DEPARTMENT OF DEFENSE
BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

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LITERATURE REVIEW

The Biological Basis of Chronic Traumatic Encephalopathy Following Blast Injury

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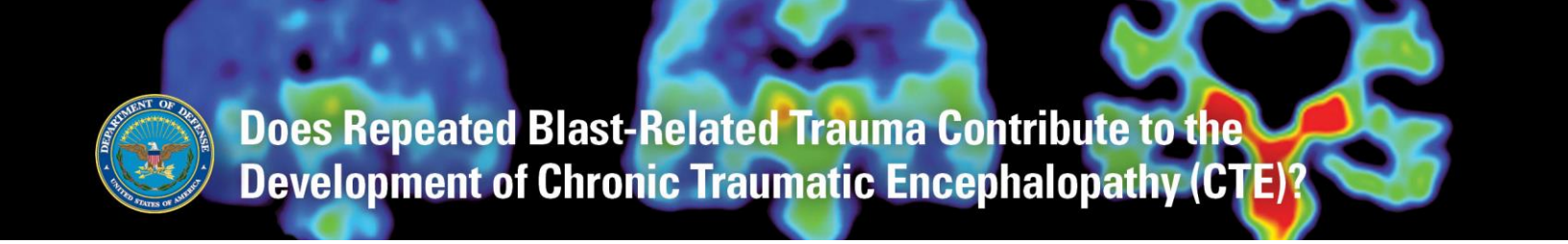

Executive Summary

To inform the 2015 International State-of-the-Science Meeting, the United States Department of Defense Blast Injury Research Program Coordinating Office requested a review of recent research literature on chronic traumatic encephalopathy (CTE). This literature review addresses specific research questions about (1) the pathophysiological basis of CTE and (2) associations between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE.
CTE is described as a neurodegenerative disorder affecting individuals exposed to head injury that can result in a range of cognitive, behavioral, and/or motor deficits. Broad scientific consensus about CTE has not been established; however, multiple academic and government organizations are investigating links between exposure to brain injuries, CTE-associated pathology, and reported clinical symptoms.

The current state of the science has generated an initial consensus on the neuropathology of CTE (NINDS, 2015). However, the evidence does not allow for a conclusive determination of whether exposure to head injury is sufficient and causative in the development of CTE pathology. All existing clinical neuropathological evidence associated with CTE has been gathered from postmortem autopsy of subjects with histories of exposure to head injury. Unique pathological characteristics of CTE have not been comprehensively determined, in part because observations of macroscopic (i.e., gross anatomical) and microscopic (i.e., molecular) abnormalities vary to some degree across different studies and research groups. Based on existing observations, research groups have proposed classification frameworks describing CTE as a progressive disease or as a collection of related neuropathologies.

Existing research does not substantively inform whether the development of CTE is potentially associated with head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast). Head injury exposure data is not consistent across case studies, which prevents systematic analysis. Many CTE studies characterize head injury exposure as exposure to sport or occupation and do not include data describing injury frequency, severity, or the time elapsed between injuries.

The incidence of CTE-associated pathology and/or symptoms in at-risk populations cannot be determined from existing literature and highlights a need for population-based studies. While the primary risk factor for CTE is thought to be exposure to head injury, additional research is needed to investigate other potential risk factors, such as genetic predisposition. The broad range of clinical symptoms associated with CTE overlap with those of multiple neurodegenerative disorders. Animal models may also offer insights to neuropathological and neurobehavioral abnormalities thought to be associated with CTE. While animal models do not accurately exhibit the neuropathology of CTE, animal

models of traumatic brain injury (TBI) may reflect some associated head injury exposure conditions (e.g., blunt force or blast-induced) and tau pathology.

Successful development of biomarkers to identify CTE pathology in living persons would benefit the research and development of potential diagnosis, prevention, and treatment strategies. Investigators are pursuing neuroimaging modalities and biospecimen analytes as potential predictive biomarkers of CTE by targeting pathophysiological phenomena associated with CTE and the biological processes affected by head injury exposure.

Because no established treatment for CTE exists, current mitigation strategies focus on preventing head injury and/or concussion. Although consensus on the understanding of CTE is still being established, researchers are investigating potential treatment approaches that target the pathophysiological mechanisms associated with CTE. Because of the neuropathological similarities with Alzheimer's disease and TBI, potential pharmacological and behavioral interventions for these conditions are also being investigated for CTE.

The current state of the science does not allow for a conclusive determination of whether exposure to head injury is associated with the development of CTE pathology or clinical symptoms. Existing clinical data are limited, observational in nature, and subject to several methodological concerns, leading some researchers to question whether CTE is a unique neurodegenerative disease. CTE has drawn significant public and media attention given the large at-risk population (e.g., military service members, contact sport athletes). Experts have noted concern over the potential clinical and legal consequences of widespread misunderstanding of CTE. In light of these factors, the need for additional research is clear, particularly population-based studies, the use of standardized pathology protocols, and the development of clinical diagnostic criteria.

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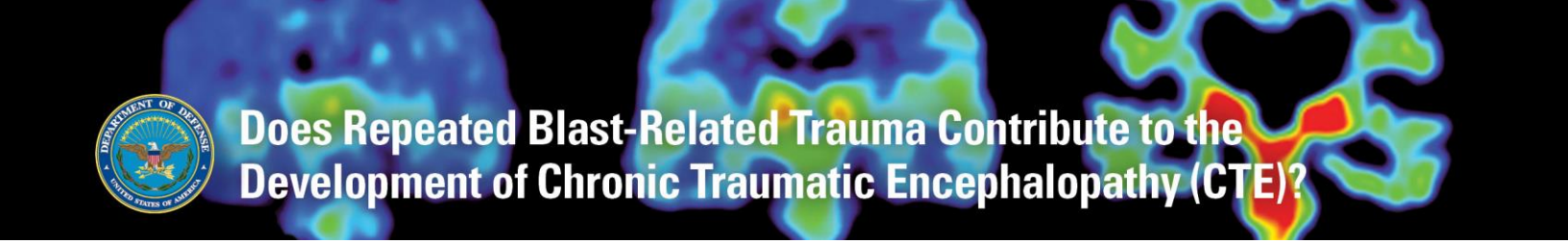


Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Purpose

The mission of the United States Department of Defense (DoD) Blast Injury Research Program Coordinating Office (Blast PCO) is to assist in fulfilling the DoD Executive Agent responsibilities and functions related to medical research to prevent, mitigate, and treat blast injuries in accordance with DoD Directive 6025.21E. The Blast PCO coordinates and manages relevant DoD medical research efforts and programs, including identifying blast injury knowledge gaps, shaping medical research programs to fill identified gaps, facilitating collaboration among diverse communities within and outside the DoD, and widely disseminating blast injury research information.

To achieve these objectives, the Blast PCO convenes an annual International State-of-the-Science (SoS) Meeting to assist in identifying knowledge gaps pertaining to key blast injury issues. These annual SoS meetings are highly focused to help determine what is known and unknown about particular blast injury topics. The topic of the 2015 International SoS Meeting is chronic traumatic encephalopathy (CTE) and how this condition may relate to head injuries arising from blast exposure. The Blast PCO requested a review of recent research literature to inform meeting participants on the current scientific knowledge of the underlying pathophysiological changes in the brain that may be associated with CTE following head injury. It seeks to address the following research questions:

- What is the current evidence describing the pathophysiological basis of CTE?
    - What biological processes following head injury are associated with the development of CTE?
    - What advances in neuroimaging or biomarkers of CTE may lead to the development of diagnostic tools or therapeutic strategies?
- What associations are known between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE?
    - Does the frequency of exposure to head injury correlate with the development of CTE?
    - Are there any known distinctions between how impact injury, nonimpact injury, and blast-induced injury are associated with the development of CTE?

Methodology

This literature review searched PubMed, the Defense Technical Information Center (DTIC), Google, and Google Scholar using search terms (see Appendix 1) to identify English language clinical and basic science articles published in the last 10 years (between 2005 and 2015, inclusive). Among DTIC documents, only those assigned for

public distribution (Distribution A) were included. Identified articles published prior to 2005 were included in the literature review only if they were determined to be potentially critical to addressing the research questions or understanding the topic. Search terms were generated in collaboration with the Blast PCO and the 2015 SoS Meeting Planning Committee. In addition to the search terms listed in Appendix 1, ad hoc searches on key principal investigators or on specific topics were performed. Publications identified in the bibliographies of reviewed articles were also included in this literature review. Table 1 lists the search inclusion and exclusion criteria for the review.

Table 1. Literature Search Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. English language articles only 2. Articles published between 2005 and 2015 (inclusive)* 3. Clinical and animal model studies 4. DTIC documents assigned Distribution A: Approved for public release: distribution unlimited	1. Articles not directly addressing research questions 2. DTIC documents not approved for public release

*Older publications were included when potentially critical to addressing the research questions or understanding the topic.

Articles meeting the inclusion criteria were further reviewed to determine whether they directly informed the research questions and merited inclusion in the literature review. Articles were reviewed for the following elements:

- Study design
- Study population (e.g., military, athletes)
- Outcome measures (e.g., histology, cognitive/behavioral symptoms)
- Results and statistics (when available)
- Conclusions, study limitations, and recommendations relevant to research questions.

Following this strategy, the literature search yielded 359 articles that met the parameters of the search terms and inclusion/exclusion criteria (see Table 1). This literature review report includes a total of 164 articles.

Neuropathology

CTE is described as a progressive neurodegenerative disorder affecting individuals exposed to head injury and resulting in cognitive, behavioral and/or motor deficits. Broad consensus on the existence of, and diagnostic criteria for, CTE has not been firmly established in the clinical and scientific community (Hazrati et al., 2013; Karantzoulis & Randolph, 2013; McCrory, Meeuwisse, Kutcher, Jordan, & Gardner, 2013; Randolph, 2014; Wortzel, Brenner, & Arciniegas, 2013); however, multiple academic research groups and government organizations are gathering and analyzing evidence that may provide significant insights about potential links between exposure to

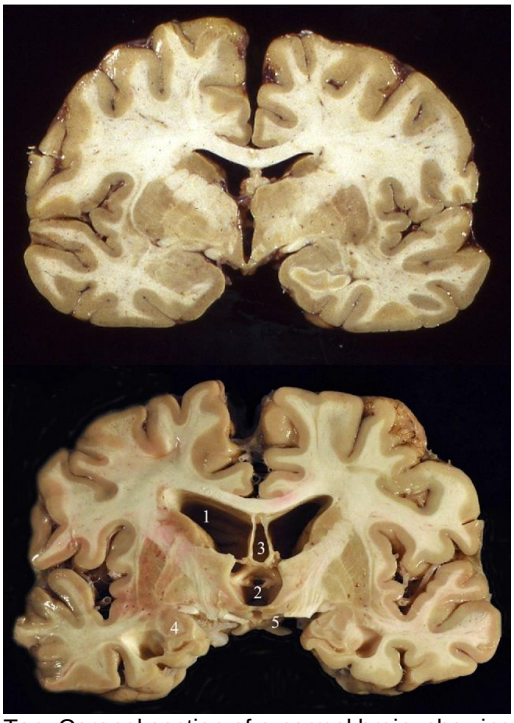
head injury and the development of CTE (Hinds, 2014; McKee et al., 2013; McKee, Stein, Kiernan, & Alvarez, 2015; Omalu, Bailes, et al., 2011; Riley, Robbins, Cantu, & Stern, 2015; Saigal & Berger, 2014). A recent National Institutes of Health (NIH) consensus workshop began to establish the pathognomonic features of CTE required for diagnosis (NINDS, 2015).

To date, all existing clinical neuropathological evidence describing CTE has been gathered from postmortem autopsy of subjects with a history of exposure to head injury (Gardner, Iverson, & McCrory, 2014). Pathological abnormalities associated with CTE include macroscopic (i.e., gross anatomical) and microscopic (i.e., cellular and molecular) changes. While CTE shares a number of characteristics with other neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Frontotemporal Lobar Degeneration (FTLD), it is thought to have unique pathological features (McKee et al., 2013, 2015; NINDS, 2015).

Macroscopic Neuropathology

Recent consensus work determined that "Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury" were supportive criteria for diagnosis of CTE (NINDS, 2015). Prior to this consensus work, multiple investigators described gross anatomical abnormalities associated in the postmortem autopsy of brains with neuropathologically confirmed CTE (McKee et al., 2015; Stern et al., 2011). These abnormalities (see Figure 1), which may result from underlying neurodegenerative processes, include an overall reduction in brain weight (Corsellis, Bruton, & Freeman-Browne, 1973), the enlargement of ventricles (Williams & Tannenberg, 1996), atrophy of functional brain structures (Roberts, Whitwell, Acland, & Bruton, 1990), cavum septum pellucidum (Hof et al., 1992), and depigmentation of the locus coeruleus and substantia nigra (Corsellis et al., 1973). Other observations describe relatively more modest gross anatomical findings in neuropathologically confirmed CTE (Wortzel, Brenner, et al., 2013), including a lack of cerebral atrophy and milder depigmentation of

Figure 1. Gross Pathology of CTE



Top: Coronal section of a normal brain, showing the expected size and relationship of the cerebral cortex and ventricles. Bottom: Coronal section from the brain of a retired professional football player showing characteristic gross pathology of CTE, including severe dilatation of ventricles II (1) and III (2) and cavum septum pellucidum (3); adapted from Stern et al, 2011; permissions pending.

the substantia nigra and locus coeruleus (Omalu, Bailes, et al., 2011; Omalu, Bailes, Hammers, & Fitzsimmons, 2010).

Microscopic Neuropathology

Postmortem examination of brains revealing microscopic pathological abnormalities associated with CTE has included histological observations thought to reflect intracellular and intercellular processes of neurodegeneration.

Tau Protein Aggregation

Abnormal aggregation of hyperphosphorylated tau protein, including neurofibrillary tangles (NFTs) and/or astrocytic tangles (ATs), is considered to be a neuropathological hallmark of CTE (Kiernan, Montenigro, Solomon, & McKee, 2015). A recent NIH consensus workshop determined that perivascular accumulation of tau proteins in neurons, astrocytes, and cell processes in an irregular pattern at the depths of cortical sulci was pathognomonic (i.e., uniquely indicative) of CTE (NINDS, 2015). Autopsy examinations of neuropathologically confirmed CTE across multiple studies describe abnormal tau aggregates in several brain areas, including superficial layers of the cerebral cortex, subcortical nuclei, and brainstem (McKee et al., 2013, 2015; Omalu, Bailes, et al., 2011; Stein, Alvarez, & McKee, 2014). However, there remain some differences in the literature about the volume and location of these tau protein aggregates (Iverson, Gardner, McCrory, Zafonte, & Castellani, 2015; Wortzel, Brenner, et al., 2013).

Tauopathies are a class of neurodegenerative diseases characterized by the aggregation of hyperphosphorylated tau protein (Takashima, 2013) that are thought to be associated with head injury (Abisambra & Scheff, 2014). The normal function of tau protein is to stabilize microtubules; however, aberrant hyperphosphorylation of tau causes the formation of protein aggregates and NFTs, which are thought to contribute to the development of CTE (Lucke-Wold et al., 2014). Other tauopathies include AD, progressive supranuclear palsy (Hauw et al., 1994; Litvan et al., 1996), Pick's disease (Rizzini et al., 2000), and Huntington's disease (Fernández-Nogales et al., 2014). Recent efforts to establish a neuropathological distinction between AD and CTE suggests that the latter is distinguished by the widespread presence of NFTs in perivascular areas, particularly at the depths of sulci, and in superficial cortical laminae and astrocytes (McKee et al., 2013; NINDS, 2015). Table 2 describes in greater detail the observed pathological differences between AD and CTE.

Table 2. Distinctions in Tau Pathology between AD and CTE

Pathological Features	AD	CTE
Tau Protein		
Six isoforms	All present	All present
3 or 4 repeat tau	Both present	Both present
Cell Origin		
Neuronal	NFTs and pretangles	NFTs and pretangles
Astrocytic	Not present	Prominent
Neuronal Domain		
Cell body	Prominent	Prominent
Dendrite	Prominent	Prominent
Axon	Sparse	Prominent
Cell Pattern		
Perivascular	Not present	Prominent NFTs and astrocytic tangles
Foci at depths of cerebral sulci	Not present	Prominent NFTs and astrocytic tangles
Irregular, patchy cortical distribution	Not present	Prominent
Cortical laminae	NFTs predominantly in laminae III and V	NFTs predominantly laminae II and III
Subpial astrocytic tangles	Not present	Prominent
Periventricular astrocytic tangles	Not present	Present
Distribution		
Mild pathology	Braak stages I and III: NFTs in entorhinal cortex, amygdala, and hippocampus	CTE stages I and II: NFTs in focal epicenters in cerebral cortex, usually frontal lobe
Advanced pathology	Braak stages IV and VI: • High densities of NFTs in widespread cortical areas and medial temporal lobe; uniform distribution • Low densities of NFTs in basal ganglia and brainstem • NFTs in mammillary bodies not present • White matter tracts relatively uninvolved	CTE stages III and IV: • High densities of NFTs in widespread cortical areas and medial temporal lobe; patchy irregular distribution • High densities of NFTs in basal ganglia, especially nucleus accumbens • Prominent p-tau pathology in white matter tracts

Adapted from McKee et al., 2013; reprint permissions pending

TAR DNA-Binding Protein 43 Aggregation

The presence of TAR DNA-binding protein (TDP-43) aggregates is another pathological abnormality observed in postmortem examination of neuropathologically confirmed CTE cases (Kiernan et al., 2015). McKee et al. (2010) were the first to report the presence of TDP-43 aggregates as a pathological feature of CTE. Distribution of these aggregates was reported in the brainstem; basal ganglia; diencephalon; medial temporal lobe; frontal, temporal, and insular cortices; and subcortical white matter.

TDP-43 functions as a transcriptional regulator in the central nervous system (Sephton, Cenik, Cenik, Herz, & Yu, 2012). Aberrant TDP-43 aggregates have also been reported in studies of other neurodegenerative diseases (Armstrong et al., 2009; Bosque, Boyer, & Priya, 2013), including Motor Neuron Disease (MND) (McKee et al., 2010), Amyotrophic Lateral Sclerosis, and FTLD (Baloh, 2011).

Beta-Amyloid Plaque Formation

The presence of beta-amyloid (Aβ) plaques has been reported at various levels and distributions in neuropathologically confirmed CTE cases (McKee et al., 2009, 2015; Omalu, Bailes, et al., 2011; Stein et al., 2015). Whether Aβ pathology has a unique association with the development of CTE has been called into question given that these peptide plaques are also associated with AD (Stein et al., 2014). However, a recent study suggests that Aβ deposition is associated with a pathological and clinical progression of CTE and in an accelerated trajectory compared to normal aging (Stein et al., 2015).

Axonal Injury

Evidence of axonal injury has been described in neuropathologically confirmed CTE cases. Multifocal axonal varicosities have been observed in the frontal and temporal cortex and in subcortical white matter tracts in the brains of CTE cases (McKee et al., 2009, 2013; Omalu, Bailes, et al., 2011). The extent of axonal injury is thought to be associated with the progression of CTE (McKee et al., 2013). Intercellular events following axonal injury, including microglial and astrocyte activation, are thought to be potential mechanistic links between TBI and CTE (Ling, Hardy, & Zetterberg, 2015; Lucke-Wold et al., 2014).

Neuroinflammation

Evidence of neuroinflammation has been reported in neuropathologically confirmed CTE cases (McKee, Daneshvar, Alvarez, & Stein, 2014; McKee et al., 2015). It is unclear whether inflammation is driving protein deposition of tau or if it is a compensatory repair mechanism of the neurodegenerative processes underlying CTE (Coughlin et al., 2015). TBI is known to induce neuroinflammation, which may persist for years in humans (Smith, Johnson, & Stewart, 2013). Neuroinflammation, which is associated with microglial and astroglial activation, may play a role in long-term neurodegeneration (Faden, Wu, Stoica, & Loane, 2015).

Classifications of CTE

Two research groups have proposed classification frameworks of CTE based on neuropathological observations. Omalu et al. (2011) describe four CTE phenotypes thought of as parallel pathologies. McKee et al. (2013) classify CTE into four stages that describe progressive neuropathological changes. These frameworks reflect an emerging understanding of the neuropathology of CTE, not rigid or absolute classifications (Wortzel, Brenner, et al., 2013). Indeed, criteria for both of these

classification frameworks is informed by the presence of Aβ plaques and related neuritic plaques despite the recent understanding that these features may not be associated with CTE (Stein et al., 2014).

In the phenotypic classification framework (see Table 3), the first phenotype of CTE is described as sparse to frequent NFTs and neuritic threads (NTs) in the cerebral cortex and brainstem (Omalu, Bailes, et al., 2011). The second phenotype also includes NFTs and NTs in the basal ganglia and cerebellum in addition to diffuse amyloid plaques. The third phenotype is defined by a combination of moderate to frequent NFTs and NTs predominately in the brainstem with none to sparse NFTs and NTs in the cerebral cortex and basal ganglia and none in the cerebellum. The fourth phenotype is defined by a combination of none to sparse NFTs and NTs in the cerebral cortex, brainstem, and basal ganglia and a lack of NFTs and NTs in the cerebellum. There are no diffuse amyloid plaques in the cerebral cortex. In all described phenotypes, there is a possibility of observing varying degrees of NFTs and NTs in the hippocampus with or without diffuse amyloid plaques.

Table 3. Phenotypic Classification of CTE

Phenotype	Characteristics
Phenotype I	• Sparse to frequent NFT and NT in the cerebral cortex and brainstem but without involvement of basal ganglia and cerebellum • No diffuse amyloid plaques in the cerebral cortex
Phenotype II	• Sparse to frequent NFTs and NTs in the cerebral cortex and brainstem and may include pathology in the basal ganglia and cerebellum • Presence of diffuse amyloid plaques in the cerebral cortex
Phenotype III	• Brainstem predominant: moderate to frequent NFTs and NTs in the brainstem nuclei, absent or sparse NFTs and NTs in the cerebral cortex, basal ganglia, and cerebellum • No diffuse amyloid plaques in the cerebral cortex
Phenotype IV	• Incipient: absent or sparse NFTs and NTs in the cerebral cortex, brainstem, and basal ganglia • No cerebellar involvement • No diffuse amyloid plaques in the cerebral cortex

Adapted from Omalu, Bailes, et al. 2011; reprint permissions pending

According to the classification framework of progressive pathological stages that McKee et al. (2013) propose (see Table 4), CTE begins focally, usually perivascularly at the depth of the sulci in the frontal cerebral cortex, as well as in the superficial layers of the cerebral cortex. The pathology develops over time to involve widespread regions of the medial cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem, and spinal cord. Stages I and II are considered to be mild pathologies and are characterized by NFTs in focal epicenters of the frontal cortices. Stages III and IV represent severe forms of CTE, with more widespread tau involvement.

Table 4. Progressive Classification of CTE

Stage	Macroscopic Pathology	Microscopic Pathology
Stage I	• Normal brain weight • Brain pathology is unremarkable	• Focal epicenters of perivascular p-tau and neurofibrillary and astrocytic tangles involving the sulcal depths and typically affecting the superior and dorsolateral frontal cortices • Approximately half of Stage I p-tau pathology also shows rare TDP-43 neurites • No presence of Aβ plaques, except in subjects over 50 years of age
Stage II	• Normal brain weight • Subtle brain pathology exhibited • Mild enlargement of the frontal horns of the lateral and third ventricles, cavum septum pellucidum, and pallor of the locus coeruleus and substantia nigra	• Multiple epicenters of perivascular foci of p-tau NFT and neurites at the depths of the sulci with localized spread from epicenters to the superficial layers of the adjacent cortex • Mild TDP-43 pathology as abnormal neurites and neuronal inclusions • No neurofibrillary p-tau involvement in the medial temporal lobe • Aβ plaques found in 19% of subjects if over 50 years of age
Stage III	• Mild reduction in brain weight • Mild cerebral atrophy with dilatation of the lateral and third ventricles • Septal abnormalities • Moderate depigmentation of the locus coeruleus and mild depigmentation of the substantia nigra • Atrophy of the mammillary bodies and thalamus	• Widespread p-tau pathology in the frontal, insular, temporal, and parietal cortices • Neurofibrillary pathology in the amygdala, hippocampus, and entorhinal cortex • Aβ plaques found in 13% of cases
Stage IV	• Marked reduction in brain weight • Atrophy of the cerebral cortex • Marked atrophy of the medial temporal lobe, thalamus, hypothalamus, and mammillary bodies • Diffuse atrophy of the white matter and thinning of the corpus callosum, particularly the isthmus • Severe thinning of the hypothalamic floor	• Severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, sparing the calcarine cortex • Severe p-tau pathology in the diencephalon, basal ganglia, brainstem, and spinal cord • Astrocytosis of the white matter • Neuronal loss in the cerebral cortex • Marked axonal loss of subcortical white matter tracts • Widespread TDP-43 deposits • Marked loss of myelinated nerve fibers

Adapted from McKee et al., 2013; reprint permissions pending

Neuropathological Diagnosis

Currently, there are no premortem diagnostic criteria for CTE. Recent proposals for postmortem CTE diagnostic criteria (McKee et al., 2013) have been followed by a recent NIH consensus workshop (NINDS, 2015), which established diagnostic criteria for CTE, supportive criteria for a diagnosis of CTE, and exclusions to a primary diagnosis of CTE (see Table 5).

Table 5. Neuropathological Criteria for Diagnosis of CTE

Required criteria for diagnosis of CTE

- Abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci

Supportive criteria for a diagnosis of CTE

- Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the third ventricle or signs of previous brain injury
- 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
- Abnormal tau (or silver-positive) neurofibrillary lesions in the hippocampus, especially in CA2 and CA4 regions, which differ from the preferential involvement of CA1 and subiculum in AD
- 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
- Tau immunoreactive in thorny astrocytes in subpial periventricular and perivascular locations

Exclusions to the diagnosis of primary CTE

- CA1 predominant neurofibrillary degeneration in the hippocampus in association with amyloid plaques, as seen in AD
- Cerebellar dentate cell loss, prominent coiled bodies in oligodendroglia, and tufted astrocytes as seen in progressive supranuclear palsy
- Severe involvement of striatum and pallidum with astrocytic plaques in cortical and subcortical structures as seen in cortical basal degeneration

Adapted from NINDS 2015; reprint permissions pending

Exposure to Head Injury

Existing clinical literature describing neuropathologically confirmed CTE does not substantively inform whether the condition is potentially associated with head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast). Data about the frequency or type of head injury exposure is not collected systematically or consistently across, or sometimes even within, CTE case series or case studies. Most CTE studies characterize head injury exposure simply as exposure to sport or occupation (e.g., football, boxing) without including data describing head injury frequency, severity, or the time elapsed between multiple injuries. Head injury exposure in these cases is assumed, but not necessarily quantified. Among the studies that do include data about the incidence of head injuries in CTE cases, including frequency, type, and/or severity, this information is gathered retrospectively from family interviews and/or medical records, which are subjective and carry other potential biases. Additionally, a high rate of duplication (i.e., re-reporting cases across multiple publications) exists in the clinical CTE literature (Maroon et al., 2015).

Head Injury Exposure Data in CTE Cases

A recent review analyzing 153 unique cases of neuropathologically confirmed CTE characterizes exposure to head injury by categorizing cases according to sports participation, Veteran status, or miscellaneous exposure types (Maroon et al., 2015). Additional information about head injury incidence (e.g., motor vehicle accidents, improvised explosive devices [IEDs]) was included when available, but not consistently across cases. The authors also note that while all neuropathologically confirmed CTE

cases had a “history of head trauma,” documentation of severity, frequency, and concussion was “highly variable” in the literature.

McKee & Robinson (2014) provide postmortem case reports for four military Veterans with pathological signs of CTE, three of which were previously reported (Goldstein et al., 2012). Exposure to head injury across the four cases is described in McKee & Robinson (2014) as exposure to blast (from single to “several”), as well as concussion symptoms and/or history, if experienced. The authors also review a single case study from Omalu, Hammers, et al. (2011) of a Veteran exposed to “multiple mortar blasts and IEDs” whose autopsy showed neuropathological changes consistent with CTE. Additionally, McKee & Robinson (2014) review 23 postmortem cases of Veterans neuropathologically diagnosed with CTE from the Boston VA Brain Bank. In this cohort, exposure to head injury is characterized by sports participation in 16 subjects, exposure to IED blast or military concussion in 5 subjects (3 of whom also played high school football), and other exposures, such as assault, motor vehicle accident, and posttraumatic epilepsy. Frequency and severity of head injury in these cases was not reported.

A case series of six retired football players from the Canadian Football League includes three with neuropathologically confirmed CTE at autopsy (Hazrati et al., 2013). These three cases are reported to have been exposed to multiple concussions; however, the authors note that additional frequency or severity information could not be determined. While clinical details of these cases were gathered retrospectively from family interviews, treating physicians, and medical records, the source of the concussion history was not specified by the authors.

The case series review by McKee et al. (2013) includes 35 football players with neuropathologically confirmed CTE for which head injury exposure information was available from structured retrospective interviews of family members. Statistical analyses among these cases finds that the family-reported number of concussions is not correlated with the pathological stage of CTE (concussion frequency data was not provided by authors). However, the number of years played, the number of years since retirement, and the age at death is correlated with CTE stage in these cases. The authors also did not report the collection of head injury exposure information for 17 football players included in the case series review who did not exhibit neuropathologically confirmed CTE. This case series also includes 21 military Veterans, 16 of whom were athletes (8 professional football players) and 9 of whom experienced combat. The authors note that three veterans sustained TBI and four were exposed to IEDs or explosive munitions.

Characterization of head injury exposure for 11 cases of neuropathologically confirmed CTE by Omalu et al. (2011) is limited to that of contact sports participation. While the

authors collected retrospective clinical symptom information through next-of-kin interviews, analysis to correlate symptoms with pathology was not performed.

McKee et al. (2009) present case reports of one football player and two boxers with neuropathologically confirmed CTE. Retrospectively collected head injury exposure information is documented for the football player (at least 11 concussions during college and the professional career, only one medically confirmed) and one of the boxers (a mild injury during the teenage years). The authors also review 47 cases previously documented in the literature, including boxing, football, and other sport activities. A review of these cases reveals that the characterization of exposure to head injury was limited to that of exposure to sport, with the exception of a soccer player (a single severe head injury) and a circus dwarf (knocked unconscious approximately a dozen times).

Frequency of Head Injury Exposure

Existing studies of neuropathologically confirmed cases do not provide evidence comparing single versus multiple head injury exposures in the development of CTE. Some investigators have explored associations between injury frequency and other neurological outcomes thought to be related to CTE; however, few firm conclusions can be drawn given mixed evidence and methodological concerns. A meta-analysis comparing the effect of exposure to multiple versus single mild TBI (mTBI) in athletes finds minimal, nonsignificant differences in cognitive function and symptom complaints between the two exposure frequencies, although secondary analysis finds poorer performance in delayed memory and executive measures in the multiple mTBI exposure group (Belanger, Spiegel, & Vanderploeg, 2010). Previously, investigators have reported an association between the number of sustained concussions and cognitive impairments, as well as self-reported clinical depression (Guskiewicz et al., 2005, 2007). However, methodological limitations attributed to errors inherent in self-reporting have subsequently put these findings in question (Kerr, Marshall, & Guskiewicz, 2012; Wortzel, Brenner, et al., 2013).

Type of Head Injury Exposure

Existing studies of neuropathologically confirmed cases do not provide evidence comparing head injury type in the development of CTE. Understanding how injury type may contribute to CTE is further complicated by observations that, in football players with pathologically confirmed CTE, some have a history of concussion and some do not (Stein et al., 2014), raising the possibility that subconcussive injury, or another exposure in the population, is potentially associated with the induction of CTE. Additionally, some football players with a documented history of multiple concussions do not exhibit neuropathologically confirmed CTE upon postmortem examination (Hazrati et al., 2013).

Investigation of blast-related CTE is relatively immature (Gandy et al., 2014), given that the first case of military CTE was reported fewer than five years ago (Omalu, Hammers,

et al., 2011). Goldstein et al. (2012) describe case studies of four military Veterans with neuropathologically confirmed CTE that, according to case history, were exposed to one or multiple IED blast exposures and/or one or multiple concussions; however, comparison between blast and nonblast injury in this limited cohort was not made. Observations by these authors in animal model data indicate that rotational forces, in addition to the blast wave, are necessary to induce injury and resulting sequelae, including CTE. Goldstein et al. (2012) also suggest that a single blast exposure may induce CTE, while other investigators have identified methodological problems with this conclusion (Wortzel, Brenner, et al., 2013). Additionally, a study by Ryu et al. (2014) includes neuropathology examinations from five Veterans exposed to blast injury that were absent the tau pathology associated with CTE.

Epidemiology

The incidence of CTE-associated pathology and/or symptoms in at-risk populations cannot be determined from existing literature, which has prompted investigators to call for population-based studies (Iverson et al., 2015; Lenihan & Jordan, 2015). Early observations in boxers estimating a prevalence of CTE at 17% (Roberts, 1969) are likely inapplicable to modern realities given changes to factors over the past several decades, including the nature of boxing, diagnostic criteria, the inclusion of other at-risk populations in the field (e.g., football), and an evolving understanding of CTE (Clausen, McCrory, & Anderson, 2005; Gardner et al., 2014; Lenihan & Jordan, 2015). Studies investigating the risk of neurodegenerative disorders secondary to repetitive head injury exposure yield mixed results (Jordan, 2014), as some investigators have observed greater rates of neurodegenerative symptoms in contact sport athletes (Guskiewicz et al., 2005; Lehman, Hein, Baron, & Gersic, 2012), while others find no increased rates in similar populations (Savica, Parisi, Wold, Josephs, & Ahlskog, 2012).

Despite inconclusive epidemiological evidence, the primary risk factor for CTE appears to be exposure to head impacts from concussive or subconcussive events. This determination is largely the result of observations that all neuropathologically confirmed CTE cases have a history of brain trauma (Baugh, Robbins, Stern, & McKee, 2014). Other factors related to or influencing injury exposure may play a role as well, including the length of boxing or professional football career (Lenihan & Jordan, 2015).

Studies of genetic CTE risk factors have primarily focused on the apolipoprotein E (ApoE) genotyping, particularly the ε4 allele, which is a known risk factor for AD (Michaelson, 2014), but when taken together, existing studies yield inconclusive evidence. ApoEε4 variations have been observed in case studies of neuropathologically confirmed CTE (Omalu, Bailes, et al., 2011), and some evidence suggests neuropathological impairment in contact sport athletes with the ApoEε4 variation (Jordan et al., 1997; Kutner, Erlanger, Tsai, Jordan, & Relkin, 2000). However, more recent studies have noted that abnormal ApoE allelic variation in CTE cases does not

appear to be greater than that of the general population (see Table 6) (Maroon et al., 2015; McKee et al., 2013).

Table 6. ApoE Allelic Distribution in Confirmed CTE Cases

ApoE Genotype	Overall Cases n (%)		Football Cases n (%)		% of Normal Population
ε3/ε3	49	(62.0%)	32	(60.4%)	58.5%
ε2/ε3	4	(5.1%)	4	(7.5%)	13.6%
ε2/ε2	0	(0.0%)	0	(0.0%)	0.3%
ε2/ε4	2	(2.5%)	1	(1.9%)	2.4%
ε3/ε4	20	(25.3%)	11	(20.8%)	22.2%
ε4/ε4	5	(6.3%)	5	(9.4%)	2.9%
Total	**80**		**53**		

Adapted from Maroon et al. 2015; reprint permissions pending

Clinical Manifestations

Numerous clinical symptoms have been associated with CTE, which are often variable and nonspecific, and that overlap with symptoms of multiple neurodegenerative disorders, including AD, PD, FTLD, MND, as well as postconcussive syndrome (Iverson et al., 2015; Lenihan & Jordan, 2015; Maroon et al., 2015). Clinical symptoms associated with CTE include chronic psychiatric illnesses (e.g., depression), headache, cognitive problems, and motor impairment (Iverson et al., 2015; Lenihan & Jordan, 2015; Maroon et al., 2015; McKee et al., 2013; Omalu, Bailes, et al., 2011). Experts have noted an extensive overlap of clinical symptoms associated with CTE and post-traumatic stress disorder in military populations (McKee & Robinson, 2014; Omalu, Hammers, et al., 2011). While suicidality is commonly reported, links between CTE and suicide have been questioned in the literature (Iverson, 2014; Maroon et al., 2015; Wortzel, Shura, & Brenner, 2013).

Investigators are working to establish clear links between clinical changes and CTE neuropathology. McKee et al. (2013) correlates clinical findings with a proposed framework of progressive neuropathological staging for CTE. Additionally, Stern et al. (2013) proposes two types of clinical presentation variants, one termed “behavior/mood” and one termed “cognitive.” Stein et al., (2015) subsequently reported that the cognitive variant may be associated with Aβ deposition. While the broad range of symptoms associated with CTE has been questioned as clinically meaningless (Randolph, 2014), investigators have recently suggested diagnostic criteria for CTE (Jordan, 2013; Victoroff, 2013), including the proposal of Traumatic Encephalopathy Syndrome (Montenigro et al., 2014; Montenigro, Bernick, & Cantu, 2015).

To address existing questions about links between CTE neuropathology and clinical/behavioral changes, established diagnostic criteria for longitudinal studies are needed (Antonius et al., 2014). Additionally, numerous methodological gaps in the existing body of case reports must be addressed. Data reporting is inconsistent across case studies, and a high rate (43%) of duplication (i.e., re-reporting cases across

multiple publications) has been described (Maroon et al., 2015). Conclusions derived from case studies, which are often referred to researchers by families with concerns about neurobehavioral problems (Antonius et al., 2014), are limited by the significant likelihood of selection (ascertainment) biases (Daneshvar et al., 2011; Maroon et al., 2015). Additionally, premortem symptom data, which is often derived from interviews with family members, is not objective and is subject to recall biases (McCrory, Zazryn, & Cameron, 2007).

Animal Models

Animal models may offer insights into neuropathological and neurobehavioral abnormalities thought to be associated with CTE. To date, few investigators have developed animal models designed to reflect CTE specifically (Goldstein et al., 2012; Petraglia, Plog, Dayawansa, Dashnaw, et al., 2014), which highlights opportunities for further preclinical research (Goldstein, McKee, & Stanton, 2014). However, certain animal models of TBI may be useful because they reflect some injury exposure conditions associated with CTE, such as blunt force or blast-induced TBI.

Animal models of blunt force-induced TBI are commonly used to study single and repetitive closed head injury (Ojo, Mouzon, & Crawford, 2015). Injury is induced in an anesthetized animal from impact to the skull or scalp (with or without a protective plate). The impact can be generated by dropping a weight through a tube positioned above the head or by using an electromagnetically or pneumatically powered probe (Mouzon et al., 2012; Petraglia, Plog, Dayawansa, Dashnaw, et al., 2014). The specific pathology and behavioral effects observed in each model vary with the impact severity, frequency, anatomical site, age, and linear or rotational movement of the head.

Existing animal models of blast-induced TBI include the shock-tube and open-field model. The shock-tube model induces injury by delivering highly reproducible blast waves from a gas-driven pneumatic tube system to the head of an anesthetized animal. Some investigators secure the neck, head, torso, and abdomen of the animal to minimize movement and tertiary blast effects (Cernak et al., 2011). Others use a Kevlar vest to protect the thorax of the anesthetized animal from the blast shock wave (Long et al., 2009). The open-field model typically involves placing anesthetized animals in compartments on a platform in close proximity (e.g., 4 to 7 meters) to an ordinance (e.g., TNT) and then exposing the animal to blast waves from a controlled explosion (Rubovitch et al., 2011). Recently, application of a lithotripsy machine has been developed to generate shock waves that induce brain injuries in mice (Divani et al., 2015).

Neuropathological Analysis

Animal models of blunt force-induced and blast-induced TBI described above have revealed few histological abnormalities consistent with observations in neuropathologically confirmed CTE cases.

Tau

Animal model research characterizing tau aggregation in the brain following TBI results in inconsistent findings. Several studies in rodents demonstrate an increase in tau following single impact TBI (Goldstein et al., 2012; Liliang et al., 2010; Luo et al., 2014; Perez-Polo et al., 2015) or blast-related TBI (Goldstein et al., 2012). Other studies fail to demonstrate a difference in tau aggregation when comparing single-impact TBI and sham-injury groups (Gama Sosa et al., 2014; Mannix et al., 2013; Mouzon et al., 2014).

Similarly, animal model studies investigating the impact of repeated TBI on tau aggregation in the brain report mixed findings. Animals exposed to repeated TBI did not have elevated brain levels of phosphorylated tau (as measured by immunohistochemistry, ELISA, and western blot) 24 hours, 34 days, 10 weeks, 4 months, 6 months, and 12 months postinjury (Bolton & Saatman, 2014; Mouzon et al., 2014; Xu et al., 2014). However, other studies reported that repeated TBI increases tau levels in the brain postinjury (Arun et al., 2013; Kane et al., 2012; Luo et al., 2014; Namjoshi et al., 2014; Zhang, Teng, Song, Hu, & Chen, 2015). Of these studies that found increased tau postinjury, one reported region-specific increases (cortex, amygdala, and hippocampus) of tau immunoreactivity in up to six months following repeated TBI (Petraglia, Plog, Dayawansa, Dashnaw, et al., 2014).

One reason rodent models do not accurately reflect the neuropathology of confirmed CTE cases may be that the endogenous rodent tau aggregates differently from the human protein. In an attempt to generate a more precise rodent model of head injury, two mouse models expressing human tau isoforms have been created. The hTau mouse expresses all six human tau isoforms (Andorfer et al., 2003), and the T44 mouse expresses the shortest human tau isoform (Ishihara et al., 2001). In hTau mice, Ojo et al. (2013) demonstrated increased expression of phosphorylated tau 21 days after repetitive injury; however, tau expression in these animals did not increase after a single head injury.

Axonal Injury

Axonal injury is a common neuropathological consequence of closed head injury (Johnson, Stewart, & Smith, 2013; Povlishock & Katz, 2005). Because axonal injury and subsequent intercellular events, including activation of microglia and astrocytes, are thought to be potential mechanistic links between TBI and CTE (Ling et al., 2015; Lucke-Wold et al., 2014), animal models may provide a means to study these associations.

Traditionally, axonal injury was thought to be limited to acute periods following head injury; however, recent evidence has identified axonal degeneration in human brains many years postinjury (Johnson, Stewart, Begbie, et al., 2013; Johnson, Stewart, & Smith, 2013). Evidence of chronic axonal injury indicates a potential pathology contributing to chronic symptoms of CTE. In closed head injury animal models, the presence of persistent axon damage with corresponding activation of astrocytes and microglial cells has been described in mice subjected to single and repetitive mTBI exposure (Donovan et al., 2014; Fidan et al., 2015; Luo et al., 2014; Mierzwa, Marion, Sullivan, McDaniel, & Armstrong, 2015; Mouzon et al., 2014). Activation of astrocytes and microglial cells suggestive of CTE pathology also appears to be a common feature of blast injuries in rodents (Goldstein et al., 2012; Sajja et al., 2014; Svetlov et al., 2010).

Neurobehavioral Analysis

Animal model studies have also described neurobehavioral abnormalities reflecting clinical manifestations thought to be associated with CTE. Two common neurobehavioral tests used with rodent models are the Morris water maze test for cognitive assessment (i.e., spatial learning and memory) (Vorhees & Williams, 2006) and the accelerating rotarod test for motor assessment (i.e., balance and sensorimotor coordination) (Hamm, Pike, O'dell, Lyeth, & Jenkins, 1994). Multiple investigators have demonstrated cognitive (Laurer et al., 2001; Meehan, Zhang, Mannix, & Whalen, 2012; Petraglia, Plog, Dayawansa, Chen, et al., 2014) and motor (Laurer et al., 2001; Mouzon et al., 2012) deficits in animal models following exposures to impact-related TBI. Neurobehavioral deficits have also been observed following blast-related TBI exposure in rodents (Goldstein et al., 2012; Koliatsos et al., 2011; Long et al., 2009; Säljö, Bolouri, Mayorga, Svensson, & Hamberger, 2009).

Additionally, animal model studies have explored the impact of TBI exposure frequency on neurobehavioral abnormalities. Numerous investigators have demonstrated that multiple TBI impact-related exposures result in more pervasive and long-lasting neurobehavioral deficits when compared to single-exposure injuries (Laurer et al., 2001; Meehan et al., 2012; Mouzon et al., 2012, 2014; Petraglia, Plog, Dayawansa, Chen, et al., 2014). Studies also suggest greater cognitive impairments when the interval between multiple impacts to the head is shorter (Longhi et al., 2005; Mannix et al., 2013).

Biomarkers

Successful development of objective *in vivo* biomarkers could enable the identification of CTE pathology in living persons, which would greatly enhance understanding of the underlying biological mechanisms and would inform potential diagnostic, treatment, and prevention strategies. Investigators are pursuing neuroimaging modalities and biospecimen analytes as potential predictive biomarkers of CTE.

Neuroimaging

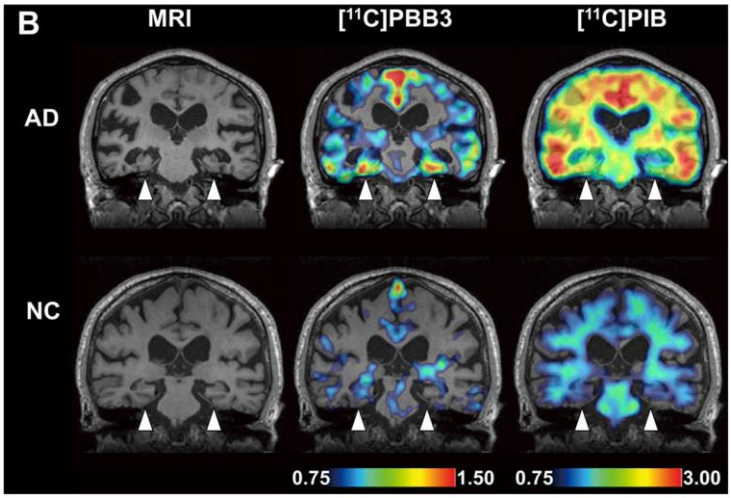
There are no longitudinal studies correlating *in vivo* neuroimaging data directly with postmortem CTE-associated pathology. Current neuroimaging research relevant to CTE biomarkers generally focuses on two approaches. One approach is the detection of molecules associated with CTE pathology (e.g., tau, Aβ). The second approach is detecting structural or molecular changes associated with head injury, which is thought to contribute to the development of CTE.

Positron Emission Tomography

Positron emission tomography (PET) can detect the presence and distribution of specific molecules using trace amounts of radioactive ligands that bind to molecules of interest. Investigators are developing PET radioligands to image pathology associated with CTE (Turner et al., 2013), including aggregations of tau (Villemagne & Okamura, 2014) and Aβ (Barrio, Hunag, & Cole, 1999). PET is also being used to assess changes in metabolic activity in the brain associated with exposure to head trauma.

Several PET radioligands targeting tau have shown potential as CTE biomarkers, and some are being investigated in clinical trials. For example, Maruyama et al. (2013) demonstrated that the [^{11}C]PBB3 radioligand exhibits specificity for tau in transgenic mouse models and human subjects with probable AD (see Figure 2). Investigators are conducting a Phase II clinical trial to determine whether [^{11}C]PBB3 can detect tau aggregates in patients with a history of TBI (National Institute of Mental Health, 2015).

Figure 2. PET Accumulation of [^{11}C]PBB3



Coronal [^{11}C]PBB3 PET scan of patients with probable AD and controls (Maruyama et al., 2014)

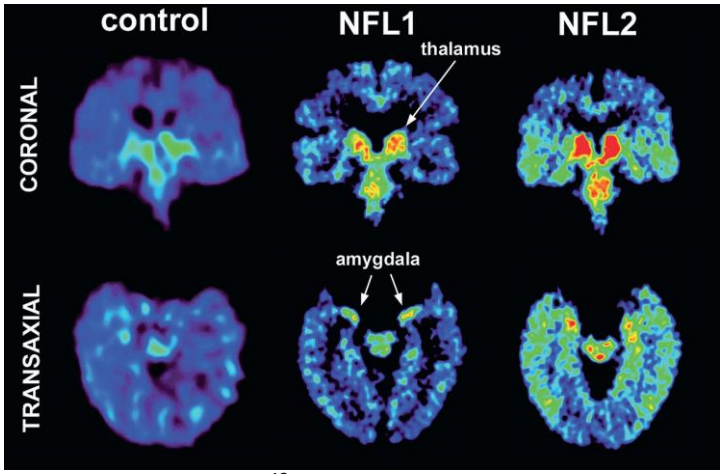
Additionally, [^{18}F]T807 and [^{18}F]T808 are two related radioligands with high affinity and selectivity for hyperphosphorylated tau in humans (Chien et al., 2013, 2014). Multiple

clinical trials are investigating the use of [^{18}F]T807 as a potential biomarker of CTE (Avid Radiopharmaceuticals, 2015; Di Carli, 2015; Molecular NeuroImaging, 2015).

PET imaging of tau faces several challenges (Villemagne, Fodero-Tavoletti, Masters, & Rowe, 2015). Tau protein aggregates are intracellularly expressed, which requires the corresponding ligand to cross the blood–brain barrier and cell membrane to bind. Tau aggregates are also subject to several post-translational modifications that alter the ultrastructural conformation of the aggregates and affect radioligand binding. Tau ligands have an affinity for Aβ aggregates as well, which poses a challenge for characterization of CTE pathology as both protein aggregates may be present in different anatomical locations and Aβ pathology is significant in AD. Nevertheless, at least six new classes of tau radioligands have been developed, each with different levels of affinity and specificity to tau relative to Aβ (Shah & Catafau, 2014).

PET imaging of Aβ aggregates has been demonstrated using a [^{18}F]FDDNP radioligand (Barrio et al., 1999); however, unlike [18F]T807, binding is relatively nonselective and also labels NFTs (i.e., tau) (Smid et al., 2013). In football players with a history of head injury exposure, [^{18}F]FDDNP PET demonstrates increased signaling in the amygdala and subcortical brain regions (see Figure 3), which is potentially indicative of CTE (Small et al., 2013). Barrio et al. (2015) describe differences in [^{18}F]FDDNP signal patterns between football players with mTBI and Veterans with blast-induced mTBI. These observations suggest that the radioligand may be useful in identifying and characterizing CTE. The [^{18}F]FDDNP radioligand also binds with extracellular Aβ plagues and intracellular NTFs in patients with AD (Shoghi-Jadid et al., 2002; Smid et al., 2013) and Down's syndrome (Nelson, Siddarth, & Kepe, 2011), so discrimination between tauopathies must rely on regional signal differences.

Figure 3. PET Imaging in Retired NFL Players



Coronal and Transaxial [^{18}F]FDDNP PET Scan of Retired NFL Players (Small et al., 2013)

PET imaging with [^{18}F]FDG PET can measure the glucose metabolic activity, which reflects the functional states of brain structures (Turner et al., 2013). [^{18}F]FDG PET imaging has found hypometabolism (relative to controls) in the brain regions of boxers, which is thought to be affected by impacts to the side of the head, including the frontal lobe anterior to Broca's area, the posterior cingulate cortex, the posterior parietal lobe, and the cerebellum (Provenzano et al., 2010). This pattern of hypometabolism differs from other types of TBI exposures, such as motor vehicle accidents and falls, which affect orbitofrontal and anterior temporal lobe areas. However, the hypometabolism of the posterior cingulate cortex and the posterior parietal lobes is similar to that seen in patients with AD, which may be responsible for the AD-like cognitive decline seen in boxers (Bonte, Harris, Roney, & Hynan, 2004). Unlike boxers, patients with AD do not typically show hypometabolism in the cerebellum, which may be unique to boxers presenting with AD-like cognitive impairments. Together, these results suggest that [^{18}F]FDG PET could potentially be used as a biomarker for TBI-related neurodegenerative processes resulting from exposure to head injury.

Researchers have also pursued the use of PET to characterize TBI-related neuroinflammation through use of radioligands selective for activated microglia. Elevated uptake of [^{11}C]R-PK11195, which binds to a transmembrane protein expressed in activated microglia, was observed in the brains of patients with moderate to severe TBI from several months to years postinjury (Folkersma et al., 2011; Ramlackhansingh et al., 2011). Increased binding of [^{11}C]-DPA-713, a second-generation radioligand with greater specificity for activated microglia, was observed in the brain regions associated with TBI of nine former NFL players compared to controls (Coughlin et al., 2015).

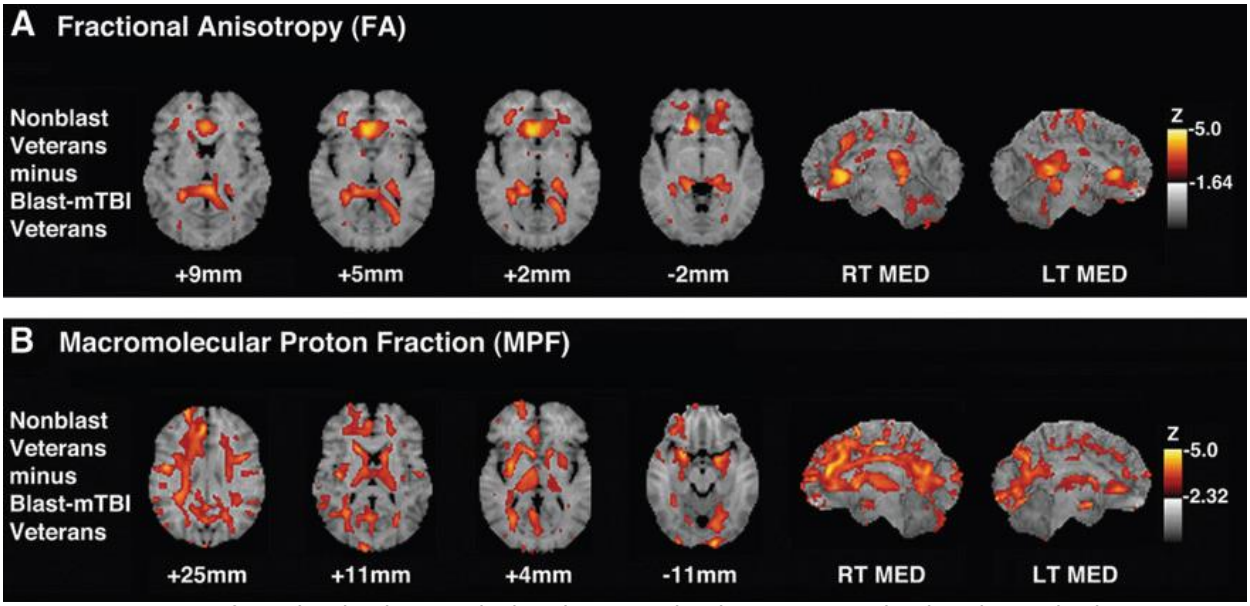
Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) can visualize white matter axon tracts, in turn enabling investigators to detect abnormalities not visible on conventional magnetic resonance imaging or computed tomography imaging methodologies (Turner et al., 2013). DTI revealed significant white matter changes in a high-school contact sport athlete following a single concussion (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012). Furthermore, significant white matter changes can be detected in contact sport athletes exposed to multiple subconsussive injuries in the absence of clinically evident concussion (Bazarian et al., 2014, 2012). DTI findings have also supported a link between axonal abnormalities and executive impairment following TBI (Lipton et al., 2009).

Several DTI studies that have investigated white matter integrity in Veterans with exposure to blast- and/or impact-related injuries report different findings. Some studies detect abnormalities in multiple, diffuse areas (see Figure 4) (Davenport, Lim, Armstrong, & Sponheim, 2012; Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015; Morey et al., 2013; Petrie et al., 2014), while MacDonald et al. (2013) report abnormalities restricted to the cerebellum. Detection of spatially heterogeneous areas of decreased

fractional anisotropy may indicate a potential DTI-based biomarker for blast-related mTBI (Jorge et al., 2012). In contrast, one recent DTI study found no significant differences in white matter integrity between Veterans exposed to blast-related injury and controls (Levin et al., 2010).

Figure 4. DTI Measurements in Veterans



DTI measurements of Fractional Anisotropy (FA) and Macromolecular Proton Fraction (MPF) mapping in Veterans with or without blast-induced mTBI. (A) FA (metric of white matter structural integrity) is reduced in the right genu of the corpus callosum of blast-induced mTBI. (B) MPF values (metric of white matter myelin compositional integrity) are lower in blast-induced mTBI in multiple brain regions. Image from Petrie et al., 2014.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive method of measuring brain chemistry *in vivo* that can be applied to detect changes in brain metabolites following TBI (Gavett et al., 2011; Turner et al., 2013). Common brain metabolites altered by brain injury that MRS can detect include decreased N-acetyl aspartate (NAA; indicating neuronal damage), increased choline (Ch) and lipid (indicating membrane damage and diffuse axonal injury), increased combined glutamate and glutamine (Glx; indicating excitotoxic effects of the brain) and increased myo-inositol (indicating brain injury from membrane damage and/or as a result of astrocytosis) (Gavett et al., 2011).

One-dimensional (1D) MRS has demonstrated a significant decrease in Glx and NAA in the primary motor cortex and NAA in the prefrontal cortex in concussed athletes as compared with nonconcussed athletes (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2009). In retired professional athletes with CTE symptoms, 1D MRS has found increased levels of Ch and Glx when compared to age-matched, healthy controls (Lin et al., 2010). Use of advanced spectroscopy methods, specifically two-dimensional localized correlated spectroscopy, illustrated changes in Glx and Ch typically captured

with conventional 1D MRS, but also recorded increases in phenylalanine and fucose from the brains of former athletes, which cannot be measured by 1D MRS (Gavett et al., 2011; Lin et al., 2015). While imaging changes in these brain metabolites using MRS may help describe pathological changes following single or repetitive brain injury, it can be difficult to distinguish between natural changes with aging and those of injury (Tremblay et al., 2013).

Researchers have been investigating MRS to study the effects of blast injury in Veterans. Reductions of NAA relative to brain metabolites Ch and creatine (Cr), NAA/Ch and NAA/Cr ratios, respectively, are thought to indicate brain injury (Signoretti et al., 2008). Significant hippocampal reductions of NAA/Ch and NAA/Cr have been observed in Veterans when compared to controls (de Lanerolle et al., 2014; Hetherington et al., 2014).

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) can investigate structural and functional changes of the brain following brain injury (Bruce et al., 2015; Gandy et al., 2014). Researchers have used fMRI to evaluate functional disruptions in both concussive and subconcussive injury groups, even in the absence of overt clinical symptoms (Talavage et al., 2010). Given its ability to detect deficits in subconcussive injury, fMRI may hold promise for future investigations of CTE-related changes (Gavett et al., 2011).

Biospecimens

Effective biospecimen-based biomarkers would provide a more accessible, cost-effective, and deployable method for identifying CTE *in vivo* than neuroimaging modalities that are resource intensive and located in fixed brick-and-mortar facilities. There are few studies focused on biospecimen-based CTE biomarkers, in part due to the pathological and symptological similarities to established neurodegenerative diseases (Turner et al., 2013). However, investigators have been pursuing the measurement of proteins and/or microRNAs found in cerebrospinal fluid (CSF) or blood plasma as potential biomarkers of TBI, which may lend insight into identification of CTE pathology *in vivo* (Baugh et al., 2012; Mez, Stern, & McKee, 2013).

Cerebrospinal Fluid

While CSF is considered a potential source of TBI biomarker identification given its direct contact with the brain and nervous system (Turner et al., 2013), the lumbar puncture required to sample CSF poses obvious disadvantages. Research on CSF biomarkers of TBI focus on axonal proteins, such as neurofilament light and tau (DeKosky, Blennow, Ikonomovic, & Gandy, 2013). A longitudinal study of amateur boxers demonstrates increased CSF levels of neurofilament light and tau after bouts (Zetterberg & Blennow, 2015). While the increases of neurofilament light suggested dose dependency (increases were more pronounced in boxers who sustained several head punches), the utility of this marker is called into question given that protein levels returned to normal after three months of no bouts. Additional studies in amateur boxers

have described increases in CSF proteins, in particular neurofilament light, tau, and glial fibrillary acidic protein (GFAP), that correlated with exposure to head trauma (Neselius et al., 2012, 2013; Zetterberg, Hietala, & Jonsson, 2006). The number of days in which the proteins remained elevated varied, indicating that they may be best used as markers of acute injury. Additional studies are needed to validate blast biomarkers and determine the most effective time to take CSF samples following exposure.

Blood Plasma

While blood-based biomarker sampling poses lower risk than the lumbar punctures that CSF approaches require, plasma biomarkers have their drawbacks, including (1) dilution of the brain-specific protein by the large volume of plasma and in the extracellular fluid of peripheral organs, (2) degradation of the biomarker candidate by blood proteases, (3) clearance of the protein by hepatic metabolism or renal excretion, and (4) analyses of brain proteins in blood that can be confounded by release of the same protein from peripheral tissues (DeKosky et al., 2013). Recent research has identified several potential blood plasma-based biomarkers of TBI. Serum levels of S-100β were increased in patients with severe TBI and demonstrate a strong correlation to clinical outcome (Anderson, Hansson, Nilsson, Dijlai-Merzoug, & Settergren, 2001; Naeimi, Weinhofer, Sarahrudi, Heinz, & Vécsei, 2006). Additionally, the ratio of GFAP to ubiquitin carboxy-terminal hydrolase-L1 in plasma may be characteristic of a focal or diffuse TBI (Mondello et al., 2012) and may change after multiple concussive or subconcussive head injuries. This ratio may potentially offer insight into the development of CTE (Turner et al., 2013). Transient, severity-dependent, and time-dependent elevations of tau levels in serum were detected following TBI in rats (Liliang et al., 2010). Additionally, Olivera et al. (2015) reported elevated concentrations of plasma tau protein in military personnel with TBI.

Another plasma-based TBI biomarker of potential relevance to CTE is neuron-specific enolase (Zetterberg et al., 2009). Elevated levels of this protein were detected in boxers after they abstained from boxing for two months when compared to healthy controls. However, S-100β, brain-derived neurotrophic factor, and heart-type fatty acid binding protein did not change. These results suggest that neuron-specific enolase may remain elevated for an extended period of time postinjury and could be a useful biomarker for diagnosing athletes and patients who have suffered multiple concussive and subconcussive head injuries.

Treatment and Prevention Strategies

There is no established treatment for CTE, and for this reason, current mitigation strategies focus on prevention of head injury and/or concussion (DeKosky et al., 2013; Jordan, 2014). While protective headgear can prevent severe injuries (e.g., penetrating injury, skull fracture, intracranial hemorrhage), helmets do not appear to mitigate the incidence or severity of sports-related concussion (Harmon et al., 2013; McCrory,

Meeuwisse, Aubry, et al., 2013). Some investigators have suggested that the use of helmets in sports enables or promotes aggressive play and increases the risk for head injury (Herring et al., 2011). Other prevention strategies in sports include rule changes and return-to-play guidelines (McCrory, Meeuwisse, Aubry, et al., 2013). The DoD is also developing return-to-activity guidelines for service members following mTBI (McCulloch et al., 2015).

Although consensus on the understanding of CTE is still being established and diagnostic criteria are still under development, researchers are investigating potential treatment approaches. Several animal model studies target tau pathology as a potential intervention strategy. Kondo et al. (2015) blocked tauopathy progression in mice with the application of an antibody that interrupted an early stage of tau development, termed “cistauosis,” following TBI. Recent work describing the impact of acetylation on tau aggregation suggests a potential therapeutic target for CTE (Cook, Carlomagno, et al., 2014; Cook, Stankowski, Carlomagno, Stetler, & Petrucelli, 2014). Additionally, pharmacologic inhibition of a metabolic enzyme (monoacylglycerol lipase) in a mouse model of repetitive closed-head injury reduced several neuropathological hallmarks of CTE, including tau phosphorylation and TDP-43 protein aggregation (Zhang et al., 2015). Because of the neuropathological similarities with AD and TBI, potential pharmacological and behavioral interventions for these conditions could also be applied to CTE (Antonius et al., 2014; Levin & Bhardwaj, 2014).

Discussion

CTE represents a major potential public health issue considering the number of athletes, service members, and Veterans exposed to single and/or multiple concussive and/or subconcussive head injuries. The current state of the science has generated an initial consensus on the neuropathology of CTE (NINDS, 2015). However, the evidence does not allow for a conclusive determination of whether exposure to head injury is sufficient and causative in the development of CTE pathology. Existing clinical data are limited, observational in nature, and subject to methodological concerns. These realities have led some investigators to question whether existing data are adequate to confirm CTE as a unique neurodegenerative disease (Iverson et al., 2015; Karantzoulis & Randolph, 2013; Randolph, 2014).

Existing neuropathological evidence describes abnormalities in the brain following exposure to head injury that may be associated with CTE development and that may reflect underlying biological processes. Recent consensus establishing perivascular tau aggregation in cortical sulci depths as unique indications of CTE represents the most conclusive pathological evidence to date (NINDS, 2015). Pathophysiological mechanisms explaining how tau aggregation causes or contributes to clinical symptoms of tauopathies, including AD, have yet to be determined, and it is not definitively established whether or how tau pathology drives or causes clinical manifestations of

CTE (Iverson et al., 2015). More broadly, it is still not clear what other macroscopic and microscopic (e.g., Aβ, TDP-43) pathological findings are unique to CTE, given that autopsy reports are inconsistent (Karantzoulis & Randolph, 2013) and that these pathological findings are also associated with aging (McCrory, Meeuwisse, Kutcher, et al., 2013) and multiple other neurodegenerative diseases (Karantzoulis & Randolph, 2013).

Identification of biomarkers enabling *in vivo* detection of CTE pathology would advance ongoing research needs. Investigators are working to develop neuroimaging and biospecimen-based biomarkers, targeting the pathophysiological mechanisms associated with CTE (e.g., tau aggregates) and the biological processes following head injury exposure. Premortem identification of CTE could potentially benefit prevention and treatment. Current preclinical and clinical development of therapeutic or rehabilitative strategies are also targeting pathophysiological mechanisms associated with CTE and the biological processes following head injury exposure.

Existing clinical evidence does not inform whether variations in head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast) are differentially associated with CTE. Data about frequency or type of head injury exposure is not collected systematically or consistently across, or sometimes even within, CTE case series or case studies. Most CTE studies characterize head injury exposure simply as exposure to sport or occupation (e.g., football, boxing) without including data describing head injury frequency, severity, or the time elapsed between injuries.

Other fundamental questions exist about the links between exposure to head injury, CTE-associated pathology, and clinical symptoms. For example, evidence does not conclusively support that retired athletes exhibit a unique neurodegenerative pathology or have higher rates of associated clinical symptoms (Randolph, 2014). Alternative hypotheses have been described recently by Iverson et al. (2015), such as the possibility that neurotrauma reduces a cerebral reserve normally protecting persons from development of neurodegenerative disorders, or that tau pathology is clinically silent such that symptoms are due to other, potentially multifactorial, causes.

Research Needs

Limitations to the conclusions that can be drawn about links between exposure to head injury, CTE-associated pathology, and clinical symptoms stem in part from the characteristics of existing evidence and methodological issues. For example, postmortem CTE autopsy cases, which are often referred to researchers by families with concerns about neurobehavioral problems (Antonius et al., 2014), are limited by significant selection (ascertainment) biases (Daneshvar et al., 2011; Karantzoulis & Randolph, 2013; Maroon et al., 2015). Data about the clinical symptoms associated with

CTE are retrospective and often derived from interviews with family members, which make the data subjective and limited by recall biases (McCrory et al., 2007).

CTE has drawn significant public and media attention given the large at-risk population (e.g., military service members, contact sport athletes). Experts have noted concern over the potential clinical and legal consequences of a widespread misunderstanding of CTE (Wortzel, Brenner, et al., 2013). Given these factors, the need for additional research is clear and investigators have called for specific actions (Iverson et al., 2015; Montenigro et al., 2014; Randolph, 2014):

- Initiation of cross-sectional, prospective, longitudinal, and/or epidemiological studies; initial work could compare retired athletes to demographically matched controls without exposure to head injury and assess whether a higher risk for clinical symptoms is supported; additional work could investigate links between CTE-associated pathology and observed clinical symptoms
- Development of standardized protocols for studying pathology, including establishing control data
- Development of clinical diagnostic research criteria
- Continued biomarker development, such as determining whether PET imaging can detect differences in tau between groups with and without head injury exposure, with different clinical manifestations, including comorbidities (as well as control subjects)

Appendices

Appendix 1: Search Terms

Condition		Pathology	Outcome Measure(s)	Study Population(s)
Alzheimer's disease	Motor neuron disease	Activated kinases	Assessment	Animal models
Auditory	Neurodegeneration	Apolipoprotein E (ApoE) genotype	Computational models	Athletes
Behavioral disorder	Neurodegenerative	Astrocytes	Diagnostic	Boxing
Blast event	Parkinsonism	Astroglial tangles	Diffraction spectrum imaging or DSI	Breacher
Blast exposure	Post-concussion syndrome or PCS	Axonopathy	Diffusion Tensor Imaging or DTI	Football
Chronic TBI	Post-traumatic stress disorder or PTSD	Beta-amyloid	Magnetic Resonance Imaging or MRI	International Space Program
Chronic traumatic encephalopathy or CTE	Potentially concussive event or PCE	Biomarker	Screening	Military
Cognition	Proteinopathies	Epigenetics	Positron Emission Tomography or PET	NASA
Cognitive deficits	Repetitive head injury	Glymphatics	Treatment	NCAA
Concussion	Suicide	Microglia		NFL
Headache/ migraine	Tauopathy	Neuroendocrine		Occupational blast
Head trauma	Traumatic brain injury or TBI	Neurofibrillary tangles		Post-mortem
Hearing	Traumatic encephalopathy	Neuropathology		Sports
Inflammation	Vascular injury	Neurosensory		Soccer
Late effects of TBI	Vertigo or dizziness	TDP-43		Veteran
Mild traumatic brain injury or mTBI	Eye, retina, optic nerve, retinal ganglion cells, photoreceptors			

Appendix 2: Selected Acronyms and Abbreviations

Aβ	Beta-amyloid
AD	Alzheimer's disease
ApoE	Apolipoprotein E
ATs	Astrocytic tangles
BBB	Blood–brain barrier
Blast PCO	DoD Blast Injury Research Program Coordinating Office
Ch	Choline
Cr	Creatine
CSF	Cerebrospinal fluid
CTE	Chronic traumatic encephalopathy
DoD	Department of Defense
DTI	Diffusion tensor imaging
DTIC	Defense Technical Information Center
FA	Fractional Anisotropy
fMRI	Functional magnetic resonance imaging
FTLD	Frontotemporal lobar degeneration
GFAP	Glial fibrillary acidic protein
Glx	Glutamine
MND	Motor neuron disease
MPF	Macromolecular proton fraction
MRS	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NFTs	Neurofibrillary tangles
NIH	National Institutes of Health
NINDS	National Institute for Neurological Disorders and Stroke
NTs	Neuritic threads
PD	Parkinson's disease
PET	Positron emission tomography
pTau	Phosphorylated tau
SoS	State of the science
TBI	Traumatic brain injury
TDP-43	TAR DNA-binding protein-43

Appendix 3: References

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