The Spectrum of Concussion: Recovery Time, Treatment and Rehabilitation, and Possible Long-Term Effects on Brain Health

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Disclosures

Reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to mild TBI and sport-related concussion at meetings, scientific conferences, and symposiums.

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

Co-investigator, collaborator, or consultant on grants relating to mild TBI.

Former Independent Research Contractor (via General Dynamics) for the Defense and Veterans Brain Injury Center.

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Topics

- Observable Features and Acute Effects
- Predictors of Clinical Recovery
- Treatment and Rehabilitation
- Possible Long-Term Effects on Brain Health
- Chronic Traumatic Encephalopathy (CTE)

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Section I

Observable Features and Acute Effects

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By definition, a sport-related concussion is a mild traumatic brain injury.

By consensus, sport-related concussions are characterized by normal structural neuroimaging.

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Pathophysiology

- Complex interwoven cellular and vascular changes
- **Multilayered Neurometabolic Cascade**
- Under certain circumstances, cells degenerate and die

Primary Mechanisms

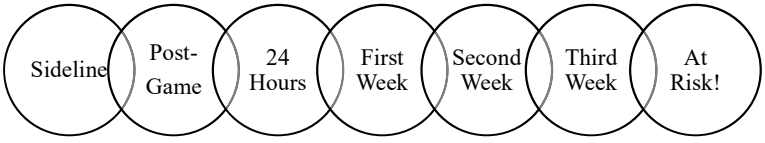
- Ionic shifts
- Abnormal energy metabolism
- Diminished cerebral blood flow
- Impaired neurotransmission

Fortunately, the brain undergoes dynamic restoration

Basic Principles

- Concussion is a clinical diagnosis
- Tests do not diagnose concussion, they measure certain aspects of how a concussion affects a person
- There are tremendous individual differences in how people are affected by a concussion

Assessment Timeline



Sideline and Post-Game

Observation and Examination

Observable Features

- Loss of Consciousness (uncommon)
- Balance Disturbance (e.g., "Bambi legs" on the ice)
- Amnesia (retrograde and/or anterograde; often very brief)
- Disorientation
- Confusion/Attentional Disturbance
  - Slowness to answer questions or follow directions
  - Easily distracted
  - Poor concentration
- Vacant Stare / "Glassy-Eyed"
- Inappropriate/confused Playing Behavior

Common Initially Reported Sideline Symptoms

- Headache
- Dizziness
- Some form of mental status disturbance, such as mental clouding, confusion, or feeling slowed down

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Post-Concussion Scale: Symptoms Endorsed Acutely

- 260 acutely concussed high school and college athletes
- All assessed within 5 days
- Mean = 2.0 days; SD = 1.2 days
- 88% assessed within 3 days

(Lovell et al., 2006)

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Most Common Symptoms

- Headaches (78.5%)
- Fatigue (69.2%)
- Feeling slowed down (66.9%)
- Drowsiness (64.2%)
- Difficulty concentrating (65.8%)
- Feeling mentally foggy (62.3%)
- Dizziness (61.2%)

(Lovell et al., 2006)

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Least Common Symptoms

- Nervousness (21.2%)
- Feeling more emotional (17.7%)
- Sadness (15.0%)
- Numbness or tingling (14.6%)
- Vomiting (8.8%)

(Lovell et al., 2006)

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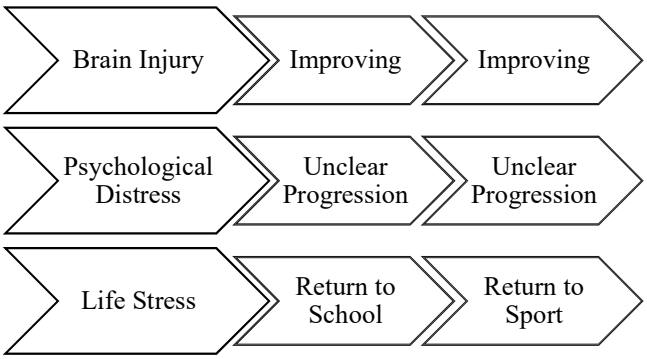
Conceptualizing Symptoms Over Time

(individual differences in how symptoms change over time)



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Acute and Subacute Concussion Symptoms

Remember:

Symptoms in the first two weeks following a concussion can be worsened by other factors, such as a neck injury, vestibular injury, psychological distress, and life stress.

Slow Recovery: Some Risk Factors

- Vestibular + Anxiety
- Stress, Worry, Depression
- Chronic Headaches
- Multiple Prior Concussions

Section II

Predictors of Clinical Recovery

Predictors of Clinical Recovery

- Results from a Systematic Review
- Preliminary Results from a Large Observational Study of High School Students and Division III Collegiate Athletes

Clinical Recovery

- For most concussed athletes, cognitive deficits (Williams et al., 2015; Kontos, et al., 2014), balance (McCrea et al., 2003; Nelson, LaRoche, et al., 2016), and symptoms (Nelson, Guskiewicz, et al., 2016) improve rapidly during the first two weeks following injury.
- Many past studies, particularly those published prior to 2005, concluded that most athletes recover from concussion and return to sports within 10 days (McCrea et al., 2003; Bleiberg, et al., 2004; Pellman, et al., 2004).

Studies over the past decade illustrate that the large majority of athletes appear to recover clinically within one month.

Some have persistent symptoms beyond a month. There might be multiple underlying causes and contributors to those persistent symptoms.

Possible Predictors or Effect Modifiers of Clinical Outcome

- Pre-injury differences
  - Sex
  - Age
  - Genetics
  - Neurodevelopmental conditions (e.g., ADHD, LD)
  - Migraine history (personal or family)
  - Mental Health history (personal or family)
  - Concussion History
- Initial injury severity/acute symptoms (e.g., LOC, PTA, retrograde amnesia)
- Post-injury clinical differences
  - Severity of cognitive deficits
  - Development of headaches, migraines, depression
  - Dizziness and/or oculomotor functioning

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Literature Review on Predictor Variables

- Examine factors that might be associated with, or influence, clinical recovery.
  - Clinical recovery is defined functionally as a return to normal activities, including school and sports, following injury.
  - Operationally it encompasses a resolution of symptoms and a return to clinically normal balance and cognitive functioning.
- Defining Predictors and Modifiers (a "Third Variable" in a disease model)
  - Effect modification
  - Intermediary (causal pathway)
  - Confounding (not on causal pathway)

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Methodological Differences in the Literature

Methodological differences in:

- Outcomes (e.g., symptom resolution, cognition, balance, return to sports, return to school)
- Time between injury and outcome (e.g., days to several months)
- Settings (e.g., high school, college, specialty clinic, emergency department)
- Number of modifiers examined in each study (e.g., 1-47)
  - Univariate
  - Multivariate

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Considerations:
Greater Pre-Injury/Baseline Symptom Reporting

- Females (Brown et al., 2015; Iverson et al., 2015)
- Athletes with a history of ADHD (Iverson et al., 2015; Nelson et al., 2015), learning disability (Zuckerman et al., 2013; Elbin et al., 2013), mental health treatment (Iverson, 2015), substance use treatment (Iverson et al., 2015), migraine treatment (Iverson et al., 2015), headache treatment (Brooks et al., 2016).
- Individuals with multiple prior concussions (Iverson et al., 2015; Brooks et al., 2016).
- Some athletes without any of these prior conditions report concussion-like symptoms in their daily lives (Iverson et al., 2015), potentially related to stress (Edman et al., 2012), depression (Covassin et al., 2012), or insufficient sleep (McClure et al., 2014).

Predictors of clinical recovery from concussion: a systematic review

Review

OPEN ACCESS

Predictors of clinical recovery from concussion: a systematic review

Grant L Iverson,[1,2] Andrew J Gardner,[3] Douglas P Terry,[1,2] Jennie L Ponsford,[4] Allen K Sills,[5] Donna K Broshek,[6] Gary S Solomon[7]

Objective

Review the factors that might be associated with, or influence, clinical recovery from concussion.

Clinical Recovery – a return to normal activities, including school and sports, following injury. Encompasses resolution of symptoms and return to normal balance and cognitive functioning.

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PRISMA

- 7,648 initially identified
- 4,777 after duplicate removals
- 101 full-text articles and 13 conference abstracts ultimately included

Study Inclusion Criteria

1. Published by June 2016
2. Examined clinical recovery from concussion

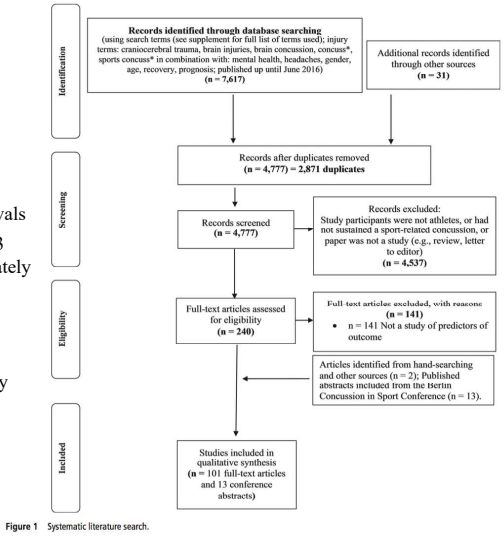

Figure 1 Systematic literature search.

Caveats for Interpreting Results

- Results of all predictors were mixed.
- Many initial studies examined outcome during the first 2 weeks post-injury, while more recent studies examined those who are slow to recover (e.g., > 1 month).

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Mixed Evidence For All Potential Predictors

Predictor of Clinical Recovery	Studies supporting it as a predictor of recovery	Studies not supporting it as a predictor of recovery
Age (younger age)	7	24
Sex (female sex)	17	27
History of Concussions	20	21
Prior Psychiatric History	7	1
Personal Migraine History	1	9
Family Migraine History	1	2
ADHD	1	10
Learning Disability	1	7
Loss of Consciousness	9	22
Post-Traumatic Amnesia	9	16
Retrograde Amnesia	5	5
Greater Acute/Subacute Symptoms	21	3

Younger Age
(Systematic Review)

Yes

Chermann (2014) 25741414; Field (2003) 12756388; Terwilliger (2016) 26421452; Covassin (2012) 22539534; Majerske (2008) 18523563; Pellman (2006) 16462480; Zuckerman (2012) 23227435

No

Lau (2012) 21841522; Hang (2015) 26430968; McDevett (2015) 26502998; Nelson (2016) 26974186; Asplund (2004) 15523205; Chrisman (2013) 23252433; Vargas (2015) 25643158; Nelson (2016) 26974186; Morgan 2015 25745949; Meehan 2010 20716683; Meehan (2013), 23628374; McCrea 2013, 23058235; Lee (2013) 24063601; Baker (2015) 26084537; Greenhill (2016) 27005467; Nelson (2016) 27164666; Corwin (2014) 25262302; Preiss-Farzenagan (2009) 19627902; Heyer (2016) 27056449; Kontos (2012) 22503738; Kriz (2016) 26781190; Miller (2016) 26684762; Ellis 2015 26359916

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Age

- There is some, but not definitive, support for a gradient age and level of play effect with clinical recovery being fastest in professional athletes, followed by college athletes, followed by high school athletes.
- No age effects in several studies, including some large-scale studies (Nelson, Guskiewicz, et al., 2016; Nelson, Tarima, et al., 2016).
- In the large multicenter Canadian study (Zemek et al., 2016), children presenting to the ED following injury, the rates of those having persistent symptoms > 4 weeks:
  - Ages 5-7=17.9%, ages 8-12=26.3%, ages 13-17=39.9%.

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Preliminary Results from Prospective Observational Studies of Concussion Recovery in High School and Division III Student Athletes

Paul Berkner, D.O., Project Director

Recovery Curve Graphs Interspersed with Findings from the Systematic Review

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Methods

- Head Injury Tracker (HIT)
  - Free online/smartphone application
  - Completed by athletic trainer or school nurse
  - Following a concussion, the following information is collected:
    - Demographics (e.g., age, sex, sport played)
    - Self-reported health history variables (e.g., pre-injury history of migraines, ADHD, depression, or concussion)
    - Scenario (e.g., practice vs. game; in season vs. out of season)
    - Injury date
    - 22-Item Post-Concussion Symptom Scale score at the time of the evaluation
    - Date of return to academics (full days, no accommodations).
    - Date of return to athletics (finished return to play protocol).

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Methods

- 1,451 athletes sustained concussions
  - 183 were not sports-related injuries, 3 were 20-year-old high school students.
- Final sample N=1,265 sustained a sport-related concussion.
  - High School: 485 athletes (45.8% girls)
    - Boys: football (39.5%), soccer (22.4%), ice hockey (9.5%), lacrosse (7.2%), basketball (6.8%) and several other sports (14.6%).
    - Girls: soccer (45.0%), basketball (10.8%), spirit squad (cheerleading; 10.8%), field hockey (7.7%), and several other (25.7%).
  - College: 780 athletes (40.4% women)
    - Men: football (38.1%), rugby (15.7%), ice hockey (12.7%), lacrosse (12.3%), soccer (7.7%), and several other sports (13.5%).
    - Women: ice hockey (21.0%), rugby (21.0%), soccer (19.0%), basketball (6.3%), volleyball (6.3%), lacrosse (6.0%), and several other sports (20.4%).

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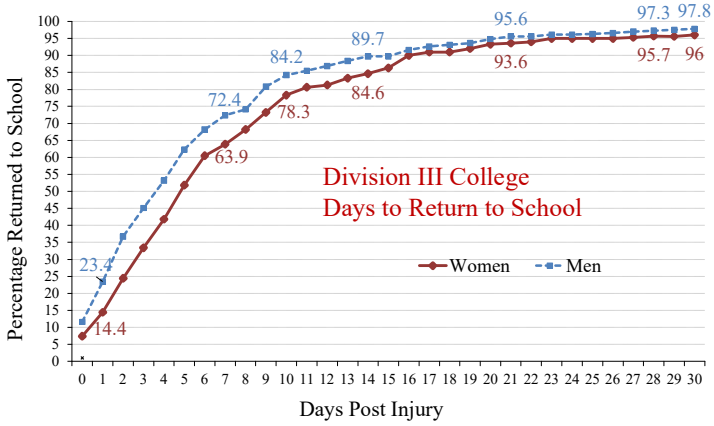

Women took longer to return to academics (MW U=51529, p=.001).

7 days (63.9% vs. 72.4%, χ^2=5.84, p=.016); 14 days (84.6% vs. 89.7%, χ^2=4.00, p=.045); 21 days (93.6% vs. 95.6%, χ^2=1.28, p=.258)

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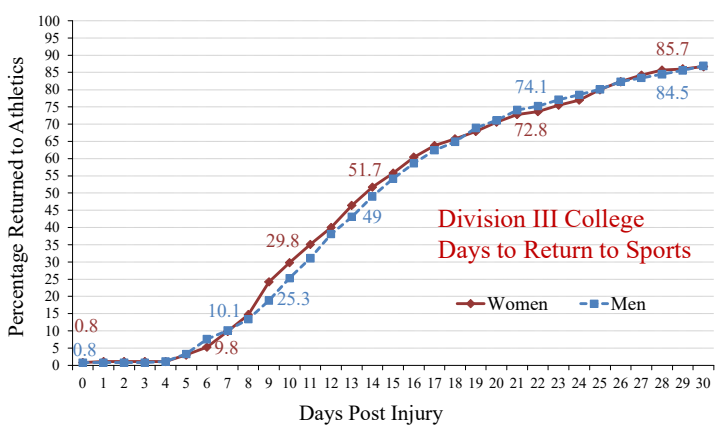

There were no group differences in recovery rates when examining return to athletics (ps>.05).

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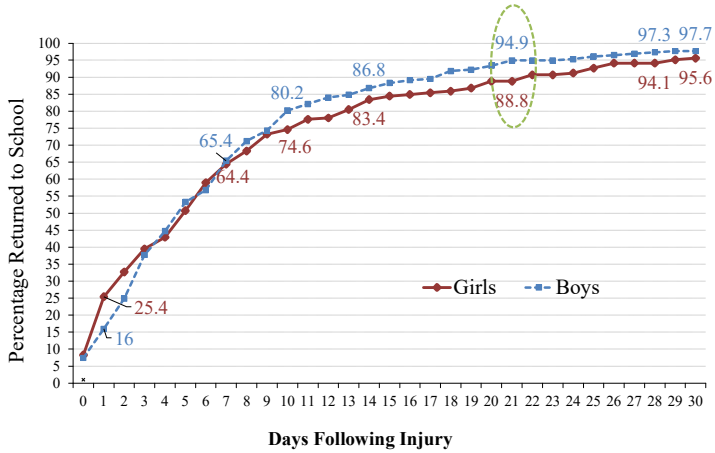
High School: Days to Return to School



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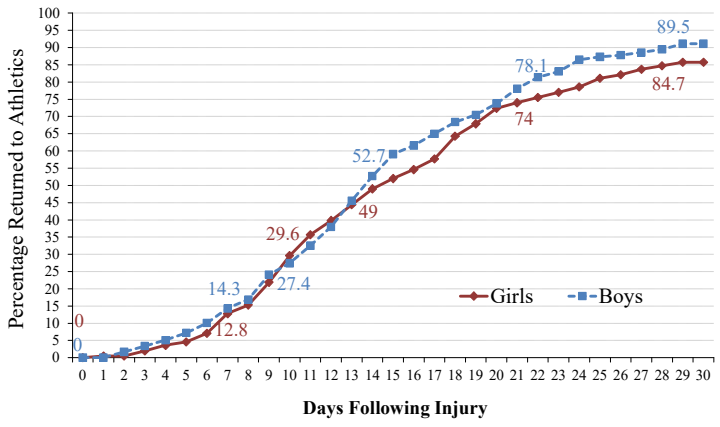
High School: Days to Return to Sports



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Female Sex
(Systematic Review)

Yes

Baker (2016) 26378093; Berz 2013 23703518; Henry 2016 26445375; Kostyun 2015 25553213; Bock 2015; 26243160; Zuckerman 2014 24206343; Covassin 2012 22539534; Covassin 2013 24197616; Covassin 2016 26950073; Majerske 2008 18523563; Colvin 2009 19460813; Eisenberg 2013 23753087; Ellis 2015 26359916; Miller 2016 26684762; Preiss-Farzenagan (2009) 19627902 (in adults); Heyer (2016) 27056449

No

Chermann 2014 25741414; Moor 2015 25883871; Hang 2015 26430968; Nelson 2016 26974186; Mayers 2013 23686028; Asplund 2004 15523205; Black 2016 26862834; Chrisman 2013 23252433; Zuckerman 2016 27032916; Zuckerman 2012 23030348; Vargas 2015 25643158; Terwilliger 2016 26421452; Morgan 2015 25745949; Frommer 2011 21214354; Baker 2015 26084537; McDevett 2015 26502998; Nelson (2016) 27164666; Lax (2015) 26362811; Ono (2016) 26672026; Preiss-Farzenagan (2009) 19627902 (in children/adolescents); Covassin (2007) 17762747; Kontos (2012) 22503738; Wasserman (2015) 26546304; Yang (2015) 25649775

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Sex

- Comparable number of studies show positive and negative findings that worse outcomes are associated with female sex
- Some large-scale and epidemiological studies indicate that girls and young women are at greater risk for having symptoms that persist for more than a month (e.g., Wasserman et al., 2016; Zemek,et al., 2016; Kostyun et al., 2016).
- The extent to which recovery is slower/outcomes are worse for females is still unclear.

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Prior Concussions
(Systematic Review)

Yes

Hang (2015) 26430968; Nelson (2016) 26974186; Guskiewicz (2003) 14625331; Castile (2011) 22144000; Chrisman (2013) 23252433 (football only); Zuckerman (2016) 27032916; Morgan (2015) 25745949; Covassin (2013) 23959963; Kerr (2014) 26535354; Colvin (2009) 19460813; Iverson (2006) 16537266; Miller (2016) 26684762; Wasserman (2015) 26546304; Slobounov (2007) 17762746; Benson (2011) 21502355; Corwin (2014) 25262302

No

Asken (2016) 27111584; Barlow (2011) 21904694; Moor (2015) 25883871; Brown (2014) 24394679; Lau (2012) 21841522; Mautner (2015) 25353721; McDevett (2015) 26502998; Vargas (2015) 25643158; Terwilliger (2016) 26421452; McCrea (2013) 23058235; Erlanger (2003) 12650417; Majerske (2008) 18523563; Baker (2015) 26084537; Ellis (2015) 26359916; Field (2003) 12756388; Makdissi (2013) 23479491; Pellman (2006) 16462480; Gibson (2013) 23758286; Heyer (2016) 27056449; Miller (2016) 26684762; Chrisman (2013) 23252433 (non-football only)

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Prior Concussions

- Many studies find an association between prior concussions and worse clinical outcomes.
- A greater number of studies **have not** found that prior concussions are associated with worse outcomes.
- Still likely a significant modifier because:
  - Prior history of concussion is a risk factor for future concussions (Abrahams et al., 2012)
  - Prior concussions are associated with greater pre-injury symptom reporting in some athletes (Abrahams et al., 2012; Iverson et al., 2015)
  - Some large-scale studies show an association between concussion history and increased risk for symptoms lasting more than four weeks (e.g., Castile et al., 2012; Miller et al., 2016; Wasserman et al., 2016)

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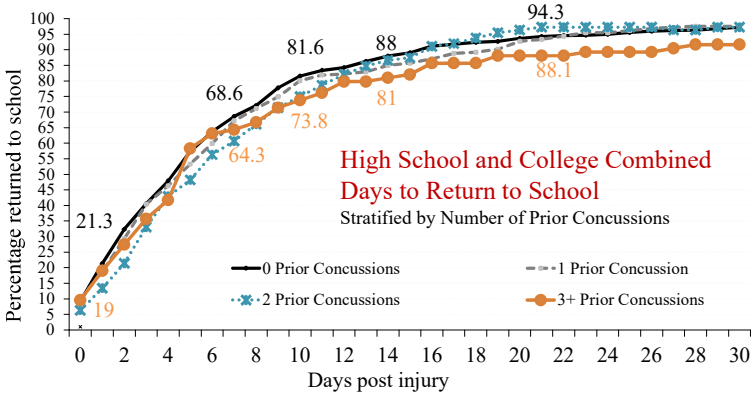

- No significant differences in return to school [$\chi^2(3)=4.56$, $p=.21$].

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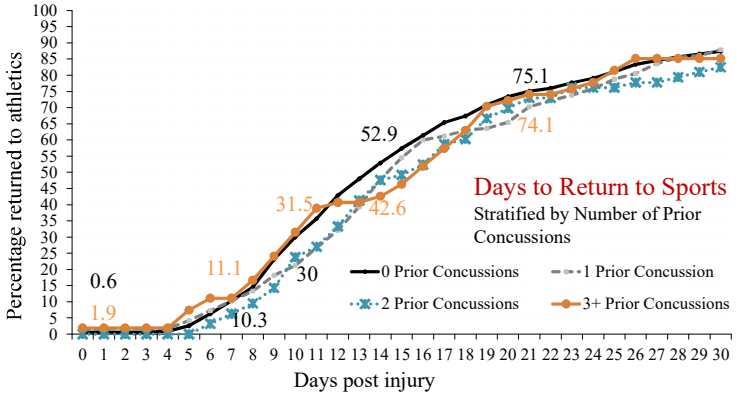

With regard to days to return to sports, the groups significantly differed, $X^2(3)=8.043$, $p=.045$. Follow-up KS tests showed that those 3+ prior concussions took longer to return to athletics compared to the groups with no prior concussions ($Z=2.080$, <.001) and 1 prior concussion ($Z=1.734$, $p=.005$).

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Health History
(Systematic Review)

- **Mental Health History**
  - Almost all studies suggest worse outcome.
- **ADHD History**
  - Almost all studies **do not** suggest worse outcome.
- **Learning Disability History**
  - Almost all studies **do not** suggest worse outcome.
- **Personal Migraine History**
  - Almost all studies do not suggest worse outcome.
  - One large well-designed study reported that a personal history of migraine is associated with risk for symptoms lasting more than four weeks (Zemek et al., 2016).

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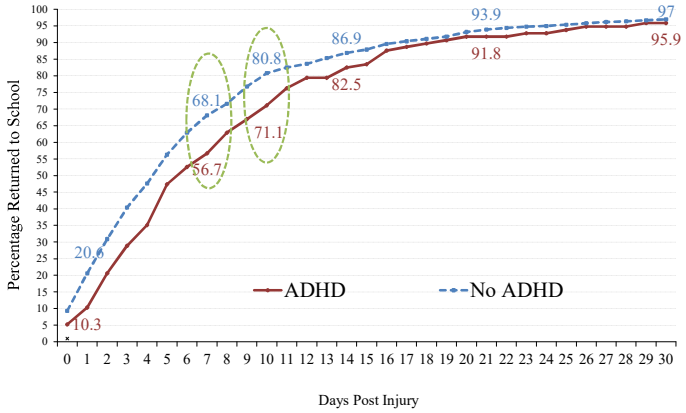
Pre-Injury ADHD: Days to Return to School
(High School and College Combined)



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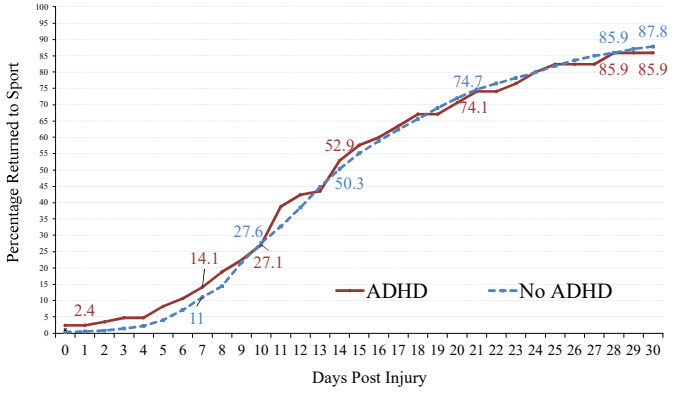
Pre-Injury ADHD: Days to Return to Sports
(High School and College Combined)



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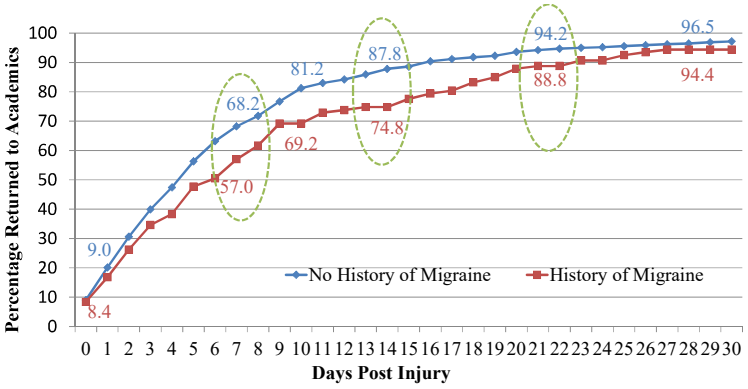
Pre-Injury Migraine: Days to Return to School
(High School and College Combined)



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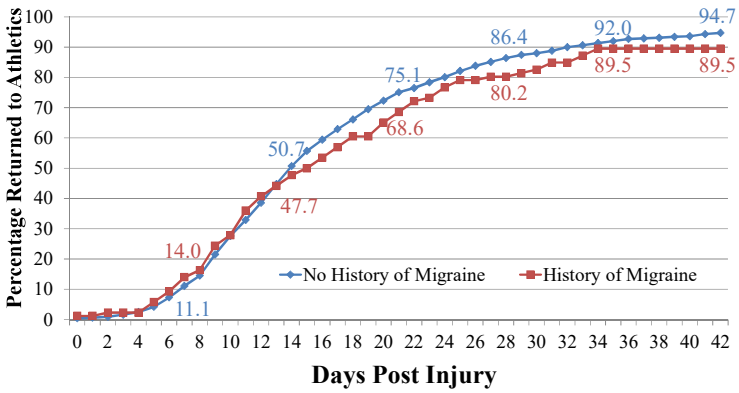
Pre-Injury Migraine: Days to Return to Sports



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Injury Severity
(Systematic Review)

- **Loss of consciousness**
  - Some studies report positive findings that LOC is associated with worse outcomes, but most do not find an association with LOC.
- **Post-traumatic amnesia/"amnesia"**
  - Mixed, but more studies do not find association with worse outcomes.
- **Retrograde amnesia**
  - Less frequently studied.
  - Consistently associated with worse outcome in the first 10 days following injury.

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Greater Acute Symptoms
(Systematic Review)

Yes

Chermann (2014) 25741414; Brown (2014) 24394679; Hang (2015) 26430968; Resch (2015) 26565424; Castile (2011) 22144000; Chrisman (2013) 23252433; Zuckerman (2016) 27032916; Meehan (2014) 25381296; Meehan (2013) 23628374; McCrea (2013) 23058235; Benson (2011) 21502355; Greenhill (2016) 27005467; Makdissi (2013) 23479491; Nelson (2016) 27164666; Merritt (2015) 25685959; Prichep (2013) 22588360; Heyer (2016) 27056449; Iverson (2007) 17304003

No

Barlow (2011) 21904694; Moor (2015) 25883871; Morgan (2015) 25745949

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Acute Clinical Findings
(Systematic Review)

- **Acute/sub-acute symptom burden**
  - Associated with worse outcome
  - Of all possible predictors, it was the most consistently associated with worse outcome.
- **Acute/Subacute Post-injury Headaches**
  - Almost all studies suggest worse outcome.

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Conclusions

- Strongest/most consistent predictor of slow recovery: more severe acute/subacute symptoms after injury.
- Those with preinjury mental health problems or migraines seem to be at a slightly increased risk for persistent symptoms.
- Those with ADHD/learning disabilities do not seem to be at an increased risk for persistent symptoms.
- Teenagers may be at the highest risk for persistent symptoms.
- Girls have a higher likelihood of prolonged recovery.

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Section III

Treatment and Rehabilitation

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Resources for Treatment and Rehabilitation

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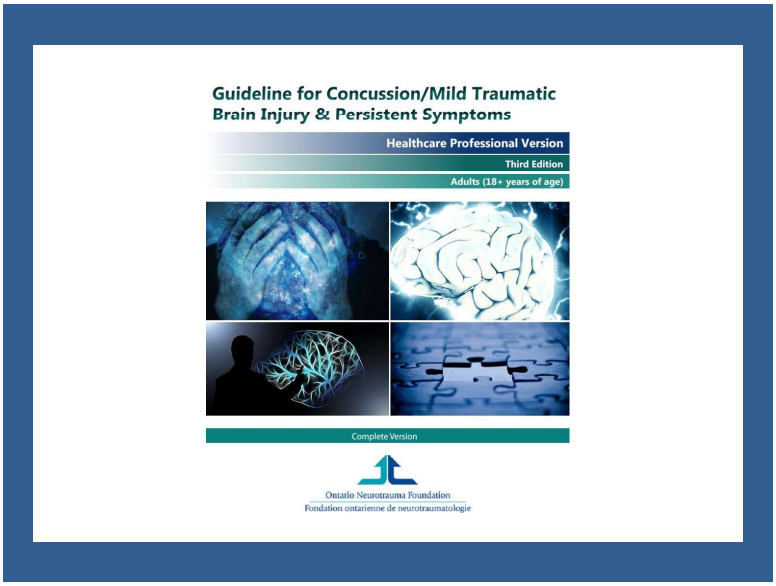

Rest and treatment/rehabilitation following sport-related concussion: a systematic review

Review

Rest and treatment/rehabilitation following sport-related concussion: a systematic review

Kathryn J Schneider,[1] John J Leddy,[2] Kevin M Guskiewicz,[3] Tad Seifert,[4] Michael McCrea,[5] Noah D Silverberg,[6] Nina Feddermann-Demont,[7,8] Grant L Iverson,[9] Alix Hayden,[10] Michael Makdissi[11,12]

Objective

Evaluate the evidence regarding rest and active treatment/rehabilitation following concussion.

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Study Inclusion Criteria

- Original research
  - Randomized clinical trials (RCTs), quasi-experimental studies, case series, case cross-overs & studies, cohort & case control
- Reported sport-related concussion as diagnosis.
- Evaluated the effect of either rest or active treatment/rehabilitation.

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PRISMA

28 studies included
- 9 rest
- 19 active treatment

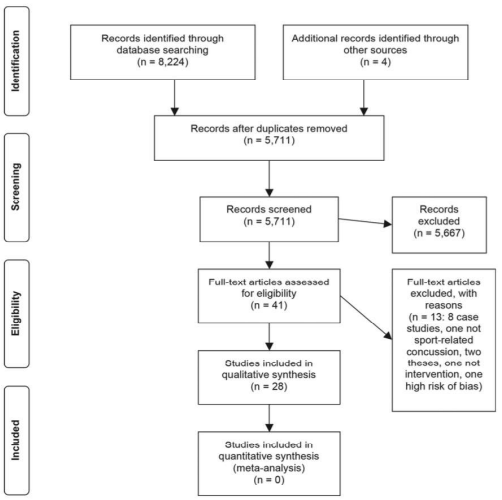

Figure 1 PRISMA flow diagram as follows: Records after duplicates removed 5710; records screened 5710 and Records excluded 5669.

Treatments with Reported Positive Effects

- Multimodal Physical Therapy
  - Combination of several types of physical therapy
- Subsymptom Threshold Aerobic Exercise Training
  - Aerobic exercise (e.g., walking, jogging, stationary bike) that does not exacerbate symptoms
- Medical Treatments
  - amitriptyline, amantadine, peripheral nerve blocks

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Treatment: Rehabilitation

- Cervical and Vestibular Rehabilitation
  - Positive effects for youth and adults with persisting dizziness, neck pain, and headaches.
- Vestibular Rehabilitation
  - May be appropriate for individuals with persistent vestibular (i.e. balance, dizziness) problems.
- Exercise and Manual Therapy (muscle & joint manipulation/mobilization)
  - May be beneficial in cases of ongoing cervical spine pain and cervicogenic headaches.

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Treatment: Exercise

- For adults and adolescents with persistent symptoms following concussion, exercise programs that meet the following criteria are likely safe and beneficial.
  - ✓Closely monitored
  - ✓Subsymptom – intensity and duration does not exacerbate symptoms
  - ✓Submaximal – light aerobic exercise
- Example: Light aerobic exercise a few times a week

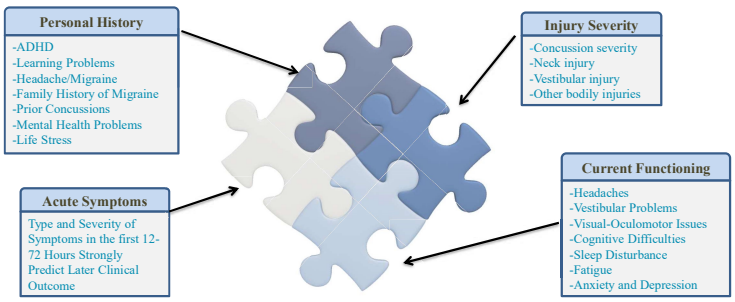
Treatment: Collaborative Care and Medical

- Collaborative treatments may be beneficial.
  - Example: cognitive-behavioral therapy (CBT), school accommodations, & pharmacotherapy (treatment by means of drugs)
  - Limited evidence for symptom resolution & improvement of health-related quality of life in youth.
- No/minimal evidence supporting medical treatments.

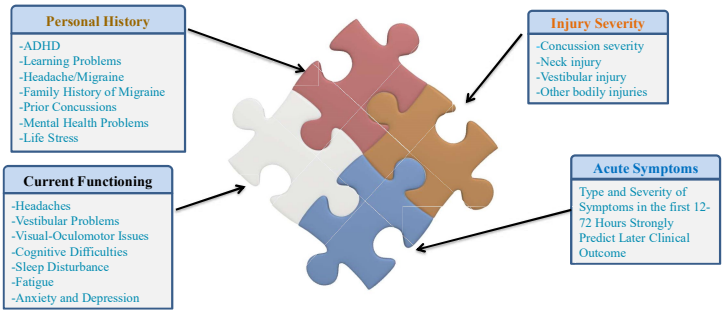
Future Directions

- Determining the optimal or preferred amount of rest (including defining rest, activity restrictions, and activity resumption)
- Determining the role of exercise as a component of active rehabilitation (including when to begin, frequency, intensity, and other parameters)
- Tailoring specific treatment and rehabilitation strategies for specific problems (including when to initiate, frequency, and duration)

The Promise of Precision Rehabilitation



Precision Rehabilitation



Section IV

Possible Long-Term Effects on Brain Health & Chronic Traumatic Encephalopathy

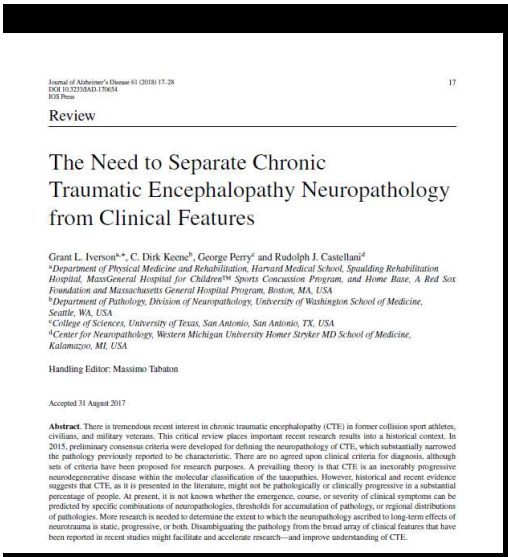
A systematic review of potential long-term effects of sport-related concussion

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
DOI 10.3233/JAD-170654
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

Handling Editor: Massimo Tabaton

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 portion of the 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

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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.

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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, Wauke... Wisconsin, Milwaukee, WI; [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.

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Chronic Traumatic Encephalopathy

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Neuroscience and Biobehavioral Reviews 56 (2015) 276–293

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

ELSEVIER

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]

CrossMark

J Neuropathol Exp Neurol
Vol. 74, No. 6
June 2015
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

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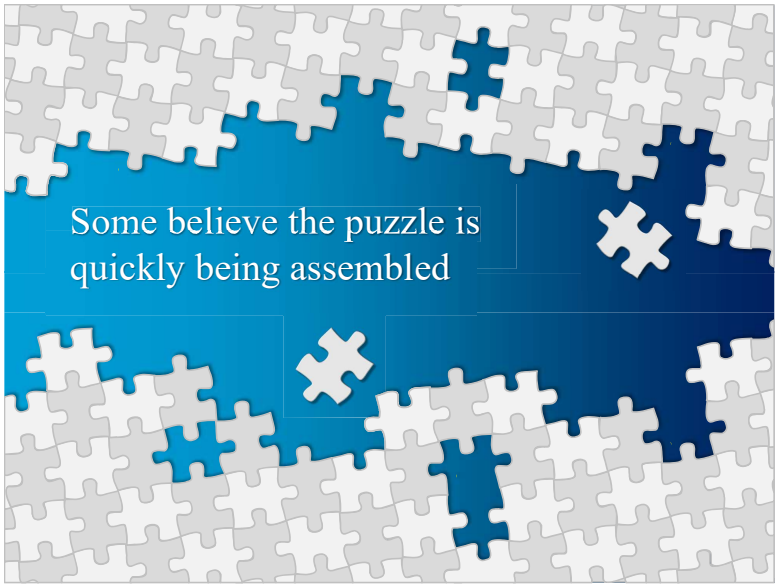

Some Important Unanswered Questions Relating to CTE

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.

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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.

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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

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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.

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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).

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Neuropathology

Neuropatholgy

Psychological Medicine, 1973, 3, 270–303

The aftermath of boxing[1]

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE*

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

Received February 8, 1991/Revised, accepted June 3, 1991

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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

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- 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.

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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.

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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

Received: 15 October 2015 / Revised: 29 November 2015 / Accepted: 29 November 2015 / Published online: 14 December 2015

Gross Pathologic Features	Microscopic Neuropathology
*Cavum Septum Pellucidum	Neuronal Loss
Lateral or *Third Ventriele 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	

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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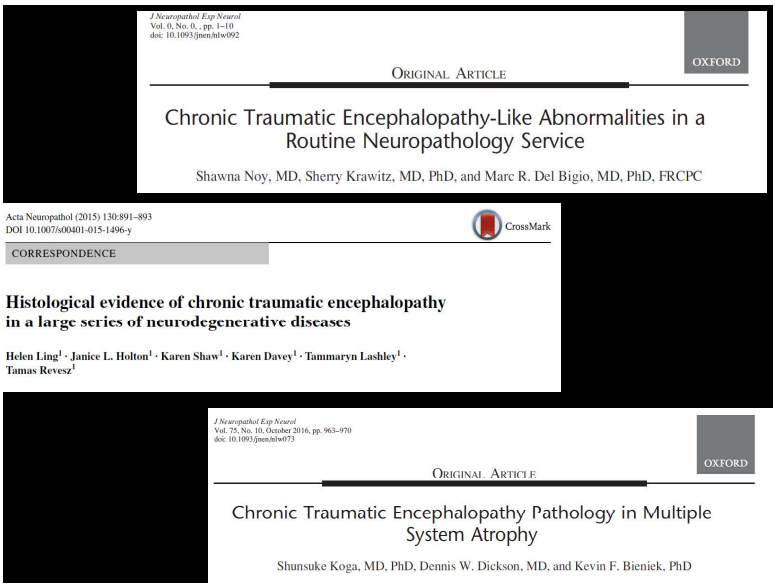

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Vol. 0, No. 0, , pp. 1–10
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OXFORD

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

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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]

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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

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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).

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- 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.

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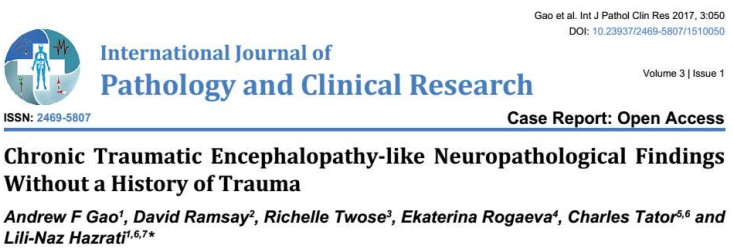
CTE-Like Pathology in ALS



Gao et al. Int J Pathol Clin Res 2017, 3:050
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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.

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.

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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.

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Review Article

Chronic Traumatic Encephalopathy and Suicide: A Systematic Review

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ORIGINAL ARTICLE

Suicide in professional American football players in the past 95 years

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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

Body Mass Index, Playing Position, Race, and the Cardiovascular Mortality of Retired Professional Football Players

Sherry L. Baron, MD[a,*], Misty J. Hein, PhD[b], Everett Lehman, MS[b], and Christine M. Gersic[b]

A Study Focused on Neurodegenerative Diseases

Former NFL Players

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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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."

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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

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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).

© 2012 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2012;87(4):335-340

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."

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Second Study: No Increased Risk

ARTICLE IN PRESS

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; Hayden B. Hasegawa, BA; Amanda K. 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

Topics

- Observable Features and Acute Effects
- Predictors of Clinical Recovery
- Treatment and Rehabilitation
- Possible Long-Term Effects on Brain Health
- Chronic Traumatic Encephalopathy (CTE)

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Mixed Evidence For All Potential Predictors of Outcome

Predictor of Clinical Recovery	Studies supporting it as a predictor of recovery	Studies not supporting it as a predictor of recovery
Age (younger age)	7	24
Sex (female sex)	17	27
History of Concussions	20	21
Prior Psychiatric History	7	1
Personal Migraine History	1	9
Family Migraine History	1	2
ADHD	1	10
Learning Disability	1	7
Loss of Consciousness	9	22
Post-Traumatic Amnesia	9	16
Retrograde Amnesia	5	5
Greater Acute/Subacute Symptoms	21	3

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- Strongest/most consistent predictor of slow recovery: more severe acute/subacute symptoms after injury.
- Those with preinjury mental health problems or migraines seem to be at a slightly increased risk for persistent symptoms.
- Those with ADHD/learning disabilities do not seem to be at an increased risk for persistent symptoms, although emerging research might identify modest increased risks.
- Teenagers may be at the highest risk for persistent symptoms.
- Girls have a higher likelihood of prolonged recovery.

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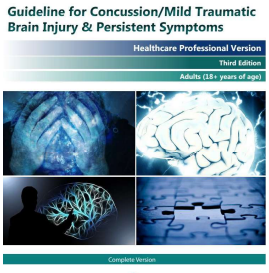
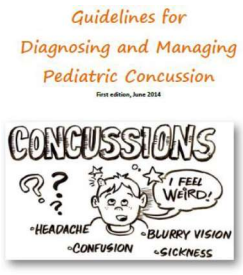
Resources for Treatment and Rehabilitation



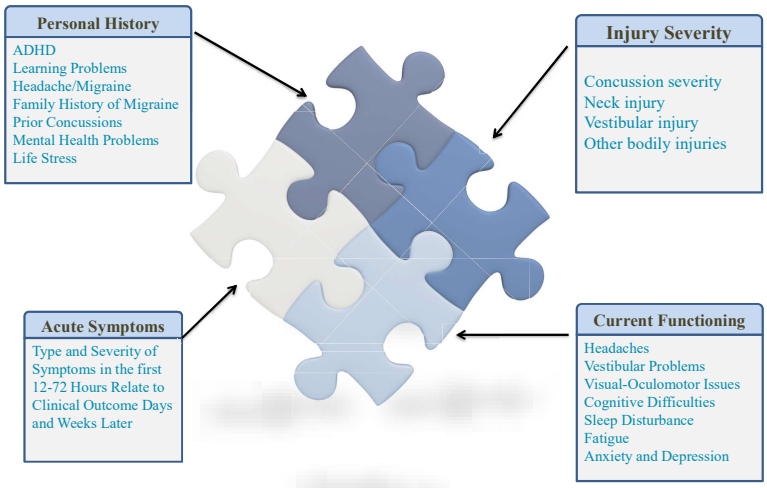


American Medical Society for Sports Medicine position statement: concussion in sport

Kimberly G Harmon,[1] Jonathan A Drezner,[1] Matthew Gammons,[2] Kevin M Guskiewicz,[3] Mark Halstead,[4] Stanley A Herring,[1] Jeffrey S Kutcher,[5] Andrea Pana,[6] Margot Putukian,[7] William O Roberts[8]

Endorsed by the National Trainers' Athletic Association and the American College of Sports Medicine

Precision Rehabilitation



Possible Long-Term Effects

- 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.

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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

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- 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

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Thank you

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