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Chronic Traumatic Encephalopathy (CTE), Alzheimer's, Dementia and Chronic degenerative brain diseases: where does rugby and contact sport fit into this picture?

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Word & page count: 3629 words, 10 pages

Introduction

Concussion is defined as a pathophysiological brain injury elicited by a direct or indirect impact to the head transmitting biomechanical forces to the brain. Concussion is often followed by spontaneous deficits in neurological function, including headaches, dizziness and balance problems, which can resolve within 24 hours to 7 days^{50,75}. Prolonged concussion signs and symptoms occur in a certain subset of individuals, which can even last several months following a concussion⁴².

In the United States, an estimated 5.3 million people live with a disability or long-term impairment following hospitalised traumatic brain injuries or TBI (including those from concussion)⁸⁴. A surprisingly high annual estimate of 1.6 – 3.8 million concussions were attributed to sports⁴⁴, and concussion incidence is probably even higher in reality, as concussion is often under-reported⁸⁸.

Rugby is a collision sport which involves frequent body contact and has a global participation of more than 5 million players. A high incidence range of 1.4 – 4.0 concussions per 1000 player hours in professional rugby union^{15,77} surpasses the incidence rate in American football but equates to that of elite ice hockey⁴¹, both of which are high-impact contact sports. Concussion can also result in time loss from game play with up to 57 days/1000 hours in a single season¹⁵. As a consequence of TBI (including concussions), catastrophic and fatal outcomes have occurred in rugby. In South African Rugby Catastrophic TBI had an average incidence of 0.19 per 100 000 Junior players (95% CI 0 to 0.56) and 0.62 per 100 000 Senior players (95% CIs 0 to 2.01) in the period 2008-2011 resulting in 4 fatalities recorded over this period¹⁷. The potential adverse effects of sustaining a serious concussion or traumatic brain injury emphasises the need to investigate potential strategies to reduce the incidence, associated risk and time lost from sport.

Current return-to-play guidelines advise players to return to physical activity once they are asymptomatic and where neurocognitive function has returned to normal baseline values. Guidelines also advise a minimum rest of 24 - 48 hours applied following the head knock. Vulnerable groups, such as youth athletes or individuals with persistent symptoms, are conservatively managed with a *minimum* 1 week rest from all physical and mental activities^{47,50}. World Rugby and SARU regulations and guidelines are even stricter and apply longer rest periods before attempting the graduated return to play process^{11,65,89,90}.

Neurocognitive testing (e.g. ImPACT, CogState Sport, SCAT3, Headminders), in addition to symptom resolution, is used as a measure of brain function recovery and assists Medical Doctors in making return to play decisions in players, following a concussion⁵⁰. Although evidence for the effect of concussion history and general cognition is conflicting^{19,27,79}, there is tenuous support for suggesting that there is a relationship between increased concussion history and decreased specialised cognitive skills (e.g. poor motor control)^{8,9,23,25}.

These functional neurocognitive deficits, reflected as concussion signs and symptoms, may partly be due to neurodegenerative microstructural changes following concussive injury¹⁰. It is therefore, theoretically possible that multiple concussions result in repeated neuropathology (e.g. neurodegeneration), thereby exacerbating neurocognitive deficits.

The aim of this review is to analyse current evidence for the potential role of sports-related concussion in potential pathologies including chronic traumatic encephalopathy, neuro-inflammation, neurodegeneration and psychiatric disorders.

Table 1: A list of abbreviations used in this review article

AD – Alzheimer’s disease
ALS – Amyotrophic Lateral Sclerosis
CTE – Chronic Traumatic Encephalopathy
MND – Motor Neuron disease
PD – Parkinson’s disease
TBI – Traumatic Brain Injury

Chronic Traumatic Encephalopathy (CTE)

In the 1920s, the signs of neurological impairment due to brain injury in boxers were originally recognised and collectively labelled as “punch drunk” syndrome or more formally, *dementia pugilistica*⁴⁸.

Dementia pugilistica was clinically characterised by motor, memory, speech and behavioural disturbances, and linked to repetitive head impacts. Symptoms would worsen over time and the more severe signs (including depression and Parkinsonian symptoms) were more commonly observed after retiring from high impact contact sports⁴⁸.

More than 40 years later, an innovative study identified the associated neuropathology in post-mortem brain tissue of retired boxers²⁴. They identified a neuropathology, with cerebral atrophy, neurofibrillary and astrocytic tangles, distinct from other neurodegenerative diseases.

Consequently, the term chronic traumatic encephalopathy (CTE) was adopted, with an estimated prevalence of 17% in former boxers who had sustained a concussion⁷¹.

Importantly, approximately, 40-50% of individuals from the general population who sustained a traumatic brain injury may present with neurological impairments and neurodegeneration³⁸. However, the exact incidence of CTE in sport and the general population is still currently unknown.

Post-mortem autopsy reports and clinical history of former athletes, military veterans, and psychiatric patients who sustained brain injuries or were exposed to frequent head impacts, display a distinct neuropathology which has become characteristic of CTE^{52,56,62-64}. The gross pathology of CTE is distinguished by the location of cerebral atrophy, including sections of the cerebral hemispheres, temporal lobe, thalamus and brainstem. The microscopic degeneration of neurofibrillary and glial tangles is spread predominantly in the superficial cortical layers and irregularly in the frontal and temporal cortices.

CTE is a slow, progressive tauopathy with deposits of hyperphosphorylated tau protein and rarely, the diffuse amyloid plaques^{52,56}. Additionally, TDP-43 proteinopathy was identified in athletes with CTE-associated pathology⁵⁵.

The clinical signs of CTE vary between individuals and are broadly categorised into speech, memory, behavioural and motor abnormalities⁵². Some aspects of CTE pathology (e.g. cerebral atrophy and neurofibrillary tangles) and clinical signs (e.g. poor speech and memory) are similar to Alzheimer's disease and some other neurodegenerative diseases^{4,32,36}.

The mechanisms of damage that occur after a concussion can partly be attributed to the dysregulation of cerebral protein metabolism, elevated release of excitatory neurotransmitters, release of inflammatory markers and ischemia-inducing neuronal death^{7,39}. The neuropathology and adverse clinical signs associated with CTE could possibly be attributed to this cascade of toxicity.

Functional neurological deficits, including poor motor control, speech, learning and memory difficulties, occur following a concussion⁵⁰ and, in some cases, can persist leading to post-concussion syndrome⁷³. Consequently, these prolonged neurological deficits seen following a concussion could provide further support for a possible link between CTE, concussion and cumulative head impacts.

Furthermore, all the former athletes identified with CTE participated in contact sports with high collision exposure (often boxing and American football). In rugby, two case studies of CTE pathology were observed in a 57-year-old former amateur rugby union player and a 77-year-old former professional Australian rules rugby player; and both presented signs of cognitive decline in their early-to-mid 50s as well as tau neurofibrillary pathology in both autopsies^{57,80}. In addition, CTE was reported in two former athletes who played both rugby and American football⁵³. Although CTE has only been identified in a handful of former players associated with rugby, it is possible that a similar neuropathology could be observed given the number of high-speed, high-impact collisions in rugby³¹.

It is, however, impetuous to definitively interpret the previous case studies as reliable evidence supporting an integral role for sports related concussions in the CTE development progression. There currently are no incidence data or direct associated evidence to accurately quantify or contextualize the plausible risk of CTE, derived from contact sport-related concussions.

Neuro-inflammation

A forceful impact to the brain causes primary and secondary injury phases, with the primary phase induced by the biomechanical impact forces within the skull and the secondary phase, elicited by the primary phase, which results in a complex cascade of neurochemical events⁴⁹. This secondary phase causes toxic hyperactivation of neurons disturbing the energy state of the brain and subsequently elicits a neuro-inflammatory response^{76,78,82}.

The fine-tuned balance between beneficial and deleterious effects of the neuro-inflammatory mediators is vital for neurological sequelae following brain injury, and thereby plays a distinct role in potentially adverse outcomes⁷⁴.

Numerous inflammatory signalling mediators, including chemokines, pro-inflammatory cytokines and anaphylatoxins, seem to contribute to the exacerbation of the secondary injury phase following brain injury. The regulation and expression of these mediators can result in: the detrimental features of blood-brain-barrier damage, cerebral oedema, chemotaxis and cell death; or the regenerative features of an accumulation of progenitor cells, hyper-release of astrocytes (astrogliosis) and neuroprotection (reviewed previously⁷⁴).

Although many of the previous literature reported neuro-inflammation in non-sport-related brain injuries or animal models, there is case report evidence for neuro-inflammation in sports concussion^{18,20}.

Diffuse or malignant cerebral oedema (sometimes referred to as second impact syndrome) has previously been reported, following a concussion, in youth athletes^{18,20}. Malignant cerebral oedema is characterised by brain swelling, haematoma and sometimes even death⁸⁷. However, there is currently very little evidence to associate neuro-inflammatory mediators with malignant cerebral oedema.

The mechanism which modulates the neuro-inflammatory response between beneficial and detrimental outcomes is currently unknown. It has only been theorised that repetitive brain impacts can cause dysregulation of inflammatory signalling mediators, which in turn contributes to the neuropathology associated with CTE and other neurodegenerative diseases²⁸.

Neurodegenerative diseases

Neurodegeneration is pathological cell death that occurs in the brain leading to atrophy and loss of neural connections. Alzheimer's disease (AD) is a progressive, widespread neurodegenerative disease. Although often termed an aging disease, the less-common hereditary familial AD can also occur in younger age groups⁷⁰. Globally, an estimated 17 million people have AD^{29,70}, however, the comparative incidence in sporting populations is currently unknown.

Autopsies of former, high impact contact sport players display neuropathology somewhat similar to neurodegenerative diseases, particularly AD^{52,62}.

Similarly to CTE, ischaemia, brain metabolic dysfunction, cerebral protein dysregulation and inflammatory marker release potentially plays a role in neuronal death following a concussion^{7,39}. Additionally, widespread deposits of β -amyloid protein plaques and neurofibrillary tangles are hallmark features of AD.

These microscopic changes plausibly could contribute to the adverse outcomes associated with AD, including memory, speech and behavioural abnormalities. A meta-analysis of case-control studies reported an association between TBI and AD risks³⁰. Contrastingly, population cohort studies reported an association between TBI and dementia risk, but not specifically AD^{45,86}. Dementia is a clinical sign of AD⁷⁰ but is also common to other neurodegenerative diseases such as frontotemporal dementia³⁶.

Autopsy case studies report a remarkably similar tauopathy in both CTE and AD in contact sport players, who sustained severe brain injury^{52,62}. Clinically, some features including dementia and memory abnormalities are also shared between CTE and AD. Moreover, sequence changes within the *APOE* gene were associated with AD risk, β -amyloid protein deposits and having a history of previous concussion^{43,46,83}. These previous genetic association studies highlight individuals with a specific genetic profile which may predispose to AD.

A subset of vulnerable individuals may exist, who are at risk for CTE, neuro-inflammation, dementia or have a genetic predisposition to AD-related pathology. Therefore, these vulnerable individuals could be more susceptible to the development of AD, particularly, if exposed to multiple concussions.

Parkinson's disease (PD), motor neuron disease (MND) and epilepsy are some of the other neurodegenerative disorders often proposed as possible outcomes following brain injury, with the exception of epilepsy which has also been suggested to impair concussion recovery^{1,55,58}.

PD has a localised dopaminergic neuronal cell death in the substantia nigra and chiefly impairs motor control. Similarly to neurodegenerative disorders AD and CTE, repetitive concussions initiate secondary injuries implicated in the development of the PD pathology². A rat model of TBI reported a PD-like pathology¹, while case reports have identified Parkinsonian symptoms in contact sport players with CTE pathology^{52,64}. There is a slight indication that brain injury, especially chronic exposure, could influence predisposition to motor control abnormalities in later life, but there is insufficient evidence to relate this to progression into PD.

MND, also known as amyotrophic lateral sclerosis (ALS), has an annual incidence of 1.5 – 2 per 100 000 population, with 50% of patients dying within 3 years post onset⁶¹. MND is a selective loss of motor neurons leading to muscle atrophy, weakness and spasticity⁶¹, with intellect and sensory function often remaining functional.

There are a range of possible mechanisms for the development of MND; including bacterial toxin, heavy-metal toxicity, environmental, occupational and excitotoxicity of neurons^{5,59,60}. In addition, 5 - 10% of patients inherit familial MND in an autosomal dominant nature⁷².

Biochemically, TDP-43 proteinopathy was identified in athletes with both CTE and MND pathology⁵⁵. Another study reported a motor system decline with age in previously concussed former athletes⁹. Although published data of MND in athletes are uncommon, an Italian study reported MND in former soccer players (concussion history was not reported) and, an autopsy case study observed MND, associated with CTE, in former American football players who experienced a history of mild traumatic brain injury^{22,56}. Although there were no published reports on MND in rugby, anecdotally and from media reports MND has previously been observed in rugby players; however, the correlation to concussion history is unknown. Concussion may result in signs of motor loss similar to MND progression; however, insufficient evidence exists to implicate concussion in the aetiology of MND.

Convulsions or seizures are observed in certain cases immediately following a concussion^{50,85}. Epilepsy is a neurodegenerative disorder characterised by seizures and was suggested to modulate concussion severity.

In contact sports, concussion-induced convulsions seem to be transient and non-epileptic with rapid normalisation of neurocognitive deficits⁵¹. Therefore, epilepsy does not seem to be a potential modifier of concussion severity, nor does current evidence implicate concussion in the development of epilepsy⁴⁷. However, athletes with a pre-existing epileptic condition should be appropriately monitored and managed by a neurologist.

Dementia

Dementia often accompanies neurodegenerative diseases, including AD⁷⁰. Advanced cognitive impairment, particularly in memory functioning, is a hallmark feature of dementia^{67,68}. An annual rate of 1 – 2% of healthy, aged individuals will present with dementia²⁶. Although dementia and dementia-related diseases (such as AD) were not associated with multiple concussions, an earlier age of onset for AD was observed in athletes with a concussion history compared to the general male population³⁴. Case studies and neurocognitive studies showed dementia, memory impairment or signs of neurocognitive decline in athletes exposed to repetitive concussions or head impacts, such as boxers and American football players^{13,14,37,52,54,64,81}. An association between repetitive concussions or head impacts and dementia or dementia-like decline appears likely.

Co-morbid psychiatric disorders

Depression is one of the most common psychiatric disorders observed in individuals following a brain injury and occurs in approximately 42% of patients³⁵. Depression is characterised with persistent low mood, self-esteem and sometimes suicidal thoughts^{3,6}. In case studies, signs of violence and erratic behaviour are reported in some individuals diagnosed with CTE pathology and exposed to repetitive concussions or head impacts^{33,52,62,63}.

In addition to behavioural disturbances, clinical depression was diagnosed in former football players who experienced multiple concussions³³. A 9-year prospective study reported a dose-response relationship between the number of self-reported previous concussions and depression risk in retired athletes⁴⁰. Neuroimaging studies have also shown brain activity changes corresponding to depression in brain injured athletes²¹.

Notably, the psychological and quality of life effects of retirement, non-brain related injuries, narcotics, alcohol use, performance-enhancer drugs, and other environmental factors are important modulators for mental health^{50,69}. Therefore, the extent of the role of brain injury in depression is uncertain. The supporting evidence and debilitating nature of depression warrants further investigation of the potential influence of concussion on later life mental health.

Discussion

Selected neuropathological and clinical features are common between CTE, neuro-inflammation, neurodegenerative diseases and to a certain extent, psychiatric disorders (Figure 1); however, there are distinct differences in aetiology between these disorders. As a result it is near impossible to isolate a single causative mechanism, such as concussion.

Realistically, it is more likely that concussion, in part, is involved in the progression of many of these tauopathies, degenerative diseases and psychiatric disorders.

There is even less certainty on the grey area of repetitive impacts as a causative factor, as this has been postulated mostly due to the high impact nature of contact sports (e.g. rugby, American football), without strong epidemiological evidence to support this claim.

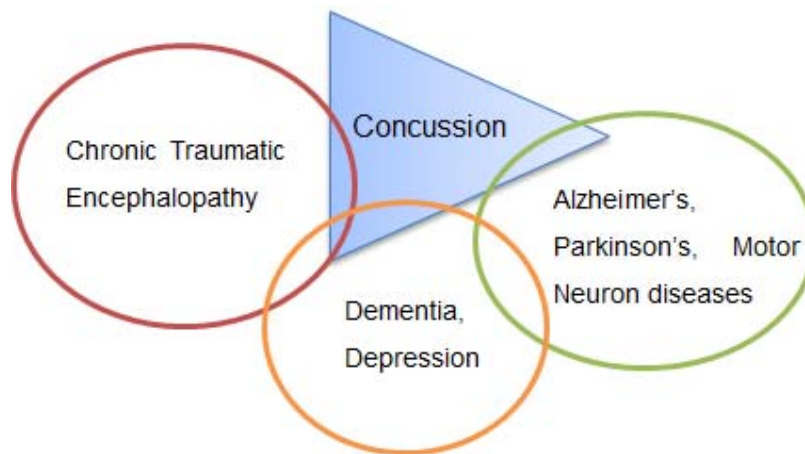


Figure 1: A simplified illustration of the possible interaction between concussion, chronic traumatic encephalopathy, Alzheimer's disease, Parkinson's disease, motor neuron diseases, dementia and depression.

Furthermore, it is currently unknown whether the number, force magnitude or direction of impact, solely or in combination, modulates progression of neurodegeneration. As is necessary with multi-faceted disorders, e.g. CTE or AD, the external contributing factors (e.g. prior clinical history, family history, violent environment) and internal factors (e.g. heritable traits, innate behaviour) must not be overlooked and may play a greater role in disease progression than concussion or repetitive impacts on their own.

Notably, the evidence for neuropathology and neurocognitive decline, resulting from TBI, may not be solely or directly relatable to sports concussions which are often the milder brain injury form^{16,50}. Specifically, albeit that there are few documented cases associated with rugby players, a direct causative link between chronic neurodegenerative disorders and rugby union has not yet been established.

Furthermore, the neuropathology and cognitive decline, often associated with dementia and AD, is also observed in apparently healthy, aged individuals¹². Therefore, it is currently debatable whether or not rugby-associated brain injury accelerates the cognitive decline which is typically associated with the normal aging process.

Presently no definitive statements of repetitive concussion and sub-concussive impacts and neurological disorders can be made. Current efforts of injury prevention programmes within sports are commendable⁶⁶ but increased fervour in investigating the unanswered questions regarding the potential role of concussion in later life mental health is imperative.

References

1. ACOSTA, S. A, TAJIRI, N., DE LA PENA, I., BASTAWROUS, M., SANBERG, P. R., KANEKO, Y. AND BORLONGAN, C. V. Alpha-synuclein as a Pathological Link between Chronic Traumatic Brain Injury and Parkinson's disease. *J Cell Physiol* September :1–34. 2014. doi:10.1002/jcp.24830
2. ACOSTA, S. A, TAJIRI, N., SHINOZUKA, K., ISHIKAWA, H., GRIMMIG, B., DIAMOND, D. M., DIAMOND, D., SANBERG, P. R., BICKFORD, P. C., KANEKO, Y. AND BORLONGAN, C. V. Long-term upregulation of inflammation and suppression of cell proliferation in the brain of adult rats exposed to traumatic brain injury using the controlled cortical impact model. *PLoS One* 8,1 :e53376. 2013.
3. AMERICAN PSYCHIATRIC ASSOCIATION. *The Diagnostic and Statistical Manual of Mental Disorders: DSM 5*. bookpointUS, 2013.
4. AREZA-FEGYVERES, R., ROSEMBERG, S., CASTRO, R. M. R. P. S., PORTO, C. S., BAHIA, V. S., CARAMELLI, P. AND NITRINI, R. Dementia Pugilistica with Clinical Features of Alzheimer's Disease. *Arq Neuropsiquiatr* 65,3-B :830–833. 2007.
5. ARMON, C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. *Neuroepidemiol* 22,4 :217–228. 2003.
6. BARLOW, D. AND DURAND, V. *Abnormal psychology: An integrative approach*. Cengage Learning, 2011.
7. BAZARIAN, J. J., BLYTH, B. AND CIMPELLO, L. Bench to Bedside : Evidence for Brain Injury after Concussion — Looking beyond the Computed Tomography Scan. *Soc. Acad. Emerg. Med.* 13,2 :199–214. 2006.
8. DE BEAUMONT, L., BRISSON, B., LASSONDE, M. AND JOLICOEUR, P. Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj.* 21,6 :631–644. 2007.
9. DE BEAUMONT, L., TREMBLAY, S., HENRY, L. C., POIRIER, J., LASSONDE, M. AND THÉORET, H. Motor system alterations in retired former athletes: the role of aging and concussion history. *BMC Neurol.* 13, :109. 2013.
10. BIGLER, E. D. Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. *Arch Clin Neuropsychol* 18,6 :595–621; discussion 623–7. 2003.
11. BOKSMART. *BokSmart Concussion Guidelines*. *BokSmart* 2012. at <www.BokSmart.com>
12. BRAAK, E., GRIFFING, K., ARAI, K., BOHL, J., BRATZKE, H. AND BRAAK, H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *Eur. Arch. Psychiatry Clin. Neurosci.* 249,S3 :s14–s22. 1999.

13. BREEDLOVE, E. L., ROBINSON, M., TALAVAGE, T. M., MORIGAKI, K. E., YORUK, U., O'KEEFE, K., KING, J., LEVERENZ, L. J., GILGER, J. W. AND NAUMAN, E. A. Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J. Biomech.* 45,7 :1265–72. 2012.
14. BREEDLOVE, K. M., BREEDLOVE, E. L., ROBINSON, M., POOLE, V. N., III, J. R. K., ROSENBERGER, P., RASMUSSEN, M., TALAVAGE, T. M., LEVERENZ, L. J. AND NAUMAN, E. A. Detecting Neurocognitive and Neurophysiological Changes as a Result of Subconcussive Blows in High School Football Athletes. *Athl. Train. Sport. Heal. Care* 6,X :1–9. 2014.
15. BROOKS, J. H. M., FULLER, C. W., KEMP, S. P. T. AND REDDIN, D. B. Epidemiology of injuries in English professional rugby union: part 1 match injuries. *Br. J. Sports Med.* 39,10 :757–66. 2005.
16. BROOKS, J. H. M., FULLER, C. W., KEMP, S. P. T. AND REDDIN, D. B. Epidemiology of injuries in English professional rugby union: part 1 match injuries. *Br J Sport. Med* 39,10 :757–66. 2005.
17. BROWN, J. C., LAMBERT, M. I., VERHAGEN, E., READHEAD, C., VAN MECHELEN, W. AND VILJOEN, W. The incidence of rugby-related catastrophic injuries (including cardiac events) in South Africa from 2008 to 2011: a cohort study. *BMJ Open* 3,2 :1–10. 2013.
18. BRUCE, D. A., ALAVI, A., BILANIUK, L., DOLINSKAS, C., OBRIST, W. AND UZZELL, B. Diffuse cerebral swelling following head injuries in children: the syndrome of 'malignant brain edema'. *J Neurosurg* 54,2 :170–8. 1981.
19. BRUCE, J. M. AND ECHEMENDIA, R. J. History of multiple self-reported concussions is not associated with reduced cognitive abilities. *Neurosurgery* 64,1 :100–6; discussion 106. 2009.
20. CANTU, R. C. AND VOY, R. Second impact syndrome: a risk in any contact sport. *Physician Sport.* 23,6 :27–34. 1995.
21. CHEN, J.-K., JOHNSTON, K. M., PETRIDES, M. AND PTITO, A. Neural Substrates of Symptoms of Depression Following Concussion in Male Athletes With Persisting Postconcussion Symptoms. *Arch Gen Psychiatry.* 65,1 :81–89. 2008.
22. CHIO, A., CALVO, A., DOSSENA, M., GHIGLIONE, P., MUTANI, R. AND MORA, G. ALS in Italian professional soccer players: the risk is still present and could be soccer-specific. *Amyotroph. Lateral Scler.* 10,November 2008 :205–209. 2009.
23. COLLINS, M. W., GRINDEL, S. H., LOVELL, M. R., DEDE, D. E., MOSER, D. J., PHALIN, B. R., NOGLE, S., WASIK, M., CORDRY, D., DAUGHERTY, M. K., SEARS, S. F., NICOLETTE, G. AND INDELICATO, P. Relationship between concussion and neuropsychological performance in college football players. *JAMA* 282,10 :964 – 970. 1999.
24. CORSELLIS, J. A. N., BRUTON, C. J. AND FREEMAN-BROWNE, D. The aftermath of boxing. *Psychol. Med.* 3,03 :270–303. 1973.
25. COVASSIN, T., ELBIN, R., KONTOS, A. AND LARSON, E. Investigating baseline neurocognitive performance between male and female athletes with a history of multiple concussion. *J Neurol, Neurosur Psych* 81,6

- :597–601. 2010.
26. DALY, E., ZAITCHIK, D., COPELAND, M., SCHMAHMANN, J., GUNTHER, J. AND ALBERT, M. Predicting Conversion to Alzheimer Disease Using Standardized Clinical Information. *Arch Neurol* 57,5 :675–680. 2000.
 27. ELBIN, R. J., COVASSIN, T., HAKUN, J., KONTOS, A. P., BERGER, K., PFEIFFER, K. AND RAVIZZA, S. Do brain activation changes persist in athletes with a history of multiple concussions who are asymptomatic? *Brain Inj.* 26,10 :1217–1225. 2012.
 28. FADEN, A. I. AND LOANE, D. J. Chronic Neurodegeneration After Traumatic Brain Injury: Alzheimer Disease, Chronic Traumatic Encephalopathy, or Persistent Neuroinflammation? *Neurotherapeutics* :1–8. 2014. doi:10.1007/s13311-014-0319-5
 29. FERRI, C. P., PRINCE, M., BRAYNE, C., BRODATY, H., FRATIGLIONI, L., HALL, K., HASEGAWA, K., HENDRIE, H., HUANG, Y., JORM, A., MENEZES, P. R., RIMMER, E., SCAZUFCA, M. AND DISEASE, A. Global prevalence of dementia : a Delphi consensus study. *Lancet* 366,9503 :2112–2117. 2010.
 30. FLEMINGER, S., OLIVER, D. L., LOVESTONE, S. AND 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.
 31. GABBETT, T. J., JENKINS, D. G. AND ABERNETHY, B. Physical collisions and injury in professional rugby league match-play. *J Sci Med Sport* 14,3 :210–5. 2011.
 32. GOEDERT, M. in *Apolipoprotein E and Alzheimer’s Disease* :103–125. Springer, 1996.
 33. GUSKIEWICZ, K. M., MARSHALL, S. W., BAILES, J., MCCREA, M., JR, H. P. H., MATTIHEWS, A. M. Y., MIHALIK, J. R. AND CANTU, R. C. Recurrent Concussion and Risk of Depression in Retired Professional Football Players. *Med Sci Sport. Exerc* 39,6 :903–910. 2007.
 34. GUSKIEWICZ, K. M., MARSHALL, S. W., BAILES, J., MCCREA, M., CANTU, R. C., RANDOLPH, C. AND JORDAN, B. D. Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players. *Neurosurgery* 57,4 :719–726. 2005.
 35. JEFFREY S. KREUTZER EUGENE GOURLEY, R. T. S. The prevalence and symptom rates of depression after traumatic brain injury: a comprehensive examination. *Brain Inj.* 15,7 :563–576. 2001.
 36. JOHANSON, A. AND HAGBERG, B. Psychometric characteristics in patients with frontal lobe degeneration of non-Alzheimer type. *Arch. Gerontol. Geriatr.* 8,2 :129–137. 1989.
 37. JOHNSON, B., NEUBERGER, T., GAY, M., HALLETT, M. AND SLOBOUNOV, S. Effects of Subconcussive Head Trauma on the Default Mode Network of the Brain. *J Neurotrauma* :1–24. 2014. doi:10.1089/neu.2014.3415
 38. JOHNSON, V. E., STEWART, J. E., BEGBIE, F. D., TROJANOWSKI, J. Q., SMITH, D. H. AND STEWART, W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136,Pt 1 :28–42. 2013.
 39. KATAYAMA, Y., BECKER, D. P., TAMURA, T. AND HOVDA, D. A. Massive increases in extracellular potassium and

- the indiscriminate release of glutamate following concussive brain injury. *J. Neurosurg.* 73,6 :889–900. 1990.
40. KERR, Z. Y., MARSHALL, S. W., HARDING, H. P. AND GUSKIEWICZ, K. M. Nine-year risk of depression diagnosis increases with increasing self-reported concussions in retired professional football players. *Am. J. Sports Med.* 40,10 :2206–12. 2012.
 41. KOH, J. O., CASSIDY, J. D. AND WATKINSON, E. J. Incidence of concussion in contact sports: a systematic review of the evidence. *Brain Inj.* 17,10 :901–917. 2003.
 42. KUTCHER, J. S. AND ECKNER, J. T. At-risk populations in sports-related concussion. *Curr. Sports Med. Rep.* 9,1 :16–20. 2010.
 43. LAMBERT, J., PASQUIER, F., COTTEL, D., FRIGARD, B. AND AMOUYEL, P. A new polymorphism in the APOE promoter associated with risk of developing Alzheimer ' s Disease. *Hum Mol Genet* 7,3 :533–540. 1998.
 44. LANGLOIS, J. A, RUTLAND-BROWN, W. AND WALD, M. M. The epidemiology and impact of traumatic brain injury: a brief overview. *J. Head Trauma Rehabil.* 21,5 :375–8. 2006.
 45. LEE, Y.-K., HOU, S.-W., LEE, C.-C., HSU, C.-Y., HUANG, Y.-S. AND SU, Y.-C. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. *PLoS One* 8,5 :e62422. 2013.
 46. LENDON, C. L., HARRIS, J. M., PRITCHARD, A. L., NICOLL, J. A. R., TEASDALE, G. M. AND MURRAY, G. Genetic variation of the APOE promoter and outcome after head injury. *Neurology* 61,5 :683–685. 2003.
 47. MAKDISSI, M., DAVIS, G., JORDAN, B., PATRICIOS, J., PURCELL, L. AND PUTUKIAN, M. Revisiting the modifiers: how should the evaluation and management of acute concussions differ in specific groups? *Br. J. Sports Med.* 47,5 :314–20. 2013.
 48. MARTLAND, H. S. Punch drunk. *JAMA* 91,15 :1103–1107. 1928.
 49. McCLAIN, C., COHEN, D., PHILLIPS, R., OTT, L. AND YOUNG, B. Increased plasma and ventricular fluid interleukin-6 levels in patients with head injury. *J Lab Clin Med* 118,3 :225. 1991.
 50. MCCRORY, P., MEEUWISSE, W. H., AUBRY, M., CANTU, B., DVORAK, J., ECHEMENDIA, R. J., ENGBRETSSEN, L., JOHNSTON, K., KUTCHER, J. S., RAFTERY, M., SILLS, A., BENSON, B. W., DAVIS, G. A., ELLENBOGEN, R. G., GUSKIEWICZ, K., HERRING, S. A., IVERSON, G. L., JORDAN, B. D., KISSICK, J., McCREA, M., MCINTOSH, A. S., MADDOCKS, D., MAKDISSI, M., PURCELL, L., PUTUKIAN, M., SCHNEIDER, K., TATOR, C. H. AND TURNER, M. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Br J Sport. Med* 47,5 :250–258. 2013.
 51. MCCRORY, P. R., BLADIN, P. F. AND BERKOVIC, S. F. Retrospective study of concussive convulsions in elite Australian rules and rugby league footballers: phenomenology, aetiology, and outcome. *BMJ* 314,January :171–174. 1997.
 52. MCKEE, A., CANTU, R. AND NOWINSKI, C. Chronic traumatic encephalopathy in athletes: Progressive

- tauopathy after repetitive head injury. *Neuropathol Exp Neurol* 68, :709–735. 2009.
53. MCKEE, A. C., STEIN, T. D., NOWINSKI, C. J., STERN, R. A., DANESHVAR, D. H., ALVAREZ, V. E., LEE, H.-S., HALL, G., WOJTOWICZ, S. M., BAUGH, C. M., RILEY, D. O., KUBILUS, C. A., CORMIER, K. A., JACOBS, M. A., MARTIN, B. R., ABRAHAM, C. R., IKEZU, T., REICHARD, R. R., WOLOZIN, B. L., BUDSON, A. E., GOLDSTEIN, L. E., KOWALL, N. W. AND CANTU, R. C. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136,1 :43–64. 2013.
 54. MCKEE, A. C., CANTU, R. C., NOWINSKI, C. J., HEDLEY-WHYTE, T., GAVETT, B. E., BUDSON, A. E., VERONICA, E., LEE, H., KUBILUS, C. A. AND STERN, R. A. Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy following Repetitive Head Injury. *J Neuropathol Exp Neurol* 68,7 :709–735. 2010.
 55. MCKEE, A. C., GAVETT, B. E., STERN, R. A., NOWINSKI, C. J., CANTU, R. C., KOWALL, N. W., PERL, D. P., HEDLEY-WHYTE, E. T., PRICE, B., SULLIVAN, C., MORIN, P., LEE, H., CAROLINE, A., DANESHVAR, D. H., WULFF, M. AND BUDSON, A. E. TDP-43 Proteinopathy and Motor Neuron Disease in Chronic Traumatic Encephalopathy. *J Neuropathol Exp Neurol* 69,9 :918–929. 2010.
 56. MCKEE, A. C., STERN, R. A., NOWINSKI, C. J., STEIN, T. D., ALVAREZ, V. E., DANESHVAR, D. H., LEE, H.-S., WOJTOWICZ, S. M., HALL, G., BAUGH, C. M., RILEY, D. O., KUBILUS, C. A., CORMIER, K. A., JACOBS, M. A., MARTIN, B. R., ABRAHAM, C. R., IKEZU, T., REICHARD, R. R., WOLOZIN, B. L., BUDSON, A. E., GOLDSTEIN, L. E., KOWALL, N. W. AND CANTU, R. C. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136,1 :43–64. 2012.
 57. MCKEE, A. C., DANESHVAR, D. H., ALVAREZ, V. E. AND STEIN, T. D. The neuropathology of sport. *Acta Neuropathol.* 127, :29–51. 2014.
 58. MILLER, H. Mental Sequele of Head Injury. in *Proc Royal Soc Med* 59, March :257–261. 1966.
 59. MILLER, R. G., MITCHELL, J. D. AND MOORE, D. H. Riluzole for amyotrophic lateral sclerosis (ALS)/ motor neuron disease (MND) (Review). *Cochrane Database Syst Rev* 3 :1–34. 2012.
 60. MITCHELL, J. D. Heavy metals and trace elements in amyotrophic lateral sclerosis. *Neurol. Clin.* 5,1 :43–60. 1987.
 61. MITCHELL, J. D. AND BORASIO, G. D. Amyotrophic lateral sclerosis. *Lancet* 369, :2031–2041. 2007.
 62. OMALU, B. I., DEKOSKY, S. T., HAMILTON, R. L., MINSTER, R. L., KAMBOH, M. I., SHAKIR, A. M. AND WECHT, C. H. Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery* 59,5 :1086–92; discussion 1092–3. 2006.
 63. OMALU, B. I., FITZSIMMONS, R. P., HAMMERS, J. AND BAILES, J. Chronic traumatic encephalopathy in a professional American wrestler. *J. Forensic Nurs.* 6,3 :130–6. 2010.
 64. OMALU, B. I., DEKOSKY, S. T., MINSTER, R. L., KAMBOH, M. I., HAMILTON, R. L. AND WECHT, C. H. Chronic Traumatic Encephalopathy in a National Football League Player. *Neurosurgery* 57,1 :128–134. 2005.
 65. PATRICIOS, J. When can a player safely return to play following a concussion? *BokSmart* at <<http://images.supersport.com/content/SAferreturn2015.PDF>>

66. PATRICIOS, J. BokSmart - South African Rugby's National Rugby Safety and Injury Prevention Program. *Am J Sport. Med* 13,3 :142–144. 2014.
67. PETERSEN, R. C., STEVENS, J. C., GANGULI, M., TANGALOS, E. G., CUMMINGS, J. L., DEKOSKY, S. T. AND EXAMINATION, M. S. Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). *Neurology* 56,9 :1133–1142. 2001.
68. PETERSEN, R. C., DOODY, R., KURZ, A., MOHS, R. C., MORRIS, J. C., RABINS, P. V., RITCHIE, K., ROSSOR, M., THAL, L. AND WINBLAD, B. Current Concepts in Mild Cognitive Impairment. *Arch Neurol.* 58,12 :1985–1992. 2001.
69. RAFTERY, M. Concussion and chronic traumatic encephalopathy: International Rugby Board's response. *Br J Sport. Med* 48,2 :79–80. 2014.
70. REITZ, C., BRAYNE, C. AND MAYEUX, R. Epidemiology of Alzheimer disease. *Nat. Rev. Neurol.* 7,3 :137–52. 2011.
71. ROBERTS, A. H. Brain damage in boxers: a study of the prevalence of traumatic encephalopathy among ex-professional boxers. Pitman Medical & Scientific Publishing Company, Limited, 1969.
72. ROTHSTEIN, J. D. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. *Ann. Neurol.* 65 Suppl 1, :s3–9. 2009.
73. SAVOLA, O. AND HILLBOM, M. Early predictors of post-concussion symptoms in patients with mild head injury. *Eur. J. Neurol.* 10, :175–181. 2003.
74. SCHMIDT, O. I., HEYDE, C. E., ERTEL, W. AND STAHEL, P. F. Closed head injury — an inflammatory disease ? *Brain Res. Rev.* 48, :388–399. 2005.
75. SCHNEIDER, K. J., MEEUWISSE, W. H., KANG, J., SCHNEIDER, G. M. AND EMERY, C. A. Preseason Reports of Neck Pain, Dizziness, and Headache as Risk Factors for Concussion in Male Youth Ice Hockey Players. *Clin J Sport. Med* 0, :1–6. 2013.
76. SHULTZ, S. R., MACFABE, D. F., FOLEY, K. A, TAYLOR, R. AND CAIN, D. P. Sub-concussive brain injury in the Long-Evans rat induces acute neuroinflammation in the absence of behavioral impairments. *Behav. Brain Res.* 229,1 :145–52. 2012.
77. SHUTTLEWORTH-EDWARDS, A. B., NOAKES, T. D., RADLOFF, S. E., WHITEFIELD, V. J., CLARK, S. B., ROBERTS, C. O., ESSACK, F. B., ZOCCOLA, D., BOULIND, M. J., CASE, S. E., SMITH, I. P. AND MITCHELL, J. L. G. The comparative incidence of reported concussions presenting for follow-up management in South African Rugby Union. *Clin J Sport Med* 18,5 :403–9. 2008.
78. SMITS, M., DIPPEL, D. W. J., HOUSTON, G. C., WIELOPOLSKI, P. A, KOUDSTAAL, P. J., HUNINK, M. G. M. AND VAN DER LUGT, A. Postconcussion syndrome after minor head injury: brain activation of working memory and attention. *Hum. Brain Mapp.* 30,9 :2789–803. 2009.
79. SOLOMON, G. S. AND KUHN, A. Relationship between concussion history and neurocognitive test

- performance in National Football League draft picks. *Am J Sport. Med* 42,4 :934–9. 2014.
80. STEWART, W., McNAMARA, P. H., LAWLOR, B., HUTCHINSON, S. AND FARRELL, M. Chronic traumatic encephalopathy: a potential late and under recognized consequence of rugby union? *QJM Int J Med* February :1–5. 2015. doi:10.1093/qjmed/hcv070
 81. TALAVAGE, T. M., NAUMAN, E. A, BREEDLOVE, E. L., YORUK, U., DYE, A. E., MORIGAKI, K. E., FEUER, H. AND LEVERENZ, L. J. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J Neurotrauma* 31,4 :327–38. 2014.
 82. TANG-SCHOMER, M. D., PATEL, A. R., BAAS, P. W. AND SMITH, D. H. Mechanical breaking of microtubules in axons during dynamic stretch injury underlies delayed elasticity, microtubule disassembly, and axon degeneration. *FASEB J.* 24,5 :1401–10. 2010.
 83. TERRELL, T. R., BOSTICK, R. M., ABRAMSON, R., XIE, D., BARFIELD, W., CANTU, R., STANEK, M. AND EWING, T. APOE , APOE Promoter , and Tau Genotypes and Risk for Concussion in College Athletes. *Clin J Sport Med* 18, :10–17. 2008.
 84. THURMAN, D., ALVERSON, C., DUNN, K., GUERRERO, J. AND SНИЕZEK, J. Traumatic brain injury in the United States: A public health perspective. *J Head Trauma Rehabil.* 14,6 :602–15. 1999.
 85. VESPA, P. M., NUWER, M. R., NENOV, V., RONNE-ENGSTROM, E., HOVDA, D. A., BERGSNEIDER, M., KELLY, D. F., MARTIN, N. A. AND BECKER, D. P. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *J Neurosurg* 91, :750–760. 1999.
 86. WANG, H.-K., LIN, S.-H., SUNG, P.-S., WU, M.-H., HUNG, K.-W., WANG, L.-C., HUANG, C.-Y., LU, K., CHEN, H.-J. AND TSAI, K.-J. Population based study on patients with traumatic brain injury suggests increased risk of dementia. *J. Neurol. Neurosurg. Psychiatry* 83,11 :1080–5. 2012.
 87. WETJEN, N. M., PICHELMANN, M. A AND ATKINSON, J. L. D. Second impact syndrome: concussion and second injury brain complications. *J. Am. Coll. Surg.* 211,4 :553–7. 2010.
 88. WILLIAMSON, I. AND GOODMAN, D. Converging evidence for the under-reporting of concussions in youth ice hockey. :128–133. 2006. doi:10.1136/bjism.2005.021832
 89. WORLD RUGBY. World Rugby Regulation 10. 2015. at <<http://images.supersport.com/content/wrReg10.pdf>>
 90. WORLD RUGBY. World Rugby Concussion Guidance. *World Rugby* 5, 2015.