Published in final edited form as:

Alzheimers Dement. 2019 June ; 15(6): 799–806. doi:10.1016/j.jalz.2019.03.003.

Brain atrophy in primary age-related tauopathy is linked to transactive response DNA-binding protein of 43 kDa

Keith A. Josephs^{a,*}, Melissa E. Murray^b, Nirubol Tosakulwong^c, Stephen D. Weigand^c, David S. Knopman^a, Ronald C. Petersen^a, Clifford R. Jack Jr.^d, Jennifer L. Whitwell^d, and Dennis W. Dickson^b

^aDepartment of Neurology, Mayo Clinic, Rochester, MN, USA

^bDepartment of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

^cDepartment of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

^dDepartment of Radiology, Mayo Clinic, Rochester, MN, USA

Abstract

Introduction: Primary age-related tauopathy (PART) is characterized by the presence of neurofibrillary tangles and absent-minimal β -amyloid deposition. Transactive response DNA-binding protein of 43 kDa (TDP-43), a third protein, has recently garnished a lot of attention in Alzheimer's disease where it is associated with memory loss and amygdala and hippocampal atrophy. We aimed to determine whether TDP-43 is associated with brain atrophy in PART.

Methods: We assessed the frequency of TDP-43 in PART and performed voxel-level analysis in SPM12, as well as region-of-interest analysis using linear regression modeling, controlling for variables of interest, to assess for associations between TDP-43 and brain atrophy.

Results: Of 116 PART cases, 31 (26.7%) had TDP-43. The presence of TDP-43 was associated with significantly greater amygdala, hippocampal, and anterior temporal atrophy in both the region-of-interest and the voxel level analyses.

Discussion: TDP-43 is associated with greater brain atrophy in PART.

Keywords

PART; TDP-43; MRI; Hippocampus; Atrophy; Tauopathy

1. Introduction

Primary age-related tauopathy (PART) [1] is a pathological entity characterized by the presence of tau-positive neurofibrillary tangles (NFTs) relatively confined to limbic regions and absent-minimal β -amyloid pathology. A diagnosis of PART requires a Braak NFT stage IV [2] (usually III or lower) and a Thal β -amyloid phase 2 [3] or a Consortium to

*Corresponding author. Tel.:+(507)-538-1038; Fax:+(507)-538-6012. josephs.keith@mayo.edu.

Declaration of interests: K.A.J., M.E.M., N.T., S.D.W., D.S.K., R.C.P., J.L.W., and D.W.D. receive research support from the US National Institutes of Health (NIH).

Establish a Registry for Alzheimer's disease (CERAD) β -amyloid ($A\beta$) stage of 0 or 1 [1]. Primary age-related tauopathy can be further subclassified pathologically as definite PART and possible PART depending on whether $A\beta$ is absent or present, respectively. A diagnosis of definite PART requires a Thal phase of 0 (no plaques of any kind anywhere) or, alternatively, a CERAD stage of 0 (no neuritic plaques in frontal, temporal, parietal, occipital neocortex). A diagnosis of possible PART requires a Thal phase of 1 or 2 (plaques are found in neocortex or extend to entorhinal or hippocampus but do not extend beyond the hippocampus) or a CERAD stage of 1 (at most scant neuritic plaques are identified in frontal, temporal, parietal, and occipital neocortex).

Cases with a diagnosis of PART may have normal cognition up to the time of death and are considered to have had asymptomatic PART (definite or possible) or may have been cognitively impaired before death and are considered to have had symptomatic PART [4]. As a result, there are four different categories of PART: asymptomatic definite PART, symptomatic definite PART, asymptomatic possible PART, and symptomatic possible PART. It should be pointed out that cases currently diagnosed as symptomatic part can have mild cognitive impairment or can be demented. Hence, the degree of cognitive impairment is not taken into account in symptomatic PART. Previously, cases with Braak stage of I-IV and absent-minimal $A\beta$ pathology, and those that were demented and typically very old, were diagnosed as having NFT-predominant dementia [5], NFT-predominant form of senile dementia [6], or senile dementia with tangles [7]. All such cases are now subsumed under the rubric of PART, specifically symptomatic PART.

Similar to the case in Alzheimer's disease, cognitive impairment in PART has been shown to be related to the severity/distribution of NFT pathology [8-10]. We have also demonstrated that NFT pathology is related to the presence of hippocampal atrophy in PART [9]. However, in Alzheimer's disease, we and others have demonstrated that a protein known as transactive response DNA binding protein of 43 kDa (TDP-43) occurs in a large proportion of cases and is associated with worse memory loss [11-13], hippocampal atrophy [11], and faster rates of hippocampal atrophy [14]. TDP-43 is found in cases of PART [9,15], and hence, it is possible that it may also be associated with neurodegeneration when it coexists with PART.

In a previous study, in which the primary analysis was assessing the association of NFT distribution with cognition and brain atrophy in 52 cases of asymptomatic definite PART, we also examined whether TDP-43 had any effect on brain atrophy as a secondary analysis [9]; we had excluded cases with symptomatic definite PART, symptomatic possible PART, and asymptomatic possible PART. In that study, we did not observe an association between TDP-43 and brain atrophy in definite asymptomatic PART. However, given that TDP-43 is strongly associated with the presence of cognitive impairment [11-13], we may have inadvertently limited our ability to find any association between TDP-43 and PART in general. We now set out to determine whether TDP-43 is associated with brain atrophy across the entire spectrum of PART, that is, asymptomatic definite PART, symptomatic definite PART, asymptomatic possible PART, and symptomatic possible PART.

2. Methods

2.1. Subject selection

We identified all cases in our pathological database that had been recruited and prospectively followed up in the Mayo Clinic Alzheimer's Disease Research Center, Alzheimer's Disease Patient Registry, or the Mayo Clinic Study of Aging who had died with a brain autopsy between January 1999 and December 2015, had a Braak NFT stage I-III [2] and a CERAD stage of 0-1 [16], and had a volumetric brain magnetic resonance imaging (MRI) scan completed before death. Given that we were including cases with a CERAD stage of 1 (scant neuritic plaques), the fact that the criteria for PART emphasizes Braak stage I-III, and the need to have as pure a sample of PART as possible, we opted not to include cases with Braak NFT of IV because the vast majority would have more than scant amounts of A β deposition and would straddle the boundary with intermediate probability Alzheimer's disease [4,17]. All cases with a pathological diagnosis of a frontotemporal lobar degeneration (FTLD) [18], progressive supranuclear palsy [19], corticobasal degeneration [20], or Lewy body disease [21] were excluded. We did not have any cases diagnosed with chronic traumatic encephalopathy. A total of 116 cases that had all undergone apolipoprotein (APOE) epsilon E genotyping were identified.

All cases had undergone a neurological evaluation during life and were categorized as cognitively unimpaired, having mild cognitive impairment [22], dementia of the Alzheimer's type [23], or a non-Alzheimer's dementia at the last visit before death. For each participant, determination of cognitively normal status was based on consensus agreement between the study coordinator, examining physician, and neuropsychologist who evaluated the participant, taking into account education, prior occupation, and visual or hearing deficits and reviewing all other participant clinical information. Clinical measures that were captured during life included the Mini-Mental State Examination [24] and Clinical Dementia Rating Scale Sum of Boxes [25].

This study was approved by the Mayo Clinic Institutional Review Board. Before death, all subjects or their proxies had provided written consent for brain autopsy examination.

2.2. Pathological analysis

All cases had undergone pathological examination according to the recommendations of the CERAD [16], and each were assigned a Braak NFT stage [2] using modified Bielschowsky silver stain. Modified Bielschowsky stain was used for Braak NFT staging to maintain consistency within our database. The left hemibrain was fixed per protocol, and paraffin block sections were stained with hematoxylin and eosin and modified Bielschowsky. Immunohistochemistry was performed using antibodies for alpha-synuclein (LB509; 1:200; Zymed, San Francisco, CA), phospho-tau (AT8; 1:1000; Endogen, Woburn, MA), and A β (6 F/3D; 1:10; Novocastra Vector Labs, Burlingame, CA). The presence of degenerative hippocampal sclerosis [26] (i.e., neuronal loss in the CA1 and subicula regions of the hippocampus in the presence of TDP-43 immunoreactivity), Lewy bodies, and vascular disease (large infarcts, microinfarcts, hemorrhages, amyloid angiopathy) was determined.

2.3. TDP-43 screening

All cases were screened for the presence of TDP-43 immunoreactivity in the amygdala and hippocampus [11,27]. Specifically, the amygdala and hippocampus were screened using a polyclonal antibody (MC2085) that recognizes a peptide sequence in the 25-kDa C-terminal fragment using a DAKO Autostainer (DAKO Cytomation, Carpinteria, CA) and 3, 3'-diaminobenzidine as the chromogen. Sections were reviewed (by D.W.D., M.E.M., and K.A.J.) to assess for the presence of any TDP-43 immunoreactive lesions including neuronal cytoplasmic inclusions, dystrophic neurites, and neuronal intranuclear inclusions typically reported in FTLTD [18, 28], as well as less common lesions such as perivascular inclusions [29] and TDP-43 associated with NFT [30]. We also determined TDP-43 stage I-VI based on the published criteria [11,31].

2.4. MRI analyses

All patients had undergone a standard MRI protocol during life, as previously described [32]. All patients were scanned on a GE scanner using the same standardized protocol. There was no significant difference in GE scanner model or software between the groups. All our scanners undergo a standardized quality control calibration procedure daily, which monitors geometric fidelity over a 200-mm volume along all three cardinal axes, signal-to-noise, and transmit gain and maintains the scanner within a tight calibration range. All MRI scans underwent corrections for intensity inhomogeneity and gradient unwarping [33] before analysis. Voxel-level comparisons of MRI gray matter volumes were performed using SPM12. All MRI scans were normalized to the Mayo Clinic Adult Lifespan Template (<https://www.nitrc.org/projects/mcalt/>) and segmented into gray matter, white matter, and cerebrospinal fluid using the Mayo Clinic Adult Lifespan Template and priors via unified segmentation [34]. Gray matter images were modulated and smoothed with an 8-mm full-width at half maximum smoothing kernel. Voxel-level t-tests were performed to compare the TDP-43(+) and TDP-43(-) PART cases, with age at death, Braak NFT stage, and total intracranial volume (TIV) included as covariates. Results were assessed using a cluster-level correction for multiple comparisons at $P < .05$.

We also used FreeSurfer version 5.3.0 [35] to measure volumes of the amygdala, hippocampus, lateral temporal cortex (inferior, middle, superior temporal cortex), parietal (inferior parietal, supramarginal, and isthmus cingulate cortex) and lateral superior frontal cortex, and outputted TIV to allow for the correction of head size [36]. In this analysis, we combined right and left hemisphere volumes.

For both the voxel-level analysis and the region of interest analysis, if more than one MRI had been performed, we analyzed the MRI closest to death.

2.5. Statistical analyses

We compared demographic, pathological, and clinical variables between TDP-43(+) and TDP-43(-) cases using Fisher's Exact or Wilcoxon rank-sum tests where appropriate. $P < .05$ was considered statistically significant. We also fitted a linear regression on log-transformed volume adjusting for age at death, TIV, and Braak NFT stage to assess for relationships between TDP-43 and brain volume (the amygdala, hippocampus, lateral

temporal cortex, parietal cortex, and frontal cortex). For this analysis, we combined right and left hemisphere volumes.

All analyses were performed using R statistical software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of the 116 PART cases, 31 (26.7%) screened positive for TDP-43 (TDP-43(+)) while the remaining 85 PART cases were TDP-43 negative (TDP-43(-)). Demographic, pathological, and clinical details of the 31 TDP-43(+) PART cases and the 85 TDP-43(-) PART cases are shown in Table 1. There was a higher number of female patients among the TDP-43(+) cases than among the TDP-43(-) cases ($P = .05$). The TDP-43(+) cases were older at the time of MRI scan than the TDP-43(-) cases ($P = .04$). There were no differences in pathological features between those with and without TDP-43. Of the 31 TDP-43(+) cases, 11 (35%) had hippocampal sclerosis. The most frequent TDP-43 stage was stage 1 (involvement of the amygdala only occurred in 15 cases; 48%). Ten percent of the cases were stage 6 involving the frontal cortex. It should be pointed out that in most cases, the burden of TDP-43 deposition was scant to minimal regardless of stage. In fact, there were a handful of regions considered affected where a single TDP-43 immunoreactive inclusion was identified. In addition, in most cases, the lesion type was perivascular [29]. TDP-43 associated with NFT known as TDP-43 type β [37] was the least common type of lesion observed. There was no significant difference in the final clinical diagnoses rendered before death or in the Mini-Mental State Examination [38] or Clinical Dementia Rating Scale sum of boxes [39] scores at the last examination before death.

In the voxel-level MRI analysis, we found that the TDP-43(+) cases had smaller gray matter volumes in an area encompassing the left hippocampus, amygdala, and anterior temporal lobe than the TDP-43(-) cases (Fig. 1). In the region-level analysis, we found the presence of TDP-43 to be associated with smaller volumes of the amygdala and hippocampus, as well as the lateral temporal lobe (Table 2, Fig. 2). Our analysis showed that TDP-43(+) cases, on average, had an estimate of -8.38% (-15.6%, -1.19%) less amygdala volume than TDP-43(-) cases ($P = .02$). For the hippocampus, TDP-43(+) case, on average, had an estimate of -10.9% (-17.4%, -4.43%) less hippocampal volume than TDP-43(-) cases ($P = .001$). For lateral temporal cortex, TDP-43(+) cases, on average, had an estimate of -6.92% (-13.3%, -0.54%) less lateral temporal volume than TDP-43(-) cases ($P = .03$). We did not see significant differences in parietal and superior frontal cortices.

4. Discussion

In this study that included asymptomatic and symptomatic definite and possible PART, we found convincing evidence, in two different imaging analyses, that TDP-43 is associated with brain atrophy in the amygdala and hippocampus, as well as in the lateral temporal neocortex.

In our previous study, we had limited our PART cohort to asymptomatic definite PART, that is, cases without any A β deposition (Thal phase 0) that were cognitively normal at the time

of final evaluation before death [9]. We did not see any effect of TDP-43 on brain atrophy in that study. The biggest difference between our previous PART study and this PART study is the inclusion of cases with cognitive impairment. In retrospect, it is no surprise that we did not find any evidence for an association between TDP-43 and brain atrophy in asymptomatic definite PART because cases without cognitive impairment will likely have less brain atrophy and a much more narrow range of volumes. Furthermore, because TDP-43 is associated with cognitive impairment, we would have essentially excluded the effect of TDP-43. The present study provides a more representative cohort of PART cases by including both symptomatic and asymptomatic cases. In this cohort, we found TDP-43 to be strikingly associated with amygdala and hippocampal atrophy. This finding is identical to what we have found in cases diagnosed with higher burdens of A β deposition and NFT distribution, that is, intermediate to high probability Alzheimer's disease [17]. Therefore, regardless of whether PART is separate from Alzheimer's disease or PART is a part of Alzheimer's disease [40], TDP-43 is associated with medial temporal lobe atrophy across the entire range and in all combinations of A β and NFT deposition. We have previously demonstrated that TDP-43 is also associated with faster rates of amygdala and hippocampal atrophy in Alzheimer's disease (i.e., those with higher levels of A β deposition and NFT distribution [Braak IV-VI]), and it is very likely that TDP-43 is also associated with faster rates of amygdala and hippocampal atrophy in PART; however, future longitudinal studies will be needed to address this hypothesis.

We also found some evidence for TDP-43 to be associated with atrophy in other regions of the temporal lobe, with lateral temporal identified in the region-level analysis and anterior temporal regions identified in the voxel-level analysis. This may reflect the fact that more than one-third of the TDP-43(+) cohort had a high TDP-43 stage (stage IV-VI), reflecting spread of TDP-43 into the temporal cortex. It should be pointed out that TDP-43 deposition in the anterior temporal lobe has been reported [41]. We did not, however, see any TDP-43 associations with parietal and frontal regions, possibly due to the fact that these regions are either not involved, minimally involved, or involved later in the TDP-43 staging scheme [31,42]. Another interesting finding from our voxel-level analysis was the asymmetry of the atrophy observed in the TDP-43(+) cases. The result suggests that in PART, there is a predilection for TDP-43 to be associated with atrophy of the left anteromedial temporal lobe structures compared with the right. We do not have a biological explanation for this finding of asymmetry, and autopsy studies are unhelpful in this regard as autopsy studies almost always assess only one brain hemisphere. Interestingly, we found TDP-43 to be associated with a bilateral pattern of atrophy in Alzheimer's disease (Braak NFT stage IV-VI) [11]. It should be pointed out that TDP-43 in the FTLDS is often associated with asymmetric atrophy. TDP-43 type A pathology, due to mutations in the *granulin* gene, and TDP-43 type C pathology that is associated with a clinical diagnosis of semantic dementia, are associated with striking asymmetric atrophy [43,44]. In fact, in TDP-43 type C pathology, atrophy targets the anteromedial temporal lobe atrophy similar to what we see in PART. Over time, however, we observe spreading of the atrophy to involve the right anteromedial temporal lobe [45]. It remains to be determined whether we see a similar pattern of spread over time of the TDP-43-associated atrophy in PART.

In this study, we found the frequency of TDP-43 deposition to be 27%. This is similar to the frequency of 29% that we reported in asymptomatic definite PART [9] and the frequency reported in definite PART from another group (32%) [46]. With that said, in our experience, the frequency of TDP-43 in PART is significantly lower than the frequency in Alzheimer's disease. In Alzheimer's disease, we and others have found frequencies of TDP-43 deposition in the range of 50%-70%, when the amygdala is screened [11,42,47,48]. In fact, one study reported a frequency even greater than 70% in Alzheimer's disease [49]. We applied the TDP-43 staging scheme in the 31 TDP-43(+) cases in this study. We found 67% of the cases were TDP-43 stage 1-3, of which a vast majority (48%) were stage 1 [31]. This is much lower than the frequency we found in asymptomatic definite PART in which 100% of the cases were stage 1-3 [9]. Two other studies have applied the TDP-43 staging scheme in PART [15,46]. In one of those studies [15], the investigators reported a similar spread of TDP-43 to ours, with TDP-43 being most frequent in the amygdala, followed by hippocampus, neocortex, and basal ganglia [15]. However, in the other study [46], a high frequency of isolated TDP-43 in the medulla was reported. In fact, in that second study, the medulla was the most affected region, although the amygdala had been screened. We do not have an explanation for the difference in the regional predilection between both the studies. Future collaborative studies are now needed to further understand these differences observed between different centers.

We did find 10% of our PART cases to involve TDP-43 stage 6. Given that we did not identify any stage 4-6 cases in our previous study of asymptomatic definite PART in which A β was not present, the findings from this present study suggest that TDP-43 may be more widely distributed in PART in the presence of A β , that is, those with possible PART. This observation is unlikely to be driven by the APOE ϵ 4 genotype given that the frequency of the ϵ 4 genotype in definite PART was 20% [9], which is similar to the frequency of 19% occurring in this study. The difference is also unlikely to be due to age at death because although older age has been reported to be associated with higher TDP-43 stage [46], the average age of death in the asymptomatic definite PART cohort and this cohort was identical at 91 years. One possible explanation could be the inclusion of symptomatic cases in this study as symptomatic PART is more likely in the presence of amyloid [8]. This may suggest that symptomatic PART may be linked to TDP-43 extending beyond limbic regions. Given our recent report of two types of TDP-43, type α and type β , and that type α is characterized by higher TDP-43 stages [37], it is possible that TDP-43 in symptomatic PART is different from TDP-43 in asymptomatic definite PART.

The only difference in demographic features in PART was that cases with TDP-43 were associated with female sex. This is most likely due to the fact the cases with TDP-43 were older at death, as there is a well-known association between female sex and older age at death. It is unlikely that female sex was driving our findings, however, as it is male sex that has been shown to be associated with smaller hippocampal volumes [50]. The only difference in pathological lesions identified between those with and without TDP-43 was the presence of degenerative hippocampal sclerosis (HpScl) being higher in those with TDP-43. This finding is unsurprising, however, given that, by definition, degenerative HpScl requires the presence of TDP-43 [26]. In addition, although we used this definition of HpScl in our study with the intention of distinguishing HpScl that is degenerative in nature from HpScl

associated with epilepsy [51] and with vascular disease [52], not everyone in the field agrees with this definition.

In summary, we have demonstrated that TDP-43 is associated with brain atrophy, particularly focused in the left anteromedial temporal lobe structures, in PART. Taken together with previous findings of TDP-43 being associated with atrophy in Alzheimer's disease, it is now apparent that TDP-43 is associated with brain atrophy across the entire spectrum of A β - and NFT-related pathologies. This should be considered when interpreting the presence of neurodegeneration [53] both in patients with and without evidence of A β deposition.

Acknowledgment

This study was funded by the following grants from the US National Institutes of Health (National Institute on Aging): R01 AG037491, P50 AG16574, and U01 AG006786. The authors thank the families of the patients who donated their brains to science and thus allowed completion of this study. The authors would also like to acknowledge Dr. Hugo Botha, Mayo Clinic, Rochester, MN, for the creation of Fig. 1.

References

- [1]. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): A common pathology associated with human aging. *Acta Neuropathol* 2014;128:755–66. [PubMed: 25348064]
- [2]. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991;82:239–59. [PubMed: 1759558]
- [3]. Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 2002;58:1791–800. [PubMed: 12084879]
- [4]. Jellinger KA, Alafuzoff I, Attems J, Beach TG, Cairns NJ, Crary JF, et al. PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. *Acta Neuropathol* 2015;129:757–62. [PubMed: 25778618]
- [5]. Ulrich J, Spillantini MG, Goedert M, Dukas L, Stahelin H. Abundant neurofibrillary tangles without senile plaques in a subset of patients with senile dementia. *Neurodegeneration* 1992;1:257–84.
- [6]. Bancher C, Egnesperger R, Kosel S, Jellinger K, Graeber MB. Low prevalence of apolipoprotein E epsilon 4 allele in the neurofibrillary tangle predominant form of senile dementia. *Acta neuropathologica* 1997;94:403–9. [PubMed: 9386771]
- [7]. Jellinger KA, Bancher C. Senile dementia with tangles (tangle predominant form of senile dementia). *Brain Pathol* 1998;8:367–76. [PubMed: 9546293]
- [8]. Besser LM, Crary JF, Mock C, Kukull WA. Comparison of symptomatic and asymptomatic persons with primary age-related tauopathy. *Neurology* 2017;89:1707–15. [PubMed: 28916532]
- [9]. Josephs KA, Murray ME, Tosakulwong N, Whitwell JL, Knopman DS, Machulda MM, et al. Tau aggregation influences cognition and hippocampal atrophy in the absence of beta-amyloid: A clinico-imaging-pathological study of primary age-related tauopathy (PART). *Acta Neuropathol* 2017;133:705–15. [PubMed: 28160067]
- [10]. Jefferson-George KS, Wolk DA, Lee EB, McMillan CT. Cognitive decline associated with pathological burden in primary age-related tauopathy. *Alzheimers Dement* 2017;13:1048–53. [PubMed: 28322204]
- [11]. Josephs KA, Whitwell JL, Weigand SD, Murray ME, Tosakulwong N, Liesinger AM, et al. TDP-43 is a key player in the clinical features associated with Alzheimer's disease. *Acta Neuropathol* 2014;127:811–24. [PubMed: 24659241]
- [12]. Nag S, Yu L, Wilson RS, Chen EY, Bennett DA, Schneider JA. TDP-43 pathology and memory impairment in elders without pathologic diagnoses of AD or FTL. *Neurology* 2017;88:653–60. [PubMed: 28087828]

- [13]. Wilson RS, Yu L, Trojanowski JQ, Chen EY, Boyle PA, Bennett DA, et al. TDP-43 pathology, cognitive decline, and dementia in old age. *JAMA Neurol* 2013;70:1418–24. [PubMed: 24080705]
- [14]. Josephs KA, Dickson DW, Tosakulwong N, Weigand SD, Murray ME, Petrucelli L, et al. Rates of hippocampal atrophy and presence of postmortem TDP-43 in patients with Alzheimer's disease: A longitudinal retrospective study. *Lancet Neurol* 2017;16:917–24. [PubMed: 28919059]
- [15]. Zhang X, Sun B, Wang X, Lu H, Shao F, Rozemuller AJM, et al. Phosphorylated TDP-43 staging of primary age-related tauopathy. *Neurosci Bull* 2019;35:183–92. [PubMed: 30382507]
- [16]. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991;41:479–86. [PubMed: 2011243]
- [17]. Working group. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute working group on diagnostic criteria for the neuropathological assessment of Alzheimer's disease. *Neurobiol Aging* 1997;18:S1–2. [PubMed: 9330978]
- [18]. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. *Acta Neuropathol* 2010;119:1–4. [PubMed: 19924424]
- [19]. Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology* 1994;44:2015–9. [PubMed: 7969952]
- [20]. Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, et al. Office of rare diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol* 2002;61:935–46. [PubMed: 12430710]
- [21]. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. *Neurology* 2005;65:1863–72. [PubMed: 16237129]
- [22]. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183–94. [PubMed: 15324362]
- [23]. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9. [PubMed: 21514250]
- [24]. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. *Arch Gen Psychiatry* 1983;40:812. [PubMed: 6860082]
- [25]. Mattis S Dementia rating scale: Professional Manual 1988. Odessa, FL: Psychological Assessment Resources; 1988.
- [26]. Murray ME, Cannon A, Graff-Radford NR, Liesinger AM, Rutherford NJ, Ross OA, et al. Differential clinicopathologic and genetic features of late-onset amnesic dementias. *Acta Neuropathol* 2014;128:411–21. [PubMed: 24899141]
- [27]. Hu WT, Josephs KA, Knopman DS, Boeve BF, Dickson DW, Petersen RC, et al. Temporal lobar predominance of TDP-43 neuronal cytoplasmic inclusions in Alzheimer disease. *Acta neuropathologica* 2008;116:215–20. [PubMed: 18592255]
- [28]. Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, et al. A harmonized classification system for FTL-D-TDP pathology. *Acta Neuropathol* 2011;122:111–3. [PubMed: 21644037]
- [29]. Lin WL, Castanedes-Casey M, Dickson DW. Transactivation response DNA-binding protein 43 microvasculopathy in frontotemporal degeneration and familial Lewy body disease. *J Neuropathol Exp Neurol* 2009;68:1167–76. [PubMed: 19816201]
- [30]. Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann Neurol* 2007;61:435–45. [PubMed: 17469117]

- [31]. Josephs KA, Murray ME, Whitwell JL, Tosakulwong N, Weigand SD, Petrucelli L, et al. Updated TDP-43 in Alzheimer's disease staging scheme. *Acta Neuropathol* 2016;131:571–85. [PubMed: 26810071]
- [32]. Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain* 2008;131:665–80. [PubMed: 18263627]
- [33]. Jovicich J, Czanner S, Greve D, Haley E, van der Kouwe A, Gollub R, et al. Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. *Neuroimage* 2006;30:436–43. [PubMed: 16300968]
- [34]. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005;26:839–51. [PubMed: 15955494]
- [35]. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002;33:341–55. [PubMed: 11832223]
- [36]. Whitwell JL, Crum WR, Watt HC, Fox NC. Normalization of cerebral volumes by use of intracranial volume: Implications for longitudinal quantitative MR imaging. *AJNR Am J Neuroradiol* 2001;22:1483–9. [PubMed: 11559495]
- [37]. Josephs KA, Murray ME, Tosakulwong N, Weigand SD, Serie AM, Perkerson RB, et al. Pathological, imaging and genetic characteristics support the existence of distinct TDP-43 types in non-FTLD brains. *Acta Neuropathol* 2019;137:227–38. [PubMed: 30604226]
- [38]. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98. [PubMed: 1202204]
- [39]. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* 1993;43:2412–4.
- [40]. Duyckaerts C, Braak H, Brion JP, Buee L, Del Tredici K, Goedert M, et al. PART is part of Alzheimer disease. *Acta Neuropathol* 2015;129:749–56. [PubMed: 25628035]
- [41]. Nag S, Yu L, Boyle PA, Leurgans SE, Bennett DA, Schneider JA. TDP-43 pathology in anterior temporal pole cortex in aging and Alzheimer's disease. *Acta Neuropathol Commun* 2018;6:33. [PubMed: 29716643]
- [42]. Josephs KA, Murray ME, Whitwell JL, Parisi JE, Petrucelli L, Jack CR, et al. Staging TDP-43 pathology in Alzheimer's disease. *Acta Neuropathol* 2014;127:441–50. [PubMed: 24240737]
- [43]. Whitwell JL, Jack CR Jr, Parisi JE, Senjem ML, Knopman DS, Boeve BF, et al. Does TDP-43 type confer a distinct pattern of atrophy in frontotemporal lobar degeneration? *Neurology* 2010;75:2212–20. [PubMed: 21172844]
- [44]. Rohrer JD, Geser F, Zhou J, Gennatas ED, Sidhu M, Trojanowski JQ, et al. TDP-43 subtypes are associated with distinct atrophy patterns in frontotemporal dementia. *Neurology* 2010;75:2204–11. [PubMed: 21172843]
- [45]. Whitwell JL, Anderson VM, Scahill RI, Rossor MN, Fox NC. Longitudinal patterns of regional change on volumetric MRI in frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* 2004;17:307–10. [PubMed: 15178942]
- [46]. Elobeid A, Libard S, Leino M, Popova SN, Alafuzoff I. Altered proteins in the aging brain. *J Neuropathol Exp Neurol* 2016;75:316–25. [PubMed: 26979082]
- [47]. Josephs KA, Whitwell JL, Tosakulwong N, Weigand SD, Murray ME, Liesinger AM, et al. TAR DNA-binding protein 43 and pathological subtype of Alzheimer's disease impact clinical features. *Ann Neurol* 2015;78:697–709. [PubMed: 26224156]
- [48]. Ihara R, Vincent BD, Baxter MR, Franklin EE, Hassenstab JJ, Xiong C, et al. Relative neuron loss in hippocampal sclerosis of aging and Alzheimer's disease. *Ann Neurol* 2018;84:741–53. [PubMed: 30246887]
- [49]. McAleese KE, Walker L, Erskine D, Thomas AJ, McKeith IG, Attems J. TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing. *Brain Pathol* 2017;27:472–9. [PubMed: 27495267]
- [50]. Jack CR Jr, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, et al. Age, Sex, and APOE epsilon4 effects on memory, brain structure, and beta-Amyloid across the adult life span. *JAMA Neurol* 2015;72:511–9. [PubMed: 25775353]

- [51]. Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. *N Engl J Med* 2017;377:1648–56. [PubMed: 29069555]
- [52]. Ferrer I, Vidal N. Neuropathology of cerebrovascular diseases. *Handb Clin Neurol* 2017;145:79–114. [PubMed: 28987197]
- [53]. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. *Alzheimers Dement* 2018;14:535–62. [PubMed: 29653606]

RESEARCH IN CONTEXT

1. Systemic review: The authors reviewed literature using PubMed for all studies on primary age-related tauopathy (PART) and for all studies that had assessed for association between transactive response DNA-binding protein of 43 kDa (TDP-43) and brain atrophy in Alzheimer's disease. TDP has been shown to be associated with brain atrophy in Alzheimer's disease, but one study of PART limited to asymptomatic β -amyloid negative PART did not find an association. No study had assessed for the association of TDP-43 and brain atrophy across the entire spectrum of symptomatic and asymptomatic definite and possible PART.
2. Interpretation: In this study across the entire spectrum of PART, we found the presence of TDP-43 to be associated with greater atrophy of the left amygdala, hippocampus, and anterior temporal lobe.
3. Future directions: The finding extends the importance of TDP-43 across all neurofibrillary tangle-related diseases including PART. Future studies are now needed to determine the effect of TDP-43 in PART and whether dementia in PART is largely due to TDP-43.

Fig. 1.

Voxel level analysis comparing PART cases with and without TDP-43. Three dimensional cut-out brain renders demonstrate atrophy (shown in red) in a region involving the left amygdala, hippocampus, and anterior temporal lobe in TDP-43(+) cases compared to TDP-43(-) cases. Images shown corrected for multiple comparisons at the cluster level at $P < .05$. Abbreviations: TDP-43, transactive response DNA-binding protein of 43 kDa; PART, primary age-related tauopathy.

Fig. 2.

Association between TDP-43 and brain volumes. The plot shows the confidence interval and degree of significance shown as distance from the vertical line at 0 after fitting a linear regression model adjusting for Braak NFT stage, age at death, and total intracranial volume. Abbreviations: TDP-43, transactive response DNA-binding protein of 43 kDa; NFT, neurofibrillary tangle.

Table 1

Demographic, clinical, and pathological features

Variable of interest	TDP-43(+) PART (N = 31)	TDP-43(-) PART (N = 85)	P value
No. of female cases, n (%)	17 (55)	28 (33)	.05
No. of APOE ε4 carriers, n (%)	6 (19)	14 (16)	.78
Age at scan, yrs	85 (75, 93)	82 (62, 99)	.04
Age at death, yrs	91 (76, 98)	86 (62, 103)	.07
Pathology information			
TDP-43(+) HpScl, n (%)	11 (35)	0 (0)	N/A
TDP-43(-) HpScl, n (%)	20 (65)	0 (0)	
Lewy body disease, n (%)	3 (15)	16 (23)	.55
TDP-43 distribution, n (%)			
Stage 1	15 (48)		
Stage 2	1 (3)		
Stage 3	4 (13)		
Stage 4	2 (6)		
Stage 5	6 (19)		
Stage 6	3 (10)		
NFT distribution, n (%)			>.99
Braak NFT stage 1	5 (16)	15 (18)	
Braak NFT stage 2	16 (52)	44 (52)	
Braak NFT stage 3	10 (32)	26 (31)	
β-amyloid, n (%)			.51
CERAD stage 0	22 (71)	53 (62)	
CERAD stage 1	9 (29)	32 (38)	
Vascular disease, n (%)	6 (30)	25 (36)	.79
Clinical information			
Last diagnosis, n (%)			.39
Cognitive normal	18 (60)	50 (60)	
MCI	5 (17)	15 (18)	
Alzheimer's dementia	3 (10)	2 (2)	

Variable of interest	TDP-43(+) PART (N = 31)	TDP-43(−) PART (N = 85)	P value
Other dementia	4 (13)	16 (19)	
MMSE	25 (4, 30)	27 (10, 30)	.38
CDRSUM	0.0 (0.0, 18.0)	0.0 (0.0, 17.0)	.98

NOTE. Data shown are n (%) or median (range).

Abbreviations: APOE, apolipoprotein; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; CDRSUM, Clinical Dementia Rating Scale sum of boxes; HpScl, hippocampal sclerosis; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NFT, neurofibrillary tangles; TDP, transactive response DNA-binding protein; PART, primary age-related tauopathy; N/A, not available.

Table 2Estimates (95% CI) with *P* values from linear regression results

Region-of-interest	Estimate (95% CI)	<i>P</i> value
Amygdala	−8.38 (−15.6, −1.19)	.02
Hippocampus	−10.9 (−17.4, −4.43)	.001
Lateral temporal	−6.92 (−13.3, −0.54)	.03
Parietal	−3.77 (−10.6, 3.09)	.28
Superior frontal	−4.21 (−10.7, 2.29)	.20

Abbreviations: CI, confidence interval.