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United States Senate

Hearing on "Current Issues in American Sports:
Protecting the Health and Safety of American Athletes"

Wednesday, May 17, 2017

Introduction

Mr. Chairman, Ranking Member Nelson, and distinguished Members of the Committee, it is a great honor to appear before you today for this hearing on “Current Issues in American Sports: Protecting the Health and Safety of American Athletes.” I am a Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology at Boston University School of Medicine. I am also the Director of the Clinical Core of the Boston University (BU) Alzheimer’s Disease and CTE Center, one of 29 Alzheimer’s research centers funded by the National Institute on Aging. For the past 30 years, I have been conducting clinical neuroscience research, primarily focused on the cognitive, mood, and behavioral changes of aging, in general, and in neurodegenerative diseases, in particular. I have been on the faculties of the University of North Carolina School of Medicine, Brown Medical School, and, for the past 13 years, BU School of Medicine. In my role in the BU Alzheimer’s Disease and CTE Center, I oversee all clinical research pertaining to Alzheimer’s disease (AD), including studies aimed at the diagnosis, genetics, prevention, and treatment of this devastating cause of dementia.

Chronic Traumatic Encephalopathy (CTE)

You may be asking, “Why is an Alzheimer’s disease specialist testifying at a hearing on *Protecting the Health and Safety of American Athletes*?” The answer is, in short, that repetitive hits to the head, such as those incurred through American tackle football and other contact sports, can have long-term negative consequences to brain health, including the development of another neurodegenerative disease, chronic traumatic encephalopathy or CTE. In 2008, I co-founded the BU Center for the Study of Traumatic Encephalopathy (now referred to as the BU CTE Center) with Dr. Ann McKee, Dr. Robert Cantu, and Mr.¹ Christopher Nowinski. Since that time, my research has focused on the long-term consequences of repetitive brain trauma in athletes, including CTE, a progressive neurodegenerative disease that can lead to dramatic changes in mood, behavior, and cognition, eventually leading to dementia. It is similar to Alzheimer’s disease, but it is a unique disease, easily distinguished from AD and other diseases through post-mortem neuropathological examination (McKee et al., 2013; 2016). CTE has been found in individuals from ages 16-98, including youth, college, and professional contact sport

¹ Christopher Nowinski will formally receive his Ph.D. in Behavioral Neurosciences from Boston University School of Medicine on the day following this Hearing (May 18, 2017).

athletes (e.g., football, hockey, soccer, and rugby players, as well as boxers), military service members exposed to blast trauma and other brain injuries, and others with a history of repetitive brain trauma, such as a physically abused woman, developmentally disabled head bangers, and seizure disorder patients. (See **Table 1**)

CTE has been known to affect boxers since the 1920s (previously referred to as “punch drunk” or dementia pugilistica). The post-mortem neuropathological characteristics were first clearly described in the 1970’s by Corsellis et al. (1973). In 2002, CTE was diagnosed neuropathologically in a former professional football player for the first time (i.e., Mike Webster of the

Table 1. All cases of neuropathologically confirmed cases of CTE have had a history of repetitive brain trauma.
Professional football players
College football players
High school football and other contact sport athletes
Professional soccer players
Semiprofessional soccer player
Professional rugby players
Boxers
Mixed martial art athlete
Combat military service members

Pittsburgh Steelers). That case and subsequent discoveries of CTE in other deceased former NFL players led to growing media attention on CTE. Until recently, I have stated publicly that the scientific knowledge of CTE is in its infancy. However, due to important new scientific

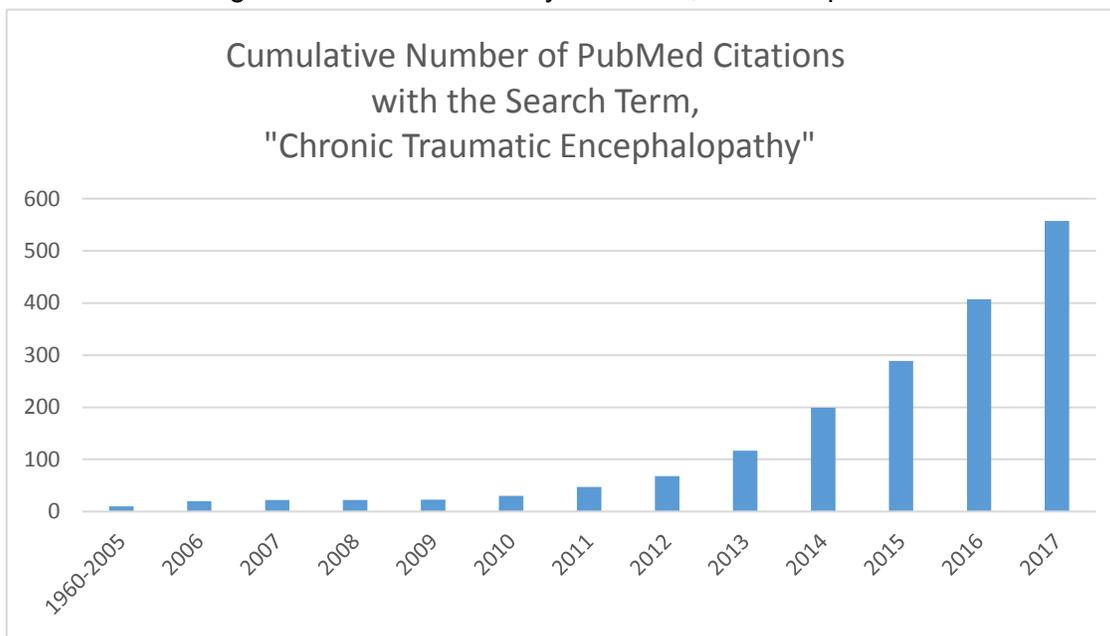


Figure 1

discoveries about CTE, along with an exponential increase in the number of publications in medical/scientific journals focusing on CTE (See **Figure 1**), I am led to think that we are now in the “toddlerhood” of our scientific knowledge about this disease.

CTE Neuropathology

What is currently known about CTE is based primarily on post-mortem examinations of brain tissue, and interviews from the family members of the deceased athletes. My colleague, Dr. Ann McKee, and her team have examined more brains of individuals with a history of repetitive brain trauma than any group in the world. What these studies have shown is that, in some individuals, repetitive brain trauma triggers a cascade of events in the brain leading to progressive destruction of the brain tissue. The hallmark feature of CTE is the build-up of an abnormal form of a protein called *tau* (See **Figure 2**; based on the work of Dr. McKee). The tau protein becomes hyperphosphorylated (referred to as p-tau) and, rather than serve its vital role in the structure and function of brain cells, it becomes toxic, eventually destroying the cells. In 2015, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) convened a consensus conference panel of seven independent neuropathologists with specific expertise in neurodegenerative tauopathies (McKee et al., 2016). The group of experts agreed that CTE is a unique disease, only seen in individuals with a history of repetitive brain trauma. Further, they agreed that the pathognomonic lesion of CTE (i.e., the changes in the brain that are uniquely found in CTE and can be used to diagnose it) is an irregular deposition of p-tau around small blood vessels at the depths of the cortical sulci (i.e., the valleys of the cerebral cortex). This pattern of p-tau was agreed to be distinct from any other neurodegenerative tauopathy, including Alzheimer’s disease and frontotemporal lobar degeneration. As the disease advances, the disease spreads to other areas of the brain, leading to progressive destruction of brain tissue (i.e., atrophy). The changes in the brain from CTE can begin years, or even decades, after the last brain trauma or end of athletic involvement.

CTE is not prolonged post-concussion syndrome, nor is it the cumulative effect of concussions or mild traumatic brain injuries. Rather, **CTE is not a “brain injury,” per se; CTE is a neurodegenerative disease** that appears to begin earlier in life, at the time of exposure to repetitive head impacts, but the symptoms often begin years or decades after the brain trauma and continue to worsen as the individual ages. Importantly, there have been numerous cases of

neuropathologically-confirmed later stage **CTE without any history of symptomatic concussions**, but with extensive exposure to “subconcussive” trauma (see below).

The Clinical Features of CTE

Depending upon the areas of the brain destroyed by the disease, CTE can lead to a variety of changes in cognitive, behavioral, mood, and often motor functioning (See **Table 1**). As

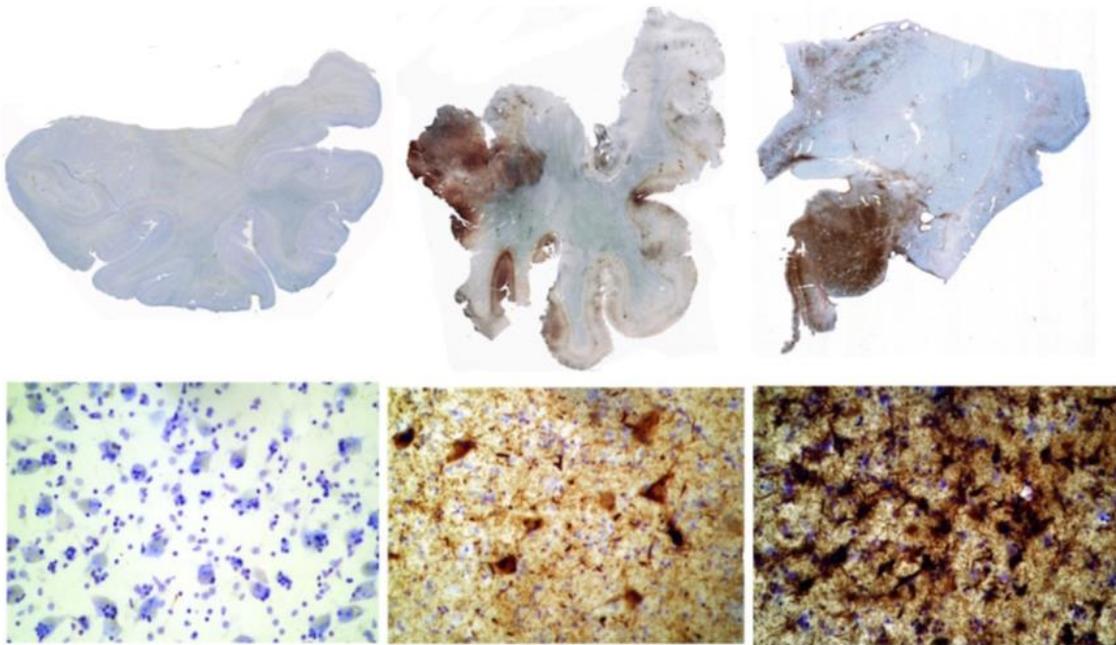


Figure of CTE Neuropathology. Left Top: Section of brain of 65 year old healthy man demonstrating no evidence of abnormal tau depositions. Left Bottom: Microscopic enhancement of same brain sample demonstrating no evidence of tau neurofibrillary tangles that would have shown up as brown from immunostain. Middle Top: Section of brain from 45 year old John Grimsley, a former NFL football player who had a five year decline in functioning (e.g., poor memory, short fuse) prior to his death from an accidental gunshot wound; brown areas are abnormal tau deposits. Middle Bottom: Microscopic enhancement of Grimsley's brain demonstrating neurofibrillary tangles. Right Top: Section of brain of 73 year old former professional boxer who died in a nursing home with clinical diagnosis of dementia pugilistica after several year decline in functioning; brown areas demonstrate widespread tau deposition. Right Bottom: microscopic enhancement of boxer's brain demonstrating widespread tau deposits

Figure 2

cognitive impairment worsens, the individual typically demonstrates progressive dementia, i.e., memory and other cognitive dysfunction severe enough to impair independence in activities of living. Although the cognitive changes in CTE are very similar to those in Alzheimer's disease, many individuals with CTE develop the significant changes in mood and behavior relatively early in life (Stern, et al., 2013). This can lead to significant distress for the individual with CTE as well as their family, friends, and other loved ones. These mood and behavioral impairments

associated with CTE are often misdiagnosed and attributed to routine psychiatric disorders, stress, substance abuse, or pre-existing personality traits. Although there can be many potential underlying causes for changes in mood and behavior in individuals in their 20's-50's, it is also known that the areas of the brain damaged in CTE could lead to these problems, including depression, impulsivity, emotional lability, irritability, and behavioral dyscontrol. Based on reviews of the published case reports and other literature, along with our own research of the reported clinical features of CTE in neuropathologically-confirmed cases (Stern et al., 2013), our group published provisional Research Diagnostic Criteria for the clinical presentation of CTE, referred to as *Traumatic Encephalopathy Syndrome or TES* (Montenigro et al., 2014). An important aspect of these proposed diagnostic criteria is the use of objective biological tests (i.e., biomarkers), when they are available and validated, to indicate that CTE is the underlying disease for the clinical presentation. This diagnostic approach is similar to that currently accepted in the research community for the clinical diagnosis of Alzheimer's disease, including Mild Cognitive Impairment (MCI) due to Alzheimer's disease and dementia due to Alzheimer's disease.

Table 1. Clinical Features of Chronic Traumatic Encephalopathy

Behavioral Features	Mood Features	Cognitive Features	Motor Features
Explosivity	Depression	Memory impairment	Parkinsonism
Loss of control	Hopelessness	Executive dysfunction	Ataxia
Short fuse	Anxiety	Lack of insight	Dysarthria
Aggression and rage	Irritability	Perseveration	Gait Disturbance
Impulsivity	Labile emotions	Impaired attention	Tremor
Physical/verbal violence	Apathy	Poor concentration	Masked facies
Paranoid delusions	Loss of interest	Language difficulties	Rigidity
		Dementia	Muscle weakness

Although there are have been tremendous gains in our understanding of CTE during the last decade, there remain many important questions (see **Table 2**). Most of these questions cannot easily be answered until CTE can be diagnosed during life. **However, we cannot wait until CTE can be diagnosed during life to begin to examine the short-term and long-term neurological consequences of repetitive head impacts in athletes.**

Table 2. What are the Important Questions to Address?
How common is CTE?
Is CTE a critical public health issue?
Will the incidence of CTE increase over the next few decades?
Above and beyond having a history of repetitive head impacts, what are the risk factors for CTE?
Do genetics play a role in determining who gets CTE or how severe it is?
What types of brain trauma exposure increase risk?
Is there a certain age in childhood or adolescence when the brain is more vulnerable to repetitive head impacts, increasing CTE risk?
Does everyone with CTE pathology have cognitive and neuropsychiatric impairments?
Do all people with early stage neuropathological CTE (i.e., focal perivascular p-tau in sulcal depths) progress and develop symptoms?
Are all of the clinical features thought to be associated with CTE specifically related to CTE p-tau neuropathology?
Can we distinguish between Alzheimer's disease and CTE by clinical examination?
How can we treat the symptoms of CTE effectively?
Can we modify the disease course of CTE if we intervene early?
Can CTE be prevented?

Concussions are the Tip of the Iceberg: Importance of Subconcussive Trauma

The Centers for Disease Control and Prevention (CDC) estimates as many as 3.8 million concussions occur in the U.S. each year through sports and recreational activities. It is clear that a single sports-related concussion can result in significant physical, emotional, and cognitive symptoms and signs. Although the majority of concussions resolve within a few weeks, 10-30% result in prolonged recovery (i.e., post-concussion syndrome). However, at some point, a single concussion is likely to completely resolve and result in no long-term consequences. It is likely that concussions are only the “tip of the iceberg,” when it comes to long-term neurological problems, in general, and CTE, in particular. What is significantly more common than symptomatic concussions are “subconcussive” hits. This subconcussive trauma is believed to occur when there is impact to the brain with adequate force to have an effect on neuronal functioning, but without immediate symptoms and signs of concussion. Some sports (e.g., American tackle football) and positions (e.g., lineman) are very prone to these impacts. The most common method used to quantify the number of these subconcussive impacts involves helmets outfitted with accelerometers, devices that measure the linear, lateral, and rotational forces of impacts. Numerous studies have been published over the past 10 years, primarily in tackle football at the high school and college level. For example, a study by Broglio

and colleagues (2011) found that high school football players received, on average, 652 hits to the head in excess of 15g of force in a *single* season. One player received 2,235 hits. The average number of hits in college players is even greater. There is now growing evidence that even after one season, repetitive subconcussive trauma can lead to cognitive, physiological, and structural changes to the brain (e.g., Abbas et al., 2015; Davenport et al., 2014, 2016; Helmer et al., 2014; McAllister et al., 2012; Breedlove et al., 2012; Poole et al., 2015; Kawata et al., 2017). One recent study of youth (8-12 year olds) tackle football by researchers at Wake Forest University (Bahrami et al., 2016) had rather striking results. In this study, the players underwent a special type of MRI scan, referred to as diffusion tensor imaging (DTI), prior to the season, and then again following the football season. The players wore helmets with accelerometers during the course of the season. Without including any players with symptomatic, diagnosed concussions, the researchers found that players who experienced greater cumulative head impact exposure (i.e., more hits above a g-force threshold across the season) had more changes in the integrity of the white matter of the brain. Research studies such as these provide strong support that there are short-term neurological consequences of repetitive subconcussive trauma.

Cumulative Head Impact Exposure

One thing we do know about CTE is that every case of post-mortem diagnosed CTE has had one thing in common: a history of repetitive brain trauma (Bieniek et al., 2015). This means that the repetitive brain trauma is a necessary factor in developing this disease. However, it is not a sufficient factor. That is, not everyone who hits their head repeatedly will develop this progressive brain disease. There are additional, as yet unknown, variables that lead to CTE, such as genetic susceptibility or specific aspects of the exposure to the brain trauma (e.g., severity and type of trauma, amount of rest between hits, total duration of exposure to trauma, cumulative number of head impacts, age of first exposure). An important next step in CTE research is to examine the specific aspects of head impact exposure, vis-à-vis risk for later life neurological changes.

Similar to measuring and modeling “exposure” to toxins in the environment or in the workplace, our group has been employing the approaches and techniques used in Exposure Science to guide our examination of exposure to head impacts through tackle football. We recently published a study evaluating the relationship between the estimated cumulative number

of head impacts received playing amateur football and later life mood, behavioral, and cognitive functioning (Montenegro et al., 2016). In this study, we developed the cumulative head impact index (CHII), using a sample of 93 former high school and college American football players, with an average age of 47. The CHII was calculated from an algorithm based on the number of seasons played, position(s) played, levels played (youth, high school, college), and estimated head impact frequencies from published helmet accelerometer studies. The total number of hits was not meant to reflect merely the number of “concussions,” but, rather, all impacts above a minimum force, including those referred to as subconcussive hits. The average number of total impacts estimated to have been received by participants in our study was 7,742, a number that is consistent with the range of cumulative impacts expected for former high school and college football players based on previous published helmet accelerometer studies. We found a strong, **dose-response relationship between the estimated total number of head impacts experienced through youth, high school, and college football and the risk of developing clinically-meaningful cognitive, mood, and behavioral impairments later in life. Figures 3 and 4** depict the dose-response relationships between the CHII and later-life depression and cognitive impairment, respectively. In layman’s terms, the more hits to the head a football player received in his career, the more likely he was to have impaired cognitive functioning, as well as depression, apathy, and behavioral regulation difficulties.

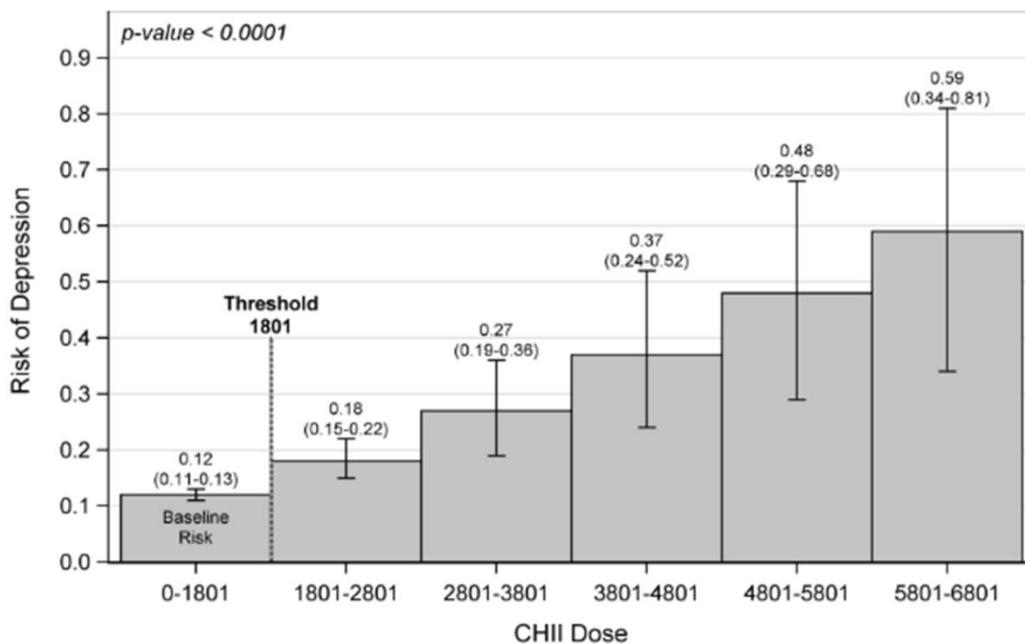


Figure 3

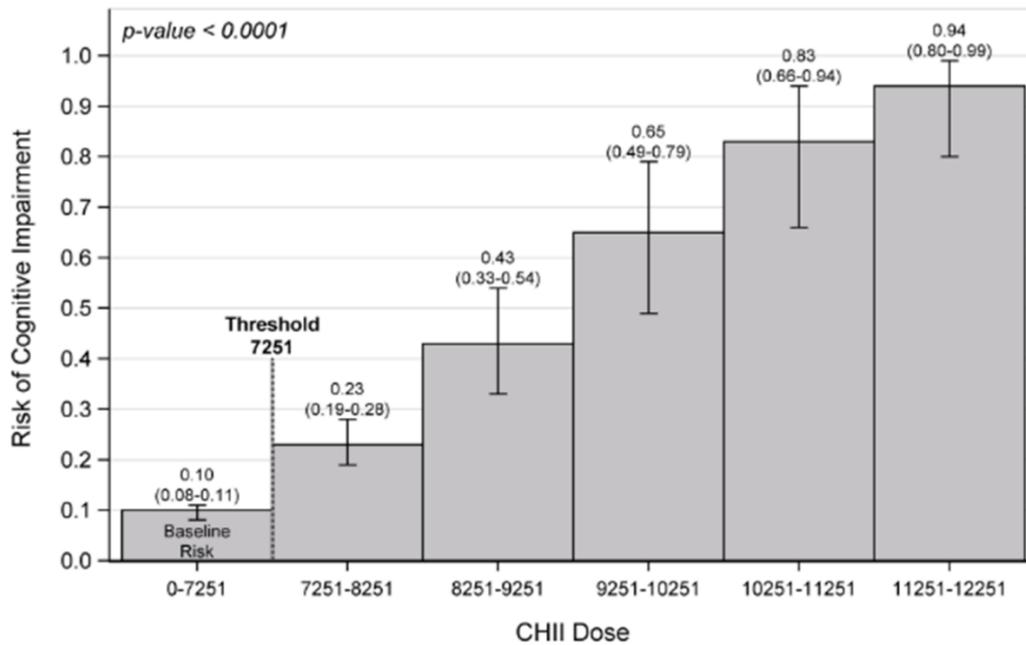


Figure 4

We have also found significant relationships between greater lifetime exposure to head impacts in football (using the CHII metric) and objective biomarkers of possible overall neurodegeneration in former NFL players between the ages of 40-69 years. For example, in one study (Alosco et al., 2016), the greater the exposure level (i.e., the amount of estimated head impacts), the higher the amount of total tau protein in blood, as determined by a state-of-the-art blood test using ultrasensitive single-molecule array (Simoa) assays ($p = 0.014$; see **Figure 5**). Other studies from our group have found significant relationships between the estimated overall exposure to head impacts and the amount of atrophy of specific areas of the brain (using magnetic resonance imaging [MRI]), as well as alterations in brain chemistry (using magnetic resonance spectroscopy [MRS]). The relationship between the total years playing football and the severity of postmortem tau pathology in CTE has also been reported (Cherry et al., 2016).

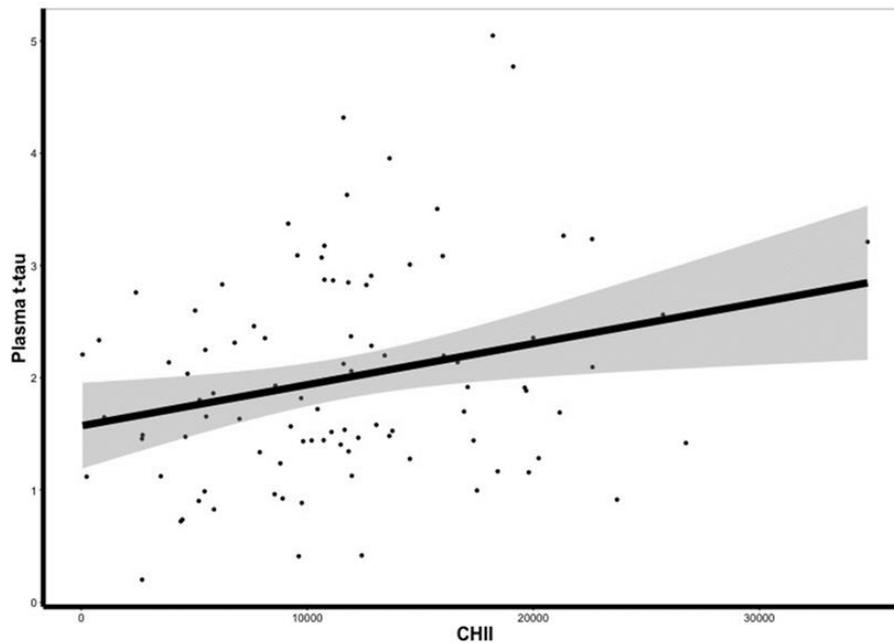


Figure 5

Age of First Exposure to Tackle Football

The brain undergoes significant maturation and development during childhood, with several brain structures and functions reaching their peaks or plateaus of development during the period leading up to age 12 (see **Table 3**). Our group conducted a study to investigate whether or not there is a relationship between experiencing repeated hits to the head during this critical period of brain development and cognitive difficulties later in life (Stamm et al., 2015). Participants in this study were former NFL players ages 41-65 who were part of my NIH-funded DETECT study at Boston University. The former players were divided into two groups: those who began playing tackle football before age 12 and those who began at age 12 or older. We examined their performance on tests of memory and mental flexibility. We found that even after accounting for the total number of years they played football, those who began playing before age 12 performed significantly worse on all tests we measured. This suggests that being hit in the head repeatedly through tackle football during a critical time of brain development is associated with later-life cognitive difficulties. In a subsequent similar study (Stamm et al., 2015) of the same sample of former NFL players, conducted in collaboration with my colleagues, Drs. Martha Shenton and Inga Koerte at Brigham and Women's Hospital in Boston, we examined the relationship between the age of first exposure to tackle football and the structural integrity of the

corpus callosum, the large white matter fiber tracts connecting the two hemispheres of the brain. The former players underwent MRI scans with diffusion tensor imaging (DTI) which showed that subjects who began playing football before age 12 were found to have significantly altered integrity of the anterior portions of the corpus callosum at middle-age, compared to those who began playing football at age 12 or older.

The participants in these studies were all former NFL players, which limits the ability to apply these findings to other groups of athletes. However, in another investigation from our group, we studied former football players who only played up through high school or college, and we found that those who began playing tackle football before age 12 had significantly greater impairments in mood and behavior as adults, compared with those who began playing at age 12 or older. More research is needed to study this question in athletes who played other sports, and female athletes, as females generally reach milestones of brain development earlier than males.

Table 3. Important Neurodevelopmental Milestones Between the Ages of 8-12

Neurodevelopmental Milestone	Age	Exemplar Reference
Peak amygdala and hippocampal volume	9-12	Uematsu et al. 2012
Regional peak gray matter volumes	10-12	Giedd et al. 1999
Regional peak cortical thickness	8-11	Shaw et al. 2008
Microstructural maturation of the genu and splenium of the corpus callosum	8-12	Lebel et al. 2008
Peak myelination rate	11-12	Thatcher 1991
Peak cerebral blood flow	10-12	Epstein 1999
Beginning of cerebral glucose metabolism decline	10	Chugani et al. 1987

Diagnosing CTE During Life

Our group at BU and other scientists from around the country and abroad are conducting research to develop methods of accurately diagnosing CTE during life. Fortunately, because CTE is similar to Alzheimer's disease and other neurodegenerative disorders, we can exploit the incredible discoveries and advances in diagnostic tests developed for these other disorders in recent years to accelerate our ability to diagnose CTE during life. Once we can accurately diagnose CTE, we will be able to more clearly address the important questions listed above in **Table 2**. We will be able to differentiate between CTE and other causes of cognitive and

behavioral change, including Alzheimer's disease, Frontotemporal Dementia, PTSD, persistent symptoms from previous repetitive or single concussions, "routine" depression and aggressive behavior, and others. We will be able to measure more clearly the true incidence and prevalence of the disease. We will be able to determine more accurately the risk factors (including genetic and exposure variables) for developing CTE. Perhaps most importantly, we will be able to begin clinical trials for the treatment and prevention of CTE, as new anti-tau compounds (as well as other disease modifying treatments) move through the pharmaceutical development pipeline. And, similar to Alzheimer's disease and other neurodegenerative diseases, the earlier a disease modifying treatment can be initiated, the more likely it will be successful in slowing the progression of symptoms. That is, once a disease has resulted in too much destruction of brain tissue, it may be too late to intervene successfully (i.e., the destroyed tissue cannot be regenerated). Therefore, early detection of the disease, before symptoms manifest, can potentially prevent the symptoms from ever appearing. However, it is likely that not all CTE will be able to be prevented and, therefore, there will always be need for successful methods of treating and slowing the progression of symptoms.

Development of Biomarkers for CTE Diagnosis

In 2011, I was fortunate to receive a grant co-funded by the National Institute of Neurologic Diseases and Stroke, the National Institute of Aging, and the National Institute of Childhood Health and Development (Grants #s R01NS078337 and R56NS078337) for a study referred to as, "Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests" (DETECT). The goals of the DETECT study (which was the first grant ever funded by NIH to study CTE) were to examine the later-life clinical presentation of former NFL players at high risk for CTE, and to begin to develop *in vivo* biomarkers for CTE. The DETECT study concluded in 2015 and involved a total of 96 symptomatic former NFL players and 28 same-age asymptomatic controls without head trauma history. All research participants underwent extensive brain scans, lumbar punctures (to measure proteins in cerebrospinal fluid), electrophysiological studies, blood tests (e.g., for genetic studies and novel potential biomarkers), and in-depth neurological, neuropsychological, and psychiatric evaluations. In addition, Dr. Martha Shenton of the Brigham and Women's Hospital and I received Department of Defense funding for a related study to examine a promising new Positron Emission Tomography (PET) ligand (developed and owned by Avid Radiopharmaceuticals) that is

designed to attach to abnormal forms of tau protein, such as those found in CTE. I also received a separate grant from Avid Radiopharmaceuticals to examine that same PET scan, in conjunction with colleagues from Banner Alzheimer's Institute and Mayo Clinic Arizona. Results from the DETECT study have been very promising, resulting in preliminary support for potential blood biomarkers of CTE (e.g., Alosco et al., 2017; Stern et al., 2016; See **Figure 6**), as well as a variety of potential MRI and MRS biomarkers (e.g., Koerte et al., 2016). In addition, preliminary analyses of the tau PET data are encouraging.

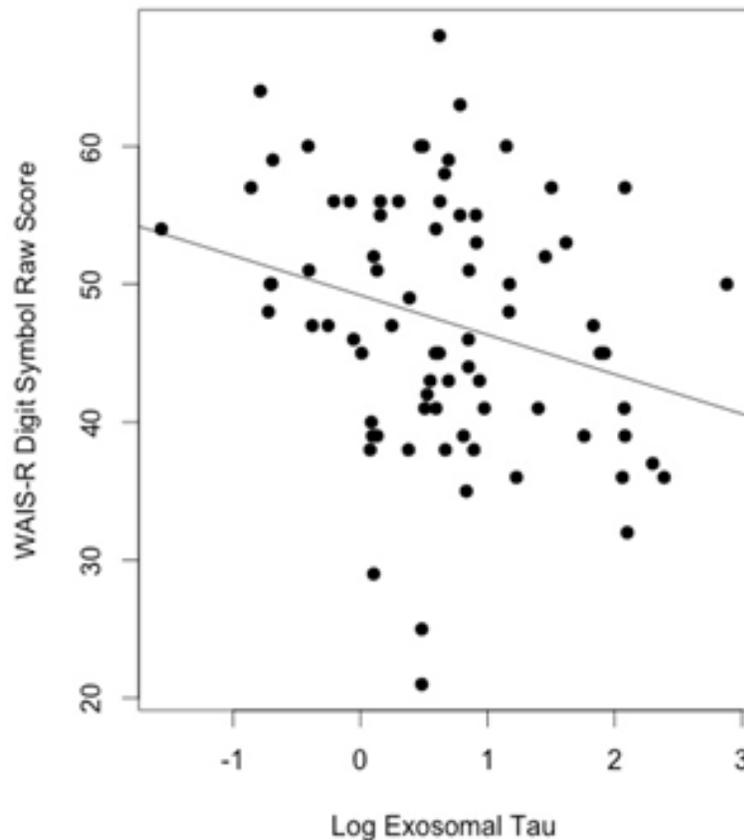


Figure 6. Significant relationship between the amount of plasma exosomal tau and worse performance on a complex cognitive test.

The DETECT study was just the first step. Much more research is needed, including studies with longitudinal designs and much larger and more diverse samples, the inclusion of newer techniques and technologies, as well as post-mortem validation of the findings during life.

DIAGNOSE CTE Research Project

In December 2015, I, along with three co-principal investigators (Jeffrey Cummings, M.D., from the Cleveland Clinic; Eric Reiman, M.D., from Banner Alzheimer’s Institute; Martha Shenton, Ph.D., from Brigham & Women’s Hospital), were honored to receive a \$16 million collaborative research grant funded by the National Institute of Neurological Disorders & Stroke (U01NS093334), entitled, “Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors.” The goals of the project are summarized in **Table 4**.

Table 4. DIAGNOSE CTE Research Project Goals

- | |
|--|
| 1. Collect and analyze neuroimaging and fluid biomarkers for the <i>in vivo</i> detection of CTE |
| 2. Characterize the clinical presentation of CTE |
| 3. Examine the progression of CTE over a three-year period |
| 4. Refine and validate diagnostic criteria for the clinical diagnosis of CTE |
| 5. Investigate genetic and head impact exposure risk factors for CTE |
| 6. Share project data with researchers across the country and abroad |

To study the clinical presentation, diagnostic criteria, biomarkers, and risk factors of CTE requires expertise across many disciplines, including neurology, neuropsychology, psychiatry, neuroimaging, molecular medicine, neuropathology, exposure science, genetics, biostatistics, bioinformatics, engineering, and others. This project brings together a network of approximately 50 scientists from 10 major research institutions from across the country, including Banner Alzheimer’s Institute in Arizona, BU Schools of Medicine and Public Health, Brigham and Women’s Hospital (Harvard Medical School), Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Mayo Clinic Arizona, New York University (NYU) Langone Medical Center and NYU School of Medicine, VA Puget Sound, University of Washington, Molecular NeuroImaging (New Haven, CT), and the Neuroinformatics Research Group and Central Neuroimaging Data Archive (CNDA) at Washington University School of Medicine (in St. Louis).

This 7-year, longitudinal, multicenter investigation, referred to as the **Diagnostics, Imaging, And Genetics Network for the Objective Study & Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project**, is well underway. In total, we will examine 240 former professional football players, former college football players, and healthy controls (without history of contact sports of brain trauma), between the ages of 45-74.

Participants will undergo extensive testing over a three-day period at one of four sites (see **Table 5**), and then return three years later for a follow-up evaluation. Examinations include: Advanced MRI and MRS imaging; two brain PET scans to measure abnormal tau and amyloid protein deposits, respectively; lumbar punctures, to measure proteins and other substances in cerebrospinal fluid; blood and saliva collection, to measure proteins and other compounds using state-of-the-art analyses; extensive neuropsychological, neuropsychiatric, neurological, and motor examinations; and genetic testing, as part of risk factor analyses. We are fortunate to have an **External Advisory Board** made up of Key Opinion Leaders, including David Knopman, M.D., External Advisory Board Chair (Professor of Neurology, Mayo Clinic), Col. Dallas Hack, M.D. (Ret.) (Medical Leader, One Mind), Brian Hainline, M.D. (Chief Medical Officer, National Collegiate Athletic Association), Mike Haynes (Member of Pro Football Hall of Fame, President and founder, Mike Haynes & Assoc.), Thomas McAllister, M.D. (Chair, Department of Psychiatry, Albert Eugene Stern Professor of Clinical Psychiatry; Indiana University School of Medicine), Arthur Toga, M.D. (Provost Professor; Director of the Institute for Neuroimaging and Informatics, University of Southern California), and Michael Weiner, M.D. (Professor of Medicine, Radiology, Psychiatry, and Neurology, University of California San Francisco). **We are confident that based on the results of this study, along with scientific advances in the diagnosis of other neurodegenerative diseases, CTE will be able to be accurately diagnosed during life within the next 5-10 years.**

<u>Arizona</u> Mayo Clinic-Scottsdale Site PI: Charles Adler, M.D., Ph.D. <ul style="list-style-type: none">PET scans at Banner Alzheimer's Institute, Phoenix	<u>Boston</u> BU School of Medicine Site PI: Robert Stern, Ph.D. <ul style="list-style-type: none">MRI's at Brigham and Women's Hospital
<u>Las Vegas</u> Site PI: Charles Bernick, M.D. Cleveland Clinic Lou Ruvo Center for Brain Health	<u>New York</u> Site PI: Laura Balcer, M.D., M.P.H. New York University Langone Medical Center

Concussions, Repetitive Subconcussive Head Impacts, and CTE

Over the past 10 years, there have been tremendous strides made in sports concussion awareness, prevention, detection, and management. These gains have resulted in improved public health and have likely saved the lives of many American athletes. Continued efforts must

be made to better detect concussion using objective tests, to reduce risk for concussion, and to educate players, parents, coaches, medical staff, and the public as a whole, about the concussions. However, I am concerned that **there is confusion regarding the difference between concussion and CTE**. A concussion is an acute brain injury, which, if managed appropriately, results in transient symptoms, without long-term consequences. CTE, on the other hand, is a neurodegenerative disease that has only been diagnosed in individuals with a history of repetitive head impacts. As stated above, the disease appears to begin at the time of exposure to those repetitive impacts but often does not result in any symptoms until years or decades following the cessation of the exposure (i.e., ending involvement in the sport). It also appears that it is the overall exposure to repetitive head impacts (including the much more common subconcussive trauma) that results in later life neurological disorders, including CTE. In short, concussion and CTE are very distinct, and yet, there seems to be widespread confusion about this. My hope is that the national discussion about brain trauma in football and other contact sports can **shift from a focus primarily on “concussion” to the much more common and, potentially more problematic, subconcussive trauma**. In other words, the big hits and symptomatic concussions can be easily observed, counted, and, with appropriate societal effort, reduced. However, the repetitive, subconcussive hits are currently viewed as fundamental to certain sports (e.g., routine plays in American tackle football, heading in soccer), but may have a greater negative overall impact on public health.

Tackle Football History

American tackle football began in the late 19th century. It was originally played without any protective headgear and then thin leather helmets were worn. However, it was not until the 1950s and 1960s that hard plastic helmets with facemasks were used. The helmets were developed to prevent skull fractures (which they did and continue to do extremely well), but they also allowed individuals to hit their head repeatedly against their opponent without feeling pain, thus possibly creating a sense of invincibility and also portraying minimal safety concerns. In the 1960s and early 1970s, children started to play organized American tackle football when Pop Warner youth football became popular nationally. From a public health perspective, the first individuals who played youth football are currently in their late 50s and 60s, and the first individuals who played college football with hard plastic helmets and facemasks are currently in their mid-70s. Aside from boxing, there does not seem to be any other activity that human

beings have been involved with that includes exposure to hundreds, thousands, or even tens of thousands of head impacts. Although boxing has been around for hundreds of years, it was not until the mid-20th century that it involved extensive exposure to repetitive head impacts. It was at that time that the padded glove was used routinely (initially meant as a means of protecting the hands from injury, but also resulted in increased numbers of blows to the head). Therefore, it is only in the past 55-65 years that large numbers of human beings have been exposed to repetitive head impacts. While the epidemiology of CTE is unknown, it is possible that millions of living older adults are currently at high risk for CTE or other long-term neurological conditions due to their history of exposure to repetitive head impacts.

Decision-Making Regarding Participation in Tackle Football

With increased knowledge of the potential short-term and long-term risks of repetitive head impacts and other injuries incurred through tackle football, adult athletes should be able to make informed decisions about participating. However, the issue of youth participation is quite different because children's brains are not yet fully developed, especially the frontal lobes, the parts of the brain responsible for complex thought, planning, judgement, abstract thinking, and decision-making. As such, children and adolescents are not able to weigh the long-term risks and benefits of playing tackle football (Bachynsky, 2016). Parents and other adults involved in the decision-making process and in setting policies often search for guidance from professional organizations, such as groups of medical and scientific experts. One such organization is the American Academy of Pediatrics (AAP) and its Council on Sports Medicine and Fitness which, after reviewing the literature regarding tackling and football-related injuries (including concussions, subconcussive trauma, and CTE), published a Policy Statement, as part of the AAP "Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children." (Council on Sports Medicine and Fitness, 2015). At the end of their review, they provided the following summary (with *italics* added for emphasis):

Removing tackling from football altogether would likely lead to a decrease in the incidence of overall injuries, severe injuries, catastrophic injuries, and concussions. The American Academy of Pediatrics recognizes, however, that the *removal of tackling from football would lead to a fundamental change in the way the game is played. Participants in football must decide* whether the potential health risks of sustaining these injuries are outweighed by the recreational

benefits associated with proper tackling. (Council on Sports Medicine and Fitness, 2015; p. e1426)

It is my opinion that if making a fundamental change to the way a game is played would likely decrease injuries, severe injuries, catastrophic injuries, and brain injuries (i.e., concussions), then perhaps there should be a recommendation that such a fundamental change should be made. And, similar to Bachynsky (2016), in his editorial in the New England Journal of Medicine critiquing the AAP Policy Statement, I strongly believe that youth are not capable of making their own decisions about participation in a game with these known short-term and long-term risks. Therefore, parents, guardians, school officials, leagues, coaches, state Departments of Health, and other key decision-makers, require ongoing, up-to-date scientific/medical information and guidance, not merely from the media or from groups with potential financial conflicts of interest or other biases.

Consensus Statements developed at conferences sponsored and organized by institutions with financial conflicts of interest (e.g., Fédération Internationale de Football Association [FIFA], Federation for Equestrian Sports [FEI], International Olympic Committee [IOC], International Ice Hockey Federation [IIHF]), and written by experts in concussion and brain injury, rather than in neurodegenerative diseases, may not necessarily result in accurate summaries and recommendations regarding the relationship between repetitive head impacts and CTE. One example of a Consensus Statement published by a less biased group of clinicians and scientists (including several with expertise in neurodegenerative diseases and neuroscience) is the “Expert Consensus Document” resulting from a one-day meeting convened by Safe Kids Worldwide, the Alzheimer’s Drug Discovery Foundation, and the Andrews Institute for Orthopedics and Sports Medicine (Carmen et al., 2015). Based on their review of the literature pertaining to CTE, they concluded that CTE is a “disease associated exclusively with repetitive head trauma,” that “...long sporting careers are not required for CTE development, and that youth athletes represent an at-risk population.” (p. 233)

Continued discussion and collaboration amongst expert scientists and clinicians about the current state of scientific knowledge regarding short-term and long-term consequences of repetitive head impacts in contact sports is critically needed. Governmental organizations (e.g., NIH, Department of Defense, Centers of Disease Control and Prevention, Department of

Veteran's Affairs) which serve as the primary funders of biomedical research can and should take the lead, by convening expert panels to help guide future scientific discovery in this area, as well as to provide the public with accurate, unbiased, state-of-the science summaries and recommendations aimed at issues pertinent to improving public health.

Increased Funding for CTE Research

In order to tackle the complex issue of CTE, we must continue to expand upon current approaches to conducting research in neurodegenerative disease. We must continue to break down the traditional silos of individual research labs, research institutions, and disciplines, and begin to conduct multidisciplinary, collaborative, and translational research, bringing together the very best scientists, novel methodologies, and state-of-the-art technology. Most importantly, we cannot forget that our research must focus on reducing individual human suffering and improving public health. Alas, this requires tremendous financial support. There is the possibility that millions of Americans are at risk for developing CTE and other long-term neurological complications from exposure to repetitive head impacts in the sports they participated in during youth, high school, and college, over the past six decades. However, there remain critical questions in need of answers and gaps in our scientific knowledge are in need of filling. **We must do everything we can to continue to reap the profound benefits of American sports while also assuring that we protect the health and safety of former, current, and future American athletes.**

Summary

In summary, many of our most cherished American sports, such as tackle football, soccer, and hockey, involve repetitive blows to the head, often resulting in changes to brain structure and function, even after just one season of play. This exposure to repetitive head impacts (often without any experience of symptomatic concussions) potentially leads to a degenerative brain disease with later life impairments in behavior, mood, and cognition, as well as the development of dementia and lack of independent functioning. Therefore, it is imperative that we: (1) determine who may be at increased risk for CTE and other long-term consequences of the repetitive head impacts experienced by athletes at all ages; (2) develop methods of accurately diagnosing CTE during life (perhaps even before symptoms); and (3) create and test

methods of slowing the progression of the disease, treating its symptoms, and even preventing the onset of symptoms altogether. I want to close by thanking the Committee for your interest in addressing this important issue and for your continued commitment toward protecting the health and safety of all athletes.

References Cited

- Abbas K, Shenk TE, Poole VN, Robinson ME, Leverenz LJ, Nauman EA, Talavage TM. Effects of repetitive sub-concussive brain injury on the functional connectivity of Default Mode Network in high school football athletes. *Dev Neuropsychol*. 2015; 40:51-6
- Alosco ML, Tripodis Y, Jarnagin J, Baugh CM, Martin B, Chaisson CE, Estochen N, Song L, Cantu RC, Jeromin A, Stern RA. Repetitive head impact exposure and later-life plasma total tau in former National Football League players. *Alzheimers Dement (Amst)*. 2016 Dec 10;7:33-40.
- Bachynski, K.E. Tolerable Risks? Physicians and Youth Tackle Football. *NEJM* 2016;374:405-407.
- Bahrami, N., Sharma, D., Rosenthal, S., Davenport, E. M., Urban, J. E., Wagner, B., . . . Maldjian, J. A. (2016). Subconcussive Head Impact Exposure and White Matter Tract Changes over a Single Season of Youth Football. *Radiology*, 160564. doi: 10.1148/radiol.2016160564
- Bieniek, K. F., Ross, O. A., Cormier, K. A., Walton, R. L., Soto-Ortolaza, A., Johnston, A. E., . . . Dickson, D. W. (2015). Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathol*, 130(6), 877-889. doi: 10.1007/s00401-015-1502-4
- Breedlove EL, Robinson M, Talavage TM, Morigaki KE, Yoruk U, O'Keefe K, King J, Leverenz LJ, Gilger JW, Nauman EA. Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J Biomech*. 2012 Apr 30;45(7):1265-72.
- Broglio, S. P., Eckner, J. T., Martini, D., Sosnoff, J. J., Kutcher, J. S., & Randolph, C. (2011). Cumulative head impact burden in high school football. *J Neurotrauma*, 28(10), 2069-2078. doi: 10.1089/neu.2011.1825
- Carman, A.J., Ferguson, R., Cantu, R., Comstock, R.D., Dacks, P.A., DeKosky, S.T., Gandy, S., Gilbert, J., Gilliland, G., Gioia, G., Giza, G., Greicius, G., Hainline, B., Hayes, R.L., Hendrix, H., Jordan, B., Kovach, J., Lane, R.F., Mannix, R., Murray, T., Seifert, T., Shineman, D.W., Warren, E., Wilde, E., Willard H., & Fillit, H.M. Expert Consensus Document: Mind the gaps—advancing research into short-term and long-term neuropsychological outcomes of youth sports-related concussions. *Nat. Rev. Neurol*. 2015; 11:230–244
- Cherry, J. D., Tripodis, Y., Alvarez, V. E., Huber, B., Kiernan, P. T., Daneshvar, D. H., . . . Stein, T. D. (2016). Microglial neuroinflammation contributes to tau accumulation in chronic traumatic encephalopathy. *Acta Neuropathol Commun*, 4(1), 112. doi: 10.1186/s40478-016-0382-8
- Chugani, H.T., Phelps, M.E. and Mazziotta, J.C. (1987). Positron emission tomography study of human brain functional development. *Ann Neurol* 22, 487-497.

- Corsellis, J. A., Bruton, C. J., & Freeman-Browne, D. (1973). The aftermath of boxing. *Psychol Med*, 3(3), 270-303.
- Council on Sports Medicine and Fitness. Tackling in youth football. *Pediatrics* 2015;136: e1419-30.
- Davenport EM, Apkarian K, Whitlow CT, Urban JE, Jensen JH, Szuch E, Espeland MA, Jung Y, Rosenbaum DA, Gioia GA, Powers AK, Stitzel JD, Maldjian JA. Abnormalities in Diffusional Kurtosis Metrics Related to Head Impact Exposure in a Season of High School Varsity Football. *J Neurotrauma*. 2016 Dec 1;33(23):2133-2146. Epub 2016 May 18.
- Davenport EM, Whitlow CT, Urban JE, Espeland MA, Jung Y, Rosenbaum DA, Gioia GA, Powers AK, Stitzel JD, Maldjian JA. Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. *J Neurotrauma*. 2014 Oct 1;31(19):1617-24.
- Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C. and Rapoport, J.L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2, 861-863.
- Helmer KG, Pasternak O, Fredman E, Preciado RI, Koerte IK, Sasaki T, Mayinger M, Johnson AM, Holmes JD, Forwell LA, Skopelja EN, Shenton ME, Echlin PS. Hockey Concussion Education Project, Part 1. Susceptibility-weighted imaging study in male and female ice hockey players over a single season. *J Neurosurg*. 2014 Apr;120(4):864-72.
- Kawata K, Rubin LH, Takahagi M, Lee JH, Sim T, Szwanki V, Bellamy A, Tierney R, Langford D. Subconcussive Impact-Dependent Increase in Plasma S100 β Levels in Collegiate Football Players. *J Neurotrauma*. 2017 Apr 27. [Epub ahead of print]
- Koerte, I. K., Hufschmidt, J., Muehlmann, M., Tripodis, Y., Stamm, J. M., Pasternak, O., . . . Shenton, M. E. (2016). Cavum Septi Pellucidi in Symptomatic Former Professional Football Players. *J Neurotrauma*, 33(4), 346-353. doi: 10.1089/neu.2015.3880
- Lebel, C., Walker, L., Leemans, A., Phillips, L. and Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage* 40, 1044-1055.
- McAllister, T. W., Flashman, L. A., Maerlender, A., Greenwald, R. M., Beckwith, J. G., Tosteson, T. D., Turco, J. H. (2012). Cognitive effects of one season of head impacts in a cohort of collegiate contact sport athletes. *Neurology*, 78(22), 1777-1784. doi: 10.1212/WNL.0b013e3182582fe7
- McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., . . . group, T. C. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*, 131(1), 75-86. doi: 10.1007/s00401-015-1515-z
- McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., Daneshvar, D. H., . . . Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, 136(Pt 1), 43-64. doi: 10.1093/brain/aws307
- Montenigro, P. H., Alosco, M. L., Martin, B. M., Daneshvar, D. H., Mez, J., Chaisson, C. E., . . . Tripodis, Y. (2016). Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. *J Neurotrauma*. doi: 10.1089/neu.2016.4413
- Montenigro, P. H., Baugh, C. M., Daneshvar, D. H., Mez, J., Budson, A. E., Au, R., . . . Stern, R. A. (2014). Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimers Res Ther*, 6(5), 68. doi: 10.1186/s13195-014-0068-z
- Poole VN, Breedlove EL, Shenk TE, Abbas K, Robinson ME, Leverenz LJ, Nauman EA, Dydak U, Talavage TM. Sub-concussive hit characteristics predict deviant brain metabolism in football athletes. *Dev Neuropsychol*. 2015 Jan;40(1):12-7

- Shaw, P., Kabani, N.J., Lerch, J.P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., Giedd, J.N. and Wise, S.P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci* 28, 3586-3594.
- Stamm, J. M., Bourlas, A. P., Baugh, C. M., Fritts, N. G., Daneshvar, D. H., Martin, B. M., . . . Stern, R. A. (2015). Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology*, 84(11), 1114-1120. doi: 10.1212/WNL.0000000000001358
- Stamm, J. M., Koerte, I. K., Muehlmann, M., Pasternak, O., Bourlas, A. P., Baugh, C. M., . . . Shenton, M. E. (2015). Age at First Exposure to Football Is Associated with Altered Corpus Callosum White Matter Microstructure in Former Professional Football Players. *J Neurotrauma*, 32(22), 1768-1776. doi: 10.1089/neu.2014.3822
- Stern, R. A., Daneshvar, D. H., Baugh, C. M., Seichepine, D. R., Montenigro, P. H., Riley, D. O., McKee, A. C. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology*, 81(13), 1122-1129. doi: 10.1212/WNL.0b013e3182a55f7f
- Stern, R. A., Tripodis, Y., Baugh, C. M., Fritts, N. G., Martin, B. M., Chaisson, C., . . . Taylor, D. D. (2016). Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy. *J Alzheimers Dis*, 51(4), 1099-1109. doi: 10.3233/jad-151028
- Thatcher RW. Maturation of the human frontal lobes. Physiological evidence for staging. *Developmental Neuropsychology* 1991; 7: 397-419
- Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M. and Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PLoS One* 7, e46970.