 stage ≥ 2) is associated with increased rates of HA as previously described [22], but also TDP-43 limited to amygdala (TDP-43 stage 1). Our results are in keeping with recent evidence of association between TDP-43 restricted to amygdala and grey matter loss in the entorhinal cortex, hippocampus, and temporal pole, the regions that have reciprocal projections to the amygdala and might undergo atrophy as a result of anterograde trans-synaptic degeneration [47].

In this study we further our results and now show that there is no evidence that Braak NFT stage and hence tau modifies the effect of TDP-43 on the rate of hippocampal neurodegeneration. In fact, our findings indicate that the two factors are essentially orthogonal in this cohort. This finding supports our previous hypothesis that tau and TDP-43 exhibit their maximum effect on hippocampus at different time-points in the disease [22]. Tau might be associated with hippocampal neurodegeneration earlier in the course of the disease, given that acceleration in the atrophy rates has been associated with increasing NFT stage in absence of TDP-43 or where TDP-43 deposition was limited to amygdala [22], whereas TDP-43 does not show this relationship with NFT stage [22].

Fig. 2. Effects for neuritic amyloid stage, Braak NFT stage, and TDP-43 stage based on models fit within last diagnosis prior to death. Effect shown is based on a one-level higher stage. Results are represented as estimates and 95% confidence intervals. Models reported here were simplified from the primary analysis and did not include terms for gender or Lewy bodies.

When we analyzed our data by clinical diagnosis we found the TDP-43 associations to be somewhat more pronounced in the clinical Alzheimer's dementia group for cross-sectional hippocampal volumes. The lack of a clear TDP-43 association with HA among cognitively unimpaired patients is consistent with a previous study that found no association between TDP-43 and hippocampal volume in patients that were cognitively unimpaired [48]. It is difficult to interpret the associations within the MCI group given the larger variability, although the effect sizes were

more similar to the cognitively unimpaired group than the clinical Alzheimer's dementia group. Unfortunately, our data are not conclusive as to whether the TDP-43 effect on hippocampal volumes is specific to those with clinical Alzheimer's dementia. The Braak NFT stage effect is interesting. The similarity in the effect sizes across clinical groups for the cross-sectional and longitudinal analyses supports the notion that Braak NFT associations are not truly different across the clinical phenotypes. The results for the amyloid-clinical diagnosis associations

Table 3
Pairwise *p*-values comparing cross-sectional and longitudinal effects between subgroups for the log-volume and volume models

	Log-volume model					
	CU* versus MCI [†]	CU versus cAD [‡]	CU versus Other	MCI versus cAD	MCI versus Other	cAD versus Other
Cross-sectional effects						
Amyloid (1 level higher) [¥]	0.82	0.005	0.25	0.05	0.32	0.25
Braak NFT stage (1 level higher)	0.91	0.32	0.76	0.56	0.92	0.55
TDP-43 stage (1 level higher)	0.61	<0.001	0.87	0.10	0.55	0.002
Longitudinal rate effects						
Amyloid (1 level higher)	0.63	0.12	0.12	0.60	0.39	0.59
Braak NFT stage (1 level higher)	0.81	0.65	0.37	0.91	0.35	0.22
TDP-43 stage (1 level higher)	0.98	0.11	0.52	0.25	0.61	0.58
	Volume model					
	CU* versus MCI [†]	CU versus cAD [‡]	CU versus Other	MCI versus cAD	MCI versus Other	cAD versus Other
Cross-sectional effects						
Amyloid (1 level higher) [‡]	0.90	0.004	0.19	0.06	0.30	0.39
Braak NFT stage (1 level higher)	0.85	0.23	0.66	0.53	0.89	0.54
TDP-43 stage (1 level higher)	0.71	0.02	0.70	0.23	0.52	0.008
Longitudinal rate effects						
Amyloid (1 level higher)	0.50	0.45	0.22	0.82	0.66	0.43
Braak NFT stage (1 level higher)	0.79	0.51	0.43	0.83	0.38	0.18
TDP-43 stage (1 level higher)	0.72	0.77	0.68	0.52	0.50	0.81

These *p*-values need to be interpreted in the context of Fig. 2 since the same effect size can be significant or not depending on the subgroup size. *CU, cognitively unimpaired. [†]MCI, mild cognitive impairment. [‡]cAD, clinical Alzheimer's dementia. [¥]Amyloid- β neuritic plaque stage, CERAD A1-3.

Fig. 3. Estimates and 95% confidence intervals for the modification of the effect of a higher level of TDP-43 on atrophy. The values shown quantify the difference in atrophy associated with a higher level of TDP-43 for each covariate contrast. Estimates are obtained from adding a single three-way (covariate $\times$ TDP $\times$ time) interaction to the primary log-volume or volume model. The age effect shown is for a 10-year older age at death. The effects for A β stage and Braak NFT stage are for a one-level higher stage.

are challenging to interpret. We observed an association between cross-sectionally smaller hippocampi and higher neuritic amyloid stage in patients with clinical Alzheimer's dementia which is biologically plausible and has been reported in the literature [49]. However, our finding of cross-sectionally larger hippocampal volumes with increasing neuritic plaque stage in cognitively unimpaired group is counterintuitive.

Several neuroimaging studies that use amyloid positron emission tomography as a measure of A β burden report no association between A β and hippocampal volumes in asymptomatic patients and/or patients with MCI [50] or weak association with HA [51–56] with stronger evidence in cases of subcortical versus cortical A β deposition [57]. CERAD neuritic plaque staging used in this study assesses only

Table 4

Likelihood ratio *p*-values from tests of whether age, gender, *APOE*, amyloid stage, Braak NFT stage, or Lewy bodies modify the effect of a higher level of TDP-43 stage on hippocampal atrophy

Term	Log model* <i>p</i>	Volume model† <i>p</i>
Age at death, y	0.28	0.68
Gender	0.13	0.68
<i>APOE</i> ε4 carrier	0.04	0.16
Aβ neuritic plaque stage	0.20	0.43
Braak NFT stage	0.61	0.86
Lewy bodies	0.24	0.39

*Estimates are expressed in terms of percentages. †Estimates are expressed in terms of mm³.

cortical deposition of Aβ with subcortical regions not included for screening [37] in contrast to Thal phases [58] and therefore might not represent a direct association between Aβ and atrophy in subcortical regions, e.g., hippocampus. This nuance could have contributed to the ambiguity of the results.

Female gender in cognitively impaired subjects has been reported to be associated with smaller hippocampal volumes cross-sectionally [14, 59] as well as accelerated rates of HA compared to men [14]. Increase in HA rates in women has been shown to be associated with low levels of Aβ and high levels of tau in the cerebrospinal fluid of the patients [14]; it is worth mentioning though that this latter study was not in an autopsy cohort. In our study we also found smaller hippocampal volumes in females cross-sectionally; however, gender was not associated with rate of hippocampal neurodegeneration. There are several possible explanations why our findings are discordant with previously published reports. First, we did not limit our cohort to any specific clinical diagnosis and instead included all clinical diagnoses (even cognitively normal or so-called resilient patients) whereas in these other studies the finding that female gender accelerated HA was specific to subjects with a clinical diagnosis of MCI or dementia, but not in healthy controls. Second, female gender has been found to be associated with more

severe AD pathology, particularly NFT burden [60]. Given that tau is associated with HA [22] as seen with our current results, it is possible that the gender differences in the rate of atrophy were driven by tau and possibly even TDP-43 which was not included in the analyses of previous studies.

APOE ε4 carriers had smaller hippocampal volumes cross-sectionally which is consistent with previous studies [16, 17], but we did not find clear evidence that carriers had greater rates of HA. However, our model with a three-way interaction including *APOE* (i.e., *APOE* × TDP-43 × time) suggested a greater atrophy rate (by ~0.3%) with increasing TDP-43 stage in those with an *APOE* ε4 allele. Given the fact that only one of our models found statistically significant TDP-43 effect modification by *APOE* ε4, this finding might be equivocal. The lack of an independent effect of *APOE* ε4 allele on rate of HA appears discordant with past studies where cognitively impaired *APOE* ε4-carriers had accelerated rates of HA [16, 17]. Perhaps since all individuals in this study had Aβ, the independent effects of *APOE* on hippocampal volume rates were reduced. Again, we did not limit our cohort to cognitively impaired individuals. Interestingly, *APOE* ε4 carrier status did not have an effect on hippocampal volumes or rate of HA in cognitively intact individuals [16] suggesting that the presence of the *APOE* ε4 allele is not a strong determinant of neurodegeneration in this population. Moreover, it has been reported that the ε4 allele is a possible risk factor of TDP-43 [61–63]. Therefore, given that the studies that reported the effect of *APOE* ε4 on rate were purely clinical and did not include an autopsy cohort [16, 17], it is possible that TDP-43 or tau were confounders of the associations with hippocampal neurodegeneration. The exact mechanisms by which TDP-43 and *APOE* ε4 interplay warrant further study.

We found an association between field strength and hippocampal volume cross-sectionally, with 3T scans having smaller hippocampi compared to 1.5 T. Earlier

Table 5
Estimates and 95% confidence intervals for the modification of the effect of a higher level of TDP-43 on atrophy model

Term	Log-volume model*	Volume model†
Age at death (10 y)	−0.1 (−0.3, 0.1)	−1.8 (−13.0, 9.4)
Female versus male	0.1 (−0.2, 0.5)	2.9 (−17.1, 23.0)
<i>APOE</i> ε4+ versus ε4−	−0.3 (−0.7, 0.0)	−4.9 (−24.9, 15.1)
Aβ neuritic plaque stage (1 level greater)	−0.1 (−0.4, 0.1)	−1.0 (−14.9, 12.9)
Braak NFT stage (1 level greater)	0.0 (−0.1, 0.2)	2.2 (−6.1, 10.4)
Lewy bodies (present versus absent)	0.2 (−0.1, 0.6)	7.1 (−13.7, 28.0)

*Estimates are expressed in terms of percentages. †Estimates are expressed in terms of mm³.

studies showed no significant differences in volume-try in 3T versus 1.5T scans [64–67]; however, a more recent study using a larger sample size and MRI scans from multiple sites participating in Alzheimer’s Disease Neuroimaging Initiative also demonstrated greater HA detected by 3T versus 1.5T which was attributed to improved signal-to-noise ratio in 3T allowing for a better grey and white matter separation [68]. Longitudinally, associations between field strength and rate of HA were equivocal since only the log-transformed model showed associations between field strength and rates of atrophy, but not the absolute volume model. Absence of the effect of field strength on the rates of HA might be due to standardization of the field strength in the longitudinal analyses where rates of HA were calculated within series of scan with the same field strength. Overall, previous studies have shown that using both 1.5T and 3T scans are appropriate for detection of degree and rate of HA [67, 68]. Mixing the scans from different field strengths also has been shown to not drastically reduce the power of detection of neurodegenerative change compared to using scans from the same scanner only [67]. However, the use of a higher field strength (3T and above) might be more advantageous for calculation of fine-scale features, e.g., hippocampal subfields [68–70].

Our study did not reveal associations between increasing neuritic A β stage, the presence of LBs and increased degree and rate of HA which is consistent with previously reported data [24–29, 31, 32]. Presence of LBs as well as neuritic A β stage also did not show any modification of the neurodegenerative effect of TDP-43.

As expected, older age was associated with smaller hippocampal volumes [1, 7, 8]; however, our findings regarding its effect on the rate of HA were counterintuitive. Older age at death was associated with slower rates of hippocampal neurodegeneration. This is consistent with work from the Alzheimer’s Disease Neuroimaging Initiative that showed that in cognitively unimpaired patients the rates of HA accelerated with age, whereas in patients with MCI and dementia rates of HA were lower in older individuals [71]. It is also consistent with studies that have shown that younger age is associated with greater tau burden on PET imaging and greater rates of cortical atrophy and tau deposition in AD [72–78]. Younger age may, therefore, predispose to a more aggressive disease course in AD. However, this phenomenon could also be explained by the threshold effect where once a certain level of protein aggregation is reached, no further aggregation leads to slower decline. We also

cannot rule out the possibility of some selection bias whereby older patients with greater rates of atrophy may be too severe to enter a research study due to poorer cognitive reserve.

Longitudinal design, extensive phenotyping of the sample, and the use of clinical, imaging, and pathological data strengthen the results of the present study. However, the findings should be interpreted taking into account the limitations. First, our study cohort included only participants who had ADNC at autopsy which limits generalizability of the results to cases without A β . Second, the patients enrolled in our ADRC, ADPR, and MCSA are predominantly white, hence we were unable to evaluate the effect of race/ethnicity on the rates of HA. Third, associations between cross-sectional hippocampal volumes and neuritic plaque stages across different clinical groups need to be validated in a different cohort in which both associations with CERAD stages and Thal phases are analyzed. Lastly, while thorough quality control checks were performed on the FreeSurfer data, we did not perform a systematic inspection of all hippocampal segmentations which may have introduced variability into our data.

This study provides further evidence that neurodegeneration occurring in the hippocampus of patients with ADNC is multifactorial, and is dependent on age, gender, *APOE* ϵ 4 carrier status, and aggregation of TDP-43 and tau; the latter two also clearly increase the rate of atrophy. TDP-43 has similar associations with atrophy across ages, gender, presence of LBs, A β , and Braak NFT stages, but its associations are slightly augmented in *APOE* ϵ 4 carriers. There is always the notion that the absence of evidence is not the same as evidence of absence, but the idea that TDP-43 behaves similarly regardless of other pathologies appears to be a good working model. This information is pertinent, especially once a TDP-43 biomarker becomes available, and can aid in clinical prognosis and disease management for patients with probable AD.

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