Published in final edited form as:

Nat Rev Neurol. 2019 March ; 15(3): 179–183. doi:10.1038/s41582-018-0114-8.

Chronic traumatic encephalopathy — confusion and controversies

Douglas H. Smith^{1,*}, Victoria E. Johnson¹, John Q. Trojanowshi^{2,3,4}, and William Stewart^{5,6}

¹Department of Neurosurgery, Penn Center for Brain Injury and Repair, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

²Department of Pathology and Laboratory Medicine, Institute on Aging, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

³Institute on Aging, University of Pennsylvania, Philadelphia, PA, USA.

⁴Center for Neurodegenerative Disease Research, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

⁵Department of Neuropathology, Queen Elizabeth University Hospital, Glasgow, UK.

⁶Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK.

Abstract

The term chronic traumatic encephalopathy (CTE) has recently entered public consciousness via media reports and even a Hollywood movie. However, in contrast to general impressions, the incidence of CTE is unknown, the clinical diagnostic criteria have not been agreed upon and the current neuropathological characterization of CTE is acknowledged as preliminary. Additionally, few studies have compared the pathologies of CTE with those of other neurodegenerative disorders or of age-matched controls. Consequently, disagreement continues about the neuropathological aspects that make CTE unique. Furthermore, CTE is widely considered to be a consequence of exposure to repeated head blows, but evidence suggests that a single moderate or severe traumatic brain injury can also induce progressive neuropathological changes. These unresolved aspects of CTE underlie disparate claims about its clinical and pathological features, leading to confusion among the public and health-care professionals alike.

In little more than a decade, the term chronic traumatic encephalopathy (CTE) has emerged into public consciousness via intense media coverage. The issue has even spawned numerous documentaries and is the subject of a Hollywood movie in which a neuropathologist is the protagonist¹. This media attention has helped to increase awareness of an important public health concern but has often included inaccurate or confusing

* smithdou@pennmedicine.upenn.edu.

Author contributions

All authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

descriptions of the fundamental aspects of CTE, thereby causing undue alarm. For example, news stories have implied a link between suicide and brain pathologies in former athletes, but no evidence supports this association. Other reports suggest that degenerative brain disease is almost inevitable for participants in some sports^{2,3}, but the actual incidence of CTE remains unknown⁴. Furthermore, despite the widely held impression that the neuropathology of CTE has been fully characterized, current consensus neuropathological criteria are acknowledged as only preliminary, in part because these criteria are based on a limited number of selected cases⁵. As a consequence, many disparate claims about the clinical and pathological features of CTE continue to confuse not only the general public, but also health-care professionals. Nonetheless, behind the hyperbole, a long history of CTE (FIG. 1) points the way forward to a better understanding of the association between traumatic brain injury (TBI) and late neurodegeneration.

In this Perspectives article, we examine the history of CTE from its first description as a neuropsychiatric entity in boxers through to current understanding of its neuropathological characteristics from a wide range of TBI exposures. We also address areas where the public perception of CTE and the scientific literature do not align, and the associated controversies.

History versus headlines

Although the term CTE has only recently entered the public vocabulary, an association between repeated head blows and early dementia has been recognized for over 90 years. In 1928, Martland first described the chronic neuropsychiatric sequelae of boxing as the ‘punch drunk’ syndrome⁶, which was later referred to as dementia pugilistica. Multiple subsequent reports elaborated on these early observations and generated a somewhat consistent and characteristic clinical picture^{7–10}, which included psychiatric symptoms, emotional lability, personality changes, memory impairment and dementia, pyramidal and extrapyramidal dysfunction, and cerebellar impairment. In 1969, a comprehensive study of 224 randomly selected, living professional boxers demonstrated that 17% exhibited a “relatively stereotyped clinical pattern” consistent with a degree of neurological impairment¹¹.

Despite this long experience with dementia pugilistica, it has now been subsumed into CTE, a clinical entity that is more encompassing but is also more vague, a problem that has resulted in misunderstanding and controversy. Particular confusion has arisen around symptoms such as suicidality, aggression and disinhibition, which were not characterized in dementia pugilistica but have been described in contemporary series of non-boxer athletes for whom a diagnosis of CTE was made at autopsy^{3,12}. This issue could be exacerbated by the fact that, at present, CTE is defined by neuropathology rather than formal clinicopathological correlation. In addition, the general perception that athletes are at increased risk of suicide and dementia associated with repetitive mild TBI-induced neuropathology seems to be based on multiple high-profile media reports rather than on evidence from adequately powered and unbiased scientific studies. Indeed, in a study of retired American National Football League (NFL) players who were followed up until 2013, the suicide rate was actually lower among this population than would have been expected among a comparable US population¹³. However, in more recent studies the reported suicide rate among individuals with autopsy-diagnosed CTE has been higher than anticipated³. If

confirmed, this observation could indicate a recent change in suicidality among former NFL athletes, an area that will require careful exploration. Prospective studies of athletes involved in contact sports other than boxing are currently underway, which might help to resolve the incidence of CTE and its neuropsychiatric profile, including suicidality, and determine whether these characteristics differ from those observed long ago in boxers.

Not new, just newly publicized

Despite several decades of suspicion that boxing could lead to progressive neurodegeneration, the neuropathology of a boxer with dementia was not described until the report of Brandenburg and Hallervorden in 1954 (REF.¹⁴). Two decades later, in a landmark autopsy study of former professional and amateur boxers, Corsellis and colleagues detailed stereotypical neuropathological findings associated with dementia pugilistica¹⁵ that continue to be elaborated today. However, these observations raised little interest from the public or the research community, perhaps owing to the misperception that boxing is unique with regards to head impacts and repetitive mild TBI.

Despite media claims and the narrative of the movie *Concussion*¹ CTE is not a new disease entity; recognition that the condition can occur in contact sports and contexts other than boxing is what is new. In particular, neuropathological findings similar to those previously described in boxers have been reported in players of American football, ice hockey, soccer and rugby^{12,16–21}, and in military personnel^{22,23}. In addition, identification of similar pathology in individuals who have experienced a single moderate or severe TBI^{24,25} (see Neurodegeneration after a single TBI below) has drawn attention to the possibility that CTE-like pathology can be associated with the full spectrum of TBI severities.

Tangled impressions about tau

Features of tau pathology that might characterize CTE have been identified, but disagreement exists about the validity of this histopathological characterization. Current evidence suggests that the distribution of neurofibrillary tangles in TBI-associated neurodegeneration is distinct from that in other neurodegenerative diseases. In multiple accounts of CTE in the past three decades^{12,16–23,26}, cortical pathology has been described as a patchy distribution of hyperphosphorylated tau deposits in neurons and glia, typically in perivascular locations and with a preferential distribution towards the depths of cortical sulci. These observations form the core of the current consensus criteria for the neuropathological diagnosis of CTE⁵. However, remarkably few cases have been described in the literature, and these consensus criteria are acknowledged as being preliminary, in part because they are based on the review of autopsy samples from just ten selected individuals.

Whether the distribution of neurofibrillary tangles is sufficient to diagnose a neuropathologically distinct neurodegenerative disorder, regardless of the clinical syndrome or previous exposure to TBI, remains unclear. Notably, a review of tissue samples from the Queen Square Brain Bank (London, United Kingdom) identified the so-called pathognomonic tau pathology of CTE in 12% of individuals from whom tissue was examined, regardless of whether the individual had a history of neurodegenerative disease²⁷.

However, all individuals in whom CTE pathology was present in this study had previously been exposed to TBI. On this basis, the tau pathology that is currently considered as being characteristic of CTE might indicate exposure to TBI but not necessarily neurodegenerative disease per se. Furthermore, the fact that the number of cases evaluated to date is limited means that attempts to stage neurodegenerative disease on the basis of neurofibrillary tangle distribution must remain speculative^{12,28}. These uncertainties are reinforced by disparities between pathological descriptions. For example, early studies of pathology in boxers identified that tau pathology was most abundant in the medial temporal lobe¹⁵, whereas subsequent studies suggest relative sparing of the medial temporal lobe^{5,12,18,19}.

Tau is not alone

In contemporary reports, the designation of CTE has often been based on the presence of tau pathology alone⁵. Neurofibrillary tangles are undoubtedly one of the most consistently described pathologies in patients with CTE^{12,25}, but historic accounts and other contemporary case series make clear that post-TBI neurodegeneration is a multifaceted pathology (FIG. 2); the additional pathologies that have been described are discussed below. In the future, the constellation of neuropathological changes that are linked with a history of exposure to TBI will continue to expand, as has been the case for many other neurodegenerative diseases. Nonetheless, on the basis of current evidence, we might already embrace the concept that CTE is not associated with a singular neuropathology.

Amyloid- β .

Amyloid- β (A β) pathology has frequently been identified alongside tau pathologies in post-TBI neurodegeneration²⁹. In a re-examination of Corsellis' original series with further cases added, 19 of 20 former boxers were found to have diffuse A β plaques³⁰. Case series of non-boxer athletes have also demonstrated a high prevalence of A β pathology, which increases with higher age at death^{3,25,31}. As such, whether A β pathology in CTE is directly linked to a history of exposure to TBI or is simply related to age remains to be elucidated. Notably, individuals with A β pathology also had clinical symptoms of cognitive impairment. Given that a limited number of cases have been examined and age-matched controls have not been used, further studies are undoubtedly required to determine the role of A β pathology in CTE before concluding that this pathology is incidental.

TDP43.

Evidence suggests that the 43 kDa transactive response (TAR) DNA-binding protein (TDP43) is involved in post-TBI neurodegeneration. In some conditions, TDP43 translocates from the nucleus to the cytoplasm, where it can become polyubiquitinated and hyperphosphorylated to form pathological inclusion bodies³². TDP43 is increasingly recognized as a major disease-associated protein in several neurodegenerative conditions, including frontotemporal lobar dementia and amyotrophic lateral sclerosis (ALS)^{32,33}, and as a minor component in various other conditions, such as Alzheimer disease (AD) and Parkinson disease^{34–36}. Autopsy studies of former boxers, American football players and hockey players have identified neuronal cytoplasmic TDP43 inclusions and distinctive 'grain-like' profiles in the surrounding neuropil in multiple regions^{5,37,38}. In a small number

of patients with ALS, autopsy studies have identified the tau pathology of CTE alongside TDP43 pathology^{12,38}. However, these few observations are not enough to conclude that the observed pathology represents an ALS-like variant of CTE (a condition that has been referred to as CTE plus motor neuron disease) or simply ALS with coincident CTE-like tau pathology.

Atrophy.

Acute and chronic axon degeneration after a single, severe TBI have been extensively documented, but white matter changes after repetitive mild TBI have also been observed in association with evidence of gliosis, foci of white matter degeneration or rarefaction^{15,39,40}, and patchy loss of myelin staining^{15,28,39,41}. Similarly, evidence of neuroinflammation has been observed, albeit in few case series^{15,28,40,42,43}. In addition, brain atrophy is frequently reported in boxers, often in the frontal and temporal lobes and the cerebellum^{8,15,41,44,45}. In most descriptions of CTE in boxers^{8,15,25,39,40,42} and in many non-boxer athletes^{12,21,25}, the pathologies observed include abnormalities of the septum pellucidum, including cavum septum pellucidum, which are often associated with ventricular dilatation.

Neurodegeneration after a single TBI

Substantial epidemiological evidence demonstrates that exposure to just a single moderate to severe TBI is associated with an increased risk of late neurodegeneration^{4,25,46–51}. In the reports to date, which have typically been based on retrospective studies, the dementia that follows a single TBI is often classified as AD-like, although none of these studies have included confirmation of the neuropathology at autopsy. Consequently, the presumption that AD follows a single moderate to severe TBI is, at best, speculative. Nonetheless, the idea that repetitive mild TBI leads to CTE but that a single moderate to severe TBI leads to AD is often put forward⁵². However, a series of studies show that almost all of the neuropathological changes described in boxers and non-boxer athletes as a result of repetitive mild TBI can also be observed in some individuals years after surviving a single moderate or severe TBI^{24,25,53,54}.

Can CTE follow a single TBI?

Analysis of non-selected brain tissue samples from individuals in the Glasgow Traumatic Brain Injury Archive (United Kingdom) who survived for 1 year after a single moderate or severe TBI revealed a greater density and wider distribution of both neurofibrillary tangles and A β plaques in ~30% of patients with TBI than in age-matched controls who had not experienced a TBI²⁴. However, these proteinopathies followed different temporal courses.

Pathological examination within months of a single moderate or severe TBI did not reveal the presence of any neurofibrillary tangles⁵⁵, yet abundant neurofibrillary tangles were observed beyond 1 year²⁴, suggesting that the processes that drive the formation of neurofibrillary tangles after TBI might progress over months to years. By contrast, A β pathology after a single moderate or severe TBI seems to develop much faster. Notably, in a large animal model of TBI⁵⁶ and in a study of human brain tissue⁵⁷, a unique mechanism of A β production after TBI has been linked to progressive axonal pathology. Specifically,

massive accumulation of amyloid precursor protein, presenilin 1 and β -secretase in damaged axons shortly after injury triggers formation of A β within the axon membrane compartment⁵⁸.

This extensive genesis and release of A β from lysing axons might account for the A β plaques that are seen in autopsy samples^{59,60} and in surgically excised brain tissue from patients in the acute phase following a moderate or severe TBI⁶¹. These A β plaques can be observed within hours of injury and are associated with polymorphisms in the genes that encode apolipoprotein E⁶² and neprilysin⁶³. By contrast, few A β plaques are found in the brains of individuals who survive a single moderate or severe TBI several months after the injury, but beyond 1 year, plaques reappear at a higher density than in age-matched controls²⁴. In these individuals, fibrillar A β plaques were observed in addition to diffuse plaques. Notably, chronic neuroinflammation has been observed to last for decades after a single moderate or severe TBI, in association with ongoing white matter loss and axonal degeneration⁵³, which might have a role in the formation of late A β plaques.

The TDP43 proteinopathy observed in some people who have experienced repetitive mild TBI does not seem to develop in patients who survive a single moderate or severe TBI⁶⁴ (FIG. 2). This observation raises the intriguing possibility that some pathological processes are shared across the spectrum of TBI severity whereas others differ.

Conclusions and the evolution of CTE

Ninety years since Martland's original description of the 'punch drunk' syndrome⁶, numerous key questions about CTE remain unanswered. By all accounts to date, the clinicopathological heterogeneity of CTE rivals that of AD and other neurodegenerative disorders. To allow meaningful clinical research to progress, there is a pressing need to achieve consensus about the clinical and neuropathological operational diagnostic criteria for CTE. In parallel, the question of whether the pathologies that have been described after a single moderate or severe TBI are the same as the pathologies that develop after repetitive mild TBI needs to be answered. More studies are needed to resolve this question, but on the basis of the current literature, the pathologies associated with survival of TBI seem to be as heterogeneous as the forms of TBI themselves. Considering the many shared pathological features that have been described, the changes could indicate a TBI dose effect, whereby a threshold that triggers neurodegenerative cascades can be reached as a result of one severe TBI or the cumulative effects of multiple mild TBI. Notably, whether exposure to repeated head impacts without a diagnosis of TBI — so-called subconcussive blows — can also trigger neurodegeneration remains to be determined.

While we await full and rigorous characterization of CTE, the current evidence does not support the widely accepted premise that it is exclusively a tauopathy that occurs only in people who have been exposed to repetitive mild TBI. Neither does the evidence support the idea that neurodegeneration after exposure to a single moderate or severe TBI is inevitably AD. Unquestionably, CTE encompasses a broader range of neuropathologies and outcomes after TBI of varying severity, and time will tell whether the condition is a distinct disease entity or is linked with other neurodegenerative processes such as AD. However, as CTE has

become embedded in the public consciousness and is fortified by the media, we are obliged to continue with the term. Meanwhile, the words of Corsellis from his original account of boxers over four decades ago are as relevant now as they were then: “most of the trenchant views that are expressed about the vulnerability, as well as the immunity, of the brain in [sport] are still based more on supposition than on fact”¹⁵.

Acknowledgements

The authors' work is supported by funding from the US National Institute of Neurological Disorders and Stroke of the NIH under award numbers R01 NS092398, R01NS094003 and R01NS038104.

References

- Landesman P Concussion [film]. (Columbia Pictures, 2015).
- Ward J, Williams J & Manchester S 110 N.F.L. brains. NYTimes <https://www.nytimes.com/interactive/2017/07/25/sports/football/nfl-cte.html> (2017).
- Mez J et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA 318, 360–370 (2017). [PubMed: 28742910]
- Wilson L et al. The chronic and evolving neurological consequences of traumatic brain injury. Lancet Neurol. 16, 813–825 (2017). [PubMed: 28920887]
- McKee AC et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol. 131, 75–86 (2016). [PubMed: 26667418]
- Martland H Punch drunk. J. Am. Med. Assoc 91, 1103–1107 (1928).
- Critchley M Medical aspects of boxing, particularly from a neurological standpoint. BMJ 1, 357–362 (1957). [PubMed: 13396257]
- Mawdsley C & Ferguson FR Neurological disease in boxers. Lancet 2, 795–801 (1963). [PubMed: 14052038]
- Spillane JD Five boxers. BMJ 2, 1205–1210(1962). [PubMed: 13990135]
- Millsbaugh J Dementia pugilistica. U.S. Nav. Med. Bull 35, 297–303 (1937).
- Roberts AH Brain Damage in Boxers: a Study of the Prevalence of Traumatic Encephalopathy Among Ex-Professional Boxers (Pitman Medical & Scientific Publishing, 1969).
- McKee AC et al. The spectrum of disease in chronic traumatic encephalopathy. Brain 136, 43–64 (2012). [PubMed: 23208308]
- Lehman EJ, Hein MJ & Gersic CM Suicide mortality among retired national football league players who played 5 or more seasons. Am. J. Sports Med. 44, 2486–2491 (2016). [PubMed: 27159317]
- Brandenburg W & Hallervorden J Dementia pugilistica with anatomical findings [German], Virchows Arch. Pathol. An at. Physiol. Klin. Med 325, 680–709 (1954).
- Corsellis JA, Bruton CJ & Freeman-Browne D The aftermath of boxing. Psychol. Med 3, 270–303 (1973). [PubMed: 4729191]
- Omalu BI et al. Chronic traumatic encephalopathy in a national football league player: part II. Neurosurgery 59, 1086–1092 (2006). [PubMed: 17143242]
- Omalu BI et al. Chronic traumatic encephalopathy in a National Football League player. Neurosurgery 57, 128–134 (2005).
- McKee AC et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J. Neuropathol. Exp. Neurol 68, 709–735 (2009). [PubMed: 19535999]
- Geddes JF, Vowles GH, Nicoll JA & Revesz T Neuronal cytoskeletal changes are an early consequence of repetitive head injury. Acta Neuropathol. 98, 171–178(1999). [PubMed: 10442557]

20. Ling H et al. Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. *Acta Neuropathol.* 133, 337–352(2017). [PubMed: 28205009]
21. Stewart W, McNamara PH, Lawlor B, Hutchinson S & Farrell M Chronic traumatic encephalopathy: a potential late and under recognized consequence of rugby union? *QJM* 109, 11–15 (2016). [PubMed: 25998165]
22. Omalu B et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurg. Focus* 31, E3 (2011).
23. Goldstein LE et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci. Transl Med* 4, 134ral60 (2012).
24. Johnson VE, Stewart W & Smith DH Widespread tau and amyloid- β pathology many years after a single traumatic brain injury in humans. *Brain Pathol.* 22, 142–149 (2012). [PubMed: 21714827]
25. Smith DH, Johnson VE & Stewart W Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat. Rev. Neurol* 9, 211–221 (2013). [PubMed: 23458973]
26. Hof PR, Knabe R, Bovier P & Bouras C Neuropathological observations in a case of autism presenting with self-injury behavior. *Acta Neuropathol.* 82, 321–326 (1991). [PubMed: 1759563]
27. Ling H et al. Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases. *Acta Neuropathol.* 130, 891–893 (2015). [PubMed: 26497674]
28. Omalu B et al. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 69, 173–183 (2011). [PubMed: 21358359]
29. Johnson VE, Stewart W & Smith DH Traumatic brain injury and amyloid- β pathology: a link to Alzheimer's disease? *Nat. Rev. Neurosci* 11, 361–370 (2010). [PubMed: 20216546]
30. Roberts GW, Allsop D & Bruton C The occult aftermath of boxing. *J. Neurol. Neurosurg. Psychiatry* 53, 373–378(1990). [PubMed: 2191084]
31. Stein TD et al. β -amyloid deposition in chronic traumatic encephalopathy. *Acta Neuropathol.* 130, 21–34 (2015). [PubMed: 25943889]
32. Neumann M, Kwong LK, Sampathu DM, Trojanowski JQ & Lee VM TDP-43 proteinopathy in frontotemporal lobar degeneration and amyotrophic lateral sclerosis: protein misfolding diseases without amyloidosis. *Arch. Neurol* 64, 1388–1394 (2007). [PubMed: 17923623]
33. Neumann M et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 314, 130–133 (2006). [PubMed: 17023659]
34. Chen-Plotkin AS, Lee VM & Trojanowski JQ TAR DNA-binding protein 43 in neurodegenerative disease. *Nat. Rev. Neurol* 6, 211–220 (2010). [PubMed: 20234357]
35. Geser F, Martinez-Lage M, Kwong LK, Lee VM & Trojanowski JQ Amyotrophic lateral sclerosis, frontotemporal dementia and beyond: the TDP-43 diseases. *J. Neurol* 256, 1205–1214 (2009). [PubMed: 19271105]
36. Josephs KA et al. Rates of hippocampal atrophy and presence of post-mortem TDP-43 in patients with Alzheimer's disease: a longitudinal retrospective study. *Lancet Neurol.* 16, 917–924(2017). [PubMed: 28919059]
37. King A et al. Abnormal TDP-43 expression is identified in the neocortex in cases of dementia pugilistica, but is mainly confined to the limbic system when identified in high and moderate stages of Alzheimer's disease. *Neuropathology* 30, 408–419 (2010). [PubMed: 20102526]
38. McKee AC et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J. Neuropathol. Exp. Neurol* 69, 918–929 (2010). [PubMed: 20720505]
39. Payne EE Brains of boxers. *Neurochirurgia (Stuttg.)* 11, 173–188(1968). [PubMed: 5729752]
40. Saing T et al. Frontal cortex neuropathology in dementia pugilistica. *J. Neurotrauma* 29, 1054–1070 (2012). [PubMed: 22017610]
41. Neuburger KT, Sinton DW & Denst J Cerebral atrophy associated with boxing. *AMA Arch. Neurol. Psychiatry* 81, 403–408 (1959). [PubMed: 13636508]
42. Nowak LA, Smith GG & Reyes PF Dementia in a retired world boxing champion: case report and literature review. *Clin. Neuropathol* 28, 275–280 (2009). [PubMed: 19642506]
43. Cherry JD et al. Microglial neuroinflammation contributes to tau accumulation in chronic traumatic encephalopathy. *Acta Neuropathol. Commun* 4, 112 (2016). [PubMed: 27793189]

44. Grahmann H & Ule G Diagnosis of chronic cerebral symptoms in boxers (dementia pugilistica & traumatic encephalopathy of boxers) [German], *Psychiatr. Neurol. (Basel)* 134, 261–283 (1957). [PubMed: 13494597]
45. Drachman D & Newall K Case 1 2–1999 —a 67-year-old man with three years of dementia. *N. Engl. J. Med* 340, 1269–1277 (1999). [PubMed: 10210712]
46. Guo Z et al. Head injury and the risk of AD in the MIRAGE study. *Neurology* 54, 1316–1323 (2000). [PubMed: 10746604]
47. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S & Giora A Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* 74, 857–862 (2003). [PubMed: 12810767]
48. Nordstrom P, Michaelsson K, Gustafson Y & Nordstrom A Traumatic brain injury and young onset dementia: a nationwide cohort study. *Ann. Neurol* 75, 374–381 (2014). [PubMed: 24812697]
49. Wang HK et al. Population based study on patients with traumatic brain injury suggests increased risk of dementia. *J. Neurol. Neurosurg. Psychiatry* 83, 1080–1085 (2012). [PubMed: 22842203]
50. Plassman BL et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology* 55, 1158–1166 (2000). [PubMed: 11071494]
51. Gardner RC et al. Dementia risk after traumatic brain injury versus nonbrain trauma: the role of age and severity. *JAMA Neurol.* 71, 1490–1497 (2014). [PubMed: 25347255]
52. DeKosky ST, Blennow K, Ikonovic MD & Gandy S Acute and chronic traumatic encephalopathies: pathogenesis and biomarkers. *Nat. Rev. Neurol* 9, 192–200 (2013). [PubMed: 23558985]
53. Johnson VE et al. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136, 28–42 (2013). [PubMed: 23365092]
54. Hay J, Johnson VE, Smith DH & Stewart W Chronic traumatic encephalopathy: the neuropathological legacy of traumatic brain injury. *Annu. Rev. Pathol* 11, 21–45 (2016). [PubMed: 26772317]
55. Smith C, Graham DI, Murray LS & Nicoll JA Tau immunohistochemistry in acute brain injury. *Neuropathol. Appl. Neurobiol* 29, 496–502 (2003). [PubMed: 14507341]
56. Smith DH et al. Accumulation of amyloid β and tau and the formation of neurofilament inclusions following diffuse brain injury in the pig. *J. Neuropathol. Exp. Neurol* 58, 982–992 (1999). [PubMed: 10499440]
57. Smith DH, Chen XH, Iwata A & Graham DI Amyloid β accumulation in axons after traumatic brain injury in humans. *J. Neurosurg.* 98, 1072–1077 (2003). [PubMed: 12744368]
58. Chen XH et al. Long-term accumulation of amyloid- β , β -secretase, presenilin-1, and caspase-3 in damaged axons following brain trauma. *Am. J. Pathol* 165, 357–371 (2004). [PubMed: 15277212]
59. Roberts GW, Gentleman SM, Lynch A & Graham DI β A4 amyloid protein deposition in brain after head trauma. *Lancet* 338, 1422–1423 (1991). [PubMed: 1683421]
60. Roberts GW et al. β amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 57, 419–425 (1994). [PubMed: 8163989]
61. Ikonovic MD et al. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. *Exp. Neurol* 190, 192–203 (2004). [PubMed: 15473992]
62. Nicoll JA, Roberts GW & Graham DI Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid β -protein following head injury. *Nat. Med* 1, 135–137 (1995). [PubMed: 7585009]
63. Johnson VE et al. A neprilysin polymorphism and amyloid- β plaques after traumatic brain injury. *J. Neurotrauma* 26, 1197–1202 (2009). [PubMed: 19326964]
64. Johnson VE, Stewart W, Trojanowski JQ & Smith DH Acute and chronically increased immunoreactivity to phosphorylation-independent but not pathological TDP-43 after a single traumatic brain injury in humans. *Acta Neuropathol.* 122, 715–726 (2011). [PubMed: 22101322]

Fig. 1|. Historical timeline of developments and the cumulative number of published cases of dementia pugilistica and CTE.

The association between exposure to brain injury in boxing and the risk of neurodegenerative disease was first reported in 1928. Since the first description of the pathology in a former American National Football League player in 2005, a marked increase in case identification and reporting has been seen. Nevertheless, the cumulative number of unique chronic traumatic encephalopathy (CTE) cases reported is currently just over 300.

Fig. 2|. Neuropathologies identified as being associated with neurodegeneration after TBI. For both repetitive mild traumatic brain injury (TBI) and single moderate or severe TBI, post-mortem neuropathology studies have identified tau and amyloid- β ($A\beta$) pathologies, brain atrophy, axonal degeneration and persistent neuroinflammation. However, thus far, 43 kDa transactive response (TAR) DNA-binding protein (TDP43) pathology has only been identified after repetitive mild TBI.