Clinical diagnosis and risk factors for chronic traumatic encephalopathy

https://hdl.handle.net/2144/19056

Boston University
CLINICAL DIAGNOSIS AND RISK FACTORS FOR CHRONIC TRAUMATIC ENCEPHALOPATHY

by

PHILIP HOMES MONTENIGRO

B.S., Boston University, 2009

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy 2016
Approved by

First Reader
_________________________________________________________
Robert A. Stern, Ph.D.
Professor of Neurology, and Neurosurgery, Anatomy and Neurobiology

Second Reader
_________________________________________________________
Yorghos Tripodis, Ph.D.,
Professor of Biostatistics

Third Reader
_________________________________________________________
Jennifer Luebke, Ph.D.
Professor of Anatomy and Neurobiology
“Case-histories are in fact the medical equivalent of the measurement of quantities in the pure sciences.” —Ernst Jokl, M.D., circa 1941

“The college health authorities are conscious of the pathology of the ‘punch-drunk’ boxer. Just how much one should permit recurrence of cerebral concussion in college athletes is a matter of opinion.” —Augustus Thorndike, M.D., circa 1952

“Physical education is one of the youngest children of science, unknown in its scope not only to the general public but to the majority of educated people. There are few whose concept of its medical implications enables them to apply our present knowledge. Physical education and sport are today still based on empiricism, not on scientific information, and many years must elapse before a rational attitude determines our policy.” —Ernst Jokl, M.D., circa 1941
DEDICATION

To the family and friends whose unceasing love, support, and patience made it possible for me to thrive:

Mr. & Mrs. Crowell
Bradley Crowell
Meridith Crowell
Kyle Crowell
Sarah Michelle Fairfield
Dr. Jonathan Rothenberg
Donna Homes Montenigro
Marjorie Lowe
Dr. John Polk
ACKNOWLEDGMENTS

With deepest gratitude and humility, I acknowledge my indebtedness:

To my primary mentor of six years, Dr. Robert A. Stern, for believing in me and aiding in my growth as both a scientist and a professional. I thank him for always encouraging my curiosity and for providing me with the very best opportunities and resources to explore it.

To co-mentor Dr. Yorghos Tripodis, for showing me how to take day dreams and whip them into statistical measurable quantities. Your willingness as a teacher and patience as a mentor has had a profound impact on my technical and scientific knowledge.

To co-mentor Dr. Robert C. Cantu, for providing me with so many opportunities to succeed and teaching me to execute and publish. Thank you for being a great mentor and friend over the past six years.

To Dr. Jennifer Luebke, who coached me over the years. Thank you for being a stabilizing force throughout my academic maturation. I will be forever grateful.

To Dr. Alexander Lin, for agreeing to “cross the pond” to BU and take time out of your schedule to be on my dissertation committee. Thank you.

To Dr. Elizabeth R. Whitney for agreeing to be the chair of my committee, and for cultivating my genuine appreciation for the art of teaching in the anatomy lab.

To the Boston University Department of Anatomy and Neurobiology, I have benefitted greatly from your excellence and standards in training and education.

To my colleagues and peers at the BU Alzheimer’s Disease and CTE Center,
including Julie S, Christine B, Daniel S, Dan D, Dan C, Brandon G, Dave R, Kim C, Eric S, Nate, Pat, Lauren, Alyssa,, and countless others, your passion and dedication to this field of study is inspiring, it has been a privilege to have known and worked beside you. A special thanks to Danielle Eble for her encouragement.

To the BUSPH Data Core, especially Brett Martin and Christine Chaisson, for your precision and excellence in data science and management. I can’t imagine having done this without you.

To the participants, donors, and family members, who gave a great deal to help this research become realized, your gift is priceless and I thank you. Especially to my better half and partner, Sarah Michelle Fairfield, for putting up with me these past three years and sticking around for more. Thank you for being a sounding board when I need it, an editor, and a best friend.
ABSTRACT

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by a pathognomonic distribution of hyperphosphorylated tau accumulations in neurons, astrocytes, and cell processes, situated around vessels at the depths of cortical sulci. Case reports of CTE pathology exhibit a common exposure to repetitive head impacts (RHI), suggesting that RHI are a necessary factor in the disease’s etiology. Currently, it is only possible to definitively diagnose CTE after death using histopathological techniques and consensus-based neuropathological diagnostic criteria recently established by the National Institute of Health and National Institute of Neurological Disorders and Stroke. Though considerable progress has been made in characterizing the neuropathology of CTE, less is known about the clinical aspects of the
disease. Specifically, additional research is needed to identify disease-specific clinical manifestations, clinicopathological correlations, and a means of diagnosis during life, all of which are critical to developing future epidemiological studies, preventative measures, and treatment trials. Moreover, it is not yet known which specific aspects of RHI exposure (type, frequency, duration) are causally linked to developing clinically meaningful neurological impairments or CTE neuropathology, nor have studies identified risk-modifying factors, such as genotype (e.g. APOE).

The objective of this dissertation’s published works was to systematically address these gaps in knowledge. First, to define a common clinical presentation of CTE, we conducted a retrospective analysis of medical records and semi-structured next-of-kin reports of 36 former athletes with autopsy-confirmed CTE without comorbid neurodegenerative disease. We then published clinical diagnostic criteria for CTE based on a systematic review of clinical features exhibited in 202 former athlete cases and a pooled analysis of 83 neuropathologically confirmed CTE cases. In subsequent analyses, we operationalized clinical criteria to investigate specific clinicopathological associations between tau, amyloid beta, age, APOE genotype, and clinical outcomes and utilized the clinical criteria to explore potential risk-factors related to RHI from boxing and football. Lastly, we developed a metric to quantify cumulative RHI exposure in retired, living, football players. Using this metric, our study was the first to indicate a causal relationship between cumulative RHI exposure and risk of later life cognitive, mood, and behavioral impairment. These studies are preliminary, and our results require replication and validation in larger, longitudinal prospective studies.
# TABLE OF CONTENTS

Title ................................................................................................................................. i
Copyright Page ............................................................................................................. ii
Reader’s Approval Page ............................................................................................... iii
Epigraph ...................................................................................................................... iv
Dedication ................................................................................................................... v
Acknowledgements ................................................................................................... vi
Abstract ..................................................................................................................... viii
Table of Contents ..................................................................................................... x
List of Tables ........................................................................................................... xiii
List of Figures .......................................................................................................... xiv
List of Abbreviations .............................................................................................. xv

**Introduction and General Overview** ....................................................................... 1

**Chapter 1. Clinical Presentation of Chronic Traumatic Encephalopathy** .............. 9
  *Introduction* ........................................................................................................... 9
  *Methods* ............................................................................................................... 10
  *Results* ............................................................................................................... 12
  *Discussion* ......................................................................................................... 19
  *References* ......................................................................................................... 26

**Chapter 2. Clinical Subtypes of Chronic Traumatic Encephalopathy, Literature Review and Proposed Research Diagnostic Criteria for Traumatic Encephalopathy Syndrome** ................................................................. 30
  *Introduction* ........................................................................................................ 30
  *Literature Search Methods* ................................................................................ 36
  *Results of Literature Review* ............................................................................. 37
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Beta-Amyloid Deposition in Chronic Traumatic Encephalopathy</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Methods</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Results</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>108</td>
</tr>
<tr>
<td>4</td>
<td>Clinical Features of Repetitive Traumatic Brain Injury and Chronic</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>Traumatic Encephalopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>Traumatic Brain Injury</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>Chronic Traumatic Encephalopathy</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>Boxing and American Football</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>Case Studies</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>Conclusions and Future Directions</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>154</td>
</tr>
<tr>
<td>5</td>
<td>Cumulative Head Impact Exposure Predicts Later-Life Depression,</td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>Apathy, Executive Dysfunction, and Cognitive Impairment in Former</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High School and College Football</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>Methods</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>188</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Conclusion</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td><strong>Discussion and Future Directions</strong></td>
<td>206</td>
<td></td>
</tr>
<tr>
<td>Cumulative Bibliography</td>
<td>215</td>
<td></td>
</tr>
<tr>
<td>Curriculum Vitae</td>
<td>241</td>
<td></td>
</tr>
</tbody>
</table>
LIST OF TABLES

1.1 Description of sample by initial clinical presentation ........................................ 14
1.2 Clinical features and course by initial clinical presentation .................................. 16
1.3 Specific clinical features by initial clinical presentation ...................................... 17
2.1 Summary of published cases describing the clinical features of CTE .................. 40
2.2 Summary of Clinical Features of CTE ................................................................. 45
3.1 Frequency of Aβ deposition in CTE ................................................................. 85
3.2 APOE allele frequencies in CTE ....................................................................... 88
Supp. 3.1 Characteristics of subjects examined by immunohistochemistry and ELISA .. 90
3.3 Clinical, exposure, and pathological findings in CTE with and without Aβ .......... 100
3.4 CTE Stage and frequency of Aβ deposition by sport or military history ............ 101
4.1 International classification for diseases 10th revision criteria for PCS ................. 117
4.2 Diagnostic and statistical manual of mental disorders 4th edition criteria for PCS ... 117
4.3 Symptoms of chronic traumatic encephalopathy .............................................. 132
4.4 General diagnostic criteria for traumatic encephalopathy ................................. 135
4.5 Criteria for diagnostic subtypes with modifiers ............................................... 136
4.6. Chronic traumatic encephalopathy likelihood criteria ..................................... 136
4.7 Comparison CTE clinicopathological features in boxers versus football players ... 146
5.1 Demographics .................................................................................................... 167
5.2 Exposure variables ............................................................................................ 169
5.3 Summary of data collected from review of helmet-accelerometer studies .......... 172
5.4 Calculation of the Cumulative Head Impacts Index ......................................... 175
5.5 Behavior, mood, and cognition outcome measures .......................................... 182
5.6 Change point thresholds from baseline constant risk to dose-response relation .... 183
Supp 5.1 Predicted probabilities of impairment with 95% CI for different doses ....... 185
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Section</th>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Comparison of tau pathology in CTE and AD</td>
<td>3</td>
</tr>
<tr>
<td>3.1 Aβ neuritic plaques in CTE and normal aging</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>3.2 Tau and Aβ concentrations within the sulcal depths and gyral crests</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>3.3 Total levels of Aβ in subjects with AD, CTE-AD, or CTE (ELISA)</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>3.4 Interaction between Aβ, age, and CTE stage</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>3.5 Ptau2311evels as measured by ELISA</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>4.1 Pathophysiology of second-impact syndrome</td>
<td></td>
<td>119</td>
</tr>
<tr>
<td>4.2 Representative diffusion tensor imaging tracking in a motor pathway</td>
<td></td>
<td>127</td>
</tr>
<tr>
<td>4.3 Left thalamus volume and years of professional fighting in retired boxers</td>
<td></td>
<td>128</td>
</tr>
<tr>
<td>4.4 Impact mechanics in boxing and football</td>
<td></td>
<td>143</td>
</tr>
<tr>
<td>4.5 Neuropathology and cerebellar degeneration in a boxer and a football player</td>
<td></td>
<td>151</td>
</tr>
<tr>
<td>5.1 Illustration depicting the relationship of CHII to risk of impairment</td>
<td></td>
<td>180</td>
</tr>
<tr>
<td>5.2 Predicted impairment with 95% CI for different doses of cumulative exposure</td>
<td></td>
<td>184</td>
</tr>
<tr>
<td>Discussion</td>
<td>Dissertation Synthesis</td>
<td>211</td>
</tr>
</tbody>
</table>
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Aβ</td>
<td>Amyloid β Peptide</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid Precursor Protein</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CSTE</td>
<td>Center for the Study of Traumatic Encephalopathy</td>
</tr>
<tr>
<td>C9ORF72</td>
<td>Chromosome 9 Open Reading Frame 72</td>
</tr>
<tr>
<td>CTE</td>
<td>Chronic Traumatic Encephalopathy</td>
</tr>
<tr>
<td>CTEC</td>
<td>Chronic Traumatic Encephalopathy Center</td>
</tr>
<tr>
<td>CTE-AD</td>
<td>Chronic Traumatic Encephalopathy with AD</td>
</tr>
<tr>
<td>CERAD</td>
<td>Consortium To Establish A Registry Of AD</td>
</tr>
<tr>
<td>CHII</td>
<td>Cumulative Head Impact Index</td>
</tr>
<tr>
<td>DP</td>
<td>Diffuse Plaques</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>GRN</td>
<td>Progranulin</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MAPT</td>
<td>Microtubule-Associated Protein Tau</td>
</tr>
<tr>
<td>NP</td>
<td>Neuritic Plaques</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PCS</td>
<td>Post-Concussion Syndrome</td>
</tr>
<tr>
<td>p-tau</td>
<td>Hyperphosphorylated Tau</td>
</tr>
<tr>
<td>ptau231</td>
<td>Tau Phosphorylated at Threonine 231</td>
</tr>
</tbody>
</table>
RBT.................................................................Repetitive Brain Trauma
RHI...............................................................Repetitive Head Impacts
RTBI ..............................................................Repetitive Traumatic Brain Injury
SIS.................................................................Second Impact Syndrome
TES-BMv............................................................TES Behavioral/Mood Variant
TES-COGv............................................................TES Cognitive Variant
TES-Dv ............................................................TES Dementia Variant
TES-MIXv ..........................................................TES Mixed Variant
TBI .................................................................Traumatic Brain Injury
TES ...............................................................Traumatic Encephalopathy Syndrome
Introduction and General Overview

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that is most often reported in postmortem autopsies of individuals exposed to repetitive head impacts, such as former boxers and American football players. The neuropathology of CTE is characterized by accumulations of hyperphosphorylated tau in a pattern that is distinct from other forms neurodegenerative tauopathy, including Alzheimer’s disease (see Figure 1). In the past decade, considerable progress has been made in the postmortem neuropathological characterization of CTE. In February of 2015, an expert panel convened by the National Institutes of Health (NIH) and the National Institute of Neurological Disorders and Stroke (NINDS) met at Boston University and successfully published the first set of consensus-based neuropathological diagnostic criteria for CTE [2]. The primary criteria for diagnosis involves “p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern [1].” Additional supportive features related to p-tau include: 1.) neurofibrillary tangles (NFTs) preferentially affecting superficial cortical layers II–III, 2.) NFTs and dendritic swellings preferentially affecting the CA2/CA4 of the hippocampus and p-tau immunoreactive lesions, 3.) neuronal and astrocytic aggregates in subcortical nuclei, 4.) thorny astrocytes in the glial limitans, subpial, and periventricular regions, and 5.) grain- and dot-like structures. Gross findings that were supportive of a diagnosis consisted of disproportionate dilatation of the third ventricle, septal abnormalities (e.g., cavum), mammillary body atrophy, and signs of previous traumatic injuries. These criteria represent an important development in the
study of long-term outcomes related to brain trauma [3]. Notably, published case reports of CTE pathology that meet these criteria all share a common history of exposure to repetitive head impacts (RHI).
Figure 1. Comparison of hyperphosphorylated tau progression in CTE and AD.

Figure 1. The characteristic neuropathologic findings of chronic traumatic encephalopathy including p-tau neurofibrillary tangle accumulations involving (a) superficial cortical layers that are commonly situated at the depths of the (b) cerebral sulci and in (c) perivascular spaces. (d) The microscopic p-tau pathology is often found in the relative absence of amyloid neuritic plaques. Comparatively, the cortical laminar distribution of p-tau pathology in AD typically involves the (e) deeper layers and is found neither (f) in the depths of the cerebral sulci nor (g) perivascularly. Additionally, AD pathology involves (h) neuritic amyloid plaques with concomitant p-tau neurofibrillary tangles. Figure previously published in Annual Reviews of Clinical Psychology 2015 [1].
Despite considerable progress in characterizing CTE’s neuropathology, little is known about its clinical aspects and etiology during life [4]. There has been a lack of quantitative evidence associating the neuropathological features of CTE to clinical impairments before death [5]. Moreover, while RHI exposure is necessary for CTE neuropathology, it is not yet known what specific aspects of exposure (type, frequency, duration) are causally linked to the development of neurological impairment and CTE. Further research is needed to identify disease-specific clinical presentations, clinicopathological associations, and risk-factors. To address these important issues, a critical next step involves defining clinically practical measurements of RHI exposure and devising criteria to diagnose neurological impairment from RHI and CTE in vivo. Having clinical criteria that can accurately identify CTE in a living person will be necessary to conduct future treatment and prevention trials, as well as perform epidemiological research to determine incidence and prevalence [6].

The main objective of the dissertation’s published works was to systematically address these gaps in knowledge.

The first chapter [7] focused on identifying the clinical presentation specific to CTE using semi-structured questionnaires with next-of-kin informants and medical record review of 36 neuropathologically confirmed cases of CTE without comorbid neurodegenerative disease. A triad of symptoms from three clinical domains – behavior, mood, and cognition – were identified in more than 70% of cases [7]. In chapter two [8] we propose clinical diagnostic criteria for CTE based on a systematic review of clinical features exhibited in 202 former athlete cases and a pooled analysis of clinical features
reported in 83 neuropathologically confirmed CTE cases [8]. Like many other
neurodegenerative diseases (e.g. Alzheimer’s disease, amyotrophic lateral sclerosis
frontotemporal dementia, multiple sclerosis, etc), the clinical symptoms in our CTE
sample clustered into distinct recurring phenotypes (i.e., clinical subtypes) [8]. Of the 84
pooled CTE cases, the initial symptoms and presentation at disease onset were reported in
54. Analysis of the initial presenting symptoms in the remaining 54 cases confirmed and
extended the observations made in chapter one [7] having also demonstrated the presence
of subtypes, including: a subtype group with behavioral/mood symptom onset at an
earlier age (32%), a subtype group with cognitive symptom onset at a later age (28%),
and a mixed symptom onset subtype group (40%) [8].

With clinical diagnostic criteria operationalized in our sample, we performed
quantitative analyses of the clinical features associated with CTE neuropathology in both
chapters three [9] and four [10]. In chapter three [9], specific clinicopathological
associations were assessed between tau, amyloid beta, age, APOE status, and the clinical
outcomes designated by our clinical presentation and diagnostic criteria [7,8]. We
hypothesized that subject specific modifiers, like ApoE4 genotype, would increase the
risk of manifesting one clinical subtype over another [9]. We also hypothesized that the
presence of co-morbid neuropathological lesion, such as amyloid beta plaques or Lewy
bodies, would significantly alter the severity and progression of CTE tauopathy [9]. In
chapter four, we tested the hypothesis that neuropathologically confirmed CTE cases with
histories of cumulative exposure to RHI from different contact sports, such as boxing and
American football, would have significant differences in the frequency of certain clinical
manifestations and regional severity CTE tauopathy [10].

In the final chapter [11] we develop a metric to quantify cumulative repetitive head impact exposure from amateur football, which we term the cumulative head impact index (CHII). We used this index to examine the relationship between cumulative exposure to RHI and the risk of later-life depression, apathy, behavioral dysregulation, executive dysfunction, and cognitive impairment among former high school and college football players [11]. We found a strong, threshold dose-response relationship between estimated exposure and risk of impairment. Moreover, this new single index of cumulative head impact exposure was shown to be a better and stronger predictor of later life risk of impairment than previously studied measures, including: total years or seasons played, age at first exposure, and number of reported concussions. Using an instrumental variable analysis, we provide the first statistical evidence of a causal relationship between RHI and later-life impairment [11].
References


Chapter 1
Clinical Presentation of Chronic Traumatic Encephalopathy

Copyright © 2013, American Academy of Neurology

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau) [1,2]. To date, CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to explosive blast, and others subjected to repetitive brain trauma (RBT), including concussive and subconcussive injuries [1-5]. All reported neuropathologically confirmed cases of CTE have had exposure to RBT. However, not all individuals with histories of RBT develop CTE, indicating that additional risk factors, including genetics, likely play a role in the neuropathogenesis of this disease. For example, it has been suggested that the apolipoprotein E (ApoE) ε 4 allele may increase susceptibility for CTE [6].

Previously published descriptions of the clinical presentation of CTE vary. Case reports of presumptive CTE (formerly termed dementia pugilistica or “punch-drunk” when thought limited to boxers [4]) indicated a constellation of clinical features, including impairments in cognition, behavior, and mood, and in some cases, chronic headache and motor and cerebellar dysfunction. Several case reports of boxers suggested two forms of presentation: (1) younger onset, with initial behavioral and mood
disturbance, but with minimal cognitive and motor features; and (2) older onset, with
greater cognitive impairment, and, often, motor disturbance [4,7-10]. In advanced cases,
CTE is associated with dementia, although it is unclear whether the clinical presentation
of CTE dementia is different from that associated with Alzheimer’s disease (AD) or other
age-related neurodegenerative disorders [11-13]. Herein, we describe the clinical
presentation, course, and ApoE genotype of a sample of 36 athletes with
neuropathologically confirmed CTE.

Methods

Subjects. The brains of 81 subjects in the Boston University Center for the Study
of Traumatic Encephalopathy (CSTE) brain bank met recently published criteria for the
neuropathologic diagnosis of CTE [1]. For the current study, 45 cases were excluded due
to: (1) primary exposure to RBT from non-athletic activities; (2) inability to contact next-
of-kin to conduct an interview; and (3) presence of comorbid motor neuron disease [14],
neurodegenerative disease, or other significant neuropathology. Seven were military
veterans with unknown or no athletic history, 10 had no next-of-kin contact, and 28 had
comorbid neuropathologic disease. Of the 36 remaining subjects, 28 were included in a
previous report1 and 8 were new cases.

CTE Neuropathological Staging. The cases were categorized into the four-stage
rating scale of CTE (I=least severe, IV=most severe) based on the severity of p-tau
pathology, as previously reported [1]. Diagnosis and staging were conducted blind with
respect to medical history, ApoE genotype, and informant interview.

**Interview and Medical Record Review.** History and clinical presentation were obtained through postmortem telephone interviews with next-of-kin by a neuropsychologist (RAS) blinded to neuropathological findings and ApoE genotype status. Medical records were available and reviewed for 23 cases. The semi-structured interview was based on previous studies of postmortem dementia diagnosis made by interviews with family members [15,16]. Information queried during the interview included: demographics; cause of death; and athletic, military, medical, neuropsychiatric, and social/occupational histories. The interview included specific questions regarding dementia, depression, changes in cognition, behavior, mood, and motor functioning, as well as instrumental activities of daily living. Responses were qualitatively summarized into an overall assessment of the subject’s presentation and course of symptoms and functioning. The number of informants interviewed per case ranged from 1-7 (median=2), with each interview lasting approximately 60 minutes. Interviews were conducted at a median time of 4 months following time of death.

**ApoE Genotyping.** DNA was extracted from brain tissue samples using a Qiagen QIAamp DNA extraction kit (Quiagen, Valencia, CA). Two single-nucleotide polymorphisms (SNPs; NCBI SNPs rs429358 and rs7412) were examined using TaqMan assays (Applied Biosystems, Foster City, CA). Allelic discrimination was automated using the manufacturer’s software. Positive controls, consisting of DNA of each of the
six possible APOE genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4), were included on each plate and genotyped with restriction isotyping.

**Statistical Analyses.** Between-group differences were examined by independent sample T-tests. Chi-square analyses were used for between group comparisons for categorical data. ApoE genotype analyses comparing CTE cases with population norms [17] were conducted with the Chi-square goodness of fit test. A probability level of \( p=.05 \) was used throughout. All statistical analyses were conducted with IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY).

**Standard Protocol Approvals, Registrations, and Patient Consents.** Approvals for brain donation, post-mortem clinical record review, interviews with family members, and neuropathological evaluation, were provided by the Institutional Review Boards of Boston University Medical Center and the Bedford VA Hospital.

**Results**

Table 1 summarizes the demographics, cause of death, athletic history, neuropathological stage, and ApoE genotypes of the sample. All subjects were male athletes, with 6 (17%) African American and 1 (3%) of Hispanic origin. There were 29 football players (22 who played professionally, 4 who only played through college, and 3 who only played through high school), 3 professional hockey players, 1 professional wrestler, and 3 boxers (1 professional, 2 amateur). Of the football players, the most
common position played was lineman (48%), followed by running back (21%),
linebacker (10%), and smaller numbers of other positions. There were no quarterbacks or
kickers. Of the 36 subjects, 3 (8%) were asymptomatic. Tables 2 and 3 describe the
clinical features and course of the remaining 33 subjects.
Table 1.1 Description of Sample by Initial Clinical Presentation

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (N=36)</th>
<th>Behavior/Mood Group (N=22)*</th>
<th>Cognition Group (N=11)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Death</strong>&lt;br&gt;(M±SD, range)</td>
<td>56.8±21.9&lt;br&gt;(17-98)</td>
<td>51.4 ±18.5&lt;br&gt;(21-84)*</td>
<td>69.2±21.8&lt;br&gt;(34-98)*</td>
</tr>
<tr>
<td>Cause of Death,%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Illness = 41.8</td>
<td></td>
<td>Systemic Illness = 49.8</td>
<td>Systemic Illness = 27.3</td>
</tr>
<tr>
<td>Accidental OD = 13.9</td>
<td></td>
<td>Accidental OD = 18.2</td>
<td>Accidental OD = 9.1</td>
</tr>
<tr>
<td>Dementia-Related = 13.9</td>
<td></td>
<td>Dementia-Related = 9.1</td>
<td>Dementia-Related = 27.3</td>
</tr>
<tr>
<td>Suicide = 16.7</td>
<td></td>
<td>Suicide = 18.2</td>
<td>Suicide = 18.2</td>
</tr>
<tr>
<td>Injury = 8.4</td>
<td></td>
<td>Injury = 4.5</td>
<td>Injury = 18.2</td>
</tr>
<tr>
<td>Years of Education&lt;br&gt;(M±SD, range)</td>
<td>15.0±2.4&lt;br&gt;(10-20)</td>
<td>14.5±2.4&lt;br&gt;(10-18)</td>
<td>15.7±1.4&lt;br&gt;(13-18)</td>
</tr>
<tr>
<td>Football as Primary Sport, %</td>
<td>80.6</td>
<td>72.7</td>
<td>90.9</td>
</tr>
<tr>
<td>Total Years of Football Played&lt;br&gt;(M±SD, range)</td>
<td>15.3±6.4&lt;br&gt;(3-25)</td>
<td>14.4±6.5&lt;br&gt;(3-25)</td>
<td>18.2±5.9&lt;br&gt;(5-24)</td>
</tr>
<tr>
<td>Neuropathological Severity Stage, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I = 8</td>
<td></td>
<td>Stage I = 9.1</td>
<td>Stage I = 0</td>
</tr>
<tr>
<td>Stage II = 28</td>
<td></td>
<td>Stage II = 31.8</td>
<td>Stage II = 9.1</td>
</tr>
<tr>
<td>Stage III = 31</td>
<td></td>
<td>Stage III = 31.8</td>
<td>Stage III = 36.4</td>
</tr>
<tr>
<td>Stage IV = 33</td>
<td></td>
<td>Stage IV = 27.3</td>
<td>Stage IV = 54.5</td>
</tr>
<tr>
<td>ApoE Genotype, b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε2/ε2=0</td>
<td></td>
<td>ε2/ε2 = 0</td>
<td>ε2/ε2 = 0</td>
</tr>
<tr>
<td>ε2/ε3=3</td>
<td></td>
<td>ε2/ε3 = 4.5</td>
<td>ε2/ε3 = 0</td>
</tr>
<tr>
<td>ε2/ε4=0</td>
<td></td>
<td>ε2/ε4 = 0</td>
<td>ε2/ε4 = 0</td>
</tr>
<tr>
<td>ε3/ε3=63</td>
<td></td>
<td>ε3/ε3 = 63.6</td>
<td>ε3/ε3 = 54.5</td>
</tr>
<tr>
<td>ε3/ε4=26</td>
<td></td>
<td>ε3/ε4 = 27.3</td>
<td>ε3/ε4 = 27.3</td>
</tr>
<tr>
<td>ε4/ε4=9</td>
<td></td>
<td>ε4/ε4 = 4.5</td>
<td>ε4/ε4 = 18.2</td>
</tr>
</tbody>
</table>

*3 subjects were asymptomatic; percentages within initial feature group are based on the percent of symptomatic subjects.

b1 subject did not have ApoE genotyping

OD=Overdose

*Statistically significant between-group difference, p < 0.05
Eleven of the symptomatic cases were reported to have initial changes in cognitive functioning (e.g., episodic memory impairment, executive dysfunction) prior to behavioral or mood disturbance. Initial changes in behavior (e.g., explosivity, impulsivity, violence) prior to mood or cognitive disturbance were reported in 13 subjects. Mood changes (e.g., depression, hopelessness) were reported as the initial feature in 9 subjects. None of the subjects had motor disturbance as their initial feature. The subgroups with initial behavioral symptoms and mood changes were similar in age of initial presentation, age of death, and neuropathological stage, and were combined into a behavior/mood group (n=22). Subjects whose initial difficulties involved cognitive functioning comprised a cognition group (n=11). Tables 1-3 describe demographics and clinical features for the behavior/mood and cognition subgroups.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic Subjects (N=33)¹</th>
<th>Behavior/Mood Group (N=22)¹</th>
<th>Cognition Group (N=11)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Progressive Course</td>
<td>90.9%</td>
<td>86.4%</td>
<td>100%</td>
</tr>
<tr>
<td>% with Dementia at Death</td>
<td>30.3%</td>
<td>18.2%*</td>
<td>54.5%*</td>
</tr>
<tr>
<td>Age First Clinical Feature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed (yrs) M ± SD (range)</td>
<td>42.5 ± 17.8 (19-82)</td>
<td>34.5 ± 11.6 (19-59)*</td>
<td>58.5 ± 17.7 (31-82)*</td>
</tr>
<tr>
<td>Duration of Clinical Features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(yrs) M ± SD (range)</td>
<td>14.9 ± 12.9 (0-51)</td>
<td>17.0 ± 14.3 (0-51)</td>
<td>10.7 ± 8.5 (1-30)</td>
</tr>
<tr>
<td><strong>Initial Clinical Domain (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>33.3%</td>
<td>--</td>
<td>100%</td>
</tr>
<tr>
<td>Behavior</td>
<td>39.4%</td>
<td>59.1%</td>
<td>--</td>
</tr>
<tr>
<td>Mood</td>
<td>27.3%</td>
<td>40.9%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Clinical Domain(s) Ever Observed During Life (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>93.9%</td>
<td>90.9%</td>
<td>100%</td>
</tr>
<tr>
<td>Behavior</td>
<td>75.8%</td>
<td>86.4%*</td>
<td>54.5%*</td>
</tr>
<tr>
<td>Mood</td>
<td>84.8%</td>
<td>95.4%*</td>
<td>63.6%*</td>
</tr>
<tr>
<td>Motor</td>
<td>30.3%</td>
<td>27.3%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Cognition &amp; Behavior</td>
<td>75.8%</td>
<td>86.4%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Cognition &amp; Mood</td>
<td>81.8%</td>
<td>90.9%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Cognition &amp; Motor</td>
<td>30.3%</td>
<td>27.3%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Behavior &amp; Mood</td>
<td>72.7%</td>
<td>86.4%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Behavior &amp; Motor</td>
<td>27.3%</td>
<td>27.3%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Mood &amp; Motor</td>
<td>30.3%</td>
<td>27.3%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Cognition, Behavior &amp; Mood</td>
<td>72.7%</td>
<td>86.4%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Cognition, Behavior &amp; Motor</td>
<td>27.3%</td>
<td>27.3%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Cognition, Mood &amp; Motor</td>
<td>30.3%</td>
<td>27.3%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Behavior, Mood &amp; Motor</td>
<td>27.3%</td>
<td>27.3%</td>
<td>27.3%</td>
</tr>
<tr>
<td>All Four Domains</td>
<td>27.3%</td>
<td>27.3%</td>
<td>27.3%</td>
</tr>
<tr>
<td>% with History of Headaches</td>
<td>34.4%</td>
<td>38.1%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Death by Suicide</td>
<td>18.2%</td>
<td>18.2%</td>
<td>18.2%</td>
</tr>
<tr>
<td>% History of Substance Abuse</td>
<td>39.4%</td>
<td>36.4%</td>
<td>45.5%</td>
</tr>
</tbody>
</table>

¹Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.

*Statistically significant, p < 0.05
**Table 1.3. Specific Clinical Features by Initial Clinical Presentation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic Subjects (N=33)</th>
<th>Behavior/Mood Group (N=22)</th>
<th>Cognition Group (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory Impairment</td>
<td>84.8%</td>
<td>77.3%</td>
<td>100%</td>
</tr>
<tr>
<td>Executive Dysfunction</td>
<td>78.8%</td>
<td>72.7%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Attention Difficulties</td>
<td>72.7%</td>
<td>63.6%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Language Impairment</td>
<td>57.6%</td>
<td>54.5%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Visuospatial Difficulties</td>
<td>54.5%</td>
<td>54.5%</td>
<td>54.5%</td>
</tr>
<tr>
<td><strong>Behavioral Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explosivity</td>
<td>57.6%</td>
<td>72.7%*</td>
<td>27.3%*</td>
</tr>
<tr>
<td>Impulse Control Problems</td>
<td>45.5%</td>
<td>54.5%</td>
<td>27.3%</td>
</tr>
<tr>
<td>“Out of Control”</td>
<td>51.5%</td>
<td>63.6%*</td>
<td>27.3%*</td>
</tr>
<tr>
<td>Physically Violent</td>
<td>51.5%</td>
<td>68.2%*</td>
<td>18.2%*</td>
</tr>
<tr>
<td>Verbally Violent</td>
<td>48.5%</td>
<td>73.6%*</td>
<td>18.2%*</td>
</tr>
<tr>
<td>Disinhibited Speech</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Disinhibited Behavior</td>
<td>3.0%</td>
<td>0%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Socially Inappropriate</td>
<td>3.0%</td>
<td>0%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Paranoia</td>
<td>18.2%</td>
<td>22.7%</td>
<td>9.1%</td>
</tr>
<tr>
<td><strong>Mood Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadness/Depression</td>
<td>63.6%</td>
<td>86.4%*</td>
<td>18.2%*</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>15.2%</td>
<td>13.6%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Manic Behavior/Mania</td>
<td>3.0%</td>
<td>4.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Suicidal Ideation/Attempts</td>
<td>30.3%</td>
<td>31.8%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>63.6%</td>
<td>72.7%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Apathy</td>
<td>6.1%</td>
<td>9.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

13 subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.

*Statistically significant between-group difference, p < 0.05
Ten subjects were diagnosed with dementia; 4 were clinically diagnosed with AD, 4 with “dementia pugilistica” or “football-related” dementia, and 2 with unspecified dementia. All had stage IV CTE. Of the 10, 7 exhibited cognitive symptoms initially, 2 exhibited mood symptoms initially, and 1 initially presented with behavior changes. The mean age of symptom onset for the dementia group was 57.7 (SD=18.3; range 25-82) and the mean age of dementia diagnosis was 72.6 (SD=8.5, range 56-83). The mean length of time between dementia diagnosis and death was 8.0 years (SD=5.5, range <1-15). Four subjects with dementia had gait difficulties, 3 had a history of falls, and 1 had a history of tremor. Two (20%) subjects with dementia had a history of headaches, compared with 11 (44%) subjects without dementia. All 10 subjects had both memory and executive impairment, 7 had language deficits, and 2 had visuospatial difficulties. Six of the 10 were characterized by behavioral impairment, predominantly described as having a “short fuse” or being “out of control.” Four of the 10 were physically violent and 2 were verbally violent. Although 1 subject demonstrated disinhibited behavior, none of the subjects had disinhibited speech or socially inappropriate behaviors. Of the 7 who were reported to have mood disturbance, 2 had predominantly sadness/depressive symptoms and 2 had anxiety symptoms. The only 2 subjects in the entire sample reported to have had apathy were in the dementia group.

The proportions of ApoE genotypes (i.e., ε4 homozygotes, combined ε4 homozygotes and heterozygotes, and ε4 non carriers) in our CTE sample were significantly different from those found in an age-matched normative sample [17], ($\chi^2 [2] = 6.63, p < .05$). A binomial test revealed that the primary difference between our CTE
sample and population norms was a greater proportion of ε4 homozygotes in our sample (p < .05). When examining the two initial presentation groups, there were no differences between the behavior/mood group and the age matched normative sample ($\chi^2 [2] = 0.46$, $p > .05$). However, there were proportionally more ε4 homozygotes in the cognition group than expected ($\chi^2 [2] = 13.3$, $p < .05$). The relative proportions of ApoE genotypes in our 10 subjects with dementia were not significantly different from those seen in AD [$18$] ($\chi^2 [2] = 1.52$, $p > .05$).

**Discussion**

Consistent with earlier reports of boxers [4,7-10], our findings suggest that there may be two different clinical presentations of CTE, with one initially exhibiting behavioral or mood changes, and the other initially exhibiting cognitive impairment. The behavior/mood group demonstrated symptoms at a significantly younger age than the cognition group. Although almost all subjects in the behavior/mood group demonstrated cognitive impairments at some point, significantly fewer subjects in the cognition group demonstrated behavioral and mood changes during the course of their illness. There were distinctions between the two groups regarding specific features present in each domain. The behavior/mood group was significantly more explosive, out of control, physically and verbally violent, and depressed than the cognition group. Whereas all subjects in the cognition group were reported to have impaired episodic memory, approximately one quarter of the behavior/mood group did not have memory difficulties. Subjects in the cognition group were significantly more likely to progress to dementia than those in the
behavior/mood group but were also significantly older at the time of death. Given the small sample size in this study, however, it is unclear if these two these apparently distinct clinical subtypes are representative of all individuals with CTE. In addition, the subsample of cases with dementia is also small, thus limiting the generalization of the presentation of CTE dementia. Further research is needed to clarify and validate these findings.

We examined the potential role of the ApoE ε4 allele as a susceptibility factor for CTE. Our findings indicate that there were significantly more ε4 homozygotes in the sample than expected in a normal, age-matched population. Furthermore, this effect was largely driven by the cognition group: 2 of 11 subjects in the cognition group and 1 of 22 subjects in the behavior/mood group was homozygous for the ε4 allele. In addition, 1 of the 10 CTE subjects diagnosed with dementia during life was ε4 homozygous. Although interpretation and generalization of these results is difficult due to the small sample, the proportion of ε4 homozygosity is in contrast to population norms in which ε4 homozygosity only occurs in 1-3% of the general population [17], and more consistent with the 10% of patients with AD who are ε4 homozygous [18]. The ApoE ε4 variant is the largest known genetic risk factor for sporadic AD [18]. It has been associated with beta-amyloid, but not tau, deposition in cognitively normal aging [19]. ApoE ε4 has also been associated with greater severity of cognitive deficits and longer recovery time following traumatic brain injury (TBI) and RBT in a variety of populations, including boxers and professional football players [20-24], and may increase the risk for clinical dementia following TBI [25]. It has been hypothesized that the ApoE ε4 isoform may
have direct neurotoxic effects leading to mitochondrial dysfunction and cytoskeletal changes, resulting in increased risk for neurodegeneration [26]. Despite the small sample size and other limitations in the current study, future research on the role of ApoE in CTE risk appears warranted. However, other potential susceptibility genes also merit consideration, including mutations to the microtubule-associated protein tau (MAPT) gene, the progranulin (GRN) gene, and the chromosome 9 open reading frame 72 (C9orf72) gene. Moreover, additional non-genetic risk factors for CTE should be examined in future research, including studies to determine what specific aspects of RBT exposure (e.g., types, severity, frequency, initial age, and duration of trauma) are associated with CTE, as well as what potential lifestyle variables (e.g., diet, exercise, obesity, steroid use) are associated with the disease initiation and variability in presentation.

It is noteworthy that motor features, including parkinsonism, were not common in our sample. This is in contrast to some earlier descriptions of CTE in boxers, in which these motor features were quite prominent [4]. However, our findings are consistent with other case reports of predominantly younger onset boxers, in which motor disturbance was not common [4,7-10]. It is not clear why some individuals with CTE develop motor features and others do not. One possibility may be the differences in the biomechanics of injury. For example, in boxing, angular acceleration and torsional injury involving the brainstem and cerebellum is thought to be a pathogenic mechanism of traumatic brain injury following a hook or jab to the jaw, whereas transverse and linear acceleration and deceleration injury are more characteristic of football dynamics [27,28]. As a result,
degeneration of brainstem structures that produce parkinsonism, such as the substantia nigra, might occur earlier in the course of disease in boxers. In contrast, football players might develop substantia nigra degeneration later in the course of their disease, at a time when widespread cortical and basal ganglionic degeneration mask the development of motor disturbance. Related mechanisms of injury leading to CTE have been suggested by recent experimental studies of blast neurotrauma [3].

Although many of the symptoms of CTE are similar to AD and other causes of dementia [11,29] there are factors that appear to clinically differentiate CTE from other age-related neurodegenerative diseases. For example, behavioral changes observed early in the course of CTE could be confused with the behavioral variant of frontotemporal dementia (bvFTD), especially in a patient in his or her 50’s without any significant memory impairment. However, common changes in bvFTD typically include disinhibited and inappropriate behavior and speech, as well as apathy [30]; these symptoms were not frequent in our case series. In addition, the progressive memory impairment observed in over 80 percent of our CTE cases, and in all 10 of the subjects with dementia, could lead to an inaccurate diagnosis of AD when the underlying disease is CTE [12].

It is not clear what neuropathological changes may lead to the two possible clinical presentations observed in this study. It is unlikely that the small, focal cortical p-tau lesions found in stage I and II CTE produce clinically meaningful behavioral and mood symptoms. However, these features may be associated with the neurofibrillary tangles in the locus coeruleus and amygdala found in younger subjects in a previous
The memory and executive dysfunction in the older cognition group may be due to the more extensive degenerative changes in the hippocampus and frontal cortices seen in CTE stages III and IV [1]. It is possible, however, that some of the features evident in the younger behavior/mood group were due to persistent post-concussion syndrome (PCS) [31], with unresolved or even progressive [32] axonal damage resulting from the initial traumas. Axonal injury has been shown in all neuropathological stages of CTE, ranging from multifocal, perivascular axonal varicosities in the cortex and white matter in stages I–II, to more extensive, diffuse axonal loss in the cortex and white matter in stages III–IV [1]. Recent reports have demonstrated that repetitive subconcussive trauma is associated with white matter abnormalities on diffusion tensor imaging [33,34] and abnormal functional MRI tests [35]. Additional findings indicate that there may be persistent and progressive inflammation and white matter degeneration following even a single TBI [36]. Further research is required to delineate these clinicopathologic relationships.

Three subjects in our case series were asymptomatic. One of these cases was only 17 years old and had stage I neuropathology. Both of the other two cases were much older football players (one in 40’s, one in 80’s), had stage II neuropathology, and were homozygous for ApoE ε3. Both also had advanced graduate degrees, were very successful in their professional careers, and were described as extremely intelligent. Although speculative, these findings raise the possibility that cognitive reserve [37] may play a role in protecting against the clinical manifestations of CTE. A recent report suggests that cognitive reserve may mitigate cognitive decline in older individuals with
earlier life TBI [38]. Future research examining the roles of cognitive reserve, genetics, and environmental factors in determining resilience to clinical manifestations and the progression of p-tau pathology will help elucidate the pathobiology of CTE.

Although these findings are based on the largest cohort of subjects with neuropathologically confirmed CTE without comorbidities studied to date, interpretation and generalizability of these results is limited by several factors. First, the overall sample size is small, and caution should be taken when generalizing these results to the larger population of athletes or to the overall clinical presentation of CTE. In addition, there are inherent selection biases imposed in a postmortem brain donation study. For example, families choosing to donate may be more likely to have witnessed symptoms during life. This could lead to reports of more severe symptoms than a typical CTE population, and could account for only having three asymptomatic cases. From the broader CTE cohort in the CSTE brain bank, we selected a smaller sample by eliminating individuals with comorbid pathology and only including athletes; this restriction may further limit the generalizability of our findings. Results from this study should not be interpreted in terms of population prevalence or generalized to living athletes with CTE. In addition, there is the potential for reduced reliability and validity of retrospective reports from family members following the death of a loved one. However, several studies have demonstrated adequate reliability and validity of these verbal autopsies in a variety of patient populations, including those with dementia [15,16] and psychiatric disorders [39]. There also may be differences in the accuracy of informant reports when comparing younger and older subjects. That is, informants of older subjects were asked
to recall early- or mid-life events possibly resulting in reduced accuracy compared to the informants of younger subjects. Finally, there was no comparison group of former athletes without CTE. This may limit the ability to draw conclusions that the clinical presentation described is specifically due to the effects of CTE. In our available dataset of subjects whose tissue had been examined at the BU CSTE brain bank, there was not an adequate number of subjects without CTE to make such a comparison. For example, 34 of 35 former professional football players had neuropathologically confirmed CTE [1]. Future research is needed to clarify the clinical presentation of CTE. The development of biomarkers (e.g., blood, CSF, neuroimaging, and tau-specific radiotracers) will result in the ability to detect and diagnose CTE during life and subsequent studies of risk factors, epidemiology, and treatment [40].
References


Chapter 2
Clinical Subtypes of Chronic Traumatic Encephalopathy: Literature Review and Proposed Research Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by the accumulation of hyperphosphorylated tau protein (p-tau) in neurons and astrocytes in a pattern that is unique from other tauopathies, including Alzheimer's disease (AD) and frontotemporal lobar degeneration. The p-tau deposition initially occurs focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci. It then spreads to involve superficial layers of adjacent cortex, eventually resulting in widespread degeneration of the medial temporal lobes, frontal lobes, diencephalon, and brainstem [1,2]. Unlike AD, there is a paucity of beta amyloid neuritic plaques. CTE has been found most often in professional athletes involved in contact sports (e.g., boxing, American football) who have been subjected to repetitive blows to the head resulting in concussive and subconcussive trauma [3,4]. Neuropathologically confirmed CTE has been reported in individuals as young as 17 and in athletes who only played sports through high school or college. It also has been found in non-athletes who have experienced repetitive head impacts, including epileptics, developmentally disabled individuals who head bang, and victims of physical abuse [2]. Moreover, CTE has been neuropathologically diagnosed in military service members previously deployed in Iraq and Afghanistan with histories of repetitive brain trauma [2,5]. At this time, it is not
completely clear if all cases of neuropathologically confirmed CTE would demonstrate a progressive course if they lived long enough.

All cases of neuropathologically confirmed CTE reported to date have had a history of repetitive head impacts, although there has been some suggestion that a single traumatic brain injury (TBI) may also lead to the neuropathological changes of CTE [6]. Although head impacts appear to be necessary for the initiation of the pathogenetic cascade that eventually leads to neurodegeneration, the history of head impacts is not sufficient and additional risk factors (including genetic susceptibility markers) remain unknown. The incidence and prevalence of CTE are also unknown, though the number potentially affected could be quite large. Every year between 1.6 and 3.8 million individuals in the U.S. experience a sports-related concussion [7], with the number of youth sports-related concussions growing in recent years [8]. The incidence of repetitive subconcussive blows (i.e., hits to the head that produce enough force to hamper neuronal integrity, but do not result in clinical concussion symptoms) is much greater [9]. For example, a study by Broglio and colleagues found that high school football players receive an average of 652 hits to the head per season that exceed 15 g of force [10]. With over one million high school students playing American football each year, and with the size and speed of football players increasing [11], the public health impact of CTE may be quite significant in future years.

In vivo diagnosis of CTE is needed to conduct research on risk factors and epidemiology and to perform clinical trials for prevention and treatment. Sensitive and specific biomarkers for CTE are currently being developed and include structural and
neurochemical imaging techniques and positron emission tomography (PET) with new ligands that selectively bind to p-tau [4,12,13]. These approaches hold promise to detect underlying neuropathological changes of CTE. However, the clinical features directly associated with these changes have only recently been described and have been based on retrospective reports of family members of deceased individuals who receive a neuropathological diagnosis of CTE [2,14].

In a recent paper from our group [14], we examined the clinical presentation of 36 adult males selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy Brain Bank. The cases were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had family member informants who provided retrospective reports of history and clinical features. The semi-structured “psychological autopsies” were conducted blind to the subjects’ neuropathological findings. Three of the 36 subjects were asymptomatic. In the remaining 33 symptomatic subjects, a triad of cognitive, behavioral, and mood impairments was found, with cognitive changes reported for almost all subjects at some time in the course of disease. However, two relatively distinct clinical presentations emerged: one group had initial features involving behavior (i.e., explosivity, physical and verbal violence, being “out of control,” impulsivity) and/or mood (i.e., depression, hopelessness) (n=22), and another group had initial features involving cognition (i.e., episodic memory impairment, executive dysfunction, poor attention and concentration) (n=11). Symptom onset for the “behavior/mood group” occurred at a significantly younger age than the “cognition group.” Most subjects in the behavior/mood group
eventually developed cognitive difficulties, though significantly fewer subjects in the
cognition group eventually demonstrated behavioral and mood changes. Significantly
more subjects in the cognition group developed dementia than those in the
behavior/mood group. Less than one third of the sample had reported motor features,
including parkinsonism.

Although the study by Stern and colleagues involved the largest case series to
date of neuropathologically confirmed cases of CTE without comorbid conditions and
with clinical histories, the sample size was small and the generalizability of the findings
was hampered by the potential bias of a sample comprised of former athletes whose
family members agreed to their brain donation [14]. This limitation notwithstanding, the
finding of two possible clinical subtypes of CTE was consistent with previous literature.

In the present paper, we provide a review of the world’s literature on the clinical features
exhibited by athletes with histories of repetitive head impacts. Following the literature
review, we provide proposed research diagnostic criteria for “traumatic encephalopathy
syndrome,” derived from this literature review, and from our own research into the
clinical presentation of CTE [1,2,14]. As described below, these criteria are meant to
initially characterize what is known to date and provide a foundation for developing more
precise clinical criteria informed by on-going and future research and clinical review.

**Historical Terms for CTE.** In his seminal 1928 paper in the *Journal of the
American Medical Association*, Martland [15] used the term “punch drunk” to describe
boxers suffering from symptoms he believed to be related to the repetitive blows they
received in the ring. Since that time, various terms have been used to describe the clinical syndrome associated with repetitive head impacts, predominantly in studies of boxers. In 1934, Parker published a paper in which he referred to the traumatic encephalopathy of pugilists [16]. In 1937, Millspaugh first used the term dementia pugilistica [17] that is still currently used by clinicians and researchers. Other terms coined through the decades include traumatic encephalitis [18], cumulative encephalopathy of the boxer [19], psychopathic deterioration of pugilists [20], chronic boxer’s encephalopathy [21], and traumatic boxer’s encephalopathy [22]. In 1949, Critchley first used the designation, chronic traumatic encephalopathy [23], or CTE, though later modified it to chronic progressive traumatic encephalopathy [24], because several cases apparently progressed from an early mild state to severe dementia [23-25]. Johnson [26] suggested the latter term erroneously implies progression is inevitable. In his case-series, little to no deterioration is reported in half of the cases followed over 5 years. In a recent reviews of the literature, Victoroff (alone [27] and with Baron [28]) suggested using the more general and inclusive term “traumatic encephalopathy.”

In 2005, Omalu and colleagues [29] described the first case of neuropathologically confirmed CTE in an American football player. Since that time, there has been increasing public attention to this disease, and reports of CTE in deceased football players, including several well-known athletes, have prompted a tremendous focus on what is commonly referred to as football’s “concussion crisis.” The scientific community also has become dramatically more aware of CTE since it was discovered in American football players. For example, a PubMed search using the terms “chronic
traumatic encephalopathy,” “traumatic encephalopathy,” “dementia pugilistica,” or “punch drunk” resulted in 14 publications in the five year period ending in December 2001 compared with 116 publications in the five year period ending in December 2013.

**Early Concepts Regarding Subtypes.** In a 1950 editorial for the *British Medical Journal*, Jokl [30] stressed that CTE was not a single syndrome but rather two kinds of chronic impairment, with either predominant “behavioral-psychopathic or neurological-psychiatric” features. He described the behavioral-psychopathic subtype as involving “viciousness,” “murder committed from jealousy,” and delinquency. In contrast, he described the neurological-psychiatric subtype as involving cognitive deficits, dementia, and motor impairment [30-32]. Grahmann and Ule [33](1957) described three general subtypes: (1) a progressive dementia that typically involved cognitive impairment and developed following a latency from the time of boxing retirement; (2) a stable neurological presentation temporally and etiologically related to the head impacts and not representative of a progressive disease; and (3) a paranoid and psychotic subtype absent of cognitive changes. Critchley maintained that there were three commonly recurring presentations of CTE that resembled, but could be distinguished from: (1) neurosyphilis (e.g., psychopathy, altered personality, and later dementia), (2) multiple sclerosis (e.g., scanning speech, tremor, progressive cognitive decline), and (3) frontal lobe tumor (e.g., executive impairments, headache, and eye ache) [23]. He later added a fourth presentation: striatal parkinsonian (e.g., masked facial features, tremor) [24]. In a study of 17 retired boxers, Johnson [26] described four different “organic psychosyndromes,”
including cognitive problems with progressive dementia, behavioral issues related to “morbid jealousy,” behavioral issues related to rage and personality disorders, and mood and behavioral disturbance related to persistent psychosis.

**Literature Search Methods.**

To examine previous literature describing the clinical presentation of CTE associated with exposure to head impacts through sports participation, we conducted a literature search utilizing PubMed, PubMedCentral, and MEDLINE databases. Search terms included: *chronic traumatic encephalopathy; punch drunk; traumatic encephalopathy; dementia pugilistica; chronic boxer’s encephalopathy; chronic progressive traumatic encephalopathy; psychopathic deterioration of pugilists; and repetitive brain injury*. In addition, bibliographies of recent literature reviews were cross-referenced [1,27,34-39]. It should be noted that most online databases are limited to articles published since the 1950s. Because essential work in this field began in 1928, archival research was carried out by hand and international works were obtained with assistance from the Boston University Medical Library Interlibrary Loan Department. Materials retained included: articles; reviews; dissertations; society transactions; association reports; and book chapters. To be reasonably confident about the diagnoses used, several criteria were used to determine inclusion in this review: (1) only case series, and not individual case reports were included; (2) adequate information must be provided in the report to allow classification of cases as confirmed CTE, probable CTE, or possible CTE, using Jordan’s criteria [35,40,41]; and (3) only cases involving athletes were
Results of Literature Review

Following the exclusion of papers and cases that did not meet the above criteria, the literature review resulted in 202 cases from 20 published case series, 4 books, and 1 medical dissertation. The cases are summarized in Table 1 [2,16,22-26,29,31-33,42-54]. Nineteen cases were published before 1950, 29 cases were published in the 1950s, 49 were published in the 1960s, 13 were published in the 1970s, 4 were published in the 1980s, 19 were published in the 1990s, and 69 were published since 2000. Using Jordan’s criteria [35], we approximated that 29 would have possible CTE, 90 would have probable CTE, and 83 would have definite CTE. Of the entire sample, 141 were boxers, 54 were American football players, five were ice hockey players, and two were professional wrestlers. The clinical features described in all of the cases were classified into one of four categories: behavioral, mood, cognitive, and motor. Table 2 summarizes the clinical features most commonly described across all cases. In 68% of cases, the course of the clinical syndrome was described as progressive. In cases where a distinction in clinical syndrome was made, the behavioral and mood features were reported to be more stable, whereas the cognitive features were described as progressive, often resulting in dementia. Compared with cases described as progressive, cases described as stable were substantially younger. A large number of cases had a period of latency of several years between the end of exposure to head impacts and the presentation of clinical signs and symptoms. In neuropathologically confirmed cases, authors
described the initial clinical presentation as involving mood and/or behavioral disturbance without cognitive impairment in 28%, as having cognitive impairment without concurrent mood or behavioral difficulties in 32%, and as having initial mixed cognitive and mood/behavioral disturbance in 40%.

In recent years, some authors have made the distinction between “classic CTE” and “modern CTE” [34,36]. For example, McCrory and colleagues [36] define the classic CTE syndrome based on the clinical descriptions from Roberts [49] and the neuropathological reports from Corsellis and colleagues [50]. Based on these earlier cases of boxers, classic CTE is described as having prominent motor features, including gait disturbance, dysarthria and pyramidal problems, but without progressive cognitive, behavioral, or mood changes [36]. However, it is important to note that in his monograph, Roberts [49] clarifies that he is intentionally focusing on the description and quantification of motor signs related to neurological lesions, reducing his focus on “the evidence of dementia or personality change” which he viewed as occurring in a subset of cases [49]. In contrast, “modern CTE” [34,36], defined as any case report published in 2005 or later, is characterized by predominant mood and behavioral symptoms, as well as later progressive cognitive deficits and dementia, but with less prevalent motor features.

We view this distinction between the earlier and more recent descriptions of the clinical presentation of CTE as largely an artifact of different sources of trauma exposure (that is, predominantly boxers in the “classic” cases and predominantly football players in the “modern” cases).

To explore this issue, we examined further the cases of neuropathologically
confirmed pure CTE described in the series of McKee and colleagues [2] and compared the presence of motor features reported for the deceased professional boxers to those reported for the professional football players. The percentage of professional boxers with motor features (71%) far exceeded that of professional football players (13%). Additionally, it was found that in cases with the most advanced stage of CTE neuropathology, there was a striking difference in the presence of cerebellar pathology in professional boxers (83%) and professional football players (57%). The likely cause of this may be related to the differences in the biomechanics of the head trauma that is experienced through the practice of these two different sports [14].
Table 2.1. Summary of published cases describing the clinical features of Chronic Traumatic Encephalopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Total</th>
<th>Behavioral</th>
<th>Mood</th>
<th>Cognition</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parker (1934) [16]</td>
<td>Boxers (n=3)</td>
<td>Social inappropriateness Childish behavior</td>
<td>Anxiety Labile emotions Fatigue</td>
<td>Reduced intelligence Memory impairment Impaired attention Visuospatial difficulties</td>
<td>Ataxia Clonus Dragging gait Dysarthria Muscle weakness Spasticity Tremor</td>
</tr>
<tr>
<td>Herzog (1938) [42]</td>
<td>Boxers (n=7)</td>
<td>Boastfulness Personality changes Impulsiveness Loss of control</td>
<td>Apathy Flat affect</td>
<td>General cognitive impairment Memory difficulties Perseveration Language difficulties Alogia Dementia</td>
<td>Dysarthria Masked facies Shuffling gait Truncal ataxia</td>
</tr>
<tr>
<td>Knoll et al (1938) [43]</td>
<td>Boxers (n=3)</td>
<td>Personality changes</td>
<td>Apathy Flat affect Loss of interest Prolix</td>
<td>General cognitive impairment Memory impairment Visuospatial difficulties Alogia Dementia</td>
<td>Ataxia Dysarthria Masked facies</td>
</tr>
<tr>
<td>Jokl (1941) [31] and Jokl and Guttmann (1933) [32]</td>
<td>Boxers (n=3)</td>
<td>Boastfulness Childish behavior Paranoid delusions Personality changes Physical violence Psychosis Short fuse Explosivity</td>
<td>Apathy Depression Euphoria Fatigue Flat affect Insomnia Irritability Labile emotions Loss of interest</td>
<td>Reduced intelligence Executive dysfunction Memory impairment Impaired attention Altered concentration Language</td>
<td>Ataxia Dysarthria Masked Facies Muscle weakness Shuffling gait Tremor Unsteady gait</td>
</tr>
<tr>
<td>Study</td>
<td>Group</td>
<td>Symptoms</td>
<td>Cognitive Function</td>
<td>Other Neurological Findings</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>--------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Schwarz (1953) [44]</td>
<td>Boxers (n=3)</td>
<td>Personality changes, Short fuse, Explosivity</td>
<td>Fearfulness, Irritability, Labile emotions</td>
<td>Memory impairment, Altered concentration, Language difficulties, Ataxia, Dysarthria, Masked facies, Muscle weakness, Stamping gait, Tremor, Unsteady Gait</td>
<td></td>
</tr>
<tr>
<td>Soeder &amp; Arndt (1954) [45]</td>
<td>Boxers (n=5)</td>
<td>Boastfulness, Disinhibited behavior, Inappropriate speech, Paranoia, Personality changes, Physical violence, Psychosis, Short fuse, Explosivity, Social inappropriateness</td>
<td>Apathy, Depressed mood, Euphoria, Fatigue, Flat affect, Insomnia, Mania, Mood swings, Prolix</td>
<td>General cognitive impairment, Executive dysfunction, Memory impairment, Impaired attention, Altered concentration, Language difficulties, Alogia, Clonus, Dysarthria, Masked facies, Rolling gait, Tremor, Truncal ataxia, Unsteady gait</td>
<td></td>
</tr>
<tr>
<td>Grahmann &amp; Ule (1957) [33]</td>
<td>Boxers (n=4), Confirmed CTE (n=1)</td>
<td>Childish behavior, Disinhibited behavior, Disinhibited speech, Impulsivity, Loss of control, Physical violence, Personality changes, Short fuse, Explosivity, Social inappropriateness</td>
<td>Apathy, Depressed Euphoria, Labile emotions, Fatigue, Flat affect, Irritable Mood swings, Prolix</td>
<td>General cognitive impairment, Executive dysfunction, Memory impairment, Impaired attention, Altered concentration, Language difficulties, Dementia, Dysarthria, Swaying gait, Masked facies</td>
<td></td>
</tr>
<tr>
<td>Muller (1958)</td>
<td>Boxers (n=3)</td>
<td>Social isolation, Personality</td>
<td>Fatigue, Irritability, General cognitive, Dysarthria, Unsteady</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Changes in Behavior</td>
<td>Impairments</td>
<td>Gait</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Spillane (1962) [46]</td>
<td>Boxers (n=5)</td>
<td>Childish behavior, Disinhibited behavior, Impulsivity</td>
<td>Anxiety, Depressed mood, Euphoria, Mania, Mood swings</td>
<td>Ataxia, Dysarthria, Dragging gait, Muscle weakness, Tremor, Unsteady gait</td>
<td></td>
</tr>
<tr>
<td>Mawdsley &amp; Ferguson (1963) [22]</td>
<td>Boxers (n=10)</td>
<td>Impulsivity, Loss of control, Physical violence, Psychosis, Paranoid delusions, Personality changes, Short fuse, Explosivity, Social inappropriateness, Verbal violence</td>
<td>Apathy, Depression, Insomnia, Irritability</td>
<td>Ataxia, Dysarthria, Dragging gait, Masked Facies, Muscle weakness, Tremor, Unsteady gait</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Boxers (n)</td>
<td>Short fuse</td>
<td>Visuospatial difficulties</td>
<td>Dementia</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Payne</td>
<td>1968</td>
<td>(n=6)</td>
<td>Disinhibited behavior Impulsivity Paranoid delusions Physical violence Psychotic Verbal violence</td>
<td>Depressed mood Labile emotions Insomnia Mania Mood swings Suicidal ideation</td>
<td>General cognitive impairment Reduced intelligence Altered concentration Visuospatial difficulties Memory impairment</td>
</tr>
<tr>
<td>Johnson</td>
<td>1969</td>
<td>(n=17)</td>
<td>Loss of control Paranoid delusions Personality changes Psychotic Short fuse Explosivity Verbal violence</td>
<td>Anxiety Labile emotions Irritability</td>
<td>General cognitive impairment Reduced intelligence Memory impairment Dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts</td>
<td>1969</td>
<td>(n=11)</td>
<td>Lack of insight Paranoid delusions Psychosis Short fuse Explosivity</td>
<td>Apathy Depression Euphoria Flat affect Labile emotions</td>
<td>Reduced intelligence Executive dysfunction Memory impairment Perseveration Impaired attention Altered concentration Language difficulties Dysgraphia Visuospatial difficulties Dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corsellis</td>
<td>1973</td>
<td>(n=13)</td>
<td>Childish behavior Paranoid delusions Personality changes Short fuse</td>
<td>Anxiety Labile emotions Irritability</td>
<td>General cognitive impairment Reduced intelligence Memory impairment</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Symptoms</td>
<td>Disorders</td>
<td>Cognitive Deficits</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Sabharwal (1987) [51]</td>
<td>Boxers (n=4)</td>
<td>Inappropriate speech, depression, irritability, labile mood, mood swings</td>
<td>Dementia, reduced intelligence memory impairment</td>
<td>Ataxia, spasticity, dysarthria</td>
<td></td>
</tr>
<tr>
<td>Jordan (1997) [52]</td>
<td>Boxers (n=19)</td>
<td>Disinhibited speech, disinhibited behavior, depression, irritability, flat affect, mania</td>
<td>Impaired attention, altered concentration, memory impairment</td>
<td>Ataxia, clonus, dysarthria, spasticity, tremor, unsteady gait</td>
<td></td>
</tr>
<tr>
<td>Omalu (2005, 2006, 2010) [29,53,54]</td>
<td>Football &amp; Wrestling (n=5) Confirmed CTE (n=5)</td>
<td>Paranoid delusions, anxiety, labile mood, irritability, insomnia, depression</td>
<td>General cognitive impairment, memory impairment, language difficulties, executive dysfunction, impaired attention</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mckee et al, (2013) [2]</td>
<td>Boxing, American football, ice hockey, wrestling (n=64) Confirmed CTE (n=64)</td>
<td>Explosivity, aggression, impulsivity, suicidality, mood swings</td>
<td>Memory impairment, executive dysfunction, impaired attention, language difficulties, visuospatial dementia</td>
<td>Dysarthria, gait, disturbance, parkinsonism</td>
<td></td>
</tr>
</tbody>
</table>
## Table 2.2: Summary of Clinical Features of CTE Found in the Literature

<table>
<thead>
<tr>
<th>Behavioral features</th>
<th>Mood features</th>
<th>Cognitive features</th>
<th>Motor features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explosivity</td>
<td>Depression</td>
<td>Dementia</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Loss of control</td>
<td>Hopelessness</td>
<td>Memory impairment</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Short fuse</td>
<td>Suicidality</td>
<td>Executive dysfunction</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Anxiety</td>
<td>Lack of insight</td>
<td>Gait Disturbance</td>
</tr>
<tr>
<td>Aggression</td>
<td>Fearfulness</td>
<td>Perseveration</td>
<td>Tremor</td>
</tr>
<tr>
<td>Rage</td>
<td>Irritability</td>
<td>Impaired attention and concentration</td>
<td>Masked facies</td>
</tr>
<tr>
<td>Physical violence</td>
<td>Labile emotions</td>
<td>Language difficulties</td>
<td>Rigidty</td>
</tr>
<tr>
<td>Verbal violence</td>
<td>Apathy</td>
<td>Dysgraphia</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Inappropriate speech</td>
<td>Loss of interest</td>
<td>Alogia</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Boastfulness</td>
<td>Fatigue</td>
<td>Visuospatial difficulties</td>
<td>Clonus</td>
</tr>
<tr>
<td>Childish behavior</td>
<td>Flat affect</td>
<td>General cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>Insomnia</td>
<td>Reduced intelligence</td>
<td></td>
</tr>
<tr>
<td>inappropriateness</td>
<td>Mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibited speech</td>
<td>Euphoria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibited behavior</td>
<td>Mood swings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid delusions</td>
<td>Prolix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social isolation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Previously Published Diagnostic Criteria. To date, there have been two published sets of diagnostic criteria for the clinical diagnosis of CTE. The first diagnostic criteria, proposed by Jordan [35,40,41], were developed specifically to represent the likelihood of underlying CTE neuropathology. As such, the following four diagnostic classifications are used: (1) definite CTE ("any neurological process consistent with the clinical presentation of CTE along with pathological confirmation"); (2) probable CTE ("any neurological process characterized by two or more of the following conditions: cognitive and/or behavioral impairment; cerebellar dysfunction; pyramidal tract disease or extrapyramidal disease; clinically distinguishable from any known disease process and consistent with the clinical description of CTE"); (3) possible CTE ("any neurological process that is consistent with the clinical description of CTE but can be potentially explained by other known neurological disorders"); and (4) improbable CTE ("any neurological process that is inconsistent with the clinical description of CTE and can be explained by a pathophysiological process unrelated to brain trauma") [35].

In contrast to Jordan’s diagnostic criteria, which are focused on the prediction of underlying CTE neuropathology, the diagnostic criteria of Victoroff [27] are focused on a broad set of clinical signs and symptoms representing a diverse set of possible etiologies and are not meant to predict underlying CTE neuropathology. These provisional research diagnostic criteria for clinically probable traumatic encephalopathy (TE) and clinically possible TE were based on the frequency of clinical symptoms and signs reported in TE case reports published between 1928 and 2010. The Victoroff criteria represent an
important addition to the literature but have several limitations. For example, for a
diagnosis of clinically probable TE, there is a requirement for two symptoms and three
signs. However, there is tremendous overlap and redundancy between the symptoms and
the “neurobehavioral signs,” including the use of the following terms included as both
symptoms and signs: memory loss, irritability, apathy, impulsivity, depression, lability,
euphoria, paranoia, and others. Another required criterion for clinically probable TE is
the “persistence of both symptoms and signs for at least two years after the traumatic
exposure” [27]. This is not consistent with numerous cases of neuropathologically
confirmed CTE for which a delayed onset of the clinical presentation is often observed,
representing the neurodegenerative nature of the disease [2,14]. An additional limitation
to the Victoroff criteria is the lack of any subtyping of the clinical presentation. That is,
the same diagnosis of clinically probable TE could be given to an 80 year old with
memory loss, mental slowing, headache, and nystagmus, and to a 22 year old with
depression, anxiety, irritability, and anger. This lack of diagnostic subtyping for a
condition with such clinically diverse signs and symptoms would reduce the utility of the
criteria for research aimed at elucidating specific clinico-pathological relationships or
clinical trials requiring greater specificity of diagnosis to assure meaningful target
outcomes. The criteria are presented in a single table without accompanying descriptive
prose, making implementation of the criteria potentially subject to individual
interpretation. Finally, the Victoroff criteria do not include or recommend the future use
of objective diagnostic tests, such as neuroimaging or other potential biomarkers, to
improve upon the diagnostic accuracy, specificity, or ability to detect CTE during life.
Proposed Research Diagnostic Criteria for TES and CTE

We propose research diagnostic criteria that address many of the limitations of the previously published criteria by Jordan [35,40,41] and Victoroff [27]. These new criteria are derived from the previous literature on CTE reviewed above, as well as the specific findings from the studies by Stern and colleagues [14] and McKee and colleagues [2] on the clinical presentation of neuropathologically confirmed cases of CTE. The term, “traumatic encephalopathy syndrome” (TES) was selected instead of “chronic traumatic encephalopathy” (CTE) for the following reasons: (1) we view the designation, “CTE” as a neuropathologically defined disease (which is defined by the characteristic deposition of p-tau pathology) rather than a clinical syndrome; (2) TES is meant to describe the clinical presentation of CTE as well as other possible long-term consequences of repetitive head impacts (e.g., chronic or progressive axonopathy without tauopathy), but is not meant to include the acute or post-acute manifestations of a single concussion, post-concussion syndrome, or moderate-to-severe TBI; (3) the use of the word, “chronic” in CTE inaccurately connotes a stable condition, rather than a progressive disorder [27]; and (4) the inclusion of the term “syndrome” appropriately describes the cluster of clinical features that make up this condition. The proposed research diagnostic criteria for TES include five general criteria, three core clinical features, and nine supportive features, that are used to define subtypes of TES: a behavioral/mood variant, a cognitive variant, a mixed variant, and TES dementia. The modifiers “progressive course,” “stable course,” and “unknown/inconsistent course” are used to describe the clinical course, and if specific motor signs are evident, the additional modifier “with motor features” is
The selection of the five general criteria was based on the literature reviewed above and was designed to favor sensitivity over specificity. This decision is consistent with the previously published diagnostic criteria [27,35], and is appropriate at this early stage of clinical research into this area. To be included as a core clinical feature, the sign or symptom must have been reported in a minimum of 70% of the cases in the Stern et al. study [14] of neuropathologically confirmed cases of pure CTE. This is in contrast to the algorithm employed in the Victoroff [27] diagnostic criteria for which a sign or symptom was included if it was present in at least 7% of the case reports he reviewed from the literature. The nine supportive features were selected to increase specificity once the general criteria are met and are based on features reported in the previous literature.

The clinical diagnosis of TES is not meant to imply a certainty of underlying CTE neuropathological changes (for example, p-tau accumulation). Rather, TES is meant to be a diagnosis of a clinical syndrome associated with a history of repetitive brain trauma. It is expected that some individuals with TES do indeed have CTE neuropathological changes. However, it is also possible that some individuals with TES have other underlying causes of their clinical presentation, including, but not limited to, progressive white matter degeneration [55] or AD. For this reason, a separate diagnostic classification for “possible CTE,” “probable CTE,” and “unlikely CTE” is included, based on the presence of additional supportive features, such as biomarkers, which indicate the degree to which the underlying etiology of the clinical presentation of TES is likely due to the CTE pathophysiological process. Finally, we offer six cases (see boxes) as exemplars of
the implementation of the TES criteria; each case is a composite of several patients, created specifically for this purpose.

At this time, risk factors for CTE (above and beyond brain trauma) remain unknown. Amongst possible variables under investigation by our group and other labs include: the quantity and/or severity of the brain trauma, the initial age and overall duration of head impact exposure, lifestyle factors, and genetic susceptibility. Based on current research findings, it is expected that TES is the clinical manifestation of underlying damage or dysfunction of cortical and/or subcortical brain structures and is associated with a history of repetitive brain trauma, including both symptomatic concussions and subconcussive trauma. Although some investigators have suggested that a single moderate to severe TBI may lead to CTE [37] and/or AD [56], at this time the use of the clinical diagnosis of TES is meant to be used for individuals with repetitive impacts to the head, as defined below. We have included a requirement for a specific minimal amount of exposure to head impacts. This is based on previous findings of post-mortem confirmed CTE cases [1,2,5,50] and will be subject to future revisions as additional research is conducted on exposure variables.
General Criteria for Traumatic Encephalopathy Syndrome.

All five criteria must be met for a diagnosis of TES:

1) History of multiple impacts to the head (or to the body resulting in impulsive force transmitted to the head). Multiple impacts are defined based upon (a) the types of injuries and (b) the source of exposure.

a) Types of injuries:

i) Mild traumatic brain injury (mTBI) or concussion, defined according to the Zurich 2012 Consensus Statement on Concussion in Sport [57] as a “complex pathophysiological process affecting the brain, induced by biomechanical forces…caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive' force transmitted to the head…the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness.” History of this form of trauma can be based on documented records from health care providers or on self- or informant-reports, after being given an appropriate definition of “concussion [58].” If there is no reported exposure to other repetitive hits to the head, there should be a minimum of 4 documented mild traumatic brain injuries or concussions.

ii) Moderate/severe (TBI), defined as having loss of consciousness of at least 30 minutes, alteration of consciousness/mental state of more than 24 hours, post-
traumatic amnesia of more than 24 hours, and Glasgow Coma Scale score of less than 13 [59]. If there is no reported exposure to other repetitive hits to the head, there should be a minimum of two moderate/severe TBIs.

iii) “Subconcussive” trauma, defined as biomechanical force to the head or body similar to, or less than, that required for symptomatic concussion, but without symptoms and clinical presentation consistent with concussion [3,4].

b) Source of exposures:

i) Involvement in “high exposure” contact sports (including, but not limited to, boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer) for a minimum of 6 years, including at least 2 years at the college level (or equivalent) or higher.

ii) Military service (including, but not limited to, combat exposure to blast and other explosions as well as non-combat exposure to explosives or to combatant or breach training).

iii) History of any other significant exposure to repetitive hits to the head (including, but not limited to, domestic abuse, head banging, vocational activities such as door breaching by police).

iv) For moderate/severe TBI, any activity resulting in the injury (e.g., motor vehicle accident).

2) No other neurological disorder (including chronic residual symptoms from a single TBI or persistent post-concussion syndrome) that likely accounts for all clinical features, although concomitant diagnoses of substance abuse, post-traumatic stress
disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases (for example, AD and frontotemporal dementia) or a combination of these can be present.

3) Clinical features must be present for a minimum of 12 months. However, if treatment (for example, “antidepressant” medication) results in an improvement in select symptoms, the clinician should use her/his best judgment to decide whether the symptoms would have persisted or progressed if treatment had not been initiated.

4) At least one of the core clinical features must be present and should be considered a change from baseline functioning.

5) At least two supportive features must be present.

**Core Clinical Features of Traumatic Encephalopathy Syndrome.**

At least one of the core clinical features must be present.

1) **Cognitive.** Difficulties in cognition:

   a) as reported either by self or informant, by history of treatment, or by clinician’s report of decline; and

   b) substantiated by impairment on standardized mental status or neuropsychological tests of episodic memory, executive function and/or attention, as defined by scores of at least 1.5 SD below appropriate norms.

2) **Behavioral.** Being described as emotionally explosive (for example, having a “short fuse,” or “being out of control”), physically violent, and/or verbally violent, as reported either by self or informant, by history of treatment, or by clinician’s report. A formal diagnosis of intermittent explosive disorder would meet this criterion but is
not necessary.

3) **Mood.** Feeling overly sad, depressed, and/or hopeless, as reported either by self or informant, by history of treatment, or by clinician’s report. A formal diagnosis of Major Depressive Disorder or Persistent Depressive Disorder would meet this criterion though is not necessary.

### Supportive Features of Traumatic Encephalopathy Syndrome.

A minimum of two of the following features must be present for a diagnosis of TES:

1) **Impulsivity.** Impaired impulse control, as demonstrated by new behaviors, such as excessive gambling, increased or unusual sexual activity, substance abuse, excessive shopping or unusual purchases, or other similar activities.

2) **Anxiety.** History of anxious mood, agitation, excessive fears, or obsessive compulsive behavior (or both), as reported by self or informant, history of treatment, or clinician’s report. A formal diagnosis of anxiety disorder would meet this criterion though is not necessary.

3) **Apathy.** Loss of interest in usual activities, loss of motivation and emotions, and/or reduction of voluntary, goal-directed behaviors, as reported either by self or informant, history of treatment, or clinician’s report.

4) **Paranoia.** Delusional beliefs of suspicion, persecution, and/or unwarranted jealousy.

5) **Suicidality.** History of suicidal thoughts or attempts, as reported either by self or informant, history of treatment, or clinician’s report.

6) **Headache.** Significant and chronic headache, with at least one episode per month for
a minimum of 6 months.

7) *Motor Signs.* Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism. If present, the modifier, “with motor features” should be used (see below).

8) *Documented Decline.* Progressive decline in function and/or a progression in symptoms and/or signs, based upon repeated formal testing, clinician examination, or other formal measurement (for example, informant questionnaire) for a minimum of one year.

9) *Delayed Onset.* Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure. It should be noted, however, that individual cases may begin to develop the clinical features of TES during their period of head impact exposure (for example, while still actively involved in a collision sport), especially older individuals or those who have been engaged in the high-exposure activity for many years. It may also be difficult to differentiate the clinical presentation of prolonged or persistent post-concussion syndrome (pPCS) from that of TES. Therefore, there could be cases for whom there is overlap of resolving pPCS and the initial features of TES, thus masking any delayed onset of TES.

**Traumatic Encephalopathy Syndrome Diagnostic Subtypes**

1) *TES behavioral/mood variant (TES-BMv)*

   a) Behavioral or mood core features (or both) without cognitive core features.
2) **TES cognitive variant (TES-COGv).**
   a) Cognitive core features without behavioral and/or mood core features.

3) **TES mixed variant (TES-MIXv).**
   a) Both cognitive core features and behavioral or mood core features (or both).

4) **TES dementia (TES-D)**
   a) Progressive course of cognitive core features with or without behavioral or mood core features (or both).
   b) Evidence of “functional impairment,” defined as cognitive impairment (or cognitive impairment exacerbated by behavioral or mood impairment or both) that is severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living.
   
   The determination of functional impairment is based on clinician’s judgment, taking into account informant reports as well as consideration of individual differences with regard to level of expected responsibility and daily challenges.
   c) If the clinical presentation is not distinguishable from that of dementia due to AD or another neurodegenerative disease (for example, frontotemporal dementia), both diagnoses may be given, either with one being “primary” and the other being “secondary,” or with the term “mixed” used if neither is presumed primary.

**“With Motor Features” Modifier.** For each TES subtype, the modifier “with motor features” should be added if the individual demonstrates dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of
Clinical Course. For each TES subtype, one of the following additional modifiers should be selected: ‘stable course’, to be used when the history or objective testing (or both) indicates that there has been little if any change in symptoms, signs, or other measures; ‘progressive course’, to be used when there is a clear indication of progressive worsening of clinical features for at least a 2-year period; and ‘unknown/inconsistent course,’ to be used when either there is too little information available about the clinical course or the course has been inconsistent, with periods of stability, worsening, and/or improvement. By definition, TES dementia has a progressive course and does not require this modifier.

“Possible CTE ” and “Probable CTE.” As stated above, CTE is a neuropathological diagnosis, whereas TES is a clinical diagnosis. As with other neurodegenerative diseases, such as AD, it is not possible at this time to diagnose the underlying disease with certainty during life. However, again as with other neurodegenerative diseases and in keeping with the diagnostic criteria for CTE proposed by Jordan [35,40,41], we propose provisional diagnostic classifications of ‘probable CTE’, ‘possible CTE’, and ‘unlikely CTE’. Because the scientific study of the clinical presentation of CTE is only in its infancy, it is not yet possible to create meaningful diagnostic criteria for ‘probable CTE’ based solely on clinical features and course, such as those employed for the National Institute on Aging-Alzheimer’s Association (NIA-AA) AD diagnostic criteria for
probable AD dementia [60], a condition that has been carefully studied for many decades. Rather, we propose, as a starting point, several potential in vivo biomarkers for CTE that can be used to support a provisional diagnosis of ‘probable CTE’. This diagnosis would be analogous to the NIA-AA diagnosis of probable AD dementia with evidence of the AD pathophysiological process [60]. However, because of the early stage of research into potential CTE biomarkers, we refrain from using this type of nomenclature. The following list of potential biomarkers for underlying CTE is meant only as a guideline at this early point in CTE diagnostic research. Many of these biomarkers are the focus of current research but have not yet been formally validated. Future biomarker validation studies will likely add to or delete (or both) items on this list. Moreover, we do not in any way recommend that the specific tests used for these potential biomarkers be conducted for clinical purposes at this time.

_Potential Biomarkers for the Diagnosis of Probable Chronic Traumatic Encephalopathy._

1) _Cavum septum pellucidum_. Report of cavum septum pellucidum, cavum vergae, or fenestrations based on neuroimaging study.

2) _Normal beta amyloid cerebrospinal fluid (CSF) levels_. CSF beta amyloid levels in the normal range for age and not diminished as would be suggestive of Alzheimer’s disease.

3) _Elevated CSF p-tau/tau ratio_. CSF p-tau/total tau ratio above the normal range for age.
4) **Negative amyloid imaging.** PET amyloid imaging (for example, florbetapir and flutemetamol) in the normal range, not suggestive of AD.

5) **Positive tau imaging.** PET paired helical filament tau imaging suggestive of abnormal tau deposition. It should be noted that this remains an experimental procedure and requires additional validation prior to its use as a research tool for diagnostic purposes.

6) **Cortical Thinning.** Based on magnetic resonance imaging (MRI) measurement, evidence of abnormal cortical thinning indicative of neurodegeneration.

7) **Cortical atrophy.** Based on MRI or computed tomography, generalized cortical atrophy beyond what is expected for age, and, in particular, frontal, thalamic, hippocampal, and/or amygdalar atrophy.

**Chronic Traumatic Encephalopathy Classification.**

1) **Probable CTE.** Meets classification for any TES subtype, progressive course; does not meet diagnostic criteria for another disorder more consistently than TES; and has a minimum of one positive potential biomarker for CTE.

2) **Possible CTE.** Meets classification for any TES subtype, progressive course, and (1) has not undergone any potential biomarker testing, (2) has had negative results on one or more biomarkers with the exception of PET tau imaging (that is, if a negative PET tau imaging finding, the current classification would be “unlikely CTE”), or (3) meets the diagnostic criteria for another disorder that, on its own, could account for the clinical presentation..
3) *Unlikely CTE*. Does not meet TES diagnostic criteria or has had a negative PET Tau Imaging scan or both.

**Case A.** A 45-year-old married man with a history of playing multiple contact sports, including soccer (ages 5 to 13), hockey (ages 7 to 12), and football (ages 9 to 22) presented to his primary care physician. He played college football at a Division 1 university and was an offensive lineman. He had no reported or formally diagnosed concussions, although when provided with a definition of concussion, he stated that he likely had 20 to 30 throughout high school and college. Since graduating from college, he has worked as an auditor for state government. His work performance evaluations had been routinely positive, although for the past two years they have been marred by reports of ‘careless errors’, reduced productivity, and one episode of yelling at his immediate supervisor. His wife of 16 years reports that he has had a 5- to 7-year history of worsening behavior, with frequent episodes of having a ‘short fuse’ and losing his temper with their two young children. Though always a social drinker, he has had frequent episodes of binge drinking over the past 2 to 3 years. She states that his personality has changed from a kind, even-keeled, loving man to an argumentative, explosive, and moody individual. Both he and his wife state that he was high-functioning, without any cognitive, mood, and behavioral problems during the time period between college and about age 35. He recently underwent formal neuropsychological evaluation that demonstrated moderately impaired sustained attention, mildly impaired delayed recall on a word list, and moderately impaired executive functioning as measured by a card-sorting
test. All other areas of functioning were within the normal range. A self-report measure of syndromal depression indicated mild to moderate severity. Other than the recent work-performance evaluations, there were no other reports of significant functional decline. The result of a recent brain MRI was unremarkable other than some mild, scattered white matter abnormalities. Other medical history, laboratory findings, and neurological examination were unremarkable. Diagnosis: TES-MIXv, progressive course; possible CTE.

**Case B.** A 31-year-old single female Army veteran was referred to the VA Medical Center Behavioral Health Clinic for a 14-month history of suicidal thoughts, agitation, and aggressive behavior. She had reached the rank of staff sergeant and was a logistics specialist. She was honorably discharged 1 year ago, began working in her family’s grocery store, but had to stop working 6 months ago because of her neuropsychiatric symptoms. She had two deployments to Afghanistan and denied being directly involved in combat. However, she reported that 20 months prior to her discharge, she was thrown off a truck when it struck an improvised explosive device. She was told she landed on her head and lost consciousness for 2 to 3 minutes. Upon regaining consciousness, she reported ‘seeing stars’ and had a headache that lasted 3 to 4 days. She denied these symptoms to the medic when questioned and remained on active duty. About 3 months later, a heavy box fell on her head, throwing her to the floor. She denied loss of consciousness but was nauseated and had balance difficulties for several hours. She complained of being in a fog and irritable for 2 days following the accident. Her tour of
duty ended 2 weeks later and she returned home. Other than those two injuries, she
denied any TBIs or concussions. These symptoms completely cleared, and she described
her functioning, including her mood, as ‘completely fine’ between that time and about 14
months ago. Prior to enlisting, she was an avid ice hockey player, having played since the
age of 5, and was the captain of her high school team. Her medical and psychiatric
histories were unremarkable, and laboratory results of tests ordered by her primary care
physician were normal. At the current evaluation, a mental status examination was
conducted and the results were generally within normal limits. She denied having any
cognitive complaints. A psychiatric interview revealed significant overall distress, with
suicidal ideation without any active plan. Her primary complaints included poor sleep,
sadness, anxiety, agitation, and being overly aroused by loud noises. She denied having
any flashbacks or night terrors. A sibling was interviewed and corroborated the
description and history but added that for the past year she had been verbally aggressive
and explosive, frequently yelling at family members for no apparent reason, and that
these episodes seemed to turn off and on without any warning. The sibling stated that
these abnormal behaviors have been somewhat consistent over the past year. A PTSD
specialist examined the patient, reported that she would not meet criteria for PTSD, and
questioned whether the symptoms were residual from her TBIs in Afghanistan. The result
of a brain MRI was unremarkable. Diagnosis: TES-BMv, stable course; possible CTE.

Case C. A 59-year-old man presented to his primary care physician with complaints
of progressive memory and concentration problems. Prior to going to college, the patient
entered the Army, where he boxed competitively for 4 years. He did not experience any combat. He was an avid rugby player in college and continued playing in formal competitive clubs until the age of 54, when he stopped because of a cervical disk injury. He received an MBA and had been a successful business consultant. He was divorced at the age of 45 and lived alone. He reported one concussion at the age of 30, when he briefly lost consciousness during a rugby game, although he stated he got his ‘bell rung’ countless times in boxing and rugby. He reported to his primary care physician that he had been having difficulty remembering details of conversations and meetings at work and that this was beginning to interfere with his productivity. His medical history was significant for the cervical disk injury and for migraine headaches for many years. He was referred to a local academic medical center memory clinic, where a formal neuropsychological evaluation demonstrated moderately impaired performance on a word list recall task, compared with age and education norms, as well as severely impaired fine motor dexterity. All other areas were intact, although his performance on a measure of psychomotor speed and response set maintenance was slightly below expected levels given his history. A neurological examination revealed mild bilateral resting tremor and mild upper extremity rigidity. An MRI scan was read as normal, and all laboratory findings were within normal limits. As part of a clinical research study, he was given two PETs: one with a new tau radiotracer and another with an amyloid tracer. Results indicated no meaningful amyloid uptake, although his tau scan was abnormal with scattered increased tracer uptake in the dorsolateral frontal cortex and the medial temporal lobes. Diagnosis: TES-COGv, with motor features, progressive course; probable
Case D. A 69-year-old former National Football League (NFL) football player was seen in consultation following a 10-year progressive decline. He had seen several physicians and had been given multiple diagnoses, including frontaltemporal dementia and dementia due to AD. He had played professional football for 9 years as a linebacker. He began playing football in high school and played for a Division 1 college for 4 years, playing both as a linebacker and as an offensive lineman. Following retirement from the NFL, he had a successful career in commercial real estate until he was forced to retire at the age of 62 because of ‘poor decision-making and judgment’. His wife of 25 years stated that, in retrospect, he was demonstrating poor memory and judgment for about 3 years prior to his retirement and that these problems had progressively worsened through the years. She stated that he also began having significant difficulties with multi-tasking and ‘numbers’ at age 61 and was having difficulty with household finances and hobbies. After retirement, he became increasingly withdrawn and refused to socialize. In contrast to his previous jovial and easy-going manner, he became verbally aggressive toward his wife and children, ‘blowing up over small things’. On two occasions, he became physically aggressive toward his wife, requiring her to call the police. He never demonstrated any disinhibited or socially inappropriate behavior, nor was there any report of hallucinations or movement disturbance. In the past 2 years, his functioning has worsened; he now has no ‘short-term memory’, watches television all day long, and has an erratic sleep cycle. He is functionally impaired in all instrumental activities of daily
living as well as in some basic activities of daily living. His medical history is significant for a myocardial infarction at age 54, hypertension, severe arthritis, and multiple lumbar disk surgeries. There is no family history of dementia. Upon examination, he was disoriented to time and place, was perseverative, and could not recall recent current events. He exhibited some frontal release signs, although the result of his motor examination was otherwise normal. His Mini-Mental Status Exam score was 9, and his Clinical Dementia Rating was 2.0. A neuropsychological evaluation was conducted and demonstrated severe episodic memory impairment as well as profoundly impaired performance on most tests of executive functioning. In contrast, attentional capacity was within normal limits and language was relatively intact. A brain MRI revealed significant global atrophy with marked hippocampal atrophy as well as a cavum septum pellucidum. An amyloid PET scan demonstrated only minimal uptake, not commensurate with the degree of dementia. Diagnosis: TES-D; probable CTE.

Case E. A 31-year-old male stockbroker saw his primary care physician because of an 18-month history of recurrent headaches, irritability, agitation, and a worsening ‘short fuse’. He had been taking oxycodone (left over from previous oral surgery) for his headache pain. He was referred to a neurologist, who specialized in headache and who diagnosed him with tension headache. However, when asked if he had ever had headaches previously, the patient reported that he frequently had them as a teenager after his varsity high school football games and when he played rugby for 2 years in college. Because of this history of prior exposure to repetitive head impacts and possible
symptomatic concussions, the neurologist referred him to a psychiatrist colleague to
evaluate him for possible depression and suicidality, based on the neurologist’s belief that
the patient might have CTE; he had recently attended a talk on sports injuries. The
consulting psychiatrist interviewed the patient, who acknowledged that he had frequent
suicidal ideation following the breakup of his marriage about 1 year earlier but that these
thoughts had now diminished. Although the patient formally met criteria for TES-BMv,
the psychiatrist felt that the headache symptoms, suicidality, short fuse, and irritability
were likely associated with the divorce. The patient was prescribed citalopram as well as
regular therapeutic massage for his tension headache and was seen in 3 months, at which
time he reported substantial improvement of his mood and behavioral symptoms and a
complete resolution of his headaches. Diagnosis: adjustment disorder, persistent with
mixed anxiety and depressed mood; unlikely CTE.

**Case F.** An 81-year-old widowed man enrolled in a research study examining the
long-term consequences of TBI. He reported having sustained a moderate TBI in a motor
vehicle accident at the age of 46 with loss of consciousness for approximately 1 hour. He
was hospitalized for 3 days because of confusion and memory difficulties that mostly
resolved prior to discharge. He was unable to return to work as a high school physical
education teacher and coach for several weeks because of continued cognitive
difficulties, headache, and balance problems. He reported that, once he returned to work,
he ‘didn’t feel normal’ for several months. He continued working until retirement at age
60. He played high school and college football and reported having had his ‘bell rung’
'all the time'. According to his adult son (with whom he lived), he was 72 when he began having memory problems that gradually progressed over the course of 5 to 6 years. In the past few years, the memory problems worsened significantly, such that he could not recall events that occurred more than an hour earlier. In addition, he had worsening problems with judgment, decision-making, multi-tasking, and word-finding. He no longer drove and was dependent in most areas of instrumental activities of daily living. He lacked interest in all activities and appears ‘depressed’ according to his son. His medical history was significant for prostate cancer, controlled hypertension, arthritis, and glaucoma. Two brothers died in their 80s with ‘dementia’. Neuropsychological testing revealed significant impairments in episodic memory, confrontation naming, psychomotor speed, and many aspects of executive functioning. Research-based MR revealed frontal and temporal atrophy and a pronounced cavum septum pellucidum; diffusion tensor imaging and tractography demonstrated significant reductions in corpus callosum fiber bundles. PET amyloid imaging showed elevated uptake consistent with AD. Diagnosis: dementia due to AD pathophysiological process and TES-D, mixed; possible CTE.

**Discussion**

The current proposed research diagnostic criteria for TES are meant to be a starting point that should be modified and updated as new research findings in the field become available and as future research using these criteria are published. These proposed criteria are not meant to be used for a clinical diagnosis or as evidence of an underlying disease.
Rather, they should be viewed as research criteria that could be employed in studies of the underlying causes, risk factors, differential diagnosis, prevention, and treatment of TES. Future studies comparing these proposed diagnostic categories with post-mortem neuropathological diagnoses, as well as with appropriate in vivo biomarkers for CTE and other conditions, will help lead to the transition from ‘research’ criteria to ‘clinical’ criteria. It also would be critical for these proposed criteria to undergo a formal expert consensus approval process, such as that used for the NIA-AA Diagnostic Guidelines for Alzheimer’s Disease [60].

One important factor that must be addressed in future iterations of these criteria is that of base rates. That is, the population prevalence of most of the core clinical features and many of the supplemental features of TES presented below is relatively high. Therefore, it is possible to meet criteria for TES and yet have an idiopathic disorder or a situationally based condition that is unrelated to the earlier history of head impact exposure. The inclusion of supportive features is meant to reduce this lack of specificity to a degree, but, at this time, we acknowledge that these criteria will likely result in very high sensitivity at the expense of specificity. With the utilization of future research findings and subsequent criteria revisions, it is likely that the specificity will increase. An important additional issue regarding the use of these criteria involves the impact of litigation or disability determination (or both) on the validity of symptom reporting and neuropsychological test performance. It is therefore recommended that this issue be taken into account when interpreting the individual’s self-reported functioning and test performance and that formal symptom validity checking be conducted as part of any formal evaluation. Until
future research yields accurate biomarkers and allows clarification and modification of the proposed criteria, the decision as to whether an individual meets the TES diagnostic criteria and associated ‘probable CTE’ diagnostic criteria should be left up to the individual researcher, clinician, or, preferably, a multidisciplinary diagnostic adjudication process.

**Conclusions**

The long-term consequences of repetitive head impacts have been known since the beginning of the 20th century. Although the clinical presentation of CTE is varied and non-specific, there are adequate reports to date to suggest that there may be two clinical subtypes: one subtype involving primarily behavioral or mood features (including explosivity or violence) or both, and the other involving cognitive deficits (including impairments in episodic memory, executive functioning, and attention). Many individuals progress to dementia, with impaired functional independence, and some individuals develop motor impairments (including parkinsonism, ataxia, and dysarthria). We propose research diagnostic criteria for TES that we hope will facilitate research into this area. There are expected limitations to the development of diagnostic criteria based primarily on a relatively small number of case reports. The goal of proposing these criteria at this time is to facilitate research in this nascent area of study. It is expected that these criteria will undergo modification and revision as new research findings become available, additional biomarkers are validated, and future research using these criteria are published.
References


18. Ravina A. Traumatic encephalitis or punch drunk. La Presse Médicale. 1937;45:1362–1364.


Chapter 3

Beta-Amyloid Deposition in Chronic Traumatic Encephalopathy

Copyright © 2015, Springer-Verlag Berlin Heidelberg (outside the USA)

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease likely caused by repetitive traumatic brain injury (RTBI). Many contact sports have now been linked to CTE, including American football, boxing, hockey, soccer, and rugby. In addition, we have found CTE in military personnel exposed to an explosive blast [10, 29]. The clinical features of CTE typically manifest years or decades after the initial RTBI and consist of impairments in mood (depression, suicidality, irritability), behavior (explosivity, violence, impulsivity), cognition (impaired memory, executive dysfunction, diminished concentration), and motor functioning (parkinsonism, dysarthria, gait changes, weakness) [32, 33, 46]. The reported clinical symptoms following RTBI can vary widely, and different subtypes have been identified in neuropathologically confirmed cases of CTE [46]. Research clinical diagnostic criteria have recently been proposed [32], but investigations to establish reliability and diagnostic accuracy in predicting underlying CTE pathological changes are ongoing [32]. In some cases the clinical features can overlap with and be clinically indistinguishable from those of Alzheimer’s disease (AD). An analysis of neuropathologically confirmed CTE without co-morbid disease demonstrated that in 11% of subjects overall and in 40% of demented
subjects the clinical presentation is indistinguishable from AD. Moreover, as in AD, there is a spectrum of pathology in CTE, and some, but not all, subjects with pathological CTE will have dementia or CTE-related clinical symptoms [46]. A more complete understanding of the pathology may help explain and predict the clinical outcomes.

CTE is a tauopathy characterized by neurofibrillary tangles, tau-positive astrocytes, and tau-positive cell processes that preferentially involve the cortical sulci, medial temporal lobe, diencephalon, and brainstem. In CTE the tau pathology is characteristically perivascular, most pronounced at the sulcal depths, and preferentially involves the superficial cortical layers. This pattern of tau pathology is distinct from other tauopathies, including Alzheimer’s disease. Recently, the US National Institute of Neurological Disorders and Stroke convened a panel of expert neuropathologists to establish consensus criteria for CTE [42]. It was determined that the pathognomonic lesion in CTE was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci, and that CTE could be reliably distinguished from other tauopathies including AD, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, Guamanian Parkinsonism Dementia Complex, and primary age-related tauopathy [4].

The role of Aβ in CTE has been controversial. At one point, Aβ deposition was thought to be a universal feature [39], but subsequent analyses found Aβ pathology within only a subset of individuals. In our reported cohort of 68 athletes and military veterans with CTE, 44% had some deposition of primarily diffuse plaques, and 10% met the criteria for AD [30]. Some epidemiologic evidence exists that suggests moderate to
severe TBI is a risk factor for AD [13, 24, 27, 38] although most reports linking TBI and AD have relied on a clinical diagnosis of probable AD without neuropathological verification and a definitive link has yet to be established [17]. It has been shown that acutely following TBI, amyloid precursor protein (APP) and Aβ increase in tissue and CSF, and there can be rapid formation of diffuse Aβ plaques in the cortex [9, 16, 36, 40, 41]. Therefore, the release of Aβ into surrounding tissue following injury may be a basis for plaque formation [41, 43]. The relation of Aβ deposition in CTE to genetic factors, other pathological lesions, and to the clinical course has yet to be determined.

Here we set out to test the hypotheses that Aβ deposition is altered in CTE compared to a control population, Aβ accumulation in CTE differs from AD, and the presence of diffuse or neuritic plaques increases pathological severity and worsens clinical outcomes in CTE. To test these hypotheses we examined the brains of 114 participants with a history of RTBI and compared the pattern of neuropathological lesions in subjects with and without Aβ to each other, to the brains of individuals with neuropathologically confirmed AD without a known history of RTBI, and to the reported pathology of a large non-selected autopsy cohort of 2,332 normal aging cases [2].

**Materials and Methods**

**Subjects.** A total of 114 subjects were evaluated from Boston University’s Chronic Traumatic Encephalopathy Center including former athletes, military veterans, and civilians with a history of repetitive mild traumatic brain injury. Next of kin provided written consent for participation and brain donation. Institutional review board
approval for brain donation was obtained through the Boston University Medical Center and the Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA. Institutional review board approval for post-mortem clinical record review, interviews with family members, and neuropathological evaluation was obtained through Boston University Medical Center. The brains from an additional 319 subjects from the Boston University AD Center were included for comparative analysis.

Clinical assessment. Concussion and RTBI history, history of cognitive and behavioral changes and clinical status leading up to death were determined through post-mortem interviews with next of kin performed by physicians, neuropsychologists, and doctoral candidates trained to assess for RTBI, dementia, and neurodegenerative diseases (J.M., T.S., D.H.D., P.H.M., and R.A.S.). Interviewers were blind to the results of the neuropathological examination at the time of interview, and the neuropathologists were blind to the results of the clinical interviews at the time of neuropathological examination and diagnosis. Informants were interviewed before receiving the results of the neuropathological examination. The interview was semi-structured and conducted by telephone. Medical record review was also performed (J.M., T.S., P.K., D.H.D, P.H.M, T.D.S., A.C.M, and R.A.S.). Recorded clinical measures included the presence or absence of CTE symptoms including mood, behavioral, or cognitive changes (reviewed in [32]), age of symptom onset, presence of symptoms associated with parkinsonism (e.g. tremor, bradykinesia, rigidity, gait disturbance, ataxia, dysarthria, dysphagia), and behavioral or cognitive variant of CTE [46]. We recorded dementia status using a
conservative definition of dementia based on a diagnosis made during life. In the subset
of AD subjects selected for ELISA and Aβ plaque burden, subjects and their informants
were asked during life about a history of contact sports play or head injury including
RTBI and those without such history were selected for comparison.

Pathological Diagnoses

Chronic traumatic encephalopathy. The diagnosis and staging of CTE followed
the definitions and criteria described previously [30] and adapted to include: (i)
perivascular foci of hyperphosphorylated tau immunoreactive neurons, astrocytes, and
cell processes; (ii) irregular cortical distribution of hyperphosphorylated tau
immunoreactive neurons and astrocytes with a predilection for the depths of cerebral
sulci; and (iii) hyperphosphorylated tau-positive neurons in the cerebral cortex located
preferentially in the superficial layers. Supportive features include: (iv) clusters of
subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal
ganglia and brainstem. CTE stages varied from I to IV based on the extent and severity
of tau pathology as previously described [30]. Briefly, Stage I CTE is characterized by
isolated perivascular foci of hyperphosphorylated tau within neurons, astrocytes, and cell
processes present at the sulcal depths. In stage II the tau pathology extends to involve the
superficial cortical layers into the gyral crest. In stage III there is additional involvement
of the parietal and temporal lobes as well as medial temporal lobe tau pathology (i.e.
hippocampus, amygdala, entorhinal cortex). By stage IV all cortical lobes are involved
with severe tau pathology though it is still most severe at the sulcal depths and around
blood vessels. In addition, there is abnormal tau accumulation within the diencephalon, brainstem, and cerebellum.

*Alzheimer’s disease.* Neuropathological diagnosis of AD required an intermediate or high degree of neuropathological changes as defined by the ABC score. Subjects with AD changes had a low degree of neuropathological change as defined by the ABC score [15, 34]. Neuritic and diffuse plaques were assessed with Bielschowsky silver staining and using the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) scoring system for plaque pathology [31].

*Lewy body disease.* The presence or absence of Lewy bodies was determined by immunohistochemical staining for alpha-synuclein. The regions examined in each case included the olfactory bulb, medulla, substantia nigra, amygdala, hippocampus, and cingulate gyrus.

*Immunohistochemistry.* Human tissue was fixed in periodate-lysine-paraformaldehyde, and tissue blocks were paraffin-embedded and cut at 10 µm for immunohistochemistry. Antigen retrievals were performed by formic acid treatment for 2 min for Aβ antibodies. Sections were incubated at 4oC overnight with antibodies to phosphorylated PHF-tau (AT8; Pierce Endogen, Rockford IL; 1:2,000), Aβ1-40 (AB5074P; EMD Millipore, Billerica, MA; 1:2000), Aβ1-42 (AB5078P; EMD Millipore; 1:2000), alpha-synuclein (rabbit polyclonal; Chemicon, Temecula, CA; 1:15,000), and pTDP-43 (pS409/410 mouse monoclonal; Cosmo Bio Co, Tokyo, Japan; 1:2,000). For determination of Aβ deposition in the medial temporal lobe (section of the hippocampal
formation, parahippocampal gyrus, transentorhinal region, and portions of occipitotemporal gyrus), the monoclonal anti-\( \text{A}\beta \) antibody (Clone 4G8; Covance, Dedham, MA, 1:100,000) was used. After three washes with PBS (pH 7.4), sections were treated with biotinylated secondary antibody and labeled with a 3-amino-9-ethylcarbazol HRP substrate kit (Vector Laboratories). Sections were counterstained with Gill's Hematoxlin (Vector Laboratories H-3401) and then coverslipped with Permount mounting medium.

**Quantitative ELISA Measurement of \( \text{A}\beta \) and tau.** The buffer conditions, protease inhibitors, and centrifugation protocols have been reported previously [51]. Briefly, a 4mm tissue punch was used to isolate and remove gray matter from the gyral crests and sulcal depths of the middle frontal gyrus and neighboring sulci and superior temporal gyrus and sulcus. Brain tissue was homogenized in 5-fold volume of 5M Guanidine Hydrochloride/50mM Tris-HCL, pH 8.0, with protease inhibitors (Thermo Scientific, 78439) and phosphatase inhibitors (Sigma, P5726 and P0044). Tissue was homogenized using a mechanical homogenizer for 25 strokes followed by ultrasonic disruption on ice. The homogenates were shaken at room temperature overnight. Samples were diluted 10 fold with 0.4% Block Ace (Dainippon Pharmaceuticals Co, Japan) and centrifuged at 14,000rpm for 15 min at 4oC. Enzyme-linked immunosorbent assay (ELISA) was performed for \( \text{A}\beta 1-38, 1-40, \) and 1-42 using a multiplex plate from Meso Scale Discovery (MSD, Rockville, MD) as well as for levels of phosphorylated tau (Thr231) following the manufacturer’s instruction.
Aβ plaque deposition was determined using Aβ1-40 and Aβ1-42 immunostaining and quantified as reported previously [37]. Briefly, digital images were captured at 200x magnification and a threshold optical density was obtained, which discriminated staining from background. The amyloid burden was defined as the total percentage of cortical surface area covered by either Aβ1-40 or Aβ1-42 deposition over three sections and was calculated for the bottom third of the sulcus (depth of the sulcus) and the top third of the gyrus (gyral crest).

**APOE Genotyping.** DNA was extracted from brain tissue samples using a Qiagen QIAamp DNA extraction kit (Qiagen, Valencia, CA). Two single nucleotide polymorphisms (National Center for Biotechnology Information SNPs rs429358 and rs7412) were examined using TaqMan assays (Applied Biosystems, Foster City, CA). Allelic discrimination was automated using the manufacturer’s software. Positive controls, consisting of DNA of each of the 6 possible APOE genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4), were included on each plate and genotyped with restriction isotyping.

**Statistical methods.** Both SPSS version 20.0 (IBM Inc., Chicago, Illinois) and SAS version 9.3 (SAS Institute, Cary, North Carolina) were utilized for statistical analyses. Significance was set a priori at alpha = 0.05. Neuropathologically confirmed CTE tauopathy cases were divided into two subgroups based on the presence or absence of Aβ plaques and further distinguishing between diffuse and neuritic types. Group
comparisons were based on demographic (e.g., age at death), clinical (e.g., symptom onset, presentation subtype), genotype (APOE), exposure (e.g., sport, RTBI history), and lesion (e.g., Aβ, LBD, TPD-43) characteristics. Spearman’s rank order correlation was used to determine the statistical association between CTE stage and all linear variables of interest. For non-linear independent variables, the Wilcoxon–Mann–Whitney U test was used for independent variables with only two groups (e.g. presence of neuritic plaques). A two-sample chi-square test weighted by sample size and a logistic regression model were used to compare the frequency of Aβ deposition in the medial temporal lobe by age in our CTE cohort to a published non-selected community-based autopsy series of 2,332 subjects [2]. The chi-square statistical method is nonparametric and therefore makes no assumptions about the population distribution. Linear regression analysis was performed to determine the relationship of Aβ deposition and age at death and CTE stage. The interaction effect between age and Aβ pathology in predicting CTE stage was calculated when appropriate. Logistic regression models were used to generate odds ratios (OR) while adjusting for age and CTE stage when appropriate.

Results

Beta-Amyloid Pathology in CTE, AD, and Aging. We first set out to determine whether the frequency of plaques differed in our cohort of CTE versus AD and normal aging. Beta-amyloid plaques can be either diffuse or neuritic as defined by the presence of abnormal tau-positive neurites. In our cohort of 114 subjects with CTE (mean age at death = 60 yrs, all men), we found Aβ deposition in the form of diffuse plaques in 52%
with Aβ immunostaining and neuritic plaques (CERAD > 0) in 36% using Bielschowsky silver staining. The percent of cases with both diffuse and neuritic Aβ deposition increased with CTE stage (Table 1). When compared to AD subjects from the Boston University’s AD Center, stage IV CTE had a similar frequency of diffuse Aβ plaques. However, there were significantly fewer neuritic plaques in stage IV CTE compared to AD (Table 1, Z = -9.94, p < 0.001).

The mean age at death was significantly higher in CTE subjects with Aβ plaques compared to those without (Figure 1a and Table 3). To evaluate the age-dependent increase of Aβ deposition in our CTE cohort and to determine whether it differs from normal aging, we grouped the age at death of our subjects into decades and plotted the frequency of cases positive for Aβ deposition in the medial temporal lobe (available in n = 104 subjects) as assessed by the anti-Aβ antibody 4G8 (Figure 1b). Aβ pathology first appeared in CTE cases aged 41 to 50, with a frequency that was significantly higher in later decades (Figure 1b). The odds of developing Aβ pathology in CTE increased 2.7 fold for every decade (p < 0.0001). A clear age-dependent increase in Aβ plaque deposition was also reported in the medial temporal lobe using identical methods in a non-selected community-based autopsy series of 2,332 subjects [2]. When compared to this normal aging population, the frequency of Aβ deposition in our CTE cohort was higher in CTE subjects in the decades between the 50s and 90s and significantly higher for CTE subjects in their 60s (χ² = 13.7, p < 0.001) and 70s (χ² = 7.76, p = 0.005), and the overall risk of developing plaque pathology was higher for the CTE group (Figure 1b). In fact, the odds of developing plaque pathology were 3.8 times higher in CTE than
in normal aging (p < 0.0001). To test the hypothesis that the Aβ plaque frequency in CTE and normal aging are not derived from a common distribution we performed a weighted two-sample chi-square test. Importantly, this demonstrated a distinct distribution of Aβ by age in the CTE cohort compared to normal aging ($\chi^2 = 721$, p < 0.0001). This suggests that Aβ deposition in CTE is not simply accelerated aging, but rather a distinct process with altered dynamics.

<table>
<thead>
<tr>
<th>Table 3.1. Frequency of Aβ deposition in CTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>CTE (all)</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>AD</td>
</tr>
</tbody>
</table>

CTE, Chronic traumatic encephalopathy; DP, diffuse plaques; NP, neuritic plaques; AD, Alzheimer's disease
* % of both $\varepsilon 4$ heterozygotes and homozygotes out of those cases with genotypes (n=82)
Figure 3.1. The presence of neuritic Aβ plaques (NPs, CERAD > 0) was associated with age at death and was accelerated in CTE. a Subjects with neuritic plaques were significantly older at death than those without neuritic plaques (CERAD = 0). b When compared to the gradual age-dependent increase in the frequency of Aβ plaques in the medial temporal lobe of a non-selected autopsy series [2], the frequency of Aβ plaques in CTE is significantly higher in subjects in their 60 s (*\(\chi^2 = 13.7, p < 0.001\)) and 70 s (**\(\chi^2 = 7.76, p = 0.005\)).
**APOE ε4 Allele is Enriched in CTE Subjects with Aβ.** We next set out to determine whether the proportion of APOE ε4 was enriched in CTE cases overall and in those with Aβ versus those without. First, we tested the hypothesis that the proportion of ε4 alleles is elevated in our CTE cohort overall. Although there were more ε4 alleles in the overall CTE cohort (20%) when compared to an age-matched normative sample (15% from [28]), the difference was not quite significant (Table 2, $Z = 1.48, p = 0.069, z$-test). Similar to what was reported previously in a subset of these cases [46], there was a significantly greater proportion of ε4 homozygotes ($Z = 1.94, p = 0.026$) and a non-significant increase in heterozygotes in the overall CTE cohort compared to the normative sample. To test the hypothesis that the ε4 proportion is elevated in CTE subjects with Aβ, but not in those without, we compared the proportions of these different groups to a control population [28]. In CTE subjects without either diffuse or neuritic plaques, the proportion of ε4 alleles (14%) was not significantly different from population norms (15%). However, the proportion of ε4 alleles was significantly greater than a control population in CTE subjects with diffuse plaques (27%, $Z = 2.92, p = 0.002$) or neuritic plaques (25%, $Z = 2.01, p = 0.022$). We also examined the other APOE allele frequencies. In CTE subjects with diffuse plaques there was a decrease in the number of ε3 alleles (65%) compared to the control population (77%, $Z = -2.51, p = 0.012$). Differences in the ε2 allele frequency were not detected (Table 2). Finally, to directly test the hypothesis that the ε4 allele is associated with Aβ in our CTE cohort, we performed a Fisher’s exact test and found that ε4 was significantly associated with the presence of diffuse plaques ($p = 0.035$), but not quite for neuritic plaques ($p = 0.086$).
<table>
<thead>
<tr>
<th>Group</th>
<th>ε2 allele count n(%)</th>
<th>p-value (Z score)*</th>
<th>ε3 allele count</th>
<th>p-value (Z score)* n(%)</th>
<th>ε4 allele count</th>
<th>p-value (Z score)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTE overall</td>
<td>12 (7.3%)</td>
<td>0.726 (-0.348)</td>
<td>120 (73%)</td>
<td>0.298 (-1.04)</td>
<td>32 (20%)</td>
<td>0.069 (1.48)</td>
</tr>
<tr>
<td>CTE without Aβ</td>
<td>5 (6.4%)</td>
<td>0.596 (-0.534)</td>
<td>64 (82%)</td>
<td>0.258 (1.13)</td>
<td>11 (14%)</td>
<td>0.386 (-0.294)</td>
</tr>
<tr>
<td>CTE with DPs</td>
<td>6 (7.0%)</td>
<td>0.711 (-0.368)</td>
<td>56 (65%)</td>
<td><strong>0.012 (-2.51)</strong></td>
<td>23 (27%)</td>
<td><strong>0.002 (2.92)</strong></td>
</tr>
<tr>
<td>CTE with NPs</td>
<td>3 (5.4%)</td>
<td>0.459 (-0.742)</td>
<td>39 (70%)</td>
<td>0.219 (-1.23)</td>
<td>14 (25%)</td>
<td><strong>0.022 (2.01)</strong></td>
</tr>
<tr>
<td>Population norms, ages 42-70 yrs [28]</td>
<td>758 (8.1%)</td>
<td></td>
<td>7205 (77%)</td>
<td></td>
<td>1439 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

*APOE*, apolipoprotein E gene; CTE, chronic traumatic encephalopathy; DPs, diffuse plaques; NPs, neuritic plaques; significant p-values in bold (Z test vs population norms), *two-tailed, **one-tailed
**Sulcal Versus Gyral Aβ Levels.** If traumatic injury influences the deposition of Aβ, we would hypothesize that more Aβ would be present at the sulcal depths due to the putative stress concentration there [45]. Therefore, we next examined a subset of cases that met the neuropathological criteria for both AD and CTE (CTE-AD; Supplementary Table 1) for differences in Aβ levels at the sulcal depths of the middle frontal sulcus versus the gyral crests. We also examined subjects with CTE and neuritic plaques that did not reach the full criteria for an AD diagnosis (CTE+NPs). These groups were compared to subjects without any history of RTBI or professional contact sports play, including those with pathologically diagnosed AD, and to those with neuritic plaques that did not have AD (AD changes; Supplementary Table 1). In subjects with only AD, there was no difference in Aβ1-40 or Aβ1-42 plaque deposition between the sulcus and the gyrus (Figure 2). However, in CTE-AD subjects, the Aβ1-40 plaque burden was significantly greater in the sulcus compared to the gyral crest (t = 2.21, p = 0.029, Student’s t-test), but this difference was not present for Aβ1-42. The Aβ1-42 plaque burden was similar between AD and CTE-AD subjects. In contrast, there was a significantly lower Aβ1-40 plaque burden in the gyral crest in CTE-AD compared to AD subjects (Figure 2, t = -2.80, p = 0.013). Subjects with AD changes and subjects with CTE+NPs had similar plaque burden levels for both Aβ1-40 and Aβ1-42 in both the gyrus and the sulcus, and all were significantly less compared to the AD subject groups (p < 0.05, Student’s t-test).

To determine whether total levels of various species of Aβ were elevated in the sulcus compared to the gyrus in subjects with CTE compared to those without, we next
used ELISA to measure the total levels of Aβ1-38, Aβ1-40, and Aβ1-42 isolated from the sulcal depths of the middle frontal cortex and compared them to levels in the gyral crests. Similar to the data on Aβ plaque burden, we found significantly more Aβ1-40 in the sulcus compared to the gyrus in CTE-AD subjects (paired t = 1.965, p = 0.045) and no difference between sulcal and gyral levels of Aβ1-42 (Figure 3). Surprisingly, we also found a trend of elevated Aβ1-40 levels in the middle frontal sulcus compared to the gyrus of AD subjects without a history of RTBI; however, this did not reach significance (t = 2.16, p = 0.059, paired t-test). As expected, subjects with CTE without neuritic plaques had very low levels of Aβ1-38, Aβ1-40, and Aβ1-42 (Figure 3).

### Supplementary Table 3.1. Characteristics of subjects examined with immunohistochemistry and ELISA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>IHC (ELISA)</th>
<th>Average age (yr)</th>
<th>Braak &amp; Braak NFT Stage</th>
<th>CERAD plaque density</th>
<th>CTE Stage Mean±SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>13 (10)</td>
<td>79</td>
<td>V-VI</td>
<td>Moderate to Frequent</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CTE-AD</td>
<td>9 (8)</td>
<td>70</td>
<td>V-VI</td>
<td>Moderate to Frequent</td>
<td>3.5±0.2</td>
<td></td>
</tr>
<tr>
<td>AD changes</td>
<td>9 (-)</td>
<td>93</td>
<td>0-III</td>
<td>Sparse to Moderate</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CTE+NPs</td>
<td>7 (-)</td>
<td>81</td>
<td>0-III</td>
<td>Sparse to Moderate</td>
<td>3.6±0.2</td>
<td></td>
</tr>
<tr>
<td>CTE</td>
<td>5</td>
<td>65</td>
<td>0-III</td>
<td>None</td>
<td>3.4±0.2</td>
<td></td>
</tr>
</tbody>
</table>

AD, Alzheimer's disease; CTE-AD, Chronic traumatic encephalopathy with Alzheimer's disease; NPs, neuritic plaques; NFT, neurofibrillary tangle
Figure 3.2. Aβ and tau pathologies were concentrated within the sulcal depths as compared to the gyral crests of the dorsolateral frontal cortex in CTE-AD.

Figure 2. a–d Immunostaining for tau showed a greater accumulation of tau-positive neurons, astrocytes, and cell processes in the sulcus of CTE-AD subjects (d) as compared to the gyrus (c), but no difference in AD subjects (a, b). e–l Immunostaining for Aβ1-40 and Aβ1-42 showed no difference between the gyrus (e, i) and sulcus (f, j) of AD subjects. However, there were a greater number of plaques in the sulcus of subjects with CTE-AD (h, l) as compared to the gyrus (g, k) although the difference in Aβ1-40 was most pronounced (k, l). Scale bar 200 μm. (m, n) Quantitation of the percent amyloid burden showed significantly increased Aβ1-40 (m), but not Aβ1-42 (n) within the sulcus compared to the gyrus in the dorsolateral frontal cortex of CTE-AD subjects (*p = 0.029, Student’s t test). There was no difference between sulcal or gyral plaque burden for Aβ1-40 or Aβ1-42 in subjects with AD, AD changes, or CTE with neuritic plaques (CTE+NPs).
Figure 3.3. Total levels of Aβ in subjects with AD, CTE-AD, or CTE alone as measured by ELISA. Subjects with both CTE and AD (CTEAD) had a significantly higher Aβ1-40 burden within the sulcus compared to the gyrus (*p = 0.045, paired t test). There was no difference between sulcal or gyral Aβ1-42 levels in subjects with AD or CTEAD. Subjects with CTE alone had low levels of Aβ1-38, Aβ1-40, and Aβ1-42 that were not significantly different between sulci and gyri.
**Effect of Aβ on CTE tauopathy.** To test the hypothesis that the development of Aβ pathology relates to an increased severity and progression of CTE tauopathy, several regression analyses were employed. The CTE stage is a measure of the degree and distribution of tau pathology [30] and was significantly increased in subjects with co-morbid neuritic plaque pathology (Figure 4a). In the overall CTE cohort, age was also significantly associated with CTE stage. Therefore, we also tested for an interaction between neuritic plaques and age on CTE stage. The overall linear regression model showed that CTE stage was significantly predicted by neuritic plaques (β = 2.43, p = 0.018) when adjusted for age (β = 0.029, p = 0.001) and the two-way interaction (age x neuritic plaque, β = -0.028, p = 0.047). Taken together, Aβ pathology and age accounted for almost half of the total variance in the progressive development of CTE stage (r² = 0.47) although the contribution of age to the development of CTE tau pathology had a small effect (β coefficient < 0.25). Figure 4b illustrates the nature of this interaction by separately plotting the regression of age and CTE stage in subjects with neuritic plaques versus those without. Notably, there was a significant association between age at death and CTE stage in subjects lacking neuritic plaques (β = 0.032, p < 0.001), but not in CTE subjects with neuritic plaques (β = 0.004, p = 0.740). The slope of the linear regression line between age and CTE stage was significantly greater in CTE subjects without neuritic plaques compared to those with neuritic plaques (F = 4.147, p = 0.044). This demonstrates that the presence of neuritic plaques modifies the relationship between age and CTE stage. When broken down by decade, CTE stage was significantly increased in subjects in their 60s with neuritic plaques, but not younger subjects (Figure 4c). After
at age 70, the average CTE stage plateaued to near its maximum level for subjects both with and without NPs. To examine this relationship even further, we employed binary logistic regression and found the odds of a case progressing to the most severe stage of CTE, stage IV tauopathy, was 3.90 times higher in subjects presenting with co-morbid neuritic plaques compared to those without (p = 0.008) while adjusting for age. Overall, this data demonstrates that the presence of neuritic plaques was associated with more severe CTE-related tauopathy independent of age.

Quantitative levels of tau phosphorylated at threonine 231 (ptau231) were also measured by ELISA in the middle frontal cortex in a subset of subjects (Supplementary Table 1). Ptau231 was significantly increased in CTE subjects with neuritic plaques compared to those without (Figure 5, t = 2.10, p = 0.045) and was further increased in CTE-AD subjects. CTE-AD subjects had similar levels of ptau231 as AD subjects despite an average age at death almost a decade earlier (70 years in CTE-AD versus 79 years in AD). This further supports the hypothesis that Aβ deposition is associated with more severe tau pathology in CTE.
Figure 3.4. CTE subjects with neuritic Aβ plaques (CERAD > 0) had an accelerated tauopathy. a The median CTE stage was significantly greater in CTE subjects with neuritic plaques (*p < 0.001, Mann–Whitney U test). b Scatter plots of CTE tau pathology (stage) versus age are shown with separate regression lines for subjects without neuritic plaques (CERAD = 0) and those with neuritic plaques (CERAD > 0). There was a significant correlation between age and CTE stage in subjects without neuritic plaques, but not in CTE subjects with neuritic plaques. The slope of the regression line between age and CTE stage was significantly greater (p = 0.044) in CTE subjects without compared to those with neuritic plaques. c The increase in CTE stage in subjects with neuritic plaques was significant in the 7th decade of life (*p < 0.002, Mann–Whitney U test), while older subjects had similarly elevated CTE stages.
Figure 3.5. Levels of tau phosphorylated at threonine 231 (ptau231) in the middle frontal gyrus measured with ELISA. Subjects with CTE and neuritic Aβ plaques (CTE + NPs) had significantly more ptau231 than subjects with CTE alone (p = 0.045). Subjects with CTE and AD (CTE-AD) had the greatest amount of ptau231 and had levels similar to subjects with Braak & Braak stage V-VI AD (AD, n = 4, Student’s t-test).
Clinical and mTBI Exposure Associations. We next set out to determine whether the presence of Aβ was associated with worse clinical outcomes. First, we found no significant difference between the number of years of athletic exposure. Subjects with diffuse or neuritic plaques did have an increased number of reported concussions compared to CTE subjects without Aβ, but this difference was not significant (Table 3). Both the age at death and the age at symptom onset were significantly greater in CTE subjects with Aβ (either diffuse or neuritic plaques) compared to those without Aβ (Table 3, p < 0.001).

There was a significantly greater frequency of dementia in subjects with Aβ compared to those without. A logistic regression analysis controlling for age shows that dementia remained significantly enriched in the CTE with Aβ subgroups (Table 3). In fact, the odds of developing dementia were 3.9 times higher in persons with diffuse plaque pathology (OR= 3.93, p = 0.013) while controlling for age (p < 0.001) and 4.5 times higher in persons with neuritic pathology (OR = 4.45, p = 0.012) while controlling for age (p < 0.001). In addition, the proportion of subjects with CTE clinical symptoms was greater in those subjects with either diffuse or neuritic plaques (neuritic: p = 0.028, Pearson χ2 test), although this difference was not significant when controlling for age (Table 3).

Two distinct clinical presentations of CTE have been reported: some subjects present with cognitive symptoms (cognitive variant) and others present with behavioral or mood symptoms (behavioral-mood variant) [46]. The frequency of the cognitive variant was increased in CTE subjects with Aβ, but this difference did not reach
Motor symptoms including parkinsonism have been reported in a subset of CTE subjects. Moreover, Lewy body disease has been associated with Aβ deposition [11]. We therefore tested whether Aβ is associated with Lewy body disease and parkinsonism in our CTE cohort. We found a significantly higher frequency of both Lewy body disease pathology and parkinsonism in CTE subjects with Aβ compared to those without. A logistic regression analysis controlling for age shows that both Lewy body pathology (neuritic: OR = 5.01, p = 0.009; diffuse: OR = 7.09, p = 0.019) and parkinsonism (diffuse: OR = 8.86, p = 0.050) are significantly enriched in the CTE with Aβ subgroups (Table 3).

The CTE cohort is a heterogeneous group with multiple comorbidities, including a history of substance abuse (present in 44% of subjects, n = 94) and symptoms of depression (65%). To test whether these comorbidities may influence the association of Aβ with dementia, parkinsonism, and Lewy body disease, we performed a logistic regression analysis controlling for them. Aβ deposition was still significantly associated with dementia, parkinsonism, and Lewy body disease, but neither a history of substance abuse nor symptoms of depression were significantly associated (data not shown). Furthermore, to test whether these comorbidities are associated with Aβ deposition in the CTE cohort, we performed a logistic regression analysis with the presence of diffuse plaques as the dependent variable and found a positive association with age (β = 0.081, p < 0.001), but a non-significant negative association with a history of substance abuse (β = -0.762, p = 0.148) and symptoms of depression (β = -0.088, p = 0.874). Results were
similar for neuritic plaques suggesting that substance abuse and depression do not influence Aβ deposition in the CTE cohort.

Because forces associated with RTBI likely differ with the type of exposure, we hypothesized that Aβ deposition would also differ with the type of exposure. Thus we compared Aβ plaque deposition across CTE subjects with different exposure histories, specifically boxing, American football, hockey, and military combat (Table 4). Overall, we found that boxers in our series had a significantly greater CTE stage when compared to football players, hockey players, or military veterans (Table 4, Mann-Whitney U test). The boxers also had the greatest frequency of neuritic plaques (50%) compared to football players (34%), hockey players (40%), and military veterans (33%), although the difference was not significant. Similarly, boxers had a greater, but non-significant, frequency of diffuse plaques compared to football or hockey players or military veterans (Table 4).
<table>
<thead>
<tr>
<th></th>
<th>CTE</th>
<th>CTE with DPs</th>
<th>CTE with NPs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean±SEM</td>
<td>n</td>
</tr>
<tr>
<td>Age at death</td>
<td>55</td>
<td>48.2 ± 2.6</td>
<td>59</td>
</tr>
<tr>
<td>Athletic exposure</td>
<td>51</td>
<td>15.0 ± 1.0</td>
<td>46</td>
</tr>
<tr>
<td>Concussion no.</td>
<td>48</td>
<td>11.5 ± 3.0</td>
<td>41</td>
</tr>
<tr>
<td>Age at Sx onset</td>
<td>43</td>
<td>36.2 ± 2.3</td>
<td>42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CTE</th>
<th>CTE with DPs</th>
<th>CTE with NPs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freq (+/-)</td>
<td>Freq (+/-)</td>
<td>p**</td>
</tr>
<tr>
<td>CTE Sx</td>
<td>76% (37/12)</td>
<td>90% (43/5)</td>
<td>0.059</td>
</tr>
<tr>
<td>Dementia</td>
<td>20% (10/39)</td>
<td>73% (35/13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognitive variant</td>
<td>58% (23/17)</td>
<td>76% (31/10)</td>
<td>0.067</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>2.1% (1/48)</td>
<td>25% (12/36)</td>
<td>0.001</td>
</tr>
<tr>
<td>LBD pathology</td>
<td>3.7% (2/52)</td>
<td>35% (19/35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDP-43 pathology</td>
<td>67% (37/18)</td>
<td>84% (48/9)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

For statistical tests, CTE with DPs compared to CTE without DPs (labeled CTE in table) and CTE with NPs compared to CTE without NPs (data not shown).

DP, diffuse plaques, NP, neuritic plaques;
*Student's t-test; **Pearson χ² test; ^logistic regression controlling for age.
Table 3.4. CTE Stage and frequency of Aβ deposition by sport or military history

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean age at death (yr)</th>
<th>CTE stage Mean±SEM</th>
<th>p-value*</th>
<th>APOE ε4 % (+/-)*</th>
<th>DP Freq (%)</th>
<th>NP Freq (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxing</td>
<td>10</td>
<td>67</td>
<td>3.80±0.13</td>
<td>-</td>
<td>29% (2/5)</td>
<td>70%</td>
<td>50%</td>
</tr>
<tr>
<td>Football</td>
<td>88</td>
<td>61</td>
<td>2.78±0.11</td>
<td>0.002</td>
<td>35% (22/41)</td>
<td>51%</td>
<td>34%</td>
</tr>
<tr>
<td>Hockey</td>
<td>5</td>
<td>57</td>
<td>2.60±0.40</td>
<td>0.012</td>
<td>40% (2/3)</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Military</td>
<td>9</td>
<td>55</td>
<td>2.22±0.12</td>
<td>0.002</td>
<td>20% (1/4)</td>
<td>44%</td>
<td>33%</td>
</tr>
</tbody>
</table>

DP, diffuse plaques, NP, neuritic plaques;
*Mann-Whitney U test compared to boxing;
*% of both ε4 heterozygotes and homozygotes out of those cases with genotypes
Discussion

Here we show that Aβ plaque deposition was present in 52% of all subjects with pathologically diagnosed CTE in our series (mean age at death=60 yrs). We find that Aβ deposition occurred at a younger age and at an accelerated rate in our cohort of subjects with a RTBI history and a neuropathological diagnosis of CTE when compared to a community-based autopsy series [2] (Figure 1b). In addition, there were elevated levels of Aβ1-40 within the sulcus compared to the gyrus in subjects with CTE-AD. When Aβ plaques were present in CTE, they were significantly associated with more severe tau and Lewy body pathology and worse clinical outcome independent of the effect of age.

While it is possible that the presence of Aβ simply represents the development of co-morbid Alzheimer's disease pathology, Aβ deposition occurred at an accelerated rate in subjects with a neuropathological diagnosis of CTE when compared to a community-based cohort (Figure 1b), which suggests that exposure to RTBI or the presence of hyperphosphorylated tau might be a modifying factor in Aβ accumulation. In fact, a weighted two-sample chi-square test demonstrated that the age-dependent distribution of Aβ was significantly different in our CTE cohort compared to normal aging ($\chi^2 = 721, p < 0.001$), suggesting that RTBI is not simply accelerating an aging process, but is altering the normal dynamics of Aβ deposition. All the subjects in our CTE cohort were men, which is not the case in the normal aging cohort. However, men develop Aβ pathology at a significantly slower rate than women [2], suggesting that the actual increase in frequency of Aβ deposition in CTE may be greater than what we report. There was a high frequency of substance abuse history (44%) and symptoms of depression (65%) in
the CTE cohort. However, neither of these comorbidities was significantly associated with Aβ deposition, suggesting that other factors drive plaque formation in CTE. Moreover, the pattern of Aβ deposition was altered in CTE-AD subjects with elevated levels of Aβ1-40 at the sulcal depths compared to the gyral crests. This sulcal predilection of Aβ corresponds to regions of axonal injury in gyrencephalic animals after acceleration-deceleration injury [44], which may be a result of stress concentration at the sulcal depths following trauma [3]. Altogether, these findings suggest that repetitive mild traumatic injury may accelerate and alter Aβ accumulation and deposition.

The presence of Aβ was associated with disease progression in CTE. Subjects with neuritic plaques had a significantly increased stage of CTE tauopathy even when controlling for age. Although an association between neuritic plaques and advanced tau pathology might be expected given that neuritic plaques require tau-positive neurites and are associated with neurofibrillary tangles in AD, the pattern of tau pathology associated with the various CTE stages is unique, and an association between Aβ deposition and tauopathy severity in CTE has not previously been shown. We further found that levels of ptau231 in CTE were increased in the presence of Aβ. Along with this increase in tau pathology, there was a significantly higher frequency of dementia in the presence of Aβ with the age-adjusted odds of developing dementia in CTE 4.5 times higher in persons with Aβ pathology than without. Taken together, this suggests that CTE with Aβ pathology is a distinct subtype of CTE—one that has a more aggressive pathology and clinical course.

Deposition of Aβ is strongly associated with Lewy body disease, the formation of
alpha-synuclein inclusions, and higher levels of insoluble alpha-synuclein [11, 20]. In vitro studies have shown that Aβ promotes the formation of alpha-synuclein oligomers and polymers as well as inclusions in transfected cell lines [25]. In our CTE cohort we found a significant association of Aβ with LBD even when controlling for age. Moreover, the age-adjusted odds for developing parkinsonism was 8.9 times higher in CTE subjects with diffuse Aβ deposition compared to those without Aβ. Thus, Aβ may lead to Lewy body pathology and parkinsonism in addition to causing a more severe tauopathy in CTE.

The ε4 allele of APOE is a common genetic factor that appears to render individuals susceptible to Aβ deposition. The APOE ε4 allele is a major risk factor for Alzheimer's disease with homozygotes possessing a more than 10-fold greater risk for developing AD dementia and heterozygotes a threefold greater risk [8, 26]. In clinical control populations, the ε4 allele is associated with biomarkers indicating greater Aβ deposition [35, 50]. Moreover, the ε4 allele is associated with increased Aβ levels following TBI [6], and several studies have demonstrated worse clinical outcomes in ε4 carriers following a traumatic brain injury or concussion [19, 21, 23, 48]. Here we show that the APOE ε4 allele was significantly associated with Aβ deposition in CTE. In fact, when subjects with Aβ were excluded, there was no significant difference in the proportion of ε4 alleles between CTE and population norms although our sample size was small. Although additional effects of the ε4 allele cannot be ruled out, it may be that the ε4 allele increases the likelihood of Aβ accumulation and deposition following RTBI and this, in turn, worsens the pathological and clinical outcomes.
Although CTE is a distinct disease, there are similarities to AD. Trauma has long been thought to be a risk factor for developing AD, and moderate to severe TBI has been shown to acutely increase Aβ levels and plaque formation [36, 16]. An increased percentage of Thioflavin-S-positive plaques has been shown in subjects many years after single TBI compared to age-matched controls, suggesting that even a single TBI may accelerate and alter Aβ deposition [18]. Axonal injury is a proposed source of elevated Aβ in acute and moderate to severe TBI, and we found increased Aβ at the depths of sulci in CTE where there is also evidence of significant axonal injury in animal models of mild TBI. This suggests that the axonal injury provoked by mild TBI might also alter the chronic deposition of Aβ in CTE. We found increased Aβ1-40 at the sulcal depths compared to the gyral crests, but the level of Aβ1-42 was unchanged in subjects with both CTE and Alzheimer's disease. The reason for this difference is unclear. Neuritic plaques are composed of both Aβ1-40 and Aβ1-42 while diffuse plaques are composed of Aβ1-42 [5, 12, 14]. Therefore, the increase in Aβ1-40 may result in more neuritic plaques in CTE.

Abundant genetic and experimental evidence suggests that Aβ can lead to the abnormal phosphorylation and accumulation of tau [1]. Our finding that the deposition of Aβ in CTE was associated with more severe tau pathology supports the hypothesis that Aβ can accelerate a tauopathy. These findings have important implications for diagnosing CTE before death. The interpretation of blood and cerebrospinal fluid biomarkers and Positron Emission Tomography (PET) neuroimaging using both amyloid and tau ligands will need to consider the possibility of Aβ pathology in persons older than
There also may be differences in tau and amyloid pathology depending on the type of traumatic exposure. Studies in boxers using anti-Aβ immunohistochemistry with formic acid pretreatment demonstrated diffuse cortical Aβ plaques in 27 of 28 (96.4%) subjects [39, 49]. In contrast to the original reports of CTE in boxers, the majority of cases in our cohort were football players. The nature, frequency, and intensity of traumatic impacts in different sports may lead to differences in CTE pathology. Here we show that boxers had a significantly greater CTE stage compared to football players, hockey players, or military veterans (Table 4). There was also a trend toward greater frequency of Aβ deposition in boxers although the difference was not significant, which may be due to the small sample size.

There are several limitations to our study. This is an autopsy-based study involving a heterogeneous cohort of individuals with a history of RTBI that came largely by self or family referral. The study subjects may not be representative of the entire RTBI population. Moreover, the clinical histories are retrospectively obtained and are subject to bias. Our subjects lived in the United States, and although the prevalence of AD does not vary much between the USA and European countries [47], it is unknown how differences in ethnicity may affect Aβ deposition. Ethnic differences have been shown to affect ε4 allele frequency. For instance, a recent study showed ε4 frequency increased with latitude [22]. We compared our cohort to a large meta-analysis that included data from multiple countries [28], and other US-based studies found similar ε4 allele frequencies [7, 50], supporting the use of this control population. Future
longitudinal, prospective studies are needed to address the frequency and type of pathologies present in population-based cohorts and to obtain less restrictive clinical histories and evaluations. Better quantitation of subject exposure to RTBI and correlation to in vivo biomarkers as well as neuropathological diagnoses at autopsy will be critical to clearly understand the role of RTBI on Aβ aggregation and deposition and CTE pathogenesis.

Overall, our work suggests that CTE with Aβ pathology is a distinct pathological subtype of CTE that shows a greater degree of tauopathy, a greater likelihood of LBD, and has a worse clinical outcome compared with CTE without Aβ. RTBI may alter and accelerate the deposition of Aβ in some individuals, and Aβ, in turn, may accelerate tau and Lewy body pathologies and worsen the clinical course in CTE. It remains to be determined whether individuals susceptible to Aβ deposition can be identified in life with biomarkers, what genetic factors, in addition to APOE ε4, may influence susceptibility to Aβ deposition, and what minimum burden of head trauma is necessary for induction of CTE and modulation of Aβ deposition.
References


Neuroscience. 2006;143:461–475.


Chapter 4

Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy

Copyright © 2015, International Society of Neuropathology

Introduction

The Participating in contact sports is thought to increase an individual’s risk for later-life impairments and neurodegeneration. Both active and retired athletes who report multiple concussions are significantly more likely to have problems with depression, emotional liability, executive function, attention and memory. In a study commissioned by the National Football League (NFL), it was reported that retired players were 20 times more likely than age-matched controls to receive a diagnosis of dementia, Alzheimer’s disease (AD), cognitive impairment or related memory impairment disorders [93]. Lehman et al, for the National Institute for Occupational Safety and Health, found that neurodegeneration was listed as the cause of death three times more often in NFL players than in the general US population [46,47]. Mounting evidence suggests chronic traumatic encephalopathy (CTE) may be the major underlying etiology in these reports. In fact, a recent study with the National Alzheimer’s Coordinating Center Uniform Data Set reported an atypical, tau predominant pathology in cases of suspected AD after grouping participants with significant traumatic brain injury (TBI) histories [73]. Recently, the Chronic Traumatic Encephalopathy Center (CTEC) added 68 new cases of CTE to the
literature [52], which doubled the number of cases reported in the world’s literature. Of the 68 new cases, it is particularly concerning that six cases of neuropathologically confirmed CTE were identified in high school level athletes [17]. As a result, the National Institutes of Health and the National Institute of Neurological Disorders and Stroke (NINDS) have teamed up with investigators to provide financial support for multicenter and multidisciplinary investigations into this condition. The purpose of this article is to review (i) the acute effects of sports-related TBI, including clinical criteria for concussions, post-concussion syndrome (PCS); second impact syndrome (SIS) (ii); the chronic effects of sports-related TBI, including CTE (iii); review new clinical diagnostic criteria for CTE; and (iv) provide clinical and pathological details from two cases of neuropathologically confirmed CTE from a professional football player and a professional boxer.

**Traumatic Brain Injury**

*Concussion.* The word “concussion” derives from the Latin *concutere*, meaning “to shake violently.” Concussions are just that—a shaking of the brain inside the skull, which alters the alertness of the injured person or produces symptoms that fall into four major categories: (i) Somatic: headaches, nausea, vomiting, balance and/or visual problems, dizzy spells and issues such as sensitivity to light and noise. (ii) Emotional: sadness to the point of depression (even suicide), nervousness and irritability. (iii) Sleep disturbance: sleeping more or less than usual and trouble falling asleep. (iv) Cognitive: difficulty concentrating, troubles with memory, feeling mentally slow or as if in a fog that will not
Changes in alertness can be relatively mild (slightly dazed) or profound (unconscious), yet both situations fall within the definition of concussion. Although concussion is often classified as a form of mild TBI (MTBI), when the profound potential effects are considered, many clinicians do not view a concussion as a necessarily mild injury. It is, however, generally agreed that: (i) Both direct and indirect head trauma produce linear and rotational forces on the brain, with rotational forces being the most injurious [14]. (ii) Concussions do not typically cause structural changes seen on routine imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI) scan, but rather exert their pathological changes at the microscopic and biomechanical levels from the brain being shaken within the skull [13]. (iii) Following a concussive event, there is a destructive pathophysiological and biomechanical response that initiates a chain of neurometabolic and neurochemical reactions that include [79]:

- Activation of inflammatory response.
- Imbalance of ionic concentrations.
- Increase in the excitatory amino acids.
- Dysregulation of neurotransmitter release and synthesis.
- Imbalance of mitochondrial functions and energy metabolism.
- Productions of free radicals.

(iv) While an individual prognosis cannot be determined, all concussions are initially managed with both cognitive and physical rest [12, 15, 31]. (v) Following a concussive event, even after resolution of all symptoms, there may be long-lasting, ultrastructural
and functional brain alteration as shown by [79]:

- Susceptibility weighted imaging MRI.
- Diffusion tensor imaging (DTI) MRI.
- Functional MRI.
- Magnetic resonance spectroscopy MRI.
- Positron emission tomography MRI.

(vi) Because of the unique features of the maturing brain, young athletes are more vulnerable to the effects of a concussion than adults [32, 76].

Post-Concussion Syndrome. While there are two well-recognized definitions of PCS [2, 65] (Tables 1 and 2), most clinicians recognize PCS as the persistence of concussion symptoms lasting beyond a month.

Individuals at increased risk for this condition include athletes with multiple concussions, those with concussions in close proximity to each other and athletes subjected to a double hit such as a direct helmet-to-helmet hit and then the head hitting the ground as the athlete falls [18]. At even higher risk is an athlete that experiences additional head trauma while they are symptomatic from a prior concussion through the course of the same game or match. PCS is usually very debilitating, but it typically clears up in a matter of months. Although rare, there are reports where post-concussion symptoms take as long as 5 years to clear up after trauma [18]. For those who are able to recover from PCS, especially those with shorter courses, many are able to safely return to competitive sports. For those who do not recover, it is presently not possible to rule out incipient CTE.
### Table 4.1. International classification for diseases 10th revision clinical criteria for post-concussion syndrome

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Head injury usually severe enough to cause loss of consciousness within 4 weeks of symptom onset</td>
</tr>
<tr>
<td>B.</td>
<td>Preoccupation with symptoms and fear of brain damage with hypochondrial concern and adaptation of sick role</td>
</tr>
<tr>
<td>C.</td>
<td>Three from below</td>
</tr>
<tr>
<td></td>
<td>Headache, dizziness, malaise, fatigue, noise intolerance</td>
</tr>
<tr>
<td></td>
<td>Irritability, depression, anxiety, emotional lability</td>
</tr>
<tr>
<td></td>
<td>Concentration, memory or intellectual deficit without neuropsychological evidence of deficit</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Reduced alcohol intolerance</td>
</tr>
</tbody>
</table>

### Table 4.2. Diagnostic and statistical manual of mental disorders fourth edition criteria for post-concussion syndrome

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>History of severe concussion</td>
</tr>
<tr>
<td>B.</td>
<td>Neuropsychological evidence of attention or memory impairment</td>
</tr>
<tr>
<td>C.</td>
<td>At least three of the following occurring shortly after injury lasting for 3 months</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Sleep impairment</td>
</tr>
<tr>
<td></td>
<td>Irritability or aggression</td>
</tr>
<tr>
<td></td>
<td>Anxiety, depression, or labile affect</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Personality Change</td>
</tr>
</tbody>
</table>
Second-Impact Syndrome. The most concerning concussion-related problem is SIS. Autoregulation, the process by which our brain normally maintain a constant blood flow, is the basis of this serious condition. When the brain’s blood pressure rises, there is a concurrent restriction in the diameter of arterioles. When the blood pressure falls, the opposite occurs: arterioles dilate, or relax, to maintain constant blood flow (Figure 1A–C).

SIS disrupts autoregulation (Figure 1D). Instead of constricting when blood pressure is normal or elevated, arterioles dilate and allow blood to rush through. The result: a massive inflow of blood to the brain accompanied by an equally dramatic increase in intracranial pressure—a highly dangerous situation, which often leads to brain herniation and death. The patients who survive are almost always severely disabled.

Each year, a few athletes lose their lives to SIS, although the exact number is unclear. Since 1987, the senior author of this paper has been involved in a research study that tracks catastrophic injuries causing death, permanent brain injury or spinal cord damage among high school and college football players in the United States. During a 13-year interval, 15 cases of SIS were identified out of 94 cases of catastrophic head injury [9]. In that study, approximately 40% of athletes were kept on the field despite having concussion symptoms. With a greater commitment to keeping players with concussion symptoms off the field, deaths from SIS could be drastically reduced or eliminated.
**Figure 4.1.** Autoregulation of brain arterioles and pathophysiology. Baseline (A): When blood pressure is normal, brain arteriole blood vessels are neither constricted nor dilated. Increased blood pressure (B): The brain seeks to maintain a constant blood flow. The brain arteriole blood vessels constrict. Decreased blood pressure (C): As pressure falls, brain arteriole dilation occurs. Blood flow to the brain remains unchanged. Dysautoregulation or second impact syndrome (D): A serious disruption occurs. The brain acts as if blood pressure is low when it is not low; it is normal or may be elevated. Brain arteriole blood vessels dilate and blood rushes into the brain and results in a massive rise in intracranial pressure. Within minutes, the brain can herniate, resulting in coma.
Subconcussive Brain Trauma. A concussion is well recognized as an etiological factor for a spectrum of neurological conditions, including PCS and risk for developing CTE, a neurodegenerative disorder occurring later in life. The role of subconcussive head trauma, defined as head trauma that does not result in recognized concussion symptoms or signs, is not well known. In our published work from the Center for the Study of Traumatic Encephalopathy at Boston University Medical School, we have seen cases of CTE in deceased athletes who never had a recognized concussion. These athletes had, however, sustained many thousands, often more than 10,000 subconcussive blows during their athletic career [53]. For athletes who have sustained concussions, our experience tells us that the risk of CTE occurrence correlates best with total head trauma, including both concussive and subconcussive blows [52].

Recent publications clearly point to the damaging effects of repetitive subconcussive trauma in male contact sport athletes when compared with age-matched male noncontact sport athletes [16]. Significant abnormal changes in DTI MRI, including fractional anisotropy (FA) and mean diffusivity, were observed in contact sport athletes. Abnormalities were most robust in the corpus callosum, external capsule and inferior fronto-occipital fasciculus areas of the brain containing long myelinated axonal fiber tracts. These abnormal findings were not only seen preseason in the contact vs. noncontact groups, but increased when the groups were compared with preseason to postseason. An alarming finding, this preseason-postseason difference suggests long-term effects from the repeated head trauma associated with playing just one season of a contact sport. A study of 50 Division I football players compared with 25 matched
controls found that the volume of the hippocampus (part of the brain important for memory) was reduced by 15%–25% in the football players [77]. This diminished brain volume reflected neuronal loss and was correlated with decreased cognitive activity and reaction time. The study further found hippocampus size to be inversely correlated with an athlete’s total years of play. These findings suggested that subconcussive hits have a harmful effect on young brains. These data validate the idea that brain injury can occur from the repetitive impacts sustained in contact sports, even in the absence of clinically apparent TBI. These subconcussive hits still impart resultant linear and rotational accelerations on the brain as it violently shakes inside the skull.

What makes the author’s findings so compelling and concerning is that in the last year alone, multiple reports in peer-reviewed journals have shown significant differences in preseason vs. post-season values in contact sport athletes using a variety of tests. These findings have included metabolic brain function as measured by functional MRI [87], neurocognitive testing (ImPACT) [87] and structural breakdown of the blood–brain barrier as manifested by S100B protein in the blood [50] structural changes seen on DTI imaging [46]. While the majority of these studies have involved American football players, some have included soccer and hockey athletes.

This demonstrates that all head trauma, even at the subconcussive level, can result in brain damage in susceptible individuals. It can be argued that the subconcussive group may have included some unrecognized concussions. It is necessary to carry out additional studies beyond the immediate postseason, up to 3, 6 or 12 months, to see in what percentage the abnormalities persist and result in permanent injury.
**Cumulative Exposure.** In those exposed to repetitive head trauma, there are several possible long-term outcomes that may occur: (i) none, that is, there is no appreciable neurological signs or symptoms; (ii) static deficits that are a result of the head trauma but do not progress; and (iii) a neurodegenerative process, with the repetitive head trauma as either a risk factor (eg, AD) or cause of, for example, CTE. To characterize the clinical features associated with repetitive head trauma, there may be no better groups to examine than football players and boxers. These athletes, particularly those who make it to the professional level, are exposed to thousands of blows to the head over the course of many years. Quantifying such exposure is among the major challenges in the field of TBI. Research efforts are underway to define “clinically practical” measurements of blows to the head among contact sport athletes. For now, the “gold standard” for determining a lifetime history of TBI is retrospective self-reports or proxy reports obtained in a structured interview. These include the NINDS common data elements and recommendations from the Center for Disease Control and Prevention [23, 24, 34]. The researchers at the CTEC developed novel questionnaires to obtain athletes’ athletic and concussion histories and to provide meaningful and accurate estimates of overall repetitive TBI (RTBI) exposure [5, 6, 70]. While there are inherent limitations of retrospective self-reports, numerous studies have demonstrated their usefulness in evaluating the association between long-term RTBI exposure and latent impairments with an acceptable level of reliability [23, 45]. For example, the CTEC recently reported a link between previous football experience and executive dysfunction in older retired football players [74]. In their study, 64 retired college and professional football players
were compared with healthy adults. Subjects were administered the Behavior Rating Inventory of Executive Function, adult version, to evaluate nine areas of executive functioning with scores compared with published age-corrected normative scores for healthy adults. Relative to healthy adults, the football players indicated significantly more problems overall, as well as on seven of the nine clinical scales, including inhibit, shift, emotional control, initiate, working memory, plan/organize and task monitor. These symptoms were greater in athletes aged 40 and older, indicating that although RTBI experienced by football players is associated with both short-term and long-term self-reported executive dysfunction, these symptoms may develop or worsen in the fifth decade of life.

In the absence of a direct measure of a subject’s cumulative trauma exposure, there are several potential surrogates, such as number of fights, fights per year, number of knockouts and years of fighting, that have been utilized in studies with boxers. Among football players, the total number of seasons, primary position and level achieved (high school, college, professional) have been utilized as well. However, each of these variables may actually have a slightly different influence on the development of long-term impairments and underlying neuropathology, including CTE. Number of fights, for example, may act as a proxy for amount of training. Some have postulated that the effects of repeated blows to the head—even at a subconcussive level—that occur during sparring may play an important role in causing cumulative brain injury as the boxing match itself. Investigations using electroencephalography (EEG) and CT in professional boxers reported a stronger association between total number of years/bouts fought than to the
total number of knockouts (KOs), implicating cumulative subconcussive effects [19, 72]. Frequency of fighting may be a complementary variable that requires consideration; fighting more frequently may reduce the time the brain has to fully recover from prior trauma and be a risk factor that interacts with number of fights. On the other hand, when the period of unconsciousness exceeds 1 minute, KO may reflect the more severe end of the spectrum of MTBI. However, in the majority of cases where loss of consciousness (LOC) is only seconds, LOC is not correlated with a severe MTBI. While the number of KOs sustained in sanctioned professional fights can be tracked from commonly available records, KOs that may have occurred at other times are harder to trace.

Aside from the specific aspects of RTBI exposures (eg, severity, location and frequency), the timing of exposure in relation to brain maturation may also influence long-term outcomes. Recently, Cantu and Hyman hypothesized that the age at which an individual is first exposed to RTBI could play a major role in the pathological cascade that leads to CTE [13]. In the book “Concussions and Our Kids [13],” the authors provide a theoretical groundwork for why certain developmental ages are particularly vulnerable to the effects of RTBI. Experimental evidence to support this hypothesis first appeared in a study of amateur boxers in 1971 [39]. In this study, Jedlinksi et al demonstrated a stronger correlation between neurological presentations and pathological EEG ($r = 0.47$), and psychiatric findings ($r = 0.60$) in boxers who began their fighting careers at age 15, 16 or 17, showing a stepwise change in the association with each year [39]. Since this publication, there has been little additional research into the subject of “age at first contact sport exposure.” Having identified this gap [13], a new study lead by Julie Stamm
[83] demonstrated similar findings in American style football players. In this study, an association was made between participation in tackle football prior to age 12 and a greater cognitive impairment later in life; this was determined based on objective neuropsychological tests in a sample of 41 former NFL players (ages 40–69).

In a another recent study group of 730 National Collegiate Athletic Association Division I Football Championship Series athletes, it was demonstrated that while there were no significant differences between position groups in the number of diagnosed concussions, there were significant differences between position groups in the number of undiagnosed concussions (P = 0.008) and “dings” (P < 0.001), with offensive linemen reporting significantly greater numbers than any other positions [3]. It is therefore reasonable to suggest that positions with greater risk of concussion have a greater likelihood for cumulative and latent neurodegeneration. Indeed, Lehman et al attempted to subgroup NFL players into “speed” and a “non-speed” groups for analysis, but were limited by the available sample size [48]. To date, no method has been shown to reliably predict which athletes are likely to develop late-life impairments and CTE disease, other than to roughly classify risk as involvement in contact sports [47].

A contemporary study designed to better understand the effect of repetitive head trauma on clinical and subclinical outcomes is the Professional Fighters Brain Health Study (PFBHS). The PFBHS is a longitudinal study of active professional fighters (boxers and mixed martial arts), retired professional fighters and age-/education-matched controls [6]. The main objective of the PFBHS is to determine the relationships between measures of head trauma exposure, along with other potential modifiers and changes in
brain imaging and neurological/behavioral function over time. Initial results from the PFBHS indicate that increased exposure to head trauma, as measured either by number of professional fights or years of professional fighting, is associated with imaging and performance findings. Because of its ability to potentially reflect white matter integrity, MRI-based DTI has been studied in many different groups exposed to repetitive head trauma. In the PFBHS, a relationship was found between number of KOs and DTI measures in several white matter and subcortical grey matter regions [75]. Moreover, striking changes were seen in transcallosal motor pathways. These fibers transverse a long distance, and given the torsional movement of the brain that can occur with head trauma, may be particularly susceptible to injury. Specifically, in 17 active fighters—scanned two times with approximately 1-year interval—transverse diffusivity ($P = 0.055$) and FA ($P = 0.018$) in a motor pathway, defined by DTI tracking from the left M1 seed, were significantly related to number of professional fights over a period of a year (see Figure 2).

While findings have been reported in a variety of sports and military settings, there is no uniform method for DTI analysis that can be applied at an individual level on differing MRI equipment. Measurement of MRI volumes may be a more practical tool, as methods for automated volumetrics are commercially available. Cross-sectional analysis of over 200 active fighters have shown significant correlations between higher number of fights or years of fighting and lower volumes of the thalamus and caudate (see Figure 3) [5].

Overall, these findings cannot be interpreted as being indicative of risk for any
specific long-term outcome (e.g., CTE). However, additional research examining the relationship between different potential RTBI exposure variables (e.g., age of first exposure, subconcussions, years of fighting) and neuropathologically confirmed CTE lesions is warranted.

**Figure 4.2.** A representative diffusion tensor imaging tracking in a motor pathway. Tracking was conducted from the left M1 seed in 17 paired fighters.
Figure 4.3. Left thalamus volume and years of professional fighting in retired boxers.
**Chronic Traumatic Encephalopathy**

**Historical Context.** As a result of its early discovery in boxers, CTE has been variously referred to as “cumulative encephalopathy of the boxer [20],” “chronic progressive traumatic encephalopathy [27]” and “chronic traumatic encephalopathy [26, 62]” to reflect its trauma etiology and clinical presentation. In the earlier half of the 20th century, it was suggested that the punch-drunk condition was unique to the sport of boxing. The first neuropathologically characterized case of CTE was reported by Brandenberg and Hallervorden in 1954 [10]. As additional cases appeared [21, 33], an association formed between the blows endured from boxing and the subsequent development of neurofibrillary tangle predominant dementia. Augustus Thorndike MD, a Massachusetts General Hospital with the Harvard University Athletic Department (1952) declared in the New England Journal of Medicine: "The college health authorities are conscious of the pathology of the 'punch-drunk' boxer. Just how much one should permit recurrence of cerebral concussion in college athletes is a matter of opinion" (p. 556) [88].” New research shows that CTE is more common in former contact sport athletes than previously realized. Interest in this condition has grown considerably since 2005, following the first post-mortem autopsy report characterizing the pathological hallmarks of CTE in a professional football player [64]. Additional neuropathological evidence of CTE has been reported in many sports other than professional boxing and football, including professional soccer, mixed martial arts, rugby, ice hockey, wrestling and baseball [52, 53, 84].

**CTE with Motor Neuron Disease (MND).** MND has been reported in a subset of
cases with CTE [54, 57]. It is not yet clear whether the pathology in these cases represents a variant of CTE or CTE with overlapping comorbid disease. Recent data suggest that professional American football players have more than four times the risk of dying from amyotrophic lateral sclerosis (ALS) MND than age- and gender-matched controls [47]. Our recent review of the world’s literature [61] uncovered the first case of CTE MND ever reported [57] with pathological evidence to support the link between sport-related RTBI and atypical ALS. Meyers et al reported clinical and neuropathological findings from a 41-year-old retired professional boxer who presented clinically with signs of progressive motor weakness [57]. The subject had a significant boxing history, with a career that began at age 14 and included only two known KOs, which were verified by the Pennsylvania Boxing Commission. This case is historically important because the findings reported by Meyers et al corroborate the findings reported in our more recent case series [52, 54]. In 2010, the members of the CTEC reported the first case series with neuropathologically confirmed CTE and ALS in two football players and one boxer (54). Among our recent series of 68 cases, approximately 11% demonstrated pathological evidence of MND [52]. The predominant presentation (63%) involved motor weakness, atrophy and fasciculations in addition to cognitive and behavioral symptoms.

**Preclinical CTE.** Analogous to other neurodegenerative diseases, there were neuropathologically confirmed CTE cases in our sample that lacked overt clinical symptoms or impairment [52, 81]. As is the case in preclinical AD, developing methods
to identify persons at this early stage of CTE disease is crucial for investigating preventative methods and treatments. Additionally, preclinical cases could provide invaluable information about the etiology and development of symptoms in living individuals. Several studies in boxers and football players support the interpretation that asymptomatic head trauma can cause long-term brain damage that may only become apparent once the normal aging process has contributed to neuronal degeneration [89].

**Clinical Symptoms of CTE.** The symptoms associated with CTE pathology typically manifest in one of four clinical domains: (i) cognitive, (ii) behavior, (iii) mood and (iv) motor [61, 86]. Table 3 summarizes the clinical symptoms identified in our recent systematic review of 202 previously published cases of male athletes with histories of RTBI that met review criteria for possible, probable and neuropathologically confirmed CTE [61]. The sample included 141 boxers, 54 American football players, 5 ice hockey players and 2 professional wrestlers, making this the largest pooled case review of the clinical features in CTE to date. Progression was identified in 137 cases (68%), most often reported in cognitive symptoms, resulting in dementia. The cases described as “stable” were notably younger in age. Symptoms typically manifest 8–10 years after initial RTBI. The clinical course of CTE is slow, much slower than AD or Frontotemporal dementia, with a progression rate estimated at 11–14 years between pathological stages [52].
<table>
<thead>
<tr>
<th>Cognitive Features</th>
<th>Behavioral Features</th>
<th>Mood Features</th>
<th>Motor Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>aMemory impairment</td>
<td>aPhysical violence</td>
<td>aDepression</td>
<td>bAtaxia</td>
</tr>
<tr>
<td>aExecutive dysfunction</td>
<td>aVerbal violence</td>
<td>aHopelessness</td>
<td>bDysarthria</td>
</tr>
<tr>
<td>aImpaired attention</td>
<td>aExplosivity</td>
<td>bSuicidality</td>
<td>bParkinsonism</td>
</tr>
<tr>
<td>bDysgraphia</td>
<td>aLoss of control</td>
<td>bAnxiety</td>
<td>bGait</td>
</tr>
<tr>
<td>Lack of insight</td>
<td>aShort fuse</td>
<td>bFearfulness</td>
<td>bTremor</td>
</tr>
<tr>
<td>Perseveration</td>
<td>aImpulsivity</td>
<td>bIrritability</td>
<td>bMasked facies</td>
</tr>
<tr>
<td>Language difficulties</td>
<td>aParanoid delusions</td>
<td>bApathy</td>
<td>bRigidity</td>
</tr>
<tr>
<td>Dementia</td>
<td>Aggression</td>
<td>bLoss of interest</td>
<td>Weakness</td>
</tr>
<tr>
<td>Alogia</td>
<td>Rage</td>
<td>Labile emotions</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Visuospatial difficulties</td>
<td>Inappropriate speech</td>
<td>Fatigue</td>
<td>Clonus</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Boastfulness</td>
<td>Flat affect</td>
<td></td>
</tr>
<tr>
<td>Reduced intelligence</td>
<td>Childish behavior</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Socially inappropriate</td>
<td>Mania</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disinhibited behavior</td>
<td>Euphoria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personality changes</td>
<td>Mood swings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychosis</td>
<td>Prolix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social isolation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aCore diagnostic clinical feature, defined as any feature that appeared in 70% or more of the neuropathologically confirmed CTE cases without comorbid disease.

*bSupportive diagnostic feature, defined as any feature that appeared in neuropathologically confirmed CTE cases without comorbid disease.

Table adapted from Montenigro et al [61] with permission.
Clinical Subtypes of CTE. Similar to other neurodegenerative conditions, the clinical features in CTE are heterogeneous. Stern et al, identified two relatively distinct clinical presentations: one consisting of behavioral and mood symptoms with an earlier age at onset [mean age at onset 34.5 standard deviation (SD) = 11.6] and another consisting of cognitive impairment with a later age at onset (mean age at onset 58.5, SD = 17.7) [86]. Among cases with initial behavioral and mood symptoms, 86% progressed to include cognitive symptoms whereas only 46% of cognitive cases developed behavior and mood symptoms. In addition to the two subtypes described in Stern et al, Montenigro et al identified an additional “mixed subtype” (mean age at onset 43.0, SD = 14.0) in neuropathologically confirmed cases where the predominant presentation was neither behavioral-mood or cognitive, but rather a combination of the two [61]. Consistent with recent subtype descriptions [61, 86], earlier studies in boxers also reported having identified recurring subtypes in the presentation of CTE. Classifications identified in the earlier literature [61] were based on various clinical features, including initial presentation, progression, age at onset and occurrence of dementia. For example, Ernst Jokl (founder of the American College of Sports Medicine) distinguished between the two types of chronic impairment in punch-drunk boxers, namely a “behavioral-psychopathic” type and a “neurological-psychiatric” one [60]. The former involved cases with presentations involving “viciousness,” “murder committed from jealousy” and “delinquency.” Research involving these subtypes represents an opportunity to refine risk-factor definitions, develop targeted prevention strategies and someday assess treatment responsiveness.
Clinical Diagnostic Criteria. To date, the only definitive means of diagnosing CTE is through post-mortem autopsy. However, the ability to diagnose CTE during life is critical to conduct epidemiologic studies on CTE and to eventually plan treatment trials. To address this gap, Montenigro et al proposed new clinical research diagnostic criteria for CTE [61] that overcome the limitations identified [49, 58] in the previous criteria [40, 43, 44, 92]. The new criteria are based on a systematic review of the previous literature, as well as on the clinical features reported in neuropathologically confirmed cases of CTE without comorbid disease [52, 53, 86]. The proposed diagnostic criteria include five general criteria, three core clinical features and nine supportive features to identify the “traumatic encephalopathy syndrome” (TES). The term TES is used to describe the “syndrome” of clinical features that comprise this condition when the underlying pathology is speculative (Table 4). Criteria for the behavioral/mood variant, cognitive variant, mixed variant and TES dementia phenotypes are also provided (Table 5). Additional biomarker evidence is required to indicate the likelihood that the etiology underlying TES is caused by the CTE pathology. Several potential biomarkers for “probable CTE,” “possible CTE” and “unlikely CTE” are proposed based on recent and ongoing biomarker research (Table 6) [4, 59, 80]. Additional research is needed to validate the usefulness of the proposed biomarkers for CTE. Efforts to validate the utility of the proposed clinical criteria [61] are currently underway (Table 4–6).
Table 4.4. General diagnostic criteria for traumatic encephalopathy [61]

<table>
<thead>
<tr>
<th>All five criterion (1-5) must be met for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. History of multiple impacts</strong></td>
</tr>
<tr>
<td><strong>Types of injuries</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Source of exposures</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>2. Other neurological disorder that likely accounts for all clinical features</strong></td>
</tr>
<tr>
<td><strong>Exclude if</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Can be present</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>3. Clinical features must be present for a minimum of 12 months</strong></td>
</tr>
<tr>
<td><strong>4. “Core clinical features” of traumatic encephalopathy syndrome</strong></td>
</tr>
<tr>
<td><strong>At least one must be present</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>5. “Supportive features” of traumatic encephalopathy syndrome</strong></td>
</tr>
<tr>
<td><strong>At least two must be present</strong></td>
</tr>
</tbody>
</table>
### Table 4.5. Criteria for diagnostic subtypes with modifiers [61]

**A. TES diagnostic variants**

<table>
<thead>
<tr>
<th>Select one</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Cognitive’</td>
<td>Cognitive core features without behavioral/mood.</td>
</tr>
<tr>
<td>‘Behavioral/mood’</td>
<td>Behavioral/mood core features without cognitive.</td>
</tr>
<tr>
<td>‘Mixed’</td>
<td>Both cognitive and behavioral/mood core features.</td>
</tr>
<tr>
<td>‘Dementia’</td>
<td>Progressive cognitive core &amp; functional impairment.</td>
</tr>
</tbody>
</table>

**B. “With motor features” modifier**

| ‘With motor features’ | Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait change, falls, and/or other features of parkinsonism. |

**C. Clinical course modifier**

<table>
<thead>
<tr>
<th>Select one</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Stable’</td>
<td>History or tests indicate little if any change.</td>
</tr>
<tr>
<td>‘Progressive’</td>
<td>Clear indication of progression over 2 years.</td>
</tr>
<tr>
<td>‘Unknown/inconsistent’</td>
<td>Unknown or inconsistent information</td>
</tr>
</tbody>
</table>

---

### Table 4.6. Chronic Traumatic Encephalopathy (CTE) likelihood criteria [61]

**‘Probable CTE’**

- Does not satisfy criteria for another disorder more consistently
- Meets classification for any TES variant.
- Progressive course.

- **At least one positive ‘potential biomarker’**
  - Positive PET tau imaging.
  - Negative PET amyloid imaging.
  - Normal beta amyloid CSF levels.
  - Elevated CSF p-tau/tau ratio.
  - Cavum septum pellucidum.
  - Cortical thinning or atrophy.

**‘Possible CTE’**

- May satisfy diagnostic criteria another disorder.
- Meets classification for any TES variant.
- Progressive course.
- No testing or one negative biomarker except for PET tau.

**‘Unlikely CTE’**

- Does not meet General criteria (1-5) for TES.
- Or has had negative PET tau imaging.
Treatment and Disease Management. The treatment of CTE is currently theoretical and remains to be validated with prospective treatment trials. Treatment and management are likely to vary from case to case. Once deficits related to CTE appear, rehabilitation and medications to treat specific symptoms may still be useful [49]. For behavioral and/or mood issues (e.g., aggression, violence) potentially useful treatments may include antipsychotics, lithium, antidepressants, sedatives, anxiolytics, anticonvulsants, opiate antagonists and beta blockers [22, 56]. To reduce drug-induced extrapyramidal symptoms, risperidone and other neuroleptics drugs can be useful to treat behavioral issues (i.e., psychotic behavior) [56]. In a limited number of cases treated for psychotic symptoms, medications such as trifluoperazine were effective [22, 36]. Methylphenidate may be used to treat apathy, as well as cognitive symptoms [35, 49]. Anti-parkinsonian medications have had mixed results in case reports [41, 56]. One case report documented successful stereotactic surgical treatment of parkinsonian features [7]. Cholinergic dysfunction is thought to underlie cognitive impairments in CTE [90], however, the use of anti-cholinergic treatments (e.g., tacrine, donepezil) for CTE remains speculative and further investigation is required [42, 66]. In another case report, verbal memory, but not visual memory, improved following treatment with physostigmine and lecithin [42]. Additionally, there are no known preventative interventions for CTE, although it has been suggested that treatments demonstrating effectiveness for AD and TBI might also show promise for CTE [49]. For example, one candidate is amantadine, which is considered to be a safe and effective treatment for severe TBI [68]. Recent preliminary investigations have suggested that nonpharmacological interventions may
benefit contact sport athletes. Studies of professional football players report statistically significant improvements in neurocognitive function for up to 6 months with dietary supplementation (e.g., omega-3 fatty acids) [1, 78]. Additional research is needed to determine whether or not reported improvements were maintained in the long term [49]. Because of the severe behavioral mood manifestations of this disease, counseling and cognitive behavioral therapy may also help to mitigate the aberrant behavioral and mood manifestations of this disease [49].

**CTE then and Now.** Recently, certain authors have made a distinction between “classic” and “modern” descriptions of CTE [30, 51]. The “classic” entity, proposed by McCrory et al., is defined by the cases reported by Roberts and Corsellis et al. in their boxing subjects [25, 71]. This particular description highlighted early cases that had prominent motor features, including dysarthria, difficulties with gait and pyramidal problems. It was noted that early reports in boxers identified progression in “the physical signs and problems, but not the cognitive deficits” (p. 2) [30], which is the distinguishing factor from what are considered to be “modern” CTE cases. Alternatively, “modern” cases (i.e., cases published after 2004) are characterized by prominent mood, behavior and progressive cognitive features, but with a reduced frequency of motor symptoms. Our assessment of the evidence suggests that this distinction between “classic” and “modern” CTE presentations is largely an artifact of review bias. The first source of this bias involves the “classic CTE” article by Roberts, who writes: “more attention has been paid, intentionally, to the clinical signs which indicate lesions of cerebellar, pyramidal
and extra-pyramidal systems, than to the evidence of dementia or personality change (for) lesions in these systems are readily comparable. Leaving aside for later consideration the question of dementia and psychiatric disturbance, which undoubtedly occurs” (p. 47) [71]. This methodological limitation prevents any reasonable inferences about the frequency of behavior, mood and cognitive symptoms in classic cases. Although, “in the first case described,” Roberts emphasized that in addition to motor features “dementia had clearly progressed over the years” with “development of a paranoid illness” (p. 44) [71]. This evidence does not support the definition of “classic” CTE, rather it suggests that some of the perceived differences in symptoms reported in earlier cases were caused by the methodological limitations and biased review. For instance, the distinction between “classic” and “modern” presentations also does not account for possible group effects related to different sport exposures, that is, the “classic” presentation is derived from boxers while the “modern” presentation is predominantly derived from American football players [61]. It is our hypothesis that sport-specific differences in exposure alter the course and severity of certain clinical manifestations in CTE. In the sections that follow, we explore our hypothesis by re-examining the CTE case evidence in boxers and football players previously reported by McKee et al [52, 53] and provide two detailed clinical and pathological case reports from two professional level athletes, a former US professional lightweight boxing champion and an American NFL player.
Boxing and American Football

Trauma Risk Factors for CTE. All reported neuropathologically confirmed CTE cases have a significant history of brain trauma, usually repetitive, which suggests that RTBI is a necessary factor in acquirement of CTE degenerative pathology. Not every case of CTE has a history of concussions, leading to the belief that subconcussive impacts may be sufficient to induce neuronal degeneration and subsequent neurodegeneration. Alternately, not every individual that is exposed to RTBI, either concussive or subconcussive, necessarily develops CTE [37]. It is not known what specific aspect of exposure (sport, age, level, position, severity, frequency and mechanics) influences the risk of acquiring CTE. The threshold of damage required for induction and progression of tau pathology is likely multifactorial and may incorporate genetic, environmental and/or nutritional factors [85]. Most of what we know about CTE comes from limited information provided in post-mortem case series. Investigations with confirmed cases have identified factors that influence the severity [52] and phenotype [86] of CTE pathology. In American football players with neuropathologically confirmed CTE, there is a positive correlation with the severity of pathology and the total number of years played (Spearman’s test, r = 0.805, P < 0.0001), as well as years since retirement (Spearman’s test, r = 0.753, P < 0.0001) and age at death (Spearman’s test, r = 0.806, P < 0.0001) [52]. Conversely, informant-reported number of concussions (Spearman’s test, r = 0.259, P = 0.184), years of education (Spearman’s test, r = 0.258, P = 0.134) and lifetime steroid use (Wilcoxon–Mann–Whitney test, P = 0.731) were not significantly correlated. In boxers with neuropathologically confirmed CTE, the severity of the tau
pathology appears to correlate with the total number of years exposed [53].

**Impact Type and Biomechanics.** The types of impacts athletes endure differ by sport. However, each impact is composed of both linear and rotational forces [13, 14]. Rotational acceleration (Figure 4A,B) occurs when a force is eccentric or tangential to the center of gravity of the head. In boxing, when a punch is directed toward the lateral side of an opponent’s face (i.e., “hook punch”) or chin (i.e., “upper cut”), the force of the impact will cause the head to twist and rotate outward along the fixed spinal axis (Figure 4A) [13, 38]. The sudden rotational acceleration of the skull and hyperextension of the neck causes brain deformation at mechanically rigid inflection points, such as the cerebellopontine angle (Figure 4B). Regions of the brain that are composed of multiple tissue types with different tensile strengths near rigid boney structures, such as the midbrain, are particularly vulnerable to shearing forces that stretch and injure vessels, axons and glia. The greatest risk a boxer faces for concussion is the result of impacts that generate rotational accelerations, such as the hook punch [8]. Linear acceleration (Figure 4C,D) occurs when a force is applied directly through the center of gravity of the head, such as in the anterior to posterior direction [14, 67]. Investigations with accelerometers placed in helmets have shown that the majority of impacts in American-style football occur from helmet-to-helmet impacts at the top-front of the helmet (Figure 4C). This is true of all levels (e.g., youth, high school, college, professional) and positions, with the exception being the quarterback position. The forces generated in this type of impact are absorbed at the point of origin, which is nearest the frontal lobes (anterior), and
transmitted through the brain, down to the brainstem and cerebellum (posterior) (Figure 4D). The helmet-to-helmet impacts in American football generate a larger net linear acceleration experienced by the frontal lobes, when compared with the net rotational acceleration generated by the hook punch in boxing [91]. The significance of impact differences between sports on long-term consequences and neurodegeneration is not yet known. Cumulative exposure to different impact types has the potential to influence the onset, type, location, severity and progression of underlying neuropathology.
Figure 4.4. Impact mechanics in boxing and football. Hook punch (A). Primarily rotational acceleration (B). Helmet-to-helmet impact (C). Primarily linear acceleration (D). Figures A and C each depict the impact type that typically leads to injury, including concussions, for each sport, respectively. Figures B and D depict the biomechanics of each impact, including the predominant acceleration involved and its transmission into brain.
CTE in Boxers and American Football Players. As the types of impact and predominant forces differ between sports (Figure 4), it was hypothesized [61] that the phenotype of CTE would also differ with the type of sport exposure. Some authors question whether the underlying pathology between CTE in American football players and boxers is really the same [8, 30, 51, 63]. To explore this issue and to test our hypothesis, we compared the frequency and severity of motor symptoms in addition to cerebellar pathology in professional boxers and professional American football players with neuropathologically confirmed CTE previously described by McKee et al [52]. Because of the spectrum of pathology in CTE stages I through IV, cases were grouped into early CTE (stages I and II) and late CTE (stages III and IV). In CTE, neurofibrillary tangle (NFT) lesions progress from a multifocal state (stage II) to a widespread state (stage III) [55]. This grouping allowed us to be reasonably confident that any significant difference between groups was caused by the differences in sport exposure and not the natural progression of CTE disease (Table 7).

Our analysis found that the proportion of boxers with motor symptoms (parkinsonism, gait changes and dysarthria) was significantly greater (Table 7, $P < 0.05$, Fisher’s exact test) than the proportion in American football players. The proportion of boxers identified with NFT pathology in their cerebellum dentate (71%) was also greater than American football players (57%), although this trend did not quite reach significance. However, we also compared the proportion of cases that had severe (++/+++)$NFT pathology in the cerebellum dentate and found that boxers had significantly more severe NFT deposition (Table 7, $P < 0.05$, Fisher’s exact test) than
American football players. The lack of significance in frequency of cerebellar involvement between the two sports suggests either one of two possibilities: (i) our sample size was too small to detect the difference or (ii) the severe NFT deposition in the cerebellum dentate of boxers reached clinical thresholds for motor symptoms, whereas in football players it did not. In summary, the results of our secondary analysis (Table 7) of previously reported CTE cases [52] supports the hypothesis that impacts in boxing cause greater strain to the midbrain and cerebellum (Figure 4B) than and therefore having a greater frequency of motor symptoms in boxers with confirmed CTE than football players. This was also evidenced by the severity of CTE NFT pathology in the cerebellum dentate. Although preliminary, these results suggest that different biomechanic exposure profiles influence the risk for specific CTE phenotypes and alter the underlying pathological severity.
### Table 4.7. Comparison CTE clinicopathological features in boxers versus football players.

<table>
<thead>
<tr>
<th>Novel (secondary) analysis of previously reported cases in McKee et al [52]</th>
<th>Pro Football</th>
<th>Pro Boxing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late stage CTE (III-IV)</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Mean decade age at symptom onset</td>
<td>50-60</td>
<td>50-60</td>
</tr>
<tr>
<td>Mean decade age at time of death</td>
<td>70-80</td>
<td>80-90</td>
</tr>
<tr>
<td>Late stage CTE “with motor* features”</td>
<td>18.8% (3/16)(^b)</td>
<td>83% (5/6)(^b)</td>
</tr>
<tr>
<td>Late stage CTE with cerebellar dentate NFTs</td>
<td>57% (12/21)</td>
<td>71% (5/7)</td>
</tr>
<tr>
<td>Late stage CTE with severe (++/+++) dentate NFTs</td>
<td>17% (2/12)(^b)</td>
<td>80% (4/5)(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Motor symptoms include parkinsonism, gait changes, and dysarthria, unrelated to MND.

\(^b\)Statistically significant difference in the proportions between-groups (Fisher’s Exact Test).

NFT = neurofibrillary tangles
Case Studies

The history and clinical presentation of the following cases were obtained through post-mortem telephone interviews with family members while the interviewer remained blind to neuropathological diagnosis and apolipoprotein E status. Semi-structured interviews and well-characterized informant questionnaires were utilized in combination with medical records. For a detailed description of the methods used, see Stern et al [86]. Post-mortem pathological analysis and diagnosis methods are described in McKee et al [52].

NFL Player, Case 1. Clinical history: 56-year-old Caucasian male with a history of high blood pressure and a basal ganglia cerebral vascular accident at 54 and death from a myocardial infarction at age 56. He participated in American football for a total of 17 years, beginning at age 12, and played for 7 years in the NFL at the running back and full back positions. He endured approximately 20 concussions, 10 in the NFL level and five in college. Two concussions resulted in loss of consciousness. At 54, he awoke with symptoms of leg weakness and an MRI demonstrated “a small lacunar infarct to the basal ganglia.” Post-stroke changes were mild and stable, with slowness in movement and complaints of fatigue. After 3 months of rest, he returned to his work as a bank vice president and did well. Around the time that he retired from the NFL, he began to experience recurring posterior headaches, with onset at age 32. Family informants reported that his mood changed in his mid-30s and indicated that he struggled with feelings of sadness and depression. His depression was further supported with the
informant short version of the geriatric depression scale (GDS) [11] (total GDS = 6), as well as having been prescribed with Wellbutrin. In the year prior to death, he developed a sense of worthlessness and hopelessness. His behavior was characterized as emotionally explosive and easily frustrated. He would often have sudden angry reactions and “little things would set him off.” Overall, he had a “short fuse” and was easily frustrated. Difficulties with rage did not worsen; however, in the year prior to his death, he began acting out of character, becoming somewhat detached and started listening to old music. Post-stroke neurology follow-up visits indicated improvement in motor symptoms and family informants reported no new symptoms in the time leading up to his death. A change in his cognitive function was observed by family informants during the 5 years leading up to his death. The family version of the cognitive difficulties scale identified mild to moderate cognitive difficulties in short-term memory, attention and concentration and language [28, 82]. Several of these changes were reported to have occurred prior to his stroke and with progression. In contrast, results on the functional activities questionnaire (total score = 0) and the modified AD8 informant interview for dementia (total score = 1) did not indicate significant functional impairment or dementia [29, 69]. He did not serve in the military nor did he receive a diagnosis related to dementia, parkinsonism or AD.

Clinical diagnosis [61]: TES mixed variant; progressive course; possible CTE.

Pathological findings: brain weight was 1550 g. Gross findings include a corpus callosum that is thinned throughout its extent, ventricular enlargement, pallor of the substantia nigra and pallor of the locus coeruleus. Microscopic (Figure 5A–D) findings were
diagnostic of CTE [52] and included numerous tau-immunoreactive NFTs, neurites and astrocytic tangles in the perivascular, sulcal depth, superficial cortical, subpial and glial distribution. No beta-amyloid protein was found. Pathology diagnoses [52]: CTE stage III/IV; vascular disease.

**Boxer, Case 2.** Clinical history: 61-year-old Caucasian male with a history of hepatitis C virus and significant liver cirrhosis that led to a transplant at age 58. The subject died from liver failure and complications of pneumonia. He was a former professional boxer and a US lightweight boxing champion. His boxing career began when he was 8, lasting a total of 26 years. He went on to win the Golden Gloves championship and was ranked the top US lightweight boxing champion for several years, with a total of 36 professional bouts in his 12 years at the professional level. He retired at age 34. Over the course of his career, he reported that he had suffered multiple concussions with only one with loss of consciousness, although the specific number of concussions he experienced is not known. He was also involved in one motor vehicle accident at the age of 56, at which time he experienced headaches, backache and signs of a concussion. A noncontrast brain CT scan found no acute intracranial process and therefore he “did not require medical care.” His brain CT did, however, discover that his ventricles and sulcal spaces showed prominent “cerebral atrophy,” including decreased attenuation within the periventricular white matter suggestive of small vessel disease, both of “uncertain significance.” There was also evidence of chronic fractures in the nasal and orbital bones. He did not serve in the military nor did he receive a diagnosis related
to dementia, parkinsonism or AD. Family informants described him as being violent and hot-headed since childhood, but noted that his behavior deteriorated significantly starting at age 30, with onset of impulsivity, spousal abuse, intermittent explosivity and generally being out of control. In his early 50s, his mood was depressed and he developed feelings of hopelessness and worthlessness. At age 55, cognitive symptoms related to executive dysfunction became apparent to the family. At age 56, an altercation with his daughter lead to a formal psychiatric consultation, which noted he had “increased memory problems (frequently forgets placement of personal items and previous conversations),” as well as worsening dysphoria, irritability and paranoid delusions that his girlfriend was attempting to kill him. He also suggested that the boxing association had officially diagnosed him with “pugilistic dementia.” In his late 50s he reported falling at home from “feeling unsteady and weak.” Motor impairments were obvious in the year prior to his death; he was never diagnosed with parkinsonism or ALS, however, he lost ability to speak, developed dysphagia for food and liquids and his handwriting deteriorated.

Clinical diagnosis [61]: TES mixed variant; with motor features; progressive course; probable CTE. Pathological findings: brain weight was 1230 g. Gross findings include generalized atrophy of the cerebral cortex, atrophy, atrophy of the fornix, cavum septum (1.0 cm), multiple septal fenestrations posteriorly and atrophy of the thalamus and mammillary bodies. There was pallor in the substantia nigra and locus coeruleus. Microscopic (Figure 5E–H) findings were diagnostic of CTE [52] and included numerous tau-immunoreactive NFTs, neurites and astrocytic tangles in the perivascular, sulcal depth, superficial cortical, subpial and glial distribution. No beta-
amyloid protein was found. The *tau pathology in the substantia nigra, basis pontis and cerebellum* was particularly severe. There was mild proliferation of protoplasmic astrocytes consistent with hepatic disease. *Pathological diagnosis* [52]: CTE with classic microscopic of stage III/IV with mild transactive response DNA binding protein (TDP-43) proteinopathy.
Neuropathology and cerebellar degeneration in a former professional boxer and football player. Case 1 (A–D): A 56-year-old former National Football League (NFL) player had chronic traumatic encephalopathy (CTE) characterized by phosphorylated tau-positive neurofibrillary tangles present at the sulcal depths (A, AT8 immunostain). His cerebellum appeared intact with a well-populated Purkinje cell layer (B, Bielschowsky silver stain) and dentate nucleus (C, Luxol hematoxylin and eosin). There was no phosphorylated tau accumulation present within the dentate nucleus (D).

Case 2 (E–H): A 61-year-old former professional boxer had a similar degree of CTE-related tauopathy (E, AT8 immunostain). In fact, both the NFL player and the boxer met neuropathological criteria [49] for CTE stage III tauopathy. However, in contrast to the NFL player, there is marked degeneration within the cerebellum with marked Purkinje cell loss (F, Bielschowsky silver stain; arrowhead, Basket cell processes without Purkinje cells “empty Baskets”). There is also loss of neurons within the dentate nucleus (G), which contains scattered phosphorylated tau-positive neurons (H, arrow) and processes (H, arrowhead). These two cases illustrate the need for careful clinical phenotyping and demonstrate the utility of recently published criteria [61]. Scale bars, A, C, E and G, 100 μm; B and F, 100 μm; D and H, 50 μm.
Conclusions and Future Directions

Participating in a contact sport is now thought to increase an individual’s risk for later-life impairment and possibly developing CTE. CTE has been diagnosed in a wide range of individuals with a history of head trauma, including American football players, soccer and hockey players, boxers, wrestlers and soldiers who have received battlefield injuries. It has even been reported in athletes as young as 17, who only played sports in high school or college. Given the wide range of people that are diagnosed and the recent increase in reported cases, CTE is likely more prevalent than previously thought. To date, the only definitive means to diagnose CTE is through post-mortem autopsy. The neuropathological features of CTE are increasingly well-characterized, yet the clinical aspects of CTE require further elucidation. There is an urgent need for methods that can reliably diagnose CTE during life. To address this gap, new clinical research diagnostic criteria for CTE were proposed and studies to validate its utility are ongoing.
References


86. Stern RA, Daneshvar DH, Baugh CM, Seichepine DR, Montenigro PH, Riley DO, Fritts NG, Stamm JM, Robbins CA, McHale L, Simkin I, Stein TD, Alvarez VE,


Chapter 5
Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School And College Football Players

Copyright © 2016, Mary Ann Liebert, Inc

Introduction

Repetitive head impacts (RHI) refer to the cumulative exposure to recurrent concussive and subconcussive events [1-6]. A concussive event is a direct or indirect impact to the head of sufficient intensity to produce overt clinical symptoms that typically resolve within days or weeks [5], but can persist for months [7] or more than one year [8]. The mechanisms of concussion are believed to involve shearing and tensile forces to axons that occur during the impact induced acceleration, deceleration, and rotational forces of the brain [9]. A subconcussive event is similar in that it also involves a transfer of mechanical energy to the brain at enough force to injure axonal integrity, but does not result in clinical symptoms [1-4, 10, 11]. However, the intensity of impact necessary to trigger this potential neuronal damage is not known and whether there are levels of impact that are benign to neuronal functioning has also not been determined.

The investigation of RHI has most commonly been in the setting of contact sports, such as American football. Over 4.5 million amateur athletes participate in tackle football each year [12, 13], and this sport has one of the highest rates of concussion [14, 15]
Surveys of high school and college athletes show that around 50% of football players suffer a concussion each year, and more than 30% sustain multiple concussions [14, 16, 17]. Subconcussive events are likely even more frequent, as helmet-based accelerometer studies estimate that amateur football players average 600 subconcussive impacts per season in high school and over 1000 at the collegiate level [3]. The high prevalence of concussive and subconcussive events in amateur football players is concerning given their reported association with acute [18-20] and chronic [21-25] neurological consequences. Repetitive subconcussive blows (measured by helmet accelerometer sensors recording events that exceed 14.4g [10]) are associated with pre- to post-season cognitive decline [10, 26], functional brain alterations (e.g., reduced neurophysiological health) [10, 26, 27], and microstructural white matter brain changes [28] in high school football players.

Although research on this topic still is limited, cumulative concussive as well as subconcussive impacts may be a key contributor to later-life neurological consequences, including the neurodegenerative disease, chronic traumatic encephalopathy (CTE) [29]. Importantly, 16% of pathologically confirmed cases of CTE have no reported history of concussion [30], highlighting the potential long-term risks of subconcussive injury. In addition, although CTE has been described predominantly in former professional contact sport athletes, a recent study of deceased amateur athletes and controls found that a history of contact sport involvement was the greatest risk factor for CTE neuropathology [31]. Various exposure metrics (e.g., age of first exposure to football [32-34], duration of football play [11, 35-37], concussion history [21-25]) have been linked to later-life
cognitive and neurobehavioral disturbances in former football players and other contact
sport athletes. These different metrics may reflect different aspects of RHI exposure, each
with slightly different effects on the brain [11, 35].

A direct relationship between RHI and long-term clinical outcomes has been
difficult to formally test due to the lack of validated tools to quantify cumulative RHI
exposure [38]. Quantifying RHI exposure is methodologically challenging given that it
involves a self-reported assessment of multiple events that occur throughout one’s
athletic career. Thus far, research on RHI and long-term outcomes has relied on single,
indirect metrics based on a subject’s history of traumatic brain injury (TBI) that involves
retrospective self-reports or proxy reports using a structured interview containing
validated scales [39-41]. These scales include those recommended by the National
Institute of Neurological Disorders and Stroke (NINDS) common data elements and the
Center for Disease Control (CDC) [42]. Despite known limitations, numerous studies
have demonstrated the usefulness of retrospective report in predicting long-term
consequences following multiple concussions [21, 22, 43]. While short-term head impact
exposure could be quantified prospectively with the placement of accelerometers in the
helmets of athletes, this approach does not estimate cumulative exposure over one’s
athletic career, which is speculated to be of primary importance for predicting later-life
impairments and CTE [44, 45]. In response to this need, Kerr et al. recently proposed the
Head Impact Exposure Estimate (HIEE) [46], which estimates a football player’s total
hours of contact exposure, excluding exposure prior to high school, using self-report
interview. However, the HIEE has not been validated in a model with clinical outcomes.
In our study, we developed and validated a metric to estimate an athlete’s total cumulative exposure to RHI from football, referred to as the cumulative head impacts index (CHII). To derive the CHII we combined two sources of information: a) individual self-report measures of athletic exposure; and b) extrapolated objective measures based on position(s) played, obtained from published helmet-accelerometer studies. Our metric includes estimates for youth, high school and collegiate level exposure, and incorporates percentages for all positions played (i.e. primary, secondary, tertiary, etc.). The purpose of this study was to evaluate the relationship between the CHII and later-life cognitive, behavioral, and mood impairment. Additionally, we compared the predictive validity of the CHII against three other individual exposure metrics, namely total season/years played, age at first exposure, and overall concussion history [21-23, 25, 32, 33, 43, 47]. We hypothesized that cumulative head impact exposure would have a measurable threshold, above which the risk of developing later life clinically-meaningful cognitive, mood, and behavioral impairment increases significantly.
Materials and Methods

Study Design. This present sample was part of a larger ongoing study, the Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND) study, at the Boston University Alzheimer’s Disease and CTE Center. LEGEND is a longitudinal study to assess potential risk factors for short- and long-term consequences of RHI. Participation involves annual telephone-based cognitive assessments, web-based measures of mood, behavior, and cognition, and saliva sampling for APOE genotyping. The LEGEND research protocol was approved by the Institutional Review Board of Boston University Medical Campus and written consent was obtained from all LEGEND participants. Study participation was open to adults, age 18 or older, who were either active or former athletes, across all sports and levels of play. There is no active recruitment program for LEGEND. Rather, this is a convenience sample in which potential subjects learn of the study through descriptions on the investigators’ websites and through word-of-mouth. Therefore, the LEGEND sample should not be viewed as being representative of all athletes. Detailed descriptions of the LEGEND protocol have been previously published [25, 47, 48].

Participants. Of the 800 participants in the LEGEND dataset at the time of analysis, 93 former amateur football players met the following inclusion and exclusion criteria: 1) highest level of football played was at high school or college; 2) no concussion sustained in the year prior to their initial evaluation (to diminish potential effect of acute brain injuries on clinical outcome measures); and 3) no participation in
another contact sport (i.e., amateur wrestling, boxing, bull riding, diving, horse jumping, ice hockey, karate, lacrosse, martial arts, mixed martial arts, entertainment wrestling, rugby, and soccer). The final sample included 17 former high school football players and 76 former collegiate football players. Demographic characteristics of the sample are in Table 1.

<table>
<thead>
<tr>
<th>Table 5.1. Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Formal education (years)</td>
</tr>
<tr>
<td>Education (terminal degree N%)</td>
</tr>
<tr>
<td>High School / GED</td>
</tr>
<tr>
<td>Bachelor’s / Associates / etc</td>
</tr>
<tr>
<td>Master’s or Doctorate</td>
</tr>
<tr>
<td>Working Full or Part Time N(%)</td>
</tr>
<tr>
<td>Marital Status Married N(%)</td>
</tr>
<tr>
<td>Body Mass Index</td>
</tr>
<tr>
<td>Handedness-Right N(%)</td>
</tr>
<tr>
<td>Military history N(%)</td>
</tr>
</tbody>
</table>

*Wilcoxon two sample test. Numbers in parentheses are standard deviations except when otherwise indicated.
Health & Athletic History. Participants were administered a structured questionnaire that has been used previously [25, 32, 47], and was designed to collect retrospective information about the participant’s lifetime athletic experience, past medical history, and concussion history. Questions about athletic experience captured variables regarded by the literature as being potential predictors of brain trauma, such as: 1) sports played [11, 49], 2) age at first exposure to tackle football [32-34], 3) levels of play [50-53] (youth, high school, college, professional), 4) number of seasons played at each level [27, 28, 54], 5) total years played [23, 35-37], 6) all positions [55-58] played for each sport (1st, 2nd, 3rd etc.) at each level, 7) percentage of game time played at each position [46, 58], and 8) age at retirement from the sport [36].

The self-reported number of concussions was obtained, after participants were read a “modern” definition of concussion, based on the CDC statement on sports-related concussion [59] and the Third International Conference on Concussion in Sport held in Zurich [60]. The concussion history characteristics of the sample are provided in Table 2. Since the distribution of self-reported concussions is highly skewed, we used the log of concussions in all subsequent analyses to normalize the distribution. Participants were also asked to report their age at first exposure (AFE) to tackle football and the total number of seasons they played (i.e., duration of football play) (Table 2). For our analysis, participant’s AFE was converted into a dichotomous variable: AFE before age 12 and AFE at age 12 or above. Age 12 was selected as the cutoff based on our previous work on AFE as an exposure metric associated with later-life clinical and structural changes [32, 33]. For duration of play, we used seasons rather than years because for some athletes a
year of football involved both a fall and spring season.

<table>
<thead>
<tr>
<th>Table 5.2. Exposure variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total Sample N=93</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>High School N=17</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>College N=76</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>p-value</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>*Concussion history Median (IQR)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>20 (3)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>10 (13)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>20 (39)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0.0431*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CHII</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5805.7 (3091.2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3237.6 (1932.4)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>6384.4 (3015.4)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>&lt;.0001*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age at first exposure (years)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>10.9 (2.7)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>10.8 (2.7)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>11.0 (2.7)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0.884</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Average years of youth football</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3.3 (2.5)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3.4 (2.3)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3.3 (2.5)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0.931</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Seasons of football play</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>11.1 (4.2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>7.1 (3.1)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>12.0 (3.1)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Time since retirement (years)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>26.3 (14.2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>26.4 (12.2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>26.3 (14.4)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0.971</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>*Wilcoxon two sample test; *Interviewers read participants a current definition of concussion methods described elsewhere [47] and asked to estimate their concussion history based on that definition; *Cumulative Head Impacts Index. Numbers in parentheses are standard deviations except when otherwise indicated. IQR = inter-quartile range.</td>
</tr>
</tbody>
</table>

**Cumulative Head Impact Exposure Index (CHII).** The CHII was developed as an estimate of an athlete’s total cumulative exposure to RHI from football. To derive an individual’s CHII we combined data from two sources of information: a) individual self-report measures of athletic exposure obtained from the LEGEND questionnaire at each level played (youth, high school, college), such as number of seasons played, positions played at each level (primary, secondary, and tertiary), and the proportion of the season’s total game time played at each position; and b) a measure of estimated head impacts received per season, based on data from published helmet accelerometer studies that report the frequency of head impacts per season by position and level of play (See below.
Published Accelerometer Studies Used to Determine Frequency of Head Impacts by Position and Level of Play. To obtain estimates of the frequency of head impacts by position and level of play, we performed a systematic review of the literature (using Pubmed) on helmet accelerometer studies, using the following keywords/search terms: HITS system, 6DOF, accelerometers, helmet-sensor, football, youth, high school, and college. Studies that satisfied the following a priori inclusion criteria were selected:

1. Head Impacts were measured during every practice and game for the entire season.
2. Level of play (youth, high school, college) was identified.
3. Head impact frequencies were reported for positions of play.
4. Any impact event with a peak linear acceleration less than 10g was excluded from analysis. A minimum cutoff of 10g ensures the elimination of non-impact events (e.g., jumping) from the calculation of head impact frequency [37, 63-65 56, 66].

Table 3 provides a summary of key data-points obtained from each accelerometer study that met our inclusion criteria. The participants in the studies summarized in Table 3 were active in both games and practices. Since most players at youth level play at multiple positions, we include a single number to reflect exposure for all seasons each player spent at youth level. There was a single high school study identified that grouped together certain positions, such as linesmen, regardless of whether they played at offensive or defensive positions. Since many players at the high school level would interchangeably
play at both offense and defense, using a similar exposure metric for these positions is a realistic assumption [61]. Impact frequencies from these studies was pooled and weighted, whenever possible, to derive averages weighted by each study’s sample size. These weighted averages are estimates of the impact frequencies per position at the different levels of play (youth, high school, college).
Table 5.3. Summary of data collected from review of helmet-accelerometer studies

<table>
<thead>
<tr>
<th>Level</th>
<th>Position</th>
<th>Study</th>
<th>Minimum acceleration</th>
<th>N</th>
<th>Mean/ Median</th>
<th>Weighted mean impacts per season</th>
</tr>
</thead>
<tbody>
<tr>
<td>College</td>
<td>DL</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>29</td>
<td>1086</td>
<td>871</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mihalik et al 2007 [55]</td>
<td>10.0 g</td>
<td>13</td>
<td>965</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>49</td>
<td>718</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LB</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>29</td>
<td>846</td>
<td>685</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mihalik et al 2007 [55]</td>
<td>10.0 g</td>
<td>9</td>
<td>655</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>47</td>
<td>592</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DB</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>34</td>
<td>487</td>
<td>417</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mihalik et al 2007 [55]</td>
<td>10.0 g</td>
<td>12</td>
<td>731</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>55</td>
<td>306</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OL</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>46</td>
<td>960</td>
<td>728</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mihalik et al 2007 [55]</td>
<td>10.0 g</td>
<td>22</td>
<td>921</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>75</td>
<td>543</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OB/RB</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>23</td>
<td>459</td>
<td>412</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mihalik et al 2007 [55]</td>
<td>10.0 g</td>
<td>12</td>
<td>589</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>37</td>
<td>326</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WR</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>16</td>
<td>305</td>
<td>237</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mihalik et al 2007 [55]</td>
<td>10.0 g</td>
<td>5</td>
<td>501</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>30</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QB</td>
<td>Crisco et al 2010 [57]</td>
<td>14.4 g</td>
<td>8</td>
<td>305</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crisco et al 2011 [62]</td>
<td>10.0 g</td>
<td>14</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>QB</td>
<td>Broglio et al 2011 [61]</td>
<td>15 g</td>
<td>4</td>
<td>467</td>
<td>467</td>
</tr>
<tr>
<td></td>
<td>WR/DB</td>
<td>Broglio et al</td>
<td>15 g</td>
<td>28</td>
<td>372</td>
<td>372</td>
</tr>
</tbody>
</table>
Player positions selected by our study participants were grouped, whenever necessary, in accordance with position groups as reported in the selected helmet-accelerometer studies and cross-referenced with position groups as characterized by relevant and authoritative publications [58,114]. DL = defensive linemen, LB = linebackers, DB = defensive backs, OL = offensive linemen, OB/RB = offensive backs or running backs, WR = wide receivers, QB = quarterbacks, WR/DB = wide receivers and defensive backs (cornerbacks and safeties), DL/OL = linemen. For more detailed information see references listed in table.

<table>
<thead>
<tr>
<th></th>
<th>2011 [61]</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RB/LB</td>
<td>Broglio et al 2011 [61]</td>
<td>15 g</td>
<td>27</td>
<td>619</td>
</tr>
<tr>
<td>DL/OL</td>
<td>Broglio et al 2011 [61]</td>
<td>15 g</td>
<td>41</td>
<td>868</td>
</tr>
<tr>
<td>Youth</td>
<td>All positions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daniel et al 2012 [56]</td>
<td>10 g</td>
<td>7</td>
<td>107</td>
</tr>
</tbody>
</table>

The CHII was calculated from the self-report variables and weighted impact frequencies using the equations outlined in Table 4. A hypothetical case is provided to illustrate the calculation of the CHII: Mr. A is a 42 year old male who reports having participated in football at the youth, high school and collegiate levels.

A. In college, Mr. A reported that he played a total of 3 seasons. His primary position for his college team was linebacker (LB); he reported having no secondary or tertiary positions of play. He estimated having participated in 85% percent of game downs as a linebacker. Thus, his college CHII was: (85%) x (685 impacts per season for LB from Table 5) x (3 seasons) = 1,747.

B. In high school, Mr. A reported that he played for all 4 seasons. His primary position for his high school team was also LB; he reported having a secondary position playing the offensive line (OL) as a guard. Of all the games in high school, he estimated having participated in 40% percent of game downs as a LB and 30% as OL. Thus, his high school CHII was: [(40%) x (619 impacts per season for LB) x (4 seasons)] + [(30%) x (868 impacts per season for OL) x (4 seasons)] = 2,032.

C. Lastly, Mr. A reported that he played 4 seasons of football prior to high school. He reported having played as an OL throughout his youth participation. He estimated that he participated in 90% game downs for all 4 seasons. Thus, his youth CHII was: (90%) x (107 impacts per season for any position) x (4 seasons) = 385.

His overall CHII = (A + B + C) = (1,747 + 2,032 + 385) = 4,164.
### Table 5.4. Calculation of the Cumulative Head Impacts Index

<table>
<thead>
<tr>
<th>YOUTH</th>
<th>% games played at 1&lt;sup&gt;st&lt;/sup&gt; position</th>
<th>X</th>
<th>Position’s weighted average # impacts per season</th>
<th>X</th>
<th>Total # of youth seasons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% games played at 2&lt;sup&gt;nd&lt;/sup&gt; position</td>
<td>X</td>
<td>Position’s weighted average # impacts per season</td>
<td>X</td>
<td>Total # of youth seasons</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% games played at 3&lt;sup&gt;rd&lt;/sup&gt; position</td>
<td>X</td>
<td>Position’s weighted average # impacts per season</td>
<td>X</td>
<td>Total # of youth seasons</td>
</tr>
<tr>
<td></td>
<td>= [A]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIGH SCHOOL</th>
<th>% games played at 1&lt;sup&gt;st&lt;/sup&gt; position</th>
<th>X</th>
<th>Position’s weighted average # impacts per season</th>
<th>X</th>
<th>Total # of youth seasons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% games played at 2&lt;sup&gt;nd&lt;/sup&gt; position</td>
<td>X</td>
<td>Position’s weighted average # impacts per season</td>
<td>X</td>
<td>Total # of youth seasons</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% games played at 3&lt;sup&gt;rd&lt;/sup&gt; position</td>
<td>X</td>
<td>Position’s weighted average # impacts per season</td>
<td>X</td>
<td>Total # of youth seasons</td>
</tr>
<tr>
<td></td>
<td>= [B]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COLLEGE</th>
<th>% games played at 1&lt;sup&gt;st&lt;/sup&gt; position</th>
<th>X</th>
<th>Position’s weighted average # impacts per season</th>
<th>X</th>
<th>Total # of youth seasons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% games played at 2&lt;sup&gt;nd&lt;/sup&gt; position</td>
<td>X</td>
<td>Position’s weighted average # impacts per season</td>
<td>X</td>
<td>Total # of youth seasons</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% games played at 3&lt;sup&gt;rd&lt;/sup&gt; position</td>
<td>X</td>
<td>Position’s weighted average # impacts per season</td>
<td>X</td>
<td>Total # of youth seasons</td>
</tr>
<tr>
<td></td>
<td>= [C]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Head Impacts Index = [A] + [B] + [C]
Clinical Outcomes & Measures.

The following set of instruments administered to LEGEND participants were selected for the current study: (1) Brief Test of Adult Cognition by Telephone (BTACT) [67]; (2) Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A) [68]; (3) Center for Epidemiologic Studies - Depression Scale (CES-D) [69]; and (4) Apathy Evaluation Scale (AES) [70]. Each of these measures were chosen a priori based on their previous use in studies of TBI and concussion (BRIEF-A [25, 71, 72]; AES [73-75]; CES-D [76-78]; BTACT [79]), and on the availability of validated cut-off scores suggesting clinically meaningful impairment [68, 73, 80-82].

Brief Test of Adult Cognition by Telephone (BTACT) [67, 79]. The BTACT is an objective measure of cognitive function administered by telephone. The benefits and validity of cognitive test batteries administered by telephone are well-documented [79, 83]. The BTACT requires 20 minutes to complete and consists of 6 subtests that measure episodic verbal memory (Immediate and Delayed Rey Auditory-Verbal Learning Test), working memory (Digits Backward), verbal fluency (Animals Categorical Fluency), task-switching (Red/Green Test), inductive reasoning (Number Series), and processing speed (Backward Counting) [67]. A global composite score was derived with the bi-factor approach, which has an overall improved validity over the single-factor approach and is better able to distinguish between persons with a lifetime history of head injury [79]. Age and gender corrected scores were scaled relative to a healthy normative sample. Objective cognitive impairment was defined as 1.5 standard deviations below the normative mean [82, 84].
The Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A) [68]. Participants completed an online version of the BRIEF-A questionnaire, a well-validated 75-item measurement of executive function behavior in activities of daily living. Participants rate “how often each of the 75 following behaviors has been a problem?” in the past month on a three-point Likert scale (1 = never, 2 = sometimes, 3 = often); higher scores indicate a greater degree of dysfunction. We used the global measure of executive function (Global Executive Composite [GEC]), as well as two factor-based measures of cognitive regulation (Meta-cognition Index [MI]) and behavioral-emotional regulation (Behavioral Regulation Index [BRI]). Raw scores are converted into standardized age-adjusted T-scores (M=50, SD=10). T-scores ≥1.5 standard deviations of the normative mean (T-scores ≥ 65) are considered clinically impaired [68].

The Center for Epidemiologic Studies - Depression Scale (CES-D) [69]. The CES-D is a 20-item self-report measure of depression symptoms that was developed and validated by the National Institute of Mental Health [69]. Participants rate their depression symptom severity in the past week on a four-point Likert scale that ranges from “none of the time” to “all of the time.” Higher scores indicate more severe depressive symptoms, with an established total CES-D cutoff score ≥ 16 reliably indicating clinically meaningful depression [80, 81].

Apathy Evaluation Scale (AES) [70]. The AES is an 18-item self-report measure of apathy over the past four weeks. Participants rate their apathetic emotions, thoughts, and behaviors in the past 4 weeks on a four-point Likert scale that ranges from “not at all
characteristic” to “very characteristic.” Higher total AES scores indicate worse apathy, with an established cutoff total AES score ≥ 34 reliably indicating clinically meaningful apathy [73].

**Statistical Modeling.**

*Group Comparisons.* The former high school and collegiate football player groups were compared using two sample t-tests for continuous normal variables, Wilcoxon two-sample tests for non-normal continuous variables, and chi-square tests for categorical or dichotomous variables.

*Regression Modeling.* To test our study hypothesis we modeled each dichotomous outcome measure (probability of impairment or not) with our predictor metric (CHII). This model is illustrated in Figure 1. We first identified a point (threshold-dose) at which the magnitude of the relationship (slope) changes from a zero magnitude (B1=0) to a non-zero magnitude (B2>0). The change-point threshold shows the conversion of the relationship from a baseline risk of playing football to a dose-response relationship above which higher exposure to head impacts can lead to higher risk of impairment [85]. The change point was identified using a Bayesian hierarchical model estimated by Markov Chain Monte Carlo (MCMC) method with 30,000 simulations implemented in PROC MCMC in SAS 9.4 [85]. An important contribution in modeling head impact exposure to long-term outcomes is the incorporation of concussion history into the model. Since a head impact is a necessary condition for a concussion, we cannot estimate the effect of head impacts by controlling for concussions in a simple regression setup. This
relationship between predictors where a value of one variable is directly caused by another is often described as endogenous [86]. If endogeneity exists between variables within our model, the following two problems would occur: (1) a linear regression model that includes both the CHII and concussion history would give invalid inference, and (2) the estimates of the slopes from such a regression model would be biased. To address the inference and bias problems caused by endogeneity we used an “instrumental variable model” with log concussions as the instrument [87]. The instrumental variable model can be described as a two-stage regression. In the first-stage regression, we estimate the effect of the log of the number of concussions on the CHII, while in the second-stage regression we use the predicted values from the first stage to estimate the effect of the CHII on the probabilities of impairment for each of the outcomes. Both regressions included age and education as covariates. Next, we applied the instrumental variable model using a bivariate probit model. The estimated effect of cumulative head impacts derived from this instrumental variable model is equivalent to an effect estimated among the compliers from a study where exposure was prospectively randomized [88]. Thus, an instrumental variable model allows for causal inference from observational data with large measurement error. Furthermore, the instrumental variable approach reduces the measurement error of the estimates of frequency of head impacts by position and level of play. Since the studies used to estimate these frequencies are independent from the LEGEND study, their measurement error is uncorrelated from the self-reported concussions in LEGEND. Therefore, in this instance, concussions become an ideal instrument to calibrate and reduce the measurement error of head impacts exposure.
Similar approaches in different settings have been used in econometric and clinical therapeutic studies [90,91].

**Figure 5.1. Illustration depicting the relationship of CHII to risk of impairment**

![Diagram](image)

**Figure 5.1.** Schematic of the dose-response model with a constant baseline risk of later-life impairment (Baseline gradient of slope = 0) below the cumulative head impact threshold-dose and with increasing probability of impairment (Dose-Response gradient of slope > 0) above that threshold-dose.
Comparison to other exposure metrics. We also examined total seasons played and age of first exposure (AFE) as simple exposure metrics that have demonstrated a significant relationship with clinical outcomes in other studies [11, 32, 33, 35, 36]. Total season played and AFE were independently added to our bivariate probit model with age and education as covariates. Next, we modeled clinical outcomes with concussion history in a separate univariate probit model, with age and education included as covariates.

Results

Participant Demographics & Group Comparisons. Participant demographics (Table 1), exposure variables (Table 2), and outcome measures (Table 5) were compared across the two highest levels of play, i.e., high school and college. The college-level group had significantly more years of education (t-test=3.58, p-value=0.0005), more seasons played (t-test=4.85, p-value<0.0001), a greater number of concussions (Wilcoxon=592.5, p-value=0.0431), and a higher CHII (t-test=2.47, p-value=0.0156. All other group comparisons were nonsignificant. Mean scores on the BTACT, an objective measure of cognitive function, indicated that the entire sample was, on average, cognitively normal (Table 5).
Table 5.5. Behavior, mood, and cognition outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Total Sample N=93</th>
<th>High School N=17</th>
<th>College N=76</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Behavioral Regulation Index of the BRIEF-A</td>
<td>64.1 (15.9)</td>
<td>64.4 (16.0)</td>
<td>64.0 (16.0)</td>
<td>0.93</td>
</tr>
<tr>
<td>Metacognition Index of the BRIEF-A</td>
<td>64.5 (16.9)</td>
<td>62.2 (14.8)</td>
<td>65.0 (17.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>Global Executive Composite of the BRIEF-A</td>
<td>65.3 (16.9)</td>
<td>64.2 (15.0)</td>
<td>65.6 (17.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression Scale</td>
<td>21.7 (15.5)</td>
<td>21.7 (17.9)</td>
<td>21.7 (15.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Apathy Evaluation Scale</td>
<td>35 (11.5)</td>
<td>34.2 (12.5)</td>
<td>35.2 (11.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Brief Test of Adult Cognition by Telephone</td>
<td>0.04 (0.9)</td>
<td>-0.11 (1.1)</td>
<td>0.08 (0.90)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.

**CHII Exposure & Risk of Impairment.** The CHII was calculated for all 93 participants, and the means for former high school and collegiate football players are listed in Table 2. The CHII change-points listed in Table 6 indicate the threshold number of impacts, above which a dose-response relationship is initiated between exposure (CHII) and the risk of impairment. Figure 2 shows the predicted probabilities of impairment for different doses of exposure. The baseline risk of impairment significantly increases linearly after a change-point as exposure increases in all outcomes. (See supplementary Table 1 for a tabular summary of the data depicted in Figure 2).

Specifically, we find that the risk of impairment increases steadily every 1000 impacts, or about twice the sample’s average’s season number of impacts (545) above the baseline change-point. For all outcomes, the risk of developing clinically meaningful impairments in mood, behavior, and cognition increased considerably with two additional seasons.
worth of head impacts. For example, we found that adding 10 seasons of impacts above
the baseline threshold increased a subject’s risk of developing objective cognitive
impairment by 25 fold.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Clinical Domain</th>
<th>Threshold for Dose-Response (*Median CHII)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral Regulation Index of the BRIEF-A</td>
<td>Behavior</td>
<td>2216</td>
<td>1537-8120</td>
</tr>
<tr>
<td>Metacognition Index of the BRIEF-A</td>
<td>Metacognition</td>
<td>2393</td>
<td>1571-6682</td>
</tr>
<tr>
<td>Global Executive Composite of the BRIEF-A</td>
<td>Executive Function</td>
<td>1850</td>
<td>1523-2011</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression Scale</td>
<td>Depression</td>
<td>1801</td>
<td>1514-2010</td>
</tr>
<tr>
<td>Apathy Evaluation Scale</td>
<td>Apathy</td>
<td>2160</td>
<td>1536-5754</td>
</tr>
<tr>
<td>Brief Test of Adult Cognition by Telephone</td>
<td>Cognition</td>
<td>7251</td>
<td>1754-9788</td>
</tr>
</tbody>
</table>

*The Median and 95% CI from 30,000 Markov Chain Monte Carlo simulations. Change-point thresholds represent the median number of impacts above which there is a predictive dose-response relationship between head impacts and clinically meaningful measures of impairment.

BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.
Figure 5.2. (A-F) Each dichotomous outcome measure (A-F; probability of impairment) was fit using a bivariate probit, instrumental variable model adjusted for both age and education as well as our predictor variable of interest (CHII). Baseline Risk refers to the risk of impairment at the CHII dose range below the thresholds identified in Table 6. Above these thresholds, a significant linear dose-response relationship between CHII exposure and later-life clinical impairment was found for all outcomes. See supplemental Table 1 for tabular data.
Supplemental Table 5.1. Predicted probabilities of impairment with 95% CI for different doses of cumulative exposure

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>*Baseline CHII</th>
<th>Baseline + 1000</th>
<th>Baseline + 2000</th>
<th>Baseline + 3000</th>
<th>Baseline + 4000</th>
<th>Baseline + 5000</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavior (BRI)</strong></td>
<td>CHII Dose</td>
<td>0-2216</td>
<td>2216-3216</td>
<td>3216-4216</td>
<td>4216-5216</td>
<td>5216-6216</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment</td>
<td>0.11(0.11-0.12)</td>
<td>0.26(0.19-0.34)</td>
<td>0.36(0.24-0.50)</td>
<td>0.47(0.29-0.66)</td>
<td>0.58 (0.34-0.79)</td>
<td></td>
</tr>
<tr>
<td><strong>Meta-cognition (MI)</strong></td>
<td>CHII Dose</td>
<td>0-2393</td>
<td>2393-3393</td>
<td>3393-4393</td>
<td>4393-5393</td>
<td>5393-6393</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment</td>
<td>0.12(0.12-0.13)</td>
<td>0.27(0.18-0.39)</td>
<td>0.37(0.21-0.56)</td>
<td>0.48(0.25-0.72)</td>
<td>0.59(0.29-0.84)</td>
<td></td>
</tr>
<tr>
<td><strong>Executive Function (GEC)</strong></td>
<td>CHII Dose</td>
<td>0-1850</td>
<td>1850-2850</td>
<td>2850-3850</td>
<td>3850-4850</td>
<td>4850-5850</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment</td>
<td>0.10(0.09-0.10)</td>
<td>0.23(0.16-0.32)</td>
<td>0.33(0.20-0.48)</td>
<td>0.44(0.25-0.65)</td>
<td>0.55(0.30-0.79)</td>
<td></td>
</tr>
<tr>
<td><strong>Depression (CES-D)</strong></td>
<td>CHII Dose</td>
<td>0-1801</td>
<td>1801-2801</td>
<td>2801-3801</td>
<td>3801-4801</td>
<td>4801-5801</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment</td>
<td>0.12(0.11-0.13)</td>
<td>0.27(0.19-0.36)</td>
<td>0.37(0.24-0.52)</td>
<td>0.48(0.29-0.68)</td>
<td>0.59(0.34-0.81)</td>
<td></td>
</tr>
<tr>
<td><strong>Apathy (AES)</strong></td>
<td>CHII Dose</td>
<td>0-2160</td>
<td>2160-3160</td>
<td>3160-4160</td>
<td>4160-5160</td>
<td>5160-6160</td>
<td>0.0161</td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment</td>
<td>0.15(0.14-0.16)</td>
<td>0.29(0.17-0.44)</td>
<td>0.38(0.19-0.61)</td>
<td>0.48(0.20-0.77)</td>
<td>0.57(0.21-0.88)</td>
<td></td>
</tr>
<tr>
<td><strong>Cognition (BTACT)</strong></td>
<td>CHII Dose</td>
<td>0-7251</td>
<td>7251-8251</td>
<td>8251-9251</td>
<td>9251-10251</td>
<td>10251-11251</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment</td>
<td>0.10(0.08-0.11)</td>
<td>0.43(0.33-0.54)</td>
<td>0.65(0.49-0.79)</td>
<td>0.83(0.66-0.94)</td>
<td>0.94(0.80-0.99)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age and education. *Baseline refers to the risk of impairment at the CHII dose range below the change-point thresholds listed in Table 6. At and below these
thresholds risk of impairment is at a constant baseline. Above the threshold, there is a
dose-response relationship between increasing CHII exposure and the risk of clinical
impairment. All outcome measures were transformed into dichotomous variables
(impairment or not) using established cut-off points. These results identify the risk of
developing clinically meaningful impairment in later-life from exposure to impacts from
amateur football.
Other Exposure Metrics & Risk of Impairment. We added alternate exposure metrics to our bivariate probit model to test whether other metrics might be better at predicting clinical outcomes and/or whether they might eliminate the predictive significance of the CHII. Total seasons of play and AFE did not add independently to our bivariate probit model, nor did they eliminate the significance of the CHII for predicting clinical outcomes. When added to the model with the CHII, participants with AFE<12 showed some increase in the risk for impairment but did not achieve significance on any outcome after adjusting for CHI: GEC ($\beta =0.41$, p-value=0.2542), MI ($\beta =0.36$, p-value=0.3456), BRI ($\beta =0.56$, p-value=0.073), CES-D ($\beta =0.49$, p-value=0.1771), AES ($\beta =0.33$, p-value=0.4170), BTACT ($\beta =0.81$, p-value=0.1427). Interestingly, when controlling for CHI, increasing the total number of seasons played reduced the risk for clinical impairment: BRI ($\beta =-0.11$, p-value=0.0183), MI ($\beta =-0.09$, p-value=0.0847), GEC ($\beta =-0.07$, p-value=0.1586), CES-D ($\beta =-0.09$, p-value=0.1224), AES ($\beta =-0.07$, p-value=0.2011), BTACT ($\beta =-0.03$, p-value=0.6390). The significant negative association between total seasons played and BRI is consistent with previous research demonstrating a neurobehavioral benefit from regular exercise [92-94]. The betas ($\beta$ indicates the magnitude and direction of the relationship between the predictor, AFE or total seasons, and the risk for impairment in a model that also takes into account a quantitative estimate of CHI exposure. For example, positive betas indicate a positive association between exposure and impairment, such that increasing exposure was associated with an increased probability of impairment.

Lastly, we explored the role concussion history had on predicting clinical
outcomes and compared its predictive power to that of the CHII. Because of the endogeneity problem previously described (i.e., that head impacts are a necessary factor for both the CHII and concussions) we could not simply include concussion history as a covariate in our CHII model. The spearman correlation between concussion history and the CHII was 0.22 (p-value=0.02). Therefore, we ran a univariate probit model with age and education as covariates, in order to evaluate the predictive power of concussions on the probability of impairment. The estimates were: BRI (β =0.50, p-value=0.0109), MI (β =0.41, p-value=0.0255), GEC (β =0.48, p-value=0.0138), CES-D (β =0.48, p-value=0.0195), AES (β =0.30, p-value=0.0717), BTACT (β =0.43, p-value=0.1526). Compared to the CHII, concussion history was limited to predicting self-reported changes in behavioral regulation (BRI), cognition (MI), executive dysfunction (GEC), and depression (CES-D), but not apathy (AES), or objective cognitive dysfunction (BTACT). Even for the significant outcomes (BRI; MI; GEC; CES-D), concussion history was found to have less predictive power than the CHII.

Discussion

We developed a metric of cumulative exposure to RHI from football, the CHII, a measure that includes self-reported exposure and estimated quantitation of head impacts based on published helmet accelerometer studies. The CHII was used to examine the relationship between cumulative RHI exposure and later-life cognitive, mood, and behavioral impairment in a sample of former football players whose highest level of play was either high school or college. Subjects denied having played any other contact sport.
at any time. The mean CHII of 5,806 total impacts for our sample is consistent with the range of cumulative impacts expected for former high school and college football players [3]. We found that the CHII strongly predicts later-life clinical outcomes, outperforming other individual metrics such as concussion history, age at first exposure to tackle football, and total duration of play, suggesting that it is a useful metric to estimate lifetime RHI exposure.

We view this study as an initial examination of the CHII and our findings of the relationship between earlier RHI exposure and later life impairments should be considered preliminary due to several limitations described below. Moreover, this was not a study of CTE or neurodegeneration; our outcome measures focused on clinically-meaningful levels of cognitive, mood, and behavior impairment and did not include any biomarkers of underlying disease or injury. This study does, however, underscore the importance of subconcussive trauma in the development of later life neurological impairment. The number of self-reported concussions predicted impairment in fewer outcomes than the CHII. Compared to the CHII, concussion history did not significantly predict apathy or objective cognitive dysfunction (BTACT). These findings are consistent with previous imaging studies of amateur athletes which demonstrated that changes in brain functional imaging occurred after a single season of cumulative asymptomatic impacts without concussion [10, 26, 27] and post-mortem studies that indicate 16% of former contact-sport athletes with pathologically verified CTE had no concussion history [30, 36]. These studies together with our current findings highlight the critical need to evaluate prospectively the potential risk and later-life consequences of exposure to
repetitive asymptomatic blows to the head (i.e., subconcussive impacts).

This study is the first in the literature to demonstrate a threshold dose-response relationship between estimated cumulative head impact exposure from football and later-life risk for cognitive and neurobehavioral impairment. We found that after a threshold, the risk for impairment increased with additional impacts. Similar findings of a threshold dose-response from RHI have been reported in studies of soccer and boxing [35, 95-97]. Specifically, our results show that the risk of developing behavioral dysregulation, executive dysfunction, depression, and apathy nearly doubled with 2800 additional impacts above the threshold. Our findings also show that increasing the CHI dose from 7200 to 11200 increased the risk for objective cognitive impairment by a considerable nine fold.

Interestingly, the dose-response threshold for cognitive function was much higher relative to other outcomes. Though speculative, it is possible that changes in mood and behavior reflect a different underlying mechanism or areas of structural impairment than cognitive changes, and that the cognitive changes reflect the evolution and progression of underlying CTE pathology [36, 98]. This is consistent with previous imaging studies in soccer players, wherein a lower threshold for detecting microstructural brain changes from soccer heading was identified compared to the threshold for memory impairment on neuropsychological evaluation [95]. Furthermore, in CTE, individuals with cognitive symptoms present later in the clinical course than behavioral impairments [98]. Our findings indicate that below identified thresholds, accumulated impacts have no apparent effect on the risk for cognitive or neurobehavioral impairment. However,
individuals had a baseline constant risk below the threshold. This baseline risk does not suggest that safety below the threshold is assumed. Moreover, our study design does not allow us to determine a safe time to cease RHI exposure, i.e., quit football. Furthermore, the baseline risk and the threshold likely depend on several subject-specific factors such as possible genetic susceptibility, body mass index, socioeconomic status, cognitive reserve, etc [99]. Large, well-controlled, prospective, longitudinal research that distinguishes threshold effects and baseline risk in football is clearly needed to identify maximum exposure levels for each player’s safety. Such research would ultimately facilitate the development of safety guidelines that could minimize the risk of adverse effects on the brain in football.

Considering the public health implications of our study, there is also a need to investigate any causal evidence between RHI exposure and clinical impairment. Establishing cause indicates the possibility of intervention. We utilized the Bradford-Hill criteria for evaluating causal inference in observational studies [100] and our findings are suggestive of a causal relationship between cumulative head impact exposure and later-life clinical impairment. We analyzed eight Bradford-Hill criteria in our model: strength, dose-response, consistency, plausibility, coherence, experiment, reversibility, temporality, and specificity. Strength of association between our predictor, the CHII, was very strong on all six measures of clinical impairment and higher than any other exposure predictor. The dose-response criterion is of particular importance in disorders that exhibit a latent onset, and this was supported by the present study [101]. Regarding consistency of association, the dose-response relationship has also been shown in boxers [94, 102-
The plausibility of association is supported by human and animal studies that show cumulative subconcussive impacts and axonal injury and blood brain barrier damage [10, 11, 28, 93, 104-107]. Since 1928, a relationship has been hypothesized between RHI and neurological disease supporting the notion of coherence of association [106]. Animal models have shown reduced numbers of impacts results in a reduced negative consequences to support experimentation of association and the reversibility of association [109-110]. Lastly, exposure must precede the outcome, which conforms to observations in all previous studies and demonstrates temporality of association.

These findings do not suggest that every individual with a history of RHI -- even exposure above the reported thresholds -- will have later life cognitive, mood, or behavioral impairments or develop a neurodegenerative disease, such as CTE. Support of a causal relationship does not imply a universal relationship. For example, a causal relationship between smoking tobacco and subsequent lung cancer has long been accepted. However, not all smokers develop lung cancer; some develop other conditions and diseases causally linked to smoking (e.g., stroke, heart disease, emphysema), and still others remain healthy throughout their lives. We hope that the use of the CHII (and subsequent iterations of this exposure metric) will result in greater clarification and validation of the causal relationship between football-related RHI and later life clinical impairment.

The current study has clear limitations. Although all the accelerometer studies used to measure RHI discarded linear accelerations below 10g, some of the studies used a slightly higher minimum cutoff to register a hit. However, small differences in cutoff
points are likely not meaningful given that the majority of recorded impacts had mean accelerations well above the minimum cutoff points (as supported by the data summarized in Table 3). For instance, the frequency of impacts per season reported by Mihalik et al., [55] was lower than the frequency reported by Crisco et al., [57] despite having used a lower cutoff (Mihalik 10g; Crisco 14.4g). Additional research using both helmet-based and head-based accelerometers is needed to develop standardized, consensus based cutoff points [66]. In addition, within the CHII, it is assumed that players are active in both games and practice, and does not take into account players who do not participate in games. Participants in our study were active players in games in high school and in college. For example, former college players in our study averaged 3.6 years of play and 50% game involvement. Therefore, because of the possible difference in RHI exposure between reserve players (who participate in all practices but limited game involvement) and starters (who participate in all practices and have extensive game involvement), and because of the potential discrepancy in the frequency and severity of RHI exposure between practices and games, our findings may not accurately reflect differences in long-term consequences between starters and reserve players. Moreover, our study evaluated only certain aspects of exposure (i.e., cumulative impacts) and did not use other possible biomechanical metrics, such as cumulative linear and rotational accelerations. The sample size of the present study was also small due to the strict inclusion and exclusion criteria. The present results will need replication in larger studies. Furthermore, despite our analytic approach, the study design is cross-sectional which limits the extent to causal inference. Our convenience sample may induce a self-selection
bias limiting the external validity of our findings. However, our instrumental variable analytic approach reduced the measurement error bias and potential confounding effects [111]. Specifically, this method allowed us to provide unbiased estimates of causal effects in our nonrandomized sample [88, 89] and is increasingly utilized in clinical studies [112-113] particularly when there are obstacles to performing a randomized controlled trial.

Future studies will be necessary to validate the CHII and improve our understanding on the long-term clinical consequences of RHI exposure. Larger studies are needed to investigate the effect of CHI exposure by age and level. Studies utilizing objective fluid and neuroimaging biomarkers will allow for a better understanding of the underlying etiology associated with CHI exposure. Case-controlled postmortem studies will also be necessary to examine the association between the CHII and CTE (and other) neuropathology. There is also the need to examine additional potential risk factors that may modify the relationship between RHI exposure and later life cognitive and neurobehavioral impairment, including, but not limited to, genetics, diet, exercise, substance use (including performance enhancing drugs), and cardiovascular risk. Finally, there is a need for similar models of cumulative RHI exposure for other contact sports, once accelerometer or some other objective measure of head impacts is more widely available.
Conclusion

We developed the CHII, a tool to quantify retrospective cumulative exposure to RHI, including subconcussive impacts. Using the CHII, we showed that RHI exposure among amateur football players is associated with later-life cognitive and neurobehavioral consequences. Although our findings raise safety concerns for participation in amateur football, prior to changes in policy and rules, prospective longitudinal research in larger samples is needed to validate the CHII and replicate and extend our associated findings.
References


2. Dashnaw ML, Petraglia AL, Bailes, JE. An overview of the basic science of concussion and subconcussion: Where we are and where we are going. Neurosurgical Focus. 2012;33, E5.


15. Guthrie RM. Emerging data on the incidence of concussion in football practice at all levels of amateur play. The Physian & Sportsmedicine. 2015;43, 333-335.


58. Baugh CM, Kiernan PT, Kershus E, Daneshvar DH, Montenigro PH, McKee AC, Stern R. Frequency of head impact related outcomes by position in NCAA Division I


63. Ng, TP, Bussone WR, Duma SM. The effect of gender and body size on linear accelerations of the head observed during daily activities. Biomedical Science Instrumentation. 2006;42, 25-30.


71. Waid-Ebbs JK, Wen PS, Heaton SC, Donovan NJ, Velozo C. The item level psychometrics of the behaviour rating inventory of executive function-adult (brief-a)


Discussion and Future Directions

Much has been learned about concussion and CTE neuropathology in recent years. Yet, the scientific study of the long-term clinical effects of repetitive head impacts, including subconcussive hits, remains in its infancy. The five published chapters of this dissertation represent important first steps towards addressing the paucity of research on this topic.

The goal of the first chapter was to quantify symptom frequencies and examine the disease-specific clinical presentation of CTE in neuropathologically confirmed cases without comorbid neurodegenerative pathology. Consistent with earlier reports in boxers, two relatively distinct clinical presentations emerged: one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance, and another group whose initial presentation developed at an older age and involved cognitive impairment. A binomial test of the proportion of APOE genotypes in our sample compared to an age-matched normative sample found that there were proportionally more ε4 homozygotes in the cognitive subtype group. These findings suggest APOE status could raise the risk of developing the cognitive manifestation of CTE in some people, though more research is needed.

In chapter two, we proposed clinical diagnostic criteria for the long-term effects of RHI and CTE. The criteria used a two-step approach to clinical diagnosis. In the first step, the presence of certain signs and symptoms were identified in order to establish an initial diagnosis of what we termed traumatic encephalopathy syndrome (TES). TES is the preferred designation at the first stage of diagnosis and is meant to be inclusive of the
full spectrum of CTE as well as other possible long-term consequences of repetitive head impacts. The selection of symptoms and signs to be used as diagnostic evidence of TES and CTE was essential to the development of our two-step diagnostic approach. In our criteria, a sign or symptom was designated as diagnostic if it occurred in a minimum of 70% of the neuropathologically confirmed CTE cases without comorbid disease, as described in chapter 1. The specificity of our first stage of diagnosis is illustrated by comparing the diagnostic threshold employed in other studies, such as the set of criteria proposed by Victoroff in 2013, where any sign or symptom that occurred in seventy percent of the cases was considered. In the next step of the two-step approach, we assessed the likelihood that TES is related to underlying CTE pathology as either TES with probable- or possible-CTE. To be diagnosed with possible-CTE, TES must have already been established but with a “progressive” course in combination with one positive potential biomarker for CTE that reflects the known neuropathological characteristics.

In chapter three we evaluated potential clinicopathological associations between tau, amyloid beta, age, APOE genotype, and clinical outcomes in heterogeneous cohort of deceased athletes with neuropathologically confirmed CTE (n=114, mean age at death=60). Generally, when amyloid β peptide (Aβ) deposition was comorbid with CTE tauopathy (52% of cases) there was a significant association with severe tauopathy and worse clinical outcomes. Also, we identified a clear clinical and pathological dichotomy between CTE cases with Aβ deposition compared to those without. Clinically, cases of CTE with Aβ had a significantly older age at symptom onset and an older age at death.
Furthermore, age adjusted logistic regression found the odds of developing dementia were 4 times higher in CTE cases with Aβ deposition (either neuritic or diffuse) and, the odds of developing parkinsonism were 9 times higher in CTE cases with diffuse Aβ deposition. The frequency of the cognitive subtype increased in CTE subjects with Aβ, but this difference was not significant. Similar to what was reported in Chapter one, there was a significantly greater proportion of ε4 allele homozygotes in our sample compared to the control population (Z = 1.94, p = 0.026). However, we extended these findings and hypothesized that ε4 allele would be elevated specifically in CTE subjects with Aβ, but not in those without. We found that there was no difference between the proportion of ε4 alleles in CTE subjects without Aβ (14%) compared to an age matched population norm (15%), but that there was a significantly increased proportion in CTE subjects with diffuse (27%, Z = 2.92, p = 0.002) or neuritic (25%, Z = 2.01, p = 0.022) Aβ plaques. A direct association between the ε4 allele and diffuse Aβ plaques in CTE was also found (p = 0.035). Pathologically, neuritic plaques were significantly associated with increased CTE tauopathy stage (β= 2.43, p = 0.018) and co-morbid Lewy body disease (OR= 5.01, p = 0.009). Lastly, to examine the direct effect of Aβ on CTE tauopathy we employed binary logistic regression and found the odds of a case progressing to the most severe stage of CTE, stage IV tauopathy, was 4 times higher in subjects presenting with co-morbid neuritic plaques compared to those without even when adjusting for age. These findings are limited by retrospective cross-section design, but have important implications for ongoing studies evaluating biomarkers for the in vivo diagnosis of CTE. Furthermore, these findings have important implications for diagnosing CTE before
death. Our results suggest possible-CTE cases may have a more severe prognosis and complicated biomarker when APOE, ε4, and amyloid beta protein deposition are comorbid with CTE tauopathy.

The fourth chapter reviewed and examined the clinical concepts associated with short- and long-term effects of RHI, with a special emphasis on the potential risk-factors for CTE. Clinical diagnostic criteria were operationalized for analyses and for the first time were applied to two neuropathologically confirmed case-reports of CTE, one a professional football player, and the other, a professional boxer. As the types of impacts and predominant forces differ between sports, we hypothesized that the clinical and pathological phenotype of CTE would also differ based on the type of sport exposure. To test our hypothesis, we compared the frequency and severity of motor symptoms and cerebellar dentate pathology between age- and CTE stage-matched groups of professional boxers and football players. In line with our hypothesis, boxers had a significantly higher frequency of motor symptoms and a greater severity of tauopathy affecting the cerebellar dentate than football players. Our results underscored the importance of cumulative exposure to RHI as a risk factor in the development and progression of CTE clinically and pathologically.

The fifth and final chapter represents an important first in examining a cause-effect relationship between exposure to repetitive head impacts through youth, high school, and college football, and later life impairments in cognition, mood, and behavior. In the absence of a direct measure of head impacts, we developed a metric to quantify cumulative repetitive head impact exposure from amateur football that we termed the
cumulative head impact index (CHII). To overcome the obstacles to conducting a randomized controlled trial involving total exposure over the course of an athlete's playing career, we utilized instrumental variable analysis with the CHII as our primary predictor. This method allowed us to examine causal relationships between cumulative exposure and the risk of depression, apathy, behavioral dysregulation, executive dysfunction, and cognitive impairment in former amateur football players. Specifically, statistical analyses, adjusted for age and education, found a strong dose-response relationship between estimated total head impact exposure and the risk of impairment.

Moreover, we found a threshold number of hits, below which there was no dose-response relationship between cumulative head impacts and risk for later life problems, but above which the greater the number of hits resulted in a greater risk for later life cognitive, mood, and behavioral impairment. It is important to note that the CHII estimated all football related hits above 10g, including the hits that did not result in the symptoms of a concussion, termed subconcussive impacts. In fact, concussion history alone did not predict objective cognitive impairment, highlighting the important role subconcussive impacts have in predicting long-term consequences. Establishing cause is important because it indicates the possibility of intervention and prevention. The focus of this study was limited to football, and there is a need for similar models of cumulative head impact exposure for other contact sports, once an accelerometer or some other objective measure of head impacts is more widely available. Our study was also limited by its small sample size. While we did demonstrate a minimum threshold of head impacts, these findings cannot be interpreted as suggesting that there is a safe number of hits for an individual as
the results were based on group findings.

**Summary.** Overall, the chapters of this dissertation addressed the need to characterize the clinical features and etiology of CTE (See Figure 1. Dissertation Synthesis). In the first two chapters, we described the clinical presentation of CTE and propose clinical diagnostic criteria. In the remaining chapters, we examined the potential risk factors and predictive exposure models for the clinical etiology of CTE during life. Additional research to refine and extend our findings using an iterative process (outlined in Figure 1) is ongoing. More specifically, studies are being planned, or are underway, that operationalize our clinical diagnostic criteria to refine our understanding of the clinical manifestations and diagnosis of CTE during life and utilize our exposure metric, the CHII, to determine if it can be used to predict a clinical diagnosis of TES and “probable” CTE.
Figure 1. Dissertation Synthesis. The clinical features of CTE are addressed in chapters one and two. The etiology of CTE clinically is examined in the remaining chapters.

Limitations. Although the limitations of each study are discussed by chapter, it is important to note that overall, these studies were limited by cross-sectional design. Future research is needed to extend our findings and further develop our proposed clinical criteria and CHII exposure metric in studies with larger samples using longitudinal, prospective experimental designs. For example, studies should be conducted that apply the CHII metric in individuals with post-mortem diagnoses of CTE or in living persons with suspected probable-CTE, once criteria and biomarkers are further refined and validated. Moreover, the analyses in this dissertation are limited by self-referral and would be appropriately described as convenience samples. The post-mortem samples from the Boston University VA Brain Bank and the clinical sample of retired football players from the Boston University CTE Center LEGEND study are limited self-referral
bias. To address this potential bias, future studies should use non-selected population based samples, for example the Framingham Heart Study. Moreover, our analyses included only males and future research studies should also include individuals of both sexes/genders.

**Key Unanswered Questions.** As the study of the clinical manifestations and etiology of CTE continues, several important questions in the field remain unanswered. For example, how common is CTE in the population? To address this question, the accuracy and validity of proposed clinical criteria and biomarkers for the diagnosis of CTE during life must be established. Once an in vivo diagnosis is possible, epidemiological research will be able to determine the population incidence and prevalence of long-term impairments related to RHI exposure and underlying CTE neuropathology. Another important question that needs to be addressed, is whether or not the tauopathy in CTE causes clinical symptoms or progression over time. Longitudinal studies that include serial neuroimaging scans specific for the hyperphosphorylated tau neuropathology of CTE (for example, PET neuroimaging with T807 for p-tau) can determine the likelihood of symptom onset and progression in living athletes. Moreover, the diagnosis of CTE during life using clinical diagnostic criteria and biomarkers would be help to differentiate the possible long-term outcomes related to prolonged exposure to RHI, including persistent PCS, primary depression, frontotemporal dementia, or Alzheimer’s disease, from CTE. A final question, why do some people exposed to RHI develop CTE whereas
others do not? To answer this question, non-selected longitudinal research is needed to refine potential risk factors of CTE, including susceptibility genes (for example, MAPT, GRN, and C9orf72), and to identify risk modifying factors such as body mass index, exercise, diet, substance use, socioeconomic background, and cognitive reserve. Future research should include a model with the CHII metric, or a variation of the CHII, as a predictor variable and incorporate additional risk- and modifying-factors to quantify their effect on the risk of developing CTE neuropathologically or probable-CTE clinically. The hope is that the use of the proposed clinical diagnostic criteria and cumulative head impact index in future studies will result in greater clarification of the modifiable, if not preventable, factors for long-term impairments related to RHI exposure and CTE.
CUMULATIVE BIBLIOGRAPHY


Bernick C, Banks SJ, Shin W, et al. Repeated head trauma is associated with smaller


Cantu R. Guidelines for return to contact sports after a cerebral concussion. The Physician & Sportsmedicine. 1986;14:75.


Casson IR, Sham R, Campbell EA, Tarlau M, Didomenico A (1982) Neurological and


Dashnaw ML, Petraglia AL, Bailes, JE. An overview of the basic science of concussion and subconcussion: Where we are and where we are going. Neurosurgical Focus. 2012;33, E5


223
Guthrie RM. Emerging data on the incidence of concussion in football practice at all levels of amateur play. The Physian & Sportsmedicine. 2015;43, 333-335.


Harrison PA, Narayan G. Differences in behavior, psychological factors, and environmental factors associated with participation in school sports and other activities in adolescence. Journal of School Health. 2003;73, 113-120.


Leigh JP, Schembri M. Instrumental variables technique: Cigarette price provided better estimate of effects of smoking on sf-12. Journal of Clinical Epidemiology. 2004;57, 284-293.


Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part II. Standardization of the neuropathologic


Mormino EC, Betensky RA, Hedden T, et al. Amyloid and APOE 4 interact to influence


Ng, TP, Bussone WR, Duma SM. The effect of gender and body size on linear accelerations of the head observed during daily activities. Biomedical Science Instrumentation. 2006;42, 25-30.


Ravina A. Traumatic encephalitis or punch drunk. La Presse Médicale. 1937;45:1362–1364.


Victoroff J. Traumatic encephalopathy: review and provisional research diagnostic


CURRICULUM VITAE

PHILIP H. MONTENIGRO
pmonte@bu.edu; (617) 784-9073
www.philipmontenigro.com
Year of Birth: 1984

EDUCATION

M.D., Ph.D.  M.D./Ph.D. Dual Degree Program (Boston, MA)  Anticipated-2018
M.D., Step-1 USMLE Board Certification, Massachusetts 2012
Ph.D., Qualified Candidate, Dept. of Anatomy and Neurobiology
Vesalius Certificate in Teaching Anatomy and Neurobiology

B.S. Boston University’s Metropolitan College (Boston, MA)  2009
Major in Biology, Concentration in neuroscience
Magna Cum Laude, Ranked in the top 10% of graduating class

HONORS AND AWARDS

Provost’s PhD Award, Office of the Provost, BU School of Medicine, For exceptional research contribution 2015
Community Service Award, BU Graduate Medical Sciences, For Vesalius Project on mTBI & homelessness 2015
Henry I Russek Student Achievement Award, For dedication and outstanding performance 2014
Community Service Award, BU Graduate Medical Sciences, For outstanding volunteer service & mentorship 2014
GMS Travel Award, BU School of Medicine, To present new diagnostic criteria for CTE at Keystone CO 2014
Sigma Xi Scientific Research Honor Society, Demonstrated noteworthy achievement in research 2014
Kappa Delta Pi International Honors Society in Education, In recognition of commitment to teaching 2014
GMS Travel Award, BU Graduate Medical Sciences, To present mTBI latent dose-effect model San Francisco 2013
Howard Gotlieb Archival Research Center Award, For a private “Punch-drunk Book Collection” 2013
Serchuck Award for Outstanding Clinical Science Poster, MSSR Symposium, Honorable Mention 2012
Medical Student Summer Research Scholarship, BU School of Medicine, Awarded to competitive applicants 2011
Alpha Sigma Lambda National Honors Society, RCC, For academic excellence while facing adversity 2006-2009


**Book Chapters**


**REFEREED ABSTRACTS**


PRESENTATIONS

2016 Clinicopathologic Phenotypes of CTE: Distinct Traumatic Risk-Factors
Montenigro PH, Cantu RC
5th International State-of-the-Science Meeting, Department of Defense, McLean VA
Oral presentation

2016 Validity of Clinical Research Criteria For CTE: The UNITE Study
Mez j, Solomon TM, Daneshvar DH, Montenigro PH, et al.
Annual Meeting American Academy of Neurology, Vancouver, BC, Canada
Oral presentation

2015 Clinical Features and Diagnosis Of Chronic Traumatic Encephalopathy
Montenigro PH
1st Neurological Disorders Summit, San Francisco CA
Oral presentation

2015 Aβ In CTE, AD, and Aging: Evidence for Non-Overlapping Etiologies
Montenigro PH, Victor Alvarez, Robert A. Stern, Ann C. McKee, Thor D. Stein
Graduate Research Symposium, Awards Luncheon, Boston MA
Oral presentation -Provost’s PhD Award

2015 Aβ in Chronic Traumatic Encephalopathy
Montenigro PH, Victor Alvarez, Robert A. Stern, Ann C. McKee, Thor D. Stein
Harvard NeuroDiscovery Center's 28th Annual Poster Symposium, Boston MA
Poster presentation

2014 Chronic Traumatic Encephalopathy: Clinical Subtypes and Diagnostic Criteria
Montenigro PH, Stern RA
National MD/PhD Student Conference, 29th Annual Meeting, Keystone CO
Poster presented
2014 Subconcussive Impacts and the Risk of Later-Life Depression and Cognitive Impairment
Montenigro PH, Baugh CM, Cantu RC, et al.,
Boston University Russek Student Achievement Day, Boston MA
Poster presented -Recipient of a Henry I. Russek Student Achievement Award
2014 Football related concussions & neurobehavioral impairment: what is the relationship?
Montenigro PH, Tripodis Y, Stern RA, Cantu RC
Global Biotechnology Congress, Boston MA
Poster presented
2014 Dose-Response Effect of Multiple Concussions on Later-Life Neurobehavioral Function
Montenigro PH, Tripodis Y, Daneshvar DH, Seichepine DR, et al.,
International Brain Injury Association’s 10th World Congress, San Francisco CA
Poster presented
2013 Statistical Analysis of Concussion History and Executive Function
Tripodis Y, Montenigro PH, Stern RA
Harvard University’s New England Symposium on Statistics in Sports, Boston MA
Poster presented
2012 Subconcussive Load Effect & Trauma Profile For Chronic Traumatic Encephalopathy
Montenigro PH, Cove C, Crowell M, Nowinski N, Cantu RC, Stern RA
BU Medical Student Summer Research Symposium, Boston MA
Poster presented -Serchuck Award with Honorable Mention

TEACHING
Boston University College of Health and Rehabilitation Sciences: Sargent College
Lecturer, by invitation of course director
1. 2015 Abnormal Psychology

Boston University’s Undergraduate Metropolitan College
Lecturer, by invitation of course directors
2. 2014 Sports Neuropsychology
3. 2013 How The Brain Works: An Introduction to Neuropsychology
4. 2012 General Psychology

Department of Anatomy and Neurobiology
Lecturer, Vesalius Program
1. 2012-2014 Gross Brain Anatomy for Medical Students
2. 2014-2015 Neuroscience for Medical Students
3. 2012-2015 Gross Anatomy for Dental Students

Boston University School of Medicine
Small Group Facilitator, by invitation of course director
1. 2012-2013 Infectious Disease, (BUSM II) Disease and Therapy
2. 2012 Medical Neuroscience, (BUSM I)

ADHOC PEER-REVIEW

2015-Present Journal of Neurotrauma,
2014-Present Neurocritical Care
2013-Present Clinical Journal of Sport Medicine
2011-2014 Yale Journal of Biology and Medicine

SOCIETY MEMBERSHIPS

American College of Sports Medicine, 2014-Present
American Association for the History of Medicine, 2014-Present
North American Society for Sport History, 2014-Present
American Academy of Neurology, 2013-Present
National Neurotrauma Society, 2013-Present
American Medical Association, 2010-Present
Massachusetts Medical Society, 2010-Present

PROFILE

Personal Website: http://philipmontenigro.com
Research Gate: https://www.researchgate.net/profile/Philip_Montenigro
BU Profile: http://profiles.bu.edu/Philip.Montenigro

Sigma Xi

First in Scholarship & Leadership

246