Football and the brain

Ann C. McKee M.D.
Professor of Neurology and Pathology  VA Boston Healthcare System
Boston University School of Medicine
Director of the CTE Program
Associate Director, Alzheimer’s Disease Center
“Shell Shock” 1916  
Frederick Mott

“Punch Drunk” “Dementia Pugilistica” 1928
First reported by Harrison Martland in 1928 in boxers  
"nearly one half of the fighters who have stayed in the game long enough"
Martland (1928) Punch drunk. JAMA 91:1103–1107

“Chronic Traumatic Encephalopathy “ 1949, 1957
Critchley M. Medical aspects of boxing, particularly from a neurological standpoint.
Br Med J 1957; 1: 357
Clinicopathological Series of 15 boxers with CTE

Corsellis, Bruton, Freeman-Browne 1973

Psychological Medicine, 1973, 3, 270-303

The aftermath of boxing

J. A. N. Corsellis, C. J. Bruton, and Dorothy Freeman-Browne

From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

Psychological Medicine, 1973, 3, 270-303
Chronic Traumatic Encephalopathy 2005, 2006

Mike Webster

Omalu, DeKosky et al. 2005, 2006

Death at 52 years
Behavioral and mood disorders
Cognitive loss
Parkinsonism
Paul Pender
World Champion boxer, Marine
Died at age 73
Severe Dementia

CTE
Control
Stage IV CTE

Bedford VAMC

p-tau pathology
Paul Pender
February 2008

Normal  John Grimsley  Boxer

Paul Pender
No p-tau  45 yo NEI  73 yo Boxer/Vet
Chronic Traumatic Encephalopathy 2009

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury

Ann C. McKee, MD, Robert C. Cantu, MD, Christopher J. Nowinski, AB, E. Tessa Hedley-Whyte, MD, Brandon E. Gavett, PhD, Andrew E. Budson, MD, Veronica E. Santini, MD, Hyo-Soon Lee, MD, Caroline A. Kubilus, and Robert A. Stern, PhD

3 cases at VA Boston/BUSM
48 other cases in the world's literature

39 boxers (76%)
5 American football players (10%)
Pathology of CTE

Brain Atrophy

Hyperphosphorylated tau (P-tau)

Normal

CTE
Severe II and III ventricular dilation
Cavum septum pellucidum
Marked medial temporal atrophy

Thinning of the posterior corpus callosum
Atrophy of the thalamus, hypothalamus and mammillary bodies

Septal fenestrations
Abnormalities of septum pellucidum
pallor of the substantia nigra
Hyperphosphorylated tau protein (p-tau)

CTE
p tau

CONTROL

CTE

frontal cortex

nucleus basalis

amygdala

entorhinal

insula

temporal cortex
Deep Nuclei

Hypothalamus
Mammillary bodies

Thalamus
Brainstem

Substantia Nigra

Locus coeruleus
Neuropathological Criteria for CTE

68 cases of CTE

1. Perivascular
2. Focal distribution at depths of sulci

McKee et al 2013

The spectrum of disease in chronic traumatic encephalopathy

P-tau lesions
Why is tau protein deposited in those brain regions?

Sulcal depth and perivascular area are regions of physical stress concentration

Cloots et al. J Mechanical Behavioral Biomedical Materials 2012 (41-52)
NINDS/NIBIB Consensus Meeting to Evaluate Pathological Criteria for the Diagnosis of CTE


Nigel Cairns, Ph.D., Rebecca Folkerth, MD, Wayne Gordon PhD, C. Dirk Keene, M.D., Irene Litvan, PhD, Ann McKee, MD, Daniel Perl, M.D., Thor Stein M.D., Ph.D., William Stewart, M.D., Jean Paul Vonsattel, M.D., Dennis Dickson, M.D, Patrick Bellgowan, MD, Debra Babcock,PhD, Walter Koroschetz, MD
In 2014, the NINDS/NIBIB launched a major effort to define the neuropathological characteristics of CTE.

First objective: evaluate the preliminary consensus criteria for the neuropathological diagnosis of CTE

Is CTE a distinct tauopathy that can be distinguished from other tauopathies?
**Methods:** The study design was based on previous successful NIH-sponsored consensus conferences for other tauopathies, specifically PSP and CBD

25 cases of various tauopathies:
- CTE (with and without Aβ)
- Alzheimer’s disease
- Progressive Supranuclear Palsy
- Corticobasal Degeneration
- Argyrophilic Grain disease
- Primary age-related tauopathy
- Guamanian Parkinson’s Dementia Complex

No clinical or demographic information was provided to the neuropathologists—including no information regarding the subjects age, gender, clinical symptoms or athletic exposure, no information on gross neuropathology.
Seven neuropathologists evaluated the digitized slides independently:

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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</thead>
<tbody>
<tr>
<td>Nigel Cairns, Ph.D.</td>
<td>Washington University, St Louis</td>
</tr>
<tr>
<td>Dennis Dickson, M.D</td>
<td>Mayo Clinic, Jacksonville</td>
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<tr>
<td>Rebecca Folkerth, MD</td>
<td>Brigham and Womens, Boston</td>
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<tr>
<td>C. Dirk Keene, M.D</td>
<td>Univ Washington, Seattle</td>
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<tr>
<td>Daniel Perl, M.D.</td>
<td>USUHS, Washington</td>
</tr>
<tr>
<td>Thor Stein M.D., Ph.D.</td>
<td>Boston Univ, Boston</td>
</tr>
<tr>
<td>Jean Paul Vonsattel, M.D.</td>
<td>Columbia Univ, New York</td>
</tr>
</tbody>
</table>

and submitted their diagnostic evaluations prior to the conference.
Results

There was good agreement within the neuropathologists who reviewed the cases (Cohen’s kappa: 0.67)

There was even better agreement between reviewers and CTE diagnosis (Cohen’s kappa: 0.78) using the proposed criteria for CTE.

91.4% of the total responses correctly identified CTE

95.7% after the clinical information and gross neuropathological features were revealed
Pathognomonic Lesion of CTE

“In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes at the depths of the depths of the cortical sulci in an irregular pattern.”
The panel also stated that:

“thus far, this pathology has only been found in individuals exposed to brain trauma, typically multiple episodes”
Low power microscopic examination often a clue to the diagnosis
CTE:
Perivascular accumulation of p-tau in NFTs, thorned astrocytes and dot-like structures
The hippocampal ptau pathology is distinctive from AD
The TDP-43 pattern is distinctive from other neurodegenerations
CTE is not ARTAG
Validation of pathological criteria for CTE risk in amateur contact sport athletes

In a review of >1,700 male brains donated over 18 years to Mayo Clinic Brain Bank, researchers found CTE pathology in 32% of contact sport athletes.

- 162 control brains without a history of brain trauma or contact sports yielded zero cases of CTE.
- 33 brains with a history of a single TBI, yielded zero cases of CTE.
- Additional evidence linking repetitive brain trauma to CTE.
Perivascular ptau lesions depth of sulcus
neurons and astrocytes

GFAP

AT8

vessel

Russ Huber, MD PhD
CTE is a distinctive tauopathy that can be distinguished from AD and age-related tauopathy by the nature and distribution of the pathology and by immunohistochemical and biochemical analyses.
Antibody against early driver of neurodegeneration *cis* P-tau blocks brain injury and tauopathy

Asami Kondo¹,², Koorosh Shahpashari³, Koochek Mannix³, Haimhua Qiu³, Juliet Moncaster⁴, Chun-Hau Chen¹,², Yandan Yao¹,², Yu-Min Lin¹,², Jane A. Driver¹,², Yan Sun⁶, Shuo Wei¹,², Man-Li Luo¹,², Onder Albayram¹,², Pengyu Huang¹,², Alexander Rotenberg⁶, Akihide Ryo⁷, Lee E. Goldstein⁴, Alvaro Pascual-Leone⁸, Ann C. McKee⁹, William Meehan¹, Xiao Zhen Zhou¹,² & Kun Ping Lu¹,²

*Cis* P-Tau

*Trans* P-Tau

*Kondo et al. Nature July 2015*
CTE: other pathology

P-TDP-43

SMI-34

IBA1

axonal injury and neuroinflammation
Beta-amyloid deposition in chronic traumatic encephalopathy

Thor D. Stein1,2,3,4, Philip H. Montenigro3,5, Victor E. Alvarez2,6, Weiming Xia7,
John F. Crary7,8,9, Yorghos Tripodis10,11, Daniel H. Daneshvar6,11,
Jesse Mez3,6, Todd Solomon3,6, Gaoyuan Meng1, Caroline A. Kubilus3,6,
Kerry A. Cormier3,6, Steven Meng3, Katharine Babcock3, Patrick Kiernan3,6,
Lauren Murphy3,6, Christopher J. Nowinski3,12, Brett Martin3,11, Diane Dixon3,11,
Robert A. Stern3,5,6,13, Robert C. Cantu5,12,13,14, Neil W. Kowall3,6,
Ann C. McKee1,2,3,4,6
Aβ deposition in CTE


- Aβ deposition in 52% of CTE subjects - never before the age of 50 years
- Age is significantly associated with Aβ in CTE
- ApoE4 allele is significantly associated with Aβ plaques in CTE
- Aβ occurs in CTE at earlier age and an accelerated rate compared to a normal aging population (p=0.025)
- Aβ in CTE is significantly associated with dementia, Parkinsonism, and LBD pathology
Microglial neuroinflammation contributes to tau pathology in CTE

Jon Cherry and Thor Stein
pTDP43 pathology in CTE

D Barnes, P Kiernan, V Alvarez, B Huber, A Dedeoglu, L Goldstein, N Kowall, T Stein, A McKee

- pTDP-43 inclusions are observed in most CTE
- There is a significant correlation between pTDP-43 score and:
  - CTE stage
  - Hippocampal sclerosis
  - Aβ plaques
  - Clinical dementia
- In CTE, pTDP43 deposits are often found in the frontal cortex, medial temporal lobe and substantia nigra
- The morphology of pTDP-43 appears to be unique in CTE
- Hippocampal sclerosis in CTE correlates with CTE stage
- 10% of CTE cases have ALS
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<tr>
<td>Boxing</td>
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<td>Rugby</td>
<td>7</td>
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<tr>
<td>Military Veterans*</td>
<td>25 (*also 60 Veteran-athletes)</td>
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<tr>
<td>Soccer</td>
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<td>Other Sport: amateur wrestling, baseball, bull riding, lacrosse, martial arts, water polo</td>
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<td><strong>TOTAL</strong></td>
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<td>CTE Diagnoses</td>
<td># CTE</td>
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<tr>
<td>Rugby</td>
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<td>Military Veterans*</td>
<td>9 (*46 Veteran-athletes)</td>
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### Neuropathological Dx: CTE

#### 184 Athletes

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McKee et al, 2013, Brain
<table>
<thead>
<tr>
<th>Stages of Tau Pathology</th>
<th>Age at Death</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>mean age: 28.3 ± 13 years</td>
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<tr>
<td>Stage II</td>
<td>mean age: 44.3 ± 16 years</td>
</tr>
<tr>
<td>Stage III</td>
<td>mean age: 56.0 ± 14 years</td>
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<tr>
<td>Stage IV</td>
<td>mean age: 77.4 ± 12 years</td>
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McKee et al, 2013, Brain
<table>
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<tr>
<th>Stages of Tau Pathology: NFL</th>
<th>Age at Death</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>mean age: 27.6 range: 23-35 years</td>
</tr>
<tr>
<td>Stage II</td>
<td>mean age: 40.0 range: 25-70 years</td>
</tr>
<tr>
<td>Stage III</td>
<td>mean age: 61.5 range: 40-89 years</td>
</tr>
<tr>
<td>Stage IV</td>
<td>mean age: 75.0 range: 60-84 years</td>
</tr>
</tbody>
</table>
143 cases of CTE in athletes: co-morbid neurodegeneration in 37%
Michael Keck
25 yo college football player

Mez et al, JAMA Neurology 2016

• 16 yrs football, 3 years division I, linebacker/ special teams
• Multiple concussions –
  persistent vision changes, memory problems, confusion, difficulty
  sleeping and headaches
• Quit football after 3 yrs college. Continued to experience memory loss,
  disorientation, difficulty with attention, concentration and word finding,
  progressively worsened over the last 2 years of life
• Depression, impulsivity and severe anger
• Died at age 25 from a staph infection
Brain weight: 1480 grams
Frontal, temporal, parietal cortex: AT8 (p-tau)
Michael Keck  Stage II CTE

PHF-tau
Tyler Sash  
27 yo former NFL player

- 16 yrs football, 2 years NFL, safety and kick coverage
- 20 concussions –
  symptoms from last concussion never completely resolved
- Subtle changes in his behavior in the NFL, more aggressive and anxious
- After NFL, impairment in attention, memory, executive function, shorter fuse, depression and apathy
- Narcotic use for chronic pain
- Death at 27 from accidental overdose
Tyler Sash 27 years old

PHF-tau
Dave Duerson

Death at age 50 years

Duerson’s Brain Trauma Diagnosed

By ALAN SCHWARTZ   Nov 3, 2016

BOSTON — The suicide of the former Chicago Bears star Dave Duerson became news simmering Monday when Boston University researchers announced that his brain had developed the same brain-wasting disease normally found in more than 90 percent of deceased players.

The diagnosis adds a new and perhaps pivotal chapter to football and raises troubling questions about concussions. Duerson died himself by gun, in the chest rather than the head, presumably so that his brain could be examined by Boston University, center for the Study of Traumatic Encephalopathy, which discovered its degeneration.

About two dozen retired N.F.L. players have been found to have the disease, known as chronic traumatic encephalopathy, but none retired upon his retirement in 2007, Dr. David H. Justice, the chairman of family brain finding normal state during his final months.

His death reminded the football community that for all the reforms in the amount of concussions and other head trauma issues in recent years, the damage to past players remains a regret of the game’s more brutal times.
Stage III CTE

Dave Duerson
69 yo former NFL player

- 28 yrs football: 4 yrs high school, 4 years division 1 college, 15 years professional primarily as quarterback
- 500+ concussions, none with LOC
- Heavy alcohol use throughout life
- Age 55: brief episode of difficulty speaking, “TIA”
- Subtle episodic memory changes at age 60, often repeated himself
- C/o Headaches, increased sensitivity to light and noise, chronic pain and tinnitus
- Mood became more sullen and withdrawn, more anxious and he developed insomnia
- Brief cognitive eval at age 65: “mild cognitive impairment”
- Death at 69 from colon cancer
69 yo former NFL player

Consensus panel clinical diagnosis:

CTE with contributions from substance abuse
Brain weight: 1318 grams
Olfactory bulb : AT8
Hippocampus

CA1                             CA4
Mammillary body  Medial geniculate nucleus
Substantia nigra
Locus coeruleus
Aβ plaques: moderate diffuse plaques, sparse neuritic plaques
Pathological Diagnoses

1. CTE, Stage IV
   - Septal fenestrations, mild generalized atrophy, most severe in frontal and temporal lobes
   - Perivascular ptau immunoreactive neurofibrillary tangles and astrocytic inclusions concentrated at the depths of the cerebral sulci with severe involvement of the medial temporal lobe structures and brainstem
   - Sparse TDP-43 neurites in CA1 hippocampus

2. Alzheimer’s changes, insufficient for diagnosis
   - Neuropathological change: Low (A3,B2,C1)
   - NIA-Reagan: Low likelihood
   - CERAD plaque density: sparse
   - Mild CAA

3. Microinfarcts, Rolandic cortex
Ken Stabler

Stage IV CTE
Sixth Annual Intensive Update in Neurology

**CTE Stages**

- **I**: Neuroinflammation, Microvasculopathy
- **II**: PHF-tau
- **III**: Neurodegeneration
- **IV**: Aβ, TDP-43

**Genetic Susceptibility and Resistance**: MAPT, ApoE

**Other Environmental Exposures**: Steroids, drugs, alcohol

**Clinical Manifestations**

- Repetitive mild trauma
- Behavioral changes
- Memory loss/cognitive impairment
- Dementia

**Aggregated Tau**

**Age**
Possible mechanisms of tau spread?

- Prion protein templating
- Glymphatic channels
- Tau secretion
  - Exosomes
- Other
## What are the critical issues in CTE?: pathology and pathogenesis

1. How to detect, diagnose and monitor CTE during life

2. What mechanisms are involved in CTE pathogenesis?

3. Is CTE reversible? Can progression be halted?

4. What are the effects of gender?

5. What is the incidence and prevalence of CTE?

6. What are the genetic susceptibility factors?

7. What is the risk for CTE in amateur and professional sports and military service?

8. How does CTE contribute to other neurodegenerative pathologies?

9. Does trauma provoke other neurodegenerations besides CTE?
### VA Boston/ Boston University/ CLF CTE Program

<table>
<thead>
<tr>
<th>BU/VA CTE Program</th>
<th>BU Goldstein Lab</th>
<th>CLF</th>
<th>Boston VA (TRACTS)</th>
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<td>Regina McGlinchey, PhD</td>
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<td>Dharmendra Goswami, PhD</td>
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### Other Institutions
- David Brody, Wash U
- Robert Brown MD, U Mass
- Nigel Cairns, PhD Wash U
- John Crary, MD, PhD Columbia
- Ramon Diaz-Arrastia, MD
- Dennis Dickson, MD Mayo Clinic
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- Garth Hall, PhD U Mass Lowell
- Lauraena Holleran, Wash U
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- Dirk Keene, MD U Wash
- Alexander Lin, PhD, BWH
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