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Review

A critical review of chronic traumatic encephalopathy

Grant L. Iverson[a,*], Andrew J. Gardner[b], Paul McCrory[c], Ross Zafonte[e], Rudy J. Castellani[d]

[a] Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, MassGeneral Hospital for Children Sports Concussion Program, & Red Sox Foundation and Massachusetts General Hospital Home Base Program, Boston, MA, USA
[b] Hunter New England Local Health District Sports Concussion Program; & Centre for Translational Neuroscience and Mental Health, School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia
[c] The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre – Austin Campus, Heidelberg, Victoria, Australia
[d] Division of Neuropathology, University of Maryland School of Medicine, USA
[e] Department of Physical Medicine and Rehabilitation, Harvard Medical School; Spaulding Rehabilitation Hospital; Brigham and Women's Hospital; & Red Sox Foundation and Massachusetts General Hospital Home Base Program, Boston, MA, USA

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ABSTRACT

Chronic traumatic encephalopathy (CTE) has been described in the literature as a neurodegenerative disease with: (i) localized neuronal and glial accumulations of phosphorylated tau (p-tau) involving perivascular areas of the cerebral cortex, sulcal depths, and with a preference for neurons within superficial cortical laminae; (ii) multifocal axonal varicosities and axonal loss involving deep cortex and subcortical white matter; (iii) relative absence of beta-amyloid deposits; (iv) TDP-43 immunoreactive inclusions and neurites; and (v) broad and diverse clinical features. Some of the pathological findings reported in the literature may be encountered with age and other neurodegenerative diseases. However, the focality of the p-tau cortical findings in particular, and the regional distribution, are believed to be unique to CTE. The described clinical features in recent cases are very similar to how depression manifests in middle-aged men and with frontotemporal dementia as the disease progresses. It has not been established that the described tau pathology, especially in small amounts, can cause complex changes in behavior such as depression, substance abuse, suicidality, personality changes, or cognitive impairment. Future studies will help determine the extent to which the neuropathology is causally related to the diverse clinical features.

Contents

* Corresponding author at: Center for Health and Rehabilitation Research, Department of Physical Medicine & Rehabilitation, Harvard Medical School, 79/96 Thirteenth Street, Charlestown Navy Yard, Charlestown, MA 02129, USA. Tel.: +1 617 952 6194.
E-mail address: giverson@mgh.harvard.edu (G.L. Iverson).

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1. Historical overview of CTE

In 1928, Martland noted that some boxers, boxing promoters, and fans were aware of a "peculiar condition" described as "punch drunk," but there had been no medical research or documentation on the deleterious effects of boxing on the brain. A fight promoter provided Martland with a list of 23 former boxers that the promoter thought had the syndrome. Martland examined and reported the details of one retired boxer who had an advanced Parkinsonian syndrome without evidence of obvious cognitive impairment. In 1934, Parker described the boxing and medical histories of three professional boxers and illustrated that they had obvious and serious neurological and neurobehavioral problems that developed during or toward the end of their extensive boxing careers. This neuropsychiatric syndrome, later called traumatic encephalopathy (Parker, 1934), dementia pugilistica (Millspaugh, 1937), and chronic traumatic encephalopathy (Critchley, 1949), continued to be described in case reports for decades. In 1969, Roberts published a book entitled *Brain Damage in Boxers: A Study of the Prevalence of Traumatic Encephalopathy Among Ex-Professional Boxers*. This book provides detailed clinical information on a random sample of 224 retired professional boxers who were registered professional boxers in England between 1929 and 1955, 11% of whom were deemed to have mild CTE and 6% were considered to have a moderate-to-severe form of the syndrome. These boxers had an enormous exposure to neurotrauma, with many having hundreds of professional fights and boxing careers lasting 20 years. Case #1 in the book, for example, began boxing at age 15 and had 50 amateur fights before turning professional at age 16. As a professional, it was estimated that he had 200 fights. Based on his analysis of this random case series of boxers, Roberts described the syndrome as predominately cerebellar or extrapyramidal, typically characterized by dysarthria and motor problems, with some cases having dementia. A few years later, Corsellis et al. (1973) made a large contribution to the literature by carefully describing the gross and microscopic neuropathology believed to be unique to dementia pugilistica in 15 boxers whose brains were stored in a brain bank (e.g., neurofibrillary degeneration, neuronal loss, 'scarring' of the cerebellar tonsils, and fenestrated cavum septum pellucidum).

In 1990, Roberts et al. re-examined the brains from the Corsellis series and additional cases and discovered, using modern immunohistochemistry techniques, that nearly all had extensive beta amyloid deposition similar to what is seen in Alzheimer's disease (AD). Roberts et al. (1990b) also identified what appeared to be neuropathology characteristic of dementia pugilistica in a woman who had reportedly been repeatedly battered. She also had significant cerebrovascular disease. In 1991, Hoff et al. identified tau in the depths of sulci in a person with autism who had a long history of head banging behavior. In 1999, Geddes et al. examined the brains of four young men who had been exposed to repetitive head injuries and emphasized that repetitive head injury in young adults is initially associated with neocortical neurofibrillary tangle formation in the absence of amyloid beta (Aβ) deposition, and the distribution of the tau pathology suggests that the pathogenesis might relate to damage to blood vessels or perivascular elements.

In 2000, Jordan published a review of the literature relating to "chronic traumatic brain injury" (CTBI). He included a broader description of chronic brain damage in boxers, with CTE and dementia being the most severe. Jordan described the clinical presentation of CTBI in its milder form as involving mild dysarthria and difficulty with balance. Those with more advanced brain damage might have ataxia, spasticity, impaired coordination, and Parkinsonism. Cognitive impairment could range from mild to dementia. He noted that behavioral changes could be diverse and include disinhibition, irritability, euphoria or hypomania, impaired insight, paranoia, and violent outbursts. He stated that it might be difficult to determine the extent to which some of the behavioral problems reflected longstanding (i.e., premorbid) personality characteristics. Jordan reported that it was unclear whether CTBI in boxers reflected a progressive neurodegenerative disease or whether it reflected the aging process superimposed on a fixed neurological injury (or both).

In 2005, Omalu et al. reported the first case of CTE in a retired National Football League (NFL) player. In 2006, they reported the second case of CTE in a former NFL player (Omalu et al., 2006). In 2009, McKee et al. identified 48 cases of CTE in the world literature and carefully documented their clinical and neuropathological characteristics. They added three new cases to the literature in that article, one of whom was a retired professional football player. In 2010, Omalu reported on another case of a former NFL football player. In this article, it was introduced for the first time that suicidality was a prominent clinical feature of CTE. This conclusion appears to be based on the fact that two of the three cases examined by Omalu et al. completed suicide. In their review of all known cases up to 2009, McKee et al. did not report that suicidality or completed suicide was a clinical feature of CTE. It was not included in their tables as a possible clinical feature or discussed as such in the article. In contrast, suicide is now widely cited as a clinical feature of CTE.

McKee et al. (2013) introduced four neuropathological stages of CTE. For the first time, they reported that CTE could be diagnosed in someone who has no clinical symptoms. Stage 1 CTE can be diagnosed based on having small focal epicenters of p-tau and no clinical symptoms, or symptoms such as headaches and mild depression. Gardner et al. (2014a) identified 158 cases of CTE in the world literature and carefully reviewed the neuropathology and clinical features of each case (see the online supplementary material). In 2014, Montenigro et al. proposed a new syndrome called Traumatic Encephalopathy Syndrome. This syndrome is extraordinarily broad in scope, encompassing people with mild depression and those with late-stage dementia. For example, if a person played high school and collegiate sports (for at least 2 years at the college level) and had current problems with depression, anxiety, and headaches, that person would meet criteria for the new Traumatic Encephalopathy Syndrome.

2. Need for a critical review

Two groups of athletes represent the vast majority of cases identified as having CTE: boxers and football players. There are reasons to be concerned about the long-term brain health of football players. It has now been established scientifically that amateur football players are exposed to large numbers of head impacts per playing season (Broglio et al., 2013; Daniel et al., 2014; Wong et al., 2014; Young et al., 2013)—so a long career in football, such as experienced by NFL players, is associated with an enormous exposure to head

trauma. There is steadily emerging evidence that some retired NFL players have mild cognitive impairment (Guskiewicz et al., 2005; Randolph et al., 2013), neuroimaging evidence of microstructural changes in white matter (Hart et al., 2013; Strain et al., 2013), functional changes in brain metabolism (Hampshire et al., 2013) and molecular changes (Coughlin et al., 2015) disproportionate to their age. In addition, considerable progress is being made in understanding the neuropathology of repetitive mild brain injuries in animal models (Angoa-Perez et al., 2014; Goldstein et al., 2014; Ojo et al., 2013; Petraglia et al., 2014a; Petraglia et al., 2014b; Zhang et al., 2015).

There has been an evolution in the description of both the neuropathology and clinical features of CTE in the past few years, especially in American football players. In the past, CTE was diagnosed in some retired boxers who presented with serious neuropsychiatric problems, dysarthria, and Parkinsonism, whereas at present it has been diagnosed in young athletes with no or mild symptoms. The etiology of the modern description of CTE generally has been assumed to be multiple concussions in sports (McKee et al., 2013; Omalu et al., 2011; Stein et al., 2014). However, CTE researchers have also asserted that a single traumatic brain injury of any severity (Omalu et al., 2011) or multiple mild TBIs in civilians or military service members (McKee et al., 2013; Omalu et al., 2011; Stein et al., 2014) can cause the disease. Recently, CTE researchers have emphasized that the more important etiology might not be concussions, but instead multiple subconcussive blows (Bailes et al., 2013; Baugh et al., 2012; Gavett et al., 2011a; Gavett et al., 2010; Gavett et al., 2011b; McKee et al., 2009; Mez et al., 2013; Stern et al., 2011). CTE researchers have noted that there are multiple additional factors that may or may not relate to the development of the neuropathology, such as genetics, gender, physiological stress, alcohol, opiates, and performance-enhancing drugs, but these factors have not been studied (McKee et al., 2014; Stein et al., 2014).

The microscopic neuropathology described in recent cases of CTE includes: (i) localized neuronal and glial accumulations of phosphorylated tau involving perivascular areas of the cerebral cortex, sulcal depths, and with a preference for neurons within superficial cortical laminae; (ii) multifocal axonal varicosities involving deep cortex and subcortical white matter; (iii) variable and often absent beta-amyloid (Aβ) deposits (generally less than that encountered in Alzheimer's disease (AD)); and (iv) TDP-43-positive inclusions and neurites (Baugh et al., 2012; Gavett et al., 2011a). Some of the described neuropathology may be encountered in other conditions, such as AD, frontotemporal dementia, progressive supranuclear palsy, and aging, but the distribution and localized nature of the p-tau lesions, such as p-tau around vessels and in depths of sulci, are considered unique and thought to set the tau pathology apart from aging, AD, or other tauopathies. The clinical features of CTE have been described as chronic psychiatric problems, substance abuse, aggression, and cognitive impairment (Baugh et al., 2012; Gavett et al., 2011a; Omalu et al., 2011; Omalu et al., 2010b). These clinical features, of course, are not unique to CTE. They are present in other psychiatric, neurological, and neurodegenerative conditions. At present, there is no way to diagnose CTE in a living person, although positron emission tomography imaging of tau is progressing rapidly (Gandy and DeKosky, 2014; Han et al., 2012; Mitsis et al., 2014; Shoup et al., 2013; Small et al., 2013; Zhang et al., 2012). Such imaging might help clarify the diagnostic dilemma, although tau may appear in association with numerous neurological conditions, opiate abuse (Ramage et al., 2005), and healthy aging (Braak and Del Tredici, 2011; Braak et al., 2011).

In contrast to AD and other dementias, there is very little research relating to CTE—and previous authors have noted that it is difficult to draw conclusions about CTE given the limited scientific evidence (Gardner et al., 2014a; Giza et al., 2013; Karantzoulis and Randolph, 2013; McCrory et al., 2013a; McCrory et al., 2013b; Randolph, 2014; Smith et al., 2013b). The neuropathology and the clinical features have not been agreed upon or codified. Following a review of the literature, Smith et al. (2013b) concluded that the small literature to date precludes formal characterization of the clinical syndrome and the pathology—and robust diagnostic criteria permitting confident differentiation of CTE and TBI-associated neurodegeneration from other neurodegenerative diseases are not available.

In the papers presenting autopsy cases, and subsequent review papers, the authors have stated unequivocally that there is unique neuropathology associated with CTE, this neuropathology is caused by neurotrauma (single or repetitive), and the neuropathology, even in small amounts, causes complex changes in behavior and cognition such as depression, anger dyscontrol, suicidality, and mild cognitive impairment (Baugh et al., 2012; Gavett et al., 2011b; McKee et al., 2009; McKee et al., 2013; Omalu, 2014; Omalu et al., 2010a; Stern et al., 2013; Stern et al., 2011). An alternative hypothesis has been articulated in the literature: neurotrauma and repetitive neurotrauma might be associated with increased risk for aging-related cognitive and behavioral changes in some people that do not reflect a completely separate disease process but rather contribute to known disease processes. That is, repetitive neurotrauma might be associated with reductions in "cerebral reserve" or "cognitive reserve", resulting in the person being more vulnerable to an earlier expression of late-life neurodegenerative disorders (Karantzoulis and Randolph, 2013; Randolph et al., 2013; Randolph and Kirkwood, 2009).

Depression has been reported as a very common clinical feature of CTE, and cognitive impairment is a cardinal clinical feature of depression (American Psychiatric Association, 1994). Anger control problems and aggression have also been cited frequently as a clinical feature of CTE. In a phone survey of 1063 former NFL players (Weir et al., 2009), individuals were asked if they have ever had attacks of anger when they lost control and broke or smashed something worth more than a few dollars, hit or tried to hurt someone, or threatened to hit or hurt someone? A substantial minority of retired NFL players between the ages of 30–49 (30.7%) and 50+ (29.3%) said yes to this question; however, the authors noted that the rate of anger dyscontrol in men in the general US population is higher (i.e., 54.8% for men between 30 and 49, and 47.2% for men aged 50+). A second alternative hypothesis is that some people have mental health, anger control, and cognitive problems that are mostly or entirely unrelated to the neuropathology that is reported to be unique to CTE (e.g., tau in the depths of sulci); these problems are due to other multifactorial causes similar to what is seen in the general population of adults who have not been exposed to repetitive neurotrauma. A third alternative hypothesis is that neuropathology unique to CTE contributes in a small but meaningful way to the development of mental health problems, personality changes, and/or cognitive difficulties. This critical review has three main sections: neuropathology, differential clinical diagnosis, and directions for future research. It is important to carefully consider neuropathology and clinical features separately because the extent to which they are related is presently unknown.

3. Neuropathology

There are many studies that support the theory that neurotrauma is associated with not only acute but also chronic microscopic neuropathology (Smith et al., 2013b; Tsitsopoulos and Marklund, 2013). Post-mortem studies prior to 2005 have reported neurofibrillary tangles (NFTs) in young and middle-aged men who were boxers, as well as one soccer player, a person with epilepsy prone to frequent falls, a circus performer, and an autistic patient

prone to frequent and forceful head-banging (Corsellis et al., 1973; Geddes et al., 1999; Geddes et al., 1996; Hof et al., 1991; Williams and Tannenberg, 1996). NFTs have been shown to be abundant in the brains of older boxers, as have Aβ plaques, the extent to which is indistinguishable from AD in some cases (Dale et al., 1991; Hof et al., 1992; Jordan, 2000; Tokuda et al., 1991). In a landmark study, and the largest study on boxers to date, Corsellis et al. (1973) reported findings in 15 boxers between the ages of 57 and 91. In this study, the authors noted the following salient findings that collectively appeared to be unique to boxers (i.e., "dementia pugilistica"): (i) neurofibrillary degeneration, particularly involving medial temporal lobe and brainstem tegmentum; (ii) neuronal loss involving the pars compacta region of the substantia nigra with occasional neurofibrillary tangles in residual neurons (but no Lewy bodies); (iii) 'scarring' of the cerebellar tonsils; and (iv) abnormalities in the septum pellucidum including cavum septum pellucidum and septal fenestrations. Some of these findings have been documented in the recent cases of CTE, but they are not considered necessary for neuropathological diagnosis. Instead, region-specific p-tau deposition is currently considered sufficient for diagnosis.

The Corsellis study codified the abnormal presence of neurofibrillary degeneration out of proportion to plaque pathology. It should also be pointed out that the studies were performed using such preparations as cresyl violet, Congo red, and silver impregnation, prior to the advent of immunohistochemistry, and prior to the better detailed understanding of the spectrum of proteinopathy as a function of age alone. A subsequent study on eight cases from the Corsellis et al. (1973) study using antibodies to Aβ demonstrated "variable numbers of morphologically diverse senile plaques in an extensive area of the cortex," raising the possibility that a subset of these cases were AD (Tokuda et al., 1991). Roberts et al. (1990a) also examined 14 of the 15 original cases in the Corsellis et al. (1973) study, and additional cases, and found that antigen retrieval with formic acid pretreatment uncovered extensive, diffuse Aβ plaques. Similar antigen retrieval procedures are now standard for immunohistochemistical workup of dementia brains, so it would be interesting to subject the original case series to blinded interpretation for the presence or absence of Alzheimer's disease changes. Co-morbidities were also prominent in this series, including alcohol abuse in at least six of the 15 cases, neurosyphilis with tabes dorsalis in one case, a cavernous malformation of the globus pallidus in one case, and hypertensive vascular disease. The subjects also boxed in the early part of the 20th century, when several hundred bouts were commonplace at the professional level. In addition, three of the 15 subjects had no known neurological illnesses prior to death, and family history of neurodegenerative disease was not commented upon in any of the case histories. In short, although it appears that neurofibrillary degeneration is increased in boxers, uncertainties persist even within dementia pugilistica per se regarding the specificity of the neurofibrillary degeneration.

Animal studies have demonstrated that TBI (Hartman et al., 2002; Tran et al., 2011) and repetitive TBI (Uryu et al., 2002) are associated with the development of Aβ plaque pathology and increased phosphorylated tau. Johnson et al. (2012) reported that approximately one-third of individuals who sustain *a single moderate or severe traumatic brain injury* (TBI) and later die of another cause had abundant and widely distributed NFTs and Aβ plaques. In their study, NFTs were present in 46% of those with a history of TBI and 34% of controls, but when subjects over 60 were excluded, NFTs were present in 34% of those with TBIs compared to only 9% of controls. Aβ plaques were found in 28% of both groups, but there was a trend toward a greater distribution and higher density of these plaques in the TBI group (Johnson et al., 2012). Interestingly, in a study of long-term survivors of TBI, this same research group (Chen et al., 2009) was the first to report that although Aβ plaques are present shortly after TBI, they were not found years after injury in their post-mortem cases, suggesting that they might actually regress over time. In another study, this group (Johnson et al., 2011) reported that there was no association between a history of single TBI in humans and abnormally phosphorylated TDP-43 (p-TDP-43) inclusions, suggesting that TDP-43 proteinopathy might differ in those with single versus repetitive neurotrauma.

In the largest study to date on the neuropathology of CTE (McKee et al., 2013), CTE was based on the following criteria: "(i) perivascular foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles; (ii) irregular cortical distribution of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci; (iii) clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem; and (iv) neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers" (McKee et al., 2013, page 45). The presence of Aβ plaques was noted in 44.1% of CTE subjects and those with Aβ plaques tended to be older. The authors noted that the "brains of 68 of the 85 subjects showed p-tau immunoreactive neurofibrillary tangles and astrocytic tangles in a pattern and neuroanatomical distribution diagnostic of CTE" and proposed a new four stage diagnostic criteria system. The pattern and distribution of neuropathology differs dramatically across the four newly proposed stages of the disease, ranging from isolated microscopic depositions of phosphorylated tau to a heavy burden of diverse and widespread microscopic and macroscopic neuropathology. Specifically, stage I and stage II CTE have isolated phosphorylated tau even on whole mount, thick sections; stage III CTE shows similarly localized cortical phosphorylated tau, with the overlay of age-related tau in the medial temporal lobe; whereas stage IV shows abundant tau in the neocortex and medial temporal lobe that might be similar to other neurodegenerative diseases such as AD and frontotemporal dementia. Aβ immunohistochemistry was performed, presumably ruling out AD in most of the stage IV cases, although similar 50 μm thick immunostains for Aβ were not presented for comparison. It is noteworthy that the criteria for CTE is particularly encompassing in that *any* localized phosphorylated tau constitutes stage I CTE or higher, and may be one of the bases for the conclusion that nearly all subjects examined to date have stigmata of CTE.

The online supplementary material provided by McKee et al. (2013) indicates both diversity and nonspecificity of the gross and microscopic neuropathology in the sample identified as having CTE. Moreover, these supplementary tables, combined with tables in the published article, provide insight into some of the similarities and differences in regard to how CTE has been described by Omalu et al. (2011) and McKee et al. (2013). In terms of gross features, Omalu et al. (2010a, 2011) reported that CTE is not characterized by atrophy (page 176 in Omalu et al., 2011 and page 132 in Omalu et al., 2010a). In the McKee et al. (2013) case series, frontal, temporal, parietal, occipital, and hippocampal atrophy was very common in cases with advanced CTE (stage IV, online supplementary Table 2). In the McKee et al. (2013) case series, p-tau immunoreactive astrocytic tangles are a defining feature of the disease—but Omalu et al. (2011) reported that these were not present in their cases (page 181). Both groups emphasize that the disease is characterized by microscopic tau pathology, and both note that a unique location for the tau is the depths of the sulci, and in superficial cortical layers. McKee et al. emphasize that another unique feature is subependymal accumulation of p-tau, whereas Omalu et al. (2011) have not found p-tau in this location (page 181). Both groups note that the distribution of p-tau differs from AD. However, neither group clearly addresses the issue of sporadic tau depositions in the brains of people in their 40s, 50s, and 60s who are cognitively and psychologically healthy, those with medical problems, and those with mild cognitive impairment. For example, limbic stage AD (stage III–IV) as defined by Braak and Braak (1991)

indicate significant neurofibrillary degeneration in the medial temporal lobe (amygdala, entorhinal cortex, hippocampal formation, inferior temporal neocortex)—brain regions emphasized and depicted in the dementia pugilistica (Corsellis et al., 1973) and CTE (McKee et al., 2009; McKee et al., 2013) literature. Half of these individuals in the Braak and Braak (1991) study had no evidence of dementia during life. In Table 1 of their article McKee et al. (2013) note that a characteristic of AD is tau pathology in the entorhinal cortex, amygdala, and hippocampus; this is not listed as characteristic of CTE although it is depicted in illustrations emphasizing CTE pathology and it is emphasized in dementia pugilistica. Omalu et al. (2011) attempt to differentiate CTE from MCI by stating that the "brains of those with MCI show topographically restricted neurofibrillary pathology limited to the entorhinal cortex, hippocampus, and amygdala accompanied by concomitant pathologic alterations, most frequently strokes, argyrophilic grains, and Lewy bodies" (page 182). Omalu et al. comments on the hippocampus appear somewhat contradictory, in that: "The hippocampus is frequently spared by tauopathy in CTE cases, whereas tauopathy first appears in the hippocampus in AD. The hippocampus for each CTE case may show none to sparse or moderate to frequent NFTs and NTs with or without diffuse amyloid plaques" (page 180). Based on the online supplementary tables provided by McKee et al. (2013), some degree of p-tau was present in the entorhinal cortex, amygdala, or hippocampus of 1/7 cases in stage I, 12/14 cases in stage II, and all the cases in stage III and IV and/or those diagnosed with a separate neurodegenerative disease. It is clear that to advance knowledge regarding CTE, it will be critical to develop specific and reproducible definitional criteria for the neuropathology and then apply those criteria to various samples of control subjects using identical methodology. This work is underway, as described below in the section on consensus-based neuropathological criteria for CTE.

In a review paper, Omalu et al. (2011) noted that Aβ plaques are usually not present in cases of CTE (page 176). In contrast, in the McKee et al. (2013) case series, Aβ deposition was present in 44.1% of the CTE cases as noted above. However, only seven cases had sufficiently severe neuropathology to meet criteria for AD by NIA-Reagan and NIA-Alzheimer Association guidelines (Montine et al., 2012; i.e., 10.3% of the CTE cases). Omalu et al. (2011) also noted that alpha-synuclein-positive Lewy bodies were not found in any of their subjects (page 176). In the McKee et al. (2013) case series, Lewy bodies were found in 15 of the CTE cases (22.1%). In addition, six cases (8.8%) met neuropathological diagnostic criteria for Parkinson's disease, frontotemporal dementia, Pick's disease, or progressive supranuclear palsy. In total, of the 68 cases with Stage I to stage IV CTE, 32 (47.1%) had some degree of neuropathology and 17 (25.0%) met criteria for severe neuropathology consistent with another neurological or neurodegenerative disease. A minority of subjects have only neuropathology suggestive of CTE.

In a review of the neuropathology of CTE, Smith et al. (2013b) noted that the depths of sulci might be biomechanically vulnerable during head trauma (and thus precipitate tau deposition), but the specificity and significance of tau in this location remains uncertain because (i) there are not large numbers of control subjects who have been examined for tau in these locations, and (ii) studies to date that have described the neuropathological features of acute TBI have not documented the pattern and distribution of tau that has been described in CTE. These authors urged caution in regard to the proposed hierarchical stages of CTE given the relatively small number of autopsy cases to date, the potential for case selection bias, and the limited data available for clinical-pathological correlation. Smith et al. also noted that Aβ pathology is a less consistent feature in CTE, compared to tau. They cautioned that amyloid plaques are observed in normal control subjects—so to associate these plaques to a history of neurotrauma requires adequate age-matched control groups, and past CTE studies have omitted control subjects entirely or included them in such small numbers or with characteristics sufficiently different from the CTE clinical cases to make them of limited relevance.

It is important to consider tau accumulation in CTE in the broader context of tau accumulation in aging and other diseases. Researchers have reported that tau depositions begin in childhood in nuclei of the lower brainstem, in particular the locus ceruleus, and progress to different regions of the brain throughout the lifespan (Braak and Del Tredici, 2012; Braak et al., 2011; Elobeid et al., 2012). In an unselected sample of 2332 autopsies between age 1 and 100, 89% of those under age 30 (93 total) had tau depositions (Braak et al., 2011). Astrocytic tau, subpial tau, subependymal tau, tau in superficial cortical neurons, tau in the medial temporal lobe, and tau in the brainstem tegmentum and spinal cord all occur with age and in AD (Braak and Braak, 1991; Braak and Del Tredici, 2011; Braak et al., 2011; Dugger et al., 2013; Munoz et al., 2007; Nishimura et al., 1995; Serrano-Pozo et al., 2011; Thom et al., 2011). The presence of NFTs in the absence of Aβ plaques has recently been termed "primary age-related tauopathy," and in these people the NFTs are mostly found in structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (Crary et al., 2014). The uniqueness of the cerebral cortical tau findings in CTE is related more to their focality, often termed "epicenters" (McKee et al., 2013), and relative distribution compared to AD and aging, which may constitute the basis for the diagnostic criteria that emphasize cortical pathology over subcortical pathology. Such focality is best demonstrated by thick (50–100 μm), whole mount sections of cerebral hemisphere as depicted in the literature (McKee et al., 2009; McKee et al., 2013). These preparations maximize sensitivity to detect phosphorylated tau, but may reduce the specificity, considering again the occurrence of tau pathology in asymptomatic patients and the overlay of normal aging (McKee et al., 2013).

There are also many studies illustrating that tau pathology (e.g., NFTs) and Aβ plaques are common in cognitively normal adults and older adults (Iacono et al., 2014; Jellinger and Attems, 2013), and in patients with mild cognitive impairment (Haroutunian et al., 2009; Markesbery, 2010; Petersen et al., 2006), in addition to AD (Hardy and Selkoe, 2002; Lazarczyk et al., 2012; Mehta, 2007). Genetic factors that predispose to phosphorylated tau deposits apart from rare kindreds with autosomal dominant frontotemporal dementia, are largely unknown, although genetic factors and in particular ApoE appear to relate more closely to Aβ plaque deposits than phosphorylated tau (Caselli et al., 2010; Vemuri et al., 2010). Interestingly, in a post-mortem study of 34 opiate abusers under the age of 40, multifocal NFTs were common, and 19% of the control subjects had NFTs in the entorhinal cortex (Ramage et al., 2005). Some retired professional athletes have a problem with opiate abuse (Cottler et al., 2011). In a second study, this research group also reported elevated levels of hyperphosphorylated tau in drug users, similar to that of elderly control subjects, but far less than is seen in AD (Anthony et al., 2010).

In a case of progressive dementia in a retired boxer, Nowak et al. (2009) reported neuropathology consistent with multiple etiologies, including dementia pugilistica, cerebral infarcts, and Wernicke–Korsakoff syndrome. Comorbid diseases were also noted by a group of Canadian researchers. Hazrati et al. examined the brains of six former Canadian Football League players who had neurological decline prior to death. Three of these individuals had neuropathological changes consistent with CTE, but they also had evidence of vascular disease and AD. The other three cases were diagnosed with AD, amyotrophic lateral sclerosis, and Parkinson's disease (Hazrati et al., 2013). In a systematic review of the literature, Gardner et al. (2014a) noted that of the 85 autopsies that have been performed in athletes over the past few years, 20% had 'pure'

neuropathology consistent with CTE as noted above, 52% had CTE plus other neuropathology, 5% had neuropathology but no CTE, and 24% had no neuropathology.

While immunolabeling with AT8 is widely used to define the cellular localization of phosphorylated tau, it is important to keep in mind not only the complexity and heterogeneity of tau inclusions (e.g., neurofibrillary tangles, pretangles, globose tangles, ghost tangles, astrocytic tangles, coiled bodies, tufted astrocytes, neuropil threads, dystrophic neurites, astrocytic plaques, etc.), but also the biology and pathobiology of tau itself that involve a complex interplay between genetic (mutations, polymorphisms), transcriptional, translational, and post-translational processes (Sobrido et al., 2003; Wolfe, 2009). At least 37 pathogenetic tau mutations have been identified, and they may be associated with diverse clinical and pathological phenotypes, resembling not only frontotemporal dementia, but also progressive supranuclear palsy, corticobasal degeneration, and Pick disease (Wolfe, 2009), the pathology of which overlaps substantially with that described for CTE. Screening for tau mutations among CTE cohorts has not been performed to date. Alternative splicing of exon 10 of the tau gene occurs sporadically or via mutation, affecting the ratio of four-repeat (four microtubule binding domain repeats, 4R) to three-repeat (3R) isoforms, which in turn tends to differ as a function of phenotype (de Silva et al., 2003). For example, 3R tau predominates in Pick disease, whereas 4R tau predominates in progressive supranuclear palsy and corticobasal degeneration. AD phosphorylated tau is comprised of a mixture of 3R and 4R tau, although 4R to 3R transition has been suggested to underlie NFT progression from pretangles to extracellular tangles (Hara et al., 2013). CTE is said to resemble AD in that relative amounts of phosphorylated tau isoforms were shown to be similar between AD and dementia pugilistica (McKee et al., 2013), although this is based on comparisons between brains of AD and only two boxers, one of which had brainstem Lewy bodies (Schmidt et al., 2001). Detailed analysis of tau isoforms is not available for the vast majority of CTE cases reported to date, nor is data addressing possible differences in the 4R/3R ratio as a function of time, age, or clinical progression.

The complexity of tau immunopathology is further highlighted by the fact that AT8 recognizes only two of >80 possible phosphorylation sites (Spires-Jones et al., 2009). In AD, for example, tau is phosphorylated at 19 sites (Augustinack et al., 2002). Some phosphorylation site-specific antibodies demonstrate evanescent pretangle epitopes, while others label phosphorylation sites in extracellular neurofibrillary tangles, while still others recognize phosphorylation sites in intraneuronal neurofibrillary tangles that appear to degrade with cell death (Augustinack et al., 2002). More than 20 protein kinases and phosphatases that regulate phosphorylation are also involved (Spires-Jones et al., 2009), which differ depending on phosphorylation site (Augustinack et al., 2002). What can be concluded, therefore, from AT8 immunohistochemistry in CTE (either on standard, automated immunostains or on whole brain, thick immunostains), is that patterns of AT8 labeling represent a small, empirical piece of data, in the backdrop of exceedingly complex biology and numerous potential morphologic variations, all of which overlaps substantially with both aging and heterogeneous diseases.

3.1. New consensus criteria for the neuropathology of CTE

The first NIH-supported consensus workshop relating to defining the neuropathological criteria for CTE occurred in Boston on February 26th and 27th of 2015. The initial findings from this consensus group were presented on the NINDS-NIH website as the "Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy" (www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm; Downloaded March 30, 2015). The neuropathology considered pathognomonic of CTE, and required for diagnosis, is abnormal accumulation of tau in neurons and glia in an irregular, focal, perivascular distribution and at the depths of cortical sulci. Many other neuropathological abnormalities were identified, especially in more severely affected brains, but those abnormalities were not considered unique to CTE.

The consensus group also defined "supportive criteria" for the neuropathological diagnosis of CTE, and noted that these criteria were more likely to be present in severely affected cases: "(i) macroscopic abnormalities such as abnormalities of the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury; (ii) abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 and 5 as in AD; (iii) abnormal tau (or silver-positive) neurofibrillary lesions in the hippocampus, especially in CA2 and CA4 regions, which differs from preferential involvement of CA1 and subiculum in AD; (iv) abnormal tau immunoreactive neuronal and astrocytic lesions in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum and substantia nigra; and (v) tau immunoreactive in thorny astrocytes in subpial periventricular and perivascular locations." The consensus group also defined, for the first time, neuropathological findings that should be considered exclusions to the primary diagnosis of CTE, as follows: "(i) CA1 predominant neurofibrillary degeneration in the hippocampus in association with amyloid plaques, as seen in AD; (ii) cerebellar dentate cell loss, prominent coiled bodies in oligodendroglia, and tufted astrocytes as seen in PSP; and (iii) severe involvement of striatum and pallidum with astrocytic plaques in cortical and subcortical structures as seen in CBD."

3.2. Conclusions

In short, CTE neuropathology relies on the focality of the cerebral cortical lesions, and includes cases with any degree of phosphorylated tau in discrete epicenters, whether clinically symptomatic or not, under the CTE umbrella. This emphasis on focal neuropathology renders comparison with dementia pugilistica difficult, because dementia pugilistica is essentially defined by the presence of neurofibrillary degeneration (especially temporal lobe) out of proportion to plaque pathology, in the presence of a boxing history. Epicenters of neurofibrillary degeneration, perivascular neurofibrillary degeneration, and preference for superficial cortical laminae were not features of the Corselis et al. series, but have been noted in cases of younger boxers (Geddes et al., 1999; Geddes et al., 1996; Hof et al., 1991). Of all cases (CTE and dementia pugilistica) reported to date in which pathological descriptions are available (Gardner et al., 2014a), a number of cases demonstrate neither focal epicenters nor neurofibrillary degeneration out of proportion to plaques. The bulk of cases described as having focal tau pathology are comprised of the recently reported CTE cases in athletes, of which only 20% had "pure" CTE pathology. It therefore appears that comparison with age-related phosphorylated tau, the overlay of comorbid diseases, the clinical signs attributable to head trauma versus other processes, and potential differences between boxers and other athletes are incompletely addressed. Before considering the CTE clinical diagnosis, it is therefore important to appreciate that many of the cases identified as having CTE had other non-specific neuropathology, and that a substantial percentage had a heavy burden of neuropathology that was sufficient to meet diagnostic criteria for a different neurodegenerative disease. It is also important to note that approximately 1 in 4 people identified as having the neuropathological features of CTE did not have significant clinical

symptoms. Conversely, approximately 1 in 4 of subjects with clinical symptoms had no demonstrable neuropathology (McKee et al., 2013).

The autopsy descriptions of the gross and microscopic neuropathology associated with CTE have included changes associated with aging, neurotrauma, and a variety of neurological and neurodegenerative diseases. Yet, the findings are described and presented as if all of the features were characteristic of the disease, and, until more recent publications, it was not clear which of these neuropathological features were considered unique to CTE. Some of the neuropathology described as characteristic of CTE in prior articles can occur in cognitively normal individuals, and it often coexists with pathologic changes in other diseases. As the case descriptions and review articles have evolved, however, the collective data to date suggests that the only consistent hallmark of CTE is p-tau accumulation in an abnormal distribution.

4. Clinical features of CTE

Through family interviews and reviews of medical records of individuals comprising post-mortem case studies, chronic psychiatric problems, substance abuse, aggression, and suicidal behavior have been linked to the neuropathology (Baugh et al., 2012; Gavett et al., 2011a; Omalu et al., 2011; Omalu et al., 2010b), although the link between completed suicide and CTE has been questioned (Iverson, 2014; Wortzel et al., 2013). McKee et al. (2013) state in their abstract: "Symptoms in stage I chronic traumatic encephalopathy included headache and loss of attention and concentration. Additional symptoms in stage II included depression, explosivity, and short-term memory loss. In stage III, executive dysfunction and cognitive impairment were found, and in stage IV, dementia, word-finding difficulty, and aggression were characteristic." Additional symptoms at each stage are set out in the text and a table in that article. Clearly, at all stages of neuropathology, the differential clinical diagnoses are complex. This is especially true in the presumed early stages of the disease, where the clinical features might be subtle, nonspecific, and even relatively common in the general population (e.g., headaches or concentration difficulty). Stage I initially appeared to be conceptualized as part of the clinical syndrome (McKee et al., 2013). However, in recent articles the authors state that the neuropathology in stage I is unlikely to cause clinical features (Stern et al., 2013) and that stage I is likely "preclinical" (McKee et al., 2014). We agree that isolated tau might be preclinical, and it is not entirely clear from the published articles to date the extent to which non-specific symptoms such as headache; difficulties with attention, concentration, and memory; and depression are linked to stage I or II neuropathology. It is also possible that some of the neuropathology in stage I, in particular, is incidental or age-related rather than representing a stage of a disease.

In the historical descriptions of CTE, there appeared to be two clinical syndromes—one that was progressive and one that did not appear to be progressive (Johnson, 1969; Roberts, 1969; Roberts et al., 1990a). In the historical descriptions, slurred and dysarthric speech, gait problems, Parkinsonism, and cognitive impairment (including dementia) were common. Detailed neuropsychological evaluations were not conducted on most of the historic cases, so whether they were truly cognitively intact is unclear. The early case descriptions contain extensive histories of psychiatric illnesses, severe substance abuse, and other medical or neurological problems. The extent to which these problems represent clinical features of CTE, one or more comorbidities, or both is difficult to determine. In a recent study of 45 retired NFL players between the ages of 30 and 60, the former athletes were not similar to these historical descriptions in that none had dysarthria, Parkinsonism, cerebellar dysfunction, or dementia (Casson et al., 2014). In an epidemiological study of neurodegenerative disease in former NFL players, they were reported to have a higher rate of dementia as a contributing cause of death than is expected in the general population (Lehman et al., 2012); however, in terms of absolute numbers only 2.1% of those who had died had dementia listed on their death certificates as a contributing cause of death (7/334), and only 0.9% had Parkinson's disease listed as a contributing cause of death (3/334). In a phone survey of a stratified random sample of 1063 former NFL players (Weir et al., 2009), individuals were asked if they had ever been diagnosed with "dementia, Alzheimer's disease, or other memory related disease." Of the retired players between the ages of 30–49, 1.9% said yes (compared to 0.1% of men in the US general population) and for former players aged 50+, 6.1% said yes (compared to 1.2% of men in the general population).

The individual autopsy case descriptions of CTE, in recent years, listed a variety of clinical features as being associated with the disease, including cognitive problems (Baugh et al., 2012; McKee et al., 2013; Omalu et al., 2011), mental health problems (Baugh et al., 2012; McKee et al., 2013; Omalu et al., 2011), personality changes and aggression (Baugh et al., 2012; McKee et al., 2013; Omalu et al., 2011), and physical problems, such as headaches (McKee et al., 2009; McKee et al., 2013; Omalu et al., 2011), Parkinsonism (Baugh et al., 2012; McKee et al., 2013; Omalu et al., 2005), and motor neuron disease (McKee et al., 2010). Most of these symptoms and problems are nonspecific; they are associated with many medical, neurological, psychiatric, and neurodegenerative conditions and disorders. Headaches, for example, are common in the general population (Lanteri-Minet et al., 2003; Rasmussen et al., 1991), and in those with depression (Chai et al., 2012), anxiety and life stress (Chai et al., 2012; Penacoba-Puente et al., 2008), sleep problems (Chai et al., 2012; Rains and Poceta, 2012), and hypertension (Chai et al., 2012; Lagman-Bartolome and Gladstone, 2014). Interestingly, researchers have recently reported that headaches are a risk factor for a later diagnosis of vascular dementia (Hagen et al., 2013) and headaches apparently are an associated feature of early-onset AD (Joshi et al., 2012; Ringman et al., 2008). It seems very unlikely, however, that headaches will emerge as a reliable and specific indicator of CTE given the high prevalence in the general population and in those with various health and mental health problems.

Poor financial decisions, financial problems, and bankruptcy have been considered a feature of CTE (Omalu et al., 2011). These problems, of course, occur in people who do not have CTE, and researchers have reported a link between personal debt and suicidal ideation (Hintikka et al., 1998; Meltzer et al., 2011). Impulse control problems, such as gambling, have also been linked to CTE (Omalu et al., 2011). Unrelated to CTE, researchers have reported that pathological gamblers are at increased risk for physical and mental health problems (Black et al., 2013). Pathological gamblers who go bankrupt are more likely to have diverse problems in their lives (work, marital, and legal), and they have increased rates of depression and substance abuse (Grant et al., 2010).

Omalu et al. (2011) described the clinical features of CTE as: (i) progressive deterioration in social and cognitive functioning (including deterioration in socioeconomic status and bankruptcy); (ii) mood and behavioral disorders (including depression, paranoia, social phobias, and suicidality), (iii) progressive deterioration in interpersonal and intrafamily relationships; (iv) criminal and violent tendencies and behavior (and sexual indiscretions); (v) abuse of alcohol and drugs; (vi) increasing religiosity; and (vii) headaches, generalized body aches, and pain. A comprehensive description of the clinical features of CTE, based on a larger case series presented by Stern et al. (2013), also lists a broad range of symptoms and problems, including cognitive features (memory impairment, executive dysfunction, attention and concentration difficulties, language impairment, and visual-spatial difficulties), behavioral features

(explosivity, impulse control problems, "out of control", physically violent, verbally violent, disinhibited speech, disinhibited behavior, socially inappropriate, and paranoia), and mood features (sadness/depression, anxiety/agitation, manic behavior/mania, suicidal ideation/attempts, hopelessness, and apathy).

5. Differential clinical diagnosis of CTE

Individuals with CTE (especially stages III and IV) are at risk for (i) having another neurodegenerative disease, or (ii) having substantial tau pathology (e.g., Braak stage III–IV). Therefore, their clinical features might be due in whole or part to another disease. In the case series identified with CTE from McKee et al. (2013) 17/68 (25%) people met neuropathologically established criteria for a disease other than CTE (as presented in Table 2). Interestingly, one case had a neuropathological diagnosis of Pick's disease, and he showed evidence of only stage I CTE neuropathology. One case had a neuropathological diagnosis of Lewy body disease and stage II CTE neuropathology. A third case had Parkinson's disease and progressive supranuclear palsy, and also had stage II CTE neuropathology. As such, these three cases showed small amounts of CTE neuropathology, but their neuropathologic diagnoses and clinical features would be much better explained by other diseases. Similarly, motor neuron disease (MND) is a progressive and uniformly fatal condition. The assignment of such cases to a new disease called CTE-MND (McKee et al., 2010) on the basis of small subcortical foci of phosphorylated tau (McKee et al., 2014) actually might be combining two separate and largely unrelated conditions. Or, it might be combining one neurodegenerative disease and one incidental pathological pattern. Research in this area is needed to better understand and document the range of neuropathology that accompanies the neuropathology that is considered unique to CTE.

6. Mild cognitive impairment

The term Mild Cognitive Impairment (MCI; Albert et al., 2011; Petersen et al., 1994; Petersen et al., 1999) has been widely used in neurology, and it is especially common in reference to memory problems in older adults. There have been hundreds of studies relating to MCI in the past decade. MCI is a condition where individuals have cognitive and memory impairment, due to diverse and often multifactorial causes, that does not substantially interfere with their daily activities. The prevalence of MCI varies considerably across studies, based on the age and clinical characteristics of the samples, ranging from 3 to 42% (Ward et al., 2012). MCI is often seen as a transitional stage between normal aging and dementia although many cases remain stable over time or even resolve. Studies suggest that those with MCI tend to progress to probable AD at a rate of approximately 10–15% per year (Grundman et al., 2004; Tabert et al., 2006), and the conversion rate appears to be predicted in part by Aβ load (Lim et al., 2014a; Lim et al., 2014b).

Cognitive impairment in the men identified as having CTE was usually determined based on an interview with a family member after the person had died. It was not based on a direct evaluation of the person using interviews, psychological testing, or cognitive testing. The cognitive features of CTE have been described in past articles as occurring across a broad spectrum, from subtle subjective difficulties to advanced dementia. What is challenging for researchers and clinicians, however, is that both subjectively experienced cognitive impairment and objectively measured impairment are present in a wide array of health, mental health, and neurological conditions. In addition, cognitive functioning declines with aging, and general medical problems (e.g., hypertension, diabetes, heart surgery), neurological problems (e.g., MS, Parkinson's disease, and severe TBI), and neurodegenerative diseases (e.g., AD and FTD) can alter the trajectory, or cause acceleration, of cognitive decline over the course of the adult lifespan. It is unclear, however, the extent to which mild repetitive neurotrauma, independently or through an interaction with genetics and other health problems, can alter the trajectory or cause acceleration of cognitive decline. Retired athletes, civilians, or veterans who have experienced repetitive neurotrauma might also have one or more other health problems that could contribute to difficulties with cognitive functioning. Therefore, in any given person, the extent to which a history of neurotrauma, or the presence of tau in specific brain regions, contributes to subjective or objective cognitive impairment can be extremely difficult to determine.

7. Alzheimer's disease and dementia

Meta-analytic reviews of the literature have revealed a statistically significant increased risk for AD in association with moderate to severe TBI in men (Fleminger et al., 2003; Mortimer et al., 1991). The relationship between TBI and dementia is complex, however, and a recent study illustrated that mild TBIs sustained at age 65 or older, and moderate-severe TBIs sustained at 55 or older, might increase a person's risk for developing dementia (Gardner et al., 2014b); but the absolute increase in risk for dementia following TBI is small, in that 8.4% of those who sustained a TBI in middle age or older adulthood went on to develop dementia compared to 5.9% of control subjects (who were followed after sustaining an injury to another part of the body) (Gardner et al., 2014b).

Some of the case studies of CTE have been examined carefully for the presence of AD, and a small percentage meet neuropathological criteria for the disease (Hazrati et al., 2013; McKee et al., 2013). Importantly, nearly all of the more advanced cases of CTE for which detailed neuropathological findings have been provided in online supplementary material (McKee et al., 2013) show considerable evidence of AD pathology. Dementia is a defining feature of late stage CTE. However, there are numerous potential causes for dementia, including AD, frontotemporal dementia, vascular dementia, Lewy body dementia, prion diseases, Huntington's disease, infectious diseases (e.g., neurosyphillis, HIV-AIDS), hydrocephalus, nutritional deficiencies, and toxic and metabolic disorders (Venketasubramanian et al., 2010). AD is the most common dementia, accounting for well over half of all cases. One in eight individuals (13%) over 65 years are diagnosed with AD, which increases to almost one in two (45%) for individuals over 85 years (Sivanandam and Thakur, 2012). There is an uncommon form of AD, referred to as "early onset" AD, which has a higher likelihood of demonstrable pathogenic mutation, most commonly presenilin 1 (Campion et al., 1999). Early onset AD appears in an individual's 40s and 50s; thus, it should be considered one of the differential diagnoses for those suspected of having CTE. A recent epidemiological study examined the relationship between TBI and early-onset dementia in men (Nordstrom et al., 2014). If one considers the risk for developing early-onset AD, prior to the age of 65, the absolute risks appear to be extremely low; in a sample of 45,249 men who sustained a TBI, only 14 developed early-onset AD (Nordstrom et al., 2014).

The enormous literature on AD is relevant to understanding the association between neuropathology at autopsy and clinical features of a disease during life. It is well known that p-tau neuropathology begins early in life and progresses over the adult lifespan (Braak et al., 2011), and that the early stage neuropathology does not correlate well with cognitive or behavioral changes in functioning (Braak and Braak, 1991; Montine et al., 2012). Postmortem brain examinations demonstrate diverse pathology. For example, in older adults clinically diagnosed as having "pure AD," fewer than 50% of these had the typical pathological features of AD. Moreover, neuropathological abnormalities are found in approximately 30–50% of cognitively normal patients (De Meyer

Table 1
Reported CTE clinical features in frontotemporal dementia and depression in men.

Reported CTE clinical features	Behavioral-variant Frontotemporal dementia	Depression in men
Cognitive features		
Memory impairment	Present (Bertoux et al., 2014; Matuszewski et al., 2006; Stopford et al., 2012)	Present (American Psychiatric Association, 2000, 2013; Zakzanis et al., 1998)
Executive dysfunction	Present (Laforce, 2013; Roca et al., 2013)	Present (American Psychiatric Association, 2000, 2013; Zakzanis et al., 1998)
Attention and concentration difficulties	Present (Stopford et al., 2012)	Present (American Psychiatric Association, 2000, 2013; Zakzanis et al., 1998)
Language impairment	Partially present, but less so in bvFTD (Rascovsky et al., 2011)	Not sufficiently studied
Visuospatial difficulties	Partially present, but less so in bvFTD (Possin et al., 2011)	Not sufficiently studied
Behavioral features		
Impulse control problems and aggression[a]	Present (Laforce, 2013; Miller et al., 2001; Rascovsky et al., 2002; Srikanth et al., 2005)	Present (Busch, 2009; Gerlock et al., 2011; Graham et al., 2012; Martin et al., 2013; Perlis et al., 2009; Shorey et al., 2012; Winkler et al., 2005)
Disinhibited behavior	Present (Laforce, 2013)	Not present (depending on how defined)
Socially inappropriate	Present (Laforce, 2013; Rascovsky et al., 2011)	Not present (depending on how defined)
Paranoia	Present (Dobson-Stone et al., 2012; Smith et al., 2013a)	Present (Collip et al., 2013)
Mood features		
Sadness/depression	Present (Srikanth et al., 2005)	Present (American Psychiatric Association, 2000, 2013)
Anxiety/agitation	Present (Srikanth et al., 2005)	Present (American Psychiatric Association, 2000, 2013)
Manic behavior/mania	Present (Srikanth et al., 2005)	Not present
Suicidal ideation/attempts	Present (Synofzik et al., 2012)	Present (American Psychiatric Association, 2000, 2013)
Hopelessness	Not sufficiently studied	Present (American Psychiatric Association, 2000, 2013)
Apathy	Present (Rascovsky et al., 2011; Snowden et al., 2011; Srikanth et al., 2005; Tagariello et al., 2009)	Present (Tagariello et al., 2009)

[a] Some examples of impulse control problems and aggression include: "explosivity," being "out of control", having a "short fuse," and being "physically violent" or "verbally violent." Omalu et al. also note: dismal business/investment performance, dismal money management, deterioration in socioeconomic status, and bankruptcy; hyperactivity, restlessness, high energy and performance drive levels without productive outcomes or results; breakdown of intimate and social relationships with spouses (including physical and emotional abuse, separation, and divorce), children, other family members, friends, and co-workers.

et al., 2010; Gelber et al., 2012; Robinson, 2011; White, 2009b). The distinction between AD and cognitively normal aging in the very old is particularly problematic (Brayne et al., 2009; Driscoll et al., 2006). In general, the literature in AD and the dementias illustrates that many patients with early stages of neuropathology do not show cognitive impairment, patients with a heavy burden of neuropathology are very likely to have cognitive impairment, and neuropathological comorbidity is very common—and this comorbidity can influence clinical features (Gelber et al., 2012; Nelson et al., 2012; Snowdon and Nun, 2003; Sonnen et al., 2007; Toledo et al., 2013; White, 2009a).

8. Frontotemporal dementia (FTD)

Frontotemporal dementia, in particular, represents a difficult clinical differential diagnoses for CTE (Baugh et al., 2012; Gavett et al., 2011b). The clinical features of CTE resemble the behavioral-variant FTD (bvFTD) which is characterized by deterioration in personality, social comportment, and cognitive functioning (Rascovsky et al., 2011). Frontotemporal dementia accounts for 5–20% of all dementias and typically has an earlier onset (Ratnavalli et al., 2002); in the 50s or 60s (Graham and Hodges, 2007). Insidious changes in personality, interpersonal conduct, and emotional regulation characterize bvFTD. Apathy, disinhibition, repetitive stereotypic behaviors, or perseveration are frequently observed. The prototypical cognitive profile illustrates relatively well preserved language and visuospatial abilities; however, higher-order, executive functions tend to be adversely affected (Piguet et al., 2011). There are no definitive biomarkers for the disease, so the diagnosis is dependent on clinical diagnostic criteria. The updated international consensus criteria for bvFTD provide detailed information about the syndrome (Rascovsky et al., 2011). When the new consensus criteria were applied to 137 cases from 16 multinational brain banks, 86% met criteria for 'possible' bvFTE and 76% met criteria for 'probable' bvFTD. In contrast, only 53% met the 1998 criteria for FTD (Rascovsky et al., 2011). Thus, the new criteria are associated with a fairly dramatic improvement in sensitivity compared to criteria in use for many years before.

FTD has been characterized by disease progression, although survival rates differ across FTD variants (behavioral-variant versus semantic dementia versus progressive nonfluent aphasia). In bvFTD the progression can vary but tends to occur more rapidly than other FTD variants. The median survival is approximately nine years from symptom onset, and 5.4 years from diagnosis (Garcin et al., 2009). Increasingly, however, frontotemporal dementia is being considered a spectrum disease rather than a disease with pure canonical subtypes (Perry and Miller, 2013; Seelaar et al., 2011)—meaning that the clinical features of the disease that have been traditionally associated with subtypes are also present to varying degrees across subtypes.

As seen in Table 1, the proposed clinical features of CTE are also clinical features of frontotemporal dementia (Bertoux et al., 2014; Dobson-Stone et al., 2012; Laforce, 2013; Matuszewski et al., 2006; Possin et al., 2011; Rascovsky et al., 2011; Roca et al., 2013; Smith et al., 2013a; Snowden et al., 2011; Srikanth et al., 2005; Stopford et al., 2012; Tagariello et al., 2009), especially bvFTD. Clearly, FTD presents a challenging differential clinical diagnosis for CTE. Moreover, diagnostic criteria for early stage CTE will need to carefully consider the known clinical features of depression, as discussed below.

9. Depression

Many men identified as having CTE had depression or chronic depression prior to their deaths. CTE researchers have written that the depression was a clinical feature of CTE, implying that it was caused by the tau pathology or other aspects of the neuropathology attributed to CTE. It is essential, however, to appreciate that the causes of depression are diverse and that depression is not uncommon across an adult man's lifespan. The extent to which the

neuropathology attributed to CTE, especially in small amounts, can cause depression de novo or worsen existing depression is currently unknown. It is known, however, that men with depression show the full spectrum of symptoms and problems that have been proposed to represent early-stage CTE clinical features (American Psychiatric Association, 2000, 2013; Busch, 2009; Corruble et al., 1996; Fava et al., 2010; Gerlock et al., 2011; Graham et al., 2012; Martin et al., 2013; Perlis et al., 2009; Shorey et al., 2012; Tagariello et al., 2009; Winkler et al., 2005), so many men with depression, and no history of repetitive neurotrauma, would appear symptomatically to have CTE (if there were established clinical diagnostic criteria for the condition).

As seen in Table 1, some of the clinical features of CTE are also core diagnostic features of depression, such as sadness, hopelessness, suicidality, and cognitive difficulties. Subjectively-experienced problems with concentration, memory, problem solving, and thinking skills are a cardinal diagnostic feature of major depressive disorder (American Psychiatric Association, 1994). Cognitive problems associated with depression are likely to significantly impair daily functioning, particularly functioning at work (Greer et al., 2010). In a study of outpatients with depression who were employed ($N = 164$), 96% endorsed difficulty with concentration and 93% reported problems with memory; these cognitive symptoms were perceived by 52% of patients to be significantly interfering with their occupational functioning (Lam et al., 2012).

Interestingly, authors of several lay and academic books suggest that men who are depressed engage in behaviors that are similar to some of the other clinical features of CTE (in Table 1 and in case descriptions in past publications), such as being irritable, angry, and aggressive—as well as engaging in risky behaviors involving sex, alcohol, drugs, and gambling (e.g., Diamond, 2005; Pollack and Levant, 1998). Researchers have also reported that anger (Busch, 2009) and irritability (Fava et al., 2010; Perlis et al., 2009) are associated with depression. Winkler et al. (2005) reported that men with depression scored significantly higher on a measure of irritability, they were more likely to overreact to minor annoyances and have anger attacks, they had lower impulse control, and they were more likely to abuse alcohol and drugs than women with depression. Based on an analysis of the National Comorbidity Survey Replication, Martin et al. (2013) noted that men reported higher rates of anger attacks/aggression, substance abuse, and risk taking compared with women. Men who engage in domestic violence often have PTSD and/or depression (Gerlock et al., 2011; Graham et al., 2012; Shorey et al., 2012). The Diagnostic and Statistical Manual of Mental Disorders-5th Edition notes that many people with depression have considerable problems with irritability (e.g., persistent anger, a tendency to respond to events with angry outbursts or blaming others, and an exaggerated sense of frustration over minor matters), and family members often notice social withdrawal or neglect of pleasurable recreational activities. In a recent large study involving sex differences in depression (Kendler and Gardner, 2014), factors related to depression in men were conduct disorder, drug abuse, childhood sexual abuse, prior history of depression, and stressful life events occurring in the past year (e.g., financial, employment, and legal).

9.1. Suicide

Suicide has recently been considered a common clinical feature of CTE (as of 2010, in the published literature). It was not considered a clinical feature in the first 80 years of writing relating to CTE. In their review of all known cases of CTE, Maroon et al. (2015) reported that all suicides have occurred after 2002, and most were former football players. At present, there are no published cross-sectional, epidemiological, or prospective studies showing a relation between contact sports, CTE, and risk of suicide. In a study of 45 retired NFL players (Casson et al., 2014), none reported a history of suicide attempts but 18% reported a lifetime history of at least mild suicidal ideation (based on information in the online supplementary tables). In a large-scale retrospective epidemiological study of retired NFL players that examined death rates associated with cardiovascular disease (Baron et al., 2012), it was noted that former NFL players were *less* likely to die by suicide than men in the general population (there were only nine reported cases of suicide between 1960 and 2007). Therefore, according to the only published epidemiological data to date, NFL players are at decreased risk, not increased risk, for completed suicide relative to the general population. In two recent reviews of the literature, it was concluded that there is insufficient scientific evidence to conclude that CTE is a risk factor for suicide (Iverson, 2014; Wortzel et al., 2013). That said, former NFL players might be at increased risk for depression (Gonzalez et al., 2010; Schwenk et al., 2007), and their rate of chronic pain and opioid use is high (Cottler et al., 2011). Depression is a well-established risk factor for suicide, but there is also evidence that patients with chronic pain are at increased risk for suicidal ideation (Ilgen et al., 2008) and for suicide (Tang and Crane, 2006). Moreover, former NFL players with depression and chronic pain are much more likely to report life stress and financial difficulty than former players without depression (Schwenk et al., 2007). Therefore, factors unrelated to CTE might place certain former athletes at increased risk for suicide.

There is a mature body of evidence suggesting that the causes of suicide are complex, multifactorial, and difficult to predict in individual cases. Childhood adversities, such as physical abuse, sexual abuse, or family violence (Bruffaerts et al., 2010); physical illnesses (Scott et al., 2010); interpersonal/family conflict (Foster, 2011); personality disorders (Arsenault-Lapierre et al., 2004); impulsivity and aggression (Gvion and Apter, 2011; McGirr and Turecki, 2007); and hopelessness (Conner et al., 2001) are risk factors for suicide. In people with alcohol problems, major interpersonal stressful life events might precipitate suicide attempts (Conner et al., 2012). In general, the rate of suicide in civilians (Sullivan et al., 2013) and the military (Armed Forces Health Surveillance Center, 2012) has increased in recent years, and suicide is also a problem that affects athletes in non-contact sports, such as cricket, baseball, power lifting, and track and field throwing events (Frith, 2001; Hundertmark, 2007; Lindqvist et al., 2013; Smith, 2011). Moreover, concern has been expressed about the rate of suicide in people from specific occupations, such as physicians (Petersen and Burnett, 2008; Schernhammer and Colditz, 2004). In adults from the general population over the age of 50, aggression (Conner et al., 2004), limited social connectedness (Fassberg et al., 2012), poor physical health (Conwell et al., 2010), and depression (Conwell et al., 2002) are associated with increased risk for suicide. TBI is also a risk factor for suicide. In a longitudinal epidemiological study of 218,300 individuals who sustained a TBI, the injury was independently related to increased risk for completed suicide, the risk was greater in those with moderate or severe TBIs compared to those with MTBIs, and those with depression or substance abuse were at the greatest risk (Fazel et al., 2014). In terms of absolute numbers, the rate of suicide was as follows: general population (0.03%), TBI and no psychiatric disorder (0.1%), TBI and a psychiatric disorder (1%), TBI and depression (1.5%), and TBI and substance abuse (1.6%).

10. New research criteria for "Traumatic Encephalopathy Syndrome" (TES)

In 2013, both Jordan (2013) and Victoroff (2013) proposed criteria for diagnosing CTE. In 2014, building upon their experience

and work at Boston University, Montenigro et al. (2014) coined a new term related to CTE, Traumatic Encephalopathy Syndrome (TES), and proposed research criteria for this syndrome. Montenigro et al. identified 202 published cases of CTE over the past 100 years, 114 were published before 1990 and 88 were published after 1990 (141 boxers, 54 American football players, 5 ice hockey players, and 2 professional wrestlers). They reviewed these cases and documented their clinical features. They estimated that 29 would have possible CTE, 90 would have probable CTE, and 83 would have definite CTE based on Jordan's criteria (Jordan, 2013).

Montenigro et al. presented research criteria for traumatic encephalopathy syndrome consisting of four proposed subtypes: (i) TES behavioral/mood variant (i.e., emotionally explosive or depressed), (ii) TES cognitive variant (based on self-report and/or collateral report and low scores on neuropsychological testing), (iii) TES mixed variant (behavioral/mood features and cognitive features), and (iv) TES dementia. The duration of the symptoms must be a minimum of 12 months. They stated that the primary source of exposure to neurotrauma, necessary to make the diagnosis of TES, is repetitive hits to the head in sports such as boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer. The person must have played the sport for a minimum of six years, with two years at the college level or higher. In the absence of exposure to a sport with repetitive blows to the head, a history of four documented mild TBIs or concussions, or two moderate/severe TBIs, is necessary. Military service members exposed to multiple blasts, and police officers who have hit their heads multiple times during door breaches, also meet their exposure criteria. To meet diagnostic criteria, patients must also have a minimum of two of the following nine "supportive features": (i) impulsivity (e.g., excessive gambling, increased or unusual sexual activity, substance abuse, or excessive shopping or unusual purchases); (ii) anxiety (e.g., anxious mood, agitation, excessive fears, obsessive behavior, or compulsive behavior; and the authors note that a formal diagnosis of anxiety disorder would meet this criterion); (iii) apathy (e.g., loss of interest in usual activities, loss of motivation, and/or reduction of voluntary, goal-directed behaviors); (iv) paranoia; (v) suicidality (thoughts or attempts); (vi) significant headache (at least one episode per month for a minimum of 6 months); (vii) motor signs (e.g., dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism); (viii) documented decline (i.e., progressive decline in functioning); or (ix) delayed onset (i.e., usually at least two years after exposure, but delayed onset is not required for diagnosis). The authors noted that TES should not be diagnosed if another neurological disorder accounts for *all* of the clinical features, but other neurological disorders can be present (e.g., frontotemporal dementia and Alzheimer's disease).

Montenigro et al. emphasize that the criteria for TES should not be used to make a clinical diagnosis or as evidence of an underlying disease; they should only be used for research. They also acknowledge that the criteria for TES will likely result in very high sensitivity at the expense of specificity. Without question, the diagnostic criteria for TES are extremely broad—virtually any man who played two or more years of football, hockey, soccer, lacrosse, wrestling, or rugby, who has depression for more than a year, will meet criteria for TES. This is because a diagnosis of depression meets criteria for a core clinical feature of TES, and having two or more of the supportive features is very common in men with depression (e.g., impulsivity, anxiety, apathy, suicidality, and headaches). Moreover, all former collegiate athletes in these sports who are diagnosed with Alzheimer's disease or frontotemporal dementia will meet criteria for TES because those two neurodegenerative diseases have overlapping diagnostic features with TES.

11. Directions for future research

There are fundamental unanswered questions about CTE. First, it has not been established scientifically that the described tau pathology in the brain, especially in small amounts, can cause depression, substance abuse, suicidality, personality changes, or cognitive impairment. Second, it is not known whether patients with chronic depression, chronic pain, problems with substance abuse, a history of anabolic steroid use, stimulants, chronic opioid medication use, heart disease, diabetes, or metabolic syndrome, singly or especially in combination, who did not play sports and have no history of repetitive neurotrauma, have tau pathology in the regions of the brain that are considered unique to CTE. It is well established that tau pathology and Aβ depositions are not unique to CTE in general, and they are found in healthy adults and adults with diverse health conditions. Research groups need to establish the extent to which the pattern of tau deposition is indeed unique to neurotrauma or repetitive neurotrauma. To our knowledge, there are no published studies involving middle-aged men with chronic depression, substance abuse problems, and other health conditions (e.g., cardiovascular disease) showing that they *do not* have similar neuropathology—so the specificity and uniqueness of the neuropathology to those with a history repetitive neurotrauma has yet to be established. Finally, it is not known whether certain genetic factors place people at increased risk for certain proteinopathies in the presence or absence of a history of repetitive neurotrauma.

Epidemiological studies on the relation between contact sports and neurodegenerative disease are needed. In a study of mortality rates in former NFL players (Lehman et al., 2012), 10 of 334 (3.0%) death certificates listed neurodegenerative disease as the underlying cause of death; this rate was three times greater than that of the general population. The total number of NFL players who had a neurodegenerative disease at the time of death was small, and the increased rate of neurodegenerative disease could have been related in part to the reduced mortality from other causes. In contrast, in a study of former high school football players (who played from 1946 to 1956), there was not an increased risk of later developing dementia, Parkinson's disease, or ALS compared with non-football-playing high school males (Savica et al., 2012). Therefore, at present, the risk for developing a neurodegenerative disease in former athletes who played football or other contact sports is unclear.

To advance research, a standardized and precise protocol for studying the neuropathology is needed (e.g., minimum sampling of brain, preferred staining methods with acceptable alternatives, reporting of results, including clinicopathologic correlations), such as what is done in AD. Controls should include clinically normal athletes and combat veterans of all ages, non-athletes and non-combat veterans of all ages, and those with a range of medical, psychiatric, neurological, and neurodegenerative conditions and diseases (Montine et al., 2012). It should also be acknowledged that extensive hemispheric sampling from front to back with whole mount, sledge microtome, free floating sections (50–100 μm) immunostained for tau (with AT8) maximizes sensitivity for detecting lesions and should be used in all cases and controls. AT8 is a clean and robust monoclonal antibody, and the accumulations are dense and insoluble with strong antigenicity, so it is essential to study heterogeneous control subjects with the same methodology—to determine specificity (and false positives). To date, no research groups have published an adequate amount of data on heterogeneous control subjects. The neuropathological criteria for CTE need to be clearly stated and the post-mortem examination methodology needs to be replicable to facilitate studying the relationship between the neuropathology and clinical characteristics.

It is increasingly apparent that some of the neuropathology that has been attributed to CTE can occur in cognitively normal

Table 2
Directions for future research.

1.	Establish clearly defined neuropathological criteria for the features believed to be unique to CTE. This work is now underway: "Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy" (www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm; Downloaded March 30, 2015).
2.	Develop a clearly defined methodology for coding and reporting the gross and microscopic features that are *not* unique to CTE.
3.	Agree on and codify regions of interest, sampling, and staining techniques.
4.	Conduct neuropathological studies of appropriate control subjects to determine if they show any of the pathological features believed to be unique to CTE. Studies of men in their 50s and 60s who have a history of chronic depression, substance abuse, and cardiovascular disease, with no known history of neurotrauma or participation in contact sports, are urgently needed.
5.	Conduct neuropathological studies on a large sample of cases with a history of neurotrauma to determine the prevalence of specific neuropathological features in a larger and more representative sample of men.
6.	Determine if the neuropathological features characteristic of CTE are present in women, and examine both the sensitivity and specificity of those features.
7.	Develop a classification system for research, for clinical features of "possible CTE." Given that the clinical features reported in the literature are diverse, nonspecific, and very similar to how depression and frontotemporal dementia manifest in men, it might not be prudent, at this point in time, to develop diagnostic criteria for "probable CTE."
8.	Conduct large clinical studies with former athletes and non-athletes to determine if a history of MTBI or repetitive non-concussive neurotrauma associated with contact sports is *independently* associated with depression, suicidality, irritability and emotional dyscontrol, or cognitive impairment after control for other factors known to be associated with these clinical symptoms.
9.	Determine if PET imaging shows a clear difference in the extent and distribution of tau in the following groups: healthy controls with no comorbidities, controls with multiple comorbidities (e.g., chronic mental health problems, substance abuse, and medical problems), adults with a remote history of one MTBI and no comorbidities, those with a history of repetitive neurotrauma and no comorbidities, and those with a history of repetitive neurotrauma and multiple comorbidities. Determine if the extent or distribution of tau is correlated with any clinical features.
10.	Research on CTE has and will elicit extraordinary media coverage, and there is a risk for public misunderstandings, iatrogenesis, or other unintended consequences. Researchers are encouraged to (i) design studies with a priori hypotheses and defined statistical analysis plans; (ii) be cautious about diverging from the analysis plan, conducting too many exploratory analyses, or being overly focused on seeking positive findings; (iii) publish findings of well-designed studies regardless of whether they are positive or negative; (iv) report findings carefully, avoid drawing conclusions that go far beyond the results of the study, and clearly delineate the limitations of the study; and (v) be cautious and circumspect when discussing research findings in the media.

individuals, and it often coexists with pathologic changes of other diseases that could account for most or all of the clinical features. Comorbidities such as AD, Lewy body disease, and cerebrovascular disease, and the nature and extent of other neuropathologic changes (e.g., TDP-43), should be documented carefully in future studies, while utilizing detailed and specific neuropathological staging (Hyman et al., 2012; Montine et al., 2012) for comorbid diseases in future studies.

In AD, it is cautioned that when a low level of AD neuropathology is present in patients with cognitive impairment, it is likely that other diseases are present and might have contributed substantially to the clinical features (Hyman et al., 2012; Montine et al., 2012). There is no reason to believe this would not also be the case for CTE. Researchers should be cautious and circumspect in their attributions of specific neuropathology to specific environmental causes and clinical features. Clinical features in AD, such as cognitive impairment, tend to be worse when in the presence of comorbidities, and it is often not possible to know at autopsy which disease process contributed substantially to the clinical features (Hyman et al., 2012; Nelson et al., 2010).

There is a need for more research on clinical features in people with a remote history of repetitive neurotrauma. The clinical features of CTE, as described in the recent literature, are so broad and nonspecific that a former athlete, veteran, or civilian with depression, substance abuse and anxiety, anger control problems and traumatic stress, mild cognitive impairment, frontotemporal dementia, or AD, singly or in combination, could be conceptualized as having CTE. As a starting point, a working definition of the clinical features of "possible CTE" is required. Directions for future research are summarized in Table 2.

12. Conclusions

CTE was originally described in boxers, most of whom presumably had long careers and many more bouts than boxers in recent decades (Roberts, 1969). The description of CTE has been expanded to include post-mortem case studies of young athletes, retired athletes, military service members, and veterans. At present, the science underlying the neuropathology, clinical features, and causal relationship between the neuropathology and clinical features in CTE is very limited, leading some authors to question whether it has been clearly established as a disease (Karantzoulis and Randolph, 2013; Randolph, 2014).

It has been asserted unequivocally that there is focally and regionally unique neuropathology caused by neurotrauma (single or repetitive), and this neuropathology, even in small amounts, causes complex changes in behavior and cognition such as depression, anger dyscontrol, suicidality, and mild cognitive impairment (Baugh et al., 2012; Gavett et al., 2011b; McKee et al., 2009; McKee et al., 2013; Omalu, 2014; Omalu et al., 2010a; Stern et al., 2013; Stern et al., 2011). As of 2013, there are now many documented cases of focal and regionally specific tau deposition. However, the mechanisms by which this tau deposition might drive or reflect progressive neurodegeneration or specific clinical features are unclear. There is an enormous and mature scientific literature on numerous biopsychosocial causes for mental health and cognitive problems in men in the general population. In contrast, there is minimal scientific evidence that supports the assertion that *small amounts* of focal or regionally-distributed tau pathology cause mental health and cognitive problems. Therefore, there are important expanded and alternative hypotheses to consider. First, repetitive neurotrauma might be associated with reductions in cerebral reserve resulting in the person being more vulnerable to an earlier expression of late-life neurodegenerative disorders (Karantzoulis and Randolph, 2013; Randolph et al., 2013; Randolph and Kirkwood, 2009). Second, small amounts of tau pathology in specific locations (e.g., depths of sulci or perivascular) might be clinically silent, and people have mental health and cognitive problems that are due to other multifactorial causes similar to what is seen in the general population of adults. Finally, the tau pathology reported to be unique to CTE contributes in a meaningful way to the development of mental health problems, personality changes, and/or cognitive difficulties. All three alternative hypotheses might be partially correct, are worthy of study, and have major clinical and societal implications.

The current state of the science does not allow us to determine the extent to which repetitive neurotrauma uniquely causes, or partially contributes to, specific clinical symptoms such as depression, personality changes, or cognitive impairment. Based on decades of research in AD and other diseases, it is apparent that early stage tau pathology is usually not considered sufficient to cause clinical symptoms or a syndrome. Moreover, retired athletes and military veterans are not immune to the medical, psychiatric, neurological,

or neurodegenerative conditions, disorders, or diseases that affect the general population. What is clear from this critical review of the literature is that the reported clinical features of CTE are very similar to the clinical features of other neurological and psychiatric conditions, especially frontotemporal dementia and depression. For example, in addition to the core diagnostic features of depression, the DSM-5 states that many people with depression have considerable problems with irritability (e.g., persistent anger, a tendency to respond to events with angry outbursts or blaming others, and an exaggerated sense of frustration over minor matters), and family members often notice social withdrawal. Martin et al. (2013) reported that men with depression have higher rates of anger attacks/aggression, substance abuse, and risk taking compared with women. Thus, the clinical features of CTE, in the absence of dementia or Parkinsonism, are very similar to the clinical features of depression in men. Therefore, if a person with a history of repetitive neurotrauma demonstrates evidence of depression, this might reflect an unrelated depression or neurodegenerative disease. Alternatively, there might be an underlying neurodegenerative disease that contributes, in a small, medium, or possibly even a large way to the depression (in a multifactorial neurobiological causal model that includes genetics, life stress, chronic pain, proinflammatory cytokines, and other factors).

The fundamental challenge is that we lack a clinical or empirical methodology for determining whether an individual's symptoms and problems are unrelated or related in a small, medium, or large way to the neuropathology of CTE versus the neuropathology associated with aging and other medical, psychiatric, neurological, and neurodegenerative diseases. Clinically silent neuropathology is widespread in normal aging. For many people neuropathological findings do not mean that they will have a clinical syndrome or even specific signs and symptoms. Neuropathological abnormalities are frequently seen in cognitively normal older adults. Simply put, an older adult might have evidence of neuropathologic change without having a syndrome, and a person with a syndrome might have diverse (not specific) neuropathology, or no structural neuropathology at all.

In summary, the aggregated human literature on CTE remains observational. There are no cross-sectional, prospective, longitudinal, or epidemiological studies that have been published to date. Therefore, when we consider the plight of former athletes, civilians, and veterans who present for clinical services with depression or evidence of dementia, it is important to be cautious and circumspect in discussing the possibility that they might have this disease. Clinicians should be aware that, at present, there are no nationally or internationally agreed upon neuropathological or clinical diagnostic criteria for CTE. Moreover, many of the case studies that have undergone detailed neuropathological examination at autopsy show macroscopic and microscopic pathology consistent with pre-clinical Alzheimer's disease, frontotemporal dementia, Lewy body disease, cerebrovascular disease, and other neurological conditions—and some of these cases have met full neuropathological criteria for one of those diseases. Therefore, a tremendous amount of research is needed to better understand if and when in the natural history there is a unique and reliable relationship between tau pathology and specific clinical symptoms—especially depression, anxiety, and suicidality.

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Conflict of interests

Grant Iverson has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to mild TBI and sport-related concussion at meetings, scientific conferences, and symposiums. He has a clinical and consulting practice in forensic neuropsychology involving individuals who have sustained mild TBIs (including professional athletes). He has received research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He has not received research support from a test publishing company in the past 3 years.

Paul McCrory is a co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several governmental organizations. He is directly employed by the National Health & Medical Research Council of Australia and is based at the Florey Institute of Neuroscience and Mental Health. He is Co-Chair of the Australian Centre for Research into Sports Injury and its Prevention (ACRISP), which is one of the International University Research Centres for Prevention of Injury and Protection of Athlete Health supported by the International Olympic Committee (IOC). He is co-chair of the International Concussion in Sport Group. He has a clinical and consulting practice in general and sports neurology. He receives book royalties from McGraw-Hill and was employed in an editorial capacity by the British Medical Journal Publishing Group from 2001 to 2008. He has been reimbursed by the government, professional scientific bodies, and sporting bodies for travel costs related to presenting research on mild TBI and sport-related concussion at meetings, scientific conferences, and symposiums. He received consultancy fees in 2010 from Axon Sports (US) for the development of educational material (which was not renewed) and has received research funding since 2001 from CogState Inc. He has not received any research funding, salary or other monies from the Australian Football League, FIFA or the National Football League. The Australian Football League funds research at the Florey Institute under a legal memorandum and Dr. McCrory does not receive any money from this industry funded research research. Dr. McCrory is a cofounder and shareholder in two biomedical companies (involved in eHealth and Compression garment technologies) but does not hold any individual shares in any company related to concussion or brain injury assessment or technology. He did not receive any form of financial support directly related to this manuscript.

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