Chronic Effects of Repetitive Concussion: Lessons Learned from Sports Concussion

Michael McCrea, PhD, ABPP
Professor and Director of Brain Injury Research
Departments of Neurosurgery and Neurology
Member, NFL Head Neck and Spine Committee
Neuropsychology Consultant, Green Bay Packers

Disclosures

- Dr. McCrea has received research funding from several federal, industry and private sources over the past 20 years.
- Dr. McCrea’s Brain Injury Research program at the Medical College of Wisconsin is currently funded by the U.S. Department of Defense, NCAA GE-NFL Head Health Challenge I, and other sources.
- Dr. McCrea is a member of the NFL Head, Neck and Spine Committee.
- Opinions provided are those of Dr. McCrea and not necessarily representative of the NFL, NCAA, GE, DoD, VA or other sources.
Old Problem

New Awareness

SRC: What’s All The Fuss About?

- Up to 3.8 million concussions due to sport and recreation per year
- Among most frequent injuries in contact and collision sports
- More than just “bell rung”
- Serious acute effects that effect function
- Urgency to “get back out there”
- Concern about lasting effects
- Lack of scientific evidence
Scientific Advances in SRC: 

Acute Effects & Recovery

MECHANISM

Minimum Threshold: How much is enough to cause brain injury?

Clinical Recovery: How long does it take for sign & symptoms to recover?

Window of Vulnerability: How long does the brain take to recover?

Driving Evidence Based Diagnosis, Assessment and Management

Acute Effects and Recovery Time Following Concussion in Collegiate Football Players

The NCAA Concussion Study

JAMA 2003; 290:2556-2563

Over 25,000 Athlete Seasons, 1,500 Concussions Studied

Context: Lack of empirical data on recovery time following sport-related concussion hampers clinical decision making about return to play after injury.

Objective: To prospectively measure immediate effects and natural recovery course relating to symptoms, cognitive functioning, and postural stability following sport-related concussion.

Design, Setting, and Participants: Prospective cohort study of 1631 football players from 15 US colleges. All players underwent preseason baseline testing on concussion assessment measures in 1999, 2000, and 2001. Ninety-four players with concussion (based on American Academy of Neurology criteria) and 56 noninjured controls underwent assessment of symptoms, cognitive functioning, and postural stability immediately, 3 hours, and 1, 2, 3, 5, 7, and 90 days after injury.

Michael McCrea, PhD
Kevin M. Guskiewicz, PhD, ATC
Stephen W. Marshall, PhD
William Barr, PhD
Christopher Randolph, PhD
Robert C. Cantu, MD
James A. Onate, PhD, ATC
Jingzhen Yang, MPH
James P. Kelly, MD
How Long Does it Take to Recover?

<table>
<thead>
<tr>
<th>Rate of Postinjury Recovery in HS and College Athletes (n=790)</th>
<th>Total (%)</th>
<th>Cumulative Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid (&lt; 1 day)</td>
<td>21.1</td>
<td>21.1</td>
</tr>
<tr>
<td>Gradual (&gt; 1 day, &lt; 7 days)</td>
<td>64.3</td>
<td>85.4</td>
</tr>
<tr>
<td>Prolonged (1 week – 1 month)</td>
<td>11.9</td>
<td>97.3</td>
</tr>
<tr>
<td>Persistent (&gt; 1 month)</td>
<td>2.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Pellman et al., (2004): PPCS 1.6% of pro football players

Association Between Recovery & Risk

80-90% Achieve Complete Recovery in 7-10 Days

75% of repeat concussions within first 7 days
• 92% of repeat concussions within first 10 days

How long is long enough?
New Frontiers in Brain Injury Science

Acute and Subacute Changes in Neural Activation during the Recovery from Sport-Related Concussion

How Long Does it Take for the Brain to Recover?

A Prospective Study of Advanced MRI Biomarkers to Determine Acute Physiological Effects and Longitudinal Recovery after Sport-Related Concussion

PI: M. McCrea
Co-I: S. Li, T. Hammeke, K. Guskiewicz, T. McAllister
Comprehensive Study of SRC

Understanding the True Natural History of Injury & Recovery

Future Directions

Sponsored by United States Department of Defense (DoD) & National Collegiate Athletic Association (NCAA)

3 Years, $30M

MTBI and PCS: Scientific Update

Michael McCrea, PhD, ABPP-CN
Evidence-based Injury Assessment, Management and Return to Play:

Good News, Bad (Not So Good) News?

Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma

Michael McCrea, PhD, ABPP-CN
Longitudinal Perspective on SRC: Potential Longterm Effects

**ACUTE INJURY**

**REPETITIVE MTBI**

Cumulative Effects:
How many is too many (or, how much is too much)?

**LONG-RANGE OUTCOME**

Neurodegeneration:
What are the long-term or late life risks?

What Happens Down the Road?

The Death of Dave Duerson: More Evidence of Concussion Dangers in Football

The Week

Is football immoral?

Lawsuit filed against NFL by players over concussions

Former Chicago Bears star joins suit against NFL

New Report Links Sports Concussion to Chronic Traumatic Encephalopathy

Evan P. Friede's career came to an end when he retired at 23 after suffering multiple concussions during his NFL career. Friede, who played for the Cleveland Browns from 1995 to 1998, has since been diagnosed with early onset dementia and has been working to raise awareness about the dangers of repetitive head trauma in sports. Friede's story has inspired others to speak out about their experiences, and there is growing recognition of the need for improved safety measures and better understanding of the long-term effects of concussions.
How Many is Too Many?
Repetitive Exposure & Cumulative Effects

ACUTE INJURY

REPETITIVE MTBI

Cumulative Effects: How many is too many (or, how much is too much)?

- Risk of concussion
- Influence on recovery
- Chronic Symptoms
- Cognitive Impairment
  - Influence on post-injury recovery
  - Persistent neurocognitive effects
- Neuropsychiatric Disorders
  - Mood disorders
  - Neurobehavioral changes
  - Suicide
- Neurodegenerative Disease
  - MCI
  - Dementia

A Different Playing Field

NFL, former players reach settlement in concussion lawsuit

The NFL And GE Announce 'Head Health Initiative' To Study The Brain And (Maybe) Save The Game Of Football
The Bigger Picture

The Story vs. The Science

How Many is Too Many?
Repetitive Exposure & Cumulative Effects

ACUTE INJURY

REPETITIVE MTBI

Cumulative Effects:
How many is too many (or, how much is too much)?

- Risk of concussion
- Influence on recovery
- Chronic Symptoms
- Cognitive Impairment
  - Influence on post-injury recovery
  - Persistent neurocognitive effects
- Neuropsychiatric Disorders
  - Mood disorders
  - Neurobehavioral changes
- Neurodegenerative Disease
  - MCI
  - Dementia (CTE)
Concussion Begets Concussion

184 total injuries/4,251 NCAA FB players (4.2%)

χ² = 30.11, df=3, P < .001

Guskiewicz, McCrea et al, JAMA 2003

Chronic Symptoms Associated with Prior Concussion Exposure

P < 0.0001, All post-hoc comparisons significant

Mean Baseline GSC Score (SD)

0 3.44 (6.50) (N=13,046)
1 5.04 (8.28) (N=3,112)
2 7.38 (11.03) (N=767)
3+ 10.38 (14.51) (N=396)

Total N = 17,321

24.7% with history of 1+ concussion
Recurrent SRC & Neuropsychiatric Disorders

Risk For Late Life Cognitive Impairment?

MTBI and PCS: Scientific Update

Recurrent Concussion and Risk of Depression in Retired Professional Football Players

Guskiewicz et al., Neurosurgery, 2005

Guskiewicz et al., Neurosurgery, 2005
**MTBI and PCS: Scientific Update**

---

**Recurrent Concussion as Risk for Dementia?**

*NFL vs. Normative AD Age Distribution*

---

**Chronic Traumatic Encephalopathy**  
*Dementia Pugilistica*

- Neurodegeneration characterized by the accumulation of tau protein that develops following repetitive mild brain injury
- First described in boxers by Martland in 1928  
- 49 neuropathologically verified cases in the world’s literature
- Suspected in non-boxing athletes…

---

NFL Mean Age: 71.7 (7.62); Median: 74.0; Range: 52-83
Repetitive Head Trauma and Neurodegenerative Disease

McKee et al, 2011

CTE & Tauopathy Associated with MTBI

Football Player: 9 years in NFL
death at age 45 years: depression, poor decision making, substance abuse

Orbital frontal    Hippocampus    Temporal    Amygdala

Hyperphosphorylated Tau Immunohistochemistry

Aβ: rare diffuse plaques

From A. McKee
The spectrum of disease in chronic traumatic encephalopathy

Michael McCrea, PhD, ABPP-CN 15
What Does it Look Like in Living Humans?

Table 2 Summary of clinical features of chronic traumatic encephalopathy 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>Dystonia</td>
</tr>
<tr>
<td>Short fuse</td>
<td>Sadness</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</td>
<td>Masked Facies</td>
</tr>
<tr>
<td>Physical violence</td>
<td>Labile emotions</td>
<td>concentration</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Verbal violence</td>
<td>Apathy</td>
<td>Language difficulties</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Inappropriate speech</td>
<td>Loss of interest</td>
<td>Dysgraphia</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Irritability</td>
<td>Fatigue</td>
<td>Alogia</td>
<td>Closus</td>
</tr>
<tr>
<td>Childish behavior</td>
<td>Flat affect</td>
<td>Visuospatial</td>
<td></td>
</tr>
<tr>
<td>Social inappropriateness</td>
<td>Insomnia</td>
<td>difficulties</td>
<td></td>
</tr>
<tr>
<td>Disinhibited speech</td>
<td>Mania</td>
<td>General cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Disinhibited behavior</td>
<td>Euphoria</td>
<td>Reduced intelligence</td>
<td></td>
</tr>
<tr>
<td>Paranoid delusions</td>
<td>Mood swings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality changes</td>
<td>Prolix</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>
</tbody>
</table>
Neuroimaging of Cognitive Dysfunction and Depression in Aging Retired National Football League Players

A Cross-sectional Study

Objective: To assess cognitive impairment and depression in aging former professional football National Football League (NFL) players and to identify neuroimaging correlates of these dysfunctions.

Design: We compared former NFL players with cognitive impairment and depression, cognitively normal retired players who were not depressed, and matched healthy control subjects.

Setting: Research center in the North Texas region of the USA and France.

Patients: Cross-sectional sample of former NFL players with and without a history of concussion sustained from the North Texas region and age-matched, and sex-matched control subjects. Thirty-two retired NFL players (mean age 51.3 years) underwent neurobehavioral and neuroimaging assessments. A subset of 20 players also underwent detailed neuroimaging imaging. Thirty control subjects were compared with imaging data acquired in healthy matched controls.

Main Outcome Measures: Neurobehavioral outcomes, clinical diagnosis of depression, neuroimaging evidence of white matter pathology, and a measure of cerebrovascular flow.

Results: Of the 14 former NFL players, 20 were cognitively normal. Participants diagnosed as having a mixed cognitive deficit (5), mild cognitive impairment (5), dementia (1), and BDD (7) depression. The two groups to whom neuroimaging data were acquired, cognitively impaired participants showed deficits in verbal language, word finding, and frontal verbal episodic memory. We found significant differences in white matter abnormality in cognitively impaired and depressed retired players compared with their respective controls. Regional blood flow differences in the cognitively impaired group (left temporo-parietal junction, left prefrontal cortex, left and right temporal cortex) were identified in regions associated with impaired cognitive performance, problems with memory, reasoning, and word finding.

Conclusions: Cognitive deficits and depression appear to be more common in aging former NFL players compared with healthy controls. These deficits are correlated with white matter abnormalities and changes in regional cerebral blood flow.

JAMA Neurol. Published online January 7, 2015. doi:10.1001/jamaneurol.2014.386

Figure 1. Ventricle comparisons of factional anisotropy (FA) differences between symptomatic retired professional football players with cognitive impairment and depression deficits (FA > 0.50) and their matched control subjects (FA > 0.50) in diffusion tensor imaging. Red includes voxels in which FA is lower in the symptomatic retired players than in controls (P < .05, corrected). All images are in a 5% log-ratio scale with the results thresholded for better visibility using the seed-based spatial statistics (SBSS) method.

Michael McCrea, PhD, ABPP-CN
“PET Scans May Reveal CTE in Living Players”

G. Small et al 2013 Amer J Geri Psych

2013: No Longer Just About a Few Old Pros

Implications Based on Global Participation
2013: The Newest Chapter

No Longer Just about the Long Haul

Chronic Symptoms Associated with Prior Concussion Exposure

P < 0.0001, All post-hoc comparisons significant

Mean Baseline GSC Score (SD)

- 0 (N=13,046) - 3.44 (6.59)
- 1 (N=3,112) - 5.04 (8.28)
- 2 (N=767) - 7.38 (11.03)
- 3+ (N=396) - 10.38 (14.51)

Total N = 17,321
24.7% with history of 1+ concussion
COMMENTARY

Mild traumatic brain injury: a risk factor for neurodegeneration

Brandon E. Gevett1, Robert A. Stern2, Robert C. Cantu2, Christopher J. Nowinski2 and Ann C. McKee2,3,4

Abstract

Recently, it has become clear that head trauma can lead to a progressive neurodegeneration known as chronic traumatic encephalopathy (CTE). Some researchers have concluded that the pathologies associated with CTE are the underlying cause of suicide and completed suicide in former athletes.

Methods: A review of the literature on contact sports and risk of completed suicide revealed only one epidemiological study with short follow-up data. Results: There are no published cross-sectional, epidemiological or prospective studies showing a relation between contact sports and risk of suicide. One published epidemiological study suggests that retired National Football League players have lower rates of death by suicide than the general population. Outside of sports, there is a cumulative body of evidence suggesting that the causes of suicide are complex, multifactorial and difficult to pin down in individual cases.

Conclusions:Future research might establish a clearer causal connection between the pathophysiology of CTE and suicide. At present, however, there is insufficient evidence to conclude that there is a strong causal relationship between the presence of these pathophysiological substrates and suicide in former athletes.

Chronic traumatic encephalopathy and risk of suicide in former athletes

Grant L. Iverson

ABSTRACT

Background: In the initial autopsy cases of chronic traumatic encephalopathy, some researchers have concluded that the pathologies associated with CTE are the underlying cause of suicide and completed suicide in former athletes.

Methods: A review of the literature on contact sports and risk of completed suicide revealed only one epidemiological study with short follow-up data. Results: There are no published cross-sectional, epidemiological or prospective studies showing a relation between contact sports and risk of suicide. One published epidemiological study suggests that retired National Football League players have lower rates of death by suicide than the general population. Outside of sports, there is a cumulative body of evidence suggesting that the causes of suicide are complex, multifactorial and difficult to pin down in individual cases.

Conclusions: Future research might establish a clearer causal connection between the pathophysiology of CTE and suicide. At present, however, there is insufficient evidence to conclude that there is a strong causal relationship between the presence of these pathophysiological substrates and suicide in former athletes.

There is a genetic susceptibility to the development of CTE and whether a single severe traumatic head injury may also be causative.

Chronic traumatic encephalopathy

CTE is a progressive tauopathy with a distinct clinical and neuropathological profile that becomes symptomatic many years after an individual experiences repeated concussive or subconcussive blows to the head. The characteristic features of CTE include extensive tau-immunoreactive neurofibrillary tangles and astrocytic tangles throughout the frontal and temporal cortices in a patchy, superficial distribution, with focal atrophy at the depths of sulci and around small vessels extensive tau neurofibrillary tangles in the limbic and paralimbic regions, diencephalon, basal ganglia and brainstem; and a relative paucity of beta-amyloid (AD) deposits, although diffuse plaques are present in roughly one-half of the cases. In advanced disease, there are also macroscopic inclusions in the form of neurofibrillary tangles, neuronal tangles and gialtangles, (2) (pseudolaminar deposition, and (2) widespread (NP) hyperphosphorylation. Therefore, by logical extension, it has been assumed that participation in contact sports results in microtrauma and subconcussive blows to the brain and body, these insults then and blocks some neuroprotective changes in the brain, thus progressive neuropathological changes cause a neuropsychiatric disease process or decreases other neurotransmitters from sports and a clear clinical picture of this neuropsychiatric disease is personally related to suicide.

REVIEW

The rate of suicide in civilians and the military has increased in recent years, and people are now more likely to die by suicide than by motor vehicle accidents. In civilians, researchers have reported that suicide rates have increased in towns of counties in relation to the worldwide economic crisis. Men are much more likely to complete suicide than women (27.3 vs. 8.1/100,000 in the USA in 2010) and the rates of suicide in men and women were significantly higher in 2010 compared to 1995.11 Men are twice as likely to commit suicide compared to other age groups, and white men (24.2/100,000 in 2010) are much more likely to commit suicide than
Prevalence and Characterization of Mild Cognitive Impairment in Retired National Football League Players

Christopher Randolph, 1 Stella Kanatous, 2 and Kevin Guskiewicz 2,3,4,5
1 Department of Neurology, Loyola University Medical Center, Maywood, Illinois
2 Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida
3 Department of Exercise Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
4 Department of Physical Medicine and Rehabilitation, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
5 Center for the Study of Retired Athletes, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Abstract
It has been hypothesized that exposure to repetitive head trauma from contact sports over a long playing career may explain the observed risk of late-life cognitive impairment. There are currently few compelling hypotheses about the possible mechanisms underlying such impairment. One is the presence of a unique neurodegenerative disorder known as "chronic traumatic encephalopathy" (CTE). The other is diminished cerebral function leading to the onset of clinical expression of age-related neurodegenerative diseases such as mild cognitive impairment (MCI) and Alzheimer's disease (AD). This present study examined the prevalence of MCI and AD in a sample of 131 retired National Football League (NFL) players. The data suggest that childhood and recent adult history of repetitive head trauma and sports may be risk factors for the development of MCI and AD. There is no evidence to date of a unique neurodegenerative disorder in retired NFL players, which may reflect delayed time to diagnosis of neocortex. The findings are consistent with prior studies, but extend the need for larger, controlled studies in this area.

Keywords: Chronic Traumatic Encephalopathy, Mild Cognitive Impairment, NFL, AD, MCI

Chronic traumatic encephalopathy in sport: a systematic review

Andrew Gardner, 1 Grant Innes, 1 Paul McCrory 1

Abstract
Objective: To provide a critical review of chronic traumatic encephalopathy (CTE) by synthesizing the range of clinical presentations, neuropathology, and the strength of evidence for CTE as a distinct syndrome.

Methods: Specific inclusion and exclusion criteria were used to select studies for review. Data was extracted where present and included study population, exposure characteristics, clinical data, neuroimaging, examination findings, cognitive assessment, investigation results and neuropathological results.

Results: A total of 86 published research studies were included in this review. Evidence was found for a distinct presentation in sport-related traumatic brain injury. The diagnostic criteria for CTE are evolving, with a focus on the clinical presentation and neuropsychological findings.

Conclusion: The clinical criteria for CTE are evolving, with a focus on the clinical presentation and neuropsychological findings. The pathologic diagnosis of CTE remains complex and requires further study.

What are the new findings?

- The definition of chronic traumatic encephalopathy (CTE) has changed from the original "classic" description seen in boxers.
- The clinical phenotype of CTE is becoming more clearly defined in vivo.
- A large scale prospective, longitudinal clinicopathological study is required to answer some of the currently unresolved issues associated with CTE.
What is CTE and Who is at Risk?

**True Incidence, Risks, Latent Pathophysiology?**

Need for prospective, longitudinal, population-based studies

What are the True Population Based Risks?

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

Rodrigo Savara, MD, MSc; Joseph E. Parnell, MD; Lester E. Wolfe, MD; Keith A. Josephs, MD, MSc; and J. Eric Ahlskog, PhD, MD

Abstract

Objective: To assess whether high school football played between 1945 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 1945 to 1956 in the high schools of Stearns County, Minnesota, plus a non-football-playing reference group of male students in the band, cheer, or class were identified. Using the medical records of the Stearns County Professional Project, we measured (from October 1, 2010, to March 30, 2011) available medical records to access 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 Stearns County, Minnesota.

Results: We found an increased risk of dementia, PD, or ALS among the 434 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 football played 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).
Future Directions

A prospective, longitudinal study of head impact exposure, neurologic health and brain imaging biomarkers in former NCAA athletes:

15 year follow-up of the original NCAA Concussion Study

Co-Principal Investigators:
Kevin Guskiewicz, PhD, ATC
UNC-Chapel Hill

Michael McCrea, PhD, ABPP
Medical College of Wisconsin

At a Crossroads

Concussion news worries parents

OTL survey finds 57 percent of parents less likely to allow kids to play football

August 26, 2012, 9:13 AM ET
By Paula Lavigne | ESPN.com

Outside the Lines’ survey finds that a majority of parents are concerned enough about news reports of concussions from playing football to keep their children away from the sport.

Looking to Science for Answers
Thank You

Michael McCrea, PhD, ABPP
Professor of Neurosurgery and Neurology
Director of Brain Injury Research
Medical College of Wisconsin

Office: 414-955-7302
Email: mmccrea@mcw.edu