2019

Characterizing a symptom profile in former athletes

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

CHARACTERIZING A SYMPTOM PROFILE IN FORMER ATHLETES

by

SYDNEY CARPENTER

B.S., Emory University, 2016

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2019

Approved by

First Reader _____

Robert A. Stern, Ph.D.
Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology

Second Reader _____

Michael L. Alosco, Ph.D.
Assistant Professor of Neurology

ACKNOWLEDGMENTS

First, I would like to acknowledge everyone at the Boston University Alzheimer's Disease and Chronic Traumatic Encephalopathy Centers. The hard work of each individual at these centers is so very important and valued.

I would especially like to express my appreciation to my advisors. Dr. Stern was such an instrumental mentor throughout this process, and I am so grateful to have had his expertise and generosity. Dr. Alosco's contributions were also so greatly appreciated during this process. I would like to recognize Dr. Stearns-Kurosawa who has been guiding me throughout my time as a graduate student. She has been very active in steering my course down the right path at each twist and turn.

Gathering data was an arduous process for this project and I cannot thank Brett Martin enough for all of his work to make this happen.

I will also take this opportunity to thank my officemates for helping me work through my daily tribulations and their continued understanding. Furthermore, I would like to thank my research coordinator Shannon Conneely for helping keep all of my meetings on track and for being an amazing resource and friend throughout this time.

Finally, for moral support and helping me through even the roughest days, I would like to thank my friends and family. You were all there to help in any way you could, even if that meant listening to my stream of consciousness at times. My roommate should be rewarded for her patience. My mother was particularly incredible throughout this process at making sure I kept my goals in sight and encouraging me to strive for my best daily.

CHARACTERIZING A SYMPTOM PROFILE IN FORMER ATHLETES

SYDNEY CARPENTER

ABSTRACT

The long-term effects of repetitive head impacts are a growing concern. Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that is associated with repetitive head impacts and is characterized by distinct neuropathological changes. Other risk factors of developing CTE are still unknown but may include age, genetics, age of first exposure to sports and type of sport. The only way to diagnose CTE is with a post-mortem analysis. Current research is focused on diagnosing CTE during life; efforts are turning towards developing a clinically diagnosable syndrome that is related to CTE prognosis. Common symptoms reported from retrospective analyses of CTE confirmed cases include cognitive difficulties as well as mood and behavior symptoms like depression and impulsivity. The goal of the present study was to define the clinical presentation of a diverse group of former athletes in an effort to categorize a clinical presentation of individuals with various head impact exposure. The individuals in the sample included contact and non-contact sport athletes, both male and female, ranging from 19 to 86 years of age. The data was based on a larger study, the Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND). In a sample of 592 participants from this study, cluster analyses identified five discrete groups of individuals based on their symptom profile. These included Asymptomatic, Mildly symptomatic, Mood symptoms, Behavior symptoms and Highly symptomatic groups. Between the groups, there was no difference in age of participants. There was no

prevalence of a certain sport in any of the clusters. Additionally, there was no significant finding regarding estimated number of head impacts and symptomatology in football players. Results showed an effect of cognitive reserve, measured by years of education. Participants in the Asymptomatic group had significantly more education. This implies that years of education may be a risk factor for decreasing one's ability to cope with neuropathology. Further research needs to be done on the connection between symptomatology and neuropathological diagnosis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AD .....Alzheimer's Disease

AES..... Apathy Evaluation Scale

ApoE-ε4 .....Apolipoprotein E-allele 4

BIS-11.....Barratt Impulsiveness Scale – Version 11

BRI ..... Behavioral Regulation Inventory

BRIEF-A..... Behavior Regulation Index of Executive Function – Adult Version

CES-D.....Center for Epidemiologic Studies Depression Scale

CHII .....Cumulative Head Impact Index

CTE.....Chronic Traumatic Encephalopathy

FAQ .....Functional Activities Questionnaire

LEGEND ....Longitudinal Examination to Gather Evidence of Neurodegenerative Disease

MI ..... Metacognition Index

NFTs ..... Neurofibrillary tangles

RHI ..... Repetitive Head Impacts

S-N-K ..... Student-Newman-Keuls

TBI .....Traumatic Brain Injury

TES ..... Traumatic Encephalopathy Syndrome

INTRODUCTION

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that is associated with repetitive head impacts (RHI) and is characterized by distinct neuropathological changes including the perivascular deposition of hyperphosphorylated tau proteins in the brain (K. Bieniek et al., 2015; B. Gavett, Stern, & McKee, 2011; A. McKee, Cairns, et al., 2016; A. McKee et al., 2009; R. Stern et al., 2011). Currently there is no way to diagnose CTE during life; a true diagnosis can only come from a post-mortem neuropathological examination (A. McKee, Cairns, et al., 2016). From these post-mortem analyses, it has been found that CTE clinically presents with cognitive, behavior, and mood disturbances (L. Hazrati et al., 2013; A. McKee, Cairns, et al., 2016; A. McKee et al., 2013; J. Mez et al., 2017; R. Stern et al., 2013).

HISTORICAL REPRESENTATION

This type of neurologic disorder caused by repetitive head impacts was introduced by Martland as *punch-drunk*, a disorder affecting boxers characterized by gait abnormalities and mental status changes. Symptoms related to the disorder were noted in almost half of boxers by Martland. Sports casters, fans and boxers themselves described the afflicted as goofy or seemingly intoxicated. The underlying neuropathology was speculated to be due to repeated blows causing multiple concussions possibly leading to progressive degenerative lesions in the affected areas. It was distinguished, however, that

fighters who moved more quickly and took fewer hits seemed to be less affected. (H. Martland, 1928; H. Parker, 1934)

There was an increase in pathologic examinations of boxers supporting this distinguishable form of neurodegenerative disease by the 1970s (J. Corsellis, Bruton, & Freeman-Browne, 1973). With the increased clinical evidence of disease and prevalence found outside of boxers, a new term *chronic traumatic encephalopathy* became used (Miller, 1966). CTE has since been categorized among athletes of other contact sports, football and soccer (H. Ling et al., 2017; A. McKee et al., 2013; B. Omalu et al., 2005), and in non-athletes with repetitive trauma to the brain, such as in epileptics (V. Puvenna et al., 2016).

NEUROPATHOLOGY

A 1973 paper studying the brains of 15 former boxers summarized common findings of the gross pathology. These included reduced brain weight, enlarged lateral and third ventricles, corpus callosum thinning, fenestrations of the cavum septum pellucidum as well as cerebellar tonsils with scarring and neuronal loss (J. Corsellis et al., 1973). McKee et al found many of these gross pathological findings within the sample of 48 cases studied in 2009 (A. McKee et al., 2009).

Microscopic neuropathologic findings are essential for the diagnosis of CTE. Recent consensus meetings have characterized a specific lesion indicative of CTE as well as supportive, non-specific features of CTE. This lesion required to diagnose CTE consists of accumulated hyperphosphorylated tau (p-tau) in neurons and astroglia around

small blood vessels that are specifically at the cortical depths of sulci in irregular patterns. This lesion is specific to the diagnosis of CTE and has only been visualized in individuals with brain trauma, usually from multiple episodes, to date. Supportive neuropathologic features include p-tau immunoreactive features such as pretangles and neurofibrillary tangles (NFTs). (A. McKee, Cairns, et al., 2016; R. Stern et al., 2011)

RISK FACTORS

Risk factors for developing CTE are derived from correlating the post-mortem diagnoses to reports of the individual's clinical behavior during life. Risk factors for CTE include playing certain sports and repetitive head impacts outside of sports, such as those from military experience or domestic violence (L. Goldstein et al., 2012; A. Jones, Britton, Blessing, Parisi, & Cascino, 2018). There are also genes thought to be associated with neurodegenerative disease that may increase an individual's risk of developing later-life problems with head trauma (B. Jordan et al., 1997).

REPETITIVE HEAD IMPACTS

Exposure to repetitive head impacts (RHI) can result in recurrent concussive and subconcussive injuries. A concussion is the result of a head impact that causes symptoms for any amount of time. Subconcussive impacts are those head impacts that do not result in concussive symptoms or any overt signs of dysfunction. These injuries can even result from rapid acceleration or deceleration (D. Smith et al., 2012). Research has recently started focusing on these repetitive subconcussive blows and their harmful long-term effects on the brain. (J. Bailes, Petraglia, Omalu, Nauman, & Talavage, 2013; S. Lakhan

& Kirchgessner, 2012). It is important to note, that there is a subset of individuals who have been pathologically diagnosed with CTE though they did not report a history of concussion. Instead, these individuals were exposed to subconcussive blows (T. Stein, Alvarez, & McKee, 2015).

RHI have been linked to short- and long-term neurologic consequences (M. Dashnaw, Petraglia, & Bailes, 2012). This type of injury associated with RHI has also been linked to cognitive deficits and even decreased olfactory function (M. Alosco, Jarnagin, et al., 2017). RHI seem to be a necessary risk factor for developing CTE (K. Bieniek et al., 2015). However, RHI are not a sufficient history to make a post-mortem diagnosis of CTE and there are many other risk factors that can contribute to the diagnosis (M. Goldfinger et al., 2018; A. McKee et al., 2009).

With recent attention turning towards monitoring sports-related brain injury, accurate measurements of risk exposure are more important than ever. The cumulative head impact index (CHII) was developed as a metric to estimate the head impacts football players are exposed to in the course of play (P. Montenigro et al., 2017). The CHII was derived from the athlete's self-reported exposure as well as an objective measure extrapolated from accelerometer studies (S. Broglio et al., 2009; T. Talavage et al., 2014) and positions played. Montenigro et al. showed a dose-response relationship between the CHII and later-life neurobehavioral impairments (2017).

EXPOSURE TO SPORTS

Boxing was the first sport implicated in this progressive neurodegenerative disease (Miller, 1966). Current research still examines boxers as well as related sports

like wrestling (B. Omalu, Fitzsimmons, Hammers, & Bailes, 2010) and martial arts (L. Lim, Ho, & Ho, 2019). There is a big push towards defining the link between boxing and CTE (P. McCrory, Zazryn, & Cameron, 2007).

The link between CTE and American football has been put in the spotlight, especially considering recent high-profile cases with media attention (K. Belson, 2017; B. Omalu et al., 2005). CTE has been confirmed in football players from the high school level up through the professional level. While the prevalence of CTE is unclear, 87% of a convenience sample including 202 former football players were neuropathologically diagnosed with CTE (J. Mez et al., 2017).

Ice hockey is another sport with pathologically confirmed cases of CTE (Maroon et al., 2015; A. McKee, Daneshvar, Alvarez, & Stein, 2014). Soccer has also been demonstrated as a risk factor of CTE with confirmed cases (L. Grinberg et al., 2016; H. Ling et al., 2017), though soccer does involve different mechanisms of brain injury than American football or ice hockey (R. Naunheim, Standeven, Richter, & Lewis, 2000). Finally, CTE has been implicated in rugby players (Stewart, McNamara, Lawlor, Hutchinson, & Farrell, 2016).

The age at which an individual's exposure to head impacts begins is also a risk factor for developing later-life problems (M. Alosco et al., 2018; V. Schultz et al., 2018; J. Stamm, Bourlas, et al., 2015; J. Stamm, Koerte, et al., 2015). A recent study found that American football players who started playing before the age of 12 had more than double the risk of clinical impairments in behavior regulation, apathy and executive function. In addition, these individuals exhibited higher levels of depressive symptoms than

participants who began playing football later than 12 years of age (M. Alosco et al., 2017).

MILITARY EXPERIENCE

Another important risk factor of developing CTE lies with military experience. Cases of military veterans with blast exposure as well as those with a history of concussive injuries have demonstrated CTE neuropathology (L. Goldstein et al., 2012; B. Omalu et al., 2011). Most military-related injury comes from blast exposure and has been associated with long-term neurologic consequences (I. Cernak et al., 2011; A. McKee & Robinson, 2014; T. Stein, Alvarez, & McKee, 2014).

CLINICAL PRESENTATION

Knowing CTE can only be diagnosed post-mortem, clinically confirmed cases of CTE have been associated with retrospective analyses of clinical presentation during life to create a picture of how CTE may present. From these studies, it has been shown that the clinical presentation associated with CTE typically displays in four domains: cognitive, behavior, mood and motor (P. Montenigro, Bernick, & Cantu, 2015). Some of the major symptoms are summarized in Table 1, though this is not an exhaustive list.

Table 1: Clinical symptomatology of CTE (adapted from Montenigro et al. 2015 and Stern et al. 2013)

Cognitive	Mood	Behavior	Motor
Impaired memory	Apathy	Impulsivity	Parkinsonism
Executive dysfunction	Depression	Disinhibition of speech/behavior	Gait
Attention difficulties	Anxiety	Paranoia	Tremor
Language difficulties	Suicidality	Verbal/physical violence	Rigidity

Frequently reported symptoms in participants with RHI include apathy, depression, behavioral dysregulation and executive dysfunction, as well as cognitive impairment (P. Montenigro et al., 2017). A recent study revealed mood and behavior symptoms in both mild and severe cases of CTE pathology (J. Mez et al., 2017). Of those symptoms, impulsivity and depressive symptoms were among the most common in all groups.

SUBTYPES OF CTE

Researchers identified two clinical subtypes of CTE with onset in different stages of life (R. Stern et al., 2013). The subtype showing initial mood and behavior symptoms

tended to have an earlier onset of symptomatology. A later onset group exhibited cognitive symptoms initially. An additional mixed subtype was later found in which participants exhibited a combination of mood, behavior and cognitive symptoms (P. Montenigro et al., 2015).

TRAUMATIC ENCEPHALOPATHY SYNDROME

A relatively new set of provisional clinical research diagnostic criteria have been termed, "traumatic encephalopathy syndrome" (TES) after a literature review of 202 pathologically confirmed CTE cases (P. Montenigro et al., 2014). TES is a term to describe the clinical features that may be due to the underlying neuropathology of CTE. The proposed diagnostic criteria include general criteria, core clinical features and supportive features. Four subtypes are specified with a behavioral/mood variant, cognitive variant, mixed variant and TES dementia.

The five general criteria include RHI with concussive and subconcussive impacts from sources including contacts sports, military experience and domestic abuse among others. It is noted that other neurological disorders may be comorbid but may not account for all clinical features. Another general criterion is that clinical features must be present for at least 12 months. At least one of the core clinical features must be present and be a marked change from baseline functioning for the individual. Two additional supportive features must also be present.

The three core criteria consist of cognitive difficulties, mood symptoms and behavior symptoms. The cognitive difficulties must be substantiated by impairment on

standardized tests in domains such as memory and executive functioning. Behavioral symptoms are characterized by explosivity and physical or verbal violence, while mood behaviors are described as depressive or related symptoms. The supportive features of TES include impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs and a documented decline in function. Additionally, it is specified that a delayed onset in symptoms after head impact exposure may be anticipated.

AGE OF ONSET

It has been estimated that symptoms relating to CTE will begin about 15 years after ending head impact exposure though it can vary from 19 years of age to over 65 (A. McKee, Alosco, & Huber, 2016). Of the two subtypes previously discussed, the younger onset group with mood and behavior symptoms averaged 35 years old, while the cognitive symptom onset group was closer to 60 years old (R. Stern et al., 2013).

COGNITIVE RESERVE

Although the onset of CTE is variable, cognitive reserve (CR) may have an impact. CR is the theory that individuals with similar neuropathology can experience different levels of impairment (Y. Stern, 2009). The variance between the individuals is specific life experiences contributing to reserve creating a difference in the way the brain is able to fight against pathology or use compensatory strategies (Y. Stern, 2002). CR describes how the brain is able to actively adapt to changes and alters brain processes in a dynamic way (J. Steffener, Brickman, Rakitin, Gazes, & Stern, 2009; E. Zarahn, Rakitin, Abela, Flynn, & Stern, 2007). There is no convenient way to measure CR holistically, so

most often it is measured using one or multiple proxies. These proxies include estimated IQ, level of educational attainment and occupational level (Y. Stern, 2002).

The concept of CR can be applied to any brain disruption including Alzheimer's disease (AD), neuropsychiatric disorders and traumatic brain injury, and has been shown to delay the onset of impairment with higher reserve (Anaya et al., 2016; S. Kesler, Adams, Blasey, & Bigler, 2003; Y. Stern, 2013). It has been suggested that CR, measured by years of education, facilitated recovery from TBI (E. Schneider et al., 2014). Recent attention has also implicated CR as a modifier of symptom profiles in individuals with confirmed CTE with higher occupational attainment predicting a later onset of cognitive, behavioral and mood impairment (M. Alosco, Mez, et al., 2017).

BIOLOGICAL DIAGNOSIS

Further risk factors of CTE lie in genetics and biomarkers that are currently being put into a new light with neurodegenerative research. Apolipoprotein E allele 4 (ApoE-ε4) abnormalities have been detected in AD patients and ApoE-ε4 gene dose has been defined as a common risk factor for late onset AD (E. Corder et al., 1993). CTE can present similarly to patients with AD in macroscopic and microscopic appearance. Both involve tauopathies as well as amyloid deposition. Apolipoprotein E allele 4 (ApoE-ε4) abnormalities is also a commonality between the two diseases (J. Ramos-Cejudo et al., 2018). Showing many other commonalities with AD, CTE researchers began investigating ApoE-ε4 expression in patients. They found an increased severity of deficits acquired from traumatic brain injury (TBI) in patients with ApoE-ε4 (B. Jordan

et al., 1997). From here, the genetic and biomarker research surrounding CTE has taken off.

Recent work by Cherry et al. discovered a protein, CCL11, that is elevated in CTE patients compared to those subjects with AD (2017). CCL11 will act as both a biomarker for CTE and a way to rule out AD as a diagnosis. (J. Cherry et al., 2017)

A potential biomarker measuring exosomal tau content in plasma has been suggested in a modern study (R. Stern et al., 2016). Levels of exosomal tau in plasma of patients with a history of playing football were significantly higher than levels in a control group of non-contact athletes. The high levels of tau also correlated with lower levels of cognitive functioning. These results could be combined with patient history of TBI and clinical symptoms to preliminarily diagnose CTE non-invasively in living patients.

SPECIFIC AIMS

In 2017, 75% of the population participated in physical activities across the United States and its territories ("BRFSS Prevalence & Trends Data: Explore by Topic | DPH | CDC," n.d.). With this heightened activity and exposure to head impacts, more research needs to be done on CTE and how this progressive neurodegenerative disease will affect individuals during life. Since there is a lack of ability to diagnose CTE, there is also lack of therapy and treatment. Current research is focused on developing a clinically diagnosable syndrome that is related to CTE prognosis. With development of *in vivo* diagnosis methods, there can be further strides to recognize CTE in living patients followed by an increase in therapeutic measures.

The goal of the present study was to define the clinical presentation of former athletes with various exposure to RHI. The main focus was on the mood and behavior profiles demonstrated by research-based outcome measures. It was hypothesized that the symptom profiles would cluster into four groups: asymptomatic, mood symptoms, behavior symptoms, and highly symptomatic with mood and behavior symptoms. Additionally, it was thought that the highly symptomatic group would largely be made up of football players. Another hypothesis of the present study, regarding age, was that the more symptomatic persons would be significantly older, while the younger individuals would show fewer symptoms. Furthermore, it was hypothesized that there would be a cognitive reserve protective effect in that participants with more years of education would exhibit fewer symptoms. A secondary hypothesis within this study was that within the

group of football players, there would be a significant effect of RHI as shown by CHII in that a higher CHII would indicate more symptomatic participants.

METHODS

PARTICIPANTS

The current study is based on data collected from an ongoing study of former and active athletes at the Boston University Alzheimer's Disease and Chronic Traumatic Encephalopathy Centers, the Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND). Previous studies have published on the LEGEND protocol (Alosco et al., 2017; Montenigro et al., 2017; Robbins et al., 2014). Although this thesis conducted thorough analysis of existing data, the description of the overall LEGEND study procedures will be summarized below. LEGEND is an ongoing longitudinal study with the purpose of recording risk factors related to RHI in former and active contact and non-contact sport athletes. The study examines short and long-term consequences that may be associated with participation in sports.

Participants complete online questionnaires and speak with a member of the study staff once a year over the phone to discuss concussions, athletic history, medical history and cognitive functioning. The online survey includes self-reported measures of mood, behavior and executive functioning. The structured telephone interview includes an objective cognitive measure, the Brief Test of Adult Cognition by Telephone (BTACT). There are also questionnaires to gather demographic information, full athletic and military history as well as substance use and medical history. The surveys are updated yearly. All study procedures were approved by the Boston University Medical Campus Institutional Review Board and participants provided informed written consent.

LEGEND participants were initially acquired through online postings, physical postings and word-of-mouth. The criteria include a history of participation in organized sports and ≥ 18 years of age. The broad parameters insure a large enough sample for data analysis.

The sample used for analysis was taken from a larger sample of subjects from the LEGEND study. The study used data from each participant's most recent visit in order to gather a more accurate, current clinical picture of the participants' symptom profiles. We included participants 18 years of age or older, with no military experience or diagnoses of epilepsy who had a history of playing organized sports at any level. Participants with military experience were excluded due to the difference in mechanisms and neuropathologic progression of brain injury compared to sports related injuries (L. Goldstein et al., 2012). Participants with seizure disorders were excluded from the present sample for similar reasoning (A. Jones et al., 2018). This left 859 unique subjects in the sample.

Additionally, all subjects who reported they had a concussion within the year of their cognitive testing were excluded, as answers would be unreliable given the possibility of persistent cognitive symptoms up to one year after injury (P. McMahon et al., 2014). Participants who were active in their primary sport in the past two years were excluded from analyses due to the possibility of continuous exposure to head trauma. From this set, only participants that completed all four outcome measures were included in the analysis. Of the 859 unique subjects in the sample, 592 met the criteria and were included in the final analyses, see figure 1 for a depiction of the sample selection.

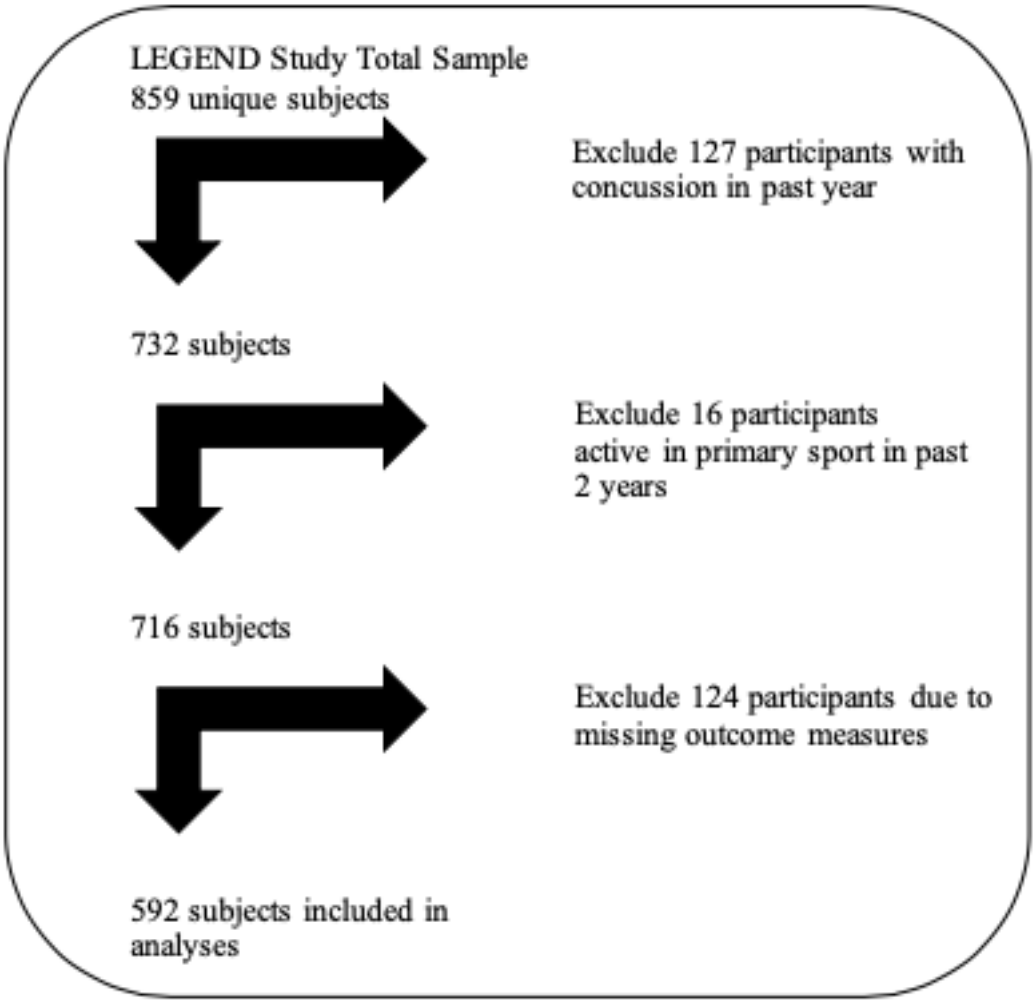

Figure 1: Flowchart of sample selection based on inclusion criteria

MEASURES

The focus of the measures administered in LEGEND is to evaluate domains that may be affected by RHI exposure (M. Alosco et al., 2017; Byrd, Dixon, & Lucke-Wold, 2018; A. McKee et al., 2013; J. Mez et al., 2017). These include the BTACT, Behavior Regulation Inventory of Executive Function-Adult Version (BRIEF-A), the Apathy

Evaluation Scale (AES), the Barratt Impulsiveness Scale-11 (BIS-11), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Functional Activities Questionnaire (FAQ). Domains tested include cognition (measured by the BTACT), executive functioning (measured by the BRIEF-A), apathy (measured by the AES), impulsivity (measured by the BIS-11), depression (as measured by the CES-D) and functional independence (measured by the FAQ). The present study included scores from the Behavior Regulation Index (BRI) collected from the BRIEF-A as well as the AES, BIS-11 and CES-D in the analyses. As this study is focused on creating a clinical picture of the mood and behavior profile of athletes, the FAQ and BTACT measures were not included in analyses. The specific tests chosen for the current study will be described in more detail below.

LEGEND Study Measures Included in Current Analyses	
Mood	Behavior
Apathy Evaluation Scale (AES)	Barratt Impulsiveness Scale-11 (BIS-11)
Center for Epidemiologic Studies Depression Scale (CES-D)	Behavior Regulation Index (BRI)

Figure 2: Categorizing LEGEND study measures

BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION-ADULT VERSION

An online version of the BRIEF-A was used to evaluate participants' executive functioning on a validated, 75-item self-report instrument (R. Roth, Isquith, & Gioia, 2005). The participants use a three-point Likert scale to rate the frequency that executive-

function behaviors are a problem. On the scale, a higher score indicates more dysfunction. Two index scores can be derived from the BRIEF-A, the Metacognition Index (MI) and the Behavior Regulation Index (BRI). As our study is focused on the mood and behavior symptom profile as opposed to the cognitive profile of our participants, we used the BRI subscale score only. A BRI T-score was derived from the raw scores using normative data. For this measure, a higher T-score indicates worse dysfunction. The BRIEF-A has been used in literature to evaluate mental health in retired contact sport athletes and this is why we chose to include this as a main measure (B. Willer et al., 2018). This measure has already been shown to be sensitive to changes in exposure to head impacts (M. Alosco et al., 2017; D. Seichepine et al., 2013).

APATHY EVALUATION SCALE

The AES is a self-report measure of apathy through domains of behavior, cognition and emotional symptoms (R. Marin, Biedrzycki, & Firinciogullari, 1991). Participants are asked to rate symptoms experienced in the past month on a four-point Likert scale. We used a total score in analyses with higher scores representing greater apathetic symptoms and scores at or above 34 are clinically meaningful (Kant, Duffy, & Pivovarnik, 1998). The AES has been shown to detect changes regarding head impacts (M. Glenn et al., 2002; B. Guercio et al., 2015; P. Montenigro et al., 2017)

BARRATT IMPULSIVENESS SCALE-VERSION 11

The BIS-11 is a 30-item scale that is self-rated using a four-point Likert scale and is used to measure impulsivity (J. Patton, Stanford, & Barratt, 1995; S. Reise, Moore,

Sabb, Brown, & London, 2013). Participants are asked to answer questions about how they think and act without spending too much time on any question. There is no time frame in which to judge the presence of behaviors, so this provides a current sample of the participant's behavior. Higher scores on the BIS-11 indicate a participant is more impulsive with a cutoff score at or above 72 indicating high impulsivity (M. Stanford et al., 2009). This scale is reliable in its evaluation of assessing impulsivity across a diverse set of cultures and samples (A. Vasconcelos, Malloy-Diniz, & Correa, 2012). This measure has previously been sensitive to changes with exposure to head impacts (S. Banks et al., 2014; V. Schultz et al., 2018).

CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE

The CES-D was completed online as a 20-item checklist measuring self-reported depressive symptoms. This measure uses a Likert four-point scale to have participants reflect on their depressive symptoms in the past week. A total score was used in analysis with higher scores reflecting worse depressive symptoms. Clinical depression is suggested at and above a score of 16 (Lewinsohn, Seeley, Roberts, & Allen, 1997). We decided to use this measure as it is validated in measuring depressive symptoms as a self-report measure (R. Gomez & McLaren, 2015). The CES-D was also chosen given its sensitivity with exposure to head impacts (Alosco et al., 2017; Montenigro et al., 2017).

DATA ANALYSIS PLAN

All analyses were performed using SPSS version 25 (*IBM SPSS Statistics for Windows*, 2017). Descriptive statistics were compiled for all demographic variables, such

as age, sex, and race. Frequencies for all outcome measures were collected and compared using histograms against a normal curve. The outcome measures were standardized using z-scores. In all cases, a z-score greater than zero indicates more dysfunction.

Cluster analyses of the outcome measures were used to identify homogenous subgroups within the larger sample. K-means iterative partitioning technique was used to cluster solutions. Cluster analyses specifying 3, 4 and 5 groups were executed, given the literature on the clinical presentation of CTE suggesting the possibility of these separate groups (P. Montenigro et al., 2015; R. Stern et al., 2013).

Descriptive features of the groups within the clusters were explored for similarities and differences. ANOVA tests were used to analyze quantitative variables. Homogeneity of variance tests were used to evaluate normality, and post-hoc analyses were done using Student-Newman-Keuls (S-N-K) tests. Chi-square tests were used to evaluate the categorical variables. Significance was set at $p < 0.05$.

RESULTS

DESCRIPTION OF THE SAMPLE

Of the 592 participants in the current sample, most were white males who identified as not Hispanic or Latino. The mean age of the sample was 46.2 years old (SD=13.16, range = 19-86).

Table 2: Description of the sample

Characteristic	Total Sample (N=592)
Sex (% male)	83.60%
Age at evaluation, mean (years)	46.22 (SD=13.16;range =19-86)
Race (% white)	92.90%
Ethnicity (% not Hispanic/Latino)	97.50%

Regarding athletic history, over half the male sample identified football as their primary or secondary sport. This left just 29.6% of males in the study without football experience. Soccer and hockey were the next most popular sports.

Table 3: Athletic experience of the sample

Sport	Percent of Total Sample (N=592)
Football	59.30%
Soccer	16.20%
Hockey	13.30%
Other	11.20%

Table 4: Football experience of the sample

Cluster Membership	Football (%)	Between Group Significance
Asymptomatic	64.7	p = 0.818
Mildly symptomatic	66.2	
Mood symptoms	69.2	
Behavior symptoms	64.3	
Highly symptomatic	72.1	

MOOD AND BEHAVIOR PROFILE OF SAMPLE

During analyses, various cluster solutions were examined. The solution with five clusters was the most clinically meaningful as it showed a clear difference between mood and behavior symptoms. Based on the profile of clusters, the following descriptive labels were given, see figure 3 for a full depiction.

Cluster one consists of the *Asymptomatic* (N=160) group. The individuals in this group had very low z-scores on all outcome-measures, indicating almost no dysfunction. These participants are not currently having trouble with symptoms related to mood or behavior based on the self-reported outcome measures.

The second cluster is made up of the *Mildly symptomatic* (N=180) group of individuals. These participants showed some dysfunction compared to the asymptomatic group; they may be experiencing mild symptoms but still remain within normal limits.

The *Mood symptoms* (N=99) group of individuals are found in cluster 3. These individuals showed higher z-scores on the CES-D and AES compared to their scores on the BRI and BIS-11.

Cluster 4 shows the *Behavior symptoms* (N=84) group with individuals showing a higher level of dysfunction, as measured by z-scores, on the BRI and BIS-11 compared to the CES-D and AES.

The last cluster revealed a *Highly symptomatic* (N=69) group showing a mixed profile. Participants in this cluster exhibited very high levels of dysfunction on all outcome measures.

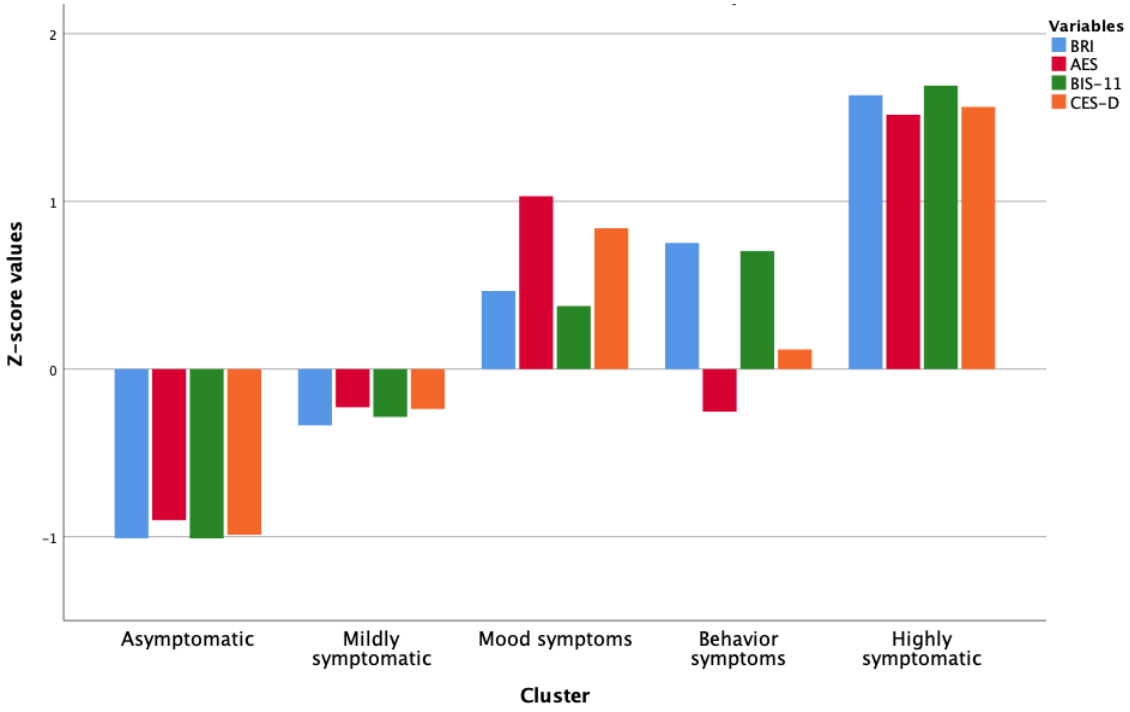

Figure 3: Cluster membership based on outcome measures; *Behavior Regulation Index (BRI), Apathy Evaluation Scale (AES), the Barratt Impulsiveness Scale-11 (BIS-11), the Center for Epidemiologic Studies Depression Scale (CES-D)*

ASSESSMENT OF DIFFERENCES

There were no significant differences suggesting football to make up the majority of any clusters. This was analyzed using a Chi square (df=4, p=0.818).

Table 5: Percent of cluster made up by football players

Cluster Membership	Football (%)	Between Group Significance
Asymptomatic	64.7	p = 0.818
Mildly symptomatic	66.2	
Mood symptoms	69.2	
Behavior symptoms	64.3	
Highly symptomatic	72.1	

Average age was not significantly different across the clusters. A one-way ANOVA was used in the analysis (df=4, p=0.181).

Table 6: Mean age of participants in each cluster

Cluster Membership	Age, mean (SD)	Between Group Significance
Asymptomatic	46.02 (13.70)	p = 0.181
Mildly symptomatic	44.46 (13.44)	
Mood symptoms	47.89 (12.73)	
Behavior symptoms	47.76 (13.95)	
Highly symptomatic	46.99 (10.20)	

There was a significant difference in the mean years of education between the clusters as measured by a one-way ANOVA (df=4, $p < 0.001$). Post-hoc S-N-K tests revealed significant differences between the groups and are included below (Figure 5). The S-N-K tests presented the significant difference between the Asymptomatic group, with the most years of education, and the Highly symptomatic group, with the least years of education. It was also revealed that the Mildly symptomatic, Mood symptom and Behavior symptom groups were not significantly different from each other; however, they were significantly different from the Highly symptomatic and Asymptomatic groups.

Table 7: Mean years of school reported by participants

Cluster Membership	Years of School, mean (SD)	Between Group Significance
Asymptomatic	17.76 (2.43)	$p < 0.001$
Mildly symptomatic	17.18 (2.23)	
Mood symptoms	16.80 (2.46)	
Behavior symptoms	16.48 (2.49)	
Highly symptomatic	15.62 (2.56)	

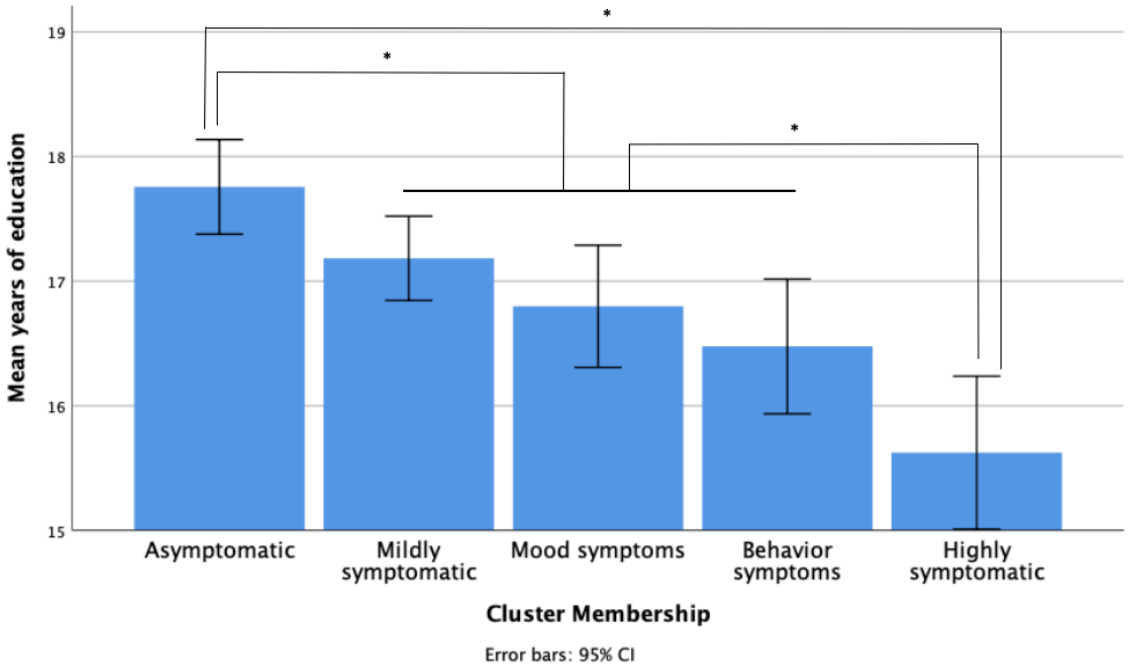

Figure 4: Mean years of education within clusters

Student-Newman-Keuls[a,b]

5-kmeans Cluster Number of Case	N	Subset for alpha = 0.05		
		1	2	3
Highly symptomatic	69	15.62		
Behavior symptoms	84		16.48	
Mood symptoms	99		16.80	
Mildly symptomatic	180		17.18	17.18
Asymptomatic	160			17.76
Sig.		1.000	.090	.089

Figure 5: Post-hoc S-N-K tests of mean years of education

Regarding the CHII, there were no significant differences between the groups, as measured by a one-way ANOVA (df=4, p=0.905). This measure was based on number of seasons played and only included football players.

Table 8: Mean CHII based on seasons of play of football players

Cluster Membership	CHII, mean	Between Group Significance
Asymptomatic	6596	p = 0.905
Mildly symptomatic	7202	
Mood symptoms	6880	
Behavior symptoms	6486	
Highly symptomatic	6654	

DISCUSSION

The goal of this study was to define the clinical presentation of former athletes. Four outcome measures were used to categorize the symptoms of the individuals. It was found that in a group of 592 participants, there were five groups in which the participants clustered with discrete symptom profiles. There were no significant differences in age, sport prevalence or CHII between the clusters. The results of the study revealed a significant difference in the mean years of school between the five clusters. These findings depict a clear grouping of clinical symptoms in former athletes. The results indicate various groups with specific symptom profiles with mood and behavior symptoms falling into separate categories.

CLUSTER RESULTS

Cluster analyses revealed five discrete groups in the sample of 592 former athletes: Asymptomatic, Mildly symptomatic, Mood symptoms, Behavior symptoms and Highly symptomatic. These results are consistent with literature showing separate subtypes of individuals having a history of head impact exposure (P. Montenigro et al., 2014; R. Stern et al., 2013). Groups of highly symptomatic and asymptomatic participants were anticipated due to the variety of the sample in experience, risk factor exposure and age. With the widespread sport experience of the sample, both contact and non-contact, it was expected to find this broad range of symptom severity.

It was originally hypothesized there would be four clusters with asymptomatic, mood symptoms, behavior symptoms and highly symptomatic groups; however, our

analyses revealed an additional fifth group that was Mildly symptomatic. This finding could be attributed to analyzing participants at different time periods after finishing their athletic careers. In connection with CTE, there may be a latency period between when an individual ends exposure to head impacts and when they begin to develop symptoms (P. Montenigro et al., 2014). This Mildly symptomatic group suggests a progression of symptoms after sport experience and exposure to head impacts. The progression of symptoms would be consistent with the progressive nature of CTE (A. McKee et al., 2009).

In regard to the mood and behavior symptoms seen in this sample, there is conjecture that the symptoms are related to underlying pathology. The neuropathologic distribution of tau deposition associated with CTE may follow the Papez circuit with serious implications to emotion (A. McKee et al., 2009; J. Papez, 1995). The early abnormalities seen in this region of the brain may account for this mood and behavior symptom profile that we see early in the progression of CTE. It is suggested that dysexecutive symptoms, as seen on the BRI, may stem from the neurofibrillary degeneration in the frontal cortex and white matter in the region (McKee et al., 2009).

Very new research is suggesting clinical implications of neuroinflammatory processes from RHI unrelated to tau pathology (M. Alosco et al., 2019). Specifically, increased neuroinflammatory markers were related to notable mood and behavior symptoms in former NFL players compared to control participants. In addition to non-tau pathology, there are other factors contributing to this mood and behavior symptom profile

that are unknown at this time. These include genetics, predisposition to psychiatric history and idiopathic mental illness.

ASSESSMENT OF DIFFERENCES RESULTS

FOOTBALL WITHIN CLUSTERS

Originally, it was hypothesized that the football players in the sample would mostly be grouped into symptomatic clusters. This was hypothesized due to the high number of RHI these athletes are exposed to in the course of competition resulting in increased brain injury (J. Mez et al., 2017). Results revealed no significant difference in the overall percentage of the group made up by football players compared to other sports. Since the sample was mostly football, it is hard to make clear conclusions.

AGE TRENDS

The present study found that there was no age difference between the Asymptomatic and Highly symptomatic groups. Beginning hypotheses were that a group of older individuals would show higher levels of symptoms. This was due to findings that symptoms may begin to develop in the fifth decade of life (D. Seichepine et al., 2013), and as CTE is a progressive disease, symptoms would be anticipated to worsen over time.

This lack of difference between clusters may potentially be due to the varied nature of our sample and assessing individuals at different time periods after stopping their athletic participation. One study found symptom onset was on average starting 14.5 years after retirement from athletic play (T. Stein et al., 2015). It is consistent, therefore, that onset of symptoms was varied, and symptom severity did not mirror the age of

participants. The finding implies the need to assess athletes of all ages for mood and behavior symptoms, as well as future available tests for brain diseases like CTE.

There is a study suggesting a connection between the time it takes for the spread of neuropathology and the delayed symptom onset (J. Kriegel, Papadopoulos, & McKee, 2018). These results would be consistent with such a theory in that it is unclear what stage each of our participants is in post-retirement.

YEARS OF EDUCATION

This study uses total years of education as a measure of CR. Results show a significant difference between the five clusters with the least symptomatic participants reporting the most years of education. This is consistent with literature that predicts a protective effect against symptoms with higher reserve (Y. Stern, 2013). Similar neuroprotective effects have been seen in AD, Parkinson's disease as well as aging (Y. Stern, 2002). Evidence also suggests the CR effect in neuropsychiatric disorders like bipolar (Anaya et al., 2016). Moreover, there was a study suggesting CR across dementia types (A. Linds et al., 2015).

Limitations to this study include the use of educational attainment as a proxy of CR. Specifically, educational attainment does not factor in the experience that individuals with the same degree can have due to the differences in educational rigor (J. Manly, Jacobs, Touradji, Small, & Stern, 2002). This sample is mostly highly educated people with college degrees, and a large part of the sample is made up of college football players. In this case, educational attainment may instead be a measure of athleticism.

Also, the significant differences in the years of school attained do not correlate to an increase in degrees achieved, making meaningful clinical conclusions difficult to obtain.

On another note, these measures do not account for genetic predispositions and personal characteristics (S. Cosentino & Stern, 2013; Krapohl & Plomin, 2016; E. Rhodes, Devlin, Steinberg, & Giovannetti, 2017). Additionally, CR measures like years of education do not account for later life experiences that may contribute to how an individual's brain is able to combat injury (A. Borenstein, Copenhaver, & Mortimer, 2006).

Stern also warns that the relationship between years of school and these measures of outcome may be unclear (2002). That is to say, it is not a cause and effect relationship and the years of school may not be causing this perceived protection against symptomatology. There is the concern brought in with socioeconomic factor and this being a confounding variable (Y. Stern, 2002). Though other studies have found this relationship between schooling and CR, it is possible that years of education may be a proxy for measuring other things like environmental risk factors (N. Anderson, Bulatao, Cohen, & National Research Council (US) Panel on Race and Ethnicity, 2004; J. Mortimer & Graves, 1993; K. Siedlecki et al., 2009).

Some of these limitations could be combatted by using multiple measures of CR, though this would introduce confounding variables. Using things like leisure activities and socioeconomic status in addition to measures like educational attainment may help create a holistic picture (Scarmeas, Levy, Tang, Manly, & Stern, 2001). There is still a need for developing dynamic measures of CR in a convenient manner.

CHII

It was expected that increasing CHII in the football only sample, would match up with increasing symptom severity as previous literature has suggested (P. Montenigro et al., 2017). Results revealed that this was not the case in our current analyses of the sample. Inconsistencies may stem from having a group with an overall higher CHII than may be seen in other samples due to the majority of football players in the sample having many years of playing. There is also a possibility that the present sample is made up mostly of older participants, in their forties, which is when it would be expected to see participants with possible CTE start showing symptoms. Another note to be made is that the study may have used an insensitive measure of CHII, as it was basing this on seasons of football played. For all of these reasons, it may not have been possible to see the trend of increased CHII leading to increased impairment within the data.

IMPLICATIONS FOR FIELD

Current research has been unable to set standards for diagnosing CTE in the living. Often, CTE is instead misdiagnosed during life as AD or dysthymic disorder. The only way to diagnose CTE, at present, is with post-mortem neuropathology studies and a complete history of RHI. Recently, research of CTE has been focused on creating a standard for diagnosing CTE in living patients. Some strides have been made using plasma protein levels and looking at genetic biomarkers. A clinical profile specific to individuals exposed to RHI would help provide standards for diagnosis during life. This study revealed that participants in a large sample of athletes fell into very discrete groups

with specific symptom profiles. Using these symptom profiles along with a full history and potential scans and or biomarkers could bring a lifetime diagnosis to fruition.

Additionally, the more that is discovered about CTE, the more it is seen how this disease may be preventable. Helmets and mouthguards are a step towards preventing serious injury, though they are not enough to reduce concussions and head impacts in sports (D. Daneshvar et al., 2011). An estimated 50% of sports-related concussions may go unreported. Athletes may be unaware of the severity associated with brain injuries and are instead motivated by their fear of being withheld from competition (M. McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). This is likely attributed to a gap in research and educational resources surrounding head impacts and long-term consequences. Since 2009, all 50 states have passed legislature addressing TBI ("Traumatic Brain Injury Legislation," n.d.). In 2017 alone, 24 states enacted legislation to prevent TBI, including in youth athletes ("Injury Prevention Legislation Database | Opioid Abuse Prevention," n.d.). Though this is not exhaustive, there are many more pieces of legislature that advocates are currently working to pass into action.

LIMITATIONS

While this study is a strong step towards further discerning a symptom profile of CTE, it does have limitations. Since LEGEND is a longitudinal study of living participants, we do not have pathology to correlate with the data. This means there is not currently a way to correlate these profiles to a diagnosis of CTE. The present study was also limited in that LEGEND does have sampling bias. It is mostly self-selected and

largely made up of football players. This may be due to a recruitment bias especially provoked by media attention on the relation between football and CTE. Additionally, all measures reported on in this study were self-report and there were no cognitive measures used in the analyses. There is no way to create an unbiased clinical picture with just the current measures.

FUTURE DIRECTIONS

In future studies, it would be ideal to have the participants complete objective measures of mood, behavior and cognition, as well as donate their brains to be correlated with the data once they pass. Having objective neuropsychological testing will create a true clinical profile that we can associate with neuropathology. This combination will lead to diagnosing CTE during life and potential implementation of therapeutic measures.

Another venture would be to collect the CHII for all sports, instead of just football. There is a need to learn about the exposure of RHI in regard to all sports. With this knowledge it may be possible to decrease the number of head impacts in the future, thus decreasing the risk of developing CTE.

CONCLUSION

Long-term effects of RHI have been clearly linked to CTE and current efforts are directed towards diagnosing this disease during life. In this study, a symptom profile was conceived for former athletes. Per these results and previous literature, we anticipate individuals with head trauma exposure to develop mood and behavior symptoms. Further research surrounding the connection between symptomatology and neuropathological diagnosis is needed.

REFERENCES

Alosco, M., Jarnagin, J., Tripodis, Y., Platt, M., Martin, B., Chaisson, C., … Stern, R. (2017). Olfactory Function and Associated Clinical Correlates in Former National Football League Players. *Journal of Neurotrauma*, *34*(4), 772–780. https://doi.org/10.1089/neu.2016.4536

Alosco, M., Kasimis, A., Stamm, J., Chua, A., Baugh, C., Daneshvar, D., … Stern, R. (2017). Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes. *Translational Psychiatry*, *7*(9), e1236. https://doi.org/10.1038/tp.2017.197

Alosco, M., Mez, J., Kowall, N., Stein, T., Goldstein, L., Cantu, R., … McKee, A. (2017). Cognitive Reserve as a Modifier of Clinical Expression in Chronic Traumatic Encephalopathy: A Preliminary Examination. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(1), 6–12. https://doi.org/10.1176/appi.neuropsych.16030043

Alosco, M., Mez, J., Tripodis, Y., Kiernan, P., Abdolmohammadi, B., Murphy, L., … McKee, A. (2018). Age of first exposure to tackle football and chronic traumatic encephalopathy. *Annals of Neurology*, *83*(5), 886–901. https://doi.org/10.1002/ana.25245

Alosco, M., Tripodis, Y., Rowland, B., Chua, A., Liao, H., Martin, B., … Lin, A. (2019). A magnetic resonance spectroscopy investigation in symptomatic former NFL players. *Brain Imaging and Behavior*. https://doi.org/10.1007/s11682-019-00060-4

Anaya, C., Torrent, C., Caballero, F., Vieta, E., Bonnin, C., Ayuso-Mateos, J., & CIBERSAM Functional Remediation Group. (2016). Cognitive reserve in bipolar disorder: relation to cognition, psychosocial functioning and quality of life. *Acta Psychiatrica Scandinavica*, *133*(5), 386–398. https://doi.org/10.1111/acps.12535

Anderson, N., Bulatao, R., Cohen, B., & National Research Council (US) Panel on Race and Ethnicity. (2004). *Ethnic Differences in Dementia and Alzheimer's Disease*. National Academies Press (US). Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK25535/

Bailes, J., Petraglia, A., Omalu, B., Nauman, E., & Talavage, T. (2013). Role of subconcussion in repetitive mild traumatic brain injury. *Journal of Neurosurgery*, *119*(5), 1235–1245. https://doi.org/10.3171/2013.7.JNS121822

Banks, S., Mayer, B., Obuchowski, N., Shin, W., Lowe, M., Phillips, M., … Bernick, C. (2014). Impulsiveness in professional fighters. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *26*(1), 44–50. https://doi.org/10.1176/appi.neuropsych.12070185

Belson, K. (2017, December 22). Aaron Hernandez Had Severe C.T.E. When He Died at Age 27. *The New York Times*. Retrieved from https://www.nytimes.com/2017/09/21/sports/aaron-hernandez-cte-brain.html

Bieniek, K., Ross, O., Cormier, K., Walton, R., Soto-Ortolaza, A., Johnston, A., … Dickson, D. (2015). Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathologica*, *130*(6), 877–889. https://doi.org/10.1007/s00401-015-1502-4

Borenstein, A., Copenhaver, C., & Mortimer, J. (2006). Early-life risk factors for Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *20*(1), 63–72. https://doi.org/10.1097/01.wad.0000201854.62116.d7

Broglio, S., Sosnoff, J., Shin, S., He, X., Alcaraz, C., & Zimmerman, J. (2009). Head Impacts During High School Football: A Biomechanical Assessment. *Journal of Athletic Training*, *44*(4), 342–349.

Byrd, M., Dixon, C., & Lucke-Wold, B. (2018). Examining the Correlation between Acute Behavioral Manifestations of Concussion and the Underlying Pathophysiology of Chronic Traumatic Encephalopathy: A Pilot Study. *Journal of Neurology and Psychology*, *6*(1), 01–04. https://doi.org/10.13188/2332-3469.1000037

Cernak, I., Merkle, A., Koliatsos, V., Bilik, J., Luong, Q., Mahota, T., … Ahmed, F. (2011). The pathobiology of blast injuries and blast-induced neurotrauma as identified using a new experimental model of injury in mice. *Neurobiology of Disease*, *41*(2), 538–551. https://doi.org/10.1016/j.nbd.2010.10.025

Cherry, J., Stein, T., Tripodis, Y., Alvarez, V., Huber, B., Au, R., … McKee, A. (2017). CCL11 is increased in the CNS in chronic traumatic encephalopathy but not in Alzheimer's disease. *PLoS ONE*, *12*(9). https://doi.org/10.1371/journal.pone.0185541

Corder, E., Saunders, A., Strittmatter, W., Schmechel, D., Gaskell, P., Small, G., … Pericak-Vance, M. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, *261*(5123), 921–923. https://doi.org/10.1126/science.8346443

Corsellis, J., Bruton, C., & Freeman-Browne, D. (1973). The aftermath of boxing. *Psychological Medicine*, *3*(3), 270–303.

Cosentino, S., & Stern, Y. (2013). Consideration of Cognitive Reserve. In *Handbook on the Neuropsychology of Aging and Dementia* (pp. 11–23). https://doi.org/10.1007/978-1-4614-3106-0_2

Daneshvar, D., Baugh, C., Nowinski, C., McKee, A., Stern, R., & Cantu, R. (2011). Helmets and Mouth Guards: The Role of Personal Equipment in Preventing Sport-

Related Concussions. *Clinics in Sports Medicine*, *30*(1), 145–163. https://doi.org/10.1016/j.csm.2010.09.006

Dashnaw, M., Petraglia, A., & Bailes, J. (2012). An overview of the basic science of concussion and subconcussion: where we are and where we are going. *Neurosurgical Focus*, *33*(6), E5. https://doi.org/10.3171/2012.10.FOCUS12284

Gavett, B., Stern, R., & McKee, A. (2011). Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma. *Clinics in Sports Medicine*, *30*(1), 179–188. https://doi.org/10.1016/j.csm.2010.09.007

Glenn, M., Burke, D., O'Neil-Pirozzi, T., Goldstein, R., Jacob, L., & Kettell, J. (2002). Cutoff score on the apathy evaluation scale in subjects with traumatic brain injury. *Brain Injury*, *16*(6), 509–516. https://doi.org/10.1080/02699050110119132

Goldfinger, M., Ling, H., Tilley, B., Liu, A., Davey, K., Holton, J., … Gentleman, S. (2018). The aftermath of boxing revisited: identifying chronic traumatic encephalopathy pathology in the original Corsellis boxer series. *Acta Neuropathologica*, *136*(6), 973–974. https://doi.org/10.1007/s00401-018-1926-8

Goldstein, L., Fisher, A., Tagge, C., Zhang, X., Velisek, L., Sullivan, J., … McKee, A. (2012). Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model. *Science Translational Medicine*, *4*(134), 134ra60-134ra60. https://doi.org/10.1126/scitranslmed.3003716

Gomez, R., & McLaren, S. (2015). The Center for Epidemiologic Studies Depression Scale: Support for a Bifactor Model With a Dominant General Factor and a Specific Factor for Positive Affect. *Assessment*, *22*(3), 351–360. https://doi.org/10.1177/1073191114545357

Grinberg, L., Anghinah, R., Nascimento, C., Amaro, E., Leite, R., Martin, M., … Nitrini, R. (2016). Chronic Traumatic Encephalopathy Presenting as Alzheimer's Disease in a Retired Soccer Player. *Journal of Alzheimer's Disease: JAD*, *54*(1), 169–174. https://doi.org/10.3233/JAD-160312

Guercio, B., Donovan, N., Munro, C., Aghjayan, S., Wigman, S., Locascio, J., … Marshall, G. (2015). The Apathy Evaluation Scale: A Comparison of Subject, Informant, and Clinician Report in Cognitively Normal Elderly and Mild Cognitive Impairment. *Journal of Alzheimer's Disease : JAD*, *47*(2), 421–432. https://doi.org/10.3233/JAD-150146

Hazrati, L., Tartaglia, M., Diamandis, P., Davis, K., Green, R., Wennberg, R., … Tator, C. (2013). Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. *Frontiers in Human Neuroscience*, *7*, 222. https://doi.org/10.3389/fnhum.2013.00222

IBM SPSS Statistics for Windows. (2017). (Version 25.0) [Windows]. Armonk, NY: IBM Corp.

Injury Prevention Legislation Database | Opioid Abuse Prevention. (n.d.). Retrieved February 10, 2019, from http://www.ncsl.org/research/health/injury-prevention-legislation-database.aspx#2017

Jones, A., Britton, J., Blessing, M., Parisi, J., & Cascino, G. (2018). Chronic traumatic encephalopathy in an epilepsy surgery cohort: Clinical and pathologic findings. *Neurology*, *90*(6), e474–e478. https://doi.org/10.1212/WNL.0000000000004927

Jordan, B., Relkin, N., Ravdin, L., Jacobs, A., Bennett, A., & Gandy, S. (1997). Apolipoprotein E epsilon 4 associated with chronic traumatic brain injury in boxing. *Jama-Journal of the American Medical Association*, *278*(2), 136–140. https://doi.org/10.1001/jama.278.2.136

Kant, R., Duffy, J., & Pivovarnik, A. (1998). Prevalence of apathy following head injury. *Brain Injury*, *12*(1), 87–92. https://doi.org/10.1080/026990598122908

Kesler, S., Adams, H., Blasey, C., & Bigler, E. (2003). Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. *Applied Neuropsychology*, *10*(3), 153–162. https://doi.org/10.1207/S15324826AN1003_04

Krapohl, E., & Plomin, R. (2016). Genetic link between family socioeconomic status and children's educational achievement estimated from genome-wide SNPs. *Molecular Psychiatry*, *21*(3), 437–443. https://doi.org/10.1038/mp.2015.2

Kriegel, J., Papadopoulos, Z., & McKee, A. (2018). Chronic Traumatic Encephalopathy: Is Latency in Symptom Onset Explained by Tau Propagation? *Cold Spring Harbor Perspectives in Medicine*, *8*(2). https://doi.org/10.1101/cshperspect.a024059

Lakhan, S., & Kirchgessner, A. (2012). Chronic traumatic encephalopathy: the dangers of getting "dinged." *SpringerPlus*, *1*, 2. https://doi.org/10.1186/2193-1801-1-2

Lim, L., Ho, R., & Ho, C. (2019). Dangers of Mixed Martial Arts in the Development of Chronic Traumatic Encephalopathy. *International Journal of Environmental Research and Public Health*, *16*(2). https://doi.org/10.3390/ijerph16020254

Linds, A., Kirstein, A., Freedman, M., Verhoeff, N., Wolf, U., & Chow, T. (2015). Trajectories of Behavioural Disturbances Across Dementia Types. *Canadian Journal of Neurological Sciences*, *42*(6), 389–394. https://doi.org/10.1017/cjn.2015.266

Ling, H., Morris, H., Neal, J., Lees, A., Hardy, J., Holton, J., … Williams, D. (2017). Mixed pathologies including chronic traumatic encephalopathy account for dementia in

retired association football (soccer) players. *Acta Neuropathologica*, *133*(3), 337–352. https://doi.org/10.1007/s00401-017-1680-3

Manly, J., Jacobs, D., Touradji, P., Small, S., & Stern, Y. (2002). Reading level attenuates differences in neuropsychological test performance between African American and White elders. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 341–348.

Marin, R., Biedrzycki, R., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Research*, *38*(2), 143–162. https://doi.org/10.1016/0165-1781(91)90040-V

Maroon, J., Winkelman, R., Bost, J., Amos, A., Mathyssek, C., & Miele, V. (2015). Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases. *PLoS ONE*, *10*(2). https://doi.org/10.1371/journal.pone.0117338

Martland, H. (1928). Punch Drunk. *Journal of the American Medical Association*, *91*(15), 1103–1107. https://doi.org/10.1001/jama.1928.02700150029009

McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported concussion in high school football players: implications for prevention. *Clinical Journal of Sport Medicine: Official Journal of the Canadian Academy of Sport Medicine*, *14*(1), 13–17.

McCrory, P., Zazryn, T., & Cameron, P. (2007). The Evidence for Chronic Traumatic Encephalopathy in Boxing. *Sports Medicine*, *37*(6), 467–476. https://doi.org/10.2165/00007256-200737060-00001

McKee, A., Alosco, M., & Huber, B. (2016). Repetitive Head Impacts and Chronic Traumatic Encephalopathy. *Neurosurgery Clinics of North America*, *27*(4), 529–535. https://doi.org/10.1016/j.nec.2016.05.009

McKee, A., Cairns, N., Dickson, D., Folkerth, R., Dirk Keene, C., Litvan, I., … Gordon, W. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica*, *131*, 75–86. https://doi.org/10.1007/s00401-015-1515-z

McKee, A., Cantu, R., Nowinski, C., Hedley-Whyte, E., Gavett, B., Budson, A., … Stern, R. (2009). Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury. *Journal of Neuropathology and Experimental Neurology*, *68*(7), 709–735. https://doi.org/10.1097/NEN.0b013e3181a9d503

McKee, A., Daneshvar, D., Alvarez, V., & Stein, T. (2014). The neuropathology of sport. *Acta Neuropathologica*, *127*(1), 29–51. https://doi.org/10.1007/s00401-013-1230-6

McKee, A., & Robinson, M. (2014). Military-related traumatic brain injury and neurodegeneration. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *10*(3 Suppl), S242-253. https://doi.org/10.1016/j.jalz.2014.04.003

McKee, A., Stein, T., Nowinski, C., Stern, R., Daneshvar, D., Alvarez, V., … Cantu, R. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, *136*(1), 43–64. https://doi.org/10.1093/brain/aws307

McMahon, P., Hricik, A., Yue, J., Puccio, A., Inoue, T., Lingsma, H., … Vassar, M. (2014). Symptomatology and Functional Outcome in Mild Traumatic Brain Injury: Results from the Prospective TRACK-TBI Study. *Journal of Neurotrauma*, *31*(1), 26–33. https://doi.org/10.1089/neu.2013.2984

Mez, J., Daneshvar, D., Kiernan, P., Abdolmohammadi, B., Alvarez, V., Huber, B., … McKee, A. (2017). Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football. *JAMA*, *318*(4), 360–370. https://doi.org/10.1001/jama.2017.8334

Miller, H. (1966). Mental after-effects of head injury. *Proceedings of the Royal Society of Medicine*, *59*(3), 257–261.

Montenigro, P., Alosco, M., Martin, B., Daneshvar, D., Mez, J., Chaisson, C., … Tripodis, Y. (2017). Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. *Journal of Neurotrauma*, *34*(2), 328–340. https://doi.org/10.1089/neu.2016.4413

Montenigro, P., Baugh, C., Daneshvar, D., Mez, J., Budson, A., Au, R., … Stern, R. (2014). Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimer's Research & Therapy*, *6*(5), 68. https://doi.org/10.1186/s13195-014-0068-z

Montenigro, P., Bernick, C., & Cantu, R. (2015). Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy. *Brain Pathology*, *25*(3), 304–317. https://doi.org/10.1111/bpa.12250

Mortimer, J., & Graves, A. (1993). Education and other socioeconomic determinants of dementia and Alzheimer's disease. *Neurology*, *43*(8, Suppl 4), S39–S44.

Naunheim, R., Standeven, J., Richter, C., & Lewis, L. (2000). Comparison of Impact Data in Hockey, Football, and Soccer. *The Journal of Trauma: Injury, Infection, and Critical Care*, *48*(5), 938–941.

Omalu, B., DeKosky, S., Minster, R., Kamboh, M., Hamilton, R., & Wecht, C. (2005). Chronic Traumatic Encephalopathy in a National Football League Player: *Neurosurgery*, *57*(1), 128–134. https://doi.org/10.1227/01.NEU.0000163407.92769.ED

Omalu, B., Fitzsimmons, R., Hammers, J., & Bailes, J. (2010). Chronic traumatic encephalopathy in a professional American wrestler. *Journal of Forensic Nursing*, *6*(3), 130–136. https://doi.org/10.1111/j.1939-3938.2010.01078.x

Omalu, B., Hammers, J., Bailes, J., Hamilton, R., Kamboh, M., Webster, G., & Fitzsimmons, R. (2011). Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurgical Focus*, *31*(5), E3. https://doi.org/10.3171/2011.9.FOCUS11178

Papez, J. (1995). A proposed mechanism of emotion. 1937 [classical article]. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *7*(1), 103–112. https://doi.org/10.1176/jnp.7.1.103

Parker, H. (1934). Traumatic Encephalopathy (`Punch Drunk') of Professional Pugilists*. *Journal of Neurology and Psychopathology*, *15*(57), 20–28.

Patton, J., Stanford, M., & Barratt, E. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–774.

Puvenna, V., Engeler, M., Banjara, M., Brennan, C., Schreiber, P., Dadas, A., … Janigro, D. (2016). Is phosphorylated tau unique to chronic traumatic encephalopathy? Phosphorylated tau in epileptic brain and chronic traumatic encephalopathy. *Brain Research*, *1630*, 225–240. https://doi.org/10.1016/j.brainres.2015.11.007

Radloff, L. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Ramos-Cejudo, J., Wisniewski, T., Marmar, C., Zetterberg, H., Blennow, K., de Leon, M., & Fossati, S. (2018). Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link. *Ebiomedicine*, *28*, 21–30. https://doi.org/10.1016/j.ebiom.2018.01.021

Reise, S., Moore, T., Sabb, F., Brown, A., & London, E. (2013). The Barratt Impulsiveness Scale - 11: Reassessment of its Structure in a Community Sample. *Psychological Assessment*, *25*(2), 631–642. https://doi.org/10.1037/a0032161

Rhodes, E., Devlin, K., Steinberg, L., & Giovannetti, T. (2017). Grit in adolescence is protective of late-life cognition: non-cognitive factors and cognitive reserve. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *24*(3), 321–332. https://doi.org/10.1080/13825585.2016.1210079

Robbins, C., Daneshvar, D., Picano, J., Gavett, B., Baugh, C., Riley, D., … Stern, R. (2014). Self-reported concussion history: impact of providing a definition of concussion. *Open Access Journal of Sports Medicine*, *5*, 99–103. https://doi.org/10.2147/OAJSM.S58005

Roth, R., Isquith, P., & Gioia, G. (2005). Behavior Rating Inventory of Executive Function--Adult Version. *BRIEF-A*. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=mmt&AN=test.2917&site=ehost-live&scope=site

Scarmeas, N., Levy, G., Tang, M., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology*, *57*(12), 2236–2242.

Schneider, E., Sur, S., Raymont, V., Duckworth, J., Kowalski, R., Efron, D., … Stevens, R. (2014). Functional recovery after moderate/severe traumatic brain injury: a role for cognitive reserve? *Neurology*, *82*(18), 1636–1642. https://doi.org/10.1212/WNL.0000000000000379

Schultz, V., Stern, R., Tripodis, Y., Stamm, J., Wrobel, P., Lepage, C., … Koerte, I. (2018). Age at First Exposure to Repetitive Head Impacts Is Associated with Smaller Thalamic Volumes in Former Professional American Football Players. *Journal of Neurotrauma*, *35*(2), 278–285. https://doi.org/10.1089/neu.2017.5145

Seichepine, D., Stamm, J., Daneshvar, D., Riley, D., Baugh, C., Gavett, B., … Stern, R. (2013). Profile of Self-Reported Problems with Executive Functioning in College and Professional Football Players. *Journal of Neurotrauma*, *30*(14), 1299–1304. https://doi.org/10.1089/neu.2012.2690

Siedlecki, K., Stern, Y., Reuben, A., Sacco, R., Elkind, M., & Wright, C. (2009). Construct Validity of Cognitive Reserve in a Multi-Ethnic Cohort: the Northern Manhattan Study. *Journal of the International Neuropsychological Society : JINS*, *15*(4), 558–569. https://doi.org/10.1017/S1355617709090857

Smith, D., Bailes, J., Fisher, J., Robles, J., Turner, R., & Mills, J. (2012). Internal jugular vein compression mitigates traumatic axonal injury in a rat model by reducing the intracranial slosh effect. *Neurosurgery*, *70*(3), 740–746. https://doi.org/10.1227/NEU.0b013e318235b991

Stamm, J., Bourlas, A., Baugh, C., Fritts, N., Daneshvar, D., Martin, B., … Stern, R. (2015). Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology*, *84*(11), 1114–1120. https://doi.org/10.1212/WNL.0000000000001358

Stamm, J., Koerte, I., Muehlmann, M., Pasternak, O., Bourlas, A., Baugh, C., … Shenton, M. (2015). Age at First Exposure to Football Is Associated with Altered Corpus

Callosum White Matter Microstructure in Former Professional Football Players. *Journal of Neurotrauma*, *32*(22), 1768–1776. https://doi.org/10.1089/neu.2014.3822

Stanford, M., Mathias, C., Dougherty, D., Lake, S., Anderson, N., & Patton, J. (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences*, *47*(5), 385–395. https://doi.org/10.1016/j.paid.2009.04.008

Steffener, J., Brickman, A., Rakitin, B., Gazes, Y., & Stern, Y. (2009). The impact of age-related changes on working memory functional activity. *Brain Imaging and Behavior*, *3*(2), 142–153. https://doi.org/10.1007/s11682-008-9056-x

Stein, T., Alvarez, V., & McKee, A. (2014). Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. *Alzheimer's Research & Therapy*, *6*(1), 4. https://doi.org/10.1186/alzrt234

Stein, T., Alvarez, V., & McKee, A. (2015). Concussion in Chronic Traumatic Encephalopathy. *Current Pain and Headache Reports*, *19*(10), 47. https://doi.org/10.1007/s11916-015-0522-z

Stern, R., Daneshvar, D., Baugh, C., Seichepine, D., Montenigro, P., Riley, D., … McKee, A. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology*, *81*(13), 1122–1129. https://doi.org/10.1212/WNL.0b013e3182a55f7f

Stern, R., Riley, D., Daneshvar, D., Nowinski, C., Cantu, R., & McKee, A. (2011). Long-term Consequences of Repetitive Brain Trauma: Chronic Traumatic Encephalopathy. *PM&R*, *3*(10S2), S460–S467. https://doi.org/10.1016/j.pmrj.2011.08.008

Stern, R., Tripodis, Y., Baugh, C., Fritts, N., Martin, B., Chaisson, C., … Taylor, D. (2016). Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy. *Journal of Alzheimer's Disease*, *51*(4), 1099–1109. https://doi.org/10.3233/JAD-151028

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y. (2013). Cognitive Reserve: Implications for Assessment and Intervention. *Folia Phoniatrica et Logopaedica*, *65*(2), 49–54. https://doi.org/10.1159/000353443

Stewart, W., McNamara, P., Lawlor, B., Hutchinson, S., & Farrell, M. (2016). Chronic traumatic encephalopathy: a potential late and under recognized consequence of rugby

union? *QJM: Monthly Journal of the Association of Physicians*, *109*(1), 11–15. https://doi.org/10.1093/qjmed/hcv070

Talavage, T., Nauman, E., Breedlove, E., Yoruk, U., Dye, A., Morigaki, K., … Leverenz, L. (2014). Functionally-Detected Cognitive Impairment in High School Football Players without Clinically-Diagnosed Concussion. *Journal of Neurotrauma*, *31*(4), 327–338. https://doi.org/10.1089/neu.2010.1512

Traumatic Brain Injury Legislation. (n.d.). Retrieved February 10, 2019, from http://www.ncsl.org/research/health/traumatic-brain-injury-legislation.aspx#2

Vasconcelos, A., Malloy-Diniz, L., & Correa, H. (2012). Systematic Review of Psychometric Properties of Barratt Impulsiveness Scale Version 11 (BIS-11), 14.

Willer, B., Tiso, M., Haider, M., Hinds, A., Baker, J., Miecznikowski, J., & Leddy, J. (2018). Evaluation of Executive Function and Mental Health in Retired Contact Sport Athletes. *The Journal of Head Trauma Rehabilitation*, *33*(5), E9–E15. https://doi.org/10.1097/HTR.0000000000000423

Zarahn, E., Rakitin, B., Abela, D., Flynn, J., & Stern, Y. (2007). Age-related changes in brain activation during a delayed item recognition task. *Neurobiology of Aging*, *28*(5), 784–798. https://doi.org/10.1016/j.neurobiolaging.2006.03.002

CURRICULUM VITAE