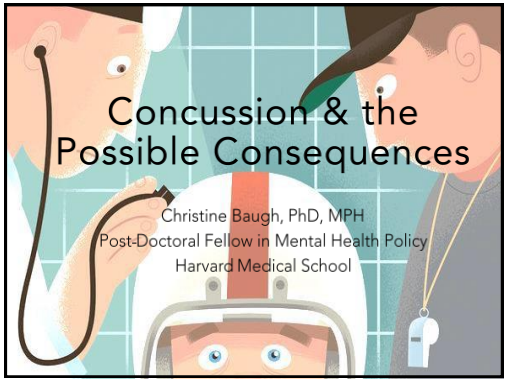
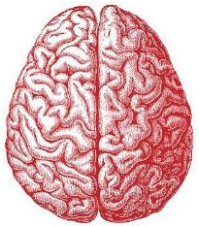



## Conflict Statement

- I have no financial conflict of interest
- All views are my own

## Roadmap

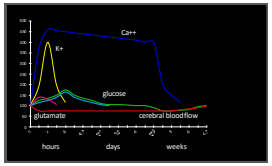


- What is a concussion
- Incidence/prevalence
- Long-term effects
- Human studies
- Animal studies
- Future directions

## Concussions

## What is a concussion?

- Diffuse
- Invisible; no biomarker
- Microscopic
- Metabolic
- Axonal
- No biomarker
- Concussion is a transient neurometabolic injury that typically resolves in under 2 weeks




## Signs & Symptoms

Acute symptoms vary:
- Time to presentation
- Duration
- Severity
- Type
- By sex, age, etc.

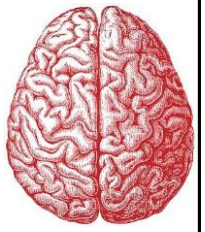
"Once you've seen one concussion… you've seen one concussion."

## Signs & Symptoms

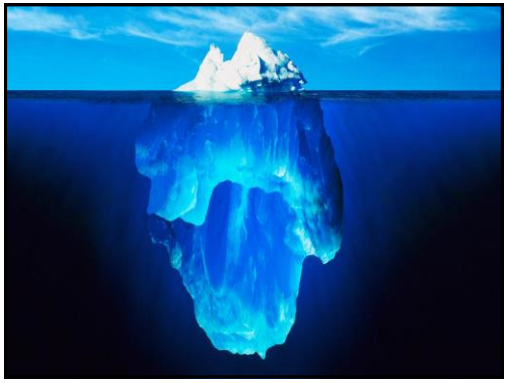
| THINKING/ REMEMBERING | PHYSICAL | EMOTIONAL/ MOOD | SLEEP DISTURBANCE |
|---|---|---|---|
| • Difficulty thinking clearly<br>• Feeling slowed down<br>• Difficulty concentrating<br>• Difficulty remembering new information | • Headache<br>• Nausea or vomiting (early on)<br>• Balance problems<br>• Dizziness<br>• Fuzzy or blurry vision<br>• Feeling tired, having no energy<br>• Sensitivity to noise or light | • Irritability<br>• Sadness<br>• More emotional<br>• Nervousness or anxiety | • Sleeping more than usual<br>• Sleeping less than usual<br>• Trouble falling asleep |

## Concussion Epidemiology

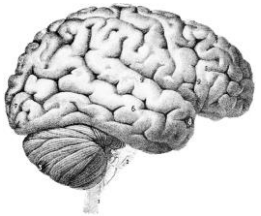
- 1.6-3.8 million concussions sustained annually in the U.S.
- Figures may be an underestimate as concussions are underreported and underdiagnosed; some studies suggest that >50% go unrecognized.
- In recent years, the number of diagnosed concussion has increased in some populations.



## More to come…



## Concussion v. repetitive brain trauma



## Chronic Traumatic Encephalopathy (CTE)

## The latest on CTE

- Neuropathological diagnosis

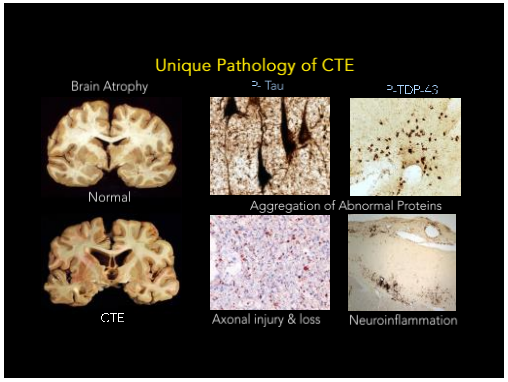
Acta Neuropathol (2016) 131:75–86
DOI 10.1007/s00401-015-1515-z

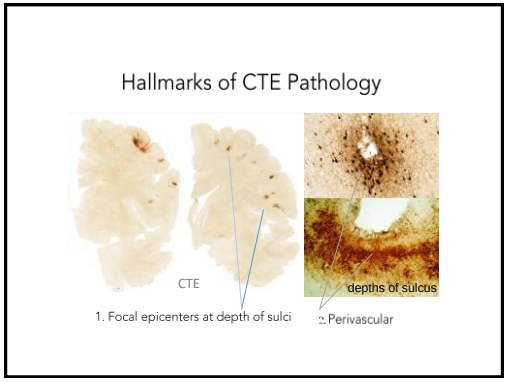
CONSENSUS PAPER

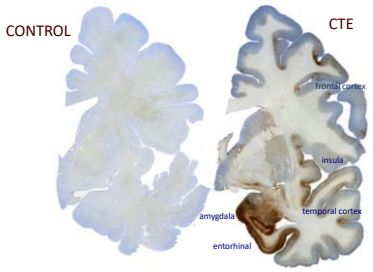
**The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy**

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[1] · Kristen Dams-O'Connor[16] · Victor E. Alvarez[1,2,3,4] · Wayne A. Gordon[16] · the TBI/CTE group

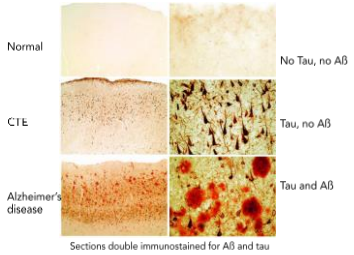
Received: 15 October 2015 / Revised: 29 November 2015 / Accepted: 29 November 2015 / Published online: 14 December 2015

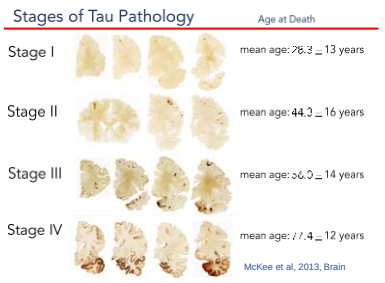





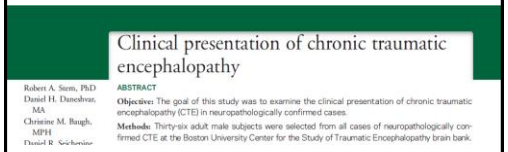

## CTE is unique neuropathology




Sections double immunostained for Aß and tau



## Clinical Presentation of CTE



Clinical presentation of chronic traumatic encephalopathy

Robert A. Stern, PhD; Daniel H. Daneshvar, MA; Christine M. Baugh, MPH; Daniel R. Seichepine

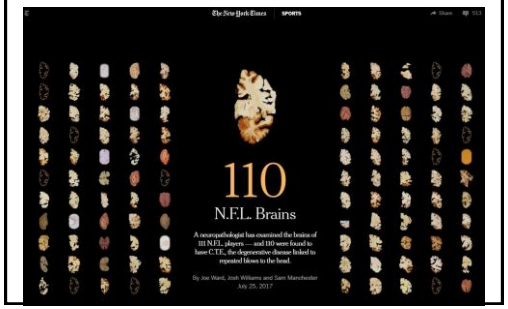
ABSTRACT

**Objective:** The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

**Methods:** Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank.

Clinical presentation less well understood.
Symptoms correlated with CTE fall in 3 domains:
- Cognition (e.g., memory difficulties)
- Mood (e.g., depression, anxiety)
- Behavior (e.g., explosivity)

## The latest on CTE



The New York Times SPORTS

110

N.F.L. Brains

A neuropathologist has examined the brains of 111 N.F.L. players — and 110 were found to have C.T.E., the degenerative disease linked to repeated blows to the head.

By Joe Ward, Josh Williams and Sam Manchester
July 25, 2017

## The latest on CTE

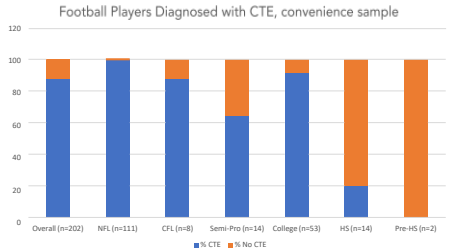
Research

JAMA | Original Investigation

**Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football**

Jesse Mez, MD, MS; Daniel H. Daneshvar, MD, PhD; Patrick T. Kiernan, BA; Bobak Abdolmohammadi, BA; Victor E. Alvarez, MD; Bertrand R. Huber, MD, PhD; Michael L. Alosco, PhD; Todd M. Solomon, PhD; Christopher J. Nowinski, PhD; Lisa McHale, EdS; Kerry A. Cormier, BA; Caroline A. Kubilus; Brett M. Martin, MS; Lauren Murphy, MBA; Christine M. Baugh, MPH; Phillip H. Montenigro, BA; Christine E. Chaisson, MPH; Yorghos Tripodis, PhD; Neil W. Kowall, MD; Jennifer Weuve, MPH, ScD; Michael D. McClean, ScD; Robert C. Cantu, MD; Lee E. Goldstein, MD, PhD; Douglas I. Katz, MD; Robert A. Stern, PhD; Thor D. Stein, MD, PhD; Ann C. McKee, MD

## The latest on CTE




Mez, Daneshvar, Kiernan, et al. July 25 2017 JAMA

## The latest on CTE

- The punchline:
  - In convenience sample of posthumously examined brains from individuals who played football, there was a high rate of CTE
  - More severe CTE was more frequently found in individuals who played at a higher level and individuals who died at an older age
- The caveats:
  - Referral bias, recall bias, no comparison group, etc.

## Gaps in knowledge

- Human studies leave many unanswered questions:
  - True incidence/prevalence of concussion
  - Incidence/prevalence of CTE; no *in vivo* diagnosis
  - Causal relationship between brain trauma and CTE
  - Causal relationship between football and/or CTE pathology and associated symptoms
  - Definitive claims of progressive nature of pathology or clinical symptoms

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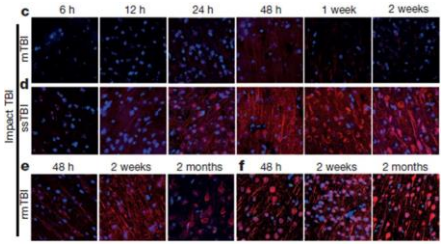
  - Definitive claims of progressive nature of pathology or clinical symptoms

## Animal model of TBI & CTE

- Weight dropped (54.3gm bolt) onto head
- Head free to rotate
- Measure loss of consciousness time
- Measure cognitive function

Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM, Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P, Rotenberg A, Ryo A, Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, Zhou XZ, Lu KP. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature. 2015; 523:431–436.

## Animal model of TBI & CTE

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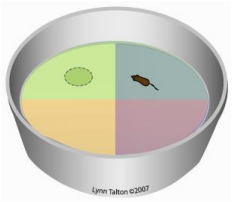


Repetitive Traumatic Brain Injury

Morris Water Maze

- ✓Hidden trials
- ✓Probe trials

Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM, Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P, Rotenberg A, Ryo A, Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, Zhou XZ, Lu KP. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature. 2015; 523:431–436.

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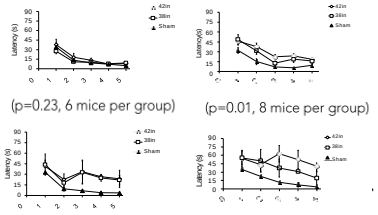
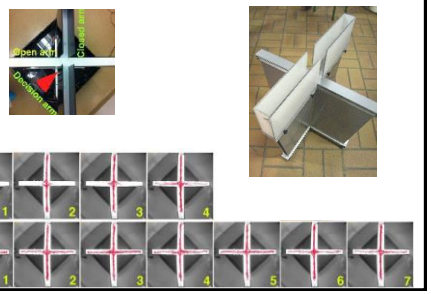



(p=0.23, 6 mice per group) (p=0.01, 8 mice per group)

(p=0.01, 5 mice per group) (p<0.01, 5 mice per group)

Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM, Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P, Rotenberg A, Ryo A, Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, Zhou XZ, Lu KP. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature. 2015; 523:431–436.

## Animal model of TBI & CTE



## Animal Model of TBI & CTE

Takeaways:

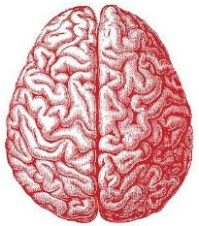
- Repeat brain injury, in short succession, *causes* CTE-like tau accumulation
- CTE-like tau accumulation *causes* some behavioral symptoms in mice
- Antibody induced removal of tau reverses behavioral symptoms to some extent

## Challenges

- Generalizability of animal model to humans unclear
- Similar experiments in humans unethical or infeasible

- Change in game/exposure over time
- Hard to find appropriate "control" group for NFL athletes for purposes of comparison
- …and many more

## Beyond CTE



- Depression
- Anxiety
- Executive Dysfunction

- Physical Activity
- Team-building
- Social Support

## Thank you

Special thanks to my many colleagues and collaborators, especially Dr. Ann McKee who shared many of the CTE images that were included in this presentation.