Chronic Traumatic Encephalopathy

Harvard Dementia Course
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Disclosures

- Psychological Assessment Resources, Inc.
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- King-Devick Test, Inc.
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- National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation
  - Consulting fees as member of Medical Science Committee
- Avid Radiopharmaceuticals
  - Research grant

Repetitive Head Impacts
Moderate-to-Severe TBI
Symptomatic mTBI/Concussion
Subconcussive Trauma
**Subconcussive Impacts**

- Impact to brain with adequate force to have an effect on neuronal functioning (possibly including: neurometabolic cascade, neuroimmune response, breakdown of blood brain barrier).
- **BUT… No Immediate Symptoms of Concussion**
- Some sports and positions very prone
  - Pro football linemen may have 1000-1500 of these hits per season, each at 20-30 g.

**Force = Mass x Acceleration**

- Athletes are getting bigger and faster!
  - Anzell et al., 2013

**Subconcussive Impacts**

- Using helmet accelerometers, Broglio and colleagues (2011) found that high school football players received, on average, 652 hits to head in excess of 15 g of force.
- One player received 2,235 hits! Studies with college players even higher.
  - Growing evidence that even after one season, repetitive subconcussive trauma can lead to cognitive, physiological, and structural changes.
- Abbas et al., 2015; Davenport et al., 2014; Koerte et al., 2012, 2014; McAllister et al., 2013; Pasternack et al., 2014; Robinson et al., 2015; Brodthahn et al., 2012; Prude et al., 2015; Stewart et al., 2017, etc.
- Wake Forest study in youth (8-12 yo) football (Bahrami et al., 2016, Radiology)
  - Players who experienced more cumulative head impact exposure had more changes in brain white matter after one season (no concussions).
Do Concussions and Subconcussive Trauma Lead to Neurodegeneration?

We Have Known About the Long-Term Consequences of Repetitive Head Impacts in Boxing for a Long Time

- **Punch Drunk**: Martland, 1928
  - “goofy,” “slug-nutty”
  - Later on, “institutionalized in an asylum”...for dementia
- **Dementia Pugilistica**: Millsapgh, 1937
- **Chronic Traumatic Encephalopathy**: Bowman & Blau, 1940; Critchley, 1957

Long-Term Consequences of Repetitive Head Impacts in American Football

- Mike Webster (who died in 2002) was the first American Football Player with Neuropathologically Diagnosed Chronic Traumatic Encephalopathy
  - Omalu et al., 2005
  - Began increased media attention to CTE
Chronic Traumatic Encephalopathy is Dementia Pugilistica

- Neurodegenerative disease, similar to Alzheimer’s disease but is unique neuropathologically and, in some ways, clinically
- CTE is associated with a history of repetitive head impacts, including concussions and subconcussive trauma
- The repetitive trauma appears to start a cascade of events in the brain that eventually leads to progressive neurodegeneration

Chronic Traumatic Encephalopathy (CTE)

- Not prolonged post-concussion syndrome
- Not the cumulative effect of concussions
- Not a “brain injury” or TBI, per se…it is a neurodegenerative disease
- The disease appears to begin earlier in life, but the symptoms often begin years or decades after the brain trauma (latency) and continue to worsen
- Numerous cases of neuropathologically-confirmed later stage CTE without any history of symptomatic concussions, but with extensive subconcussive exposure

CTE

- Like Alzheimer’s and other neurodegenerative diseases, CTE can currently only be diagnosed postmortem
- Dr. Ann McKee has examined more brains with CTE than any other neuropathologist; BU has the largest CTE brain bank (BU-VA-CLF) Brain Bank in the world
  - >300 brains examined
CTE Neuropathology

- Characterized by abundance of a misfolded, hyperphosphorylated form of tau protein:
  - Neurofibrillary tangles and astrocytic tangles
- Pathognomonic findings of CTE:
  - Tau deposits surrounding small blood vessels
  - Found at the depths of cortical sulci

Unique Pathology of CTE

What we Know:

- Tissue stained (AT8) for p-tau = brown

- CTE is a disease
- It is unique from other tauopathies
- It is only seen in people with a history of previous repetitive brain trauma
BU-VA-CLF Brain Bank has a Biased Sample Based on Who Donates Brain Tissue

- The goal is NOT to examine the epidemiology of CTE
- The goal is to describe the neuropathology and clinico-pathological correlations
- Need for a large-scale brain bank (not focused on CTE or athletes, etc.) to examine CTE neuropathology

Clinical Features of CTE as reported by next-of-kin

- Changes in Mood
  - Sadness/Depression
  - Apathy
  - Anxiety and Agitation
  - Rage
- Changes in Behavior
  - Short Fuse
  - Impulsivity (poor self-control)
  - Aggressive Behavior
Clinical Features of CTE as reported by next-of-kin

- Changes in Cognitive Functioning
  - Poor Episodic Memory (cannot make new memories, rapid forgetting, repeats stories)
  - Executive Dysfunction (e.g., Poor Judgment and Decision-Making, Impaired Organizational and Planning Skills, Poor Multi-Tasking)
- Dementia
  - Impaired functioning in activities of daily living
  - Can easily be misdiagnosed as AD Dementia

Clinical Subtypes

Early Behavioral/Mood and Later Cognitive

John Grimsley - Died at Age 45

- Houston Oilers 1984-1990; Miami Dolphins 1991-1993; Linebacker; Pro-Bowl, 1988
- Hunting/Fishing guide post NFL
- For the 5 years prior to death at age 45, he experienced worsening memory and cognitive functioning, as well as increasing "short fuse."
- Died of gunshot to chest while cleaning gun. Not suicide.
Grimsley - Neuropathology

Tom McHale - Died at age 45
A Control???

- Nine-year NFL veteran lineman
- Tampa Bay Buccaneer
- No reported concussions, so wife (and we) thought control
- But as lineman had routine subconcussive blows
- Cornell University graduate, successful restaurateur post NFL, husband and father of three boys
- Died due to drug overdose after a multi-year battle with addiction

McHale - Neuropathology
Not Just Football

• CTE in > 250 individuals, including former pro football players AND in:
  – Boxers (Dementia Pugilistica)
  – Pro Wrestling
  – Rugby
  – Pro Hockey Players (only enforcers)
  – Soccer (new paper from UK)

Not Just Pros

• College Football
• High School Football
• Military
• Ages: 17 through 80’s

Owen Thomas
UPenn Football Co-Captain (Lineman)
Played since age 9: NO Concussions
Owen Thomas
Suicide at Age 21

Suicide Caused by CTE?
• Unlikely
• Suicide is, tragically, too common in this age group
• Complex, multifactorial causes to suicide
• Thomas case showed us:
  – Early evidence of CTE at just 21 years old
  – Another case of CTE with no reported concussions

Scientific Growth versus Media and Public Attention
• Dr. McKee’s groundbreaking work on the neuropathology of CTE has had a great impact on public policy and awareness
• However, the public thinks that the science of CTE is far more advanced than it is
CTE: What We Need to Know

• Is CTE Common?
  – We just don’t know!
  – Need for longitudinal, epidemiological studies

• Why do some people get CTE and others do not?
  – All neuropathologically confirmed cases have had a history of repetitive head impacts.
  – Translation: repetitive impact exposure is a necessary but not sufficient cause of CTE
  – Not everyone who hits their head will get it!
CTE: What We Need to Know

What are the risk factors?

- Genetics (e.g., APOE, MAPT)
  - Some initial data to suggest that APOE e4 carriers may be at greater risk (Stern et al., 2013)
  - Several additional studies currently underway

CTE: What We Need to Know

What are the risk factors?

- EXPOSURE Variables
  - Severity and type of trauma
  - Amount of rest/time between hits
  - Overall duration
  - Total amount of hits
  - Age of first exposure

What, if any, are the long-term consequences of repeated head impacts occurring during critical periods of neurodevelopment?
### Neurodevelopmental Milestone

<table>
<thead>
<tr>
<th>Neurodevelopmental Milestone</th>
<th>Age</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak amygdalar and hippocampal volume</td>
<td>9-12</td>
<td>Uematsu et al. 2012; Caviness et al. 1996</td>
</tr>
<tr>
<td>Regional peak gray matter volumes</td>
<td>10-12</td>
<td>Giedd et al. 1999, 2008; Courchesne et al. 2000</td>
</tr>
<tr>
<td>Regional peak cortical thickness</td>
<td>8-11</td>
<td>Shaw et al. 2006, 2008</td>
</tr>
<tr>
<td>Microstructural maturation of the genu and splenium of the corpus callosum</td>
<td>8-12</td>
<td>Snook et al. 2005; Lebel et al. 2008</td>
</tr>
<tr>
<td>Peak myelination rate</td>
<td>11-12</td>
<td>Thatcher 1991, 1997</td>
</tr>
<tr>
<td>Peak cerebral blood flow</td>
<td>10-12</td>
<td>Epstein 1999</td>
</tr>
<tr>
<td>Beginning of cerebral glucose metabolism decline</td>
<td>10</td>
<td>Chugani et al. 1987, 1996</td>
</tr>
</tbody>
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### Age at First Exposure to Football

Stamm et al., 2015, *Neurology*

- 42 former NFL players (ages 40-69) divided into two groups based on age of first exposure (AFE) to tackle football:
  - <12 or ≥12 and matched by age
- 21 pairs
Age at First Exposure to Football
Stamm et al., 2015, Neurology

Summary
• Former NFL players who started playing tackle football before age 12 have greater current:
  – executive dysfunction (mental flexibility, planning, organization)
  – memory impairment
• …controlling for current age and for total duration of play

Are There Neuroanatomical Changes Also Associated with Age of First Exposure to Tackle Football?
Region I: Prefrontal
Region II: Premotor/Supplementary Motor
Region III: Primary Motor
Region IV: Primary Sensory
Region V: Parietal, Temporal, and Occipital

AFE <12 group displayed sig. lower FA and higher RD in the anterior CC regions compared to the AFE ≥12 group

Stamm et al. (2015) *J Neurotrauma*
Summary
*Altered White Matter Integrity*

- Former NFL players in the AFE <12 group had altered microstructure integrity of the anterior corpus callosum regions compared to those in the AFE ≥ 12 group
Limitations

- Very unique cohort of former professional football players
- What about those who only played through HS or College?

Age of First Exposure LEGEND Study
Alosco et al., under review

- 214 former football players without other contact sport history
  - High School n=43
  - College n=103
  - Professional n=63
- Measures:
  - Brief Test of Adult Cognition by Telephone (BTACT)
  - Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A)
  - Center for Epidemiologic Studies Depression Scale (CES-D)
  - Apathy Evaluation Scale (AES)
- Outcomes examined as continuous variables and dichotomized as clinically impaired or not
- Age of First Exposure:
  - Continuous and Dichotomized into <12 and ≥12 years

Age of First Exposure LEGEND Study
Alosco et al., under review

- Results
  - Multivariate mixed-effect regressions controlling for age, education, and duration of play
  - AFE to football before age 12 corresponded with >2X increased odds for clinically-impaired scores on all measures with exception of BTACT
  - No interaction between AFE and highest level of play
Limitations

• Telephone-based cognitive assessment
• Does not indicate CTE
• Is that adequate evidence to stop youth tackle football?

Next Step in Examining Exposure

• Study individuals who only had high school or college exposure to football (Not Pros)
• Estimate Cumulative Head Impact Exposure
  – Exposure Science modeling using data from previously published studies of youth, high school, and college football players with helmet accelerometers

Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players

Montenigro, Alonso, Martin, Daroff, Muz, Chaisson, Nowinski, Au, McKee, Cantu, McClean, Stern, Tripodis


• Objectives:
  1. To develop a metric to quantify cumulative RHI exposure from football, that we term the Cumulative Head Impact Index (CHII)
  2. To use the CHII to examine the association between RHI exposure and long-term clinical outcomes
Montenigro et al. (2017)

• Methods:
  – Participants: 93 former high school (n = 17) and college (n = 76) football players from the BU LEGEND Study; no other contact sport; mean age = 47.3 (SD = 13.9)
  – Measures: Telephone-administered cognitive test as well as standardized self-reported behavioral/mood scales
  – Index: CHII computed for each subject and derived from a combination of self-reported athletic history (i.e., # of seasons, position(s), levels played), and impact frequencies reported in helmet accelerometer studies.

• Results:
  – Dose-Response relationship between cumulative head impacts and later life cognitive, mood, and behavioral impairment
Diagnosis of CTE During Life is the Critical Next Step

- Differentiate between CTE and other causes of cognitive, mood, and behavioral change, including:
  - Alzheimer’s disease
  - Frontotemporal Dementia
  - PTSD
  - Persistent symptoms from previous repetitive or single mTBI
  - Idiopathic depression and aggressive behavior, etc.
- Understand the true incidence and prevalence of the disease
- Determine the risk factors (including genetic and exposure variables) for CTE

Steps Required to Diagnose CTE During Life

1. Describe the clinical features associated with neuropathologically confirmed CTE
2. Develop and begin to refine clinical diagnostic criteria
3. Develop potential “biomarkers”

Similar to Alzheimer's Disease, Biomarkers, in Addition to Clinical Evaluation, will Lead to Accurate Diagnosis of CTE During Life
DETECT

Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests

“Chronic Traumatic Encephalopathy: Clinical Presentation and Biomarkers”

Goal:
To Develop Biomarkers to Diagnose CTE During Life

Principal Investigator: R.A. Stern
NIH R01 Grants R01NS078337 and R56NS078337
funded by:
National Institute of Neurologic Diseases and Stroke
National Institute of Aging
National Institute of Childhood Health and Development

DETECT Study - Subjects

• ~100 former NFL players (CTE High Risk)
  – ages 40-69
  – positions with highest exposure to RHI
  – currently symptomatic
• 30+ controls (CTE No Risk)
  – same age
  – no brain trauma exposure
• Last DETECT Subject - October 2015
DETECT Study - Measures

- Neuroimaging (MRI, DTI, SWI, fMRI, MRS, etc.)
  - Shenton, Koerte, and Lin (BWH, Harvard)
- Lumbar Puncture (CSF Tau, beta amyloid)
- EEG (BrainScope)
- Genetics (APOE, MAPT, etc.)
- Clinical Exams (Neuro, Cognitive, Psych, Motor)
- When we started, there were no measures of blood tau or brain tau on the horizon

Olfactory Function and Associated Clinical Correlates in Former National Football League Players
Alosco et al., 2017, J Neurotrauma

- Former NFL players had worse B-SIT scores relative to controls (p = 0.0096)
- In the former NFL players, lower B-SIT scores correlated with greater behavioral/mood impairment (p = 0.0254) and worse psychomotor speed/executive functioning (p = 0.0464) after controlling for age and education.

MRI Measures of Cavum Septi Pellucidi (CSP)
Koerte et al., 2015, J Neurotrauma (M. Shenton, BWH)

- Former NFL group had a higher rate of CSP, a greater length of CSP, and a greater ratio of CSP length to septum length
- Additionally, in the NFL group, a greater length of CSP was significantly associated with decreased performance on a list learning task
Several Important Findings from the DETECT Study Using MRI/MRS

- Neurodegeneration/Atrophy
- Specific structural abnormalities (CSP)
- Functional dysconnections
- Inflammation
- Biochemical metabolite alterations
- But, nothing specific to CTE due to the lack of ability to detect tau in brain

DETECT PET Study

*Funding by Avid Radiopharmaceuticals*

- AV 1451 PET Tau Imaging and Florbetapir PET Amyloid Imaging added to DETECT protocol.
- 20 former NFL and 10 controls
- (VERY) Preliminary Findings
- But...larger study including subjects from Banner Alzheimer's Institute and Mayo Clinic-Arizona about to be submitted for publication

A Blood Test???
Plasma Exosomal Tau

- Exosomes are cell-derived “nanovesicles” present in biological fluids, including blood, saliva, cerebrospinal fluid and urine
- Mirror the features of the parent cell, including the proteins inside (e.g., p-tau from neurons!)
- Very stable and make a “liquid” biopsy possible
- And…they cross the blood-brain barrier!

Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy

Robert A. Stern1,2,3,5,6, Stephen T. Yankner1, Christine M. Baugh1, Jennifer G. Finn2, Bard M. Karp1,2, Christine Channer1,2, Robert C. Conti3,2, James A. Joy2, and Mark H. Ste-Marie1,2,5,6

- 78 former NFL and 16 controls from DETECT

Stern et al. (2016) Plasma Exosomal Tau

- NFL group had higher exosomal tau than the control group (p < .0001)
• Within the NFL group, higher exosomal tau associated with:
  \( \diamond \text{worse memory (p = 0.01)} \)
  \( \diamond \text{worse psychomotor speed (p = 0.01)} \)

Stern et al. (2016) - Plasma Exosomal Tau

Plasma Exosomal Tau

• Very preliminary! Many limitations and need for refinement, replication, and post-mortem validation; currently underway with Dr. Tsuneya Ikezu and others
• Will always require extra steps of exosome isolation, making it less likely to be a first-step, routine screening test
• Need for direct measures of tau in blood
• Starting point: total tau in plasma

Repetitive head impact exposure and later-life plasma total tau in former NFL players

• 96 former NFL players (ages 40-69) and 25 same-age controls from DETECT
• Plasma total tau (t-tau):
  - Ultrasensitive single-molecule array (Simoa) assays
  - Simoa HD-1 analyzer (Quanterix).
• Cumulative Head Impact Index (CHI) quantified RHI exposure
• Clinical Evaluation:
  - Comprehensive cognitive and neuropsychiatric test battery
Plasma t-tau Study (cont)

• Results
  – No significant group differences in plasma t-tau between the former NFL players and controls
  – But, former NFL players exhibited more extreme plasma t-tau concentrations;
    • 12 Ss t-tau level ≥3.56 pg/mL
    • No control subject had a t-tau level above ≥3.56 pg/mL
  – No relationship between plasma t-tau and clinical measures...But...

Greater Exposure to Repetitive Head Impacts Associated with Higher Later-Life Concentrations in Plasma Total Tau (p = 0.014)

DIAGNOSE CTE
Research Project

Diagnostics, Imaging, And Genetics Network
for the Objective Study & Evaluation of
Chronic Traumatic Encephalopathy
Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors

$16 Million grant funded by the National Institute of Neurological Disorders & Stroke (U01NS093334)

7-Year Multicenter Study
Principal Investigators
Robert Stern, Ph.D., Boston University (Contact PI)
Jeffrey Cummings, M.D., Cleveland Clinic
Eric Reiman, M.D., Banner Alzheimer’s Institute
Martha Shenton, Ph.D., Brigham & Women’s Hospital

50 Collaborators
10 Research Institutions

Collaborating Institutions
- Banner Alzheimer’s Institute
- Boston University Schools of Medicine and Public Health
- Brigham and Women’s Hospital, Harvard Medical School
- Cleveland Clinic Lou Ruvo Center for Brain Health
- Mayo Clinic Arizona
- Molecular Neuroimaging
- NYU School of Medicine
- University of Washington
- VA Puget Sound
- Washington University School of Medicine

External Advisory Board
- David Knopman, M.D., Advisory Board Chair
  Professor of Neurology, Mayo Clinic
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  Montana Governor, One Mind
- Brian Harline, M.D.
  Chief Medical Officer, National Collegiate Athletic Association
- Mike Haynes
  Member of Pro Football Hall of Fame
  President and founder, Mike Haynes & Associates
- Thomas McCullough, M.D.
  Chief, Department of Psychiatry
  Assistant dean of Psychiatry, Indiana University School of Medicine
- Arthur Tops, M.D.
  Founding Scientific Director of the Institute for Neuroimaging and Informatics (INI)
  University of Southern California
- Michael Weiner, M.D.
  Professor of Medicine, Radiology, Psychiatry, and Neurology, University of CaliforniaSan Francisco
Aims

DIAGNOSE CTE Research Project

1. Collect and analyze neuroimaging and fluid biomarkers for the in vivo detection of CTE
2. Characterize the clinical presentation of CTE
3. Examine the progression of CTE over a three-year period
4. Refine and validate diagnostic criteria for the clinical diagnosis of CTE
5. Investigate genetic and head impact exposure risk factors for CTE
6. Share project data with researchers across the country and abroad

High Exposure Group
120 Former NFL Players
Asymptomatic, Symptomatic, Dementia

Medium Exposure Group
60 Former College Players
Asymptomatic, Symptomatic, Dementia

Control Group
60 No-Contact Sport/no TBI Controls
All Asymptomatic

Biomarkers
Fluid: CSF & Blood, Saliva
Neuroimaging: MRI, DTI, fMRI, MRS, PET - amyloid, & PET - tau

Clinical Diagnosis
Traumatic Encephalopathy Syndrome
Behavior/Mood, Cognitive, Mixed, Dementia Subtypes
& Chronic Traumatic Encephalopathy Probable, Possible, Unlikely

Clinical Exams
Neurocognitive, Mood, Behavior, & Motor Tests

Risk Assessment:
Head Impact Exposure & Genetic Polymorphisms
Disease Course:
Clinical and Biomarker Characteristics
Consensus Statement on Diagnostic Criteria

Sites

Arizona
Mayo Clinic-Scottsdale
Site PI: C. Adler
• PET scans at Banner Alzheimer's Institute, Phoenix

Las Vegas
Site PI: C. Bernick
Cleveland Clinic Lou Ruvo Center for Brain Health

Boston
BU School of Medicine
Site PI: R. Stern
MFA at Brigham and Women's Hospital

New York
Site PI: L. Balcer
New York University Langone Medical Center
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- Tsuneya Ikezu

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- Ofer Pasternack
- Manfa Shehata

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- Chris Blevins
- Cliff Robbins

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- Andreas Jeromin (Quanterix)
- Mark Mintun (Avid)
- John Mize (Carolina)
- Mike Pontecorvo (Avid)
- Henrik Zetterberg (U. Gothenburg)
- Jing Zhang (U. Wash.)

And all the athletes and families who participate in our research