# Chronic Traumatic Encephalopathy (CTE), Alzheimer's, Dementia and Chronic degenerative brain diseases in contact sport – Evidence-based review

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**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[54]. Concussion is often followed by changes in neurological function, including physical symptoms such as headaches, dizziness and balance problems, cognitive difficulties, emotional changes and sleep disturbances. Most may resolve within 24 hours to 7 days[54,83] but sometimes can take much longer.

Prolonged concussion signs and symptoms occur in a certain subset of individuals, which can even last several months following a concussion[46]. The presence of loss of consciousness (LOC), occurring in only about 10% of concussions[35], and amnesia were initially thought to be determinants of severity and prolonged recovery. However, the duration and nature of all post-concussive symptoms seems more predictive of concussion recovery than amnesia or LOC in isolation[54].

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)[93]. Concussions commonly result from vehicle accidents, falls, military duty and sport. A surprisingly high annual estimate of 1.6 – 3.8 million concussions were attributed to sports[48], and concussion incidence is probably even higher in reality, as concussion is often under-reported[97].

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[15,85] surpasses the incidence rate in American football but equates to that of elite ice hockey [45], 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 season[15].

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 period [17]. 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 the neurocognitive deficits, measured using a variety of clinical tools, have returned to normal baseline values. Guidelines also advise a minimum rest of 24 - 48 hours, following the head knock; with more conservative guidelines for younger athletes.

Vulnerable groups, such as youth athletes, individuals with persistent symptoms or those with other modifying factors, are conservatively managed with a *minimum* 1 week rest from all physical and mental activities and the focus for children is to return to school as well as sport[51,54]. World Rugby and SARU regulations and guidelines are even stricter and apply longer rest periods before attempting the graduated return to play process[11,72,98,99].

Clinical screening tools (SCAT3, SCOAT)[25,74,88] and computerised neurocognitive testing (e.g. ImPACT, CogState Sport, Headminders), are used as measures of brain function recovery and may help guide Medical Doctors in making return to play decisions in players, following a concussion[54].

Some studies have linked reduced neurocognitive ability (including executive, visual & motor function) to sustaining multiple previous concussions in asymptomatic athletes[8,9,24,27] and other, prospective, large sample size studies, reported no association between general cognitive ability and multiple concussions[20,29,87]. Although evidence for the effect of concussion history and general cognition is conflicting, there is tenuous support for suggesting that there might be a relationship between increased concussion history and decreased specialised cognitive skills (e.g. poor motor control).

These functional neurocognitive deficits, reflected as concussion signs and symptoms, may partly be due to neurodegenerative microstructural changes following concussive injury[10]. It is therefore theoretically possible that multiple concussions could 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 pathology including chronic traumatic encephalopathy, neuro-inflammation, neurodegeneration and psychiatric disorders.

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

| Abbreviations |
| --- |
| 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 impairments due to brain injury in boxers were originally recognised and collectively labelled as "punch drunk" syndrome or more formally, *dementia pugilistica*[52].

*Dementia pugilistica*, initially thought to occur in boxers only, 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 sports[52].

These symptoms were also recognised in military personnel exposed to blast-related head injury[65], thus broadening the affected population from boxers to non-sport individuals as well.

More than 40 years later, an innovative study identified the associated neuropathology in the post-mortem brain tissue of retired boxers[26]. They described a neuropathology with cerebral atrophy, neurofibrillary and astrocytic tangles distinct from other neurodegenerative diseases. Further autopsy studies observed this neuropathology not only in boxers and soldiers but also in circus acrobats, American football players, a wrestler, military veterans, autistic patients, a physically abused victim and an epileptic[56,60,69–71]; which further broadened the affected population to other contact sports and individuals who sustained severe TBI as well.

As a consequence of the distinctive neuropathology and to cluster the neuropathological findings in this cohort, the term chronic traumatic encephalopathy (CTE) was adopted. An estimated prevalence of 17% of former boxers who sustained a concussion developed CTE[79], while approximately 40-50% of those, in the general population, who sustained a traumatic brain injury may present with neurological impairments and neurodegeneration[42]. However, the exact incidence of CTE in sport and the general population is currently unknown.

Post-mortem autopsy reports and clinical histories of former athletes, military veterans, and psychiatric patients who sustained brain injuries or were exposed to frequent head impacts; all display a distinct neuropathology which has become characteristic of CTE.

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 with irregular distribution in the frontal and temporal cortices.

CTE is a slow, progressive tauopathy with deposits of hyperphosphorylated tau protein and rarely, the diffuse amyloid plaques[56,60]. Additionally, TDP-43 proteinopathy was identified in athletes with CTE-associated pathology[59].

The clinical signs of CTE vary between individuals and are broadly categorised into speech, memory, behavioural and motor abnormalities[56]. 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[4,34,40].

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 and ischemia-inducing neuronal death[7,43]. The insult to the brain elicits hyperactivation of brain regions causing a metabolic imbalance, which further creates an environment for dysregulated deposition of proteins (e.g. hyperphosphorylated tau) and release of inflammatory markers to assist in healing[7,86,91]. The combination of hyperactivation, metabolic imbalance and protein deposition becomes toxic, possibly leading to neuronal cell death and the associated neurocognitive impairment (Figure 1). The neuropathology and adverse clinical signs of CTE could possibly be attributed to this cascade of toxicity.
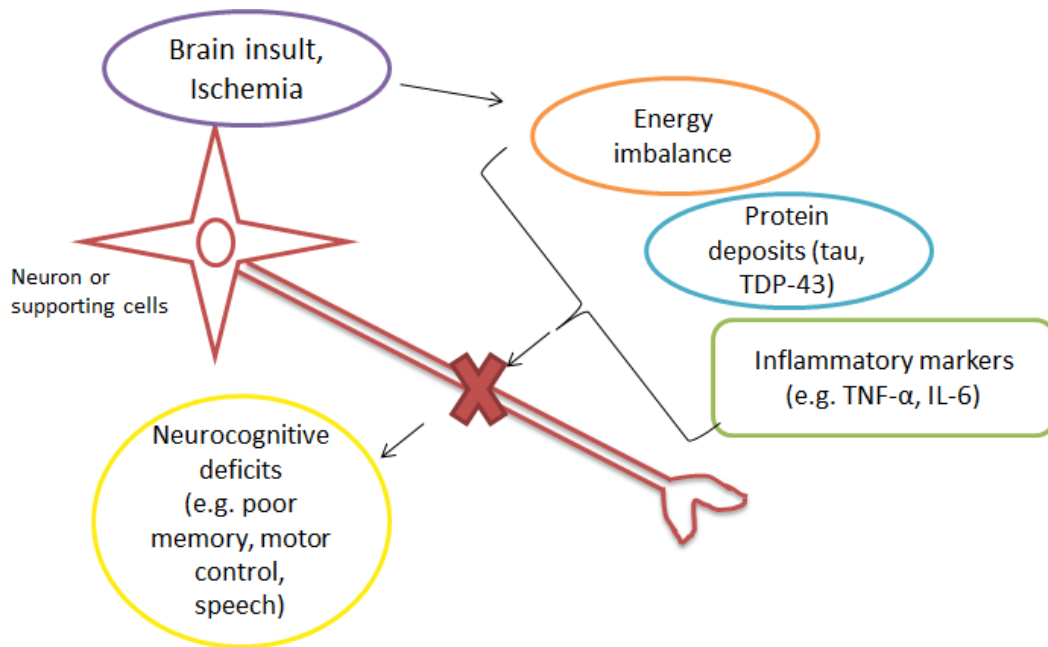


Figure 1: A summary of the proposed neurodegenerative pathways involved in the development of neurocognitive deficits following a concussion (brain insult)[7,43,86,91]. TDP-43 - TAR DNA-binding Protein of approximately 43 kd, TNF-α – Tumour Necrosis Factor, IL-6 – Interleukin-6

As previously mentioned, the post-mortem neuropathology of CTE was identified in individuals exposed to brain injury or cumulative head impacts. All the former athletes identified with CTE participated in contact sports with high collision exposure (e.g. boxing, American football). In rugby, CTE neuropathology was observed in a 57-year-old former amateur rugby union player who suffered cognitive decline over 5 years until his death due to respiratory failure[89]. Notably, he had a family history of neurological disorders suffered by his mother and maternal uncle. Another CTE case study of a 77-year-old former professional Australian rules rugby player also showed cognitive decline in his mid-50s which worsened to severe dementia by his 60s[61]. Both presented signs of cognitive decline in their early-to-mid 50s and tau neurofibrillary pathology in the autopsies[61,89]. In addition, CTE was reported in two former athletes who played both rugby and American football[57]. Although CTE has only been identified in a handful of former players associated with rugby[57,61,89], it is possible that a similar neuropathology could be observed given the number of high-speed, high-impact collisions in rugby[33].

Furthermore, functional neurological deficits, including poor motor control, speech, learning and memory difficulties, occur following a concussion[54] and, in some cases, can persist, leading to post-concussion syndrome[81]. Consequently, these prolonged neurological deficits seen following a concussion could provide further support for a possible link between CTE, concussion and cumulative head impacts.

It is, however, impetuous to definitively interpret the previous case studies as reliable evidence supporting an integral role of sport-related concussions in the development and progression of CTE.

There are currently no incidence data or direct associated evidence to accurately quantify or contextualize the plausible risk of CTE derived from contact sport and likewise, there is no direct associative evidence to do the same for CTE and concussions in contact sports.

The potential influence of performance enhancing drugs, alcohol use, mental health and genetic predisposition on developing CTE must be noted[38,77]. Consequently, the roles of concussion, and sub-concussive impacts (defined as a head impact without clinical concussion signs and symptoms but with concussion-associated neurocognitive deficits) in isolation, in the development of CTE is currently ill-defined and unknown.

**Neuro-inflammation**

A forceful impact to the brain causes primary and secondary injury phases, with the primary phase induced by the biomechanical forces within the skull, and the secondary phase, elicited by the primary phase, which results in a complex cascade of neurochemical events[53].

This secondary phase causes toxic hyperactivation of neurons which imbalances the energy state of the affected brain regions and subsequently elicits a neuro-inflammatory response to assist in preventing infection or repairing affected tissue[53,84,86,91].

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 outcomes (Figure 2). An intensified neuro-inflammatory response, with elevated signalling molecules (e.g. TNF-α), can easily become deleterious and toxic for surrounding nerve tissue[82].
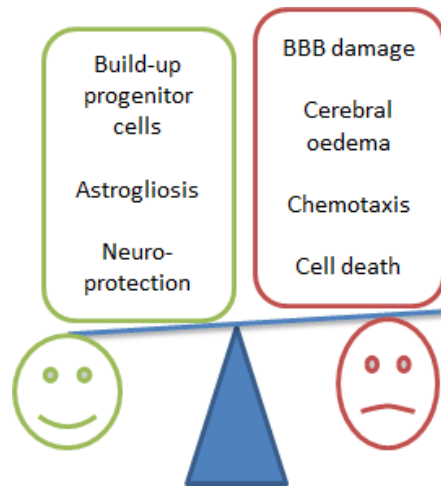


*Figure 2: The balance between beneficial (left panel) and adverse (right panel) effects of neuro-inflammation following a concussion*[53,82]. BBB – Blood brain barrier

There are numerous inflammatory signalling mediators that are involved following a brain injury including chemokines, pro-inflammatory cytokines and anaphylatoxins. These mediators seem to contribute to 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 accumulation of progenitor cells, hyper-release of astrocytes (astrogliosis) and neuroprotection (reviewed previously[82], Figure 2).

Although many of the previous literature reported neuro-inflammation in non-sport related brain injuries or animal models, there is case study evidence for neuro-inflammation in sports concussion[18,21].

Diffuse or malignant cerebral oedema (sometimes referred to as "second impact syndrome") has previously been reported, following a concussion, in youth athletes[19,21]. Malignant cerebral oedema is characterised by brain swelling, haematoma and sometimes even death[96]. 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 could contribute to the neuropathology associated with CTE and other neurodegenerative diseases[30].

**Neurodegenerative diseases**

*Alzheimer's disease*

Neurodegeneration is a process of pathological cell death that occurs in the brain leading to atrophy and loss of neural connections within the nervous system. Alzheimer's disease (AD) is a progressive, widespread neurodegenerative disorder, predominantly occurring in the elderly (> 60 years old). Although often considered a disease of aging, the less-common hereditary familial AD can also occur in younger age groups[78].

An estimated 17 million people globally have AD[31,78], however, the comparative incidence in sporting populations is currently unknown. Autopsies of former high impact, contact sport players display neuropathology somewhat similar to neurodegenerative disorders, particularly AD[56,69].

Hypoxia can, in part, lead to brain metabolic dysfunction, resulting in an imbalance of the brain energy state and thereby depriving nervous tissue of energy[43]. With the energy state of the brain compromised, widespread deposits of β-amyloid protein plaques and neurofibrillary tangles occur in the brain. A neuro-inflammatory response is activated by the protein deposits and, as previously discussed, can play a role in cell death and dysfunctional nerve signalling. Moreover, these microscopic changes plausibly can contribute to the resulting adverse outcomes including memory, speech and behavioural abnormalities associated with AD.

A meta-analysis of case-control studies reported an association between TBI and AD risk, however, no association was observed when analysing a subset of recent studies only[32]. Population cohort studies reported an association between TBI and risk of developing dementia, but not specifically AD[49,95].

Dementia is often an integral clinical sign of AD[78] but is also common to other neurodegenerative diseases such as frontotemporal dementia[40].

Autopsy case studies report a remarkably similar tauopathy in both CTE and AD in contact sport players, who sustained severe brain injury[56,69]. Clinically, some features including dementia and memory abnormalities are also shared between AD and CTE. Furthermore, sequence changes within the *APOE* gene were associated with AD risk, β-amyloid protein deposits and having a history of previous concussion[47,50,92]. 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.

*Other neurodegenerative diseases*

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[1,59,63].

PD has a localised and progressive cell death of the dopaminergic neurons in the substantia nigra and chiefly impairs motor control. A rat model of TBI reported a PD-like pathology in the substantia nigra[1]. Similarly to neurodegenerative disorders AD and CTE, repetitive concussions initiate secondary injuries implicated in the development of the PD pathology[2]. In addition, case reports have identified Parkinsonian symptoms in former, contact sport players with CTE pathology[56,71]. There is a slight indication[2,56,71] 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 the progression into PD.

MND, also known as amyotrophic lateral sclerosis (ALS) or colloquially as Lou Gehrig's disease, has an annual incidence of 1.5 – 2 per 100 000 population, with 50% of patients dying within 3 years post onset[67]. MND is a selectively progressive loss of lower and upper motor neurons leading to denervated muscle atrophy, weakness and spasticity[67]. The intellect and sensory function often remains functional, however, some MND cases experience associated central nervous system degeneration, such as frontotemporal dementia[68]. Generally, the clinical signs include debilitating facial and limb weakness; often with respiratory muscle denervation resulting in fatality[80].

There are a range of possible mechanisms for the development of MND; from bacterial toxins, heavy-metal toxicity, environmental, occupational and excitotoxicity of neurons[5,64,66]. In addition, 5 - 10% of patients inherit familial MND in an autosomal dominant nature[80].

Biochemically, TDP-43 proteinopathy was identified in athletes with both CTE pathology and MND[59]. Another study reported a motor system decline with age in previously concussed former athletes[9]. 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 injury[23,60]. 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[54,94]. Epilepsy is a neurodegenerative disorder characterised by seizures and was suggested to modulate concussion severity. Epilepsy results in a lack of inhibition of neuronal activity leading to neuronal over-excitation and subsequent excitotoxic cell death.

In contact sports, concussion-induced convulsions seem to be transient, non-epileptic with rapid normalisation of neurocognitive deficits[55]. Therefore, epilepsy does not seem to be a potential modifier of concussion severity, nor does current evidence implicate concussion in the development of epilepsy[51]. However, athletes with a pre-existing epileptic condition should be appropriately monitored and managed by a neurologist.

*Dementia*

Dementia often accompanies neurodegenerative diseases, including AD[78]. Advanced cognitive impairment, particularly in memory functioning, is a hallmark feature of dementia[75,76]. An annual rate of 1 – 2% of healthy, aged individuals will present with dementia while 10 – 20% of patients with mild cognitive impairment (MCI) will convert per year[28,62]. MCI is classified, usually in older individuals, as a cognitive decline (often in memory) greater than normal aging but less advanced than dementia[75,76]. In former football athletes (mean age: 54 years old), clinically diagnosed MCI and self-reported memory deficits were associated with having a history of previous concussion. 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 than for the general male population[37]. 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[13,14,41,56,58,71,90]. An association between repetitive concussions or head impacts and dementia or dementia-like decline seems 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 patients[39]. Depression is a type of mood disorder that is clinically characterised with persistent low mood, self-esteem, disinterest in normally pleasurable activities and sometimes even suicidal thoughts[3,6]. In case studies, signs of violence and erratic, uncharacteristic behaviour are reported in some individuals diagnosed with CTE pathology and those exposed to repetitive concussions or head impacts[36,56,69,70].

In addition to behavioural disturbances, clinical depression was diagnosed in former football players who experienced multiple concussions[36]. A 9-year prospective study reported a dose-response relationship between the number of self-reported previous concussions and depression risk in retired athletes, after adjusting for physical health[44]. Neuroimaging studies have also shown brain activity changes corresponding to the limbic-frontal depression model in brain injured athletes[22].

It must be noted that the psychological and quality of life effects of retirement, non-brain related injuries, narcotics, alcohol use, performance-enhancement drugs, and other environmental factors are important modulators of mental health[54,77]. As the extent to which these external factors may modulate the risk of depression or other mood disorders is unknown, the role of brain injury in depression is still uncertain. However, the behavioural and mood disturbances that can occur following acute concussions[54] and the 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; however, there are distinct differences in aetiology between these disorders. Although these disorders are related to brain damage, their multifactorial nature constrains proper investigation of the isolated role of concussion and repetitive head impacts in their causation. Hereditary-linked neurodegeneration, mental health history, narcotics, alcohol use, performance-enhancing drugs and other environmental factors are some of the modulators of the development of neurological and psychiatric disease[6,54,77].

Notably, the long term neurological sequelae have been investigated in both TBI and the milder form, concussion. However, the aetiology, symptom presentation and incidence, in sport, differ between TBI and concussion. Concussion is more common in contact sport than moderate to severe TBI[16,54]. Therefore, the evidence for neuropathology and neurocognitive decline, resulting from TBI, may not be directly applicable to sports concussion. Furthermore, the neuropathology and cognitive decline, often associated with dementia and AD, is also observed in apparently healthy, aged indiviuals[12].

All these neurological diseases and pathologies could interact, and some can even be associated. There are also numerous contributing factors which influence these pathologies and disorders (Figure 3). As a result it is 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 some 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 any epidemiological evidence currently available to support this claim.

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 an even greater role in disease progression than concussion or repetitive impacts on their own.
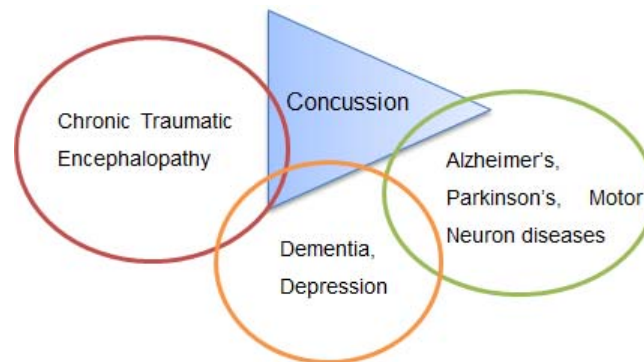


*Figure 3: A simplified illustration of the possible interaction between concussion, chronic traumatic encephalopathy, Alzheimer's disease, Parkinson's disease, motor neuron diseases, dementia and depression.*

Presently no definitive statements on the relationships between repetitive concussions and sub-concussive impacts and neurological disorders can be made. Recent media attention on CTE and head impacts can undermine the on-going efforts of concussion awareness and education[77], especially at this infantile stage of our understanding of the underlying mechanisms of CTE and other neurological disorders. Current efforts of injury prevention programmes within sports are commendable[73] but increased fervour in investigating the unanswered questions regarding the potential role of concussion in later life mental health is imperative.

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