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OXFORD

ORIGINAL ARTICLE

Differential Vulnerability of Hippocampal Subfields in Primary Age-Related Tauopathy and Chronic Traumatic Encephalopathy

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Abstract

Chronic traumatic encephalopathy (CTE) is a tauopathy associated with repetitive mild head impacts characterized by perivascular hyperphosphorylated tau (p-tau) in neurofibrillary tangles (NFTs) and neurites in the depths of the neocortical sulci. In moderate to advanced CTE, NFTs accumulate in the hippocampus, potentially overlapping neuroanatomically with primary age-related tauopathy (PART), an age-related tauopathy characterized by Alzheimer disease-like tau pathology in the hippocampus devoid of amyloid plaques. We measured p-tau burden using positive-pixel counts on immunohistochemically stained and neuroanatomically segmented hippocampal tissue. Subjects with CTE had a higher total p-tau burden than PART subjects in all sectors ($p = 0.005$). Within groups, PART had significantly higher total p-tau burden in CA1/subiculum compared to CA3 ($p = 0.02$) and CA4 ($p = 0.01$) and total p-tau burden in CA2 trended higher than CA4 ($p = 0.06$). In CTE, total p-tau burden in CA1/subiculum was significantly higher than in the dentate gyrus; and CA2 also trended higher than dentate gyrus ($p = 0.01$, $p = 0.06$). When controlling for p-tau burden across the entire hippocampus, CA3 and CA4 had significantly higher p-tau burden in CTE than PART ($p < 0.0001$). These data demonstrate differences in hippocampal p-tau burden and regional distribution in CTE compared to PART that might be helpful in differential diagnosis and reveal insights into disease pathogenesis.

Key Words: Aging, Chronic traumatic encephalopathy, Primary age-related tauopathy, Repetitive head impacts, Tauopathy.

INTRODUCTION

Abnormal accumulation of hyperphosphorylated tau (p-tau) in the human brain is the key pathological feature of a spectrum of conditions termed tauopathies (1). Alzheimer disease (AD) is a common secondary tauopathy characterized by

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comorbid amyloid-β pathology; other tauopathies include chronic traumatic encephalopathy (CTE), which is associated with exposure to repetitive head impacts, and an age-associated tauopathy, primary age-related tauopathy (PART) (2). While there are neuropathological features that enable delineation of the tauopathies, overlaps in symptomatology, neuroanatomical vulnerability, cellular features, molecular changes, and genetic risk are barriers to the identification of specific pathogenetic pathways that might enable the development of novel biomarkers and therapeutics. Understanding the differential hippocampal neuroanatomical vulnerability to p-tau pathology in PART and CTE has the potential to improve diagnosis, provide mechanistic insights, and inform therapeutic strategies (3).

The hippocampal formation, a component of the limbic system, is a complex multifunctional brain region in the medial aspect of the temporal lobe that has critical roles in learning, memory, and cognition (4). The hippocampal formation consists of several histologically distinct and functionally specialized subfields, including the dentate gyrus, cornu ammonis (CA), and subiculum. The subfields are selectively vulnerable in different neurodegenerative tauopathies. For example, the dentate gyrus is selectively involved in Pick disease, a 3 microtubule-binding domain (3R) dominant tauopathy; CA2 is involved in 4 microtubule-binding domain repeat (4R)-dominant tauopathies, including progressive supranuclear palsy; and CA1 involvement is predominant in AD, a combined 3R/4R tauopathy (5–7). Recent refinements in neuropathological criteria for PART and CTE have allowed clearer delineation of these entities (8, 9), although both are reported to exhibit high levels of phosphorylated tau (p-tau) in CA2 and other hippocampal sectors (10–14).

The goal of this study was to compare the regional hippocampal p-tau pathology in CTE and PART. To accomplish this, we used age- and sex-matched cases from each entity, as defined by recent neuropathological consensus criteria, and segmented the hippocampus into subfields on digitized whole slide images of immunohistochemically stained brain tissue sections (9). We then deployed a quantitative positive pixel burden measure of p-tau pathology that we previously found to be highly predictive of clinical outcomes in PART (15). Using this computational approach to measure p-tau pathology minimized bias and highlighted neuropathological-related differences in p-tau neurofibrillary degeneration.

MATERIALS AND METHODS

Subjects

Postmortem human brain tissue was obtained from former American football players, following a comprehensive neuropathological workup using the published NINDS-NIBIB criteria for the diagnosis of CTE in 2021 and staged using the McKee criteria which we found to be highly correlated with exposure and symptomatology (9, 16, 17). Next-of-kin provided written consent for participation and brain donation. IRB approval for brain donation was obtained through the Boston University School of Medicine and VA Boston Healthcare System. CTE cases were selected based on the availability of paraffin-embedded hippocampal sections at the level of the lateral geniculate nucleus. PART cases were selected from a collection derived from domestic and international brain banks and were also taken at the level of the lateral geniculate nucleus (15, 18). Neuropathological inclusion and exclusion for PART cases have been detailed elsewhere (11, 18). The PART cases were sex-matched to the CTE group but given that PART is associated with aging and the CTE cases available were ascertained from younger donors, the samples could not be individually age-matched. There was, however, no statistical difference between the average age of each group. All PART subjects had a CERAD score of 0 (19) and a Braak stage of 0–IV (20) to represent the full range of age-related tau pathology.

Immunohistochemistry

Whole mount immunohistochemistry was performed as previously described using the CP13 antisera, a generous gift of Dr. Peter Davies (21). Formalin-fixed paraffin-embedded tissue sections (5 μm in thickness) mounted on charged slides were baked at 70°C and immunohistochemistry was performed on a Leica Bond III (Leica Biosystems, Buffalo Grove, IL) for all cases. Antigen retrieval was done using citric acid buffer for 1 hour followed by primary antibody incubation for 40 minutes. Slides were stained for phospho-tau (AT8; MN1020, Thermo Fisher Scientific, Waltham, MA). Because the Leica bond III can only stain 30 slides per batch, each batch included a case of severe AD, CERAD plaque score 2, Braak stage VI to ensure uniform pixel staining intensity.

Segmentation of the Hippocampal Subfields

A hematoxylin and eosin slide counterstained with Luxol fast blue (LH&E) was prepared using routine protocols to assist in segmentation. All slides were scanned using an Aperio CS2 Scanner (Leica Biosystems, Buffalo Grove, IL) at 20× magnification and digital analysis including segmentation of the subfields and pixel counting (see below) was done using the ImageScope v12.3 software (Leica Biosystems). Given that no validated standardized protocol exists for hippocampal segmentation on routine neuropathological staining, we developed the following protocol to maximize uniformity and reproducibility (Fig. 1). The subregions of the hippocampus were defined based on cell morphology and density. LH&E-stained hippocampal sections were scrutinized and compared to an adjacent AT8-immunostained section. Then segmentation was performed. The cornu ammonis 2 (CA2) was first annotated with the medial and lateral boundaries drawn encompassing the most compact region. The cornu ammonis 4 (CA4) boundaries were drawn closing the opening of the dentate and circling only cell bodies within the dentate gyrus. The cornu ammonis 3 (CA3) was drawn as the area between CA4 and CA2. The cornu ammonis 1 (CA1) and subiculum were combined (termed CA1/sub) and drawn from CA2 to the recess of the hippocampal fissure where a straight line was drawn. The CA layers included in the annotation were the stratum oriens, stratum pyramidale, stratum lucidum, stratum radiatum, stratum lacunosum, and stratum moleculare ending

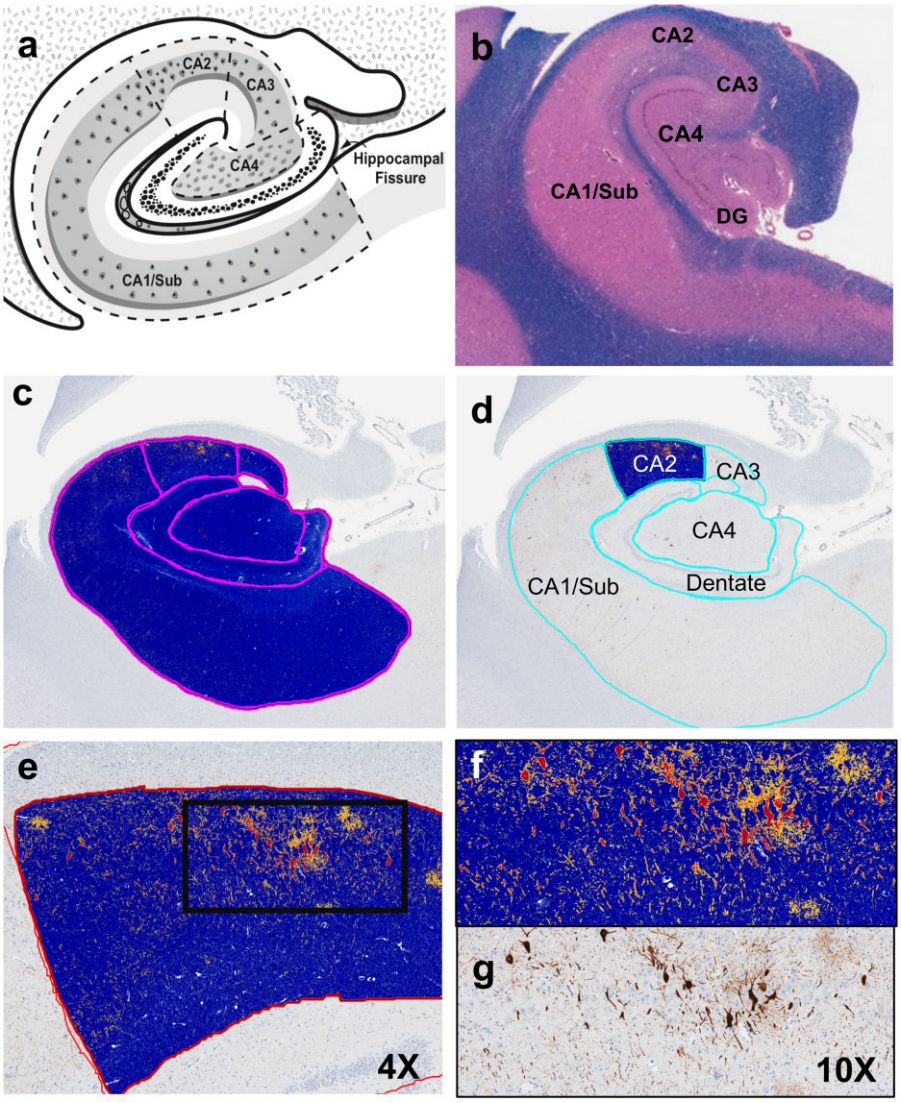

FIGURE 1. Neuroanatomical segmentation strategy and p-tau burden quantification. **(a)** Schematic illustrating the hippocampal subregions. **(b)** Representative Luxol fast blue-counterstained hematoxylin and eosin section (LH&E) from a control showing the hippocampal subregions. **(c)** Example of a fully segmented hippocampal formation following application of the positive pixel algorithm. **(d)** Example of quantification of the positive pixel count algorithm in CA2. **(e)** Higher-power images of CA2 are shown at 4× **(f, g)** as well as 10× showing that the pixel thresholds capture intracellular tangles (red) threads and dots (orange and yellow). The example case shown above had a diagnosis of PART.

at the hippocampal sulcus. The dentate gyrus was outlined with the outer boundary at the hippocampal sulcus (following blood vessels) and inner boundary in CA4 not including the cell bodies.

Computer-Assisted Quantitative Assessment of Hyperphosphorylated Tau (p-Tau) Burden

The Aperio positive pixel count algorithm (version 9) was used to quantify p-tau burden (Fig. 1). The parameters of the algorithm were defined by the user based on the intensity of the signal in the positive control AD case run in each staining batch and the thresholds remained the same for each case. The output values were low (proxy for delicate threads), medium (proxy for dense/coarse threads), and high intensity (proxy for neurofibrillary tangles [NFTs]) pixels. P-tau burden was assessed in 2 ways. First, each p-tau positive pixel contained in the subregion was divided by the total pixels (p-tau positive and negative) contained in the subregion producing a 0-1 p-tau burden score (1 indicating the entire region was positive, and 0 no positive pixels). Second, we used the p-tau burden score and divided it by the total p-tau positive pixels in the entire hippocampus (CA1/subiculum, CA2, CA3, CA4, and dentate) divided by the total pixels (p-tau positive and negative). This value represented a proportion of p-tau intensity. A score greater than 1 indicated that the region had more total

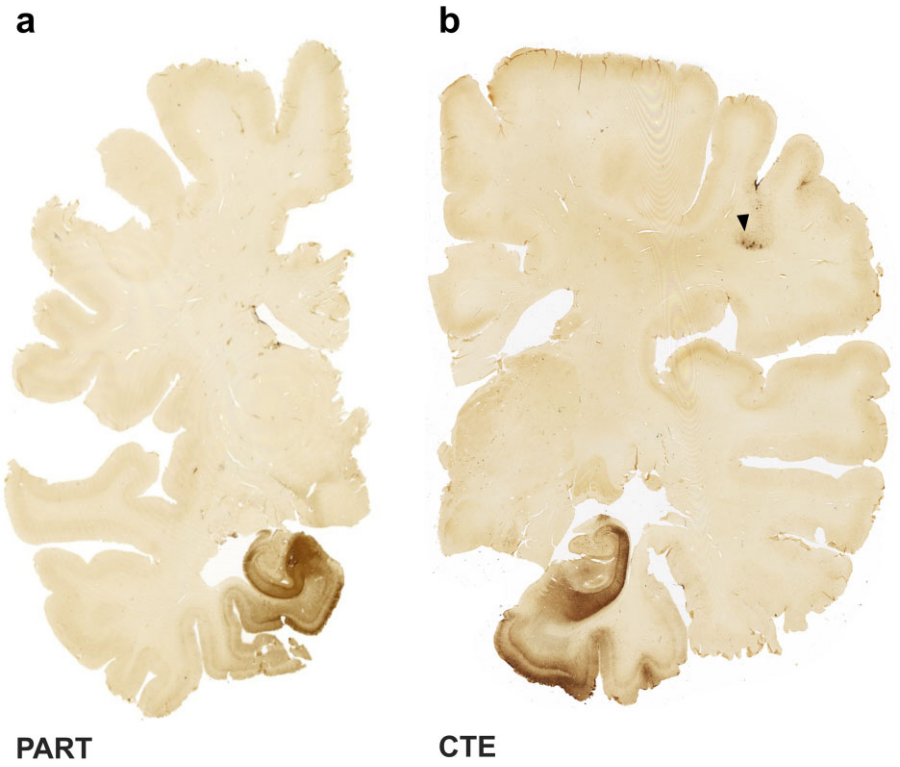

FIGURE 2. Selective vulnerability of the hippocampal formation in PART and CTE. **(a)** Whole mount hemibrain stained for p-tau from a 92-year-old woman with PART showing significant p-tau burden confined to the medial temporal lobe with scant neocortical p-tau (CP13 antisera). **(b)** A 67-year-old male professional football player with CTE stage 3 with low cortical p-tau burden and scattered cortical lesions (see arrow).

p-tau relative to the entire hippocampus, with the rational that the relative proportion of p-tau could assist in differentiating the 2 conditions when viewing a slide at a low magnification.

Statistical Analysis

Data were statistically analyzed and visualized using the statistical software GraphPad Prism 8 (San Diego, CA). P-tau burden across hippocampal subregions were compared within PART and CTE groups using Kruskal-Wallis one-way analysis of variance. The hippocampal subregional total p-tau burden (modeled to consider p-tau burden in the entire hippocampus) was compared in PART versus CTE using the Mann-Whitney test. Statistical significance was defined as $\alpha < 0.05$ (2-tailed).

RESULTS

Overlapping Medial Temporal Lobe Neurofibrillary Pathology in PART and Advanced CTE

Neuropathologically, PART has NFTs predominantly in the medial temporal lobe in the absence of or with sparse neuritic β-amyloid pathology (Fig. 2). CTE displays patchy perivascular p-tau pathology at the depths of the cortical sulci in early disease stages and extends to include diffuse neurofibrillary p-tau pathology in the medial temporal lobe in more advanced stages (17, 21).

Selective Vulnerability of Hippocampal Regions in PART and CTE

For the quantitative analyses, 32 neuropathologically confirmed PART and 32 neuropathologically confirmed CTE cases were included (Table). The overall median age at death of the cohort was 72.5 years with a range of 25–84 years. There was no significant difference between the average age of each cohort and most of the cases in each cohort were between 66 and 85 years old (78.1% in PART, 65.6% for CTE). All cases were male. Four PART cases were cognitively impaired, whereas 18 CTE cases had clinical evidence of cognitive impairment. The average age of the CTE subjects with cognitive impairment was 72.38 and 10 of those cases had a CERAD score of 1. All the PART and 56.2% of the CTE lacked neuritic plaques (CERAD 0). The remaining 40.6% CTE cases had sparse neuritic plaques (CERAD A1). Nineteen of the PART cases had a Braak NFT stage of I–II and 9 were III–IV. Four cases in the PART group were designated Braak 0 with too few p-tau positive neural structures to categorize as Braak I. Twenty-four of the CTE cases had a CTE stage of III–IV and 8 were stage I–II.

CTE cases had significantly higher p-tau burden in the hippocampus compared to PART cases across all comparisons

TABLE. Patient Data

	PART	CTE	Total
Clinical features			
Sample size, *n*	32	32	64
Average age of death (range)	74 (55–82)	70 (25–84)	
25–45 (%)	0 (0)	4 (12.5)	4 (6.5)
46–65 (%)	7 (21.9)	7 (21.9)	14 (22.6)
66–85 (%)	25 (78.1)	21 (65.6)	46 (74.2)
Sex, male (%)	32 (100)	32 (100)	64
Cognitively impaired* (%)	4 (12.5)	18 (60)	22 (35.5)
Neuropathological features			
CERAD score (%)†			
No neuritic plaques (C0)	32 (100)	18 (56.2)	50 (79.4)
Sparse (C1)	0 (0)	13 (40.6)	13 (20.6)
Moderate (C2)	0 (0)	0 (0)	0 (0)
Frequent (C3)	0 (0)	0 (0)	0 (0)
Braak stage (%)			
0	4 (12.5)	NA	—
I–II	19 (59.4)	NA	—
III–IV	9 (28.1)	NA	—
V–VI	0 (0)	NA	—
CTE stage (%)			
I–II	NA	8 (25)	—
III–IV	NA	24 (75)	—

NA, not applicable.
*Two CTE cases have unknown cognitive status.
†One CTE case has unknown CERAD stage.

(Fig. 3), although there were unique subregion differences. In PART, there was a significantly higher total p-tau burden in CA1/subiculum compared to CA3 ($p = 0.02$) and CA4 ($p = 0.01$). Total p-tau burden trended higher in CA2 than CA4 ($p = 0.06$). All other total p-tau burden comparisons amongst subregions of the hippocampus in PART were not different. In CTE, we saw that CA1/subiculum had significantly higher total p-tau burden than dentate ($p = 0.01$). CA2 p-tau burden showed a trend toward higher total p-tau burden compared to the dentate ($p = 0.06$). All other comparisons amongst subregions of the hippocampus were not significantly different in the CTE group. The data suggest regional differences in p-tau burden in each disease.

Differences in Regional Vulnerability between PART and CTE

Finally, we examined differences in subfield regional vulnerability using a model that accounted for the total p-tau burden observed across the entire hippocampus (Fig. 4). We observed that subfields CA3 and CA4 had significantly higher p-tau burden in CTE compared to PART ($p < 0.0001$ in both cases). PART cases had significantly higher total p-tau burden in CA1 than CTE cases ($p = 0.005$). Total p-tau burden did not differ in CA2 ($p = 0.68$) and dentate ($p = 0.26$) between PART and CTE. The data suggest a distinctive regional signature when adjusting for the total burden across the entire hippocampus, with relatively more p-tau in CA3 and CA4 in CTE than in PART.

DISCUSSION

The ability to differentiate ubiquitous aging-related changes from preventable causes of injury has numerous implications (22). This is exemplified by PART and CTE, two tauopathies with both similar and divergent clinical and neuropathological profiles (8, 9, 11, 14, 21, 23). In CTE, there is a strong and independently replicated link with repetitive head impacts (24, 25), and its pathological signatures have been observed across the adult lifespan independent of age. By contrast, PART is observed in the brains of advanced age (26) and has not been associated with a specific environmental exposure. To our knowledge, this study is the first to directly compare the selective p-tau deposition in the hippocampus in these two tauopathies. Our findings suggest that there is a divergent pattern of regional vulnerability in the hippocampus that distinguishes CTE from PART.

Previous work has highlighted regional p-tau deposition in the hippocampus in PART (11–13) and CTE (10, 14). Jellinger (12) reported that PART diverges from AD in that there are more p-tau positive neurons in CA2 than CA1. We also observed selective vulnerability of CA2 to p-tau pathology in PART (11). However, a small quantitative study by Zhang and colleagues found that CA1 and subiculum had the highest p-tau burden in PART, followed by entorhinal cortex, CA2/3 (which were combined and possibly obscured potential differences), CA4, and the dentate (13). Selective vulnerability of CA2 has also been reported in CTE (11, 14). Furthermore, a high p-tau burden across the entire hippocampal formation except for the dentate gyrus has been observed in CTE (14). Here, our quantitative analysis showed a striking vulnerability of the CA1/subiculum and CA2 for p-tau pathology in CTE compared to other subfields. Neuroimaging studies in suspected CTE cases have reported the CA1/subiculum to be highly atrophic (27). Our analysis revealed a significantly higher p-tau burden in the CA1/subiculum in PART compared to CTE, and a higher p-tau burden in CA3 and CA4 in CTE, which is consistent with recent work (9).

Although there are similarities, these findings suggest that the hippocampal p-tau pathology in CTE and PART can be differentiated neuropathologically, a distinction that has been previously questioned (28). These data also provide more information about the diagnostic features of CTE in addition to the pathognomonic lesion. These selective patterns of hippocampal involvement in PART and CTE might be useful in the interpretation of neuroimaging studies, for example tau PET tracers that are increasingly being applied to CTE (29). It is unclear why CA1/subiculum and CA2 are selectively vulnerable in PART and CTE and understanding the cellular or molecular factors native to these neuronal populations might be helpful in understanding the pathogenesis of these tauopathies.

There are several limitations to this study. The sample size was limited due to the inherent restrictions of autopsy studies. The PART subjects were from a collection derived from many brain banks, while the CTE cases all came from

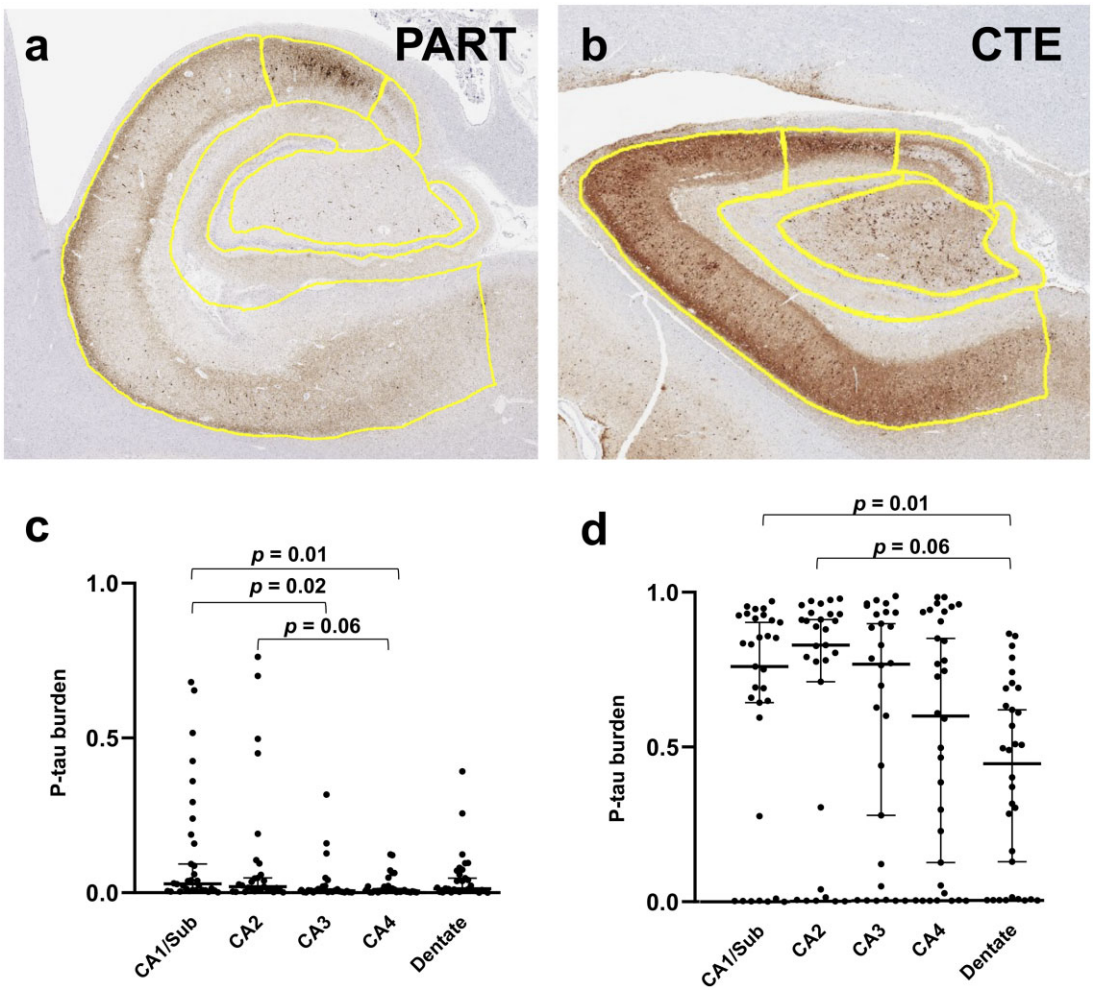

FIGURE 3. Quantitative assessment of selective hippocampal vulnerability in PART and CTE. **(a, b)** Examples of a whole slide images of hyperphosphorylated tau (p-tau, AT8) immunolabeled hippocampal sections from subjects with PART and CTE annotated using our segmentation protocol. **(c, d)** P-tau burden was measured in each subfield using positive pixel counts and modeled to consider burden across the entire hippocampal formation. Comparisons were performed using Kruskal-Wallis one-way analysis of variance.

one center, which might have introduced bias. The dataset was restricted to males due to the less frequent reporting of CTE in females. Future studies including female CTE brain donors, such as have been reported in the context of intimate partner violence (30, 31), are needed. Segmentation of the hippocampus is also challenging on routine paraffin sections. Specialized techniques (e.g., thick sections), could assist in providing the highest degree of confidence in accurate segmentation. In addition, there are numerous co-pathologies that occur alongside CTE and PART, which might have influenced our findings; additional multidimensional analyses will be helpful to address this. Specifically, some CTE cases had neuritic plaques, implying an additional neuropathological diagnosis of AD neuropathologic change. It could also be inferred that some of the older CTE cases had age-related tau deposition and the results of this study should be viewed in this context. To overcome these issues, we anticipate that the use of digital approaches including AI and machine learning will enable larger and more granular, quantitative analyses of multiple brain regions, including the entorhinal cortex and amygdala, to understand the differences between pathological and age-related neurodegenerative features of both these conditions. Nevertheless, these data show striking and robust differences between CTE and PART in the hippocampus that are consistent with previous publications.

In summary, in a cohort of age- and sex-matched PART and CTE subjects, we demonstrated a divergent pattern of regional p-tau vulnerability in the hippocampal subfields. These data represent a deep analysis of two unique tauopathies and might assist those practicing diagnostic neuropathology as well as provide insights into their differing pathogeneses.

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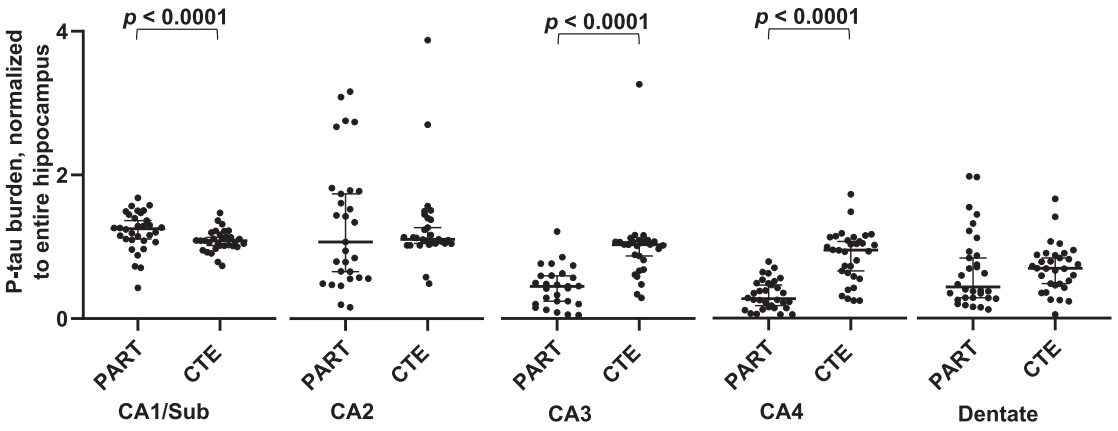

FIGURE 4. Differences in subfield regional vulnerability in PART and CTE accounting for the total p-tau burden in the entire hippocampus. Total p-tau positive pixels were modeled to consider the total hippocampus proper p-tau. Comparisons were performed using a Mann-Whitney test.

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