

Chronic traumatic encephalopathy and athletes



William Meehan III, MD
 Rebekah Mannix, MD,
 MPH
 Ross Zafonte, MD
 Alvaro Pascual-Leone,
 MD, PhD

Correspondence to
 Dr. Meehan:
william.meehan@childrens.harvard.edu

ABSTRACT

Recent case reports have described athletes previously exposed to repetitive head trauma while participating in contact sports who later in life developed mood disorders, headaches, cognitive difficulties, suicidal ideation, difficulties with speech, and aggressive behavior. Postmortem discoveries show that some of these athletes have pathologic findings that are collectively termed chronic traumatic encephalopathy (CTE). Current hypotheses suggest that concussions or perhaps blows to the head that do not cause the signs and symptoms necessary for making the diagnosis of concussion, so-called subconcussive blows, cause both the clinical and pathologic findings. There are, however, some athletes who participate in contact sports who do not develop the findings ascribed to CTE. Furthermore, there are people who have headaches, mood disorders, cognitive difficulties, suicidal ideation, and other clinical problems who have neither been exposed to repeated head trauma nor possessed the pathologic postmortem findings of those currently diagnosed with CTE. The current lack of prospective data and properly designed case-control studies limits the current understanding of CTE, leading to debate about the causes of the neuropathologic findings and the clinical observations. Given the potential for referral and recall bias in available studies, it remains unclear whether or not the pathologic findings made postmortem cause the presumed neurobehavioral sequela and whether the presumed risk factors, such as sports activity, cerebral concussions, and subconcussive blows, are solely causative of the clinical signs and symptoms. This article discusses the current evidence and the associated limitations. **Neurology® 2015;85:1504-1511**

GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **CTE** = chronic traumatic encephalopathy; **FTD** = frontotemporal dementia; **TDP-43** = TAR DNA-binding protein 43.

Recent case reports have described athletes previously exposed to repetitive head trauma while participating in contact sports who later in life developed mood disorders, headaches, cognitive difficulties, suicidal ideation, difficulties with speech, and aggressive behavior.¹⁻¹¹ Some were discovered, postmortem, to have certain pathologic findings that have become collectively termed chronic traumatic encephalopathy (CTE).⁷⁻¹² These observations have led to the hypothesis that concussions or perhaps blows to the head that do not cause the signs and symptoms necessary for making the diagnosis of concussion, so-called subconcussive blows, cause both the clinical and pathologic findings.¹⁻⁶ There are, however, some athletes who participate in contact sports who do not develop the clinical and pathologic findings ascribed to CTE. Furthermore, there are people who have headaches, mood disorders, cognitive difficulties, suicidal ideation, and other clinical problems who have neither been exposed to repeated head trauma nor possessed the pathologic postmortem findings of those currently diagnosed with CTE. Thus, some experts have pointed out that association does not necessarily mean causation.¹³ Nearly all of what we have learned regarding CTE has come from case reports and case series. The current lack of prospective data and properly designed case-control studies limits

Editorial, page 1442

From the Micheli Center for Sports Injury Prevention (W.M.), Waltham; the Brain Injury Center (W.M., R.M.), Sports Concussion Clinic, Division of Sports Medicine (W.M.), and Division of Emergency Medicine (W.M., R.M.), Boston Children's Hospital; the Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital (R.Z.), Massachusetts General Hospital, Brigham and Women's Hospital; and the Berenson-Allen Center and Division of Interventional Cognitive Neurosciences, Department of Neurology (A.P.-L.), Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

the current understanding of CTE, leading to debate about the causes of the neuropathologic findings and the clinical observations. The purpose of this article is to discuss the current evidence and frame the debate.

Although the term CTE is relatively new, some of the clinical and pathologic findings were described nearly a century ago. In 1928, Dr. Harrison S. Martland¹⁴ described a clinical condition in boxers who were known at the time as being punch drunk. He noted that some boxers, most often sluggers, a class of boxers who often absorb multiple blows to the head while waiting to deliver a decisive knockout blow, frequently developed unsteady gait, mental confusion, slowed muscular response, hesitant speech, tremors, dragging of the leg or foot when ambulating, and facial characteristics similar to those seen in Parkinson disease. He believed the syndrome resulted from a single or repeated blows to the head or jaw, which caused hemorrhages in the deeper portions of the cerebrum. Martland¹⁴ noted that the condition was more common in “second rate fighters used for training purposes,” and that duration of exposure to boxing appeared to be associated with a higher likelihood of developing these features.

Later authors also noted a predisposition for the condition among less skilled fighters, and made further observations, noting that the condition was irreversible and progressive, advancing steadily, even after retirement from boxing.¹⁵ Pathologic correlates were soon investigated, and the term punch drunk gave way to the terms dementia pugilistica and traumatic encephalopathy, as authors noted pathologic abnormalities such as cerebral atrophy, particularly of the frontal lobes,^{15,16} presumably a result of repeated cerebral injuries sustained over long boxing careers.^{14,16,17} The causal relationship between boxing and CTE, however, remained a matter of dispute and controversy.¹⁵

The pathologic findings associated with the disorder were further characterized in a case series of 15 boxers whose brains were studied postmortem by Corsellis et al.¹⁷ These authors described cerebral atrophy, atrophy of the mammillary bodies, thinning of the hypothalamic floor, enlargement of the lateral and third ventricles, cavum septum pellucidum with fenestrations,

and loss of pigment in the substantia nigra. While a cavum septum pellucidum can be considered a normal variant, these authors pointed out that the relative width of the cavum septum pellucidum in boxers was approximately 3–5 times that found in nonboxers. Furthermore, boxers had highly fenestrated septae in disproportionate numbers to the nonboxing population: while a fenestrated septum was present in 77% of boxers studied, it was only noted in 3% of nonboxers. These same authors described an increase in astrocytes and the presence of neurofibrillary tangles throughout the frontal and temporal cortex, prominent in the uncus and hippocampus. Unlike the pattern seen in Alzheimer disease, neurofibrillary tangles were seen in the absence of senile plaques.¹⁷

The brains studied by Corsellis et al. were re-examined in the late 1980s by Roberts et al.,¹⁸ who discovered large numbers of diffuse β -amyloid plaques. Summarizing the previous reports on dementia pugilistica, Roberts et al.¹⁸ described 3 clinical stages, consisting of (1) affective disturbances and psychotic symptoms; (2) social instability, psychiatric symptoms, memory loss, and the development of parkinsonism; and (3) general cognitive dysfunction and pyramidal tract disease. Many authors since that time have noted similar progressive symptomatology among former and current boxers,^{19–23} although, as of yet, there are no prospective longitudinal studies tracking the progression.

Interest in traumatic encephalopathy surged in the early part of this century, coinciding with the publication of case reports of the disease in American football players.^{8,9} These case reports described former National Football League players who, after their playing careers, displayed cognitive impairment, mood disturbances, depression, suicidality, and parkinsonism. Although findings differed among these former players, they all were noted at autopsy to have findings similar to those reported previously for boxers, including loss of pigment in the substantia nigra, cerebral atrophy, diffuse amyloid plaques, neurofibrillary tangles, and tau-positive neuritic threads in the neocortical areas.^{8,9} These initial case reports were soon followed by other case reports and case series of athletes, including boxers, American football players, and wrestlers,

and nonathletes who had repeated brain trauma such as abuse victims, veterans, autistic patients with head-banging behavior, and a circus clown.^{7,10–12,24,25} In an extensive case series of 47 cases of CTE published in 2009, McKee et al.¹² retrospectively reported similar clinical features, such as memory and behavior disturbances, parkinsonism, speech difficulties, and gait abnormalities, associated with cerebral and mammillary body atrophy, dilation of the lateral ventricles, fenestrations of the septum pellucidum, tau-positive neurofibrillary tangles, astrocytic tangles, and neuritic threads. β -amyloid, however, was an inconsistent feature, occurring in fewer than half of the cases they reported.¹² As other case series were reported, β -amyloid continued to be an inconsistent finding.^{10,11,25,26}

This renewed interest in CTE has led to heightened concerns over traumatic brain injuries sustained by athletes, particularly those playing American football and other contact sports. Still, numerous questions remain unanswered, particularly, given the retrospective design of these studies with the potential for referral and recall bias, whether or not the pathologic findings made postmortem cause the presumed clinical signs and symptoms. In addition, it remains uncertain whether the presumed risk factors such as sports activity, cerebral concussions, and subconcussive blows are solely causative of the clinical signs and symptoms.

DEFINITION OF CTE Despite the renewed interest in studying CTE, a standard, precise, and quantifiable definition is lacking. Different case reports, case series, and review articles use varying definitions. In particular, some definitions specify that CTE occurs as a consequence of repetitive mild traumatic brain injury,⁷ or following a single, severe traumatic brain injury,^{14,27} while others note that CTE is currently thought to be caused by repeated exposure to brain trauma.^{5,12,28} Some criteria limit the definition to athletes who played either amateur or professional contact sports.²⁹

While there may not be a standard, accepted definition, there are certain characteristics that are common to nearly all definitions of CTE. Most modern definitions of CTE describe it as a neurodegenerative disease associated with repetitive mild traumatic brain injuries.^{5,7,12,27,29} Most definitions suggest a possible clinical syndrome characterized by memory disturbance, behavior changes, parkinsonism, gait abnormalities,

speech abnormalities, and mood disturbance. Pathologically, most definitions include cerebral and temporal lobe atrophy, ventriculomegaly, enlarged cavum septum pellucidum with frequently fenestrated septum, and extensive tau-immunoreactive pathology.^{5,7,12,17,27,29} Several authors note that CTE is associated with β -amyloid deposition, especially in those with a history of boxing.^{14,15,18,23,29} Most experts agree that, at present, the definitive diagnosis can only be made postmortem.^{28,30}

CLINICAL CHARACTERISTICS Although there are, as of yet, no prospective, longitudinal studies demonstrating this, clinically, CTE is described as a progressive cognitive, motor, and mood decline. Early symptoms include memory problems and confusion, depressive symptoms, suicidal ideation, headaches, and behavior changes revealing poor impulse control and short temper with aggression.^{12,28,30–32} As reported in the case series, patients develop worsening executive functioning, trouble with language, increasingly aggressive behavior, and motor disturbance. Some patients develop parkinsonian signs, including masked facies and tremor. Severe impairments of social functioning and frank dementia can occur.^{12,28,30,32}

CTE is not considered to be a linear progression from concussion or even postconcussive syndrome, but rather, as its own entity that typically arises insidiously, years after exposure to repetitive brain traumas, and progresses slowly over years or decades.^{12,28–32} Some consider CTE a diagnosis of exclusion.^{21,30} Others note that all cases are from individuals with a history of repetitive brain trauma.²⁸

Comorbidities that have been described with CTE can lead to specific clinical symptoms. Pituitary gland atrophy has been associated with CTE and can lead to neuroendocrine findings. Given the high prevalence of Alzheimer disease (AD), a mixed pathology and clinical picture combining CTE or AD has been postulated.^{7,30} Molecular studies have suggested that repeated trauma can increase the toxicity of TAR DNA-binding protein 43 (TDP-43), a key pathologic marker of ubiquitin-positive forms of frontotemporal dementia (FTD) and associated with amyotrophic lateral sclerosis (ALS).^{7,26,30} Studies have also revealed an increased risk of FTD and ALS in individuals exposed to repetitive brain trauma.^{7,33–35} The nonspecific nature of the symptoms currently ascribed to CTE and the association with these other comorbidities makes the clinical diagnosis of CTE challenging.

PATHOLOGIC CHARACTERISTICS Grossly, CTE is characterized by cortical atrophy, particularly in the frontal and medial temporal lobes, enlarged lateral and third ventricles, hippocampal atrophy, cavum septum pellucidum, often with a fenestrated septum,

Table Proposed pathologic criteria of chronic traumatic encephalopathy

McKee et al. ⁷	Omalu et al. ²⁹
Perivascular foci of phosphorylated tau, immunoreactive astrocytic tangles, and neurofibrillary tangles	Sparse to frequent neurofibrillary tangles and neuropil threads in cerebral cortex, brainstem with or without neurofibrillary tangles and neuropil threads in subcortical nuclei and basal ganglia, no neurofibrillary tangles in the cerebellum, and no diffuse amyloid plaques in the cerebral cortex
Irregular cortical distribution of phosphorylated tau, immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci	Combination of sparse to frequent neurofibrillary tangles and neuropil threads in the cerebral cortex and brainstem with or without neurofibrillary tangles and neuropil threads in subcortical nuclei and basal ganglia, no neurofibrillary tangles and neuropil threads in the cerebellum, and sparse to frequent amyloid plaques in the cerebral cortex
Clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem	Combination of moderate to frequent neurofibrillary tangles and neuropil threads in brainstem nuclei, no to sparse neurofibrillary tangles and neuropil threads in cerebral cortex and subcortical nuclei and basal ganglia, no neurofibrillary tangles and neuropil threads in the cerebellum, and no diffuse amyloid plaques in the cerebral cortex
Neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers	Combination of no to sparse neurofibrillary tangles and neuropil threads in the cerebral cortex, brainstem, and subcortical nuclei/basal ganglia; no neurofibrillary tangles and neuropil threads in the cerebellum; and no diffuse amyloid plaques in the cerebral cortex

dilated perivascular spaces, atrophy of the diencephalon and mammillary bodies, and pallor of the substantia nigra.^{17,28,30,32,36,37}

On a cellular level, CTE is characterized by numerous tau-positive neurofibrillary tangles, neuropil neurites, and astrocytic tangles in the frontal, temporal, and insular cortices, diencephalon, basal ganglia, and brainstem, with predilection for the depths of cortical sulci and perivascular areas.^{12,26,28,29,38,39} In addition, some experts have reported accumulations of TDP-43 as neuronal and glial inclusions, neurites, and intranuclear inclusions.^{7,28,40}

The pathologic diagnosis of CTE may be complicated by skip phenomenon, whereby neurofibrillary tangles and neuropil threads are absent in many areas in the cortex and intermittently present in other areas within the same lobe in an irregular fashion involving both gyri and sulci.²⁹ β -amyloid is associated with some cases of CTE, particularly in those with an exposure to boxing,^{12,18,38,41–43} but, as noted above, this finding is described inconsistently.^{12,25–27,32}

Recently, attempts have been made to specify the pathologic criteria of CTE (table). In addition, the NIH held a consensus conference in February 2015 to define the pathologic criteria of CTE. The report from that conference states, “In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci,” further stating, “consensus was that abnormal tau immunoreactivity in neurons and glia, in an irregular, focal, perivascular distribution and at the depths of cortical sulci, was required for the diagnosis of CTE.”⁴⁴

In an attempt to integrate clinical, gross pathologic, and cellular pathologic findings, McKee et al.⁷ have defined 4 stages of CTE. The authors note that

this staging correlates with duration of exposure to American football, survival after American football exposure, and age at death. It is important to point out, however, that the staging is ultimately based on a mixed population of individuals—not all former football players—and further studies are needed to relate the clinical and pathologic stages to history and history of trauma. Furthermore, the clinical assessment was performed postmortem through interviews with the next of kin. Nonetheless, the proposed stages offer a useful framework.

Stage I: Perivascular phosphorylated tau neurofibrillary tangles in focal epicenters at the depth of sulci in the superior, superior lateral, or inferior frontal cortex, clinically associated with headaches, loss of attention, and problems with concentration.

Stage II: Neurofibrillary tangles in superficial cortical layers adjacent to focal epicenters, in the nucleus basalis of Meynert, and in the locus coeruleus, clinically associated with depression and mood swings, explosivity, loss of attention, problems with concentration, headaches, and short-term memory loss.

Stage III: Mild cerebral atrophy, septal abnormalities, ventricular dilation, a sharply concave contour of the third ventricle, and depigmentation of the locus coeruleus and substantia nigra, with dense phosphorylated tau pathology in medial temporal lobe structures, widespread regions of the frontal, septal, temporal, parietal, and insular cortices, the diencephalon, the brainstem, and the spinal cord, clinically associated with cognitive impairment, memory loss, executive dysfunction, loss of attention, problems with concentration, depression, explosivity, and visuospatial abnormalities.

Stage IV: Further cerebral, medial temporal, hypothalamic, thalamic, and mammillary body atrophy,

septal abnormalities, ventricular dilation, and pallor of the substantia nigra and locus coeruleus, with phosphorylated tau pathology including in widespread regions of the neuraxis including the white matter, prominent neuronal loss and gliosis of cerebral cortex, and hippocampal sclerosis, clinically associated with dementia, profound short-term memory loss, executive dysfunction, loss of attention, problems with concentration, explosivity, aggression, paranoia, depression, impulsivity, and visuospatial abnormalities. The most advanced cases at this stage are associated with decreased brain weight and more severe cognitive abnormalities.⁷

Currently, these pathologic characteristics can only be detected postmortem. Efforts are being made, however, to detect the pathologic correlates of chronic repetitive brain trauma, and CTE specifically, in vivo, using radiographic techniques.^{40,45–48} At present, such technology is in its nascent stages, and has yet to be validated by comparison to pathologic findings.

HYPOTHESES Several hypotheses have been proposed to explain CTE, nearly all of which stem from the belief that single or repeated blows to the head result in the clinical and pathologic findings described. In his 1928 article “Punch drunk,” Martland¹⁴ proposed the following hypothesis:

I am of the opinion that in punch drunk there is a very definite brain injury due to a single or repeated blows on the head or jaw which cause multiple concussion hemorrhages in the deeper portions of the cerebrum...These hemorrhages are then replaced by a gliosis or degenerative progressive lesion in the areas involved.

Other hypotheses suggest that repeated blows lead to shear trauma to the axons resulting in increased membrane permeability and ion shifts as described by Giza and Hovda.^{49,50} This, in turn, leads to calcium influx and the subsequent release of caspases and calpains, triggering tau phosphorylation and aggregation.⁴⁹

Blaylock and Maroon⁴¹ have recently suggested that immune excitotoxicity may be the underlying mechanism that results in CTE pathology. They have proposed that some initial head trauma primes the microglia for subsequent injury. Although both proinflammatory and anti-inflammatory cytokines and chemokines are released acutely after traumatic brain injury, microglia are initially in a largely proinflammatory state, switching later to a reparatory state. If, however, additional head trauma occurs, the hypothesis contends that microglia remain in a proinflammatory, excitotoxic mode, releasing cytokines, chemokines, and the inflammatory excitotoxins glutamate, aspartate, and quinolinic acid. These, in turn, lead to progressive neurodegeneration and the

deposition of hyperphosphorylated tau protein, resulting in neurofibrillary tangle formation.

Such ideas about complex cascades with multiple different pathogenic mechanisms involved are reminiscent of current thinking about other neurodegenerative disorders such as AD. In both AD and CTE, protein folding status for tau has been argued to play potentially an important role. Cis-tau has been found to be extremely toxic^{51–53} and may represent the initial insult activating a cascade that can lead to CTE in certain individuals or AD in others. Some research has suggested that axonal degeneration after traumatic brain injury, as opposed to being simply an acute or subacute response to injury, may persist for years, even in the absence of β -amyloid plaques, and may result from chronic inflammation.^{54,55} While axonal degeneration has been noted to occur even in the absence of β -amyloid plaques, survivors of traumatic brain injury often do have β -amyloid plaques years after the trauma.⁵⁶ These discrepant findings may be a result of changing pathophysiology, over time, after traumatic brain injury. The pathologic events leading from head trauma to CTE, however, remain poorly understood.

On a more gross structural level, McKee et al.¹² propose that concussive impacts result in fluid waves within the lateral ventricles that place a shear stress on the septum pellucidum resulting in an enlarged cavum septum and septal fenestrations. In addition, they propose that ischemia contributes to the development of CTE, noting that tau pathology occurs at the depths of sulci. They propose damage to the blood–brain barrier and release of neurotoxins contributes to the perivascular nests of tau-immunoreactive neurofibrillary tangles and neuropil neurites.¹²

Nearly all investigators describing CTE thus far propose an association between head trauma and the clinical and pathologic correlates.^{7–12,14–18,23,24,26,29,32} Some authors have noted increased disease in those with longest durations and highest burdens of exposure.^{14,23,31} Associations between other variables and disease burden, however, have also been proposed, including genetics, style of play, the manner in which concussions were managed in the past, psychiatric and other mental health disorders, alcohol and drug use, obesity, age-related changes to the brain, and coexisting dementing illnesses.^{13,57} In particular, *APOE* ϵ genotypes have been proposed as associated with a higher disease burden.^{8,10,23,25,32} In general, these case series are not designed to evaluate the effect of confounders on pathologic outcomes.

DISCUSSION The work discussed above has brought several important findings to light. We know that some athletes exposed to repetitive brain trauma develop neuropsychological difficulties later in life. We know that some athletes exposed to repetitive

brain trauma have the pathologic findings described above. We further know that some athletes with exposure to repetitive brain trauma have both neuropsychological difficulties and the pathologic findings noted above. There is, however, a lack of prospective data and properly designed case-control studies, thus limiting our current understanding of CTE.

Some authors have correctly pointed out that association does not necessarily mean causation.¹³ It remains to be determined whether or not those former athletes who have the pathologic findings used to define CTE have a higher prevalence of the clinical symptoms than those athletes exposed to contact sports who do not have the pathologic findings. It may be that exposure to repetitive brain trauma causes the pathologic findings noted above, and that these changes to the brain result in the neuropsychological and physical findings described as CTE. It may be, however, that exposure to repetitive brain trauma results in long-term neuropsychological difficulties even in the absence of hyperphosphorylated tau or β -amyloid deposits,⁵⁸ and that these pathologic findings are associated with, but not causative of, the signs and symptoms. This would explain, in part, the different patterns of pathology noted by different investigators, and the fact that some asymptomatic individuals are noted to have the pathologic findings of CTE post-mortem.⁷ It may also be that the pathologic findings are causative of the signs and symptoms of CTE, but that they do not result exclusively from exposure to repetitive brain trauma. It is possible that repetitive trauma interacts with multiple other person-specific factors to shift those with higher levels of vulnerability to a clinical decline or to the expression of another clinical syndrome at an earlier age than is typical.

Our current understanding of CTE is limited by sampling bias, since most studies almost exclusively include contact sport athletes and others exposed to repetitive brain trauma. Furthermore, there is likely a self-selection bias, as families whose loved ones had what they believe were the effects of multiple blows sustained during athletics are more likely to donate their brains to this research.²⁸

Despite the validity of some of these criticisms, the value of this work must not be overlooked. The scientific method dictates that in our quest to discover the truth we must (1) make an observation, (2) develop an hypothesis that explains the observation, (3) test that hypothesis in varying situations, and (4) reach a conclusion based on the findings of those tests. The investigators cited throughout this article have made insightful and important observations.^{7-10,12,14,17,18,25-27,29} They and others have developed some hypotheses to explain these observations.^{12,14,17,18,29,41,49} We must now test these hypotheses and, if necessary, develop new hypotheses, to further define the disease, and to develop

strategies for diagnosing and treating those at risk. Ideally, future studies will (1) compare the pathologic findings of those exposed to repetitive brain trauma to those without repetitive brain trauma and (2) compare the neuropsychological symptoms of those exposed to repetitive brain trauma who have pathologic findings to those exposed to repetitive brain trauma who do not have the pathologic findings. Only then can we quantify the true contribution of exposure to repetitive brain trauma and the presence of hyperphosphorylated tau or β -amyloid deposits to clinical observations.

AUTHOR CONTRIBUTIONS

All authors contributed to the review of the literature, interpretation of the literature, and preparation of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

W. Meehan receives royalties from ABC-Clio publishing for the sale of his book, *Kids, Sports, and Concussion: A Guide for Coaches and Parents* and royalties from Wolters Kluwer for working as an author for *UpToDate*. His research is funded, in part, by a grant from the National Football League Players Association and by philanthropic support from the National Hockey League Alumni Association through the Corey C. Griffin Pro-Am Tournament. R. Mannix is funded by the NIH (T32 HD40128-11A1) and a Boston Children's Hospital Pilot Studies Grant. R. Zafonte receives support from a grant from the National Football League Players Association and is also supported, in part, by NIH/EKS-NICHD R24 HD065688, USAMRMC W81XWH-08-2-0159, NIDRR-H133A120085, DOD W81XWH-11-2-0210, and the Gordon Foundation to Treat Paralysis. A. Pascual-Leone is also supported, in part, by grants from the Sidney R. Baer Jr Foundation, the NIH (R01HD069776, R01NS073601, R21 MH099196, R21 NS082870, R21 NS085491, R21 HD07616) and Harvard Catalyst/The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758). Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync, and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with EEG and MRI. His research is also funded, in part, by a grant from the National Football League Players Association. All funding sources provided salary support only; the content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the NIH, the National Football League Players Association, or the Sidney R. Baer Jr Foundation. None of the funding sources reviewed the data or manuscript. None was involved in data collection, analysis, interpretation, design, or recruitment. Go to Neurology.org for full disclosures.

Received February 19, 2015. Accepted in final form May 20, 2015.

REFERENCES

1. Bailes JE, Petraglia AL, Omalu BI, Nauman E, Talavage T. Role of subconcussion in repetitive mild traumatic brain injury. *J Neurosurg* 2013;119:1235-1245.
2. Broglio SP, Eckner JT, Paulson HL, Kutcher JS. Cognitive decline and aging: the role of concussive and subconcussive impacts. *Exerc Sport Sci Rev* 2012;40:138-144.
3. Breedlove EL, Robinson M, Talavage TM, et al. Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J Biomech* 2012;45:1265-1272.

4. Bazarian JJ, Zhu T, Blyth B, Borrino A, Zhong J. Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. *Magn Reson Imaging* 2012;30:171–180.
5. Gavett BE, Cantu RC, Shenton M, et al. Clinical appraisal of chronic traumatic encephalopathy: current perspectives and future directions. *Curr Opin Neurol* 2011;24:525–531.
6. Killam C, Cautin RL, Santucci AC. Assessing the enduring residual neuropsychological effects of head trauma in college athletes who participate in contact sports. *Arch Clin Neuropsychol* 2005;20:599–611.
7. McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 2013;136:43–64.
8. Omalu BI, DeKosky ST, Hamilton RL, et al. Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery* 2006;59:1086–1092; discussion 92–93.
9. Omalu BI, DeKosky ST, Minster RL, Kambh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery* 2005;57:128–134; discussion 34.
10. Omalu BI, Fitzsimmons RP, Hammers J, Bailes J. Chronic traumatic encephalopathy in a professional American wrestler. *J Forensic Nurs* 2010;6:130–136.
11. Omalu BI, Hamilton RL, Kambh MI, DeKosky ST, Bailes J. Chronic traumatic encephalopathy (CTE) in a National Football League Player: case report and emerging medicolegal practice questions. *J Forensic Nurs* 2010;6:40–46.
12. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009;68:709–735.
13. McCrory P, Meeuwisse WH, Kutcher JS, Jordan BD, Gardner A. What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes? *Br J Sports Med* 2013;47:327–330.
14. Martland HS. Punch drunk. *J Am Med Assoc* 1928;91:1103–1107.
15. Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. *Br Med J* 1957;1:357–362.
16. Miller H. Mental after-effects of head injury. *Proc R Soc Med* 1966;59:257–261.
17. Corsellis JA, Bruton CJ, Freeman-Browne D. The aftermath of boxing. *Psychol Med* 1973;3:270–303.
18. Roberts GW, Allsop D, Bruton C. The occult aftermath of boxing. *J Neurol Neurosurg Psychiatry* 1990;53:373–378.
19. Bailey DM, Jones DW, Sinnott A, et al. Impaired cerebral haemodynamic function associated with chronic traumatic brain injury in professional boxers. *Clin Sci* 2013;124:177–189.
20. Drew RH, Templer DI, Schuyler BA, Newell TG, Cannon WG. Neuropsychological deficits in active licensed professional boxers. *J Clin Psychol* 1986;42:520–525.
21. Jordan BD. Chronic traumatic brain injury associated with boxing. *Semin Neurol* 2000;20:179–185.
22. Jordan BD, Matser EJ, Zimmerman RD, Zazula T. Sparring and cognitive function in professional boxers. *Phys Sportsmed* 1996;24:87–98.
23. Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *JAMA* 1997;278:136–140.
24. Goldstein LE, Fisher AM, Tagge CA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med* 2012;4:134ra60.
25. Omalu B, Hammers JL, Bailes J, et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurg Focus* 2011;31:E3.
26. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* 2010;69:918–929.
27. Omalu BI, Bailes J, Hammers JL, Fitzsimmons RP. Chronic traumatic encephalopathy, suicides and parasuicides in professional American athletes: the role of the forensic pathologist. *Am J Forensic Med Pathol* 2010;31:130–132.
28. Baugh CM, Stamm JM, Riley DO, et al. Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav* 2012;6:244–254.
29. Omalu B, Bailes J, Hamilton RL, et al. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 2011;69:173–183; discussion 83.
30. Saule M, Greenwald BD. Chronic traumatic encephalopathy: a review. *Rehabil Res Pract* 2012;2012:816069.
31. Costanza A, Weber K, Gandy S, et al. Review: contact sport-related chronic traumatic encephalopathy in the elderly: clinical expression and structural substrates. *Neuropathol Appl Neurobiol* 2011;37:570–584.
32. Stern RA, Riley DO, Daneshvar DH, Nowinski CJ, Cantu RC, McKee AC. Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. *PM R* 2011;3:S460–S467.
33. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? *Eur J Epidemiol* 2005;20:237–242.
34. Binazzi A, Belli S, Uccelli R, et al. An exploratory case-control study on spinal and bulbar forms of amyotrophic lateral sclerosis in the province of Rome. *Amyotroph Lateral Scler* 2009;10:361–369.
35. Chio A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 2005;128:472–476.
36. Handratta V, Hsu E, Vento J, Yang C, Tanev K. Neuroimaging findings and brain-behavioral correlates in a former boxer with chronic traumatic brain injury. *Neurocase* 2010;16:125–134.
37. Orrison WW, Hanson EH, Alamo T, et al. Traumatic brain injury: a review and high-field MRI findings in 100 unarmed combatants using a literature-based checklist approach. *J Neurotrauma* 2009;26:689–701.
38. Blennow K, Hardy J, Zetterberg H. The neuropathology and neurobiology of traumatic brain injury. *Neuron* 2012;76:886–899.
39. Mandelkow EM, Mandelkow E. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. *Cold Spring Harb Perspect Med* 2012;2:a006247.
40. Small GW, Kepe V, Siddarth P, et al. PET scanning of brain tau in retired national football league players: preliminary findings. *Am J Geriatr Psychiatry* 2013;21:138–144.
41. Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy—A unifying hypothesis. *Surg Neurol Int* 2011;2:107.

42. Tokuda T, Ikeda S, Yanagisawa N, Ihara Y, Glenner GG. Re-examination of ex-boxers' brains using immunohistochemistry with antibodies to amyloid beta-protein and tau protein. *Acta Neuropathol* 1991;82:280–285.
43. Uryu K, Laurer H, McIntosh T, et al. Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. *J Neurosci* 2002;22:446–454.
44. Stroke NINDa. Report from the first NIH consensus conference to define the neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Available at: <http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm>. Accessed March 31, 2015.
45. Gandy S, DeKosky ST. [18F]-T807 tauopathy PET imaging in chronic traumatic encephalopathy. *F1000Res* 2014;3:229.
46. Koerte IK, Ertl-Wagner B, Reiser M, Zafonte R, Shenton ME. White matter integrity in the brains of professional soccer players without a symptomatic concussion. *JAMA* 2012;308:1859–1861.
47. Poole VN, Abbas K, Shenk TE, et al. MR Spectroscopic evidence of brain injury in the non-diagnosed Collision sport athlete. *Dev Neuropsychol* 2014;39:459–473.
48. Poole VN, Breedlove EL, Shenk TE, et al. Sub-concussive hit characteristics predict deviant brain metabolism in football athletes. *Dev Neuropsychol* 2015;40:12–17.
49. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin Sports Med* 2011;30:179–188, xi.
50. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train* 2001;36:228–235.
51. Nakamura K, Greenwood A, Binder L, et al. Proline isomer-specific antibodies reveal the early pathogenic tau conformation in Alzheimer's disease. *Cell* 2012;149:232–244.
52. Nakamura K, Zhen Zhou X, Ping Lu K. Cis phosphorylated tau as the earliest detectable pathogenic conformation in Alzheimer disease, offering novel diagnostic and therapeutic strategies. *Prion* 2013;7:117–120.
53. Nakamura K, Zhou XZ, Lu KP. Distinct functions of cis and trans phosphorylated tau in Alzheimer's disease and their therapeutic implications. *Curr Mol Med* 2013;13:1098–1109.
54. Chen XH, Johnson VE, Uryu K, Trojanowski JQ, Smith DH. A lack of amyloid beta plaques despite persistent accumulation of amyloid beta in axons of long-term survivors of traumatic brain injury. *Brain Pathol* 2009;19:214–223.
55. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 2013;136:28–42.
56. Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol* 2012;22:142–149.
57. Watanabe T, Elovic E, Zafonte R. Chronic traumatic encephalopathy. *PM R* 2010;2:671–675.
58. Mannix RM, Meehan WP, Mandeville J, et al. Clinical correlates in an experimental model of repetitive mild brain injury. *Ann Neurol* 2013;74:65–75.

Neurology[®]

Chronic traumatic encephalopathy and athletes

William Meehan III, Rebekah Mannix, Ross Zafonte, et al.

Neurology 2015;85;1504-1511 Published Online before print August 7, 2015

DOI 10.1212/WNL.0000000000001893

This information is current as of August 7, 2015

Updated Information & Services	including high resolution figures, can be found at: http://www.neurology.org/content/85/17/1504.full.html
Supplementary Material	Supplementary material can be found at: http://www.neurology.org/content/suppl/2015/10/24/WNL.0000000000001893.DC1.html
References	This article cites 57 articles, 12 of which you can access for free at: http://www.neurology.org/content/85/17/1504.full.html##ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://www.neurology.org/content/85/17/1504.full.html##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Trauma http://www.neurology.org/cgi/collection/all_trauma Brain trauma http://www.neurology.org/cgi/collection/brain_trauma
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/addir.xhtml#reprintsus

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2015 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

