

RESEARCH ARTICLE

The relationship between hippocampal amyloid beta burden and spatial distribution of neurofibrillary degeneration

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Abstract

Introduction: Neurofibrillary degeneration in Alzheimer's disease (AD) typically involves the entorhinal cortex and CA1 subregion of the hippocampus early in the disease process, whereas in primary age-related tauopathy (PART), there is an early selective vulnerability of the CA2 subregion.

Methods: Image analysis-based quantitative pixel assessments were used to objectively evaluate amyloid beta (A β) burden in the medial temporal lobe in relation to the distribution of hyperphosphorylated-tau (p-tau) in 142 cases of PART and AD.

Results: Entorhinal, CA1, CA3, and CA4 p-tau deposition levels are significantly correlated with A β burden, while CA2 p-tau is not. Furthermore, the CA2/CA1 p-tau ratio is inversely correlated with A β burden and distribution. In addition, cognitive impairment is correlated with overall p-tau burden.

Discussion: These data indicate that the presence and extent of medial temporal lobe A β may determine the distribution and spread of neurofibrillary degeneration. The resulting p-tau distribution patterns may discriminate between PART and AD.

KEYWORDS

Alzheimer's disease, amyloid beta, image analysis, neurodegeneration, neurofibrillary degeneration, primary age-related tauopathy, tau

Highlights

- Subregional hyperphosphorylated-tau (p-tau) distribution is influenced by hippocampal amyloid beta burden.
- Higher CA2/CA1 p-tau ratio is predictive of primary age-related tauopathy-like neuropathology.
- Cognitive function is correlated with the overall hippocampal p-tau burden.

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common underlying cause of cognitive impairment worldwide. The neuropathologic diagnosis of AD is dependent on the presence of amyloid beta ($A\beta$) plaques and abnormal hyperphosphorylated tau (p-tau) immunoreactive neurofibrillary degeneration, both of which are thought to progress through the brain in well-characterized patterns. While there is some degree of p-tau present in almost all individuals > 20 years of age, this remains largely of low burden and regionally confined to the brainstem and subcortical nuclei in younger adults.^{1,2} Neurofibrillary degeneration progresses from the medial temporal region to the neocortex in six successive Braak stages,³ while $A\beta$ progresses from neocortex to limbic structures, brainstem, and cerebellum in five Thal phases.⁴ These changes are thought to be interrelated, and can be used to assess the overall severity of AD neuropathologic change (ADNC) in *post mortem* brain tissue.⁵

Primary age-related tauopathy (PART) is a term describing an $A\beta$ -independent tauopathy characterized by 3R- and 4R-tau positive paired helical filaments (AD-type neurofibrillary tangles) that includes cases previously described as "tangle-only senile dementia," "tangle-predominant senile dementia," and "age-related neurofibrillary degeneration," as well as non-demented individuals harboring tauopathy with a similar neuroanatomical distribution. The neurofibrillary degeneration in PART is largely confined to the medial temporal region, roughly corresponding to Braak stages I–IV. Recent evidence has suggested that this hierarchical progression of neurofibrillary degeneration does not correspond as well to cognitive status in PART as it does in AD.^{6,7} Two general categories of PART are currently recognized: "definite PART," which consists of Braak stage I–IV neurofibrillary degeneration in the absence of any $A\beta$ deposition (Thal phase 0 and Consortium to Establish a Registry for Alzheimer's Disease [CERAD] neuritic plaque [NP] score "absent"), and "possible PART," which consists of Braak stage I–IV neurofibrillary degeneration with Thal phase 1–2 $A\beta$ deposition and/or CERAD NP score "sparse."⁸ Recent studies have demonstrated an early selective vulnerability for neurofibrillary degeneration in the CA2 hippocampal subregion, in contrast to AD, where the neurofibrillary degeneration is most severe in the entorhinal cortex and CA1 subregion initially, with relative sparing of CA2 until later in the disease course.^{7,9} It has also been suggested that non-demented elderly individuals without senile plaques may be separated into distinct groups: one with prominent CA2 neurofibrillary degeneration and one with a greater burden of disease in the entorhinal and CA1 subregion with relative CA2 sparing.^{10,11} Other differences between AD and PART have been described, including apolipoprotein E (APOE) allele status and MAPT haplotypes,^{12,13} although there has long been debate as to whether PART simply represents part of the ADNC spectrum.^{14,15}

In this study, we examine the relationship between medial temporal lobe $A\beta$ deposition and the neuroanatomical distribution of p-tau. Using image analysis-based assessments of whole slide images of immunohistochemically stained tissue sections, we objectively determined the positive pixel counts of $A\beta$ and p-tau to explore how the p-tau

RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors reviewed the literature using online journal sources. The distribution of neurofibrillary degeneration and amyloid beta ($A\beta$) deposition in Alzheimer's disease (AD) have been studied thoroughly (Braak stages and Thal phases). However, how hyperphosphorylated tau (p-tau) distribution differs in relation to $A\beta$ deposition has not. Relevant literature is appropriately cited.
- 2. Interpretation:** Although it is known that $A\beta$ and tau interact and work synergistically in AD, it is unclear how or why. By studying primary age-related tauopathy and AD cases with varying degrees of $A\beta$ burden, we have demonstrated that the amount of hippocampal $A\beta$ deposition may dictate regional neurofibrillary degeneration distribution.
- 3. Future Directions:** This article describes the development of AD-type pathologic changes, as well as what normal aging may look like in comparison, which could be translated to imaging studies and used for diagnostic purposes, in addition to histopathologic analysis of $A\beta$ and tau in additional brain regions and spatial multiomic studies.

burden in individual hippocampal subregions is affected by increasing $A\beta$ burden. Our results suggest that the two processes are linked at the level of the hippocampus, resulting in divergent "PART-like" and "ADNC-like" patterns of hippocampal pathology.

2 | METHODS

2.1 | Patient samples

One hundred forty-two autopsy cases from the previously described multi-institutional PART working group (PWG) cohort were used.^{6,7,16–19} The participants, 46% male, ranged in age from 61 to 108 years (mean age 89.5 ± 0.9 years), Braak stage from I to V, Thal phase from 0 to 4, and CERAD NP score "absent" to "frequent" (Table 1). Fifty individuals had a diagnosis of "definite" PART (Braak stage I–IV, Thal phase 0, and CERAD NP score "absent"), 73 individuals had a diagnosis of "possible" PART (Braak stage I–IV and Thal phase 1–2 and/or CERAD NP score "sparse"), and 19 individuals had a diagnosis of ADNC (Braak stage I–VI, Thal phase 3–5, and/or CERAD NP score "moderate" or "frequent") to represent the full spectrum of p-tau and $A\beta$ pathology in the entorhinal cortex and hippocampal subregions.^{5,7,8} Clinical exclusion criteria included patient age < 50 years and presence of frontotemporal dementia, movement disorder, or motor neuron disease.⁷ Cognitive information, including Clinical Dementia Rating (CDR) Global Score, was available for 98 subjects.

TABLE 1 Overview of demographic, clinical, and pathologic features

Thal phase	n	Age (years)	% Male	Braak stage			CERAD NP score		Cognitive status*		
				I–II	III–IV	V–VI	None	Sparse+	Normal	MCI	Dementia
0	53	88.3 ± 1.6	54%	7	46	0	50	3	28	9	5
1	32	87.9 ± 2.0	44%	0	32	0	31	1	14	12	5
2	46	93.8 ± 0.9	46%	4	41	1	30	16	11	6	10
3	8	89.2 ± 4.2	33%	2	4	2	4	4	2	1	3
4	3	91.6 ± 1.3	0%	0	3	0	1	2	0	1	1
5	0	–	–	–	–	–	–	–	–	–	–
Total	142	89.5 ± 0.9	46%	13	126	3	116	26	55	19	24

*Only a portion of cases had cognitive data available.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MCI, mild cognitive impairment; NP, neuritic plaque.

2.2 | Immunohistochemistry

Histological staining methods have been described previously.⁷ Briefly, hippocampal sections (level 7)²⁰ and middle frontal gyrus sections were available for each case. Formalin-fixed paraffin-embedded (FFPE) tissue sections (5 µm thick) were mounted on charged slides and baked at 70°C. Luxol Fast Blue/hematoxylin & eosin (LFB/H&E), Bielschowsky silver stain, phospho-tau (p-tau) immunohistochemistry (IHC; AT8; MN1020, Thermo Fisher Scientific), and Aβ IHC (6E10; SIG-39320, Covance, Inc.) were performed on all sections on a Leica Bond III automated stainer (Leica Biosystems), according to the manufacturer's protocols. All slides were imaged to generate whole slide digital images using an Aperio CS2 scanner (Leica Biosystems) at 20x magnification at The University of Texas Southwestern Medical Center (Dallas, TX). For each case, Braak stage (0–V)³, Thal phase (0–4)⁴, and CERAD NP score ("absent"–"frequent")⁵ were reassessed in a previous publication using appropriate consensus criteria to ensure consistency in diagnoses.⁷ The relative density of p-tau and Aβ in each hippocampal subregion (entorhinal cortex, CA1/subiculum, CA2, CA3, and CA4) were assessed by a semi-quantitative scoring system (0–3), as previously described.⁷

2.3 | Computer-assisted assessments of p-tau and Aβ

Segmentation of hippocampal subfields (entorhinal cortex, CA1/subiculum–CA4 subregions) was performed on scanned hippocampal sections, using Aperio ImageScope software.^{6,16} For p-tau analysis, CA2 was defined neuroanatomically with boundaries drawn at the most compact region of cornu ammonis neurons. CA4 was defined as the region enclosed by the dentate gyrus. CA3 was defined as the region between CA2 and CA4. CA1/subiculum was defined as the region between CA2 and the hippocampal fissure, and included stratum oriens to stratum moleculare (Figure 1A–F and M–R). For Aβ analysis, the hippocampus proper (subiculum, CA1–4, dentate gyrus) and adjacent entorhinal region were assessed as separate and combined regions (Figure 1G–L and S–X), as previously described.⁶ Defects in the sections (including artifacts such as tears and folds) and other

features (including perivascular hemosiderin, iron, and calcifications) which may cause false positive or false negative pixel counts were excluded where possible using the Aperio ImageScope Negative Pen Tool (Figure 1H and Figure 1T).

p-tau and Aβ burdens were determined using Aperio ImageScope positive pixel count (Version 9) using default parameters (intensity threshold for weak positive pixels [upper limit] = 220, intensity threshold for weak positive pixels [lower limit] = 175, intensity threshold for medium positive pixels [lower limit] = 100, intensity threshold for strong positive pixels [lower limit] = 0), and the same thresholds were used for each slide.^{6,16} In each measured region, the number of medium and strong positive pixels and total pixels were recorded and used to create a ratio from 0 to 1 of positive pixels/total pixels of both p-tau and Aβ, termed the positive pixel percentage (PPP). For validation, we first performed these analyses on the positive control ADNC case run with each staining batch to ensure consistency.^{6,16} Pairs plotting was performed in R using the ggplot2 and Ggally packages.

2.4 | Statistical analysis

All statistical analysis was performed using GraphPad Prism version 9 (GraphPad Software, Inc.). Correlations among Aβ burden, Thal phase, Braak stage, age, and p-tau levels and ratios were made using linear regression modelling using Pearson correlation coefficient. Comparisons between diagnostic groups (i.e., Aβ burden and CA2/CA1 p-tau ratio in ADNC vs. PART) were performed using Student's *t* test. Statistical significance was set at $\alpha = 0.05$.

3 | RESULTS

3.1 | Interaction between hippocampal Aβ burden and p-tau burden and distribution

In cases with greater hippocampal Aβ burden (determined by PPP of the combined hippocampus proper and entorhinal region), the

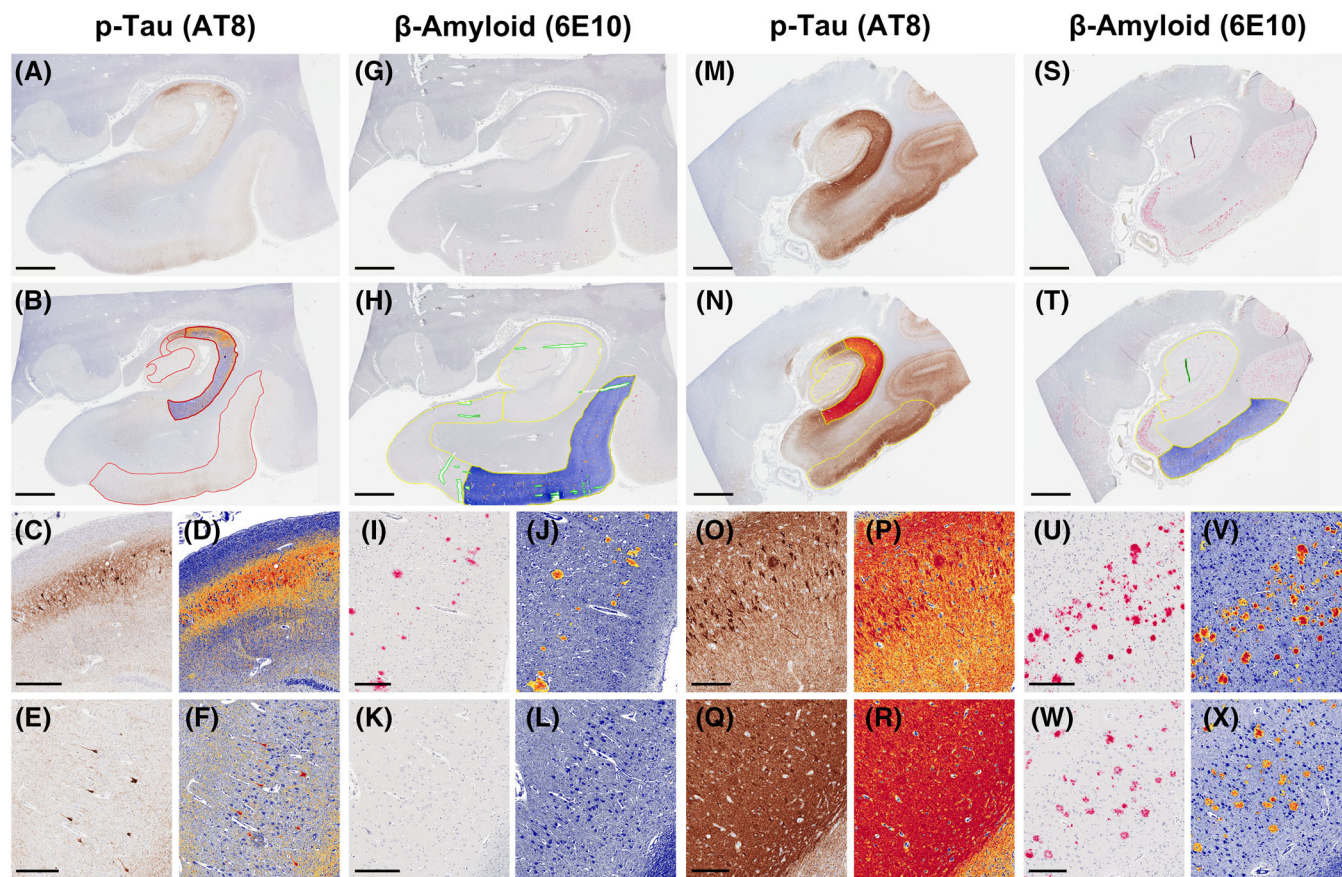


FIGURE 1 Demonstration of neuroanatomical segmentation and quantification of hyperphosphorylated tau (p-tau) and amyloid beta ($A\beta$) immunopositive pixels in $A\beta$ negative (primary age-related tauopathy-like) and positive (AD neuropathologic change-like) subjects. A-B, p-tau quantification in the first subject (CA1 subregion segmentation highlighted), showing high-power views of the CA2 (C-D) and CA1 (E-F) hippocampal subfields. G-H, $A\beta$ quantification in the first subject (entorhinal cortex segmentation highlighted), showing high-power fields of the entorhinal cortex (I-J) and CA1 hippocampal subfield (K-L). M-N, p-tau quantification in the second subject (CA1 subregion segmentation highlighted), showing high-power views of the CA2 (O-P) and CA1 (Q-R) hippocampal subfields. S-T, $A\beta$ quantification in the second subject (entorhinal cortex segmentation highlighted), showing high-power fields of the entorhinal cortex (U-V) and CA1 hippocampal subfield (W-X). Scale bars for (A-B), (G-H), (M-N), and (S-T) = 3 mm. Scale bars for (C-F), (O-P), (U-X) = 400 μ m. Scale bars for (I-L) = 300 μ m. Scale bars for (Q-R) = 500 μ m

overall hippocampal p-tau burden (determined by PPP of the combined hippocampus proper and entorhinal region) was significantly higher (Pearson's $r = 0.35$; $P < 0.0001$; Figure 2A-L and Figure 3A). In addition, the p-tau burden was positively correlated with $A\beta$ burden in the entorhinal region ($r = 0.24$; $P = 0.0036$) and the CA1 ($r = 0.37$; $P < 0.0001$), CA3 ($r = 0.26$; $P = 0.0018$), and CA4 ($r = 0.20$; $P = 0.0220$) hippocampal subfields, but not the CA2 hippocampal subfield ($r = 0.03$; $P = 0.6845$; Figure 3B-F). The CA2/CA1 p-tau ratio was significantly lower with increasing $A\beta$ burden ($r = -0.35$; $P = 0.0019$; Figure 2M-N and Figure 4A) as well as with increasing Thal phase ($r = -0.30$; $P = 0.0013$; Figure 4B). The CA2/CA1 p-tau ratio was also inversely correlated with the $A\beta$ burden in the hippocampus proper ($r = -0.20$; $P = 0.0197$; Figure 4C), as well as the hippocampus proper/combined hippocampus proper and entorhinal $A\beta$ ratio ($r = -0.17$; $P = 0.0418$; Figure 4D). These data suggest that the p-tau burden and the spatial distribution of p-tau

within the hippocampus are related to both the overall level of $A\beta$ present, as well as the progression of amyloid from neocortex (Thal phase 1) to entorhinal cortex to hippocampus proper. The overall p-tau burden significantly increased with patient age ($r = 0.28$; $P = 0.0025$); however, the CA2/CA1 p-tau ratio was not significantly correlated with age ($r = -0.04$; $P = 0.6767$; Figure S1 in supporting information).

Cases that qualified as ADNC based on a combination of Braak stage, Thal phase, and CERAD NP score⁵ had no significant difference in age compared to definite PART (90.3 ± 2.0 vs. 88.3 ± 1.5 ; $P = 0.4523$) and combined definite and possible PART (89.5 ± 1.0 ; $P = 0.7620$). ADNC cases had significantly higher $A\beta$ burden compared to cases that qualified as definite PART (0.11 ± 0.01 vs. 0.004 ± 0.001 PPP; $P < 0.0001$) and combined definite and possible PART (0.02 ± 0.003 PPP; $P < 0.0001$; Figure 5A-B), as well as significantly higher overall p-tau burden compared to definite PART (0.30 ± 0.03 vs. 0.19 ± 0.01 PPP;

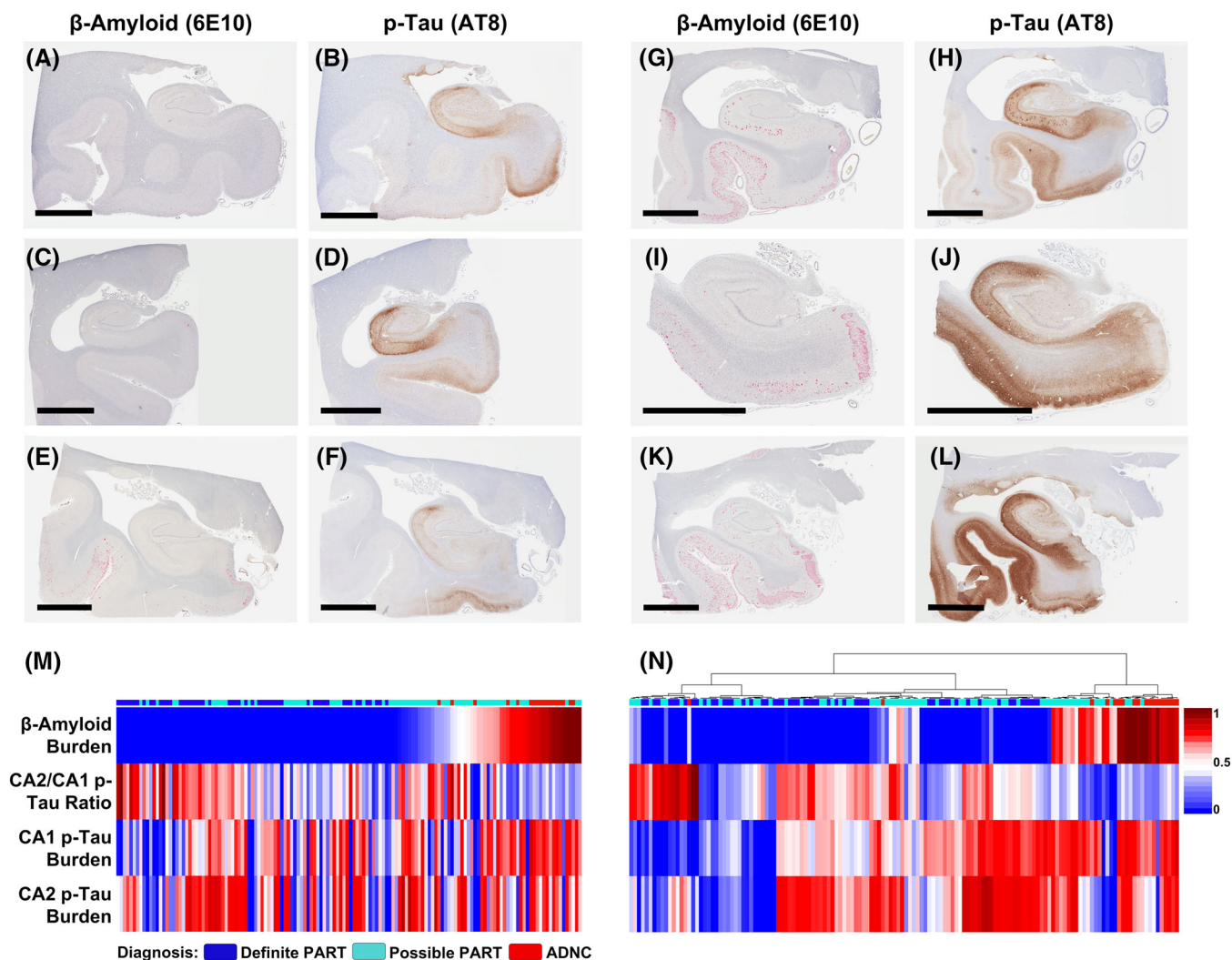


FIGURE 2 Paired images of hyperphosphorylated tau (p-tau) and amyloid beta ($A\beta$) immunohistochemical stains from six representative cases: 3 primary age-related tauopathy-like with minimal $A\beta$ deposition (A-F) and 3 AD neuropathologic change-like with greater $A\beta$ deposition (G-L), illustrating a trend toward higher overall hippocampal p-tau burden and lower CA2/CA1 p-tau ratio with higher $A\beta$ burden. Scale bar in all panels = 6 mm. Heatmaps demonstrating the CA2/CA1 p-tau ratio, as well as CA1 and CA2 p-tau burdens in relation to $A\beta$ burden in individual cases (M) ranked by $A\beta$ burden and (N) ranked by hierarchical clustering using a Euclidean distance metric. Note: all measured values were normalized to fit a 0–1 scale by dividing each value by the highest value to allow for heatmap comparison

$P = 0.0002$) and combined definite and possible PART (0.20 ± 0.01 PPP; $P = 0.0002$; Figure 5C-D). ADNC cases had a significantly higher CA1 p-tau burden compared to definite PART (0.30 ± 0.03 vs. 0.19 ± 0.02 PPP; $P = 0.0024$) and combined definite and possible PART (0.23 ± 0.01 PPP; $P = 0.0251$), but did not differ in terms of CA2 p-tau burden compared to definite PART (0.25 ± 0.03 vs. 0.26 ± 0.02 PPP; $P = 0.8721$) or combined definite and possible PART (0.27 ± 0.01 PPP; $P = 0.6046$). ADNC cases had a significantly lower CA2/CA1 p-tau ratio compared to definite PART (0.92 ± 0.16 vs. 1.45 ± 0.12 PPP; $P = 0.0202$) and combined definite and possible PART (1.33 ± 0.07 PPP; $P = 0.0413$; Figure 5E-F). In addition, ADNC cases had a significantly lower CA2/entorhinal p-tau ratio compared to definite PART (0.84 ± 0.15 vs. 1.87 ± 0.26 PPP; $P = 0.0288$), although there was only a non-significant trend toward this compared to combined definite and possible PART ($P = 0.1433$).

Only 3 cases that met criteria for ADNC had a CA2/CA1 p-tau ratio greater than 1 (16%), compared to 37 cases of definite PART (69%; $P = 0.0002$) and 80 cases of combined definite and possible PART (65%; $P < 0.0001$). In addition, receiver operating characteristic (ROC) curves demonstrated that the CA2/CA1 p-tau ratio discriminates between ADNC and definite PART (area under the curve [AUC] = 0.81; $P = 0.0002$; Figure 5G) and combined definite and possible PART (all PART; AUC = 0.75; $P = 0.0007$; Figure 5H). Pairs plot of $A\beta$ and sub-regional p-tau burdens demonstrated separate peaks between ADNC and definite/possible PART cases in terms of $A\beta$ burden, overall p-tau burden, entorhinal p-tau burden, and CA1 p-tau burden, while CA2 p-tau burden has overlapping peaks, suggesting two separate histomorphologic entities within this overall cohort. Similar findings were observed between $A\beta$ -positive and $A\beta$ -negative cases (Figure S2 in supporting information).

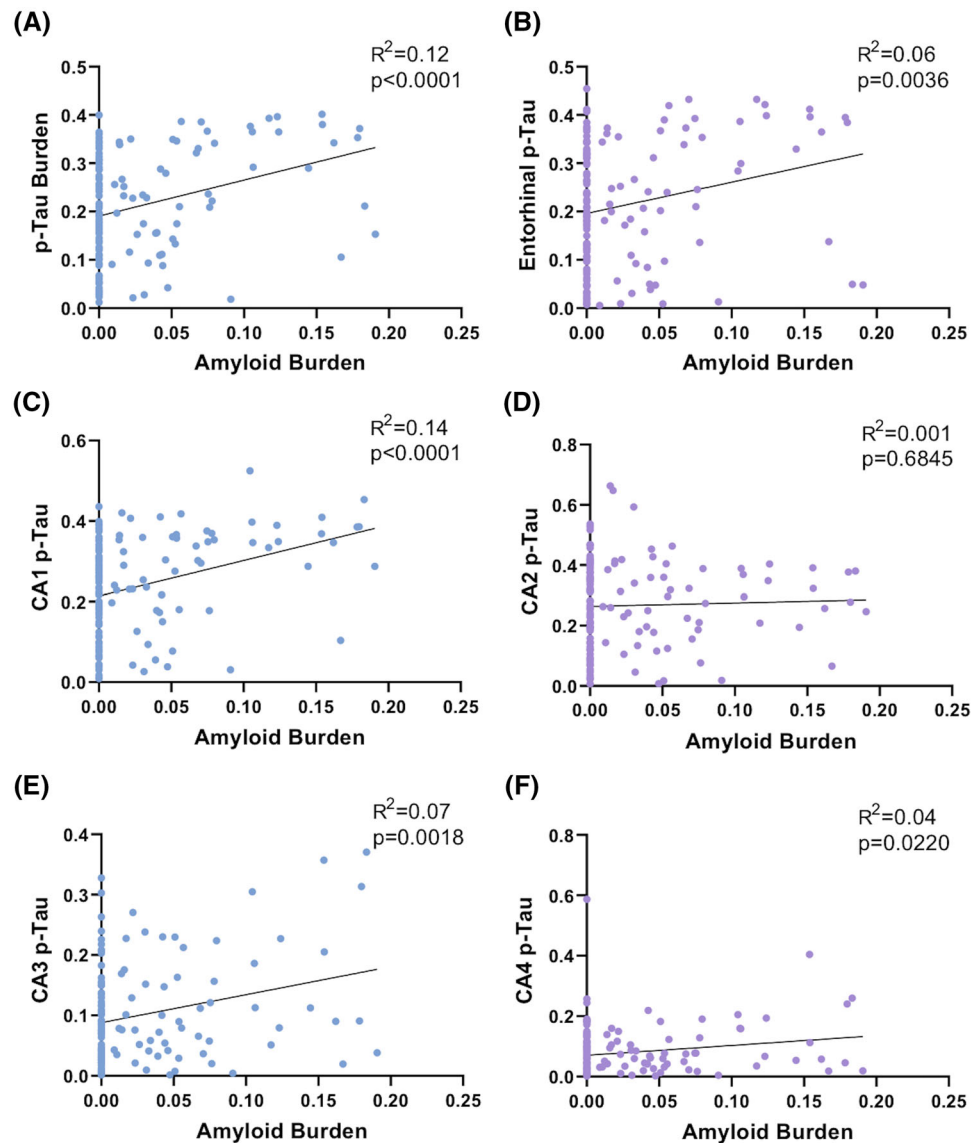


FIGURE 3 Hyperphosphorylated tau (p-tau) burden in each hippocampal subregion except CA2 correlates with hippocampal amyloid beta ($A\beta$) burden. Linear correlation between hippocampal $A\beta$ burden and (A) overall hippocampal p-tau burden, (B) entorhinal p-tau burden, (C) CA1 p-tau burden, (D) CA2 p-tau burden, (E) CA3 p-tau burden, and (F) CA4 p-tau burden

3.2 | Comparison of semiquantitative and quantitative methods

To compare the Aperio ImageScope-generated quantitative measurements against previously established semiquantitative measurements, we established a direct correlation between Thal phase and overall $A\beta$ burden PPP ($r = 0.69$; $P < 0.0001$; Figure S3A in supporting information), Braak stage and overall p-tau burden PPP ($r = 0.57$; $P < 0.0001$; Figure S3B), and CA2/CA1 p-tau ratio (determined by previous semiquantitative scoring systems^{7,21}) and quantitative CA2/CA1 p-tau ratio ($r = 0.64$; $P < 0.0001$; Figure S3C), confirming the validity of both techniques. These data also suggest, however, that there is a great deal of variation in hippocampal $A\beta$ burden in Thal phase 2 and p-tau burden in Braak stages III and IV, suggesting that the quantita-

tive measures may be better at capturing the full extent of hippocampal pathology than more topographical measurements such as Thal phase and Braak stage (Figure S3A-B).

3.3 | Clinical correlations

Clinical data in the form of CDR Global Scores were available for 98 of the subjects included in this study. There was a non-specific trend toward increasing CDR with increasing hippocampus proper/entorhinal cortex $A\beta$ ratio and overall $A\beta$ burden ($r = 0.14$; $P = 0.1464$; Figure 6A). CDR was significantly correlated with the overall p-tau burden ($r = 0.20$; $P = 0.0385$) (Figure 6B), but not CA2/CA1 p-tau ratio ($r = 0.14$; $P = 0.3082$), CA1 p-tau burden ($r = 0.17$;

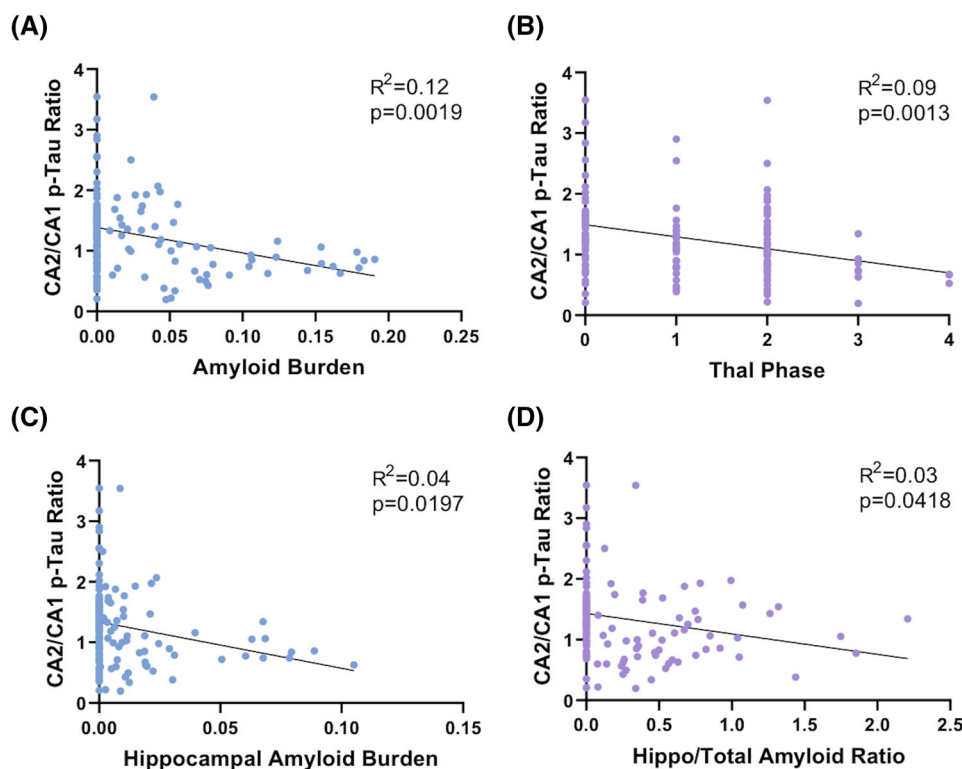


FIGURE 4 The CA2/CA1 hyperphosphorylated tau (p-tau) ratio is inversely correlated with amyloid beta ($A\beta$) deposition. Correlation of CA2/CA1 p-tau ratio with (A) $A\beta$ burden in the overall combined hippocampus and entorhinal cortex, (B) Thal phase, (C) $A\beta$ burden in the hippocampus proper only (excluding entorhinal cortex), and (D) hippocampal/total $A\beta$ ratio

$P = 0.0850$; Figure 6C), or CA2 p-tau burden ($r = 0.14$; $P = 0.0939$; Figure 6D). There was also a significant direct correlation between patient age at death and CDR ($r = 0.26$; $P = 0.0060$), although this may be related to the direct correlation between age and overall p-tau burden (Figure S1) or the tendency to accumulate additional comorbidities with increasing age.^{22,23} No significant correlations were found among p-tau, $A\beta$, or CDR in terms of APOE allele status or MAPT haplotype within this dataset.

4 | DISCUSSION

PART is a $A\beta$ -independent tauopathy with different clinical,^{24–27} radiographic,^{28,29} morphologic,^{7–9} and genetic^{12,13,17,27} profiles compared to ADNC, although there remains controversy over the exact relationship between these two processes.^{14,15} Neurofibrillary degeneration in ADNC progresses almost invariably from the medial temporal lobe to the neocortex in stereotypical Braak stages,³ while the $A\beta$ deposition begins in the neocortex and progresses through the limbic system and into the brainstem and cerebellum,⁴ often initially coexisting in the same space at the level of the entorhinal cortex and hippocampus, although recent imaging data suggests that there may be multiple distinct potential patterns of p-tau progression through the brain, complicating our understanding of this process.³⁰ In contrast, while PART may exist in the presence of minimal $A\beta$ deposition,^{7,8} the neurofibrillary degeneration is thought to be a $A\beta$ -independent

process, and generally does not progress past the medial temporal lobe (Braak I–IV).^{7,8,31} Within the hippocampus, morphological differences have been noted between the two processes as well. ADNC tends to affect the entorhinal cortex and CA1 hippocampal subfields initially, while PART frequently displays early neurofibrillary degeneration in the CA2 subfield with less severe entorhinal and CA1 p-tau deposition.^{7,9,21} Clinically, it is unclear if PART pathology alone correlates with significant cognitive symptoms. In PART cohorts, cognitive impairment does not appear to be related to Braak stage (as it is in AD), but appears to be affected primarily by the overall p-tau burden in the hippocampus and entorhinal cortex (Figure 6) as well as other comorbidities, including hippocampal atrophy, cerebrovascular disease, white matter abnormalities, the presence of aging-related tau astroglialopathy, and the degree of limbic-predominant age-related TDP-43 encephalopathy neuropathologic change.^{6,7,18,32} Furthermore, there is evidence that the hippocampal pathology in PART and early AD may develop asymmetrically in some individuals, which may provide a source of cognitive reserve.²¹ In addition, anterior temporal lobe atrophy in neuropathologically confirmed PART cases negatively correlated with performance on the Boston Naming Test, suggesting there may be clinical deficits in PART related to confrontational word retrieval.²⁸ Although the exact function of the hippocampal CA2 subregion is not known, it has been proposed to be involved in social memory³³ and encoding face–name pairs.³⁴

In addition to the early involvement of the CA2 hippocampal subregion and the general absence of $A\beta$ deposition in PART, we previously

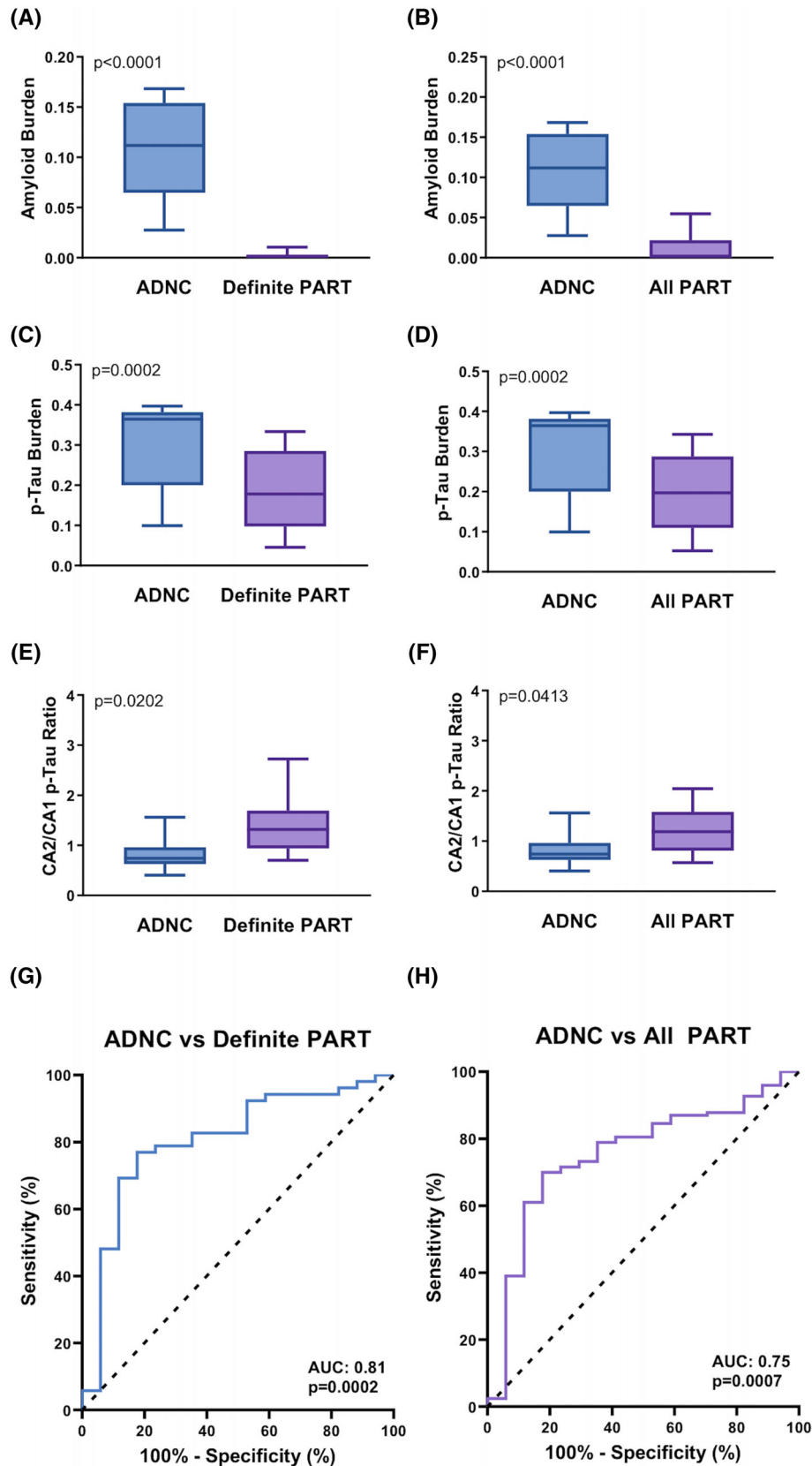


FIGURE 5 Comparison of amyloid beta ($A\beta$) and hyperphosphorylated tau (p-tau) burden in Alzheimer's disease neuropathologic change (ADNC) and primary age-related tauopathy (PART) cases. ADNC versus definite PART and all PART cases in terms of (A-B) overall $A\beta$ burden, (C-D) overall p-tau burden, and (E-F) CA2/CA1 p-tau ratio. Receiver operating characteristic curves demonstrating the predictive value of CA2/CA1 p-tau ratio in discriminating between (G) ADNC and definite PART and (H) ADNC and combined definite and possible PART (all PART)

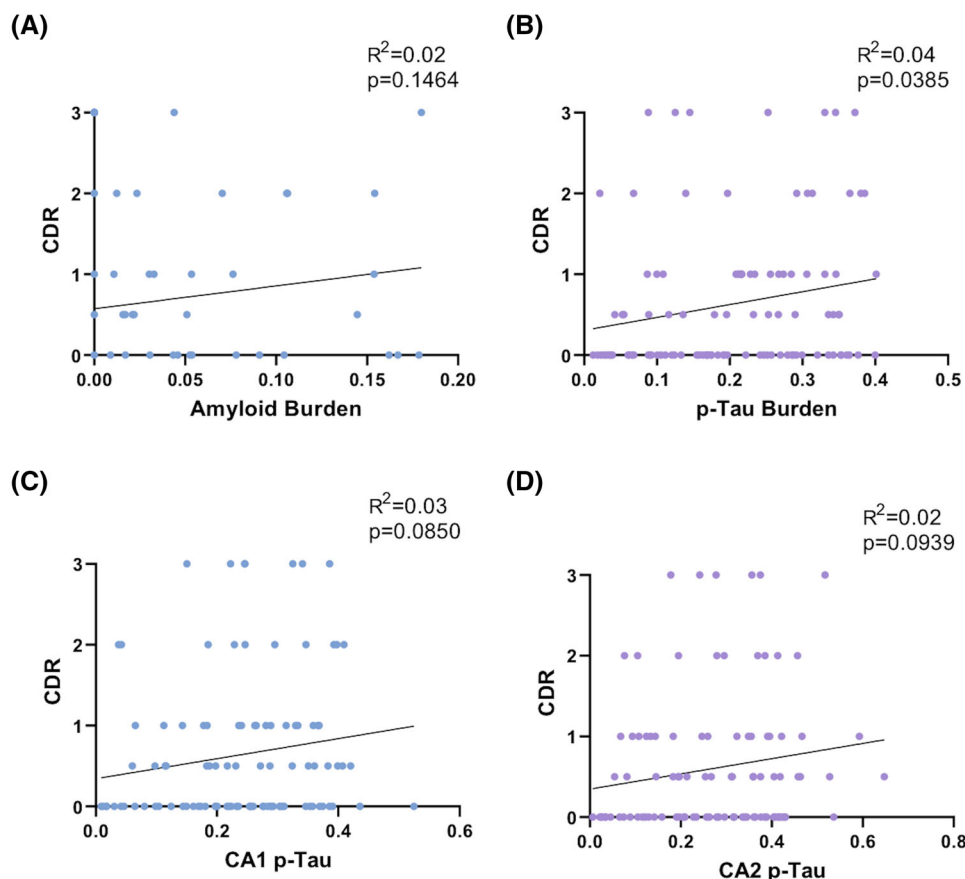


FIGURE 6 Clinical and quantitative pathology comparisons. A, Amyloid burden and Clinical Dementia Rating (CDR), (B) overall hyperphosphorylated tau (p-tau) burden and CDR, (C) CA1 p-tau burden and CDR, and (D) CA2 p-tau burden and CDR, demonstrating a significant correlation only between CDR and overall p-tau burden

noted that there was an inverse relationship between the semiquantitatively measured CA2/CA1 p-tau ratio and Thal phase, and that Thal phase 3 cases with CERAD NP scores of “absent” had significantly higher CA2/CA1 p-tau ratio than subjects with CERAD NP scores of “sparse” to “frequent,”⁷ suggesting that there is a relationship between the A β burden and the hippocampal distribution pattern of p-tau. Here, we used image analysis to quantitatively measure the level of A β and p-tau in the entorhinal cortex and hippocampal subfields to further explore the interaction between the two aggregated proteins at the level of the hippocampus. These data indicate that the level of A β is significantly correlated to the level of p-tau in the entorhinal cortex and all of the individual hippocampal subfields except CA2 (Figure 3), and the CA2/CA1 p-tau ratio is inversely correlated with the A β burden (Figure 4A). The quantitatively assessed CA2/CA1 p-tau ratio is also inversely correlated with Thal phase, A β burden in the hippocampus proper (excluding the entorhinal cortex), and the A β hippocampus proper/combined hippocampus proper and entorhinal cortex ratio (Figure 4B–D). This suggests that the presence of A β at the level of the hippocampus may in part be responsible for the distribution pattern of p-tau, and that the amount and location of A β influences the deposition of p-tau. Subjects with greater A β burden and A β progression from the entorhinal cortex into the hippocampal proper (AD-like)

are more likely to have higher entorhinal and CA1 p-tau deposition compared to CA2 (in an AD-type distribution), whereas subjects with absent or more restricted A β burden (PART-like) are more likely to have a higher CA2/CA1 p-tau ratio (Figure 2). Further evidence for A β burden influencing the vulnerability of CA2 comes from the fact that A β -independent 4R-tauopathies, such as progressive supranuclear palsy and corticobasal degeneration, tend to preferentially affect CA2.³⁵

An alternative explanation to the concept that A β burden in the medial temporal lobe dictates the regional spread of neurofibrillary degeneration in the hippocampus is that the specific spatial deposition of p-tau may dictate the amount and location of A β plaques (i.e., early deposition of CA2 p-tau is somehow “protective” against A β deposition). In either scenario, there is a strong correlation between the A β plaque burden and the neurofibrillary degeneration burden and pattern, suggesting that these two proteins may initially interact with one another within the medial temporal lobe. Interestingly, we have shown previously that proteins specifically related to A β processing are upregulated in neurofibrillary tangle (NFT)-bearing neurons of symptomatic AD patients, but not in normal non-NFT-bearing neurons in the same patients, or NFT-bearing neurons of resilient, cognitively intact individuals, and the microenvironments surrounding NFT-bearing neurons

in subjects with dementia have higher levels of proteins related to inflammation and lower levels of proteins associated with healthy synapses.³⁶ This suggests that the interaction between A β and p-tau may play some role in the development of overall hippocampal pathology as well as cognitive symptoms,³⁷ although only overall p-tau burden was found to have a significant effect on cognition in the study cohort (Figure 6).

Imaging studies have found an association between regional A β accumulation and p-tau aggregation.^{38,39} The working model is that extracellular A β plaques increase neuronal excitability, triggering tau hyperphosphorylation and dissociation from microtubules, secreted as soluble p-tau, which is thought to “seed” other neurons leading to NFT accumulation. It is unclear how definite PART would fit within this model as it does not display A β accumulation, yet still harbors NFTs, unless PART and AD have different mechanisms for p-tau accumulation.

It has also been suggested that PART may simply represent an early step in the spectrum of AD with p-tau–predominant features, or a stage of AD before significant A β has yet been deposited, and with time these individuals would develop A β plaques and have a decreasing CA2/CA1 p-tau ratio.¹⁴ This is unlikely, given that PART patients have numerous diverging patterns from AD,^{7,8,15} there is no age difference between subjects diagnosed as definite or possible PART and ADNC in this cohort, and the CA2/CA1 ratio does not decrease (become more “ADNC-like”) with increasing patient age. Moreover, PART subjects are often older than subjects with clinical and pathological evidence of AD (representing the “oldest old”), suggesting that these individuals will likely never develop into ADNC.^{15,40} PART patients in this study with relatively high CA1 p-tau burden (or overall p-tau burden) and/or higher Global CDR often still maintain a CA2/CA1 p-tau ratio > 1 and lack significant hippocampal A β deposition, arguing for the existence of a discrete neuropathologic pattern associated with PART and against the idea that these individuals are simply in the process of developing ADNC. In addition, patients with relatively high hippocampal A β burden compared to their p-tau burden (“early AD” or pre-clinical AD patients) also have preferential entorhinal and CA1 neurofibrillary degeneration instead of early CA2 p-tau deposition, again suggesting two distinct patterns between PART and AD populations.

In summary, these data demonstrate that there is a significant relationship between hippocampal A β and p-tau deposition, where both the amount of A β pathology and the location of A β plaques appear to affect the overall severity and distribution of neurofibrillary degeneration within individual hippocampal subregions. These patterns differ between cases with ADNC and cases with definite or possible PART. Within the context of previous data, these findings suggest that there may be an interaction between A β and p-tau that could ultimately influence cognitive outcome.

AUTHOR CONTRIBUTIONS

Conception of the work: J.M.W., T.E.R.; design of the work: J.M.W., T.E.R.; acquisition/analysis/interpretation of the data: J.M.W., W.G.,

K.F., M.A.I., E.K., T.E.R.; obtained materials and cases: C.L.W., J.F.C.; drafted the work or substantially revised it: J.M.W., C.L.W., J.F.C., T.E.R.; all authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The results presented in this paper have not been published previously in whole or part. The authors declare that they have no competing interests. [Author disclosures](#) are available in the supporting information.

CONSENT FOR PUBLICATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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