Chronic Traumatic Encephalopathy: Historical Origins and Current Perspective

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Annu. Rev. Clin. Psychol. 2015. 11:309–30

First published online as a Review in Advance on January 12, 2015

The *Annual Review of Clinical Psychology* is online at clinpsy.annualreviews.org

This article's doi: 10.1146/annurev-clinpsy-032814-112814

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Keywords

chronic traumatic encephalopathy, concussion, traumatic brain injury, neurodegenerative disorders, football, history

Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that is most often identified in postmortem autopsies of individuals exposed to repetitive head impacts, such as boxers and football players. The neuropathology of CTE is characterized by the accumulation of hyperphosphorylated tau protein in a pattern that is unique from that of other neurodegenerative diseases, including Alzheimer's disease. The clinical features of CTE are often progressive, leading to dramatic changes in mood, behavior,

and cognition, frequently resulting in debilitating dementia. In some cases, motor features, including parkinsonism, can also be present. In this review, the historical origins of CTE are revealed and an overview of the current state of knowledge of CTE is provided, including the neuropathology, clinical features, proposed clinical and pathological diagnostic criteria, potential in vivo biomarkers, known risk factors, and treatment options.

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INTRODUCTION

Each year 1.6 to 3.8 million sports-related concussions occur in the United States; most of these concussions are suffered by football players (Langlois et al. 2006). The incidence of subconcussive impacts—impacts that may cause neuronal dysfunction in the absence of concussive symptoms—is far greater (Bailes et al. 2013). Considering that more than 200 million Americans are involved in organized sports (Daneshvar et al. 2011a), the long-term consequences of sports-related concussive and subconcussive brain trauma may represent a major public health concern. Though a spectrum of chronic neurological injuries may occur, a primary concern involves the neurodegenerative disease known as chronic traumatic encephalopathy (CTE) (Jordan 2013). CTE is considered one of the tauopathies, neurodegenerative diseases marked by an accumulation of hyperphosphorylated tau protein, leading to neuronal destruction and accompanying symptoms. Alzheimer's disease (AD) is the most common of the tauopathies; however, CTE is both neuropathologically and clinically distinct from AD and the other similar diseases. As we describe below, the clinical features of CTE included mood, behavioral, and cognitive impairments that often result in progressive

dementia. In some cases, motor features, including parkinsonism, can also be present. Although CTE was described more than 70 years ago (Bowman & Blau 1940), the prevalence of the disease is still unknown, and an in vivo diagnosis is not currently possible. The goal of the present review is to summarize what is known about CTE and clarify controversy regarding the disease.

HISTORY: FROM PUNCH-DRUNK BOXERS TO THE MEDIA HYPE OF DECEASED PROFESSIONAL FOOTBALL PLAYERS

In 1928, Harrison Martland famously introduced the term "punch-drunk" into the medical literature to describe a peculiar condition occurring among prize fighters (Martland 1928a,b). Martland used terms such as "goofy," "slug nutty," and "cuckoo" to describe the behavior early on in punch-drunk cases, adding that, "later on . . . marked mental deterioration may set in necessitating commitment to an asylum" (Martland 1928b, p. 1103). The previous year, Osnato & Giliberti (1927) studied 100 clinical cases of concussion and pathologically examined one case of acute traumatic brain injury (TBI). The case with microscopic evidence was from a man who suffered a TBI without visible laceration, fracture, or contusion, and who died within 36 hours of the accident. Pathological examination revealed small petechial hemorrhages scattered throughout the corpus callosum and pons, microscopic evidence of parenchymal degeneration situated around vessels and glial cells, uneven staining in cortical pyramidal cells, and uneven staining of cerebellar Purkinje cells. The microscopic picture resembled a pattern of perivascular pathology previously found in epidemic encephalitis. On the basis of their review of the literature to date and the microscopic findings in their case, Osnato & Giliberti (1927) concluded that brain injury, even without fracture, may result in the initiation of chronic injury such that "in a few instances complete resolution does not occur, and there is a strong likelihood that secondary degenerative changes develop"; they believed these cases of "postconcussion neuroses" should therefore be called "traumatic encephalitis" (Osnato & Gilberti 1927, p. 211; see also Martland 1928b, p. 1104). Osnato (1929) later renamed this constellation of pathology following head injury traumatic encephalopathy.

The term chronic traumatic encephalopathy was coined by Bowman & Blau (1940) when they described the case of a 28-year-old professional boxer in their chapter "Psychotic States Following Head and Brain Injury in Adults and Children" (see Brock 1940). Upon presentation to the psychiatric division of Bellevue Hospital, the boxer's wife reported that for the two previous years the patient had exhibited increasingly childish behavior and was occasionally depressed. Though the patient wanted to return to professional boxing, the boxing commissioner refused him on account of his poor mental health. The patient was described as having paranoia, including feelings of being poisoned, stalked, and deceived. He also was involved in violent assaults and had been arrested for shouting at strangers. He lacked insight into his condition, had poor orientation, could not grasp simple concepts, and had poor short-term memory. It is also notable that the patient abstained from alcohol and that he experienced many knockouts during his boxing career. The authors initially diagnosed this young boxer with traumatic encephalopathy; however, after seeing that his condition remained unimproved over 18 months, they changed their diagnosis to reflect this, and the term chronic traumatic encephalopathy was born. The chapter by Bowman & Blau (1940) was written specifically to establish a standard classification system for mental disorders caused by trauma (p. 312).

These early cases demonstrate that mood and behavioral symptoms have been reported in boxers as part of the long-term consequences of repetitive head impacts for more than 75 years. Some researchers have suggested that the disease suffered by boxers is distinct from that suffered by football players (Gardner et al. 2014, McCrory et al. 2013). These theories are centered on the belief that retired American footballers exhibit a predominance of mood and

behavioral disturbances, whereas boxers predominantly have motor symptoms (Gardner et al. 2014, McCrory et al. 2013). The symptoms reported by Bowman & Blau (1940), among others, do not support this view. Martland himself notes that "more than 60% of professional pugilists (boxers) who have been fighting longer than five years develop enough mental and emotional changes to be considered 'punchy'" (Martland 1943, p. 294). Martland (1943) advised readers that the condition is best described by Carroll, who writes that fighters who remain in the ring longer than five years "develop mental and emotional changes, which are obvious to people who knew them previously" (Carroll 1936, p. 709). More recently, Jordan writes that in boxers, "Behavioral changes encountered can include disinhibition, irritability, euphoria or hypomania, impaired insight, paranoia, and violent outbursts" (Jordan 2000, p. 180).

It is likely that modern researchers (Gardner et al. 2014, McCrory et al. 2013) overlooked mood and behavioral features in historical cases because two of the larger and influential studies on boxers (Corsellis et al. 1973, Roberts 1969) focused mainly on motor symptoms, intentionally ignoring the presentation of mood and behavioral features. Roberts writes, "More attention has been paid, intentionally to the clinical signs and symptoms which indicate lesions of cerebellar, pyramidal and extrapyramidal systems, than to the evidence of dementia or personality change . . . leaving aside for later consideration the question of dementia and psychiatric disturbance, which undoubtedly occur in some cases" (Roberts 1969, p. 47). Similarly, Corsellis et al. (1973) state, "Perhaps the more intriguing problems, however, are raised by the psychological components of the syndrome. These have rarely been looked at in the detail accorded to the neurological side" (p. 299). To account for the full presentation, both authors cite Johnson (1969) who named four organic psychosyndromes that he attributed to boxing: chronic amnesic state, dementia, rage reactions in personality disorder, and the morbid jealousy syndrome (pp. 47–49). Evidence suggests that some of the perceived differences in symptoms between classic and modern cases are due to the methodological differences in influential studies. For instance, if the participants in one study are predominantly boxers and in another study football players, then differences may be observed because of differences in the biomechanics of head trauma that may influence the location or severity of pathology in the brain (for further discussion, see Montenigro et al. 2014).

In further characterizing the current understanding of CTE, it is important to note that although CTE was only recently diagnosed neuropathologically in football players, the chronic effects of head trauma in American football have long been noted. Evidence demonstrates that as far back as 1893, the public was aware that long-term consequences of head trauma could result from playing American football. **Figure 1** shows US Naval Academy midshipman and football player Joseph M. Reeves, who, after being cautioned by a physician that another blow to his head would cause traumatic insanity, hired an Annapolis shoemaker to fashion the first-ever football helmet. This parallels an account given by Martland in one of his lesser-known works, wherein he states, "While this disease (punch drunk) is most commonly observed in pugilists it is not entirely confined to this sport, but may be seen in wrestlers, and not uncommonly in footballers" (Martland 1943, p. 294). Indeed, many authors who first characterized the long-term consequences of head trauma in boxers also noted these symptoms in American football players. Bowman & Blau (1940) attributed the mental deterioration of CTE to "repeated frequent head injuries occurring in certain types of professional pugilists and football players" (p. 343). Osnato & Giliberti (1927) raised the possibility that traumatic encephalopathy might occur in "young men knocked out during football and other games" (p. 214). Carroll (1936) observed that "punch drunk is said to occur among professional football players also" (p. 709).

Case reports of punch drunk dementia among football players began to appear in the 1930s. The first of these reports described a young football player who "forged checks and did things suggesting the behavior of psychopathic personality" and the "condition we sometimes find in

Figure 1

First football helmet. Photo depicts an 1894 intramural football team at the US Naval Academy. A handwritten note on the back of the original photograph states, "Navy football team in which cadet Reeves wore first helmet—1894." Joseph M. Reeves was the captain of the team. Image used with permission from Corbis Corporation.

pugilists . . . pummeled about the head" (Homeopath. Med. Soc. State PA 1933). Following this case report, the *New York State Journal of Medicine* published an editorial entitled "Punch-Drunk Boxers and Football Players," which reported that participation in any sport in which multiple head injuries occur, as in football, can cause a condition similar to punch-drunkenness such that "attention, concentration, and memory suffer permanently" (Health Dig. 1936, p. 1654). One year later, Frank Scully, a former Columbia football star, reported that he tracked down former football teammates and had uncovered varying degrees of dementia, vagrancy, and motor deficiencies in seven of his classmates (Scully 1937a,b). Scully stated that the concern for boxers is "multiplied many times if applied to football" (Scully 1937b, p. 35). He proposed the terms stumble-backs and stumble-bums to better reflect the etiology of punch-drunkenness in football players (Scully 1937b). This historical evidence demonstrates that the long-term consequences of repeated head trauma in football players were recognized long before the recent explosion in media interest. It also shows that prominent researchers who first attributed punch-drunkenness to the effects of boxing

observed the same clinical symptoms in football players. However, this issue in football players did not reach prominence again until 2005, when an autopsy demonstrated neuropathological changes consistent with CTE in a retired National Football League (NFL) player (Omalu et al. 2005).

In this case, neuropathologist Bennet Omalu examined the brain of former Pittsburgh and Kansas City NFL player Mike Webster after his death from a heart attack in 2002. Though a gross examination revealed that the brain looked normal, Omalu decided to fix the brain and study it microscopically given Webster's history of cognitive and neuropsychiatric problems (after retirement from football, he had developed significant memory impairment and depression, became homeless, and apparently was fully demented prior to his death) (Fainaru-Wada & Fainaru 2013). Omalu identified an accumulation of hyperphosphorylated tau (p-tau) and reasoned that Webster was suffering from something similar to the punch-drunk syndrome described in boxers (Fainaru-Wada & Fainaru 2013). After colleagues confirmed his findings, he published his results in *Neurosurgery* in an article titled "Chronic Traumatic Encephalopathy in a National Football League Player" (Omalu et al. 2005). Since that time, the brains of several additional well-known former professional football players have been examined posthumously and diagnosed with CTE. CTE has become almost a household term in large part because of the highly publicized autopsy findings after the deaths of former football players including Junior Seau, Dave Duerson, Jovan Belcher, and John Mackey. In contrast to the heightened public awareness of CTE, the actual science of CTE remains in its infancy, with a great deal to be learned about its incidence, prevalence, risk factors, and diagnosis.

LONG-TERM CONSEQUENCES OF HEAD TRAUMA: EPIDEMIOLOGICAL RESEARCH

All cases of neuropathologically confirmed cases of CTE to date have had one thing in common: a history of repetitive head impacts (McKee et al. 2013, Mez et al. 2013). In addition, neuropathological evidence of CTE has never been found in anyone without a history of head impacts. This suggests that although head trauma is a necessary variable for developing the disease, it is not sufficient. That is, not everyone who experiences repetitive head impacts will get this disease. Risk factors above and beyond merely having a history of head impacts are not yet known. The proportion of former NFL players whose brains have been examined neuropathologically and found to have CTE is staggering. However, these data cannot be used to estimate incidence and prevalence rates because of the inherent biases involved in brain donation decisions. There currently are no accepted and accurate methods of diagnosing CTE during life, and because CTE shares many clinical features with other neurodegenerative and psychiatric conditions, differential diagnosis of CTE is not yet possible (Gavett et al. 2010, Stern et al. 2011). Moreover, because CTE is not listed as a cause of death in the *International Classification of Diseases*, it has been hypothesized that some patients with CTE have been inaccurately classified as having other neurodegenerative disorders on death certificates and in epidemiological studies (Gavett et al. 2010, Lehman et al. 2012). This hypothesis has led several authors to examine the epidemiology of long-term consequences of repetitive head impacts by indirect methods, such as survey studies of former football players.

In their investigation of the long-term effects of football participation, Guskiewicz et al. (2005) identified a relationship between a higher number of concussions and a range of subsequent neurological problems. In this study, 2,552 former NFL players responded to a general health questionnaire, and results showed that players with a history of concussion scored significantly

worse on the mental component scale than players without a concussion ($p = 0.001$). A second questionnaire, which was administered to 758 NFL respondents and 641 of these players' spouses or close relatives, indicated that retired players who reported three or more concussions had a fivefold higher prevalence of being diagnosed with mild cognitive impairment.

Further analysis of Guskiewicz and colleagues' (2005) data suggested a link between recurrent concussion and depression. Guskiewicz et al. (2007) found that those with a reported history of three or more concussions were three times more likely to be diagnosed with depression. There was also a significant linear trend for increasing diagnosis with concussion incidence across the 1, 2, and 3+ concussions groups ($p < 0.005$). Although recent studies have demonstrated that retrospective self-report of concussion is subject to poor reliability (Delaney et al. 2002, Kerr et al. 2012), the dose-response relationships identified within both studies should not be discounted.

In an effort to overcome the limitations of retrospective self-reporting, Lehman et al. (2012) analyzed mortality rates within NFL players to demonstrate long-term consequences of participation in football. This study examined neurodegenerative causes of death (i.e., AD, Parkinson's disease, and motor neuron disease) for 3,439 retired NFL players and showed that mortality rates for NFL players were significantly lower than those of age-matched US males (0.53) but that the incidence of neurodegenerative disease was significantly higher [underlying cause standardized mortality rate (SMR) 2.83, confidence interval (CI) 1.36–5.21; contributing cause SMR 3.26, CI 1.90–5.22]. The authors pointed out that because CTE was not an available option for cause of death at that time and because few clinicians even knew about CTE, it was possible, if not likely, that many of the deaths reported to have been caused by AD were actually caused by CTE (Lehman et al. 2012).

An increased risk of neurodegenerative disease with head trauma has also been demonstrated outside of the realm of athletics. A meta-analysis of 15 case-control studies by Fleminger et al. (2003) established a significant link between a history of head injury (no specific population; only those injuries resulting in a loss of consciousness) and the development of AD [odds ratio (OR) 1.58, 95% CI 1.21–2.06; $p = 0.001$). In addition, during 1996 and 1997, Plassman et al. (2000) prospectively examined medical records of World War II US Navy and Marine male veterans and showed that those who had experienced head trauma with a loss of consciousness had a significantly increased risk of both AD (HR 2.00, 95% CI 1.03–3.90) and dementia (HR 2.23, 95% CI 1.30–3.81). When the severity of head trauma was graded as mild, moderate, or severe, there was a significant dose-response trend in the increased incidence of both AD and dementia ($p = 0.0013$ and <0.01, respectively). Notably, when the demented group was limited to those without a primary diagnosis of AD ($n = 21$), head injury was still associated with an increased risk of dementia (HR 3.23, 95% CI 1.33–7.82). This suggests that head trauma not only results in the increased risk for or progression of AD-like symptoms but other causes of dementia also.

Some investigators have suggested that CTE is likely to have been misdiagnosed as another neurodegenerative disease (Lehman et al. 2012). Gavett et al. (2010) noted that in almost all of the studies investigating TBI and subsequent AD risk, AD was diagnosed without neuropathological verification, and the majority of reports were based on clinical diagnostic criteria that may lack the specificity to rule out other causes of dementia. In further support of the hypothesis that cases of CTE have been misdiagnosed, Beach et al. (2012) demonstrated that of the 526 individuals diagnosed with AD from the National Alzheimer's Coordinating Center, 88 did not meet criteria for AD after later neuropathological examination.

Using a method similar to that of Beach et al. (2012) (comparing clinical diagnoses with postmortem neuropathological data from the National Alzheimer's Coordinating Center) Sayed et al. (2013) showed that despite an in vivo clinical diagnosis of AD, in some cases clinical and

neuropathological evidence were not consistent with this disease. This investigation compared patients with dementia who had a history of TBI to patients with a clinical diagnosis of probable AD but without TBI. Although the majority of those in the TBI group were given a clinical diagnosis of probable or possible AD (40% and 14%, respectively, with 30% undetermined), patients with TBI were significantly more likely to experience depression, anxiety, irritability, and motor disorders than were those without a history of TBI. The authors concluded that some TBI patients diagnosed as having AD in life demonstrated clinical features that are consistent with CTE. Autopsy data were available for 20 of the 62 patients in the TBI group and for 16 non-TBI patients. TBI cases had significantly lower amyloid angiopathy scores than non-TBI cases, and they had comparable levels of tauopathy. Given that CTE is predominantly a tauopathy that differs from AD in part because of a paucity of amyloid, Sayed et al. (2013) concluded that the patients with TBI presented with features consistent with CTE rather than AD.

NEUROPATHOLOGICAL FINDINGS OF CHRONIC TRAUMATIC ENCEPHALOPATHY

In a 2009 study, 47 previously reported cases of neuropathologically confirmed CTE were reviewed (McKee et al. 2009). To date, an additional 110 cases of CTE have been neuropathologically diagnosed at the Veterans Association-Boston University-Sports Legacy Institute Brain Bank (McKee & Robinson 2014). The common feature in all cases involves a unique pattern and distribution of p-tau accumulation. Although there is some degree of pathological overlap with other neurodegenerative diseases, the pattern of p-tau accumulation clearly distinguishes CTE from AD, age-related changes, and other neurodegenerative tauopathies (McKee et al. 2009, 2013).

Corsellis et al. (1973) were among the first to describe the neuropathology of CTE in their case series of 15 retired boxers. Some of the more specific neuropathological features of CTE were described in additional case studies. For example, a case study of a 23-year-old boxer by Geddes et al. (1996) found a peculiar perivascular distribution of neurofibrillary tangles (NFTs) in the frontal lobe, with relative sparing of the medial temporal lobes and hippocampus. From this case study it was concluded that frontal lobe perivascular NFT accumulation represented the earliest neuropathological change associated with repetitive brain trauma. Hof et al. (1992) first identified the predilection of NFTs to accumulate in the neocortical superficial layers II and III in CTE, a finding in contrast to the known neuropathology of AD, in which the neocortical laminar distribution involves the deeper layers.

In 2013, the largest series of neuropathologically confirmed CTE cases was published (McKee et al. 2013), and pathological staging criteria were proposed to evaluate the severity of p-tau pathology in individual cases. First, p-tau accumulates as perivascular neurofibrillary tangles, astrocytic tangles, and neurites at the depths of the cerebral sulci. It then spreads from the depths of the sulci to adjacent superficial cortical layers, with marked degeneration of the medial temporal lobes, frontal lobes, diencephalon, and brainstem in the later stages. The specific regional areas of p-tau pathology and the unique accumulation at the depths of the cortical sulci and surrounding small blood vessels is quite distinct from AD (see **Figures 2** and **3**).

It has been suggested that factors other than repetitive head impacts could also be responsible for this pattern of pathology. The most commonly suggested alternative explanations include substance abuse and the normal degenerative process of aging (McCrory et al. 2007, 2013). Although it is true that cause-and-effect relationships between the number of head impacts or amount of brain trauma and the extent of pathology of CTE have yet to be established, there are good reasons to reject these alternative explanations. No other disease has been known to produce the pattern

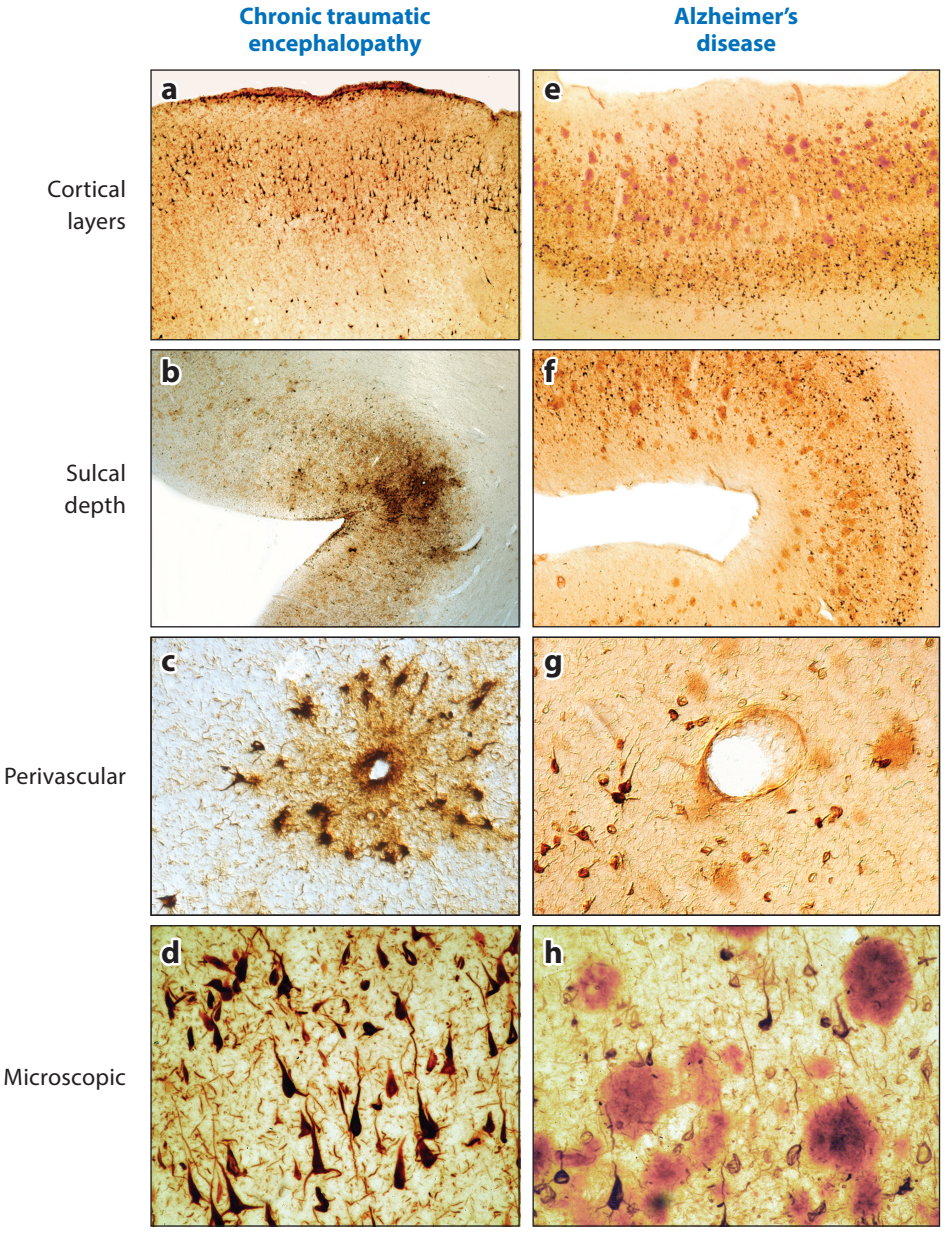

Figure 2

The characteristic neuropathological findings of chronic traumatic encephalopathy (McKee et al. 2013) include p-tau neurofibrillary tangle accumulations involving (*a*) superficial cortical layers that are commonly situated at the depths of the (*b*) cerebral sulci and in (*c*) perivascular spaces. (*d*) The microscopic p-tau pathology is often found in the relative absence of amyloid neuritic plaques. Comparatively, the cortical laminar distribution of p-tau pathology in Alzheimer's disease (AD) typically involves the (*e*) deeper layers and is found neither (*f*) in the depths of the cerebral sulci nor (*g*) perivascularly. Additionally, AD pathology involves (*h*) neuritic amyloid plaques with concomitant p-tau neurofibrillary tangles. Figure courtesy of Dr. Ann McKee.

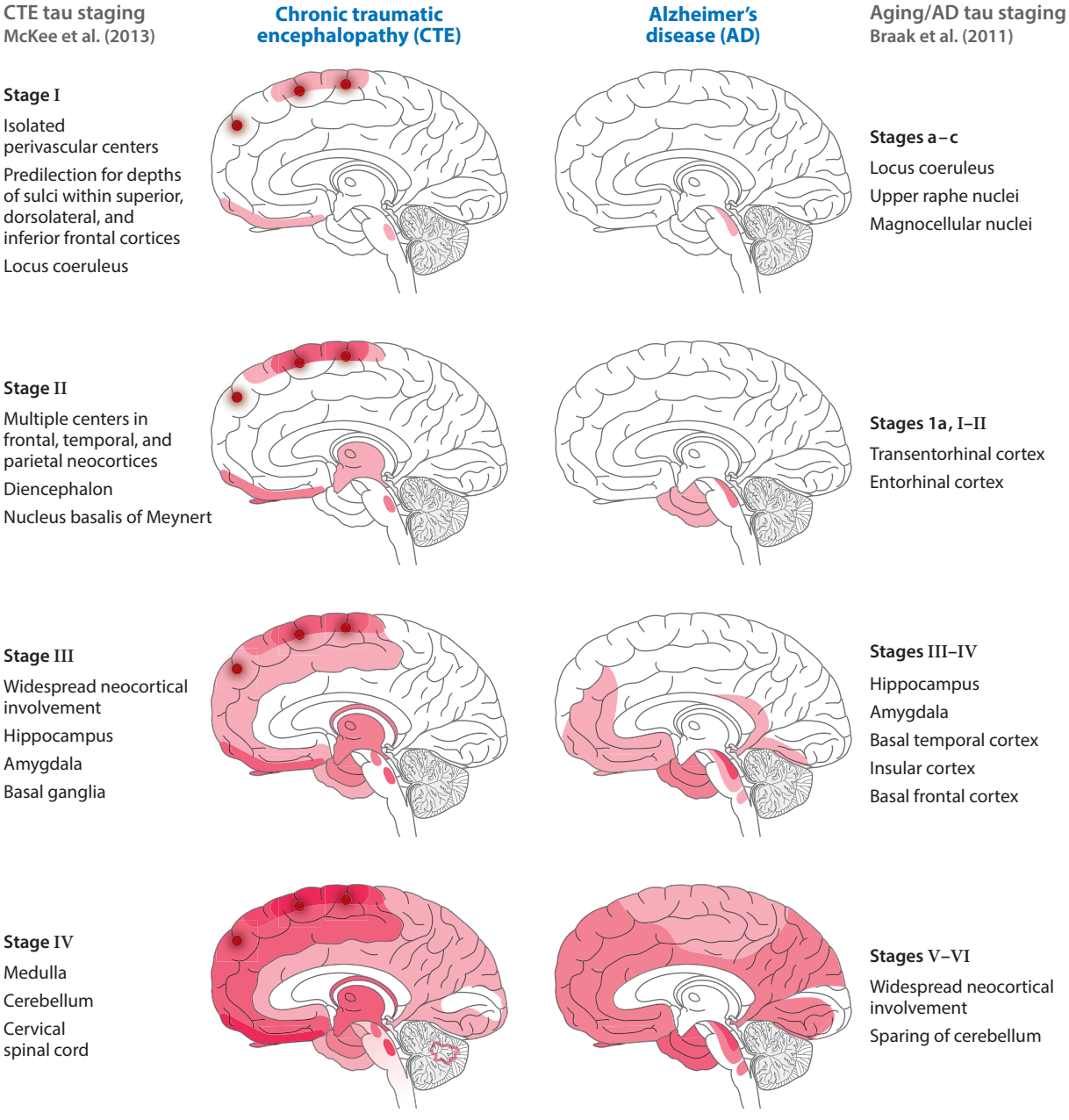

Figure 3

Comparison of hyperphosphorylated tau progression. In chronic traumatic encephalopathy (CTE) the abnormal accumulation of hyperphosphorylated tau first appears in the neocortex and locus coeruleus (CTE stage I), then involves the diencephalon (CTE stage II), next the medial temporal lobe (CTE stage III), and finally is widespread throughout the neocortical, brainstem, and cerebellar regions (CTE stage IV). This is in contrast to Alzheimer's disease (AD), where the tau pathology first occurs in the brainstem (Braak stages a–c), next involves the entorhinal cortex (stages 1a, 1b, I-II), then more widespread involvement of the medial temporal lobe (stages III-IV), and finally widespread involvement of the neocortex (stages V-VI). This schematic figure is based on information reported in Braak et al. (2011), McKee et al. (2013), and Stein et al. (2014).

of p-tau pathology that CTE produces. Corsellis et al. (1973) demonstrated that the pattern of pathology associated with excessive alcohol use (i.e., Wernicke's encephalopathy) was not the same as the p-tau pathology described in CTE. Autopsy studies, including one of 2,333 nonselected individuals, show that in normal aging p-tau pathology begins in the brainstem, next involves the medial temporal lobe, and only later substantially involves neocortex (Braak et al. 2011). This is in sharp contrast to the distribution of p-tau pathology noted in the brains of persons sharing a common history of exposure to repetitive brain trauma, in which the early stages of p-tau pathology involve the cortex and later stages involve the medial temporal lobe (McKee et al. 2013).

CLINICAL PRESENTATION OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Clinical Domains

The clinical presentation of CTE was recently described in a sample of 36 neuropathologically confirmed CTE cases (Stern et al. 2013) and in a pooled analysis of 202 published studies (Montenigro et al. 2014). In the study by Stern et al. (2013), the clinical features of 36 deceased former athletes (including 22 football players) without evidence of comorbid pathology were described through retrospective semi-structured interviews of next-of-kin informants and from medical record reviews. All clinical interviews were conducted blind to the neuropathological diagnosis, and all neuropathological diagnoses were made blind to the clinical history. Of the 36 subjects, 33 were symptomatic and exhibited a triad of cognitive, behavioral, and mood impairments. To corroborate and develop these findings, Montenigro et al. (2014) reviewed the literature on the clinical features exhibited by athlete cases with histories of repetitive head impact and provided the largest pooled case analysis of clinical features in CTE to date. The clinical features in all of the cases were classified into one of four domains: cognitive, behavioral, mood, and motor. **Table 1** summarizes the clinical features most commonly reported across all cases. The clinical course was described as progressive in 68% of cases. Stable cases were notably younger. In a majority of cases, several years elapsed between the cessation of sports-related exposure and the appearance of symptoms.

Subtypes

Stern et al. (2013) identified two relatively distinct clinical presentations of CTE. The first presented initially with behavioral and/or mood features and had a younger age of onset. The second initially had cognitive features and developed at an older age. To corroborate and validate these findings, Montenigro et al. (2014) identified studies in which subtypes were noted in the presentation. In addition to the two subtypes described in Stern et al. (2013), Montenigro et al. (2014) added a mixed subtype, wherein the predominant presentation was neither behavioral/mood nor cognitive but rather a combination of the two. In our diagnostic criteria, we selected the term traumatic encephalopathy syndrome (TES) rather than chronic traumatic encephalopathy for the following reasons: (*a*) we view CTE as a neuropathologically defined disease and not a clinical syndrome, (*b*) TES describes the clinical features presentation of CTE as well as other conditions representing the long-term consequences of repetitive head impacts, (*c*) we believe that the use of the term chronic in CTE inaccurately connotes a stable condition rather than a progressive disease, and (*d*) the use of the word syndrome appropriately connotes a cluster of clinical features that define a condition. On the basis of our previous research and literature reviews, we chose the following diagnostic subtypes: TES behavioral/mood, TES cognitive, TES mixed, and TES dementia.

Table 1 Summary of clinical features in chronic traumatic encephalopathy

Features			
Cognitive	**Behavioral**	**Mood**	**Motor**
Memory impairment	Physical violence	Depression	Ataxia
Executive dysfunction	Verbal violence	Hopelessness	Dysarthria
Impaired attention	Explosivity	Suicidality	Parkinsonism
Dysgraphia	Loss of control	Anxiety	Gait
Lack of insight	Short fuse	Fearfulness	Tremor
Perseveration	Impulsivity	Irritability	Masked facies
Language difficulties	Paranoid delusions	Apathy	Rigidity
Dementia	Aggression	Loss of interest	Muscle weakness
Alogia	Rage	Labile emotions	Spasticity
Visuospatial difficulties	Inappropriate speech	Fatigue	Clonus
Cognitive impairment	Boastfulness	Flat affect	
Reduced intelligence	Childish behavior	Insomnia	
	Socially inappropriate behavior	Mania	
	Disinhibited speech	Euphoria	
	Disinhibited behavior	Mood swings	
	Personality changes		
	Psychosis		
	Social isolation		

Table adapted with permission from Montenigro et al. (2014).

Diagnostic Criteria

Prior to 2014, two initial clinical diagnostic criteria for CTE had been proposed (Jordan 1992, 1998, 2013; Victoroff 2013). Although the publications of these criteria were important developments in the field, neither sets of criteria have been widely adopted, due in part to operational limitations (Levin & Bhardwaj 2014, Mez et al. 2013). To address these limitations and incorporate recent advances in knowledge concerning the clinical presentation and progression of CTE, updated research diagnostic criteria have been proposed (Montenigro et al. 2014). Common to each criteria is the presence of distinct clinical features that must be identified in order to establish a clinical diagnosis. A major update to the new criteria involves the method of selecting symptoms and signs to be clinically diagnostic of CTE. For example, Victoroff (2013) selected any sign or symptom that occurred in at least 7% of the previously published cases he identified for review. In comparison, to be included as a core clinical feature in Montenigro et al. (2014), a sign or symptom was selected if it occurred in a minimum of 70% of the neuropathologically confirmed CTE cases previously described (Stern et al. 2013). Additional updates include clear operational standards and nomenclature, provisional exposure levels, supportive features, subtype designations, progression designations, and a dimensional diagnostic hierarchy for CTE diagnosis (i.e., probable, possible, or unlikely) based largely on potential biomarker findings (Montenigro et al. 2014).

BIOMARKERS FOR THE IN VIVO DIAGNOSIS OF CHRONIC TRAUMATIC ENCEPHALOPATHY

As described in previous sections, at this time the diagnosis of CTE can only be confirmed postmortem by the presence and pattern of p-tau neurofibrillary tangles. This is critical because the locations of deposition in CTE differ from those in AD (see **Figures 2** and **3**). Therefore,

methods that can accurately localize p-tau deposition represent the best hope for diagnosing CTE in vivo. Currently, there are no objective, validated in vivo biomarkers specific for CTE, although promising studies are currently under way. Although still in nascent stages of development, we briefly summarize some of these efforts.

Neuroimaging

Advancements in neuroimaging techniques have recently uncovered neurological injury and pathology in individuals that previously had been undetected (Abbas et al. 2014, Breedlove et al. 2012). Although methods of detecting p-tau deposition have only recently been used in humans (see below), other proxy markers of the neurodegenerative changes of CTE may be possible (Baugh et al. 2012, Koerte et al. 2015, Ng et al. 2014). Although such methods cannot detect p-tau accumulations, insidious changes and chronic injuries related to brain trauma can be identified. If combined with another biomarker, such as cerebrospinal fluid (CSF), such imaging methods are likely to have improved diagnostic usefulness for CTE.

Functional magnetic resonance imaging. Blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) uses the contrast between oxygenated and deoxygenated blood to provide an indirect measure of the amount of neural activity within specific regions of the brain. Thus, BOLD fMRI provides the hemodynamic response to neural activity (Slobounov et al. 2012). A number of studies using fMRI have shown differences in BOLD response between controls and athletes with a history of head trauma. Ford et al. (2013) measured cerebral blood flow while retired NFL players concurrently performed memory tasks. Memory testing indicated a trend for a reduction in performance with concussion (see figure 3 in Ford et al. 2013). Hart and colleagues (2013) also measured a number of cognitive outcomes in retired NFL players and concluded that for those in the impaired group, problems such as word finding, memory, and naming corresponded with areas within the brain that mediated these functions. As in the findings of Ford et al. (2013), these areas also included the temporal and parietal lobes.

Although such studies using fMRI show promise in identifying areas of the brain that may demonstrate changes in activation after a career of head impacts, much further research is required before this method can be used as a valid biomarker of CTE during life. For a diagnosis from BOLD data, it may be necessary to observe consistent patterns of activity within specific regions and associate these patterns with performance on tasks that are known to reliably decline with the development of CTE.

Diffusion tensor imaging. Diffusion tensor imaging (DTI) is a noninvasive technique that uses MRI to indicate the diffusion of water within brain tissue. Scalar measures (for example, fractional anisotropy scaled between 0 and 1) are applied to quantify this directional diffusion. Given that the movement of water generally occurs directionally along axons, these measures can be applied to indicate disruption or demyelination of axonal tissue. Because such disruption is thought to increase diffusion or reduce the directionality of this water movement, a lower measure of fractional anisotropy suggests damage to white matter microstructures (Ng et al. 2014). CTE is associated with axonal disruption and loss (McKee et al. 2013); therefore, DTI is a relevant tool in the assessment of brain disease (Baugh et al. 2012, Koerte et al. 2015). For example, Shin et al. (2014) demonstrated that increased mean diffusivity and decreased fractional anisotropy in the white matter of boxers and mixed martial arts fighters were strongly associated with the amount of knockouts the fighter had experienced. Strain et al. (2013) examined 26 former NFL players with DTI and found that white matter FA was negatively correlated with severity of depression symptoms.

Volumetric MRI. High-resolution T1 volumetric MRI scans may aid in the diagnosis of CTE because rates of neuronal loss have been correlated with p-tau, but not beta-amyloid, deposition (Small et al. 2013). Studies have recently demonstrated correlations between head impacts in athletes and the reduction in volume of specific brain regions (Bernick & Banks 2013, Singh et al. 2014). Singh et al. (2014) compared the hippocampal volume of young American football players with and without at least one clinically diagnosed concussion to age-matched non-football-player controls. MRI showed that players with and without a history of concussion had smaller hippocampal volumes than controls had, and players with a history of concussion had smaller hippocampal volumes than players without concussion had (both $p < 0.001$). Left hippocampal volumes were also significantly correlated with years of football experience. Preliminary findings from Bernick & Banks (2013) show that in boxers and mixed martial arts fighters, exposure to head impact is associated with smaller volume in a number of brain regions, including the caudate, putamen, and amygdala. For fighters with more than five years of experience, there was a 1% reduction in caudate volume per additional year of professional fighting ($p < 0.001$).

Positron emission tomography. Positron emission tomography (PET) is a nuclear imaging technique that can detect specific infused radiolabeled tracer. The most common PET approach is one that uses 2-deoxy-2-(18F)-fluoro-D-glucose (FDG) as a measure of regional differences in metabolism. To date, two studies have used FDG PET in individuals at risk for CTE, including a study of boxers (Provenzano et al. 2010) and an analysis of combat military service members suffering from multiple blast exposures (Peskind et al. 2011). Hypometabolism in the cerebellum was found in both studies, and in the study of boxers, hypometabolism was also present in the posterior cingulate and the frontal lobes. In contrast, in the blast trauma study, there was hypometabolic activity in the medial temporal lobe and pons.

A key development in recent years in the establishment of biomarkers for AD has been the use of PET ligands specifically targeting beta-amyloid, such as Food and Drug Administration–approved [18F] florbetapir (Landau et al. 2013). These PET studies are appropriately used to rule out AD when there is little or no uptake of the amyloid tracer. Because of this, they may be effective in the diagnosis of CTE by ruling out AD as the underlying cause of an individual's neurocognitive impairment when there is a history of substantial exposure to repetitive head impacts, as was recently demonstrated in a case study by Mitsis and colleagues (2014) of a former NFL player.

However, the more accurate approach would be to use a ligand that specifically targets p-tau. Small et al. (2013) used the ligand 2-(1-{6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) in a study of five retired NFL players with history of cognitive and mood symptoms and found significant uptake of the tracer. However, FDDNP is a rather old ligand that is infrequently used because it binds to multiple proteins, including tau and amyloid. The authors argue that the distribution of binding in the football players was consistent with that expected in CTE rather than amyloid deposition in AD. Unfortunately, their conclusion is inconsistent with the known neuropathologic findings in these two diseases (**Figures 2** and **3**).

More recently, PET ligands that specifically target p-tau have been developed and used in humans. The most promising of these is [18F]-T807, which has a high affinity and selectivity for tau over beta-amyloid (Chien et al. 2013). This ligand is now being used in several clinical trials, including two with former football players. It is hoped that the use of a combination of two PET ligands, one selective for amyloid (with an expected negative finding) and one selective for tau (with an expected positive finding), will eventually result in a highly accurate diagnosis of CTE.

Fluid Biomarkers

Although neuroimaging methods, particularly PET, may prove valuable for the in vivo diagnosis of CTE, they have limitations due to cost, time, and the accessibility of the equipment required to perform such imaging (Turner et al. 2012). Therefore, it is important to find methods that can provide simple and cost-effective diagnosis, evaluation of treatment outcome, or risk assessment. It has been suggested that fluid biomarkers may serve as a tool by which CTE may be efficiently diagnosed (Turner et al. 2012). Fluid biomarkers are usually obtained by extraction of blood or CSF. Although such methods present advantages in relative simplicity, it is yet to be established whether there are signatures within bodily fluid that can accurately characterize the general long-term consequences of repetitive head impacts or the specific neurodegenerative disease of CTE. Although a number of studies have researched fluids for the acute effects of head trauma in athletes (Bazarian et al. 2014, Marchi et al. 2013, Neselius et al. 2012, Otto et al. 2000), there is currently a paucity of studies aimed at determining biomarkers that indicate the development and progression of CTE. Future studies are needed with existing methods for measures of CSF tau, p-tau, and amyloid as well as newly developed methods for plasma or exosome-based measures of tau (Kapogiannis et al. 2015, Shahim et al. 2014).

RISK FACTORS FOR CHRONIC TRAUMATIC ENCEPHALOPATHY

Potential Genetic Risk Factors

A number of studies have uncovered genetic risk factors for AD (Farrer et al. 1997) and poor long-term cognitive outcome after a severe TBI (Teasdale et al. 1997). Given the similarities between the clinical features of AD and CTE, it has been hypothesized that similar genetic factors may also predispose certain individuals to an increased risk of the development of CTE pathology (Baugh et al. 2012, Gandy & Dekosky 2012). The major gene implicated is the apolipoprotein E (*APOE*) ε4 allele (Finnoff et al. 2011). Three *APOE* alleles (ε2, ε3, and ε4) code for three ApoE isoforms. ApoE assists with maintaining neural integrity and recovery after a brain injury. However, although the *APOE* ε3 allele promotes neurite growth, the ε4 allele inhibits it (Finnoff et al. 2011). Crawford et al. (2009) suggested that poor outcomes associated with the ε4 allele are less likely to result from the activation of neurodegenerative mechanisms and more likely to result from a loss of reparative capabilities following TBI.

In those without TBI, the increased risk of AD in carriers of the ε4 allele has been demonstrated. A meta-analysis by Farrer et al. (1997) showed that the ε4 allele represents a major risk factor for AD in all ethnic group studies, across all ages between 40 and 90, and in both men and women.

Studies of individuals with a history of TBI also indicate that the ε4 allele may be a risk factor for poor outcome. These studies have greater relevance to CTE because they involve a longer follow-up period in comparison with a number of other studies with no greater than an eight-month follow-up after TBI (Friedman et al. 1999; Teasdale et al. 1997, 2005; Zhou et al. 2008). In a prospective study of 543 participants ages 40 to 85 years, Sundström et al. (2007) demonstrated that, in combination with the *APOE* ε4 allele, a mild TBI conferred a significant increase in the risk of dementia. In a study of 30 boxers with a mean age of 49 $\pm$ 16.5 years, Jordan et al. (1997) showed greater cognitive impairments for boxers who carried the ε4 allele. For fighters with more than 12 fights of exposure, mean chronic brain injury scale scores were 3.9 $\pm$ 2.3 for those with the ε4 allele compared with 1.8 $\pm$ 1.2 for those without (a higher score is indicative of greater impairment). Another study of 53 current American football players (mean age 27.1 $\pm$ 2.6 years)

showed that older players with the ε4 allele scored lower on cognitive tests than players without the allele, or less-experienced players of any genotype, scored (Kutner et al. 2000).

A possible explanation for this association between ε4 allele carriers and the lower cognitive scores seen in athletes with increasing age is an increased susceptibility of ε4 carriers to trauma-induced neurodegenerations, including CTE. In fact, elevated ε4 proportions in a cohort of athletes with pathologically confirmed CTE have been demonstrated (Stern et al. 2013). Further research is necessary to determine the mechanism through which ε4 mediates an effect on CTE.

Head Impact Exposure Factors

It is accepted that head impact is the primary risk factor for the development of CTE, but the type and duration of exposure required to induce CTE is still unknown. The characterization of head impact exposure leading to adverse long-term outcomes has long been an issue for clinicians, with Thorndike (1952, p. 556) noting, "The college health authorities are conscious of the pathology of the 'punch-drunk' boxer. Just how much one should permit the recurrence of cerebral concussion in our college athletes is a matter of opinion." There is a sense of urgency for the dangers of head impacts to be better quantified given the large numbers of participants in sports that involve contact. This is of further importance when one considers that approximately 3 million American youths participate in tackle football (Powell & Barber-Foss 1999). Although cerebral concussion was until recently considered the main head impact risk factor important to quantify for later assessment of long-term consequences, our understanding is evolving. Recent research has demonstrated that impacts do not necessarily need to cause immediate symptoms (i.e., concussion) in order to produce changes in the brain (Bazarian et al. 2014, Talavage et al. 2010). A host of recent prospective studies in current athletes have used DTI to identify demyelination or disruption of axonal tissue in the absence of a clinically diagnosed concussion (Bazarian et al. 2014, Davenport et al. 2014, Koerte et al. 2012, Lipton et al. 2013, McAllister et al. 2014).

Although these studies of acute outcomes after asymptomatic head impacts are not indicative of long-term degeneration of CTE, a number of studies have investigated such chronic outcomes. As briefly discussed above (see Volumetric MRI section), a recent study by Singh et al. (2014) showed that players both with and without a history of concussion had smaller hippocampal volumes than those who had never played football. In addition, volumes were inversely related to mean body mass index for each group (nonfootball controls 24.9 $\pm$ 6, football players without concussion 27.4 $\pm$ 3.6, and football players with concussion 30.7 $\pm$ 4.5; R. Singh, personal communication), making a smaller hippocampal volume for football players even more remarkable. This is further strengthened by the fact that although every neuropathologically confirmed case of CTE has had a significant history of repetitive head impacts, not all cases have a documented history of concussion (McKee et al. 2013). Neuropathological evidence also shows that the number of seasons played by deceased American football players, but not the number of family-reported concussions, was significantly correlated with pathological stage of CTE ($p < 0.001$ and $p = 0.184$, respectively) (McKee et al. 2013). These studies suggest that multiple head injuries in sport, whether accompanied by symptoms or not, can cause chronic, negative neurophysiological and neuropsychological outcomes.

Age of first exposure to head impacts may also be a risk factor for CTE, with a possible increased risk of later life dysfunction for those who sustain sports-related head trauma in developmental years. Although the acute signs and symptoms of a concussion are clinically similar in children and adults, the mechanism of neural tissue damage after head impact appears to be different in the developing brain (Shah et al. 2006, Teasdale et al. 2005). These changes are likely due to differences between adults and children in the structure of the brain (e.g., lower myelination of

the axons within younger brains), the skull, and the supporting musculature (Mueller 2001, Prins & Hovda 2003). A number of studies support this hypothesis. One prospective longitudinal study found that children who experienced a mild TBI requiring hospitalization before age 10 years displayed increased hyperactivity/inattention and conduct disorder between the ages of 10 and 13 in comparison with children who had not experienced a mild TBI, as rated by both their mothers and their teachers (McKinlay et al. 2002). Another study of 45 adults, with an average age at injury of 8.9 years, found that those who experienced posttraumatic amnesia for at least 30 minutes had statistically significant decreases in measures of attention and memory more than two decades later (Hessen et al. 2006). In a review concerning the long-term consequences of head trauma on development, these results prompted Daneshvar et al. (2011b) to suggest that the age at which an individual begins experiencing head injury might play a role in the development of CTE.

A recent study (Stamm et al. 2015) has indicated that there is an association between participation in tackle football prior to age 12 and greater later-life cognitive impairment measured using objective neuropsychological tests. These findings were based on a study of 41 former NFL players (ages 40–69) and suggest that exposure to repeated head impacts during a neurodevelopmental window of vulnerability may increase the risk of later-life neurocognitive impairment. However, these findings cannot be interpreted as being indicative of CTE risk per se. Future studies examining the age of first exposure to repetitive head impacts and neuropathologically confirmed CTE are warranted.

CONCLUSION: WHAT WE THINK WE KNOW AND WHAT WE NEED TO KNOW NEXT

Much has been learned about the neuropathological and clinical aspects of CTE in recent years. However, the scientific study of CTE remains in its infancy. Critical questions remain unanswered, such as: How common is CTE? Why do some people develop this neurodegenerative disease whereas others with similar histories of repetitive brain trauma do not? How can this disease be prevented or treated? To address these and other important issues, necessary next steps are to develop methods to diagnose CTE during life and to further study the reliability, diagnostic accuracy, and utility of the recently published diagnostic criteria for TES and CTE. However, as with other neurodegenerative diseases such as AD, accurate in vivo diagnoses will require well-validated biomarkers for the disease. Future studies are therefore needed to examine direct measures of tau deposition in the brain (e.g., PET ligands for p-tau) as well as fluid biomarkers of tau (e.g., plasma, CSF, brain-derived exosomal tau) and proxy biomarkers of the disease, such as advanced neuroimaging studies (e.g., DTI, magnetic resonance spectroscopy, fMRI). Once a combination of clinical diagnostic criteria and accurate biomarkers is validated, future research of the risk factors (e.g., exposure variables, genetic polymorphisms), clinical course, prevention, and treatment will be possible. These studies may include large-scale longitudinal epidemiological investigations as well as prospective clinico-pathological studies. Clinical trials for disease modification, including treatment and prevention studies, could be conducted. Compounds are already being used in human trials aimed at preventing the accumulation of p-tau or removing it once it is in the brain. Other compounds aimed at reducing the inflammation involved in diseases such as CTE are also being developed. Additional clinical trials of existing pharmacological and behavioral approaches to treat specific features of CTE could also be initiated. We anticipate great strides in this area of research over the next several years. With the potentially large public health impact of CTE, there is an urgency to move ahead with these advances as quickly as possible.

DISCLOSURE STATEMENT

P. Montenigro, D. Corp, and T. Stein are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

R. Cantu receives compensation from the National Football League as senior advisor to the Head, Neck and Spine Committee, from the National Operating Committee on Safety of Athletic Equipment as chairman of the Scientific Advisory Committee, and from the Sports Legacy Institute as cofounder and medical director for talks given and research conducted. He receives royalties from Houghton Mifflin Harcourt and compensation for expert legal opinions.

R. Stern acknowledges funding support from NIH grants R01 NS078337, R01 CA129769, P30 AG13846, U01 AG10483, and U01 AG015477 and Department of Defense grant PT120012P1. He receives research support from Eli Lilly, Eisai, and Avid Radiopharmaceuticals. He is also a paid consultant to Athena Diagnostics and Janssen Alzheimer's Immunotherapy, and he receives royalties from Psychological Assessment Resources for the publication of neuropsychological tests.

ACKNOWLEDGMENTS

D. Corp acknowledges funding support from an Endeavor Research Fellowship awarded by the Australian Government Department of Education. T. Stein acknowledges funding support from the Department of Veterans Affairs, Veterans Health Administration, Clinical Sciences Research and Development Merit Award; Alzheimer's Association (NIRG-305779); and NIH grant P30 AG13846. Figures were designed with the help of graphic artist Benjamin Michaels (**benpmichaels@gmail.com**).

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