Chronic Traumatic Encephalopathy: A Critical Review

Grant L. Iverson, Ph.D.
Professor, Department of Physical Medicine and Rehabilitation,
Harvard Medical School;
Director, MassGeneral Hospital *for* Children™ Sport Concussion Program; &
Associate Director of the Traumatic Brain Injury Program,
Home Base, A Red Sox Foundation and Massachusetts General Hospital Program

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Disclosures

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Consulting practice in forensic neuropsychology involving individuals who have sustained mild TBIs, including former athletes.

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- Harvard Football Players Health Study (NFLPA)

A systematic review of potential long-term effects of sport-related concussion

Review

OPEN ACCESS

A systematic review of potential long-term effects of sport-related concussion

Geoff Manley,[1] Andrew J Gardner,[2] Kathryn J Schneider,[3] Kevin M Guskiewicz,[4] Julian Bailes,[5] Robert C Cantu,[6] Rudolph J Castellani,[7] Michael Turner,[8] Barry D Jordan,[9] Christopher Randolph,[10] Jiří Dvořák,[11] K. Alix Hayden,[12] Charles H Tator,[13] Paul McCrory,[14] Grant L Iverson[15]

Journal of Alzheimer's Disease 61 (2018) 17–28
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IOS Press

Review

The Need to Separate Chronic Traumatic Encephalopathy Neuropathology from Clinical Features

Grant L. Iverson[a,*], C. Dirk Keene[b], George Perry[c] and Rudolph J. Castellani[d]
[a]*Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, MassGeneral Hospital for Children™ Sports Concussion Program, and Home Base, A Red Sox Foundation and Massachusetts General Hospital Program, Boston, MA, USA*
[b]*Department of Pathology, Division of Neuropathology, University of Washington School of Medicine, Seattle, WA, USA*
[c]*College of Sciences, University of Texas, San Antonio, San Antonio, TX, USA*
[d]*Center for Neuropathology, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI, USA*

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Accepted 31 August 2017

Abstract. There is tremendous recent interest in chronic traumatic encephalopathy (CTE) in former collision sport athletes, civilians, and military veterans. This critical review places important recent research results into a historical context. In 2015, preliminary consensus criteria were developed for defining the neuropathology of CTE, which substantially narrowed the pathology previously reported to be characteristic. There are no agreed upon clinical criteria for diagnosis, although sets of criteria have been proposed for research purposes. A prevailing theory is that CTE is an inexorably progressive neurodegenerative disease within the molecular classification of the tauopathies. However, historical and recent evidence suggests that CTE, as it is presented in the literature, might not be pathologically or clinically progressive in a substantial percentage of people. At present, it is not known whether the emergence, course, or severity of clinical symptoms can be predicted by specific combinations of neuropathologies, thresholds for accumulation of pathology, or regional distributions of pathologies. More research is needed to determine the extent to which the neuropathology ascribed to long-term effects of neurotrauma is static, progressive, or both. Disambiguating the pathology from the broad array of clinical features that have been reported in recent studies might facilitate and accelerate research—and improve understanding of CTE.

At present, it is not known whether the emergence, course, or severity of clinical symptoms can be predicted by specific combinations of neuropathologies, thresholds for accumulation of pathology, or regional distributions of pathologies.
More research is needed to determine the extent to which the neuropathology ascribed to long-term effects of neurotrauma is static, progressive, or both.
Disambiguating the pathology from the broad array of clinical features that have been reported in recent studies might facilitate and accelerate research—and improve understanding of CTE.

This lecture, by design, focuses as much or more on what is not known than what is known

Topics

- Survey Studies
- Neuroimaging
- Chronic Traumatic Encephalopathy
- Suicide
- Alzheimer's Disease

There are Reasons to be Concerned About Long-Term Brain Health

Brain Health of Contact Sport Athletes

- American Football are exposed to a tremendous number of head impacts over the course of a single season.
- Researchers have reported differences in
  - the microstructure of white matter using diffusion tensor imaging (DTI),
  - neural activation using functional magnetic resonance imaging (fMRI),
  - endogenous neurochemistry using magnetic resonance spectroscopy (MRS) in several studies of current and retired professional athletes.

Structural Imaging

JOURNAL OF NEUROTRAUMA 33:346–353 (February 15, 2016)

DOI: 10.1089/neu.2015.3880

Cavum Septi Pellucidi in Symptomatic Former Professional Football Players

Inga K. Koerte,[1,2,*] Jakob Hufschmidt,[1,3,*] Marc Muehlmann,[1,2] Yorghos Tripodis,[4–6] Julie M. Stamm,[1,5,7] Ofer Pasternak,[1] Michelle Y. Giwerc,[1] Michael J. Coleman,[1] Christine M. Baugh,[5,8] Nathan G. Fritts,[5] Florian Heinen,[3] Alexander Lin,[1,9,10] Robert A. Stern,[5,6,7,11,+] and Martha E. Shenton[1,9,12,+]

Brain Imaging and Behavior (2016) 10:792–798
DOI 10.1007/s11682-015-9442-0

ORIGINAL RESEARCH

Cortical thinning in former professional soccer players

Inga K. Koerte[1,2,3] · Michael Mayinger[1,2] · Marc Muehlmann[1,2,3] · David Kaufmann[2,4] · Alexander P. Lin[1,5] · Denise Steffinger[2] · Barbara Fisch[2] · Boris-Stephan Rauchmann[1,2] · Stefanie Immler[6] · Susanne Karch[7] · Florian R. Heinen[6] · Birgit Ertl-Wagner[2] · Maximilian Reiser[2] · Robert A. Stern[8] · Ross Zafonte[9] · Martha E. Shenton[1,5,10]

Survey Studies: Subgroups with Depression and MCI

Kevin M. Guskiewicz, Ph.D., A.T.C.
Departments of Exercise and Sport Science and Orthopedics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina,

Stephen W. Marshall, Ph.D.
Departments of Epidemiology and Orthopedics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina,

CLINICAL STUDIES

ASSOCIATION BETWEEN RECURRENT CONCUSSION AND LATE-LIFE COGNITIVE IMPAIRMENT IN RETIRED PROFESSIONAL FOOTBALL PLAYERS

OBJECTIVE: Cerebral concussion is common in collision sports such as football, yet

Clinically Relevant

CLINICAL SCIENCES

Recurrent Concussion and Risk of Depression in Retired Professional Football Players

KEVIN M. GUSKIEWICZ[1,2], STEPHEN W. MARSHALL[2,3], JULIAN BAILES[4], MICHAEL MCCREA[5,6], HERNDON P. HARDING JR[7], AMY MATTHEWS[1], JOHNA REGISTER MIHALIK[1], and ROBERT C. CANTU[8,9]

Departments of [1]Exercise and Sport Science, [2]Orthopedics, and [3]Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Department of Neurosurgery, West Virginia University School of Medicine, Morgantown, WV; [5]Neuroscience Center, Waukesha Memorial Hospital, Waukesha, WI; [6]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI; [7] [8]Neurosurgery Service, Emer Hospital, Boston, MA

Current Physical and Mental Health of Former Collegiate Athletes

Zachary Y. Kerr,* PhD, MPH, J.D. DeFreese,† PhD, and Stephen W. Marshall,*‡§ PhD

Investigation performed at The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Survey: Mild Cognitive Impairment

- 2,552 retired NFL players
- 1.3% (n=33) reported a physician diagnosis of Alzheimer's disease
- Of the 758 who were age 50 or greater, 2.9% (n=22) reported a physician diagnosis of mild cognitive impairment
- Of the 641 former players who had a spouse or close relative complete a questionnaire, 12.0% (n=77) were identified as having significant memory problems.

- Former players with 3+ concussions during their playing career had a 5-fold greater risk of MCI diagnosis after age 50 compared to those with no prior concussions.

Chronic Traumatic Encephalopathy

Neuroscience and Biobehavioral Reviews 56 (2015) 276–293

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Review

A critical review of chronic traumatic encephalopathy

Grant L. Iverson[a,*], Andrew J. Gardner[b], Paul McCrory[c], Ross Zafonte[e], Rudy J. Castellani[d]

J Neuropathol Exp Neurol

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pp. 00–00

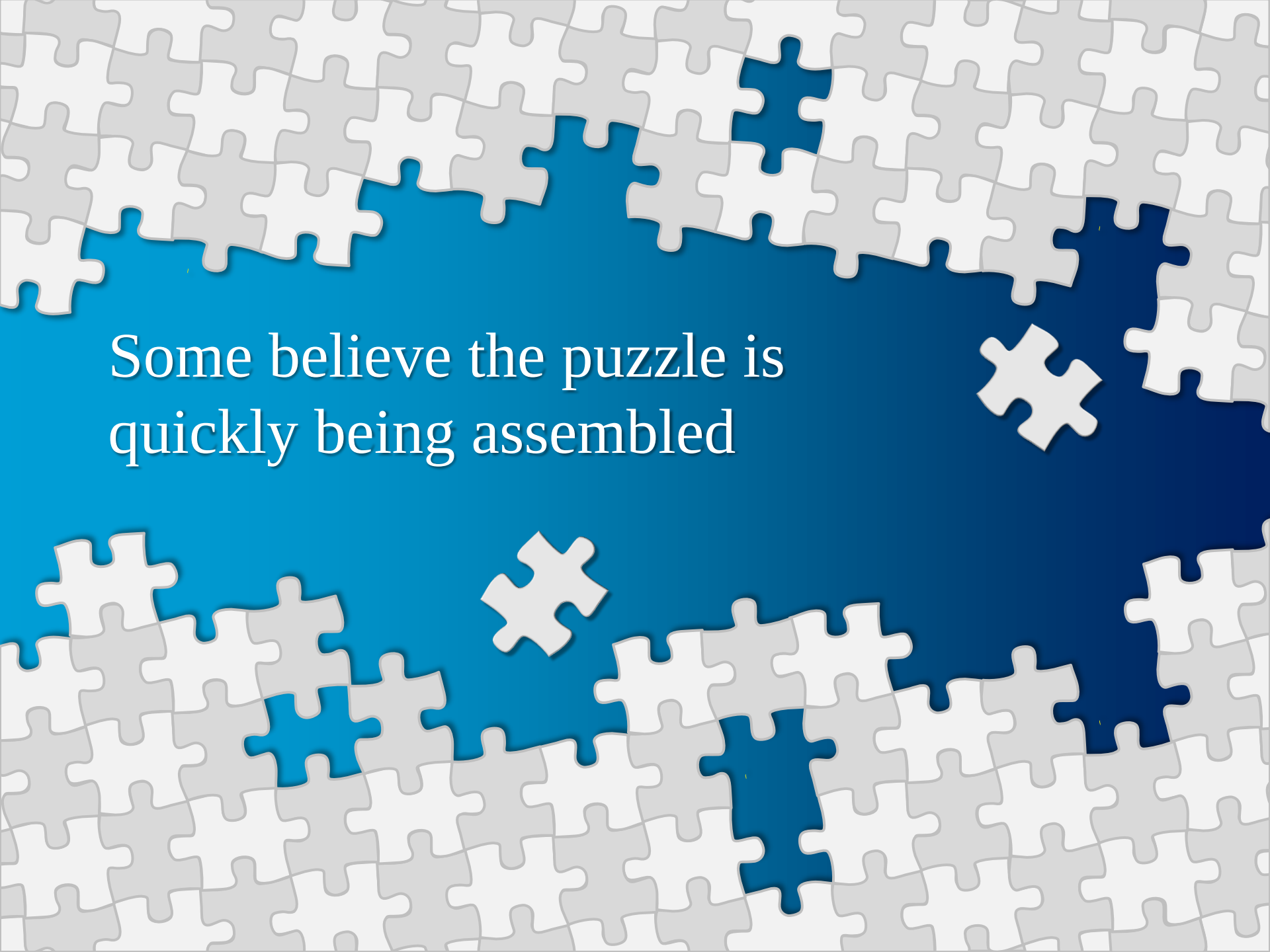
REVIEW ARTICLE

Chronic Effects of Mild Neurotrauma: Putting the Cart Before the Horse?

Rudy J. Castellani, MD, George Perry, PhD, and Grant L. Iverson, PhD

Extraordinary and Unprecedented Media Attention toward CTE

In my experience, clinicians, researchers, and the general public think that the state of the science is much more advanced than it is


Some believe the puzzle is
quickly being assembled

Some Important Unanswered Questions Relating to CTE

1. Prevalence
2. Genetic or other risk factors
3. Resilience factors
4. Clinical diagnostic criteria
5. Extent to which the neuropathology causes specific clinical symptoms or problems
6. Extent to which the neuropathology is progressive
7. Extent to which the clinical features are progressive

Poorly Understood & No Diagnostic Criteria

- Chronic traumatic encephalopathy (CTE) has been poorly understood for more than 80 years.
- Clinical Features: slurred and dysarthric speech, gait problems, Parkinsonism, cognitive impairment, and dementia
- Prior to early 2015, there were no widely accepted or empirically-evaluated diagnostic criteria for either the neuropathology or the clinical features.

From 1929-2012, there was only 1 large study

- Roberts (1969) published a book entitled *Brain Damage in Boxers: A Study of the Prevalence of Traumatic Encephalopathy Among Ex-Professional Boxers*. This book provides detailed clinical information on a random sample of 224 retired professional boxers.

Roberts (1969)

- 11% were deemed to have mild CTE
- 6% were considered to have a moderate-to-severe form of the syndrome
- Roberts described what appeared to be two syndromes, one appeared static and one progressive

Thought to be a Neurological Condition Affecting Boxers

- CTE was thought to be found almost entirely in boxers prior to 2005.
- There were isolated case reports of dementia pugilistica in people who were not boxers, including a battered woman in 1990.
- Omalu and colleagues published the first case of a retired NFL player in 2005, and the second case in 2006.

Evolution of the Diagnosis

- There has been a fairly dramatic evolution of both the neuropathology and clinical features of CTE in the past few years, especially as described in American football players.

- In the past, CTE was diagnosed in some retired boxers who presented with obvious and serious problems, such as neuropsychiatric symptoms and Parkinsonism, whereas at present it has been diagnosed in young athletes with no or mild symptoms (McKee et al., 2013).

Neuropathology

Neuropatholgy

Psychological Medicine, 1973, **3**, 270–303

The aftermath of boxing[1]

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE[2]

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

SYNOPSIS The brains of **15** retired boxers have been studied and the lives of the men concerned have been investigated in retrospect. A characteristic pattern of cerebral change has been identified which appears not only to be a result of the boxing but also to underlie many features of the punch-drunk syndrome.

Neurofibrillary degeneration, neuronal loss, ‘scarring’ of the cerebellar tonsils, and fenestrated cavum septum pellucidum.

Tau in Depths of Sulci

Acta Neuropathol (1991) 82: 321 – 326

Acta Neuropathologica

Case report

Neuropathological observations in a case of autism presenting with self-injury behavior*

P. R. Hof[1,2], R. Knabe[3], P. Bovier[3], and C. Bouras[3]

[1]Fishberg Research Center for Neurobiology and [2]Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY 10029, USA
[3]Department of Psychiatry, IUPG Bel-Air, 100 Av. Bel-Air, University of Geneva School of Medicine, CH-1225 Chêne-Bourg, Geneva, Switzerland

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doi:10.1093/brain/aws307 Brain 2013: 136; 43–64 | 43

BRAIN
A JOURNAL OF NEUROLOGY

The spectrum of disease in chronic traumatic encephalopathy

Ann C. McKee,[1,2,3,4,5] Thor D. Stein,[1,5] Christopher J. Nowinski,[2,4,6] Robert A. Stern,[2,3,4,7] Daniel H. Daneshvar,[2,4] Victor E. Alvarez,[2,4] Hyo-Soon Lee,[3,4] Garth Hall,[8] Sydney M. Wojtowicz,[1,2] Christine M. Baugh,[2,4] David O. Riley,[2,4] Caroline A. Kubilus,[3,4] Kerry A. Cormier,[1] Matthew A. Jacobs,[2,4] Brett R. Martin,[9] Carmela R. Abraham,[3,10] Tsuneya Ikezu,[3,4,11] Robert Ross Reichard,[12] Benjamin L. Wolozin,[3,4,11] Andrew E. Budson,[1,3,4] Lee E. Goldstein,[3,4,12,13,14,15] Neil W. Kowall[1,3,4,5,*] and Robert C. Cantu[2,6,7,16,*]

McKee et al. 2013

- Described macroscopic features
- Described microscopic features
- Conceptualized four stages of pathology
- Discussed clinical features associated with the stages

- Stage 1 CTE can be diagnosed based on having small focal epicenters of p-tau and no clinical symptoms, or symptoms such as headaches and mild depression.

- This represented a fundamental change in that now a person can be said to have a degenerative neurological disease in the absence of serious physical, cognitive, behavioral, or psychological problems.

Gross Pathologic Features	Microscopic Neuropathology
Cavum Septum Pellucidum	Neuronal Loss
Lateral or Third Ventricle Enlargement	Hippocampus
Frontal Atrophy	Entorhinal Cortex
Temporal Atrophy	Amygdala
Diencephalon Atrophy	Locus Coeruleus
Basal Ganglia Atrophy	Substantia Nigra
Brainstem Atrophy	Medial Thalamus
Cerebellar Atrophy	TAR DNA-binding protein 43 (TDP-43)
Thinning of the Hypothalamic Floor	Frontal Cortex
Shrinkage of the Mammillary Bodies	Medial Temporal Cortex
Pallor of the Substantia Nigra	Hippocampus
Hippocampal Sclerosis	Amygdala
Reduced Brain Weight	Insular Cortices
	Basal Ganglia
Microscopic Neuropathology	Thalamus
Amyloid Beta (Aβ) Deposition (variable)	Hypothalamus
Multifocal Axonal Varicosities	Brainstem
Frontal and Temporal cortex	Hyperphosphorylated Tau
Subcortical white matter	Perivascular in the neocortex
Deep white matter tracts	Depths of sulci
Diffuse Axonal Loss	Superficial layers of cerebral cortex
Subcortical White Matter	
White Matter Tracts	

Described as “characteristic” of CTE in subsequent review papers

ARTAG Pathology Characterized as CTE Pathology

In previous review papers and studies, perivascular, subpial, and periventricular p-tau has been described as characteristic of CTE (McKee et al., 2009; McKee et al., 2010; McKee & Robinson, 2014; McKee et al., 2013; Mez, Stern, & McKee, 2013; Montenigro, Corp, Stein, Cantu, & Stern, 2015; Omalu, 2014; Omalu et al., 2011; Riley, Robbins, Cantu, & Stern, 2015; Stern et al., 2013; Stern et al., 2011).

However, p-tau in these regions has recently been reported to be characteristic of "age-related tau astrogliopathy (ARTAG)" (Kovacs et al., 2016) and “primary age-related tauopathy” (PART; Crary et al., 2014), which blurs the distinction between neuropathology characteristic of CTE and age-related p-tau deposits.

Liu *et al. Acta Neuropathologica Communications* (2016) 4:59
DOI 10.1186/s40478-016-0330-7

Acta Neuropathologica Communications

LETTER TO THE EDITOR Open Access

ARTAG in the basal forebrain: widening the constellation of astrocytic tau pathology

Alan King Lun Liu, Marc H. Goldfinger, Hayleigh E. Questari, Ronald K. B. Pearce and Steve M. Gentleman*

J Neuropathol Exp Neurol
Vol. 0, No. 0, 2016, pp. 1–19
doi: 10.1093/jnen/nlx007

OXFORD

ORIGINAL ARTICLE

Evaluating the Patterns of Aging-Related Tau Astrogliopathy Unravels Novel Insights Into Brain Aging and Neurodegenerative Diseases

Gabor G. Kovacs, MD, PhD, John L. Robinson, BS, Sharon X. Xie, PhD, Edward B. Lee, MD, PhD, Murray Grossman, MD, EdD, David A. Wolk, MD, David J. Irwin, MD, Dan Weintraub, MD, Christopher F. Kim, Theresa Schuck, BA, Ahmed Yousef, BA, Stephanie T. Wagner, Eunran Suh, PhD,Vivianna M. Van Deerlin, MD, PhD, Virginia M.-Y. Lee, PhD, and John Q. Trojanowski, MD, PhD

Acta Neuropathol (2016) 131:75–86
DOI 10.1007/s00401-015-1515-z

CONSENSUS PAPER

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

Ann C. McKee[1,2,3,4,5] · Nigel J. Cairns[6] · Dennis W. Dickson[7] · Rebecca D. Folkerth[8] · C. Dirk Keene[9] · Irene Litvan[10] · Daniel P. Perl[11] · Thor D. Stein[2,3,4,5] · Jean-Paul Vonsattel[12] · William Stewart[13] · Yorghos Tripodis[3,14] · John F. Crary[15] · Kevin F. Bieniek[7] · Kristen Dams-O'Connor[16] · Victor E. Alvarez[1,2,3,4] · Wayne A. Gordon[16] · the TBI/CTE group

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Gross Pathologic Features	Microscopic Neuropathology
*Cavum Septum Pellucidum	Neuronal Loss
Lateral or *Third Ventricle Enlargement	Hippocampus
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Temporal Atrophy	Amygdala
Diencephalon Atrophy	Locus Coeruleus
Basal Ganglia Atrophy	Substantia Nigra
Brainstem Atrophy	Medial Thalamus
Cerebellar Atrophy	TAR DNA-binding protein 43 (TDP-43)
Thinning of the Hypothalamic Floor	Frontal Cortex
*Shrinkage of the Mammillary Bodies	*Medial Temporal Cortex
Pallor of the Substantia Nigra	*Hippocampus
Hippocampal Sclerosis	*Amygdala
Reduced Brain Weight	Insular Cortices
	Basal Ganglia
Microscopic Neuropathology	Thalamus
Amyloid Beta (Aβ) Deposition (variable)	Hypothalamus
Multifocal Axonal Varicosities	Brainstem
Frontal and Temporal cortex	Hyperphosphorylated Tau
Subcortical white matter	Perivascular in the neocortex
Deep white matter tracts	**Depths of sulci
Diffuse Axonal Loss	*Superficial layers of cerebral cortex
Subcortical White Matter	
White Matter Tracts	

White: Previously claimed as “characteristic”, Red: Consensus-based “pathognomonic”, Yellow: Consensus-based “supportive”

Recent Findings

- CTE Pathology:
  - In Women (Ling et al., 2015),
  - In those with Multiple System Atrophy (Koga et al., 2016),
  - In people with substance abuse and no known neurotrauma (Noy et al., 2016),
  - In people with no substance abuse and no known neurotrauma (Noy et al., 2016),
  - In a man with ALS and no known neurotrauma (Gao et al., 2017)

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doi: 10.1093/jnen/nlw092

OXFORD

ORIGINAL ARTICLE

Chronic Traumatic Encephalopathy-Like Abnormalities in a Routine Neuropathology Service

Shawna Noy, MD, Sherry Krawitz, MD, PhD, and Marc R. Del Bigio, MD, PhD, FRCPC

Acta Neuropathol (2015) 130:891–893
DOI 10.1007/s00401-015-1496-y

CrossMark

CORRESPONDENCE

Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases

Helen Ling[1] · Janice L. Holton[1] · Karen Shaw[1] · Karen Davey[1] · Tammaryn Lashley[1] · Tamas Revesz[1]

J Neuropathol Exp Neurol
Vol. 75, No. 10, October 2016, pp. 963–970
doi: 10.1093/jnen/nlw073

OXFORD

ORIGINAL ARTICLE

Chronic Traumatic Encephalopathy Pathology in Multiple System Atrophy

Shunsuke Koga, MD, PhD, Dennis W. Dickson, MD, and Kevin F. Bieniek, PhD

Canadian Study: Noy and Colleagues

J Neuropathol Exp Neurol
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ORIGINAL ARTICLE

Chronic Traumatic Encephalopathy-Like Abnormalities in a Routine Neuropathology Service

Shawna Noy, MD, Sherry Krawitz, MD, PhD, and Marc R. Del Bigio, MD, PhD, FRCPC

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Canadian Study

- Examined 111 brains in a routine neuropathology service.
- Ages: 18-60 (to reduce pre-clinical neurodegenerative disease findings)
- Only one subject had a history of sports participation.

- 4.5% had CTE pathology (3 cases of Stage I and 2 cases of Stage II).

- However, they made the important observation that there is no lower bound for classifying Stage I CTE pathology, so if they included tiny amounts of pathology characteristic of Stage I, an additional 34 cases were identified (30.6% of the sample).

- Therefore, of the total sample, 35.1% had some degree of mild CTE pathology.

- Factors that were associated with the presence of CTE pathology were age, history of traumatic brain injury, and substance abuse.

- Some of the cases had no known history of traumatic brain injury.

- There was no association between CTE pathology and psychiatric illness in this sample.

CTE-Like Pathology in ALS

Gao et al. Int J Pathol Clin Res 2017, 3:050
DOI: 10.23937/2469-5807/1510050

International Journal of
Pathology and Clinical Research

Volume 3 | Issue 1

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Case Report: Open Access

Chronic Traumatic Encephalopathy-like Neuropathological Findings Without a History of Trauma

*Andrew F Gao[1], David Ramsay[2], Richelle Twose[3], Ekaterina Rogaeva[4], Charles Tator[5,6] and Lili-Naz Hazrati[1,6,7]**

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CTE: Clinical Features

Symptoms and Problems Attributed to CTE Have Evolved Over the Past Few Years

- Broad and diverse symptoms and problems have now been attributed to CTE (e.g., headaches, anxiety, depression, suicide, and dementia).

- The symptoms and problems attributed to CTE are similar to depression and to behavioral-variant frontotemporal dementia.

Montenigro *et al. Alzheimer's Research & Therapy* 2014, **6**:68
http://alzres.com/content/6/8/68

alzheimer's research&therapy

REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

Philip H Montenigro[1], Christine M Baugh[2], Daniel H Daneshvar[3], Jesse Mez[4], Andrew E Budson[4,5], Rhoda Au[2,6], Douglas I Katz[2,7], Robert C Cantu[8,9] and Robert A Stern[1,4,2,8*]

New Diagnosis: Traumatic Encephalopathy Syndrome

- In 2014, Montenigro and colleagues proposed a new syndrome called Traumatic Encephalopathy Syndrome.

- This syndrome is extraordinarily broad in scope, encompassing people with depression, anger control problems, and those with late-stage dementia.

Examples of Breadth of TES Diagnosis

- If a person played high school and collegiate sports (for at least 2 years at the college level) and had:
  - Depression + Anxiety + Headaches
  - Depression + Suicidality + Anxiety
  - Depression + Suicidality + Headaches
  - Anger Control Problems + Anxiety + Headaches
  - Anger Problems + Excessive Gambling + Headaches
  - Mild Cognitive Impairment + Depression + Anxiety
  - Dementia + Apathy + Parkinsonism

Suicide

- In 2010, Omalu and colleagues introduced in the published literature that suicidality was a prominent clinical feature of CTE.

- This conclusion appears to be based on the fact that two of the three cases examined by Omalu completed suicide.

- It had been introduced in the media, however, hundreds of times prior to the publication of this article.

Suicide was not a Feature in the Roberts (1969) Book or in the McKee et al. (2009) Review of All Known Cases

- In their published review of all known cases up to 2009, McKee and colleagues did not consider suicidality to be associated with, or a clinical feature of, CTE.
- It was not included in their extensive tables as a possible clinical feature or discussed as such in the article.
- In contrast, suicide is now widely cited in the literature as a clinical feature of CTE.

Suicide

- Suicide was not considered a clinical feature in the first 80 years of writing relating to CTE.
- There were no confirmed cases of suicide in the Roberts (1969) random sample of retired boxers. 1 person had a suspicious cause of death.
- At present, there are no published cross-sectional, epidemiological, or prospective studies showing a relation between contact sports, CTE, and risk of suicide.

Review Article

Chronic Traumatic Encephalopathy and Suicide: A Systematic Review

Hal S. Wortzel,[1,2] Robert D. Shura,[1,3] and Lisa A. Brenner[1,2]

[1] *Departments of Psychiatry, Neurology, and Physical Medicine and Rehabilitation, Veterans Integrated Service Network (VISN) 19 Mental Illness, Research, Education and Clinical Center, Denver Veterans Affairs Medical Center, Denver, CO 80220, USA*
[2] *Departments of Psychiatry and Neurology, University of Colorado School of Medicine, Denver, CO 80045, USA*
[3] *Department of Psychology, Marshall University, Huntington, WV 25755, USA*

Correspondence should be addressed to Hal S. Wortzel; hal.wortzel@ucdenver.edu

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 DOI: 10.1080/02699052.2016.1202451

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ORIGINAL ARTICLE

Suicide in professional American football players in the past 95 years

David Webner[1] & Grant L. Iverson[2]

[1]*Department of Family Medicine, Crozer-Keystone Health System, Philadelphia, PA, USA and* [2]*Department of Physical Medicine and Rehabilitation, Harvard Medical School; Spaulding Rehabilitation Hospital; Mass General Hospital for Children Sport Concussion Program; & Red Sox Foundation and Massachusetts General Hospital Home Base Program, Boston, MA, USA*

Suicide and Chronic Traumatic Encephalopathy

Grant L. Iverson, Ph.D.

For nearly 80 years, suicidality was not considered to be a core clinical feature of chronic traumatic encephalopathy (CTE). In recent years, suicide has been widely cited as being associated with CTE, and now depression has been proposed to be one of three core diagnostic features alongside cognitive impairment and anger control problems. This evolution of the clinical features has been reinforced by thousands of media stories reporting a connection between mental health problems in former athletes and military veterans, repetitive neurotrauma, and CTE. At present, the science underlying the causal assumption between repetitive neurotrauma, depression, suicide, and the neuropathology believed to be unique to CTE is inconclusive. Epidemiological evidence indicates that former National Football League players, for example, are at lower, not greater, risk for suicide than men in the general population. This article aims to discuss the critical issues and literature relating to these possible relationships.

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Short report

Chronic traumatic encephalopathy and risk of suicide in former athletes

Grant L Iverson

Former NFL Players have a Lower Risk for Death by Suicide than Men in the General Population

Suicide Mortality Among Retired National Football League Players Who Played 5 or More Seasons

Everett J. Lehman,*† MS, Misty J. Hein,† PhD, and Christine M. Gersic†
Investigation performed at the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio, USA

Background: There is current disagreement in the scientific literature about the relationship between playing football and suicide risk, particularly among professional players in the National Football League (NFL). While some research indicates players are at high risk of football-related concussions, which may lead to chronic traumatic encephalopathy and suicide, other research finds such a connection to be speculative and unsupported by methodologically sound research.

Purpose: To compare the suicide mortality of a cohort of NFL players to what would be expected in the general population of the United States.

Study Design: Cohort study; Level of evidence, 3.

Methods: A cohort of 3439 NFL players with at least 5 credited playing seasons between 1959 and 1988 was assembled for statistical analysis. The vital status for this cohort was updated through 2013. Standardized mortality ratios (SMRs), the ratio of observed deaths to expected deaths, and 95% CIs were computed for the cohort; 95% CIs that excluded unity were considered statistically significant. For internal comparison purposes, standardized rate ratios were calculated to compare mortality results between players stratified into speed and nonspeed position types.

Results: Suicide among this cohort of professional football players was significantly less than would be expected in comparison with the United States population (SMR = 0.47; 95% CI, 0.24-0.82). There were no significant differences in suicide mortality between speed and nonspeed position players.

Conclusion: There is no indication of elevated suicide risk in this cohort of professional football players with 5 or more credited seasons of play. Because of the unique nature of this cohort, these study results may not be applicable to professional football players who played fewer than 5 years or to college or high school players.

Keywords: suicide; football; National Football League; concussion

A Study Focused on Neurodegenerative Diseases

Former NFL Players

SPAULDING REHABILITATION NETWORK

HARVARD MEDICAL SCHOOL

MASSACHUSETTS GENERAL HOSPITAL

Lehman et al., 2012
Same Cohort of 3,439 Retired Players with 334 Deaths as Used by Baron et al, 2012

Neurodegenerative causes of death among retired National Football League players

Everett J. Lehman, MS
Misty J. Hein, PhD
Sherry L. Baron, MD
Christine M. Gersic

ABSTRACT

Objective: To analyze neurodegenerative causes of death, specifically Alzheimer disease (AD), Parkinson disease, and amyotrophic lateral sclerosis (ALS), among a cohort of professional football players.

Methods: This was a cohort mortality study of 3,439 National Football League players with at least 5 pension-credited playing seasons from 1959 to 1988. Vital status was ascertained

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MASSACHUSETTS GENERAL HOSPITAL

Lehman et al., 2012

- “The neurodegenerative mortality of this cohort is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher.”

- “These results are consistent with recent studies that suggest an increased risk of neurodegenerative disease among football players.”

The Raw Data

- Of the 334 death certificates reviewed, the number of times neurodegenerative diseases were listed as an underlying or contributing cause of death were as follows:
  - Alzheimer's Disease/Dementia = 7
  - Parkinson's Disease = 3
  - ALS = 7

MAYO CLINIC

ORIGINAL ARTICLE

High School Football and Risk of Neurodegeneration: A Community-Based Study

Rodolfo Savica, MD, MSc; Joseph E. Parisi, MD; Lester E. Wold, MD; Keith A. Josephs, MD, MST, MSc; and J. Eric Ahlskog, PhD, MD

Abstract

Objective: To assess whether high school football played between 1946 and 1956, when headgear was less protective than today, was associated with development of neurodegenerative diseases later in life.

Methods: All male students who played football from 1946 to 1956 in the high schools of Rochester, Minnesota, plus a non–football-playing referent group of male students in the band, glee club, or choir were identified. Using the records-linkage system of the Rochester Epidemiology Project, we reviewed (from October 31, 2010, to March 30, 2011) all available medical records to assess later development of dementia, Parkinson disease (PD), or amyotrophic lateral sclerosis (ALS). We also compared the frequency of dementia, PD, or ALS with incidence data from the general population of Olmsted County, Minnesota.

Results: We found no increased risk of dementia, PD, or ALS among the 438 football players compared with the 140 non–football-playing male classmates. Parkinson disease and ALS were slightly less frequent in the football group, whereas dementia was slightly more frequent, but not significantly so. When we compared these results with the expected incidence rates in the general population, only PD was significantly increased; however, this was true for both groups, with a larger risk ratio in the non–football group.

Conclusion: Our findings suggest that high school students who played American football from 1946 to 1956 did not have an increased risk of later developing dementia, PD, or ALS compared with non–football-playing high school males, despite poorer equipment and less regard for concussions compared with today and no rules prohibiting head-first tackling (spearing).

High School Football Players Compared to Band, Glee Club, and Choir (1946-1956)

- "We found no increased risk of dementia, PD, or ALS among the 438 football players compared with the 140 non-football-playing male classmates."

- "Parkinson disease and ALS were slightly less frequent in the football group, whereas dementia was slightly more frequent, but not significantly so."

Second Study: No Increased Risk

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MAYO CLINIC

ORIGINAL ARTICLE

High School Football and Late-Life Risk of Neurodegenerative Syndromes, 1956-1970

Pieter H.H. Janssen; Jay Mandrekar, PhD; Michelle M. Mielke, PhD; J. Eric Ahlskog, PhD, MD; Bradley F. Boeve, MD; Keith Josephs, MD; and Rodolfo Savica, MD, PhD

JAMA Neurology | Original Investigation

Association of Playing High School Football With Cognition and Mental Health Later in Life

Sameer K. Deshpande, BS; Raiden B. Hasegawa, BA; Amanda R. Rabinowitz, PhD; John Whyte, MD, PhD; Carol L. Roan, PhD; Andrew Tabatabaei; Michael Baiocchi, PhD; Jason H. Karlawish, MD; Christina L. Master, MD, CAQSM; Dylan S. Small, PhD

Editorial
Supplemental content

IMPORTANCE American football is the largest participation sport in US high schools and is a leading cause of concussion among adolescents. Little is known about the long-term cognitive and mental health consequences of exposure to football-related head trauma at the high school level.

OBJECTIVE To estimate the association of playing high school football with cognitive impairment and depression at 65 years of age.

DESIGN, SETTING, AND PARTICIPANTS A representative sample of male high school students who graduated from high school in Wisconsin in 1957 was studied. In this cohort study using data from the Wisconsin Longitudinal Study, football players were matched between March 1 and July 1, 2017, with controls along several baseline covariates such as adolescent IQ, family background, and educational level. For robustness, 3 versions of the control condition were considered: all controls, those who played a noncollision sport, and those who did not play any sport.

EXPOSURES Athletic participation in high school football.

MAIN OUTCOMES AND MEASURES A composite cognition measure of verbal fluency and memory and attention constructed from results of cognitive assessments administered at 65 years of age. A modified Center for Epidemiological Studies' Depression Scale score was used to measure depression. Secondary outcomes include results of individual cognitive tests, anger, anxiety, hostility, and heavy use of alcohol.

RESULTS Among the 3904 men (mean [SD] age, 64.4 [0.8] years at time of primary outcome measurement) in the study, after matching and model-based covariate adjustment, compared with each control condition, there was no statistically significant harmful association of playing football with a reduced composite cognition score (−0.04 reduction in cognition vs all controls; 97.5% CI, −0.14 to 0.05) or an increased modified Center for Epidemiological Studies' Depression Scale depression score (−1.75 reduction vs all controls; 97.5% CI, −3.24 to −0.26). After adjustment for multiple testing, playing football did not have a significant adverse association with any of the secondary outcomes, such as the likelihood of heavy alcohol use at 65 years of age (odds ratio, 0.68; 95% CI, 0.32-1.43).

CONCLUSIONS AND RELEVANCE Cognitive and depression outcomes later in life were found to be similar for high school football players and their nonplaying counterparts from mid-1950s in Wisconsin. The risks of playing football today might be different than in the 1950s, but for current athletes, this study provides information on the risk of playing sports today that have a similar risk of head trauma as high school football played in the 1950s.

Cognitive and depression outcomes later in life were found to be similar for high school football players and their non-playing counterparts from the mid-1950s in Wisconsin.

Conclusions

- Neuroimaging studies show modest evidence of macrostructural, microstructural, functional, and neurochemical changes in some athletes.
- Some former athletes in contact, collision, and combat sports suffer from depression and cognitive deficits later in life.
- There is an association between these deficits and a history of multiple concussions in some studies.
- Former athletes are not at increased risk for death by suicide.

- Former high school American football players do not appear to be at increased risk for later life neurodegenerative diseases according to two studies.

- Retired professional American football players may be at increased risk for mild cognitive impairment.

- An increased risk for neurodegenerative diseases in retired American football players is suggested in one study examining death certificates, but more research is needed.

- It is important to appreciate, however, that survey studies of former collegiate and professional athletes indicate that the majority of people rate their functioning as normal and consistent with the general population

Some Important Unanswered Questions Relating to CTE

1. Prevalence
2. Genetic or other risk factors
3. Resilience factors
4. Clinical diagnostic criteria
5. Extent to which the neuropathology causes specific clinical symptoms or problems
6. Extent to which the neuropathology is progressive
7. Extent to which the clinical features are progressive