Bridging the Gap Between CTE and Alzheimer's: A CTE Focused Review of Tau-Related Frontal and Hippocampal Pathology in CTE and Alzheimer's Disease

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Chronic Traumatic Encephalopathy (CTE) and Alzheimer's disease (AD) are progressive neurodegenerative disorders that share abnormal tau accumulation but differ in their underlying causes. CTE is associated with repetitive head impacts, commonly observed in contact-sport athletes and military personnel, while AD is primarily associated with aging, amyloid-beta (Aβ) accumulation, and tau pathology. Both disorders produce cognitive impairment and affect brain regions involved in memory and executive function, including the hippocampus and frontal cortex. This focused review analyzed 33 studies investigating tau and amyloid-beta pathology through postmortem immunohistochemistry, molecular profiling, cerebrospinal fluid analysis, tau PET imaging, and structural analysis of hippocampal and frontal brain regions. Of these studies, 28 were included in the final synthesis based on relevance and available data. A single PubMed search was performed using predefined Boolean search strategies, including literature published through October 1, 2025. A major limitation of this review is the use of a single database, which may have excluded relevant studies. Findings indicate that CTE is characterized by perivascular tau accumulation at cortical sulcal depths with involvement of frontal and medial temporal regions. In the hippocampus, CTE demonstrates greater involvement of the CA2, CA3, and CA4 subfields, whereas AD shows greater tau accumulation in the CA1 region and subiculum. Differences in tau isoform composition have also been observed, with CTE containing both 3R and 4R tau while AD is primarily associated with paired helical filament tau. Additional pathological features in CTE include vascular alterations, blood-brain barrier disruption, astrocytic changes involving markers such as AQP4 and GFAP, and frequent TDP-43 accumulation. These findings suggest that regional tau distribution, molecular characteristics, and associated pathologies may help distinguish CTE from AD. Further research into region-specific biomarkers and noninvasive diagnostic methods may improve early detection and understanding of trauma-related neurodegeneration.

Keywords: Chronic Traumatic Encephalopathy, Alzheimer's Disease, Tau Pathology, Hippocampal Subfields, Frontal Lobe, Biomarkers, Neurodegeneration, Traumatic Brain Injury

Introduction

Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative brain disorder mostly caused by repetitive brain injuries. Often seen publicly through post-NFL career American football players or military personnel, CTE is distinct from other brain injuries as even multiple non-concussive hits to the head over time lead to the development of CTE. Modern day CTE was originally called "punch drunk syndrome" and later "dementia pugilistica" in boxers.[1,2] This classification has had profound impacts in the sports medicine and military (specifically veterans exposed to large blasts) communities with ongoing investigations into pathophysiology, diagnostic criteria, and potential therapeutic approaches.[3]

CTE has been notoriously difficult to diagnose in living patients. Current symptoms include a series of cognitive alterations (Lack or deficiency of episodic memory, executive function, and attention), behavioral (Enhanced verbal outbursts or physical aggression), and severe mood swings.[4] Different research groups have identified distinct diagnostic criteria but a distinctive treatment does not currently exist. Current diagnostic studies are based on historic neutral studies involving an investigation into a patient's history of head impacts, symptomatology present for at least 12 months, and exclusion

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of other clinical disorders.[5–7] Repeated head injury is the only known common symptom in around 97.4% of patients among the more than 645 CTE cases reported throughout the literature; which has expanded to Musk oxen, bighorn sheep and computational models.[7] Associations have been observed between cognitive decline, demographic variables (younger age at first exposure), and cumulative head impact index. An established dose–response relationship links the cumulative duration of participation in contact sports. Additionally, carriers of the APOEε-4 allele exhibit a heightened vulnerability to cognitive decline after repeated head impacts.[1]

Traumatic encephalopathy syndrome (TES) is a disorder classification to represent the clinical manifestation of CTE. While this represents improvements in awareness for CTE, the false positive rate for CTE remains high currently at around 54% of cognitively normal individuals receiving a TES diagnosis[8]. CTE continues to only be formally diagnosed through post mortem autopsy[9].

During autopsies, the confirmation of CTE is confirmed through an accumulation of phosphorylated tau entanglements[10,11],the primary symptom of Alzheimer's disease[12] Additionally, there is reported regression of the neocortex in CTE patients identified in postmortem examinations. Recent advances in extracellular vesicles, diagnostic imaging and fluid biomarkers for Alzheimer's can provide valuable insight into cross-compatible biomarkers for CTE. Advances in radiotracers for Alzheimer's including flortaucipir F-18 fluorinated positron-emission tomography (PET) could potentially serve as a diagnostic tool, although cross disorder specificity is reported as remaining poor[13]. With multiple tracers, regional patterns and volume differences between disorders have not been clarified[9].

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of beta-amyloid plaques and tau protein tangles, which disrupt neuronal communication, impair microtubule function, and ultimately lead to cell death. Pathological changes typically begin in the hippocampus, a brain region critical for memory encoding and consolidation, and gradually spread to other cortical areas, including the frontal lobes, which govern executive functions such as planning, decision-making, attention, and working memory. Clinically, AD manifests as memory loss, confusion, impaired judgment, mood disturbances, and difficulties performing daily activities. Established risk factors include advanced age, genetic susceptibility, vascular or metabolic conditions, and a history of head injury, highlighting partial overlap with risk factors observed in chronic traumatic encephalopathy (CTE)[14].

Focusing on the hippocampal and frontal lobes provides insight into how neurodegenerative processes compromise cognitive function. These regions are highly interconnected, allowing for coordinated memory storage, retrieval, and higher-order cognitive control. Studying patterns of protein accumulation, neuronal atrophy, and functional connectivity in these areas not only informs the progression of AD but also helps in identifying potential biomarkers and therapeutic targets. Moreover, understanding regional vulnerability helps distinguish AD from other tau-related disorders, such as CTE, where pathological changes may follow different regional patterns within the brain.

Although CTE and AD arise from distinct etiologies and exhibit different patterns of neuropathology, both disorders share hallmark features, including tau related neuronal degeneration and progressive declines in cognition, behavior, and daily function. Investigating the mechanisms by which beta-amyloid and tau proteins affect neural circuits is essential for improving early detection strategies and developing targeted therapeutic approaches. Recent advances in diagnostic imaging, fluid biomarkers, and cellular vesicle research in AD offer potential translational insights for CTE, particularly for identifying cross-disorder biomarkers and further clarifying overlapping pathophysiological processes[13].

Methodology

A systematic review was performed according to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA 2020 [`https://www.prisma-statement.org/`]). Our research exclusively utilized anonymized data, with no collection of personal information or involvement of human subjects. The study protocol was not registered. Standard protocol approvals, registration, and patient consents are not applicable to this review.

Data sources and search strategy

A systematic search was conducted using PubMed on November 3, 2025, covering all indexed literature up to October 1, 2025, with no language restrictions. Two Boolean search strategies were used to identify region-specific studies: ("Chronic traumatic encephalopathy") AND ("Alzheimer's" OR "Alzheimer") AND ("Frontal Lobe") for frontal lobe–focused studies,and ("Chronic traumatic encephalopathy") AND ("Alzheimer's" OR "Alzheimer") AND ("Hippocampus") for hippocampal studies. Duplicates were removed manually, and gray literature, conference abstracts, and preprints were excluded. Study selection followed predefined inclusion criteria, with disagreements resolved through discussion. The selection process is shown in the PRISMA table (Table 3). Included studies were organized by search strategy into two tables: Table 1 (Frontal lobe focus) and Table 2 (Hippocampus focus) (Tables 1–2). Extracted data included

study design, sample size, population, brain region, tau outcomes, and other biomarkers when available.

Data Extraction and Organization

Data extraction was performed by a single reviewer (DW) using a standardized approach across all included studies and evaluated by a second reviewer (AB). Relevant study characteristics and findings were systematically recorded, including study type (e.g., postmortem histopathology, molecular analysis, PET imaging, cerebrospinal fluid (CSF) biomarker study, or case report), examined brain regions, tau pathology characteristics when reported, imaging or molecular findings, clinical characteristics, and major conclusions relevant to the relationship between CTE and Alzheimer's disease. Extracted findings were organized by evidence type and summarized in Supplementary Table 1 and 2 to facilitate comparison across studies and identify recurring pathological patterns. To maintain consistency, the same extraction criteria were applied to all included studies.

Eligibility criteria

Risk of bias assessment

The quality and risk of bias of all eligible studies were evaluated individually by DW, with any disagreements resolved through discussion with AB until consensus was reached. Given the heterogeneous study designs included in this review encompassing postmortem pathology, molecular studies, neuroimaging, and case reports, a strictly diagnostic accuracy framework was not fully applicable. Therefore, limitations are presented narratively to allow for a more transparent and design-appropriate appraisal.

Several methodological vulnerabilities were identified across the included literature. First, ascertainment bias was a consistent concern, as brain-bank donor samples are largely self-selected through family donation, which may overrepresent individuals with severe or symptomatic disease and limit generalizability. Second, exposure misclassification was present in many CTE studies, where head impact histories were predominantly self-reported or obtained from next-of-kin, introducing potential recall and reporting bias. Third, survivor bias may affect findings, as individuals who survive long enough to be diagnosed or to donate tissue may not be representative of the broader CTE population. Finally, co-pathology confounding was a recurring limitation, as many CTE cases presented with concurrent neurodegenerative pathologies, complicating the attribution of tau-related findings to CTE alone. These limitations were considered collectively when interpreting the findings of this review.

Results

Tau Pathology in the Frontal Lobe

Severity and Molecular Characteristics of Frontal Lobe Tau

Studies using postmortem brain tissue have repeatedly identified substantial tau accumulation in the frontal cortex of individuals exposed to repetitive head impacts. A large-scale study of 180 male brain donors, primarily former American football players, demonstrated moderate-to-severe neurofibrillary tau tangle burden in the dorsolateral frontal cortex.[15] Additional molecular analysis in a cohort of 207 former contact-sport athletes examined specific tau phosphorylation patterns, where a specific phosphorylated tau epitope, p-tau202, was found to be significantly increased by approximately 3.2-fold in the dorsolateral frontal cortex of high-stage Chronic Traumatic Encephalopathy (CTE) cases compared to controls. Notably, this study also found that amyloid-β levels were a significant predictor of a different tau isoform, p-tau396, which was increased in Alzheimer's disease.[16] This CTE-specific tau forms a unique C-shaped protofilament structure with a distinctive β-helix and hydrophobic cavity, which differentiates it from the tau folds observed in Alzheimer's disease.[17] Furthermore, early tau conformations and specific phosphorylation sites are detected perivascularly, providing a biochemical signature that distinguishes CTE from other tauopathies.[18]

Distinct Spatial Distribution and Vascular Association

One defining feature of CTE pathology is the characteristic distribution of tau within the frontal cortex. The pathognomonic lesion is characterized by abnormal hyperphosphorylated tau in neurons and astroglia accumulating around small blood vessels at the depths of cortical sulci.[19] This perivascular tau is predominantly found in cortical layers II and III.[20] The relationship between vasculature and tau pathology is reinforced by a study of 41 male brain donors, which used 3D imaging to reveal that increased microvascular branching and coverage in the sulci of the dorsolateral frontal cortex were directly correlated with p-tau pathology.[21] This perivascular tau accumulation is linked to vascular injury and inflammation, with markers such as ICAM1, VCAM1, and CRP being elevated and co-localizing with p-tau.[22]

Clinical and Pathological Progression

The accumulation of tau in the frontal lobe is progressive and correlates with clinical severity. In a comprehensive study of 364 brain donors, p-tau burden was quantified across 11 brain regions and was found to increase with CTE stage, with the highest levels seen in Stage IV, which correlated strongly with the presence of dementia. This study also reported that Alzheimer's pathology and Lewy bodies were present in subsets of cases, indicating that co-morbid pathologies are common.[23] This progressive tau accumulation, in the context of

Table 1 Supplemental table of results and data extraction (Frontal lobe focus).

Author/Year	Design	Sample Size	Population	Brain Region	Method	Major Tau Finding	Other Biomarkers	Limitations
Falcon et al., 2019	Postmortem case series	3	Retired football player + 2 former boxers with stage IV CTE	Cortical sulci, cortical layers II–III	Neuropathology	Hyperphosphorylated tau in neurons, astrocytes, and perivascular regions in cortical layers II–III	C-shaped tau protofilaments with β-helix structure distinguishing CTE from AD	Very small sample size
Fowler et al., 2025	Case-control study	50 (32 veterans, 18 controls)	Blast-related mTBI veterans and civilian controls	Gray-white matter junction, sulci, white matter	MRI, molecular/astrocytic markers	AQP4 upregulation at gray-white matter boundaries and sulci associated with injury patterns	GFAP elevation, perivascular space enlargement, glymphatic dysfunction	Indirect relation to tau pathology
Falcon et al., 2023	Postmortem cohort	364	Brain donors (mostly former athletes with CTE)	11 brain regions	Histopathology, p-tau quantification	p-tau increases with CTE stage; highest in Stage IV and correlates with dementia	Alzheimer pathology, Lewy bodies, APOE ε4 association	Postmortem cross-sectional design
Zivanov et al., 2023	Postmortem cohort	41	CTE low-stage, high-stage, and controls	Dorsolateral frontal cortex sulci	Histopathology, vascular analysis	p-tau density highest in sulci and correlates with disease stage	Microvascular branching and vessel remodeling	Moderate sample size
Falcon et al., 2022	Postmortem cohort	16	Confirmed CTE cases	Cortical sulci	Immunohistochemistry	Neuronal p-tau forms neurofibrillary tangles; astrocytic tau minor	N/A	Small sample size
Zivanov et al., 2020	Postmortem cohort	156	RHI-exposed sports/military individuals	Cortical sulci	Histopathology, vascular markers	Perivascular p-tau in sulci linked to RHI severity and duration	ICAM1, VCAM1, CRP elevation; BBB leakage	Observational postmortem study
Masiulis et al., 2019	Postmortem case study	1	Former Australian football player with CTE + AD pathology	Cortical sulci, hippocampus	Neuropathology	Extensive perivascular p-tau in neurons and astrocytes; mixed tau isoforms	TDP-43 inclusions, amyloid-β plaques	Single case
Falcon et al., 2019 (early tau study)	Postmortem cohort	9–11 + controls	CTE vs AD vs controls	Cortical sulci	Immunohistochemistry	Early tau conformations (PAD, TOC1, pS422) in perivascular lesions	N/A	Small sample size
Falcon et al., 2018	Clinical imaging + neuropathology cohort	11	Former athletes with TES symptoms	Cortical sulci, hippocampus, brainstem	Tau PET, MRI, histopathology	Perivascular tau tangles in cortical layers II–III; spread across brain regions	TDP-43 (> 85%), amyloid-β (up to 43%)	Small imaging cohort
Cherry et al., 2016	Postmortem cohort	17	Contact sports/military exposure	Frontal + temporal cortex	Neuropathology	Perivascular p-tau in cortical layers II–III; spreads to limbic regions	N/A	Postmortem design
Zhang et al., 2020	Structural neuropathology study	3	Corticobasal degeneration cases	Frontal + subcortical regions	Cryo-EM structural analysis	4R tau forms unique four-layered filament fold distinct from CTE/AD	No Aβ or TDP-43 pathology	Small sample size
Gu et al., 2017	Postmortem cohort	180	Former athletes with RHI exposure	Dorsolateral frontal cortex	Histopathology	Widespread p-tau in sulci and perivascular regions	Gliosis, neuroinflammation; no major Aβ difference	Cross-sectional postmortem
De Simoni et al., 2018	Postmortem case series	8	Former professional boxers	Cortical sulci	Neuropathology	Widespread p-tau in neurons, astrocytes, neurites in sulci	Gliosis, microglial activation; minimal amyloid-β	Small cohort
McKee et al., 2016	Consensus pathology study	25	Mixed tauopathy cases	Cortical sulci, perivascular regions	Neuropathology consensus	Defines CTE hallmark: perivascular p-tau at sulcal depths	TDP-43 inclusions	Descriptive consensus paper

repetitive head-impact exposure, is associated with the cognitive, behavioral, and motor decline observed in CTE.

Tau Pathology in the Hippocampus

Regional Susceptibility and Subfield Vulnerability

Tau pathology in the hippocampus of CTE patients shows a distinct and selective pattern of involvement. A key finding from a study of 171 older adult men was a preferential accumulation of hyperphosphorylated tau in the hippocampal CA2 region, which was present in approximately 29.9% of cases.[24] This pattern differs from the distribution typically observed in other tauopathies, including AD. A direct comparison of 9 individuals with CTE and 6 with Alzheimer's disease (AD) confirmed this pattern, revealing that CTE cases exhibited higher tau densities in the CA2/3 and CA4 hippocampal subfields, whereas AD was associated with higher tau in the CA1 subfield and subiculum. This study also noted that amyloid-β pathology was measured but did not contribute significantly to the tau isoform levels observed.[25]

Table 2 Supplemental table of results and data extraction (Hippocampus focus).

Author/Year	Design	Sample Size	Population	Brain Region	Method	Major Tau Finding	Other Biomarkers	Limitations
Falcon et al., 2019	Postmortem case series	3	Former football player and boxers with stage IV CTE	Cortical sulci, cortical layers II–III	Cryo-EM, neuropathology	C-shaped tau protofilaments; perivascular hyperphosphorylated tau in neurons and astrocytes	Structural tau differences vs AD	Very small sample size
Fowler et al., 2025	Case-control cohort	50 (32 veterans, 18 controls)	Blast-related mTBI veterans and civilians	Gray-white matter junction, sulci, white matter	MRI, immunohistochemistry, molecular assays	AQP4 dysregulation linked to glymphatic dysfunction and regions vulnerable in tauopathies	GFAP elevation, perivascular space increase	Indirect link to tau pathology
Falcon et al., 2023	Large postmortem cohort	364	Former athletes with CTE	11 brain regions	Histopathology, p-tau quantification	p-tau burden increases with CTE stage and correlates with dementia	APOE $\varepsilon 4$, coexisting AD/Lewy pathology	Postmortem cross-sectional design
Zivanov et al., 2023	Postmortem cohort	41	CTE (low/high stage) and controls	Dorsolateral frontal cortex sulci	Histopathology, vascular analysis	p-tau highest in sulcal regions and correlates with severity	Increased microvascular branching	Moderate sample size
Falcon et al., 2022	Postmortem cohort	16	Confirmed CTE cases	Cortical sulci	Immunohistochemistry	Neuronal p-tau increases with disease stage; minor glial tau	Minimal astrocytic/oligodendrocytic tau	Small cohort
Cherry et al., 2021	Postmortem comparative study	15 (9 CTE, 6 AD)	CTE vs AD donors	Hippocampal subfields	Tau isoform mapping	CTE shows more tau in CA2/3 & CA4; AD in CA1/subiculum	Amyloid-β present but not driving tau pattern	Small sample size
Namsaraeva et al., 2024	Proteomic postmortem study	20	ADNC, PART, CTE donors	Hippocampus, entorhinal cortex	Proteomics	Region-specific p-tau epitope differences across tauopathies	Inflammation, proteostasis, synaptic proteins altered	No absolute tau quantification
Farrell et al., 2022	Postmortem cohort	107	PART vs CTE cases	Hippocampus	Digital pathology	CTE shows higher hippocampal p-tau than PART	No major additional biomarkers	Limited biomarker scope
McKee et al., 2016	Consensus neuropathology study	25	Mixed tauopathy cases	Cortical sulci, perivascular regions	Histopathology consensus definition	Defines CTE hallmark: perivascular p-tau in sulcal depths	TDP-43 inclusions	Descriptive /consensus study
Marquie et al., 2019	Pilot imaging study	33 (23 athletes, 10 controls)	Living former athletes	Cortical regions	Tau PET (Flortaucipir)	Mild/inconsistent increased tau PET uptake in athletes	Amyloid PET negative differences	Small sample; variability
Bieniek et al., 2021	Postmortem cohort	14	Former athletes	Cortex, hippocampus, brainstem	Neuropathology	Majority show CTE-like tau pathology	Amyloid plaques in minority	Small cohort
Farrell et al., 2021	Cohort imaging study	124	ADNI participants	Whole brain	PET, MRI, FDG-PET	Study focuses on neurodegeneration; tau not quantified	Amyloid, glucose metabolism, atrophy	No tau-specific data
Cheng et al., 2024	Animal model study	Not specified	Tau transgenic mice	Hippocampus, cortex	Molecular/biochemical assays	p-tau associated with synaptic mitochondria dysfunction	Synaptic loss markers	Animal model limits translation
Iverson et al., 2025	Postmortem cohort	171	Older adult men (football vs non-contact)	Hippocampus (CA2)	Histopathology	CA2 p-tau accumulation in subset of cases	Age association noted	Observational postmortem design
Mann et al., 2021	Animal model	Not specified	Tau transgenic mice + CCI injury	Hippocampus	TBI model + immunohistochemistry	Persistent AT8-positive tau after injury	Gliosis, synaptic loss	Animal model
Moszczynski et al., 2018	Postmortem cohort	207	Contact sport athletes	Frontal cortex	Biochemical assay	p-tau increases with CTE stage and exposure	Amyloid-β associations	Cross-sectional design
van Amerongen et al., 2023	Case report + review	1 (+13 reviewed)	Former soccer player	Frontal cortex, hippocampus	Neuropathology	Severe CTE tau pathology with astroglial involvement	TDP-43 inclusions	Single case report
Craven et al., 2018	Animal model	Not specified	Tau transgenic mice	Hippocampus	Western blot, staining	Increased tau tangles with zinc modulation	Zinc depletion in brain	Animal model
Alosco et al., 2023	PET-autopsy correlation study	3	Former American football players	Cortex, limbic system, thalamus	PET + postmortem histology	Strong correlation between tau PET and postmortem p-tau	Amyloid PET included	Extremely small sample size
Lepreux et al., 2015	Case report	1	Former boxer with dementia	Cortex, hippocampus, brainstem	Neuropathology	Extensive tau pathology resembling AD/CTE overlap	TDP-43 inclusions	Single case
Kochanek et al., 2013	Animal study	11 rats	TBI-exposed rats	Hippocampus, cortex	Blast injury model	Neuroinflammatory response similar to AD pathways	Cytokines, oxidative stress markers	Animal model
Gyoneva et al., 2015	Animal model	Not specified	CCR2 knockout mice	Brain-wide	TBI + molecular analysis	Increased tau phosphorylation after CCR2 deletion	Reduced lesion size	Animal model
Yu et al., 2024	Cellular model	Not specified	Neuron cultures	In vitro hippocampal neurons	Cell transfection	Mutant tau disrupts synaptic function	Synaptic dysfunction markers	In vitro model
Tagge et al., 2018	Animal + postmortem study	1 human + mice	Teen athletes + mouse model	Cortex, hippocampus	Histology + injury model	Early p-tau after injury spreads over time	BBB disruption, gliosis	Mixed model design
Johnson et al., 2011	Animal model	Not specified	Rats with TBI	Axonal regions	Histopathology	Increased tau phosphorylation after injury	APP accumulation, mitochondrial dysfunction	Preclinical model

Table 3 PRISMA 2020 table for inclusion of selected studies.

PRISMA Screening Stage	CTE Studies (n)	AD Studies (n)
Records Identified from PubMed	19	36
Records Screened	19	36
Reports Sought for Retrieval	19	36
Reports Assessed for Eligibility	19	36
Excluded (Review Articles)	2	6
Excluded (Did not assess tau pathology or other relevant biomarkers of neurodegeneration)	5	14
Studies Included in the Review	**12**	**16**

Overall Hippocampal Tau Burden in CTE

The overall burden of tau pathology in the hippocampus is significantly elevated in CTE. A large analysis of 107 individuals demonstrated that CTE cases had a significantly higher overall hippocampal phosphorylated tau burden compared to those with Primary Age-Related Tauopathy. (PART) across all hippocampal sectors.[25] These findings suggest that individuals with CTE may exhibit greater hippocampal tau burden than individuals with age-related tau accumulation alone.

Isoform Composition and Co-existing Pathologies

The tau pathology in the CTE hippocampus involves both 3R and 4R tau isoforms. The same study comparing CTE and AD also noted that the tau isoform composition in CTE can shift, being 4R-predominant in mild disease and becoming 3R-predominant in severe cases.[26] Furthermore, hippocampal pathology in CTE is often accompanied by other proteinopathies. TDP-43 positive cytoplasmic inclusions are frequently observed in the hippocampus and amygdala, being present in over 85% of cases, which may contribute to clinical symptoms.[19,27] Several studies have reported cases in which CTE pathology occurs alongside Alzheimer's-related changes. One case report of a former professional Australian football player revealed extensive tau pathology alongside amyloid-β plaques (CERAD C2), illustrating how these pathologies can co-occur and complicate clinical diagnosis.[27] A separate study of former athletes also reported the presence of amyloid-β in up to 43% of older CTE patients.[27] However, in vivo imaging of former professional athletes with cognitive symptoms showed no significant differences in amyloid-β PET uptake compared to the control groups, suggesting that tau may be the primary driver of symptoms in many cases.[28]

Discussion

The findings of this focused review demonstrate that although Chronic Traumatic Encephalopathy (CTE) and Alzheimer's disease (AD) are both tauopathies, they differ substantially in the regional distribution of tau pathology, the biological mechanisms that drive disease progression, and their associated clinical features. Across the studies included in this review, CTE consistently showed tau deposition within the dorsolateral frontal cortex, where abnormal phosphorylated tau accumulates around small blood vessels at the depths of the cortical sulci. This perivascular pattern distinguishes CTE from other neurodegenerative disorders and reflects the close relationship between repetitive head trauma and the development of tau pathology.

In contrast, Alzheimer's disease follows a different pathological pattern. Rather than beginning within the frontal cortex, tau accumulation typically starts in the hippocampus, particularly within the CA1 region and subiculum, before spreading throughout additional cortical areas as the disease progresses. Unlike CTE, Alzheimer's disease is more strongly associated with aging, amyloid-β deposition, and genetic risk factors. These differences suggest that although both disorders involve abnormal tau aggregation, they arise through distinct biological processes and affect different neural networks during the earliest stages of disease.

Another consistent finding across the reviewed studies was the relationship between vascular injury, neuroinflammation, and tau pathology in CTE. Multiple investigations identified increased expression of inflammatory markers alongside perivascular tau deposits, supporting the hypothesis that repetitive head impacts disrupt the neurovascular environment and promote pathological tau accumulation. Although the precise mechanisms remain incompletely understood, the available evidence indicates that vascular dysfunction may contribute to both the initiation and progression of CTE. This association is less prominent in Alzheimer's disease, where tau pathology appears to develop primarily through age-related neurodegenerative mechanisms rather than repeated mechanical injury.

Regional differences within the hippocampus further distinguish CTE from Alzheimer's disease. The studies included in this review consistently reported greater tau accumulation within the CA2, CA3, and CA4 hippocampal subfields in CTE, whereas Alzheimer's disease showed more extensive involvement of the CA1 region and subiculum. These findings suggest that the two disorders selectively affect different hippocampal circuits despite sharing tau as a common pathological feature. The selective vulnerability of these regions may also help explain differences in memory impairment, executive dysfunction, and behavioral symptoms observed between the two diseases.

The reviewed literature also demonstrates that CTE

frequently occurs alongside additional neuropathological changes, including TDP-43 proteinopathy and, in some individuals, amyloid-β deposition. While these coexisting pathologies may contribute to disease severity and clinical variability, they do not appear to explain the characteristic regional distribution of tau observed in CTE. Instead, the evidence suggests that repetitive head trauma initiates a disease process that remains neuropathologically distinct from Alzheimer's disease, even when overlapping pathological features are present.

Further Implications and Future Research:

Early Detection and Biomarkers

A major challenge in CTE research is the lack of reliable methods to diagnose the disease during life. Currently, confirmation of CTE depends on postmortem examination, making it difficult to identify individuals who may be at risk before severe symptoms appear. Future studies should investigate whether tools such as tau PET imaging, cerebrospinal fluid analysis, and blood-based phosphorylated tau measurements can identify early pathological changes. Developing these biomarkers could improve disease monitoring and allow researchers to better understand how CTE progresses over time.

Vascular Protection and Neuroinflammation

The association between perivascular tau accumulation, vascular changes, and inflammatory markers such as ICAM1, VCAM1, and CRP suggests that blood vessel injury may contribute to CTE development. Further research should examine whether protecting the blood–brain barrier, maintaining microvascular function, or reducing chronic inflammation can influence tau accumulation. These approaches may provide new strategies for slowing cognitive and behavioral changes associated with CTE.

Region-Specific Investigations

The selective involvement of hippocampal subfields, including CA2–CA4, and the dorsolateral frontal cortex highlights the importance of studying regional differences in CTE pathology. Future investigations should continue examining how tau isoforms, additional proteinopathies, and structural changes vary between brain regions. This information may help improve disease classification and guide future approaches for treatment and patient management.

Tracking disease progression

Because most current CTE research relies on postmortem studies, the timeline of disease development remains unclear. Long-term studies following individuals with repeated head impact exposure are needed to determine how trauma contributes to changes in tau accumulation, tau isoforms, and copathologies such as TDP-43. These studies may help establish stronger connections between exposure history, biological changes, and later cognitive outcomes.

Comparative Insights with Alzheimer's Disease

Comparing CTE and Alzheimer's disease provides insight into how similar proteins can contribute to different patterns of neurodegeneration. Although both disorders involve tau pathology, differences in tau structure, distribution, and associated pathologies may reveal why their clinical presentations differ. Continued comparison between these diseases may help identify shared biological pathways and improve the development of disease-specific biomarkers.

Public Health and Safety Applications

Improving our understanding of CTE has important implications for individuals exposed to repetitive head impacts, including athletes and military personnel. Research on risk factors, disease progression, and protective strategies can contribute to improved safety guidelines and monitoring programs. Reducing unnecessary head trauma and identifying individuals at higher risk may help decrease the long-term neurological consequences associated with repeated injury.

AI Usage Disclosure

At the initial stage of developing the manuscript, generative AI was used to assist with the preliminary organizational structure of the manuscript. It was used as a starting-point structuring aid and not as a substitute for the research, literature review, analysis, interpretation of findings, or authorship of the work.

No generative AI was used for any revisions made after the second draft. All revisions following the second draft, including subsequent restructuring, rewriting, clarification of the methodology and results, and preparation of the manuscript for NHSJS, were completed by the authors based on our own research, analysis, writing, and feedback from the editorial and mentorship process.

Both authors confirm that the final manuscript represents our own work and that we take responsibility for its contents.

Author Contributions

Day-Liin Williams: Conceptualization, literature search and analysis, data extraction, synthesis of the reviewed literature, interpretation of findings, and primary drafting and writing of the manuscript. Day-Liin developed the central research ideas and conducted the literature review underlying the manuscript.

Aleks Bogoniewski: Supervision and mentorship, methodological guidance, scientific interpretation, manuscript organization and restructuring, and substantive revision. Aleks provided guidance on the scientific framing and structure of the manuscript, identified areas requiring further investigation, and assisted in refining the presentation of the research and its findings.

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