Received: 28 October 2021 | Accepted: 27 January 2022

DOI: 10.1111/ene.15270

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Antemortem basal forebrain atrophy in pure limbic TAR DNA-binding protein 43 pathology compared with pure Alzheimer pathology

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Funding information
Miguel Servet" program, Grant/Award Number: CP19/00031; Instituto de Salud Carlos III – IFondo Europeo de Desarrollo Regional, Grant/Award Number: PI20/00613; Bundesministerium für Bildung und Forschung, Grant/Award Number: 01KX2130

Abstract

Background and purpose: Currently, the extent of cholinergic basal forebrain atrophy in relatively pure limbic TAR DNA-binding protein 43 (TDP-43) pathology compared with relatively pure Alzheimer disease (AD) is unclear.

Methods: We compared antemortem magnetic resonance imaging (MRI)-based atrophy of the basal forebrain and medial and lateral temporal lobe volumes between 10 autopsy cases with limbic TDP-43 pathology and 33 cases with AD pathology on postmortem neuropathologic examination from the Alzheimer's Disease Neuroimaging Initiative cohort. For reference, we studied MRI volumes from cognitively healthy, amyloid positron emission tomography-negative subjects ($n = 145$). Group differences were assessed using Bayesian analysis of covariance. In addition, we assessed brain-wide regional volume changes using partial least squares regression (PLSR).

Results: We found extreme evidence (Bayes factor $[BF]_{01} > 600$) for a smaller basal forebrain volume in both TDP-43 and AD cases compared with amyloid-negative controls, and moderate evidence ($BF_{01} = 4.9$) that basal forebrain volume was not larger in TDP-43 than in AD cases. The ratio of hippocampus to lateral temporal lobe volumes discriminated between TDP-43 and AD cases with an accuracy of 0.78. PLSR showed higher gray matter in lateral temporal lobes and cingulate and precuneus, and reduced gray matter in precentral and postcentral gyri and hippocampus in TDP-43 compared with AD cases.

Conclusions: Atrophy of the cholinergic basal forebrain appears to be similarly pronounced in cases with limbic TDP-43 pathology as in AD. This suggests that a clinical trial of the efficacy of cholinesterase inhibitors in amyloid-negative cases with amnestic dementia and an imaging signature of TDP-43 pathology may be warranted.

KEYWORDS
AD pathology, autopsy, cholinergic deficit, imaging signature, limbic TDP-43, MRI

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

INTRODUCTION

Presence of TAR DNA-binding protein 43 (TDP-43) in the medial temporal lobe and limbic system is a frequent copathology of Alzheimer disease (AD) that was found to be associated with an amnestic dementia phenotype, more pronounced hippocampus atrophy [1], and faster progression of brain atrophy compared with AD pathology alone [2]. In 2019, an international consensus group defined a neuropathological entity of limbic TDP-43 even in absence of AD pathology, which was named neuropathological change of limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) [3]. It remains controversial whether LATE-NC is only part of a neuropathological continuum between AD and TDP-43 pathology or represents the pathological basis of a distinct nosological entity called LATE [4,5].

Albeit a large range of studies have investigated clinical and brain changes associated with combined TDP-43 and AD pathology, comparisons of patterns of brain atrophy in relatively pure limbic TDP-43 pathology (i.e., without significant AD pathology) compared with relatively pure AD pathology (i.e., without relevant TDP-43 pathology) are still rare. Particularly, we lack studies on differences in the degree of cholinergic basal forebrain atrophy in limbic TDP-43 cases without significant AD pathology. The early and selective atrophy of cholinergic neurons in the basal forebrain of AD cases [6] serves as the pathogenic rationale for the symptomatic cholinergic treatment of AD dementia [7]. Thus, demonstration of a similar degree of cholinergic basal forebrain atrophy in limbic TDP-43 cases compared with AD would inform regarding whether cholinergic treatment may be beneficial in these cases.

Two recent developments make this question even more relevant. First, evidence suggests that fluorodeoxyglucose positron emission tomography (FDG-PET)-based markers may be useful to determine whether limbic TDP-43 pathology is present [8]. Such a signature could be used to confirm the presence of limbic TDP-43 pathology in the setting of clinical diagnostics. Second, with the advent of targeted amyloid therapies, such as the antiamyloid antibody aducanumab, approved by the US Food and Drug Administration (FDA) in June 2021 for the treatment of AD, testing for the presence or absence of amyloid pathology using PET or cerebrospinal fluid (CSF) will become increasingly common in the diagnostic workup of individuals with amnestic dementia. The question arises of whether people with amnestic dementia syndromes who are amyloid-negative and have an imaging signature of limbic TDP-43 should still receive antidementia treatment with a cholinesterase inhibitor even though their biomarker signature precludes the presence of AD pathology. For practical purposes, the question is whether clinical and pathologic data can provide evidence that a clinical trial of cholinesterase inhibitors for limbic TDP-43 pathology without significant AD pathology is or is not warranted.

Here, we used the latest data freeze of the Alzheimer's Disease Neuroimaging Initiative (ADNI) autopsy cohort (May 2021) consisting of 81 cases to identify subsets of relatively pure limbic TDP-43 or pure AD cases. We compared the extent of atrophy of the cholinergic basal forebrain between the two groups based on the last available antemortem magnetic resonance imaging (MRI) scan. We used a Bayesian approach that allowed us to directly quantify the evidence for or against a volume difference. In addition, we performed hypothesis-driven analyses of medial temporal lobe volumes to extend previous findings of a synergistic effect of limbic TDP-43 pathology together with AD pathology. We also examined whether lateral temporal lobe volumes were relatively preserved based on previous findings that lateral temporal lobe glucose metabolism was relatively spared in amnestic dementia cases with autopsy-confirmed TDP-43 pathology and hippocampal sclerosis as well as in tau-PET-negative dementia cases [9]. We investigated whether a ratio between the volumes of the medial temporal lobe and the lateral temporal lobes could serve as a potential volumetric signature to distinguish limbic TDP-43 and AD cases. Finally, we used partial least squares regression to examine brain-wide gray matter volume changes in limbic TDP-43 compared with AD cases.

METHODS

Data source

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu/). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the FDA, private pharmaceutical companies, and nonprofit organizations, with the primary goal of testing whether neuroimaging, neuropsychological, and other biologic measurements can be used as reliable in vivo markers of AD pathogenesis. A fuller description of ADNI and up-to-date information are available at www.adni-info.org.

All procedures performed in the ADNI studies involving human participants were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the ADNI studies.

Study participants

We retrieved the last available MRI scans of 81 ADNI subjects who had come to autopsy between 2007 and 2021. For comparison, we also retrieved the MRI data of a group of 145 healthy control participants from ADNI who were amyloid negative according to the global evaluation of the corresponding amyloid-sensitive AV45-PET scan.

Detailed inclusion criteria for the antemortem diagnostic categories can be found at the ADNI web site (http://adni.loni.usc.edu/methods/). Cognitively normal subjects had Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), had a Clinical Dementia Rating (CDR) = 0, were nondepressed, did

not have mild cognitive impairment (MCI), were nondemented, and reported no subjective memory concerns. MCI subjects had MMSE scores between 24 and 30 (inclusive); a subjective memory concern reported by subject, informant, or clinician; objective memory loss measured by education-adjusted scores on delayed recall, a CDR = 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living; and absence of dementia. At inclusion into the ADNI cohort, subjects with AD dementia had initial MMSE scores between 20 and 26 (inclusive) and a CDR = 0.5 or 1.0, with impaired activities of daily living, and fulfilled National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for clinically probable AD [10].

Neuropathological assessments

All neuropathological evaluations in the ADNI cohort are performed through the central laboratory of the ADNI neuropathology core (http://adni.loni.usc.edu/about/#core-container) [11]. The neuropathological procedures follow previously established guidelines [12] that are captured in the format of the Neuropathology Data Form Version 10 of the National Alzheimer Coordinating Center (https://www.alz.washington.edu/NONMEMBER/NP/npform10.pdf).

Here, we applied established rating scales for the presence of TDP-43 pathology and AD pathology, respectively. Cases were classified as relatively pure TDP-43 if they had TDP-43 pathology in at least two of the four regions of amygdala, hippocampus, entorhinal/inferior temporal cortex, or neocortex (TDP-43 sum score ≥ 2), and a National Institute on Aging/Alzheimer's Association AD neuropathologic change (ADNC) score < 2, indicating no or low presence of AD pathology. In contrast, cases were classified as pure AD if they had an ADNC score ≥ 2, indicating at least moderate presence of AD pathology, and a TDP-43 sum score of 0, indicating no TDP-43 pathology in any of the four regions. Hippocampal sclerosis was assessed as well, indicating presence of unilateral or bilateral involvement.

Imaging data acquisition

Detailed acquisition and standardized preprocessing steps of ADNI imaging data are available at the ADNI website (https://adni.loni.usc.edu/methods/). Structural MRI scans were acquired on multiple 1.5-T and 3-T MRI scanners using scanner-specific T1-weighted sagittal three-dimensional magnetization-prepared rapid acquisition gradient echo sequences. MRI scans undergo standardized preprocessing steps aimed at increasing data uniformity across the multicenter scanner platforms (see https://adni.loni.usc.edu/methods/ for detailed information on multicentric MRI acquisition and preprocessing in ADNI).

Imaging data preprocessing

Images were preprocessed using Statistical Parametric Mapping software version 12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London) implemented in MATLAB 2019. MRI images were segmented into different tissue types and spatially normalized to the Montreal Neurological Institute (MNI) template as implemented in the CAT12 toolbox.

Medial as well as inferior and lateral temporal lobe volumes, including hippocampus and inferior and middle temporal gyrus, were derived from the spatially normalized MRI scans using the Hammers atlas masks. We localized the cholinergic space of the basal forebrain based on a cytoarchitectonic map of basal forebrain cholinergic nuclei in MNI space, derived from combined histology and MRI of a postmortem brain, as described previously [13]. All volumes were scaled to each individual's total intracranial volume.

Statistical analysis

We used Bayesian Student *t*-test to compare volumes between healthy control, TDP-43, and AD groups, after covarying out age, sex, and time between MRI scanning and death from the volumes. We used BF hypothesis testing to compare the alternative hypothesis of an effect against the null hypothesis (i.e., the assumption that there is no effect of group, H_0) [14,15], as implemented in Jeffreys' Amazing Statistics Program (v0.14.3), available at jasp-stats.org.

For basal forebrain volume, our alternative hypothesis was that BF was larger in TDP-43 than in AD cases; for hippocampal volume, the alternative hypothesis was that the volume was smaller in TDP-43 than in AD cases; and for inferior and middle temporal lobe volume, the alternative hypothesis was that volume was larger in TDP-43 than in AD cases.

We report the BF_{01} quantifying evidence in favor of the null hypotheses. BF hypothesis testing inferences are mutually consistent with each participant's data contribution through continuous updating of the prior distribution [15]. Three conclusions are possible within the Bayesian framework [15]: support for either alternative hypothesis ($BF_{01} \leq 0.33$), support for the null hypothesis ($BF_{01} > 3$), or inconclusive evidence (BF_{01} between 0.33 and 3).

We used the area under the receiver operating characteristic (ROC) curve (AUC) to estimate the volume's ability to predict group membership (TDP-43 vs. AD). ROC analysis was done using the library ROCnReg in R, allowing for Bayesian estimates of credibility intervals for the areas under the ROC curves and calculation of conditional ROC curves.

Finally, to determine the structural covariance of the group membership with brain-wide regional gray matter volumes, we used partial least squares (PLS) analysis [16]. This approach operates on the covariance between brain voxels and allows assessment of an integrated network of brain regions that together covaries with some external measure [17], here, the group membership. PLS yields a new set of variables, the so-called latent variables (LVs),

where each LV identifies a pattern of brain regions structurally connected with group. Each voxel of the brain has a weight on each LV, called the salience of this voxel on the LV. The significance of each LV has been assessed using permutation tests with 100 permutations at a $p < 0.05$ threshold. In addition, we used bootstrap estimation (with 100 bootstrap iterations) to determine the reliability of the saliences for the brain voxels determining each LV. The bootstrap ratios of salience follow a standard z-score distribution, where a ratio of >1.96 corresponds to a p value of <0.05, and a ratio of >2.58 to a p value of <0.01. In contrast to univariate analysis, the permutation tests and the saliences were determined in a single analytical step so that there is no need for multiple comparison correction.

RESULTS

Demographics

From the 81 cases available, we identified 10 cases with a TDP-43 sum score ≥ 2 and an ADNC score < 2, labeled TDP-43 cases, and 33 cases with a TDP-43 score = 0 and an ADNC score ≥ 2, labeled AD cases. An additional five cases had TDP-43 in only one region (three in entorhinal inferior temporal cortex and two in amygdala), that is, TDP-43 score = 1. Four of these cases had an ADNC score of 3, and one case had an ADNC score of 1. We excluded these five cases from the analysis.

Of the 10 TDP-43 cases, one had unilateral hippocampal sclerosis, and two had hippocampal sclerosis where laterality had not been assessed. None of the AD cases had hippocampal sclerosis. Demographics of both pathologically defined groups are displayed in Table 1. The amyloid-negative healthy control participants from ADNI who served as reference group for basal forebrain volume had 72 women and 73 men; mean age was 73.0 years, with a 95% credibility interval between 72.0 and 74.0 years.

Volume differences and group separation

We found extreme evidence in favor of smaller volumes of basal forebrain and hippocampus in both the TDP-43 and AD cases compared with the amyloid-negative healthy control group, with BFs > 600 in favor of a group difference.

We found moderate evidence ($BF_{01} = 4.925$) that age-, sex-, and time to death-adjusted basal forebrain volume was not larger in TDP-43 than in AD cases (Figure 1). Evidence was absent for an effect of a smaller hippocampus volume ($BF_{01} = 0.973$) in TDP-43 cases than in AD cases (Figure 2). We found moderate evidence in favor of a larger inferior and middle temporal gyrus volume in TDP-43 cases compared with AD cases ($BF_{01} = 4.396$; Figure 3). Consistent with strong evidence for a smaller ratio of hippocampus to inferior and lateral temporal lobe volumes in TDP-43 than in AD cases ($BF_{10} = 11.23$), this ratio yielded an AUC of 0.784 (95% credibility interval = 0.591–0.92) discriminating between TDP-43 and AD cases. Figure 4 depicts the conditional AUC and its 95% credibility interval depending on the subjects' age at MRI.

When field strength was additionally regressed out of the residual volume scores, the effects of volumetric group differences between TDP-43 and AD cases remained essentially unchanged (data not shown).

Pattern of gray matter atrophy in TDP-43 cases compared with AD cases

In structural covariance analysis using PLS, the LV of pathological group on gray matter volume yielded a singular value of 111.95, with $p < 0.03$ using 100 permutations. TDP-43 group was associated with higher gray matter volumes at a bootstrap ratio > 3.1 ($p < 0.002$) in a network encompassing left predominant inferior and middle temporal gyrus as well as bilateral anterior cingulate, precuneus, and cuneus (Figure 5). Reduced gray matter in TDP-43 cases compared with AD

TABLE 1 Demographics of autopsy sample

Characteristic	AD group, $n = 33$	TDP-43 group, $n = 10$
Clinical diagnoses, CN, MCI, ADD[a]	2/17/14	2/6/2
Sex, female/male[b]	11/22	2/8
Age at MRI, years, mean (95% CI)[c]	78.0 (75.6–80.4)	81.7 (76.2–87.2)
Time between MRI and death, years, mean (95% CI)[d]	2.4 (1.5–3.2)	3.1 (0.9–5.2)
MMSE score at last clinical examination, mean (95% CI)[e]	15.7 (12.9–18.5)	22.0 (18.5–25.5)

Abbreviations: AD, Alzheimer disease; ADD, AD dementia; CI, confidence interval; CN, cognitively normal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; TDP-43, TAR DNA-binding protein 43.

[a]Bayes factor in favor of no dependency between pathological groups and clinical diagnoses, $BF_{10} = 0.365$; that is, a dependency between pathological groups and clinical diagnoses is 1/0.365 = 2.7 times less likely than the independence of both factors.

[b]Bayes factor shows no conclusive evidence, $BF_{10} = 0.494$.

[c]Bayes factor shows no conclusive evidence, $BF_{10} = 0.749$.

[d]Bayes factor shows no conclusive evidence, $BF_{10} = 0.431$.

[e]Bayes factor shows no conclusive evidence, $BF_{10} = 2.3$.

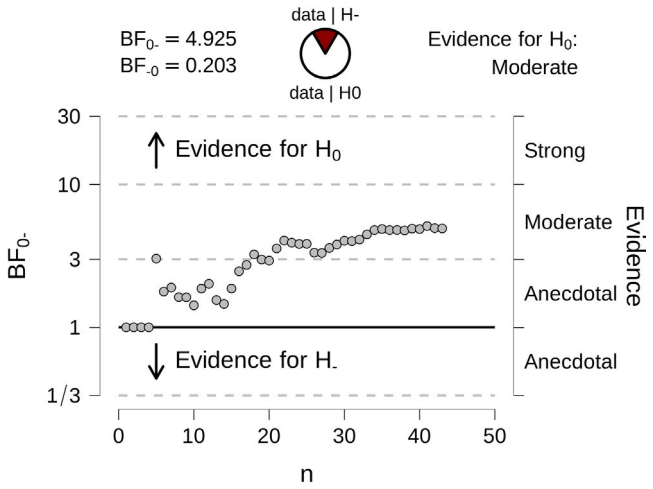

FIGURE 1 Basal forebrain volume in TAR DNA-binding protein 43 (TDP-43) versus Alzheimer disease (AD) cases. The probability wheel on top contrasts the posterior probabilities for the data under the assumption of presence (H_1) or absence (H_0) of an effect of TDP-43 versus AD. The scatterplot on the bottom demonstrates the internal coherence of Bayesian hypothesis testing; each individual participant contributes to the updating of the prior distribution, and the subsequent inference based on the posterior distribution (shown on the right-hand y-axis). The evidence for H_{0-}, that is, basal forebrain volume not smaller in AD cases than in TDP-43, starts to become moderate, that is, Bayes factor (BF) > 3, with number of cases sequentially included into the analysis being 21 and higher. After the inclusion of 21 cases, the moderate evidence level for the absence of an effect remains stable [Colour figure can be viewed at wileyonlinelibrary.com]

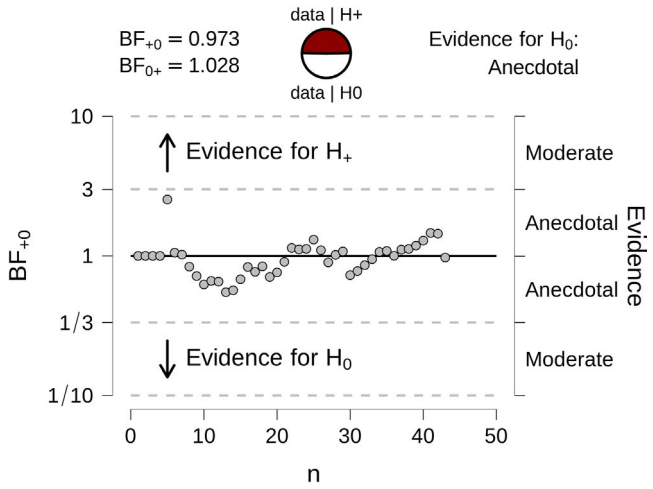

FIGURE 2 Bilateral hippocampus volume in TAR DNA-binding protein 43 (TDP-43) versus Alzheimer disease (AD) cases. Probability wheel (for details, see legend of Figure 1) and sequential plot of the Bayes factor (BF) for the data under the assumption of presence (H_1) or absence (H_0) of an effect of more atrophied hippocampus volume in TDP-43 cases compared with AD cases are shown. The sequential plot shows that the evidence is inconclusive across all numbers of cases included, with the BF between 1/3 and 3 [Colour figure can be viewed at wileyonlinelibrary.com]

cases was only visible at a bootstrap ratio of −1.96 ($p = 0.05$), with spatially very restricted involvement of precentral and postcentral gyri and hippocampus.

DISCUSSION

Here, we studied antemortem brain volume differences between autopsy cases with relatively pure limbic TDP-43 pathology and those with relatively pure AD pathology, with a focus on the volume of the cholinergic basal forebrain. We found extreme evidence that basal forebrain volume was reduced in both the TDP-43 and the AD cases compared with amyloid-negative healthy controls, and moderate evidence that the basal forebrain volume in TDP-43 cases was at least as much atrophied as in AD cases, suggesting involvement of this brain area not only in AD but also in limbic TDP-43 pathology. If confirmed in subsequent studies, these data would suggest that limbic TDP-43 pathology may also be accompanied by a cholinergic deficit. The evidence is currently restricted to MRI-based basal forebrain volume as a structural surrogate marker of cholinergic degeneration [18], so our results cannot confirm a cholinergic deficit in limbic TDP-43 cases but rather warrant further investigation of cholinergic involvement in limbic TDP-43 pathology.

Hippocampus atrophy is well established in cases with AD pathology and concomitant TDP-43 pathology [2,19], even when controlling for the degree of tangle and neuritic plaque pathology [20]. Our data replicate these findings in relatively pure limbic TDP-43 cases. Our data, however, showed inconclusive evidence for more pronounced hippocampus atrophy in pure limbic TDP-43 cases compared with pure AD cases. This observation is supported by the data-driven partial least square analysis, which showed only spatially very restricted effects of atrophy in hippocampus in TDP-43 versus AD cases. Of note, the number of cases is relatively small, so that larger samples will be required for confirmation.

In contrast, we found moderate level evidence that the basal forebrain volume was not more preserved in limbic TDP-43 cases than in AD cases. Evidence from frontotemporal lobar degeneration (FTLD) cases, including a subset of pathologically confirmed cases, suggested atrophy of the basal forebrain based on antemortem MRI scans in FTLD with tau pathology cases, and to a lesser degree also in frontotemporal dementia with TDP-43 pathology cases compared with controls [21]. The clinical phenotypes of limbic TDP-43 and FTLD-TDP-43 differ, but both still may belong to a continuum between AD pathology and TDP-43 pathology. Interestingly, TDP-43-positive inclusions in basal forebrain neurons were found in a subset of 11 of 33 patients who died with amyotrophic lateral sclerosis even in the absence of a clinical FTLD phenotype [22]. Atrophy of the basal forebrain in TDP-43 cases does not necessarily imply that TDP-43 pathology involves the basal forebrain directly, but it could also result from degeneration of medial temporal lobe and cortical target areas of cholinergic projections. Several studies, however, also found TDP-43 pathology in the basal forebrain

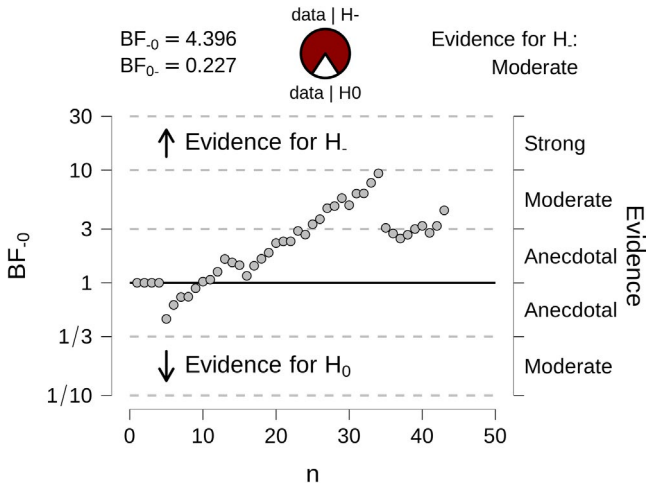

FIGURE 3 Bilateral inferior and middle temporal gyrus volume in TAR DNA-binding protein 43 (TDP-43) versus Alzheimer disease (AD) cases. Probability wheel (for details, see legend of Figure 1) and sequential plot of the Bayes factor (BF) for the data under the assumption of presence (H_1) or absence (H_0) of an effect of less atrophied lateral temporal lobe volume in TDP-43 cases compared with AD cases are shown. The sequential plot shows that a moderate level of evidence for H_1 is reached and holds after about 25 cases have been included [Colour figure can be viewed at wileyonlinelibrary.com]

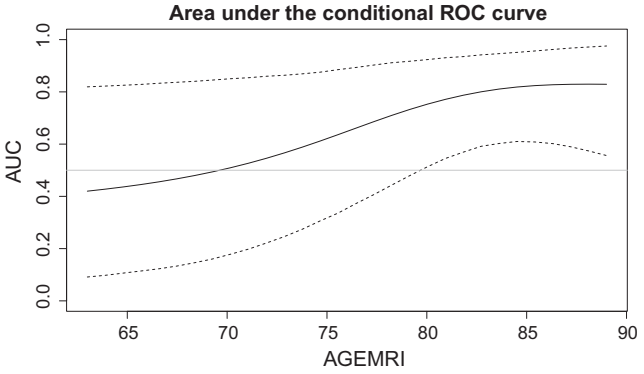

FIGURE 4 Area under the receiver operating characteristic (ROC) curve (AUC) for bilateral hippocampus to inferior and middle temporal gyrus ratio conditional on the subjects' age. Dotted lines indicate the 95% credibility interval for the AUC. AGEMRI, age at magnetic resonance imaging in years

as a possible downstream event from different primary pathologies, including cortical pathology of massive infarct or hemorrhage [23], chronic traumatic encephalopathy [24], and hippocampal sclerosis [25]. These studies may point to a propensity of the basal forebrain as a target site for TDP-43 pathology under different primary pathologies. In conclusion, our data agree with the notion that the cholinergic basal forebrain is atrophied in limbic TDP-43 pathology as well, either reflecting a direct involvement by TDP-43 pathology or resulting from primary involvement of target regions. This finding would provide some rationale for future investigation of the clinical efficacy of cholinesterase inhibitors in people with a limbic TDP-43 signature even in the absence of AD pathology biomarkers.

Previous evidence from FDG-PET studies suggests that the ratio of reduced hippocampus metabolism to preserved lateral temporal lobe metabolism may be useful to discriminate TDP-43 cases from cases with pure AD [8]. Here, we studied whether the ratio of MRI-based volumes of bilateral hippocampus to lateral temporal lobe may be a useful proxy for this metabolic signature. Our region of interest and complementary data driven partial least square regression analysis showed moderate evidence for a relative preservation of the lateral temporal lobe gray matter volume and subsequently strong evidence for a more reduced hippocampus to lateral temporal lobe volume ratio in TDP-43 with AD cases. Consistently, ROC analysis revealed a moderate accuracy of group separation, with an AUC of 0.78. This is similar to a recent study finding that the ratio of inferior-to-medial temporal gray matter volume could distinguish between TDP-43-positive and TDP-43-negative autopsy cases with AD pathology, with an AUC of 0.74 [19]. This level of accuracy would not be sufficient to make a diagnosis in individual cases but could be useful to identify those amyloid-negative cases with an amnestic dementia syndrome for which a more detailed diagnosis by FDG-PET is warranted. With the advent of CSF markers of TDP-43 pathology currently under development [26], in the future, the MRI signature may be useful to identify those patients who should undergo lumbar puncture as a possibly more specific marker than FDG-PET. Not surprisingly, the conditional ROC analysis showed that the accuracy of group separation greatly increased with age, so that a relevant degree of accuracy was only reached at and above an age of 75 years. This is consistent with the observation that limbic TDP-43 pathology is more frequent in greater age [3] so that a limbic TDP-43-like MRI signature may not be able to discriminate the only very few young TDP-43 cases from their AD age peers. Based on larger datasets, novel approaches from machine learning may still be able to derive a relevant group separation even with very few index cases in the young age group by using oversampling methods [27]. However, the current number of cases was much too small to apply such approaches.

We need to consider several limitations of this study. First, the number of cases was small. We used Bayesian analysis, which allowed us to monitor the level of evidence sequentially as the number of cases was increased. Thus, the results for basal forebrain and lateral temporal lobe volumes appeared to be robust, as evidence converged at a moderate level of evidence even before the maximum number of available cases had been included. Similar to the basal forebrain, we found hippocampal volumes to be reduced in the TDP-43 and AD groups compared with controls. However, the evidence for hippocampus volumes being smaller in the TDP-43 group compared to the AD group remained inconclusive, requiring future study in larger samples. Obviously, the small number of cases renders our group separation analysis a first indication of the possible usefulness of the MRI signature, but larger samples are needed to establish its usefulness. The temporal delay between the last MRI scan and death varied greatly between cases. We do not anticipate, however, that this would result in a

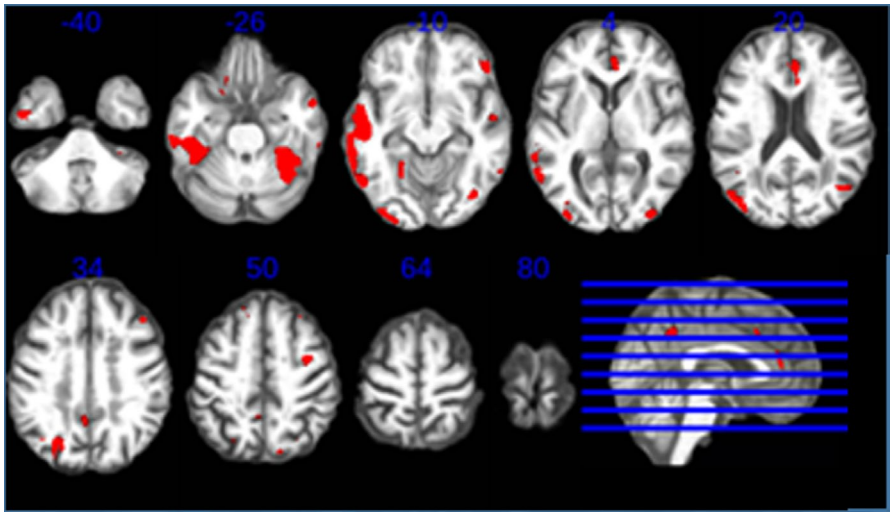

FIGURE 5 Association of pathological group with cortical gray matter as determined using partial least square analysis. Latent variable-representing brain regions where cortical gray matter volume was higher in TAR DNA-binding protein 43 than in Alzheimer disease cases (at a bootstrap ratio >3.1) are projected on a magnetic resonance imaging scan in Montreal Neurological Institute (MNI) standard space. Axial sections go from MNI coordinate z = −40 to z = 80. Upper numbers indicate the level of the axial section according to the MNI space z coordinate. Colored voxels represent a significant bootstrap ratio of $p < 0.002$. Right of image is right of brain (viewed from superior) [Colour figure can be viewed at wileyonlinelibrary.com]

large bias, as significant AD pathology or TDP-43 pathology can be expected to have been absent already at the time of antemortem examination, if it was also absent later, at the time of autopsy.

In summary, we found evidence for an at least similar degree of atrophy of the basal forebrain in limbic TDP-43 cases without relevant AD pathology as in relatively pure AD pathology. These data suggest that a clinical trial of the efficacy of cholinesterase inhibitors may be justified in amyloid-negative cases with amnestic dementia and an imaging signature of TDP-43 pathology. Our data provide further indication that an MRI signature of relatively reduced hippocampus volume with preserved lateral temporal lobe volume may be a useful proxy for a more invasive and costly assessment of the metabolic signature on FDG-PET. Given the small number of cases and the indirect structural imaging approach, we want to point out again that our findings should not be interpreted as confirmatory but that they justify future testing of the hypothesis of a cholinergic deficit in limbic TDP-43. Finally, our data show the ability of Bayesian analysis to provide quantitative evidence for either the presence or absence of an effect given the data, which is more informative than just accepting or rejecting the null hypothesis of no effect based on classical *p*-values [28].

ACKNOWLEDGMENTS

Data collection and sharing for this project were funded by the ADNI (National Institutes of Health grant U01 AG024904) and Department of Defense (DOD) ADNI (DOD award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica, Biogen Idec, Bristol-Myers Squibb, Eisai, Elan Pharmaceuticals, Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche and its affiliated company Genentech, Fujirebio, GE Healthcare, IXICO, Janssen Alzheimer Immunotherapy Research & Development, Johnson & Johnson Pharmaceutical Research & Development, Medpace, Merck & Co, Meso Scale Diagnostics, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer, Piramal Imaging, Servier, Synarc, and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. The work was supported by a grant to S.J.T. within the CureDem funding of the Federal Ministry of Research (grant number 01KX2130). M.J.G. is supported by the Miguel Servet program (CP19/00031) and a research grant (PI20/00613) of the Carlos III Health Institute–European Regional Development Fund. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

S.J.T. has participated on scientific advisory boards for Roche Pharma, Biogen, Grifols, Eisai, and MSD, and has received lecture fees from Roche and MSD. M.J.G. declares no conflicts of interest.

AUTHOR CONTRIBUTIONS

Stefan J. Teipel: Conceptualization (equal), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), resources (equal), software (lead), supervision (lead), writing–original draft (lead). **Michel J. Grothe:** Conceptualization (equal), data curation (supporting), formal analysis (supporting), methodology (equal), writing–review & editing (supporting).

RESEARCH INVOLVING HUMAN PARTICIPANTS

All procedures performed in the ADNI study were in agreement with the ethical standards of the institutional research committees and the 1975 Helsinki Declaration and its later amendments.

INFORMED CONSENT

Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the ADNI study.

DATA AVAILABILITY STATEMENT

Data used for the current analysis from the ADNI cohort are freely available from the ADNI website (http://adni.loni.usc.edu/data-samples/access-data), including autopsy data and MRI scans. Processed MRI scans are available upon request through the corresponding author of this article.

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How to cite this article: Teipel SJ, Grothe MJ. Antemortem basal forebrain atrophy in pure limbic TAR DNA-binding protein 43 pathology compared with pure Alzheimer pathology. *Eur J Neurol*. 2022;29:1394–1401. doi:10.1111/ene.15270