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Kenneth Perrine, Ph.D., 1 Jacqueline Helcer, M.S., M.A., 2,3 Apostolos John Tsiouris, M.D., 4 David J. Pisapia, M.D., 5 Philip Stieg, Ph.D., M.D. 1

1 Department of Neurological Surgery
   Weill Cornell Medical College
   525 E. 68th Street, Box 99
   New York, NY, USA, 10065
2 Department of Psychiatry
   Harvard Medical School
   25 Shattuck Street
   Boston, MA, USA, 02115
3 Department of Psychiatry
   Massachusetts General Hospital
   55 Fruit Street
   Boston, MA, USA, 02114
4 Department of Clinical Radiology, NYPH – Weill Cornell Medical College
   525 E. 68th Street, Starr 630C
   New York, NY, USA, 10065
5 Department of Pathology and Laboratory Medicine
   Weill Cornell Medical College
   1300 York Avenue
   New York, NY, USA, 10065

Corresponding Author:
Kenneth Perrine, Ph.D.
krp2003@med.cornell.edu
Weill Cornell Medical College
525 E. 68th St., Box 99
New York, NY 10021, USA

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Abbreviations and Acronyms
AD, (Alzheimer’s Disease); ALS, (Amyotrophic Lateral Sclerosis); APOE, (apolipoprotein); CERAD, (Consortium to Establish A Registry for Alzheimer’s Disease); CT, (Computed Tomography); CTE, (Chronic Traumatic Encephalopathy); DTI, (Diffusion Tensor Imaging); FA, (Fractional Anisotropy); FLAIR, (Fluid Level Attenuated Inversion Recovery); fMRI, (Functional Magnetic Resonance Imaging); FTD, (Frontotemporal Dementia); MPRAGE, (Magnetization-Prepared Rapid Gradient-Echo); MRI, (Magnetic
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Highlights:
- Chronic Traumatic Encephalopathy (CTE) is a type of tauopathy seen at autopsy
- CTE may result from concussion or subconcussive blows to the head
- Stages of CTE with an accompanying set of clinical features have been proposed
- The prevalence of CTE is unknown given sampling bias in the brains examined
- The current article reviews evidence for multiple factors associated with CTE

ABSTRACT

Chronic Traumatic Encephalopathy (CTE) evolved from the term “dementia pugilistica” describing the dementia found in many boxers to its current use in describing the dementia and depression sometimes found in athletes subjected to multiple concussions or sub-concussive
blows to the head. Concurrently, the neuropathology evolved to specify a unique type of tauopathy found in perivascular spaces at the depth of sulci and other features not typically seen in neurodegenerative tauopathies. Four stages of CTE have been proposed, with four corresponding clinical syndromes of Traumatic Encephalopathy Syndrome. However, it remains unclear whether this is a syndrome unique to repetitive head trauma, especially in contact sports, as the epidemiology has been difficult to establish. In particular, research to date suffers from a “denominator” problem in not establishing the total number of potential cases at risk for developing CTE. The current review examines the evidence to date for these syndromes, and contributing or complicating factors affecting the neuropathology, neuroimaging, and clinical presentations associated with them.
INTRODUCTION

A dramatic increase in the discussion of concussions and brain pathology in contact sport athletes occurred in the last decade, both in the popular press and in the scientific literature. Chronic Traumatic Encephalopathy (CTE) is implicated as a neurodegenerative condition resulting from the repetitive head trauma often sustained by participation in contact sports such as football and boxing. The first description of a disorder predating the term CTE dates back to 1928, when a “punch drunk” syndrome in 23 boxers was described by Martland. The term then evolved to “traumatic encephalopathy” in 1934, “dementia pugilistica” in 1937, and finally, Chronic Traumatic Encephalopathy by Critchley in 1949. This original description of CTE was characterized by cerebellar or extrapyramidal disorders with dysarthria and motor deficits, and was sometimes accompanied by dementia. Roberts et al. reported in 1990 that 17% of 224 retired boxers had CTE. Jordan reviewed the literature on boxers through 2000 and reported clinical phenomenon of cerebellar and extrapyramidal signs along with cognitive and behavioral problems. He noted that it was unclear whether the signs and symptoms observed were indicative of a neurodegenerative disorder or a neurologic disorder exacerbated by aging. Other instances of CTE had been reported in non-boxers, including patients with repeated head banging or battery.

CTE is thought to result from multiple concussions or repetitive head trauma, which are more prevalent in athletes in contact sports. Coupled with substantial media attention surrounding sport-related concussions, the research focus is dominated by investigations of CTE in deceased football players. Renewed interest in CTE began when Omalu reported finding evidence of CTE in three retired football players. McKee reported similar findings in 3 new subjects when reviewing the world literature on CTE including one football player, followed by
numerous reports and case studies of evidence of CTE in athletes, veterans, and others exposed to repetitive head trauma.\textsuperscript{8,12-17}

The neurobehavioral changes associated with CTE reportedly involve a wide spectrum of pathologies, such as depression severe enough to lead to suicide, substance abuse, emotional instability, aggressiveness, poor impulse control, irritability, and advanced dementia.\textsuperscript{16,17} Similar to other neurodegenerative disorders, the cognitive difficulties seen in patients with CTE typically have a gradual, progressive course and can include significant memory impairment, executive dysfunction, language difficulties, and motor disturbances. The onset of behavioral and cognitive symptoms is generally years after exposure to repetitive trauma and often presents in midlife (e.g., after retirement from sports).\textsuperscript{16,17} However, neuropathologic changes can be seen at a microscopic level in patients with a single traumatic brain injury (Omalu, 2011) or as early as adolescence (i.e., in high school football players) in some case reports.\textsuperscript{8}

Just as the demographics of CTE evolved from boxers to football players and other contact sport athletes, the observed pathological features have also expanded from gross morphological changes such as cavum septi pellucidi to specific locations involving p-tau, and from clinical phenomena with extrapyramidal signs and Parkinsonian-like dementia to a very broad spectrum of neurobehavioral disorders. The various definitional shifts since the first description of CTE raise important questions about our current understanding of CTE that remain unanswered: Is the modern description of CTE a new, distinct disorder or is modern CTE merely a variant of the same essential pathological process initially described in the classic CTE of boxers? Or is CTE a variant or co-morbidity of other unrelated more essential neurodegenerative conditions such as frontotemporal dementia (FTD) and Alzheimer’s disease (AD) to which individuals with exposure to trauma may have increased susceptibility?
Some of the challenges in studying CTE include the fact that there appears to be great variability in the clinical presentation of CTE across studies, as well as signs and symptoms that overlap with other neurodegenerative conditions. Second, there is considerable heterogeneity in the histopathological changes cited for CTE with four “stages” and four “phenotypes” associated with histopathological findings. Third, as most studies acknowledge, many of the brains examined for CTE were donated explicitly because of the presence of neurobehavioral symptoms prior to death, resulting in a pronounced selection bias. Related to these problems and perhaps more importantly with respect to the public’s perception of the disease and how CTE may influence policy, the current literature based on case studies suffers from a “denominator problem”. That is, there is still an absence of sufficient epidemiological evidence of CTE from a broad, randomly sampled population of retired athletes with and without concussions or subconcussive blows. The current review will explore these issues in more detail to present the evidence of CTE as a unique neuropathological disorder accompanied by distinctive clinical presentations with a presumptive cause of concussions or multiple subconcussive blows to the head.

Pathophysiology of Head Injury

Despite the advances made in the neuropathological findings of CTE, mechanistic information correlating particular clinical features with anatomical abnormalities is still missing. It is feasible that the motor symptoms previously seen in boxers with CTE are reflective of injuries to the pyramidal tracts, extrapyramidal system, or cerebellum. However, the injury mechanisms behind the other cognitive and behavioral manifestations of CTE are less clear. For example, Stern\textsuperscript{16} described some apparent clinical presentations of CTE in his study of athletes
and attempted to differentiate them from symptoms seen in other dementias. However, he did not relate how the clinical features may be correlated with the presence and degree of tauopathy, whereas this association is established in other dementias, such as FTD and Alzheimer’s. The impact of p-tau depositions in scattered perivascular spaces on depression and cognitive deficits is also unclear. For example, some studies show that depression \(^{19,20}\) and word finding difficulty lateralizes to injury to the left hemisphere, and a predominance of p-tau in the left hemisphere would be expected to relate to associated deficits in these domains. However, lateralization is discussed in CTE, further obscuring the mechanism causing depression and language deficits.

Similarly, little is known about the pathophysiology of concussions and the anatomical correlates of its clinical features. Our knowledge on why concussions cause loss of consciousness, photosensitivity, headaches, fatigue, poor concentration and other symptoms is limited.\(^{21}\) Thus, in order to understand the mechanisms that contribute to the clinical features of CTE, a more thorough comprehension of the physiology of concussions is needed. Moreover, studies are mixed on whether concussions and mild TBI are distinct clinical entities, rather than milder forms of moderate to severe TBI.\(^{21,22}\) Animal models help clarify some physiological processes in the acute stages, but still do not paint a full picture.\(^{23-28}\)

**Neuropathology of CTE**

There is substantial diversity in the clinical history and presentation of those patients who are ultimately assigned a pathologic diagnosis of CTE, and many clinical symptoms may overlap with those of other neurodegenerative diseases. Studies suggest that CTE is indeed a neuropathologically distinct entity from disorders such as AD, Parkinson’s disease, FTD,
sporadic amyotrophic lateral sclerosis (ALS), and other neurodegenerative diseases. Even so, considerable heterogeneity exists across individual cases of CTE.

The initial neuropathology described CTE in boxers. In 1973, Corsellis et al. examined 15 boxers with “dementia pugilistica” and described the neuropathological substrate of CTE as involving (a) neurofibrillary tangles in the absence of plaques, particularly involving the medial temporal lobe and brainstem tegmentum, (b) neuronal loss in the substantia nigra, occasionally with neurofibrillary tangles, (c) scarring of the cerebellar tonsils, and (d) cavum septi pellucidi.29

Considering that beta amyloid deposition has variably been considered a distinguishing feature of CTE relative to AD, several studies have sought to further characterize beta amyloid in CTE cases. The cases initially examined by Corsellis et al. were later re-examined by Roberts et al. for beta amyloid. This study revealed extensive, diffuse-type beta amyloid plaques that had not been observed previously using less sensitive techniques. McKee et al. found beta amyloid deposition, an essential feature of AD, in 40-45% of CTE cases.12 Further efforts to characterize beta amyloid deposition in CTE cases by Stein et al. found beta amyloid deposition in 52% of CTE patients. Importantly, this study distinguished between the diffuse plaques observed with immunohistochemical staining (seen in 52% patients) versus neuritic plaques as assessed by silver staining (36% of patients), the plaques which are also quantified to assess the CERAD or “C” score for neuritic plaques in AD cases. The number of neuritic plaques seen even in “late stage” CTE cases (with or without concomitant AD-diagnostic pathology) was significantly lower than those found in pure AD controls. Additionally, distributional differences in amyloid deposition were observed in CTE cases versus controls.

Geddes et al., in an effort to detect early changes in CTE, examined the brains of 5 young adults in their twenties with a history of repetitive head trauma secondary to varied
causes. Chronic neuropathological changes were found in four cases. Cases 1 and 2 (the two boxers) were the most affected, while changes in cases 3 and 5 were much less frequent. The pathology included argyrophilic, tau-positive neocortical NFTs, occasionally solitary except in cases 1 and 2, in which they were more numerous and arranged in groups predominantly around small intracortical blood vessels. The authors concluded that the perivascular topography of NFTs in cases 1, 2 and 4 suggests that a vascular association might be important, and the fact that NFTs were often seen around penetrating vessels in the depths of sulci suggests a predominantly ischemic etiology. These CTE cases showed tau deposition in a prominent perivascular distribution, and an absence of beta amyloid deposition using immunohistochemical techniques, a pattern of neurodegenerative changes consistent with prior characterizations of neurodegenerative changes in CTE and a pattern distinct from that typically seen in AD.15

Gardner et al.31 performed a systematic review of 85 athlete autopsies and found that only 20% had “pure” CTE, 52% appeared to have CTE plus other neuropathology, 5% had no CTE, and 24% had no observed neuropathology, leading the authors to stress the heterogeneity of the disease. However, despite the heterogeneity in pathology and clinical history seen in patients with CTE, the first NINDS/NIH workshop to define neuropathological criteria for a pathologic diagnosis of CTE32 was able to define the following common pathognomonic feature of CTE: “p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of cortical sulci.” In particular, neurofibrillary degeneration in CTE tends to localize primarily in sulcal depths with irregular distribution in the frontal and temporal cortices, in prominent periventricular, perivascular, and subpial distribution, as well as in the superficial cortex (cortical layers II and III).12 CTE thus defined may represent a unique neuropathological
entity, based primarily on modern immunohistochemical techniques showing accumulations of p-tau in a topographical distribution that is distinct from other tauopathies.

TDP-43 accumulation has also been demonstrated in CTE in recurrent locations. Accumulation of this protein is characteristic of both ALS and frontotemporal lobar degeneration (FTD).\textsuperscript{13,14,34} It has more recently been identified as a common pathologic finding associated with CTE.\textsuperscript{13} However, the causal relationship between the multifocal tauopathy and the clinical symptoms remains poorly understood.\textsuperscript{31} It is conceivable that CTE may represent a more sophisticated pathological diagnosis than the older “dementia pugilistica” terminology, or a series of different neuropathologies.

In the largest study on CTE neuropathology samples to date, McKee et al.\textsuperscript{8} examined the brains of 85 former athletes, military veterans, and civilians with a history of repetitive traumatic brain injuries, finding evidence of CTE in 68 male subjects. Of these, 33 were retired NFL players and only 16 were considered to have “pure” CTE neuropathology (i.e., without overlapping neurodegenerative conditions). McKee et al.\textsuperscript{8} posited that the observed changes in CTE evolve from perivascular foci at the depths of sulci in the cerebral cortex, perhaps representing those areas of the cortex with increased mechanical susceptibility to injury, and then spread gradually to the superficial layers of the lateral convexities, medial temporal lobe, diencephalon, basal ganglia, brainstem, and spinal cord. Localization of these neuropathological changes is reportedly distinct from what is typically seen in other tauopathies including AD and FTD. For example, in CTE, although the specific tau isoforms are indistinguishable from AD,\textsuperscript{12} the abnormal distribution and perivascular clustering of tau in the depths of sulci and early involvement of neocortical foci suggest a distinct core pathology.\textsuperscript{12} There is also a greater density of NFTs and glial tangles (GTs) in CTE compared to other tauopathies.\textsuperscript{35}
Stages of CTE

Furthermore, McKee et al. proposed four progressive stages of CTE and specified the primary neuropathological features dependent upon each stage of degeneration (Figure 1). In stage 1, brains are typically of normal weight and show focal epicenters of perivascular p-tau, NFTs, neutrophil neurites, and astrocytic tangles involving the sulcal depths especially of the superior and dorsolateral frontal cortices. Occasional p-tau immunoreactive glia and glial processes, TDP-43 neurites, and white matter reactive microglia clusters with axonal swellings are also found.

Stage 2 brains are typically of normal weight with more frequent epicenters at the depths of the sulci and NFTs scattered throughout superficial cortical layers as well as locus coeruleus and substantia innominata. The lateral and third ventricles are often mildly enlarged, along with a cavum septi pellucidi and pallor of the locus coeruleus and substantia nigra.

In stage 3, the brain is typically reduced in weight with mild cerebral atrophy and ventricular dilatation. Septal abnormalities are more common. There is depigmentation of the locus coeruleus and substantia nigra, as well as atrophy of the mammillary bodies, thalamus, and hypothalamus. Thinning of the corpus callosum is also typical. P-tau pathology is widespread in the broader cortical areas, and NF pathology is seen in the olfactory bulbs, amygdala, hippocampus, hypothalamus, mammillary bodies, nucleus basalis of Meynert, substantia nigra, dorsal and median raphe nuclei, locus coeruleus, and entorhinal cortex.

Stage 4 brains have a marked reduction in weight due to generalized cerebral cortical atrophy of the medial temporal lobe, thalamus, hypothalamus, and mammillary bodies. Septal abnormalities are seen in most cases. Complete depigmentation of the locus coeruleus and substantia nigra can be seen. Severe p-tau pathology affects most regions of the cerebral cortex.
and the medial temporal lobe, though sparing the calcarine cortex. Severe p-tau pathology is also seen in the diencephalon, basal ganglia, brainstem and spinal cord. Marked axonal loss of subcortical white matter tracts is also evident.

Limitations to Stages

There are several limitations to this study and the proposed stages. First, not all cases that were examined in this study showed all criteria for all stages. Rather, the staging descriptions represent a collection of features seen together across multiple cases with the essential feature of tau distribution and severity as perhaps the underlying abnormality defining a given stage. For example, some staging features were only found in a minority of cases cited as showing CTE, making the identification of stage-defining criteria complex.

Secondly, these stages arose from multiple case studies of the brains examined, and are therefore based on cross-sectional rather than longitudinal data. It is conceivable that each stage could represent distinct disease processes rather than a progressive disease. In the absence of longitudinal data, it is difficult to predict whether the pathology would progress in sequential stages as defined.

Third, the contribution of other variables to each presentation requires larger, prospective, and longitudinal studies. Age, psychiatric or substance use history, family or genetic risk factors, and/or other comorbid neurodegenerative conditions that may have contributed to each individuals’ neuropathological classification within a “stage” need to be considered.

Fourth, it is well established that tau pathology and beta amyloid depositions can be found in adults who are healthy or have diverse health conditions, and therefore are not unique to CTE, although the topography of pathology may be different in CTE. However,
performing longitudinal histopathological studies is basically impossible unless sequential brain biopsies were performed, given the lack of specific in vivo p-tau biomarkers.

Older studies with boxers did not show any such progression,\textsuperscript{38,39} and Gardner et al.\textsuperscript{31} noted that classic CTE does “not appear to advance in a predictable and sequential series of stages”. Therefore, it should be emphasized that the pathological “stages” of CTE are descriptive and the implication that one stage mechanistically follows another is a hypothesis requiring further study.

Finally, a key limitation is the relatively limited number and characterization of control subjects. As the authors note, it would be ideal to expand such control groups and include individuals with dementia and depression who have never had subconcussive blows or other head trauma as well as athletes of comparable age with a history of concussion but no neurobehavioral changes to counter the inherent selection bias. A subsequent study by Bieniek et al.\textsuperscript{40} attempted to reduce selection bias in the athletic population by screening more broadly a neurodegenerative brain bank. In this study they found cortical tau pathology consistent with CTE in 32\% of 66 athletes with a history of contact sports as compared to 0\% of 198 age-matched controls in the same bank. Omalu et al.\textsuperscript{18} also proposed a histopathological classification of CTE with many similarities to McKee’s stages. He did not report a marked accumulation of \(\tau\)-immunoreactive astrocytes as a hallmark feature, whereas McKee did\textsuperscript{8,12,18}

It is also unclear how frequently neuropathologists use the specific stains\textsuperscript{32} shown to adequately identify the presence of abnormalities said to be specific to CTE in non-athletes, normal elderly individuals, or in those with other pathologies unique to similar neurodegenerative disorders (e.g., AD, FTD, ALS).
Several researchers explored the development of CTE histopathology in animal models. Mild traumatic brain injury was induced by controlled blasts, direct impact, or percussion techniques, and the animals were followed for up to six months with histopathology. Although p-tau developed in several of the studies, especially in mice with tau mutations predisposing them to accumulation, the distributions did not resemble those seen in human histopathology. Specifically, deposition of p-tau in perivascular regions in the depths of the sulci has not been confirmed in animal models. Rather, the findings contradict the data from that in human CTE cases, and show tau depositions in the hippocampus.

The National Institute of Neurological Diseases and Stroke cautioned that a causal relationship between the multifocal tauopathy observed in CTE and antecedent clinical symptoms remains poorly understood. It is likely that CTE as it is currently defined represents a more inclusive pathological diagnosis that encompasses those cases earlier designated as “dementia pugilistica”, classically described in boxers, and is now associated with patients with other forms of trauma including patients with a history of other contact sports.

Clinical presentation

The heterogeneity in the clinical presentations of CTE further obscures its operationalization and distances researchers from defining a set of distinct diagnostic criteria. Case reports show variable neurobehavioral and neurocognitive changes, but without any definitive core criteria. Efforts to define the clinical diagnostic criteria of CTE are hindered by a lack of prospective studies with living subjects. The evidence to date relies solely on retrospective reviews of case reports and next of kin interviews, without a review of medical records, limiting their validity. Apparently, most of the brains submitted for detailed autopsy
with stains to detect tau phenotypes and TDP-43 were sent to centers by relatives of the deceased who were distressed by the patient’s clinical depression or dementia. It is not clear how many of the brains reported as having CTE were submitted by families of decedents with no history of mental disorders or dementia. Consequently, reliance on histories of psychiatric problems, neurological disorders, or co-morbidities without medical record verification cannot be regarded as reliable. And as already noted, these studies are cross-sectional, rather than longitudinal. However, what can be inferred from the current data is that the clinical presentation of CTE involves symptoms in at least one of three possible domains: cognition, behavior/mood, and motor functioning.

The cognitive and behavioral symptoms of CTE are nonspecific in that they are frequently seen in the general population as well as in other medical, psychiatric, and neurological disorders. For example, some of the cognitive features seen (i.e., impaired concentration, language, and memory, as well as executive dysfunction, visuospatial difficulties, and dementia) are common in other neurodegenerative conditions, as well as in normal aging. The motor features seen in boxers (e.g., dysarthria, spasticity, ataxia, tremors, gait disturbance) resemble those of individuals with Parkinson’s disease. The behavioral manifestations (i.e., apathy, aggression, impulsivity, depression, delusions, and suicidality) are seen in the general population or psychiatric disorders and are hallmark features of some neurodegenerative conditions (e.g., FTD). Iverson et al. found that high school athletes with no history of concussion reported one or more concussion symptoms with 19% of boys and 28% of girls showed enough symptoms to resemble a diagnosis of post-concussion syndrome.

The absence of a definitive clinical diagnostic criteria makes it challenging to clinically differentiate CTE from other neurodegenerative diseases. For example, it is unclear whether the
dementia from CTE is distinct from the tauopathy phenotype of frontotemporal dementias (FTD), as most of the signs and symptoms cited as evidence for CTE can be found in criteria for FTD. Episodic memory impairments seen in some cases of CTE could also be confused with those seen in Alzheimer’s disease (AD), just as motor features seen in other cases of CTE could be confused with Parkinsonian syndromes. Despite the frequent overlap in symptoms, there are some distinctions in the clinical presentations of CTE that help differentiate CTE from non-traumatic neurodegenerative disorders (e.g., AD, FTD, Parkinson’s). 

Stern et al. examined the clinical presentation of CTE in 36 subjects with neuropathologically confirmed CTE with retrospective reports of their clinical presentations. The results of the study suggested the existence of two distinct clinical presentations of CTE. One (n=22) had initial changes in behavior (n=13) or mood (n=9) prior to the onset of cognitive disturbances and with an earlier age of onset (n =22), and the other with initial changes in cognition and an older age of onset (n = 11). There was also an understated third group of who were asymptomatic (n = 3). The behavior/mood group was thought to be distinct from FTD in that cases of disinhibition and inappropriate behavior were not seen in this sample. However, this contradicts the description of these patients as “explosive, out of control, physically and verbally violent, and depressed” (p. 1125). Furthermore, the onset of behavioral changes with later developed cognitive changes is one of the hallmarks of FTD. Memory disturbances were predominant in subjects in the cognitive group who were also older, but three-quarters of the behavior/mood group also had significant memory impairments.

There were no motor features in the subjects, which diverges from previous cases of such symptoms in boxers but is consistent with a distinction of the clinical presentation between football players and boxers. Boxers have predominantly motor symptoms, such as ataxia,
dysarthria, and parkinsonism.\textsuperscript{6} In contrast, cognitive and neurobehavioral features predominate in football players with histopathological evidence of CTE, with very few motor features. This stark difference is also reflected in the neuropathology, with studies finding more cerebellar scarring in boxers compared to football players.\textsuperscript{47} Stern et al. suggested that these differences could be attributable to the variance in the biomechanics of the injuries, specific to the nature of each sport. For example, some studies found that although boxers may sustain more angular acceleration and torsional injuries, while football players may be more likely to sustain transverse and linear acceleration/deceleration injuries,\textsuperscript{48} more research is needed to determine if there actually are differences in injury mechanisms between these two contact sports. These findings suggest that it cannot be concluded that repetitive brain trauma in multiple contexts will certainly cause CTE.

Another major challenge is determining a causal relationship between clinical features and neuropathological abnormalities. They are not consistently correlated, and experimental evidence is lacking that links the specific neuropathological features of CTE to the clinical presentation presented in the literature. CTE neuropathology has been found in subjects who were clinically asymptomatic.\textsuperscript{8,16,35,49} Other neuropathological abnormalities similar to CTE and Alzheimer’s diseases are also found in samples of asymptomatic older adults.\textsuperscript{50} Conversely, many subjects who initially presented with the cognitive and behavioral symptoms consistent with a traumatic encephalopathic syndrome were later found to lack the neuropathological changes of CTE at autopsy.\textsuperscript{8,21} The inability to determine causality given these disparities highlights the need to design further studies that address moderating variables and attempt to mitigate methodological limitations.
McKee et al. proposed four stages of *clinical* CTE corresponding to the proposed four stages of the *neuropathological* progression of CTE, and described common clinical features seen at each stage. Initially, Stage I symptoms were said to include headaches and decreased attention and concentration. Stage II symptoms were said to progress to depression, explosivity, and memory loss, and then to executive dysfunction and cognitive impairment in stage III. Finally, individuals in stage IV were said to exhibit word-finding difficulty, aggression, and dementia. In their more recent studies however, the authors state that individuals with stage I neuropathology are unlikely to be symptomatic at all and that subjects with stage II pathology may also be asymptomatic.

**Traumatic Encephalopathy Syndrome**

In 2014, a new diagnosis in order to classify the clinical presentation of CTE, termed Traumatic Encephalopathy Syndrome (TES), was proposed. The general proposed criteria for TES includes: 1) a history of multiple head impacts (defined by injury and exposure type), 2) an exclusion of any neurologic disorder that could account for clinical features, but with the caveat that, “concomitant diagnoses of substance abuse, post-traumatic stress disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases (for example, AD and frontotemporal dementia) or a combination of these can be present”, 3) symptoms must be present for at least 12 months, 4) the presence of at least one of the core clinical features (i.e., cognitive, behavioral, mood) representing a change from baseline functioning, and 5) the presence of at least two supportive features (e.g., impulsivity, anxiety, apathy, paranoia,
suicidality, headache). Given that a history of ADHD or a learning disability is regarded as an antecedent risk factor, perhaps it should be excluded from a diagnosis of TES.\textsuperscript{55,62}

The rationale for designating TES as distinct from CTE was to separate the observed neurobehavioral symptoms from the neuropathological underpinnings. Since CTE can only be diagnosed through confirmation of neuropathological abnormalities postmortem, similar to AD, the introduction of TES would allow for an \textit{in vivo} classification. However, the proposed syndrome is significantly far-reaching and broad in that it encompasses many individuals with a history of head injuries, ranging from those with subconcussive trauma, itself broadly defined as “biomechanical force to the head or body” that does not lead to concussive symptoms,\textsuperscript{54} to those with two or more severe TBIs. It also broadly encompasses individuals from mild depression to late stage dementia. For example, an individual with subconcussive blows, perhaps from contact sports, who also had problems with depression, anxiety, and headaches, would meet criteria for TES. Victoroff\textsuperscript{63} noted the absence of an operational definitions of CTE and TES, and after reviewing 92 boxers and 4 football players suggested the adoption of provisional diagnostic criteria for CTE research. Montenigro et al.\textsuperscript{64} presented clinical features thought to relate repetitive traumatic brain injury with CTE that could be used in research, emphasizing the use of clinical signs and symptoms present in more than 70\% of reported cases of CTE. Reams et al.\textsuperscript{65} recently published a comprehensive set of diagnostic criteria to establish a clinical diagnosis of TES in living patients without necessitating the use of autopsy proven changes. A flow chart was created that incorporates trauma exposure, repetitive head trauma, comorbid conditions, onset, progression over time, evidence for other neurodegenerative disease, presence of cognitive decline documented by neuropsychological testing, and one or more clinical features of TES.
These precise criteria should help researchers develop a better clinical construct for the diagnosis of TES.

**Comorbidities and Moderating Variables**

An attempt to attribute clinical features solely to concussive or subconcussive blows sustained during play would need to account for comorbidities that may contribute to and confound the neuropathology and clinical presentation of CTE. Asken et al. stressed that biopsychosocial factors can have a strong influence of the clinical manifestations of CTE, including the athlete’s developmental environment, neurodevelopmental disorders, normal aging, adjustment to retirement, drug and alcohol abuse, surgeries and anesthesia, and sleep disturbances. For example, in the early case descriptions of retired boxers, many had extensive psychiatric histories (e.g., severe substance abuse), as well as other psychiatric, medical, or neurological comorbidities. The same is true for the more recent CTE studies. Some studies have not adequately controlled for or addressed certain factors (e.g., genetic, lifestyle) that could help account for the neuropathological or neurobehavioral symptoms seen in NFL players, or that may make players more susceptible to developing neurodegenerative conditions.

The extent to which athletes’ family histories of neurodegenerative conditions or potential genetic risk contributes to the neuropathology and clinical presentation of CTE is still unknown. It has been suggested that the apolipoprotein (ApoE) ε4 allele may increase susceptibility for CTE. In fact, Jordan et al. found the APOE ε4 allele to be overrepresented among boxers diagnosed with CTE. However, the precise relationship or mechanisms involved in determining
the magnitude of genetic risk on CTE is yet to be determined. Prospective studies could consider genetic testing for the ApoE ε4 allele, along with investigation of other genes that merit consideration, as well as more rigorous reviews of family pedigrees.

Family socioeconomic background, including income, education, occupation, access to medical care, and early cognitive stimulation significantly affects adult functioning. Socioeconomic background is associated both with childhood disorders such as learning disabilities or ADHD, which in turn affect the functioning of professional athletes and influences later expression of neurodegenerative disorders.

Another potentially important variable is professional athletes’ use of anabolic steroids or other performance enhancing drugs (PEDs). The NFL began testing for PEDs in 1987, with approximately 6 to 7 percent of 2,600 players testing positive for anabolic steroid use in that first year. The adverse physical and psychiatric effects of PEDs are well documented across studies with numerous case reports of violence, aggression, mania, and suicide discussed in the media. In high doses, PEDs are associated with manic-like affective symptoms (e.g., hostility and aggressiveness, mood swings, poor impulse control), cognitive symptoms (e.g., deficits in memory, attention, and orientation), and psychosis. Steroid withdrawal can result in depression and suicidal ideation. Given that they are illegal, it is difficult to determine the true prevalence of PEDs in NFL players. However, several former players admitted to PED use, some of whom were also diagnosed with CTE. For example, Mike Webster, who committed suicide and was the first NFL player found to have CTE, was among those with an unequivocal history of steroid use. Another former player, Steve Courson, asserted in his autobiography that 75 percent of his teammates on the offensive line used steroids. These assertions certainly raise
questions about the effect of PEDs on the development of CTE in former players, or at the very least, marks the importance of controlling for such variables when possible.

In addition to the use of PEDs, the use of other illicit or prescription drugs may be worthy of attention as well. Opioid abuse in particular is especially prevalent in NFL players, both during play and post-retirement. Opioid abuse can also contribute to significant psychiatric disorders. Cottler et al. conducted a telephone survey of 644 retired NFL players from the 2009 Retired Players Association Directory, finding that 52% (n=336) of retired NFL players reported opioid use during their NFL careers, with 71% of those reporting misuse. Compared to players who only used the medications as prescribed, misusers were found to be more likely to have poor overall health at retirement. Furthermore, undiagnosed concussions, which were reported by 81% of the sample, were found to be the strongest predictor of opioid misuse. It would thus be prudent for CTE researchers to consider the potential neurological and neurobehavioral impacts of these drugs.

The varying lifestyle factors of NFL players, both while playing and later when retired, make it crucial to consider alternative explanations or theories for their neurobehavioral presentation. The additive effects of substance abuse can certainly have an effect on individuals’ mood and behavior, but there are other unique circumstances that are particularly relevant to elite athletes. For example, many elite athletes can become depressed after they retire, merely as a result no longer being in the limelight or having focused nearly all of their life to one objective and then abruptly stopping that pursuit. Torre reported that as many as 78% of retired NFL players develop financial hardship within 2 years of retirement. Financial difficulties in conjunction with substance abuse problems could cause or exacerbate major depression. Additionally, normal aging should be considered when examining later-life neurobehavioral
functioning \textsuperscript{66}, especially given the increased risk of subsequent dementia after TBI. \textsuperscript{86,87} Asken et al. \textsuperscript{66} also noted that the higher incidence of surgeries, most with general anesthesia, may impact the risk of later neurodegenerative disorders, and that sleep disorders also contribute to the development of dementia.

To best clarify the effects of concussions on dementia or neurodegeneration, other variables such as comorbid illnesses (e.g., heart disease, diabetes, metabolic syndrome), lifestyle factors (e.g., diet, stress), age at trauma, and other specific aspects of head injuries (e.g., severity, frequency, type, duration of trauma) should also be investigated as any of these could potentially initiate or exacerbate tau aggregation. \textsuperscript{15,31,34,44,52,67} Future studies should thus consider implementing genetic testing, collecting rigorous family history data, and more thoroughly investigating the association between these factors and CTE-related proteinopathies.

**Neuroimaging**

Given that the diagnosis of CTE is a post-mortem neuropathological diagnosis, currently there are no retrospective studies reviewing any structural or advanced neuroimaging biomarkers in patients diagnosed posthumously with the disease. However, as with all traumatic brain injury, the objectives of neuroimaging should include the better characterization and classification of brain injuries, prognostication, and identifying patients that would benefit from early specialist referral.

Currently, structural MRI is the primary imaging modality for subacute to chronic TBI. \textsuperscript{88} It is sensitive for detecting and characterizing brain injuries, particularly cerebral atrophy in chronic TBI. The literature is most complete for moderate to severe TBI, where cerebral atrophy
is a consistent finding.\textsuperscript{89-91} Three-dimensional isotropic short echo spoiled gradient-recalled echo (SPGR) and magnetization-prepared rapid gradient-echo (MPRAGE) sequences can be used to assess TBI-associated cerebral atrophy.\textsuperscript{91-94} A few studies correlated the severity of injury with chronic cerebral atrophy\textsuperscript{95} and functional outcomes to post-TBI cerebral atrophy,\textsuperscript{90,96-98} although only weak correlations were found between the patterns of atrophy and their neurocognitive sequelae.\textsuperscript{91,94}

Relatively new structural MRI techniques such as susceptibility weighted imaging (SWI), which uses the magnitude component of the T2* gradient echo data and the phase of the MRI signal to increase sensitivity, are exquisitely sensitive to identifying blood products within the brain, showing approximately 30\% more hemorrhagic lesions when directly compared to CT.\textsuperscript{99} The number, size, and location of MRI abnormalities are correlated with the severity of TBI in the chronic stage and were used to predict clinical outcomes among patients with early posttraumatic vegetative state.\textsuperscript{100}

Additional advanced neuroimaging techniques assessing chronic traumatic brain injury include diffusion tensor imaging (DTI) to determine axonal integrity,\textsuperscript{101} magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) to examine brain metabolism, and functional magnetic resonance imaging (fMRI) to evaluate brain function.\textsuperscript{19,26,101-110} Intense research in DTI over the past 10 years demonstrated the utility of DTI in identifying TBI-associated changes in the cerebral white matter in group-based analyses, some of which correlate with injury outcomes.\textsuperscript{107,111} However, there is insufficient evidence for the use of DTI to characterize, diagnose and/or prognosticate at the individual patient level.\textsuperscript{107,111,112} Although DTI remains a very promising imaging technique and continues to be the subject of intense research interest, the accuracy and precision of the test in individual patient is unknown.
Although some neuroimaging studies show evidence of alterations in brain structure, function, and metabolism in football players, none demonstrated a direct link to CTE. With regard to white matter changes, Strain et al.\textsuperscript{101} used DTI to examine 26 retired NFL players, and found a significant association between depression symptom severity and disruption of white matter integrity. However, they were unable to determine the presence of CTE in the sample. Hart et al.\textsuperscript{103} performed a small cross-sectional study of retired NFL players and found that those with cognitive impairment and depression showed diffusely reduced fractional anisotropy (FA) values within the cerebral white matter on DTI that were not evident in matched controls or in the unimpaired retired NFL players. Retired impaired NFL players also demonstrated an increase in deep white matter lesions on T2-weighted FLAIR when compared to matched controls but not when compared to the unimpaired retired NFL players. Given the small number of subjects and the study design, this study can only conclude that white matter abnormalities identified on DTI are correlated with cognitive impairment and depression. Hampshire et al.\textsuperscript{102} reported abnormal functional changes on fMRI in the activation of the dorsal frontoparietal network of retired NFL players when compared to healthy controls; however, the former NFL participants already had complaints of cognitive deficits, creating a significant selection bias. Furthermore, only small differences were noted between the retired players and controls on a computerized test of executive functioning.\textsuperscript{102} A few studies investigated metabolic disturbances in athletes post-concussion using MRS. Results examining young athletes with concussions showed disturbances in brain metabolism after a single concussion, both in the acute and chronic phases.\textsuperscript{108,113} Small prospective cross-sectional and case-control longitudinal cohort studies show spectroscopic metabolite levels with neuropsychological outcomes in moderate-to-severe TBI. Decreased NAA is significantly correlated with poor outcomes in most of these studies.\textsuperscript{114-116}
Although neuroimaging may show promise in identifying future biomarkers for CTE, the scientific rigor in most of the currently published neuroimaging studies is significantly limited. Larger future prospective and well-controlled studies are needed that relate neurocognitive measures to imaging biomarkers to inform interpretations of causal mechanisms.

**Epidemiology**

Data on the epidemiology of CTE in football players are limited due to a “denominator problem”. To date there broad samples of populations such as retired NFL players are lacking, and there are no completed longitudinal or prospective studies with sufficient sample sizes. Early case reports of classic CTE in boxers are not necessarily generalizable to other populations such as NFL players due to the differing nature of the sport already noted by CTE researchers, small sample sizes, non-controlled confounding variables (e.g., psychiatric or medical comorbidities), changes in sport safety procedures (e.g., abolishment of bare-knuckle boxing, increased medical monitoring), and limited immunohistochemical technologies. Indeed, the incidence of CTE specific to a broad range of athletes with varying degrees of head injury is presently unknown.\textsuperscript{31}

The most important risk factor for CTE is hypothesized to be increased exposure to concussions and subconcussive blows.\textsuperscript{12,31,34,44} For football players, this risk may depend on the total number of games and contact practices, number of hits, position played, pre-existing conditions, genetic risk (e.g., family history of neurodegenerative conditions), age they began playing, career duration, and age of retirement. Gardner et al.\textsuperscript{31} calculated a rough estimate of the incidence of CTE using the number of cases obtained in a given period versus the number of athletes who died during the same period, thus finding it to be less than 4% of NFL players. If all professional athletes at risk were to be used as the “denominator”, then the estimated incidence
rate drops to less than 0.01%. Of course these estimates cannot account for the number of athletes who might have had neuropathological changes of CTE but who were never referred to autopsy, irrespective of their clinical phenotype.

Conclusions

At present, the available evidence underlying the mechanisms of the neuropathology and clinical features of CTE is still limited. The fundamental challenge is that there are no published prospective, longitudinal, or comprehensive epidemiological studies. Therefore there is as yet insufficient epidemiological or experimental evidence to ascertain the extent to which an individual’s particular clinical presentation is related to CTE-specific neuropathology versus neuropathology associated with other entities including, in some cases, the aging process. Despite initially proposed consensus criteria for a neuropathological diagnosis of CTE, the considerable heterogeneity of histopathological changes seen in CTE and the practical aspect of using the criteria across institutions and laboratories will require time to implement consistently. Some researchers question the establishment of CTE as a single distinct entity given the heterogeneity of the neuropathology and clinical features described as CTE.

The precise relationship of CTE to the proposed potentially causative risk factor of multiple subconcussive blows remains unclear, especially given the limited comparisons to relevant control groups. There is a lack of autopsies on non-demented and psychologically intact athletes with equivalent concussive histories. The problem of selection bias is especially significant given that many of the brains diagnosed with CTE were donated by families of individuals who committed suicide or had overt neurobehavioral features, with reported mental health issues or dementia. This selection bias is compounded by the problems inherent in
subjective retrospective reporting of clinical symptoms, often without adequate objective medical record documentation.

Biopsychosocial factors, including those from childhood, time spent playing contact sports, and later activities, significantly affect the development of the type of psychiatric and neurodegenerative disorders now being attributed to the effects of concussions or subconcussive blows and CTE. Childhood history including socioeconomic factors, learning disabilities, and ADHD, adult factors such as psychiatric disorders and drug, alcohol, opioid, and PED abuse, and post-career variables including adjustment to retirement and financial stress all contribute to functioning in middle age and later life. A biopsychosocial model incorporating these factors should be applied when studying CTE. 66,117

Rule changes in football will presumably result in fewer concussions, making prospective studies more challenging. However, there is a need for more longitudinal and prospective research on retired athletes with head injuries in order to better control for potential moderating variables, utilize more appropriate control groups, and eliminate selection bias. Capturing and following an in vivo history of clinical features from living athletes in addition to postmortem assessments will improve the ability to study CTE. Future studies should specifically utilize control groups that include individuals with depression and dementia and larger samples of athletes, but without a history of head trauma. For example, a good control group would be body builders, who have a similar body habitus and history of steroid use to that of American football players but who often have little to no history of concussions. It would also be prudent for researchers to clarify overlapping terminology, so as to avoid confusion. For example, the term “footballer” is sometimes used interchangeably to describe both soccer players and American football players in the CTE literature. 7,21,118,119
With the growing development of brain banks of individuals irrespective of their neurological history (e.g., at the National Institute of Child Health and Human Development, the Tissue Bank for Development Disorders at the University of Maryland, and the Sports Legacy Institute in Boston) the hope is that there will be a greater ability to conduct controlled epidemiological studies of CTE in athletes vs. non-athletes, those with vs. without concussion histories, and those with more robustly annotated clinical data (i.e., those bolstered by medical records and not solely reliant on non-medical sources).

Many groups and funding agencies are now endeavoring to identify biomarkers for p-tau that could help identify potential living individuals with CTE who could be followed longitudinally through death and autopsy. This effort could provide valuable information on the progression of CTE, and neuroimaging studies are showing particular promise. The upside to the media emphasis on concussions is a growing awareness among athletes, as well as a greater willingness to recognize or admit to concussions. This awareness in turn should improve the reliability of scientific studies, as well as the accuracy of incidence rates and perhaps in the future, clearer risk factors (e.g., age of greatest vulnerability, etc). Furthermore, the NFL and the NCAA are increasingly committed to educating players about concussions and encouraging them to participate in empirical studies, all of which should help advance our knowledge on the relationship between sports-related injuries and CTE. Taken together, although there is insufficient empirical evidence to date to determine for certain the extent to which concussive or subconcussive blows contribute to neuropathological or neurobehavioral changes in the future, this area of research is rapidly growing, and numerous studies are currently underway.
REFERENCES


Figure 1. The distribution of pathological tau accumulation in 4 stages. 50-µm tissue sections were stained using the CP-13 antibody for phosphorylated tau. McKee et al., The spectrum of disease in chronic traumatic encephalopathy, Brain 2013: 136; 43–64, by permission of Oxford University.
Disclosure- Conflict of Interest

None of the authors has a conflict of interest.