Traumatic brain injuries

Kaj Blennow[1,2], David L. Brody[3], Patrick M. Kochanek[4], Harvey Levin[5,6], Ann McKee[7,8], Gerard M. Ribbers[9,10], Kristine Yaffe[11,12] and Henrik Zetterberg[1,2,13]

Abstract | Traumatic brain injuries (TBIs) are clinically grouped by severity: mild, moderate and severe. Mild TBI (the least severe form) is synonymous with concussion and is typically caused by blunt non-penetrating head trauma. The trauma causes stretching and tearing of axons, which leads to diffuse axonal injury — the best-studied pathogenetic mechanism of this disorder. However, mild TBI is defined on clinical grounds and no well-validated imaging or fluid biomarkers to determine the presence of neuronal damage in patients with mild TBI is available. Most patients with mild TBI will recover quickly, but others report persistent symptoms, called post-concussive syndrome, the underlying pathophysiology of which is largely unknown. Repeated concussive and subconcussive head injuries have been linked to the neurodegenerative condition chronic traumatic encephalopathy (CTE), which has been reported post-mortem in contact sports athletes and soldiers exposed to blasts. Insights from severe injuries and CTE plausibly shed light on the underlying cellular and molecular processes involved in mild TBI. MRI techniques and blood tests for axonal proteins to identify and grade axonal injury, in addition to PET for tau pathology, show promise as tools to explore CTE pathophysiology in longitudinal clinical studies, and might be developed into diagnostic tools for CTE. Given that CTE is attributed to repeated head trauma, prevention might be possible through rule changes by sports organizations and legislators.

Traumatic brain injuries (TBIs) can affect people of all ages and are a major cause of death and disability, with an incidence of ~10 million people worldwide[1]. TBIs can include penetrating injuries (in which an object breaches the skull and dura, with direct damage to the brain parenchyma) and closed-head injuries (in which the skull and dura remain intact)[2]. TBIs can be categorized into mild, moderate and severe based on clinical factors, such as the duration and severity of consciousness (if present), the presence of amnesia and neurological symptoms, and the results of structural brain imaging (such as CT or MRI)[3] (BOX 1). Moderate and severe TBI are neurosurgical and intensive care concerns.

Mild TBI and concussion are interchangeable terms for the least severe form of TBIs and represent 80–90% of cases[4]. Mild TBI is defined on clinical grounds and conceptualized in clinical criteria outlined by different working groups that largely are compatible with each other[4–6]. Mild TBI is typically caused by blunt non-penetrating head trauma and results in transient symptoms that are detected through clinical observations, patient self-reporting or observations by witnesses (when available). Symptoms are highly variable and can include physical (for example, nausea and vomiting, dizziness and headache), cognitive (for example, poor concentration and memory problems) and behavioural (for example, irritability and emotional lability) symptoms as well as loss of consciousness. According to the American Congress of Rehabilitation Medicine criteria, CT of the brain, as well as a routine neurological examination, might (or might not) be normal[5]. The clinical criteria for the classification of mild TBI can be found in BOX 1. No single test is available to assist making a clinical diagnosis of mild TBI.

Symptoms of mild TBI resolve within 7–10 days in 80–90% of cases and most patients with post-concussive symptoms will show resolution of their symptoms within 1–12 weeks. The recovery period after sports concussion might be shorter, as athletes are typically in better physical condition than patients with non-sports-related mild TBI. Patients with non-sports-related mild TBI more often have pre-existing behavioural, psychiatric and/or substance abuse problems that increase their susceptibility to injury and might prolong recovery[7,8], although sports-related TBIs might result from lower mechanical forces than non-sports-related TBIs. Patients with persisting symptoms (>3 months) are diagnosed with post-concussive syndrome (PCS)[9]. The symptoms of PCS are highly variable (BOX 2), which makes determining the prevalence of this disorder difficult to calculate, but has been estimated at 10–15% of patients with concussion[9].

Correspondence to K.B.
Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, SE-43180 Mölndal, Sweden.
kaj.blennow@neuro.gu.se

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Author addresses

[1]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, SE-43180 Mölndal, Sweden.
[2]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden.
[3]Department of Neurology, Washington University School of Medicine in Saint Louis, St. Louis, Missouri, USA.
[4]Department of Critical Care Medicine, Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
[5]Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas, USA.
[6]Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA.
[7]Department of Veterans Affairs, VA Boston Healthcare System, Boston, Massachusetts, USA.
[8]Departments of Neurology and Pathology & Laboratory Medicine, Boston University School of Medicine, Boston, Massachusetts, USA.
[9]Department of Rehabilitation Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands.
[10]Rijndam Rehabilitation Center, Rotterdam, The Netherlands.
[11]Departments of Psychiatry, Neurology, Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA.
[12]Department of Veterans Affairs, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA.
[13]Institute of Neurology, University College London, London, UK.

Repeated mild TBIs and subconcussive head impacts have been associated with the development of chronic traumatic encephalopathy (CTE), particularly in contact sports athletes and military veterans[10]. Notably, CTE is a neuropathological diagnosis that requires post-mortem examination, given that no established or validated clinical criteria and no biomarkers to support the diagnosis ante mortem are available, but criteria for the clinical counterpart — traumatic encephalopathy syndrome (TES) — have recently been suggested[11]. A progressive neurological condition in retired boxers called 'punch drunk syndrome', which was believed to be linked to repetitive head blows, was initially described in 1928 (REF. 12), following which the condition was called 'dementia pugilistica' (REF. 13), before being referred to as CTE in the 1940s[14–16]. In 1973, a neuropathological study showed that dementia pugilistica was associated with widespread neurofibrillary tangles (NFTs) in the brain[17], which were later known to be composed of aggregates of paired helical filament (PHF)-tau. The first case report of CTE in a former American football player was described in 2005 (REF. 18), following which CTE pathology was identified in other contact sports athletes, such as ice hockey, soccer and rugby players and wrestlers. CTE pathology has also been documented in soldiers exposed to explosive blasts, although the number of cases is limited[19]. Amyloid-β (Aβ) plaques have been found in ~50% of CTE cases and are significantly associated with age and the inheritance of the *APOE* (which encodes apolipoprotein E) ε4 allele[20].

This Primer discusses mild TBI and concussion in adults, together with the relationship between mild TBI and PCS and CTE. We regard TBIs as a spectrum of severities, with mild TBI being the least intense, instead of separate entities. However, other types of injuries (such as contusions or haemorrhages) can occur in severe TBI owing to the more-extensive mechanical forces involved. The data from mild TBI (including those in athletes) have not been evaluated in either humans or animal models to the extent that moderate-to-severe TBI has been studied. However, we find it unlikely that there is any pathophysiological distinction between the different TBI severities and think it plausible that the same underlying cellular and molecular processes are involved, just to different degrees.

Epidemiology

The incidence of hospital-admitted TBIs has been estimated at ~262 cases per 100,000 individuals in a meta-analysis from 16 European countries[21]. The US Centers for Disease Control and Prevention have reported an increase in the number of TBI-related emergency department visits from 567 cases per 100,000 individuals in 2000 to 824 cases per 100,000 individuals in 2010 (REF. 22). The incidence of TBI has increased in middle-income and low-income countries, which is mostly attributable to inadequate motor vehicle and traffic laws and safety regulations[23]. The true incidence of TBI is probably higher than the reported data, given that the incidence of mild TBI, which probably accounts for 80–90% of all TBIs, is underestimated in most studies[4]. A large, state-wide, population-based study conducted in the United States has reported that >40% of participants had at least one TBI during their lifetime[24].

The most common causes of TBIs of any severity are falls and road traffic accidents, which together account for >50% of all cases[21,22,25]. The rate of TBIs tends to be higher among men than among women, with the peak incidence among adults in the oldest (>75 years) age groups[21,22,25]. Surveillance data indicate that the incidence of sports-related TBI visits to emergency rooms in the United States is 152 cases per 100,000 individuals, with almost two-thirds occurring in children and young adults <19 years of age and numbers increasing in both males and females[26]. In addition, military service members represent a unique at-risk group owing to training and combat-related activities[27]; according to the US Defense and Veterans Brain Injury Center, >22,000 service members sustained a TBI in 2015, of which 82% were mild.

Studies have shown that the negative outcomes of TBIs (for example, disability, poor life satisfaction and memory impairment) increase in prevalence with increasing TBI severity[24]. Such studies have also suggested an association between TBIs and the risk of dementia. Indeed, a meta-analysis of 15 case–control studies reported an association between head injury and the risk of Alzheimer disease (odds ratio: 1.58; 95% CI: 1.21–2.06)[28]. However, these studies are based on patients with clinically diagnosed Alzheimer disease, which are unreliable and did not involve patients with Alzheimer disease confirmed on autopsy or with biomarkers (such as Aβ PET or cerebrospinal fluid (CSF)). Thus, the type of dementia associated with TBI is unclear. In addition, although several studies have demonstrated a dose–response relationship, such that the risk of dementia increases with increasing severity of TBI[29,30], the risk of dementia associated

Box 1 | **Definition and classification of traumatic brain injuries**

Traumatic brain injuries (TBIs; see the table) are induced structural injuries and/or physiological disruptions of brain function as a result of an external force, resulting in acute onset or worsening of at least one of the following clinical signs immediately following the event:

- A period of loss, or a decreased level, of consciousness
- Loss of memory for events immediately before or after the injury
- Alteration in mental state at the time of the injury (such as feeling dazed, confused or uncertain about what is happening, having difficulty in thinking clearly or responding appropriately to mental status questions)
- Neurological deficits (for example, weakness, loss of balance and/or change in vision) that may or may not be transient, and an intracranial lesion

	Mild TBI	Moderate TBI	Severe TBI
Structural brain imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness (duration)	0–30 minutes	30 minutes to 24 hours	>24 hours
Altered mental state (duration)	≤24 hours	>24 hours	>24 hours
Post-trauma amnesia (duration)	≤1 day	1–7 days	>7 days
Glasgow Coma Scale[96] score	13–15*	9–12*	<9*

Classification presented by the US Department of Veterans Affairs and the US Department of Defense concussion or mild TBI Working Group[3]. A patient meeting the criteria in more than one category is classified into the higher severity level, and patients with abnormal CT and/or MRI findings attributed to the TBI are classified as having increased severity of TBI. *Best score achieved in the first 24 hours after trauma.

with mild TBI is unknown[31]. Investigating the risk of dementia with mild TBI might be difficult as mild TBI is under-reported and the definition is often not uniform across studies[31]. Age at the time of TBI could also be an important factor for dementia risk. One study reported an interaction between age and TBI severity, such that the risk of dementia was greater among older adults with mild TBI, whereas moderate and severe TBI was associated with an increased risk of dementia across all age groups[32]. A large study on dementia risk in veterans showed that TBIs in veterans ≥55 years of age imposed a 60% increase in dementia risk, even after compensating for other risk factors and potential confounders[33].

Epidemiological evidence is also incomplete on the association between repetitive TBIs and the risk of CTE. Although cognitive and behavioural changes are reported among contact sports athletes who experience repetitive TBIs[34], no estimates for the prevalence or incidence of CTE are available. In particular, it should be noted that knowledge is lacking on the risk increase following repetitive subconcussive head impacts (without loss or impairment of consciousness) in contact sports athletes who sustain hundreds to thousands of head impacts during a season. Furthermore, that no biomarkers exist to clinically identify CTE or differentiate this disorder from Alzheimer disease or other neurodegenerative diseases is a limitation of these studies.

Mechanisms/pathophysiology

Biophysical mechanisms

Understanding how the physical forces from an external blow to the head are transmitted through the brain should shed light on the pathogenetic processes of TBI and how this disorder can affect physiological functions.

Brain damage in TBIs is caused by rotational (angular) and/or linear (translational) acceleration forces, or by blunt trauma with impact deceleration (FIG. 1). These forces generate intracranial pressure gradients through the inertia of the brain that lags behind the skull during the rapid movement. These pressure gradients generate shearing and strain forces that stretch and damage axons, leading to axonal injury, which, when multifocal, is called diffuse axonal injury (DAI)[35]. Whether different types of acceleration and deceleration forces cause axonal damage by different mechanisms is unclear; either focal strains or strains due to differences in densities between different parts of the brain (for example, the cortex and the underlying white matter) might be at play[36]. Indeed, biomechanical studies have shown that higher stress and strain forces can be observed in the bottom of the sulci in the frontal, parietal and temporal cortices[37], which also matches the location of tau pathology in CTE[38].

Exactly how shearing forces cause axonal damage is not known. However, in non-human primates, the severity of DAI was shown to be directly proportional to the severity of brain injury, which was measured by the severity of symptoms and functional outcomes[39]. Moreover, axonal injury occurs after brain acceleration or deceleration forces, not secondary to other types of injury, such as ischaemia or inflammation. The severity of concussion in contact sports is also related to the force of the impact to the head, for example, the degree of head acceleration following impact in American football[40]. In addition, in boxing, the rotational acceleration force caused by a punch increases in heavier weight classes[41]. Interestingly, a punch by a professional boxer has been estimated to generate the same force on impact as being hit by a 6 kg bowling ball rolling at 20 mph[42].

Neuropathology

Neuropathological changes found after concussion (mild TBI) include mild multifocal axonal injury together with activation of microglia (the resident innate

immune cells of the central nervous system) and microhaemorrhages[43,44]. The multifocal axonal injury typically involves the fornices, corpus callosum, subcortical white matter and cerebellum[45]. Less-consistent findings include TAR DNA-binding protein 43 (TDP43)-immunopositive neurites and small focal accumulations of PHF-tau, either as NFTs or neuropil threads[45].

The neuropathology of CTE involves both gross morphological and microscopic changes. For example, gross alterations, such as cavum septum pellucidum (a space between the layers of the septum pellucidum) or septal pellucidum fenestrations, are common pathological findings in CTE that are thought to represent traumatic damage to the septum from CSF wave shifts that occur with linear and rotational acceleration. In the recent US National Institute of Neurological Disorders and Stroke consensus criteria on CTE neuropathology[46], the pathognomonic lesion of CTE was defined as irregular, perivascular accumulation of phosphorylated tau (P-tau) aggregates in neurons and astrocytes that clustered at the depths of cortical sulci (FIG. 2). This hallmark tau lesion distinguishes CTE from other neurodegenerative tauopathies, including Alzheimer disease, progressive supranuclear palsy and argyrophilic grain disease. Tau abnormalities in CTE often involve the superficial cortical layers of the frontal, temporal and parietal cortices. TDP43 accumulation, Aβ accumulation and dot-like and spindle-shaped neurites can also be observed[38]. A staging scheme of progressive PHF-tau pathology in CTE has been proposed, which consists of four stages (stages I–IV), and will be important for studies of CTE prevalence and its relationship with the number and severity of repeated mild TBIs[47]. A recent review of >1,700 brains from a neurodegenerative disease brain bank found CTE pathology in one-third of the brains of contact sports athletes, but no CTE-type changes were found in 162 controls or in 33 individuals with a history of a single TBI[10].

Other pathological abnormalities include deposits of phosphorylated TDP43, which have been observed in 80% of cases, especially in later stages of CTE, and occasionally colocalizes with PHF-tau, axonal injury and neuroinflammation[47,48]. In addition, ~50% of CTE cases have deposition of Aβ as either diffuse or neuritic plaques (also known as senile plaques) and ~14% of CTE cases are comorbid for Alzheimer disease[20]. Brains from individuals with CTE have been shown to be fourfold more likely to have Aβ plaques and to develop plaques 10–15 years earlier than those from a community-based autopsy cohort. Moreover, the presence of Aβ plaques has been shown to be significantly associated with more-severe PHF-tau and poor clinical status before death, independent of the age of the patient[20].

Cellular and molecular pathophysiology

Axonal injury. Studies of the molecular pathophysiology of TBIs have examined many factors, including neuronal cell death, astrocyte injury, astrocyte and microglial responses, dendritic injury and synaptic dysfunction. Notably, much of the field has focused on axonal injury, especially multifocal axonal injury or DAI (FIG. 3), largely because of the clinical and experimental observations that link the severity of DAI to the extent of disability following TBIs[49]. For example, multifocal axonal injury is consistently revealed by amyloid precursor protein (APP) immunohistochemistry in TBI of all severities, given that APP accumulates at sites of axonal injury with axonal transport failure[43,44]. Moreover, the depth of coma has been shown to be directly proportional to the extent of axonal injury in the brainstems of non-human primates following rotational acceleration injury[39]; similar observations have been reported in a pig model[50]. In addition, several investigators have demonstrated a correlation between the severity of axonal injury (assessed using diffusion tensor imaging (DTI) and biomarker-based measurements of axonal injury) and outcomes in patients with mild TBI or those with more-severe injuries[51,52].

Axonal injury can be detected immediately after injury when forces of sufficient magnitude are applied to the brain. Microtubule disruption has been shown within 2 minutes after rapid stretch of the axons of cultured neurons[53], which can cause the formation of axonal varicosities (distorted and irregular axonal swellings or local dilations), as a result of failed axonal transport. Indeed, axonal varicosities are the most common manifestation of axonal injury and show accumulation of APP. Similar axonal varicosities are a hallmark of traumatic axonal injury observed in patients with TBI[54,55]. Axons in general, and microtubules specifically, might be more mechanically brittle than other structures in the nervous system, although this idea has not been rigorously tested. The dynamic instability of microtubules might also contribute to microtubule disruption and failed axonal transport in TBIs[53], but the role of microtubule disruption in other cellular structures, such as dendrites, has yet to be established.

Box 2 | **Conditions associated with traumatic brain injuries**

Subconcussive head trauma

- Head traumas that do not result in any subjective or objective symptoms
- To which degree repeated subconcussive head traumas in contact sports add to the risk of developing chronic traumatic encephalopathy (CTE) is currently unknown, but is under active investigation

Repetitive mild TBI

- Repeated episodes of concussion or mild traumatic brain injury (TBI; BOX 1)
- Primarily experienced by contact sports athletes and in military personnel who are exposed to training and/or combat
- Believed to initiate the CTE pathophysiological process

Post-concussive syndrome (also known as post-concussion disorder)

- Mild TBI that persists beyond the expected recovery period (>3 months)
- Nonspecific subjective symptoms, such as headache, fatigue, dizziness, poor concentration, sleep disturbances, anxiety, irritability and depressed mood

CTE

- Chronic neurodegenerative disorder believed to be initiated by repeated head trauma
- The term suggested for the clinical counterpart to CTE, primarily in research settings, is traumatic encephalopathy syndrome
- Both the clinical and the pathological syndromes were first described in retired professional boxers and are now also recognized in amateur and professional athletes involved in many different contact sports and in military veterans

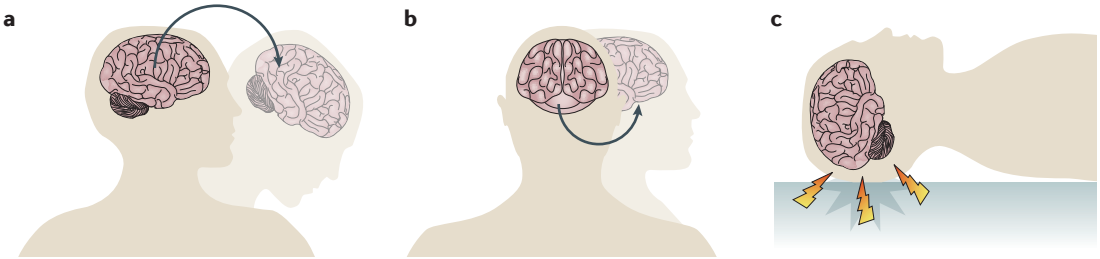

Figure 1 | **Examples of the types of forces in mild traumatic brain injury.** The central mechanisms for neuronal damage in mild traumatic brain injury (TBI) are acceleration and deceleration biomechanical forces. These forces cause strain and shearing forces on axons in the brain, which result in diffuse axonal injury. **a** | Linear (translational) acceleration occurs as a result of forces that make the head move in the anterior–posterior direction (such as hitting the front or back of the head). **b** | Rotational (angular) acceleration occurs as a result of forces that make the head rotate sideways (such as a punch to one side of the head). **c** | Impact deceleration occurs when the head forcefully decelerates, for example, when the head hits the ground. Many TBIs are caused by combinations of the above forces. Figure from REF. 221, Nature Publishing Group.

Other investigations have revealed additional manifestations of axonal injury[56,57]. For example, cytoskeletal neurofilament compaction has been observed in the brains of rats and humans with TBI[58,59]. The mechanisms underlying neurofilament compaction include disruption of the plasma membrane, which leads to increased intracellular calcium levels, activation of calpains and caspases and cytoskeletal proteolysis, including cleavage of spectrin and neurofilament side arms[60]. Another form of axonal injury involves axonal collapse and has been detected in mice after experimental mild TBI[61]. The mechanisms underlying axonal collapse remain to be determined.

Importantly, not all forms of axonal injury result in the disconnection of axons[62]; injured axons can remain connected, although whether these axons are functional is unknown. Notably, the extent of traumatic axonal injury can be greatly underestimated in studies using thick-section light microscopy, which can only visualize dilated axons and axonal varicosities. Non-dilated, injured axons require electron microscopy or ultra-thin section-based approaches for detection[63]. To our knowledge, studies using super-resolution light microscopy of injured axons have not yet been reported.

Aβ accumulation. Aβ is a key component of plaques that are found in patients with Alzheimer disease and is produced by sequential cleavage of APP by β-secretase 1 and the γ-secretase complex (with presenilin 1 constituting the active site)[64]. As previously mentioned, a link between TBIs and Alzheimer disease has been suggested. Two major hypotheses regarding the mechanisms underlying this increased risk have been proposed[65]; one states that TBIs reduce cognitive reserve such that the same pathophysiological processes underlying Alzheimer disease cause detectible symptoms at an earlier age. The second hypothesis is that TBIs directly set into motion the tau and Aβ pathophysiological processes underlying the development of Alzheimer disease (the accelerated Aβ hypothesis). These two hypotheses are not mutually exclusive.

In support of the accelerated Aβ hypothesis, diffuse Aβ plaques have been observed in some patients with severe TBI at younger ages than would be expected[66,67]. In addition, experimental TBI in pig models has been shown to cause formation of diffuse Aβ plaques and intra-axonal deposition of Aβ[68]. The origin of the diffuse plaques is unknown, but studies have indicated that the levels of soluble extracellular Aβ decrease acutely after TBI and then recover as neurological function is restored, which is probably owing to the recovery of synaptic activity[69,70]. This recovery phase might also explain the delayed increase in the levels of Aβ that is observed in the ventricular CSF in patients with acute TBI[71]. By contrast, acutely increased levels of Aβ have been observed in tissue lysates following experimental injury in mice[72]; this discrepancy might be due to partial mixing of increased intracellular and decreased extracellular Aβ pools in tissue lysates[70]. The increase in the levels of intra-axonal Aβ is believed to arise from the aberrant colocalization of APP, γ-secretase complex and β-secretase 1 at the sites of failed axonal transport[73]. Inhibition of γ-secretase prevents TBI-related intra-axonal Aβ formation in mice, but does not affect the overall severity of axonal injury[74]. Studies that investigated the pathophysiology of age-related Alzheimer disease have emphasized the role of soluble oligomeric assemblies of Aβ as key mediators of synaptic dysfunction and memory loss that underlie Alzheimer disease[75]. However, the effects of TBIs on Aβ oligomers remain to be determined.

Tau aggregation. Tau aggregates observed at post-mortem examination are a key finding in CTE. Tau is a microtubule-stabilizing protein and upregulation of tau after TBI has been hypothesized to be an aberrant attempt to stabilize microtubules that are disrupted by the trauma. An alternative hypothesis is that aberrant phosphorylation of tau leads to loss of its normal microtubule-binding function and promotes aggregation. In other contexts, Aβ aggregates might induce tau phosphorylation and aggregation[76], but in a mouse model of TBI, a 90% reduction in Aβ levels had no effect on TBI-related tau aggregation[74]. By contrast, c-jun N-terminal kinase (JNK) activation colocalized with tau aggregates and JNK inhibition reduced TBI-related tau aggregation[77]. Thus, the mechanisms underlying TBI-related tau aggregation might be distinct from the mechanisms elucidated in other contexts.

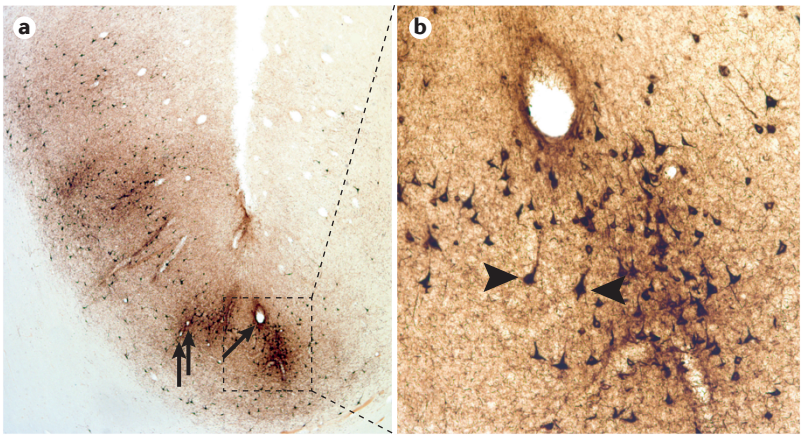

Figure 2 | **Tau pathology in chronic traumatic encephalopathy.** The diagnostic hallmark of chronic traumatic encephalopathy (CTE) neuropathology is the perivascular accumulation of hyperphosphorylated tau in neurons (as neurofibrillary tangles (NFTs) and neurites) and in astrocytes in an irregular pattern at the depths of the cortical sulci. **a** | Clusters of NFTs in an irregular perivascular pattern (arrows denote blood vessels), with dense patches located at the depths of the cortical sulci. A whole mount (50-μm-thick section) free-floating section from a 65-year-old former professional American football player. Magnification ×40. **b** | A higher magnification image that shows paired helical filament-tau immunoreactive NFTs (arrowheads) clustered around a small blood vessel. Magnification ×200.

Other pathophysiological changes. The inflammatory responses to TBI are major pathophysiological events that might affect outcomes in complex ways. Microglia are dramatically activated in the first days to a week after trauma and can either be transiently or persistently activated[78,79]. However, the mechanisms underlying microglial activation and the roles of microglia and astrocytes in debris removal, repair, recovery, progressive degeneration and long-term neurodegenerative sequelae remain to be determined[80]. Furthermore, the current categorization of microglia into M1 'classically activated' and M2 'alternatively activated' subtypes might be inadequate for the characterization of responses to TBI[81]. The soluble cytokine response is dramatic in patients with TBI[82], which supports the notion that inflammation might be a therapeutic target for TBIs, at least in severe injury[83].

After TBI, reactive oxygen and nitrogen species damage proteins, lipids and nucleic acids in the brain. Early after injury, oxidative and nitrosative stress might be due to, for example, activation of the arachidonic acid cascade or nitric oxide synthase, or mitochondrial dysfunction in severely injured regions of the brain[84], but it is not as clearly involved in less severely injured areas or in concussive injury. Specific mitochondrial lipid oxidation has recently been demonstrated and might have an important role in apoptotic cell death[85]. The effects of delayed oxidative and nitrosative stress caused by microglial and other inflammatory cellular responses are just beginning to be explored[86].

Genetic factors

Genetic factors can influence both short-term survival and long-term neurological and functional outcome after TBI by affecting several different putative pathogenetic pathways. Short-term survival might depend on genetic variants that can influence the severity of axonal injury, inflammation, blood–brain barrier disruption and neuronal survival. Long-term outcome might depend on genes that have a role in neuronal regeneration and plasticity. Indeed, studies have shown associations with outcomes following TBI between polymorphisms in genes that have a role in neuronal plasticity, for example, *BDNF* (which encodes brain-derived neurotrophic factor), and the inflammatory response, for example, the interleukin (*IL*) genes[87].

The most examined gene for short-term and long-term prognosis after TBI is *APOE*, which encodes APOE. APOE is involved in cholesterol and lipid metabolism and is a main component of plasma lipoproteins. In addition, APOE is the principal apolipoprotein in the central nervous system and is involved in the recycling of plasma lipoproteins to build new neuronal cell membranes, neurites and synapses during regeneration in response to brain injury[88,89].

APOE has three alleles (*APOE* ε2, ε3 and ε4), the most common of which is the ε3 allele. The ε4 allele is a well-established and strong susceptibility gene for risk and age of onset of Alzheimer disease[64], and might also influence prognosis or rate of progression of other brain disorders[90]. An association between poor short-term clinical outcome after TBI and the ε4 allele has been found in some studies, but these associations are weak and variable and several studies have reported no effect[87]. Preclinical studies have suggested that APOE might affect the severity of axonal injury; mice with the ε4 allele showed larger numbers of dilated, APP-stained axons than mice with the ε2 allele or ε3 allele[91]. In addition, several clinical studies have suggested that the ε4 allele predicts poor long-term (between 6 and 12 months) clinical outcome after TBI, which has been verified in a recent meta-analysis that showed an effect, particularly in severe TBI[92].

Studies examining *APOE* and the risk of eventual CTE-like symptoms are scarce. One study of retired professional boxers with high exposure to head blows revealed that carriers of the ε4 allele had more-severe symptoms of chronic brain injury (as a proxy for CTE)[93] than non-carriers. Other studies have found lower cognitive performance in high-exposure American football players who carry the ε4 allele[94] and ~50% of individuals with CTE were found to carry the ε4 allele in a small study[38]. The mechanisms underlying the putative association between *APOE* and the risk of CTE might involve isoform-dependent effects on neuronal regeneration and plasticity or be linked to a build-up of tau or Aβ pathology. In Alzheimer disease, the leading hypothesis is that Aβ aggregation and clearance are differentially regulated by the APOE isoforms[95]. Considering that Aβ plaques are preferentially found at a late stage of CTE[38], mechanisms related to β-amyloidosis are unlikely to be involved in the initiation of disease. Further large clinical studies are warranted to verify and explore the mechanisms for the association between *APOE* and eventual development of CTE, and to identify new genes that are associated with risk.

Diagnosis, screening and prevention

TBI severity

Acute TBI severity is classified primarily by the level of consciousness of the patient, which is measured by the lowest post-resuscitation Glasgow Coma Scale (GCS) score[96]. The GCS score consists of subscale scores for behaviours (such as eye opening and verbal and motor responses to questions and painful stimuli), with a higher total score indicating a higher level of consciousness of the patient. For example, the total score for the best eye opening, verbal response and motor response ranges from 3 to 15, with a sum score of 3 indicating total unresponsiveness and 15 indicating the best response (totally conscious). However, as some components of the GCS are untestable or cannot be tested reliably (for example, if the patient is intubated), clinicians are recommended to report subscale scores for individual patients[97]. In a patient in coma or with moderate impairment of consciousness, the GCS is generally repeated at specific times, especially during the initial hospitalization; once a patient's consciousness recovers to a GCS score of 15, it is not repeated. The GCS score correlates with clinical outcome and disability, but prediction is enhanced by taking into account age, pupillary reactivity and the type of pathology noted on CT and/or MRI. Thus, in the clinical setting, clinicians should consider the use of brain radiographic imaging, other neurological findings (such a pupillary response) and fluid biomarkers in addition to the GCS score for the classification of TBIs, patient monitoring, management and prognosis[97].

Clinical characteristics of PCS and CTE

Patients with symptoms that persist for several months after mild TBI are classified as PCS. However, PCS is difficult to diagnose as no objective diagnostic tools are available. In addition, symptoms of PCS (BOX 2) are common in healthy individuals, as well as in those with pre-existing psychiatric conditions, such as anxiety and depression. Furthermore, these symptoms are influenced by personality, psychological factors[9] and demographic

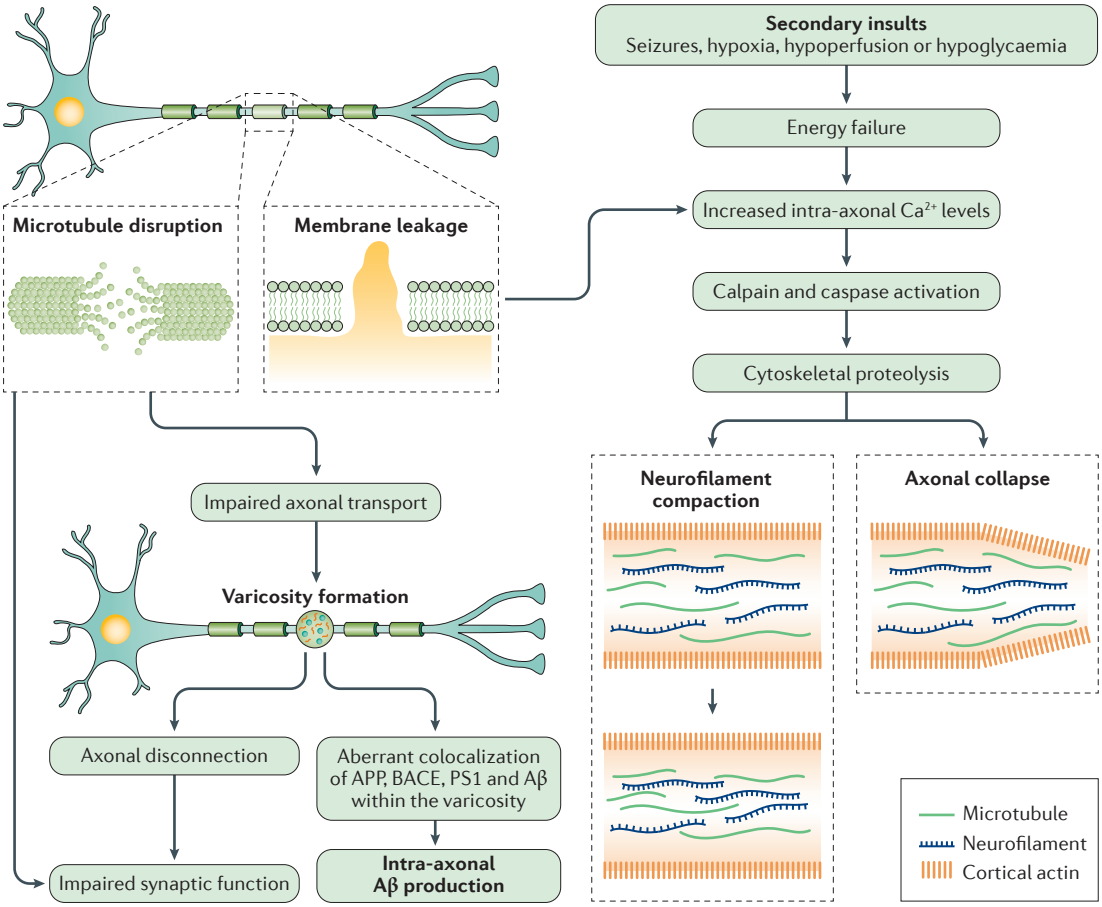

Figure 3 | **Axonal injury in traumatic brain injuries.** Axonal injury following brain trauma involves a complex set of pathophysiological events, which have been partially characterized. For example, rapid mechanical stretch can cause microtubule disruption (the nature of which is unclear) and impair axonal transport, which can cause varicosity formation. Membrane leakage can involve membrane rupture, transient poration or loss of ion channel selective permeability. The net effects of these changes can be axonal disconnection, which leads to impaired synapse function, and aberrant colocalization of amyloid-β (Aβ), amyloid precursor protein (APP), β-secretase (BACE) and presenilin 1 (PS1). APP is processed by BACE and PS1 to produce Aβ. Rapid mechanical stretch or injury can also induce another injury cascade, which begins with membrane leakage and leads to increased levels of intra-axonal calcium (Ca^{2+}), calpain-mediated and caspase-mediated spectrin proteolysis, neurofilament compaction and axonal collapse.

factors, such as social status, sex, ethnicity and alcohol use[98], which might also affect the rate of recovery after mild TBI.

As mentioned, CTE is a post-mortem diagnosis associated with varying clinical features before death and without established biomarkers. Diagnostic criteria for TES were recently suggested[11]. These criteria are based on the exclusion of other neurological disorders that could account for delayed-onset progressive cognitive, psychiatric and neurological symptoms in patients with a history of repetitive concussive or subconcussive head trauma exposures. These criteria have not been validated against neuropathology but are currently undergoing evaluation in a large longitudinal study.

Individuals who are later found to have CTE tend to have begun playing their sport during childhood and adolescence and played for >5 years. Symptoms associated with CTE can present at varying ages, but one-third of individuals are symptomatic at the time they retire from sport and, in most cases, the condition advanced slowly over several decades[38]. Retrospective descriptions of symptoms suggest three primary subtypes: first, behavioural and/or mood changes (such as irritability, depression and sleep disturbances); second, cognitive deficits (such as poor attention, memory problems, executive dysfunction and dementia); and third, a mixed-feature subtype[99]. Motor deficits (such as Parkinsonism, ataxia and dysphasia) also occur, and were described in former boxers with dementia pugilistica[17]. However, pending results of current prospective, longitudinal studies of at-risk athletes with a control group suggest that these descriptions should be interpreted as preliminary. For further details on sports-related concussion, see BOX 3.

Endocrine complications. The most common endocrine complications following TBI are related to injury of the pituitary gland. The pituitary gland itself is well protected within the sella turcica of the sphenoid bone, but the pituitary stalk (which is connected to the anterior pituitary gland and hypothalamus) is vulnerable to the mechanical forces of TBI. Post-traumatic hypopituitarism (PTHP; decreased secretion of hormones from the pituitary gland after brain injury) is found in ~30% of patients with TBI, with a higher prevalence in more-severe injuries[100]. The most common abnormalities are growth hormone deficiency and hypogonadism, whereas adrenocorticotropic hormone and thyroid-stimulating hormone deficiencies are diagnosed less often[101,102]. Indeed, a large proportion of patients with TBI have vasopressin deficiency that is severe enough to cause central diabetes insipidus in the acute phase, but this deficiency often resolves within 3 months[102,103].

PTHP can result in a multitude of acute and chronic symptoms[104]. For example, growth hormone deficiency can result in changes in body composition and reduce quality of life (QOL), including the development of depression, whereas hypothyroidism can cause weight gain, low mood and blunted cognition[104]. Most crucially, acute adrenal insufficiency can occur within days of TBI, causing hypotension, hyponatraemia and hypoglycaemia, which require immediate treatment. PTHP is also relevant in the context of mild TBI; 1% of patients with a history of concussion have growth hormone deficiency[105] and 25–30% of amateur kick-boxers and retired American football players have hypopituitarism with growth hormone and adrenocorticotropic hormone deficiencies, which might result in poor QOL, erectile dysfunction and metabolic syndrome[104,106,107]. Similarly, 42% of military personnel with previous blast-related mild TBI have abnormal levels of one or more pituitary hormones[108]. Given the subtle nature of some of the symptoms of endocrine complications, screening strategies in patients with a history of TBI have been proposed[109,110].

Imaging

CT is fast and can accurately detect essentially all life-threatening and surgically treatable intracranial haemorrhages in patients with TBI[111]. However, CT cannot detect DAI and provides only modest information about prognosis. Indeed, even if CT is part of the diagnostic criteria, many patients with mild TBI who are evaluated in the emergency department, in addition to most cases of sports concussion, do not undergo any structural brain imaging. In addition, 28% of patients with normal brain imaging on CT have lesions on MRI that is performed in the research setting within 2 weeks of the trauma, with lesions (such as contusions and/or multifocal haemorrhagic axonal injury) associated with worse outcome[112].

Box 3 | **Sports-related concussion**

Concussion in sports is diagnosed based on subjective symptoms. According to consensus diagnostic criteria, sports-related concussion or mild traumatic brain injury (TBI)[4] is a transient disturbance of brain function due to a sports-related head blow or trauma, which causes acceleration or deceleration of the head followed by the onset of post-concussive symptoms. Although loss of consciousness occurs in <10% of sports-related concussions[4], these injuries, in addition to non-sports-related mild TBI, are often followed immediately (or within minutes to hours) by the onset of one or more post-concussive symptoms.

Many athletic programmes in the United States conduct pre-season 'baseline' assessments that measure self-reported symptoms, balance and cognitive performance, which is interpreted relative to the athlete's pre-season test scores. Following sports-related concussion, this assessment is repeated to identify and grade the severity of symptoms and signs of acute concussion and the cognitive deficit relative to baseline values. Concussion symptoms and cognitive performance are monitored while the athlete completes a concussion management programme. Loss of consciousness, the duration of post-traumatic amnesia (if present), the number and severity of acute post-concussive symptoms predict time for recovery[219].

When the athlete becomes asymptomatic at rest, light exercise and cognitive activity are resumed and gradually increased. If symptoms return, the level of exercise and cognitive activity is reduced to the previous asymptomatic level[4]. Otherwise, the athlete resumes non-contact training, followed by a return to contact training and competitive play. The time from injury to return to play is 7–10 days in 85% of collegiate athletes after their first concussion, but might be delayed in athletes with persistent symptoms. In these cases, a multidisciplinary approach by health care providers with experience in sports-related concussion is important, and coexistent disorders should be considered and evaluated, for example, by neuropsychological testing and CT and/or MRI scans to exclude structural pathology. Owing to the lack of tools to grade neuronal injury, the actual time period for a safe return to play is unknown, but might be longer than imagined. Indeed, a case report of a knocked-out boxer has suggested that ongoing axonal damage and dysfunction (assessed as high levels of neurofilament light in the cerebrospinal fluid) might be extended over several months[220]. Concomitant injuries to other body regions and depression can also delay return to play.

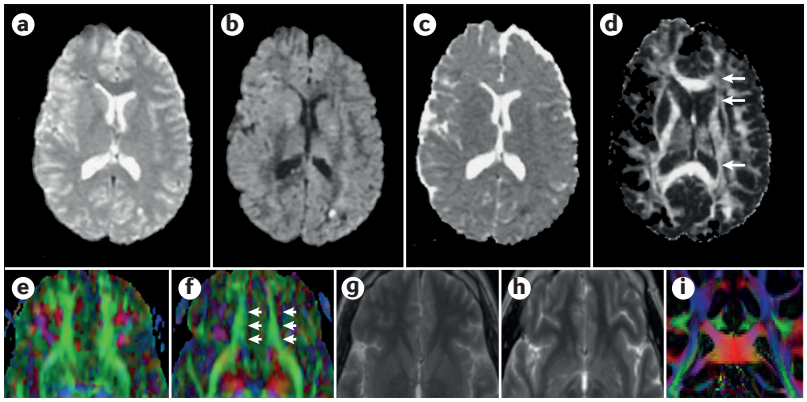

Figure 4 | **Diffusion tensor imaging for assessment of diffuse axonal injury.** Diffusion tensor imaging (DTI) MRI maps macroscopic axonal organization by measuring the diffusion of water molecules in the brain. Unlike conventional MRI sequences (T2-weighted, diffusion-weighted and trace diffusion) (parts **a–c**), DTI reveals a reduction in diffusion anisotropy (arrows; part **d**) and, therefore, evidence of axonal injury after concussive or mild traumatic brain injury (TBI). In a member of the US Military who experienced blast-related concussive TBI, DTI reveals neuronal abnormalities through a reduction in relative anisotropy (part **e**), indicated by a less-bright green colour (arrows; part **f**) that were not detected with conventional T2-weighted MRI (part **g** and part **h**). Using high spatial resolution DTI in a control without TBI, the individual white matter tracts can be distinguished from each other and from surrounding structures more clearly than using lower spatial resolution DTI seen in part **a** and part **c** (part **i**). The colours in part **i** indicate the primary direction of white matter tracts detected by DTI: green indicates anterior–posterior, red indicates right–left and blue indicates rostral–caudal. Images in parts **a–d** are from REF. 222, republished with permission of American Society of Neuroradiology, from Diffusion tensor MR imaging in diffuse axonal injury, Arfanakisa, K. *et al.*, **23**, 5, 2002. Images in parts **e–h** courtesy of C. L. Mac Donald, University of Washington, Seattle, Washington, USA, and D.L.B. Image in part **i** courtesy of L. Holleran, National University of Ireland Galway, Ireland, and D.L.B.

MRI-based techniques. MRI provides superior anatomical detail, more-sensitive detection of smaller haemorrhages and improved information about prognosis compared with CT[111]. However, MRI is less clinically available and has longer scan times than CT. Furthermore, conventional MRI sequences have little ability to detect axonal injury (FIG. 4) and are usually normal in patients with mild TBI. Consequently, extensive efforts have gone into developing improved MRI sequences that are more sensitive to axonal injury.

DTI is the leading MRI sequence for the detection of axonal injury[52,113] (FIG. 4). DTI measures the diffusion of water, which can be used to calculate the directional asymmetry (termed anisotropy) of water diffusion. Normally, the diffusion of water molecules occurs more readily parallel to the primary direction of the axons and less in perpendicular directions. Thus, healthy axons have high anisotropy. However, following axonal damage, the diffusion of water can be more hindered in the parallel direction than in perpendicular directions, such that injured axons have lower anisotropy than uninjured axons. In experimental animals, the extent of reduced anisotropy has been shown to quantitatively correlate with the extent of axonal injury, assessed using immunohistochemistry[111,114]. In addition, reduced anisotropy after TBI of all severities has been reported in a large number of clinical studies at different time points after injury, even when CT and conventional MRI showed no evidence of axonal injury[113,115]. Indeed, reductions in anisotropy in specific white matter tracts have been shown to correlate with TBI-related cognitive deficits[116] and the levels of tau in the brain extracellular space, which is a biomarker of axonal injury[117].

Limitations of DTI include its relative insensitivity to detect injury in complex white matter regions where there is not one predominant direction of the axons, inconsistencies concerning reported increases in anisotropy in some mild TBIs and the lack of spatial resolution to detect injury in small white matter tracts[118]. Furthermore, DTI needs standardization across different MRI scanners, which means that control data on each scanner is required for each study.

Novel diffusion imaging methods, such as diffusion kurtosis imaging[119], high angular resolution diffusion imaging[120], high-definition fibre tracking[121] and diffusion spectrum imaging[122], might be even more sensitive at detecting axonal injury, but probably have similar limitations as DTI. Magnetic resonance spectroscopy can resolve alterations in brain metabolism after TBIs and has been shown to correlate with metabolite concentrations and outcomes[123,124]. Functional MRI (fMRI) can also reveal alterations to the brain after TBIs, such as areas of either reduced or increased activation and altered connectivity[125]. Magnetoencephalography (MEG) detects changes in magnetic fields caused by the electrical activity of the brain. The time resolution of MEG is considerably better than fMRI and allows the resolution of fast activity and transient changes in functional connectivity. Following TBI, MEG can detect abnormalities that were not identified with DTI or conventional MRI, and results obtained from MEG can correlate with clinical outcome[126,127]. However, MEG is available at only a few centres, has limited spatial resolution (similar to DTI) and cannot yet be readily standardized between sites.

PET imaging. PET ligands have been developed that bind to aggregated Aβ and give a measure of the amount of Aβ deposits in different brain regions compared with a reference region (the cerebellum, which virtually lacks fibrillar Aβ plaques). Patients with Alzheimer disease typically show a 50–70% increased ligand retention in cortical regions compared with elderly controls[128]. Except for the ^{11}C-labelled Aβ ligand (known as Pittsburgh compound B (PiB)), which has a short half-life that hinders its use outside specialized research centres, ^{18}F-labelled amyloid tracers with longer half-lives (including florbetapir, flutemetamol and florbetaben) have also been developed.

A pilot study using PiB PET showed increased PiB retention, which reflects increased Aβ deposition, in the cortical grey matter and striata in young-to-middle-aged patients with moderate-to-severe TBI compared with controls, up to 1 year post-trauma[129]. Another small study showed increased PiB retention in the precuneus, posterior cingulate cortices and cerebella of patients with severe TBI, 11–17 months after injury[130]. PiB deposition in the posterior cingulate cortex correlated with decreasing fractional anisotropy assessed

by DTI, but ligand retention deposition was much lower than that found in patients with Alzheimer disease[130]. No studies on amyloid PET in individuals with mild TBI have been reported.

PET using ^{18}F-labelled fluorodeoxyglucose (FDG) can be used to measure glucose uptake and metabolism in different brain regions. Perturbed brain FDG-PET is found in neurodegenerative disorders, including Alzheimer disease, and psychiatric diseases, such as schizophrenia and bipolar disorder[131]. A general trend to increased glucose metabolism in variable brain regions during the acute phase, followed by a prolonged hypometabolism during the subacute-to-chronic phase has been observed in patients with moderate-to-severe TBI[132]. Mild TBI is less well-studied and findings are variable.

Several tau PET tracers with a high binding affinity and selectivity for PHF-tau deposits in the brain have been developed[133]. Tau PET is currently being evaluated in Alzheimer disease and has shown promise in monitoring the development of tau pathology and improving the understanding of the disease pathophysiology[134]. However, no clinical studies using tau PET in patients with TBI or clinically suspected CTE have been performed. Large longitudinal clinical studies in patients with TBI and patients with PCS and suspected CTE are important to learn the frequency of Aβ and tau deposits, at what point after TBI these deposits develop and how they correlate with other measures of neuronal damage, clinical symptoms, disease stage and prognosis.

Fluid biomarkers

For acute TBI, biomarkers can be used to grade the severity of brain damage, predict prognosis, guide clinical management, monitor therapeutic interventions and — in sports-related TBI — guide return-to-play decisions. CSF, serum and plasma are all of relevance for the detection of fluid biomarkers in patients with TBI, whereas biomarkers in other fluids such as saliva and urine are not yet established. Optimal biomarkers for TBI should reflect the pathophysiological processes.

CSF biomarkers. CSF sampling through a ventricular catheter from patients with severe TBI who are in need of intracranial pressure monitoring is used in clinical proof-of-concept studies to evaluate candidate CSF biomarkers. The high sensitivity of CSF biomarkers to detect even minor brain damage in patients with negative CT and/or MRI might give important information about the pathophysiology of mild TBI. Lumbar puncture might be difficult to implement in the clinic for evaluation of patients with acute mild TBI, as the procedure might be considered invasive. This concern was also noted for CSF biomarkers for early diagnosis of Alzheimer disease, but increasing scientific data supporting both the safety of lumbar puncture and the high performance of biomarkers for early diagnosis are increasing their use for diagnostic purposes of Alzheimer disease in clinical practice[135]. Candidate biomarkers for use in patients with TBI include markers of neuronal damage (for example, tau, neurofilament light (NF-L), Aβ, neuron-specific enolase (NSE; also known as γ-enolase) and spectrin-α chain (also known as αII-spectrin)), blood–brain barrier integrity, the immune response and astrocyte function (such as S100 calcium-binding protein B (S100B) and glial fibrillary acidic protein (GFAP)).

The most established CSF biomarkers for axonal injury are total-tau (T-tau) and NF-L (a structural protein that is mainly expressed in large calibre myelinated axons)[136]. Studies have shown that T-tau concentrations in the ventricular CSF correlate with lesion size and outcome in severe TBI, such that high levels indicate worse injury[136,137]. One pilot study has shown increased concentrations of T-tau and P-tau in the ventricular CSF during the acute phase of severe TBI[138]. Studies of mild TBI have shown increased concentrations of both T-tau and NF-L in the CSF, but the concentrations of NF-L increased more than T-tau, suggesting that mild TBI affects long, myelinated axons more than short, non-myelinated axons[139,140]. In addition, amateur boxers with concussions have been shown to have high levels of NF-L in the CSF after a match, even if they were not knocked-out. Higher levels of NF-L were observed with increasing numbers of hits to the head and NF-L levels reduced towards control levels after a period of rest[139,140]. Interestingly, these boxers had negative MRI scans, suggesting that the detection of increased levels of NF-L in the CSF is enough to identify even minor axonal damage.

As previously mentioned, APP and Aβ have been shown to accumulate in neurons and axons after TBI with axonal damage[15]. Ventricular CSF and brain interstitial fluid concentrations of two isoforms of Aβ (Aβ40 and Aβ42) have been shown to increase during the first week after severe TBI[71,141], particularly in patients with DAI[142]. Similar results have been obtained for soluble isoforms of APP[71]. However, no amyloid-related changes have been observed in the lumbar CSF of patients with mild TBI[139,140].

NSE is a glycolytic enzyme that is enriched in neuronal cell bodies[143]. NSE concentrations are higher in the ventricular CSF sampled within 3 days following the injury of patients with severe TBI who did not survive than in those who survived and have been shown to correlate with TBI severity in both adults and children[144,145]. However, the major limitation of assessing the levels of NSE in the CSF as a biomarker for neuronal injury is the high concentration of NSE in erythrocytes, which might contaminate the sample[146].

Spectrin-α chain is found in neuronal axons and presynaptic terminals in the brain[147]. Spectrin-α chain is proteolytically processed into fragments that have been suggested as potential TBI biomarkers both in animal experimental studies and in humans[148,149]. The levels of spectrin fragments in the ventricular CSF have been shown to correlate with clinical correlates of injury severity and predict outcomes in patients with severe TBI[150]. In addition, the levels of spectrin breakdown products in the CSF have been evaluated with the levels of ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1)[151], a de-ubiquitylating enzyme that is highly expressed in neurons[152].

Other biomarkers for TBI include markers of blood–brain barrier function and inflammatory markers of injury. An increased CSF:serum albumin ratio — a standard biomarker of blood–brain barrier dysfunction — has been reported in patients with severe TBI[153,154]. In mild TBI, no changes in the CSF:serum albumin ratio have been observed[139,155], which suggests that the blood–brain barrier remains intact or only 'opens up' transiently. A large number of studies have reported an acute-phase response in the central nervous system following severe TBI, which can be reflected by increased concentrations of pro-inflammatory cytokines, such as IL-6, IL-8 and IL-10 in the CSF[156,157].

Markers of astrocyte function might also be used as biomarkers for TBI. The levels of protein S100B — an astrocyte-enriched calcium-binding protein — are slightly increased in the CSF of amateur boxers after one or several matches, but these changes are less pronounced than those for the axonal markers T-tau and NF-L[140]. Similar results have been reported for GFAP[139,140], which is an intermediate filament that is almost exclusively expressed in astrocytes[143]. The levels of GFAP have also been evaluated in the CSF of patients with severe TBI, and when used in conjunction with clinical data can improve the predictive power of outcome models[151].

Blood biomarkers. On the basis of the CSF biomarkers above, candidate blood biomarkers for TBI include spectrin fragments, GFAP, UCHL1, S100B, T-tau and NF-L.

Standard enzyme-linked immunosorbent assays (ELISAs) for T-tau and NF-L have been transferred onto the single molecule array (Simoa; Quanterix, Lexington, Massachusetts, USA) platform, which enables the ultrasensitive measurement of these proteins in the blood[158,159]. The Simoa assay for serum NF-L levels has been shown to have a 100-fold better analytical sensitivity than standard ELISA to measure the levels of NF-L in the CSF[160]. The concentration of T-tau in plasma correlates poorly with concentrations in the CSF[161], but has been shown to be predictive of cerebral function in patients with acute hypoxic brain injury[158]. Increases in the serum levels of T-tau and P-tau have been described during the acute phase of severe TBI, following which the levels have been shown to decrease for up to 6 months but do not reach levels that are observed in controls[138]. In addition, in those with sports-related concussion, plasma T-tau levels have been found to predict return-to-play time with high accuracy[162]. Serum NF-L levels correlate strongly with the levels of NF-L in the CSF and have been shown to increase over time in American football players over the course of a season[163]. One study has shown a 30-fold increase in the serum levels of NF-L in patients with severe TBI, with higher levels of NF-L tightly correlating with DTI measures of DAI[164], suggesting that serum NF-L levels might serve as a measure of severity of axonal injury in patients with TBI.

Spectrin fragments have been shown to accumulate in damaged axons following TBIs[165]. Spectrin fragments can be measured in blood samples and levels have been shown to increase after TBIs, even in patients with mild TBI with no abnormal findings on CT[166,167], and has been suggested as a biomarker of prognosis and return-to-play time for sports-related concussion[168].

Guidelines for the use of S100B levels in the blood for the initial management of mild TBI have been published[169], which aim to reduce the number of unnecessary CT scans in patients who are at low risk of intracranial complications, such as haemorrhage or swelling, that might require neurosurgical intervention. These guidelines were recently validated in a large multicentre study; S100B had a sensitivity of 97% and a specificity of 34% for the identification of intracranial haemorrhages confirmed by CT scans[170]. However, some studies have found no change in the serum levels of S100B in patients with mild TBI and abnormal findings on CT compared with those with normal CT[171] and only minor changes in the serum levels of S100B in boxers or ice hockey players with concussion[140,162].

The levels of GFAP and UCHL1 in the blood might be used to discriminate between patients with TBI and healthy controls[172,173]. In addition, higher levels of UCHL1 and GFAP have been found in patients with TBI who have abnormalities on CT than in patients without abnormalities on CT[172,174]. A large study of patients with mild-to-moderate TBI showed that GFAP levels can be used to detect intracranial lesions on CT and to identify patients in need of neurosurgical interventions, but the performance was lower for UCHL1 (REF. 175). Another study showed similar performance for GFAP, UCHL1 and S100B to identify abnormalities on CT in patients with mild-to-moderate TBI[176]. Few studies on the use of these biomarkers in patients with mild TBI have been performed, but one study found higher levels of GFAP in patients with mild TBI and abnormalities on CT[171].

Management

Acute TBI

At the scene of injury and in the emergency centre, patients undergo an urgent assessment of the risk of developing an intracranial haemorrhage or brain swelling, which includes a brief interview and neurological examination (including GCS), to determine whether a CT scan is indicated[177,178]. Factors that should prompt referral for a CT scan include loss of consciousness or reduced sensorium after an initial lucid interval, focal neurological signs or seizures, suspected skull fracture, older age, comorbid conditions and the use of anticoagulant medication[178]. Observation for 6–8 hours in the emergency centre and repeat neurological assessment might be an alternative to CT, for example, in patients with high GCS scores and no focal neurological signs. With increasing use of anticoagulants among older adults in the general population, concern exists as to whether these patients have a greater risk of delayed intracerebral haemorrhage following mild TBI, if their initial CT is normal. However, repeat CT to detect intracerebral haemorrhage has been deemed unnecessary, except in patients with severe TBI, patients showing neurological deterioration and patients on vitamin K antagonist anticoagulation medication[179].

In the United States, following sports-related concussion, an athletics trainer or other clinician often directs clinical management (BOX 3). However, for non-sports-related mild TBI, emergency department discharge instructions provide management guidance, but follow-up is not the standard of care. Patient and caregiver education, including verbal and written instructions for identifying complications of TBI, observation by an adult for 24 hours, a regimen of rest and gradual resumption of activities, is the standard of care for mild TBI at many centres. The regimen of rest includes suspension from contact sports or other activities that risk head impacts or re-injury and initially extends to any vigorous physical activity and might also include intensive cognitive activity. The clinical management and follow-up of patients treated for mild TBI varies depending on several factors, such as the policy of the emergency department, the treating physician and the identification of risk factors for delayed recovery. Concerns about this approach to concussion management include the lack of precise definitions of rest, ambiguities in its implementation and evidence that durations of rest longer than 2–3 days might be deleterious to recovery[180]. Indeed, translational research has indicated that the gradual introduction of exercise can promote neuroplasticity after concussion[181]. However, further research is necessary to more precisely determine the duration and definition of rest depending on the injury features, concussion and head impact history, as well as pre-injury characteristics.

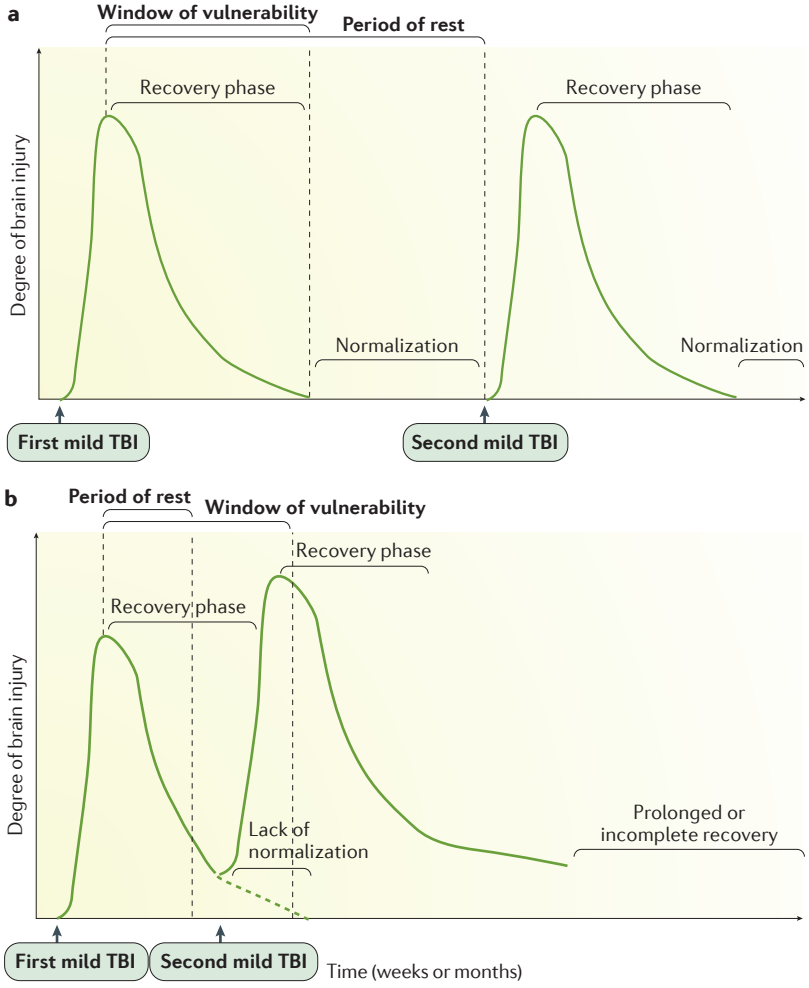

Figure 5 | **Repeated traumatic brain injuries and the proposed window of vulnerability.** After mild traumatic brain injury (TBI), the brain has increased susceptibility for a new injury during the recovery phase, termed the 'window of vulnerability'. A second mild TBI before the full resolution of pathophysiological changes following the first injury might add cumulative damage to the brain and prolong recovery from the second injury as compared with two injuries that are well-spaced apart during a prolonged period of rest. **a** | In a case of two TBIs, a second TBI that occurs after an extended period of rest, with normalization of the pathophysiological changes from the first TBI, enables normalization of the pathological changes of the second injury back to baseline (before any injury). **b** | In a case of two TBIs in which the second injury occurs during the window of vulnerability (before normalization of the pathophysiological changes of the first TBI), prolonged recovery and incomplete normalization after the second TBI might occur. This window of vulnerability is the rationale for recommending extended return-to-play periods after a concussion in contact sports athletes.

The early post-injury period is associated with the release of excitotoxic neurotransmitters, a neurometabolic crisis (due to increased energy demand of the brain despite a reduction in cerebral blood flow), inflammation and axonal dysfunction[182]. A second mild TBI that occurs before the resolution of the pathophysiological changes following the first injury might add cumulative damage to the brain and prolong recovery from the second injury[183,184]. This 'window of vulnerability' to re-injury has been cited as the rationale for prescribing rest for sports players who experience head trauma[4] (BOX 3; FIG. 5).

Persistent symptoms of CTE

With sparse prospective, longitudinal studies of athletes exhibiting persistent symptoms associated with repeated sports-related concussion and/or repetitive head impacts, few evidenced-based guidelines for the clinical management of symptoms that might be related to CTE pathology are available. Thus, the current knowledge of clinical decision making in these patients relies on retrospective clinical histories in neuropathologically confirmed cases of CTE[99].

For the development of long-term effects of repeated TBIs detected years to decades after retirement from sports, symptoms of mood and cognitive impairment and the age of the athlete relative to the typical duration of their playing career might be relevant[185]. In addition, the position played by the athlete and the number of years played professionally and in university provide an index of their exposure to repetitive head impacts

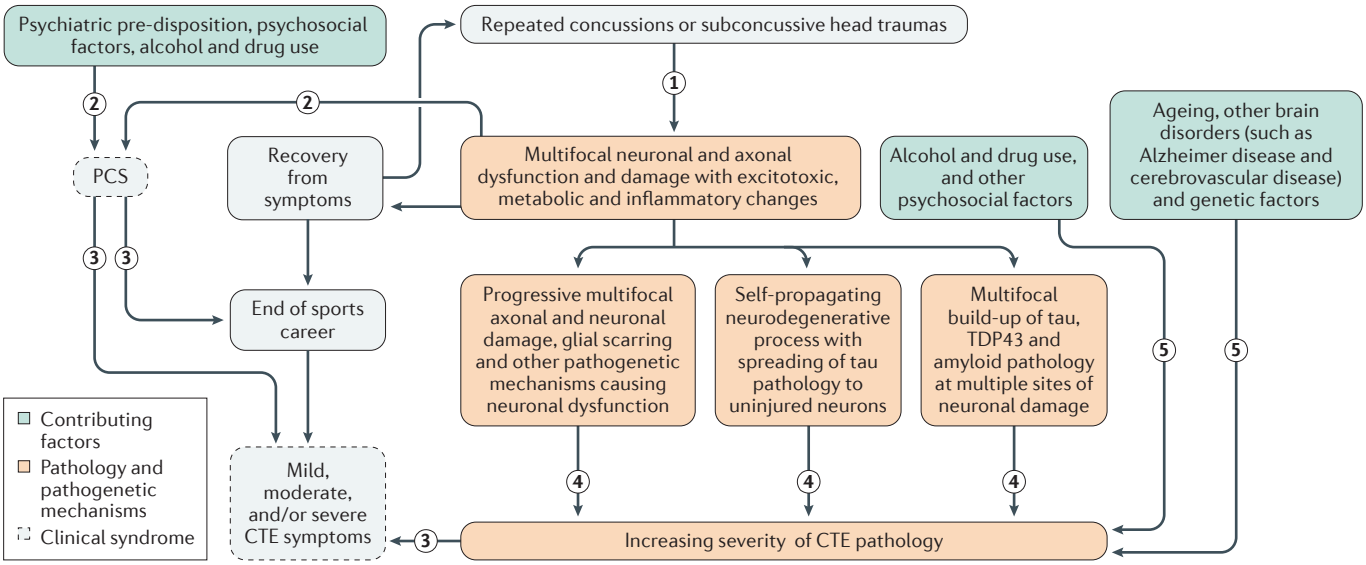

Figure 6 | **Unknowns in the clinical and pathological pathways of chronic traumatic encephalopathy.** Flowchart for the possible pathophysiological routes from repeated concussions to post-concussion syndrome (PCS) and chronic traumatic encephalopathy (CTE) pathology. Several factors regarding the pathophysiology and clinical manifestations of chronic traumatic encephalopathy (CTE) are unknown: (1) The number, temporal distribution and severity of head traumas that are needed to initiate the disease process and the percentage of contact sports athletes or military veterans who develop or escape CTE pathology and/or symptoms; (2) why some patients develop PCS and whether this is related to more-severe neuronal damage or to early CTE pathology, and to what extent contributing factors have a role; (3) whether clinically evident symptoms related to CTE pathology are preceded by mild PCS or whether there is a clinically silent period; (4) the relative importance of progressive neuronal and axonal damage versus tau, TAR DNA-binding protein 43 (TDP43) and amyloid-β (Aβ) lesions, and whether pathology spreads from damaged to undamaged neurons or whether it builds up exclusively at sites of brain damage; and (5) the degree to which contributing factors increases CTE risk and influences the clinical presentation.

that might correlate with biomarker evidence of brain injuries[163]. More detailed neurological and neuropsychological assessments, together with MRI using advanced sequences, might identify evidence of brain damage that might guide whether to consider recommending an athlete to retire from sport.

In general, many clinicians would advise an athlete to retire from contact sports after sustaining multiple (more than two) concussions, especially if the injuries were temporally contiguous, for example, within a single season. However, the evidence base for this decision is weak and there is concern that years of exposure to repetitive head impacts are sufficient to initiate a self-perpetuating neurodegenerative process. With a latent period estimated to be 8–10 years, it is likely that the initial, preclinical stage of CTE pathology is thought to be undetected by conventional imaging methodologies or clinical assessments[47]. The dilemma for the clinician and the athlete is that current evidence does not permit estimation of the threshold of exposure to repetitive TBI episodes for initiating this neurodegenerative process. Moreover, individual differences in genotype, age when exposed to contact sports and other vulnerabilities, including medical and social history, might predispose individuals to developing CTE pathology (FIG. 6). Recently developed tau ligands for PET imaging in Alzheimer disease can estimate the burden of tau in the cerebral cortex, but validation of this technique in individuals at high risk for, or symptoms that might indicate, CTE pathology is pending. In combination with other brain imaging modalities, fluid biomarkers and monitoring neurobehavioral changes, it might soon be possible to identify CTE pathology at a preclinical stage.

Quality of life

Life satisfaction following TBI can vary over time and is associated with several factors. The levels of cognitive and physical disability of the patient are related to injury severity[186], but can also include contextual factors, such as income, mood, fatigue and social participation[187,188].

In the first 6 months post-injury, patients typically report low life satisfaction with a gradual improvement over years. Locus of control (that is, the degree to which individuals believe that their health is controlled by themselves, rather than controlled by external factors) is related to health-related QOL (HR-QOL) after TBI[189]. Indeed, an externally oriented locus of control has been shown to be negatively related to HR-QOL. Locus of control, self-efficacy and coping are intertwined concepts that might serve as potential targets to improve HR-QOL. 12 months after mild TBI, symptoms and QOL are usually similar to that of healthy individuals[190]. However, in some individuals, a loss of life roles might hamper improvements in QOL or might even cause a further decline of life satisfaction.

In individuals with PCS and persistent symptoms, headaches, especially migraines, have a negative effect on QOL and might respond to medication[191]. Depression is also common following mild TBI complicated by lesions seen on brain imaging, and is around eightfold higher than expected in the general population following TBI[192] and can be treated by a combination of medication and behavioural approaches. Instructions for good sleep hygiene are recommended because sleep disturbance is a frequent sequela of mild TBI[178]. As the consequences of TBI can vary between individuals, insight into the effects of TBI experienced by patients is required. In addition, individuals with serious disabilities might report high satisfaction with life, whereas caregivers and clinicians might question their QOL. A lack of awareness, but also a re-evaluation of what matters in life, by the patient might explain such a different perspective.

Outlook

Despite considerable advances, research on mild TBI, PCS and CTE is still in its early stages, with many gaps in our knowledge still to be filled (FIG. 6). These gaps include improved knowledge of biophysical mechanisms of injury, the prevalence of CTE in contact sports athletes, as well as the precise molecular pathway from acute axonal injury to chronic and progressive neurodegeneration.

Mechanistic questions

Which forces cause brain damage in TBIs and trigger CTE? Axonal injury is probably the central mechanism in TBIs, which is accompanied by other changes, such as inflammation, metabolic crisis and oxidative stress. However, further research is needed to resolve why axons are differentially vulnerable to trauma compared with other brain structures and whether injured axons with axonal transport failure can be restored to normal. In addition, the relationship between the extent of axonal injury and recovery rate, or the development of PCS, after a single mild TBI is not known. Similarly, little is known about the number of mild TBIs or subconcussive head impacts that are needed to initiate the neurodegeneration that underlies CTE. In addition, whether blast-related TBI and CTE in military personnel is due to brain damage caused by the blast wave that progresses from the source of the explosion as a sphere of compressed and expanding gases creating high barometric pressure or whether the high velocity blast wind that follows gives a detrimental acceleration of the head with resulting axonal shearing is unknown[19]. Tools to quantify both the trauma force and the neuronal damage in mild TBI and blast injuries are required to resolve these questions.

What governs recovery after acute concussion? Why a proportion of patients develop long-lasting PCS is unclear[193]. These patients might have more-severe neuronal damage or sustain damage related to the type of impact and localization of injury, but the possible influences of psychogenic or psychosocial mechanisms remain to be examined.

What is the risk for CTE among contact sports athletes? Although repetitive subconcussive head impacts are thought to initiate the neurodegenerative process that leads to CTE[47], the number of known CTE cases is limited and the percentage of individuals participating in contact sports who will develop CTE is unknown. Thus, longitudinal epidemiological studies in contact sports athletes are needed to learn the frequency of CTE, as well as its relation to the number and severity of concussions, length of career and similar risk factors. Furthermore, examining which factors govern resiliency to CTE and resolving the possible influence on CTE risk of psychosocial factors, such as alcohol and drug abuse, and other health factors, such as obesity, diabetes mellitus and hypertension, are important.

What is the role of CTE pathology and does it propagate in the brain? Preclinical discoveries suggest that repetitive concussive and/or subconcussive brain injuries initiate tau pathology that spreads to adjacent neurons in the absence of ongoing triggering factors[194]. However, we do not know if the tau aggregates after TBI have a causal role in delayed neurodegeneration and the development of CTE, or if they are a marker of prior injury. Indeed, one neuropathology study on blast TBI in military veterans has reported axonal damage, but no tau pathology, even in patients who survive long (up to 4 years) after the blast[195]. Another study has reported distinct astrocyte scarring with dense astrogliosis in several brain areas, but no or minimal tau pathology[196]. Further studies, especially longitudinal biomarker (tau PET and CSF tau) and neuropathology studies that correlate different types of pathology in affected brain regions with disease stage in CTE, are needed to determine whether tau pathology is the cause or a bystander of neuronal dysfunction in CTE. In addition, these studies will reveal whether progression of CTE is due to the spreading of tau pathology throughout neuronal networks or whether the disease simply affects an increasing number of brain regions with increasing severity (FIG. 6).

What is the role of Aβ plaques in CTE? The involvement of brain Aβ mis-metabolism and aggregation after TBIs is supported by animal studies that have shown sequential accumulation of APP, upregulation of secretases and Aβ generation with the formation of diffuse Aβ plaques after rotational TBIs[68,197]. How TBIs induce Aβ oligomerization and aggregation, whether Aβ oligomers cause toxicity after TBI and whether Aβ plaques and intra-axonal depositions have causal roles in the increased risk of Alzheimer disease are unclear. CSF measurements and amyloid PET can monitor APP and Aβ metabolism and aggregation in patients, and will help to resolve whether Aβ aggregation is involved in CTE pathogenesis or whether it is a bystander of neuronal damage and degeneration.

Can we find an objective measure for neuronal damage in mild TBI? Some argue that the term 'concussion' should no longer be used owing to its vague definition and variable symptoms without any clinically identifiable

pathological substrate[198]. Accordingly, an unmet need exists for the development of biomarkers to identify and monitor axonal damage and other pathophysiological processes in mild TBI. However, the most studied blood biomarker, the astroglial protein S100B, has poor specificity to predict intracranial pathology that can be observed with CT, with many false-positive results[199]. In addition, S100B is present in peripheral organs and non-neuronal cell types, for example, adipose tissue and chondrocytes[200], making it responsive to peripheral injuries and multiple traumas, further limiting its clinical usefulness for TBIs. Given that the central mechanism in TBIs is axonal damage, fluid biomarkers of axonal damage, such as tau[158,162] and NF-L[159,163] in blood samples, have been developed for TBIs, but need further clinical evaluation.

Can we find tools to identify CTE in the clinic?

Symptoms associated with CTE pathology, and its suggested clinical counterpart TES, might be difficult to differentiate not only from Alzheimer disease and Parkinson disease but also from PCS and depression in younger patients[201], so diagnostic tools are highly desirable. For Alzheimer disease, numerous biomarkers are available, including Aβ PET and measurements of the levels of Aβ42 in the CSF[202], as well as the levels of T-tau, P-tau and NF-L in the CSF[135]. In addition, recent developments have resulted in promising ligands for tau PET imaging[203]. These Alzheimer disease biomarkers are also candidate CTE markers, but no clinical biomarker studies on patients with suspected CTE pathology have been conducted.

Prevention

Guidelines for return to play have been proposed by the American Academy of Neurology[204]. These state that an athlete with concussion should not return to play if they have persistent post-concussion symptoms at rest or with exertion, reduced academic or sports performance, abnormal neurological examination, neuropsychological test findings, or CT and/or MRI findings that indicate increased risk of further concussion and/or delayed neurological deterioration[204]. Strict compliance with these guidelines by field and ringside physicians might reduce both short-term and long-term suffering for contact sports athletes.

Following international consensus criteria on concussion in sports, an athlete diagnosed with concussion should not be allowed to return to play on the day of injury by the physician or other licensed health provider[4]. Owing to the nature of the sport, this is not easily applied in boxing, in which an alternative to secure the well-being of the athletes might be to introduce rules that forbid blows to the head. In addition, the Word Medical Association recommended the general ban of boxing in 2005 (REF. 205), based on the risk for brain damage and that the basic intent of boxing is to knock the opponent unconscious. However, the liability lies with sports organizations and governments to regulate rules in a way that minimizes the risk for chronic brain damage for athletes, especially for those who are underaged (<16–18 years).

Emerging treatments

Factors such as the marked heterogeneity of disease (including anatomical, physiological and genetic factors) across injury severity and the limitations of current outcome assessment tools have hindered the development of new therapies for TBIs[206]. Furthermore, successful translation of new therapies has been problematic despite the implementation of carefully designed multicentre, randomized controlled trials[207–209]. Accordingly, new clinical trial designs, such as comparative effectiveness trials, might help to define optimal care and facilitate successful randomized controlled trials[210]. Despite these challenges, several new therapies merit discussion.

Cerebral oedema with resultant intracranial hypertension is a key therapeutic target for severe TBI, but might also have a role across the injury spectrum[211]. The treatment of severe brain oedema involves CSF drainage, administration of osmolar agents and/or craniectomy. Now, molecularly guided approaches can be used to prevent the development of brain oedema rather than react to it after it is formed. Emerging treatments, such as glibenclamide, which targets sulfonylurea receptor 1-mediated ion channel opening, are in phase II clinical trials (NCT01454154)[212]. Similarly, inhibition of aquaporin 4-mediated oedema either directly or by blocking a cascade of events that are triggered by the release of high-mobility group protein B1 and the activation of Toll-like receptors, which upregulate aquaporin 4, is in preclinical testing[213]. Such approaches might improve care.

Several approaches for the treatment of mild TBI are under investigation. For example, recent preclinical studies suggest that hyperthermia (≥39 °C) at the time of injury might magnify secondary tissue damage and initiate degenerative processes, such as CTE; rapid normalization of body temperature might be neuroprotective[214]. Treatment of hyperthermia immediately after the time of injury (such as during football training camp in summer months) merits further investigation. This approach differs from the use of hypothermia given that it only entails return to normothermia. In addition, the acute accumulation and spread of a toxic *cis* P-tau protein isomer might disrupt axonal microtubule networks and lead to apoptosis, whereas treatment with a monoclonal antibody against *cis* P-tau might prevent its spread and improve outcome[215]. Finally, cellular therapies might improve outcome by either promoting new neuronal circuits or expressing trophic factors that are neuroprotective or pro-regenerative. A phase I study of autologous bone marrow mononuclear cells in children with severe TBI suggested that this approach might be feasible, safe and associated with reduced treatment intensity to maintain intracranial pressure[216].

Fostering clinical research on TBIs and CTE

To improve our understanding of TBIs and CTE pathogenesis, large longitudinal clinical studies that combine clinical evaluations with imaging, biomarker and genetic data are necessary. The Alzheimer Disease Neuroimaging Initiative (ADNI) has had a vast impact

on the understanding of Alzheimer disease[217]. For acute TBIs, the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study in the United States (NCT02119182) and the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study in Europe (NCT02210221) are two prospective observational studies examining clinical, imaging, genetic and blood biomarkers with longitudinal clinical follow-up across the TBI severity spectrum (including mild TBI). The goals of these studies are to improve methods for diagnosis and prognosis, refine outcome assessment and TBI care. For CTE, the Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) study[218] is a retrospective clinical–pathological study aiming to investigate the validity of recently proposed clinical criteria of CTE[99] and to identify clinical features that improve prediction of CTE pathology. The Diagnose CTE Research Project is a multicentre, prospective longitudinal study evaluating clinical criteria for the diagnosis of TES and fluid and imaging biomarkers for CTE, aiming to enable the diagnosis of CTE ante-mortem. These and other clinical studies are likely to improve our understanding of the pathophysiology, the ability to clinically diagnose and institute personalized therapy programmes for these disorders.

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Competing interests
K.B. has served on advisory boards for IBL International and Roche Diagnostics and provided consultation to Fujirebio Europe. K.B. and H.Z. are co-founders of Brain Biomarker Solutions. P.M.K., D.L.B., H.L., A.M., G.M.R. and K.Y. declare no competing interests.