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Distinguishing early stage chronic traumatic encephalopathy from persistent post-concussion syndrome

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**DISTINGUISHING EARLY STAGE CHRONIC TRAUMATIC
ENCEPHALOPATHY FROM PERSISTENT POST-CONCUSSION SYNDROME**

by

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I will be forever appreciative of the life lessons and experiences I have gained through playing football and hockey but will always be mindful of those less fortunate who are dealing with the neurological repercussions that contact sports can yield. This thesis is dedicated to the athletes and military personnel who deal with the debilitating effects of traumatic brain injuries every day, and to those who have allowed their legacies to live on through donation as researchers continue to explore better ways to prevent, manage, and treat the symptoms and neurologic disorders related to head trauma.

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ABSTRACT

Background

Sports-related head trauma has become a major public health concern with significant consequences including persistent post-concussion syndrome (pPCS) and chronic traumatic encephalopathy (CTE). pPCS is a condition where symptoms of single concussion persist years beyond the initial injury. CTE has been characterized as a condition with insidious onset following a latent period after substantial exposure to repetitive head impacts (RHI). Timing of symptom onset usually distinguishes these conditions, however in certain clinical situations a definitive diagnosis is not always clear. For these situations, a measurable distinguishing variable is necessary.

Literature Review

Concussions are the most common form of traumatic brain injury (TBI) and are associated with a variety of neurological symptoms that usually resolve within weeks. Post-concussion syndrome (PCS) refers to cases where symptoms continue months beyond this window, and pPCS is defined as symptoms continuing over years. These conditions are temporally related single concussive events. CTE is the hallmark condition related to RHI and remains difficult to fully characterize as it currently can only be diagnosed post-mortem. Clinical features of CTE are similar to those of pPCS with notable behavioral/mood symptoms in its earliest stages, and progression to severe

cognitive decline over time. Current research has shown executive dysfunction to be a common impairment among these conditions. The difference in level of dysfunction between them, if one exists, is yet to be measured.

Proposed Project

A cross-sectional analysis of executive function in four groups. A control without history of mTBI or football exposure (Non-Football – pPCS), a second control of asymptomatic subjects with football exposure (Football – pPCS), a group of pPCS patients with non-athletic mTBI history (Non-Football + pPCS), and a group of pPCS patients with football exposure (Football + pPCS). Executive functioning will be evaluated using the BRIEF-A assessment. Results will be compared to determine if significant differences in executive functioning exist between the groups.

Conclusions

With previous studies showing a correlation between CTE pathological stage, worsening executive function, and increased RHI exposure, further investigation into using executive function as a distinguishing variable between early stage CTE and pPCS is warranted.

Significance

Results of this study, if significant, could be applied clinically to assess risk of early stage CTE in athletes with prolonged post-concussion symptoms. If results are not significant, they may still be utilized for a better understanding of the effects of isolated mTBIs and RHI on executive functioning, and provide valuable information for ongoing longitudinal studies.

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LIST OF ABBREVIATIONS

AD.....	Alzheimer’s Disease
ADHD.....	Attention deficit/hyperactive disorder
ATP.....	Adenosine triphosphate
BRI.....	Behavior Regulation Index
BRIEF.....	Behavior Rating Inventory of Executive Function
BRIEF-A.....	Behavior Rating Inventory of Executive Function-Adult
BRIEF-A SP.....	BRIEF-A Software Portfolio
CHII.....	Cumulative Head Impact Index
CTE.....	Chronic Traumatic Encephalopathy
DSM-IV.....	Diagnostic and Statistics Manual, fourth edition
FTLD.....	Frontotemporal Lobar Degeneration
GEC.....	Global Executive Composite
ICD-10.....	International Classification of Diseases, tenth revision
LEGEND....	Longitudinal Examination to Gather Evidence of Neurodegenerative Disease
MI.....	Metacognition Index
mTBI.....	Mild Traumatic Brain Injury
NP.....	Neuropsychological
PCS.....	Post-Concussion Syndrome
pPCS.....	Persistent Post-Concussion Syndrome
p-tau.....	Hyperphosphorylated tau protein
RHI.....	Repetitive Head Impacts

TBI Traumatic Brain Injury

WHO World Health Organization

INTRODUCTION

Background

The potential long-term consequences of contact sports-related head trauma have become a significant public health concern over the last decade with a major focus on the spectrum of neurologic conditions associated with the acute and chronic implications of traumatic brain injuries (TBI) and repetitive head impacts (RHI). A great deal of this concern has centered around concussions, which are considered a subset of mild TBI (mTBI) and are the most common form of sports-related TBI. These injuries result from traumatic forces on the brain leading to a potential constellation of several neuro-cognitive symptoms which tend resolve within a week's time in the majority of cases.

In up to 30% of concussion cases however, symptoms may linger beyond the acute phase in a condition known as post-concussion syndrome (PCS).¹⁵ In up to 15% of cases, symptoms may even progress years beyond the initial injury in what is termed persistent post-concussion syndrome (pPCS).¹⁵ The clinical features of pPCS can involve many neuropsychological and cognitive components which have even been noted to be progressive in some cases, especially with regard to behavior and mood symptoms.¹² Though a variety of factors may contribute to the development and course of pPCS, the defining characteristic of this condition is its temporal link to a specific concussive event, and not the gradual development of symptoms years after injury has occurred.¹²

Another highly discussed and debated repercussion of contact sports-related head trauma is Chronic Traumatic Encephalopathy (CTE), a pathologically diagnosed syndrome of neurological damage related to extensive history of RHI exposure.¹² This

accumulation of impacts not only include the concussive events that athlete's experience over the course of a career but also subconcussive impacts, which are defined as those with enough force to inflict neuronal damage without resulting in symptomatic concussion.³² CTE has been described to elicit several neurological impairments including behavioral, mood, and cognitive symptoms similar in many ways to that of pPCS.⁷ It is a progressive condition but in contrast to pPCS, is characterized by an insidious onset of clinical features following significant exposure to RHI. In the majority of cases, these symptoms do not develop until several years after the maximal exposure period.⁷

Though CTE and pPCS have a clear clinical distinction with regard to their expected timing of symptom onset, recognition of probable early-stage CTE can become difficult in cases where individuals who have been engaged in contact sports for many years suffer a concussive event leading to the acute onset and duration of symptoms consistent with pPCS.¹² Though the clinical picture in this situation may lead to the presumed diagnosis of pPCS, it is possible that the symptoms related to concussion in these patients are bridging the latent period of what is developing CTE, or may even be masking what is a true manifestation of early stage CTE in the first place. The question of how to distinguish pPCS from early stage CTE when clinical picture and history could make arguments for either has yet to be explored.¹²

Statement of the Problem

Following the deaths of several high profile athletes and the growing public health concerns regarding risks of participating in contact sports, the past decade has seen an extraordinary amount of attention and effort being allocated to the study of CTE with numerous institutions implementing research programs in attempt to characterize the disease from a clinical standpoint. Likely the most challenging road block involved with attempting to define CTE is the fact that the disease can only be definitively diagnosed on post-mortem neuropathological examination. As a result, the clinical features that have been described in CTE have been based primarily on retrospective interviews from family members of the deceased subjects who have been neuropathologically diagnosed.⁷ In order to fully characterize CTE, its risk factors and epidemiology, and to perform clinical trials for prevention and treatment, the development of *in vivo* diagnosis for the disease is necessary.⁷

Current research is beginning to show promise in the development of sensitive and specific biomarkers for CTE which may eventually contribute to a support model for *in vivo* diagnosis. Given the fact that many common neurodegenerative diseases and other conditions such as pPCS have clinical findings that mimic or overlap with CTE, it is important to distinguish these conditions from CTE in order to truly characterize the disease and place the correct candidates into studies for future biomarkers.

Hypothesis

Patients with a history of sports-related RHI exposure and symptoms consistent with early stage CTE will have worse executive functioning compared to patients with non-sports-related pPCS.

Objectives and specific aims

The purpose of this study will be to investigate a possible distinguishing variable between early stage CTE and pPCS that is measurable. Evidence has shown that executive dysfunction is one of the earliest signs of cognitive decline associated with CTE.²³ Patients with pPCS have also been proven to exhibit impairments of executive function, however the progressive nature of cognitive decline in CTE opens the argument that these patients would eventually develop worsening executive function over time as compared to pPCS patients. If it could be established that patients with probable early stage CTE had worse executive functioning than those with pPCS, it may be possible to use this measure as a distinguishing variable in clinical assessment. Being able to distinguish or recognize probable early stage CTE versus pPCS could lead to a better understanding of the disease process of CTE and its relationship to acute concussive events and pPCS. A better understanding of CTE will help guide future studies leading to improved diagnostic methods and ultimately possible management or treatment avenues.²⁰

1. Attempt to develop a measurable variable that may aid in distinguishing early stage CTE from pPCS.

2. Analyze the effects of football related RHI exposure and non-sports-related mTBI on executive function.
3. Establish expected levels of executive function in patients with history of football exposure versus those with non-sports-related mTBI events, and develop a spectrum of clinical risk for probable early stage CTE versus pPCS.
4. Analyze progression of executive dysfunction in pPCS patients and those at higher risk of having early stage CTE.

REVIEW OF THE LITERATURE

Overview

History of Head Trauma in Sports

The link between neurological dysfunction and RHI in athletic competition was first identified in 1928 when Harrison S. Martland described a constellation of symptoms effecting professional boxers that he termed “punch drunk syndrome”.¹ This condition involved mental confusion with an unsteady gait pattern in its earliest stages, with progression to parkinsonian-like symptoms and pronounced mental deterioration requiring commitment to asylums in its most severe cases.¹ Martland concluded that since this condition was present in almost 50% of fighters and most often affected those who took considerable head punishment over their careers, there was strong evidence that some neurological disorder due to their occupation likely existed.¹

In the years following Martland’s findings, the clinical impact of RHI continued to be investigated with various terms such as “traumatic encephalopathy of pugilists”, “dementia puglistica”, and finally “chronic traumatic encephalopathy” being introduced in 1949 to define the progressive condition.²⁻⁴ In 1973, the first description of pathologic characteristics of CTE were identified in deceased boxers by Corsellis, and throughout the remainder of the 20th century, the study of CTE focused primarily on boxers.⁵ In 2005 however, the potentially serious public health implications of CTE were realized when Omalu and colleagues identified the first evidence in CTE in a professional football player.⁶ Following this finding, public interest and research in CTE escalated tremendously with evidence of CTE being found in former athletes of other contact

sports including ice hockey, soccer, rugby, and professional wrestling, as well as other individuals who had been subjected to repetitive brain trauma such as military veterans and victims of abuse.⁷

In recent years, further research and knowledge of CTE has continued to amplify public health concerns and has even led to several changes in sports programs and leagues at all levels with regard to concussion protocol and exposure to head contact. Though awareness and understanding of sports-related head trauma and RHI have grown vastly since its origins in 1928, countless questions still remain and it may be many more years until researchers and clinicians are able to truly grasp this subject matter.

Concussion

As concern for the potential long term consequences of sport-related concussions continues to grow, the necessity to understand, recognize, and adequately treat/manage concussions has become a priority for many institutions. Concussions are considered a subset of mild traumatic brain injury (mTBI) and consist of 75-95% of all TBIs.⁸

Concussions are defined as any complex pathophysiological process onset by traumatic biomechanical forces which affect the brain.¹² These traumatic forces can be caused by a direct collision with either the head, face, neck, or body with forces being transmitted to the head, and ultimately result in rapid onset of acute neurological impairments.

Concussions are a clinical diagnosis which can be identified by assessment following head trauma. The most common symptoms include headache and dizziness along with cognitive impairment such as confusion, and behavioral symptoms such as irritability.

Many other symptoms can manifest with concussion and are illustrated in Table 1. Of note, loss consciousness only occurs in 10% of concussions and should not be considered necessary for diagnosis.¹³

Table 1. Symptoms of Concussion.

Physical	Cognitive	Emotional
Headache	Confusion	Irritability
Dizziness	Disorientation	Depression
Nausea/Vomiting	Memory deficits	Anxiety
Photophobia/Phonophobia	Impaired concentration	Mood swings
Visual/Vestibular dysfunction	Feeling mentally “foggy”	Paranoia
Numbness/tingling	Loss of consciousness	Apathy
Fatigue	Amnesia	Sleep disturbance
Impaired speech		

Epidemiology

The Centers for Disease Control and Prevention (CDC) have estimated between 1.6 and 3.8 million individuals in the United States sustain a sports-related concussion every year, and the probability of an athlete sustaining a concussion in a contact sport may be as high as 20%.^{9,10} Recent data has suggested that annual concussion rates have increased over the past decade, however it has been widely speculated that this increase is a result of improved concussion awareness and education leading to increased identification and reporting.¹³ Even still, the true incidence of sports related concussions is likely higher. It has been suggested that as many as 50% of athletes fail to recognize, report, or admit to symptoms, leading some to refer to concussions in sports as a “silent epidemic”.¹³

Pathophysiology

The mechanism of injury involving concussions has evolved considerably over the past decades from merely being a “brain bruise” to a complex process involving brain and neuronal tissue, vasculature, and cellular metabolism. The primary mechanism by which concussions occur is through rapid acceleration and deceleration of the brain, including both rotational and linear acceleration, and impact deceleration.¹² The kinetic forces placed on the brain causes deformation of tissue triggering a cascade of neurochemical and metabolic events.

First, the stretching of neural tissue that occurs during brain deformation causes axonal injury or shearing which releases ions across their membranes. The disruption in axonal membrane potential causes a release of neurotransmitters, with glutamate in particular. This excitatory neurotransmitter binds to N-methyl-d-aspartate receptors causing further membrane depolarization and calcium release. The overload of calcium within tissue further disrupts axonal membrane potential, inhibiting proper function and communication between neurons. In order to restore normal axonal membrane potential, the sodium-potassium pumps are required to work at extremely high levels, which in turn elicits the need for equally high levels of oxygen and glucose for ATP production. However, decreased cerebral blood flow resulting from injury leads to a mismatch in supply and demand and inhibits the brain’s ability to properly restore normal cellular function. This process of axonal injury and neuronal dysfunction, along with neuroinflammatory responses and production of free radicals are the basis of the many signs and symptoms brought on by concussions.¹⁴

Disease course and management

In the 80-90% of sports-related concussion cases, symptoms usually resolve spontaneously within 7-10 days, though recent research has shown that this recovery period may be longer in the developing brains of children and adolescents.^{12,15}

Appropriate management of concussion can have a large influence on the length of recovery period for patients as well as the prospective implications of injury such as the development of PCS or second-impact syndrome, a potentially fatal condition.¹² The first step in management consists of recognizing injury and immediately removing the player from competition.¹³ Following evaluation by a professional healthcare provider, it is recommended that patients undergo a period of physical and cognitive rest in order to reduce the metabolic needs of the brain and allow for healing of injured tissue.¹⁶ Once an athlete is asymptomatic from initial symptoms of concussion and does not develop further complications, a gradual return to competition should be overseen. Athletes should only return to full activity until they are asymptomatic at rest and on exertion.¹²

Post-concussion syndrome

Though most athletes who suffer symptomatic concussions are able to make a full recovery to baseline within the average 7-10 day window, some are subject to symptoms that continue over a period of months or even years beyond their injury in a condition referred to as post-concussion syndrome (PCS). There are two standardized definitions of PCS. The Diagnostic and Statistics Manual, fourth edition (DSM-IV) defines PCS as cognitive deficits with attention or memory and a minimum of three or more of the following symptoms: headache, dizziness, fatigue, irritability, apathy, personality change,

or sleep or affective disturbance.¹⁵ To meet the DSM criteria for PCS, symptoms must be present for three months or greater.¹⁵ In comparison, the World Health Organization's (WHO) International Classification of Diseases, tenth edition (ICD-10) characterizes PCS as the presence of three or more of the following symptoms that must be present within the first month post-injury including: insomnia, irritability, dizziness, headache, fatigue, and difficulty with concentration or memory.¹⁵ There is little agreement between these definitions in clinical practice and as a result, determining the epidemiology and public health implications of this condition have proven to be challenging.

Epidemiology and risk factors

The percentage of adult athletes that continue to experience concussion symptoms beyond the 7-10 day time frame is reportedly in the range of 10-30%.¹⁵ Many of the symptoms that manifest acutely with concussions can endure in PCS with the most common reported symptom being headache, which in most cases is described as more frequent and longer-lasting than prior to injury.¹⁷ About half of PCS patients report dizziness, irritability, depression, and anxiety.¹⁷ With regard to cognition, short term memory loss appears to be the most common symptom. In a recent study, 25% of people diagnosed with PCS continued to report memory problems more than one year following injury.¹⁸ Overall however, most experienced clinicians tend to agree that cognitive symptoms of PCS resolve within 6 months to a year following injury in the vast majority of individuals.¹⁷

Several clinical variables have been thought to be associated with prolonged recovery from concussion and may predict the development of PCS. Some of these risk factors include younger age, female sex, unconsciousness or amnesia at time of injury, history of previous concussion, pre-existing ADHD or mood disorders, headache or dizziness at time of injury, delayed symptom onset, and initial symptom burden.¹⁵ A recent study by Tator et. al. however reported considerable heterogeneity in the clinical demographics of 221 PCS patients who were studied.¹⁹ Notably, 23.1% of patients had been diagnosed with PCS following only 1 concussion which seemed to dispel the common theory that multiple concussions increase the likelihood of developing PCS. Given these findings, further investigation into the predictors, risk factors, and process of PCS will be necessary to shape our understanding of this condition.

Persistent post-concussion syndrome

Persistent post-concussion syndrome (pPCS) is a clinical phenomenon in which patients experience neurologic and behavioral symptoms following a concussion that do not seem to resolve. The exact frequency of pPCS is unknown but reports have shown that 10-15% of concussion patients continue to be symptomatic 1 year post-injury.¹² Symptoms of pPCS are again similar to those in acute concussion and PCS, however emotional symptoms in pPCS seem particularly prominent and in some cases progressive.¹² The etiology of pPCS and reasons for why post-concussive symptoms may not resolve in certain patients is debated. Prolonged symptoms have been theorized to be related the mechanism of injury, the regions of the brain effected, or some other unknown

pathological substrate yet to be explored.²⁸ However, it has also been theorized that some cases of pPCS may be a consequence of maladjustment, depression, or unmet expectations in relation to recovery from concussion.²⁸ A study by Lange et.al. noted that patients who experience a concussion and have a recovery period complicated by major depression report more post-concussion symptoms and more severe symptoms than outpatients with depression, and patients with concussions who do not report significant depression.²⁹ This finding would suggest that depression may have a role in the prolonging of symptoms in pPCS and given the lack of an objective marker for this condition, the ability to draw a truly direct correlation between prolonged symptoms and a single concussion may be difficult.

Chronic traumatic encephalopathy

In recent years, the untimely and tragic deaths of several high profile athletes revealed to have evidence of CTE on post-mortem histopathological examination has led to an extraordinary surge in public interest and media attention regarding the disease.

Considering the amount of athletes of all ages who participate in contact sports every year, CTE has become a significant public health concern, and many institutions are implementing great efforts to characterize this disease that is still not fully understood.

As it currently agreed upon, CTE is defined as a progressive, neurodegenerative condition that develops in association with repetitive mTBI.⁷ This repetitive trauma is not simply limited symptomatic concussions, but also subconcussive blows to the head which can be quite numerous in certain contact sports, most notably football. Over one

million high school athletes participate in football each year and with the size and speed of these athletes increasing according to recent studies, the public health implications of CTE could become rather significant in the years to come.^{7, 24}

Epidemiology

The incidence and prevalence of CTE is largely unknown as cross-sectional and prospective studies are inhibited by the inability to definitively diagnose this disease in living patients.^{25,30} As a result, most epidemiological data regarding CTE has been derived retrospectively through pathological analysis of donated brains from athletes post-mortem.³⁰ To date, neuropathologically confirmed cases of CTE have been discovered in subjects as young as 14 and as old as 98, and in former athletes who did not continue contact sports beyond the high school or collegiate level.^{10, 21} Cases have also been reported in non-athletes who have been exposed to other forms of RHI, including military personnel with blast exposure, epileptic and mentally disabled patients who frequently head-bang, physical abuse victims, and even a circus clown who was recurrently shot out of a cannon.¹⁰ The majority of cases however, have been noted in athletes of high impact sports such as football, ice hockey, wrestling, soccer, boxing, and rugby.¹⁰

Retrospective studies and neuropathological examination have revealed some concerning statistics with one study finding evidence of CTE in 80% of athlete brains reviewed.²¹ However, estimates of prevalence from such subject groups are likely inflated by referral bias and may not represent the general athlete population.³⁰ The

limitation to being able to report accurate incidence and prevalence rates for CTE once again highlights the need for *in vivo* diagnostic criteria for this disease.

Subconcussive impacts

An important development in the characterization of CTE with regard to etiology has been the role of subconcussive impacts. Subconcussive injuries are defined as head impacts that involve enough force to disrupt axonal integrity but do not result in recognizable, symptomatic concussions. The intensity of impact required to cause neuronal damage is unknown, and whether there are impact levels that do not disrupt neuronal function is yet to be determined.³² These events have become notable however, due to the fact that 16% of previous CTE cases have no reported concussion history leading to the suggestion that subconcussive impacts are sufficient to initiate the disease process of CTE.¹¹

In certain contact sports, especially football, the amount of subconcussive injuries that may accumulate over the course of a career can be quite numerous. A study by Broglio et al. suggested that high school football players sustain an average of 24 head impacts per game exceeding 14 g-force.³⁰ Another study determined that offensive lineman experience over 1000 subconcussive impacts exceeding 10 g-force over a single college football season.¹¹ Similar results have been shown in male collegiate hockey players, indicating that a variety of athletes may endure a significant amount of head impacts every season.³⁰

Though it is unknown whether a specific threshold of head impacts is necessary to cause the development of CTE, there appears to be a correlation between the amount of exposure to contact sports and severity of disease. Samples reviewed by McKee and colleagues have shown that pathologic staging of CTE correlates significantly with the amount of years spent playing football.²¹ Position played also seems to have bearing on risk as studies of collegiate players suggest that offensive linemen develop more post-impact symptoms and experience more subconcussive injury compared to other positions.¹¹ Recent advances in protective equipment act to mitigate the effects of high-impact forces, however they do not alleviate the effects of rotational forces experienced with head contact. In addition, an athlete's perceived lower level of risk with helmet use may spur more risky behavior during games, leading to more severe impacts.³⁰

Pathophysiology

CTE is categorized a tauopathy which is pathologically distinct from that of Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). The neurodegeneration of CTE is associated with accumulation and widespread deposition of hyperphosphorylated tau protein (p-tau) as neurofibrillary and astrocytic tangles.¹¹ CTE has been noted for its unique pattern of distribution found to preferentially involve the sulcal depths and perivascular regions of the brain.¹¹ In addition, there is significant periventricular and subpial distribution with prominent accumulation of tau-immunoreactive astrocytes.¹¹ It has been theorized that the specific distribution of p-tau in CTE is likely due to accumulation in vulnerable areas of brain tissue that are most susceptible to injury as a

result of mTBI.¹¹ The superficial layers of the frontal and temporal cortices tend to be the first areas of the brain affected by CTE.¹¹ As the disease course progresses, p-tau deposition spreads to involve the adjacent cortices, diencephalon, and brainstem.¹¹ Beta amyloid deposition as diffuse plaques has been seen in less than fifty percent of cases which seems to distinguish CTE specifically from AD.¹¹

Pathology

As CTE is presently only diagnosed through post-mortem histopathological analysis, it is important to understand the common pathological findings and classification of this disease. From a gross anatomical perspective, CTE is characterized by atrophy of the cerebral hemispheres, thalamus, mammillary bodies, and brainstem, with ventricular enlargement and a fenestrated cavum septum pellucidum.¹⁰ Microscopically, there are extensive tau-immunoreactive neurofibrillary and astrocytic tangles, and spindle-shaped and threadlike neurites throughout the brain.¹⁰ Being a progressive disease, it is helpful to define CTE in terms of stages. McKee and colleagues have developed a commonly used outline which classifies CTE into 4 stages.¹² The pathological findings of these stages are described further in Table 3 along with their clinical associations. Progression between each stage of CTE has been estimated to be 11 to 14 years.²¹

Clinical Features

Since Martland's initial studies in the early 20th century, a plethora of different clinical signs and symptoms have been used to describe CTE. However, overall consensus seems

to agree on a core characterization of progressive deficits in behavior, mood, cognition, and motor function which seem to correlate with the anatomic distribution on neuropathology as a result of disease.²⁵ Another challenge of defining the true clinical features of CTE is the fact that most symptoms have been described retrospectively by family members of brain donors. Recently however, Montenigro et al. reviewed literature of the clinical presentations of CTE from 202 published cases and categorized the most common descriptions as summarized in Table 2.⁷

Table 2. Summary of clinical features for previous CTE cases.

Behavioral	Mood	Cognitive	Motor
Aggression	Depression	Memory impairment	Ataxia
Explosivity	Anxiety	Loss of concentration	Dysarthria
Impulsivity	Apathy	Executive dysfunction	Parkinsonism
Paranoia	Suicidality	Dementia	Tremor
Physically/verbally violent	Mood swings	Language difficulties	Gait disturbance

The review also identified two relatively distinct clinical manifestations of CTE with one group exhibiting initial features in behavior and/or mood while the other seemed to have initial features involving cognitive dysfunction. It was also noted that symptom onset for the ‘behavior/mood’ group occurred at a significantly younger age compared to the ‘cognition group’, and that most subjects in the behavior/mood group eventually

developed cognitive symptoms.⁷ Less than a third of the cases reviewed had reported motor features such as Parkinsonism.

In the majority of CTE cases, symptoms develop insidiously and generally begin 8-10 years after experiencing RHI exposure, though evidence of CTE has been found in subjects who were actively participating in contact sports at time of death.¹⁰ With regard to symptom progression, McKee et al. recently characterized the four main pathological stages of CTE with symptoms that progressively worsen with extent of pathological changes.²¹ The pathology and symptoms described in Table 3 are noted to be cumulative through disease progression.

Table 3. Neuropathology and clinical symptoms based on CTE stage.

Stage	Pathology	Symptoms
Stage I	<i>Gross:</i> None <i>p-tau:</i> Sulcal depths of frontal cortex	-Headache -Loss of concentration -Reduced attention span
Stage II	<i>Gross:</i> Mild ventricular enlargement, cavum septum pellucidum, pallor of locus coeruleus and substantia nigra <i>p-tau:</i> Subcortical white matter, medial temporal lobe, brainstem	-Pronounced behavioral/personality changes (depression, impulsive behavior) -Short term memory loss -Executive dysfunction
Stage III	<i>Gross:</i> Reduced brain weight, mild frontal/temporal atrophy <i>p-tau:</i> Diffuse in frontal, temporal, and parietal cortices, concentrated around small vessels and sulcal depths	-Further cognitive impairment -Aggression -Mood disorders
Stage IV	<i>Gross:</i> Pronounced atrophy and reduction in brain weight. Septal abnormalities <i>p-tau:</i> Severe deposition, inclusion of cerebellum and medulla	-Severe mood disorders -Language difficulties -Visuospatial difficulties -Gait/motor control impairments

As with the findings described by Montenigro et al., behavioral/mood symptoms appear to be the earliest manifestation in the majority of CTE cases with cognitive symptoms becoming more pronounced in stages II-III and motor symptoms developing in late-stage disease. Based on informant interview and previous neurological examination on patients prior to death, the earliest cognitive deficits of CTE tend to be in the areas of memory and executive function.²⁵

Executive function

Executive function is defined as the mental capacities required for effective goal-directed activity and cognitive control of behavior.³⁵ It is involved in complex mental processes such as problem solving, behavior modification in setting of new information, strategy generation, and sequencing complicated actions.³⁵ These functions are dependent on the prefrontal brain areas and on links between dorsolateral frontal and parietal cortices which, as stated previously, are regions of the brain commonly affected in the early stages of CTE progression.

Behavior rating inventory of executive function (BRIEF)

The Behavior Rating Inventory of Executive Function (BRIEF) test was developed in 2000 to assess executive function and behavior in children and adolescents with a variety of neurological conditions including autism, Tourette syndrome, TBI, and most commonly, Attention deficit/hyperactive disorder (ADHD). The BRIEF-Adult version (BRIEF-A) was developed 2005 as an extension of the original test and has been proven

to be useful in assessing older patients with neurological/psychiatric disorders, dementia, and TBI as well. The BRIEF-A consists of a 75-item questionnaire that can be completed either by the patient or an informant involved with care. Participants indicate how problematic certain behaviors have been over the previous 30 days on a 3-point scale: never (1 point); sometimes (2 points); or often (3 points).³² The overall score called the Global Executive Composite (GEC) is broken down into two indices: Behavior Regulation Index (BRI) and Metacognition Index (MI). The BRI measures ability to control behavior and emotional responses, while the MI measures ability to solve problems, plan, organize, and sustain a working memory. These indices are calculated from a total of nine clinical scales which are described in Table 4. Scores are compared to normalized data previously obtained from 1050 participants selected to proportionally represent the United States population with regard to sex, race/ethnicity, education, and geographic region.²⁷ Higher scores relative to normative data indicate more executive dysfunction, with scores 1.5 standard deviations above the mean being considered clinically significant.

Table 4. BRIEF-A Clinical scales.

Behavior Regulation Index (BRI)		Metacognition Index (MI)	
<i>Inhibit</i>	Ability to control impulses and to stop engaging in a behavior.	<i>Initiate</i>	Ability to begin an activity and to independently generate ideas or problem-solving strategies.
<i>Shift</i>	Ability to move freely from one activity or situation to another; to tolerate change;	<i>Working Memory</i>	Ability to hold information when completing a task, when encoding information, or

	to switch or alternate attention.		when generating goals/plans in a sequential manner.
<i>Emotional Control</i>	Ability to regulate emotional responses appropriately.	<i>Plan/Organize</i>	Ability to anticipate future events; to set goals; to develop steps; to grasp main ideas; to organize and understand the main points in written or verbal communication.
<i>Self-Monitor</i>	Ability to keep track of the effect of one's own behavior on other people.	<i>Task-Monitor</i>	Ability to assess one's own performance in problem solving tasks.
		<i>Organization of Materials</i>	Ability to put order in work, living, and storage spaces

Existing research

In concordance with the growing concerns on the issue of sports-related head trauma and repetitive impacts, a great deal of research and new information has been published on this subject. Several of these studies have also concentrated particularly on the effects of head trauma on executive functioning and other related aspects of neuropsychological health. The results of many of these studies have shown troubling statistics with regard to neurological deficiencies in current and former contact sport athletes, and the conclusions they have drawn continue to emphasize the necessity for further research.

In attempt to illustrate the acute and residual neuropsychological effects of sport-related mTBI, Killiam et al. studied a cohort of collegiate contact sport athletes. Participants in this study were assigned to one of four groups: non-concussed, non-recent concussed (>2 years), recently concussed (<2 years), or a control group of non-concussed/non-athletes. Subjects were assessed on executive functioning using

neuropsychological (NP) tests focused on working memory, visuospatial construction, language, and attention. Results of testing showed no difference in visuospatial construction, language, and attention among the four groups but significant deficits in working memory were identified for the concussed athletes (both recent and non-recent) relative to the control group.³³ This finding would suggest that there some degree of executive impairment in the acute and chronic periods for previously concussed athletes, however data also revealed a significant difference in this area for recently concussed relative to non-recent, suggesting a level of improvement to function over time. Of note, overall results of NP testing showed significantly lower scores for not only concussed athletes relative to non-athletes, but non-concussed athletes as well. This finding highlights the potentially large role that subconcussive impacts play in executive function impairment, especially given that no statistical differences were found between the concussed and non-concussed athletes.³³

Though these may be crucial findings, this study was limited by a small sample size and the fact that students were all selected from the same college, making data less generalizable. Participants were also asked to only list concussions that were diagnosed by a physician on screening questionnaires. This differs from protocol of more recent studies in which subjects self-report concussion history based on a modernized definition, and not just from clinical diagnoses. In this regard, it is possible that athletes in the non-concussed group may have had previous concussion as considered by current standards.

Another deficiency in the Killiam et al. study is that it did not designate a group specifically for post-concussion subjects who remained symptomatic. A more recent

study by Dale et al. however, takes this variable into account by comparing post-mTBI patients with pPCS to those without, as well as control groups that included non-mTBI patients who were experiencing symptoms consistent with PCS according to DSM-IV criteria.³⁴ The groups were designated as mTBI + PCS, mTBI – PCS, Control + PCS, and Control – PCS with the mTBI groups being ≥ 1 year post injury and the control groups having no prior history of head injury. Participants all underwent various behavioral and neurocognitive tasks to assess executive functioning.

Results revealed that the mTBI + PCS group had significantly greater error rates in cognitive tasks than all other groups, including mTBI – PCS. Comparison of all other groups were not statistically significant. With regard to executive function, the mTBI + PCS group demonstrated significant impairment in working memory and information processing speed compared to all other groups.

It could be argued that the deficiencies seen on testing for the mTBI + PCS group relative to the mTBI – PCS group may be secondary to effects of symptoms. In attempt to control for this variable, the study utilized the Control + PCS group and compared the symptoms reported in each group. While depression/anxiety symptoms did not vary between the +PCS groups, the mTBI + PCS group did have increased symptom report in sleep quality and PTSD. It was also found that symptom report (i.e. amount of sleep deprivation) correlated with decreased test results. Given this outcome, Dale et al. ultimately concluded that the executive function impairment seen in the mTBI + PCS group was most likely due a combination of symptom effect and that of the initial injury. Ultimately, further investigation on effects of sleep quality and PTSD in pPCS patients

along with longitudinal studies would prove more useful in characterizing executive dysfunction for pPCS.

Though there is limited data with respect to the longitudinal neuropsychological and cognitive outcomes of patients with history of RHI, researchers are working towards developing methods to help answer the many questions surrounding the long-term consequences of participating in contact sports. The Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND) study at Boston University's Alzheimer's Disease and CTE Center is one such study. LEGEND is designed to assess the potential risk factors involved with the short and long-term implications of mTBI and RHI exposure. Participants in this study undergo annual cognitive assessments, and internet-based measures of mood, behavior, and cognition. Participation in LEGEND is open to adults over the age of 18 who are either active or former athletes involved with any sport and level of competition. There are currently about 800 current/former athletes participating in this study.³²

As a segment of the ongoing LEGEND study, Montenigro et al. recently looked to quantify the impact of sports-related RHI on long-term neurological function. The study made use of a metric called the "cumulative head impact index" (CHII) which was generated from a combination of self-reported athletic history (amount of seasons, positions, and levels played) and impact frequencies based of previous helmet accelerometer studies which quantified frequency of head impacts per season by position and level of play.³² The study sample included 93 former high school and collegiate football players enrolled with LEGEND.

Participants completed questionnaires to assess past medical history and concussion history along with athletic history.³² They then completed several self-assessment surveys which measured levels of depression, mood, cognitive function, and executive function. The CHII calculated from athletic history served as an estimate of the total exposure to RHI participants had experienced over a lifetime of playing football. This estimate was used as a predictor metric and was modeled with each outcome of the self-assessments.³² With statistical analysis, researchers were able to identify CHII threshold points for which the risk of neurological impairment begins to increase above that of the normal population. As data also showed a correlation between increasing CHII and risk of impairment, these thresholds essentially represented change points in which a dose-response is initiated.³² These change points are listed in Table 5.

Table 5. Change Point threshold from baseline risk to Dose-Response Relation for CHII and Impairment Risk.

Clinical Domain	Threshold-mean CHII for dose-response	95% Confidence Interval
Executive Function	1850	1523-2011
Depression	1801	1514-2010
Apathy	2160	1536-5754
Cognition	7251	1754-9788

According to this data, the amount of head impacts estimated to initiate an increased risk of executive dysfunction above the normal average is 1,850.³² This impairment threshold is only achieved earlier by depression, and for a high school athlete, this level of CHII could be achieved in about 3 seasons of play.³² This risk increases with a higher CHII as illustrated in Figure 1 and with a mean CHII of 5,806 for

this study sample, the average risk of executive dysfunction was increased almost 5 fold for these athletes.

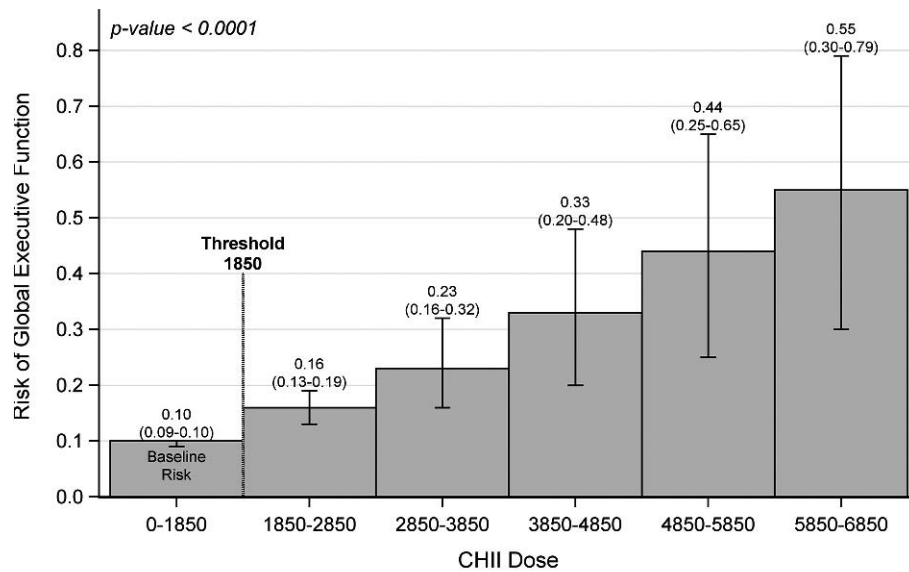


Figure 1: Dose-Response Relationship for CHII-Executive Dysfunction Risk.

The results from this study also proved CHII to be a better predictor of impairment than self-reported concussions.³² This may imply that total RHI has a greater effect on executive dysfunction than do isolated concussions, but it may also demonstrate the inaccuracy of self-reporting concussions in studies in the first place. Regarding the validity of CHII, a notable weakness is its assumption that players are active for all games and practices throughout the season.³² Regardless, the results of the study highlight the importance of subconcussive impacts in the development of neurological impairment as a correlate with duration of contact sport exposure.

Another segment of the LEGEND study by Seichepine et al. seems to illustrate the progressive nature of executive function decline in individuals with RHI exposure who are likely to be at high risk of either having or developing CTE. The study looked at executive function in college and professional football players through self-assessment using the BRIEF-A. The use of this particular measurement allowed researchers to compare results of these athletes with the normative scores for healthy adults, as well as compare the results of athletes themselves by age. The BRIEF-A test was also considered advantageous as previous research has shown it to be more sensitive in detecting early executive deficits compared to other objective measures of cognitive function.²⁷

Participants in this study included 64 current and retired football players, of which were all males ranging from 25 to 81 years of age (mean age of 47.0 and standard deviation of 13.6). Subjects were grouped by level achieved in football (college and professional) and by age (less than 40 and greater than or equal to 40). This age grouping was chosen based on evidence that cognitive decline and other profound CTE symptoms appear to develop in the fourth or fifth decades of life.²⁷ Once BRIEF-A scores were obtained, they were converted to age-appropriate *t*-scores based on normative data.

In comparing BRIEF-A results of football players and normative data for healthy adults ($t=50$), football players indicated greater decline in executive function with significant elevations on the GEC ($t(63)=5.4$; $p<0.05$), MI ($t(63)=5.3$; $p<0.05$), and BRI ($t(63)=5.2$; $p<0.05$) indices.²⁷ Analysis of the individual clinical scales also showed significant deficiencies for football players on seven of the nine scales: inhibit, shift,

emotional control, initiate, working memory, plan/organize, and task-monitor.²⁷ Across all scales, football players indicated worse functioning and had higher rates of clinically elevated scores (t -score ≥ 65) than the normative sample.²⁷ When comparing football players by age group, the ≥ 40 group showed significant differences in executive function compared to younger players with the three overall indices of GEC ($t(62)=2.7$; $p<0.05$), on the BRI ($t(56.0)=3.3$; $p=0.05$); and on the MI indices ($t(62)=2.1$; $p<0.05$) elevated as well.²⁷ These findings would suggest that executive dysfunction in football players is either a progressive component that is set in motion from onset of RHI or that it becomes significantly worsened after 40 years of age. Ultimately, longitudinal studies are necessary to better understand this data.

Though the BRIEF-A does provide several advantages in this study, a notable weakness in its use is the fact that a population of elite athletes may not be generalizable against the normative data. There are likely many differences in these groups including physical stature (height and weight), education (many players in this study attended college), overall health (heart disease, arthritis, chronic pain, orthopedic issues, use of medications), and health-related behaviors (alcohol, smoking, and illicit drugs).²⁷ Comparison of this data to non-contact athletes would strengthen the argument that executive dysfunction is a direct result of cumulative RHI.

Another weakness to consider for this study is its self-referral recruitment which may have included mostly players who were symptomatic and more concerned about their cognitive function than those who were not experiencing symptoms. If this were a major bias however, there likely would have been few scores within the normal range for

football players. In contrast, 31.3% of the players had overall scores at or below the expected value for their age.²⁷

Neuropsychological function has also been studied in individuals who have sustained multiple concussions but not in the setting of repetitive subconcussion exposure. Vynorius et al. recently assessed the effects of multiple mTBIs on self-reported cognitive difficulties, executive functioning, and mood in individuals who were not athletes. The study sample consisted of 58 young adults (mean age of 22.84 and standard deviation of 4.88) of which 29 denied history of mTBI, and 29 reporting 2 or more mTBIs in their lifetime (range 2–7).³¹ Participants in this study were also assessed on executive function using the BRIEF-A, along with two other self-report tools to assess overall cognition over the previous five years and depression in the previous two weeks.

Results of the three self-assessments showed that subjects with a history of multiple mTBIs reported a greater amount of depression symptoms, more change in cognitive function, and more problems with executive function in the previous 30 days compared to those without history of mTBI.³¹ Further analysis of the BRIEF-A results showed a significant elevation in the MI index but not in the BRI ($p=0.066$).³¹ Additionally, it was found that an increased number of mTBIs reported by individuals correlated with an increased reporting of symptoms across all measurements.³¹ These findings would indicate that individuals with history of mTBIs but without history of contact-sports related RHI also experience a level of cognitive decline and executive dysfunction which worsens with subsequent injuries.

As with the Killiam et al. study, these results were limited by a relatively small sample size and having participants as college students from a single institution. Variables such as socioeconomic status, average amount of sleep, and learning disabilities were also not addressed in the study, and these variables may have contributed to the results of the three self-assessments.³¹ Nonetheless, the findings of this study are consistent with the growing evidence that any history of head trauma, whether it be isolated mTBI events or years of RHI exposure, seem to be associated with some degree of executive dysfunction and long-term, progressive decline. How this decline differs between non-athletes with pPCS and contact sport athletes who may be experiencing early symptoms of CTE requires further investigation.

METHODS

Study design

The proposed study will be a cross-sectional analysis of executive function in non-athletes and football players using two control groups and two study groups. The first control group will consist of non-pPCS subjects without history of mTBI or contact sports exposure (Non-Football – pPCS). The second control group will involve subjects with football exposure who are without symptoms of PCS (Football – pPCS). The first study group will include pPCS patients with a non-athletic related mTBI history and no previous exposure to contact sports (Non-Football + pPCS). The final group will be comprised of pPCS patients with football related mTBI and a significant history of RHI exposure that could raise suspicion of what may ultimately be a manifestation of early stage CTE (Football + pPCS). Subjects will undergo self-assessments of executive function using the BRIEF-A assessment. Results will be compared to determine if significant differences in executive function exist between the groups. This study will work in parallel with the ongoing LEGEND study at Boston University.

Study population and sampling

The study population for the Non-Football groups will be selected from family medicine and neuropsychology practices across the New England region. Those that qualify under the specified inclusion/exclusion criteria as detailed in Table 6 will be selected to proportionally represent a variety of races, socioeconomic statuses, and educational backgrounds consistent with the United States population.

Table 6. Inclusion and Exclusion Criteria.

Non-Football – pPCS		Non-Football + pPCS	
Inclusion	Exclusion	Inclusion	Exclusion
Male, age 18-40	History of neurological disorder or learning disability	Male, age 18-40	History of neurological disorder or learning disability
	Any exposure to contact-sports, military experience, or other history of RHI	Symptoms ≥ 1 year under DSM IV criteria for PCS	Any exposure to contact-sports, military experience, or other history of RHI
	History of substance and/or alcohol abuse	History of single or multiple non-sports-related mTBI	History of substance and/or alcohol abuse
	Any history of TBI		Any TBI sustained w/in year of study
Football – pPCS		Football + pPCS	
Inclusion	Exclusion	Inclusion	Exclusion
Male, age 18-40	History of neurological disorder or learning disability	Male, age 18-40	History of neurological disorder or learning disability
Exposure to football at high school level or higher	Exposure to other contact-sports, military experience, or other history of RHI	Symptoms ≥ 1 year under DSM IV criteria for PCS	Exposure to other contact-sports, military experience, or other history of RHI
CHII ≥ 4500	History of substance and/or alcohol abuse	Exposure to football at high school level or higher	History of substance and/or alcohol abuse
	Any TBI sustained w/in year of study	CHII ≥ 4500	Any TBI sustained w/in year of study

The study population for the Football groups will be selected from the current pool of LEGEND study participants. Demographic characteristics, athletic experience, concussion history, and psychiatric history have already been obtained for these individuals, and those who meet group criteria as specified in Table 6 will also be selected to represent a variety of demographics and backgrounds consistent with the current population.

Participants of the study will be between the ages of 18-40. This parameter is necessary given the proclivity for younger CTE subjects to develop the behavior/mood symptoms that tend to mirror pPCS.⁷ It will also exclude the age groups in which cognitive symptoms of CTE are known to begin strongly manifesting based on previous evidence.⁷ Cognitive impairment may already be prominent in these individuals, which could lead to the possibility of skewed data.

Subjects for the + pPCS groups will be selected based on diagnostic criteria of the DSM-IV definition of PCS which requires changes in attention or memory and a minimum of three or more symptoms including; headache, dizziness, fatigue, irritability, apathy, personality change, or sleep or affective disturbance.¹⁵ Patients who are symptomatic for at least 1 year will be included in the study. The Non-Football group will consist of subjects with pPCS following a non-sports-related concussion (e.g. car accident). Subjects in this group may have a history of multiple concussions prior to development of pPCS, but will have no previous exposure to repetitive subconcussive impacts such as that experienced in contact-sports or military service.

Given the historically limited participation of females in football, subjects in the study will be exclusively male. The study will make use of the CHII estimate for football related RHI developed by Montenigro et al.³² Using this measurement rather than “years of contact sport exposure” would exclude participants who had played other contact sports, however its use will also control for several variables and provide a realistic estimate of RHI for participants. The minimum CHII will be 4,500 for inclusion in the Football groups. This number would equate to roughly 4 years of high school and 2 years of college football.

The sample size for this study will be based on outcome variable of BRIEF-A scores. Previous studies using the BRIEF-A have been able to use smaller sample sizes as data was compared against the test’s normative data. In comparing average scores between four independent groups however, larger sample sizes will be required. While an increase in BRIEF-A scores of 15% above the normative average are considered clinically significant, this study will consider a difference of 10% between each of the four groups to be significant. With an α -value of 0.05 and a power of 80%, the sample size required for each group will be 140.³⁶

Study variables and measures

The primary variable of this study will be exposure to football-related subconcussion. Given that all previously studied cases of CTE have involved exposure to repetitive subconcussion, including 16% with no concomitant history of symptomatic concussion, this variable should prove to play an important role in discerning potential cases of early

stage CTE and true cases of pPCS within the Football + pPCS and Non-Football + pPCS groups respectively.²²

Cumulative RHI for the Football groups will be measured with the CHII calculated from athletic history and previous accelerometer data. Participants in the study groups will undergo a one-time BRIEF-A assessment to measure level of executive functioning in the previous 30 days. Results will be converted to age-appropriate *t*-scores based on published normative data. These *t*-scores will then be compared to determine if a significant difference in executive function exists between the control and study groups as well as the study groups of Non-Football + pPCS and Football + pPCS themselves. Scores for the GEC, BRI, MI and the individual clinical cases described previously in Table 4 will all be calculated and compared. A difference of 10% on all scores and clinical scales will be considered significant.

Multiple, symptomatic concussion history among the Football and Non-Football + pPCS groups will be controlled as a variable by pairing scores for each group based on the amount of concussions sustained over a lifetime, e.g. football players with a history of 3 symptomatic concussions will be compared with non-athletes with 3 concussions. Concussion history will be self-reported on screening questionnaires with a definition used in previous LEGEND studies and consistent with current guidelines from the American Academy of Neurology.

Age as a variable will be controlled through the age adjusted *t*-scores. Other secondary variables to consider are past medical history, amount of symptoms reported, level of competition achieved in football, and severity of mTBIs.

Recruitment

Subjects from the Football groups will have previously been recruited for the LEGEND study and will only require an additional email that would include a link to a screening questionnaire. Subjects for the Non-Football groups will be recruited using flyers posted at family medicine and neuropsychology practices across New England. These flyers would direct potential subjects to an online source where the screening questionnaire could be accessed and submitted to a database.

Data collection

The BRIEF-A is a self-assessment requiring only a pencil and 10-15 minutes to complete. This assessment is currently not available online, and will be mailed to participants. For this study, one survey will be administered for each participant to assess executive function over the previous 30 days. Raw scores will be computed with the BRIEF-A Software Portfolio (BRIEF-A SP) which requires 15-20 minutes. This program will also convert raw scores into age-appropriate *t*-scores based on the published normative data as previously collected by the developers of BRIEF-A.

Data analysis

The *t*-scores for all four groups will first be compared against the normative data to identify any levels of dysfunction against the average population. Mean *t*-scores for the Non-Football, and Football groups will then be calculated, and each group will be

compared with a two-sample *t*-test in order to identify any significant differences. The *t*-scores can also be adjusted to compare level of executive dysfunction by increasing age, lifetime concussions, and total CHII within each group. These comparisons may provide evidence on how executive function declines with age, increased concussion history, and increased exposure to football.

Timeline and resources

Fall 2017	-Apply for IRB expedited review -Obtain approval to recruit in New England family medicine practices
Winter-Spring 2018	-Recruit participants
Spring 2018	-Obtain materials for the BRIEF-A assessment -Mail assessments to subjects who qualify and agree to study
Summer-Fall 2018	-Data collection
Fall 2018	-Study completion -Prepare and submit manuscript for peer review

Resources needed for this study mainly include the materials for the BRIEF-A test administration and scoring. As far as recruitment, the Football groups will already have been made available through the LEGEND study. Recruiting for the and Non-Football groups will require several co-investigators in order to solicit the use of recruitment flyers in physician’s offices. Undergraduate and graduate student volunteers interested in this area of research could be utilized to support the LEGEND personnel with mailing and receiving BRIEF-A tests, as well as administering phone calls to encourage participants to complete assessments in a timely manner.

Institutional Review Board

As LEGEND has received prior IRB approval, this proposed branch of study will be submitted for expedited review as it involves a survey to proposed additional participants of a low risk, non-vulnerable population.

CONCLUSION

Discussion

The ultimate goal of the proposed study will be to identify evidence of a possible measurable variable between early stage CTE and pPCS, as well as further define each condition as separate disease processes. It should be emphasized that this study does not specifically compare early stage CTE with pPCS however, as the lack of an *in vivo* diagnosis for CTE predicates this as a study limitation. The rationale behind the design of this proposal is based on the fact that all previously studied cases of CTE have involved a significant degree of exposure to subconcussion.²² Therefore, this design is based on the assumption that a symptomatic Football + pPCS group will likely contain more cases of early stage CTE than the Non-Football + pPCS group, which should be represented to a greater extent by true cases of pPCS. This assumption may be a limitation in itself but based on evidence from previous studies, would give the proposal's results some merit to clinical application and hopefully provide evidence that would direct future studies down the correct pathways.

Advantages of this proposal relative to similar previous studies would certainly include its sample size and generalizability. The total sample will contain a pool of both athletes and non-athletes made up of a variety of demographics and socioeconomic backgrounds. As with the Seichepine et al. study, this proposal will also be designed to investigate the nature of progression in executive dysfunction for these particular individuals. In this case however, the focus will be on the <40 year old population and include symptomatic individuals in the study groups. Results under these parameters

may provide further clues into the potential decline of executive function in pPCS patients versus those at greater risk of having early stage CTE. Any significant difference or recognizable patterns in this data may prove to be very beneficial in future studies.

Beyond the limitation of assumptions as previously stated, the proposed study includes other weaknesses that should be noted. First, it will not include female participants, and with studies showing higher prevalence of women reporting prolonged symptoms of concussion, this exclusion may prove to be a considerable limitation in data collection.¹⁹ The study will also only include athletes with exclusive exposure football which would prevent the generalizability of results with other contact sports. Finally, though the BRIEF-A has proven to yield accurate measurements of executive functioning in previous studies, it is purely a subjective measurement. The involvement of an objective assessment such as cognitive testing would likely strengthen the results of this proposed study.

Summary

With the body of evidence that has been revealed with respect to the acute and long-term effects of contact sports-related RHI, the risks of participating in these sports, especially football, can no longer be understated. The evidence in literature and statistics from current research show that neuropsychological and cognitive health can all be markedly compromised even at a young age for these athletes, and even in those who have never sustained a symptomatic concussion. The recent efforts to better diagnose, recognize,

and manage concussions and their related symptoms have supported the campaign against this “silent epidemic” but clearly the best clinical solution to prevent the detrimental, long-term consequences of RHI is to recommend against the participation in contact sports. As this is not quite an acceptable answer from a cultural stand point at present, our next best option is to continue researching these athletes and work towards finding risk factors, genetic predispositions, and *in vivo* diagnostic models for conditions such as CTE and pPCS.

Regarding the potential of distinguishing these two conditions in situations where clinical picture is questionable, it would seem that a patient’s risk of having early stage CTE over a diagnosis of pPCS would increase with amount of RHI exposure they had experienced. Whether there is a threshold of ‘years playing contact sports’ or total RHI that predicts this risk remains unknown, but the proposed study may help guide future studies in revealing that answer. As previous studies have shown that worsening CTE pathology and worsening executive functioning are both correlated with increased RHI exposure, the argument that potential early stage CTE patients with significant exposure to RHI would exhibit worse executive functioning than that of true pPCS patients certainly warrants further investigation.^{21, 32}

Clinical and/or public health significance

If results of the proposed study prove the initial hypothesis to be true, then the BRIEF-A scores obtained from this study could be applied clinically to assess a patient with pPCS symptoms and a history of contact sports exposure as to whether or not there should be

concern for early stage CTE based on level of executive functioning and scoring spectrum of the Football and Non-Football groups. Even if the results of this study do not show any significant findings between the groups, the statistics generated from it will give researchers and clinicians a better understanding and measurable expectation of the effects of RHI on executive functioning in contact sport athletes.

As has been the conclusion for many other studies on this subject, the findings of a longitudinal study will ultimately prove to be the most beneficial in characterizing CTE as a disease. The efforts to see such research through are well within the abilities of the LEGEND team at Boston University, however it may still require several years, even decades, until research yields truly tangible results. Smaller studies such as the one proposed will aid efforts of the LEGEND study and clue researchers into what level of RHI history would push the clinical picture of a symptomatic individual in the direction of probable early stage CTE rather than pPCS.

LIST OF JOURNAL ABBREVIATIONS

Alzheimers Res Ther.	Alzheimer's Research & Therapy
Arch Clin Neuropsychol.	The Official Journal of the National Academy of Neuropsychologists
Aust Fam Physician.	Australian Family Physician
Br J Sports Med.	British Journal of Sports Medicine
Curr Neurol Neurosci Rep.	Current Neurology and Neuroscience Reports
Curr Pain Headache Rep.	Current Pain and Headache Reports
Front Hum Neurosci.	Frontiers in Human Neuroscience
Front Neurol.	Frontiers in Neurology
J Am Med Assoc	The Journal of the American Medical Association
J Head Trauma Rehabil.	The Journal of Head Trauma Rehabilitation
J Neuropathol Exp Neurol.	Journal of Neuropathology and Experimental Neurology
J Neurol Psychopathol.	The Journal of Neurology and Psychopathology
J Neurosurg.	Journal of Neurosurgery
J Neurotrauma.	Journal of Neurotrauma
J Strength Cond Res.	Journal of Strength and Conditioning Research
J Vasc Interv Neurol.	Journal of Vascular and Interventional Neurology
Nat Rev Neurol.	Nature Reviews Neurology
Neurol Clin.	Neurologic Clinics
Pediatr Ann.	Pediatric Annals
PLoS ONE	Public Library of Science ONE

PM&R	Physical Medicine & Rehabilitation: The Journal of Injury, Function, and Rehabilitation
Psychol Med.	Psychological Medicine
US Naval Med Bulletin	United States Naval Medical Bulletin

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