The multi-factorial origins of Chronic Traumatic Encephalopathy (CTE) symptomology in post-career athletes: The athlete post-career adjustment (AP-CA) model

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Title: The multi-factorial origins of Chronic Traumatic Encephalopathy (CTE) symptomology in post-career athletes: The athlete post-career adjustment (AP-CA) model

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ABSTRACT

CTE has two prominent components: the pathophysiology that is detected in the brain postmortem and the symptomology that is present in the interval between retirement and end of life. CTE symptomology has been noted to include memory difficulties, aggression, depression, explosivity, and executive dysfunction at early stages progressing to problems with attention, mood swings, visuospatial difficulties, confusion, progressive dementia, and suicidality [e.g. 6-10]. There are a number of assumptions embedded within the current CTE literature: The first is the assumption that CTE symptomology reported by athletes and their families is the product of the pathophysiology change detected post-mortem [e.g. 10]. At present, there is little scientific evidence to suggest that all CTE symptomology is the product of CTE pathophysiology. It has been assumed that CTE pathophysiology causes CTE symptomology [38, 61] but this link has never been scientifically validated. The purpose of the present work is to provide a multi-factorial theoretical framework to account for the symptomology reported by some athletes who sustain neurotrauma during their careers that will lead to a more systematic approach to understanding post-career symptomology. There is significant overlap between the case reports of athletes with post-mortem diagnoses of CTE, and symptom profiles of those with a history of substance use, chronic pain, and athlete career transition stress. The athlete post—career adjustment (AP-CA) is intended to explain some of the symptoms that athletes experience at the end of their careers or during retirement. The AP-CA model consists of four elements: neurotrauma, chronic pain, substance use, and career transition stress. Based on the existing literature, it is clear that any one of the four elements of the AP-CA model can account for a significant number of CTE symptoms. In addition, depression
can be a chronic lifelong co-morbid condition that may be present prior to an athletic career, or may be developed secondary to any of the model elements as shown in Figure 1. Notably, neurotrauma is a necessary, but not a sufficient condition, for the development of CTE symptomology.

INTRODUCTION

Chronic Traumatic Encephalopathy (CTE) has recently received considerable attention in the clinical literature as well as in mainstream and popular media. In fact, it is rare that a movie is made about a specific area of clinical science while the science is ongoing, but such is the case with the movie “Concussion”; a focus on the scientific career of Dr. Bennett Omalu and his study of deceased professional athletes many of whom had donated their brains to study at the University of Pittsburgh and later at the Boston University (now the VA-BU-CLF) Brain Bank. It is the contention of Omalu and colleagues that CTE is the product of any human activity that exposes you to a “single traumatic brain injury, episodic traumatic brain injury or repetitive traumatic brain injury” [1](p. 10). Sports generally considered to generate CTE include combat sports (e.g. boxing and mixed martial arts), ice hockey, North American football, rugby union and amateur and professional wrestling [1,2]. Some have stated that it is now known that “repeated TBI can potentially lead to irreversible and progressive neurodegeneration of CTE” and can be produced by activities ranging from heading the ball in soccer to being an enforcers in ice hockey [3] (p.119). CTE has also been detected in deceased military veterans [e.g. 4].
CTE has two prominent components: the pathophysiology that is detected in the brain following death and the symptomology that is present in the interval between retirement and end of life. The pathophysiologic features have generally been defined by CTE researchers [e.g. 5, 6] to include p-tau immunoreactive astrocytic tangles and neurofibrillary tangles (NFT) that aggregate in specific locations within the brain. CTE symptomology (clinical symptoms) has been noted to include memory difficulties, aggression, depression, explosivity, and executive dysfunction at early stages progressing to problems with attention, mood swings, visuospatial difficulties, confusion, progressive dementia, and suicidality [e.g. 6-10]. CTE has been linked to the deaths of athletes in the National Football League (NFL) [e.g. 11-13] and the National Hockey League (NHL) [14]. Related to these negative outcomes are well publicized past and current legal cases initiated on behalf of retired athletes who claim that professional sports leagues should have done more to protect and inform them from these negative outcomes during their sports careers [11]. Some have stated that given the numbers of North Americans involved in contact sport, “it is clear that the risk of CTE looms as a potential public health disaster” [15] (p. 4). The concern over CTE has had a direct impact on some athletes who have decided to retire early in their careers to limit the potential for long-term negative outcomes [16].

The clinical science and presence of CTE as a mainstream concept have progressed rapidly, however, some would argue, without the measured and expected degree of scientific rigor. As a result, there are a number of assumptions embedded within the current CTE literature that may be clouding a more accurate interpretation of the findings. The first is the assumption that
CTE symptomology reported by athletes and their families is the *product* of the pathophysiology change detected post-mortem [e.g. 10]. Because the vast majority of the CTE literature is based on case studies, there has been very little information generated that objectively and intentionally demonstrates this link. The second assumption is that retired athletes are representative of the general population with the exception that their brains have sustained at least single or repetitive mild concussive or subconcussive injury. This assumption is generally incorrect. Athletes who have attained some level of success and notoriety are a unique sub-population: 1) They often experience significant physical trauma, and in some cases neural trauma, during their careers. This trauma may lead to persistent neurologic and physical problems; 2) To achieve their atypical level of success, they must sacrifice other elements of personal or social engagement and/or development. This can lead to social isolation post-career and may even lead to problematic personality (identity) development; and 3) Athletes oftentimes achieve a level of social prominence during their careers. This level of prominence diminishes or disappears following retirement. These are important factors to consider when attempting to understand why some athletes have negative outcomes following retirement.

At present, there is little scientific evidence to suggest that all CTE symptomology is the product of CTE pathophysiology. The purpose of the present work is to provide a multi-factorial theoretical framework to account for the symptomology reported by some athletes who sustain neurotrauma during their careers and that will lead to a more systematic approach to understanding post-career symptomology.
CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

CTE History

Elements of CTE pathophysiology and symptomology were historically described as a progressive neurodegenerative syndrome that occurred in boxers who had a significant history in the sport. Martland [17] was the first to describe the syndrome known as “punch drunk” that characterized some of the symptomatology attributed to the pathophysiology of CTE. While many of the signs included obvious physical symptoms such as leg dragging, Parkinsonian symptoms, and speech slowing, some of the symptomology was also consistent with CTE including cognitive deterioration and confusion. It is also evident that at the time of publication, the words “concussion” and “traumatic encephalitis” were in use to describe various forms of neurotrauma in boxers [17]. Parker [18] was among the first to use the term traumatic encephalopathy to identify a chronic disease of the nervous system observed in former boxers who sustained repeated injuries to the brain. He described early signs and symptoms such as ataxia and confusion, postcareer signs such as dysarthria, deafness, “physical slowing up,” and slow, laboured, grating, nasal speech. Symptomology included deficits in memory, attention, and concentration. An interesting note in the cases reviewed by Parker was that despite presence of substantial neurotrauma, evidenced by numerous physical signs, the deterioration did not seem to worsen over the years of follow-up [18]. These deficits were generally considered to affect professional boxers only with the “punch-drunk” syndrome... never observed in amateur boxers” [19] (p. 363). This early work was built upon by Roberts [20] who randomly sampled 250 retired boxers and showed severe pathophysiology in 5% and demonstrable lesions in 17% of cases. The often cited classic study by Corsellis et al. [21]
described a characteristic pattern of brain injury in boxers, some of whom were amateurs: a fenestrated or a cavum septum pellucidum, scarring to cerebellar tonsils and other cerebral areas, neuronal loss in substantia nigra and locus coeruleus, ventricular enlargement, thinning of the corpus callosum, and neurofibrillary tangles in cerebral cortex and temporal lobe. More recent attempts to link the current concept of CTE with boxing have been published [22, 23]. In their review of 36 published articles, Loosemore et al. [22] defined CTE as a demonstrable change in neurological signs, brain imaging, psychometric testing, electroencephalography, and other imaging. The authors concluded that a strong association between amateur boxing and chronic traumatic brain injury did not exist. They added that the neurotrauma sustained in amateur boxing was lower than other more popular sports (e.g. rugby union and equestrian) [22]. McCrory et al. [23] had a different perspective stating that both amateur and professional boxers are potentially at risk of developing CTE. Notably, both of these studies describe neurologic and cognitive deficits in boxers without the pathophysiologic confirmation of CTE.

The modern era of CTE research

The modern era of CTE study can be credited to Omalu et al.’s [24] description of neurodegenerative change in a retired NFL football athlete. The description of modern CTE cases differs from the historical reports in boxers in a number of ways. First, the more recent cases have been “autopsy confirmed” [e.g. 24]. Second, many of the athletes in current CTE studies are not boxers (e.g., American football, ice hockey, and professional wrestling) [5, 25]. Third, the modern era of CTE research has been presented by some as pathophysiologically distinct from the historical precedent described in boxing [1, 6, 8, 25-29].
A unified definition for modern CTE has been elusive. Some researchers have defined CTE related to single, episodic, or repetitive blunt force impacts to the head [5]. Others have defined CTE as developing following repetitive concussive or subconcussive events [8, 30-32]. Some have suggested that CTE can occur with no direct head trauma at all [8, 33]. Recently, an entirely new category has been proposed for research purposes; Traumatic Encephalopathy Syndrome (TES) consisting of four variants (TES behavioral/mood variant, TES cognitive variant, TES mixed variant, and TES dementia) [34].

CTE rates of incidence are unknown based on the research methodologies employed to date. Prevalence estimates vary from relatively low [3, 29, 35], to moderate [e.g. 36], with some media reports cresting 90% [12]. This has led some to suggest that CTE is likely more prevalent than previously considered [37] while other caution that CTE has been over-estimated in some athlete populations due to sampling bias [32]. As indicated in a recent NIH consensus document, most agree that a definitive diagnosis of CTE can only be made during neuropathological examination of the brain at autopsy [38, 39]. Nonetheless, it has also been argued that a diagnosis of CTE related to sports can be based on a history of repetitive clinical or subclinical concussions, evidence of disease progression, and a positive neurological exam [15]. The number of concussive or subconcussive events in these athletes is often unusually high (e.g. a mean of 20 concussions) [40].

Modern CTE Pathophysiology
Early descriptions of modern CTE pathophysiology centred on the presence of tau-positive neuritic threads, sparse intraneuronal NFTs, and cortical amyloid plaques, with little pathology in the entorhinal cortex or hippocampus [24]. It was noted that NFTs often aggregated in perivascular regions in cortical layers II and III [10]. Since that time, the identification of CTE has evolved into classification systems developed by established CTE research groups [29]. However, similar to the varied definitions for CTE, pathophysiologic criteria also vary among these classification systems.

McKee and colleagues have classified CTE into four stages [41, 42] while Omalu and colleagues [5] have developed four histomorphologic CTE phenotypes. The inconsistencies between the staging and phenotype classification schemes have generated criticism [43]. Inconsistencies between systems include variations in gross morphological atrophy and the presence or absence of p-tau immunoreactive astrocytic tangles, Aβ plaques, Lewy bodies, and subependymal accumulation of p-tau. In addition, the issue of sporadic tau depositions in various populations was not adequately addressed [43]. In an attempt to establish a consistent pathological diagnosis of CTE, the National Institutes of Health (NIH) convened a Consensus Conference to define the neuropathological criteria for CTE diagnosis [12]. The “Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy” (http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm) clearly indicated that a diagnosis of CTE can only be made during neuropathological examination of the brain at autopsy. The group consensus was that “abnormal tau immunoreactivity in neurons
and glia, in an irregular, focal, perivascular distribution and at the depths of cortical sulci, was required for the diagnosis of CTE”.

Modern CTE Symptomology
Similar to modern CTE pathophysiology, modern CTE symptomology has evolved since first described in 2005. The first descriptions were notably simple and straightforward, with the first case described by Omalu et al. [24] as resembling a dysthymic disorder, with memory and judgment problems, and Parkinsonian symptoms. Subsequent cases described by Omalu and co-workers were depicted as having significant increases in psychiatric symptoms. For example, the second case presented by this group [44] included more detailed neuropsychiatric sequelae such as becoming agitated in social situations, being reclusive (e.g. often locking himself in the house for 1 to 2 days), having unpredictable fluctuations in mood and personality, risky/ambitious/irrational business dealings, and sudden bouts of agitation and irritability with no rationale. Symptomology in subsequent cases was expanded to include distinct symptoms such as suicidality, paranoia, hyperreligiosity, and violent behavior including criminality [7, 9, 10]. Some have suggested that CTE symptomology is progressive including worsening memory impairment, executive dysfunction, management of activities of daily living (enough to impair social and/or occupational functioning), with dementia in later stages [32]. Others speculate that there may be several possible long-term outcomes following repetitive neurotrauma including no neurological signs or symptoms, static deficits, or progressive neurodegeneration [37]. In addition, some contend that sports-related (CTE) deterioration occurs in three stages: Stage 1 - Affective disturbances and psychotic symptoms; Stage 2 - Social instability,
erratic behavior, memory loss, and initial symptoms and signs of Parkinsonism; and Stage 3 - General cognitive dysfunction, the progression of dementia, speech, and gait abnormalities, or full-blown Parkinsonism [15]. CTE symptomology has been described as developing “insidiously” some years to decades after retirement or exposure to neurotrauma [31].

In relation to the pathophysiologic stages proposed by McKee et al. [6]: Stage I CTE has been associated with headache and loss of attention and concentration; Stage II CTE includes depression, mood swings, explosivity, problems with attention and concentration, headache, and short-term memory loss; Stage III includes cognitive impairment with memory loss, executive dysfunction, loss of attention and concentration, depression, explosivity and visuospatial abnormalities; Stage IV includes dementia, short-term memory loss, executive dysfunction, attention and concentration loss, explosivity and aggression [6]. The proponents of the Chronic Traumatic Encephalopathy Syndrome [34] have offered a broadened definition that includes at least one “clinical” feature and at least two “supportive” features. Clinical features include “Cognitive” (e.g. difficulties in cognition), “Behavioral” (e.g. being emotionally explosive), and “Mood” (e.g. feeling overly sad, depressed, and/or hopeless). Supportive features include: 1) Impulsivity, 2) Anxiety, 3) Apathy, 4) Paranoia, 5) Suicidality, 6) Headache, 7) Motor signs 8) Documented decline, 9) Delayed onset [34]. More recently, CTE symptoms have been categorized into four broad classifications: behavior, cognition, mood, and motor as per Table 1 [31, 35, 37]. Based on these four classifications, two major clinical variants of CTE have described, with younger patients exhibiting more pronounced behavioral or mood disturbances and older patients exhibiting cognitive impairment that overlaps with other age-
associated cognitive disorders, such as Alzheimer’s disease (AD) [31, 35, 36, 45, 46]. Notable distinctions between the two major clinical variants were that the behavior/mood group was considered to be significantly more explosive, out of control, physically and verbally violent, and depressed. On the other hand, the cognition group were reported to have impaired episodic memory, and were significantly more likely to progress to dementia (but were also significantly older at the time of death) [46].

Criticisms of CTE research

The CTE literature has received much criticism. One of the criticisms is that many of the studies used biased sampling methodologies, specifically, the inherent selection bias associated with postmortem brain donations from families who may have witnessed disturbing behavioural changes during life [46]. To their credit, the methodologic limitations of their work, such as biased sampling, have been acknowledged by some CTE researchers [32, 46, 47]. Nonetheless, the focus of CTE research has not shifted to improvements in methodology (including case controlled studies), but has continued with the existing paradigm with efforts for elucidation of molecular events responsible for the neurodegeneration [28]. As such, criticisms regarding biases continue. One such criticism involves the availability cascade - the neglect of empirical data in favor of highly publicized and emotional case findings, with perpetuation of biased perception, as has been observed in media reports [12, 45]. Further, studies that rely on the retrospective recall of clinical features by family members and friends of the deceased individuals with CTE are limited by recall bias [12]. The lack of properly matched non-injured controls has been noted [45; 48]. Davis et al. [45] correctly state that an adequate control
group should have a similar demographic profile to cases, similar history of drug exposure, and similar genetic profile. An adequate control group for CTE studies should also match for confounding factors, such as underlying depression or anxiety, genetic predisposition to psychiatric illness, or substance use [49]. The cases to date also suffer from limited case numbers and differences in methodology between research groups [48].

Further methodologic criticisms have been levied related to the quality of data and the difficulties establishing CTE incidence or prevalence [50]. Regarding prevalence, Stern and co-workers correctly stated that not all individuals with exposure to brain trauma develop neurodegenerative disease [32]. For example, a study on high school students who played American football from 1946 to 1956 did not have an increased risk of later developing dementia, Parkinson’s disease, or Amyotrophic Lateral Sclerosis compared to non–football-playing high school males [51]. In a report on the clinical and pathological case histories for 6 retired Canadian Football League (CFL) athletes who underwent CNS autopsies, repetitive concussions, positive clinical signs and symptoms of progressive neurodegenerative disease, were not inevitably associated with CTE (3 of 6 had CTE) [52]. Bieniek et al. [36] screened for CTE pathology in brains of individuals with exposure to contact sports and matched controls without such exposure from a brain bank containing neurodegenerative disorders. Of 66 patients with history of exposure to contact sports, 21 (32 %) had tau pathology consistent with CTE. No CTE pathology was observed in any control case [36]. Finally, a 41-year-old retired NFL offensive lineman who had likely many head impacts over the course of his career had no CTE changes at autopsy [28]. As Castellani [28] stated, this raises the issue of the much needed
prevalence data, as well as the resilience and plasticity of the human brain and its ability to endure significant concussive and subconcussive injuries impacts.

CTE has been linked with progressive cognitive, motor, and mood decline [38]. Some CTE researchers have noted that while CTE pathology is progressive, it remains to be determined if certain individuals are resilient or if the pathology is reversible [6]. However, Davis and colleagues [45] argued that “no scientific evidence has been presented based on prospective cohort studies to support (the) contention that CTE is a progressive entity” [45] (p. 644). Ban et al. [12] added that sampling at a single post-mortem time point is not sufficient proof of progressive disease. They reasoned that longitudinal studies with multiple time point sampling at multiple scientific centres are required to make this determination [12]. Issues related to incidence rates have also been described Iverson and colleagues [43] who stated that approximately 1 in 4 people identified as having the neuropathological features of CTE did not have significant clinical symptoms and 1 in 4 cases with clinical symptoms had no demonstrable neuropathology. Therefore, there seems to be a mismatch between pathology and symptomology for a significant number of cases.

Criticisms that some of the pathophysiology identified as characteristic of CTE may be part of the normal aging process or an element of an established neurodegenerative disease process have also been advanced. It is important to note that many degenerative diseases share the characteristic of protein tau pathology. Examples include progressive supranuclear palsy,
Down’s syndrome, dementia pugilistica, amyotrophic lateral sclerosis, postencephalitic parkinsonism, parkinsonism-dementia complex of Guam, as well as viral and metabolic disorders; therefore, the presence of tau pathology cannot be considered specific [53; 54]. For example, numerous researchers have noted that the shared pathological characteristics between Alzheimer’s disease (AD) [10, 43, 48, 49, 55] and CTE make the diagnosis difficult especially in cases older than 65 years [5]. The Aβ and NFTs found in CTE are immunocytochemically identical to those found in AD, suggesting a possible common pathogenesis [10] that may in some cases be linked to neurotrauma [55]. Further, there had until recently been only two cases where a biochemical characterization of tau has been performed and in both cases, the hyperphosphorylated tau of CTE was indistinguishable from that observed in AD [48]. This has led some to question whether the diagnoses of CTE and AD and other neurodegenerative disorders are mutually exclusive [49]. This position has been supported in a recent study that showed that in 268 neurodegenerative disease and control cases, 32 cases (11.9 %), had histological evidence of CTE. CTE pathophysiology “was highest in Progressive Supranuclear Palsy (24 %) and Parkinson’s disease (16 %), followed by controls (12.8 %), AD (10 %), Corticobasal degeneration (7.4 %), Frontotemporal lobe dementias (4.2 %) and multiple system atrophy (2 %)” [56] (p. 892). Interestingly, all cases identified with CTE had stage I or II progression and only 2 cases (0.1 %) were reported as having ‘pure’ CTE pathology [56]. Of note in this study was the number of controls that had evidence of CTE. Results such as these have prompted some to suggest that a portion of what has been labelled as CTE pathology may be confused with normal age-related change [5, 45, 50]. Frontotemporal lobe dementias (FTLD) have also been shown to share many of the pathologic and clinical features of
CTE [45]. The combined data on normal aging and FTLD have led some to conclude that CTE stages I and II may represent tau deposition seen in normal aging brains, while stages III and IV may represent forms of FTLD [45]. Finally, a recent study has demonstrated that the pathological presence and expression patterns of tau protein are not unique to CTE and exist in patients with a history of the temporal lobe epilepsy. The authors of this study caution that the overall pattern of phosphorylated tau detected in these tissues did not lend credence to the hypothesis that CTE has a unique protein tau signature [57].

In addition to concerns related to the pathologic features of CTE, CTE symptomology has also been criticized. The inclusion of the clinical feature “suicidality” has spawned much debate and commentary. Suicidality is a prominent feature in the well-publicized deaths of prominent athletes [11] and may account for much of the amplified media focus on CTE [58]. There have been many graphic and dramatic descriptions of suicide attempts, suicide, and “parasuicide” in the CTE literature [5, 7-10, 11, 44]. Suicide has been presented as “clinically associated” with CTE [6], over-represented in CTE cases [5], not uncommon [32], with the heightened suicidal risk in stark contrast to other tauopathies [35]. The association between CTE and suicide has been postulated for professional athletes [11]. Recently, concussion has also been linked to suicide [37].

The facts are that suicide is over-represented in the CTE literature with a recent review stating of 111 cases, 78 deaths were from natural causes; 19 accidental deaths, and 14 suicides [50].
However, there are a number of points to consider when regarding the pathophysiology of CTE as a cause of suicide. First, suicide was not considered a clinical feature in the first 80 years of writing relating to CTE with the first description occurring with modern CTE cases [43, 50]. Second, there is no established causal scientific link between CTE pathophysiology and suicide [43, 59]. Third, the case selection bias results in an over-representation of CTE cases with neuropsychiatric comorbidities and suicide risk factors [58]. Fourth, Iverson [59] has noted that in 10 of 52 athletes that committed suicide, 6 of 10 did not have the neuropathological features of CTE, suggesting other potential causes for these cases. Fifth, former NFL athletes are less likely to die by suicide than men in the general population [59]. A recent study has demonstrated that a cohort of NFL players with 5 or more credited seasons of play had rates of suicide that were less than half of what would be expected in a comparable sex/race/age grouping from the general US population [60]. Sixth, many of the case histories contained known risk factors for suicidality including but not limited to depression, substance abuse, chronic pain, limited social connectedness, and hopelessness [61]. Iverson has stated that depression is somewhat common in men across their lifespan, and suicidality is a cardinal diagnostic feature of major depressive disorder [61]. Therefore, when all of the evidence is considered, the link between suicide and CTE pathophysiology can be considered scientifically “premature, overly simplistic, and potentially fatalistic” [61] (p. 13) and clearly precludes any claims suggesting evidence-based relationships [58].

Another criticism related to CTE symptomology is the unverified link between symptomology and pathophysiology. CTE researchers often comment on the link between pathophysiology
and symptomology. It has been suggested that there is mounting evidence suggesting CTE may be the major underlying etiology in the deaths related to neurodegeneration in NFL athletes [37]. It has also been stated that “the symptoms of CTE, like other neurodegenerative diseases, results from the progressive decline in functioning of neurons or of the progressive neuronal death” [32] (p. S463). Others have stated that we “know that athletes who develop CTE develop a progressive neurodegeneration that typically produces clinical symptoms years to decades after retiring from the sport” [42] (p. 10). It has also been stated recently that PTSD might share biological and pathological underpinnings with CTE [42]. Efforts have been made to link the pathological changes described through stages I-IV with specific symptoms (e.g. memory and executive dysfunction related to degenerative changes in the hippocampus in advanced CTE) [15, 46]. As with many areas of CTE science, these statements have met with criticism. Castellani [28] (p. 581) put it well: “drawing mechanistic associations between tauopathy at autopsy, and psychiatric signs or complex behaviors such as suicide, explosive anger, impulse control, or posttraumatic stress disorder, appears beyond the scope of neuropathological interpretation.” Therefore, it has been assumed that CTE pathophysiology causes CTE symptomology [38, 61] but this link has never been scientifically validated. An alternative hypothesis proposed by Iverson and co-workers is that post-career symptomology is related to mental health, anger control, and thinking problems unrelated to the neuropathology of CTE. The source of these problems may be multifactorial and unrelated to neurotrauma specifically [43].
Finally, the explanation that neurotrauma is the sole or primary cause of CTE has been questioned. CTE has been described as a neuropathologically distinct, progressive tauopathy with a clear environmental etiology [10] and is the only known neurodegenerative dementia with a specific identifiable cause; in this case, head trauma [47]. However, to date, there are no published prospective studies relating to CTE that could generate data to support these statements [29]. In addition, it has been noted that psychiatric problems and cognitive impairment usually have multifactorial, not unitary causation [29]. For example, in their critical review, Iverson et al. [43] cited several studies suggesting that men with depression show the full spectrum of symptoms and problems that have been proposed to represent early-stage CTE [43]. They continue that considerable overlap exists between the clinical features of CTE and core diagnostic features of depression (e.g. sadness, hopelessness, suicidality, cognitive difficulties; problems with concentration memory, problem solving, and thinking). We are reminded that when considering the potential multifactorial bases for the symptomology reported by some athletes, that when compared to the general population, athletes lead quite different lives. Other potential factors to examine may include the effect of a relatively short and intense career, genetics, sex, age, when collision sports were started, the use of performance-enhancing drugs, and substance abuse [12].

ALTERNATIVE EXPLANATIONS FOR “CTE SYMPTOMATOLOGY” IN POST-CAREER ATHLETES

As Omalu et al. [8] have stated, most disease models are multifactorial and CTE is not an exception. But what are the most important factors to consider when studying athletes with a
substantial history in sport? Factors such as the effects of gender, genetics, and the age when impacts were first experienced have been suggested as potential mediators [8, 12, 43]. Other factors specific to the experience of athletes in contact sport should be considered. Specifically, the use of substances to manage injury and chronic pain have also been noted as potential factors [8, 12, 43]. Another element to consider is identity development in young athletes. To date, there has been relatively little attention given to how we develop athletes and the role that identity may play in symptomology post-retirement for athletes with foreclosed athletic identities. This area of study has been labeled athlete career transition stress.

Athlete Career Transition Stress

Brian Kingman, a pitcher for the Oakland A’s in the 1980s stated “There’s a saying that an athlete dies twice ... Everyone gets out of the game at some point, and it’s usually involuntary. It can be traumatic when the thing you love and have been doing so long comes to an end” [62]. Kingman’s statements are supported by a recent media survey of 763 retired NFL athletes that reported 61% have had difficulty adjusting to life after football (61%) [63]. It may be difficult for the non-elite athlete to understand the cognitive and emotional trauma that can occur following a career that has brought wealth, social prominence, and a relatively early retirement. However, the trauma is common and all too real to for elite athletes.

One potential factor may be rooted in how we form our identities. Identity theorist James Marcia stated that successful identity formation for adolescents in western contexts is often defined by a commitment to a vocation, a set of meaningful values, and a sexual identity [64].
As Kroger [64] described, there are two distinct types of commitment (achievement and foreclosure), and two of non-commitment (diffusion and moratorium). Those adopting achievement or foreclosure have made commitments to various social roles, however, identity achieved individuals have done so following a crisis or decision-making period. On the other hand, individuals with foreclosed identities have foregone the identity formation process and adopted roles and values of childhood identification figures (e.g. an NFL football player). Marcia also believed that foreclosed individuals are notable for their inflexibility and defensiveness in the face of identity challenge and are drawn to the values of a parent or strong leader who can show them the ‘right way’. They can appear to be progressing toward occupational goals and have avoided any form of serious exploration. As a result, rigid identity structures are formed which are impervious to challenge from new life situations [64].

Identity development requires an investment in time. However, to achieve elite athletic status, an individual must dedicate a significant amount of time training in their specific sport at a very young age. The timing and intensity of training varies by sport [65]. Athletic talent is often identified in elementary school and developing elite talent becomes a central preoccupation for both a child and caregivers [66]. For example, in European football (soccer), players as young as five years old have been scouted and substantial contracts have been offered to 11 year olds [67]. In American football, the recruitment process for college scholarships begins in the freshman or sophomore years (or earlier) when athletes are advised to create online profiles for potential coaches or recruiters [68]. For hockey in Canada, the first draft occurs at the Bantam level (ages 13 and 14) for recruitment to the high profile junior ranks [69]. Ballie [70]
stated that over 80% of professional hockey and baseball players were involved in competitive sport before 10 years of age. Elite gymnasts must commit to their sport during childhood with most retiring in adolescence at a time when most are beginning their search for an identity [71]. It is a widely held belief that a narrow focus on sport is necessary for competitive success. As a result, important adult figures including sport administrators and coaches may be less likely to support non-sporting activities that affect training time or focus on sport [72]. This commitment to athletic excellence at such an early age benefits the athlete from a performance perspective but may also have a significant cost in terms of identity development. In short, in order to achieve elite athletic status, it can often be difficult to be anything other than an athlete [73]. Aspiring elite athletes begin to define themselves as “an athlete”, with a near complete concentration on training and competition and a near exclusion of everything else including education, social goals, and career goals, [66, 70, 72, 73]. The definition of oneself exclusively as an athlete has been termed “athletic identity” consisting of the cognitive, affective, behavioral, and social concomitants of identifying with the athlete role [74].

Developing a foreclosed or athletic identity may translate to success in a sporting context, but may be related to a number of problems in other areas of life. For example, identity foreclosure and athletic identity were found to be inversely related to career maturity, suggesting that foreclosure and athletic identity are separate processes, both associated with inhibited post-athletic career decision making, failing to explore alternative roles and behaviors, and identifying strongly and exclusively with the athlete role [72]. Elite athletic performances are more public than most role enactments and the public reputation of most successful athletes is
generally positive. This can generate a high degree of social status and esteem causing one's public athletic reputation to become enmeshed with the athlete's overall identity [66, 75]. For some, the excitement and intensity of the experience can be addictive [75]. Some have termed the development of an identity that is strengthened by the growth of prestige combined with social and public acknowledgement as an identity variant termed the “glorified self” [76]. At its extreme, this complex depiction of self has been linked to “a greedy, catchy and toxic feeling, through which the self looks to increase its importance and escape from other dimensions into which it might develop” [76] (p. 8) and has been linked to the loss of future orientation and long-term planning [76].

For some, the transition from athlete to non-athlete may be relatively smooth [77]. Others have described retirement from sport as similar to retirement from other professions, with a percentage of athletes doing reasonably well, and others doing less well for reasons including the amount of social support, discrimination in the job market, lack of material supports and social contacts, level of education, and the availability of resources to assist them in career development or job training [78]. However, the prevalence data to date suggest that the likelihood of difficulty with transition out of sport may be significant especially for athletes with intended or actualised careers in sport [70]. In a review of the literature, Park et al. [79] stated that among 13,511 participants, 1768 (16%) reported adjustment difficulties during career transition. A study on top Canadian amateur athletes who had retired from international competition reported that 32% had a very difficult time with career transition and 46% had a moderately difficult time [73]. Another study reported that 46.2% of retired athletes reported
that a difficult retirement was "quite characteristic" or "very characteristic" of their experience [66]. In a study of young retired gymnasts, most described their disengagement from gymnastics as profoundly traumatic [71]. Therefore it appears that for some athletes, the transition to retirement can be perceived as negative and difficult.

A number of variables have been identified as important indicators of a difficult transition to retirement including “athletic identity, demographic issues, voluntariness of retirement decision, injuries/health problems, career/personal development, sport career achievement, educational status, financial status, self-perception, control of life, disengagement/drop-out, time passed after retirement, relationship with coach, life changes and balance of life” [79] (p.33). Others have noted that the type of sport involvement is important with Olympic and college athletes making smoother transitions than professional athletes [70]. Those with abrupt retirements, due to injury or being de-selected have had worse post-retirement outcomes [65, 66, 70, 80-82]. Coping style or resources may also affect post-career adjustment [78, 82-84]. However, it is the strength of the athletic identity that has been shown to be the primary factor related to career transition stress [65, 66] because of its narrowing effect on other aspects of life such as education, friend networks, sport specific social and emotional support by families, and limitation of experience and social contacts outside of sport [78].

In their review of the literature, Park et al. [79] identified 34 studies indicating that both a strong athletic identity and high tendency towards identity foreclosure were negatively associated with the quality of athletes’ career transitions. Importantly, these studies indicate
that the retired athletes experienced a *loss of identity* when they had a strong athletic identity at the time of their sport career termination requiring a longer period of time to adjust to post-sport life. Consistent with this position is a study by Webb and colleagues [66] who reported a positive relationship between the strength of athletic identity and retirement difficulty. Another study reported similar findings suggesting that individuals who maintain a strong and exclusive athletic identity up to the point of retirement may be vulnerable to career transition difficulties [83]. Conversely, those who begin the transition from athlete to non-athlete prior to retirement have reported increased levels of life satisfaction [80]. A number of other studies also point to the strength of athletic identity as a prominent factor in career transition difficulties [77, 85]. How the retirement was characterised in the media may also impact the quality of adjustment to life after elite competition [86, 87].

The qualitative research literature also contains substantial commentary on the struggle to find meaning following retirement from sport. Retired gymnasts reported feeling lost post-retirement, had difficulties with starting again in the real world/fitting in, and had deep sense of disappointment/loss that could not be faced [71, 85]. A common theme reported by athletes was that they may never find a replacement for the pleasure, intensity, and passion provided by involvement in their sport [70, 75, 85]. Athletes reported feeling unprepared, or even unwilling, to re-create their identity [75]. They also reported missing the public recognition, adoration of fans, and connection to team-mates [75]. They reported having a sense of uncertainty regarding who they were outside of their sport [71].
The literature on athletic identity and retirement from sport is relevant to the CTE literature for a number of reasons. First, while most athletes who struggle with loss of athletic identity adjust within a few years, some struggle for 10 or more years post retirement [70, 73]. This time frame is consistent with the window of symptom onset for CTE. Many of the CTE cases described to date reference retirement with most describing symptom onset as the athlete nears retirement, or within 10 years of retirement [3, 7, 9, 10, 44, 47]. Interestingly, the first case described by Omalu [44] was diagnosed with adjustment disorder, a diagnosis consistent with loss of identity following retirement. Another interesting point regarding two asymptomatic CTE cases described by Stern et al., [46] was that they obtained “advanced graduate degrees, were very successful in their professional careers, and were described as extremely intelligent.” (p.1127). The authors attributed the asymptomatic status to the fact that they were intelligent and therefore had significant “cognitive reserve”. An alternative hypothesis is that they had less developed athletic identities (seeing themselves as more than athletes), allowing them to transition into post-career life without a dramatic increase in CTE symptomology. The same general pattern of adequate post-career adjustment has been shown for ex-professional Swedish tennis players all of whom obtained employment as tennis coaches, managers, consultants and sport commentators [88].

Other parallels exist between the CTE and identity literatures regarding symptomology. For example, athletes with difficult transitions from sport related to a strong athletic identity have reported coping via substance use or abuse [87, 89], anxiety symptoms [79, 83], aggression and emotionality [73, 83] and depression [73, 75, 84, 87, 90]. In addition, there is a well-established
and substantial link between suicide and factors experienced by elite athletes post-retirement such as a loss of identity, challenges with mental health, and a loss of social support networks. For example, it is well known that individuals with affective disorders have a markedly increased risk of suicide [e.g. 91, 92]. Substance use disorders have also been linked with suicide in with a number of studies yielding odds ratio estimates ranging from 3.3 to 10.7 [91]. Further, the social isolation and low belongingness experienced by some athletes post-career have been linked to increased suicidal ideation in young adults [93, 94]. Of particular relevance, the presence of identity stress has also been reported to increase the risk of suicidal ideation [92, 95] in non-athletes and athletes. For instance, acculturative stress associated with an ethnic minority identity has been associated with depression and suicidal ideation in some college students [96]. Gender identity issues have been linked to increased rates of suicidal behaviour in youth who die by suicide [97], in transgendered veterans with gender identity disorder [98], in female college students [99], in sexual minority youth [100] and in military personnel with a history of same sex behaviour [101]. The loss of identity as a farmer has been associated with suicide and has been described as an international phenomenon [102]. Military personnel have been reported to undergo stress when transitioning to civilian life. This problem has been noted for reservists [103] and regular force members, particularly those with a foreclosed military identity [104]. A shift in identity may be particularly relevant to members of the armed forces returning from active service, who may become disconnected from the values of society and in some cases believe that their service was unappreciated [105, 106]. Brewin and Andrews [105] reported an association between negative changes in perceptions of the world, PTSD and suicidal behaviour in military veterans. It is possible that this type of stress is
experienced by in military veterans who experience neurotrauma [5]. Schmidt and West [106] liken the military identity to a strong athletic identity and discussed how both can be related to and increased risk of suicide. For athletes with a strong athletic identity, an increased rate of suicide attempts has been reported following retirement [107]. This trend may particularly relevant for athletes for masculine sports that emphasize risk-taking, including some degree of tolerance for health-compromising behaviors [108]. The latter is consistent with the recent statements of the high profile MMA fighter Rhonda Rousey who following a one-sided loss, recalled thinking “…what am I anymore if I’m not this? ... I was literally sitting there ... thinking about killing myself ... I’m nothing ... what do I do anymore?” [109]. Table 1 summarises the common symptomology for athlete career transition stress and CTE.

Chronic Pain

Chronic pain is a common problem affecting 19% of the adult population in Europe and Canada and 30% in the USA [110]. Chronic pain is a more prevalent problem in retired athletes who have sustained multiple injuries during their careers. For example, a case reported by Omalu and co-workers had numerous musculoskeletal and cartilage injuries requiring knee, elbow and shoulder surgeries [44]. Another had spinal surgery with many musculoskeletal injuries [8]. Yet another suffered chronic musculoskeletal pain and constant headaches [9]. The latter two cases had evidence of pain prescription overuse; a common problem with chronic pain patients. The link between chronic pain and abuse substance use/abuse was recently described in a study of ex-NFL athletes [111]. Nearly half (47%) of the 644 athletes polled had had three or more NFL injuries, most reported undiagnosed concussions (81%), half (55%) reported a career-ending
injury, with 6% reporting current use of an assistive mobility device. Players also reported that approximately one-third (29.4%) of their teammates misused prescription pain medication [111].

Nes et al., [112] have described the complex interactions between executive functioning, the capacity for self-regulation, and chronic pain management. They stated that self-regulatory capacity varies and is a limited resource that can be fatigued. Chronic pain management can affect self-regulatory ability resulting in cognitive difficulties, fatigue, sleep disturbance, tension, and emotional and social distress. The decrease in cognitive ability during pain flare-ups is the first indication that pain interferes with the ability to self-regulate. The potential for a downward spiral in which self-regulatory demands cause self-regulatory fatigue, reduce executive cognitive resources for further self-regulation, and thereby increase difficulty in meeting further demands occurs with increased pain symptoms. A history of repetitive neurotrauma may worsen executive functioning, resulting in problems controlling and regulating behavior, leading to additional difficulty in functioning [112].

Chronic pain has been linked to symptomology that parallels CTE cases. For example, a wide array of cognitive abilities can be affected with chronic pain including attention, concentration, speed processing, working memory, psychomotor ability, decision-making, and executive functioning [113, 114]. Post-traumatic headaches that can occur following concussion have been reported to cause confusion and loss of concentration and overuse of pain medication [115, 116]. Altered sleep patterns and sleep deprivation (that can affect mood and cognition)
are commonly reported with chronic pain [112, 117]. Chronic pain can also lead to dependence on prescription medication as reported in some CTE cases [8, 9] and in studies on chronic pain patients [118]. Emotional dysregulation including anger, irritability, sadness, and fear symptoms have been reported in those with chronic pain [112, 119]. Chronic pain has been shown to increase anxiety-like behaviour in animal models [110, 113] and anxiety symptoms in human studies [112, 119, 120]. A number of authors have reported the reciprocal relation between depression and chronic pain [113, 118, 120] and their relation to CTE [61]. The reciprocal relation between chronic pain and depression has been demonstrated in animal models [110, 113] and in chronic pain patients [112], with both linked to common dopamine pathways [110, 120]. Finally, there are links between chronic pain and suicidal behaviour [61, 118]. For example, the lifetime prevalence of suicide attempts was between 5% and 14% in individuals with chronic pain, with the prevalence of suicidal ideation being approximately 20% [121]. Other studies reported that pain was an independent risk factor for suicide, particularly among those with head pain or multiple forms of co-occurring pain [122, 123] as reported in CTE cases and retired athletes who participated in contact sport. Table 1 summarises the common symptomology for chronic pain and CTE.

Substance Use and Abuse
The unique lives of athletes can in some cases lead to the development of specific types of substance use and/or abuse. For example, following the deaths of three National Hockey League (NHL) athletes, a series of now public emails were produced by members of the NHL league office. One email stated that the role of enforcer is “not the same role as it was in the
80's and 90's... Fighters used to aspire to become regular players. Train and practice to move from 4th line to 3rd. Now they train and practice becoming fearsome fighters. They used to take alcohol or cocaine to cope... Now they take pills. Pills to sleep. Pills to wake up. Pills to ease pain. Pills to amp up. Getting them online." [14]. These statements have been supported by recently retired enforcer Daniel Carcillo speaks about substance abuse, depression and loss following his career as an NHL enforcer [124].

Evidence of substance use in sport is not limited to ex-hockey enforcers. Evidence of alcohol use, abuse, and addiction can be found in a number of the CTE case histories [e.g. 6, 7, 9]. Cottler et al. [111] reported that 52% of retired football players used opioids during their NFL career with 71% of those respondents reporting misuse. Substance abuse and addiction have been linked to accidental and intentional death in CTE cases [7, 32]. Evidence of past anabolic-androgenic steroid (AAS) abuse have been reported in CTE cases [8, 44] with at least one case revealing an exogenous testosterone source in the body at time of death [8]. It has been reported that an estimated 20% of CTE cases had a documented history of substance abuse prior to or co-morbid with symptomatic CTE presentation including the use of alcohol, prescription opioids, AAS, cocaine, methamphetamine, and cannabis [50]. CTE researchers have attempted to address this issue by suggesting that athletes may in some cases develop “problems with drug abuse as a consequence of the loss of inhibitory control caused by the neurodegenerative disease” [47] (p.183) however no objective evidence has been advanced to support this claim. Others have reported that no relation between CTE symptomology and
Steroid use [6, 37] but again, it is difficult to determine how these data were derived in the original publication based on the information provided.

Substance use, abuse, and addiction in its many forms can result in acute and long-term changes that are similar to some of the symptomology attributed solely to CTE. For instance, excessive alcohol use has been associated with the culture of certain sports and is used during and following some athletic careers [125]. It is also linked to specific elements unique to sport such as poorly developed coping strategies and injury management [125]. While not a general trend, a percentage of people will either resume alcohol abuse or will develop a new alcohol use disorder following TBI due to a combination of negative affective states, impaired decision making, social pressures, and alterations in neurochemical signaling [126]. Social stressors, such as adjustment to retirement, may cause activation of the corticotrophin releasing factor (CRF) system is necessary for this social stress-induced escalation of alcohol consumption [127].

Alcohol use is linked to general health problems such as respiratory dysfunction and infection [128]. It is also correlated with co-morbid psychiatric problems such as antisocial behavior [129] and anxiety and mood disorders, the latter being reduced with abstinence [130]. Animal models have shown that alcohol may lead to the distortion of social signals from benign to threatening which in turn can lead to the emergence of aggressive behavior [127]. Prolonged alcohol exposure has been associated with impairments in executive processes such as top-down inhibitory control, decision-making, and behavioral flexibility possibly related to altered dopamine (DA) function in pre-frontal cortex (PFC) [131,132]. Lifetime alcohol use has been
shown to correlate with reduced dorsolateral PFC and anterior cingulate cortex (ACC) gray matter density of up to 20% leading to problems with attention, decision-making, error monitoring, and impulse control [132]. It is also well-established that alcohol use is a potential risk factor for attempted and completed suicide among individuals both with and without a history of alcohol abuse or dependence, and when combined with other substances such as opiates, can lead to accidental overdose via respiratory depression [130]. Alcohol use, abuse, and alcohol-related accidental overdose have been reported in some CTE cases.

The use of recreational substances such as cannabis and cocaine also have the potential to affect symptomology in retired athletes. Moderate polydrug use such as cannabis, amphetamine, and cocaine has been shown to elevate psychiatric symptom profiles [133]. Evidence of a dose–response relation has been reported between cannabis use and psychotic outcome [134,135]. Cocaine use is related to various cerebrovascular events that can occur in every brain region and may in some cases increase the risk of developing Parkinsonism [136]. Cannabis use may affect broad cognitive domains including memory, attention, decision-making, psychomotor speed, and inhibitory control [134]. Similarly, chronic cocaine use is linked to problems with executive function, decision-making, increased impulsivity, visual perception, psychomotor speed, manual dexterity, verbal learning, memory function, insight and judgment, foresight, and disinhibition related to dopamine dysfunctions in the prefrontal cortex [134, 137]. Small but significant lingering effects have been reported for long-term cocaine abstinence over many cognitive domains [138]. Cocaine dependence may also be associated with impaired recognition of fearful facial expressions and the perception of anger
Chronic cocaine use may cause long-term hippocampal-dependent learning and memory impairments associated with elevated HPA axis activity [140] and changes in N—methyl-D-aspartate receptor activity [141].

Prescription and non-prescription opioid use in sport increases as injuries occur and associated chronic pain mounts [111]. Interestingly, opioid use has also been increasing in military populations in response to war-related injuries that exceed the rise of civilian opioid use and abuse [142]. Long-term opioid use may be associated with a number of negative outcomes including tolerance, opioid induced hyperalgesia, physical and psychological dependence, and higher rates of depression [143, 144]. Additional problems may arise when continued opioid use is expanded to manage the pain-related negative emotions associated with prolonged use leading to a spiral of use and elevated pain and dependence [145]. To add to the problem, opioids are often prescribed for pain conditions where they have little to no effect (i.e. headache) [146, 147] meaning that few of these patients will benefit and many will be exposed to significant harms [144]. Cognitive and sedative effects for those experiencing long-term opioid therapy for chronic non-malignant pain may be as high as 60% [148, 149]. Cognitive effects of prolonged opioid use include problems with attention, concentration, affect, memory, executive functioning, perception, psychomotor functioning, and delirium [148, 149]. Sedation effects can include somnolence, lethargy, and sleep disorders [148]. Delirium can occur when opioid use is initiated or following dose escalation and may be greater in patients with pre-existing cognitive impairment [148, 149]. Additional negative outcomes related to the problematic use of opioids include hypogonadism [150], depression and other mental health
diagnoses [143, 144, 149]. The risk of accidental death by overdose is increased in patients who are prescribed opioids for pain [143, 149, 151] as is suicidal ideation [118]. Finally, opioid use may have long-term effects on brain structure. Hyperphosphorylated tau positive neuropil threads, not unlike those found in CTE case studies, have been observed in a number of brain areas in those who overuse opioids [152, 153].

Anabolic androgenic steroids (AAS) are used by some athletes during their careers to improve elements of sport performance and to recover more rapidly from fatigue and injury. The increased popularity of these products has led to the development of synthetic AAS which have not undergone appropriate testing in humans or animals and therefore may represent an even more serious health risk than the more traditionally used AAS [154]. The acute effects of AAS administration have been studied prospectively in volunteer participants. Acute AAS use has been associated with increases in positive mood, negative mood (including irritability), mood swings, violent feelings, anger, and hostility, and cognitive symptoms such as distractibility, forgetfulness, and confusion [155] not attributable to prior substance abuse, familial history of mental illness, or substance abuse [155]. A subsequent prospective study administered prednisone to participants for 5 consecutive days and observed that 75% of participants developed diverse and fluctuating behavioral changes which had discrete onsets during the prednisone administration period including depression, irritability, anger, sleep problems, tearfulness, mood elevation, increased energy, confusion, with some associated changes in EEG, and significantly higher rate of errors of commission during a test of recognition memory [156]. Hypomania, aggression, or violence have been shown in occasional users [157]. Long-
term AAS use results in a more well-established presence of symptoms of aggressiveness, anxiety, depression, and potentially psychosis linked to functional change in monoamine and peptidergic systems with evidence of hippocampal involvement [158-161]. A review of the negative outcomes associated with AAS described a link between AAS use and higher rates of attempted suicide and homicide [154]. AAS-induced hypogonadism may require normalization of neuroendocrine function that can include antidepressant treatments and reversal of dependence via mechanisms shared with other addictive substances [162]. Hypogonadism induced by androgen withdrawal may occasionally produce severe depression in some men [157]. Animal models suggest that AAS has significant effects on neural systems that control reproductive function [163]. Some males regret AAS use because of the negative impact on future fertility [164].

A substantial body of evidence exists pointing to the addictive properties of AAS that have a shared neural basis with other addictive substances [154, 157, 159]. AAS dependence may share mechanisms of opioid dependence in humans and therefore it is not surprising that some retired athletes continue the use of AAS beyond the duration of their careers [154]. There is also substantial evidence to suggest that substance use, including opioids, cannabis, alcohol, amphetamines, and cocaine co-occur with AAS use [154, 157, 159]. Long-term use of AAS may result in neural damage via apoptosis [157]. In adolescents, AAS use may cause persistent changes in neural structures and neurotransmitter function that may cause increased aggressiveness and perceived threat during a social encounter [165]. Animal models have demonstrated AAS effects on the expression of NGF and its receptors in the hippocampus and
basal forebrain [166], show axonal injury and microgliosis increases when ASS use co-occurs with repetitive neurotrauma [167], and decreased performance in multiple aspects of behavioral flexibility including both set-shifting and reversal learning [168]. In humans AAS users have had significant impairments in visuospatial memory correlated to the lifetime AAS dose, problems with inhibitory control and attention, larger right amygdalas, and higher glutamine/glutamate ratios [159].

A THEORETICAL MODEL TO EXPLAIN CTE SYMPTOMATOLOGY IN RETIRED ATHLETES

It is evident that some athletes experience career transition stress (related to a strong athletic identity), chronic pain, and substance use/abuse as they enter retirement. It is also evident that there is significant overlap between the case reports of athletes with post-mortem diagnoses of CTE, and symptom profiles with those with a history of substance use, chronic pain, and athlete career transition stress. Table 1 provides a summary of research on the athletic identity/career transition stress, chronic pain, and substance use/abuse and how each independently may result in symptomology in athletes that has been attributed primarily to neurotrauma and CTE.

Figure 1 represent a theoretical model intended to explain some of the symptoms that athletes experience at the end of their careers or during retirement. Stern et al., [46] described two major clinical variants of CTE. Variant 1 described patients who died earlier, exhibited more pronounced behavioral or mood disturbances, were significantly more explosive, out of control, physically and verbally violent, and depressed. Variant 2 described patients who were older at their time of death, who exhibited cognitive impairment including impaired episodic memory,
and were significantly more likely to progress to dementia that overlaps with other age-associated cognitive disorders, such as Alzheimer’s disease (AD) [31, 35, 36, 45, 46]. The Athlete Post-Career Adjustment (AP-CA) model shown in Figure 1 is most consistent with the symptomology of the patients with Variant 1 (behavioural and mood disturbances).

Based on the existing literature, it is clear that any one of the four elements of the AP-CA model can account for a significant number of Variant 1 CTE symptoms. In addition, depression can be a chronic lifelong co-morbid condition that may be present prior to neurotrauma, or may be developed secondary to any of the model elements as shown in Figure 1. Notably, neurotrauma is a necessary, but not a sufficient condition, for the development of Variant 1 CTE symptomology because at minimum, a history of neurotrauma must be present for an individual, or a family, to suspect the CTE. It is important to recognize that the science for each of the factors within the AP-CA model have been presented as independent elements. We do not as yet have substantial information regarding how symptomology is affected when more than one element is present. For example, it is possible, that the effects of neurotrauma and chronic pain affect the emotional responses to identity transition and pain management. The exaggerated patterns of emotional response in some retired athletes may be due to the interactions between each model element. Finally and of note, there is no inclusion of a genetic factor in the AP-CA model at this time. The rationale for this exclusion is that based on the available literature, it is difficult to identify a definitive link between the APOE e4 allele and the development of CTE independent of other neurodegenerative diseases [e.g. 50].
It is hoped that the AP-CA model will allow for the development of specific hypotheses related to post-career symptomology in retired athletes. If the model holds, athletes with elevated CTE symptomology should score highly on at least one of the model elements, with the inclusion of more elements related to increased symptomology. As noted, some of the CTE cases describe precisely that.

CONCLUSIONS

In their criticisms of CTE research to date, Meehan III et al., [38] stated, “The scientific method dictates that in our quest to discover the truth we must (1) make an observation, (2) develop an hypothesis that explains the observation, (3) test that hypothesis in varying situations, and (4) reach a conclusion based on the findings of those tests.” [38] (p.1509). With this in mind, statements such as “Participating in a contact sport is now thought to increase an individual’s risk for later-life impairment and possibly developing CTE” [37] (p. 304) and “CTE is the only known neurodegenerative dementia with a specific identifiable cause; in this case, head trauma” [47] (p. 184) are highly problematic. These statements are based on highly selected case evidence and equate all symptomology with one primary mechanism. It is clear, from a thorough review of the scientific literature, that the development of symptoms post-athletic career is multi-factorial in nature and at minimum includes career transition stress mediated by athletic identity, chronic pain, and substance use/abuse.

It is necessary to separate CTE pathophysiology detected post-mortem, from the CTE symptomology that in most cases was obtained retrospectively. There is no prospective
scientific basis that can be used to support this link; only speculation based on highly selective and potentially biased case data. As scientists, we have a responsibility be thorough and accurate in our presentation of facts. To ignore the non-neurotrauma elements in the AP-CA model as important factors that have been demonstrated to cause symptomology attributed almost exclusively to CTE by some researchers is irresponsible. We must consider the unique developmental and situational factors that athletes face as they enter retirement. If we hope to limit the severity and prevalence of these problems, we must also understand that our current practices for developing athletes are problematic.

Future studies must be prospective in nature and less reliant on case data. Identification of biomarkers that can be correlated with neurotrauma are ongoing but in their early stages [169]. Unfortunately, large ongoing CTE studies such as the UNITE and LEGEND appear to be fraught with similar problems as those described here. Restricting a participant pool to only those who had a history of repetitive head impacts during sport or military careers [170] limits the identification of other factors that produce CTE pathophysiology. Case data based on the criteria developed in this manner have been inconclusive [171]. The use of convenience sampling that targets individuals with perceived problems related to participation in contact sport [172] potentially creates problems with generalizability and sampling bias. In future studies, we must invest in proper methodology and move away from a focus on case data and neurotrauma if we intend to correctly identify and address the bases for the significant symptomology experienced by some athletes following retirement. It is hoped that development of models such as AP-CA will be the first step toward development and testing of specific hypotheses in this population.
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REFERENCES


Downloaded June 23, 2016.


(data.newsday.com/projects/sports/football/life-football/)


[70] Ballie PHF. Understanding retirement from sports: Therapeutic ideas for helping athletes in transition. The Counselling Psychologist 1993;21(3):399-410.


doi:10.1017/S0033291705006719


[101] Ray-Sannerud BN, Bryan CJ, Perry NS, Bryan AO. High levels of emotional distress, trauma exposure, and self-injurious thoughts and behaviors among military personnel and


[125] Lamis DA, Baum AL, Lester D. Substance abuse and suicide in athletes. In Suicide in professional and amateur athletes: Incidence, risk factors, and prevention. David Lester and John F. Gunn III (Eds.) 2013 p.74-84.


CAPTIONS TO ILLUSTRATIONS

TABLE 1. OVERLAP IN SYMPTOMATOLOGY BETWEEN CTE, CHRONIC PAIN, SUBSTANCE USE, AND FORECLOSED ATHLETIC IDENTITY.

FIGURE 1. A THEORETICAL MODEL TO ACCOUNT FOR CTE SYMPTOMATOLOGY IN RETIRED ATHLETES.
A necessary but not a sufficient condition.
TABLES AND FIGURES

CTE Symptomatology

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<th>Other factors</th>
<th>CTE Features (e.g. Stern et al., 2013; Montenigro et al., 2015)</th>
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<td>spasticity; clonus</td>
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<tr>
<td>Athletic Identity</td>
<td>Grove et al., 1997; Werthner &amp; Orlick, 1986.</td>
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<td>Chronic Pain</td>
<td>Lane, 2000; Lane &amp; Arciniegas, 2002; Liu and Chen, 2014; Moriarity &amp; Finn, 2014; Garland, 2012; Nes et al., 2009; Braden &amp; Sullivan, 2008; Cheatle, 2011; Garland, 2012; Ilgen et al., 2008; Jarcho et al., 2012; Liu and Chen, 2014 Nes et al., 2009; Tang &amp; Crane, 2006</td>
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<tr>
<td>Substance Use/abuse</td>
<td>Cadet &amp; Bisagno, 2016; Dhingra et al., 2015; Grönbladh et al., 2016; Harned &amp; Sloan, 2016; Potvin et al., 2014; Spronk et al., 2013; Yang et al., 2016</td>
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