CTE: What is it?
What is the Relationship to Repetitive Heat Impacts (RHI)?

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Neurobiology of Aging, Vol. 14, pp. 303–307, 1993

Morphometric Image Analysis of Neuropil Threads in Alzheimer's Disease

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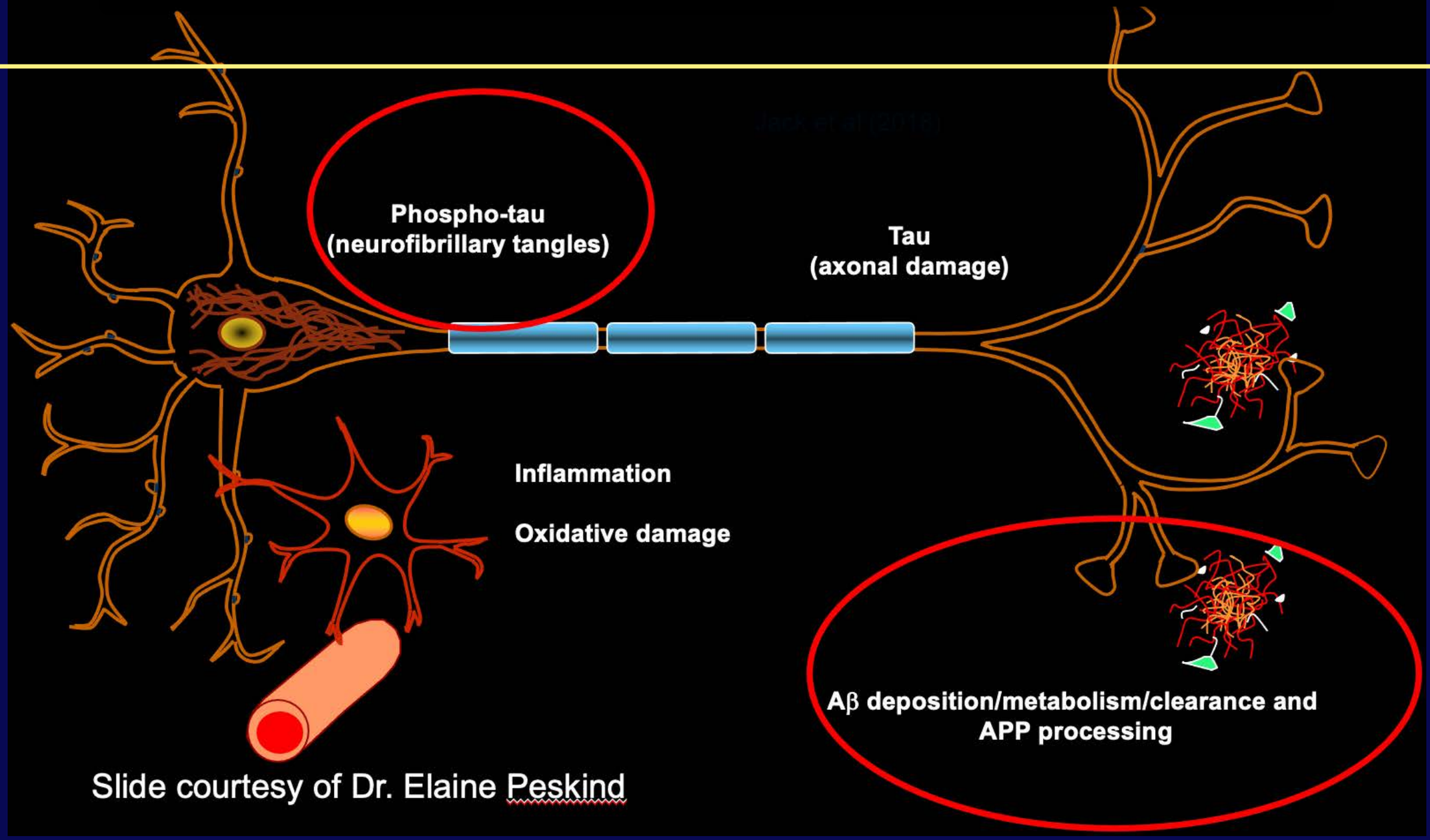
No disclosures

TBI, AD and dementia



TBI, particularly moderate-severe TBI, has long been recognized as a risk factor for Alzheimer's disease and dementia.

TBI, AD, PD, and dementia

- Most studies, not all, have found that moderate & severe TBI are associated with increased risk or earlier onset of Alzheimer's disease and dementia, particularly in those with genetic risk factors, such as one or more apolipoprotein E e4 alleles.
- Recently mild TBI has been shown to increase all-cause dementia.
- Multiple studies also report the risk of clinical Parkinson's disease (PD) is greater in those with a history of mild, moderate or severe TBI.
- Repetitive head impacts (RHI), including symptomatic concussions and asymptomatic *nonconcussive injuries,* are associated with Chronic Traumatic Encephalopathy (CTE)
- RHI is also associated with increased risk of LBD.

CTE in the news

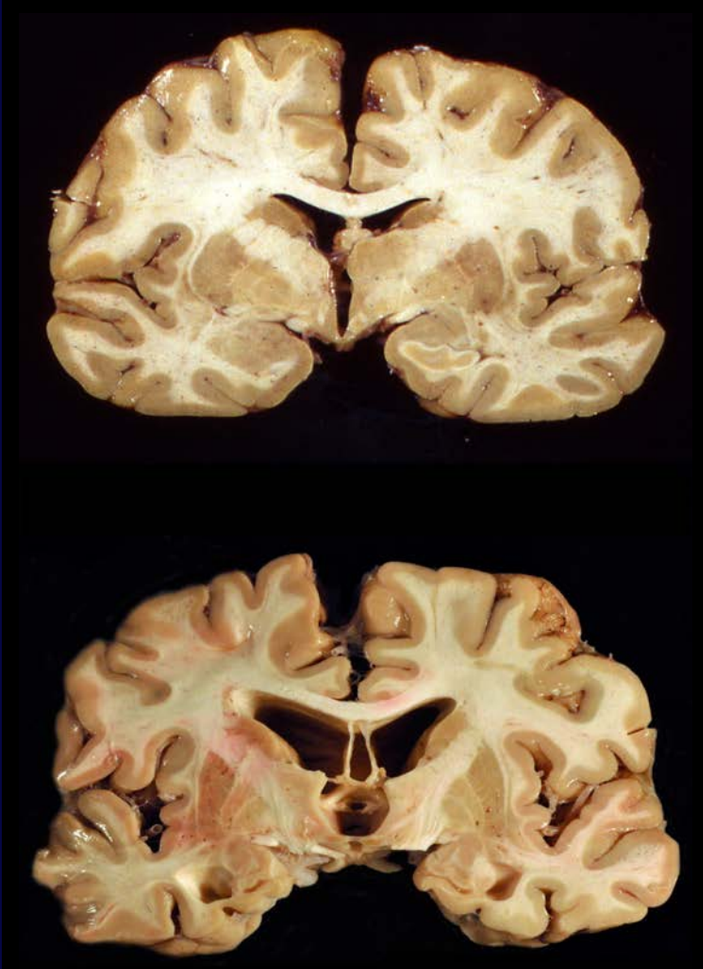
US health body rules collision sports cause CTE in landmark change

- **US National Institutes of Health acknowledge causal link**
- **Concussion in Sport Group conference takes place this week**

The Guardian, October 2022

- ***CDC:*** *"Most research suggests that CTE is caused in part by exposure to repeated traumatic brain injuries, including concussion, and repeated hits to the head, called subconcussive impacts."*

- **NINDS** statement on CTE causation updated October 2022:
- "*CTE is a delayed neurodegenerative disorder that was initially identified in post-mortem brains and research-to-date suggests,* ***is caused in part by head injuries.***"



What is CTE?

Chronic traumatic encephalopathy (CTE) is a neurodegenerative pathology associated with exposure to repetitive head impacts (RHI), including symptomatic concussions and asymptomatic *nonconcussive injuries*

CTE has been diagnosed in American football, rugby, ice hockey, soccer players, boxers, wrestlers, and individuals exposed to domestic violence, head banging, and military service-related injuries.

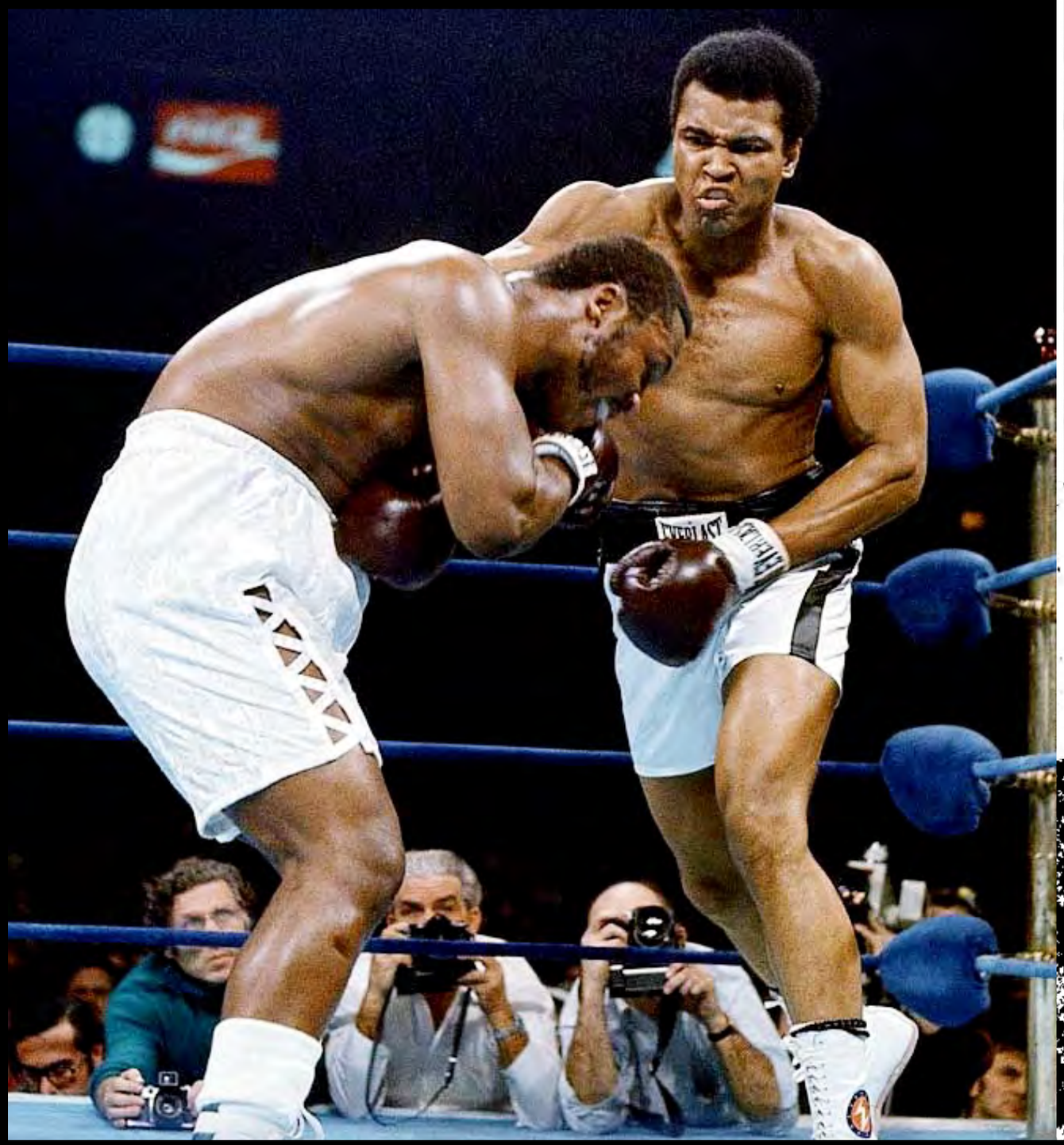
CTE can only be diagnosed after death by post-mortem brain examination. It cannot be diagnosed with certainty during life.

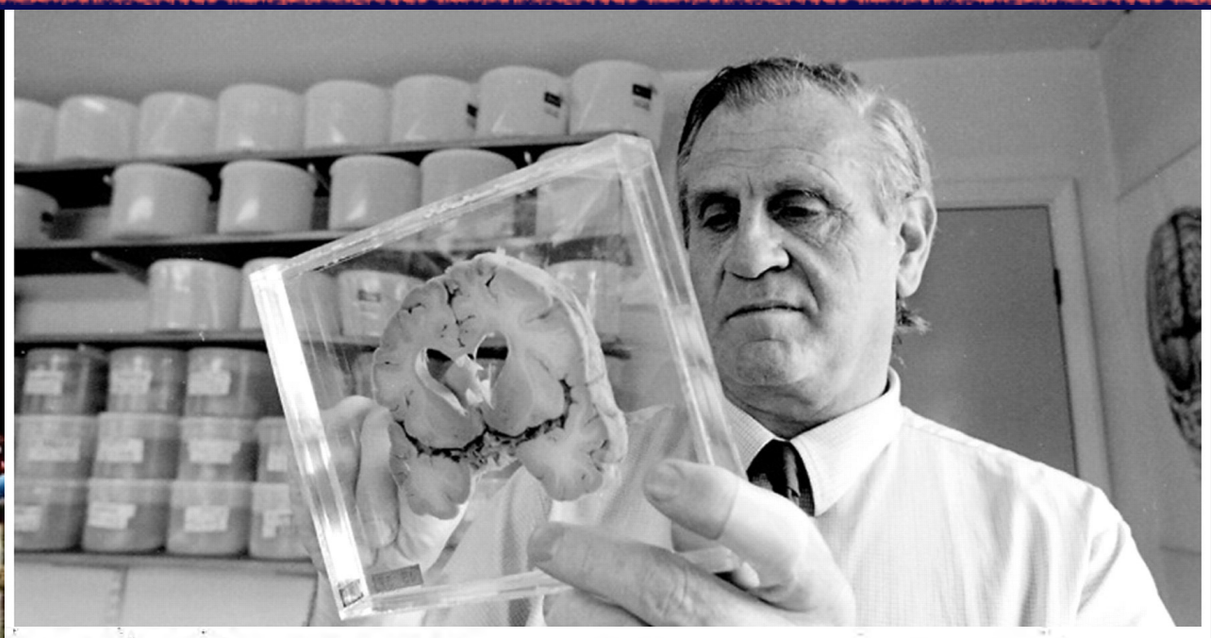
The clinical condition associated with CTE pathology is *Traumatic Encephalopathy Syndrome (TES).*

Clinicopathological Series of 15 boxers with CTE

Corsellis, Bruton, Freeman-Browne 1973

(57 to 91 years old, mean 67 yrs)





Psychological Medicine, 1973, **3**, 270–303

The aftermath of boxing[1]

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE[2]

From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

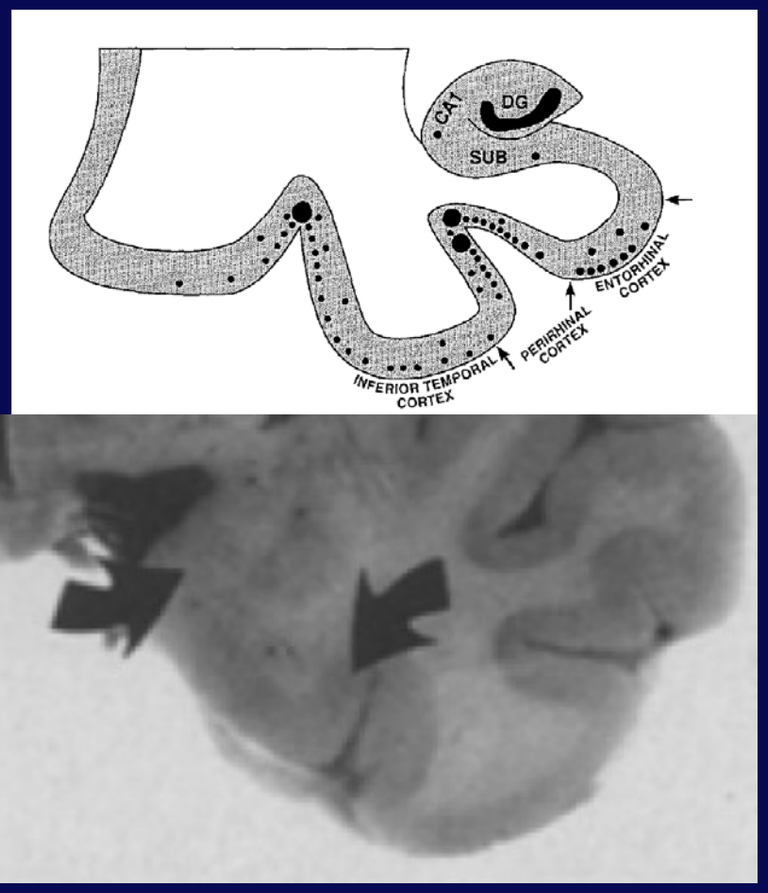
Von Braunmuhl silver: ***Neurofibrillary tangles***

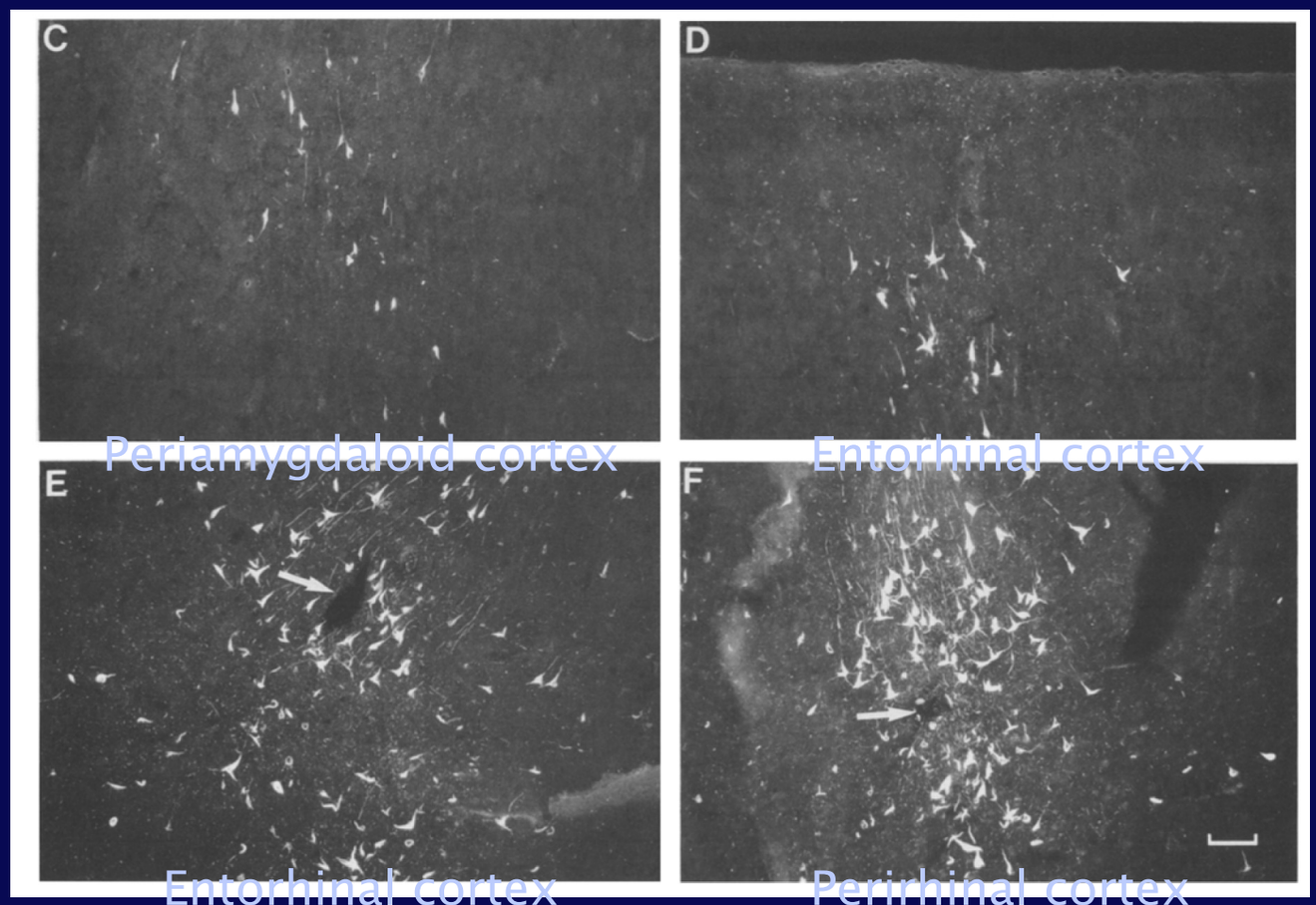
Neuropathological observations in a case of autism presenting with self-injury behavior

Hof P, Knabe R, Bovier P, Bouras C

Acta neuropathologica. 1991;82(4):321-326

Thioflavin: clusters of NFTs around blood vessels in the periamygdaloid, entorhinal and perirhinal cortex





24 year old woman No Aß

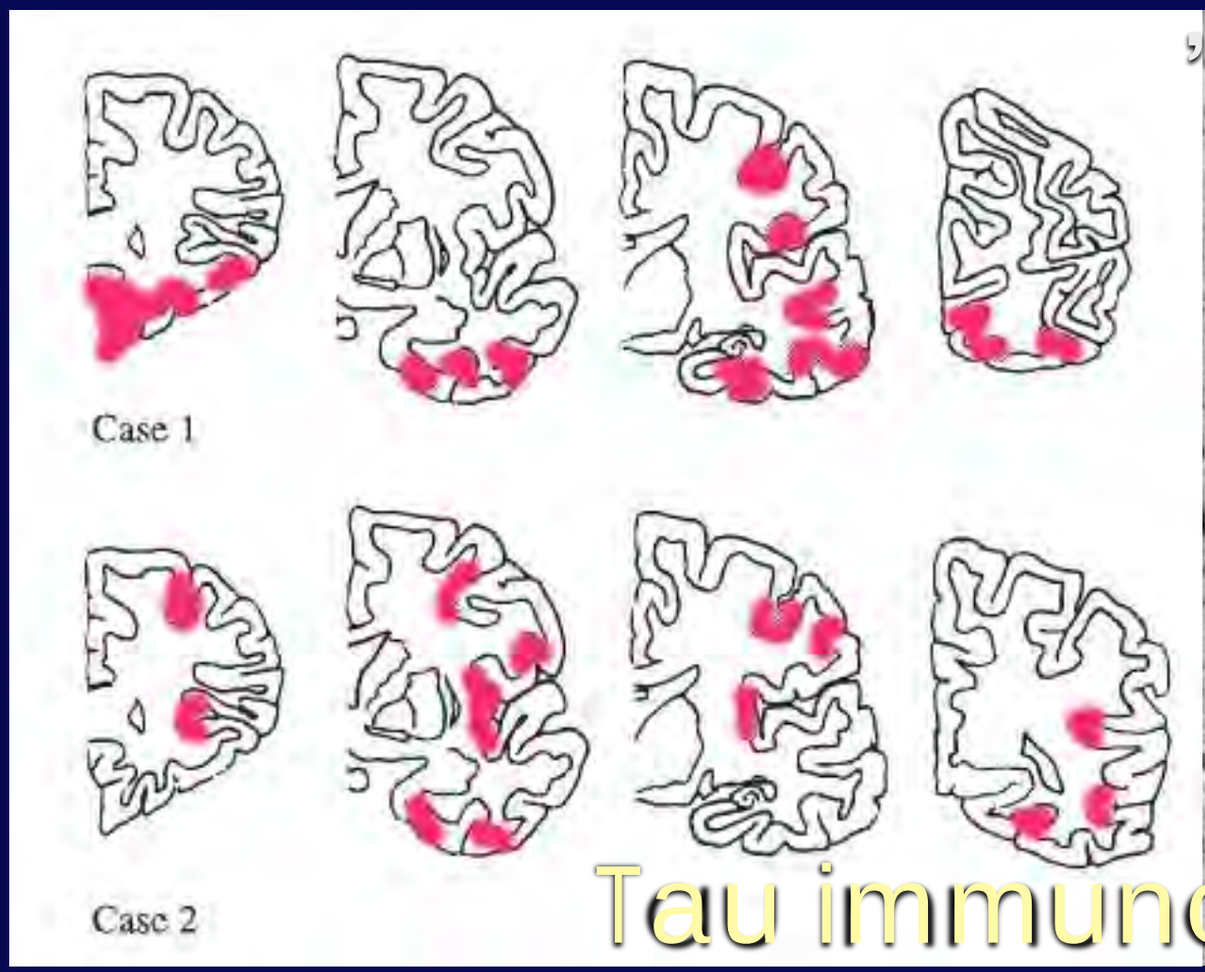
Neuronal cytoskeletal changes are an early consequence of repetitive head injury

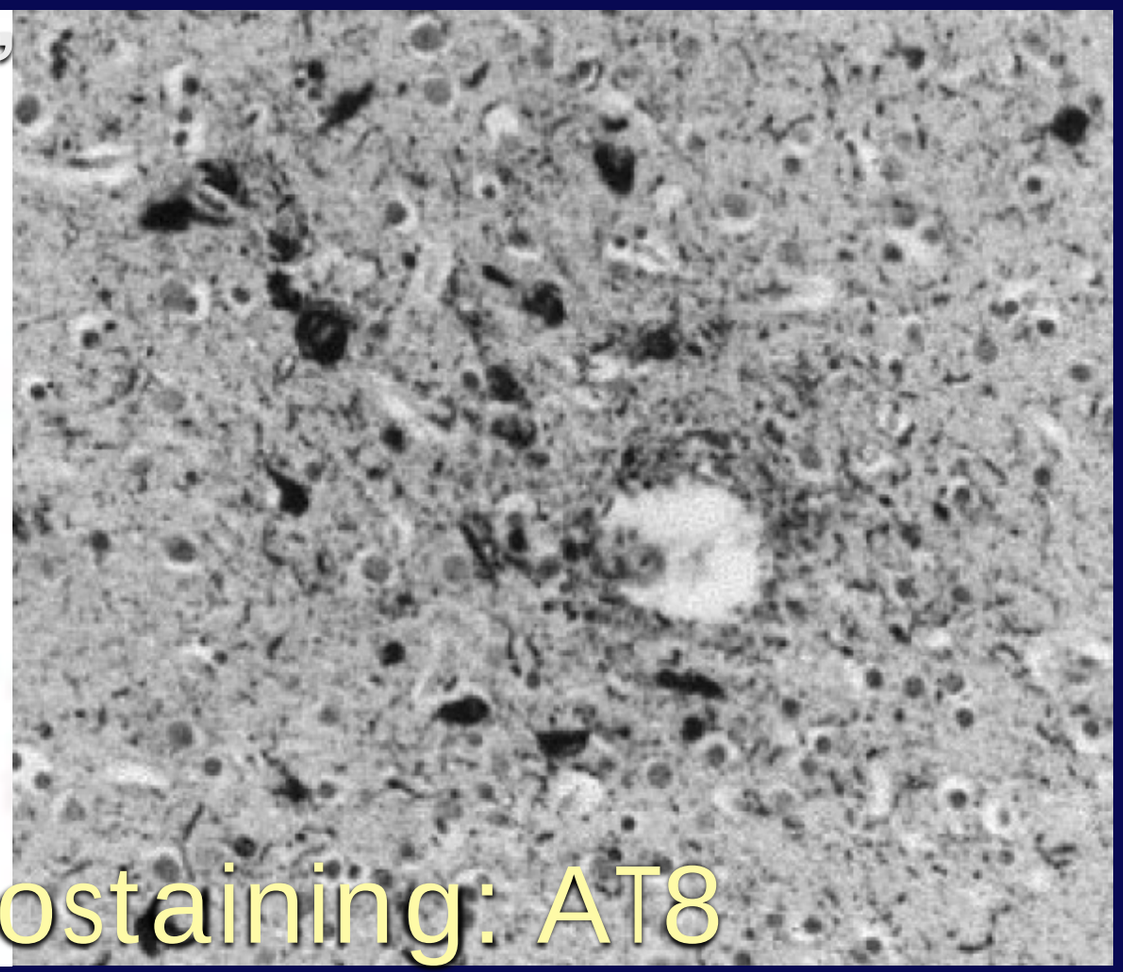
Geddes J, Vowles G, Nicoll J, Revesz T

Acta Neuropath. 1999: 98(2):171-178

5 men 23-28 years: 2 boxers, 1 rugby, 1 epileptic, 1 head-banger

21 age-matched controls





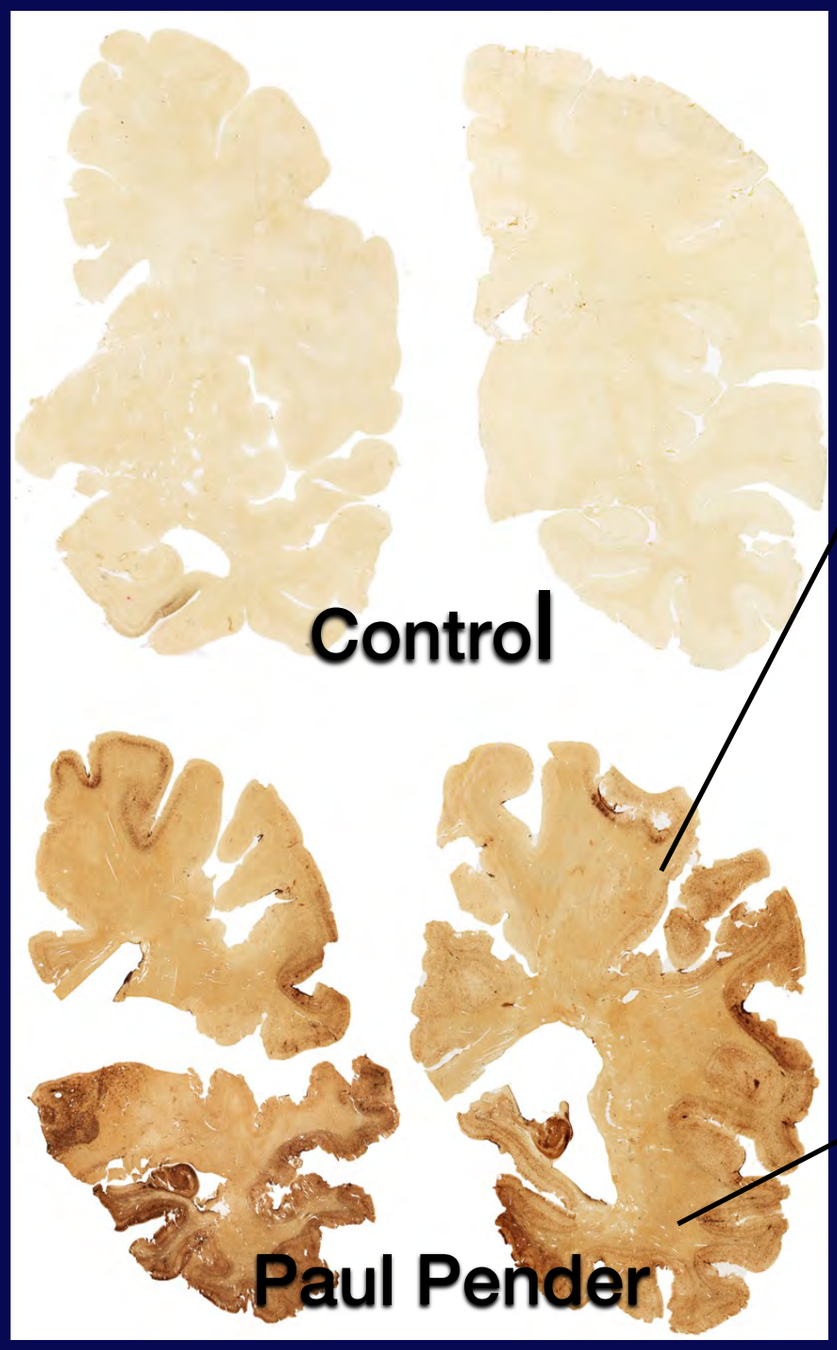
Tau immunostaining: AT8

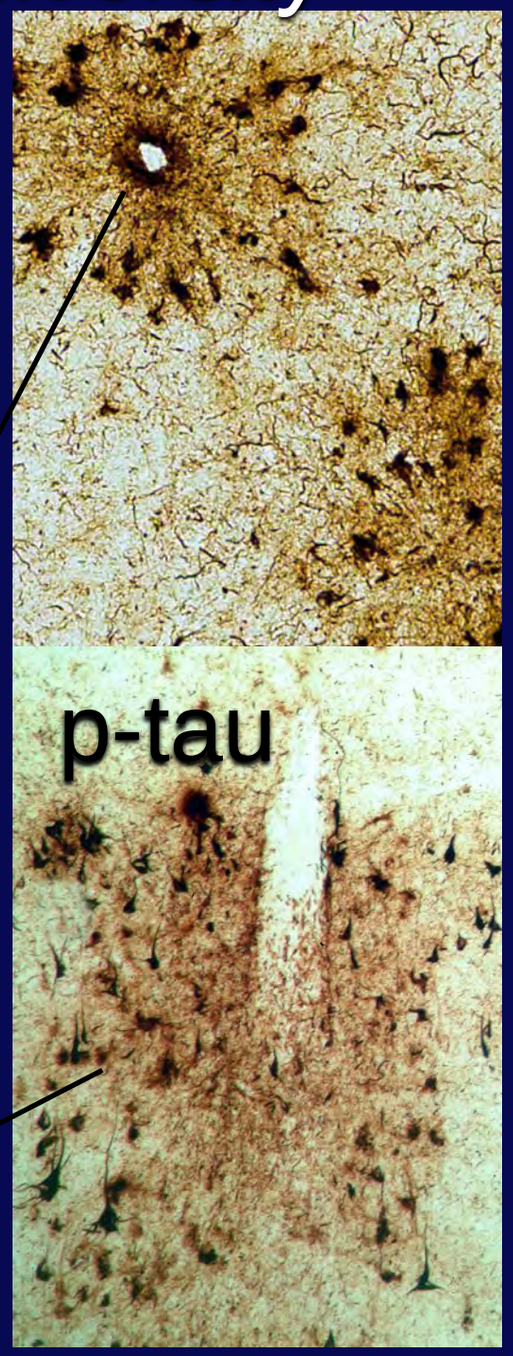
No Aß

Paul Pender (1930-2003)

First case of CTE at VA/Boston University

World Champion Boxer
Marine
Severe Dementia
Clinical diagnosis: AD





SEVERE TAUOPATHY with no Aß

McKee et al. J Neuropath Exp Neurol, 2009 68(7): 709-735

Mike Webster

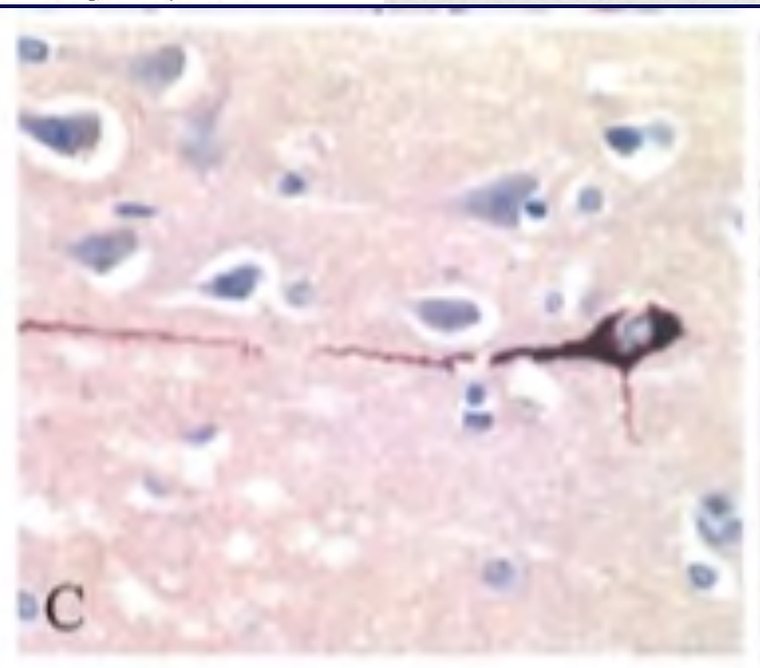
50 years old 25 years football 17 years in NFL

CHRONIC TRAUMATIC ENCEPHALOPATHY IN A NATIONAL FOOTBALL LEAGUE PLAYER

Bennet I. Omalu, M.D., M.P.H.

Departments of Pathology and Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania

OBJECTIVE: We present the results of the autopsy of a retired professional football player that revealed neuropathological changes consistent with long-term repetitive concussive brain injury. This case draws attention to the need for further studies in the cohort of retired National Football League players to elucidate the neuropathological sequelae of repeated mild traumatic brain injury in professional football.



CLINICAL:
Behavioral and mood disorder
Parkinsonism
Cognitive loss
Death at 52 years

PATHOLOGICAL:
Sparse cortical NFT
Diffuse Aß plaques
Non-specific pathology

Omalu, et al. 2005

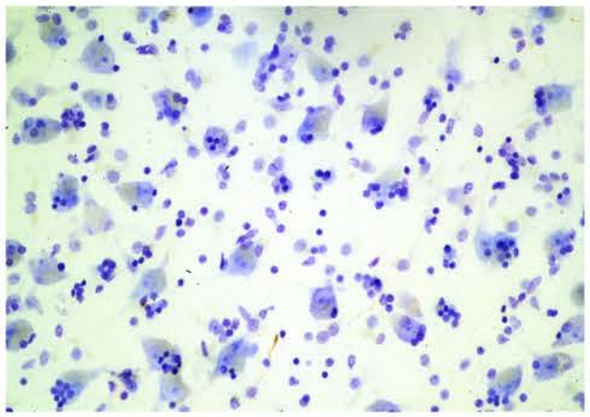
45 year old ex-NFL players

Tom McHale

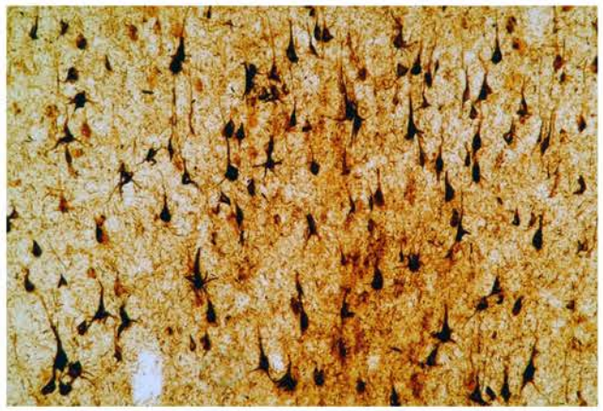
Lineman, 9 years NFL
Retired from NFL at age 32
Age 40: business failed, painkillers, short-term memory problems, depression, irritability
Age 45: death from overdose

John Grimsley

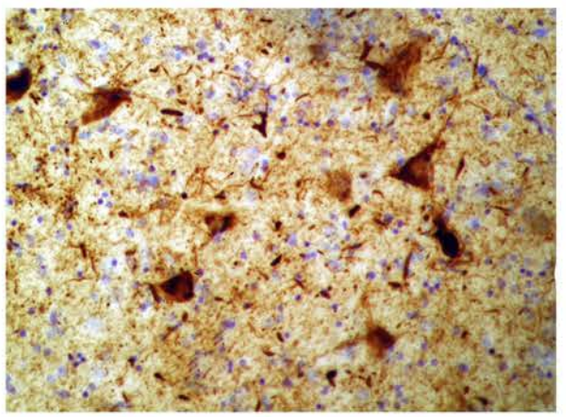
Linebacker, 9 years in NFL
Retired from NFL at age 32
Age 40: short term memory problems, attention and concentration difficulties, poor judgment
Age 45: death from accidental GSW



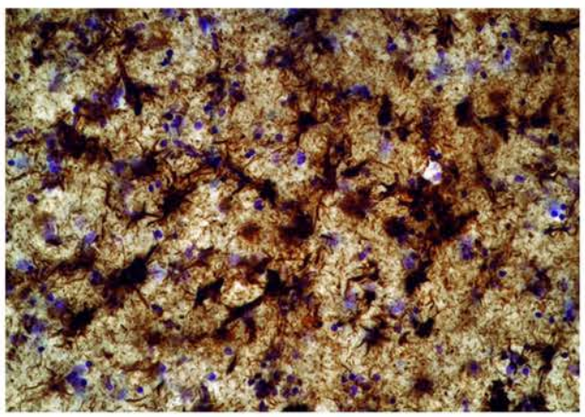
Control



Tom McHale



John Grimsley



Paul Pender

BOSTON UNIVERSITY

Department of Veterans Affairs

CONCUSSION LegacyFoundation

McKee et al. J Neuropath Exp Neurol, 2009 68(7): 709-735

Chronic Traumatic Encephalopathy (CTE)

Punch drunk *Martland JAMA 91:1103–1107, 1928*

Chronic Traumatic Encephalopathy *Critchley In: Homage a Clovis Vincent, Paris, Malonie, 1949*

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy following Repetitive Head Injury

McKee et al. J Neuropath Exp Neurol, 2009 68(7): 709-735

UNITE Brain Bank, 2008-present

To investigate the long-term consequences of TBI/RHI



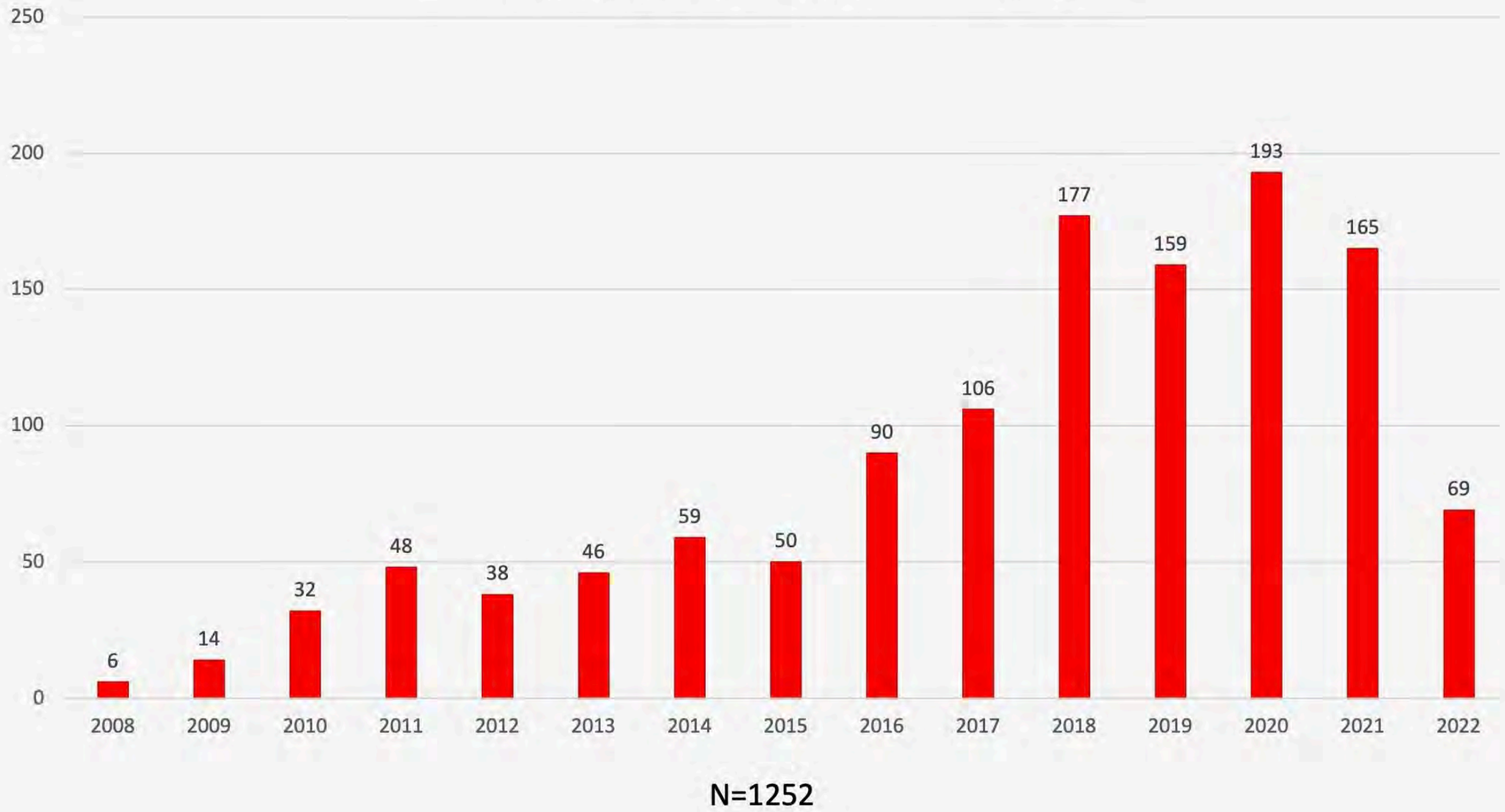




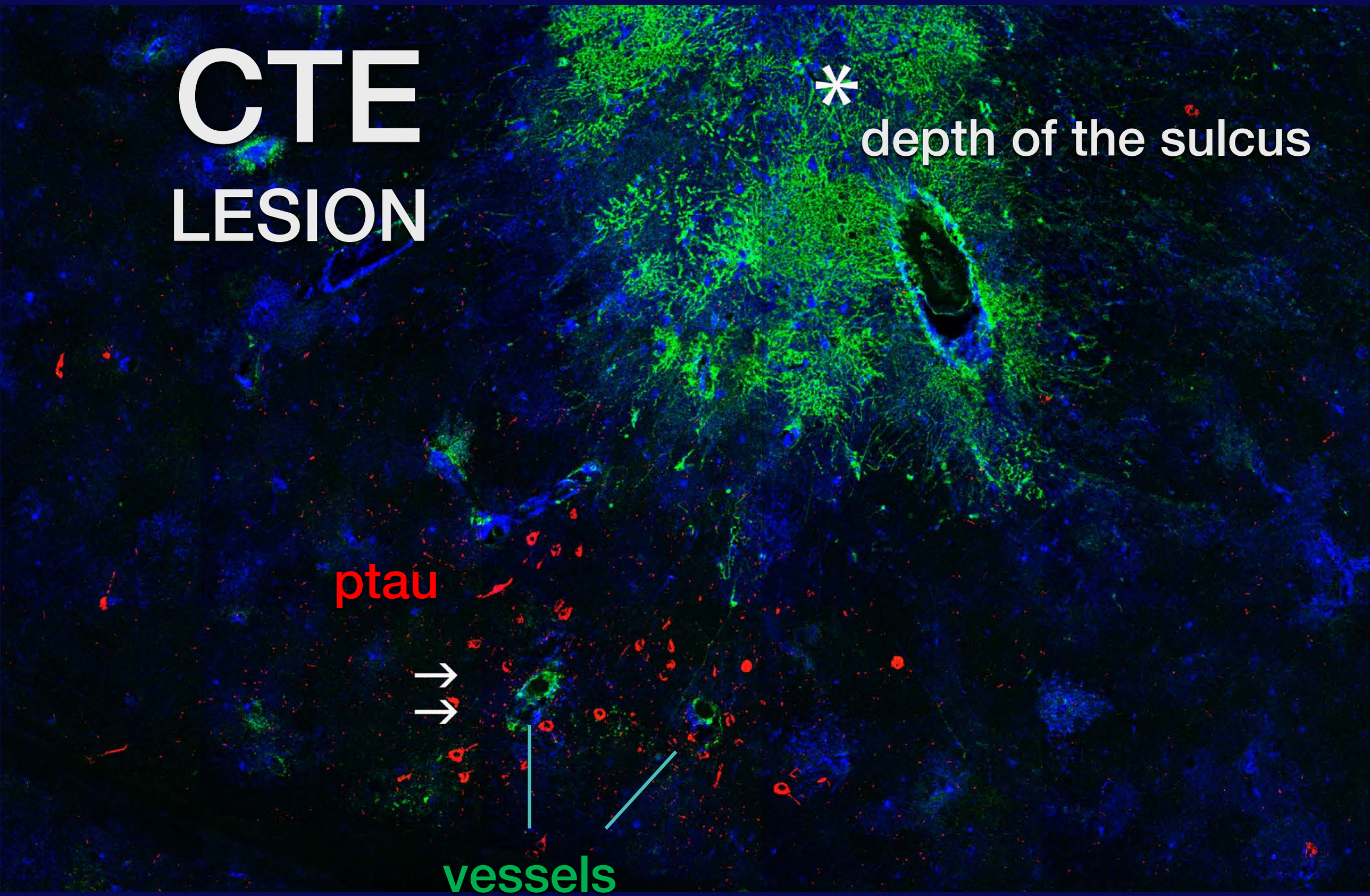



>1300 brain donors

UNITE Brain donations by year

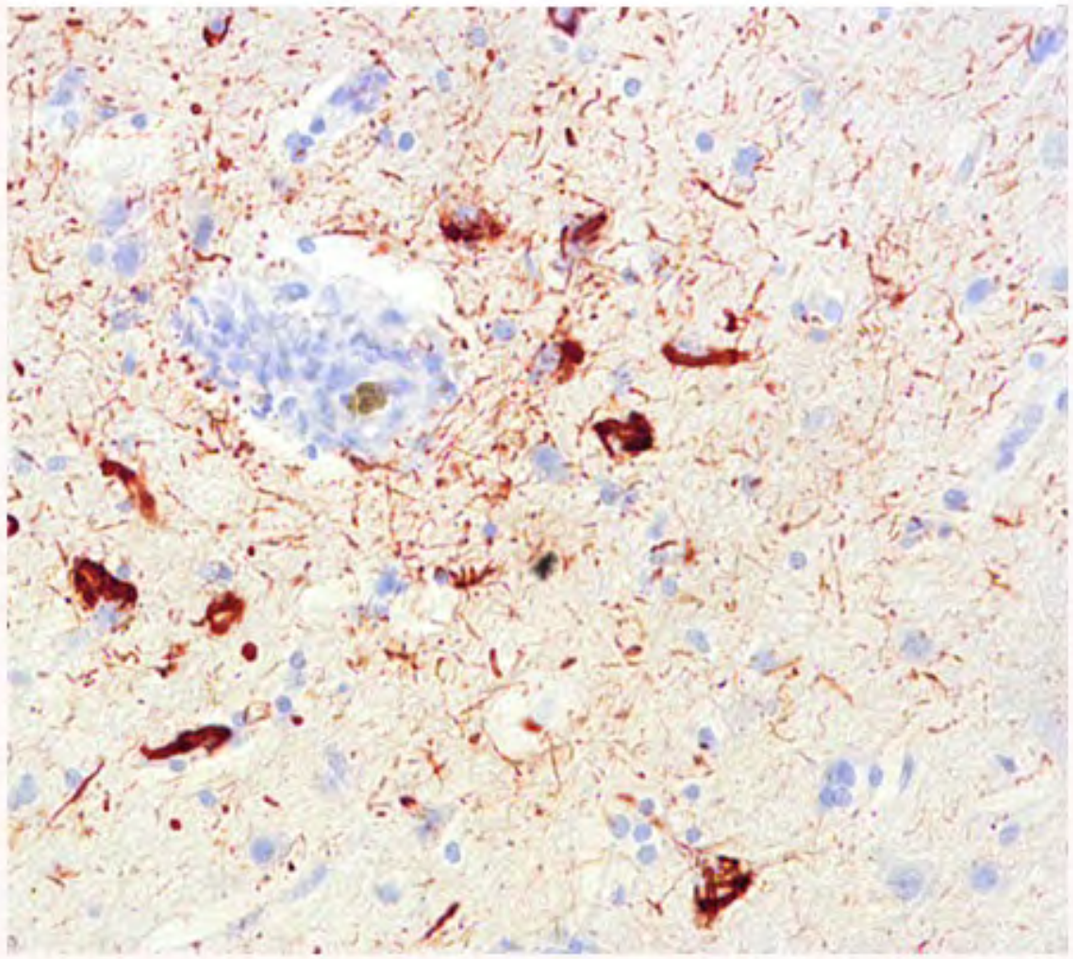


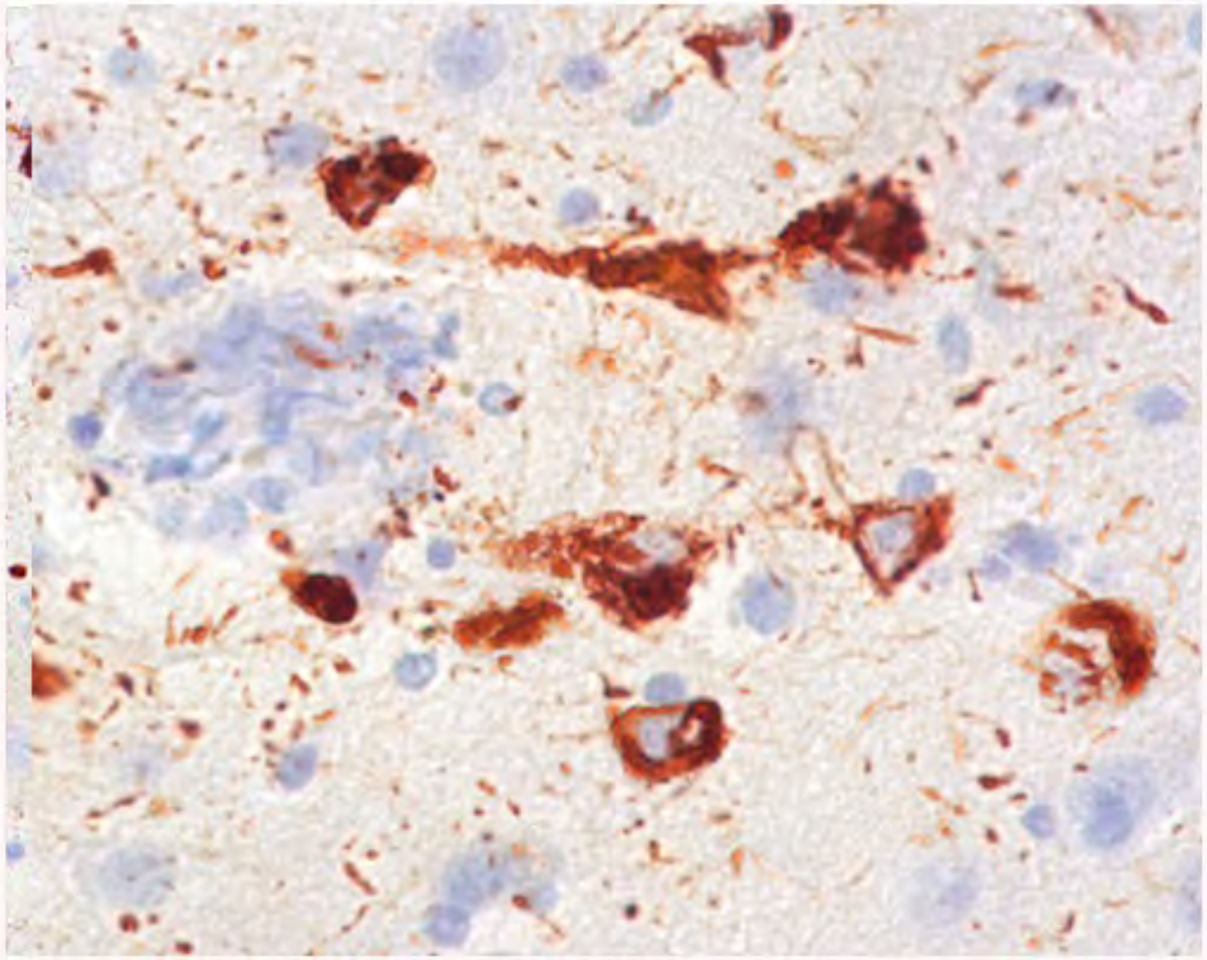
N > 1300


CTE
LESION
* depth of the sulcus
ptau
vessels

Diagnostic features of CTE:

1. Perivascular p-tau lesion (CTE lesion)

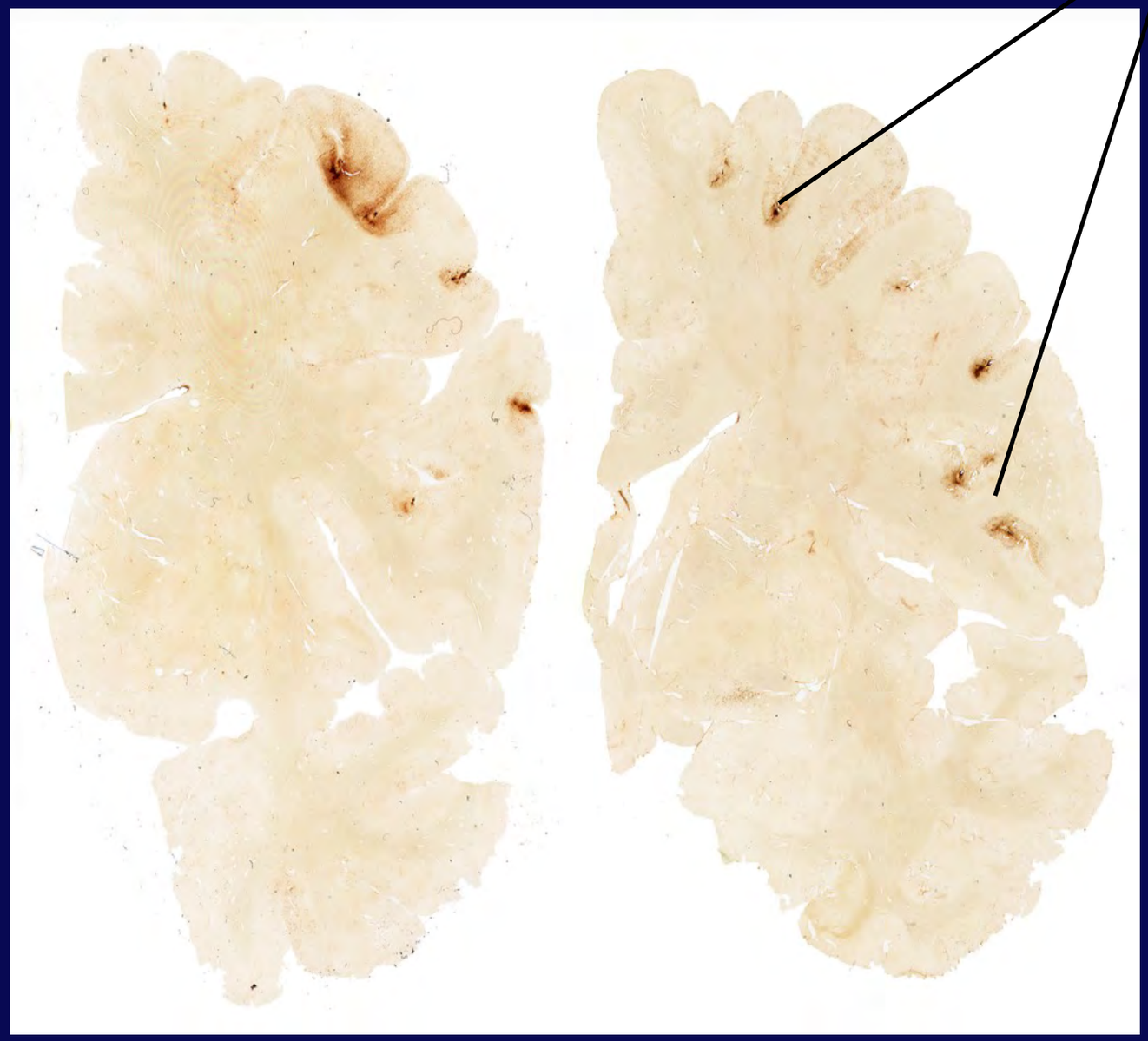




McKee et al, Brain 2013

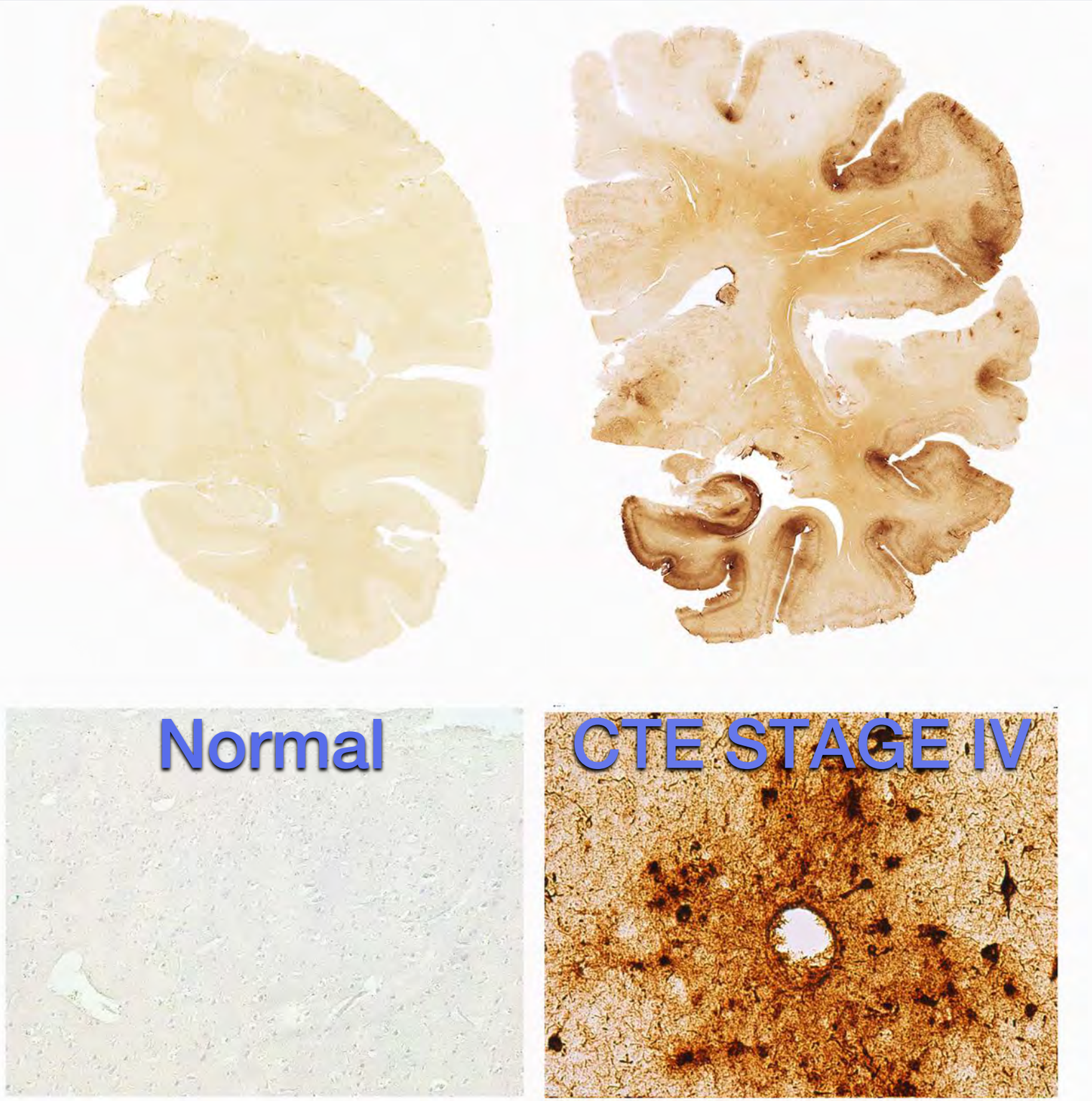
Diagnostic features of CTE:

2. CTE lesions are found at the sulcal depths



McKee et al, Brain 2013

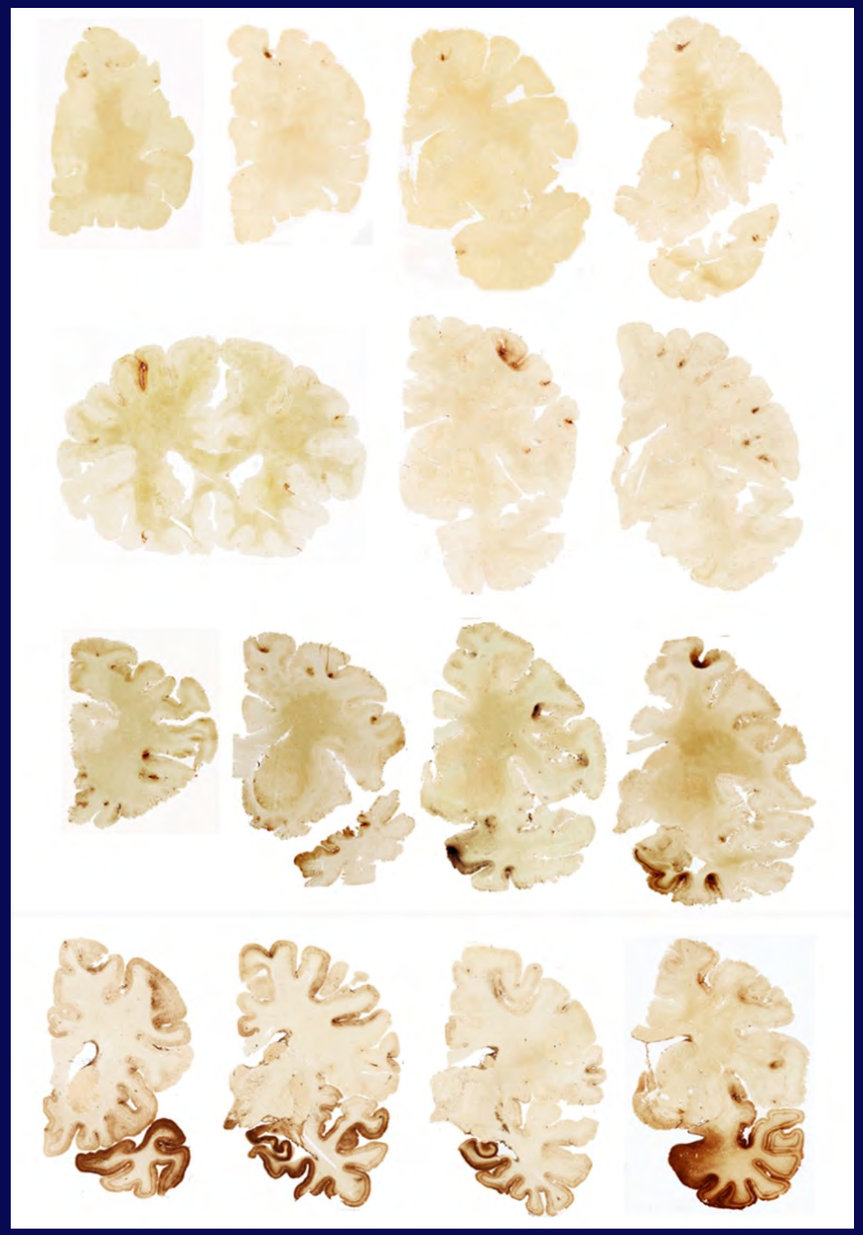
Stages of CTE severity I-IV



McKee et al, Brain 2013

Stages of Tau Pathology Age at Death

The method of staging CTE ptau pathology was based on large hemispheric 50-mm-thick slides immunostained as free-floating sections for p-tau



Stage I — m age: 28.3 + 13 yrs

Stage II — m age: 44.3 + 16 yrs

Stage III — m age: 56.0 + 14 yrs

Stage IV — m age: 77.4 + 12 yrs

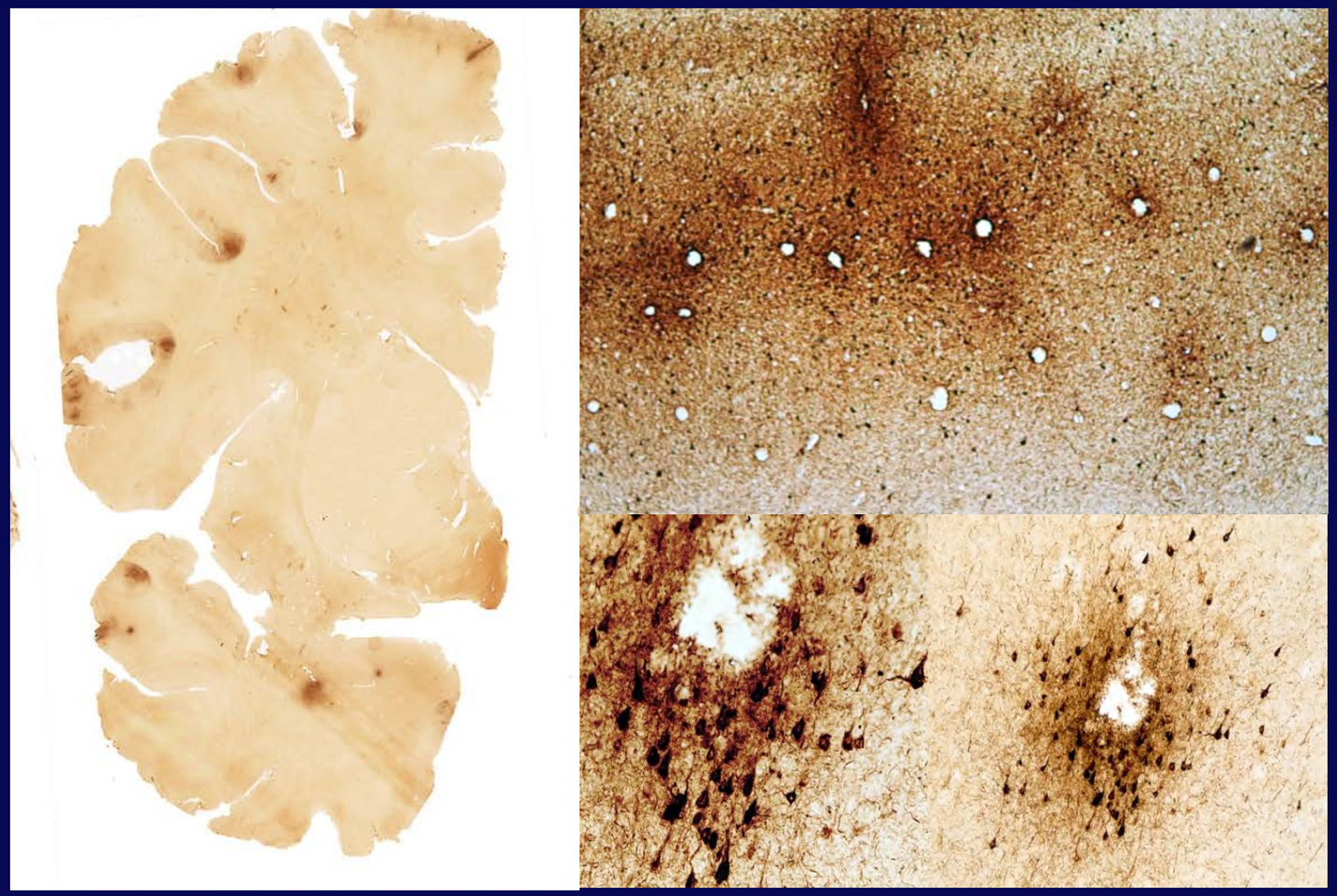
CTE stage significantly correlates with age at death and total number of years playing football

First NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of CTE

Acta Neuropathologica. 2016;131(1):75-86

Nigel Cairns, Ph.D., Rebecca Folkerth, MD, Wayne Gordon PhD, C. Dirk Keene, M.D., Irene Litvan, PhD, Ann McKee, MD, Daniel Perl, M.D., Thor Stein M.D., Ph.D., William Stewart, M.D., Jean Paul Vonsattel, M.D., Dennis Dickson, M.D, Patrick Bellgowan, MD, Debra Babcock,PhD, Walter Koroschetz, MD

Pathognomonic Lesion of CTE



"In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes at the depths of the cortical sulci in an irregular pattern."

McKee et al, Acta Neuropathologica. 2016;131(1):75-86

J Neuropathol Exp Neurol
Vol. 00, No. 00, 2021, pp. 1–10
doi: 10.1093/jnen/nlab001

ORIGINAL ARTICLE

The Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

- Confirmed the 2016 NINDS criteria,
- clarified that the pathognomonic lesion must include
- ptau in neurons

- Purely astrocytic perivascular p-tau pathology is ARTAG; not diagnostic for CTE

- A *single pathognomonic lesion* is sufficient to diagnose CTE

- When only a limited number of standard paraffin slides are available, the panel suggested an algorithm for classifying CTE as low and high stage.

Bieniek et al, JNEN 2021

ORIGINAL PAPER

Characterizing tau deposition in chronic traumatic encephalopathy (CTE): utility of the McKee CTE staging scheme

Michael L. Alosco[1,18,19,20,21] · Jonathan D. Cherry[1,2,3,4] · Bertrand Russell Huber[1,4,7] · Yorghos Tripodis[1,6] · Robert A. Stern[1,12,17] · Victor E. Alvarez[1,4,5] · Jesse Mez[1] · Thor D. Stein[1,2,3,4,5] · Ann C. McKee[1,2,3,4,5]

Association between CTE stage (n=366) :

1. *Semi-quantitative* assessments of AT8 from 14 brain regions
2. *Quantitative digital* assessment of AT8 across 7 brain regions
3. *Age at death*
4. *Dementia status*
5. *Years of American football play (proxy for cumulative RHI exposure)*

Alosco et al, Acta Neuropathologica 2021

1. Stages of CTE Correlate with Semi-Quantitative Scales of P-tau

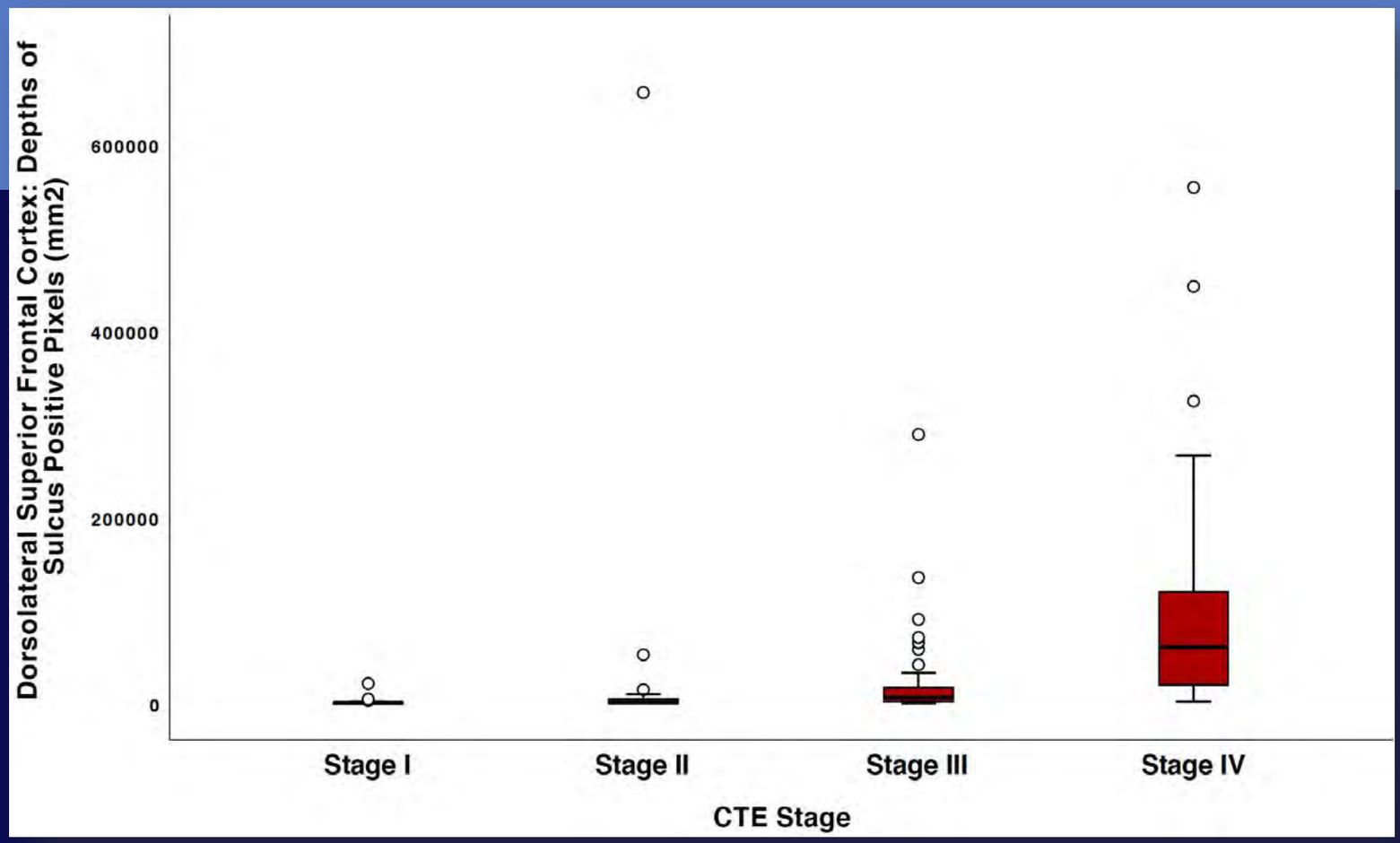
Statistically significant across all 14 brain regions:

Dorsolateral frontal cortex ($\rho = 0.65$, $p < 0.001$), Rolandic cortex ($\rho = 0.64$, $p < 0.001$), Inferior Frontal cortex ($\rho = 0.66$, $p < 0.001$), Inferior Parietal cortex ($\rho = 0.60$, $p < 0.001$), Superior Temporal cortex ($\rho = 0.63$, $p < 0.001$), Hippocampus: CA1 ($\rho = 0.51$, $p < 0.001$), CA2 ($\rho = 0.62$, $p < 0.001$), CA4($\rho = 0.66$, $p <0.001$), Entorhinal Cortex ($\rho = 0.66$, $p < 0.001$), Amygdala ($\rho = 0.72$, $p < 0.001$), Substantia Nigra ($\rho = 0.70$, $p < 0.001$),Locus Coeruleus ($\rho = 0.42$, $p < 0.001$).

2. Stages of CTE Correlate with Quantitative P-tau Density

Statistically significant across all brain regions:

DLF gyral crest ($\rho = 0.77$, $p < 0.001$), DLF depths of sulcus ($\rho = 0.73$, $p < 0.001$), CA1 ($\rho = 0.69$, $p < 0.001$), CA2/3 ($\rho = 0.66$, $p < 0.001$), CA4 ($\rho = 0.72$, $p < 0.001$), subiculum ($\rho = 0.70$, $p < 0.001$), and the LC ($\rho = 0.55$, $p < 0.001$). Example:



3. Stages of CTE Correlate with Age at Death

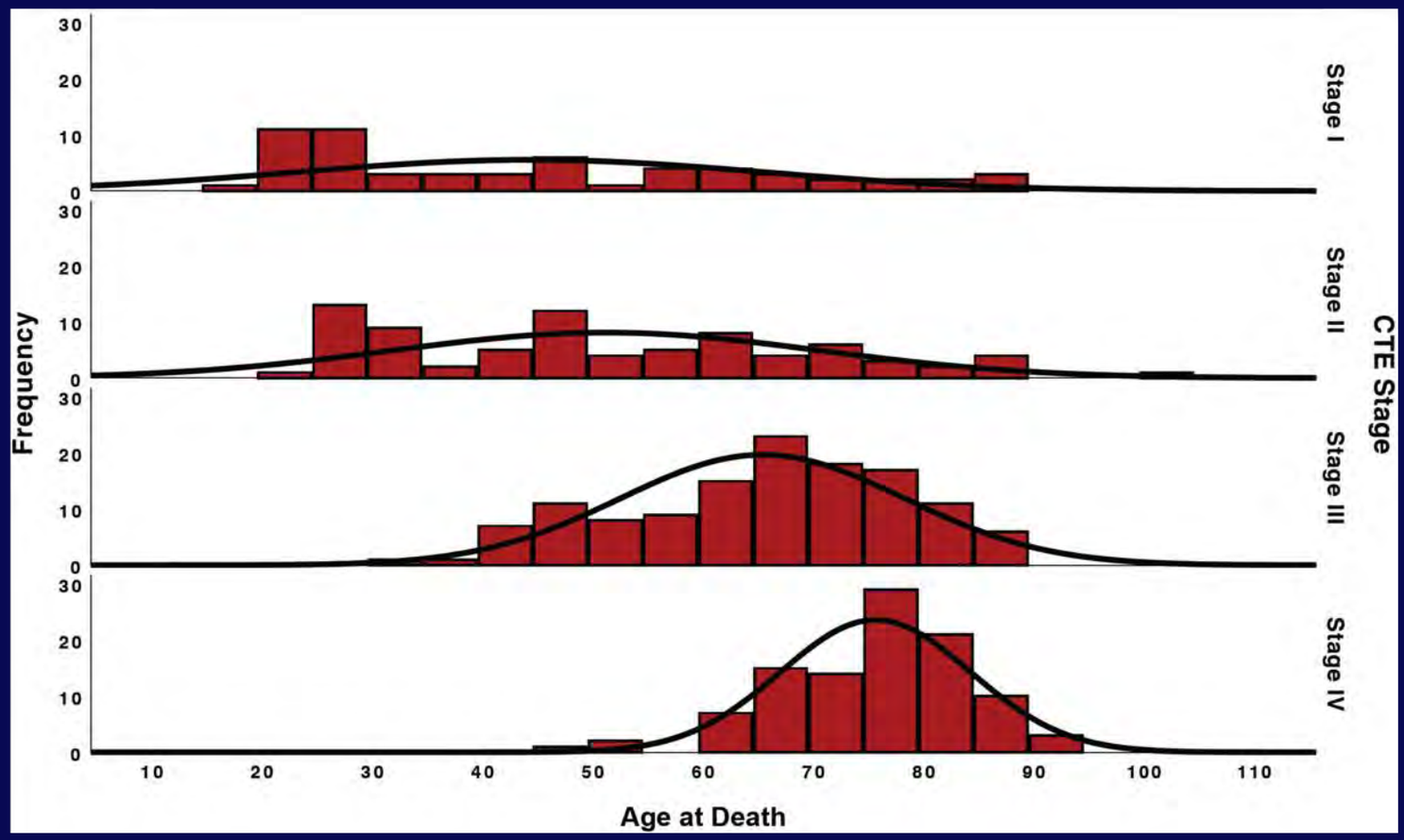
The nature, severity and distribution of CTE-related ptau pathology followed an age-dependent progression

17-100 years old

(mean = 61.75, SD = 18.97)

Age → CTE Stage

($p < 0.001$)



Age at Death	N	CTE Stage (III/IV)	DLFC	IOFC	Superior Temporal	Infer. Parietal	CA1	CA2	CA4	Entorhinal	Amygdala	SN	LC
20-29	26	0	1.12	0.54	0.88	0.81	0.27	0.04	0.15	1.02	0.90	0.37	0.85
30-39	12	1	1.50	0.92	1.58	0.92	0.83	0.17	0.58	1.00	0.92	0.42	1.33
40-49	36	15	1.78	1.06	1.44	1.25	1.06	1.00	0.86	1.67	1.25	0.86	1.94
50-59	29	16	1.83	1.07	1.90	1.21	1.55	1.24	0.93	1.90	1.66	1.28	2.17
60-69	66	49	2.14	1.61	1.97	1.73	2.00	1.88	1.71	2.30	2.00	1.76	2.45
70-79	75	66	2.23	1.85	2.21	1.76	1.77	1.97	1.88	2.55	2.33	1.85	2.20
80-89	57	47	2.16	1.93	2.12	1.88	1.93	1.81	1.89	2.47	2.35	1.95	2.16
Total	301	194	1.98	1.50	1.88	1.55	1.59	1.50	1.44	2.11	1.87	1.47	2.08

4. Stages of CTE Are Associated with Dementia Status (N = 360)

- 216 (60%) determined by consensus panel to have had ante-mortem dementia
- Binary logistic regression controlling for age showed higher CTE stage was associated with increased odds for having dementia (OR = 1.64, 95% CI = 1.19-2.27, p = 0.003); remained after controlling for neurodegenerative and vascular comorbidities

5. Stages of CTE Correlate with Years of American Football Play

Replicated our past work in this larger sample:

- Among the 305 brain donors whose primary sport was American football, more years of American football play was associated with increased odds for having a higher stage of CTE (OR = 1.10, 95% CI = 1.06-1.15, p < 0.001), controlling for age at death.

Evolution of neuronal and glial tau isoforms in chronic traumatic encephalopathy

Jonathan D. Cherry[1,2,3,4]; Soong Ho Kim[5]; Thor D. Stein[1,3,4,6]; Morgan J. Pothast[3,4]; Raymond Nicks[3,4,6]; Gaoyuan Meng[6]; Bertrand R. Huber[3,4,6]; Jesse Mez[2,3,7]; Michael L. Alosco[2,3]; Yorghos Tripodis[8]; Kurt Farrell[5]; Victor E. Alvarez[3,4,6]; Ann C. McKee[1,2,3,4,6,*]; John F. Crary[5,*]

CTE (n=99)

wide range age at death: 20-90 years

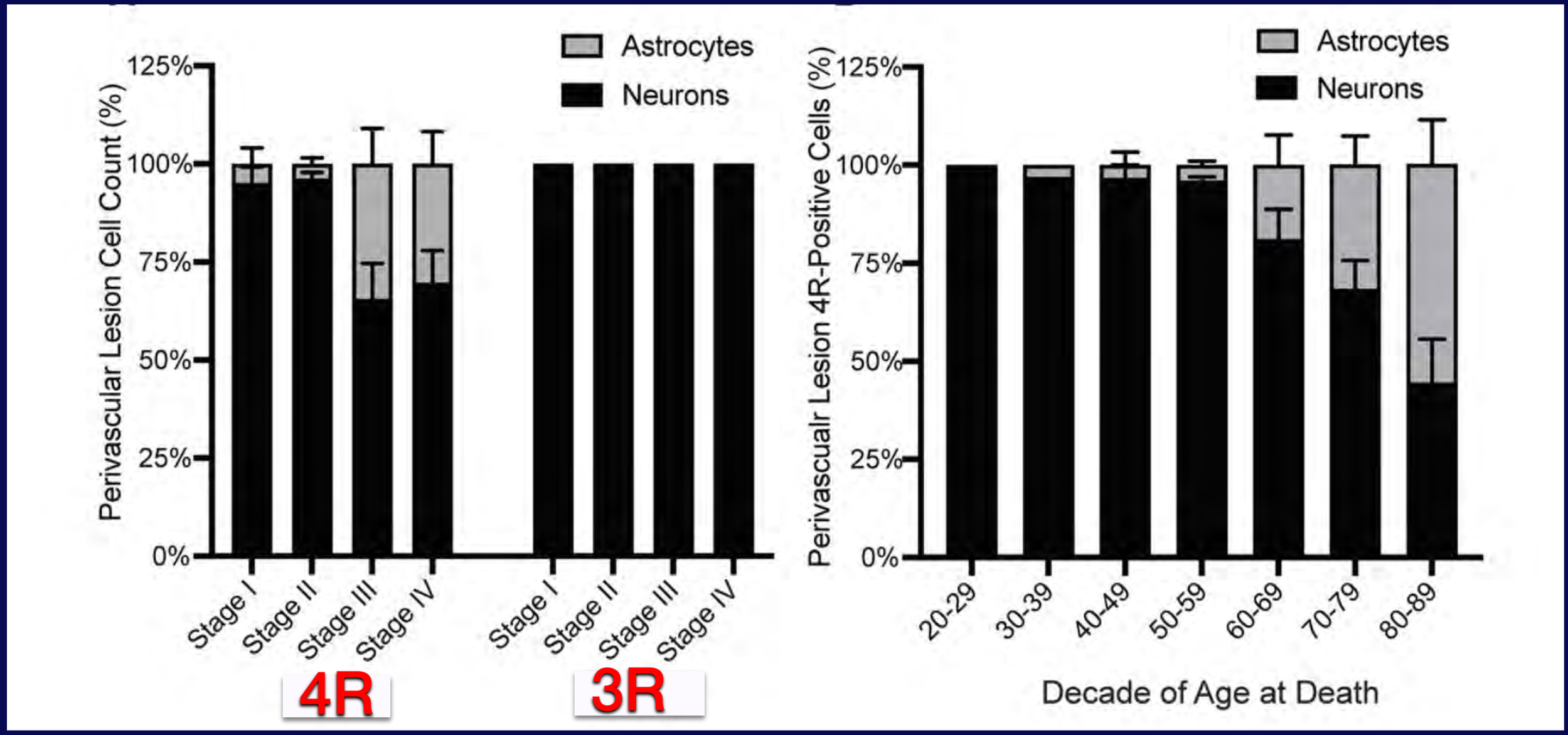
wide disease severity: CTE stage I-IV

Quantitative morphologic assessment and multiplex immunofluorescence were used to determine:

- 4R: 3R containing neurons and astrocytes within the pathognomonic CTE lesion

Cherry et al, Brain Pathology, 2020

The early CTE lesion: Neuronal, 4R tau



4R p-tau astrocytes in crease with age not pathological severity

Cherry et al, Brain Pathology, 2020

Tau pathology in CTE:

- *CTE : mixed 4R and 3R tau*
- *Neuronal tau predominates in early CTE*
- *4R neuronal tau predominates in early CTE*
- *There is a shift from 4R toward 3R tau as the severity of CTE increases*
- *4R astrocytes increase with age, not CTE severity, especially after age 60*
- *Astrocytic p-tau only 4R tau*

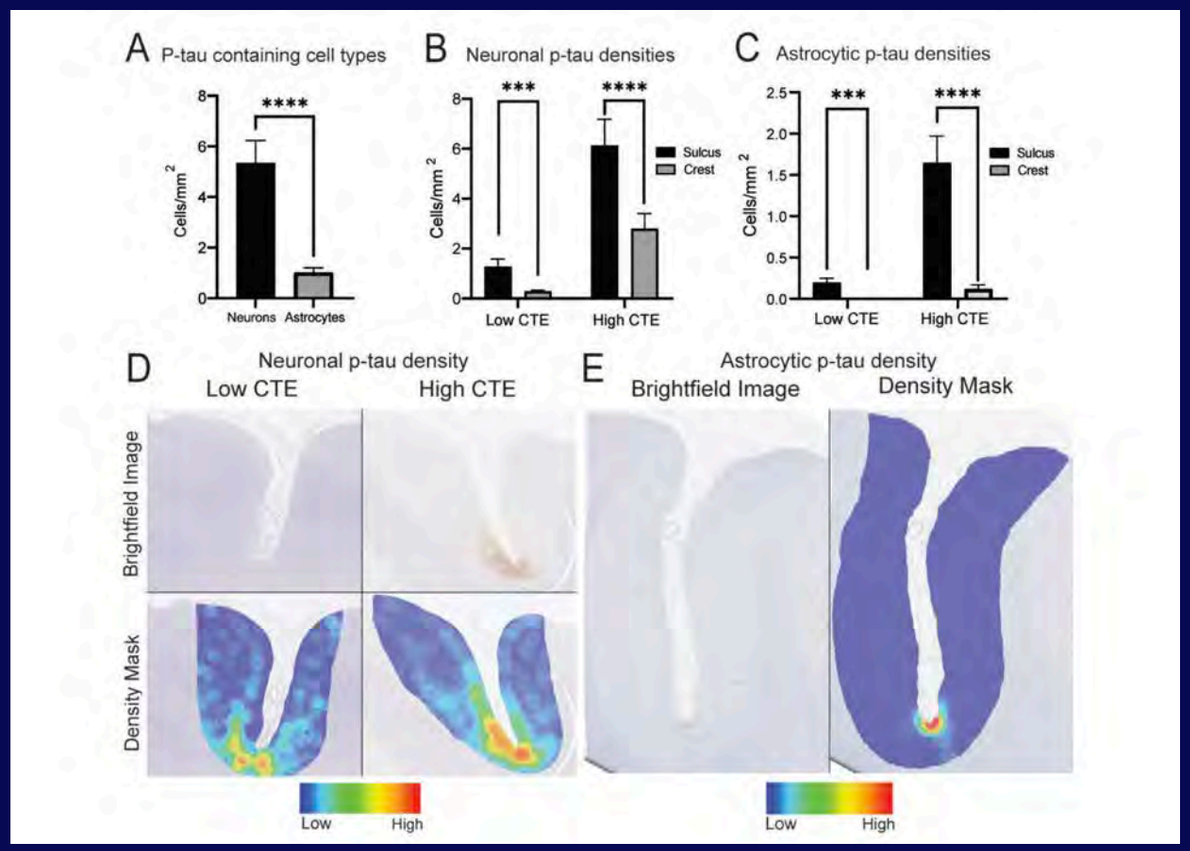
Cherry et al, Brain Pathology, 2020

ORIGINAL ARTICLE

Tau Pathology in Chronic Traumatic Encephalopathy is Primarily Neuronal

Morgane L.M.D. Butler, BSc, Erin Dixon, BS, Thor D. Stein, MD, PhD, Victor E. Alvarez, MD, Bertrand Huber, MD, PhD, Michael E. Buckland, MBBS, PhD, FRCPA, FFSc, Ann C. McKee, MD, and Jonathan D. Cherry, PhD

Quantitation of Multiplex immunofluorescent staining in CTE (n=150)



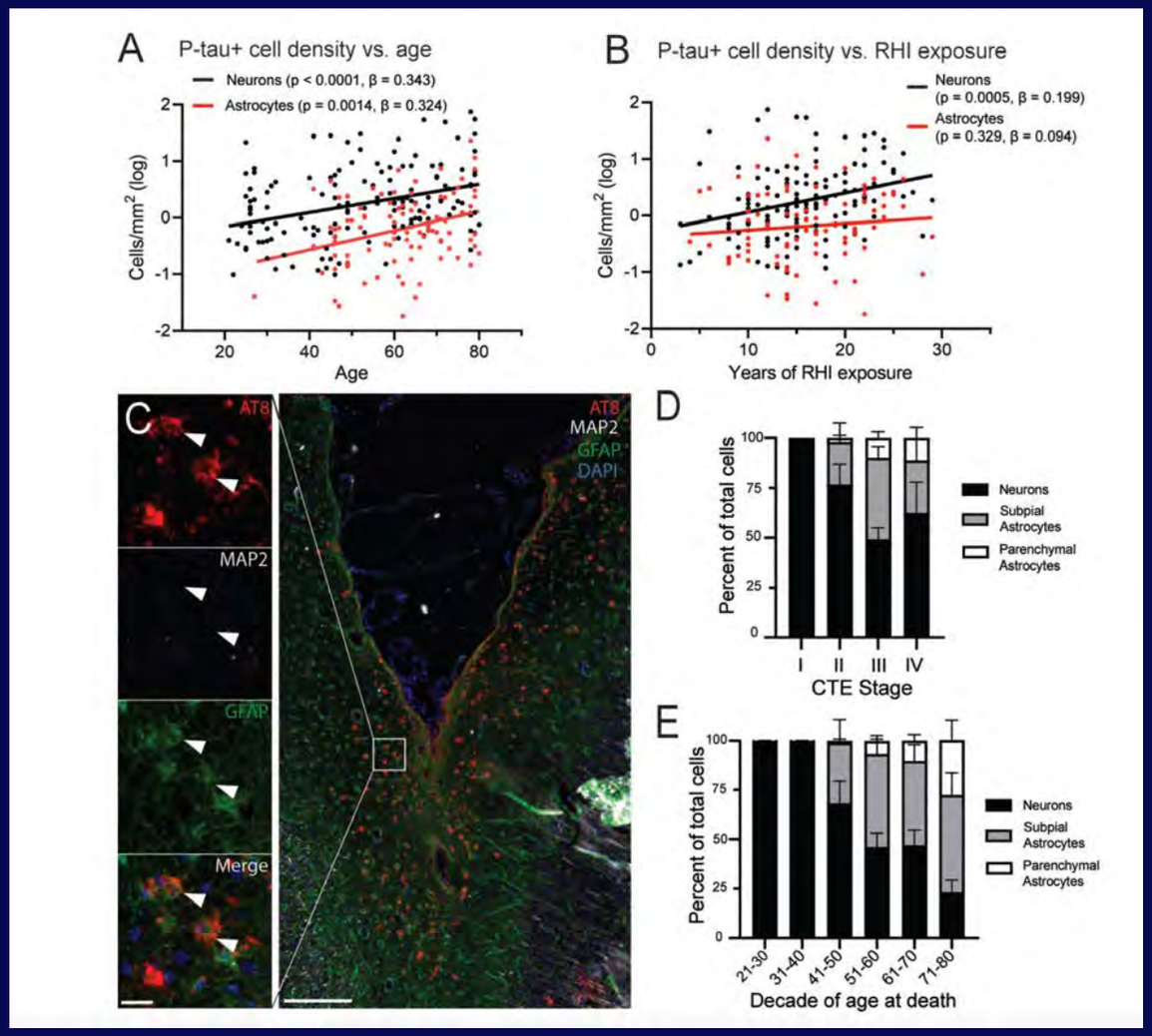
- *More neuronal p-tau was found across all cortical regions compared to astrocytic p-tau.*

- *Sulcal astrocytic ptau was primarily localized to subpial regions as thorn-shaped astrocytes, a form of age-related tau astrogliopathy.*

ORIGINAL ARTICLE

Tau Pathology in Chronic Traumatic Encephalopathy is Primarily Neuronal

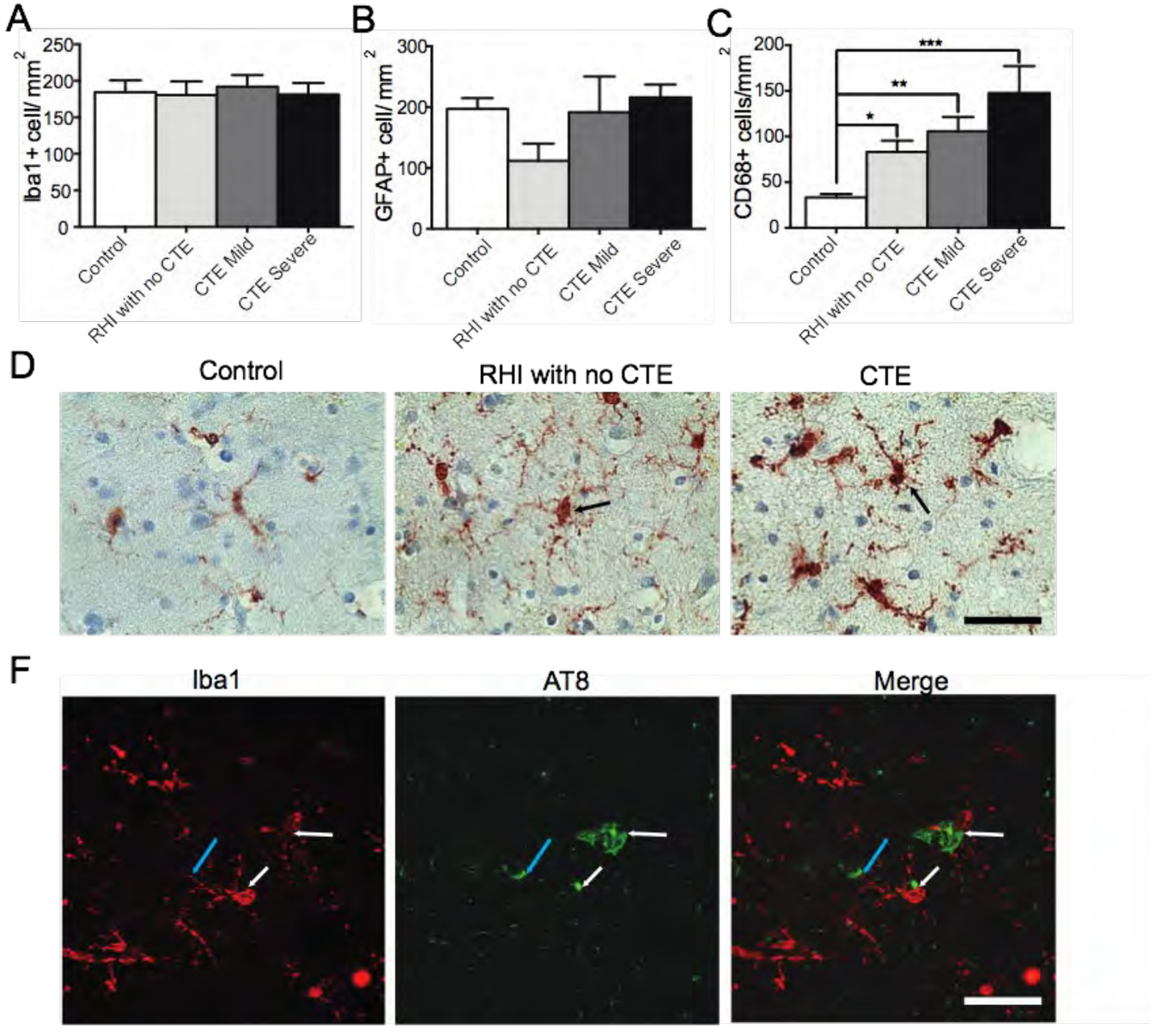
Morgane L.M.D. Butler, BSc, Erin Dixon, BS, Thor D. Stein, MD, PhD, Victor E. Alvarez, MD, Bertrand Huber, MD, PhD, Michael E. Buckland, MBBS, PhD, FRCPA, FFSc, Ann C. McKee, MD, and Jonathan D. Cherry, PhD



- *Neuronal p-tau was significantly associated with age, years of RHI exposure, and CTE severity.*
- *Astrocytic p-tau pathology was significantly associated only with age.*

Inflammatory microglia are found in the perivascular CTE lesion and contribute to the ptau pathology

Increased activated microglia in young football players w RHI (m age 32 yrs) and increase further in CTE.



Increased neuroinflammation associated with increased AT8 pathology

Iba1 positive cells surrounding AT8 positive clusters. White arrows =Iba1 cell body near tau aggregates. Blue arrow =microglia process contacting AT8 + cell

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