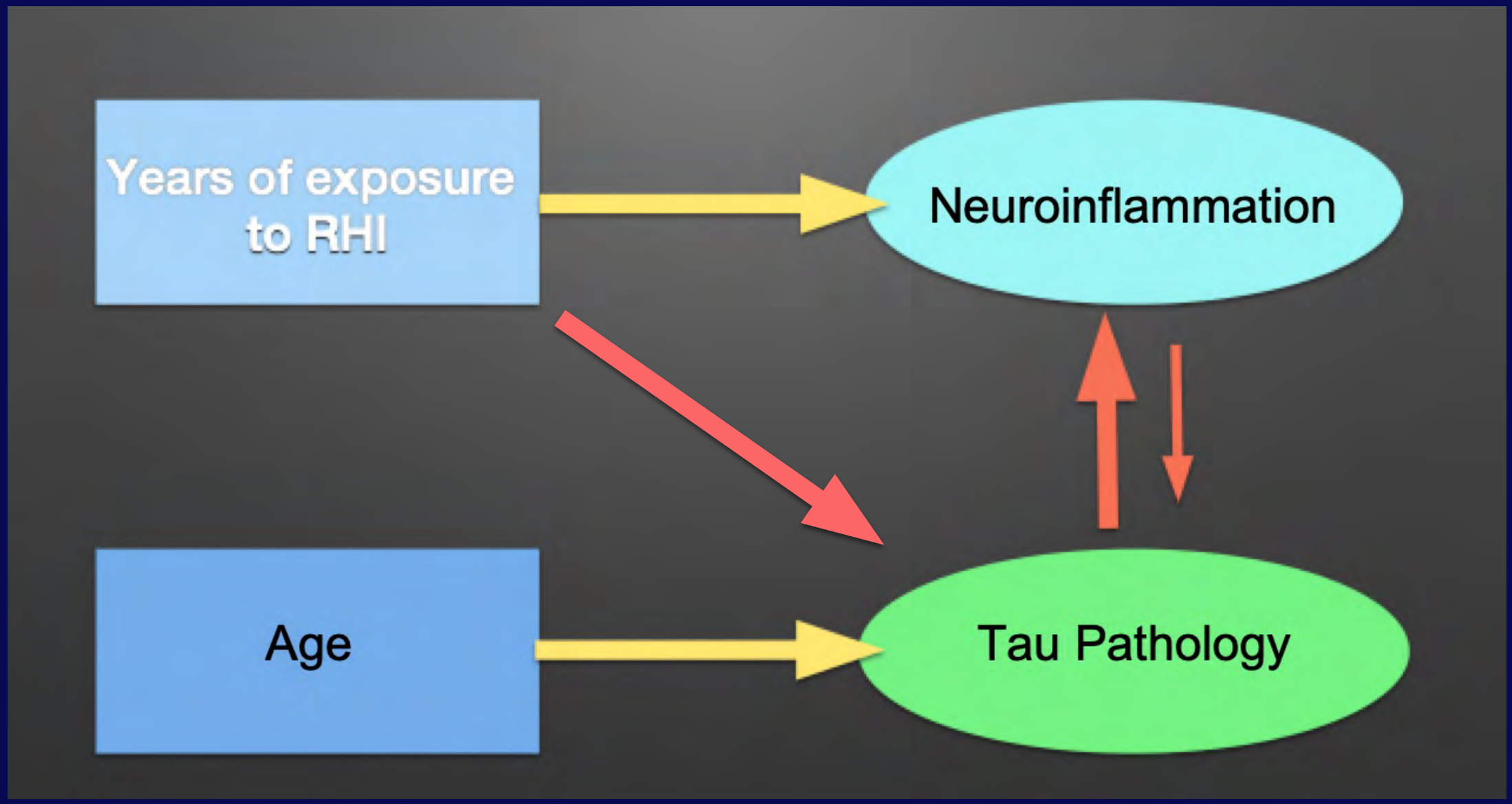
Dose-response between RHI and outcome:

Greater years of football, higher level of play predict: increased CTE severity, greater ptau burden, greater inflammation



Cherry, et al Acta Neuropath Comm 2016

JAMA Neurology | Original Investigation

Association of White Matter Rarefaction, Arteriolosclerosis, and Tau With Dementia in Chronic Traumatic Encephalopathy

Michael L. Alosco, PhD; Thor D. Stein, MD, PhD; Yorghos Tripodis, PhD; Alicia S. Chua, MS; Neil W. Kowall, MD; Bertrand Russell Huber, MD, PhD; Lee E. Goldstein, MD, PhD; Robert C. Cantu, MD; Douglas I. Katz, MD; Joseph N. Palmisano, MPH, MA; Brett Martin, MS; Jonathan D. Cherry, PhD; Ian Mahar, PhD; Ronald J. Killiany, PhD; Michael D. McClean, ScD; Rhoda Au, PhD; Victor Alvarez, MD; Robert A. Stern, PhD; Jesse Mez, MD, MS; Ann C. McKee, MD

180 football players > 40 yrs with CTE:

- Years of playing football associated with increased white matter rarefaction and p-tau NFTs
- White matter rarefaction and p-tau NFTs associated with dementia
- Arteriolosclerosis associated with dementia but not years of football.
- Dementia in CTE is likely a result of multiple neuropathologic changes associated with trauma, including white matter rarefaction and NFTs, in addition to non trauma–associated changes, such as arteriolosclerosis.

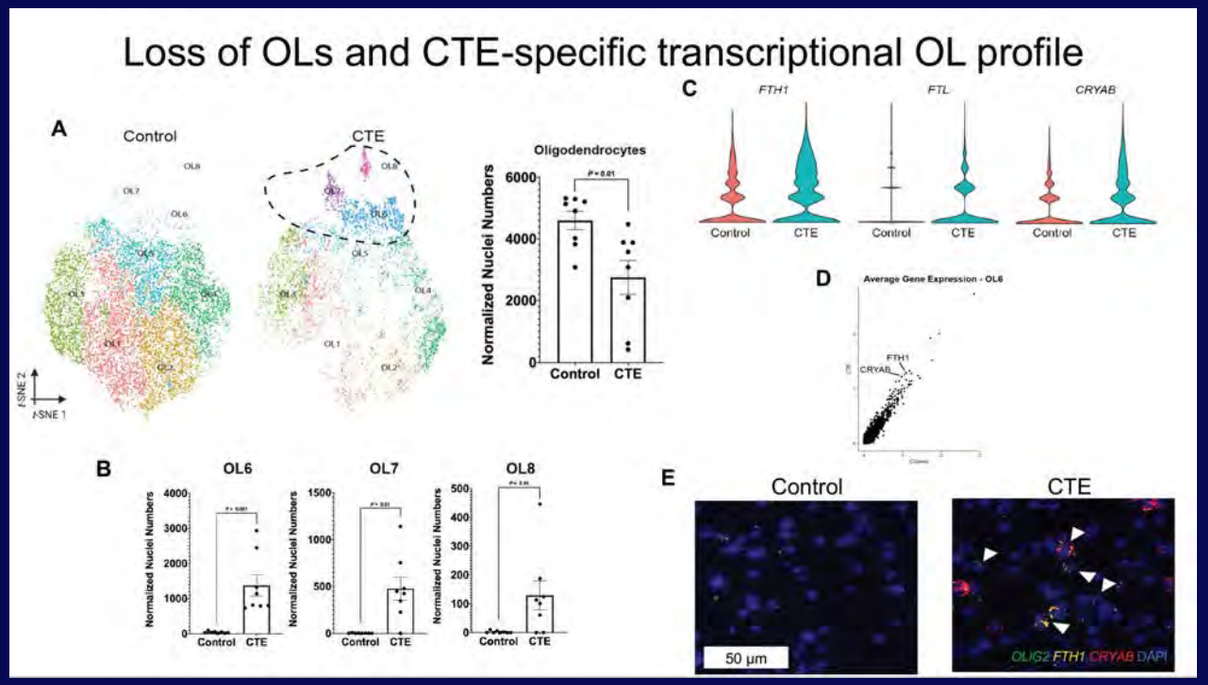
Alosco et al., JAMA Ny, 2019

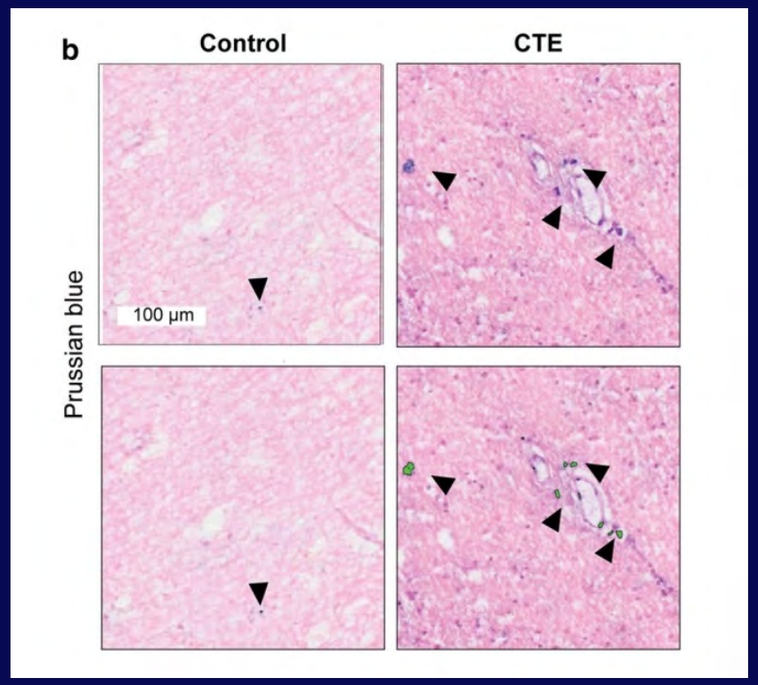
Altered oligodendroglia and astroglia in chronic traumatic encephalopathy

K. Blake Chancellor[1] · Sarah E. Chancellor[2] · Joseph E. Duke-Cohan[1] · Bertrand R. Huber[2,3,4,6] · Thor D. Stein[2,4,5,6] · Victor E. Alvarez[2,3,4,6] · Benjamin W. Okaty[1] · Susan M. Dymecki[1] · Ann C. McKee[2,3,4,5,6]

Single-nucleus RNA-seq cell nuclei from DLF white matter

- Oligodendrocytes were reduced in CTE and altered in relative proportions of subtypes compared to controls
- CTE-enriched oligodendrocytes showed more transcripts relevant to iron metabolism and cellular stress response
- CTE tissue also demonstrated excessive iron accumulation histologically





Chancellor et al, Acta Neuropath 2021

Clinical Presentation associated w CTE pathology:

Traumatic Encephalopathy Syndrome (TES)

Behavioral/mood vs. Cognitive

Behavioral tends to have a younger age at onset, m = 35 yrs;
Cognitive presentation similar to AD, older age at onset, m =59 yrs.

Most common clinical features (>70%) in pathologically verified CTE

COGNITIVE	BEHAVIORAL	MOOD	MOTOR
Memory	Physical violence	Depression	Ataxia
Executive dysfunction	Verbal violence	Hopelessness	Dysarthria
Impaired attention	Explosivity	Suicidality	Gait impairment
Dementia	Loss of control	Anxiety	Tremor
Cognitive impairment	Short fuse	Irritability	Masked facies
	Impulsivity	Apathy	Rigidity
	Paranoia	Loss of interest	
	Rage	Fearfulness	

Stern et al, Neurology 2013

Montenigro et al. Alzheimers Res Ther 2014

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

National Institute of Neurological Disorders and Stroke Consensus Diagnostic

Criteria for Traumatic Encephalopathy Syndrome

NINDS Consensus Diagnostic Criteria for TES: the clinical disorder associated with CTE pathology

1. substantial exposure to RHI from contact sports, military service, or other causes (e.g., a minimum of 5 years of football, with at least 2 years played at the high school level or beyond)
2. a progressive course of cognitive impairment (specifically in episodic memory and/or executive functioning) or neurobehavioral dysregulation (including explosiveness, impulsivity, rage, violent outbursts, and emotional lability) or both.
3. Other neurologic, psychiatric, or medical conditions cannot be fully responsible for these clinical problems, although other neurologic and psychiatric conditions may be diagnosed together with TES.
4. Biomarkers, such as PET scans and blood tests, will be integrated into the criteria to improve diagnostic accuracy in the next few years and allow appropriate use of the criteria to diagnose patients in the clinic.

Katz et al., Neurology, 2021

RESEARCH ARTICLE

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Validity of the 2014 traumatic encephalopathy syndrome criteria for CTE pathology

- *In 2014, criteria for TES were proposed for use in research settings to diagnose CTE in life.*
- To assess the reliability and diagnostic validity of TES criteria, a team of clinicians interviewed family members of 336 brain donors exposed to RHI from contact sports, military service and/or physical violence who were at risk for CTE.
- A total of 309 donors were diagnosed with TES; 244 donors had CTE pathology.
- TES criteria demonstrated sensitivity and specificity of 0.97 and 0.21, respectively.
- Cognitive symptoms (odds ratio [OR] = 3.6; 95% confidence interval [CI]: 1.2–5.1 were significantly associated with CTE pathology.
- Having AD pathology was significantly associated with reduced TES accuracy (OR = 0.27; 95% CI: 0.12–0.59).
- TES criteria provided good evidence to rule out, but limited evidence to rule in, CTE pathology. Requiring cognitive symptoms in revised criteria and using AD biomarkers may improve CTE pathology prediction.
- MM

Mez et al., Alz & Dementia, 2021

Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules

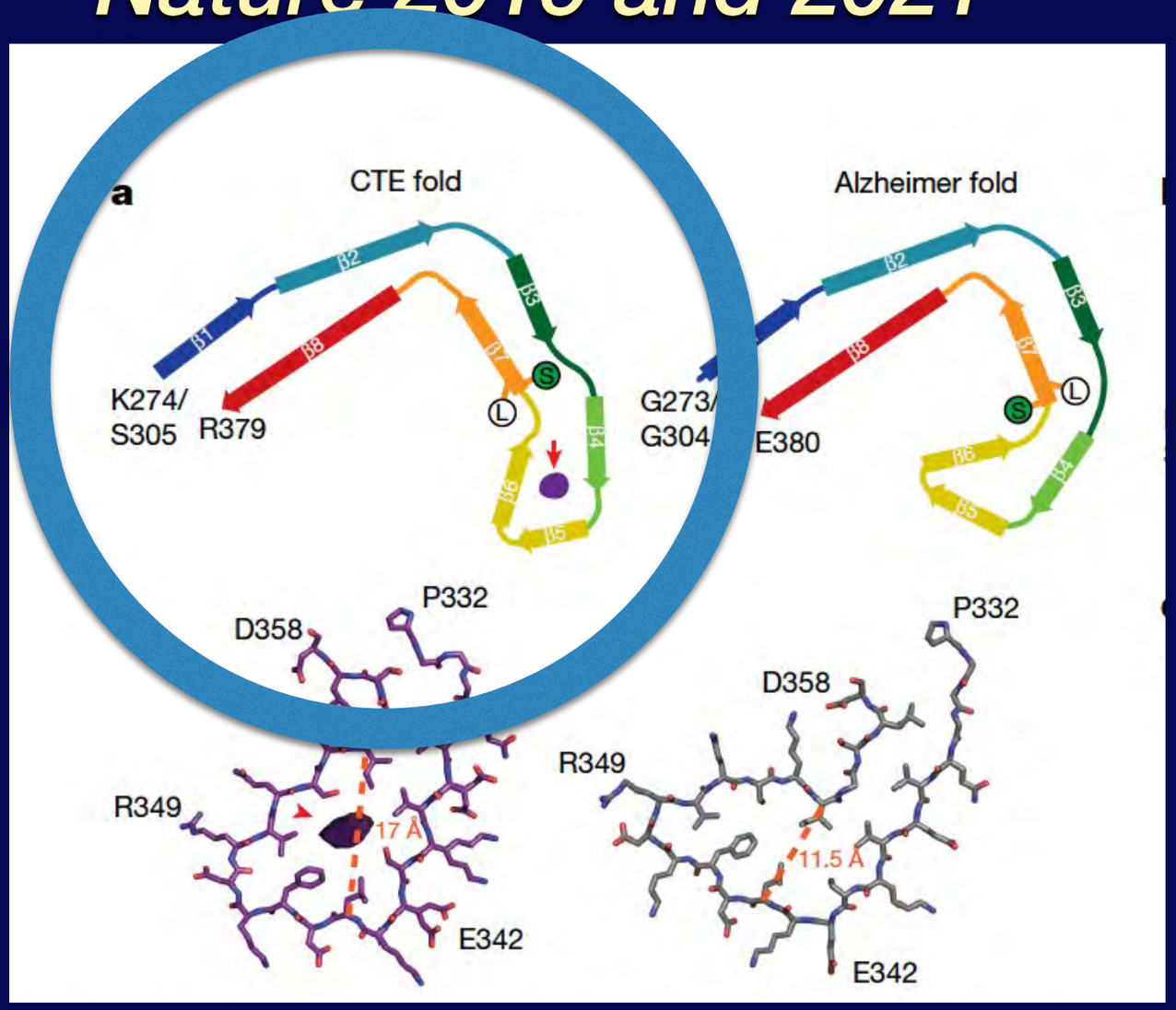
Benjamin Falcon[1], Jasenko Zivanov[1], Wenjuan Zhang[1], Alexey G. Murzin[1], Holly J. Garringer[2], Ruben Vidal[2], R. Anthony Crowther[1], Kathy L. Newell[3], Bernardino Ghetti[2], Michel Goedert[1,4]* & Sjors H. W. Scheres[1,4]*

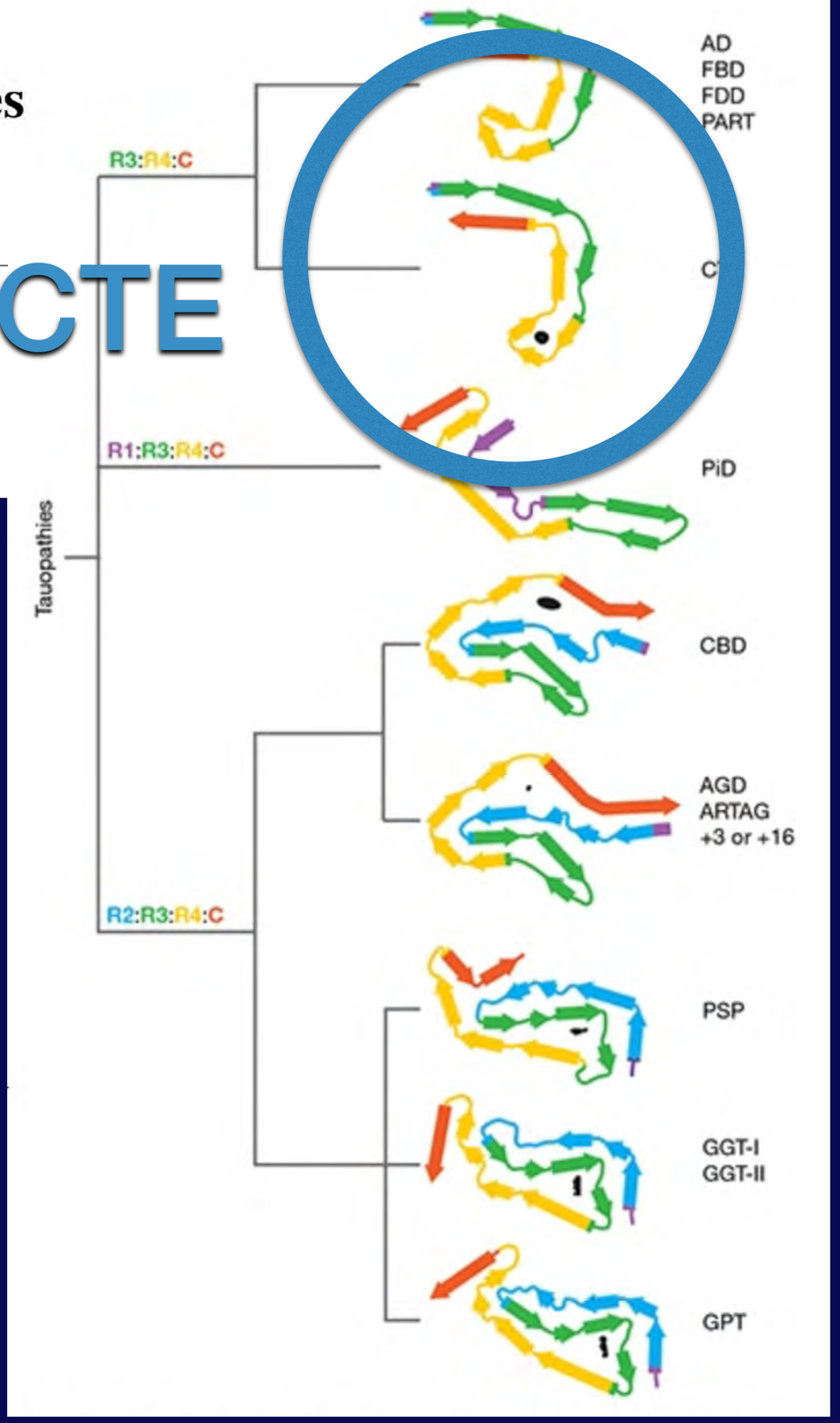
Article

Structure-based classification of tauopathies

CTE

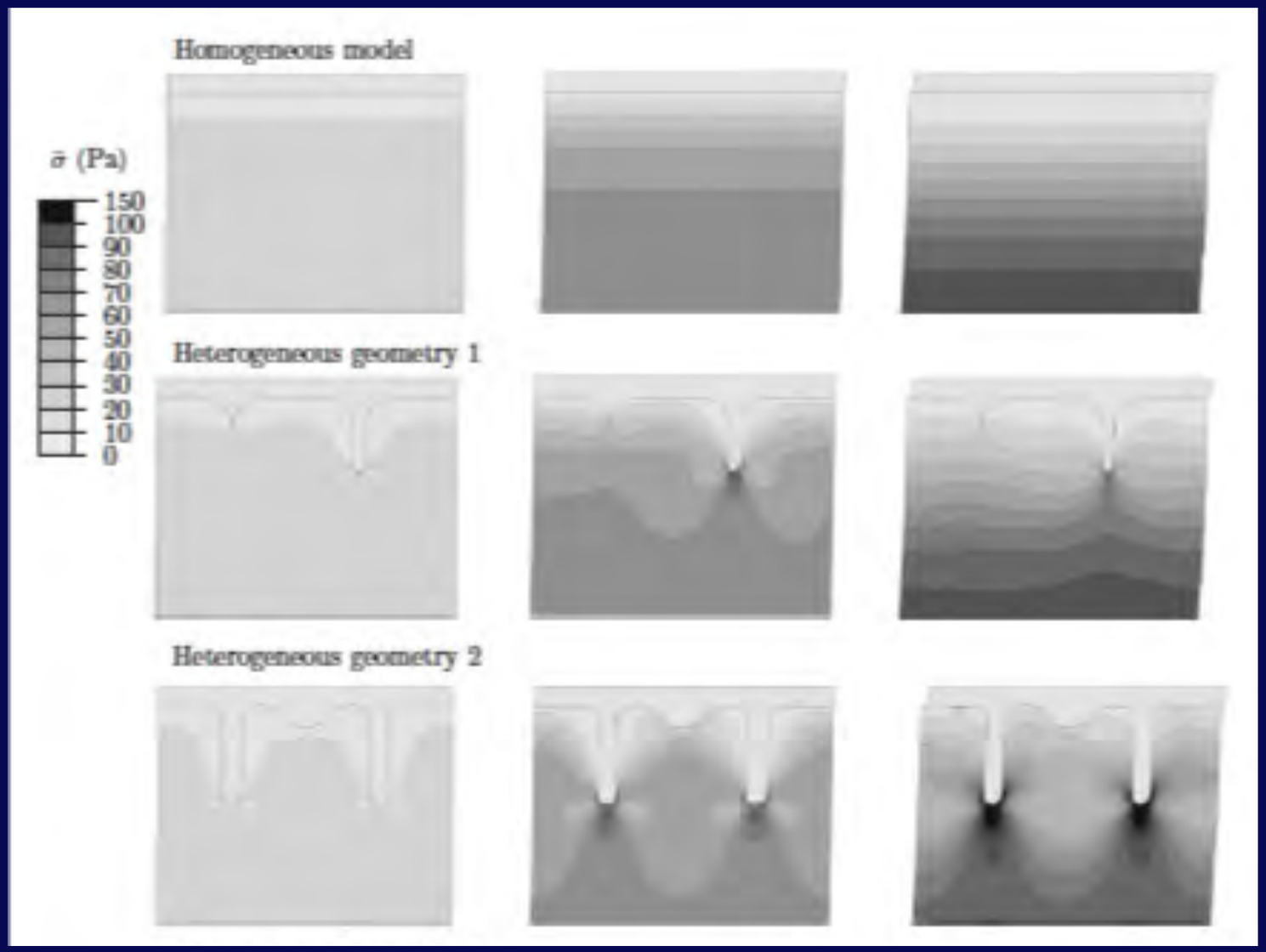
Nature 2019 and 2021

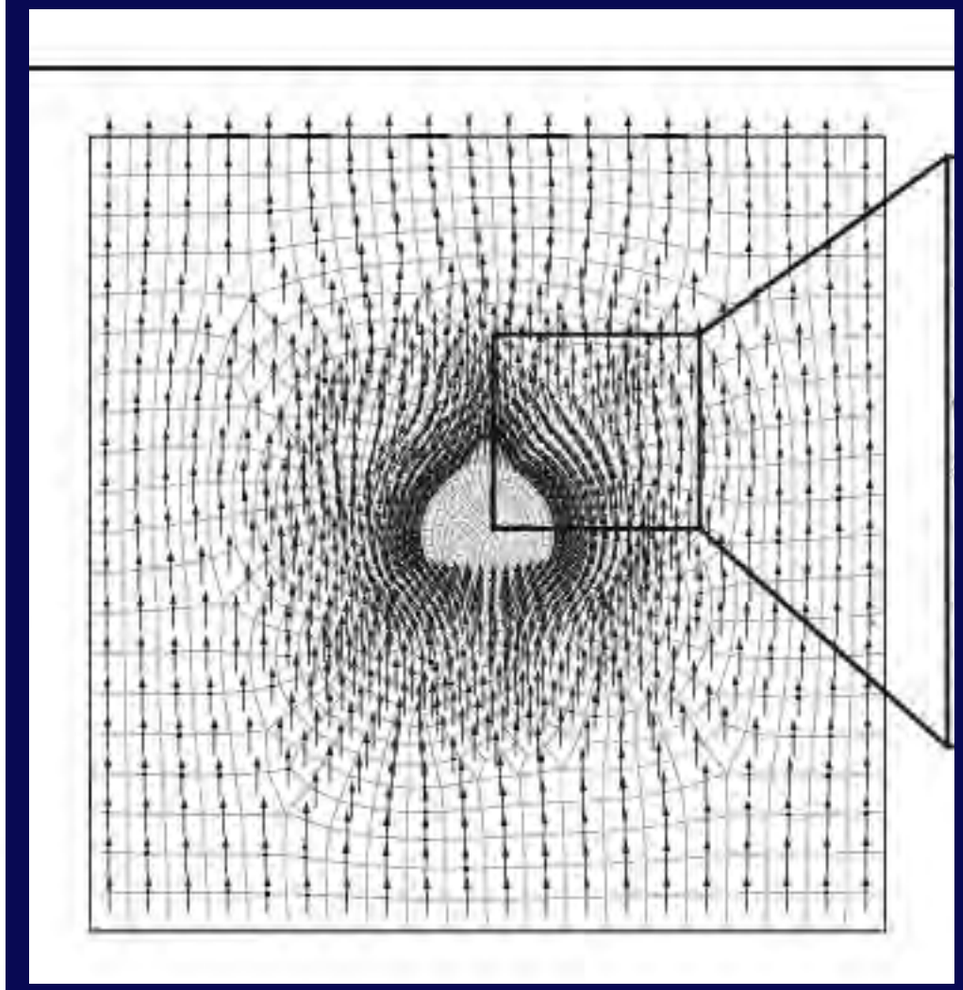




Why is ptau protein deposited in those brain regions?

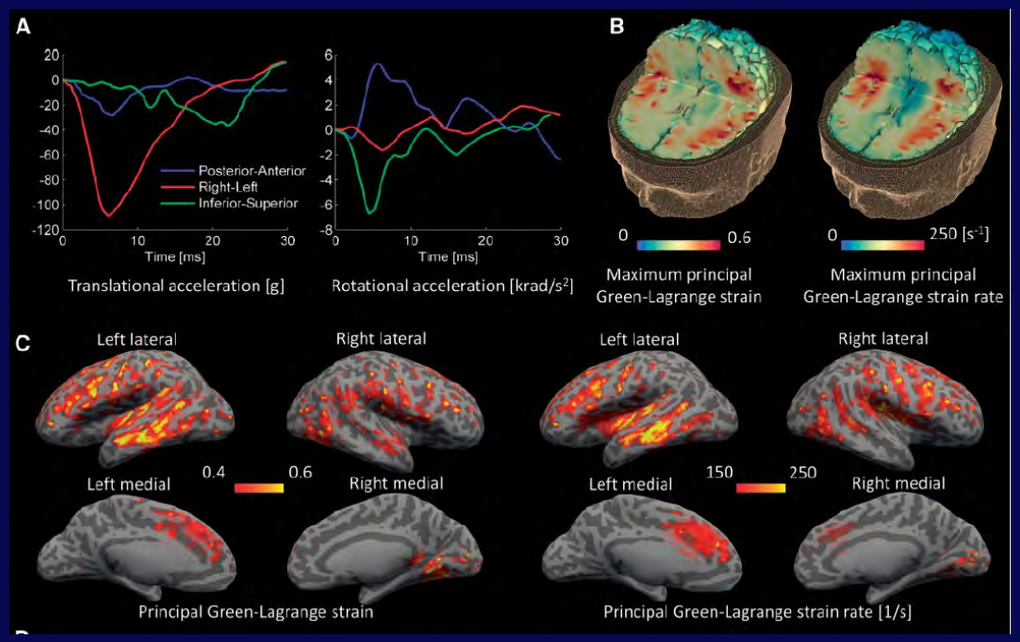
Sulcal depth and perivascular region are areas of physical stress and strain concentration during impact injury





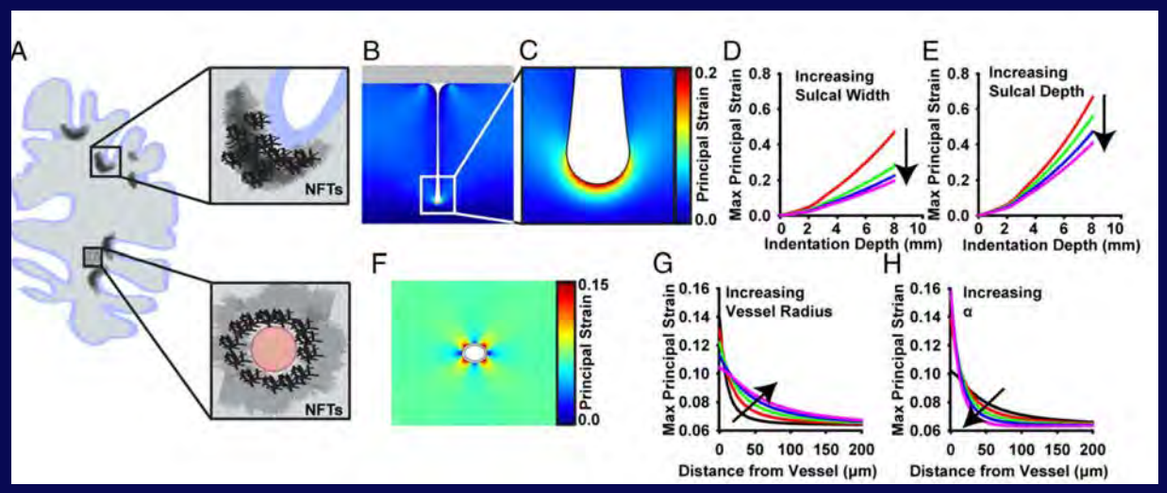
Cloots et al Annals of Biomedical Engineering, 2008
Cloots et al.J Mechanical Beh Biomed Mat 2012

Many computational and finite element model studies of head impact injury show: *greatest tissue strain and deformation occur at sulcal depth and perivascular region*



Higher strain and strain rate in sulci compared to gyri

Ghajari et al, Brain 2017, J. Biomechanics 2021



Finite element model : Greatest mechanical deformation in depth of sulcus and perivascular region.

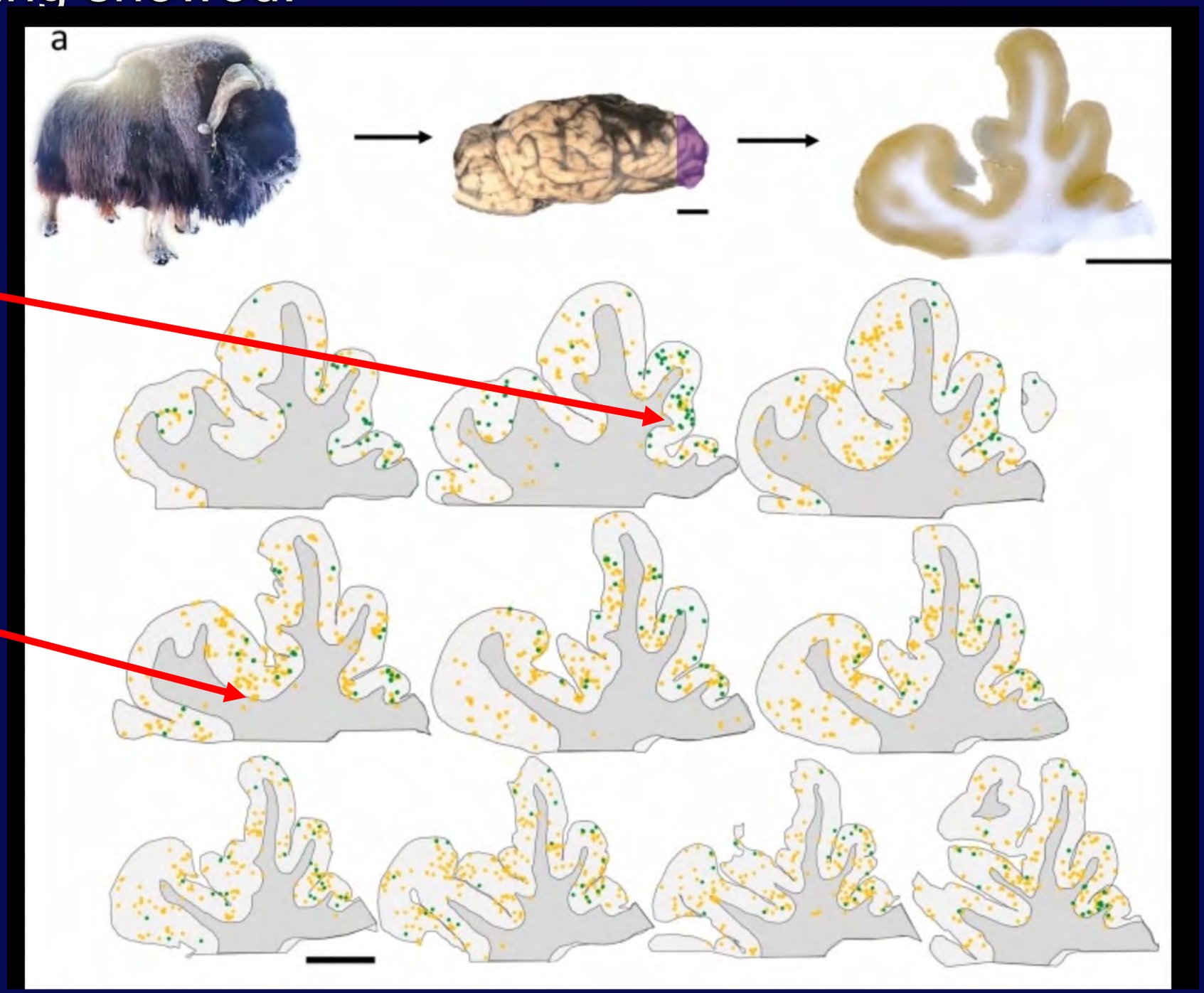
Liao et al. PNAS 2021

Studies in Muskoxen

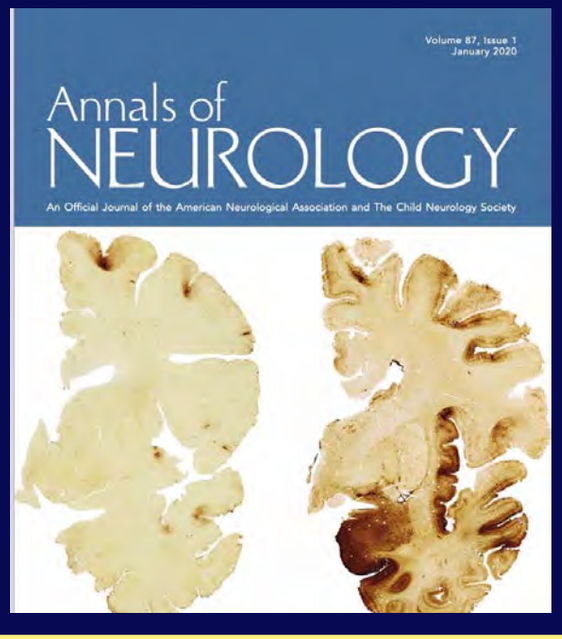
Muskoxen (*Ovibos moschatus*, *n* = 3) gyrencephalic mammals who participate in headbutting showed:

Brain shows
p-tau neuritic threads, neurites, and neurons:

superficial cortex,
sulcal depths and
occasionally
around blood vessels



Ackermans et al. Acta Neuropathol 2022



RESEARCH ARTICLE

Duration of American Football Play and Chronic Traumatic Encephalopathy

Jesse Mez, MD, MS,[1,2,3] Daniel H. Daneshvar, MD, PhD,[1,4]

Among 266 football players:

- Risk of developing CTE increased by 30 percent per year played
- For each 2.6 additional years of football, odds of developing CTE doubled
- Among those w CTE, for each additional 5.3 yrs, the odds for severe CTE doubled
- Those who played < 4.5 yrs were 10 X less likely to develop CTE than those who played longer
- Those who played >14.5 yrs were 10 X more likely to develop CTE than those who played less

Using simulation and inverse probability weighting, accounting for all degree of selection bias, the strength of the duration of play-CTE relationship remained consistent

Mez et al, Annals Neurology 2019

Original Contribution

Relationship Between Level of American Football Playing and Diagnosis of Chronic Traumatic Encephalopathy in a Selection Bias Analysis

Jessica LeClair, Jennifer Weuve, Matthew P. Fox, Jesse Mez, Michael L. Alosco, Chris Nowinski, Ann McKee, and Yorghos Tripodis*

- 290 American football players in the UNITE Brain Bank (2008 and 2019)
- After adjustment for selection bias, college-level and professional football players had 2.38 (95% simulation interval (SI)=1.16-5.94) and 2.47 (95%SI=1.46-4.79) times the risk of being diagnosed with CTE as high-school-level players, respectively
- The adjusted estimates are larger than estimates with no selection bias adjustment.
- *These findings suggest that the selection bias in the UNITE study may underestimate the risk of CTE.*

LeClaire et al J Epidemiology 2022

jama.com

July 25, 2017

Volume 318, Number 4
Pages 311-400

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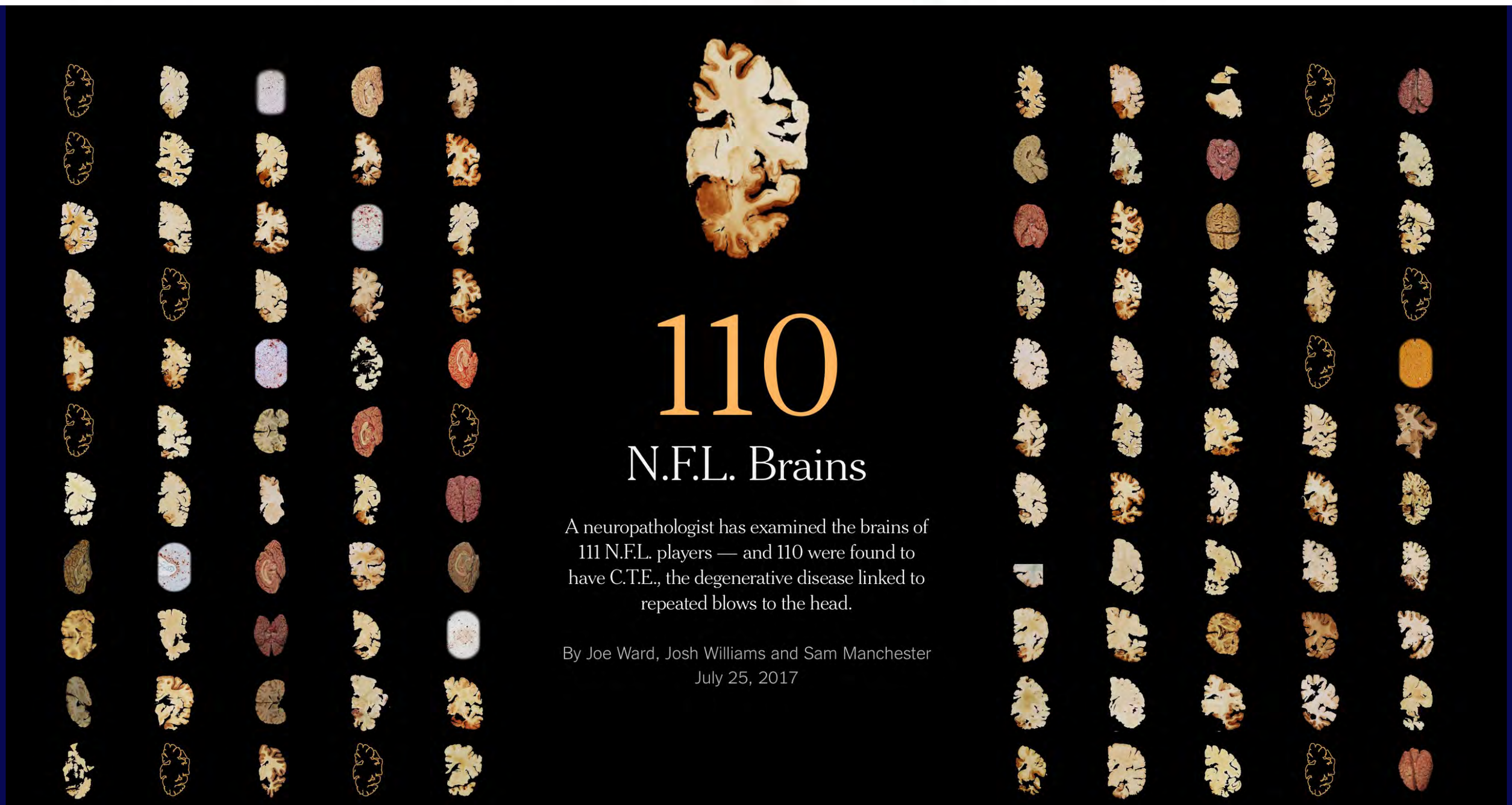
Journal of the
American Medical Association



110 N.F.L. Brains

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

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

Dr. Ann McKee, a neuropathologist, has

jama.com

July 25, 2017

Volume 318, Number 4
Pages 311-400

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Journal of the
American Medical Association

Case series of 202 American football players at all levels whose brains were donated for research

Rigorous clinical and neuropathological evaluation

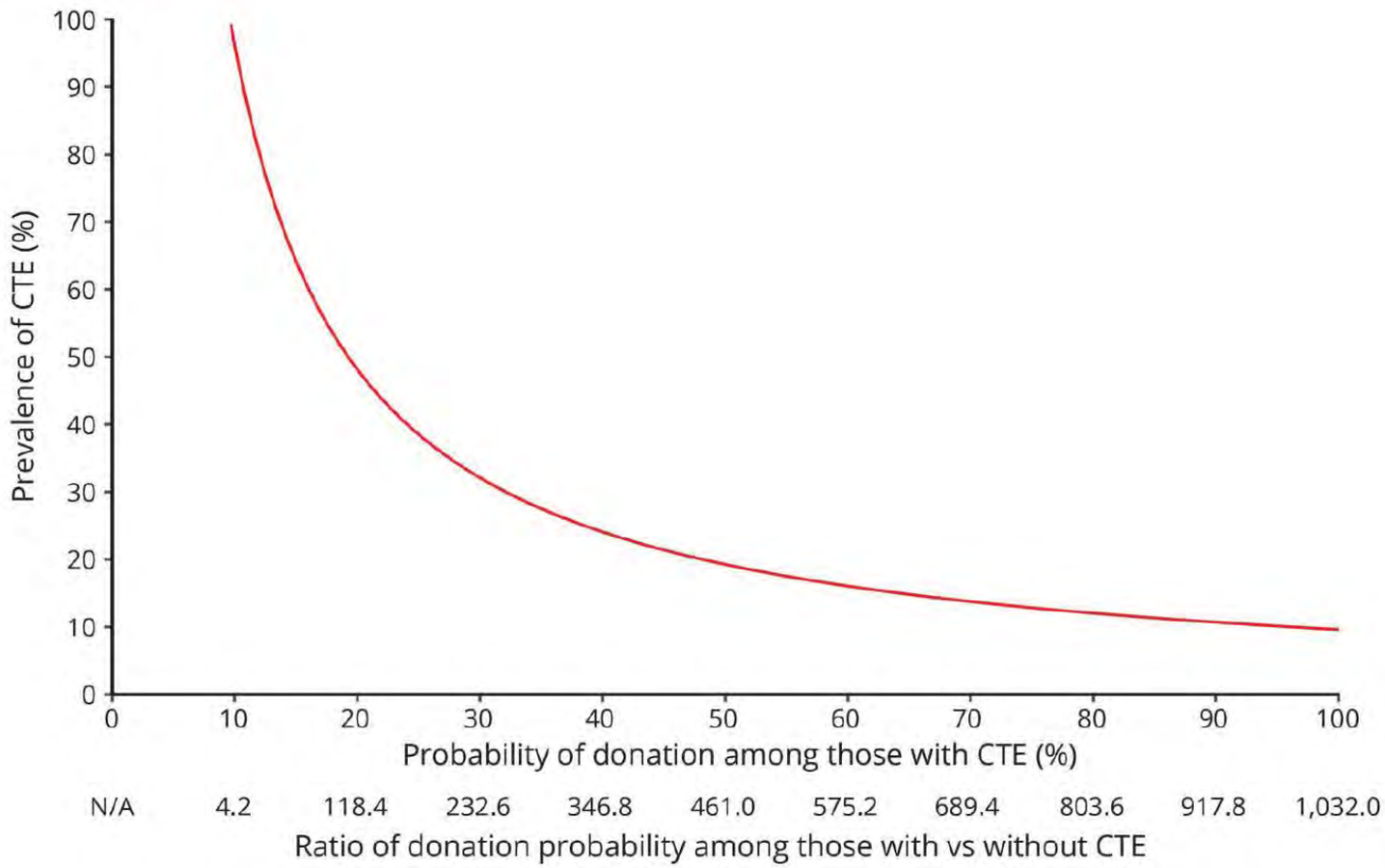
87% of the 202 brain donors were diagnosed with CTE using NINDS criteria, including:

110 of 111 NFL	***99%***
48 of 53 college	***91%***
3 of 14 high school	***21%***

Mez, Daneshvar, Kiernan et al JAMA 2017

Estimating the prevalence at death of CTE neuropathology among professional football players

Figure Prevalence of chronic traumatic encephalopathy (CTE) among deceased National Football League players under various selection conditions



The estimated prevalence of CTE in former NFL players ranges from 9.6% to near 100% depending on the proportion of players with CTE captured by the UNITE brain bank

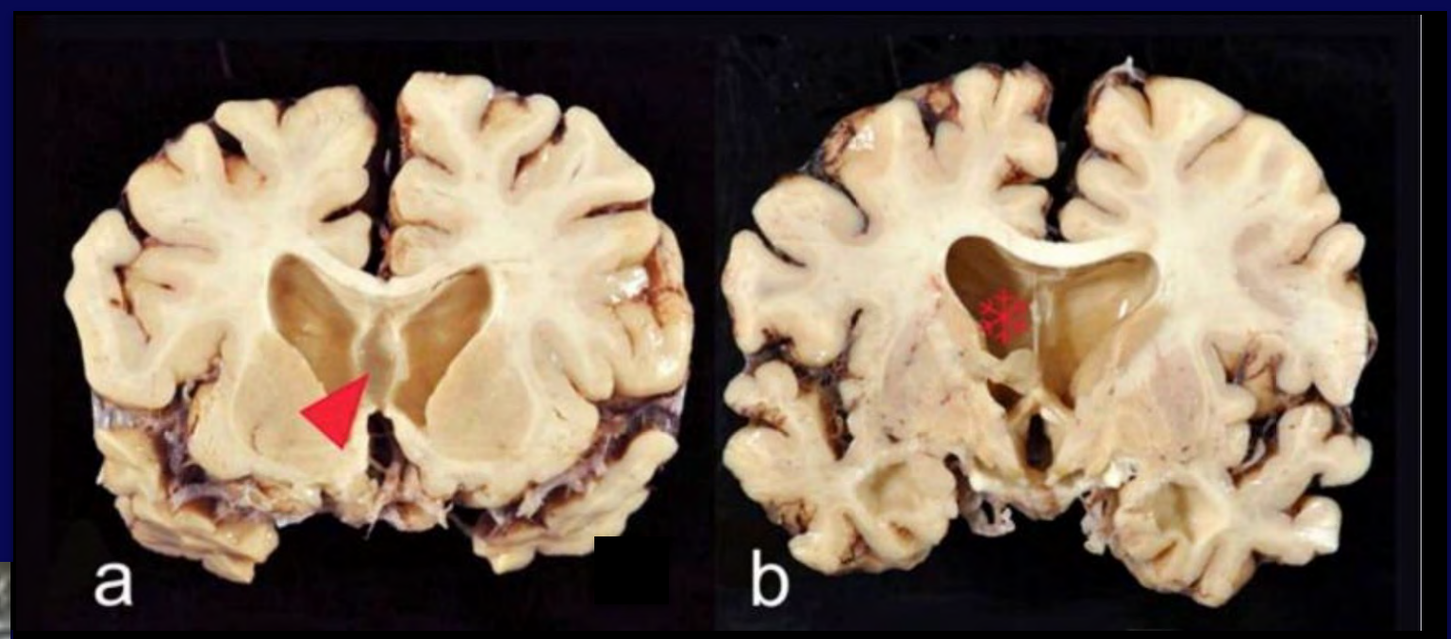
Binney and Bachynski, JAMA Neurol Nov 2018

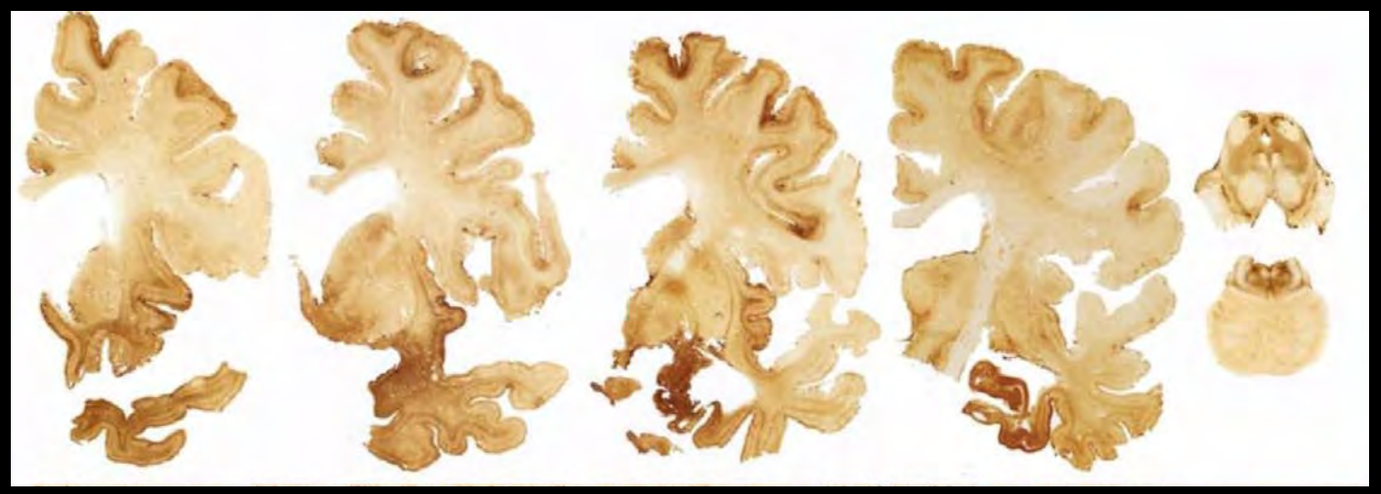
CTE in Rugby

- *Geddes et al,1999: young rugby player*
- *McKee et al, 2014: Australian rugby league player*
- *Stewart et al, 2019: 3 (of 4) rugby union players (75%)*
- *Buckner et al, 2019: 5 (of 9) rugby league players(55.6%)*

77-year-old Australian rugby player who died with severe dementia

Neuropathological dx: Stage IV CTE



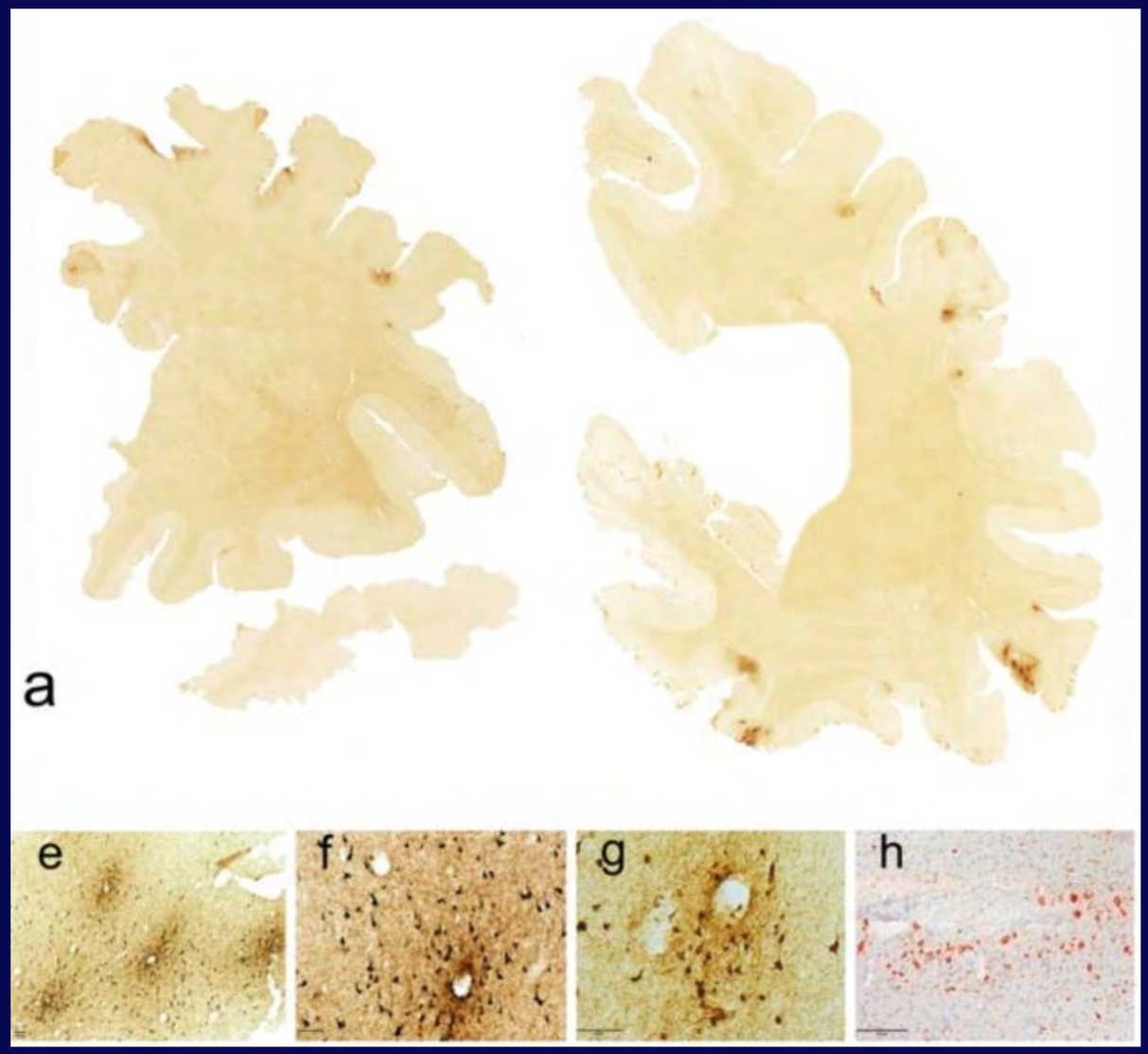


CTE in Soccer

- *McKee et al, 2014: 29 yo semi-pro soccer player*
- *Hales, et al, 2014: 80 yo professional soccer player*
- *Grinberg et al, 2016: 83 yo professional soccer player*
- *Ling et al, 2017: 6/6 professional soccer players (100%)*
- *Stewart et al, 2019: 5/7 soccer players (71%)*

29-year-old semi-professional soccer player with ALS

Neuropathological dx:
CTE II and ALS

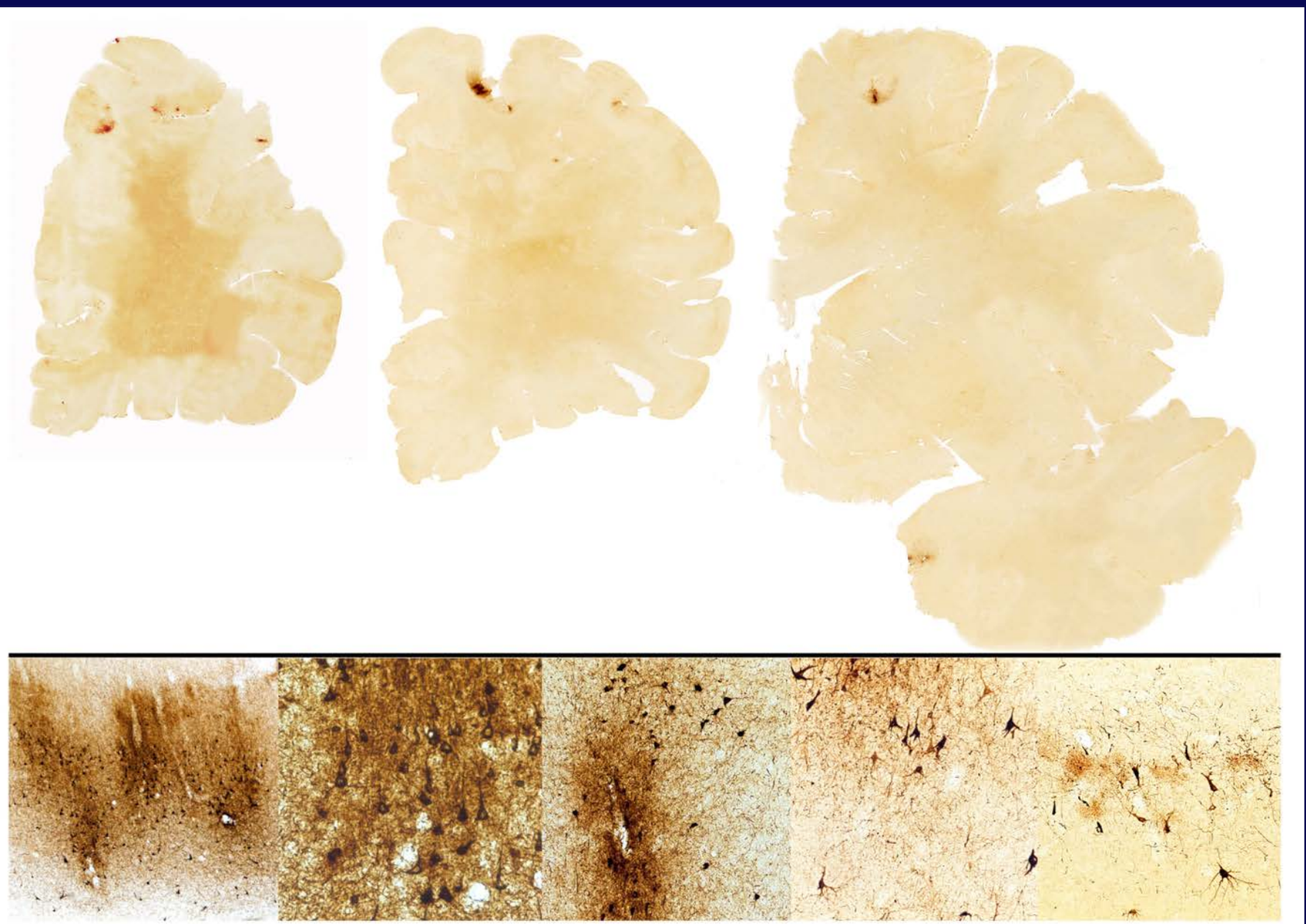


CTE in Ice Hockey

- *Schwab et al, 2019: 6 (of 11) ice hockey players (55%)*
- *Abdolmohammadi et al, 2022: 30 (of 56) ice hockey players (54%)*

Derek Boogaard,
28 yo NHL player

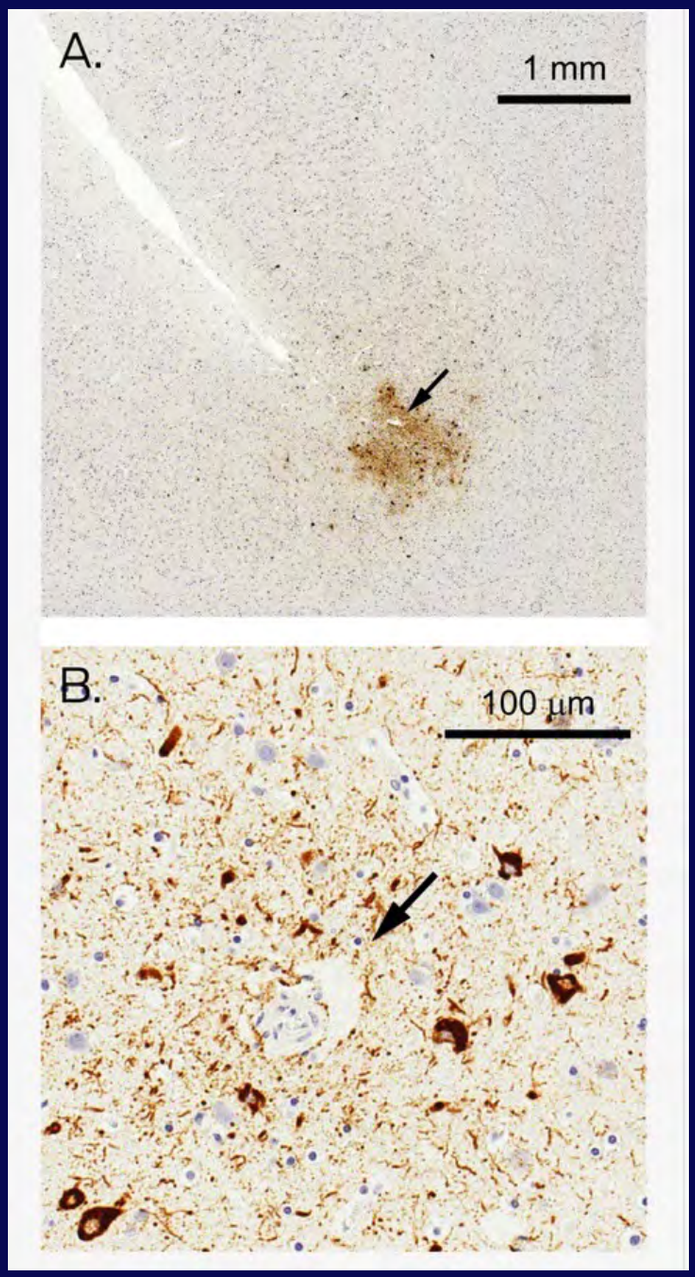
Dx: CTE II



CTE in Australian Rules Football

- *Suter et al, : 6 (of 8) Australian Rules football (75%)*
  Med J Aust 2022

Frontal cortex of a man in his early fifties with CTE



In community brain banks, CTE is rare : 0-2.8%

- *Adams et al, : 1 of 164 brain donors FHS study (0.6%)*
- *Forrest et al: 0 of 310 Vienna Trans-Danube Ageing study (0.0%)*
- *Bieniek et al: 21 of 750 donors, Mayo brain bank (2.8%)*
- *Postnupta et al: 3 of 532 donors in Seattle ACT study (0.6%)*
- *Suter et al, 2022: 18 of 180 donors Royal Prince Alfred Hospital (RPAH), in Sydney, Australia (2.2%)*
- *McCann et al, 2022, 5 of 636 Sydney Brain Bank (0.8%)*

CTE in Military Personnel

Omalu et al 2011: 27-year-old Iraqi war veteran exposed to blasts.

Goldstein et al, 2012: 4 military vets with blast exposure or concussive injury (22 to 45 years; mean, 32.3 years)

Priemer et al, CTE in the Brains of Military Personnel, NEJM, 2022

- 225 consecutive brains of military personnel, active duty and retired, irrespective of TBI history or other factors.
  Male donors average age: 48.2 years (range, 18 to 87)
  Female donors average age: 47.8 years (range, 20 to 63)
- Neuropathological examination not-standardized; NINDS guidelines for CTE were not followed

- CTE in 4.4% - roughly twice that of community brain banks

Q: Are you worried about CTE?

A: "First of all, I have been doing it a long time, so your body *gets used to the hits*. The *brain understands* the position you are putting your body into, *and my brain is wired for contact*.
I would say in some ways it's *become callus to some of the hits*".

CTE: The Solution:
What do we need to do?

- Detect CTE in the living
- Prevention – safer practices, fewer games, better acute care of head injuries
- Active monitoring of athletes at risk
- Identification of genetic susceptibility factors and gender effects
- Raise the starting age
- Develop new therapies and treatments

Genetic/ non-genetic modifiers

- ***APOE ε4*: *APOE* ε4 is associated with increased CTE severity (OR=3.96, P=0.02), p-tau density (OR=2.41 for an increase in 1 quartile, P=0.01), and dementia (OR=2.52, P=0.04). *(Atherton JAMA Neurol 2022)***

- ***TMEM106b:* Minor allele frequency was associated with reduced ptau pathology and neuroinflammation, increased synaptic protein density and reduced odds for dementia. *(Cherry 2018)***

Genetic/ non-genetic modifiers

- ***Age*:** Older age is associated worse CTE severity. *(McKee 2013, Cherry 2016, Alosco 2018)*
- ***Resilience:*** higher occupational attainment predicts later cognitive (P=0.02) and behavioral/mood (P=0.02) symptom onset *(Alosco 2016)*

How can we detect CTE during life?
Fluid biomarker candidates

- P-tau
- Total tau
- Amyloid beta
- CCL11
- sTREM2, CD68
- Neurofilament light
- Neurogranin
- Vascular biomarkers (e.g., ICAM, VCAM)
- GFAP, S100b, neuron-specific enolase (NSE), UCHL1

Neuroimaging biomarker candidates

Tau PET imaging:

Fluortaucipir has high affinity for AD tau, particularly late-stage AD

Inconclusive results in CTE, especially early CTE

Amyloid PET imaging: Used to identify AD/ rule out AD in suspected CTE patients

^{18}F-Fluorodeoxyglucose PET: mixed results, some suspected CTE have decreased metabolism in the frontal region

SPECT Imaging: cerebral blood flow reductions; non-specific

MRI:

Atrophy: frontal, insula, and anterior temporal lobes, thalamus

Corpus Callosum Thinning

Cavum Septum Pellucidum: often found in CTE; non-specific, frequent MRI finding in the general population

Flair MRI

RESEARCH ARTICLE

Association Between Antemortem FLAIR White Matter Hyperintensities and Neuropathology in Brain Donors Exposed to Repetitive Head Impacts

- 75 donors: 67 football players and 8 non-football contact sport athletes or military veterans.
- *Dementia was the most common MRI indication (64%)*

  53 (70.7%) had CTE at autopsy.
- Log Total Lesion Volume was associated with:

  White matter rarefaction (OR 2.32)

  Arteriolosclerosis (OR 2.38)

  CTE stage (OR 2.58)

  Dorsolateral frontal p-tau (OR 3.03)

  No association with Aβ
- *WMH might capture long-term white matter pathologies from RHI, including those from white matter rarefaction, p-tau, and microvascular disease.*
- Prospective imaging–pathologic correlation studies are needed.

Uretsky et al, Neurology, 2021

Associations between near end-of-life flortaucipir PET and postmortem CTE-related tau neuropathology in six former American football players

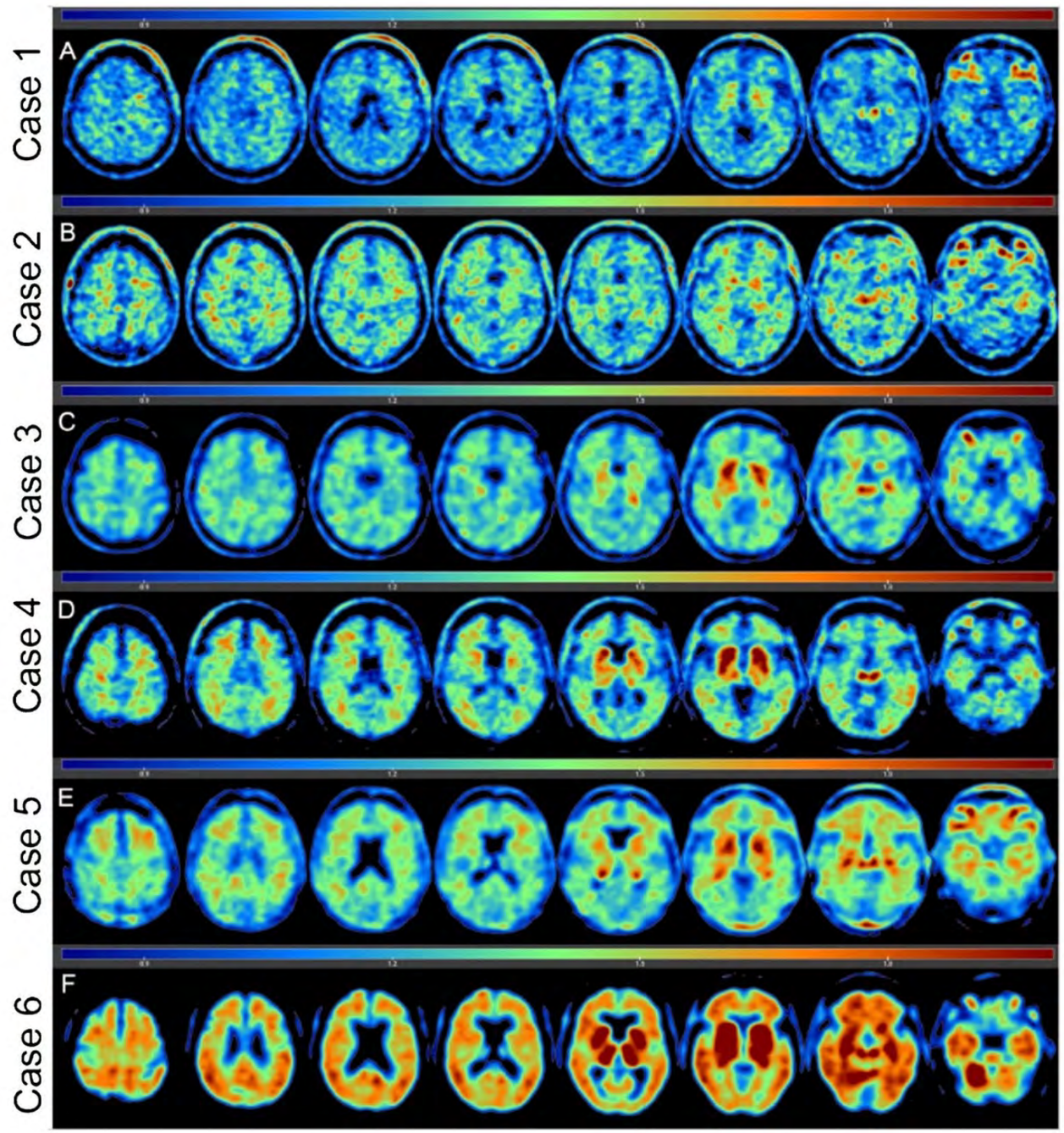
European J Nucl Med Mol Imaging 2022

Michael L. Alosco[1] · Yi Su[2] · Thor D. Stein[1,3,4,5] · Hillary Protas[6] · Jonathan D. Cherry[1,3] · Charles H. Adler[7] · Laura J. Balcer[8] · Charles Bernick[9,10] · Surya Vamsi Pulukuri[1] · Bobak Abdolmohammadi[1] · Michael J. Coleman[11] · Joseph N. Palmisano[12] · Yorghos Tripodis[1,13] · Jesse Mez[1,4] · Gil D. Rabinovici[14] · Kenneth L. Marek[15] · Thomas G. Beach[16] · Keith A. Johnson[17,18,19,20] · Bertrand Ru · Alexander P. Lin[11,25] · Sylvain Bouix[11] · Jeffrey L. Cummings · Ann C. McKee[1,3,4,5] · Robert A. Stern[1,29] · for the DIAGNOSE

4 brain donors had autopsy-confirmed CTE. 3 met criteria for TES.
2 did not have CTE at autopsy,1 met criteria for TES.

Strong association between fluortaucipir and p-tau in composite and limbic regions.

* *Flortaucipir-PET might be useful for detecting high stage CTE, but specificity for CTE is uncertain*.



Summary

Since the publication of NINDS-NIBIB criteria for the pathological diagnosis of CTE multiple international studies have reported CTE in individual exposed to RHI.

- CTE: amateur and professional athletes, including *American and Australian Rules football, soccer, rugby union, rugby league, and ice hockey players, wrestlers, boxers, bull riders, military veterans exposed to blast or impact injuries, individuals who experienced falls, domestic violence, poorly controlled epilepsy, or head-banging behavior.*
- *In 97% of reported cases, RHI from various sources is a common denominator*.
- *In studies of community populations and unselected brain banks, CTE is rare to absent (0-2.8%).*

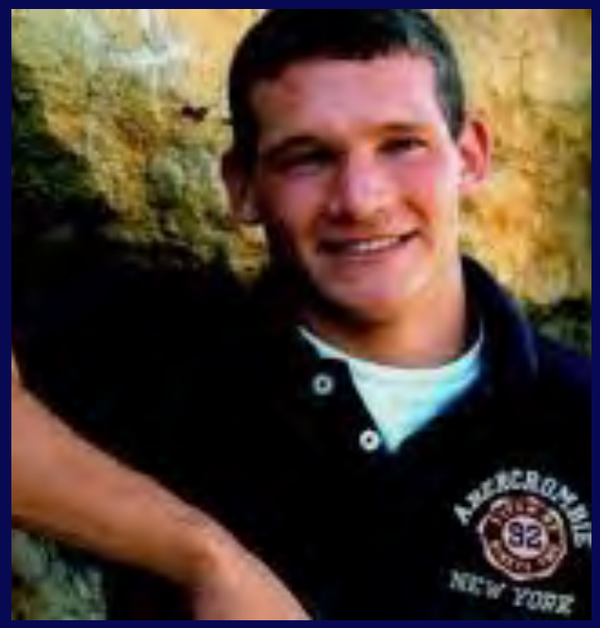
Summary

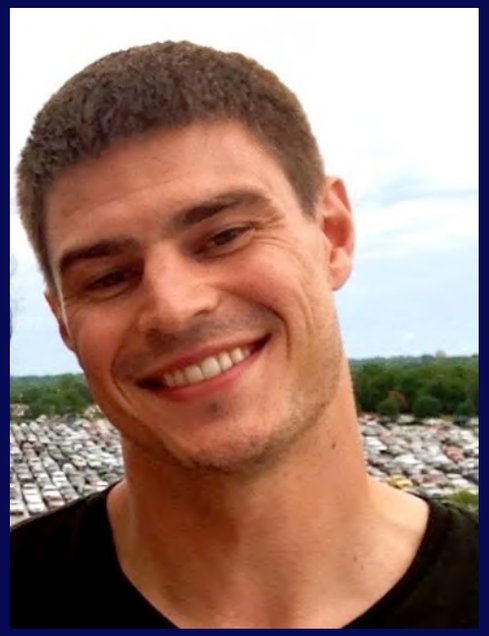
Evidence for a causal relationship between CTE and RHI:

- *Computation and finite element models show that the regions of greatest physical deformation and strain during impact injury predict the sulcal and perivascular distribution of p-tau in CTE.*
- Muskoxen, a species with gyrencephalic brains that participate in combative headbutting, show superficial, sulcal depths and perivascular p-tau.
- *There is a robust dose-response relationship between CTE and years of American football play, a relationship that remains consistent even when accounting for all levels of selection bias.*
- In addition, a recent analysis using UNITE brain bank donors found that selection bias might produce an *underestimation* of risk.

Funding sources:

Department of Veterans Affairs
NIA
NINDS
NIBIB
Nick and Lynn Buoniconti Foundation
Tau Consortium
Andlinger Foundation
WWE
NFL
NOCSAE





All the families who participated in our research

The BU CTE Center and brain bank team

Thank you!!!