Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma

HHS Dean's Lecture Series

University of North Carolina - Greensboro

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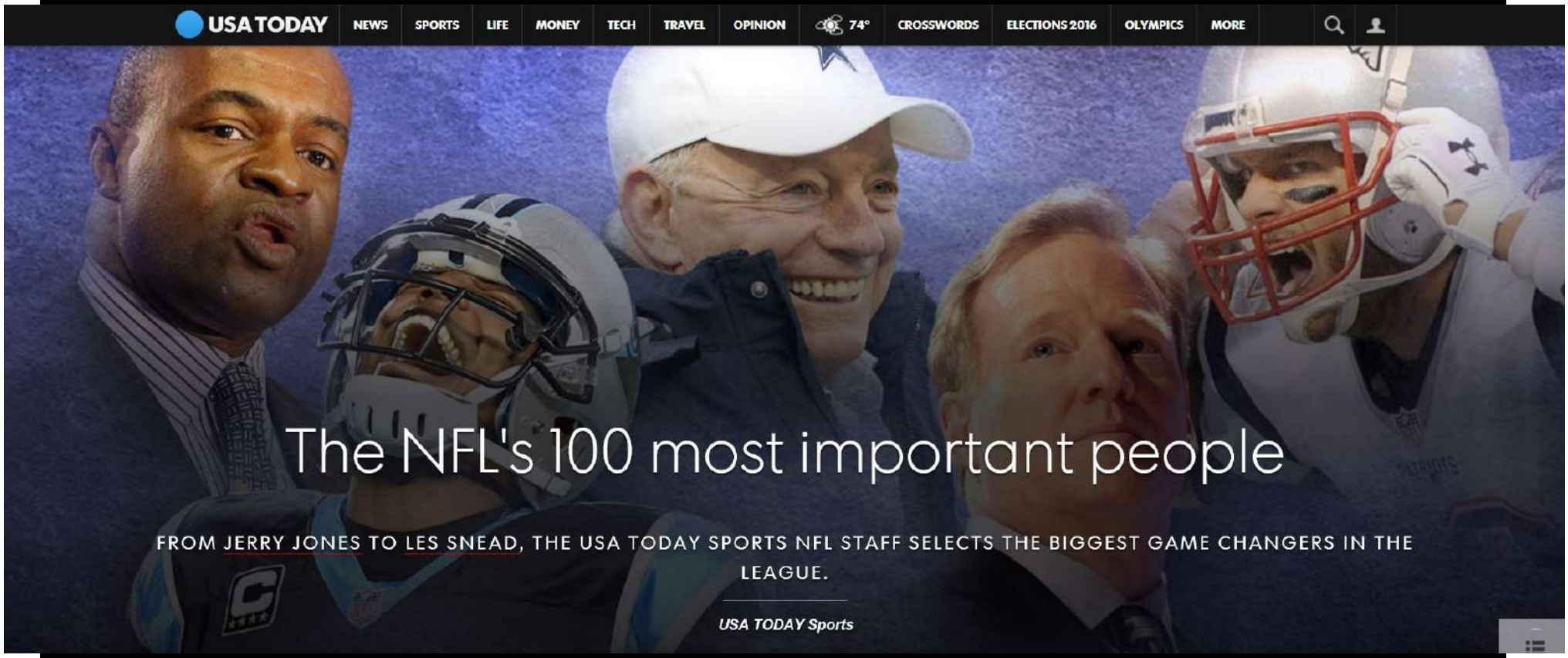
BOSTON UNIVERSITY

UNC

Disclosures

- Psychological Assessment Resources, Inc. (Royalties for Published Tests)
- Amarantus Bioscience (Medical Advisory Board Member)
- Avanir Pharmaceuticals (TBI Advisory Board Member)
- Biogen (Alzheimer's Medical Advisory Board Member)
- Eli Lilly (Member of Executive Committee for AZD3293 Alzheimer's Disease studies)
- National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation (Medical Science Committee)
- **I was a football fan…**

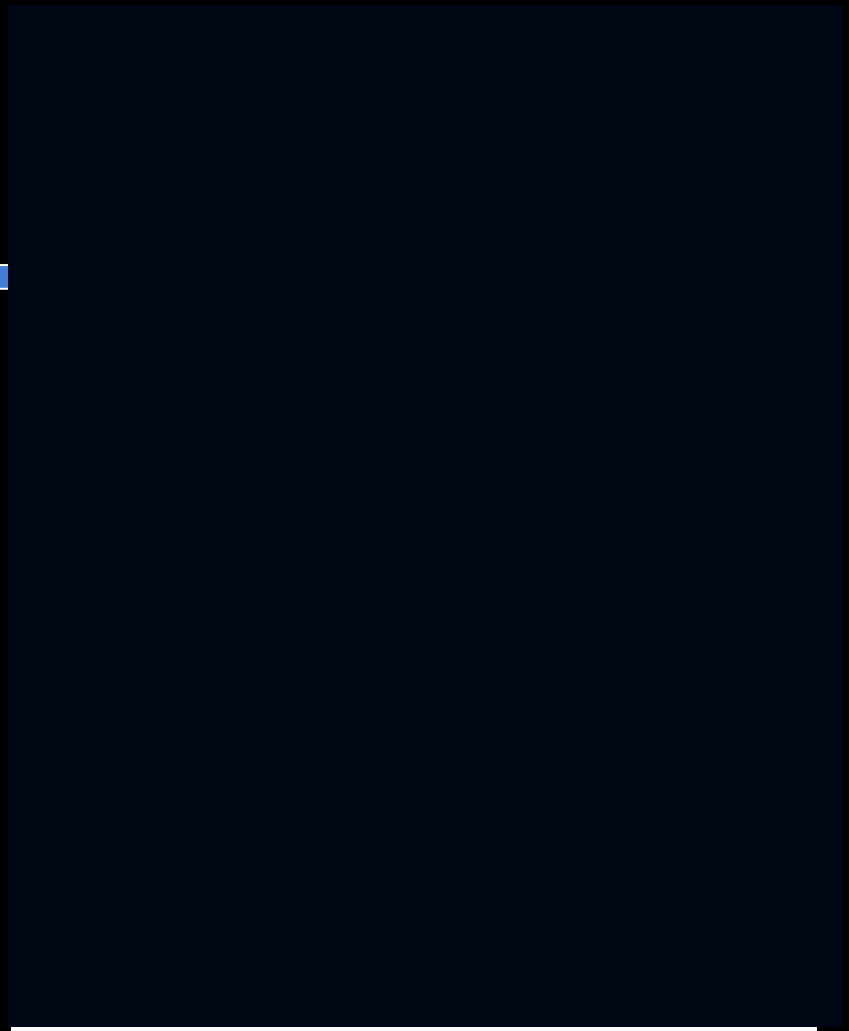

SUPER BOWL XLIX
NEW ENGLAND PATRIOTS
SUPER BOWL XLIX
SUPER BOWL XLIX



The NFL's 100 most important people

FROM JERRY JONES TO LES SNEAD, THE USA TODAY SPORTS NFL STAFF SELECTS THE BIGGEST GAME CHANGERS IN THE LEAGUE.

USA TODAY Sports

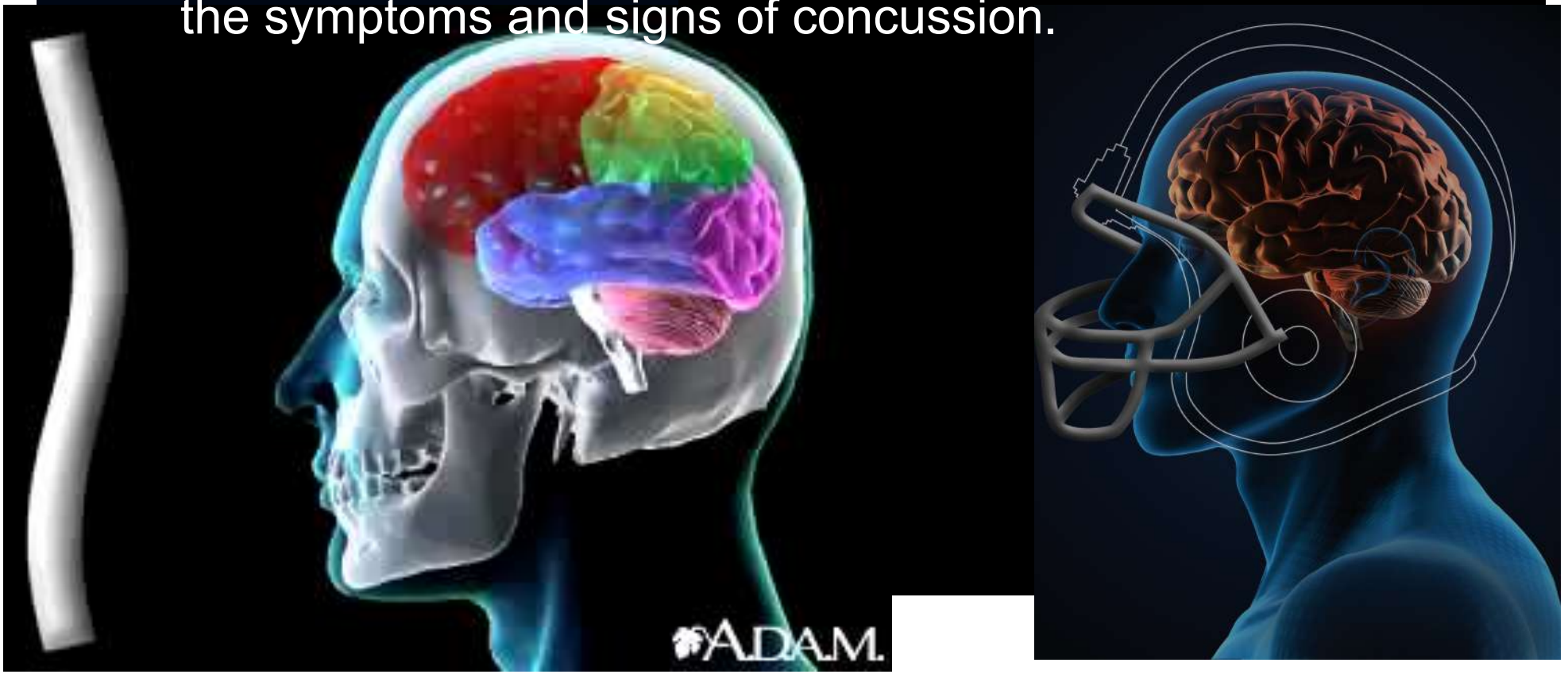


10. Tom Brady

Patriots quarterback. Since 2001, Brady has led the team to four Super Bowl titles, winning game MVP honors in three of them, and has also been the league MVP twice. He currently faces a four-game suspension for his alleged role in Deflategate. Widely regarded as the best quarterback in the game and perhaps of all time.

What is a Concussion?

- When the head or body gets hit and the brain moves quickly, it results in immediate changes to nerve cells.
- "Good stuff" leaves cells and "bad stuff" enters, all at the same time that the cells increase their energy needs but get less blood flowing to them.
- These changes to the functioning of the brain cells lead to the symptoms and signs of concussion.



Concussion

- Does not require a loss of consciousness; Less Than 10%
- Concussions cannot be seen on traditional CT or MRI
- It is NOT a bruise to the brain!
- It IS a brain injury
- Helmets do not protect the brain from concussion; helmets prevent skull fractures

Concussion Signs & Symptoms

- Results in temporary changes in:
  - Physical Functioning: headache, poor balance, blurry vision, nausea, light and noise sensitivity
  - Cognition: feeling foggy, memory problems, poor concentration, slowed thinking and reaction times
  - Mood/Behavior: depression, irritability, anxiety
  - Sleep: fatigue, insomnia, hypersomnia
- Requires cognitive and physical rest for recovery

Great Strides in Sports Concussion Prevention, Awareness, Detection, and Management

"You'd better sit out the rest of the game. You might have a concussion."

Disclosures - Continued

- I know very little about concussions!
  - My area of expertise is neurodegenerative disease
  - There is incredible expertise at UNCG in concussion detection and treatment
    - Drs. Milroy, Rhea, Wyrick, and others
- **I'm not very concerned about concussions when it comes to later life neurodegenerative disease**


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 but No Immediate Symptoms of Concussion
- Some sports and positions very prone
  - Football linemen may have 1000-1500 of these hits per season, each at 20-30 *g*.
    - Double the number for the athletes who plays both offense and defense

Force = Mass x Acceleration

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


NFL CBS

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., 2012; Pasternack et al., 2014; Robinson et al., 2015; Breedlove et al., 2012; Poole et al., 2015
- Recent Wake Forest study in youth football

The Washington Times

Scientists find signs of brain changes after just one season of youth football

By Andrew Blake - *The Washington Times - Tuesday, October 25, 2016*

Researchers are already aware of the ravaging effect repeated concussions can have on the human brain, but a new report suggests less powerful strikes to the skull may pose significant risks as well, especially among children.

Scientists studied the brain activity of 25 boys between the ages of 8 and 13 before and after a single season of tackle football, and published their findings in Monday's issue of the academic journal Radiology.

While none of the children concurred a concussion during the season, a comparison of their before and after brain scans revealed changes the researchers consider to be statistically significant.

Do Concussions and Subconcussive Trauma Lead to Neurodegeneration?


HBO 2:36
Round 2 of 12


AP

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

- Punch Drunk: Martland, 1928
- Traumatic Encephalopathy: Parker, 1934
- Dementia Pugilistica: Millspaugh, 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
  - And….led to a somewhat fictional major motion picture…

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)

What we Know:

- Not prolonged post-concussion syndrome
- Not the cumulative effect of concussions
- Not a “brain injury” or TBI, per se…it is a neurodegenerative disease, a “tauopathy”
- The disease appears to begin earlier in life, but the symptoms often begin years or decades after the brain trauma and continue to worsen

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

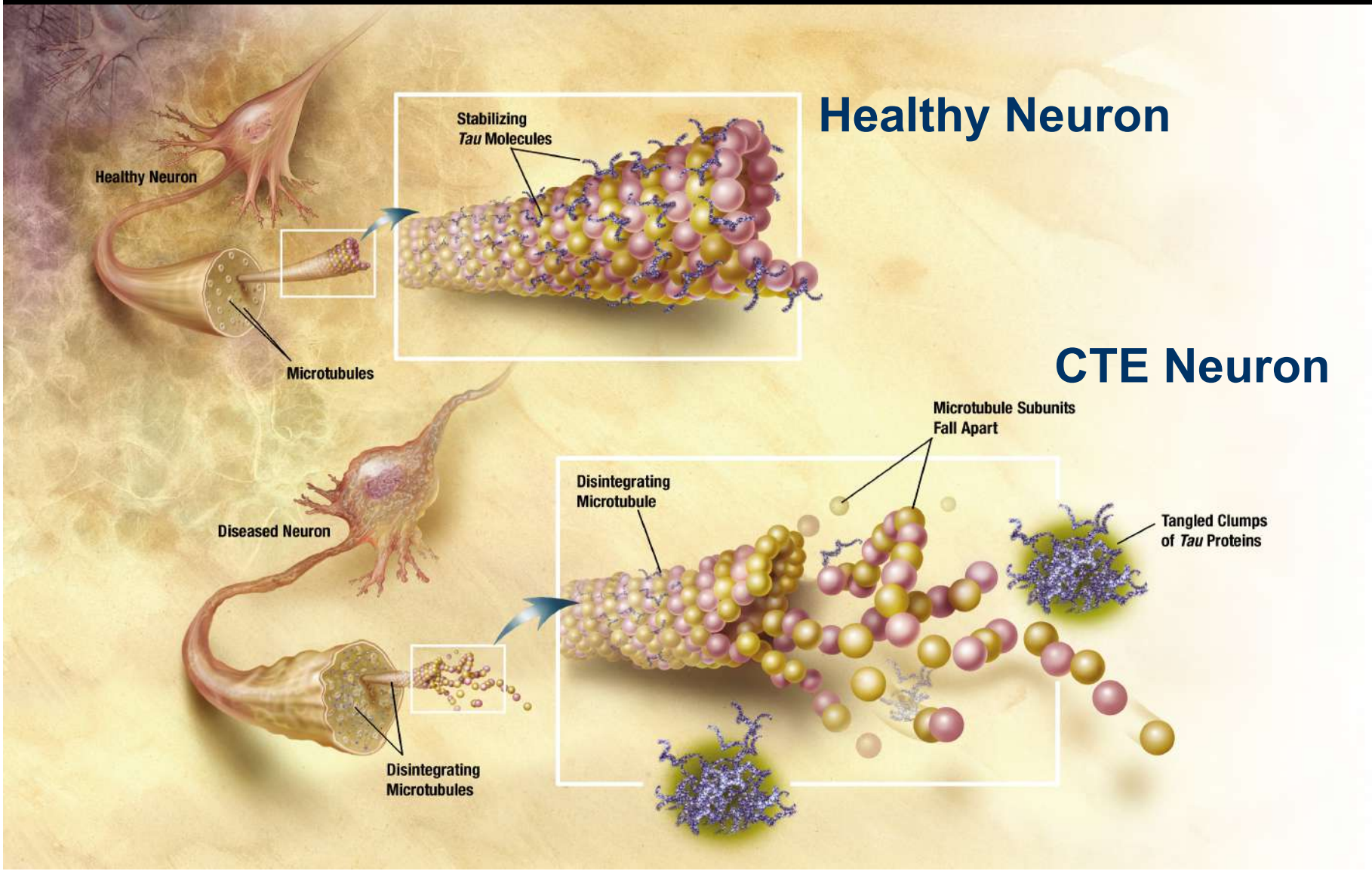
doi:10.1093/brain/aws307 Brain 2013: 136; 43–64 | 43

BRAIN
A JOURNAL OF NEUROLOGY

The spectrum of disease in chronic traumatic encephalopathy

Ann C. McKee[1,2,3,4,5], Robert A. Stern[2,3,4,6], Christopher J. Nowinski[2,4,7], Thor D. Stein[1,5], Victor E. Alvarez[2,4], Daniel H. Daneshvar[2,4], Hyo-Soon Lee[3,4], Sydney M. Wojtowicz[1,2], Garth Hall[8], 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[2,3,4,5,14,15], Neil W. Kowall1[3,4,5,*], Robert C. Cantu[2,6,7,16,*]

Microtubule-Associated Protein Tau



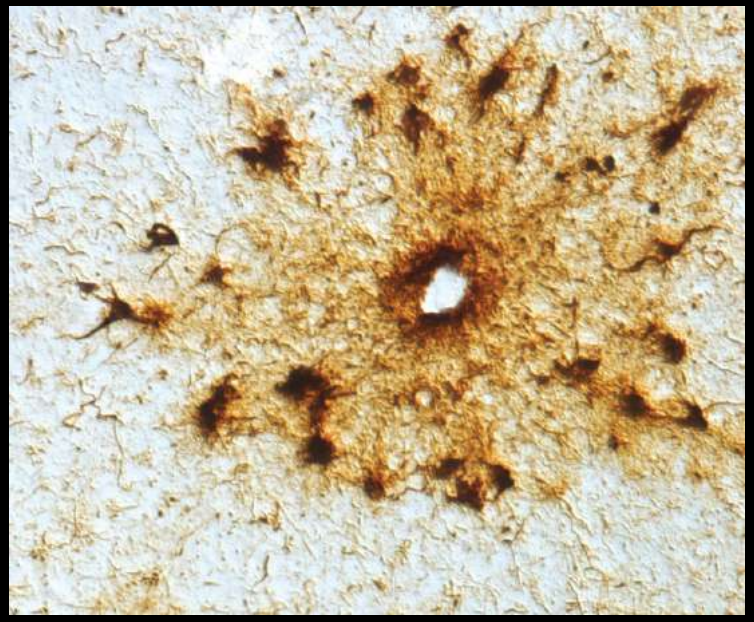
CTE Neuropathology

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

Unique Pathology of CTE
What we Know:

Tissue stained (AT8) for p-tau = brown

Perivascular



Depths of the Sulci

Spread of Destruction from Abnormal Tau

What are the Clinical Features?

Clinical presentation of chronic traumatic encephalopathy

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The Official Journal of the American Academy of Neurology

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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. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had next-of-kin informants to provide retrospective reports of the subjects' histories and clinical presentations. These interviews were conducted blind to the subjects' neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at the time of death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. *Neurology*® 2013;81:1–8

GLOSSARY

AD = Alzheimer disease; **CSTE** = Center for the Study of Traumatic Encephalopathy; **CTE** = chronic traumatic encephalopathy; **p-tau** = hyperphosphorylated tau; **RBT** = repetitive brain trauma; **TBI** = traumatic brain injury.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau).[1,2] To date, CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to

Clinical Features of CTE

- Changes in Mood
  - Sadness/Depression
  - Apathy
  - Anxiety and Agitation
  - Rage
- Changes in Behavior
  - Short Fuse
  - Impulsivity (poor self-control)
  - Aggressive Behavior
- “Change in Personality”

Clinical Features of CTE

- Changes in Cognitive Functioning
  - Poor Memory (cannot make new memories, rapid forgetting, repeats stories)
  - Poor Judgment and Decision-Making
  - Impaired Organizational and Planning Skills
  - Poor Multi-Tasking
- Dementia…what is it????
  - Does that mean they get Alzheimer's disease???

What is Dementia?

- Dementia refers to a new loss of memory and other cognitive functioning that is significant enough to get in the way of routine independent living, resulting in dependence on others.
- Dementia is not an illness or disease
- It is a clinical syndrome caused by many underlying conditions

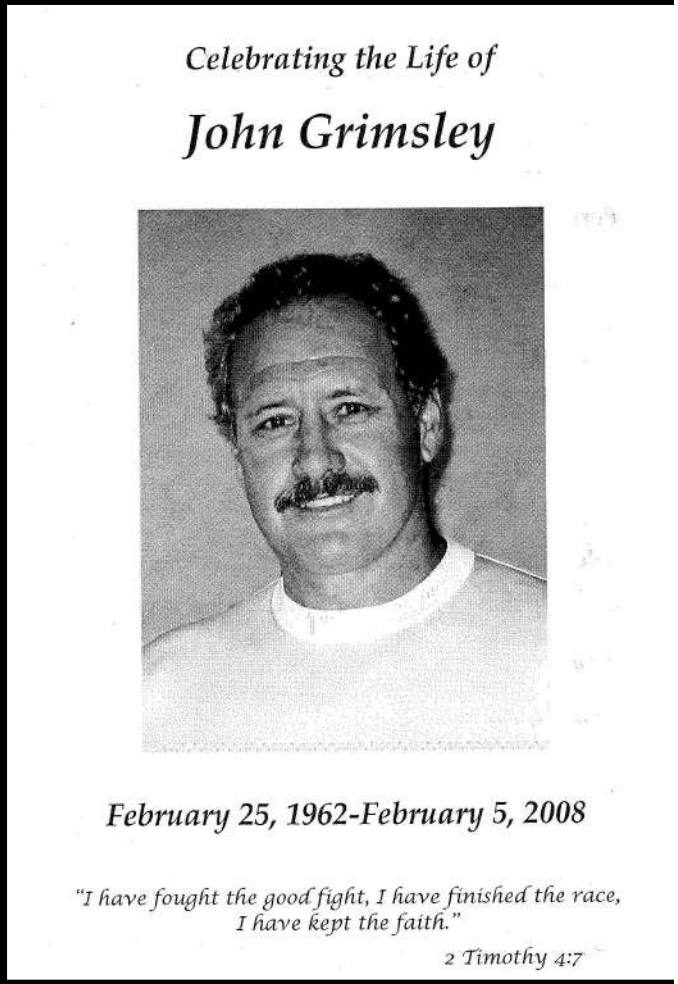
Causes of Dementia

- "Reversible"
  - Hypothyroidism
  - Vitamin B12 Deficiency
  - Clinical (Major) Depression
- Neurodegenerative/Progressive Disease
  - Vascular Dementia/Multi-Infarct
  - Frontotemporal
  - Dementia with Lewy Bodies
  - Alzheimer's Disease (75-80% of all dementia)
  - **Chronic Traumatic Encephalopathy**

First BU NFL Case

John Grimsley - Died at Age 45

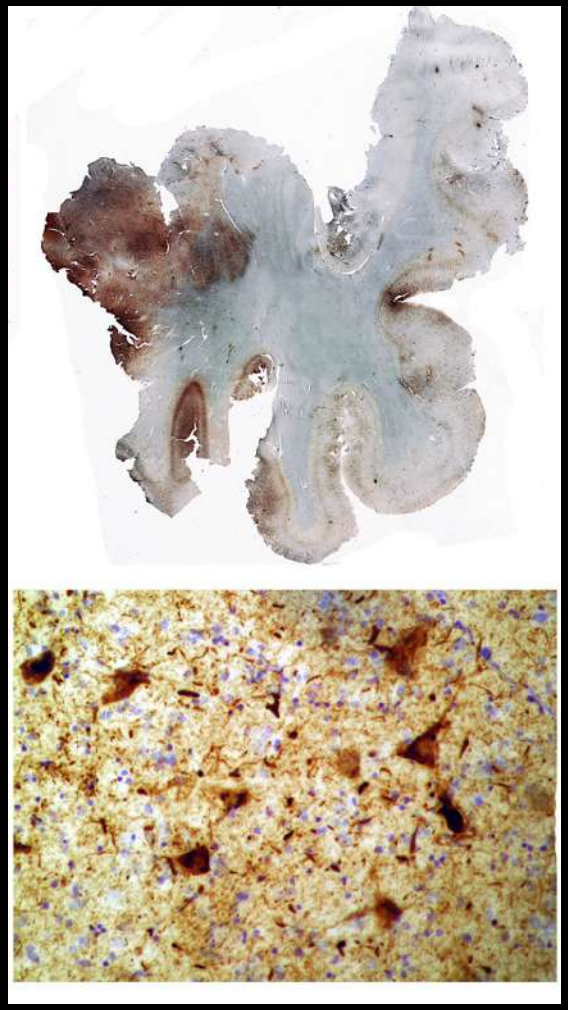
- Houston Oilers 1984-1990; Miami Dolphins 1991-1993; Linebacker; Pro-Bowl, 1988
- At least 8 concussions during NFL career.
- Hunting/Fishing guide post NFL
- For the 5 years prior to death at age 45, he experienced worsening memory and cognitive functioning, as well as increasing “short fuse.”
- Died of gunshot to chest while cleaning gun. Not suicide.



Grimsley - Neuropathology

Photoscan

Microscope



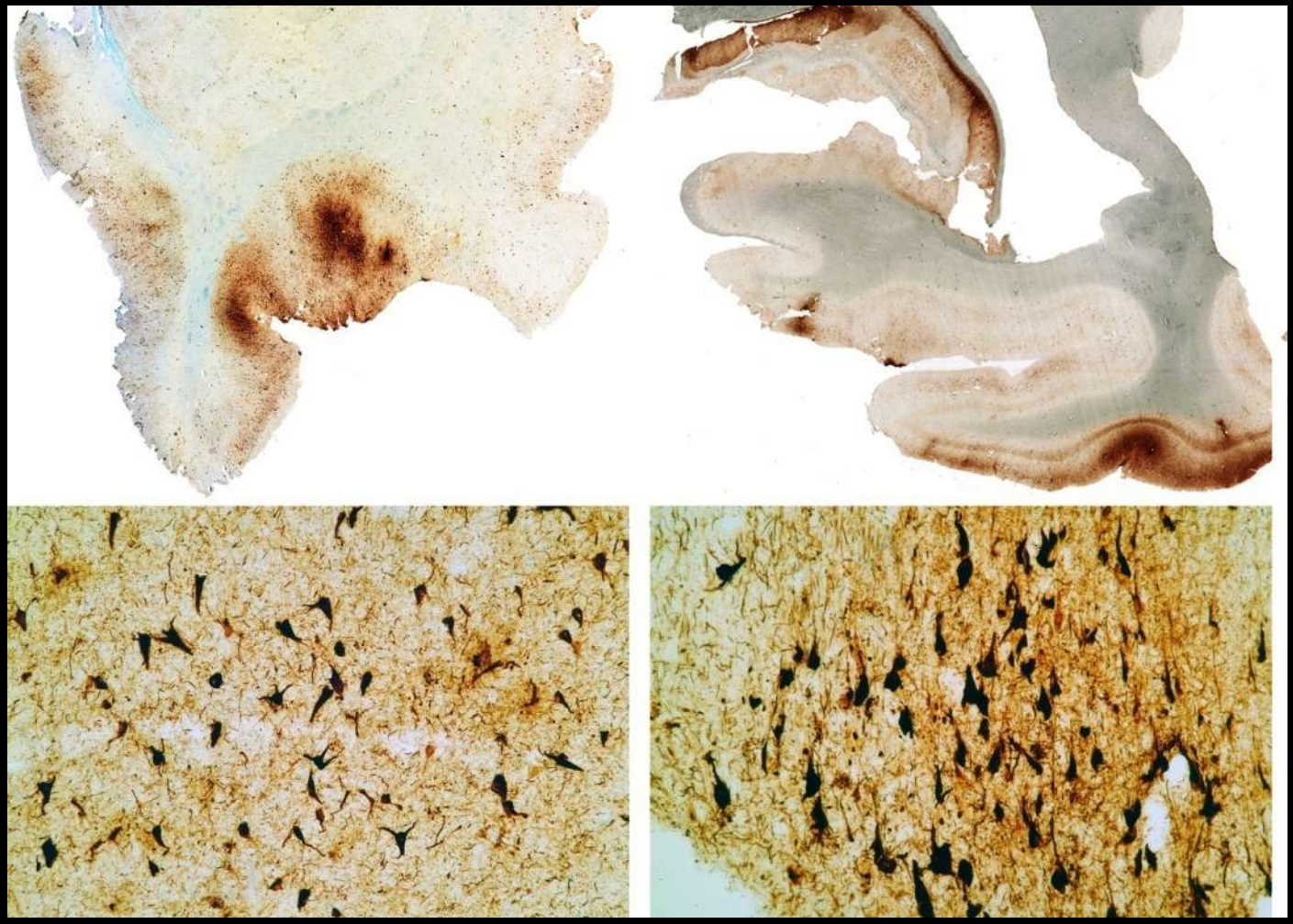
Grimsley 45 yr
old CTE


73

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

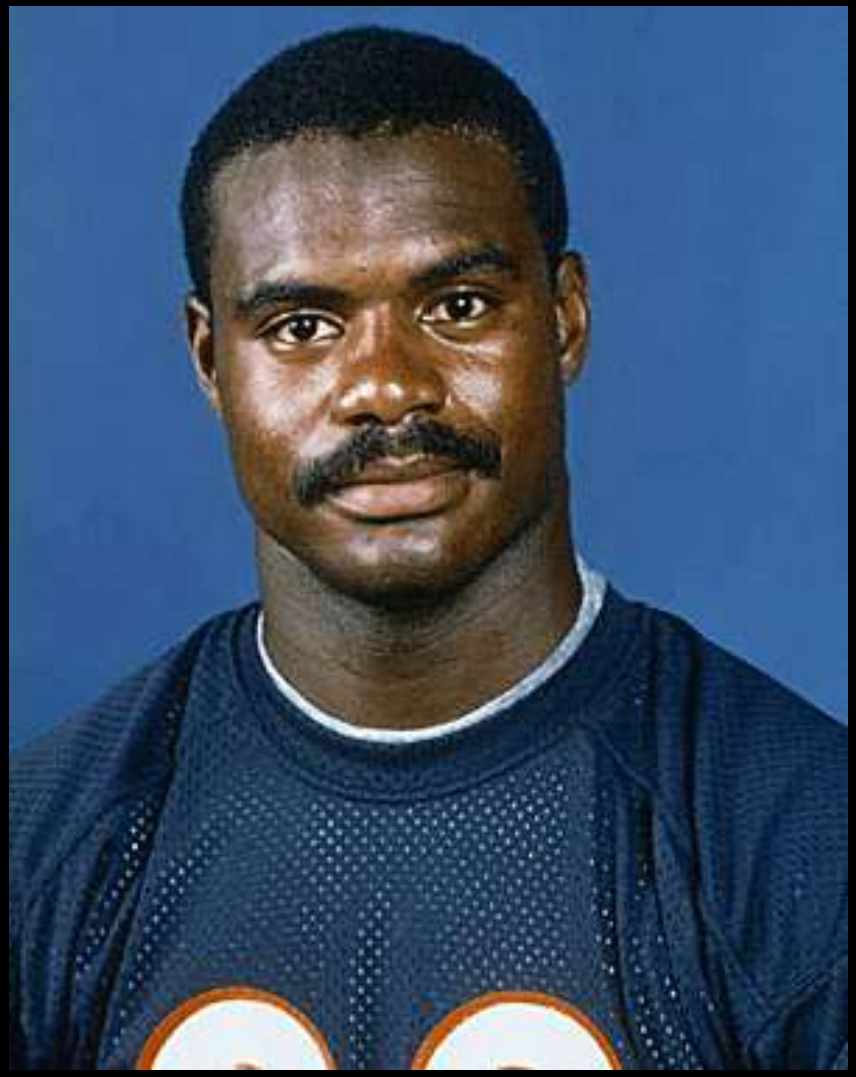
- Nine-year NFL veteran lineman
- Tampa Bay Buccaneer
- No reported concussions, so wife (and we) thought control
- But as lineman had routine subconcussive blows
- Cornell University graduate, successful restaurateur post NFL, husband and father of three boys
- Died due to drug overdose after a multi-year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

McHale - Neuropathology



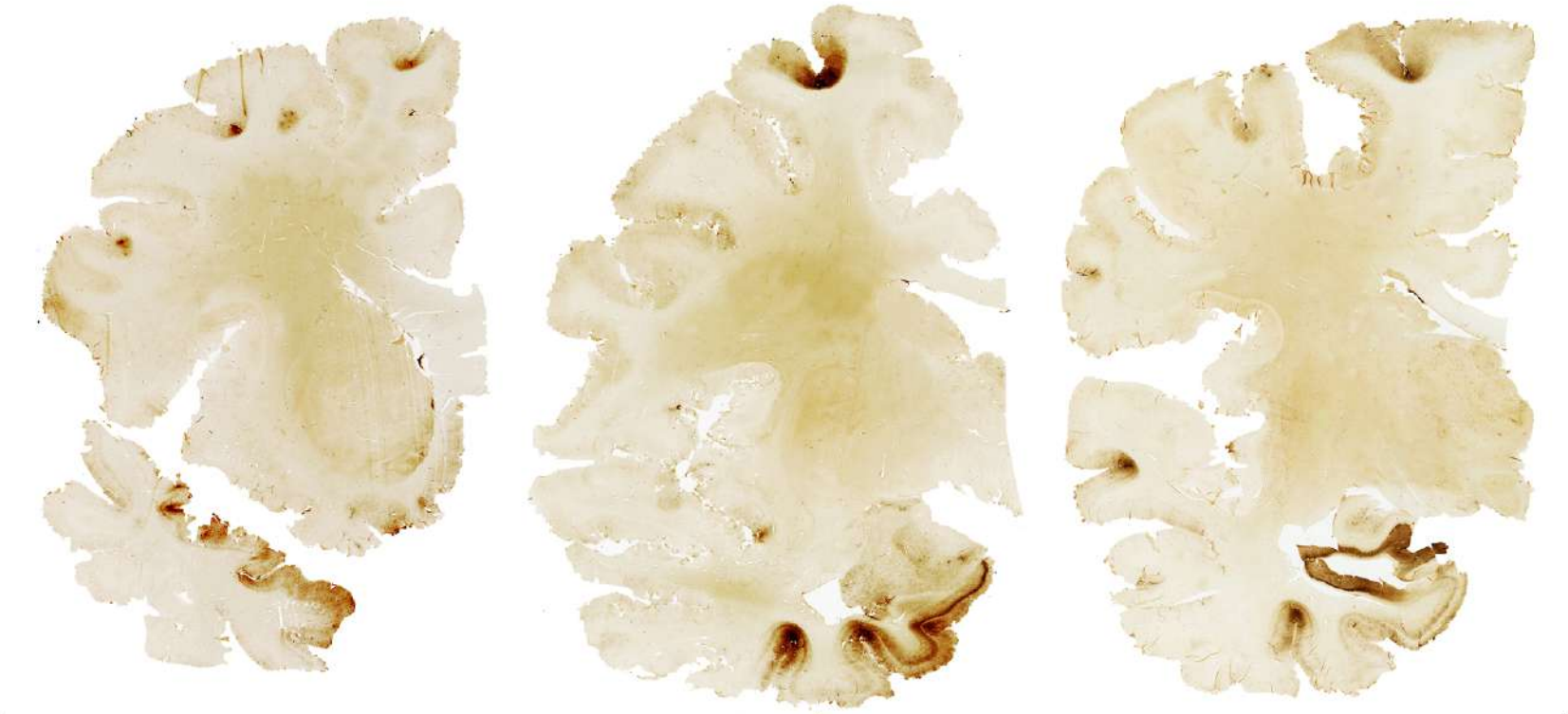
Dave Duerson

November 28, 1960 – February 11, 2011



Duerson's Clinical History

- Long-standing complaints of headaches since NFL and onward.
- Over the ~5 years prior to death, he had worsening short-term memory difficulties, as well as problems with language
- Increasingly out of control:
  - Short fuse, hot tempered, physically abusive, verbally abusive
  - Lost business, wife, and more
- Suicide: Shot himself in chest to save his brain; Suicide Note….



Dave Duerson

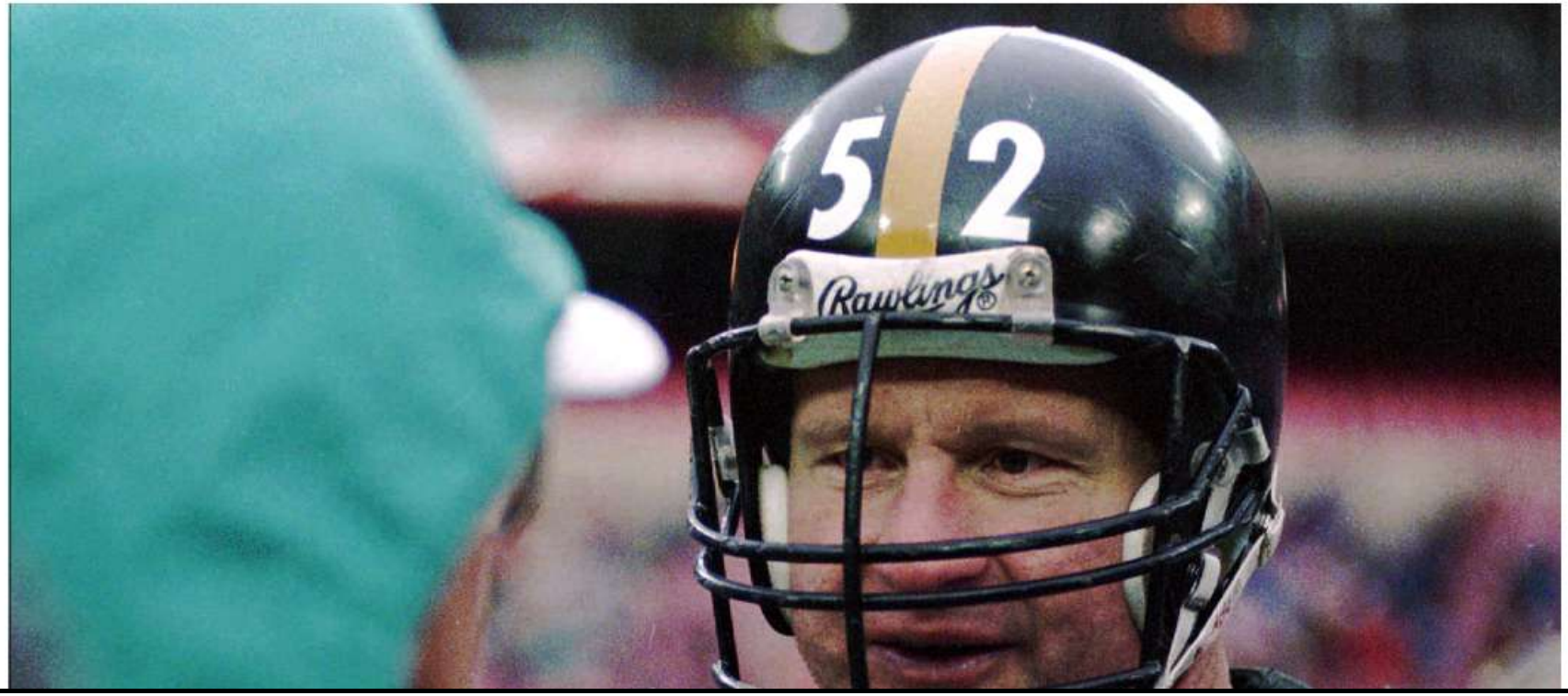
BOSTON UNIVERSITY

Department of Veterans Affairs

sportslegacy INSTITUTE

The N.F.L.'s Tragic C.T.E. Roll Call

Chronic traumatic encephalopathy, a degenerative brain disease, has been found in dozens of former N.F.L. players. Here are some of the most notable cases, along with New York Times coverage. FEB. 3, 2016 | RELATED ARTICLE



Not Just Football

- We have found CTE in ~ 250 individuals, including former pro football players AND in:
  - Boxers (Dementia Pugilistica)
  - Soccer
  - Pro Wrestling
  - Rugby
  - Pro Hockey Players (only enforcers)
    - Reggie Flemming
    - Bob Probert
    - Rick Martin
    - Derek Boogaard

Not Just Pros

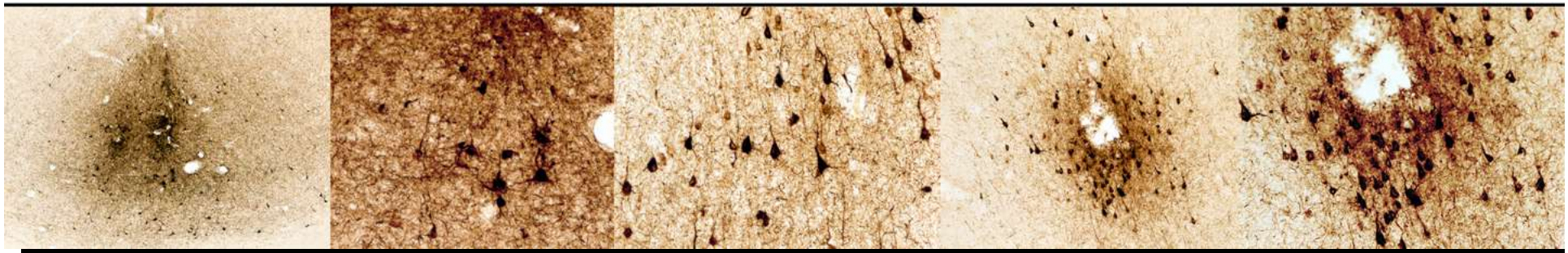
- College Football
- High School Football
- Military
- Ages: 17 through 80’s

Owen Thomas

UPenn Football Co-Captain (Lineman)

Played since age 9; NO Concussions

Owen Thomas
Suicide at Age 21

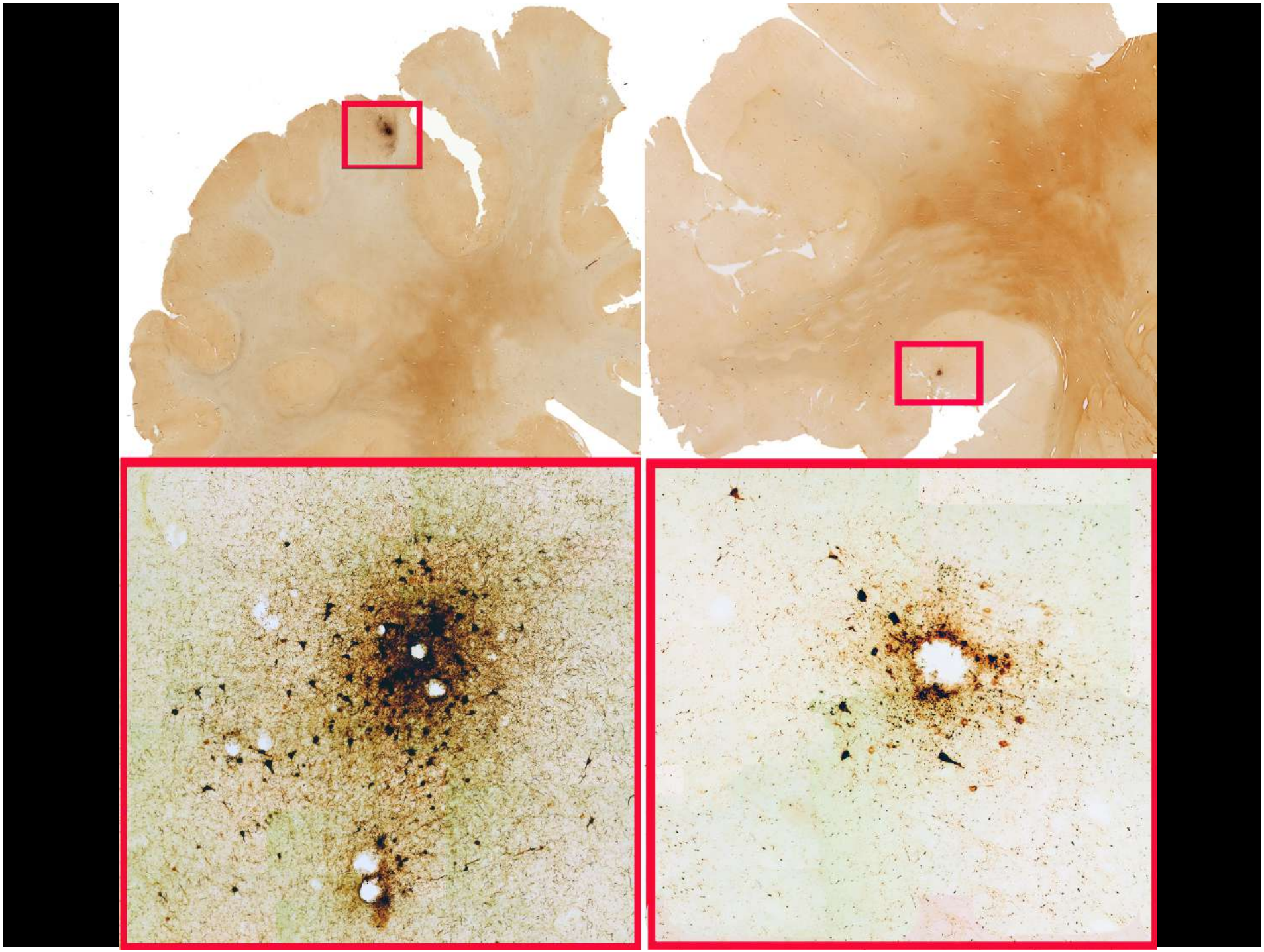


Suicide Caused by CTE?

- 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

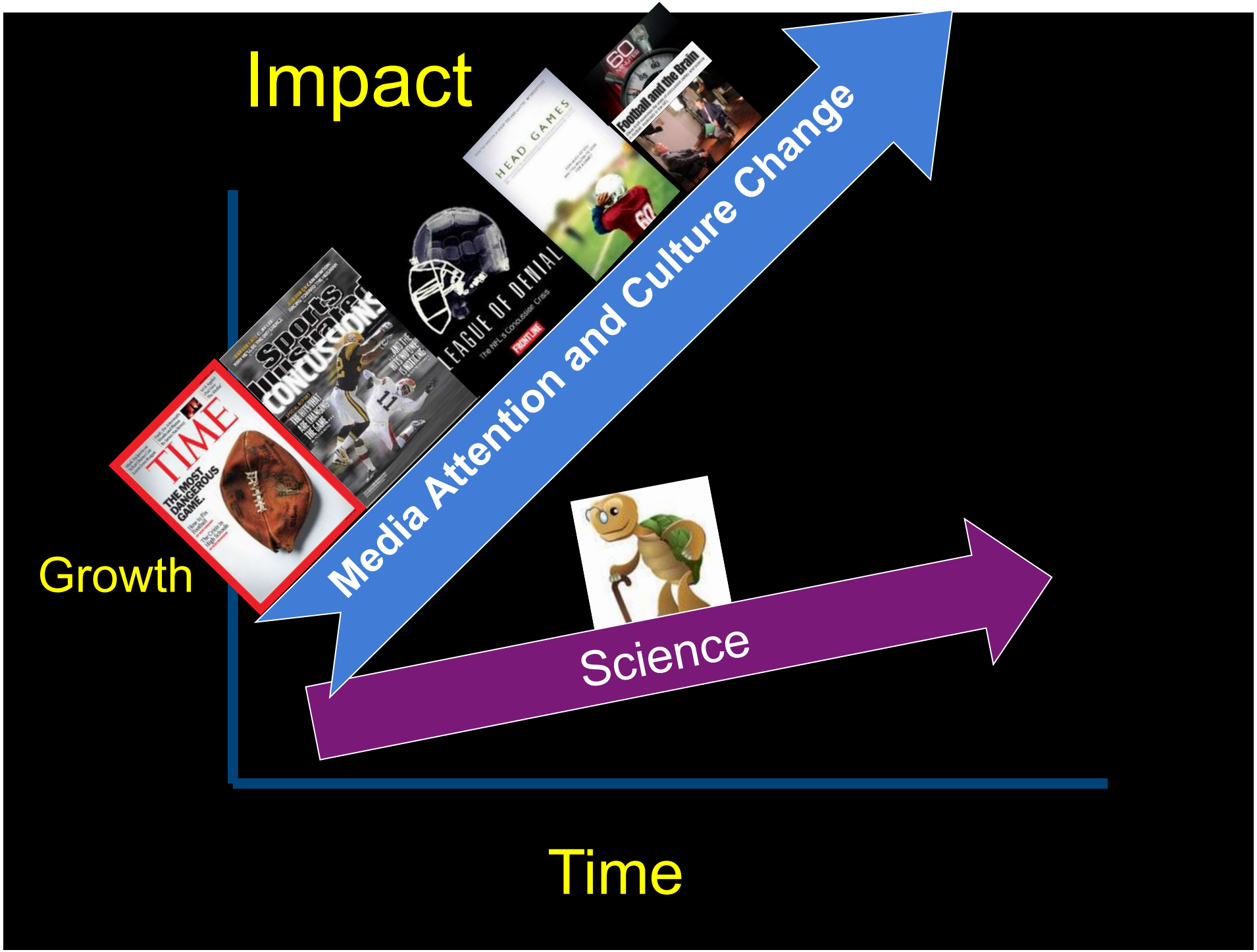
Age 18

HS Athlete



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, as well as new funding for science in the area
- However, the public thinks that the science of CTE is far more advanced than it is


Impact
Growth
Time
Media Attention and Culture Change
Science
TIME
THE MOST DANGEROUS GAME.
Sports Illustrated
CONCUSSIONS
HEAD GAMES
LEAGUE OF DENIAL
FRONTLINE
60 MINUTES
Football and the Brain

Harry's Law: "Head Games"
"BU CTE Researcher"

Law & Order SVU

Dr. Ann McKee

More CTE “Science”

- The Good Wife
- House
- CSI


J. Otte Photography

CTE Science: What We Need to Know

- **Is CTE Common?**
  - We just don't know!
  - "90 of 94 Pro Football players in BU-VA-CLF Brain Bank have had CTE"
  - Biased!!

Mayo Clinic Study

Dr. Dennis Dickson

Bieniek et al., *Acta Neuropathologica*, 2015

- Objective: To determine the presence of CTE in a large brain bank for neurodegenerative disorders for individuals with and without a history of contact sports participation.
- Methods: Available med records of 1721 deceased men reviewed for evidence of past history of TBI or participation in contact sports.

New Mayo Clinic Study
(Bieniek et al., *Acta Neuropathologica*, 2015)

- Results:
  - 21 of 66 former amateur contact sport athletes had the unique tau pathology of CTE
  - CTE pathology was only detected in individuals with documented participation in amateur contact sports

CTE: What We Need to Know

- Why do some people get CTE and others do not?
  - all neuropathologically confirmed cases 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?

Is there a Window of Neurodevelopmental Vulnerability?

Critical Neurodevelopmental Stage – 9-12

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

Age of first exposure to football and later-life cognitive impairment in former NFL players

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ABSTRACT

Objective: To determine the relationship between exposure to repeated head impacts through tackle football prior to age 12, during a key period of brain development, and later-life executive function, memory, and estimated verbal IQ.

Methods: Forty-two former National Football League (NFL) players ages 40–69 from the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study were matched by age and divided into 2 groups based on their age of first exposure (AFE) to tackle football: AFE <12 and AFE ≥12. Participants completed the Wisconsin Card Sort Test (WCST), Neuropsychological Assessment Battery List Learning test (NAB-LL), and Wide Range Achievement Test, 4th edition (WRAT-4) Reading subtest as part of a larger neuropsychological testing battery.

Results: Former NFL players in the AFE <12 group performed significantly worse than the AFE ≥12 group on all measures of the WCST, NAB-LL, and WRAT-4 Reading tests after controlling for total number of years of football played and age at the time of evaluation, indicating executive dysfunction, memory impairment, and lower estimated verbal IQ.

Conclusions: There is an association between participation in tackle football prior to age 12 and greater later-life cognitive impairment measured using objective neuropsychological tests. These findings suggest that incurring repeated head impacts during a critical neurodevelopmental period may increase the risk of later-life cognitive impairment. If replicated with larger samples and longitudinal designs, these findings may have implications for safety recommendations for youth sports. *Neurology*® 2015;84:1–7

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?

JOURNAL OF NEUROTRAUMA 32:1768–1776 (November 15, 2015)

DOI: 10.1089/neu.2014.3822

Age at First Exposure to Football Is Associated with Altered Corpus Callosum White Matter Microstructure in Former Professional Football Players

Julie M. Stamm,[1–3] Inga K. Koerte,[3,4] Marc Muehlmann,[3,4] Ofer Pasternak,[3,15] Alexandra P. Bourlas,[1,5] Christine M. Baugh,[1,6] Michelle Y. Giwerc,[3] Anni Zhu,[3] Michael J. Coleman,[3] Sylvain Bouix,[3] Nathan G. Fritts,[1] Brett M. Martin,[7] Christine Chaisson,[1,5,7,8] Michael D. McClean,[9] Alexander P. Lin,[3,10] Robert C. Cantu,[1,11–13] Yorghos Tripodis,[1,5,8] Robert A. Stern,[1,2,5,11,14,*] and Martha E. Shenton[3,15,16,*]

Region II:

Premotor/
Supplementary
Motor

Region III:

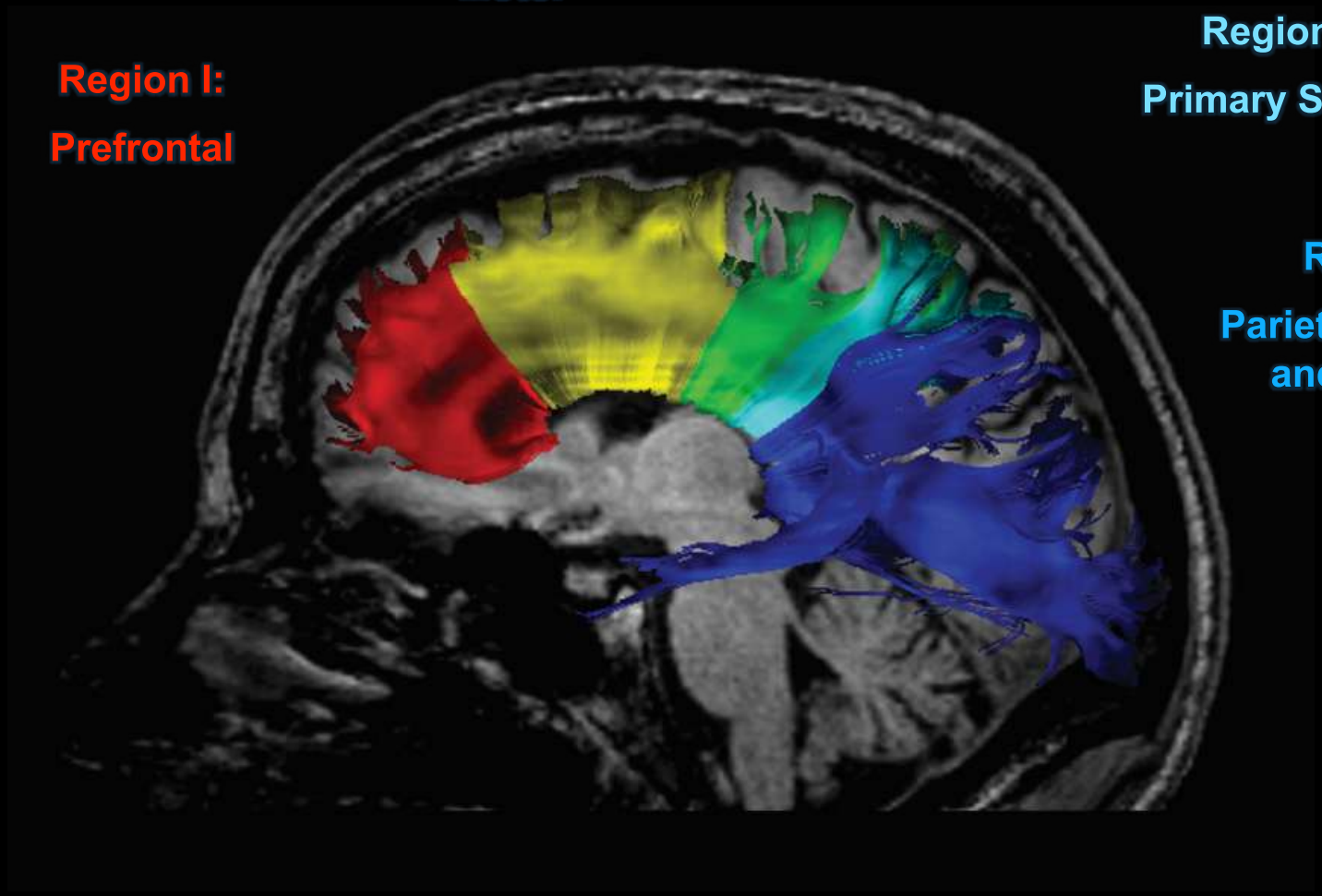
Primary Motor

Region IV:

Primary Sensory

Region I:

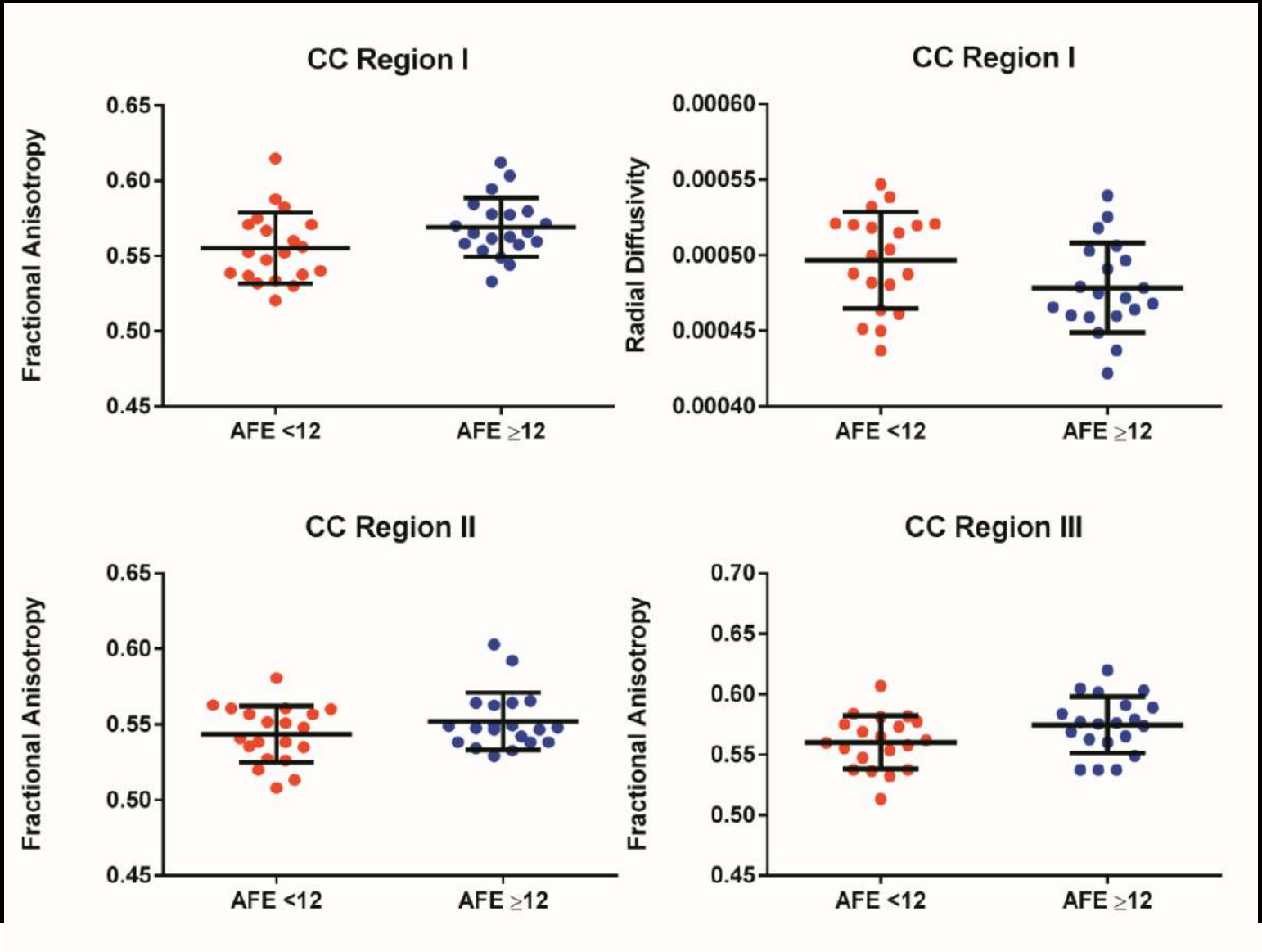
Prefrontal



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 Ingegrity

- 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

Many Limitations!

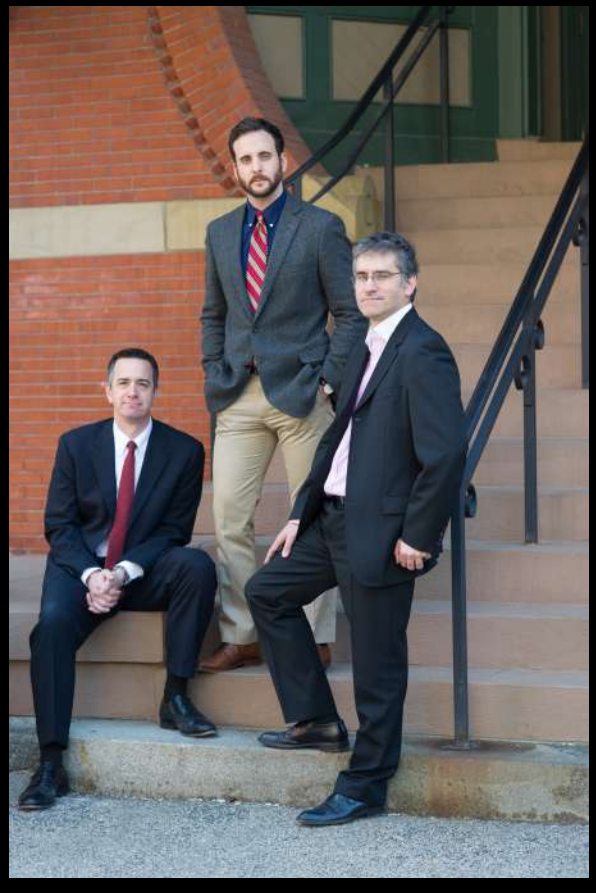
- Very unique cohort of former professional football players in middle age
- What about those who only played through HS or College?
- Are there different eras? That is, is the game played differently now than 30 years ago?
- Does not indicate CTE
- Is that adequate evidence to stop youth tackle football?


20

Next Step in Examining Exposure

- Study individuals who only had high school or college exposure to football (Not Pros)
- Estimate Cumulative Head Impact Exposure

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



Journal of Neurotrauma (2016)

Montenigro, Alosco, Martin, Daneshvar, Mez, Chaisson, Nowinski, Au, McKee, Cantu, McClean, Stern,* Tripodis*

Montenigro et al. (2016)

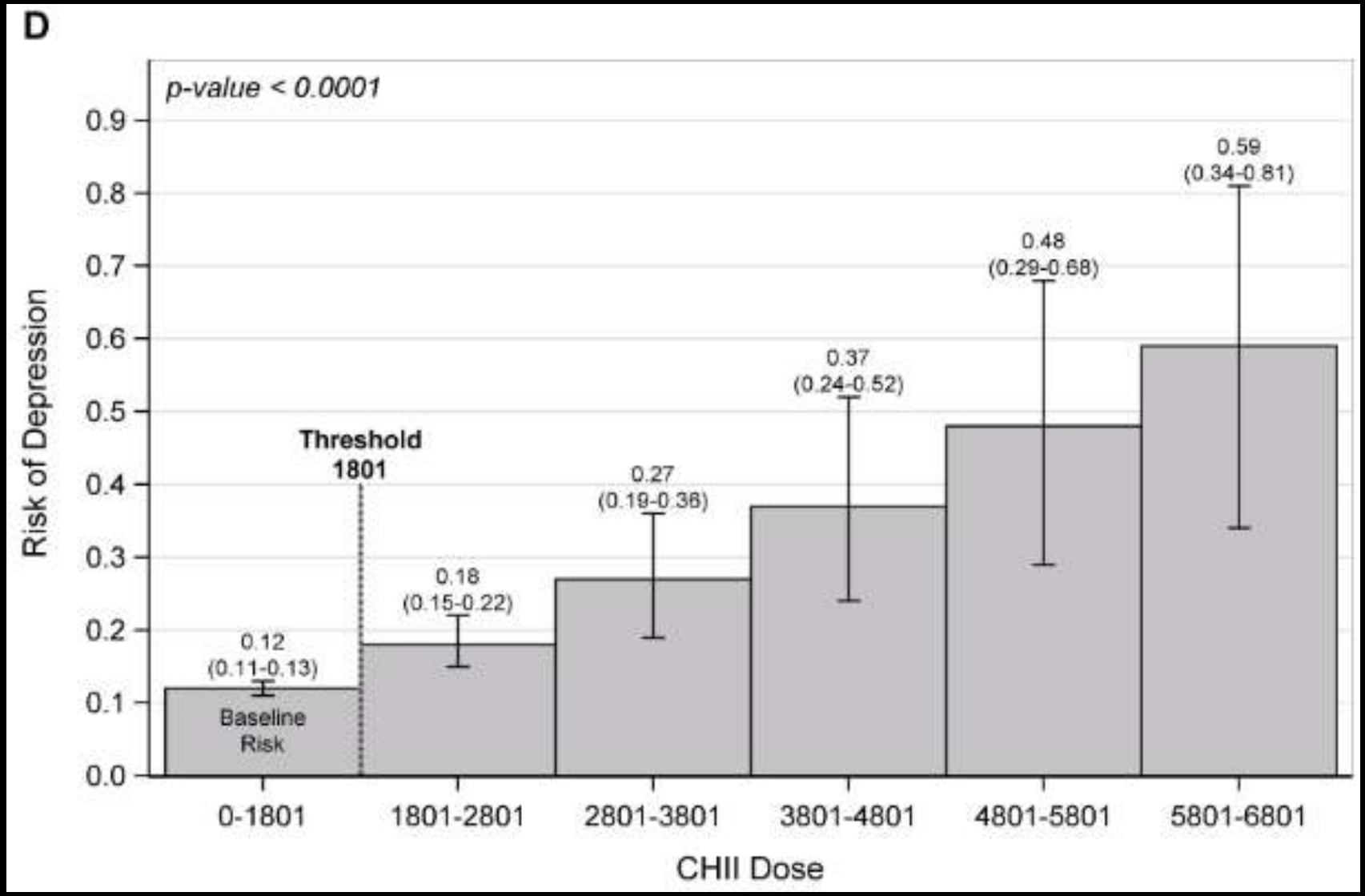
- Objectives:
  1. To develop a metric to quantify cumulative RHI exposure from football, that we term the *Cumulative Head Impact Index* (CHII)
  2. To use the CHII to examine the association between RHI exposure and long-term clinical outcomes

  ➢NOT a Study of CTE

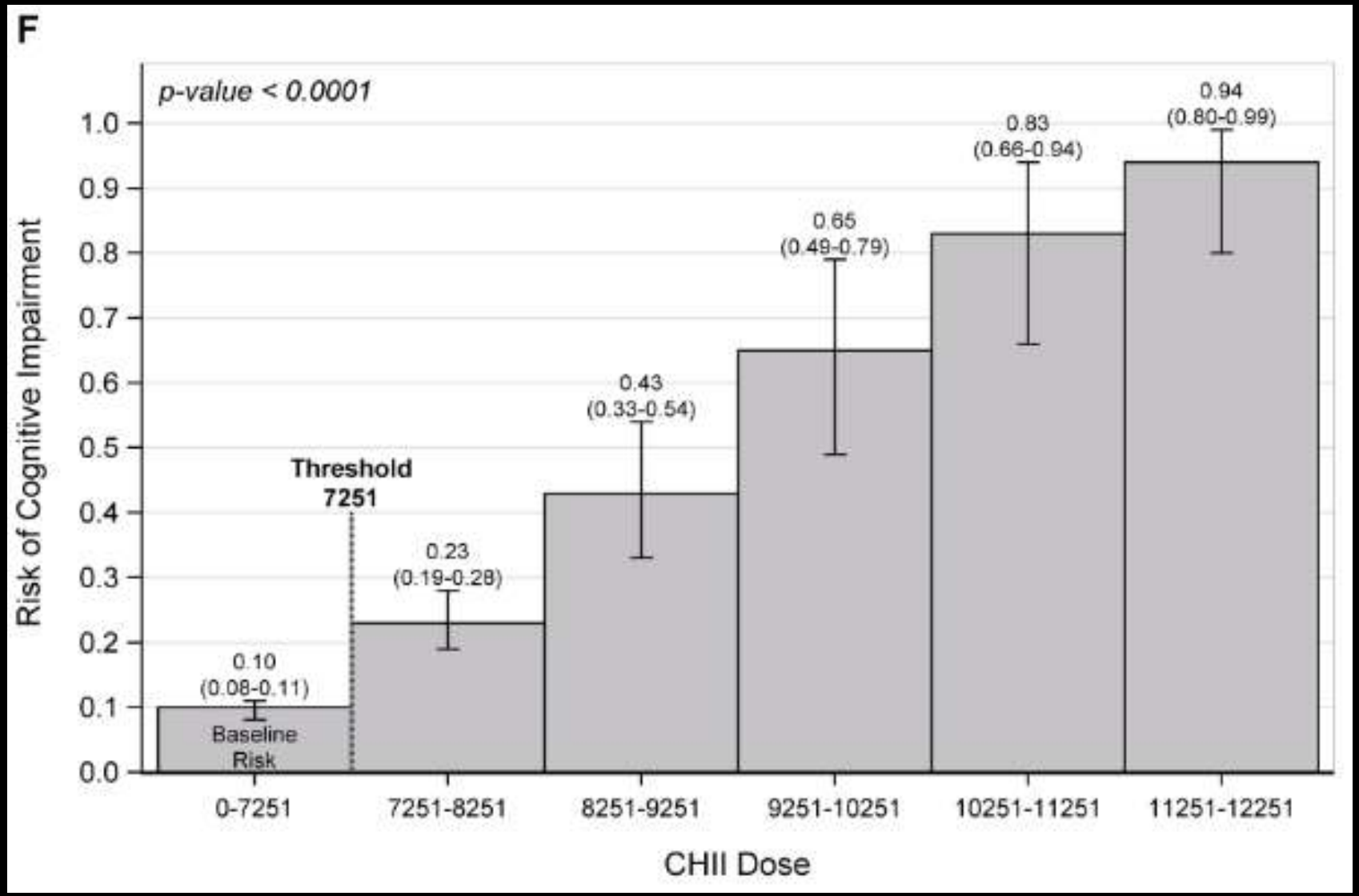
Montenigro et al. (2016)

- 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

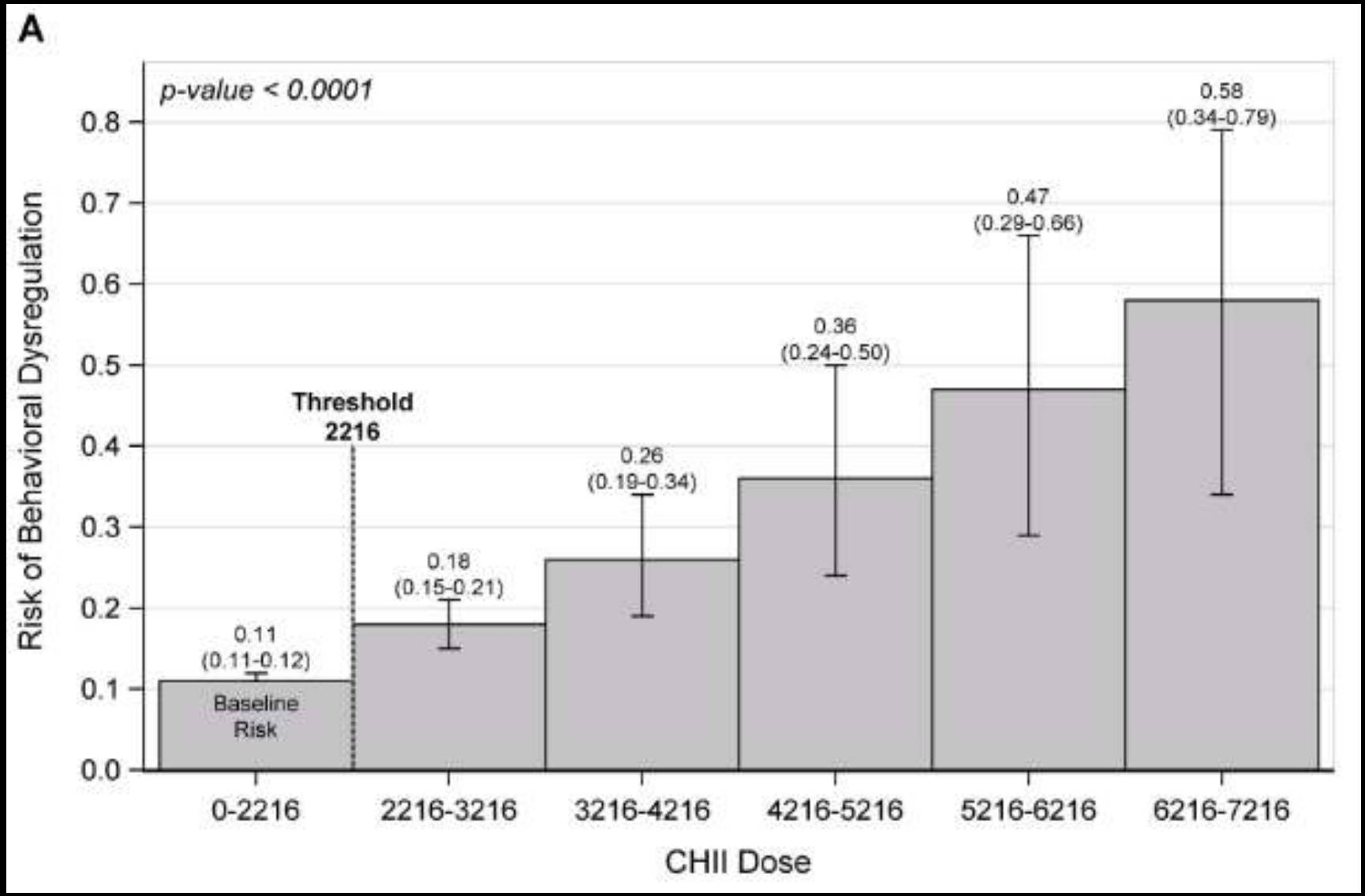
Montenigro et al (2016)



Montenigro et al (2016)

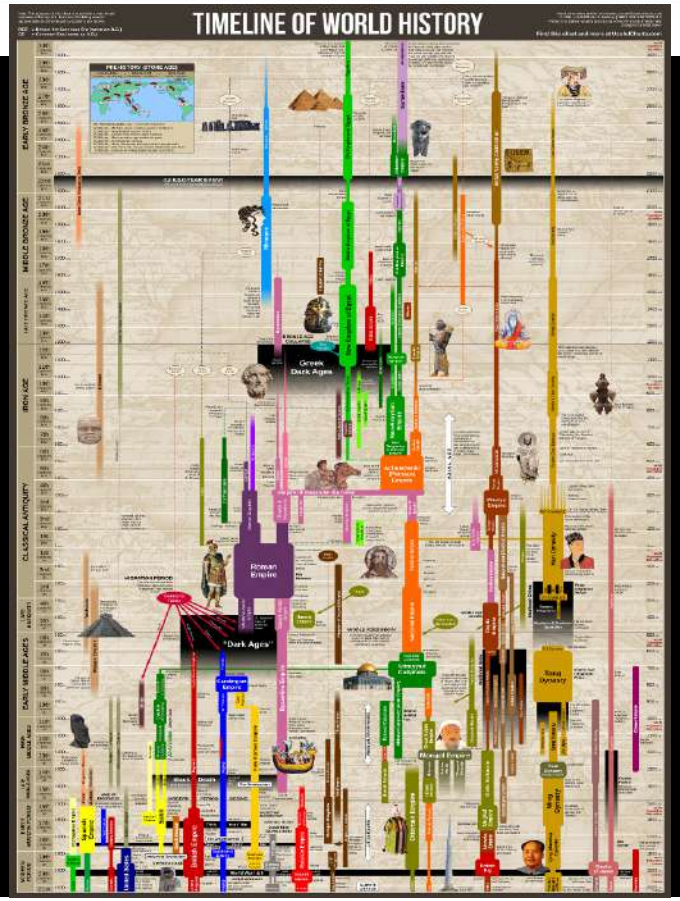


Montenigro et al (2016)



Time for a Break
Anthropology Lesson

Humans Have Been Around for 200,000 Years



History of Humans Incurring Repetitive Head Impacts?

- Padded boxing gloves
  - 1950's
- Hard football helmets with facemasks
  - 1950's-1960's
- Youth tackle football
  - Late 1960s – Early 1970s

CTE and Public Health?

- The first individuals who played college football with hard plastic helmets and facemasks are now only in their mid-70's
- The first individuals who began playing tackle football prior to high school are now only in their late 50's to early 60's
- In the 200,000 year history of humankind, it is only in the last 50-75 years that we hit our heads repeatedly and allowed our children to do so as well
- We just don't know what lies ahead…

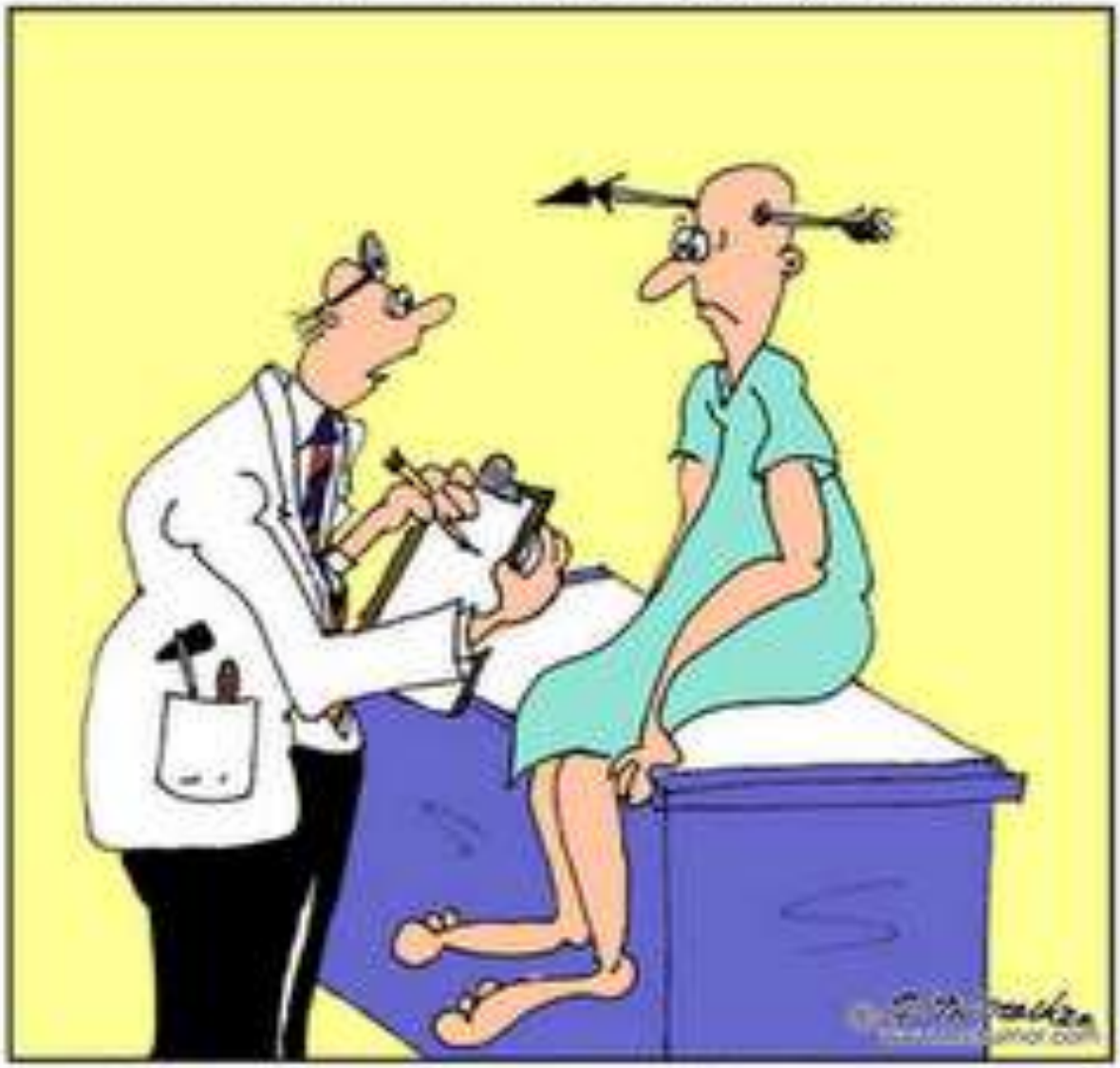
Diagnosis of CTE During Life is the Critical Next Step

- Differentiate between CTE and other causes of cognitive and behavioral change, including Alzheimer's disease, Frontotemporal Dementia, PTSD, persistent symptoms from previous repetitive or single mTBI, "routine" 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
- Begin clinical trials for treatment and prevention

Steps Required to Diagnose CTE During Life

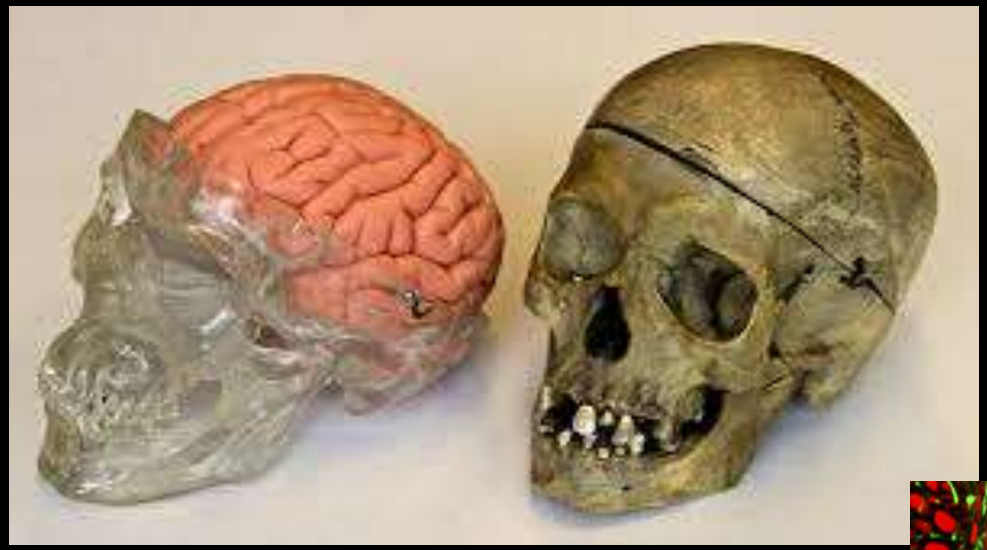
1. Describe the clinical features associated with neuropathologically confirmed CTE
   - Stern et al. (2013). Clinical presentation of Chronic Traumatic Encephalopathy. *Neurology*, 81:1122-1129.
2. Develop and begin to refine clinical diagnostic criteria
   - Montenigro et al. (2014). Clinical subtypes of chronic traumatic encephalopathy: Literature review and proposed research diagnostic criteria for Traumatic Encephalopathy Syndrome. *Alz Res Therapy*, 6:68.
   - Mez et al. (2015). Assessing clinicopathological correlation in chronic traumatic encephalopathy: rationale & methods for the UNITE study. *Alz Res Therapy*, 7, 62
3. Develop potential "biomarkers"

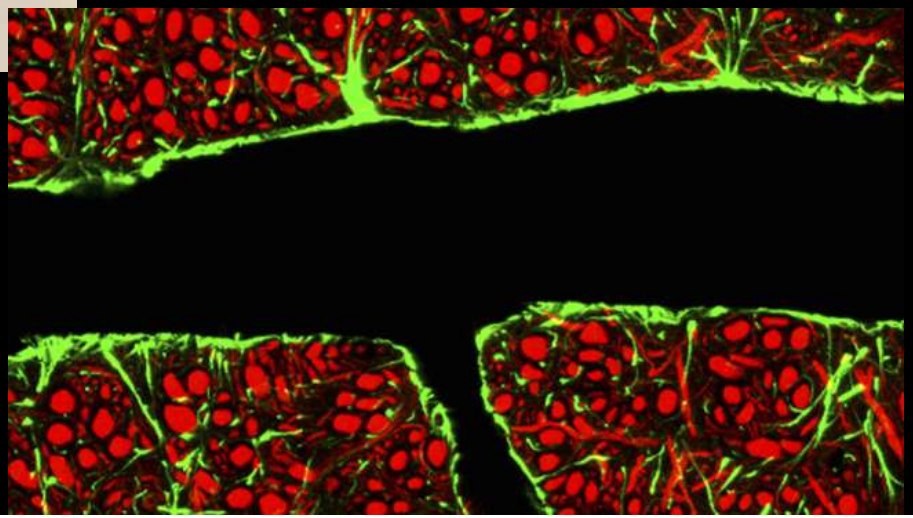
McHUMOR by T. McCracken



“Off hand, I’d say you’re suffering from an arrow through your head. But, just to play it safe, I’m ordering a bunch of biomarker tests.”

The Brain is the Only Part of the Body that Cannot Easily be Tested for Injury or Disease



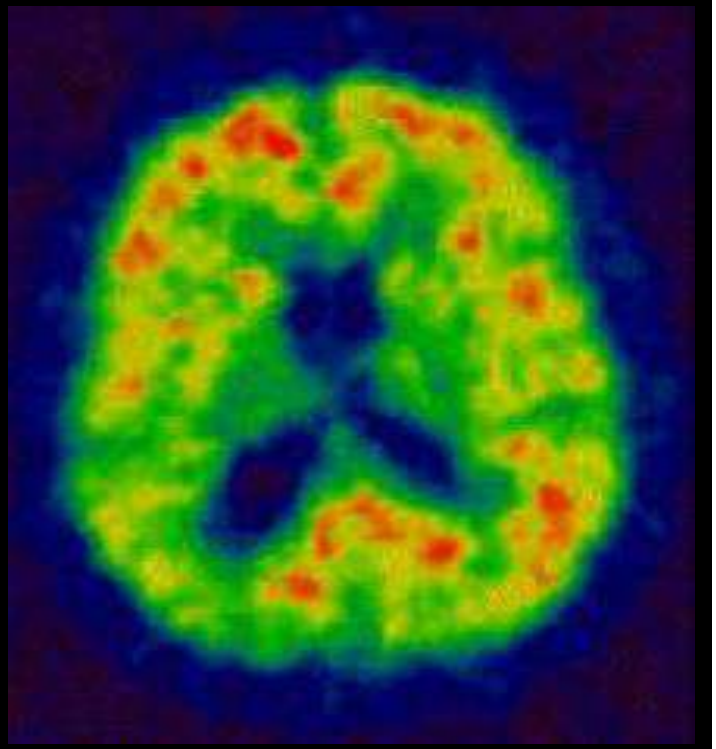


Biomarkers

- Objective biological tests of an illness, injury, condition, disease
  - Heart = EKG, cholesterol, blood pressure
  - Diabetes = blood sugar, HA1C
  - Pneumonia = Chest X-ray
  - Cancer = biopsy
  - Orthopedic injury = X-ray/MRI
  - Kidney disease = blood tests
  - Liver disease = blood tests
- Great Strides in biomarker development for Alzheimer's disease over the past decade

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

+



Biomarker Development
Step One

- Develop a great acronym!

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

Principle 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

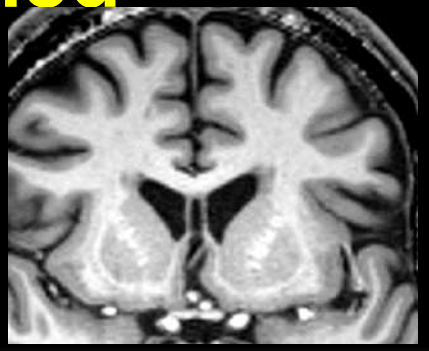
- ~100 former NFL players (CTE High Risk)
  - ages 40-69
  - positions with highest exposure to RHI
  - currently symptomatic
- 30+ controls (CTE No Risk)
  - same age
  - no brain trauma exposure
- Last DETECT Subject - October 2015

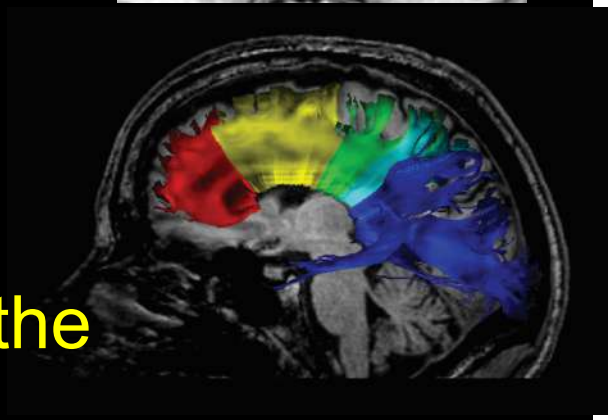
DETECT Study - Measures

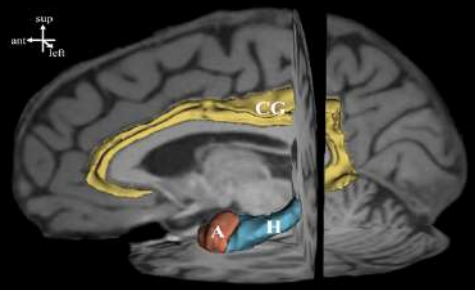
- Neuroimaging (MRI, DTI, SWI, fMRI, MRS, etc.)
  - *Shenton, Koerte, and Lin (BWH, Harvard)*
- Lumbar Puncture (CSF Tau, beta amyloid)
- EEG (BrainScope)
- Genetics (APOE, MAPT, etc.)
- Clinical Exams (Neuro, Cognitive, Psych, Motor)
- When we started, there were no measures of blood tau or brain tau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

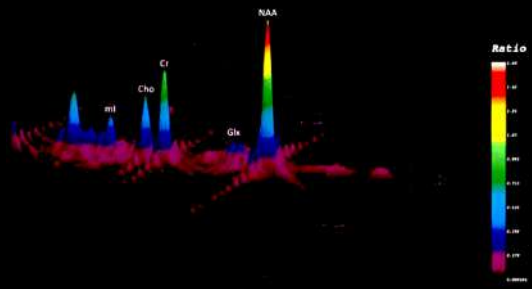
Several Important Findings from the DETECT Study Using MRI/MRS Published or to-be-Published

- 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





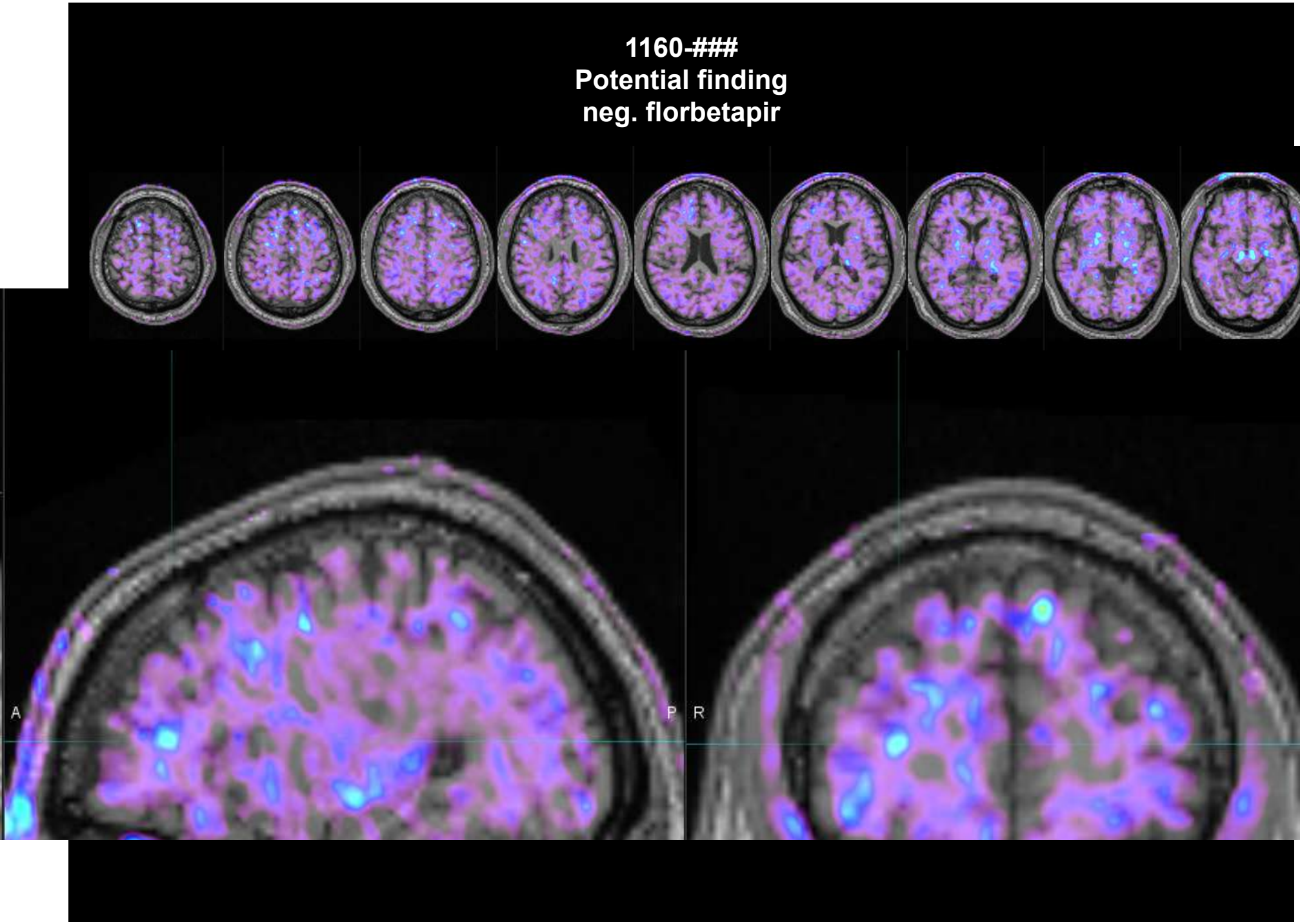




DETECT PET Study

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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Potential finding
neg. florbetapir
A
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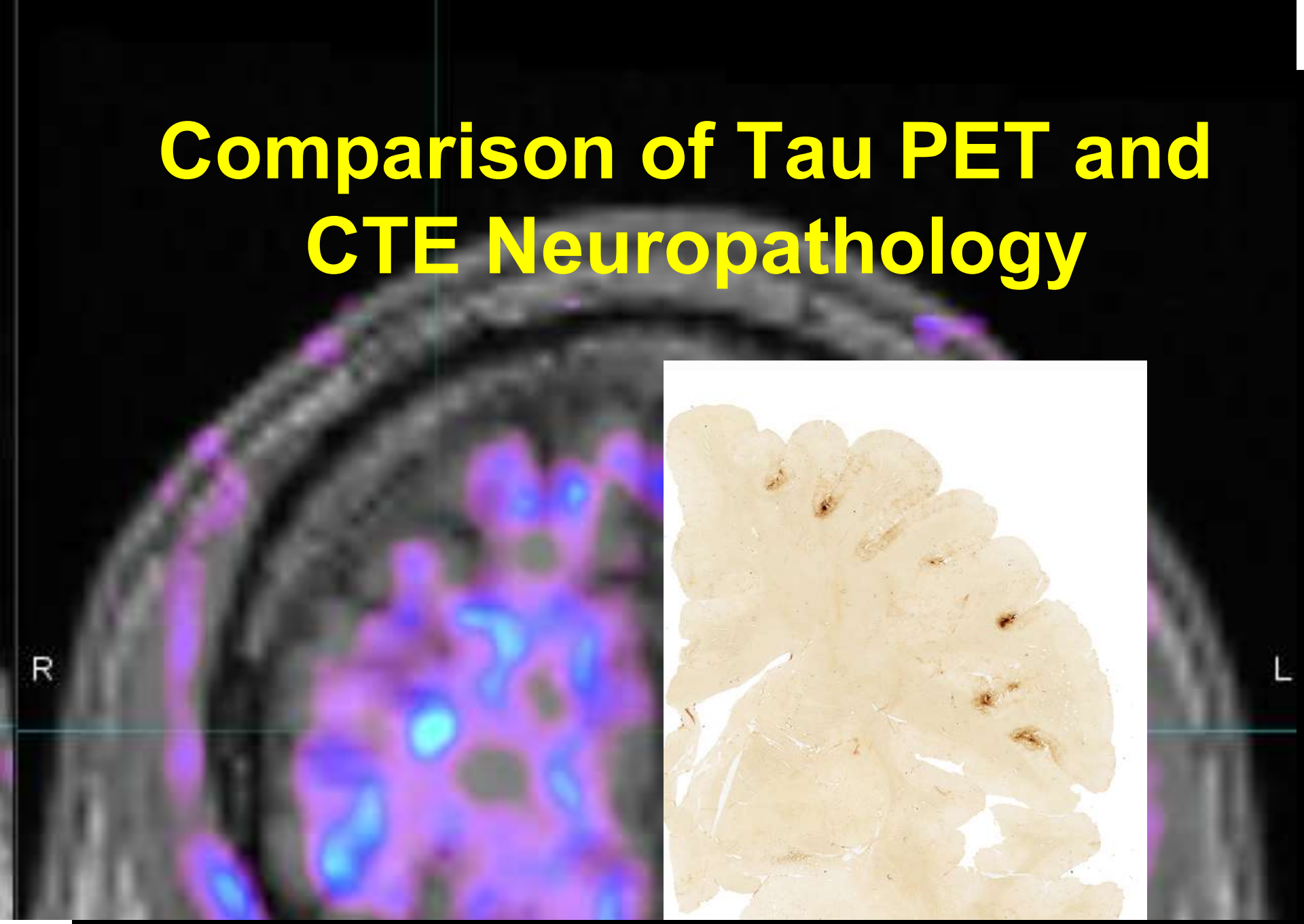
Comparison of Tau PET and CTE Neuropathology

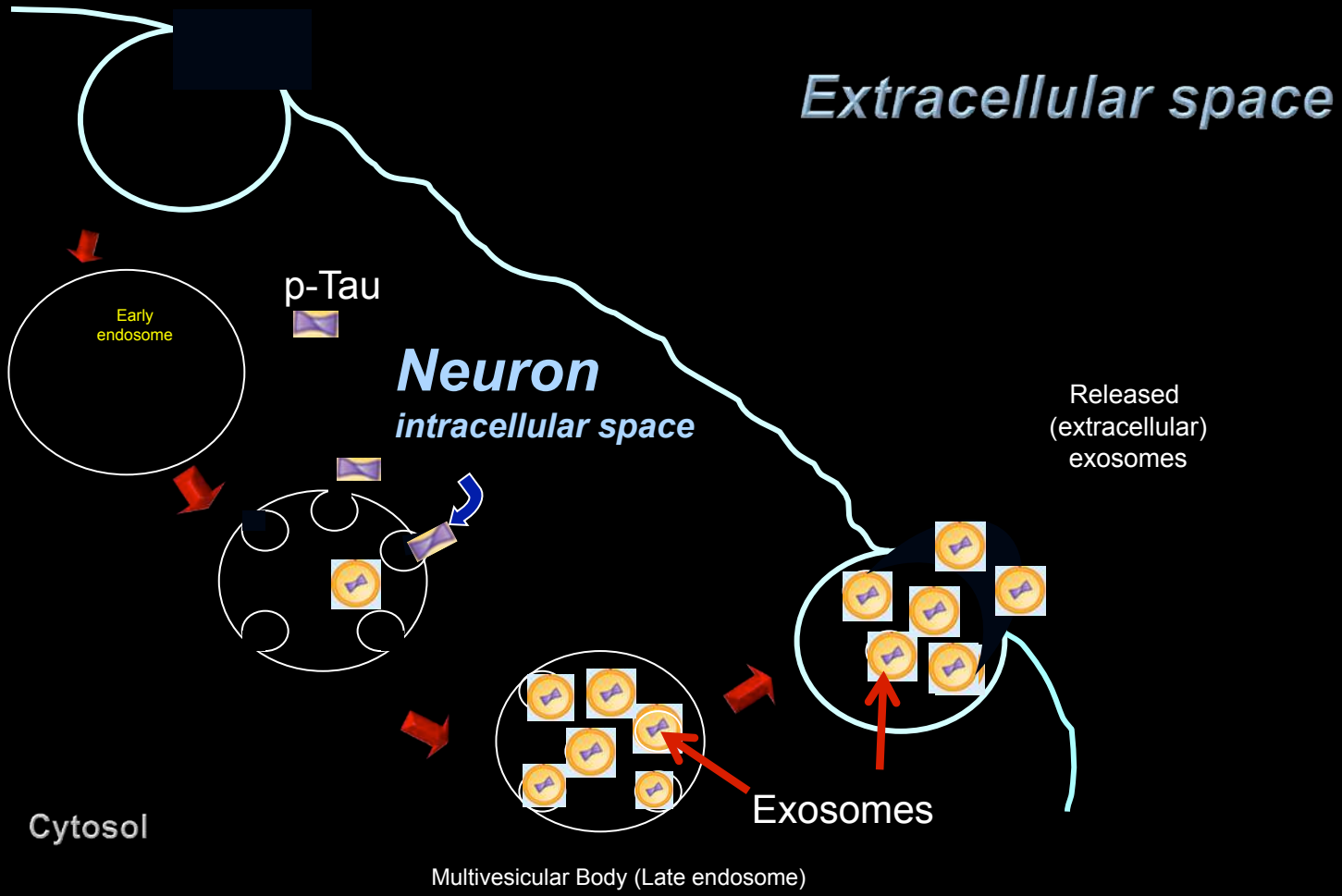


A Blood Test???

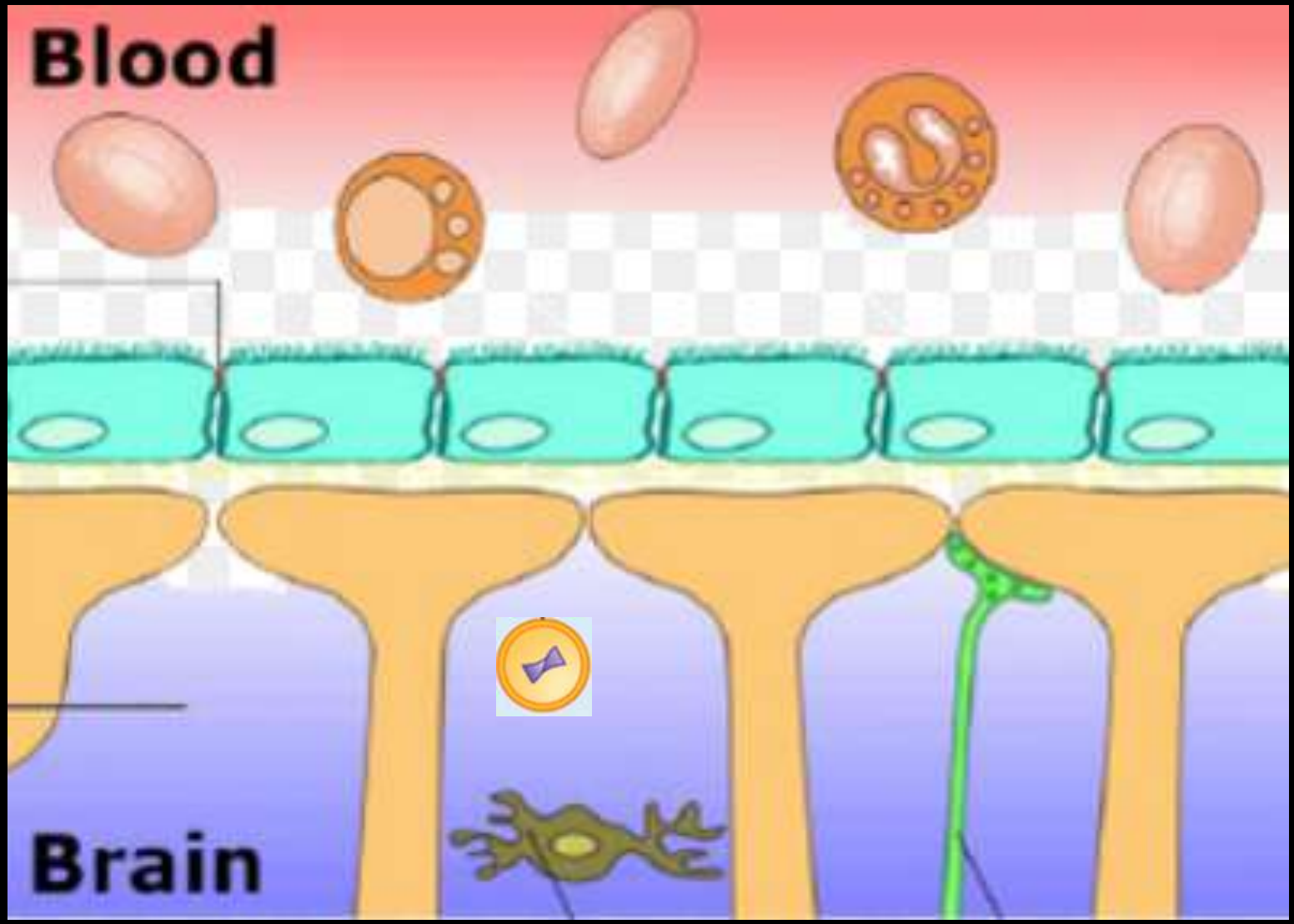
Plasma Exosomal Tau

- 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
- Very stable and make a “liquid” biopsy possible
- And…they cross the blood-brain barrier!

Generation of Neuronal Exosomes



Exosomes Cross BBB



Isolate Brain-Derived Exosomes from Plasma

"Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy"

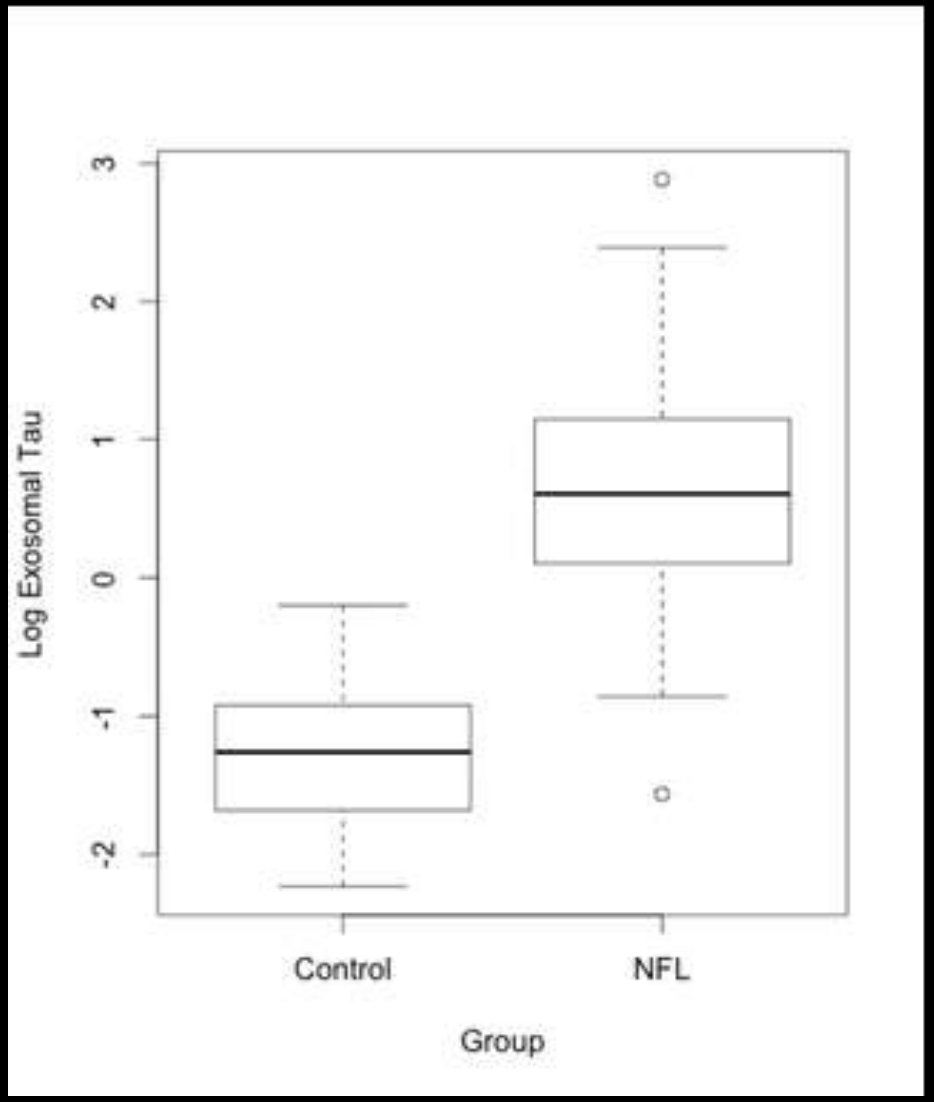
Stern, Tripodis, Baugh, Fritts, Martin, Chaisson, Cantu, Joyce, Shah, Ikezu, Zhang, Gercel-Taylor, & Taylor

J Alzheimer's Disease, 2016

- 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 ($p < .0001$)

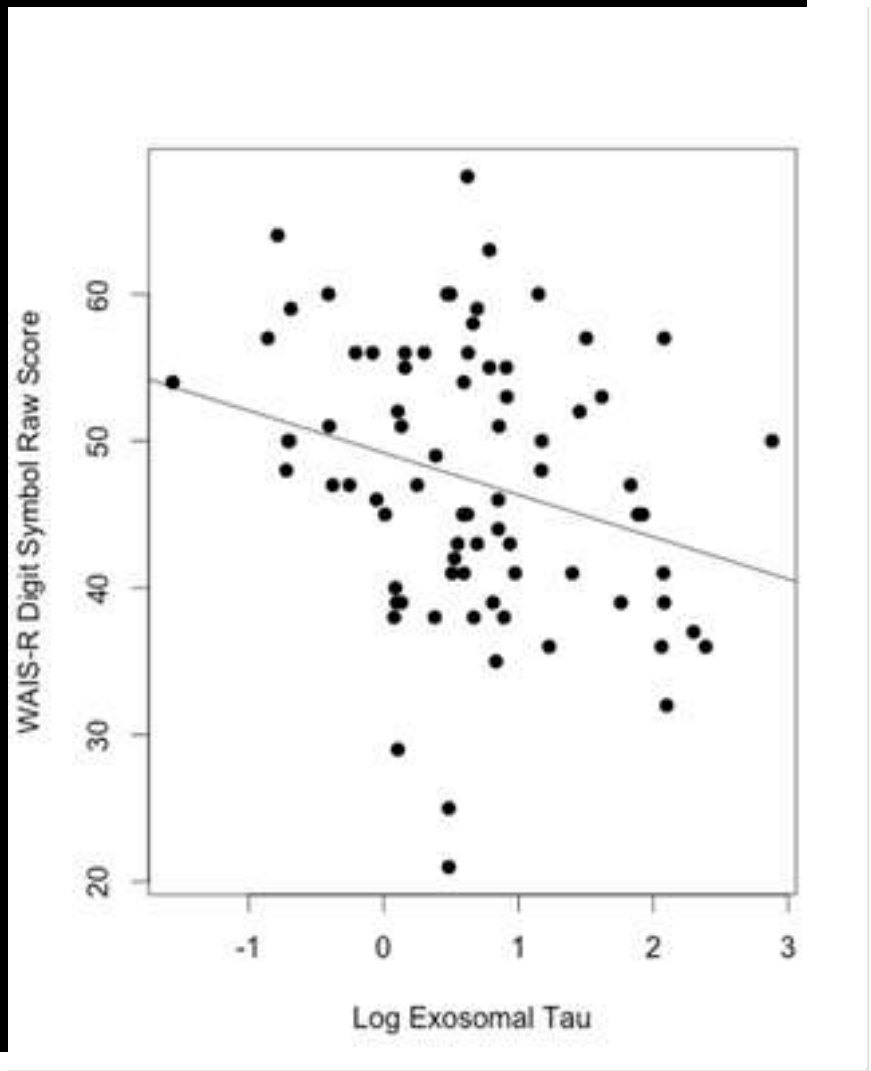


Stern et al. (2016)
Plasma Exosomal Tau

- Within the NFL group, higher exosomal tau associated with:

❖worse memory (p = 0.01)

❖worse psychomotor speed (p = 0.01)



Stern et al. (2016) 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

"Repetitive Head Impact Exposure and Later-Life Plasma Total Tau in Former NFL Players"

Alosco, Tripodis, Jarnagin, Baugh, Martin, Chaisson, Estochen, Song, Cantu, Jeromin, & Stern

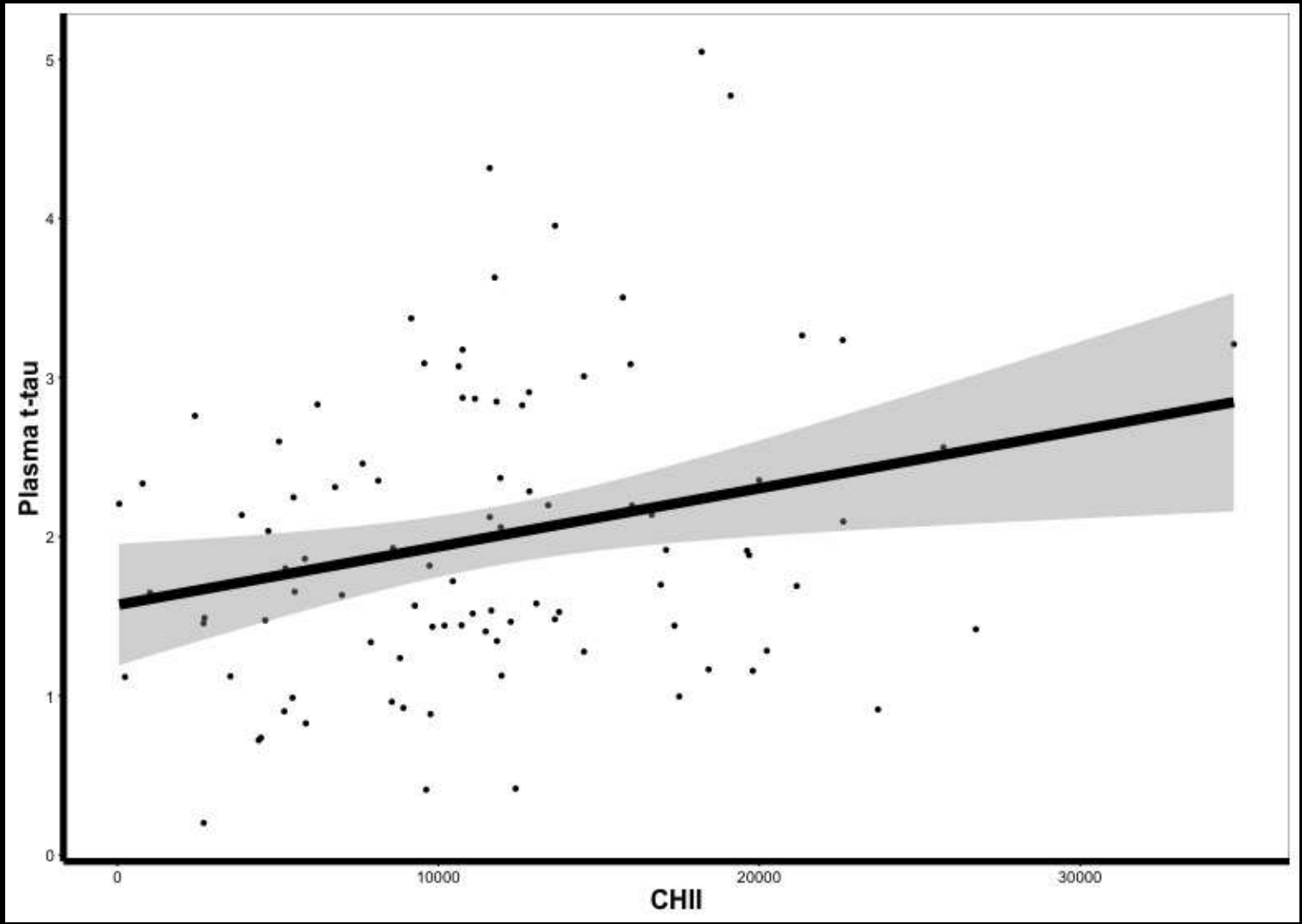
(manuscript is currently under review)

- 96 former NFL players (ages 40-69) and 25 same-age controls from DETECT
- Plasma total tau (t-tau) Simoa HD-1 analyzer (Quanterix)
- Cumulative Head Impact Index (CHII) 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)



Plasma t-tau Study (cont)

- Plasma t-tau is a general marker of neuronal injury
- New Simoa “kits” being developed to measure the “bad tau” in plasma

Next Step:
Develop another Great Acronym

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

*Not the NFL…

rd

Advisory Board

David Knopman, M.D., **Advisory Board Chair** Professor of Neurology, Mayo Clinic	**Thomas McAllister, M.D.** Chair, Department of Psychiatry Albert Eugene Stern Professor of Clinical Psychiatry; Indiana University School of Medicine
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Mike Haynes Member of Pro Football Hall of Fame President and founder, Mike Haynes & Assoc.	**Michael Weiner, M.D.** Professor of Medicine, Radiology, Psychiatry, and Neurology; University of California San Francisco

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

Aims
DIAGNOSE CTE Research Project

1. To collect and analyze neuroimaging and fluid biomarkers for the *in vivo* detection of CTE
2. To characterize the clinical presentation of CTE
3. To examine the progression of CTE over a three-year period
4. To refine and validate diagnostic criteria for the clinical diagnosis of CTE
5. To investigate genetic and head impact exposure risk factors for CTE
6. To share project data with researchers across the country and abroad

Who will be studied?

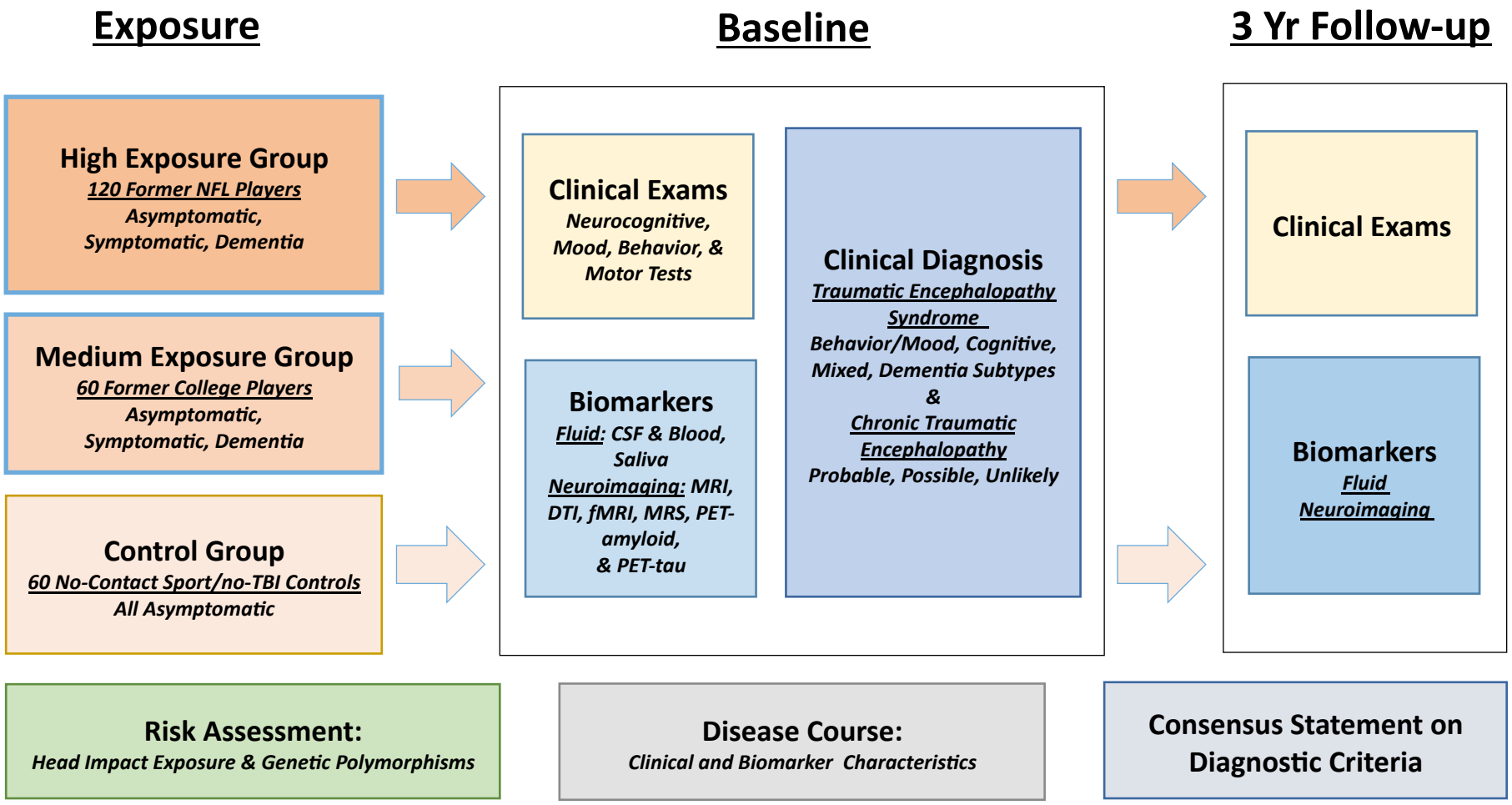
- Males between 45-74 years old
- Three groups based on history of exposure to repetitive head impacts
  - 120 Former NFL Players
    - No Symptoms
    - Mild Symptoms
    - Dementia (impaired daily functioning)
  - 60 Former College Football Players (no other contact sports)
    - No Symptoms
    - Mild Symptoms
    - Dementia
  - 60 Controls (no contact sports, TBI, mTBI, Military)
    - No Symptoms
- Spread the Word!!!!
  - www.diagnosecte.com

Where will participants be evaluated?

Arizona Mayo Clinic-Scottsdale Site PI: C. Adler • PET scans at Banner Alzheimer's Institute, Phoenix	**Boston** BU School of Medicine Site PI: R. Stern • MRI's at Brigham and Women's Hospital
Las Vegas Site PI: C. Bernick Cleveland Clinic Lou Ruvo Center for Brain Health	**New York** Site PI: L. Balcer New York University Langone Medical Center

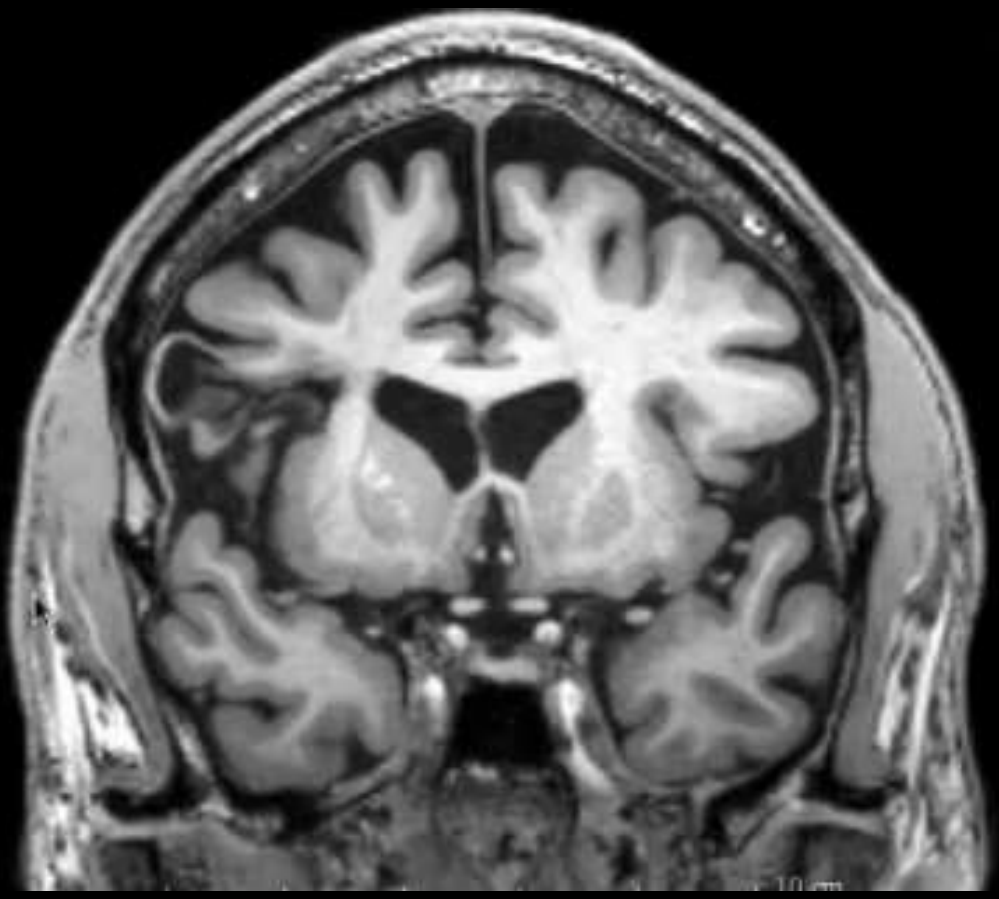
DIAGNOSE CTE Research Project

Study Design Overview



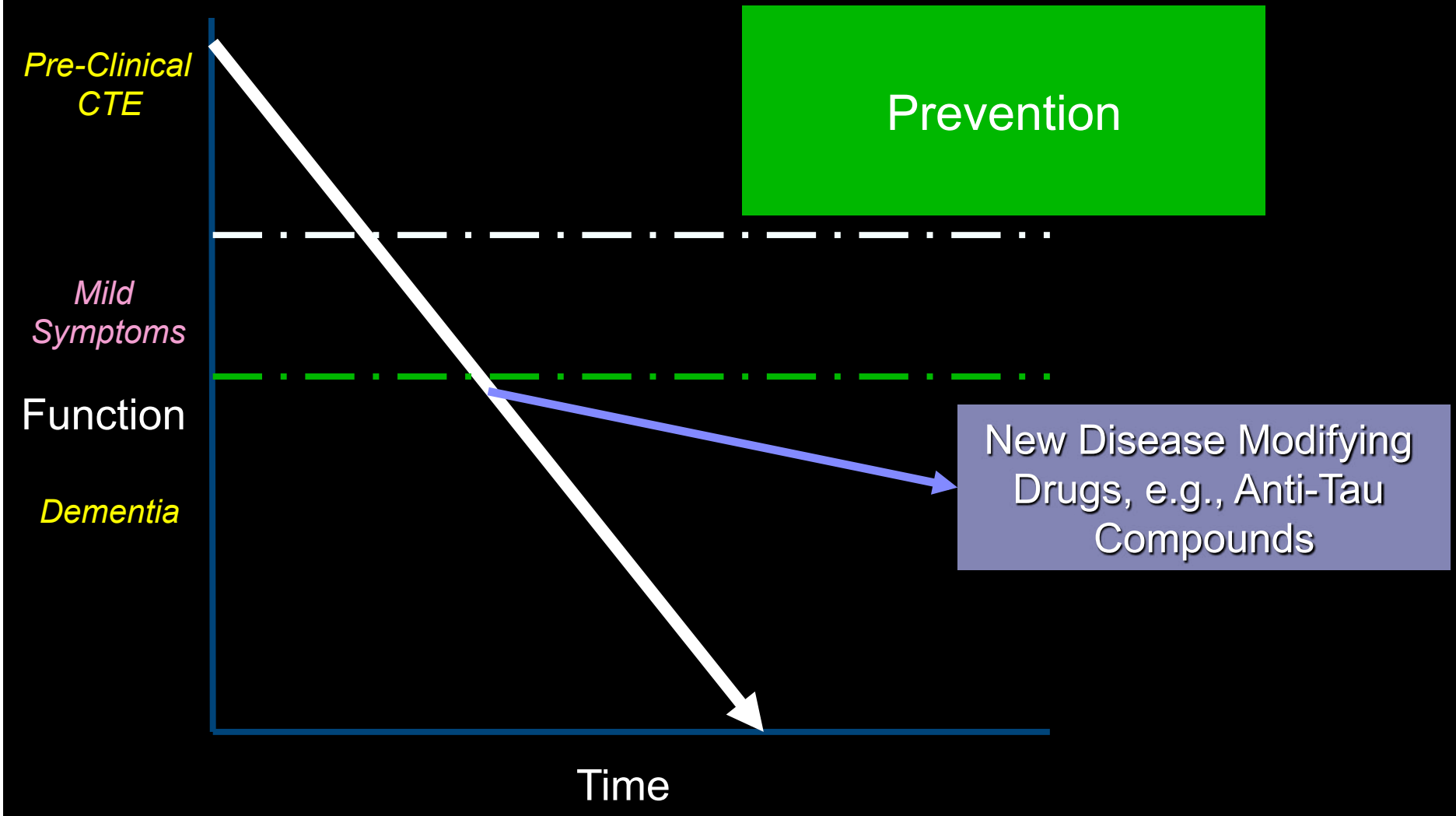
DIAGNOSE CTE Research Project

We have started!!!!

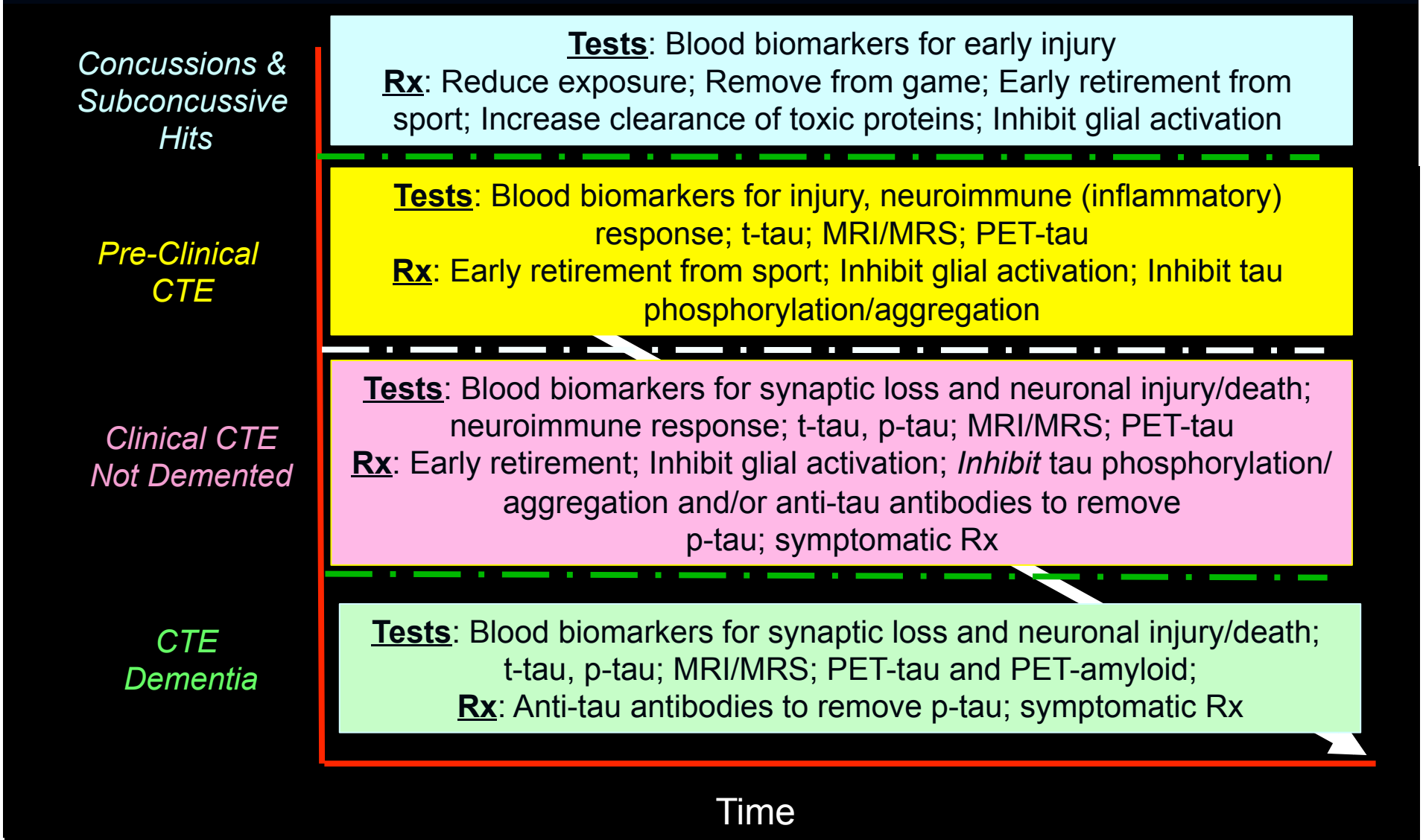


From Brigham & Women's Hospital, M. Shenton

As with AD, Early ***CTE*** Disease Modification = Prevention

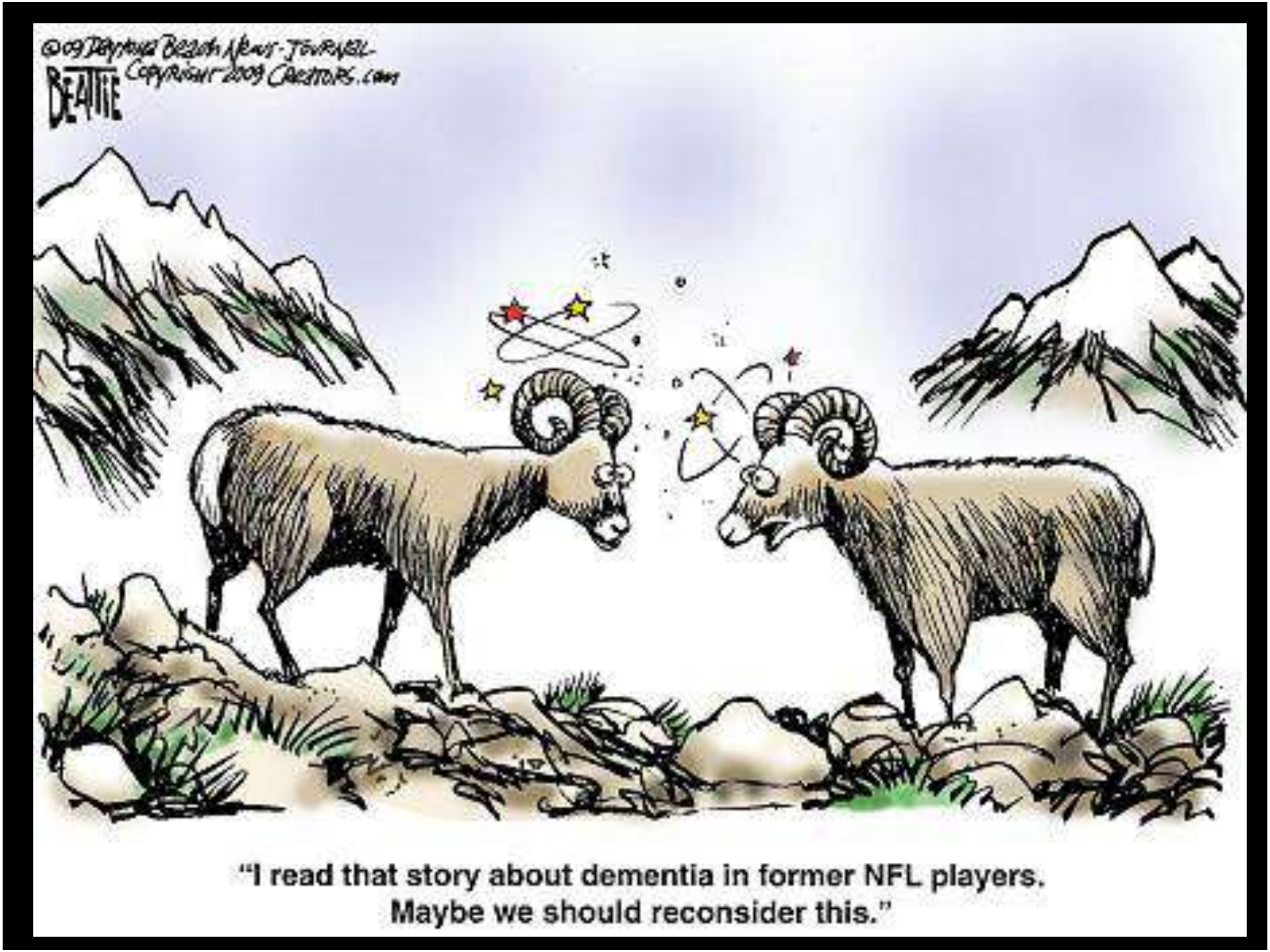


Toward Precision Health:
Prevention and Treatment of CTE



Future Research

- Once we can diagnose CTE during life, we will be able to begin clinical trials for treatment
- And, if we can detect it early in the disease course, prior to symptoms, we can conduct clinical trials for **prevention!**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BEATTIE
"I read that story about dementia in former NFL players.
Maybe we should reconsider this."

Acknowledgments

Boston University Alzheimer's Disease and CTE Center

- Mike Alosco
- Victor Alvarez
- Rhoda Au
- Christine Baugh
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- David Riley
- Fiona Rice
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- Julie Stamm
- Thor Stein
- Yorghos Tripodis
- BU GenCore

Brigham & Women's Hospital

- Inga Koerte
- Alex Lin
- Ofer Pasternack
- Martha Shenton

Concussion Legacy Foundation

- Lisa McHale
- Chris Nowinski
- Cliff Robbins

Others

- Kaj Blennow (U Gothenberg)
- Mike Devous (Avid)
- Andreas Jeromin (Quanterix)
- Mark Mintun (Avid)
- John Mann (Columbia)
- Mike Pontecorvo (Avid)
- Leslie Prichep (BrainScope)
- Eric Reiman (Banner Alzheimer's Inst)
- Les Shaw (Upenn)
- Doug Taylor (Exosome Sciences)
- John Trojanowski (Upenn)
- Henrik Zetterberg (U Gothenberg)
- Jing Zhang (U. Wash.)
- And all the athletes and families who participate in our research

CTE – ALS Connection

- Subset of individuals with CTE develop a “motor neuron disease” that would be clinically diagnosed as Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig’s Disease
- McKee et al (2010) *Journal of Neuropathology and Experimental Neurology*

The Washington Post

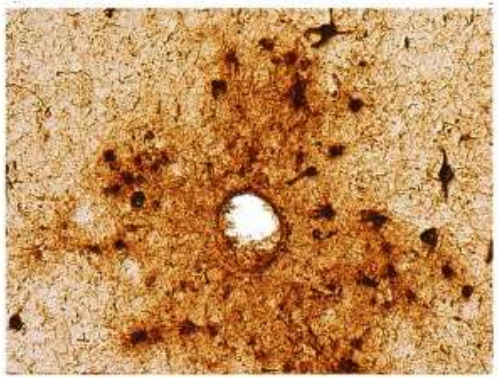
Early Lead

Former NFL player Kevin Turner's death caused by CTE, not ALS

By Jeremy Gottlieb November 3

Former NFL fullback Kevin Turner died of CTE, according to researchers at Boston University, and not ALS. (Matt Rourke/Associated Press)

Former New England Patriots and Phialdelphia Eagles fullback Kevin Turner, who played in the NFL from 1992 to 1999, died in March at age 46. Turner was diagnosed with amyotrophic lateral sclerosis in 2010, but Thursday the Boston University Brain CTE Center announced that it was a severe case of chronic traumatic encephalopathy that killed him, not ALS.



Control

Kevin Turner

BOSTON UNIVERSITY

Department of Veterans Affairs

CONCUSSION LegacyFoundation

Rugby

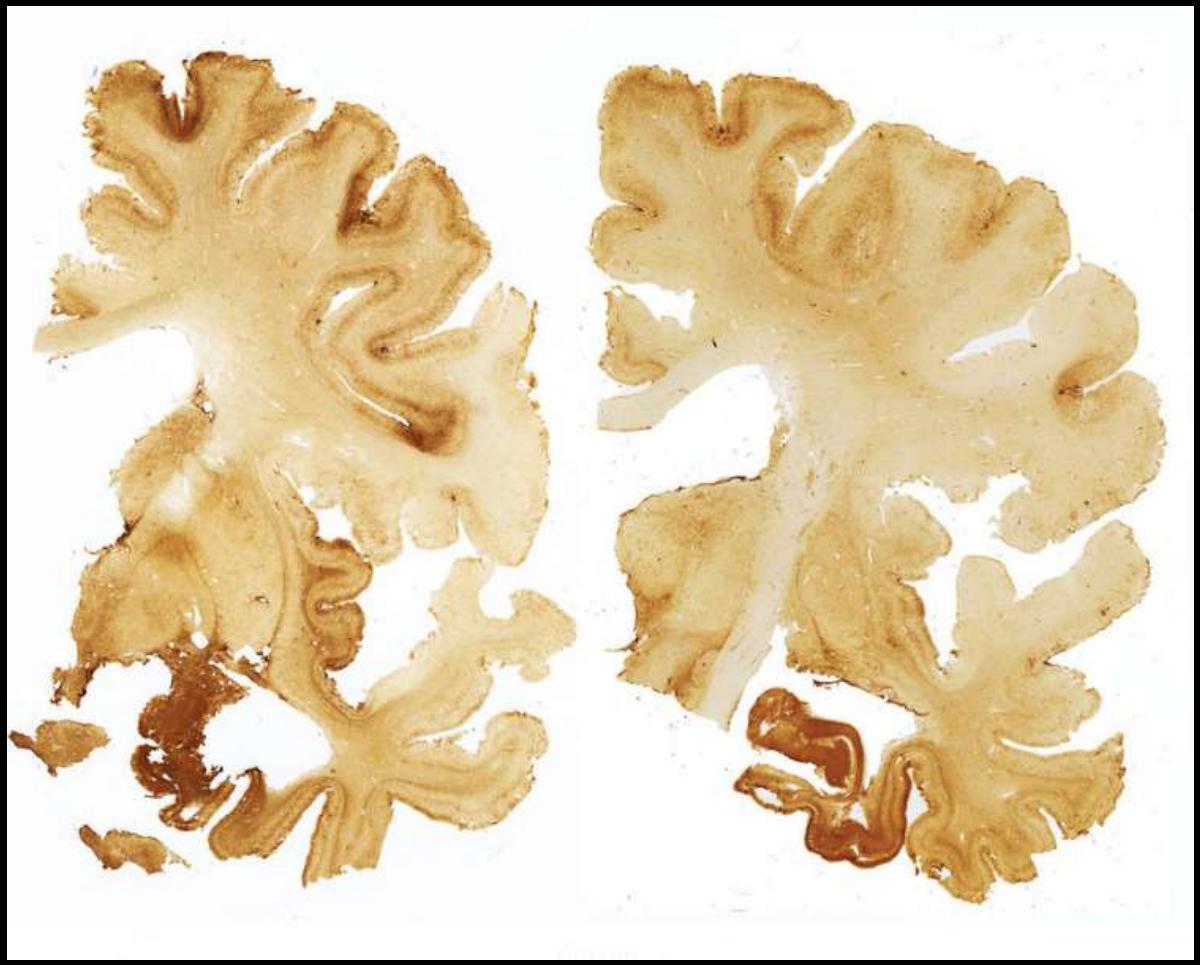
Barry (Tizza) Taylor – Age 77

Australian Rugby Player

Competitive Rugby for 19 years

235 games for Manly Rugby Union, an Australian professional team near Sydney

Tizza Taylor – Age 77
Cognitive Problems in 50's
Severe Dementia in 60's



Acta Neuropathol
DOI 10.1007/s00401-015-1515-z

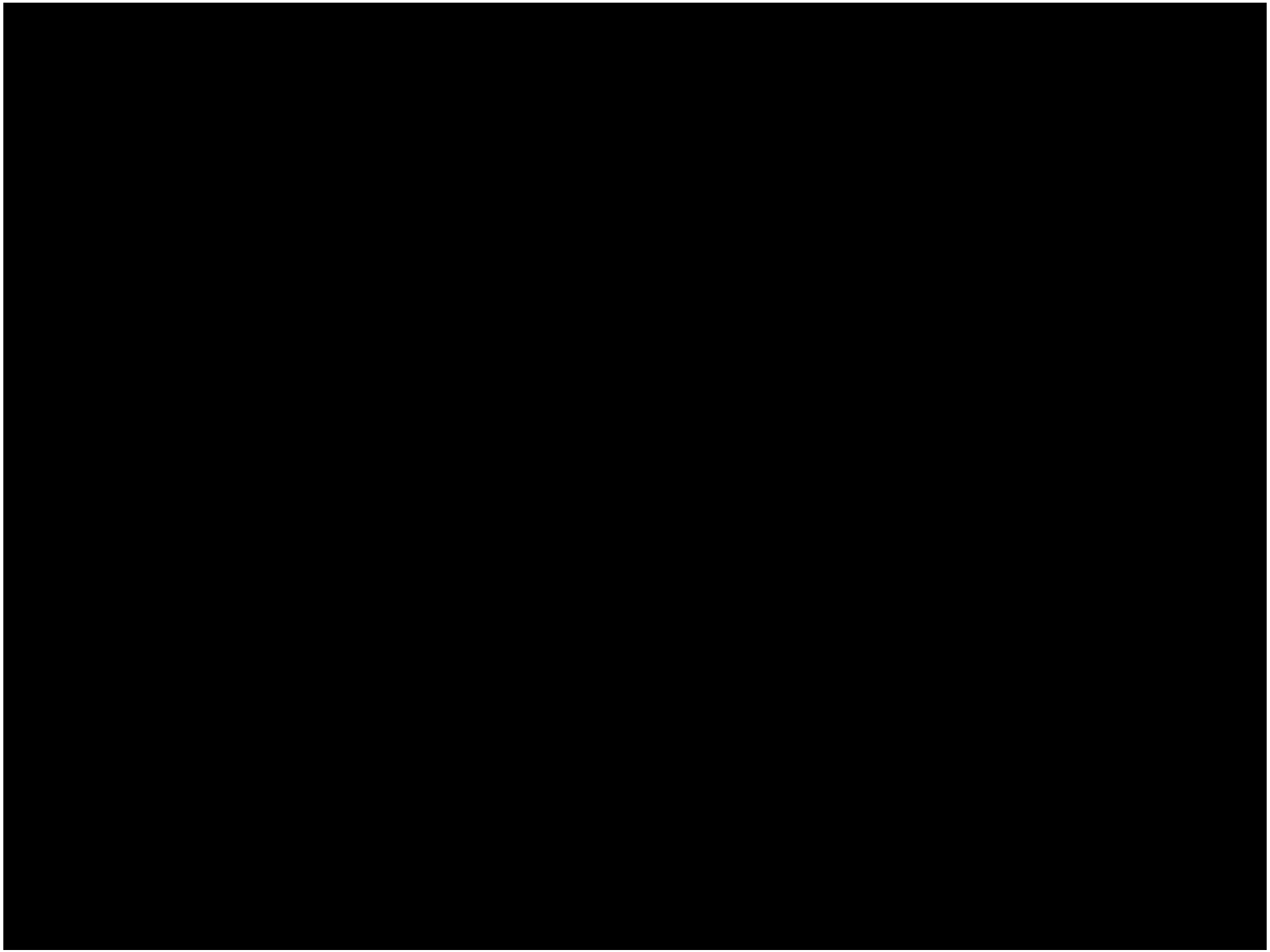
CONSENSUS PAPER

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

- CTE is a disease
- It is unique from other tauopathies
- It is only seen in people with a history of previous brain trauma, usually repetitive



BU CTE Clinical Research Funding

National Institutes of Health
NINDS R01 NS078337/R56NS078337; NINDS U01NS093334

Boston University Alzheimer's Disease Center -NIA
NIA P30 AG13846 supplement 0572063345-5

Department of Veteran's Affairs

NFL – Unrestricted Gift and Travel for study participants

NFL Players Association – Travel for study participants

JetBlue – Travel for study participants

Center for Integration of Medicine and Innovative Technology (CIMIT) - Grant

NOCSAE – Grant

Department of Defense
PHTBI W81XWH-13-2-0064

BU CTE Clinical Research Funding

Avid Radiopharmaceuticals
- A division of Eli Lilly

Quanterix (Blood Biomarkers)

Exosome Science (Blood Biomarkers)

The Boston Globe

CHRISTOPHER L. GASPER

Scientific and medical jargon aside, Kevin Turner died from playing football

NOVEMBER 5, 2016

The NFL has bigger concerns than sagging television ratings, questionable quality of play, and restive players complaining the league wants them to behave like the football version of "Westworld" robots. Those are cosmetic threats to the league's popularity. The idea that prolonged exposure to football can be fatal is an existential threat.

Kevin Turner had 25 years of exposure to head trauma while playing football.
MATT ROURKE/ASSOCIATED PRESS/FILE 2013