2013

The effects of level and duration of play on cognition, mood and behavior among former football players

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BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

THE EFFECTS OF LEVEL AND DURATION OF PLAY ON COGNITION, MOOD AND BEHAVIOR AMONG FORMER FOOTBALL PLAYERS

by

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B.A., Johns Hopkins University, 2009

Submitted in partial fulfillment of the

Requirements for the degree of

Master of Arts

2013

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ACKNOWLEDGEMENTS

I would like to thank my principle investigator, Dr. Robert A. Stern for his guidance, along with Ms. Christine Baugh, Mr. Dan Daneshvar, Mr. Cliff Robbins, Dr. Daniel Seichepeine and Dr. Yorghos Tripodis for their help and support.

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ABSTRACT

Interest in the short and long-term effects of concussions has drastically increased due to the recent high-profile deaths of former National Football League (NFL) players. However, research on this subject, especially at the youth level, has moved at a much slower rate. Second Impact Syndrome (SIS), Postconcussive Syndrome (PCS) and Chronic Traumatic Encephalopathy (CTE) are three major consequences that have the potential to negatively affect athletes participating in contact sports immediately or years after their athletic careers are over. The goal of this study is to examine whether the level of first exposure and/or duration of exposure has an effect on a player's cognition, mood and behavior years after his football career is complete. I hypothesized that the age of onset of exposure to football would have a significant effect on cognition, mood and behavior later in life, and that those who started playing football prior to high school would self-report more problems in all three domains compared to those who started playing in high school when matched for the total number of years played.

In order to test my hypotheses, analysis was completed on n=154 cases, all of whom played football at some level. Results showed that age of onset of exposure to football did have a significant effect on the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) assessment, specifically the Global Executive Composite (GEC) ($p = .018$), Behavioral Regulation Index (BRI) ($p = .014$) scores and three of the nine clinical subscales (Inhibit [$p = .025$], Shift [$p = .015$] and Self-Monitor [$p = .048$]). Age of onset of exposure to football was also found significant for the mood and behavior assessment scores, the Apathy Evaluation Scale (AES) ($p = .024$) and Center for Epidemiological Studies Depression Scale CES-D ($p = .011$). No significant difference in assessment scores was found for level of onset of exposure when matched by number of years of football played. BRIEF-A GEC, BRI and MI raw scores were significantly different than published normative data for each age group, except the 70-79 and 80-90 year olds, both of which had very small sample sizes. Significant differences in all BRIEF-A index scores and all nine clinical subscores were found for the 40-49, 50-59 and 60-69 age groups. Finding significant differences in these age groups is somewhat unsurprising, given that CTE symptoms tend to begin decades after the end of exposure. Also consistent with this idea, the 30-39 years old age group showed a significant difference with the normative data in six of the nine clinical subscales, while the 18-29 years old age group showed a significant difference in three of the nine subscales. Longitudinal studies will need to be conducted to validate these findings and further understand the relationship between level of onset of play and long-term deleterious effects as a result of repetitive brain trauma (RBT).

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LIST OF ABBREVIATIONS

Aβ	Beta Amyloid
AES	Apathy Evaluation Scale
APOE	Apolipoprotein E Gene
BRI	Behavioral Regulation Index
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Version
CES-D	Center for Epidemiological Studies Depression Scale
CDC	Centers for Disease Control and Prevention
CTBI	Chronic Traumatic Brain Injury
CTE	Chronic Traumatic Encephalopathy
CTE-MND	Chronic Traumatic Encephalopathy with Motor Neuron Disease
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revised)
ED	Emergency Department
GEC	Global Executive Composite
GPA	Grade Point Average
HS-RIO	High School Reporting Information Online
ICD-10	International Classification of Diseases, 10^{th} Revision
LEGEND	Longitudinal Examination to Gather Evidence of Neurodegenerative Disease
LOC	Loss of Consciousness

MI	Meta-Cognition Index
mTBI	Mild Traumatic Brain Injury
NFL	National Football League
NFT	Neurofibrillary Tangle
PCS	Post-concussive Syndrome
P-Tau	Hyperphosphorylated Tau Protein
RBT	Repetitive Brain Trauma
SIS	Second Impact Syndrome
SLI	Sports Legacy Institute
SLICE	Sports Legacy Institute Community Educators
TBI	Traumatic Brain Injury
TDP-43	TAR DNA-binding Protein 43

INTRODUCTION

Sports-related concussions and their resulting consequences have entered the spotlight and become a major public health concern due to the tragic deaths of some of our most beloved athletes, most recently former San Diego Chargers linebacker, Junior Seau (Bishop & Davis, 2012). As an estimated 44,000,000 children and teens participate in organized sports annually (Daneshvar et al., 2011b), the rising interest in and attention to concussions among the masses is understandable. This heightened interest has led to a rapid increase in scientific publications over the past decade (Meehan, D' Hemecourt, & Comstock, 2010). Even still, research examining the immediate and long-term effects of concussions on different age groups, especially in our youth, has not been able to keep up with the drastic increase in concern.

An estimate by the Centers for Disease Control and Prevention (CDC) states that up to 3.8 million concussions occur from sports or recreation in the United States each year, representing up to 9% of injuries in sports (Broglio et al., 2009; Daneshvar et al., 2011a; Daneshvar et al., 2011b; Gessel et al., 2007; Harmon et al., 2013; Herring et al., 2011; Langlois, Rutland-Brown, & Wald, 2006). Other studies suggest that the CDCs estimate may be an underrepresentation, claiming up to 50% of concussions go unreported potentially due to 1) the athlete's inability to recognize the seriousness of the concussion, 2) his or her desire to stay in the game and 3) the limited availability of medical personnel and certified athletic trainers with the knowledge required for concussion diagnosis, the last reason often seen among sporting events at the high school

level and younger. (Daneshvar et al., 2011b; Gessel et al., 2007; Harmon et al., 2013; Langlois et al., 2006; McCrea et al., 2004; Williamson & Goodman, 2006). McCrea et al surveyed 1532 high school football players regarding their concussion history at their football season's end, and of the 30% who reported sustaining a concussion, less than half (47%) actually reported the injury for immediate diagnosis. 40% of the athletes who did not report their concussions cited their reasoning as fear of being withheld from play (McCrea et al., 2004). This lack of understanding the seriousness of concussions has motivated the CDC and other groups, like the Sports Legacy Institute (SLI), to launch concussion awareness programs, providing educational tools geared toward medical personnel, coaches, parents and athletes involved at the high school level and below (Bagley et al., 2012; Buzzini & Guskiewicz, 2006; Covassin, Elbin, & Sarmiento, 2012; Daneshvar, et al., 2011b; Gessel et al., 2007). Multiple studies indicate an increase in yearly concussion rates of over 15% in the past 10 years (Bagley et al., 2012; Covassin et al., 2012; Daneshvar, et al., 2011b; Harmon et al., 2013; Lincoln et al., 2011). This suggests increased knowledge on the topic, leading toward improvement of concussion detection and reporting, and the success of these concussion awareness programs.

Another potential reason for the higher rate of reported concussions is the possibility that the actual number of concussions occurring has, in fact, increased. The size, strength and speed of today's athletes have no doubt increased compared to those of the past, suggesting a higher force per collision today than previously experienced (Daneshvar et al., 2011b). In the past, studies have used acceleration sensors within the helmets themselves (Reid et al., 1971), but more recently the use of sensors put in direct

contact with an athlete's head have proved to be more accurate, with one study finding that the head acceleration experienced during an impact in football is less than 10% of the helmet acceleration (Daneshvar et al., 2011a; Manoogian et al., 2006). In two separate studies, Broglio et al. determined that rotational acceleration, the majority of which result from an impact to the front of the head, is more correlated with concussion than other types of forces experienced, while impacts to the top of the head are associated with the highest impact force (Broglio et al., 2009a, 2009b). Among high school football players, the front of the head impacts are the most frequently experienced (Broglio et al., 2009a). Other studies using collegiate and professional football players suggest that these top of the head impacts occur less frequently and have forces with lower accelerations associated with them than in high school (Mihalik et al., 2007; Pellman et al., 2006). Football players at the college and professional levels may have better tackling form or increased neck strength, which may account for this difference in the frequency of top of the head impacts and the associated decreased acceleration (Mihalik et al., 2007). Although helmets and mouth guards were originally designed and are proven to protect against severe traumatic brain injury (TBI) and dental and orofacial injuries at high impact, they may not be appropriate in protecting against the lesser forces and rotational components of these impacts, which are believed to be the cause of concussion (Daneshvar et al., 2011a). Until helmets and protective gear are developed and proven to be effective at reducing the risk of concussion, rule changes, concussion education, like the CDCs Heads Up Program and SLI's Sports Legacy Institute Community Educators

(SLICE), and proper return to play (RTP) guidelines should be further established and utilized (Bagley et al., 2012; Daneshvar et al., 2011a; Herring et al., 2011).

The brain sits in the skull surrounded by cerebrospinal fluid. As a consequence, it can move at a different rate than that of the rest of the head, making it susceptible to injury (Daneshvar et al., 2011a). A concussion is described as a pathophysiological injury to the brain resulting from a force, linear and/or rotational, that is transmitted to the head by a direct or indirect hit to the head, neck, face or body (Buzzini & Guskiewicz, 2006; Daneshvar et al., 2011a; Daneshvar et al., 2011c; Harmon et al., 2013; McCrory et al., 2009; Powell & Barber-Foss, 1999). Tensile, shearing and compressive forces on the brain occur from this biomechanical impact, leading to a number of chemical events (Buzzini & Guskiewicz, 2006). Though the brain is subject to structural harm, it appears that the biochemical changes as a result of that mechanical influence produce much of the real damage to the brain's axons (Geddes et al., 1999). When the brain is injured in this fashion, a 'neurometabolic cascade' ensues, comprised of a disruption in normal metabolism, including an increase in excitatory neurotransmitter release and an imbalance of ions in the brain's axons. This dysfunction requires energy to return to normal (Barkhoudarian, Hovda, & Giza, 2011; Harmon et al., 2013). Due to a decrease in cerebral blood flow, an imbalance in the supply and demand of energy occurs (Buzzini & Guskiewicz, 2006; Harmon et al., 2013). Using rodent brain models, researchers have found that it may take more than a week for cerebral blood flow alone to be restored (Giza & Hovda, 2001). This leaves the brain vulnerable to a second, and potentially worse, consequence, such as Second Impact Syndrome (SIS). SIS, which mostly occurs

in athletes 19 years old and younger, can transpire after an initial concussion or other brain injury is followed by a second before the initial concussion's associated symptoms have subsided (Buzzini & Guskiewicz, 2006). A loss of the automatic regulation of the blood supply to the brain involved in this pathophysiological process leads to a significant increase in pressure within the skull, eventually causing coma or death (Buzzini & Guskiewicz, 2006). This vulnerability remains until normal cellular function and homeostasis is restored, which can take weeks or months (Buzzini & Guskiewicz, 2006; Harmon et al., 2013). This is one reason, among many, that concussions in younger athletes should be managed in a more conservative manner, with more cautious RTP guidelines (Cantu, Herring, & Putukian, 2007; Harmon et al., 2013; McCrory et al., 2009). It is also essential to understand that no two concussions present with the same symptoms or follow the same recovery path, making concussions even more difficult to diagnose and treat (Harmon et al., 2013). And although a concussion is sometimes referred to as a mild traumatic brain injury (mTBI), it is important to avoid using these two names interchangeably, as concussions are a subset of mTBIs (Harmon et al., 2013).

The identification and diagnosis of a concussion relies mostly on the athlete's self-report of symptoms, as well as the observations of someone trained in concussion identification and management (Cantu & Register-Mihalik, 2011; Moser & Schatz, 2012). Concussions often result in an onset of at least one acute clinical symptom in one or more of four categories: physical or somatic symptoms, cognitive symptoms, mood and behavioral changes and sleep disturbances (Harmon et al., 2013). A rapid, but short-lived onset of neurologic dysfunction occurs with clinical symptoms of concussion,

which include, but are not limited to headache, nausea or vomiting, irritability, drowsiness, nervousness or anxiety, fatigue, amnesia and loss of consciousness (LOC), suggesting a functional disturbance rather than a structural one (Daneshvar et al., 2011c; Harmon et al., 2013; Herring et al., 2011; McCrory et al., 2009). Of these symptoms of concussion, multiple studies found headache to be the most common, but as explained earlier, each concussion presents with unique signs and symptoms (Guskiewicz et al., 2000a; Guskiewicz et al., 2003b; Harmon et al., 2013; Meehan et al., 2010). It is a common misconception that a concussion is always accompanied by LOC. Though LOC used to be a defining criterion for concussion, current consensus states that LOC is present in a minority of concussion cases (Buzzini & Guskiewicz, 2006; Cantu et al., 2007). Using the High School Reporting Information Online (HS RIO) injury surveillance system, one study found LOC occurred in less than 5% of reported concussions across all high school sports (Meehan et al., 2010). Another study by Zhao et al found that out of 43,802 sports-related concussions resulting in a visit to the emergency room, 51.6% recorded no LOC (Zhao, Han, & Steiner, 2011). Furthermore, a brief LOC does not correspond to the severity of the concussion, meaning that all symptoms and their type, duration and severity, along with prolonged LOC (>1min) and any other modifiers, should be used in order to determine the severity of the concussion (Cantu et al., 2007; Herring et al., 2011).

A concussion's prognosis is dependent on a number of items, including the number of symptoms experienced, the severity of those symptoms and the athlete's concussion history (Buzzini & Guskiewicz, 2006; Herring et al., 2011). Sustaining a

concussion automatically puts you at a higher risk for sustaining another in the future (Harmon et al., 2013). In 2003, a study of football players at the collegiate level who self-reported a history of two concussions, and those with a history of three or more concussions were 2.8 and 3.5 times respectively more likely to sustain another concussion, compared to those with no history of concussion (Guskiewicz et al., 2003b). Unfortunately, a 2000 study found that 30% to 70% of football players in the United States who experience LOC during a game will return to competition in the same day, thus putting them at risk for more severe consequences (Guskiewicz et al., 2000a). Additional modifiers are used to determine the estimated recovery timeline and plan, including age and preexisting conditions, such as migraines, depression or learning disabilities (Herring et al., 2011). Neuropsychological tests have become increasingly popular in gauging recovery progress from concussion, but due to the still developing brain, it is difficult to accurately use in cases of adolescents and children (Guskiewicz & McLeod, 2011).

RTP guidelines for an athlete often depend on the recovery plan and are complex, including a number of influencing factors, such as the number and severity of past concussions, age, gender, sport played and history of head impacts (Cantu & Register-Mihalik, 2011). Arguably the most critical guideline for RTP is that no athlete should return to practice or games until all symptoms have subsided (Cantu & Register-Mihalik, 2011). Importantly, a 2011 consensus statement by team physicians revised their previous RTP guidelines to include no same-day RTP for any athlete at any level of play, emphasizing the importance of physical and cognitive rest (Herring et al., 2011). For

some, cognitive rest may mean time off from homework and school attendance with the potential to fall behind or cause a drop in the athlete's grade point average (GPA) (Moser & Schatz, 2012; Moser, Shatz & Jordan, 2005).

An athlete's head impact history may also have an important role in the decision to retire. In a 2011 report, Cantu and Register-Mihalik suggest that both concussive and subconcussive blows sustained by an athlete should impact RTP and/or the decision to retire, although no concrete number of concussions forces an athlete to ultimately end his or her career (Cantu & Register-Mihalik, 2011). The decision to retire among high school athletes can greatly affect the athlete's self-esteem, which may lead to depression and participation in poor decision making (Cantu & Register-Mihalik, 2011). Yet, avoiding the long-term consequences of multiple concussive and subconcussive blows is more important, outweighing the short-term emotional lability that may occur in these cases.

The effects of age on the susceptibility to and recovery from outcomes of concussion have only been adequately established among athletes aged 15 years or older (Harmon et al., 2013). Even though the mechanism of concussion among adults and children is similar, the effects of and recovery from concussion are different. The adult and developing brain differ drastically in terms of structure and function (Guskiewicz & McLeod, 2011). Not only are children more susceptible to concussions due to a greater head-to-body ratio, weaker muscles and thinner bones of the skull, they also prove to be more vulnerable due to structural immaturity of the brain, including a decreased number of myelinated axons and increased volume of white matter, suggesting more connectivity in the brain (Guskiewicz & McLeod, 2011). Although an adult brain may be fully

functional, a child's brain is not completely developed, especially in the areas associated with concentration, problem solving, reasoning and other skills of cognition (Guskiewicz & McLeod, 2011). The developmental stages of the brain are difficult to discern, however, one research group (Fischer & Rose, 1997) illustrated brain development by way of dynamic growth curves at approximately 4-5, 6-7 and 9-11 years of age respectively (Guskiewicz & McLeod, 2011). This understanding of brain growth and development is increasingly important with the rise in use of neuropsychological testing in assessing recovery from concussion (Guskiewicz & McLeod, 2011). Brain maturation occurs in developmental periods often referred to as "growth clusters", which occur around 2, 4, 7, 11, 15 and 20 years of age, suggesting that the results of neuropsychological tests would also change non-linearly until the age of 20 years old (Fischer & Rose, 1997; Guskiewicz & McLeod, 2011). This proves to be a problem when establishing and using baseline neuropsychological tests in order to compare post-concussion results (Guskiewicz & McLeod, 2011).

An individual who begins playing a high-risk sport, such as football before high school, and sustains a concussion during that period, will have a longer time period in which he can sustain subsequent concussions compared to an individual who experiences his first concussion in high school or even later. This extra time may lead to an increased risk for repeated concussions and thus an increased risk for the effects of multiple concussive blows, including Chronic Traumatic Encephalopathy (CTE) (Guskiewicz & McLeod, 2011). Field et al provided evidence of extended recovery time for concussion in high school athletes and those playing at the collegiate level, citing a delay in the

recovery of normal cognitive function (Field et al., 2003). More recently, it has been established that athletes at the high school level and below will have a longer recovery time to baseline compared with their collegiate counterparts (Guskiewicz & McLeod, 2011). Still, more research needs to be conducted analyzing the recovery time in athletes less than 15 years old.

Approximately 136,000 concussions happen in high school sports during the school year alone (Gessel et al., 2007; Meehan et al., 2010). In children and adolescents from the ages of 5 to 19 years old, 30% of the documented concussions are related to sports, resulting in a considerable number of visits to the emergency department (ED) (Bakhos et al., 2010; Harmon et al., 2013; Meehan et al., 2010). 144,000 ED visits for concussion between 2002 and 2006 were in children up to 19 years of age (Meehan & Mannix, 2010). In 2008 alone, sports-related concussions comprised 7.4% (44,000) of visits to the ED, about 17% between 11 and 13 year olds, nearly 58% between the ages of 14 and 18, and a little over 8% of which were among 19 to 23 years old (Zhao et al., 2011). Moreover, the highest rates of concussion per athletic exposure (where athletic exposure means one athlete's exposure to brain trauma either by playing in one game or participating in one practice) are seen in contact and collision sports, such as American football, soccer, ice hockey and lacrosse (Herring et al., 2011). In one study, Guskiewicz et al. estimated that 5.6% of high school football players experience at least one concussion in one season (Guskiewicz et al., 2000a). Keeping in mind the fact that many concussions are not reported, that number may be closer to 15% (McCrea et al., 2004). In a 3-year prospective study looking at the incidence of mTBI in high school athletes it was

found that of the 1219 mTBIs, 63.4% occurred among football players, the highest among all sports, with a rate of .59 (.19-1.04) per 1000 athletic exposures (Powell & Barber-Foss, 1999). A more recent and larger study by Lincoln et al. completed an 11-year prospective study, observing 2651 concussions in 10,926,892 athletic exposures, an incidence rate of .24 per 1000 athletic exposures (Lincoln et al., 2011). Similar to the previous study, this 2011 study showed that football accounted for more than half of the total concussions reported at an incidence rate of .60 per 1000 athletic exposures, 11 times higher than baseball, which had the lowest incidence (Lincoln et al., 2011).

The consequences of concussion are not always solely acute. One previously discussed potential danger of RTP before the athlete is asymptomatic is SIS, resulting in coma or death very soon after the second brain injury, mild or otherwise, is sustained. This is especially true for adolescents and children. Another possibility is postconcussional syndrome (PCS), also known as post-concussive syndrome and postconcussion syndrome. PCS is defined as a consequence of brain injury that leads to dysfunction in three areas: 1) somatic (i.e. headache), 2) cognitive (i.e. poor concentration or attention), and 3) psychological (i.e. no motivation or anxiety), for an extended period of time, leading to long-term burden (Daneshvar et al., 2011c; Hall, Hall, & Chapman, 2005). The International Classification of Diseases, 10th Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revised) (DSM-IV-TR) differ in their respective definitions of PCS, illustrating the difficulty to medically define this syndrome which presents with highly subjective symptoms (Hall et al., 2005). The relationship of PCS to mTBI has had a history of

mixed results and is dependent on premorbid differences, and post-injury psychological and cognitive factors (Yeates et al., 1999). 7-15% of PCS sufferers have symptoms one year after injury, with the most common symptoms consisting of a combination of all three areas of dysfunction, among which are headache, sensitivity to light and noise, depression and anxiety (Daneshvar et al., 2011c; Hall et al., 2005). However, the majority of those with PCS experience a full recovery within three to six months (Hall et al., 2005). And although initial research found a difference in symptoms and outcome for PCS among adults and children, current knowledge suggests that pediatric populations may experience similar somatic, behavioral and emotional symptoms and deficits as adults (Daneshvar et al., 2011c; Yeates et al., 1999).

The neurodegenerative disease, Chronic Traumatic Encephalopathy (CTE), is thought to be a result of repetitive brain trauma (RBT), including both concussive and subconcussive blows like that experienced during high exposure contact sports, like football, and during military service (Baugh et al., 2012; McKee et al., 2009a, 2013c; Omalu et al., 2010c). These subconcussive blows can be characterized as hits to that head that have no readily apparent signs or symptoms of concussion, but may induce the same biochemical changes within the brain (Baugh et al., 2012; Gavett, Stern, & McKee, 2011c; Gavett et al., 2011; McKee et al., 2009a; Stern et al., 2011). CTE is not thought to be the consequence of a single concussion or mTBI, but a result of a history of hits to the head that may or may not be recognized as concussive, with possible biochemical consequences accumulating over time (Baugh et al., 2012; Geddes et al., 1999; Maugans et al., 2012). CTE is also clinically distinct from (PCS) (Baugh et al., 2012; Gavet et al.,

2011a). While PCS is associated with immediate symptoms after experiencing a concussion of which are extended far past the normal recovery timeframe, but still result in full recovery, CTE symptoms typically present years or decades after participation in contact sports or other activity involving repetitive brain trauma (RBT) when the initial symptoms of concussion have since long subsided and likely remain a problem until death (Baugh et al., 2012; Daneshvar et al., 2011c; Hall et al., 2005).

CTE was originally described almost 100 years ago by Martland as "punch drunk" syndrome, in reference to boxers who experienced symptoms that he believed to be resultant of repeated brain injury from competition (Martland, 1928). Martland claimed that fighters most affected were of the "slugging type", that is, boxers who took considerable hits to the head in an attempt to knock out their opponent in one blow, or "second rate fighters" who were used to train more promising boxers (Martland, 1928). Subsequently in 1937, Millspaugh confirmed Martland's ideas, but replaced "punch drunk" for the term "dementia pugilistica" to describe the same symptoms and deficits in boxers (Millspaugh, 1937). In 1973, a 15 case series was presented, distinguishing dementia pugilistica from Alzheimer's Disease and other neurodegenerative disorders using neuropathological evidence for the first time (Corsellis et al., 1973). Later, the current use of the term CTE was established, and more contact sports and activities were associated with this neurodegenerative disease (Baugh et al., 2012; McKee et al., 2013c; Omalu et al., 2005a, 2006b). Since Corsellis et al. in 1973, CTE was found and diagnosed in the brains of other former athletes, including former football players, professional wrestlers and professional hockey players, along with a victim of domestic abuse, an

epileptic, and others who experienced repetitive brain trauma from other activities outside of sports (Gavett et al., 2011a; Geddes et al., 1999; McKee et al., 2009a; Stern et al., 2011). Omalu et al. reported the first three cases of CTE in former National Football League (NFL) players confirmed by autopsy (Omalu et al., 2005a, 2006b, 2010c). Moreover, the Boston University Center for the Study of Traumatic Encephalopathy (CSTE), through neuropathological diagnosis, has confirmed CTE in former football players, including linemen, without a history of reported concussions providing evidence that subconcussive blows may also lead to the development of CTE (Baugh et al., 2012; McKee et al., 2009a, 2013c).

CTE is characterized by hyperphosphorylated tau (p-tau) aggregation and deposition in the form of neurofibrillary tangles (NFTs), glial tangles (GTs) and neurites, which can be found throughout the cortex, with focal epicenters mainly in the superficial cortical layers surrounding blood vessels and at the depths of the sulci, along with the brain stem, spinal cord and other parts of the brain (Baugh et al., 2012; Corsellis et al., 1973; Daneshvar et al., 2011a; Gavett et al., 2010b; Gavett et al., 2011c; McKee et al., 2009a, 2013c; Omalu et al., 2005a, 2006b, 2010c; Stern et al., 2011). This irregular deposition and perivascular clustering of p-tau at the depths of the sulci distinguish p-tau deposition associated with CTE from p-tau associated with Alzheimer's Disease (AD) (McKee et al., 2009a). In cases with severe p-tau aggregation and deposition, TAR DNA-Binding Protein 43 (TDP-43) has been found to accumulate as inclusions in the brain's neurons and glial cells, and as neuritis and intranuclear inclusions, which is most prominent in the frontal and medal temporal cortices, white matter of the subcortex,

substantia nigra, amygdala, caudate, putamen, hippocampus, hypothalamus and brainstem (Baugh et al., 2012; McKee et al., 2009a, 2010b, 2013c; Stern et al., 2011). Other microscopic neuropathological findings include neuronal loss seen prominently in the amygdala, hippocampus and entorhinal cortex, and less prominent in the olfactory bulbs, locus coeruleus, substantia nigra, mammillary bodies, medial thalamus and cerebral cortex (McKee et al., 2009a). The presence of β amyloid (Aβ) deposits have been found in approximately 40-45% of neuropathologically diagnosed cases of CTE, but is necessary for an AD diagnosis, suggesting the presence of Aβ indicates a coexistence of CTE with AD (McKee et al., 2009a).

Since its establishment in 2008, the CSTE, in conjunction with the Bedford VA Hospital developed a brain bank that has extensively analyzed the brains and spinal cords of 85 donors with a history of repetitive brain trauma (McKee et al., 2013c). Gross pathological characteristics are dependent on the stage of CTE, of which there are four. General atrophy of the brain, including a decrease in brain weight is most commonly associated with more advanced stages of CTE, along with atrophy of both the frontal and temporal cortices, medial temporal lobe, thalamus, hypothalamus and mammillary bodies (McKee et al., 2013c). Commonly, the lateral and third ventricles are dilated, with thinning of the corpus callosum and cavum septum pelucidum with septal fenestrations also found (McKee et al., 2009a). The septum pellucidum is thought to be damaged by the fluid wave that is likely caused by RBT, leading to separation of the leaflets followed by filling of the space with cerebrospinal fluid (Baugh et al., 2012; Gavett et al., 2010b; McKee et al., 2009a). Stage I CTE is most commonly associated with one or two focal

epicenters of perivascular NFTs found in the depths of the sulci, with unremarkable gross abnormalities (McKee et al., 2013c). The frontal horn of the lateral or third ventricles may be mildly enlarged in stage II CTE, with an increase in the number of p-tau foci in the cortex, which spread to the superficial layers of the adjacent cortex, along with mild presence of NFTs in the amygdala and other areas of the medial temporal lobe (McKee et al., 2013c). Stage III CTE presents with a severely widespread deposition of NFTs throughout the cortex, with advancing neurofibrillary pathology in the medial temporal lobe, including the amygdala, hippocampus and locus coeruleus (McKee et al., 2013c). Gross pathology of stage III CTE includes dilation of the ventricles, possible thinning of the corpus callosum, and may also include pallor of the locus coeruleus and substantia nigra (McKee et al., 2013c). Stage IV, the most advanced stage of CTE, is associated with atrophy of the white matter and cortex and atrophy of the medial temporal lobe, thalamus, hypothalamus and mamillary bodies, along with dilated ventricles, cavum septum pellucidum with perforations or complete absence of the septum pellucidum and pallor of the locus coeruleus and substantia nigra (McKee et al., 2013c). Microscopically, neuronal loss in the cortex is prominent with NFTs widespread throughout the cerebral cortex and medial temporal lobe (McKee et al., 2013c).

Symptoms of CTE have delayed onset of 10 years or more and consist of initial symptoms found in three domains, cognitive, behavioral and mood related in nature, including short term memory loss, executive dysfunction, irritability, anger and hostility, depression, impulsivity issues and suicidality (Baugh et al., 2012; McKee et al., 2009a, 2013c; Stern et al., 2011). Symptoms associated with CTE reflect the regions affected

neuropathologically, including the cerebral cortex and limbic system (amygdala, mammillary bodies, hippocampus and other associated structures), which are related to emotion, behavior, motivation and long-term memory (Baugh et al., 2012; Gavett et al., 2011a; Stern et al., 2011). As CTE progresses, symptoms become more severe, including dementia, parkinsonism and issues with gait (McKee et al., 2013c). There is also the possibility of motor neuron involvement in an associated disease called Chronic Traumatic Encephalopathy with Motor Neuron Disease (CTE-MND), which presents with ALS-like symptoms (McKee et al., 2010b).

Table 1. Early Symptoms of Chronic Traumatic Encephalopathy.

Domain	Symptoms
Cognitive	Memory Impairment
	Executive Dysfunction (i.e. problems with planning, organization, multi-tasking, judgment)
Mood	Depression
	Apathy
	Irritability
	Suicidality
Behavior	Impulse Control (i.e. having a "short fuse", or being "out of control"
	Disinhibition
	Substance Abuse and Other Addictions
	Aggression and Violence

Table taken from Baugh et al., 2012.

There have been mixed results regarding the importance of a specific Apolipoprotein E (APOE) allele in CTE. It is understood that the Apolipoprotein E protein is an important component of lipid transport within the nervous system, providing phospholipids and cholesterol to injured nerves for membrane maintenance, repair and synapse branching and development. (Graham et al., 1999; Teasdale, Murray, & Nicoll, 2005). The three alleles of APOE, ε2, ε3 and ε4 have respective frequencies of occurrence of 7%, 78% and 15%, with ε4 homozygosity occur in 1-2% of the population

(Baugh et al., 2012; Graham et al., 1999; Laskowitz, Horsburgh, & Roses, 1998; Roses, 1996). Studies have shown that the presence of ε4 allele is associated with less branching of neurites than the ε3 allele, and additionally ε4 also has a higher binding affinity with beta amyloid (Aβ), which aggregates and deposits in the form of amyloid plaques in AD (Graham et al., 1999). Therefore, it is not surprising that some studies found an association between the ε4 allele and an increased risk of sporadic and late onset familial AD (Graham et al., 1999). There has also been evidence suggesting an association between the ε4 allele and a worse outcome following head injury (Graham et al., 1999). One study examining the relationship between the APOE ε4 allele and outcomes following acute head injury reported that the greatest outcomes were experienced by children, a striking discovery among the research among the ε4 allele and its effect on AD risk (Teasdale et al., 2005). In 1997, keeping the similarities of AD and CTE, or what they called Chronic Traumatic Brain Injury (CTBI) in mind, Jordan et al. analyzed the relationship between the APOE ε4 allele, and what they called chronic brain injury in a cohort of 30 boxers. Their cohort showed higher frequencies than the normal population of the ε4 allele, 30% with at least one ε4 allele and 3% ε4 homozygosity. Out of 30 samples, 12 were classified as probable CTE, 50% of whom had at least one ε4 allele (Jordan et al., 1997). This suggests a relationship between CTE and the APOE ε4 allele. However, without neuropathological diagnosis of CTE, no real conclusions can be made from this study. A more recent study (McKee et al., 2010b) also observed the suggested higher risk of CTE with inherited ε4 allele using neuropathologically diagnosed CTE cases, but later found with a larger sample size no statistically significant difference

between the 68 individuals diagnosed with CTE carrying at least one APOE ε4 allele and that of the general population (McKee et al., 2013c). More research is needed to fully understand the relationship between APOE ε4 and recovery from brain injury and CTE. More specifically, this research should focus on the association of the ε4 allele with recovery outcomes of brain injury, concussion and PCS, especially in adolescents and children.

OBJECTIVES

The immediate effects of concussions experienced during high-risk contact sports continue to be studied extensively. Long-term effects of concussions and RBT on cognition, mood and behavior have been studied, especially in college and professional populations. However, it is unclear whether or not starting a high-risk sport, like football, at a younger age has the same or more deleterious effects on a person's cognition, mood and behavior later in life. Considering the millions of children and teens participating in sports, a large part of our population is at risk for long-term cognitive and behavioral effects from the brain trauma they are exposed to through this participation. The goal of this study was to examine the three symptom domains: cognition, mood and behavior in former football players who started playing either before high school or during high school using the Apathy Evaluation Scale (AES), Center for Epidemiological Studies Depression Scale (CES-D) and Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) self-report assessment tools. Duration of play was also examined to account for the fact that those who start playing football earlier are more likely play longer. I hypothesized that the age of onset of exposure to football would have a significant effect on cognition, mood and behavior scores later in life, and that those who started playing football prior to high school would self-report more problems in all of the three domains compared to those who started playing in high school when matched for the total number of years played.

METHODS

Data used for this research project was taken from the Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND) study at Boston University's Center for the Study of Traumatic Encephalopathy (CSTE). The LEGEND study's goal is to understand the clinical presentation of and possible risk factors for CTE in the living by examining the three main symptom domains associated with CTE: cognition, mood and behavior. In order to participate in the LEGEND study you must be 18 years or older and have a history of participation in organized sports at any competitive level. For this study, organized sports means participation in officiated competition. Participants were recruited through the websites of the CSTE and SLI, lectures and appearances at events geared toward athletes by one of our Co-Directors and by word of mouth. If interested in participation, subjects contacted the CSTE via email or by phone, underwent eligibility screening and reviewed and provided the proper informed consent for the protocol approved by the Boston University Medical Center Institutional Review Board. Once consent was given, participants were sent a link via email to complete an online self-report questionnaire (SC) that included questions regarding cognition, mood and daily behaviors, along with demographic information and participant and family medical histories. Subsequently, a telephone interview including cognitive testing, demographic information, athletic history, military service history, concussion history, substance use history and medical history was conducted. Of those participating in the LEGEND study, only participants with some history of football

participation and those who completed a baseline self-complete questionnaire online and baseline phone interview after November 1, 2011, or participants who completed their baseline requirements before November 1, 2011, but who also completed a follow-up self-complete questionnaire and phone interview, were included in this present study. The aforementioned inclusion criteria were necessary to ensure that an age of onset of exposure to football was provided. Subjects who participated in other high-risk sports at a higher competitive level than their football participation history were also excluded.

Overall, 302 subjects from the LEGEND study had participated in football at some level. Of the 302, 148 were excluded because they did not meet the above inclusion criteria, leaving n=154 cases ranging from 23-82 years old (M = 46.7, SD = 14.5). Included were 119 cases (M = 46.06, SD = 13.87) who had an onset of exposure to football at a time prior to high school and 35 cases (M = 48.86, SD = 16.52) who had an onset of exposure to football beginning sometime in high school. Demographic information, along with athletic characteristics and concussion history of the group are listed in Table 2. Concussion history was taken during a phone interview. Participants were asked to provide an approximate number of concussions experienced during their lifetime. Then they were given the following definition of concussion:

> "Some people have the misconception that concussions only happen when you black out after a hit to the head or when the symptoms last for a while. But, in reality, a concussion has occurred anytime you have had a blow to the head that caused you to have symptoms for any amount of time. These include: blurred or double vision, seeing stars, sensitivity to light or noise, headache, dizziness or

balance problems, nausea, vomiting, trouble sleeping, fatigue, confusion, difficulty remembering, difficulty concentrating, or loss of consciousness. Whenever anyone gets a ding or their bell rung, that too is a concussion."

Participants are then asked to re-state the approximate number of total concussions they have had during their life.

Table 2. Demographics and Concussion History, n=154.

Demographics	Range	Mean (SD)
Age at Completion of Self-Complete Questionnaire	23-82	46.69 (14.50)
Number of Years in School	11-27	17.05 (2.28)
Age Started Playing Football	5-16	11.60 (2.29)
Total Number of Years Playing Football	1-26	11.72 (5.44)
Race	Frequency	Percent
White	142	92.2
Black or African American	8	5.2
Asian	1	0.6
Other	3	1.9
Education History		
Highest Degree Received	Frequency	Percent (%)
High school/GED	16	10.4
Associates or Related Certification	4	2.6
Bachelors	90	58.4
Masters or Doctoral	44	28.6
Football History		
Level at Onset of Football	Frequency	Percent (%)
Prior to High School	119	77.3
High School	35	22.7
Highest Level of Football Attained	Frequency	Percent (%)
Professional	55	35.7
Other (inc. Semi-Pro)	14	9.1
College	58	37.7
High School	25	16.2
Prior to High School	2	1.3
Concussion History	Range	Mean (SD)
Pre-Definition Total Number of Concussions	0-3500	40.82 (294.04)
Post-Definition Total Number of Concussions	0-20000	209.79 (1631.08)
Total number of LOC	0-500	6.03 (40.86)

Subjects completed an online self-complete questionnaire, which included self-report forms of the AES, CES-D and BRIEF-A. The AES is an 18-item self-report measure of apathy over the past four weeks including indicators that are behavioral, emotional and cognitive. Subjects are asked to indicate the answer that best describes their thoughts, feelings and activity using a four-point scale (not at all = 0; slightly = 1; somewhat = 2; a lot = 3). Positive statement scores (i.e. "I am interested in things") were re-scored to allow higher scores to correspond with a higher apathy response. A higher total score suggests higher apathy. An AES score ≥ 34 suggests a clinically significant level of apathy (Kant, Duffy, & Pivovarnik, 1998). The CES-D is a 20-item self-report measure to assess current depression symptoms. Participants are asked to gauge how they may have felt or behaved during the week and were asked to respond using a four-point scale (rarely or none of the time [less than 1 day per week] = 0; some, or a little of the time [1-2 days per week] = 1; occasionally, or a moderate amount of time [3-4 days per week] = 2; most, or all of the time [5-7 days per week] = 3). Positive statement scores (i.e. "I felt I was just as good as other people) were re-scored to allow higher scores to correspond with a higher depression response. A score ≥ 16 on the CES-D suggests depression in a clinical setting (Radloff, 1977).

The BRIEF-A is a 75-item self-report measure of executive function in everyday activities over the past 30 days. Subjects were asked to answer the question "during the past month, how often has each of the following behaviors been a problem?" for each of the 75 statements using a three-point scale (never=1; sometimes=2; often=3) with higher scores indicating a higher executive dysfunction. Responses to these questions will give a

participant's Global Executive Composite (GEC) score, two index scores (Metacognition Index (MI) and Behavioral Regulation Index (BRI)), along with nine clinical subscales: Inhibit, Shift, Emotional Control, Self-Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor and Organization of Materials, each of which includes 6-10 questions from the survey. These subscales contribute to the index scores, with the BRI comprised of Inhibit, Shift, Emotional Control and Self-Monitor subscales, and the MI comprised of the Initiate, Working Memory, Plan/Organize, Task Monitor and Organization of Materials subscales. Raw scores for the GEC, MI, BRI and all subscales were calculated according to the BRIEF-A Manual and age-adjusted scales were used to conclude whether or not the scores were considered clinically elevated (Roth, Isquith & Gioia, 2005). Subjects whose raw scores corresponded to age-adjusted T scores of ≥ 65 were considered to have clinically significant executive dysfunction according to normative data (Roth, Isquith & Gioia, 2005).

AES, CES-D and BRIEF-A GEC, index scores and subscales were scored according to their respective guidelines. The number of cases with clinically significant BRIEF-A raw scores were determined using age-adjusted tables published on normative data from a study of 1,050 subjects representative of the United States population on levels of sex, race, geographic region and education (Roth, Isquith & Gioia, 2005). For between-group comparisons of means within the original 154 cases, independent t-tests were performed.

Multiple regression analyses were conducted to assess the relationship of the AES, CES-D and BRIEF-A scores and subscales with age at onset of exposure of

football, age at self-complete, total number of years of football and total number of years of schooling. One sample t-tests were conducted for comparisons with normative data (Kant et al., 1998; Radloff, 1977; Roth, Isquith & Gioia, 2005). Then, the 35 subjects who began football during high school were matched with 35 of the 119 cases of whom began playing football prior to high school, matched by the total number of years of football played. An independent t-test was completed to determine that there was no difference between the two groups in duration of play (total $M = 9.73$, $SD = 5.40$; prior to high school $M = 10.04$, $SD = 5.24$; high school $M = 9.41$, $SD = 5.63$; $p = .630$) For between-group comparisons, independent t-tests for two samples were performed. For the AES, CES-D, BRIEF-A overall composite score (GEC) and two index scores (MI and BRI) an alpha level of .05 was adopted. If the GEC, MI or BRI were observed to be significant, analyses of the nine clinical subscales were performed.

RESULTS

Mean scores, standard deviations, number of clinically significant cases and percentages of clinically significant cases for the AES, CES-D and BRIEF-A for the total n=154 and the between-group analysis (prior to HS [n=119] and HS [n=35]) can be seen in Tables 3 and 4. Tables 5 and 6 show the same information for the duration of football-matched groups (prior to HS [n=35], HS [n=35]). T-tests for the independent samples indicated that the prior to high school and high school onset of exposure groups within the N=154 sample did not differ in age at self-complete or total number of years of schooling ($p = .317$ and $p = .960$, respectively). As presumed, age of onset of exposure to football and duration of football were different between the groups of interest. Multiple regression analysis suggested that the age of onset of exposure to football has a significant effect for the BRIEF-A composite GEC ($B = -2.372$, $p = .018$), one of the index scores (BRI [$B = -1.144$, $p = .014$], and three of the nine subscales (Inhibit [$B = -.285$, $p = .025$], Shift [$B = -.254$, $p = .015$], Self Monitor [$B = -.211$, $p = .048$]), along with the AES ($B = -.913$, $p = .024$) and CES-D ($B = -1.286$, $p = .011$). Total number of years of football was also significant for the CES-D ($B = -.519$, $p = .017$). Two cases were excluded in the analysis of the BRIEF-A GEC, MI index score and Plan/Organization due to missing responses that did not allow for scoring. 113 cases of the 154 (74.34%) had GEC scores that would be considered clinically significant executive dysfunction. Similarly, 13 cases (8.44%), all of whom began football prior to high school, had clinically significant AES scores, and 77 cases (50.00%) had clinically

significant CES-D scores. Means and standard deviations for BRIEF-A scores based on age group can be found in Table 7. Comparison of those means with published normative data can be found in Table 8. The AES (M = 14.46, SD = 10.72, p-value = .000) and CES-D (M = 18.69, SD = 13.80, p-value = .000) were also significant, when compared to published normative data.

The number of clinically significant cases in the duration of football-matched groups revealed relatively similar numbers for the prior to high school and high school groups, with the exception of the AES. Independent t-tests for between-group comparison of those who began football prior to high school and those who began during high school showed no significant difference in the AES, CES-D, or BRIEF-A GEC, index scores (BRI, MI), or subscales. One case was excluded in the prior to high school group in the analysis of the GEC, MI and Plan/Org scales due to too many missing responses that did not allow for scoring.

Table 3. BRIEF-A GEC, BRI, MI and AES and CES-D mean scores with clinically significant cases, n=154.

Cognition (Executive Function)				
GEC	Mean (SD)	Number with Clinically Sig. Dysfunction	Percent of Group Total	Percent of Total n=154
Total[a*]	55.16 (26.75)	113	74.34%	.
Prior to HS[b*]	55.43 (26.60)	99	84.62%	65.13%
HS[c]	54.26 (27.64)	14	40.00%	9.21%
Index Scores:				
BRI				
Total[a]	23.59 (12.51)	56	36.36%	.
Prior to HS[b]	24.09 (12.77)	46	38.66%	29.87%
HS[c]	21.89 (11.57)	10	28.57%	6.49%
MI				
Total[a*]	31.83 (16.60)	67	44.08%	.
Prior to HS[b*]	31.67 (16.22)	51	43.59%	33.55%
HS[c]	32.37 (18.04)	16	45.71%	10.53%
Mood and Behavior				
AES				
Total[a]	14.46 (10.72)	13	8.44%	.
Prior to HS[b]	14.74 (11.10)	13	10.92%	8.44%
HS[c]	13.54 (9.37)	0	0.00%	0.00%
CES-D				
Total[a]	18.69 (13.80)	77	50.00%	.
Prior to HS[b]	19.10 (13.8)	62	52.10%	40.26%
HS[c]	17.29 (13.89)	15	42.86%	9.74%

Results for the total n=154 and within group totals are given. [a] indicates n=154, [a*] indicates n=152 (2 cases excluded), [b] indicates n=119, [b*] indicates n=117 (2 cases excluded), [c] indicates n=35.

Table 4. BRIEF-A clinical subscale mean scores with clinically significant cases, n=154.

Clinical Subscales:				
Inhibit	Mean (SD)	Number with Clinically Sig. Dysfunction	Percent of Group Total	Percent of Total n=154
Total[a]	6.57 (3.43)	53	34.42%	.
Prior to HS[b]	6.76 (3.48)	43	36.13%	27.92%
HS[c]	5.94 (3.24)	10	28.57%	6.49%
Shift				
Total[a]	4.64 (2.81)	57	37.01%	.
Prior to HS[b]	4.68 (2.82)	45	37.82%	29.22%
HS[c]	4.51 (2.82)	12	34.29%	7.79%
Emotional Control				
Total[a]	8.47 (5.48)	54	35.06%	.
Prior to HS[b]	8.66 (5.61)	44	36.97%	28.57%
HS[c]	7.80 (5.05)	10	28.57%	6.49%
Self-Monitor				
Total[a]	3.91 (2.91)	41	26.62%	.
Prior to HS[b]	3.99 (3.02)	32	26.89%	20.78%
HS[c]	3.63 (2.50)	9	25.71%	5.84%
Initiate				
Total[a]	6.51 (4.00)	57	37.01%	.
Prior to HS[b]	6.43 (3.84)	42	35.29%	27.27%
HS[c]	6.80 (4.57)	15	42.86%	9.74%
Working Memory				
Total[a]	7.60 (3.85)	88	57.14%	.
Prior to HS[b]	7.54 (3.82)	69	57.98%	44.81%
HS[c]	7.83 (4.00)	19	54.29%	12.34%
Plan/Organize				
Total[a*]	7.22 (4.81)	60	39.47%	.
Prior to HS[b*]	7.22 (4.71)	45	38.46%	29.22%
HS[c]	7.20 (5.18)	15	42.86%	9.74%
Task Monitor				
Total[a]	4.87 (2.54)	56	36.36%	.
Prior to HS[b]	4.84 (2.56)	42	35.29%	27.27%
HS[c]	4.97 (2.50)	14	40.00%	9.09%
Organization of Material				
Total[a]	5.72 (3.76)	29	18.83%	.
Prior to HS[b]	5.76 (3.74)	21	17.65%	13.64%
HS[c]	5.57 (3.91)	8	22.86%	5.19%

Results for the total n=154 and within group totals are given. [a] indicates n=154, [a*] indicates n=152 (2 cases excluded), [b] indicates n=119, [b*] indicates n=117 (2 cases excluded, [c] indicates n=35

Table 5. BRIEF-A GEC, BRI, MI and AES and CES-D mean scores with clinically significant cases, n=70.

Cognition (Executive Function)				
GEC	Mean (SD)	Number with Clinically Sig. Dysfunction	Percent of Group Total	Percent of Total n=70
Total[a*]	124.34 (25.69)	28	18.18%	.
Prior to HS[b*]	124.46 (23.95)	14	9.09%	9.21%
HS[b]	124.23 (25.69)	14	9.09%	9.21%
Index Scores: BRI				
Total[a]	52.70 (11.58)	22	14.29%	.
Prior to HS[b]	53.51 (11.70)	12	10.08%	7.79%
HS[b]	51.89 (11.57)	10	28.57%	6.49%
MI				
Total[a*]	71.64 (16.12)	30	19.74%	.
Prior to HS[b*]	70.94 (14.12)	14	11.97%	9.21%
HS[b]	72.34 (18.07)	16	45.71%	10.53%
Mood and Behavior AES				
Total[a]	14.01 (10.57)	5	3.25%	.
Prior to HS[b]	14.49 (11.77)	5	4.20%	3.25%
HS[c]	13.54 (9.37)	0	0.00%	0.00%
CES-D				
Total[a]	18.91 (14.75)	34	22.08%	.
Prior to HS[b]	20.54 (15.59)	19	15.97%	12.34%
HS[b]	17.29 (13.89)	15	42.86%	9.74%

Results for the total n=70 and within group totals are given. [a] indicates n=70, [a*] indicates n=69 (1case excluded), [b] indicates n=35, [b*] indicates n=34 (1 case excluded).

Table 6. BRIEF-A clinical subscale mean scores with clinically significant cases, n=70.

Clinical Subscales:				
Inhibit	Mean (SD)	Clinically Sig. Cases	Percent of Group Total	Percent of Total n=70
Total[a]	14.24 (3.23)	22	14.29%	.
Prior to HS[b]	14.54 (3.23)	12	10.08%	7.79%
HS[b]	12.94 (3.24)	10	28.57%	6.49%
Shift				
Total[a]	10.74 (2.88)	26	16.88%	.
Prior to HS[b]	10.97 (2.96)	14	11.76%	9.09%
HS[b]	10.51 (2.82)	10	28.57%	6.49%
Emotional Control				
Total[a]	18.00 (5.05)	20	12.99%	.
Prior to HS[b]	18.20 (5.12)	10	8.40%	6.49%
HS[b]	17.80 (5.05)	10	28.57%	6.49%
Self-Monitor				
Total[a]	9.71 (2.64)	18	11.69%	.
Prior to HS[b]	9.80 (2.82)	9	7.56%	5.84%
HS[b]	9.63 (2.50)	9	25.71%	5.84%
Initiate				
Total[a]	14.53 (4.00)	28	18.18%	.
Prior to HS[b]	14.26 (3.37)	13	10.92%	8.44%
HS[b]	14.80 (4.57)	15	42.86%	9.74%
Working Memory				
Total[a]	15.67 (3.86)	38	24.68%	.
Prior to HS[b]	15.54 (3.72)	18	15.13%	11.69%
HS[b]	15.80 (4.04)	20	57.14%	12.99%
Plan/Organize				
Total[a*]	17.13 (4.76)	27	17.76%	.
Prior to HS[b*]	17.20 (5.18)	12	10.26%	7.79%
HS[b]	17.06 (4.37)	15	42.86%	9.74%
Task Monitor				
Total[a]	10.83 (2.47)	23	14.94%	.
Prior to HS[b]	10.69 (2.46)	9	7.56%	5.84%
HS[b]	10.97 (2.50)	14	40.00%	9.09%
Organization of Material				
Total[a]	13.49 (3.65)	13	8.44%	.
Prior to HS[b]	13.40 (3.43)	5	4.20%	3.25%
HS[b]	13.57 (3.91)	8	22.86%	5.19%

Results for the total n=70 and within group totals are given. [a] indicates n=70, [a*] indicates n=69 (1 case excluded), [b] indicates n=35, [b*] indicates n=34 (1 case excluded)

Table 7. Means and standard deviations of all BRIEF-A scores based on age group.

Age Range	18-29 years (n=15)		30-39 years (n=42)		40-49 years (n=36)		50-59 years (n=24)		60-69 years (n=29)		70-79 years (n=5)		80-90 years (n=3)	
Index Scores	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GEC	121.87	21.90	120.45	28.61	133.00	25.74	128.75	29.94	128.75	29.94	101.80	16.72	130.67	27.23
BRI	49.33	9.04	51.83	12.51	57.81	11.32	55.25	15.43	55.25	15.43	42.00	6.82	59.33	8.08
MI	72.53	15.67	68.62	17.40	75.19	16.52	73.50	18.47	73.50	18.47	59.80	10.28	71.33	19.43
Clinical Subscales														
Inhibit	14.73	1.79	14.55	3.30	15.50	3.33	14.88	4.22	14.88	4.22	10.40	2.07	15.33	1.15
Shift	10.27	3.22	10.31	3.03	11.17	2.24	10.96	3.67	10.96	3.67	9.20	1.10	10.67	1.53
Emotional Control	15.40	4.14	17.90	5.30	20.78	4.72	18.71	6.72	18.71	6.72	13.40	3.36	20.67	4.93
Self-Monitor	8.93	2.25	9.07	3.02	10.36	3.14	10.71	2.96	10.71	2.96	9.00	2.00	12.67	1.15
Initiate	13.93	4.43	13.64	3.82	15.58	3.82	14.92	4.65	14.92	4.65	12.40	1.95	14.67	4.51
Working Memory	15.87	3.64	14.86	3.89	16.39	3.95	16.33	4.09	16.33	4.09	12.40	3.65	17.33	4.04
Plan/Org.	17.20	4.89	16.31	4.89	18.03	4.90	17.74	5.19	17.74	5.19	14.80	3.42	14.00	4.58
Task Monitor	11.40	2.23	10.43	2.73	11.03	2.86	11.04	2.66	11.04	2.66	9.80	1.48	10.67	2.31
Organization of Materials	14.13	3.18	13.38	4.11	14.17	3.54	13.50	4.34	13.50	4.34	10.40	2.19	14.67	4.93

GEC = Global Executive Composite; BRI = Behavioral Regulation Index; MI = Metacognition Index; SD = Standard Deviation

Table 8. Comparison of raw scores between football players and normative data on the BRIEF-A. GEC =

	Football v. Healthy Adults						
	18-29 years[a]	30-39 years[b]	40-49 years[c]	50-59 years[d]	60-69 years[e]	70-79 years[f]	80-90 years[g]
GEC	.005*	.001*	.000*	.000*	.000*	.255	.137
BRI	.028*	.000*	.000*	.000*	.000*	.157	.051
MI	.007*	.003*	.000*	.000*	.000*	.559	.245
Inhibit	.000*	.000*	.000*	.000*	.000*	.824	.016*
Shift	.051	.002*	.000*	.001*	.000*	.084	.099
Emotional Control	.280	.000*	.000*	.000*	.000*	.728	.119
Self-Monitor	.901	.817	.003*	.001*	.003*	.620	.022*
Initiate	.193	.032*	.000*	.001*	.000*	.070	.256
Working Memory	.000*	.000*	.000*	.000*	.000*	.245	.088
Plan/Org.	.050*	.055	.000*	.000*	.000*	.220	.716
Task Monitor	.001*	.003*	.000*	.000*	.000*	.084	.285
Organization of Materials	.124	.349	.000*	.071	.003*	.924	.313

Global Executive Composite; BRI = Behavioral Regulation Index; MI = Metacognition Index; Normative data based on [a] n = 70; [b] n = 78; n = 86; [d] n = 78; [e] n = 65; [f] n = 70; [g] n = 78; * indicates statistically significant group differences (alpha < .05); Normative data published in the BRIEF-A manual

DISCUSSION

Through this study, I assessed executive function, mood and behavior in former football players with high exposure to repeated brain trauma using self-report assessment surveys. Consistent with my hypothesis, the age at which our subjects started playing football was found to be associated with their executive function, mood and behavior, the three symptomatic domains of CTE, years after their football careers have ended. That is, the earlier an athlete started playing football, the worse his assessment scores in executive function, mood and behavior. This early exposure to concussive and subconcussive blows to the head may produce the changes in the brain that lead to the increases in assessment scores. Duration of play was not found to significantly affect executive function, mood and behavior, further solidifying the relationship between age of onset of exposure and increased assessment scores.

Specific significant relationships with age at first exposure were the BRIEF-A GEC, BRI and three of the four clinical subscales (Inhibit, Shift and Self-Monitor) used to calculate the BRI. The GEC gauges the athlete's overall executive function. A significant relationship in the GEC suggests that there is an overall negative relationship between early exposure to football and executive function. The BRI is used to assess the athlete's regulatory control of his emotional responses and behaviors, such as proper inhibition of how the athlete thinks or acts while the MI is a representation of the athlete to solve problems in a planned an organized manner. Significant findings for the BRI and three of its four clinical subscales suggest that early exposure to football may negatively

affect an athlete's control over his behaviors and emotions before it affects his problem-solving skills. Initial age of exposure to football also significantly affected AES and CES-D scores, suggesting that an earlier start to football leads to increased apathy and depression. The number of cases with clinically significant AES scores was lower than than the number of clinically significant cases for the CES-D and main BRIEF-A scores (GEC, BRI, MI). Participation in voluntary research such as the LEGEND study involves some sort of motivation, which explains this smaller number of clinically significant cases for apathy.

No significant difference in any assessment was found between those who began playing football prior to high school and those who started playing in high school. The developmental stages of the brain include ages both prior to high school and during high school, suggesting that the brain is vulnerable at both levels of play and that there may not be a difference between levels of onset of exposure. Larger sample sizes may show a difference between the two levels of initial exposure. It may be important in future studies to examine athletes who played up through the same level, but who started either prior to high school or during high school. This would better assess the importance of level of onset of exposure and would control for the number of years of exposure for the entire sample.

Mean scores for the AES and CES-D were found to be significantly different from normative data, suggesting that a relationship between playing football and increased apathy and depression exists later in life. BRIEF-A GEC, BRI and MI were found to be significantly different for all age groups except the 70-79 and 80-90 year

olds, both groups having very small sample sizes. Significant differences in all BRIEF-A scores were found for the 40-49, 50-59 and 60-69 age groups. It is not surprising to have this result because of the nature of the symptom onset of CTE occurring 10 or more years after an athlete's football career is over. Also consistent with this idea, the 30-39 years old age group showed a significant difference with the normative data in six of the nine clinical subscales, while the 18-29 years old age group showed a significant difference in three of the nine subscales. However, these results do not necessarily mean that these cases have or will develop CTE. Those who are likely to play football may just be prone to high scores on these assessments because of their nature and personality.

There are a number of important limitations to consider with this study. The nature of enrollment in this study, along with the recent publicity of concussions and CTE, may produce a selection bias of the inclusion of individuals who are more likely to be symptomatic and who are concerned with their cognition, mood and behavior. These individuals may hope to understand what they are experiencing by volunteering to participate in the LEGEND study. This was also a highly exclusive study. Loosening the inclusion criteria might lend a better idea of the football population. Calculating the number of years played for each subject did not take into account the number of years played at a specific level. There may be a difference in playing four years in high school and two years in college compared to playing two years in high school and four years in college. Further, we did not exclude subjects with concussion and RBT history as a result of other contact sports or traumatic brain injuries (TBIs) experienced outside of sports, which may have also affected our results. The nature of self-report data for this study

required participants to retrospectively report, not only their concussion histories, but their mood and daily behaviors over a passed period of time (i.e. the past four weeks). Concussion histories, especially, are highly variable in our sample. In the future, it would be beneficial if studies used objective measures of mood, behavior and cognition in addition to the self-report information received from the participants. A way to determine accurate concussion histories and/or hit counts during practices and games will be beneficial in future research as well. Longitudinal studies are also needed to gauge these symptom domains over time and confirm this initial result.

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