TRAUMATIC BRAIN INJURY CENTER OF EXCELLENCE

RESEARCH REVIEW ON CHRONIC TRAUMATIC ENCEPHALOPATHY

PURPOSE

The purpose of this Research Review is to summarize current peer-reviewed scientific literature and expert assessment regarding the pathology, genetic pre-disposition, causes, clinical manifestations, and neuroimaging of chronic traumatic encephalopathy (CTE). Updates from the Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy (2021) and the 2019 First National Institute of Neurological Disorders and Stroke Consensus Workshop to Define the Diagnostic Criteria for Traumatic Encephalopathy Syndrome (TES) are included. Gaps and discrepancies in our understanding of CTE are discussed.

BACKGROUND

CTE is a progressive neurodegenerative disease pathologically distinct from other neurodegenerative diseases, including frontotemporal dementia and Alzheimer's disease (AD). There currently is no clinical, antemortem diagnostic profile for CTE, and the definitive diagnosis is based on a specific histopathologic pattern of phosphorylated tau (p-tau) protein deposition in the brain that can only be observed at autopsy. The cause of CTE has been attributed to repetitive head trauma, though not specifically repetitive traumatic brain injury. The clinical manifestations of a dementia-like syndrome, often accompanied by Parkinsonian and cerebellar motor signs, was first described nearly 100 years ago in former boxers (Martland, 1928). Initially called "punch drunk" syndrome (Martland, 1928), the presenting cognitive symptoms included slowed thinking, confusion, and short-term memory impairment. This syndrome was later called "dementia pugilistica" until the phrase "chronic traumatic encephalopathy" was coined in 1949 (Critchley, 1957). The onset of the clinical symptoms was noted to occur in middle age, a mean of 16 years after discontinuation of boxing, but disease progression was variable (Critchley, 1957). One early study on the prevalence of CTE among ex- professional boxers (n = 224) found that 17% had neurological symptoms consistent with the syndrome, and sub-syndromal cognitive impairment was apparent in 50% of these former

athletes (Roberts, 1969). Postmortem cerebral histopathologic studies were not available for these boxers, so it was not possible to correlate the clinical signs and symptoms with brain pathology. It was not until CTE pathology was described in a former professional American football player in 2005 that there was a concerted effort to investigate the pathology and clinical manifestations of CTE (Omalu et al., 2005; Smith et al., 2019). The findings from that study led to a sharp increase in the number of publications about CTE, particularly from the Boston University CTE Center, that postulated a link between multiple concussions and the histopathology of CTE (Eagle & Okonkwo, 2023). To be sure, that link has not been proven. There currently is a disproportionate dissemination and consumption of scientific research and popular media that support a relationship between CTE, contact sports, and military service, despite the lack of empirical findings to confirm causality (Eagle & Okonkwo, 2023; Ott et al., 2022; Wolfson et al., 2020). Given the variable CTE definitions as described below and ongoing efforts to define and reach consensus on postmortem CTE pathology, the term CTE in this review refers to the condition of interest, whether it is clinically presumed or histopathologically confirmed CTE using the most recent Consensus criteria, and, when possible, the terminology used by the article referenced is maintained.

INFORMATION

Pathology

The earliest known description of the gross pathologic manifestations of CTE are those described from studies of deceased boxers and align under the "Classic" CTE definition to include reduced brain weight, cavum septum pellucidum, enlargement of the ventricles, and thinning of the corpus callosum (Corsellis et al., 1973). The most striking neuropathological feature of CTE based on the more "Modern" CTE definition is the presence of neurofibrillary tangles (NFTs) composed of p-tau protein, which appear similar to NFTs found in AD but with specific differences in the neuroanatomical localization (Hof et al., 1992; Shively et al., 2012). Two large case series from the primary CTE labs in the United States (Dr. Ann McKee at Boston University and Dr. Bennet Omalu at University of California Davis) have demonstrated similar NFT neuropathology among the brains of former National Football League (NFL) players and other professional athletes with a history of repetitive mild TBI. The brains included in those case series were from individuals who either a) developed dementia and other clinical manifestations of suspected CTE prior to death in middle age, or b) died (many via suicide) after displaying some of the cognitive features of suspected CTE prior to the development of dementia (McKee et al., 2009; Omalu, Bailes, et al., 2011). While both labs recognize the presence of NFTs consisting of p-tau, the criteria used by each lab remain different. The Omalu lab identified 4 phenotypes, differentiated mainly by the frequency and location of NFTs and neuritic threads: 1) combination of sparse to frequent neuritic threads and NFTs in the cerebral cortex and brainstem without diffuse amyloid plaques in the cerebral cortex; 2) combination of sparse to frequent neuritic threads and NFTs in the cerebral cortex and brainstem with sparse to frequent diffuse amyloid plaques in the cerebral cortex; 3) combination of moderate to frequent neuritic threads and NFTs in the brainstem nuclei without diffuse amyloid plaques in the cerebral cortex; and 4) combination of none to sparse neuritic threads and NFTs in the cerebral cortex, brainstem, and subcortical nuclei without diffuse amyloid plaques in the cerebral cortex (Omalu, Bailes, et al., 2011). Alternatively, the McKee lab has used the following criteria to define CTE: 1) perivascular foci of p-tau immunoreactive

astrocytic tangles and NFTs; 2) irregular cortical distribution of p-tau positive astrocytic and neurofibrillary tangles with a localization to the depths of cerebral sulci; 3) astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem; and 4) NFTs in superficial layers of the cerebral cortex (McKee et al., 2013). Additionally, the McKee lab recognizes a progressive pathology from very mild (Stage I) to severe (Stage IV) (McKee et al., 2013). While these two primary investigators differ in histopathological definitions, both definitions offer greater specificity in presentation (i.e., phenotypes and stages) that is not present in the Classic CTE definition. However, neither Classic nor Modern approaches include criteria specific to clinical and behavioral manifestations associated with the observed pathology.

Given these prominent but discrepant histopathological definitions of CTE, a consensus conference sponsored by the National Institutes of Neurological Disorders and Stroke (NINDS), the Department of Defense, and the Department of Veterans Affairs was held in Boston in December 2015 to produce diagnostic criteria for CTE (McKee et al., 2016). This small group of 11 neuropathologists, neurologists, and TBI experts agreed that CTE should be defined as "…p- tau aggregates in neurons, astrocytes, and cell processes around small blood vessels in an irregular pattern at the depths of the cortical sulci"(McKee et al., 2016). Supportive criteria, defined as non-diagnostic in isolation, were identified related to p-tau pathology and provided details regarding the frequency, location, and form of p-tau aggregates. Two of the seven supportive criteria were unrelated to tau, where one specified macroscopic anatomical features and the other described inclusions and structures containing trans-activator regulatory DNA-binding protein 43 (TDP-43). While these supportive criteria were identified, consensus was only reached on the single criterion detailed above. Additionally, three non-diagnostic, non-supportive criteria were also identified and describe age-related p-tau pathology (ARTAG). Despite the description of four separate phenotypes from the Omalu lab (Omalu, Bailes, et al., 2011) and the description of four stages of CTE pathology based on severity and clinical manifestation by the McKee lab (McKee et al., 2015; McKee et al., 2013), neither classification system was supported and incorporated at the consensus conference. In 2021, the NINDS panel further refined the diagnostic criteria for CTE, evaluated criteria for a minimum diagnostic threshold, and determined the appropriateness of a staging scheme for CTE pathology (Bieniek et al., 2021). The panel upheld the minimum threshold for CTE diagnosis as "p-tau aggregates in neurons, with or without thorn-shaped astrocytes, at the depth of a cortical sulcus around a small blood vessel, deep in the parenchyma, and not restricted to the subpial and superficial region of the sulcus". Other supportive, but non-diagnostic tau and non-tau neuropathologies, were further identified. When applying the McKee progressive staging scheme to each case suspected of CTE (McKee et al., 2013), there was no unanimous consensus among the panel in its applicability to CTE diagnosis. Therefore, a provisional binary staging scheme to classify CTE case severity as "High CTE" or "Low CTE" was proposed. Using this framework, a "high" CTE stage case must show the defined and previously described pathognomonic lesion and present with five or more NFTs in multiple brain regions. A "low" CTE case is considered to have less than 5 NFTs. Since this framework proposal, studies have demonstrated its usefulness in classifying CTE cases to analyze early and late-stage effects of CTE (Babcock et al., 2022; Butler et al., 2022). Yet, others find the 2014 criteria valid and have elected to continue to use it in research (Alosco et al., 2020; Atherton et al., 2022; Mez et al., 2021; Turk et al., 2022). Diagnostic criteria continue to be discussed and refined as evidence guides.

Tau protein deposition is well known to be associated with other neurodegenerative

diseases and dementias, particularly frontotemporal dementia and Alzheimer's disease (AD). At a 2012 NINDS workshop on CTE neuropathology, it was noted that "none of the individual pathologic features (such as tau pathology) are unique to CTE, but what confers uniqueness in CTE cases is the peculiar distribution within the brain"(National Institutes of Neurological Disorders and Stroke, 2013). The processing of tau in CTE has been show to result in a molecule that is structurally different from tau present in AD (Cherry, Esnault, et al., 2021; Falcon et al., 2019), a finding which may have significant implications for attempts at antemortem diagnosis using positron emission tomography (PET) imaging techniques and tau sensitive ligands. Under non-pathological conditions, the protein tau normally regulates microtubule stability in neurons. Repetitive mild TBI is thought to result in abnormal neuronal processing of tau protein, which contributes to neuropathology such as the wide-spread deposition of cortical tau NFTs consistently observed in the brains of autopsied individuals presenting with clinical symptoms prior to death (Cherry, Babcock, et al., 2020; McKee et al., 2009). Neuroinflammation may also play a role in the development of CTE because activated microglia can contribute to p-tau deposition (Albayram et al., 2020; Makinde et al., 2017); TBI is known to induce neuroinflammation (Das et al., 2012), and inflammatory changes may persist for years post-injury in cases of moderate and severe TBI (Smith et al., 2013). A neuropathological study by Cherry et al. (2016) examined inflammatory markers in the brains of deceased individuals with CTE (n = 48), individuals with head impact history but no CTE (n = 18), and individuals without repetitive head impact (n = 16). Results showed that chronic activation of microglia is associated with both repetitive head impact and p-tau pathology. Likewise, Cherry et al. (2020) explored the role of microglia chemokine CCL2 in the brains of deceased individuals with CTE, AD, and those with no neurodegenerative disease or repetitive head injury exposure (N=261). CCL2 is produced by central nervous system cells commonly associated with repetitive head injury and CTE. Analysis indicated that for those with repetitive head injury exposure, microglia were the primary cell type around perivascular tau, and CCL2 levels increased with years of football played, the density of microglia, and CTE severity (Cherry, Meng, et al., 2020).

While tau processing may be associated with specific pathological conditions, primary age-related tauopathy (PART) is also of relevance in the discussion of CTE. In aged populations, NFTs analogous to those seen with AD but without the co-occurring amyloid plaques have been observed nearly universally postmortem (Crary et al., 2014). Recent research revealed differential p-tau burden in hippocampal regions among individuals with CTE and PART (Farrell et al., 2022). ARTAG has also been discussed related to and overlapping with CTE pathology (Forrest et al., 2019). A study of 310 autopsy cases from an aged (76-91 years) European community-based population identified no cases meeting the 2016 NINDS CTE criteria, yet ARTAG was identified in 117 cases, supporting the more common age-related proteinopathy over more rare CTE pathology (Forrest et al., 2019). A more recent study of 150 autopsy cases of adults, 21-80 years old prior to death, confirmed earlier findings that ARTAG is primarily age related and not due to repetitive head injury (Butler et al., 2022), which is consistent with recent 2021 NINDS/NIBIB consensus criteria. An Australian based brain-bank study found a low prevalence of CTE among 636 cases (0.79%) and suggested that TBI and neuropathologic changes are more likely related to increased brain aging and evidence of ARTAG, rather than CTE (McCann et al., 2022). Future studies should continue to define the clinical and pathological boundaries between PART and ARTAG from other neurodegenerative and tauopathy conditions to prevent

misdiagnosis of pathological conditions based on a ubiquitous aging phenomenon.

With the aim to diagnose CTE pathology antemortem or monitor cases of potential CTE, cerebrospinal fluid (CSF) and blood-based biomarkers have been examined in patients with a TBI history. Studies of CSF neurodegenerative biomarkers such as tau in patients with confirmed CTE have not yet been reported. However, elevated levels of tau in CSF and plasma may be associated with the accumulation of tau-reactive NFTs based on evidence from AD populations, which find that CSF p-tau concentrations appear to be a more specific marker of earlier neurodegenerative processes (Bergauer et al., 2022; Buerger et al., 2005; Hansson et al., 2006). Patients with severe TBI have transient elevations in CSF tau, which have been shown to correlate with clinical outcomes at one year post-injury (Ost et al., 2006). Olivera et al. (2015) reported on plasma tau levels measured in deployed military personnel with varied TBI status (Olivera et al., 2015). Tau levels were significantly higher in a) those reporting TBI as compared to those not reporting TBI, b) those with a medical record of TBI as compared to those with self-reported TBI, and c) those reporting three or more TBIs as compared to those reporting only one or two. Similarly, Pattinson et al. (2020) found that plasma tau concentrations were significantly elevated and correlated to symptom severity in veterans with TBI (Pattinson et al., 2020). Recently, Turk et al. (2022) found variable differences in CSF tau and amyloid beta (Aβ) between individuals with CTE compared to those with diagnosed AD and those without CTE or AD, suggesting that CSF tau measures may be able to differentiate between these neuropathological conditions (Turk et al., 2022). Alternatively, in a cohort of retired NFL players, there were no significant differences in CSF levels of total tau, p-tau, the ratio of p-tau to total tau, (Aβ), or a measure of microglial activation when compared with age-matched controls (Alosco, Tripodis, et al., 2018). However, greater repetitive head impacts in former players did correlate with elevated total tau levels, and this relationship was observed to be mediated by increased microglial activation. A number of studies have quantified fluid biomarker levels in populations with repetitive head impacts, independent of mTBI (Alosco, Mez, et al., 2018; Ge et al., 2022; Neselius et al., 2012; Neselius et al., 2013; Oliver et al., 2018; Oliver et al., 2016; Zetterberg et al., 2006), but further research on biomarkers of repetitive head impacts, longitudinal changes of these biomarkers, and markers of early neurodegenerative changes is necessary to advance the field of fluid biomarkers of CTE. In 2015, the Boston University CTE Center was awarded a multi-year grant from the NINDS to fund the research project "Diagnose, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE)". An objective of this project is to identify *in vivo* fluid and neuroimaging biomarkers for CTE (Alosco et al., 2021). This study is ongoing.

Genetic Pre-disposition

Multiple genes have been investigated for their potential role in mediating CTE pathology or symptomatology. Implicated in AD, the apolipoprotein E (*APOE*) gene, specifically the Ɛ4 allele, has also been investigated in relation to both TBI and CTE (Deng et al., 2018). More directly associated with CTE, *APOE*Ɛ4, specifically the Ɛ4 homozygote, has been reported to be overrepresented in a sample of neuropathologically confirmed CTE cases when compared to population norms (Stern et al., 2013). A recent study by Artherton et al. investigated the association between *APOE*Ɛ4 and CTE neuropathology in 364 brain donors with a history of head injury and only found a significant association between *APOE*Ɛ4 status

and CTE stage for those 65 years of age or older (Atherton et al., 2022). At the University of Toronto, investigators noted a relationship between the presence of *APOE*Ɛ4 and increased tau burden via increased uptake of the PET tau tracer, [F-18]AV-1451 (Vasilevskaya et al., 2020). Another gene under consideration for its known association with neuroinflammation and TDP-43 pathology is transmembrane protein 106b (*TMEM106B*). Exploratory genetic analysis by Bieniek et al. (2015) revealed a lower proportion of minor allele homozygotes with CTE compared to those without CTE pathology (Bieniek et al., 2015). Cherry et al. (2018) examined participants included in the Veterans Affairs-Boston University-Concussion Legacy Foundation Brain Bank who were Caucasian, had a history of playing American football, and had diagnosed CTE without significant co-morbid pathology. The presence of the *TMEM106B* minor allele, in a dose-dependent manner, was associated with lower p-tau, reduced neuroinflammation, higher synaptic density, and reduced odds of antemortem dementia (Cherry et al., 2018). Cherry et al. (2021) built on the previous work to investigate the genetic changes in the cortical sulcus vs. gyral crest. The majority of alterations in both regions was due to genes related to immune and inflammatory responses. Further, gene set enrichment analysis showed a significant decrease of immune and phagocytic biological processes for individuals with CTE (Cherry, Agus, et al., 2021). Despite recent research, there is still no clear distinction between the role of genetics in the development of CTE vs other neuropathological conditions. Therefore, more studies on the pathogenetic mechanisms behind the development of CTE are needed.

Causes of CTE

The cause or causes of CTE remain controversial. An association between CTE and brain trauma is assumed based largely on the fact that most known cases of CTE occurred in individuals with a history of head trauma, especially contact-sports athletes who had repetitive head trauma (Baugh et al., 2014; Bieniek et al., 2020; Erlanger et al., 1999). Research teams led by Dr. Ann McKee have reported on a convenience sample where 177 (87%) of 202 deceased American football players were diagnosed with CTE based on neuropathological findings, many of whom had significant behavioral and cognitive problems prior to death (Mez et al., 2017). It has been estimated that football players at certain positions, such as the offensive line, may sustain as many as 1,444 head impacts in a single season (Crisco et al., 2010). Lehman et al. (2012) reported that professional American football players exposed to high velocity injuries (e.g., non-linemen) had up to four times the rate of death from neurodegenerative diseases as the general population in the U.S. (Lehman et al., 2012). Relatedly, Zimmerman et al. (2021) observed that professional American football players exposed to high magnitude forces, but low frequencies (e.g., wide receiver, defensive back) had higher strain rates in sulci (Zimmerman et al., 2021), suggesting increased neurological risk with higher severities of head trauma. Mez et al. has described differential CTE findings associated with the level or length of play. Where mild CTE pathology was more often observed among former high school and college players, severe CTE pathology was found more often among semi-professional and professional football players, independent of position played (Mez et al., 2019, 2020; Mez et al., 2017). Yet, Schwab et al. (2021) found no association between position played and presence of CTE in 35 former professional and college level football and hockey players, 17 of which had pathologic evidence of CTE based on the 2015 consensus criteria (McKee et al., 2016; Schwab et al., 2021).

It remains unclear, however, how common the pathologic features of CTE are in those who are not athletes because there are no age-matched, non-athlete control subjects included in the largest case series. Those reports are convenience samples of individuals, mostly former contact sport athletes, identified by their families to have neurological abnormalities prior to death and who donated their brain to research. As a result, the reports suffer from a significant selection bias (Kelly et al., 2022; McKee et al., 2009; Mez et al., 2017). To date, a definitive cause-effect relationship between the degree of CTE pathology and history of brain trauma has not been demonstrated (Harmon et al., 2019; McCrory et al., 2013), despite recent suggestions of a causal relationship between repetitive head injury and CTE (Nowinski et al., 2022). Moreover, not all deceased individuals with a history of concussive or subconcussive head trauma have been found to have neuropathological features of CTE (Hazrati et al., 2013; Omalu, Bailes, et al., 2011; Stern et al., 2011). Alternatively, CTE neuropathology has been reported in persons with no subconcussive or repetitive concussive history (Bieniek et al., 2020; Iverson et al., 2019). These reports emphasize the fact that the largest and most publicized case reports of CTE are "convenience samples" with severe selection bias, and comparisons of individuals with CTE to appropriate control subjects have not been reported.

Military service members are another population that may sustain repeated head trauma and consequently remain a population of interest for ongoing CTE research. Specifically, blast exposure may be a risk factor for developing CTE (Goldstein et al., 2012; McKee & Robinson, 2014; Omalu, Hammers, et al., 2011). A recent study in a small sample of younger veterans (n = 16; mean age 35.2 years) revealed *in vivo* tau deposition on PET imaging associated with blast trauma, but not with blunt trauma or with the duration of TBI symptoms (Robinson et al., 2019). Case studies have confirmed postmortem CTE pathology in blast exposed veterans from the Iraq and Afghanistan conflicts, with blast exposed cases showing deposition of p-tau protein similar to that seen in non-blast CTE cases (Goldstein et al., 2012; Omalu, Hammers, et al., 2011). Conversely, a case series comparing cases of chronic blast exposure, acute blast exposure, chronic impact TBI, opiate exposure, and controls without known neurological disorder revealed that astroglial scarring was present in a novel neuroanatomical pattern to include tissues next to the ventricles, gray-white matter boundaries, and penetrating cortical blood vessels in only those cases with blast exposure (chronic and acute) but not chronic, blunt TBI or opiate use (Shively et al., 2016). Contrary to the previous research that focused on single TBI events, a case-control study compared brain tissue of military veterans, with a history of blast exposure with or without CTE, former American football players with a history of repetitive head injury with or without CTE, and a group of controls and found increased astrogliosis at the grey-white mater boundaries for both blast and repetitive head injury subjects, regardless of CTE status (Babcock et al., 2022).

However, just as with studies of CTE in athletes, these case studies of blast-exposed veterans suffer from selection bias since the majority of tissue samples are from select tissue repositories and come from individuals who died prematurely from suicide or drug overdose (Goldstein et al., 2012; Omalu, Hammers, et al., 2011; Priemer et al., 2022; Shively et al., 2016). Outside of blast exposure, military service alone may not be a risk factor for CTE. Tripathy et al. (2019) found no observable CTE-specific pathology in older (68.9±16 years) veterans compared to age-matched controls (Tripathy et al., 2019). There are other reports of veterans who have postmortem CTE findings, but these individuals also were athletes prior to military service and may have been exposed to repeated blunt impacts earlier in life (perhaps

in addition to Service-related exposures), thereby casting doubt on causal inferences (McKee et al., 2013; Priemer et al., 2022; Reid & Velez, 2015). With these discrepant findings, it is prudent to identify what other factors may put individuals at risk for CTE. Almost all confirmed CTE cases have been in males and an association with sex has not been studied. Medical risk factors such as PTSD, depression, anxiety, individual genetics, and family history remain unclear. Environmental factors such as alcohol and drug use and abuse, socioeconomic status, and others have not been sufficiently explored. Continued research using larger samples sizes without selection bias is warranted to further elucidate factors related to CTE pathology and severity.

Clinical Manifestations

There are no pathognomonic clinical manifestations of CTE, and the diagnosis can only be confirmed by postmortem examination (Harmon et al., 2019; Shively et al., 2021). However, reports of antemortem symptoms provided by the relatives of deceased individuals and reviews of medical records suggest that CTE may be associated with a variety of behavioral, emotional, cognitive, and neurologic symptoms (Lenihan & Jordan, 2015; Shively et al., 2021). Behavioral and emotional symptoms most commonly described include mood swings (Gardner et al., 2015), disinhibition, paranoia, irritability, violent outbursts (Lenihan & Jordan, 2015), and impulsiveness (Banks et al., 2014; D'Ascanio et al., 2018). Cognitive symptoms include episodes of confusion (Gardner et al., 2015), decreased attention and concentration (Lakhan & Kirchgessner, 2012), memory impairment, executive dysfunction, language impairment, and visuospatial difficulties (Albayram et al., 2020; Mendez, 1995). Neurologic symptoms include tremor (Gardner et al., 2015), dysarthria, mild imbalance, and gait or limb ataxia, spasticity, and parkinsonism (Mendez, 1995). These symptoms derive in part from studies of probable CTE cases in boxers and football players with a history of repeated TBI.

However, neuropsychiatric manifestations that have been attributed to CTE cannot currently be delineated from, and can be caused by, numerous medical and psychiatric conditions (Hanlon et al., 2017; LoBue et al., 2020; Shively et al., 2021). As a result, the diagnosis of clinical CTE and symptom attribution to pathology present challenges for clinicians and researchers. One case series showed that 25 of 68 confirmed CTE patients also had motor neuron disease, AD, Lewy body disease, or frontotemporal lobar degeneration (McKee et al., 2013), thereby complicating attribution of clinical symptoms to CTE pathology or other pathology. Given these challenges, four separate groups of investigators have developed distinct research diagnostic criteria for probable CTE in living persons. (Jordan, 2013; Montenigro et al., 2014; Reams et al., 2016; Victoroff, 2013), each with varying degrees of agreement between diagnostic requirements and supportive features. Studies of probable and confirmed CTE cases have identified different phenotypes (cognitive subtype vs behavior/mood subtype) potentially related to a complex long-term progression, but these studies do not agree on the earliest symptoms of CTE (Gardner et al., 2015; McKee et al., 2013; Stern et al., 2013). Other researchers have examined several specific symptoms attributed to probable CTE cases, including impulsiveness, cognitive impairment, and suicidality (Banks et al., 2014; Iverson, 2014; Randolph et al., 2013; Seichepine et al., 2013; Wortzel et al., 2013). However, the link between postmortem pathology and antemortem

symptomatology currently remains weak and insufficient for clinical use (Randolph, 2018).

Due to discordance between previously proposed criteria, with varying degrees of sensitivity and specificity for the diagnosis of Traumatic Encephalopathy Syndrome (TES) (Laffey et al., 2018), a more standardized set of criteria based on extensive peer-reviewed evidence was required. In response, an NINDS Consensus Workshop to Define the Diagnostic Criteria for Traumatic Encephalopathy Syndrome was held in April 2019. The goal of the conference was 2-fold – 1) enhance specificity of previously published TES diagnostic criteria and 2) create a diagnostic structure that facilitates amenability as research evolves. Twenty expert panelists examined clinicopathologic data and pre-morbid clinical data from 298 brain donors and through a modified Delphi process, came to consensus for most recent diagnostic criteria for TES – (1) substantial exposure to repetitive head injury, (2) core clinical features of cognitive impairment and/or neurobehavioral dysregulation (reported by self, informant, or by clinicians report), representing a significant decline from baseline functioning, with deficits in episodic memory and/or executive functioning, sustained by impaired performance on formal neuropsychological testing, with symptoms and/or observed behaviors representing poor regulation or control of emotions and/or behavior. (3) evidence of progressive worsening of clinical features over a period of at least 1 year without continued exposure to repetitive head injury or TBI, and (4) clinical features are not accounted for by another condition (Katz et al., 2021). None of the features of the 2014 TES diagnostic criteria were retained (Montenigro et al., 2014) and while considered, the state of the science for diagnostic biomarkers was considered premature for inclusion in the framework. A group of researchers have since called for the revision of TES diagnostic criteria, noting that as it currently stands, the NINDS criteria frames TES to be exclusively associated with CTE, rather than CTE being a subtype of TES. They further state that the criteria excludes symptomatic patients from a TES diagnosis, further limiting epidemiological studies, clinical treatment, and prevention research (Omalu & Hammers, 2021).

Despite the goal of the new framework to improve sensitivity of TES diagnosis, the application of the criteria may still result in reports of low prevalence (Casson & Viano, 2022) and specificity (Iverson & Gardner, 2020b, 2021). Additionally, there are varying degrees of agreement in the literature on how sensitive the TES criteria are in identifying individuals with neuropathological measures of probable CTE. Few studies fully support TES criteria as is. Ritter et al. (2022) analyzed and compared MRI characteristics to determine if those that met TES criteria displayed differentiation in MRI regional brain volumes, cognitive domains, and plasma biomarkers (Ritter et al., 2022). Researchers concluded that the application of TES criteria can differentiate those with different regional brain volumes, given the criteria for repetitive head impacts (RHI), however, validity of the research should continue to be explored. Multiple studies have demonstrated its shortcoming for specificity and clinical utility. In a study assessing the frequency of TES in 85 retired professional contact sport athletes, 56% met TES criteria, despite half of TES positive subjects being classified as "cognitively normal" (Schaffert et al., 2021). Comparably, a convenience sample of 409 men (ages 35-55 years) were surveyed on a variety of demographic, concussion, sport, and medical history characteristics to determine prevalence of probable TES. 56.2% of the sample met criteria for TES diagnosis. In addition, exposure to contact sports neurotrauma were not predictors of TES diagnosis, whereas age, chronic pain, and sleep difficulties were (Iverson et al., 2021). Behavioral diagnostic criteria (i.e. anger, alcohol and drug abuse, irritability,

suicidal ideation) for TES are broad and common in the US population (Hazrati & Schwab, 2021). Exposure to head injury from athletics or military service and a subsequent display of behavioral symptoms is not specific enough to rule out other conditions and can lead to misdiagnosis of TES (Iverson & Gardner, 2020a). A recent report on a clinicopathological series evaluating the recent 2019 TES criteria included nine individuals who had a history of repetitive head injury and underwent antemortem neuropsychological evaluations and neuropathological imaging. Six patients exhibited characteristics that met TES diagnostic criteria. Yet, while 5 of the 9 patients in the study exhibited some CTE pathology, that pathology was considered the primary cause for their pre-morbid clinical symptoms in only 2 cases. Despite a display of symptoms, 3 patients did not meet TES diagnostic criteria due to unknown head exposure. Researchers concluded that alone, the 2019 TES criteria may not be sufficient or sensitive enough to rule out other comorbidities (Asken, Tanner, VandeVrede, Casaletto, et al., 2022). Future research, specifically prospective cohort studies, are needed to refine TES diagnostic criteria and determine their validity and clinical utility.

Neuroimaging

Imaging techniques, such as PET and magnet resonance imaging (MRI), hold the most promise for the *in vivo* diagnosis of CTE (Asken & Rabinovici, 2021; Ayubcha et al., 2021; Bazarian et al., 2014; Ng et al., 2015; Pierre et al., 2021; Sharp et al., 2014). Yet, there is lack of correlation between PET findings and pathognomonic NINDS criteria for CTE. Current NINDS criteria for CTE diagnosis post-mortem requires p-tau aggregates at the depth of the cortical sulcus (Bieniek et al., 2021). However, some studies report suspected CTE cases with tau in subcortical regions. Brain tau deposits were examined in 5 retired NFL players (age 45-73 years) using FDDNP as a PET radioligand sensitive to tau (Small et al., 2013). FDDNP signals were higher in players compared with age-matched controls in all subcortical regions studied, including the amygdala. A second study by this group used FDDNP PET to examine tau deposition among suspected CTE cases (n = 14), controls (n = 28), and Alzheimer's dementia patients (n = 24) (Barrio et al., 2015). They found patterns of white matter neuropathology in the suspected CTE cases in brain regions related to the processing of emotions, mood, and behavior, and these patterns were distinct from those in the Alzheimer's dementia cases or controls. Similarly, Chen et al. (2018) examined tau deposition in military personnel (n = 7) and retired NFL players (n = 15) each with a history of mild TBI and cognitive/mood symptoms, AD patients (n = 24), and controls (n = 28) (Chen et al., 2018). Tau deposition was similar among military personnel and retired NFL players, and both groups had different tau deposition patterns than AD or control individuals. In a single player with a 22-year history of American football, a significant correlation between antemortem FDDNP PET binding and post-mortem neuropathological evidence of tau pathology that met several diagnostic criteria for CTE was reported, suggesting that FDDNP is a valid PET ligand for the detection of tau (Omalu et al., 2018).

Stern et al. (2019) utilized a different PET ligand, flortaucipir, to measure tau levels in the brains of 26 former NFL players who had cognitive, mood, or behavioral symptoms, and compared them to 32 age-matched controls with no TBI history (Stern et al., 2019). Compared with the controls, tau deposition was inferred in the former players in 3 brain regions traditionally affected by CTE: bilateral superior frontal, bilateral medial temporal, and left parietal. However, while former players reported cognitive, mood, or behavioral dysfunction,

tau deposition was not correlated with objective neurocognitive or neuropsychiatric measures (Stern et al., 2019). Dickstein et al. (2021) reported similar findings in which symptomatic Veterans exposed to improvised explosive device blasts exhibited increased retention of [18F]-AV-1451 [flortaucipir] in the frontal, parietal, and temporal regions (Dickstein et al., 2021). More recently, Alosco et al. utilized florataucipir and MRI to analyze the association of antemortem ligand uptake and post-mortem tau neuropathology in former professional (N=3) and college level (N=3) American football players (Alosco et al., 2022), all of whom are a part of the ongoing DIAGNOSE CTE Research Project (Alosco et al., 2021). An association between antemortem flortaucipir uptake and post-mortem p-tau density in the cortical, limbic, and thalamic regions was observed, but the specificity of florataucipir to p-tau was uncertain. In light of the evidence from Falcon et al. (2019) on the structural difference between CTE tau and AD tau, it is possible that the PET tau ligands, developed by the AD scientific community and utilized in studies on CTE, are not specific to the unique structural conformation of CTE tau (Falcon et al., 2019). This is supported by Marquie et al. (2019) which noted "…[18F]-AV-1451 [flortaucipir] may not have sufficient sensitivity to reliably detect and quantify tau pathology in CTE by in vivo neuroimaging, particularly when confounding AD lesions are present in the context of aging" (Marquie et al., 2019). This finding was further reinforced by work from Asken et al. who noted that plasma tau may be elevated in TES patients when AD pathology is present. However, [18F flortaucipir] may not be sensitive enough to detect CTE pathology burden (Asken, Tanner, VandeVrede, Mantyh, et al., 2022). While PET imaging holds promise for the antemortem diagnosis of CTE, precise development of ligands unique to the structural conformation of CTE tau is required (Bergauer et al., 2022; Huang et al., 2022)

Microstructural damage and supportive features of CTE can be detected with diffusion tensor imaging (DTI). Stamm et al. (2015) used DTI to evaluate the white matter of 40 retired NFL players (Stamm et al., 2015). Those who had their first exposure to tackle football before the age of 12 years had DTI findings in the corpus callosum indicative of white matter damage, and this was observed more often than in the group first exposed to tackle football after the age of 12 years. Clinically, age at exposure to tackle football also was found to be significant in a study of 211 brain donors with CTE, 126 without comorbid neurodegenerative disease, in which exposure to tackle football before the age of 12 was associated with earlier onset of cognitive and mood symptoms (Alosco, Mez, et al., 2018). Holleran et al. (2017) examined tissue samples from 10 confirmed CTE cases using DTI and found that fractional anisotropy, an indicator of axonal disruption, was negatively correlated with tau pathology. Specifically, increased tau deposition was associated with decreased fractional anisotropy, suggesting a correlation of tau deposition with white matter injury (Holleran et al., 2017). Kochsiek et al. (2021) utilized diffusion (dMRI) to measure the associations of repetitive head injury exposure to corpus callosum microstructure and total plasma tau in 75 former professional American football players. Increased axial diffusion and total plasma tau were positively correlated in this study with increased repetitive head injury. Further, increased axial diffusion, fractional anisotropy, and radial diffusion correlated with enhanced cognitive performance (Kochsiek et al., 2021). Specifically relevant to the military community, DTI may be a useful tool for understanding blast-related CTE mechanisms given observed differences in axonal injury following blast exposure vs. civilian head injury (Lindberg et al., 2022; Moyron et al., 2021).

SUMMARY

Despite the numerous clinical and preclinical studies reviewed in this paper, there remain critical gaps and considerable disagreement within the scientific community regarding the causes of CTE, association of clinical manifestations with brain pathology, prognosis, and treatment options. To date, no controlled epidemiological studies exist to establish an increased risk for CTE in former athletes (Randolph, 2014). In cases of co-occurring diagnosed CTE and another neurodegenerative disease, current practice often entails characterizing the case as CTE rather than the alternative disease, a practice that may be inappropriate for many cases if the alternate condition is the primary neuropathology (Iverson et al., 2018). In fact, it is common to have cases identified as CTE co-presenting with another proteinopathy (Ling et al., 2017; LoBue et al., 2020; McKee et al., 2015; McKee et al., 2013; Shively et al., 2021) and further research should work to more accurately categorize tissue samples with multiple patterns of protein deposition. Age-related protein deposition (i.e., PART and ARTAG) does not inherently indicate a pathological state (Crary et al., 2014; Forrest et al., 2019; McCann et al., 2022; Randolph, 2014, 2018). Additionally, there are multiple isoforms of tau in the brain and the accumulation of some types of p-tau (e.g., trans tau) may be innocuous (Randolph, 2014). Furthermore, the progressive nature of the observed pathology has not been confirmed, and the kinetics of tau specific to CTE require further research (Iverson et al., 2018). Future studies with a large number of control subjects are required to differentiate this histological relevance of p-tau and NFTs in the brains of those with and without a history of head trauma, other neurological disorders, and the effect of age as well as other demographic and medical risk factors. While current post-mortem diagnostic criteria are based on the presence of p-tau related pathology, the clinical relevancy of p-tau and NFT pathology to symptomology and behavioral presentation is currently under discussion. Studies reporting correlations between self-reported symptoms and the presence of specific histopathological findings in a diverse occupational cohort should not be taken to mean that the pathology is the cause of the symptomology (Iverson et al., 2018; Randolph, 2018). Additionally, even with the consensus criteria for clinical definition of Traumatic Encephalopathy Syndrome, there is insufficient evidence of a direct relationship between the observed postmortem neuropathology as the cause of the clinical presentation antemortem (Asken, Tanner, VandeVrede, Casaletto, et al., 2022; Iverson et al., 2018; Kelly et al., 2022; Randolph, 2018).

KEY POINTS & RESEARCH GAPS

- In cases with confirmed CTE, there is noteworthy overlap of symptomology and comorbid neuropathological conditions.
    - Lack of clear distinction between neuropathological conditions and CTE may lead to false positive diagnoses.
- New criteria for the diagnosis of TES premortem have been established, but longitudinal studies with a large number of controls are needed to increase statistical power and determine the associations between postmortem neuropathology and premortem clinical

presentation.

  - Despite recent criteria for the pre-mortem diagnosis of CTE, the definitive diagnosis is based on post-mortem histopathology.

- PET studies can detect tau for the *in vivo* diagnosis of CTE, but sensitive ligands are lacking and require further investigation.

- DTI can be used to identify some of the structural changes in the brain associated with some cases of CTE.

- Blood biomarkers, most notably p-tau, (Aβ), and NFT have been studied for their potential to diagnose CTE premortem. However, no single or combination of blood biomarkers are pathognomonic for CTE.

- Multiple genes have been explored for their role in CTE pathology, but larger prospective studies are needed to tease out pathogenetic mechanisms.

- The largest cohort studies to date have significant selection bias and findings cannot be generalized.

  - There is no distinct study investigating the role of sex on CTE pathology
  - Most studies investigate former athletes and military personnel

- The role of social determinants of health (i.e., environment, economic status, education, healthcare access) have not been explored in depth.

- No controlled epidemiological studies currently exist that establish the risk for CTE in athletes, military personnel, or others exposed to potential CTE causing events.

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REFERENCES

Albayram, O., Albayram, S., & Mannix, R. (2020). Chronic traumatic encephalopathy-a blueprint for the bridge between neurological and psychiatric disorders. *Transl Psychiatry*, *10*(1), 424. https://doi.org/10.1038/s41398-020-01111-x

Alosco, M. L., Cherry, J. D., Huber, B. R., Tripodis, Y., Baucom, Z., Kowall, N. W., Saltiel, N., Goldstein, L. E., Katz, D. I., Dwyer, B., Daneshvar, D. H., Palmisano, J. N., Martin, B.,

Cantu, R. C., Stern, R. A., Alvarez, V. E., Mez, J., Stein, T. D., & McKee, A. C. (2020). Characterizing tau deposition in chronic traumatic encephalopathy (CTE): utility of the McKee CTE staging scheme. *Acta Neuropathol*, *140*(4), 495-512. https://doi.org/10.1007/s00401-020-02197-9

Alosco, M. L., Mariani, M. L., Adler, C. H., Balcer, L. J., Bernick, C., Au, R., Banks, S. J., Barr, W. B., Bouix, S., Cantu, R. C., Coleman, M. J., Dodick, D. W., Farrer, L. A., Geda, Y. E., Katz, D. I., Koerte, I. K., Kowall, N. W., Lin, A. P., Marcus, D. S., . . . Stern, R. A. (2021). Developing methods to detect and diagnose chronic traumatic encephalopathy during life: rationale, design, and methodology for the DIAGNOSE CTE Research Project. *Alzheimers Res Ther*, *13*(1), 136. https://doi.org/10.1186/s13195-021-00872-x

Alosco, M. L., Mez, J., Tripodis, Y., Kiernan, P. T., Abdolmohammadi, B., Murphy, L., Kowall, N. W., Stein, T. D., Huber, B. R., Goldstein, L. E., Cantu, R. C., Katz, D. I., Chaisson, C. E., Martin, B., Solomon, T. M., McClean, M. D., Daneshvar, D. H., Nowinski, C. J., Stern, R. A., & McKee, A. C. (2018). Age of first exposure to tackle football and chronic traumatic encephalopathy. *Annals of Neurology*, *83*(5), 886-901. https://doi.org/10.1002/ana.25245

Alosco, M. L., Su, Y., Stein, T. D., Protas, H., Cherry, J. D., Adler, C. H., Balcer, L. J., Bernick, C., Pulukuri, S. V., Abdolmohammadi, B., Coleman, M. J., Palmisano, J. N., Tripodis, Y., Mez, J., Rabinovici, G. D., Marek, K. L., Beach, T. G., Johnson, K. A., Huber, B. R., . . . Stern, R. A. (2022). Associations between near end-of-life flortaucipir PET and postmortem CTE-related tau neuropathology in six former American football players. *Eur J Nucl Med Mol Imaging*. https://doi.org/10.1007/s00259-022-05963-x

Alosco, M. L., Tripodis, Y., Fritts, N. G., Heslegrave, A., Baugh, C. M., Conneely, S., Mariani, M., Martin, B. M., Frank, S., Mez, J., Stein, T. D., Cantu, R. C., McKee, A. C., Shaw, L. M., Trojanowski, J. Q., Blennow, K., Zetterberg, H., & Stern, R. A. (2018). Cerebrospinal fluid tau, Abeta, and sTREM2 in Former National Football League Players: Modeling the relationship between repetitive head impacts, microglial activation, and neurodegeneration. *Alzheimer's & Dementia*, *14*(9), 1159-1170. https://doi.org/10.1016/j.jalz.2018.05.004

Asken, B. M., & Rabinovici, G. D. (2021). Identifying degenerative effects of repetitive head trauma with neuroimaging: a clinically-oriented review. *Acta Neuropathol Commun*, *9*(1), 96. https://doi.org/10.1186/s40478-021-01197-4

Asken, B. M., Tanner, J. A., VandeVrede, L., Casaletto, K. B., Staffaroni, A. M., Mundada, N., Fonseca, C., Iaccarino, L., La Joie, R., Tsuei, T., Mladinov, M., Grant, H., Shankar, R., Wang, K. K. W., Xu, H., Cobigo, Y., Rosen, H., Gardner, R. C., Perry, D. C., . . . Rabinovici, G. D. (2022). Multi-Modal Biomarkers of Repetitive Head Impacts and Traumatic Encephalopathy Syndrome: A Clinicopathological Case Series. *J Neurotrauma*, *39*(17-18), 1195-1213. https://doi.org/10.1089/neu.2022.0060

Asken, B. M., Tanner, J. A., VandeVrede, L., Mantyh, W. G., Casaletto, K. B., Staffaroni, A. M., La Joie, R., Iaccarino, L., Soleimani-Meigooni, D., Rojas, J. C., Gardner, R. C., Miller, B. L., Grinberg, L. T., Boxer, A. L., Kramer, J. H., & Rabinovici, G. D. (2022). Plasma P-tau181 and P-tau217 in Patients With Traumatic Encephalopathy Syndrome With and Without Evidence of Alzheimer Disease Pathology. *Neurology*, *99*(6), e594-e604. https://doi.org/10.1212/wnl.0000000000200678

Atherton, K., Han, X., Chung, J., Cherry, J. D., Baucom, Z., Saltiel, N., Nair, E., Abdolmohammadi, B., Uretsky, M., Khan, M. M., Shea, C., Durape, S., Martin, B. M.,

Palmisano, J. N., Farrell, K., Nowinski, C. J., Alvarez, V. E., Dwyer, B., Daneshvar, D. H., . . . Mez, J. (2022). Association of APOE Genotypes and Chronic Traumatic Encephalopathy. *JAMA Neurol*, *79*(8), 787-796. https://doi.org/10.1001/jamaneurol.2022.1634

Ayubcha, C., Moghbel, M., Borja, A. J., Newberg, A., Werner, T. J., Alavi, A., & Revheim, M. E. (2021). Tau Imaging in Head Injury. *PET Clin*, *16*(2), 249-260. https://doi.org/10.1016/j.cpet.2020.12.009

Babcock, K. J., Abdolmohammadi, B., Kiernan, P. T., Mahar, I., Cherry, J. D., Alvarez, V. E., Goldstein, L. E., Stein, T. D., McKee, A. C., & Huber, B. R. (2022). Interface astrogliosis in contact sport head impacts and military blast exposure. *Acta Neuropathol Commun*, *10*(1), 52. https://doi.org/10.1186/s40478-022-01358-z

Banks, S. J., Mayer, B., Obuchowski, N., Shin, W., Lowe, M., Phillips, M., Modic, M., & Bernick, C. (2014). Impulsiveness in professional fighters. *Journal of Neuropsychiatry and Clinical Neurosciences*, *26*, 44-50.

Barrio, J. R., Small, G. W., Wong, K. P., Huang, S. C., Liu, J., Merrill, D. A., Giza, C. C., Fitzsimmons, R. P., Omalu, B., Bailes, J., & Kepe, V. (2015). In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging. *Proceedings of the National Academy of Sciences of the United States of America-Physical Sciences*, *112*(16), E2039-2047. https://doi.org/10.1073/pnas.1409952112

Baugh, C. M., Robbins, C. A., Stern, R. A., & McKee, A. C. (2014). Current understanding of chronic traumatic encephalopathy. *Current Treatment Options in Neurology*, *16*(9), 13. https://doi.org/10.1007/s11940-014-0306-5

Bazarian, J. J., Zhu, T., Zhong, J., Janigro, D., Rozen, E., Roberts, A., Javien, H., Merchant-Borna, K., Abar, B., & Blackman, E. G. (2014). Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. *PLoS One*, *9*(4), e94734. https://doi.org/10.1371/journal.pone.0094734

Bergauer, A., van Osch, R., van Elferen, S., Gyllvik, S., Venkatesh, H., & Schreiber, R. (2022). The diagnostic potential of fluid and imaging biomarkers in chronic traumatic encephalopathy (CTE). *Biomed Pharmacother*, *146*, 112602. https://doi.org/10.1016/j.biopha.2021.112602

Bieniek, K. F., Blessing, M. M., Heckman, M. G., Diehl, N. N., Serie, A. M., Paolini, M. A., 2nd, Boeve, B. F., Savica, R., Reichard, R. R., & Dickson, D. W. (2020). Association between contact sports participation and chronic traumatic encephalopathy: a retrospective cohort study. *Brain Pathol*, *30*(1), 63-74. https://doi.org/10.1111/bpa.12757

Bieniek, K. F., Cairns, N. J., Crary, J. F., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., Perl, D. P., Stein, T. D., Vonsattel, J. P., Stewart, W., Dams-O'Connor, K., Gordon, W. A., Tripodis, Y., Alvarez, V. E., Mez, J., Alosco, M. L., & McKee, A. C. (2021). The Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy. *J Neuropathol Exp Neurol*, *80*(3), 210-219. https://doi.org/10.1093/jnen/nlab001

Bieniek, K. F., Ross, O. A., Cormier, K. A., Walton, R. L., Soto-Ortolaza, A., Johnston, A. E., DeSaro, P., Boylan, K. B., Graff-Radford, N. R., Wszolek, Z. K., Rademakers, R., Boeve, B. F., McKee, A. C., & Dickson, D. W. (2015). Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathologica*, *130*(6), 877-889. https://doi.org/10.1007/s00401-015-1502-4

Buerger, K., Ewers, M., Andreasen, N., Zinkowski, R., Ishiguro, K., Vanmechelen, E., Teipel, S.

J., Craz, C., Blennow, K., & Hampel, H. (2005). Phosphorylated tau predicts rate of cognitive decline in MCI subjects: A comparative CSF study. *Neurology*, *65*, 1502-1503.

Butler, M., Dixon, E., Stein, T. D., Alvarez, V. E., Huber, B., Buckland, M. E., McKee, A. C., & Cherry, J. D. (2022). Tau Pathology in Chronic Traumatic Encephalopathy is Primarily Neuronal. *J Neuropathol Exp Neurol*, *81*(10), 773-780. https://doi.org/10.1093/jnen/nlac065

Casson, I. R., & Viano, D. C. (2022). Using the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome on 4 Cohorts of Retired Contact Sport Athletes. *Sports Health*, 19417381221139259. https://doi.org/10.1177/19417381221139259

Chen, S. T., Siddarth, P., Merrill, D. A., Martinez, J., Emerson, N. D., Liu, J., Wong, K. P., Satyamurthy, N., Giza, C. C., Huang, S. C., Fitzsimmons, R. P., Bailes, J., Omalu, B., Barrio, J. R., & Small, G. W. (2018). FDDNP-PET tau brain protein binding patterns in military personnel with suspected chronic traumatic encephalopathy. *Journal of Alzheimer's Disease*, *65*(1), 79-88. https://doi.org/10.3233/JAD-171152

Cherry, J. D., Agus, F., Dixon, E., Huber, B., Alvarez, V. E., Mez, J., McKee, A. C., Labadorf, A., & Stein, T. D. (2021). Differential gene expression in the cortical sulcus compared to the gyral crest within the early stages of chronic traumatic encephalopathy. *Free Neuropathol*, *2*. https://doi.org/10.17879/freeneuropathology-2021-3453

Cherry, J. D., Babcock, K. J., & Goldstein, L. E. (2020). Repetitive Head Trauma Induces Chronic Traumatic Encephalopathy by Multiple Mechanisms. *Semin Neurol*, *40*(4), 430-438. https://doi.org/10.1055/s-0040-1713620

Cherry, J. D., Esnault, C. D., Baucom, Z. H., Tripodis, Y., Huber, B. R., Alvarez, V. E., Stein, T. D., Dickson, D. W., & McKee, A. C. (2021). Tau isoforms are differentially expressed across the hippocampus in chronic traumatic encephalopathy and Alzheimer's disease. *Acta Neuropathol Commun*, *9*(1), 86. https://doi.org/10.1186/s40478-021-01189-4

Cherry, J. D., Meng, G., Daley, S., Xia, W., Svirsky, S., Alvarez, V. E., Nicks, R., Pothast, M., Kelley, H., Huber, B., Tripodis, Y., Alosco, M. L., Mez, J., McKee, A. C., & Stein, T. D. (2020). CCL2 is associated with microglia and macrophage recruitment in chronic traumatic encephalopathy. *J Neuroinflammation*, *17*(1), 370. https://doi.org/10.1186/s12974-020-02036-4

Cherry, J. D., Mez, J., Crary, J. F., Tripodis, Y., Alvarez, V. E., Mahar, I., Huber, B. R., Alosco, M. L., Nicks, R., Abdolmohammadi, B., Kiernan, P. T., Evers, L., Svirsky, S., Babcock, K., Gardner, H. M., Meng, G., Nowinski, C. J., Martin, B. M., Dwyer, B., . . . Stein, T. D. (2018). Variation in TMEM106B in chronic traumatic encephalopathy. *Acta Neuropathologica Communications*, *6*(1), 9. https://doi.org/10.1186/s40478-018-0619-9

Corsellis, J. A., Bruton, C. J., & Freeman-Browne, D. (1973). The aftermath of boxing. *Psychological Medicine*, *3*(3), 270-303.

Crary, J. F., Trojanowski, J. Q., Schneider, J. A., Abisambra, J. F., Abner, E. L., Alafuzoff, I., Arnold, S. E., Attems, J., Beach, T. G., Bigio, E. H., Cairns, N. J., Dickson, D. W., Gearing, M., Grinberg, L. T., Hof, P. R., Hyman, B. T., Jellinger, K., Jicha, G. A., Kovacs, G. G., . . . Nelson, P. T. (2014). Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol*, *128*(6), 755-766. https://doi.org/10.1007/s00401-014-1349-0

Crisco, J. J., Fiore, R., Beckwith, J. G., Chu, J. J., Brolinson, P. G., Duma, S., McAllister, T. W., & Duhaime, A.-C., Greenwald, R. M. (2010). Frequency and location of head impact exposures in individual collegiate football players. *Journal of Athletic Training*, *45*(6),

549-559.

Critchley, M. (1957). Medical aspects of boxing, particularly from a neurological standpoint. *British Medical Journal*, *1*(5015), 357-362.

D'Ascanio, S., Alosco, M. L., & Stern, R. A. (2018). Chronic traumatic encephalopathy: clinical presentation and in vivo diagnosis. *Handb Clin Neurol*, *158*, 281-296. https://doi.org/10.1016/b978-0-444-63954-7.00027-6

Das, M., Mohapatra, S., & Mohapatra, S. S. (2012). New perspectives on central and peripheral immune responses to acute traumatic brain injury. *Journal of Neuroinflammation*, *9*, 12. https://doi.org/10.1186/1742-2094-9-236

Deng, H., Ordaz, A., Upadhyayula, P. S., Gillis-Buck, E. M., Suen, C. G., Melhado, C. G., Mohammed, N., Lam, T., & Yue, J. K. (2018). Apolipoprotein E epsilon 4 genotype, mild traumatic brain injury, and the development of chronic traumatic encephalopathy. *Medical Sciences*, *6*(3), 21. https://doi.org/10.3390/medsci6030078

Dickstein, D. L., De Gasperi, R., Gama Sosa, M. A., Perez-Garcia, G., Short, J. A., Sosa, H., Perez, G. M., Tschiffely, A. E., Dams-O'Connor, K., Pullman, M. Y., Knesaurek, K., Knutsen, A., Pham, D. L., Soleimani, L., Jordan, B. D., Gordon, W. A., Delman, B. N., Shumyatsky, G., Shahim, P. P., . . . Elder, G. A. (2021). Brain and blood biomarkers of tauopathy and neuronal injury in humans and rats with neurobehavioral syndromes following blast exposure. *Mol Psychiatry*, *26*(10), 5940-5954. https://doi.org/10.1038/s41380-020-0674-z

Eagle, S. R., & Okonkwo, D. O. (2023). Telling the Whole Story: Bibliometric Network Analysis to Evaluate Impact of Media Attention on Chronic Traumatic Encephalopathy Research. *J Neurotrauma*, *40*(1-2), 148-154. https://doi.org/10.1089/neu.2022.0266

Erlanger, D. M., Kutner, K. C., Barth, J. T., & Barnes, R. (1999). Neuropsychology of sports-related head injury: Dementia Pugilistica to Post Concussion Syndrome. *Clinical Neuropsychology*, *13*(2), 193-209. https://doi.org/10.1076/clin.13.2.193.1963

Falcon, B., Zivanov, J., Zhang, W., Murzin, A. G., Garringer, H. J., Vidal, R., Crowther, R. A., Newell, K. L., Ghetti, B., Goedert, M., & Scheres, S. H. W. (2019). Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. *Nature*, *568*(7752), 420-423. https://doi.org/10.1038/s41586-019-1026-5

Farrell, K., Iida, M. A., Cherry, J. D., Casella, A., Stein, T. D., Bieniek, K. F., Walker, J. M., Richardson, T. E., White, C. L., Alvarez, V. E., Huber, B. R., Dickson, D. W., Insausti, R., Dams-O'Connor, K., McKee, A. C., & Crary, J. F. (2022). Differential Vulnerability of Hippocampal Subfields in Primary Age-Related Tauopathy and Chronic Traumatic Encephalopathy. *J Neuropathol Exp Neurol*, *81*(10), 781-789. https://doi.org/10.1093/jnen/nlac066

Forrest, S. L., Kril, J. J., Wagner, S., Honigschnabl, S., Reiner, A., Fischer, P., & Kovacs, G. G. (2019). Chronic Traumatic Encephalopathy (CTE) Is Absent From a European Community-Based Aging Cohort While Cortical Aging-Related Tau Astrogliopathy (ARTAG) Is Highly Prevalent. *J Neuropathol Exp Neurol*, *78*(5), 398-405. https://doi.org/10.1093/jnen/nlz017

Gardner, R. C., Possin, K. L., Hess, C. P., Huang, E. J., Grinberg, L. T., Nolan, A. L., Cohn-Sheehy, B. I., HGhosh, P. M., Lanata, S., Merrilees, J., Kramer, J. H., Berger, M. S., Miller, B. L., Yaffe, K., & Rabinovici, G. D. (2015). Evaluating and treating neurobehavioral symptoms in professional American football players: Lessons from a case series. *Neurology: Clinical Practice*, *5*(4), 285-295.

https://doi.org/10.1212/CPJ.0000000000000157

Ge, X., Guo, M., Li, M., Zhang, S., Qiang, J., Zhu, L., Cheng, L., Li, W., Wang, Y., Yu, J., Yin, Z., Chen, F., Tong, W., & Lei, P. (2022). Potential blood biomarkers for chronic traumatic encephalopathy: The multi-omics landscape of an observational cohort. *Front Aging Neurosci*, *14*, 1052765. https://doi.org/10.3389/fnagi.2022.1052765

Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X. L., Velisek, L., Sullivan, J. A., Upreti, C., Kracht, J. M., Ericsson, M., Wojnarowicz, M. W., Goletiani, C. J., Maglakelidze, G. M., Casey, N., Moncaster, J. A., Minaeva, O., Moir, R. D., Nowinski, C. J., Stern, R. A., Cantu, R. C., . . . McKee, A. C. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Science Translational Medicine*, *4*(134), 134ra160. https://doi.org/10.1126/scitranslmed.3003716

Hanlon, F. M., McGrew, C. A., & Mayer, A. R. (2017). Does a unique neuropsychiatric profile currently exist for chronic traumatic encephalopathy? *Current Sports Medicine Reports*, *16*(1), 30-35. https://doi.org/10.1249/JSR.0000000000000324

Hansson, O., Zetterberg, H., Buchhave, P., Londos, E., Blennow, K., & Minthon, L. (2006). Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: A follow-up study. *The Lancet Neurology*, *5*(3), 228-234. https://doi.org/10.1016/s1474-4422(06)70355-6

Harmon, K. G., Clugston, J. R., Dec, K., Hainline, B., Herring, S., Kane, S. F., Kontos, A. P., Leddy, J. J., McCrea, M., Poddar, S. K., Putukian, M., Wilson, J. C., & Roberts, W. O. (2019). American Medical Society for Sports Medicine position statement on concussion in sport. *Br J Sports Med*, *53*(4), 213-225. https://doi.org/10.1136/bjsports-2018-100338

Hazrati, L. N., & Schwab, N. (2021). Embracing the Unknown in the Diagnosis of Traumatic Encephalopathy Syndrome. In *Neurology* (Vol. 96, pp. 835-836). https://doi.org/10.1212/wnl.0000000000011847

Hazrati, L. N., Tartaglia, M. C., Diamandis, P., Davis, K. D., Green, R. E., Wennberg, R., Wong, J. C., Ezerins, L., & Tator, C. H. (2013). Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. *Front Hum Neurosci*, *7*, 9. https://doi.org/10.3389/fnhum.2013.00222

Hof, P. R., Bouras, C., Buee, L., Delacourte, A., Perl, D. P., & Morrison, J. H. (1992). Differential distribution of neurofibrillary tnagles in the cerebreal cortex of dementia pugilistica and Alzheimer's disease cases. *Acta Neuropathologica*, *85*,

Holleran, L., Kim, J. H., Gangolli, M., Stein, T., Alvarez, V., McKee, A., & Brody, D. L. (2017). Axonal disruption in white matter underlying cortical sulcus tau pathology in chronic traumatic encephalopathy. *Acta Neuropathologica*, *133*(3), 367-380. https://doi.org/10.1007/s00401-017-1686-x

Huang, C. X., Li, Y. H., Lu, W., Huang, S. H., Li, M. J., Xiao, L. Z., & Liu, J. (2022). Positron emission tomography imaging for the assessment of mild traumatic brain injury and chronic traumatic encephalopathy: recent advances in radiotracers. *Neural Regen Res*, *17*(1), 74-81. https://doi.org/10.4103/1673-5374.314285

Iverson, G. L. (2014). Chronic traumatic encephalopathy and risk of suicide in former athletes. *British Journal of Sports Medicine*, *48*, 162-164. https://doi.org/10.1136/bjsports-2013-092935

Iverson, G. L., & Gardner, A. J. (2020a). Risk for Misdiagnosing Chronic Traumatic Encephalopathy in Men With Anger Control Problems. *Front Neurol*, *11*, 739. https://doi.org/10.3389/fneur.2020.00739

Iverson, G. L., & Gardner, A. J. (2020b). Risk of Misdiagnosing Chronic Traumatic Encephalopathy in Men With Depression. *J Neuropsychiatry Clin Neurosci*, *32*(2), 139-146. https://doi.org/10.1176/appi.neuropsych.19010021

Iverson, G. L., & Gardner, A. J. (2021). Symptoms of traumatic encephalopathy syndrome are common in the US general population. *Brain Commun*, *3*(1), fcab001. https://doi.org/10.1093/braincomms/fcab001

Iverson, G. L., Keene, C. D., Perry, G., & Castellani, R. J. (2018). The Need to Separate Chronic Traumatic Encephalopathy Neuropathology from Clinical Features. *J Alzheimers Dis*, *61*(1), 17-28. https://doi.org/10.3233/JAD-170654

Iverson, G. L., Luoto, T. M., Karhunen, P. J., & Castellani, R. J. (2019). Mild chronic traumatic encephalopathy neuropathology in people with no known participation in contact sports or history of repetitive neurotrauma. *Journal of Neuropatholy and Experimental Neurology*, *78*(7), 615-625. https://doi.org/10.1093/jnen/nlz045

Iverson, G. L., Merz, Z. C., & Terry, D. P. (2021). Examining the Research Criteria for Traumatic Encephalopathy Syndrome in Middle-Aged Men From the General Population Who Played Contact Sports in High School. *Front Neurol*, *12*, 632618. https://doi.org/10.3389/fneur.2021.632618

Jordan, B. D. (2013). The clinical spectrum of sport-related traumatic brain injury. *Nature Reviews Neurology*, *9*(4), 222-230. https://doi.org/10.1038/nrneurol.2013.33

Katz, D. I., Bernick, C., Dodick, D. W., Mez, J., Mariani, M. L., Adler, C. H., Alosco, M. L., Balcer, L. J., Banks, S. J., Barr, W. B., Brody, D. L., Cantu, R. C., Dams-O'Connor, K., Geda, Y. E., Jordan, B. D., McAllister, T. W., Peskind, E. R., Petersen, R. C., Wethe, J. V., . . . Stern, R. A. (2021). National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome. *Neurology*, *96*(18), 848-863. https://doi.org/10.1212/wnl.0000000000011850

Kelly, J. P., Priemer, D. S., Perl, D. P., & Filley, C. M. (2022). Sports Concussion and Chronic Traumatic Encephalopathy: Finding a Path Forward. *Ann Neurol*. https://doi.org/10.1002/ana.26566

Kochsiek, J., O'Donnell, L. J., Zhang, F., Bonke, E. M., Sollmann, N., Tripodis, Y., Wiegand, T. L. T., Kaufmann, D., Umminger, L., Di Biase, M. A., Kaufmann, E., Schultz, V., Alosco, M. L., Martin, B. M., Lin, A. P., Coleman, M. J., Rathi, Y., Pasternak, O., Bouix, S., . . . Koerte, I. K. (2021). Exposure to Repetitive Head Impacts Is Associated With Corpus Callosum Microstructure and Plasma Total Tau in Former Professional American Football Players. *J Magn Reson Imaging*, *54*(6), 1819-1829. https://doi.org/10.1002/jmri.27774

Laffey, M., Darby, A. J., Cline, M. G., Teng, E., & Mendez, M. F. (2018). The utility of clinical criteria in patients with chronic traumatic encephalopathy. *NeuroRehabilitation*, *43*(4), 431-441. https://doi.org/10.3233/NRE-182452

Lakhan, S. E., & Kirchgessner, A. (2012). Chronic traumatic encephalopathy: the dangers of getting "dinged". *SpringerPlus*, *1*, 14. https://doi.org/10.1186/2193-1801-1-2

Lehman, E. J., Hein, M. J., Baron, S. L., & Gersic, C. M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology*, *79*, 1970-1974.

Lenihan, M. W., & Jordan, B. D. (2015). The clinical presentation of chronic traumatic encephalopathy. *Current Neurology and Neuroscience Reports*, *15*(5), 8. https://doi.org/10.1007/s11910-015-0541-5

Lindberg, M. A., Moy Martin, E. M., & Marion, D. W. (2022). Military Traumatic Brain Injury:

The History, Impact, and Future. *J Neurotrauma*, *39*(17-18), 1133-1145. https://doi.org/10.1089/neu.2022.0103

Ling, H., Morris, H. R., Neal, J. W., Lees, A. J., Hardy, J., Holton, J. L., Revesz, T., & Williams, D. D. (2017). Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. *Acta Neuropathologica*, *133*(3), 337-352. https://doi.org/10.1007/s00401-017-1680-3

LoBue, C., Schaffert, J., Cullum, C. M., Peters, M. E., Didehbani, N., Hart, J., & White, C. L. (2020). Clinical and neuropsychological profile of patients with dementia and chronic traumatic encephalopathy. *J Neurol Neurosurg Psychiatry*, *91*(6), 586-592. https://doi.org/10.1136/jnnp-2019-321567

Makinde, H. M., Just, T. B., Cuda, C. M., Perlman, H., & Schwulst, S. J. (2017). The role of microglia in the etiology and evolution of chronic traumatic encephalopathy. *Shock*, *48*(3), 276-283. https://doi.org/10.1097/SHK.0000000000000859

Marquie, M., Aguero, C., Amaral, A. C., Villarejo-Galende, A., Ramanan, P., Chong, M. S. T., Saez-Calveras, N., Bennett, R. E., Verwer, E. E., Kim, S. J. W., Dhaynaut, M., Alvarez, V. E., Johnson, K. A., McKee, A. C., Frosch, M. P., & Gomez-Isla, T. (2019). [(18)F]-AV-1451 binding profile in chronic traumatic encephalopathy: a postmortem case series. *Acta Neuropathol Commun*, *7*(1), 164. https://doi.org/10.1186/s40478-019-0808-1

Martland, H. S. (1928). Punch Drunk. *JAMA*, *91*(15), 1103-1107.

McCann, H., Bahar, A. Y., Burkhardt, K., Gardner, A. J., Halliday, G. M., Iverson, G. L., & Shepherd, C. E. (2022). Prevalence of chronic traumatic encephalopathy in the Sydney Brain Bank. *Brain Commun*, *4*(4), fcac189. https://doi.org/10.1093/braincomms/fcac189

McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, B., Dvorak, J., Echemendia, R. J., Engebretsen, L., Johnston, K., Kutcher, J. S., Raftery, M., Sills, A., Benson, B. W., Davis, G. A., Ellenbogen, R. G., Guskiewicz, K., Herring, S. A., Iverson, G. L., Jordan, B. D., Kissick, J., . . . Turner, M. (2013). Consensus statement on concussion in sport: The 4th International Conference on Concussion in Sport held in Zurich, November 2012. *British Journal of Sports Medicine*, *47*(5), 250-258. https://doi.org/10.1136/bjsports-2013-092313

McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., Perl, D. P., Stein, T. D., Vonsattel, J. P., Stewart, W., Tripodis, Y., Crary, J. F., Bieniek, K. F., Dams-O'Connor, K., Alvarez, V. E., Gordon, W. A., & group, T. C. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica*, *131*(1), 75-86. https://doi.org/10.1007/s00401-015-1515-z

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., Santini, V. E., Lee, H.-S., Kubilus, C. A., & Stern, R. A. (2009). Chronic traumatic encephalopathy in athletes: Progressive tauopathy after repetitive head injury. *Journal of Neuropathology and Experimental Neurology*, *68*(7), 709-735. https://doi.org/10.1097/NEN.0b013e3181a9d503

McKee, A. C., & Robinson, M. E. (2014). Military-related traumatic brain injury and neurodegeneration. *Alzheimer's & Dementia*, *10*(3 Suppl), S242-253. https://doi.org/10.1016/j.jalz.2014.04.003

McKee, A. C., Stein, T. D., Kiernan, P. T., & Alvarez, V. E. (2015). The neuropathology of chronic traumatic encephalopathy. *Brain Pathology*, *25*(3), 350-364. https://doi.org/10.1111/bpa.12248

McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., Lee, H.-S., Hall, G., Wojtowicz, S. M., Baugh, C. M., Riley, D. O., Kubilus, C. A., Cormier, K. A., Jacobs, M. A., Martin, B. R., Abraham, C. R., Ikezu, T., Reichard, R. R., Wolozin, B. L., . . . Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, *136*(1), 43-64. https://doi.org/10.1093/brain/aws307

Mendez, M. F. (1995). The neuropsychiatric aspects of boxing. *International Journal of Psychiatry in Medicine*, *25*(3), 249-262. https://doi.org/10.2190/CUMK-THT1-X98M-WB4C

Mez, J., Alosco, M. L., Daneshvar, D. H., Saltiel, N., Baucom, Z., Abdolmohammadi, B., Uretsky, M., Nicks, R., Martin, B. M., Palmisano, J. N., Nowinski, C. J., Montenigro, P., Solomon, T. M., Mahar, I., Cherry, J. D., Alvarez, V. E., Dwyer, B., Goldstein, L. E., Katz, D. I., . . . McKee, A. C. (2021). Validity of the 2014 traumatic encephalopathy syndrome criteria for CTE pathology. *Alzheimers Dement*, *17*(10), 1709-1724. https://doi.org/10.1002/alz.12338

Mez, J., Daneshvar, D. H., Abdolmohammadi, B., Chua, A. S., Alosco, M. L., Kiernan, P. T., Evers, L., Marshall, L., Martin, B. M., Palmisano, J. N., Nowinski, C. J., Mahar, I., Cherry, J. D., Alvarez, V. E., Dwyer, B., Huber, B. R., Stein, T. D., Goldstein, L. E., Katz, D. I., . . . McKee, A. C. (2019). Duration of American Football Play and Chronic Traumatic Encephalopathy. *Ann Neurol*. https://doi.org/10.1002/ana.25611

Mez, J., Daneshvar, D. H., Abdolmohammadi, B., Chua, A. S., Alosco, M. L., Kiernan, P. T., Evers, L., Marshall, L., Martin, B. M., Palmisano, J. N., Nowinski, C. J., Mahar, I., Cherry, J. D., Alvarez, V. E., Dwyer, B., Huber, B. R., Stein, T. D., Goldstein, L. E., Katz, D. I., . . . McKee, A. C. (2020). Duration of American Football Play and Chronic Traumatic Encephalopathy. *Ann Neurol*, *87*(1), 116-131. https://doi.org/10.1002/ana.25611

Mez, J., Daneshvar, D. H., Kiernan, P. T., Abdolmohammadi, B., Alvarez, V. E., Huber, B. R., Alosco, M. L., Solomon, T. M., Nowinski, C. J., McHale, L., Cormier, K. A., Kubilus, C. A., Martin, B. M., Murphy, L., Baugh, C. M., Montenigro, P. H., Chaisson, C. E., Tripodis, Y., Kowall, N. W., . . . McKee, A. C. (2017). Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*, *318*(4), 360-370. https://doi.org/10.1001/jama.2017.8334

Montenigro, R. H., Baugh, C. M., Daneshvar, D. H., Mez, J., Budson, A. E., Au, R., Katz, D. I., Cantu, R. C., & Stern, R. A. (2014). Clinical subtypes of chronic traumatic encephalopathy: Literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimer's Research & Therapy*, *6*, 17. https://doi.org/10.1186/s13195-014-0068-z

Moyron, R. B., Vallejos, P. A., Fuller, R. N., Dean, N., & Wall, N. R. (2021). Neuroimaging and advanced research techniques may lead to improved outcomes in military members suffering from traumatic brain injury. *Trauma Surg Acute Care Open*, *6*(1), e000608. https://doi.org/10.1136/tsaco-2020-000608

National Institutes of Neurological Disorders and Stroke. (2013). *Report on the Neuropathology of Chronic Traumatic Encephalopathy Workshop* http://www.ninds.nih.gov/news_and_events/proceedings/201212_CTE_workshop_report.htm

Neselius, S., Brisby, H., Theodorsson, A., Blennow, K., Zetterberg, H., & Marcusson, J. (2012). CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma.

PLoS One, *7*(4), e33606. https://doi.org/10.1371/journal.pone.0033606

Neselius, S., Zetterberg, H., Blennow, K., Marcusson, J., & Brisby, H. (2013). Increased CSF levels of phosphorylated neurofilament heavy protein following bout in amateur boxers. *PLoS One*, *8*(11), e81249. https://doi.org/10.1371/journal.pone.0081249

Ng, A. S., Rademakers, R., & Miller, B. L. (2015). Frontotemporal dementia: A bridge between dementia and neuromuscular disease. *Annals of the New York Academy of Science*, *1338*, 71-93. https://doi.org/10.1111/nyas.12638

Nowinski, C. J., Bureau, S. C., Buckland, M. E., Curtis, M. A., Daneshvar, D. H., Faull, R. L. M., Grinberg, L. T., Hill-Yardin, E. L., Murray, H. C., Pearce, A. J., Suter, C. M., White, A. J., Finkel, A. M., & Cantu, R. C. (2022). Applying the Bradford Hill Criteria for Causation to Repetitive Head Impacts and Chronic Traumatic Encephalopathy. *Front Neurol*, *13*, 938163. https://doi.org/10.3389/fneur.2022.938163

Oliver, J. M., Anzalone, A. J., Stone, J. D., Turner, S. M., Blueitt, D., Garrison, J. C., Askow, A. T., Luedke, J. A., & Jagim, A. R. (2018). Fluctuations in blood biomarkers of head trauma in NCAA football athletes over the course of a season. *J Neurosurg*, 1-8. https://doi.org/10.3171/2017.12.JNS172035

Oliver, J. M., Jones, M. T., Kirk, K. M., Gable, D. A., Repshas, J. T., Johnson, T. A., Andreasson, U., Norgren, N., Blennow, K., & Zetterberg, H. (2016). Effect of Docosahexaenoic Acid on a Biomarker of Head Trauma in American Football. *Med Sci Sports Exerc*, *48*(6), 974-982. https://doi.org/10.1249/MSS.0000000000000875

Olivera, A., Lejbman, N., Jeromin, A., French, L. M., Kim, H. S., Cashion, A., Mysliwiec, V., Diaz-Arrastia, R., & Gill, J. (2015). Peripheral total tau in military personnel who sustain traumatic brain injuries during deployment. *JAMA Neurology*, *72*(10), 1109-1116. https://doi.org/10.1001/jamaneurol.2015.1383

Omalu, B., Bailes, J., Hamilton, R. L., Kamboh, M. I., Hammers, J., Case, M., & Fitzsimmons, R. (2011). Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery*, *69*, 173-183. https://doi.org/10.1227/NEU.0b013e318212bc7b

Omalu, B., & Hammers, J. (2021). Letter: Traumatic Encephalopathy Syndrome [TES] Is Not Chronic Traumatic Encephalopathy [CTE]: CTE Is Only a Subtype of TES. In *Neurosurgery* (Vol. 89, pp. E205-e206). https://doi.org/10.1093/neuros/nyab231

Omalu, B., Hammers, J. L., Bailes, J., Hamilton, R. L., Kamboh, M. I., Webster, G., & Fitzsimmons, R. P. (2011). Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurgical Focus*, *31*(5), 10. https://doi.org/10.3171/2011.9.FOCUS11178)

Omalu, B., Small, G. W., Bailes, J., Ercoli, L. M., Merrill, D. A., Wong, K. P., Huang, S. C., Satyamurthy, N., Hammers, J. L., Lee, J., Fitzsimmons, R. P., & Barrio, J. R. (2018). Postmortem autopsy-confirmation of antemortem [F-18]FDDNP-PET scans in a football player with chronic traumatic encephalopathy. *Neurosurgery*, *82*(2), 237-246. https://doi.org/10.1093/neuros/nyx536

Omalu, B. I., DeKosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., & Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*, *57*, 128-134. https://doi.org/10.1227/01.neu.0000163407.92769.ed

Ost, M., Nylén, K., Csajbok, L., Ohrfelt, A. O., Tullberg, M., Wikkelsö, C., Nellgård, P., Rosengren, L., Blennow, K., & Nellgård, B. (2006). Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. *Neurology*, *67*, 1600-1604.

Ott, S. D., Cheema, S. K., Ryder, A., Schatz, P., Gonzalez, L. A., Duran, J., & Schulz, P. E. (2022). Information seeking behaviors and attitudes of wives of former football players regarding chronic traumatic encephalopathy. *Appl Neuropsychol Adult*, 1-8. https://doi.org/10.1080/23279095.2022.2145892

Pattinson, C. L., Shahim, P., Taylor, P., Dunbar, K., Guedes, V. A., Motamedi, V., Lai, C., Devoto, C., Peyer, J., Roy, M. J., & Gill, J. M. (2020). Elevated Tau in Military Personnel Relates to Chronic Symptoms Following Traumatic Brain Injury. *J Head Trauma Rehabil*, *35*(1), 66-73. https://doi.org/10.1097/htr.0000000000000485

Pierre, K., Dyson, K., Dagra, A., Williams, E., Porche, K., & Lucke-Wold, B. (2021). Chronic Traumatic Encephalopathy: Update on Current Clinical Diagnosis and Management. *Biomedicines*, *9*(4). https://doi.org/10.3390/biomedicines9040415

Priemer, D. S., Iacono, D., Rhodes, C. H., Olsen, C. H., & Perl, D. P. (2022). Chronic Traumatic Encephalopathy in the Brains of Military Personnel. *N Engl J Med*, *386*(23), 2169-2177. https://doi.org/10.1056/NEJMoa2203199

Randolph, C. (2014). Is chronic traumatic encephalopathy a real disease? *Curr Sports Med Rep*, *13*(1), 33-37. https://doi.org/10.1097/OPX.0000000000000170

Randolph, C. (2018). Chronic traumatic encephalopathy is not a real disease. *Archives of Clinical Neuropsychology*, *33*(5), 644-648. https://doi.org/10.1093/arclin/acy063

Randolph, C., Karantzoulis, S., & Guskiewicz, K. (2013). Prevalence and characterization of mild cognitive impairment in retired National Football League players. *Journal of the International Neuropsychological Society*, *19*(8), 873-880. https://doi.org/10.1017/S1355617713000805

Reams, N., Eckner, J. T., Almeida, A. A., Aagesen, A. L., Giordani, B., Paulson, H., Lorincz, M. T., & Kutcher, J. S. (2016). A Clinical Approach to the Diagnosis of Traumatic Encephalopathy Syndrome: A Review. *JAMA Neurol*, *73*(6), 743-749. https://doi.org/10.1001/jamaneurol.2015.5015

Reid, M. W., & Velez, C. S. (2015). Discriminating military and civilian traumatic brain injuries. *Molecular and Cellular Neuroscience*, *66*, 123-128. https://doi.org/10.1016/j.mcn.2015.03.014

Ritter, A., Shan, G., Montes, A., Randall, R., & Bernick, C. (2022). Traumatic encephalopathy syndrome: application of new criteria to a cohort exposed to repetitive head impacts. *Br J Sports Med*. https://doi.org/10.1136/bjsports-2022-105819

Roberts, A. H. (1969). *Brain damage in boxers : A study of the prevalence of traumatic encephalopathy among ex-professional boxers*. Pitman Medical & Scientific Publishing Co., Ltd,.

Robinson, M. E., McKee, A. C., Salat, D. H., Rasmusson, A. M., Radigan, L. J., Catana, C., Milberg, W. P., & McGlinchey, R. E. (2019). Positron emission tomography of tau in Iraq and Afghanistan Veterans with blast neurotrauma. *NeuroImage: Clinical*, *21*. https://doi.org/10.1016/j.nicl.2019.101651

Schaffert, J., Didehbani, N., LoBue, C., Hart, J., Rossetti, H., Lacritz, L., & Cullum, C. M. (2021). Frequency and Predictors of Traumatic Encephalopathy Syndrome in a Prospective Cohort of Retired Professional Athletes. *Front Neurol*, *12*, 617526. https://doi.org/10.3389/fneur.2021.617526

Schwab, N., Wennberg, R., Grenier, K., Tartaglia, C., Tator, C., & Hazrati, L. N. (2021). Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players. *Neurology*, *96*(14),

e1835-e1843. https://doi.org/10.1212/wnl.0000000000011668

Seichepine, D. R., Stamm, J. M., Daneshvar, D. H., Riley, D. O., Baugh, C. M., Gavett, B. E., Tripodis, Y., Martin, B., Chaisson, C., McKee, A. C., Cantu, R. C., Nowinski, C. J., & Stern, R. A. (2013). Profile of self-reported problems with executive functioning in college and professional football players. *Journal of Neurotrauma*, *30*(14), 1299-1304. https://doi.org/10.1089/neu.2012.2690

Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. *Nature Reviews Neurology*, *10*(3), 156-166. https://doi.org/10.1038/nrneurol.2014.15

Shively, S., Scher, A. I., Perl, D. P., & Diaz-Arrastia, R. (2012). Dementia resulting from traumatic brain injury: What is the pathology? *Archives of Neurology*, *69*(10), 1245-1251. https://doi.org/10.1001/archneurol.2011.3747

Shively, S. B., Horkayne-Szakaly, I., Jones, R. V., Kelly, J. P., Armstrong, R. C., & Perl, D. P. (2016). Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series. *The Lancet Neurology*, *15*(9), 944-953. https://doi.org/10.1016/s1474-4422(16)30057-6

Shively, S. B., Priemer, D. S., Stein, M. B., & Perl, D. P. (2021). Pathophysiology of Traumatic Brain Injury, Chronic Traumatic Encephalopathy, and Neuropsychiatric Clinical Expression. *Psychiatr Clin North Am*, *44*(3), 443-458. https://doi.org/10.1016/j.psc.2021.04.003

Small, G. W., Kepe, V., Siddarth, P., Ercoli, L. M., Merrill, D. A., Donoghue, N., Bookheimer, S. Y., Martinez, J., Omalu, B., Bailes, J., & Barrio, J. R. (2013). PET scanning of brain tau in retired National Football League players: Preliminary findings. *American Journal of Geriatric Psychiatry*, *21*(2), 138-144. https://doi.org/10.1016/j.jagp.2012.11.019

Smith, D. H., Johnson, V. E., & Stewart, W. (2013). Chronic neuropathologies of single and repetitive TBI: Substrates of dementia? *Nature Reviews Neurology*, *9*(4), 211-221. https://doi.org/10.1038/nrneurol.2013.29

Smith, D. H., Johnson, V. E., Trojanowski, J. Q., & Stewart, W. (2019). Chronic traumatic encephalopathy - confusion and controversies. *Nat Rev Neurol*, *15*(3), 179-183. https://doi.org/10.1038/s41582-018-0114-8

Stamm, J. M., Koerte, I. K., Muehlmann, M., Pasternak, O., Bourlas, A. P., Baugh, C. M., Giwerc, M. Y., Zhu, A., Coleman, M. J., Bouix, S., Fritts, N. G., Martin, B. M., Chaisson, C., McClean, M. D., Lin, A. P., Cantu, R. C., Tripodis, Y., Stern, R. A., & Shenton, M. E. (2015). Age at first exposure to football is associated with altered corpus callosum white matter microstructure in former professional football players. *Journal of Neurotrauma*, *32*(22), 1768-1776. https://doi.org/10.1089/neu.2014.3822)

Stern, R. A., Adler, C. H., Chen, K., Navitsky, M., Luo, J., Dodick, D. W., Alosco, M. L., Tripodis, Y., Goradia, D. D., Martin, B., Mastroeni, D., Fritts, N. G., Jarnagin, J., Devous, M. D., Sr., Mintun, M. A., Pontecorvo, M. J., Shenton, M. E., & Reiman, E. M. (2019). Tau positron-emission tomography in former National Football League players. *New England Journal of Medicine*, *380*(18), 1716-1725. https://doi.org/10.1056/NEJMoa1900757

Stern, R. A., Daneshvar, D. H., Baugh, C. M., Seichepine, D. R., Montenigro, P. H., Riley, D. O., Fritts, N. G., Stamm, J. M., Robbins, C. A., McHale, L., Simkin, I., Stein, T. D., Alvarez, V. E., Goldstein, L. E., Budson, A. E., Kowall, N. W., Cantu, R. C., & McKee, A. C. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology*, *81*, 1122-1129.

Stern, R. A., Riley, D. O., Daneshvar, D. H., Nowinski, C. J., Cantu, R. C., & McKee, A. C. (2011). Long-term consequences of repetitive brain trauma: Chronic traumatic encephalopathy. *PM&R*, *3*(10 Suppl 2), S460-467. https://doi.org/10.1016/j.pmrj.2011.08.008

Tripathy, A., Shade, A., Erskine, B., Bailey, K., Grande, A., deLong, J. J., Perry, G., & Castellani, R. J. (2019). No evidence of increased chronic traumatic encephalopathy pathology or neurodegenerative proteinopathy in former military service members: A preliminary study. *Journal of Alzheimer's Disease*, *67*(4), 1277-1289. https://doi.org/10.3233/JAD-181039

Turk, K. W., Geada, A., Alvarez, V. E., Xia, W., Cherry, J. D., Nicks, R., Meng, G., Daley, S., Tripodis, Y., Huber, B. R., Budson, A. E., Dwyer, B., Kowall, N. W., Cantu, R. C., Goldstein, L. E., Katz, D. I., Stern, R. A., Alosco, M. L., Mez, J., . . . Stein, T. D. (2022). A comparison between tau and amyloid-β cerebrospinal fluid biomarkers in chronic traumatic encephalopathy and Alzheimer disease. *Alzheimers Res Ther*, *14*(1), 28. https://doi.org/10.1186/s13195-022-00976-y

Vasilevskaya, A., Taghdiri, F., Burke, C., Tarazi, A., Naeimi, S. A., Khodadadi, M., Goswami, R., Sato, C., Grinberg, M., Moreno, D., Wennberg, R., Mikulis, D., Green, R., Colella, B., Davis, K. D., Rusjan, P., Houle, S., Tator, C., Rogaeva, E., & Tartaglia, M. C. (2020). Interaction of APOE4 alleles and PET tau imaging in former contact sport athletes. *Neuroimage Clin*, *26*, 102212. https://doi.org/10.1016/j.nicl.2020.102212

Victoroff, J. (2013). Traumatic encephalopathy: Review and provisional research diagnostic criteria. *NeuroRehabilitation*, *32*(2), 211-224. https://doi.org/10.3233/NRE-130839

Wolfson,D. I., Kuhn, A. W., Kerr, Z. Y., Brett, B. L., Yengo-Kahn, A. M., Solomon, G. S., & Zuckerman, S. L. (2020). Chronic traumatic encephalopathy research viewed in the public domain: What makes headlines? *Brain Inj*, *34*(4), 528-534. https://doi.org/10.1080/02699052.2020.1725843

Wortzel, H. S., Shura, R. D., & Brenner, L. A. (2013). Chronic traumatic encephalopathy and suicide: A systematic review. *Biomed Research International*, 6. https://doi.org/10.1155/2013/424280

Zetterberg, H., Hietala, A., Jonsson, M., Andreasen, N., Styrud, E., Karlsson, I., Edman, A., Popa, C., Rasulzada, A., Wahlund, L., Mehta, P. D., Rosengren, L., Blennow, K., & Wallin, A. (2006). Neurochemical Aftermath of Amateur Boxing [Journal Article]. *Archives of Neurology*, *63*, 4.

Zimmerman, K. A., Kim, J., Karton, C., Lochhead, L., Sharp, D. J., Hoshizaki, T., & Ghajari, M. (2021). Player position in American football influences the magnitude of mechanical strains produced in the location of chronic traumatic encephalopathy pathology: A computational modelling study. *J Biomech*, *118*, 110256. https://doi.org/10.1016/j.jbiomech.2021.110256