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Divergent magnetic resonance imaging atrophy patterns in Alzheimer's disease and primary age-related tauopathy

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ABSTRACT

Our study compared brain MRI with neuropathological findings in patients with primary age-related tauopathy (PART) and Alzheimer's disease (AD), while assessing the relationship between brain atrophy and clinical impairment. We analyzed 233 participants: 32 with no plaques ("definite" PART—BRAAK stage higher than 0 and CERAD 0), and 201 cases within the AD spectrum, with 25 with sparse (CERAD 1), 76 with moderate (CERAD 2), and 100 with severe (CERAD 3) degrees of neuritic plaques. Upon correcting for age, sex, and age difference at MRI and death, there were significantly higher levels of atrophy in CERAD 3 compared to CERAD 1–2 and a trend compared to PART ($p = 0.06$). In the anterior temporal region, there was a trend for higher levels of atrophy in PART compared to Alzheimer's disease spectrum cases with CERAD 1 ($p = 0.08$). We then assessed the correlation between regional brain atrophy and CDR sum of boxes score for PART and AD, and found that overall cognition deficits are directly correlated with regional atrophy in the AD continuum, but not in definite PART. We further observed correlations between regional brain atrophy with multiple neuropsychological metrics in AD, with PART showing specific correlations between language deficits and anterior temporal atrophy. Overall, these findings support PART as an independent pathologic process from AD.

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1. Introduction

Primary age-related tauopathy (PART) is a pathological process characterized by the presence of tau-positive neurofibrillary tangles (NFTs) and no amyloid-beta (Aβ) deposition ("definite PART") (Crary et al., 2014). Currently, the diagnosis of PART is histologically assessed by the presence of tau positive NFT with Braak staging (which can generally go from I to IV), and a Thal Aβ phase $\leq$2 or a Consortium to Establish a Registry for Alzheimer's disease (CERAD) Aβ stage of 0 (Crary et al., 2014).

Alzheimer's disease is clinically characterized by slowly progressive neurocognitive impairment predominantly characterized by short-term memory loss (typical senile Alzheimer's disease) and with disease progression, multiple neurocognitive domains can be involved, such as language impairment or mood disbalance (Kelley and Petersen, 2007). At the level of neuropathology, Alzheimer's disease diagnosis consists of grading the "ABC score," which is achieved by grading amyloid plaques (A) by Thal phases, NFT by Braak staging (B) and the neuritic plaque score by CERAD assessment (C) (Hyman et al., 2012).

Abbreviations: Aβ, amyloid-beta; AC, anterior cingulate; ADCs, Alzheimer's disease centers; AT, anterior temporal; CDR, CDR Dementia Staging Instrument; CDR-SB, clinical dementia rating sum of boxes; CERAD, Consortium to Establish a Registry for Alzheimer's disease; FI, frontoinsular; LATE, limbic-predominant age-related TDP-43 encephalopathy; MTA, medial temporal lobe atrophy; NACC, National Alzheimer's Coordinating Center; NIA-AA, National Institute on Aging and Alzheimer's Association; NFTs, neurofibrillary tangles; NP, neuritic plaque; OF, orbitofrontal; PART, primary age-related tauopathy; Post, posterior region; TDP-43, TAR DNA-binding protein 43; UDS, uniform data set.

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The clinical characteristics of patients eventually identified as having *post mortem* PART can be divided as "symptomatic" (when dementia or cognitive deterioration were present up to the time of death) or "asymptomatic" (with no cognitive deficits) (Besser et al., 2017). However, the clinical presentation and the specific types of neuropsychological deficits in PART participants are still under scrutiny. Regarding this, "definite" PART participants showed sparing of semantic memory/language compared to Alzheimer's disease, and, when stratified by global Clinical Dementia Rating (CDR), presented sparing of memory (CDR of 0.5 or 1) or attention (CDR of 2 or 3), when compared to Alzheimer's disease patients (Besser et al., 2019). Moreover, it was shown that patients with PART had slower cognitive decline than Alzheimer's disease patients across multiple neuropsychological domains (Bell et al., 2019; Teylan et al., 2020). Alzheimer's disease patients showed a significantly steeper decline after becoming clinically symptomatic than those with PART (Teylan et al., 2020) and temporal lobe atrophy in PART specifically correlated with semantic memory/language deficits (Quintas-Neves et al., 2019). Also, it was shown that PART patients had significantly slower rates of decline on measures of memory, language and visuospatial performance, when compared to Alzheimer's disease patients (Bell et al., 2019). Furthermore, PART with dementia was originally described as being a disorder that typically affects older patients than the ones with Alzheimer's disease (Crary et al., 2014), which is supported by follow-up studies that included a higher number of cases (Besser et al., 2019; Teylan et al., 2020).

Given that Alzheimer's disease is diagnosed more than 50% of the time in PART cases with mild cognitive impairment or dementia (Teylan et al., 2019), there is a need for in vivo diagnostic tools to differentiate PART from other dementias during life, particularly Alzheimer's disease, by assessing the cognitive domains involved, cerebrospinal fluid (CSF) biomarkers, and brain magnetic resonance imaging (MRI) findings, in accordance with the research framework recommended by the National Institute on Aging and Alzheimer's Association (NIA-AA), specifically the AT(N) criteria (Jack et al., 2018). In line with this, brain MRI of "definite" PART patients showed an association between Braak staging and atrophy of the left head of the hippocampus, which was correlated with the preservation of episodic memory (Josephs et al., 2017b). Moreover, MRI of "definite" PART participants showed a correlation between Braak staging and aging with atrophy of the medial temporal lobe (Quintas-Neves et al., 2019). Despite these results, few studies have assessed the relationship between brain MRI and neuropathological findings of patients with PART and Alzheimer's disease.

Here, we compared the in vivo brain MRI findings with neuropathological findings in patients with definite PART (i.e., BRAAK stage higher than 0 and CERAD = 0) and Alzheimer's disease (i.e., CERAD = 1–3), using visual rating regional atrophy scales (Harper et al., 2016). Additionally, we assessed the relationship between brain atrophy and the degree of clinical impairment in all groups, based on CDR metrics (Morris, 1993) and neuropsychological testing (Weintraub et al., 2018).

2. Methods

2.1. Participants

Data was obtained from the National Alzheimer's Coordinating Center (NACC), a repository for data collected at the Alzheimer's Disease Centers (ADCs) located across the United States of America. Such ADCs collect standardized clinical data via the Uniform Data Set (UDS) and neuropathological evaluations obtained at autopsy to the Neuropathology Data Set. The UDS and Neuropathology Data Set data have been described in detail (Beekly et al., 2007; Besser et al., 2018; Morris et al., 2006; Weintraub et al., 2009, 2018).

2.2. Selection criteria

Our sample was obtained from the September 2019 data freeze (n = 38,836 patients), which included 4192 patients with clinical UDS data within 2 years from death and neuritic plaque (NP) burden assessed at autopsy. At this point, all UDS visits of participants with MRI scans performed no more than 4 years before the date of death and who had neuropathology data available were collected (n = 334 patients); only the last UDS visit and respective brain MRI scan before death were considered for the analysis. We excluded participants: (a) with neuropathological evidence of frontotemporal lobar degeneration, Lewy body disease, amyotrophic lateral sclerosis, prion disease, or argyrophilic grains; (b) with clinical evidence of dementia with Lewy bodies, Parkinson disease, Down syndrome, Huntington disease, prion disease, corticobasal degeneration, or progressive supranuclear palsy; (c) with other brain lesions that biased atrophy assessment (e.g., brain tumor; brain herniation; vascular malformation; lymphocytic meningoencephalitis; traumatic brain injury; demyelinating disease). Patients with a BRAAK stage of 0 (without evidence of neurofibrillary tangles), and a simultaneous CERAD score of 0 (absence of neuritic plaques on autopsy) were excluded. With the application of these exclusion criteria, 233 participants remained (Table 1). PART patients were defined as having a higher BRAAK stage than 0, considered as having neuropathological evidence of varying degrees of neurofibrillary tangles, and a CERAD score of 0 (absence of neuritic plaques).

2.3. Neuropathology data

As referred above, the neuropathological data was collected by the ADCs by using a standardized Neuropathology Form on those patients who died and consented to autopsy and neuropathologic examination. With such data, participants were categorized according to the Braak stage for neurofibrillary degeneration and CERAD stage. TAR DNA-binding protein 43 (TDP-43) data was considered in a small subset of cases that had been assessed by the ADCs. Details on brain tissue preparation and staining within the NACC Neuropathology dataset have been previously described (Besser et al., 2018).

2.4. Brain MRI data

The MRI examinations were performed on 1.5T or 3T scanners, both from Philips, Siemens, or GE manufacturers. Although there were several imaging protocols performed by different centers, for our imaging analysis we used T1-weighted acquisitions in order to grade the degree of regional brain atrophy.

2.5. Image analysis

We previously applied validated visual rating scales to assess brain atrophy of the following regions: anterior cingulate, orbitofrontal, anterior temporal, frontoinsular, medial temporal, and posterior regions (Quintas-Neves et al., 2019). Here we define atrophy as cross-sectional, corresponding to the score attributed on the basis of these rating scales. As previously described by the simplified version: orbitofrontal (OF) and anterior cingulate (AC) regions were rated on the first anterior slice where the corpus callosum becomes visible; the frontoinsular (FI) was rated over three slices, starting on the first anterior slice where the anterior cingulate becomes visible and moving posteriorly; the anterior temporal (AT)

Table 1
Characterization of patients according to the density of neocortical neuritic plaques (CERAD score)

	PART	AD spectrum			
	CERAD 0 (None) (n = 32)	CERAD 1 (Sparse) (n = 25)	CERAD 2 (Moderate) (n = 76)	CERAD 3 (Severe) (n = 100)	p
Male sex, n (%)[a]	24 (75)	11 (44.0)	48 (63.2)	64 (64.0)	X^2 (3) = 11.34; p = 0.01
Age at death, mean (SD)[b]	79.0 (±11.06)	87.7 (±6.29)	82.2 (±8.84)	77.4 (±11.15)	$F(3, 229) = 8.464$, $p < 10^{-3}$
Age at last MRI, mean (SD)[c]	77.2 (±11.3)	85.9 (±5.75)	80.1 (±8.75)	75.0 (±11.1)	$F(3, 229) = 9.95$, $p < 10^{-3}$
Age MRI-death, mean (SD)[d]	2.0 (±1.05)	1.8 (±1.40)	2.1 (±1.18)	2.4 (±1.14)	$F(3, 229) = 2.557$, $p = 0.06$
CDR-SB[e]	6.6 (±5.54)	3.8 (±4.83)	5.9 (±4.57)	8.5 (±4.24)	$F(3, 229) = 9.77$, $p < 10^{-3}$
Global CDR[e]	1.2 (±0.89)	0.7 (±0.8)	1.1 (±0.75)	1.4 (±0.73)	$F(3, 229) = 8.529$, $p < 10^{-3}$
Braak stage, n (%)[f]					
None	0 (0)	0 (0.0)	1 (1.3)	0 (0.0)	
I	14 (43.8)	3 (12.0)	4 (5.3)	1 (1.0)	
II	12 (37.5)	8 (32.0)	10 (13.2)	0 (0.0)	
III	3 (9.37)	8 (32.0)	13 (17.1)	2 (2.0)	
IV	3 (9.37)	4 (16.0)	18 (23.7)	8 (8.0)	
V	0 (0.0)	2 (8.0)	17 (22.4)	24 (24.0)	
VI	0 (0.0)	0 (0.0)	13 (17.1)	65 (65.0)	
Braak stage, mean (SD)	1.8 (±0.95)	2.8 (±1.13)	3.9 (±1.5)	5.5 (±0.86)	$F(3, 229) = 100.5$, $p < 10^{-3}$

The table shows the summarized demographic characteristics of a total cohort of 245 patients, separated according to PART (CERAD 0 and BRAAK stage higher than 0) or AD spectrum with presence (CERAD 1—mild; CERAD 2—moderate; CERAD 3—severe) of neocortical neuritic plaques after neuropathological evaluation.
*$p < 0.05$ considered as significant for one-way ANOVA or χ^2 test, as appropriate.
[a]Male sex refers to the absolute mean and relative percentage of male patients in a given group, represented as n (%).
[b]Age at death is the subject age at the time of death.
[c]Age at last MRI is the subject age at the time the last MRI was performed.
[d]Age MRI-death is the difference between the subject age at the last performed MRI and time of death. These three variables are reported in years as [a] continuous variable with mean and standard deviation (SD).
[e]CDR-SB refers to the sum of boxes score from the CDR Dementia Staging Instrument and global CDR refers to the global Clinical Dementia Rating [s]core; they are both attributed to the subject in the last clinical visit and are also reported as continuous variables with mean and standard deviation.
[f]For each Braak stage (from none to VI) values are represented as number of cases and percentage of total. Data presented as n (%) and mean (±SD).

was rated at the level of the temporal pole, just anterior to where the "temporal stem" connects the frontal and temporal lobes; the medial temporal was rated according to the medial temporal lobe atrophy (MTA) score—performed on the hippocampus at the level of the anterior pons; the posterior region (Post) was rated according to the four-point posterior atrophy scale described by Koedam (Koedam et al., 2011)—overall score based on the presence of atrophy in sagittal (widening of the posterior cingulate and parieto-occipital sulcus, and atrophy of the precuneus on left and right by considering paramedian sagittal images), axial (widening of the posterior cingulate sulcus and sulcal dilatation in parietal lobes on axial images) and coronal (widening of the posterior cingulate sulcus and parietal lobes on coronal images) orientations, assessed for left and right separately (Harper et al., 2016). Two independent classifiers with 7 years and 4 years, respectively, of experience in clinical neuroradiology were responsible for rating the images. Visual raters were blind to clinical diagnosis. For each brain region scale, the average of both hemispheres was calculated and an average of both classifiers was used. In order to aid the rating process, reference images for each rating scale were provided to the classifiers based on Harper et al. (Harper et al., 2016).

2.6. Neuropsychological assessment

Local ADCs assessed participants using the CDR and the UDS version 2 neuropsychological test battery (Weintraub et al., 2009). Here, we used the global CDR, CDR-SB, and neuropsychological tests conducted at the last UDS visit prior to death. The so-called Washington University CDR was reviewed by Morris and collaborators in 1993. (Morris et al., 1993) with the purpose of staging the severity of Alzheimer's disease, and takes into consideration the following six cognitive categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care; it is based on a five point scale in which none = 0, questionable = 0.5, mild = 1, moderate = 2, and severe = 3. The global CDR is calculated using a proprietary algorithm according to clinical scoring rules, with CDR 0 = no dementia, CDR 0.5 = questionable dementia, CDR 1 = mild dementia, CDR 2 = moderate dementia and CDR 3 = severe dementia. The CDR-SB is calculated by summing the ratings of each of the six cognitive domains and it reflects a more quantitative global measure; it ranges from 0 (normal) to 18 (severe dementia) (O'Bryant et al., 2008). Several other tests of memory, executive function, language and processing speed were considered in our analysis. Executive function was assessed by the Trail Making Test (TMT) A and B, which globally tests attention, visual scanning and search skills, and psychomotor speed and coordination (Reitan, 1955); TMT A can independently assess processing speed, while TMT B assesses set switching; on both parts of this test (i.e., A and B), the total number of seconds to complete the test, the number of commission errors, and number of correct lines were recorded; the Wechsler Adult Intelligence Scale digit symbol test (WAIS) was also considered to provide an estimate of processing speed (Wechsler, 1939). Semantic memory/language was assessed by category (vegetables and animals) verbal fluency (Lezak and Lezak, 2004), consisting of a test on registering the total number of vegetables and animals named in 60 s; the Boston naming test (Kaplan et al., 1983), which also assesses the effect of language function, more precisely the confrontational word retrieval, was included in this evaluation, and consisted of showing pictures (up to 60) to the patient, and wait up to 20 seconds for the patients to name them. Attention and working memory was evaluated by Digit span forward (DSF) and

backward test (DSB) (Jensen and Figueroa, 1975), consisting on registering the ability of recalling a sequence of numbers shown, and the total length of numbers successfully achieved (DSF L and DSB L, respectively). Logical memory was evaluated using Logical Memory Immediate and Delayed Recall tests (Logical Mem; Mem Unit), in which an orally presented verbal story is asked to be recalled immediately and 20 minutes after (Abikoff et al., 1987). Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was performed as a brief cognitive screening instrument that provides a measure of global cognition.

2.7. Statistical analysis

We divided our data into four groups of participants according to the CERAD score (i.e., density of neocortical neuritic plaques): CERAD 0 (None); CERAD 1 (Sparse); CERAD 2 (Moderate); CERAD 3 (Severe); "definite" PART being considered CERAD 0. To assess potential differences between these groups in terms of baseline characteristics, one-way analysis of variance (ANOVA) was performed, followed by a Tukey post hoc analysis whenever these characteristics were significantly different between groups ($p < 0.05$). With the purpose of assessing the rating acuity between both classifiers, Spearman's correlation coefficient was calculated for the pair of classifiers per each region, and no significant differences were found between each observer. The standardized residuals for age and Braak were calculated after linear regression for sex, age difference at MRI and death and BRAAK staging or age at MRI, respectively. Correlation data analysis for regional brain atrophy scores and CDR-SB score for groups with absent (i.e., definite PART) versus present (i.e., Alzheimer's disease) neuritic plaques was performed using the linear regression model and Pearson correlation coefficients and values expressed as (R) and statistically significant values considered for $p < 0.05$. Moreover, multiple linear regression was used to compare slopes between groups for each brain area with CDR-SB as a continuous independent variable. Z-scores for each neuropsychological test were calculated by subtracting the score from the mean test score among cognitively unimpaired participants and dividing it by the standard deviation. Tests were then grouped by cognitive domains (i.e., episodic memory, attention, language/semantic memory, executive function) (Teylan et al., 2020), which were established by (Hayden et al., 2011) using factor analysis. Tests within a cognitive domain were averaged to calculate a domain z-score. A global composite score was created by averaging the domain z-scores (Global). These were then correlated with the residuals of the visual rating scores for each brain region after linear regression with age, in PART and Alzheimer's disease using the Pearson coefficient. SPSS Statistics version 26, and GraphPad Software version 9.0.0 were used for Figs. 1 and 2, and RStudio Version 1.4.1103 was used for Figs. 3 and 4.

2.8. Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent at each local ADC, and the study protocols were approved by the respective institutional review boards. The participants that contributed to the Neuropathology Data Set gave consent for autopsy. All participants provided written informed consent at each ADC.

2.9. Data availability

The datasets used and/or analyzed during the current study are available upon request on the NACC database.

3. Results

About 233 participants were included in this study: 32 with no ("definite" PART—CERAD 0 and BRAAK stage higher than 0), 25 with sparse ("possible" PART or mild Alzheimer's disease—CERAD 1), 76 with moderate (CERAD 2), and 100 with severe (CERAD 3) neuritic plaques. There was a global male predominance among groups (more than 50%), with significant changes in sex proportions across groups due to the Alzheimer's disease spectrum CERAD 1 group, where we found a slight female preponderance (Table 1). The mean age at death was significantly lower for groups CERAD 0 and 3 (79.0 ± 11.06 and 77.4 ± 11.15 years old, respectively), and higher for group CERAD 1 (87.7 ± 6.29 years old) (Table 1). Braak staging was also statistically different between groups, with a predominance of lower grades (Braak - I and II) in PART and higher grades (Braak - V and VI) in the Alzheimer's disease spectrum CERAD 3 cases (Table 1). The global CDR and CDR-SB were significantly higher for the Alzheimer's disease spectrum CERAD 3 group (1.4 ± 0.73 and 8.5 ± 4.24, respectively) (Table 1 and Supplementary Table 1).

After calculating the standardized residuals for age, sex and difference between age of death and age at MRI, there was a statistically significant higher brain atrophy on the AT in CERAD 3 versus CERAD 1 ($p < 0.01$; diff = 0.74; 95%CI [0.18; 1.31], Fig. 1C). There was a nonsignificant trend for higher atrophy in PART versus Alzheimer's disease spectrum cases with CERAD 1 ($p = 0.08$; diff = −0.63; 95%CI [−1.30; 0.04], Fig. 1C). In MTA, brain atrophy was higher in CERAD 3 versus CERAD 2 ($p < 0.01$; diff = 0.47; 95%CI [0.089; 0.84], Fig. 1E) and CERAD 3 versus CERAD 1 ($p < 0.01$; diff = 0.87; 95%CI [0.31; 1.42], Fig. 1E). There was also a nonsignificant trend in Alzheimer's disease spectrum with CERAD 3 versus PART ($p = 0.06$; diff = 0.49; 95%CI [−0.013; 0.99], Fig. 1E). For the other regions, there were no significant differences in relative atrophy between groups (Fig. 1A, B, D, F). Upon correction for Braak stage, the AT region showed a nonsignificant trend for higher brain atrophy in PART versus Alzheimer's disease spectrum cases with CERAD 1 ($p = 0.09$, diff = −0.62; 95%CI [−1.30; 0.059], Fig. 2C). For the other regions, there were no significant differences in relative atrophy between groups (Fig. 2). Since TDP-43 has been proposed to be a relevant determinant of atrophy in PART (Josephs et al., 2020), in the small subset of cases that had TDP-43 data available, we observed that indeed "TDP-43 positive / PART" showed higher relative medial temporal lobe atrophy compared to the "TDP-43 negative / PART" group ($p < 0.01$; diff = 53.03; 95%CI [10.85; 95.21]; Supplementary Fig. 1). On the other hand, we do not find statistically significant differences for the Alzheimer's disease group.

After computing the correlation between regional brain atrophy scores and CDR-SB scores for PART (CERAD 0) and Alzheimer's disease (CERAD 1–3) (Fig. 3A–F), significant correlations were found between CDR-SB and relative atrophy in all the brain regions evaluated in patients with Alzheimer's disease ($R = 0.2$, $p = 0.0045$; $R = 0.17$, $p = 0.016$; $R = 0.3$, $p = 1.4e{-}05$; $R = 0.29$, $p = 3.9e{-}05$; $R = 0.3$, $p = 1.3e{-}06$; $R = 0.34$, $p = 7.3e{-}0.7$; for AC, OF, AT, FI, medial temporal and posterior regions, respectively). On the other hand, patients with PART showed no significant correlations between relative regional brain atrophy and CDR-SB ($R = 0.23$, $p = 0.2$; $R = 0.24$, $p = 0.19$; $R = -0.07$, $p = 0.7$; $R = 0.015$, $p = 0.94$; $R = 0.034$, $p = 0.85$; $R = -0.12$, $p = 0.52$; for AC, OF, AT, FI, medial temporal, and posterior regions, respectively). Moreover, significant differences were found between the regression lines of both groups in the AT and posterior regions (Fig. 3; Supplementary Table 2). After correcting for age, brain atrophy scores were correlated with z-scores for the neuropsychological tests. We found that AD shows a widespread pattern of negative correlations

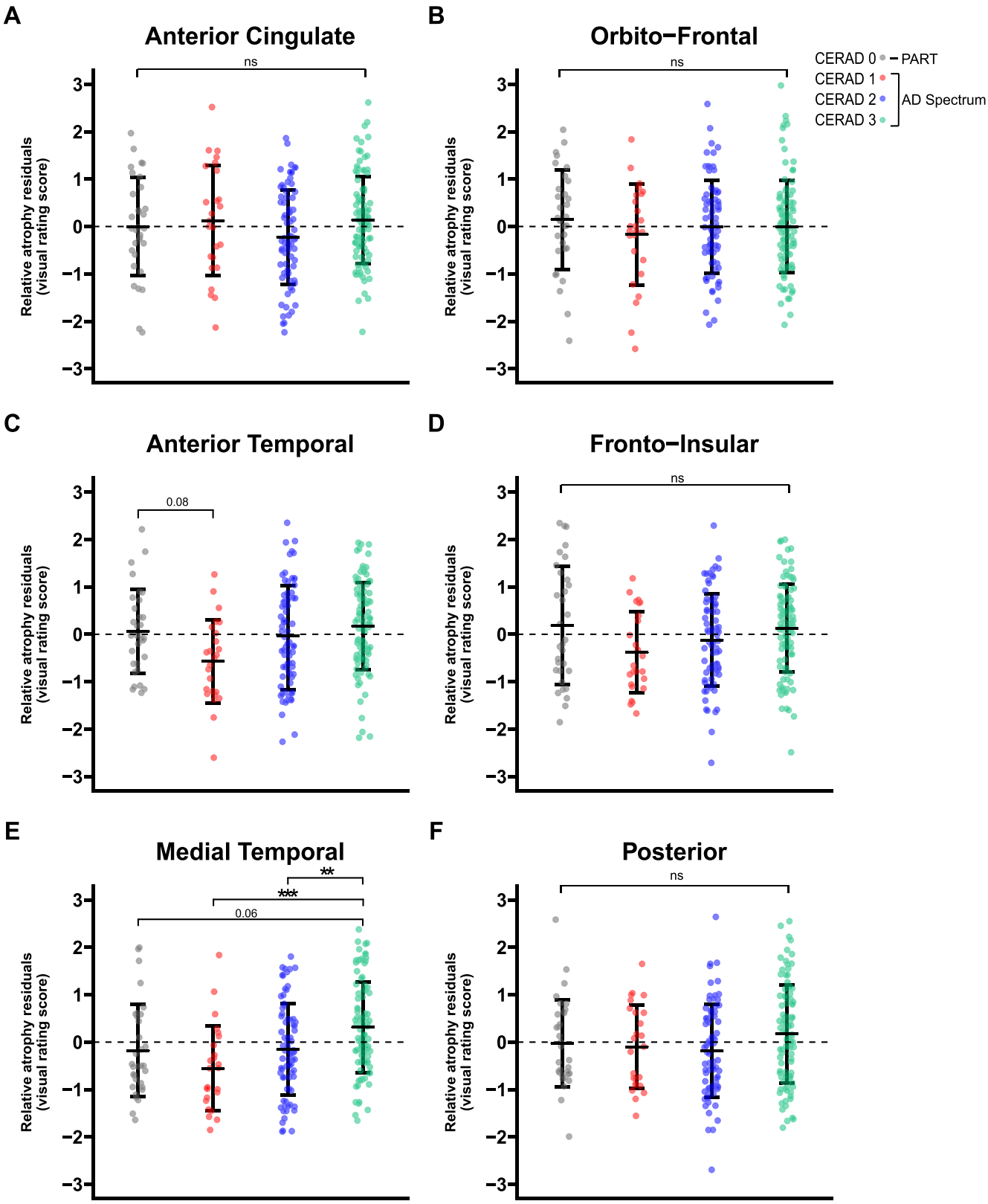

Fig. 1. Age-c relative regional brain atrophy shows differential patterns in PART and Alzheimer's disease spectrum CERAD groups. Standardized residuals corrected for age for each specific region of brain atrophy among 4 groups of participants, distributed according to PART (CERAD 0 and BRAAK stage higher than 0) or Alzheimer's disease spectrum with presence (CERAD 1—mild; CERAD 2—moderate; CERAD 3—severe) of neocortical neuritic plaques after neuropathological evaluation. The regions evaluated are (A) anterior cingulate, (B) orbitofrontal, (C) anterior temporal, (D) frontoinsular, (E) medial temporal, and (F) posterior. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. "ns" represents nonsignificant differences between groups.

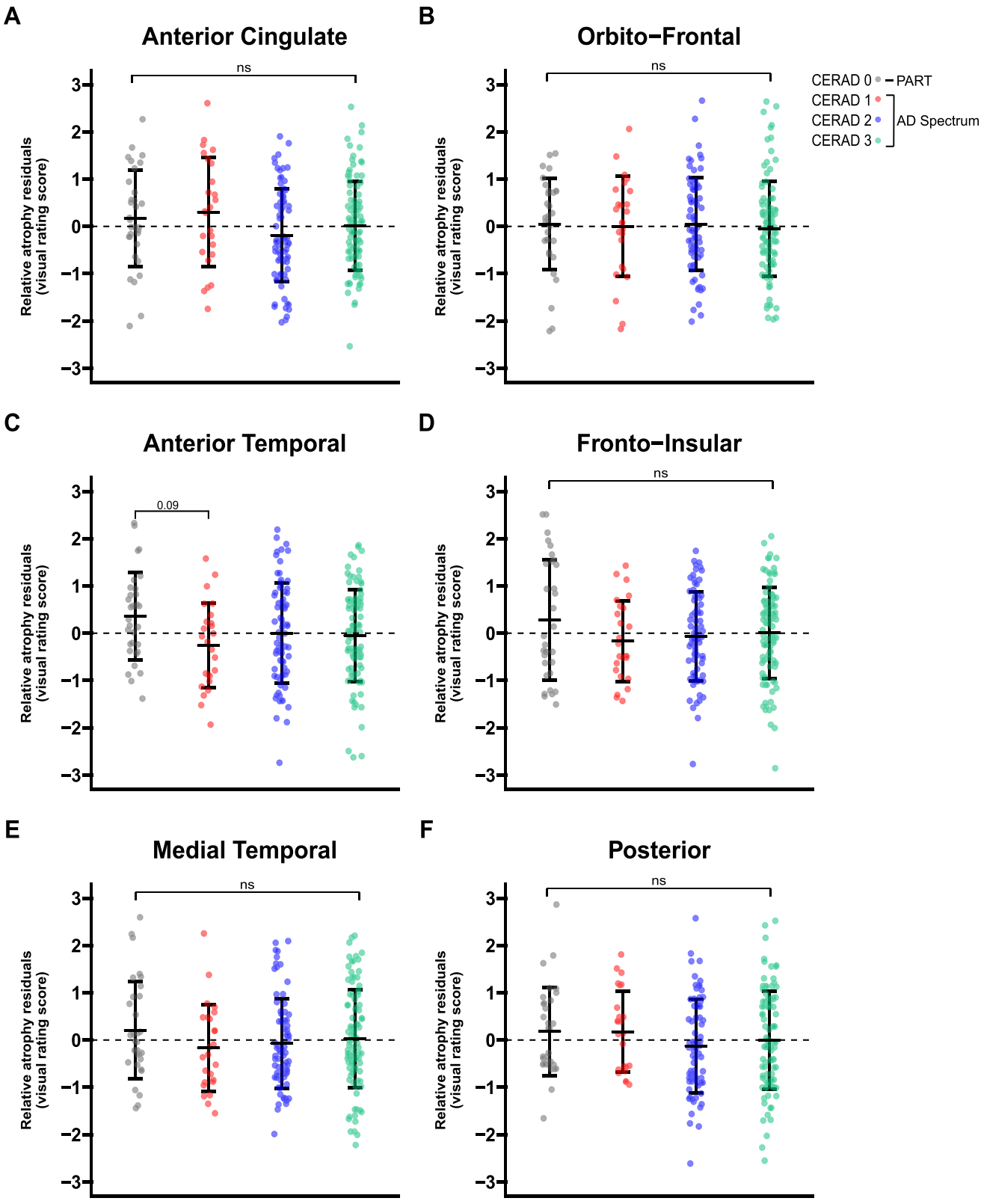

Fig. 2. Braak-corrected relative regional brain atrophy shows no significant changes in PART and Alzheimer's disease spectrum CERAD groups. Standardized residuals corrected for Braak for each specific region of brain atrophy among 4 groups of participants, distributed according to PART (CERAD 0 and BRAAK stage higher than 0) or Alzheimer's disease spectrum with presence (CERAD 1—mild; CERAD 2—moderate; CERAD 3—severe) of neocortical neuritic plaques after neuropathological evaluation. The regions evaluated are (A) anterior cingulate, (B) orbitofrontal, (C) anterior temporal, (D) frontoinsular, (E) medial temporal, and (F) posterior. * $p < 0.05$. "ns" represents nonsignificant differences between groups.

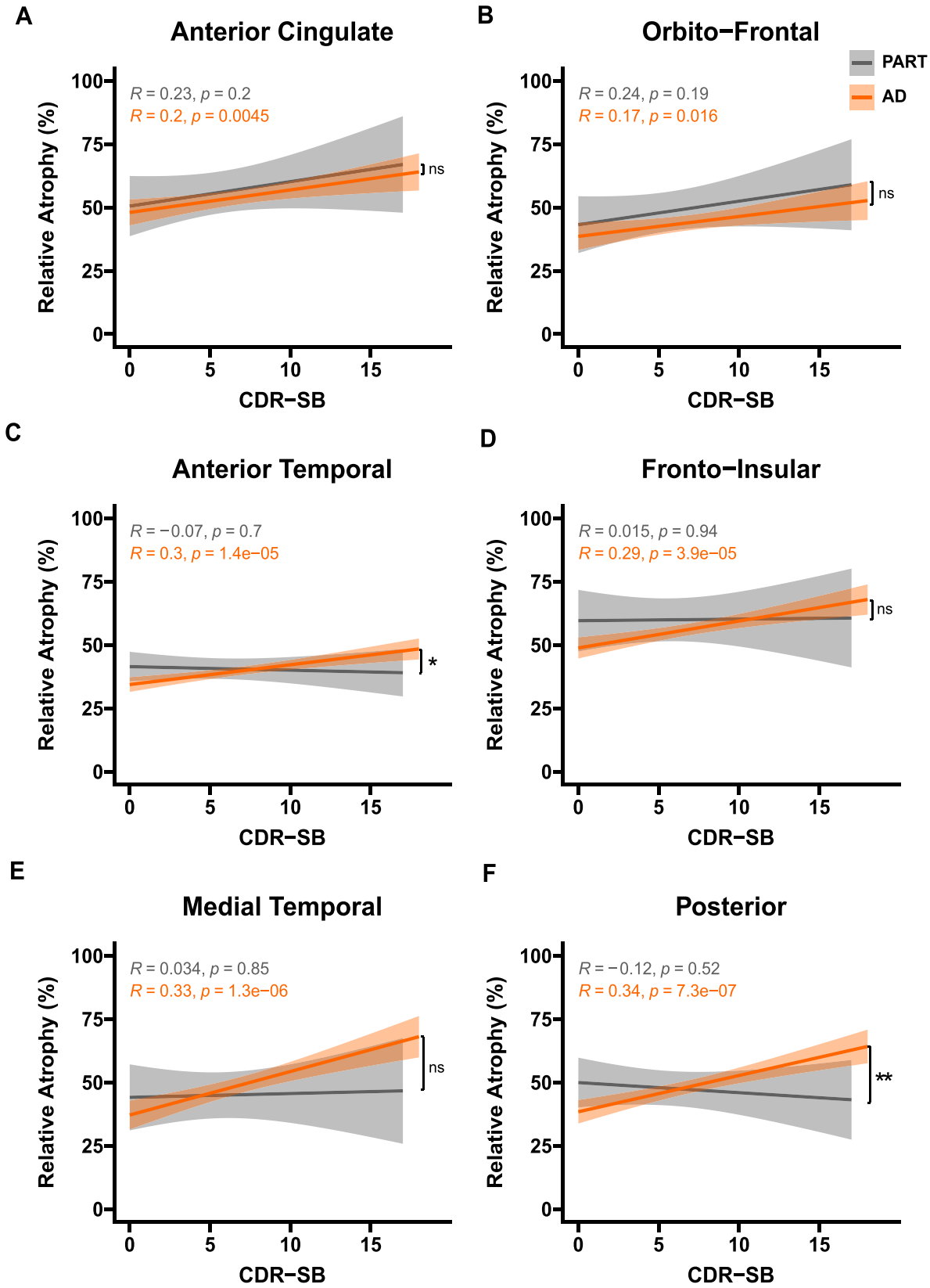

Fig. 3. Correlation analysis between relative regional brain atrophy and CDR shows differential patterns in Alzheimer's disease and PART. Pearson correlation analysis and linear regressions of relative brain atrophy per region versus CDR Dementia Staging Instrument (CDR) Sum of Boxes among 2 groups of participants, distributed according to the absence (PART) or presence (Alzheimer's disease) of neocortical neuritic plaques after neuropathological evaluation. The regions evaluated are (A) anterior cingulate (AC), (B) orbitofrontal (OF), (C) anterior temporal (AT), (D) frontoinsular (FI), (E) medial temporal, and (F) posterior. Correlation coefficients (R). p values of the correlation analysis considered significant if $p < 0.05$. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ represent statistically significant differences between the regression lines of both groups in multiple linear regression. "ns" represents nonsignificant differences between the regression lines of both groups.

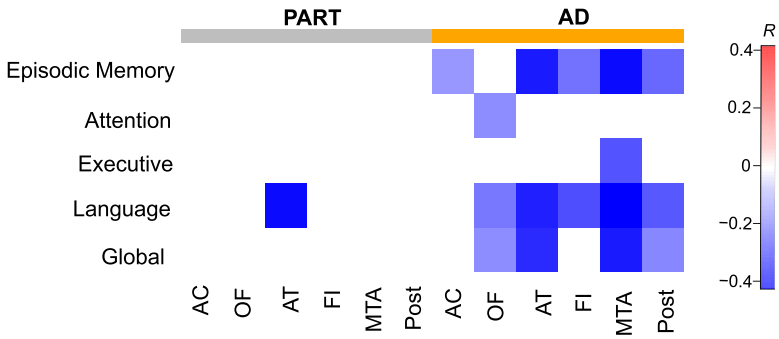

Fig. 4. Correlation analysis between relative regional brain atrophy and neuropsychological assessment shows differential patterns in Alzheimer's disease and PART. Pearson correlation analysis of relative brain atrophy residuals after linear regression with age per region versus *z*-scores of neuropsychological test composites among 2 groups of participants, distributed according to the absence (PART) or presence (Alzheimer's disease) of neocortical neuritic plaques after neuropathological evaluation. Only showing pairs with $p < 0.05$ in the correlational analysis. Color indicates *R*Pearson coefficient. Anterior cingulate (AC), orbitofrontal (OF), anterior temporal (AT), frontoinsular (FI), medial temporal (MT), and posterior (Post).

between regional atrophy and z-scores of most neuropsychological tests (Fig. 4; Supplementary Fig. 2). On the other hand, PART showed a specific negative correlation between AT atrophy and z-scores on the Boston naming test ($R = -0.554$, $p = 0.003$; Supplementary Fig. 2), which is reflected on the language composite score ($R = -0.397$; $p = 0.045$; Fig. 4). When comparing the z-scores between PART and AD, the latter group is more deeply affected in practically all tests, but not in the language composite (Table S3).

4. Discussion

The main goal of this study was to compare in vivo brain MRI findings of PART and Alzheimer's disease participants using previously validated visual rating scales that are commonly deployed in clinical settings (Harper et al., 2016). Additionally, we assessed the relationship between brain atrophy and the degree of clinical impairment, based on CDR-SB. Our results suggest that while Alzheimer's disease participants show a stepwise increase in relative age-corrected atrophy in the medial temporal lobe region with increasing CERAD scores (1 to 3), PART cases present intermediate relative atrophy levels (Fig. 1). A similar nonsignificant trend was also observed for AT regions (Fig. 1). Since there has been debate whether PART is a pre-Alzheimer's disease condition (Duyckaerts et al., 2015; Weigand et al., 2020), these findings indicate that PART could be an independent pathologic process from Alzheimer's disease (Bell et al., 2019; Besser et al., 2019; Crary et al., 2014; Josephs et al., 2020; Teylan et al., 2019, 2020).

Overall, "definite" PART patients (i.e., CERAD 0 and BRAAK stage higher than 0) showed higher mean relative age-corrected atrophy than CERAD 1 group (i.e., sparse NP—"possible" PART / mild Alzheimer's disease) in all brain regions evaluated, and lower mean relative age-corrected atrophy than the CERAD 3 group (i.e., advanced Alzheimer's disease) in the medial temporal region. This supports a more benign nature of this pathology when compared to severe Alzheimer's disease, but more severe when compared to mild Alzheimer's disease. It is interesting to observe that CERAD 1 cases are older at death, have a slight female preponderance and have lower levels of age-corrected relative atrophy when compared to the other pathological groups. This is in accordance with recent observations that show that disease onset at a younger age tends to be associated with more advanced pathology (Jack et al., 2020; Vogel et al., 2021; Whitwell et al., 2019). This suggests that CERAD 1, also considered "possible PART" by some authors, could be the basis to identify a state of Alzheimer's disease pathology resistance, while CERAD 0, corresponding to "definite PART," could represent an entirely different pathological process.

Given that NPs are only present in mild Alzheimer's disease, other pathophysiological mechanisms might explain this difference, such as deposition of TDP-43. This protein was first described in 2006 as a main component of the ubiquitinated inclusions found at autopsy of patients with frontotemporal lobar degeneration (FTLD) (Neumann et al., 2006). Over time, it has been described to be present in several other pathologies (so-called TDP-43 proteinopathies), and can be divided in two groups: primary and mixed (i.e., secondary). PART and Alzheimer's disease are considered within the mixed group. In Alzheimer's disease, TDP-43 has been found to be associated with worse memory loss (Josephs et al., 2014), atrophy of the hippocampus (Josephs et al., 2014), and faster rates of hippocampal atrophy (Josephs et al., 2017a). Concomitantly, in patients with PART, TDP-43 is strikingly associated with amygdala and hippocampal atrophy (Josephs et al., 2019), which supports TDP-43 as being associated with temporal lobe atrophy across the entire range of Aβ and NFT deposition. Interestingly, in PART patients, there seems to be a topographic predilection for TDP-43 accumulation, as more inclusions were found in the atrophic left anteromedial temporal lobe region, compared to the right (Josephs et al., 2019). This is different from what is found in Alzheimer's disease patients, where a bilateral pattern of atrophy is associated with TDP-43 (Josephs et al., 2014), and similar to what is found in FTLD type C, a disorder clinically associated with semantic dementia, as seems to be the case with PART (Josephs et al., 2017b; Quintas-Neves et al., 2019). Moreover, high TDP-43 levels in PART was associated with smaller brain volumes, faster rates of brain atrophy and acceleration of atrophy rates, more than a decade prior to death, with deceleration occurring closer to death, particularly in the hippocampus compared to neocortical regions (Josephs et al., 2020). Additionally, TDP-43 and brain atrophy association in PART occurred 3 years later than in Alzheimer's disease (Josephs et al., 2020). Even though we were only able to analyze the impact of TDP-43 in a small subset of cases, our data further supports that TDP-43 contributes to atrophy in PART, but to a lesser extent in Alzheimer's disease. Overall, these observations suggest that tau (i.e., Braak stage) and TDP-43 contribute differently to the rate of brain atrophy over time in patients with PART or Alzheimer's disease.

Globally, after controlling for Braak, we found no major differences in the mean relative atrophy of the several regions evaluated between the four groups, suggesting that atrophy patterns are mainly Braak-dependent (i.e., dependent on the NFT deposition grade) and nondependent of the Aβ deposition. Since correcting for the effect of Braak staging globally nullifies the differences between PART and Alzheimer's disease spectrum CERAD 1–3 groups,

these observations remarkably confirm the widely known correlation between tau NFTs with regional brain atrophy and cognitive deficits, when compared to Aβ plaque distribution (Nelson et al., 2012). In the AT region, we found a nonsignificant trend for higher atrophy in "definite" PART versus the CERAD 1 group. This an interesting finding, which could be partially explained by the fact that Braak staging does not consider the most anterior part of the temporal lobe for grading (Braak and Braak, 1991). The fact that PART patients show a level of atrophy comparable to higher CERAD levels indicates that tau itself can exert neurodegenerative effects in PART without the concomitant presence of neuritic plaques. This is in agreement with animal studies showing increased brain atrophy in mice overexpressing human tau and in patients with tauopathy conditions (Wang and Mandelkow, 2016).

Interestingly, patients diagnosed with PART and dementia were previously shown to be older (eighth to ninth decades) than Alzheimer's disease patients, making unlikely the Aβ deposition starting at that point (Crary, 2016; Crary et al., 2014). In our study, patients with PART presented a mean age at death significantly lower than the sparse (CERAD 1) group and not significantly different from the moderate (CERAD 2) and severe (CERAD 3) groups. Moreover, despite not being older than the CERAD 1 and 2 groups, there was a tendency for PART patients to die at the same age (77.1 $\pm$ 12.4) as patients with severe Alzheimer's disease (77.4 $\pm$ 11.2). It has been shown that PART patients have slower cognitive decline than Alzheimer's disease patients across multiple neuropsychological domains (Teylan et al., 2020). Additionally, both "definite" and "possible" PART patients exhibit longitudinal cognitive decline that increases in severity with higher levels of NFT pathology (Jefferson-George et al., 2017).

The previously mentioned differences in the patterns of atrophy between PART and Alzheimer's disease patients are potentially important, as it has been described that, although clinicians recognize a distinction in the clinical presentation between Alzheimer's disease and PART, diagnosing Alzheimer's disease less frequently in patients with PART, clinical Alzheimer's disease can be diagnosed more than 50% of the time in PART patients with mild cognitive impairment or dementia (Teylan et al., 2019). This clinical remark makes brain MRI an important tool to differentiate PART from Alzheimer's disease, or to follow longitudinally PART patients identified by other biomarkers such as CSF or PET. However, given the scarcity of PART patients with Braak stages of III and IV, this is something to be tackled by future studies. We believe that in order to validate MRI as a clinical routine tool to use in PART patients, an easy to apply and practical visual rating scale could be a relevant tool to be used. Importantly, our results are globally in accordance with what others observed using volumetric approaches (Josephs et al., 2017b).

PET studies assessing in vivo Aβ and tau deposition are overall in agreement with our results showing that concomitant Aβ and tau pathology synergizes to lead to higher levels of brain atrophy and worse clinical outcome (Jack et al., 2019; Weigand et al., 2020). However, these studies do not segregate Aβ deposition, as performed for the CERAD staging. In the present study, we identified different pathological characteristics based on different CERAD stages, and in light of recent observations in PET-MRI studies that there are 4 subtypes of tau spreading patterns that also differ in their clinical characteristics (Vogel et al., 2021), it would be interesting to assess how these CERAD stages correlate with those identified tau pathology subtypes, that challenge the concept of "typical Alzheimer's disease."

Studies that assessed cognitive status using the CDR scoring system found that within the same stratum of CDR scores, individuals with PART had relative sparing of semantic memory/language in comparison to Alzheimer's disease (Besser et al., 2019). Moreover, participants with Alzheimer's disease had a significantly steeper decline after becoming clinically symptomatic than those with PART (Teylan et al., 2020). Our results showed that overall cognition deficits (given by CDR-SB) are directly correlated with regional atrophy in patients with Alzheimer's disease, but not in patients with PART (Fig. 3A–F). Additionally, we observe significant differences between the regression lines of both groups (i.e., PART vs. Alzheimer's disease) for the AT and posterior regions. These results indicate that PART and Alzheimer's disease show different atrophy patterns, which correlate poorly with global cognitive deficits in patients with PART. This is in accordance with the previously mentioned steeper decline that Alzheimer's disease patients experience, when compared to PART (Teylan et al., 2020). This dissociation might be due to other comorbid pathologies that were shown to contribute to cognitive impairment in patients with PART, such as cerebrovascular disease (Fulcher et al., 2014). Therefore, in the future, it would be relevant to identify and characterize how brain MRI markers of vascular pathology affect the brains of patients with PART.

Additionally, our results focusing on a broader neuropsychological assessment show a focal deficit of language in PART correlating with AT atrophy, whereas in AD we find widespread correlations between regional atrophy and cognitive deficits. This is in accordance with our previous study showing that the anterior temporal region in PART correlates with semantic memory/fluency tests (Quintas-Neves et al., 2019) and other reports showing longitudinal semantic cognitive decline (Jefferson-George et al., 2017) and higher deficits in PART compared to neuropathology negative controls (Weigand et al., 2020). Importantly, the more widespread and differential pattern of cognitive impairment in Alzheimer's disease is in line with the literature (Savola et al., 2021; Teylan et al., 2020; Weigand et al., 2020).

This study had important limitations. First, it was based on a convenience, autopsy-based sample, which limits its extrapolation. The NACC database has limitations in its generalizability, given that participants tend to be more often Caucasian and more affluent than the general population. However, there was no additional selection bias of the participants considered in our sample, as we chose all eligible participants with neuropathologically defined PART or Alzheimer's disease who had an MRI available at most 4 years before death. Second, the use of visual rating scales, even when performed by trained neuroradiologists, is associated with interobserver variability. However, with training and neuroradiologic experience, using a reference visual scale during the rating process reduces this bias effect. Third, the variability in scanner manufacturers and field strengths were potential sources of biases/variability. Fourth, the patients included in our sample had incomplete clinical information on other co-morbidities that could be associated with brain atrophy, such as hypertension or dyslipidemia, or on other neuropathologic features, such as TDP-43 pathology. Fifth, Braak staging is considered an incomplete measure of tau burden and it would be beneficial to have additional quantitative measures of such parameter. However, this requires additional special staining, a process that is time-consuming and not currently performed at most centers. Furthermore, it is not available in the NACC neuropathology database (Neltner et al., 2012; Walker et al., 2017). Finally, the retrospective nature of the study is also a potential source of bias. For instance, since the only difference in selecting the participants was having performed an MRI scan, we hypothesize this contingency in patient selection, could partially explain the discrepancies in the age at death comparing with other studies using the NACC database (Teylan et al., 2019). Despite the aforementioned limitations, this study has several major strengths: the use of multicentric data on a large group of individuals across the USA, the constantly performed standard-

ized process of collecting global CDR (among other clinical variables) in every UDS visit, the use of standardized neuropathological criteria to assess pathology at autopsy (Montine et al., 2016), the preferential use of volumetric acquisitions, and a relevant number of participants with PART and Alzheimer's disease.

In conclusion, the findings of this study support the hypothesis that PART is a separate pathological process from the Alzheimer's disease "continuum." Future studies should address and expand: the independent or cumulative impact of Aβ, tau and other aggregates, such as TDP-43, on brain regional atrophy, using cases of Alzheimer's disease, PART and, eventually, the recently proposed pathological entity limbic-predominant age-related TDP-43 encephalopathy (LATE) (Nelson et al., 2019). Finally, the characterization of PET and CSF findings in symptomatic and asymptomatic PART patients could provide diagnostic biomarkers to follow their longitudinal evolution.

Disclosure statement

The authors report no conflicts of interest.

Authors' contributions

T.G.O. and J.F.C. conceived the idea. T.G.O., J.F.C., C.M., F.A., R.M., M.A.T., and M.Q. designed and planned the analysis. T.G.O. and M.Q. performed neuroimaging analysis. W.A.K., C.M., and MAT contributed with subject data.

T.G.O., M.Q., R.M., and F.A. conducted data analysis. T.G.O., M.Q., and F.A. wrote the manuscript. All authors reviewed and corrected the manuscript. All authors read and approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.04.013.

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