Traumatic Brain Injury, Concussion, and American Football.

Alvaro Pascual-Leone, MD, PhD

Berenson-Allen Center for Noninvasive Brain Stimulation & Division Cognitive Neurology • Beth Israel Deaconess Medical Center

Harvard Catalyst • Harvard Medical School

Alvaro Pascual-Leone, MD, PhD

Disclosures

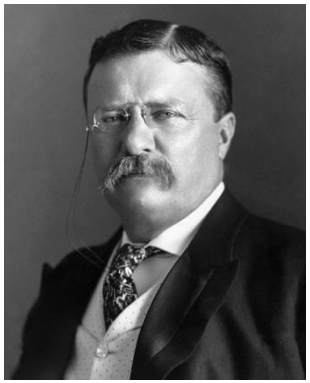
- My spouse and I have no relevant financial relations with an ACCME defined commercial interest.

American (Style) Football

American (Style) Football

More than a game

But perceptions are changing



"I would a hundred fold rather keep the game as it is now, with the brutality, than give it up. Football makes efficient leaders."

Theodore Roosevelt (1858-1919; 29th US President 1901-1909)

"I believe that football, perhaps more than any other sport, tends to instill in men the feeling that victory comes through hard — almost slavish — work, team play, self-confidence and an enthusiasm that amounts to dedication."

Dwight D. Eisenhower (1890-1969; 34th US President 1953-1961)

"I'm a big football fan, but I have to tell you, if I had a son, I'd have to think long and hard before I let him play football."

Barack Obama (1961- ; 44th US President 2009-2017)

NFL

Dave Bry column

American football is too dangerous, and it should be abolished

Dave Bry

I'd suggest recreating the game without helmets instead, but that's not going to happen, so we should all just channel our primal bloodlust elsewhere

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OPINION

Should President Obama ban football?

President Barack Obama gestures to the audience as he arrives in the East Room of the White House in Washington, Friday, Jan. 25, 2013, to announce that he will name current Deputy National Security Adviser Denis McDonough as his next chief of staff. (AP Photo/Carolyn Kaster) (AP)

"I'm a big football fan, but I have to tell you if I had a son, I'd have to think long

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President Barack Obama gestures to the audience as he arrives in the East Room of the White House in Washington, Friday, Jan. 25, 2013, to announce that he will name current Deputy National Security Adviser Denis McDonough as hi next chief of staff. (AP Photo/Carolyn Kaster) (AP)

"I'm a big football fan, but I have to tell you if I had a son, I'd have to think long

The Opinion Pages | OP-ED CONTRIBUTOR

Don't Let Kids Play Football

By BENNET OMALU DEC. 7, 2015

Some balance

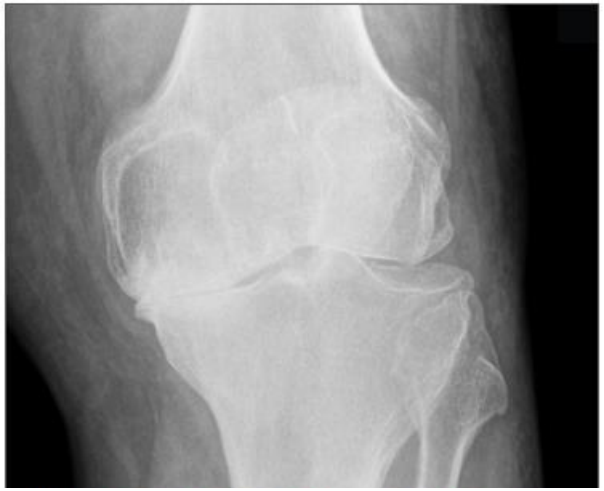
Should you let your child play contact sports like football. . . ? That involves lots of factors for each child, and is best made on an individual basis. My wife and I will let our children play any of these sports. If they begin getting multiple concussions, we will re-evaluate. . . . The scientifically established benefits of participation in organized sports outweigh the known concussion risks for my own kids."

-Michael Kirkwood, PhD

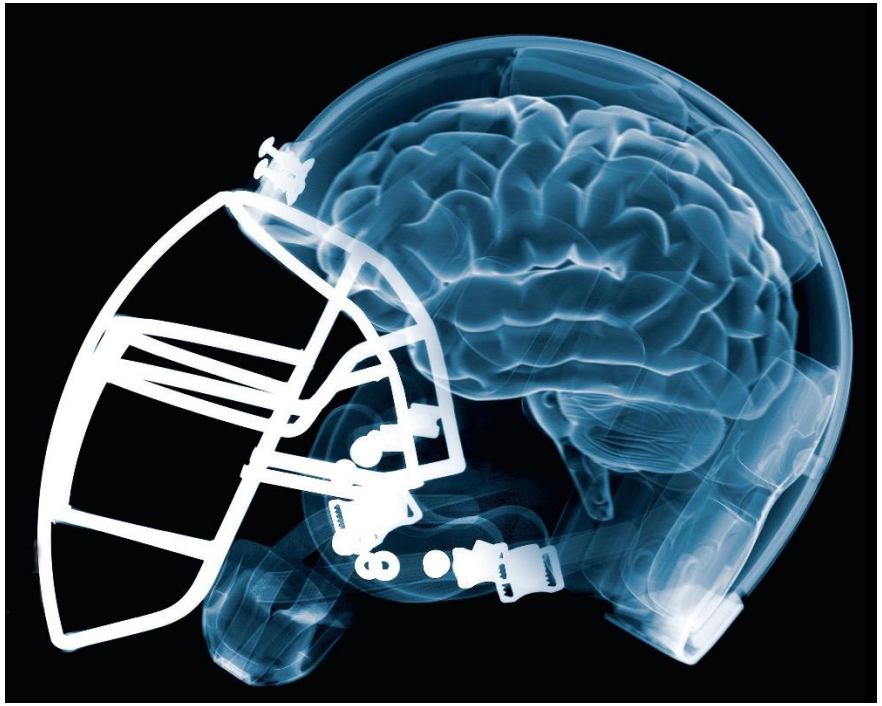
What long-term health issues impact former football players?

2013 USA Today sports survey of 293 NFL players

1. Knee Injury (ACL)
   - 46% feared a knee injury the most
   - Possibly career ending
   - Cause of lasting pain and disability
2. Chronic Pain
3. Cardiovascular health
   - HTN
   - Sudden death
4. Concussion and long term risk



Is the fear of long-term cognitive decline appropriate?



1 of every 10

Division 1 football players

believes he will suffer dementia, CTE, or Alzheimer's disease as a result of playing.

Baugh CM, et al. *J Neurotrauma*

THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

- Launched in 2014
- Multi-disciplinary investigations exploring the potential long-term health consequences of professional football
- Addressing biological, individual, and structural factors for health
- Improving methods for preventing, diagnosing, and treating injuries & medical problems associated with football.

A "One Harvard" Initiative

HARVARD CATALYST
THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Lee Nadler, MD
Principal Investigator

Alvaro Pascual-Leone, MD, PhD
Targeted Studies

Ross Zafonte, MD
Medical Navigation

Herman Taylor, MD
Player Engagement

Aaron Baggish, MD
In-person Assessment

Marc Weiskopf, MD, ScD
Epidemiology

Lydia Bergen, MPP
Executive Director, FPHS

Laura Weisel, MBA
Executive Director, Harvard Catalyst

Doug MacFadden, MS
Database Platform and Tools

Frank Speizer, MD

I. Glenn Cohen, JD
Law & Ethics Co-Lead

Holly Fernandez Lynch, JD, MBioethics
Law & Ethics Co-Lead

Bill Meehan, MD

Research Advisors N=14
Former Player Advisors N=40

Team-science in action

What does the FPHS want?

Committed to address the needs of Football Players.

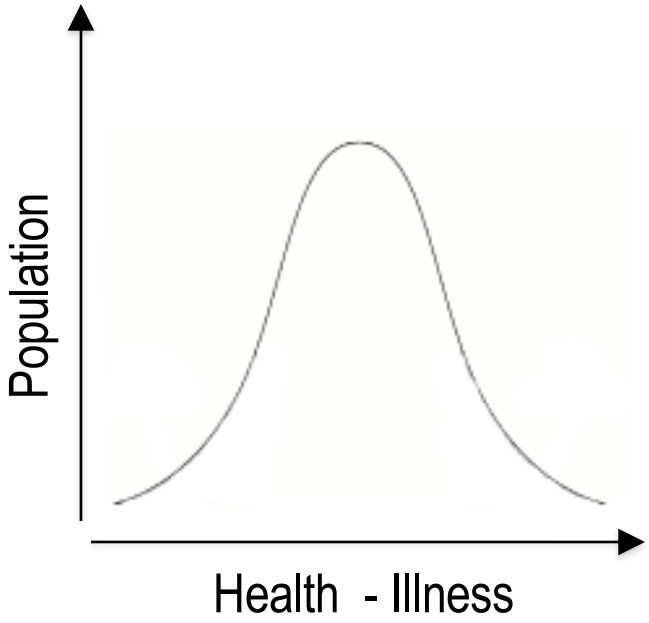
- **Understand and explain THE TRUTH to football players and their families.**
- **Translate results into NEW DIAGNOSTIC, PREVENTIVE, and THERAPEUTIC interventions to promote the health of football players.**
- **Learn from this study lessons that apply to all athletes and populations.**

Whole Player – Whole Life

Unique individuals

Physical Effort
Stress
Achievement
Social Support
Transitions

Unique Lives

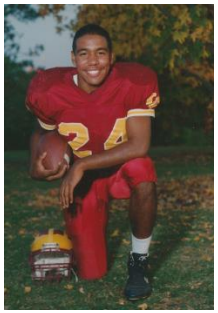


We need to understand the meaning of health and affliction in NFL players

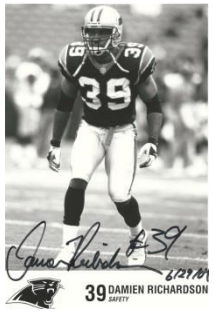
The Whole Life

Most players share the same journey

1980



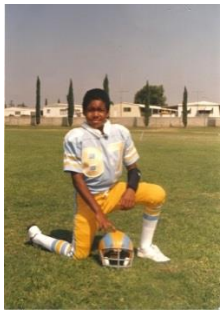
1992



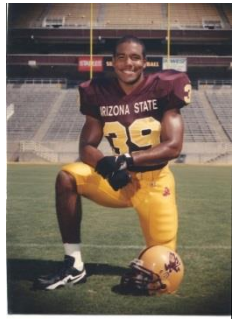
2002

Life after football

1987



1996



Shared courtesy of Damien Richardson, former NFL player

The Whole Player

Multiple individual, biological and structural factors affect the health of players.

Genetics

Development and upbringing

Environmental influences

Injuries and illnesses

Multi-organ interaction

Psychosocial influences

Healthcare system structural factors

The Whole Player, The Whole Life

PILOT STUDIES

New Prevention Strategies, Diagnostics & Treatments

Researchers working on innovative and promising developments that have the potential to impact the health of football players.

PLAYERS & SCIENTISTS

Advice and Guidance

LAW & ETHICS

Promoting Player Health Through Structural Change

Understanding the legal and ethical issues that promote and impede player health and developing responsive recommendations

POPULATION STUDIES

Health Status & Quality of Life

Using questionnaires and testing to better understand player health and wellness.

THE FOOTBALL PLAYERS HEALTH STUDY
HARVARD UNIVERSITY

Pilot Projects

Player-focused translational research.

Year One Pilot Projects

- **Bio-Enhanced ACL Repair**
  - Martha M. Murray, MD
- **Exercise Induced Cardiac Remodeling**
  - Aaron L. Baggish, MD
- **Red/Near Infrared Light for the Treatment of Concussion**
  - Michael J. Whalen, MD
  - Ross Zafonte, DO
  - Bill Meehan, MD

Year Two Pilot Projects

- **Protect When Needed (PWN) Knee Bracing**
  - Conor Walsh, Ph.D
- **Inflammation Responsive Hydrogel Depot**
  - Joerg Ermann, MD
  - Jeffrey M. Karp, Ph.D
- **Antibody Therapy for Treating Brain Injury and CTE**
  - Kun Ping Lu, Ph.D, MD
- **On-Field Brain Movement and Activity Monitoring**
  - Gary Strangman, Ph.D

Year Three Pilot Projects

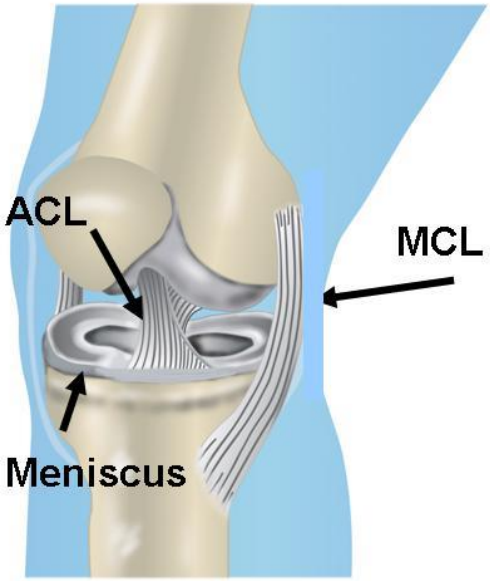
- **Modified Citrus Pectin for Osteoarthritis**
  - Christine Huang, PhD, MD
- **Cold Fluid for Obstructive Sleep Apnea**
  - Rox Anderson, MD
- **Nerve blocks for post-traumatic headaches**
  - Lexi Stillman, MD
  - Alyssa Lebel, MD
  - Pradeep Dinakar, MD

Novel Treatment for ACL Injuries: BEAR™ scaffold

Martha Murray, MD

Bridge-Enhanced ACL Repair (BEAR)

- ACL does not heal
- Reconstruction less than ideal
- Osteoarthritis with 14 years
- Natural healing preferable



Novel Treatment for ACL Injuries: BEAR™ scaffold

Martha Murray, MD

- Animal studies
- Translation to athletes
- Safety trial
- FDA pivotal study approved
- Now: larger trials, later outcomes

Untreated ACL rupture | ACL reconstruction | Bioenhanced repair

Protect-When-Needed Knee Bracing

Conor Walsh, PhD, Ata Kiapour, PhD

- Brace that has no effect normal motion
- Activates with anterior tibial translation
- Softer, more comfortable for players

Inflammation Responsive Hydrogel Depot

Joerg Ermann, MD; Jeffrey M. Karp, PhD

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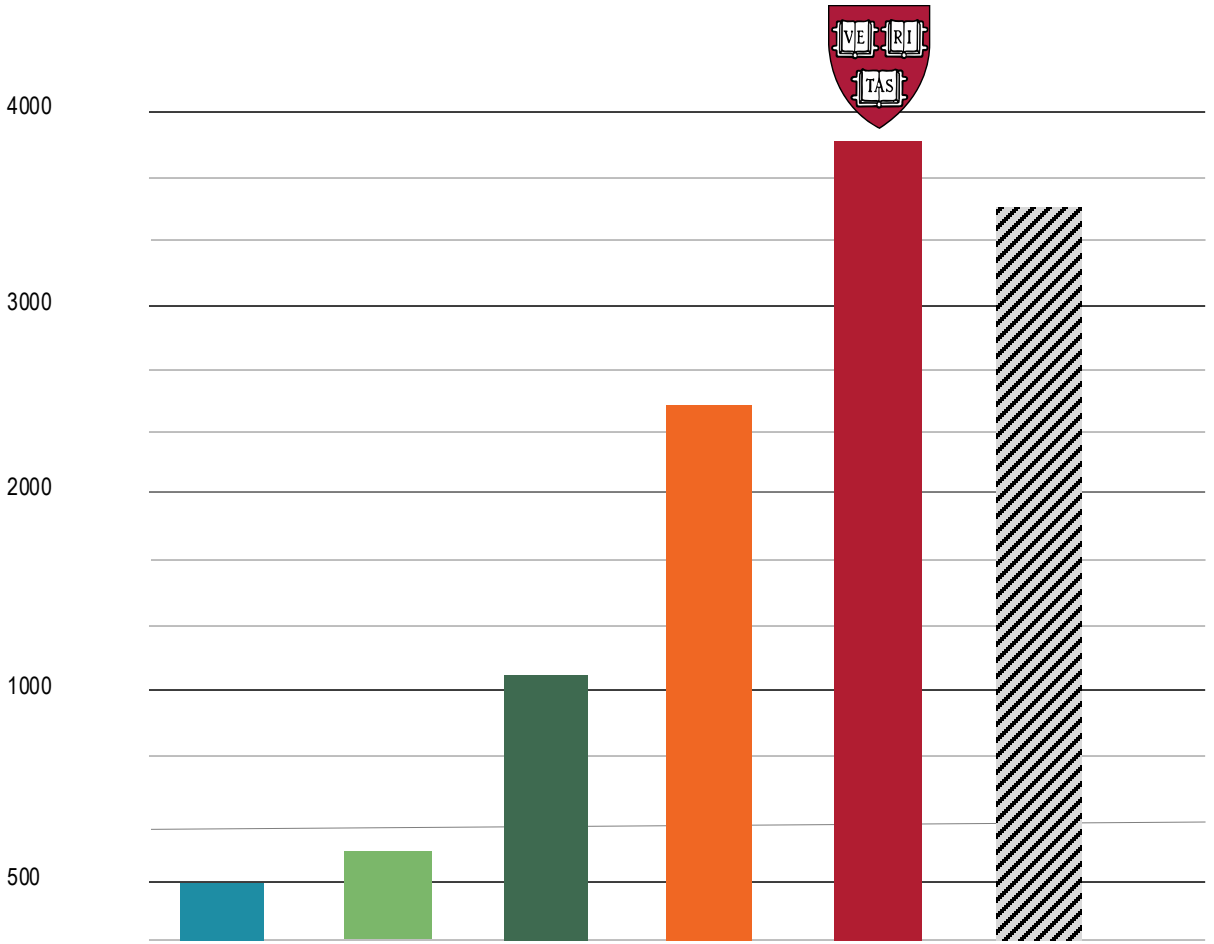
Largest Study of Living Former NFL Players
and growing…



- Prevalence and Characterization of Mild Cognitive Impairment in Retired National Football League Players (513 Players)
- Life After Football: Study of Former Players (763 Players)
- Study of Retired Former Players (1063 Players)
- Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired National Football League Players (2552 Players)
- The Football Players Health Study at Harvard University
- Neurodegenerative cause of death in retired NFL Players (3439 Players)

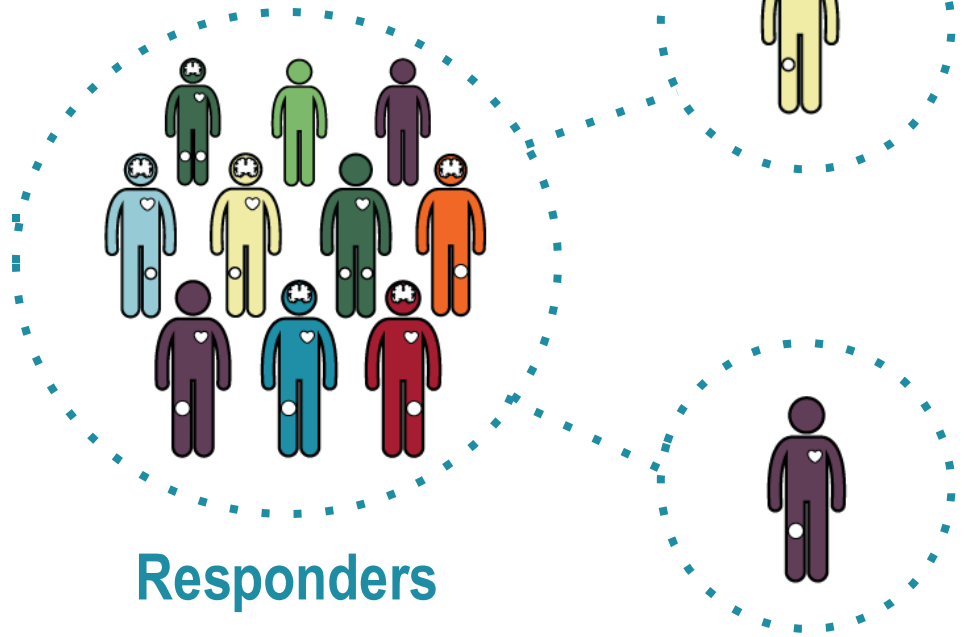
THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

>3,700 responses to date

From 1960 till today:

~15,000

reachable former NFL players



Responders

Case Control Studies

1. In-person
2. Remote

THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

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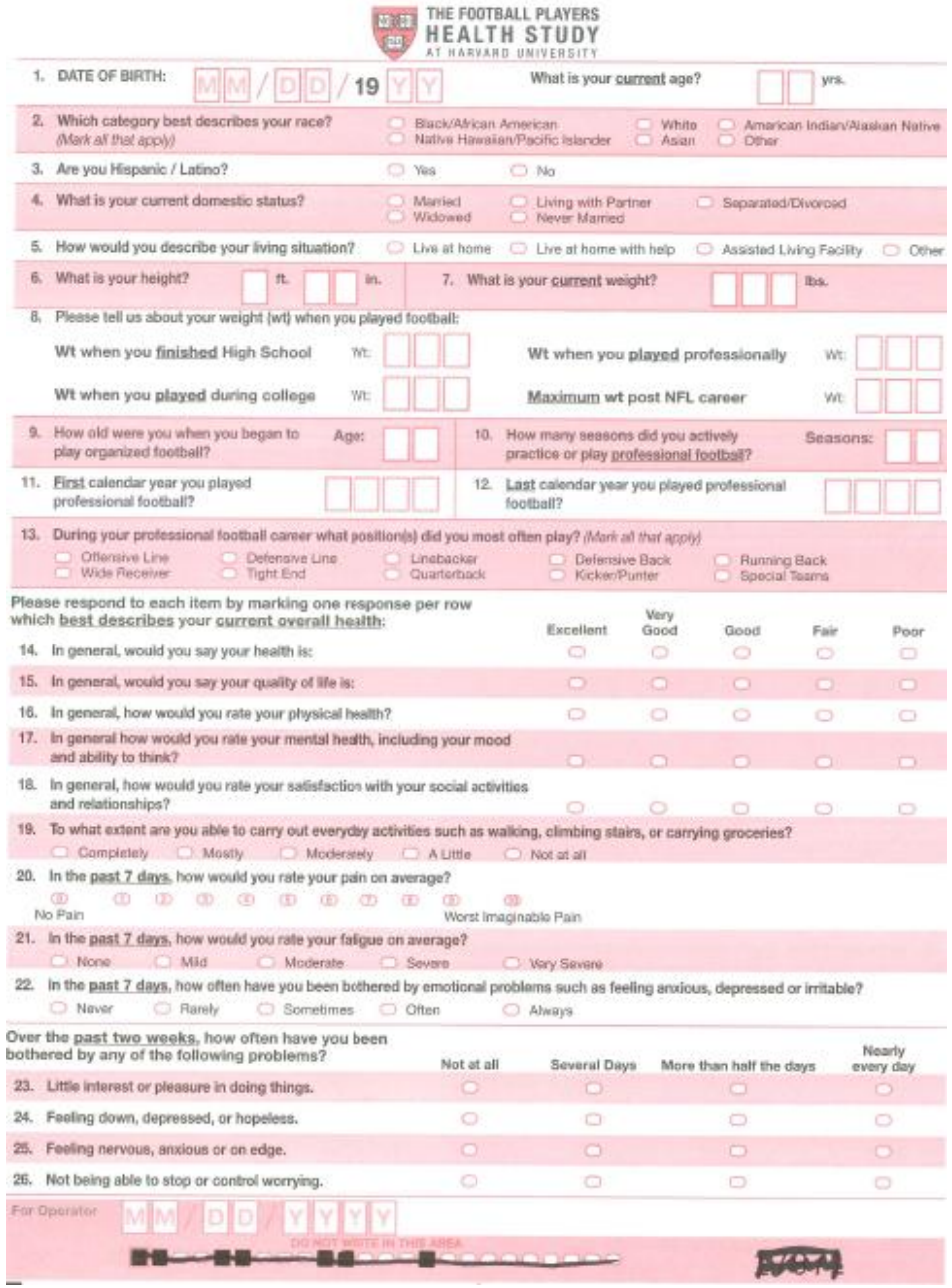


THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

1. DATE OF BIRTH: MM / DD / 19 YY — What is your current age? ___ yrs.

2. Which category best describes your race? (Mark all that apply)
Black/African American; White; American Indian/Alaskan Native; Native Hawaiian/Pacific Islander; Asian; Other

3. Are you Hispanic / Latino? Yes; No

4. What is your current domestic status?
Married; Living with Partner; Separated/Divorced; Widowed; Never Married

5. How would you describe your living situation?
Live at home; Live at home with help; Assisted Living Facility; Other

6. What is your height? ___ ft. ___ in.

7. What is your current weight? ___ lbs.

8. Please tell us about your weight (wt) when you played football:
Wt when you finished High School Wt: ___
Wt when you played professionally Wt: ___
Wt when you played during college Wt: ___
Maximum wt post NFL career Wt: ___

9. How old were you when you began to play organized football? Age: ___

10. How many seasons did you actively practice or play professional football? Seasons: ___

11. First calendar year you played professional football? ____

12. Last calendar year you played professional football? ____

13. During your professional football career what position(s) did you most often play? (Mark all that apply)
Offensive Line; Defensive Line; Linebacker; Defensive Back; Running Back; Wide Receiver; Tight End; Quarterback; Kicker/Punter; Special Teams

Please respond to each item by marking one response per row which best describes your current overall health:

	Excellent	Very Good	Good	Fair	Poor
14. In general, would you say your health is:					
15. In general, would you say your quality of life is:					
16. In general, how would you rate your physical health?					
17. In general how would you rate your mental health, including your mood and ability to think?					
18. In general, how would you rate your satisfaction with your social activities and relationships?					

19. To what extent are you able to carry out everyday activities such as walking, climbing stairs, or carrying groceries?
Completely; Mostly; Moderately; A Little; Not at all

20. In the past 7 days, how would you rate your pain on average?
0 1 2 3 4 5 6 7 8 9 10
No Pain — Worst Imaginable Pain

21. In the past 7 days, how would you rate your fatigue on average?
None; Mild; Moderate; Severe; Very Severe

22. In the past 7 days, how often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?
Never; Rarely; Sometimes; Often; Always

Over the past two weeks, how often have you been bothered by any of the following problems?

	Not at all	Several Days	More than half the days	Nearly every day
23. Little interest or pleasure in doing things.				
24. Feeling down, depressed, or hopeless.				
25. Feeling nervous, anxious or on edge.				
26. Not being able to stop or control worrying.				

For Operator MM / DD / YYYY

DO NOT WRITE IN THIS AREA

Defining Affliction & Quantifying Its Impact in our Population (n >3,700 former pro-AF athletes)

1.) Cardiometabolic disease

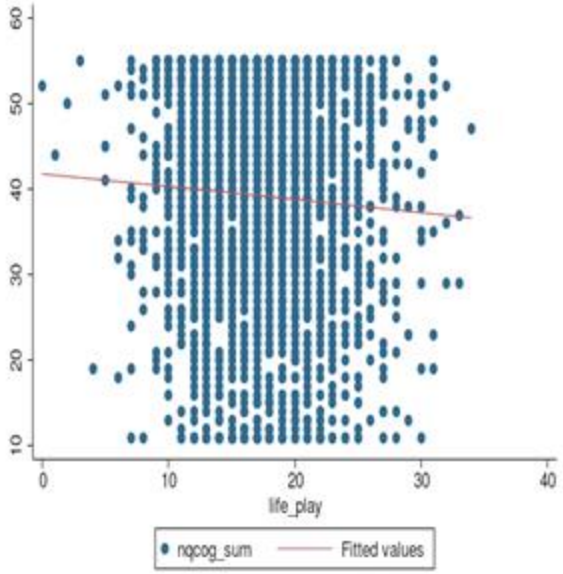
2.) Chronic pain

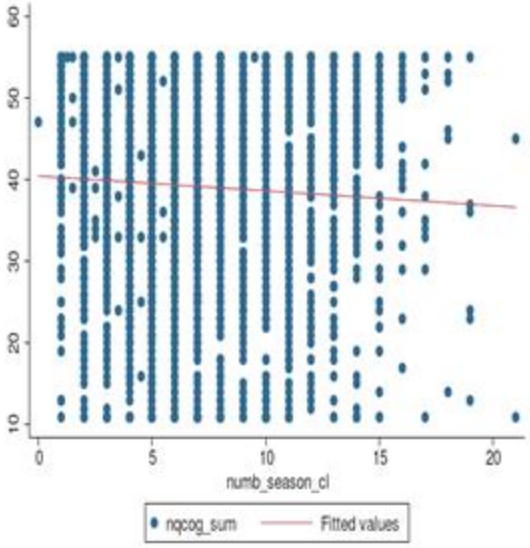
3.) Sleep disorders

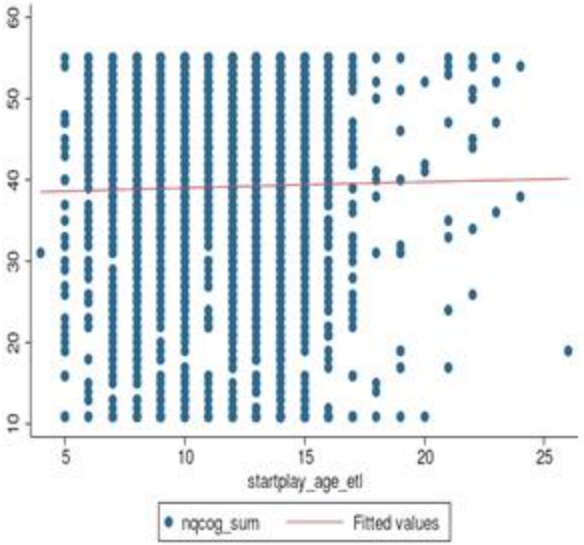
4.) Neurocognitive disorders

Subjective Cognitive Concerns in Former Football Players

NeuroQOL Sum Scores and Football Exposure







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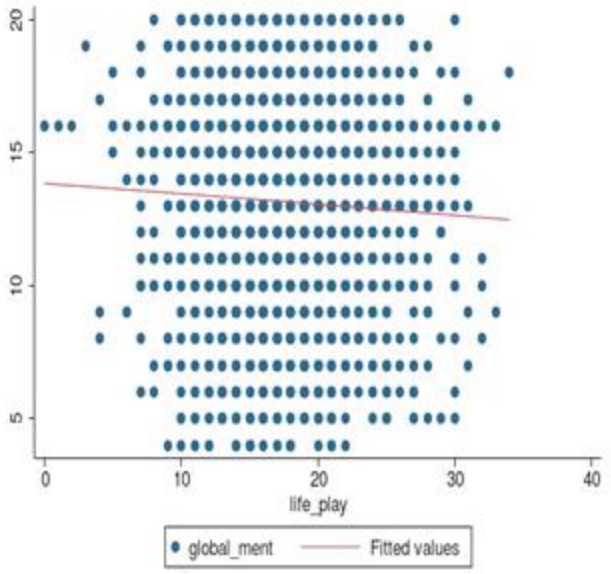
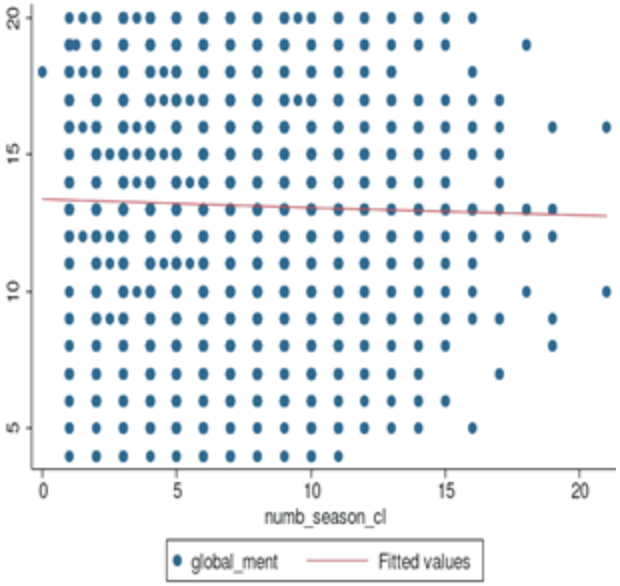
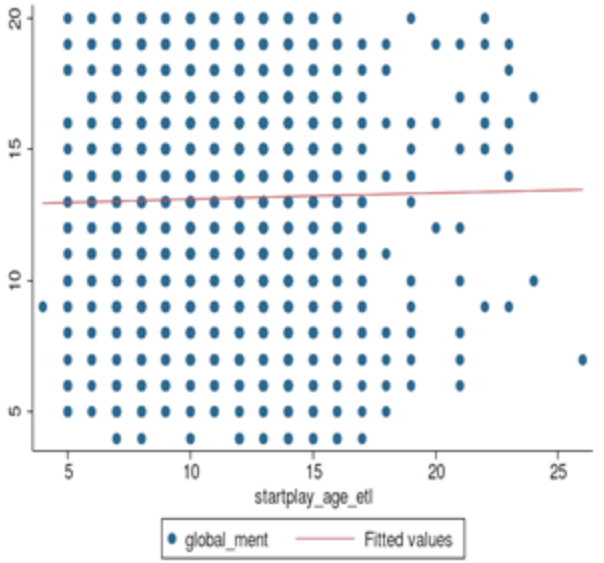
CONFIDENTIAL

Self-reported Mental Health Symptoms in Former Football Players

Global Mental Health Sum Scores and Football Exposure







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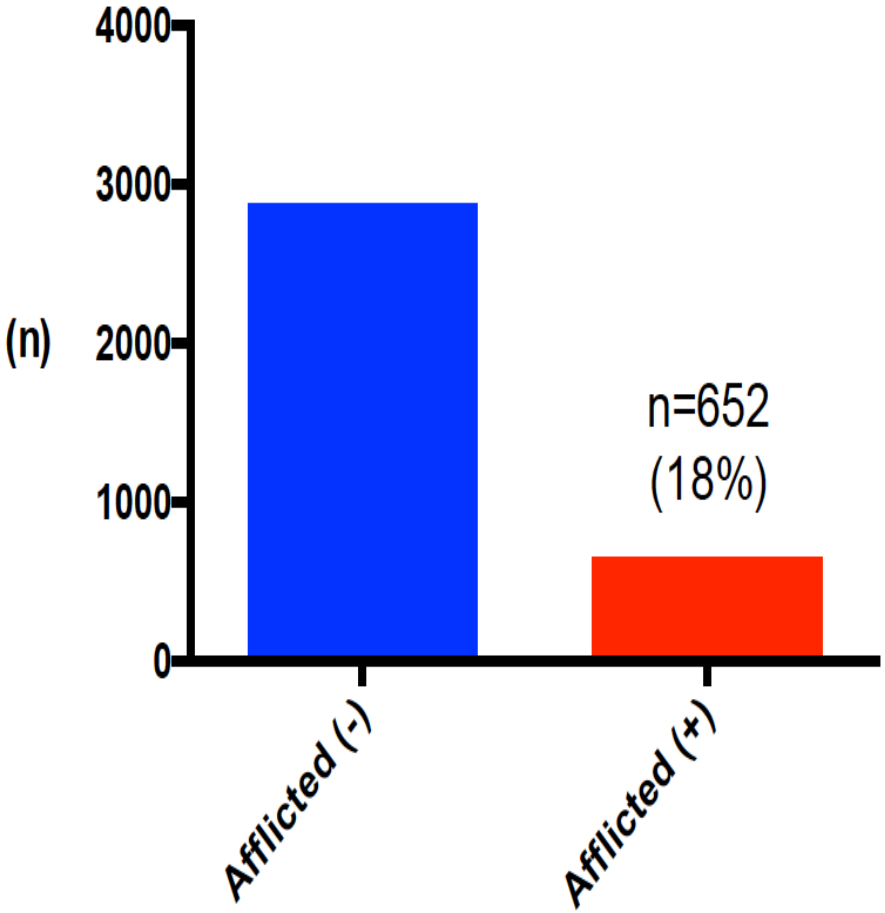
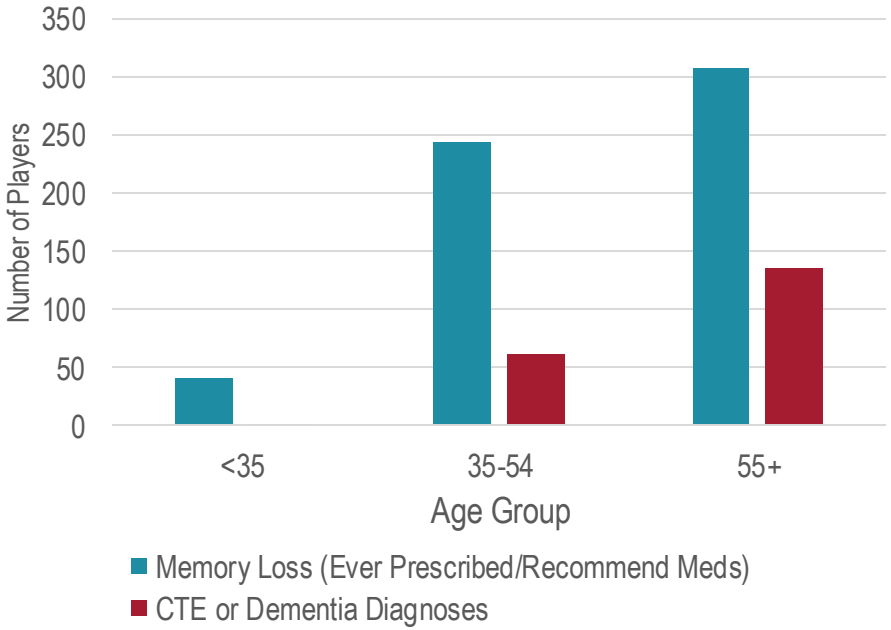
Diagnosed with or Prescribed Treatment for Dementia

THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY





Diagnosed with or Prescribed Treatment for Dementia

THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

N=1,897

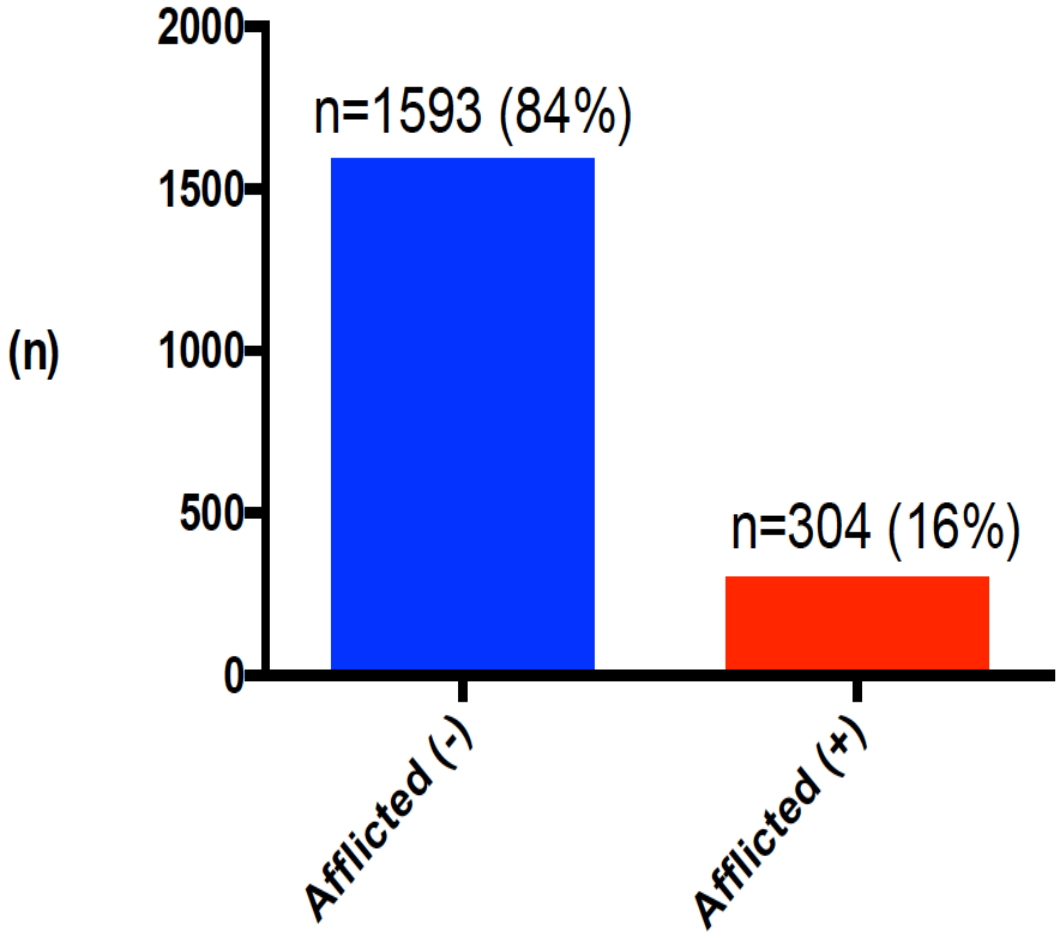
Position:
LM/NLM= 654/1253
LM/NLM= 16%/16%

Ethnicity:
Bl/Wh/Oth = 843/943/111
Bl/Wh/Oth = 21%/12%/12%

Pro Weight:
Non-Affllicted = 250 lb.
Afflicted = 246 lb.

Current Weight:
Non-Affllicted = 250 lb.
Afflicted = 257 lb.

# of Seasons Played:
Non-Affllicted = 6.5
Afflicted = 6.5



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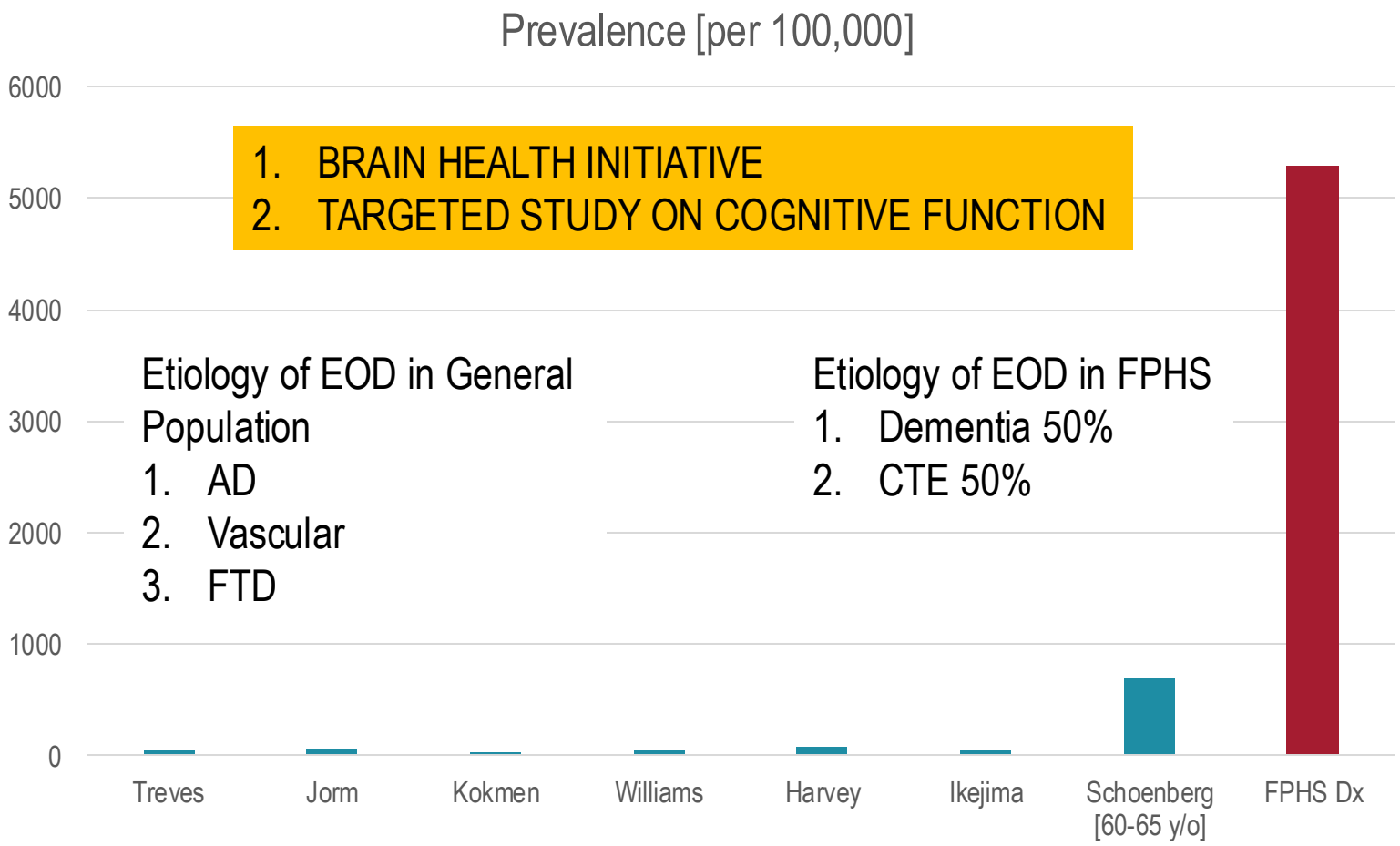
Early Onset Dementia



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Concussion definition

Altered neurological state following head trauma

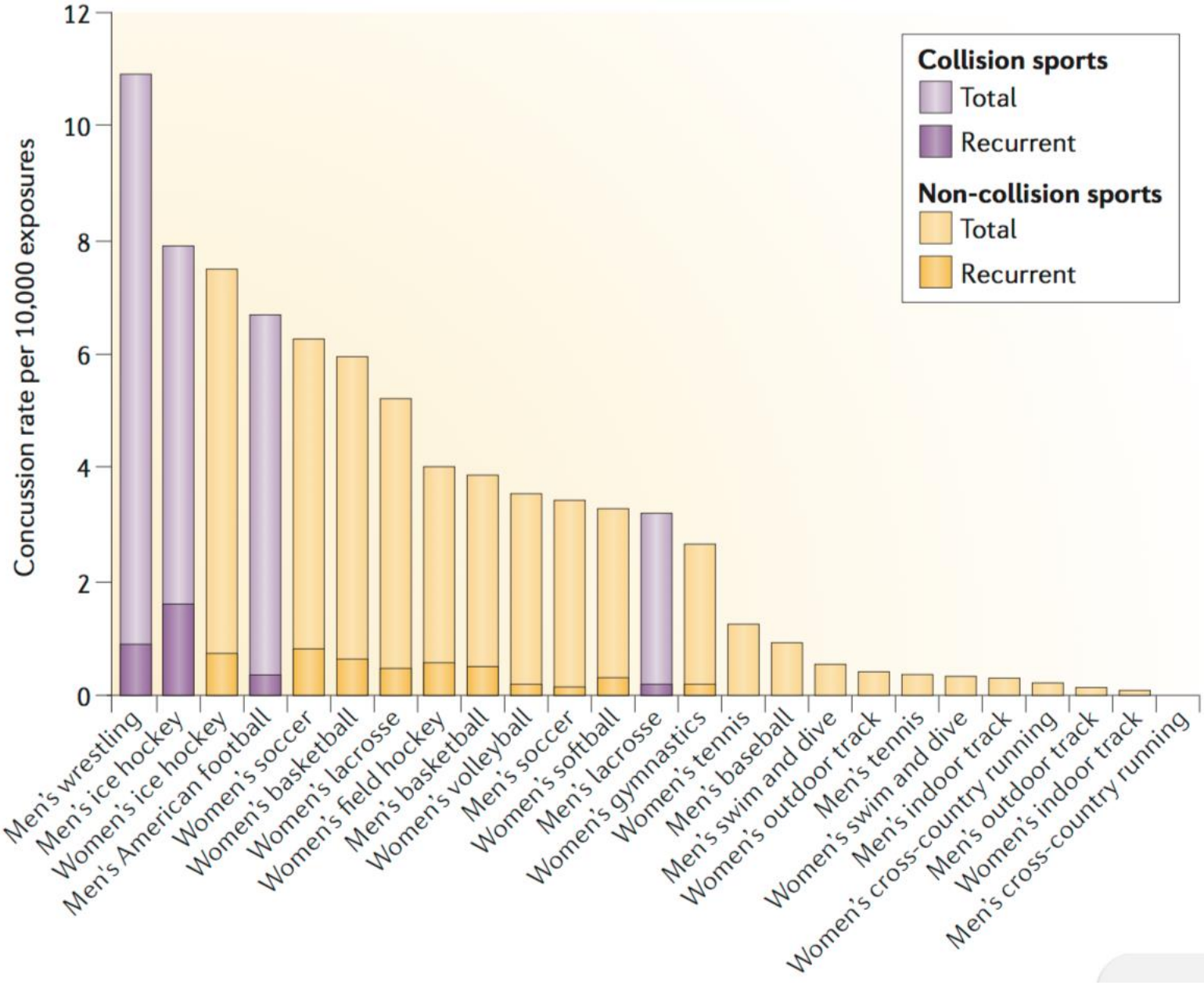
- Denny-Brown 1941: A reversible syndrome without detectable pathology
- Traumatic database 1980s: GCS 13-15
- ACRM definition: GCS 13-15, LOC < 30 mins, PTA < 24 hours, negative CT, no seizures
- AAN 1997 definition: graded based on LOC, PTA and post-traumatic confusion
- Zurich Conference 2008 and 2012: “complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces . . . Rapid onset of a short-lived impairment of neurological function that resolves spontaneously”

GLASGOW COMA SCALE

Eyes open	Spontaneously	4
	Verbal command	3
	Pain	2
Eyes do not open		1
Best motor response	Obeys commands	6
with pain	Localizes	5
	Flexes withdraws	4
	Decorticates	3
	Decerebrates	2
	No response	1
Best verbal response	Oriented	5
	Disoriented	4
	Confused	3
	Sounds only	2
	No response	1
Total		3 - 15

Concussion epidemiology

- At least 128/100,000/year
- 1.5-2.0 million civilians/year
- Probably vast under-reporting
- Bimodal age distribution – young adults and elderly
- Alcohol commonly involved
- Causes of injury
  - MVA; vehicles and pedestrian
  - Falls < 180 cm
  - Assaults and falling objects
  - Head “bumps”
  - Contact sports



Mannix et al. *Nat Neurol Rev* 2016

Mechanism of Concussion

D. Denny-Brown

SEPTEMBER, 1941.

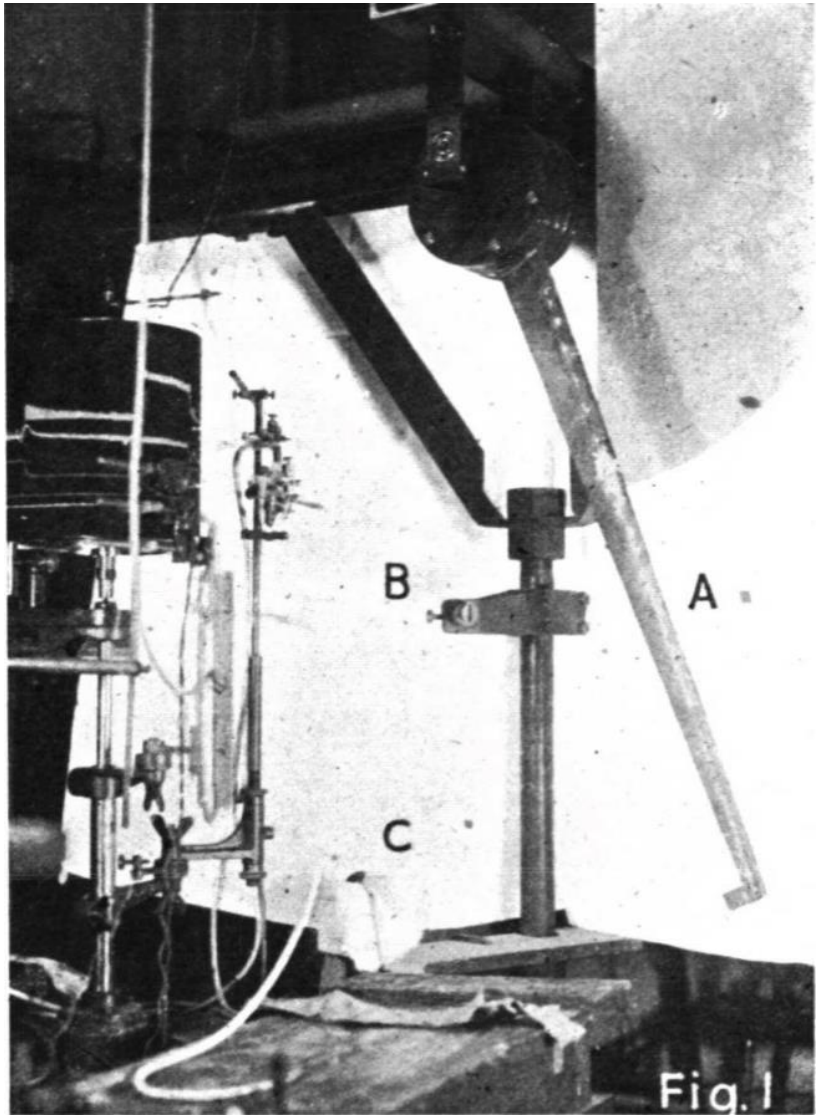
BRAIN

VOL. 64, PARTS 2 and 3.

EXPERIMENTAL CEREBRAL CONCUSSION.

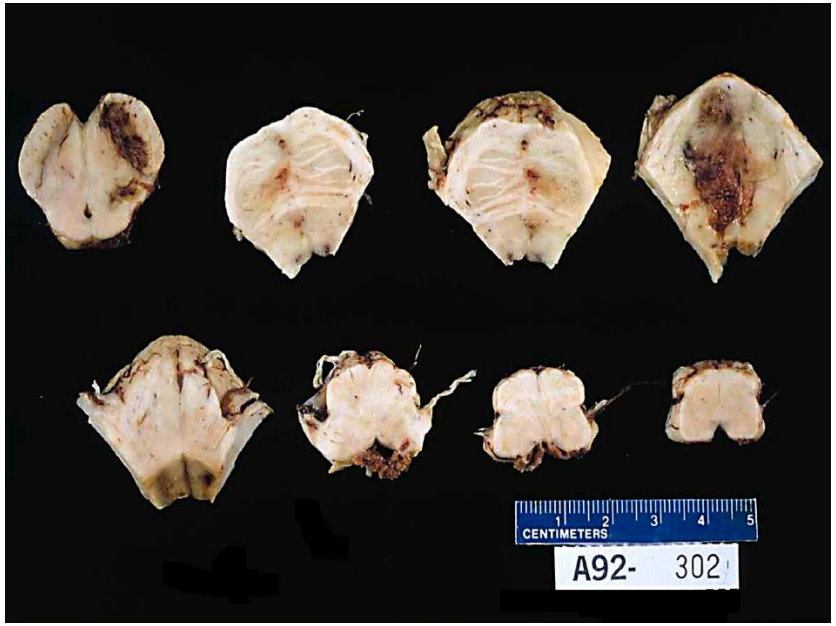
BY D. DENNY-BROWN and W. RITCHIE RUSSELL.

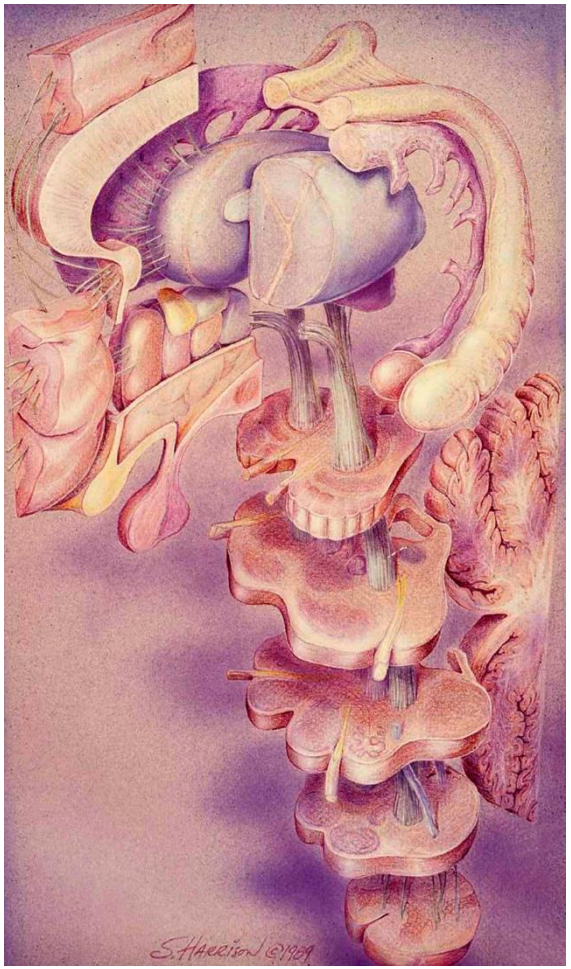
(*From the Laboratory of Physiology, Oxford.*)



Mechanism of Concussion

- Tortion around the upper brainstem
- Transient disconnection of the reticular activating system
- EEG becomes transiently flat



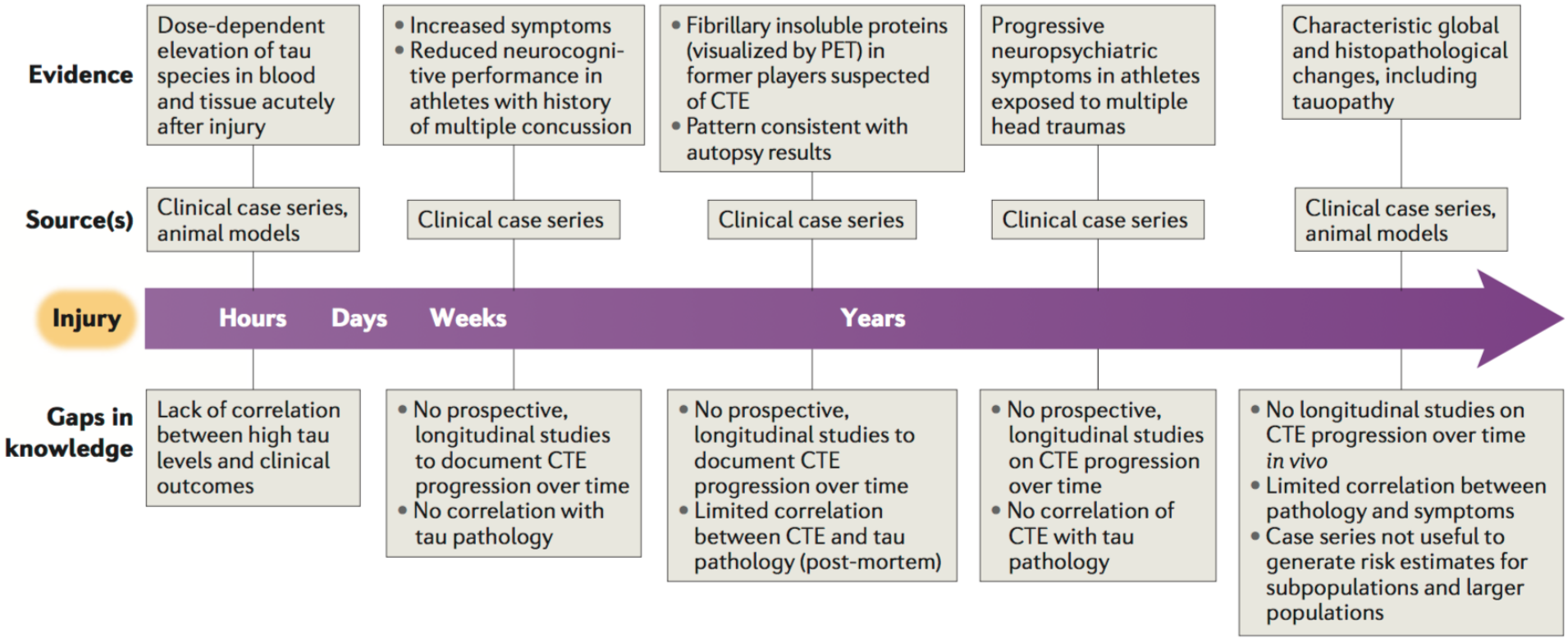


Prolonged symptoms

- <10% have persistent signs and symptoms of concussion beyond 2 weeks.
- Post-concussive Syndrome
  - Interval from injury to symptoms less than a month
  - Symptoms from at least three of the following
    - Headache, dizziness, fatigue, noise intolerance
    - Irritability, depression, anxiety, emotional lability
    - Subjective concentration, memory or intellectual difficulties without neuropsychological evidence of marked impairment
    - Insomnia / sleep disturbance
    - Reduced alcohol tolerance
    - Preoccupation with symptoms with fear of brain damage
- Patients with persistent symptoms:
  - High force mechanism of injury
  - Multiple concussions
  - Underlying neurological conditions – even age
  - Pain or psychological issues
  - Sport-related concussion

Word of caution about post-concussion syndrome

- Iverson et al. 2015
  - 32,000 high school age athletes, 19% of boys and 28% of girls reported a symptom burden resembling ICD-10 diagnosis of Post-Concussional Syndrome – WITHOUT having had a concussion.
  - Those w/pre-existing conditions even more likely to endorse sx of PCS – 21-47% for boys and 33-72% for girls
  - Strongest independent predictor for symptoms prior treatment of a psychiatric condition, migraine headaches, substance abuse, ADD/ADHD
- No difference in symptoms or functional impairments in concussion vs controls at 90 days

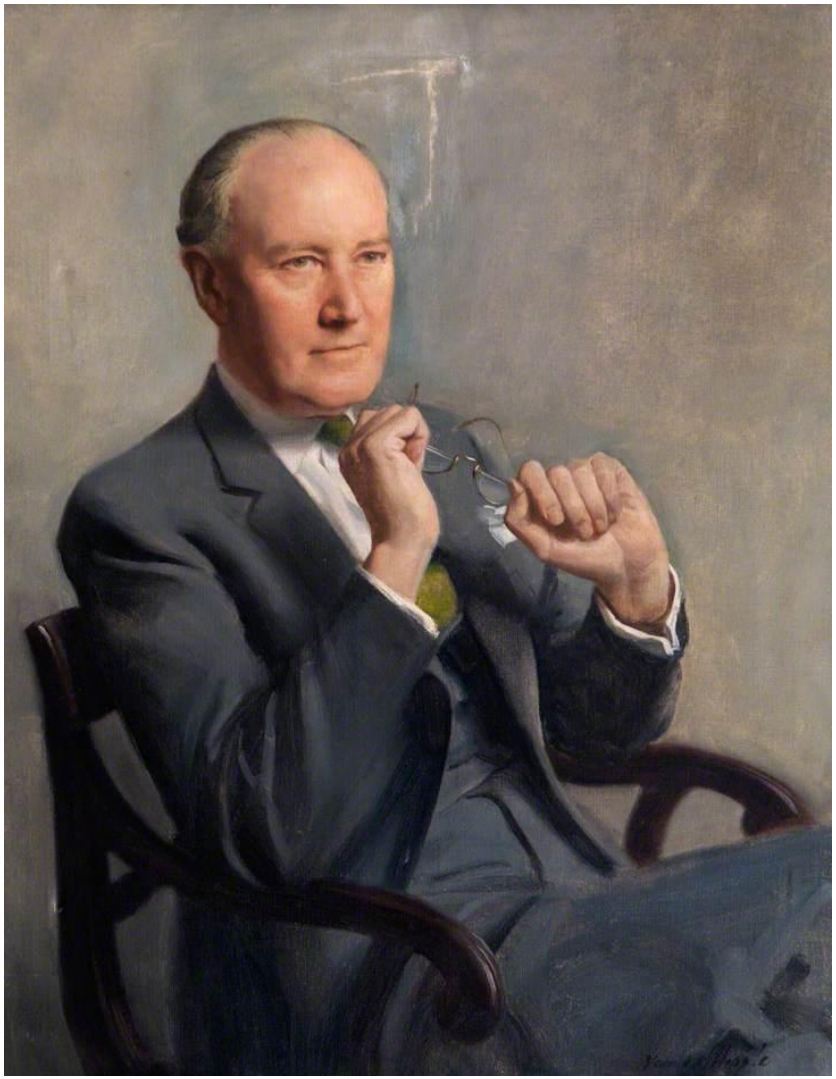


Mannix et al. *Nat Neurol Rev* 2016

Chronic (Progressive) Traumatic Encephalopathy

- Martland 1928 - Punch Drunk
  - ‘slugger’ type boxing style
  - African American
- Millspaugh 1937 – Dementia Pugilistica
- Critchley 1949 - CTE

Chronic (Progressive) Traumatic Encephalopathy



MacDonald Critchley (1900 – 1997)

"Of great interest, pathological as well as practical, is the fact that this traumatic encephalopathy is a progressive condition. Once established it not only does not permit reversibility, but it ordinarily advances steadily. This is the case even though the boxer has retired from the ring and repeated cranial traumata are at an end"

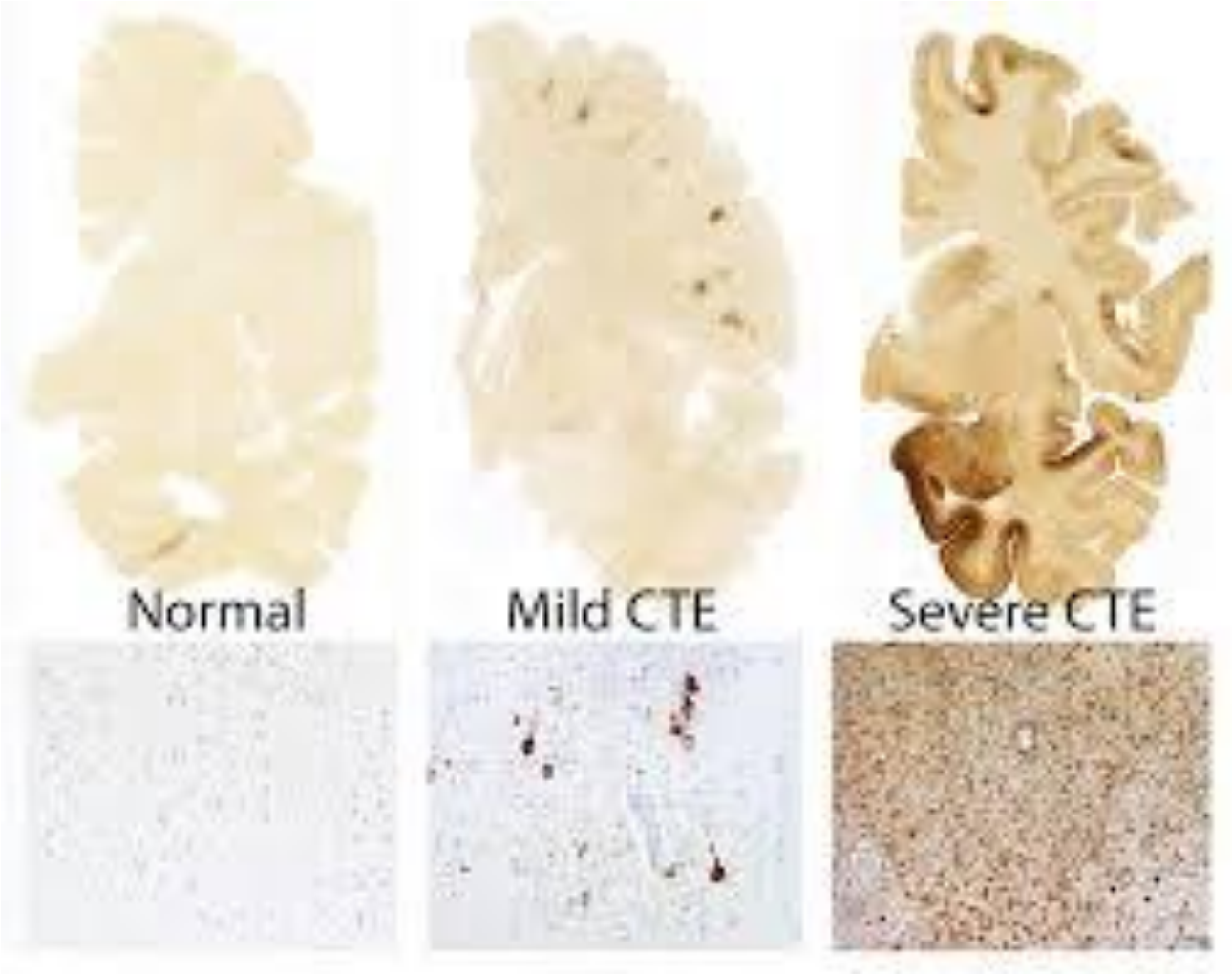
Dr. A. H. Roberts
Brain Damage in Boxers (1969)

- 250 boxers out of 16,871 registered by British Boxing Board (1929-1955)
- 6% long-term disability
- Occasionally progressive
- Questionable clinical correlate

"It has never been doubted, since it is implicit in the contest, that personal injury occurs in boxing"

"…the evidently transient incapacity usually sustained might result in permanent, slight, but cumulative damage to delicate neural structures"

Chronic (Progressive) Traumatic Encephalopathy

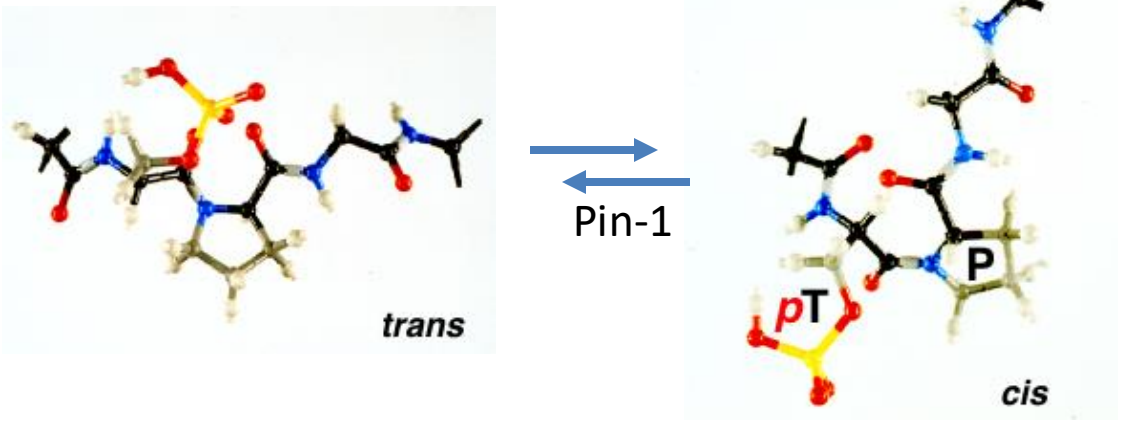


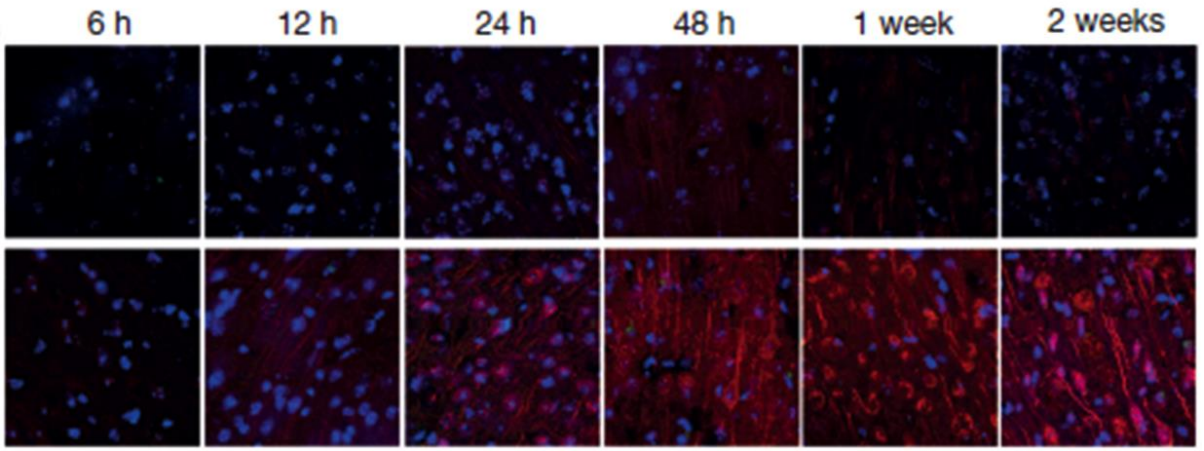
Tau-opathy

Ann McKee, Bob Stern, et al at Boston University

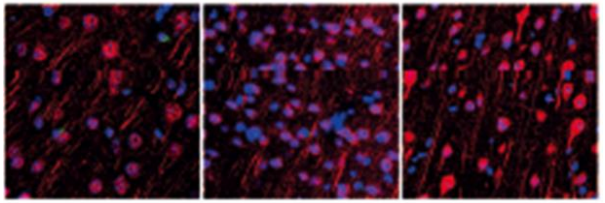
Xiao Zhen Zhou, MD
Kun Ping Lu, MD, PhD

pTau Protein Conformation





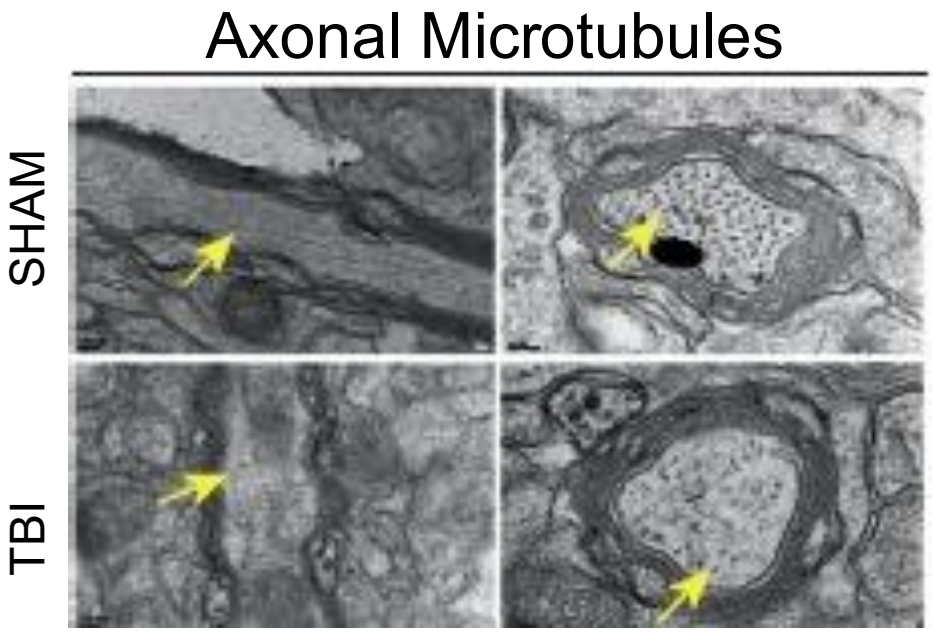
Repeated, mild TBI

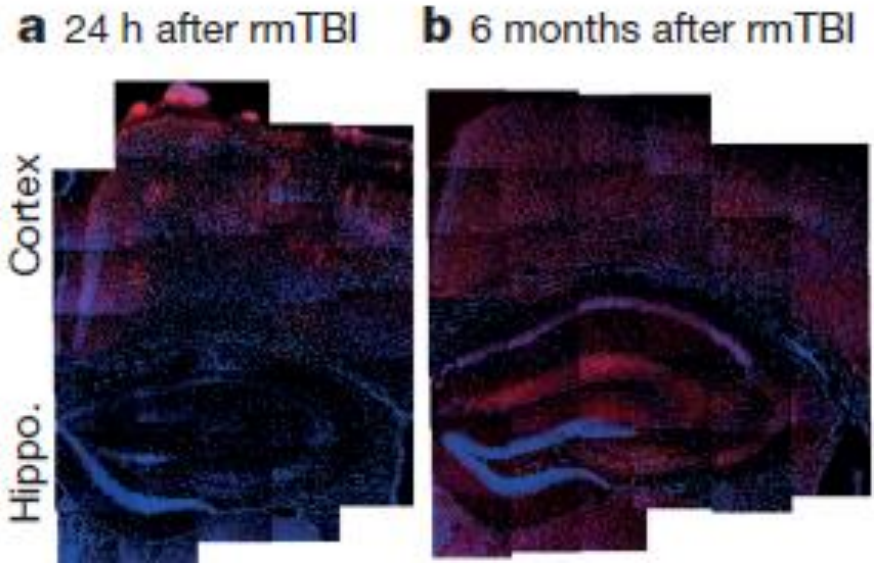


Kondo et al. *Nature* 2015

Xiao Zhen Zhou, MD
Kun Ping Lu, MD, PhD

Cis tau leads to progressive, neuronal degeneration

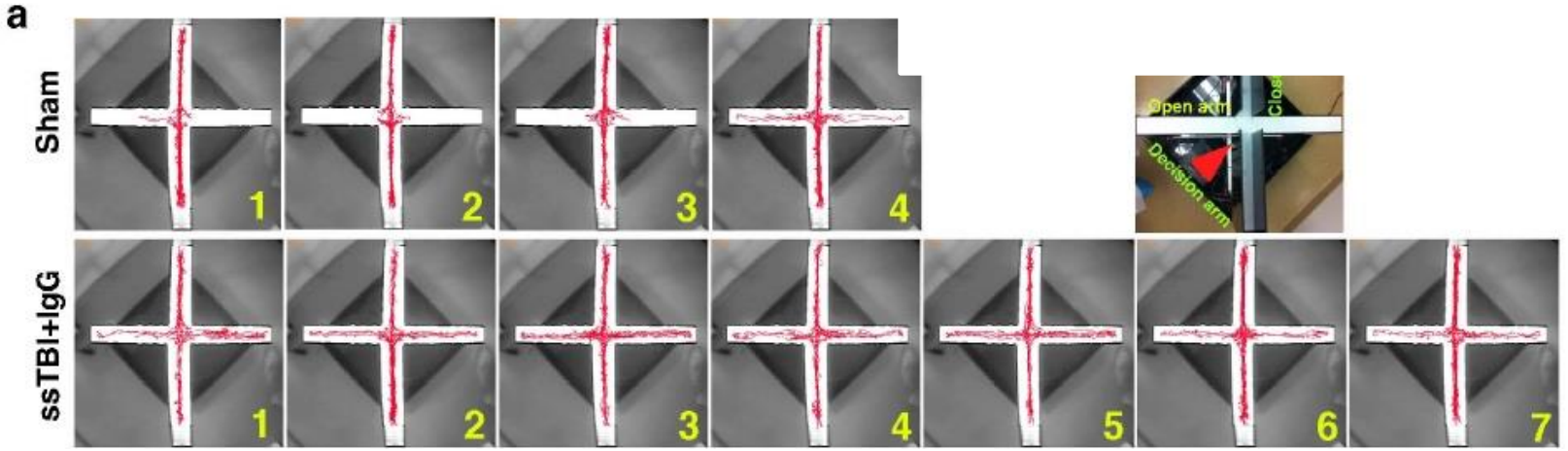




Kondo et al. *Nature* 2015

Xiao Zhen Zhou, MD
Kun Ping Lu, MD, PhD

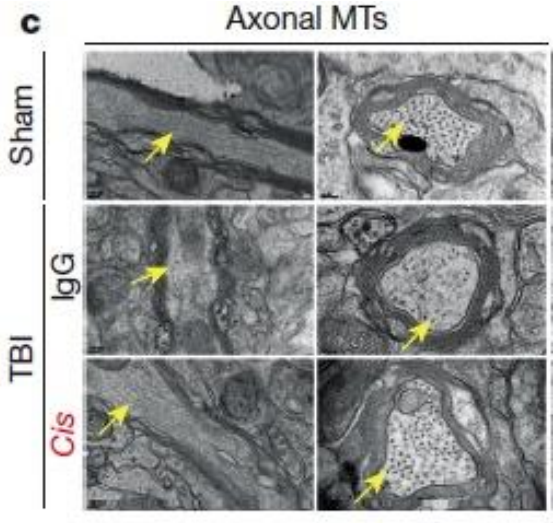
Cis tau associated with behavioral consequences (increased risk taking)

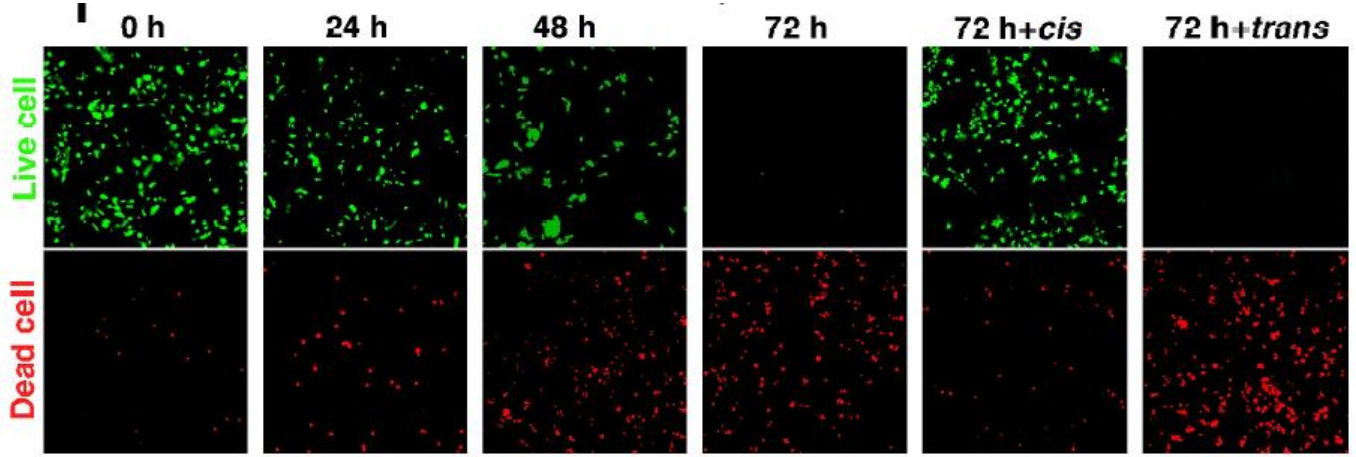


Kondo et al. *Nature* 2015

Xiao Zhen Zhou, MD
Kun Ping Lu, MD, PhD

Ab Blocks cis-Tau prevents degeneration

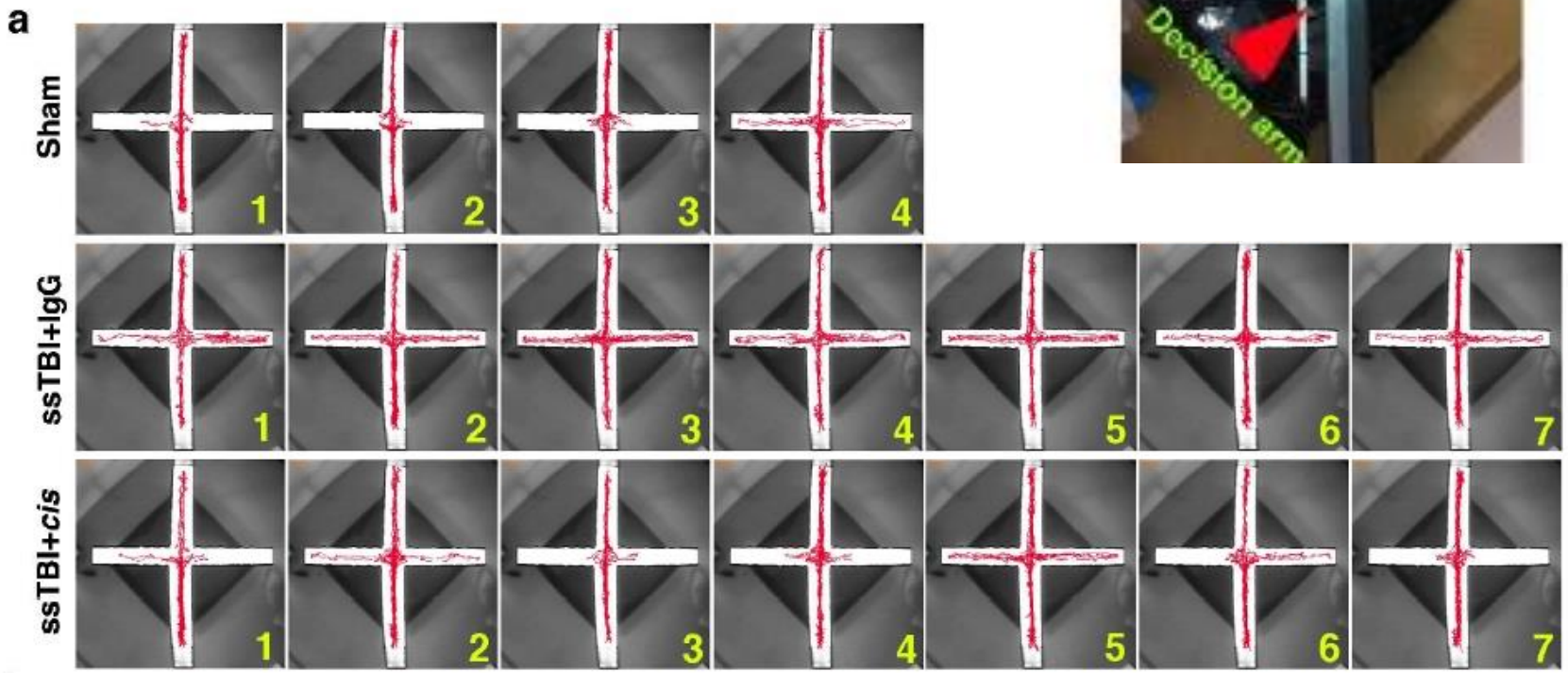




Kondo et al. *Nature* 2015

Ab Blocks cis-Tau spares neurobehavioral function

Xiao Zhen Zhou, MD
Kun Ping Lu, MD, PhD



Kondo et al. *Nature* 2015

CTE

- Repeated (mild) brain trauma can cause CTE
  - But may not be sole cause
- Tau-opathy
  - cis-pTau
  - ? Treatable by Ab

How often are there clinical correlates and what are they?

What triggers the conformational change of pTau and can it be detected and prevented?

Immunohistochemical stain for p-tau

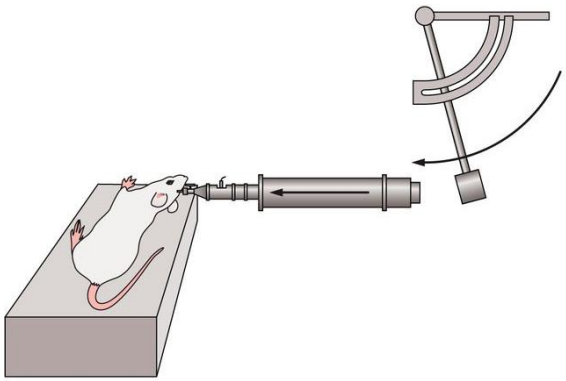
Control in NIH Neurobiobank for Neurodevelopmental Disorders Univ. Maryland

- 51 y/o
- Sudden death: pneumonia & cardiovascular complications
- Previously healthy
  - No medications
  - No EOTH or illicit drugs
- Professional boxer in youth
  - 14 fights
  - Lost 7, 2 knock out

Castellani & Perry *JAD* 2017

Animal Model of Mild TBI

Alex Rotenberg

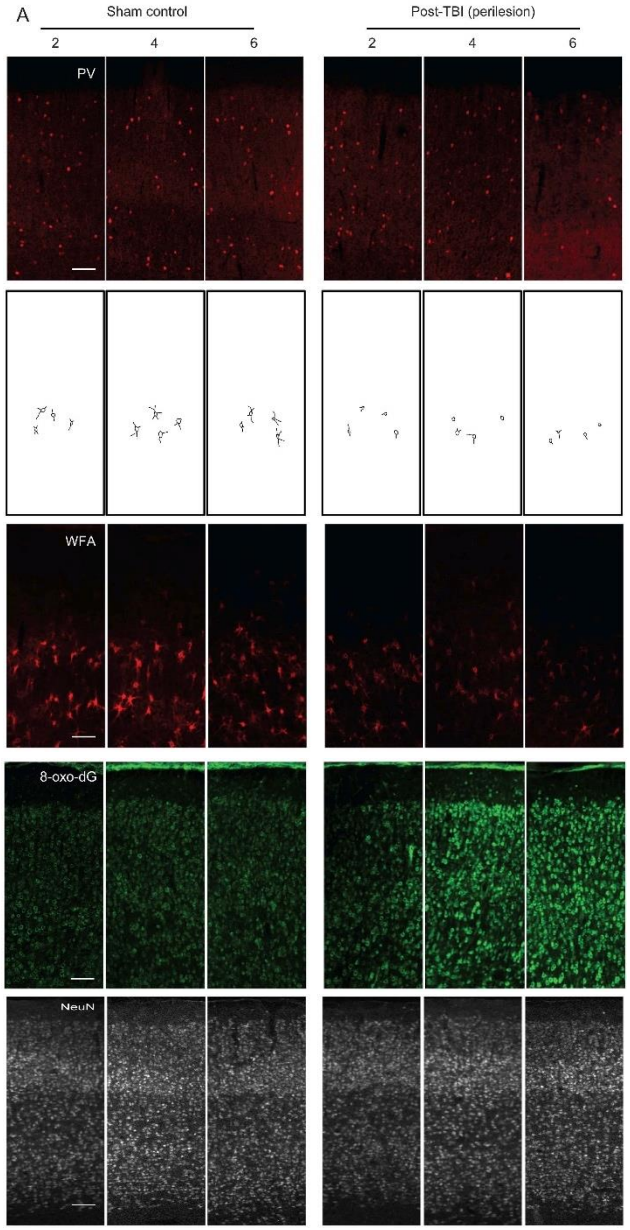


Parvo-albumin positive (PV+) Cell Loss

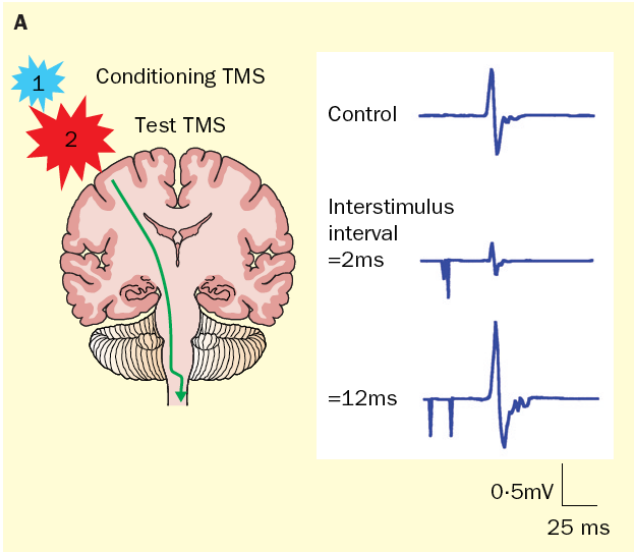
PeriNeuralNet (PNN) Damage

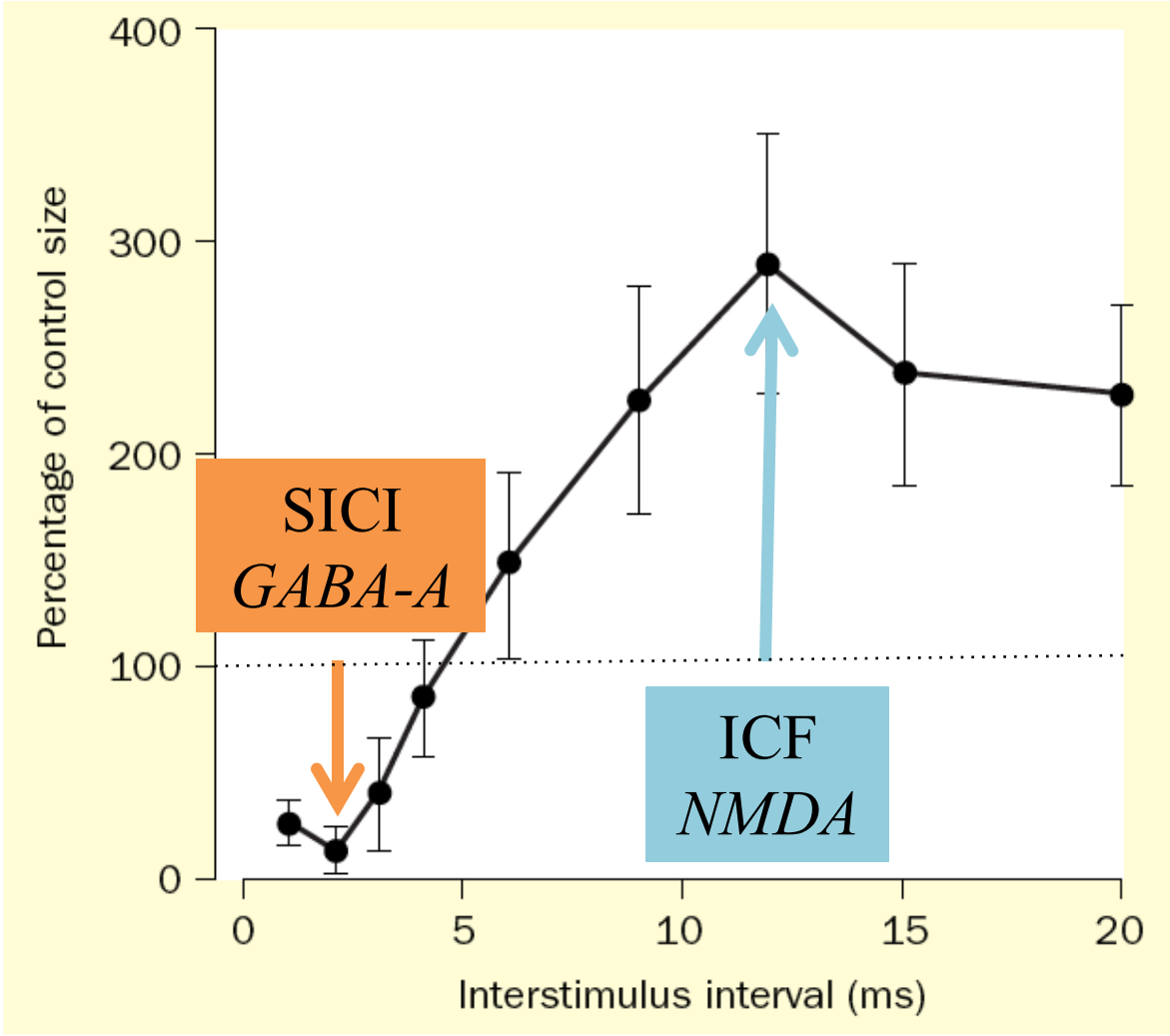
Increased Oxidative Stress

Neuronal cell count unchanged



Paired-Pulse Transcranial Magnetic Stimulation



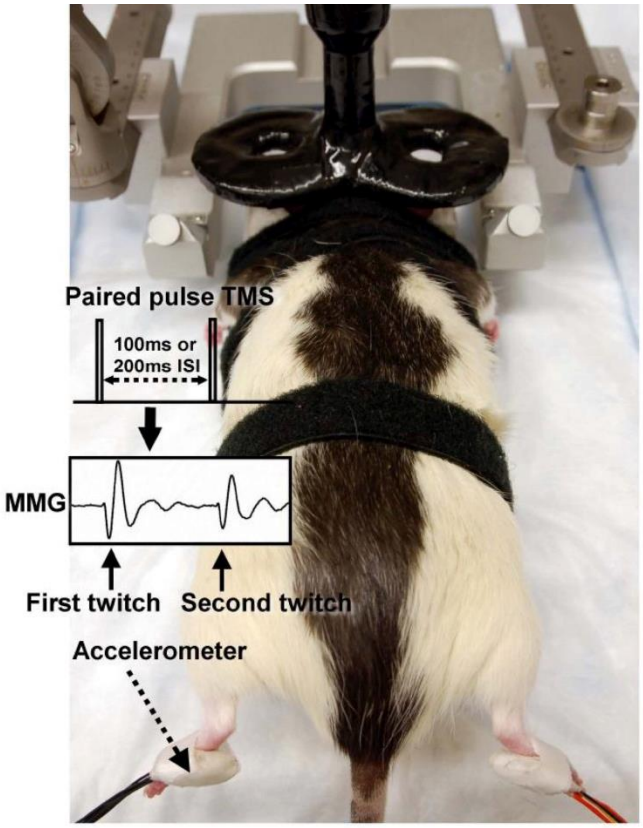


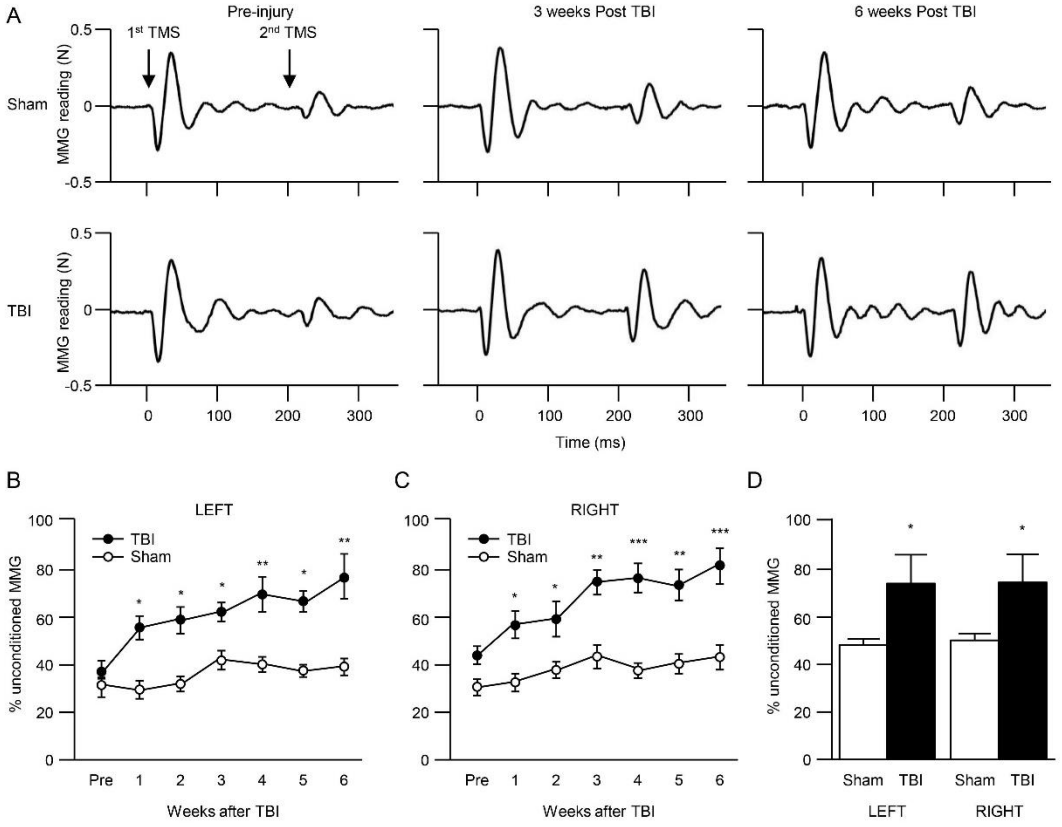
Kobayashi et al *Lancet Neurol* 03

Alex Rotenberg

Animal Model of Mild TBI:

Abnormal E/I balance demonstrable by ppTMS

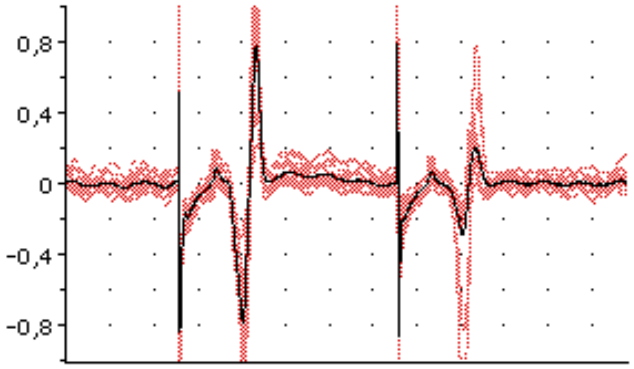




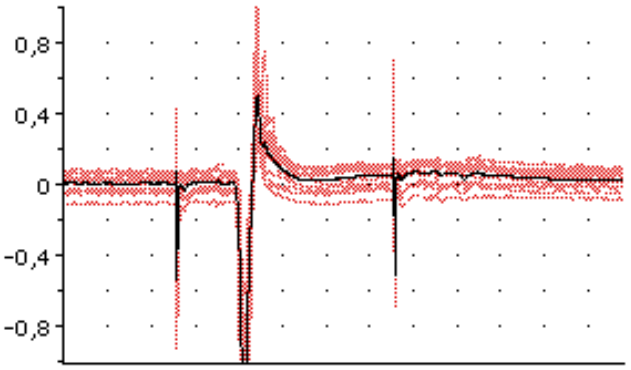
Concussion / mild TBI: Long Interval Intracortical Inhibition

Translatable Biomarker

Control

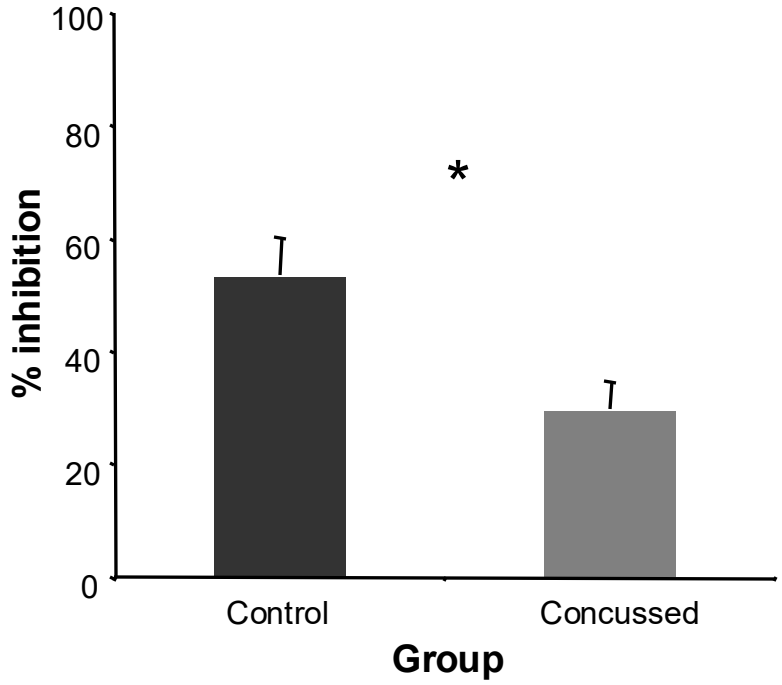


Concussed



Hugo Theoret

Long Interval Cortical Inhibition
GABA-B mediated



De Beaumont et al. *Neurosurgery* (2008)

Brain Trauma

Disruption of PNN

Loss of PV+ cells

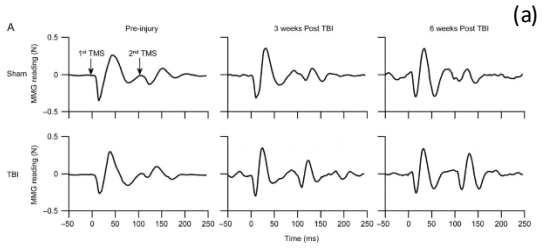
Alteration of intrinsic brain rhythms

Conformational changes in p-Tau

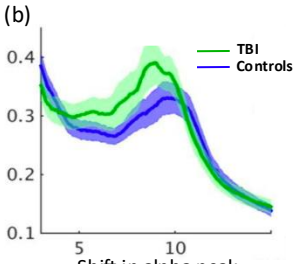
Cis-pTau toxicity and accumulation

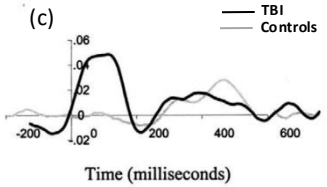
Neuronal Cell Death & Breakdown of brain networks

paired pulse TMS
Loss of ICI



EEG
Loss of Gamma Activity
Alpha Slowing

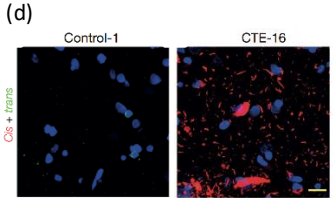




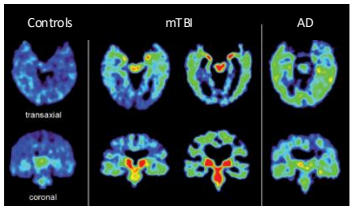
Decreased evoked gamma

CSF
cis p-Tau elevation

PET
Tau Deposition

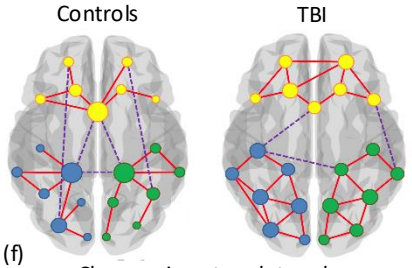


Blue= DNA Red= cis-TAU Green= trans-TAU

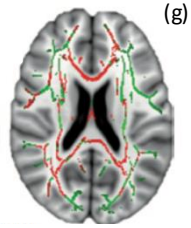


TAU binding at PET imaging

MRI (e.g. rsfcMRI & DTI)
Loss of Connectivity
Atrophy



Changes in network topology



White matter disconnection

Pathophysiological Processes

Translational Biomarkers & Interventional Targets

Whole Player

Multiple Chronic Conditions

Aaron Baggish, MD

Affliction Counts
0, n=805
4, n=23
3+4, n=130

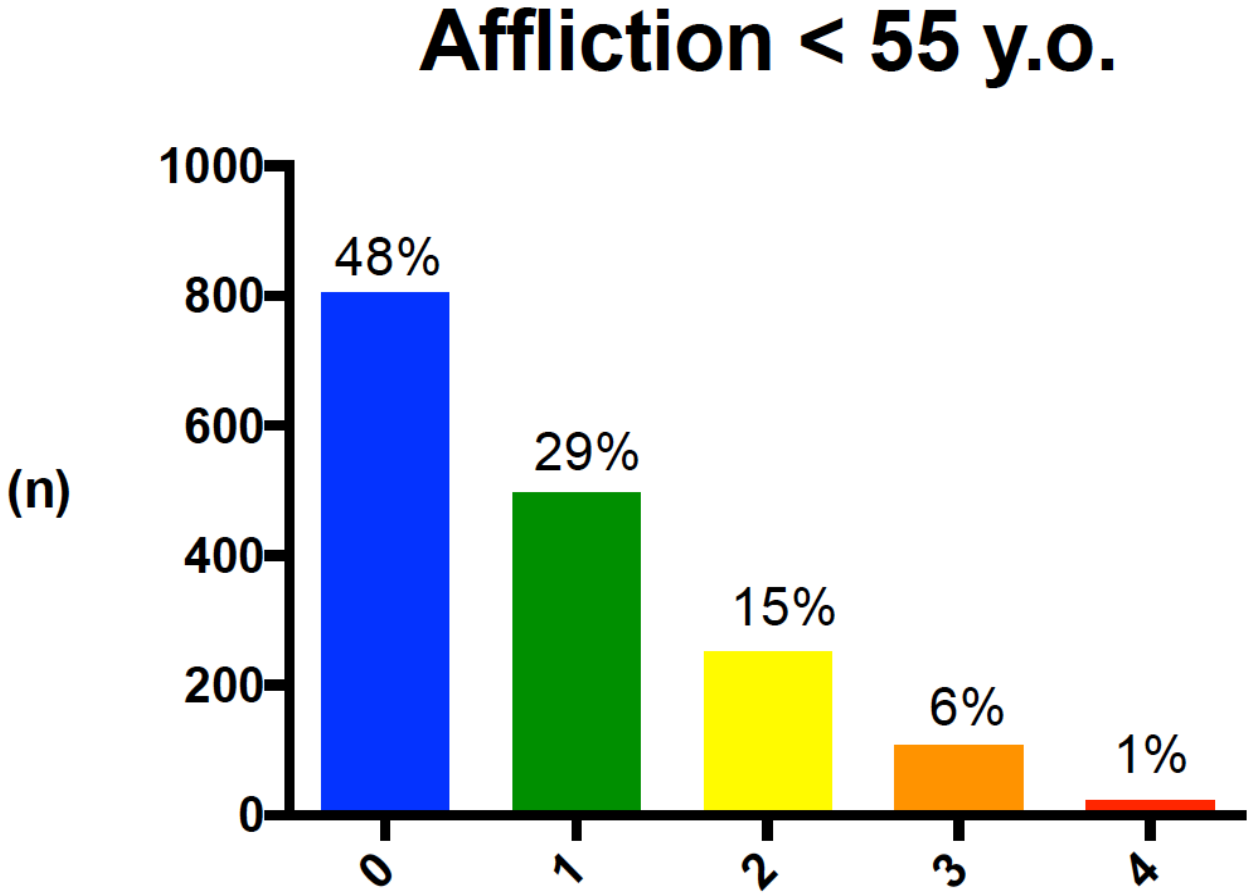
Determinants:

-Weight

- Field Position

- Ethnicity

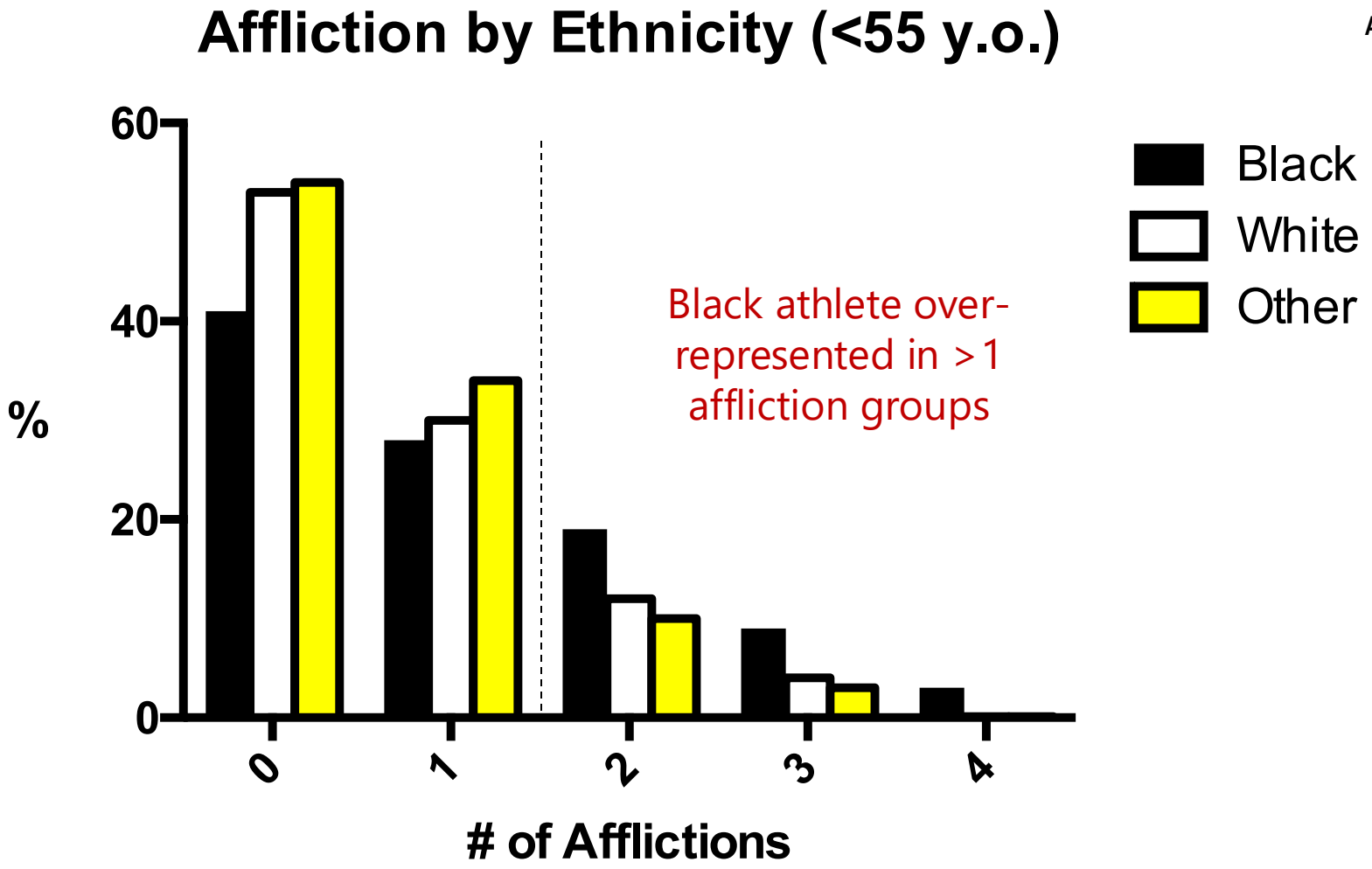
- ? Career length



THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

Multiple Chronic Conditions

Aaron Baggish, MD



THE FOOTBALL PLAYERS HEALTH STUDY AT HARVARD UNIVERSITY

CONFIDENTIAL

Multiple Chronic Conditions

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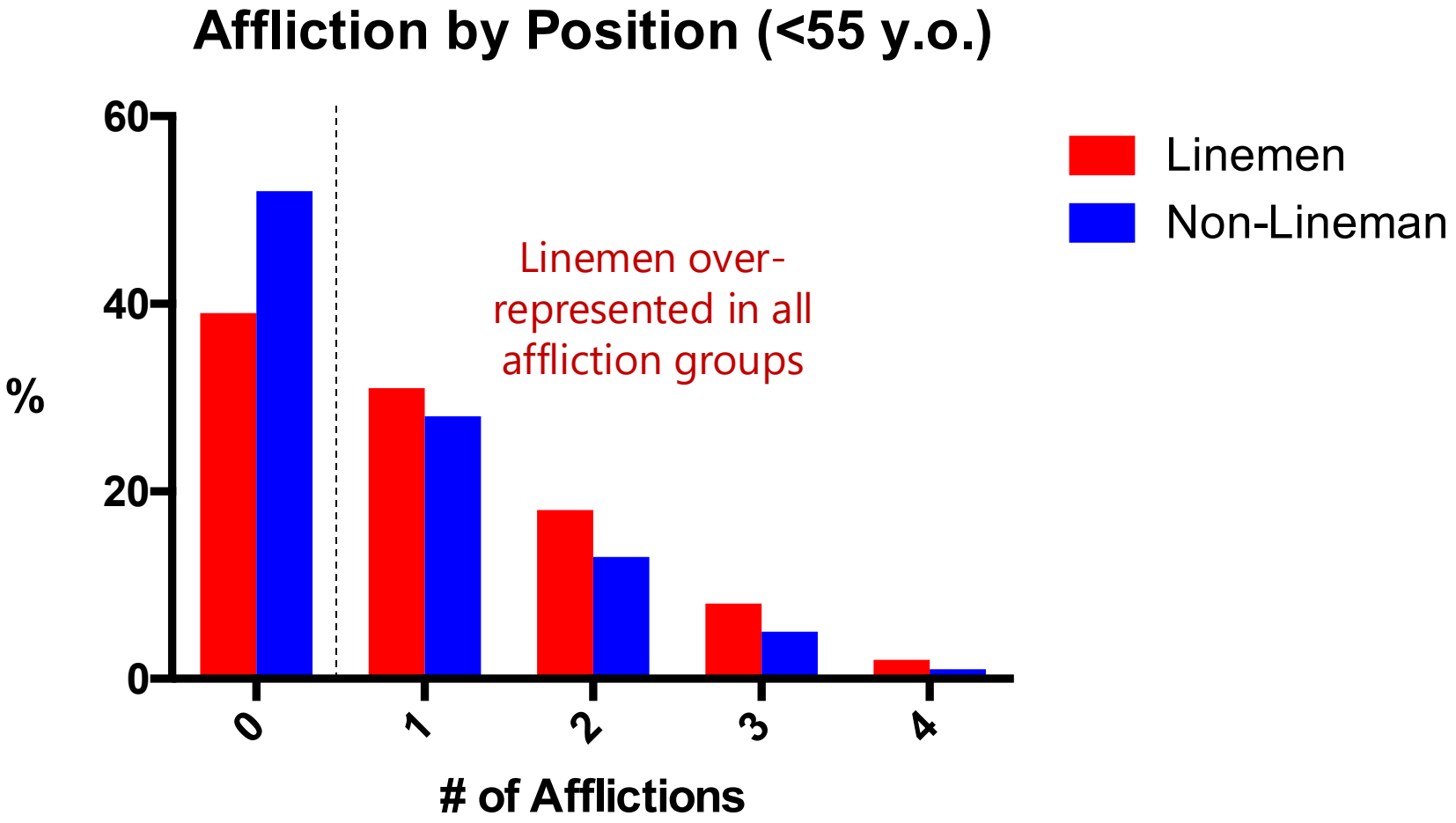

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Multiple Chronic Conditions

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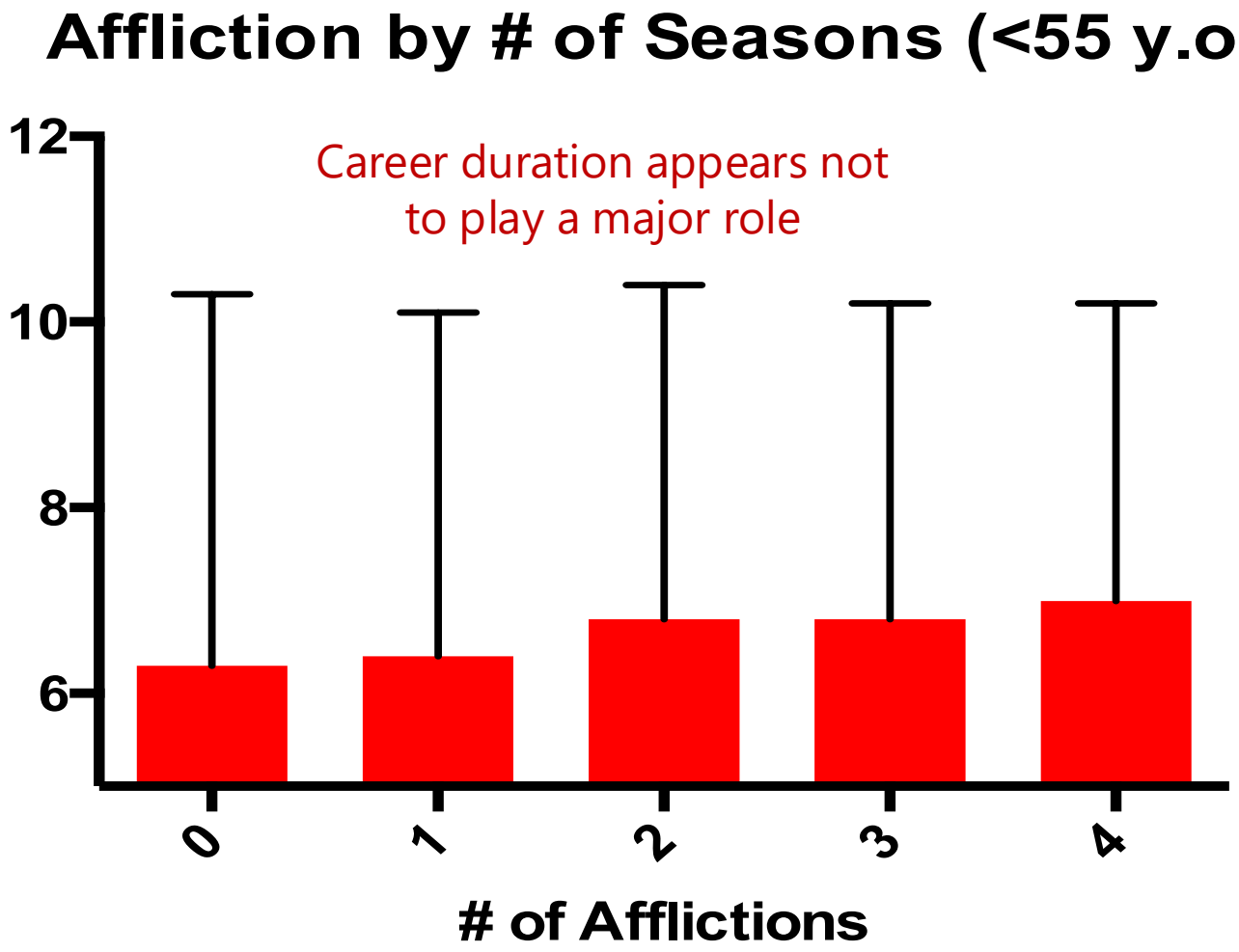

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Traumatic Brain Injury, Concussion, and American (Style) Football.

1. Progressive tau-opathy is a possible consequence of repeated brain trauma (concussions, subconcussive blows)
2. The clinical correlates of such pathological tau deposition remains unclear
3. We need to more fully understand the range of health consequences of exposure to football, how to detect them early, and how to prevent (minimize) their consequences
4. As in all of medicine (and in life) one must weigh the relative benefits and risks of any activity - to do that properly, more research and public education is critical