New Insights into the Detection of Chronic Traumatic Encephalopathy During Life
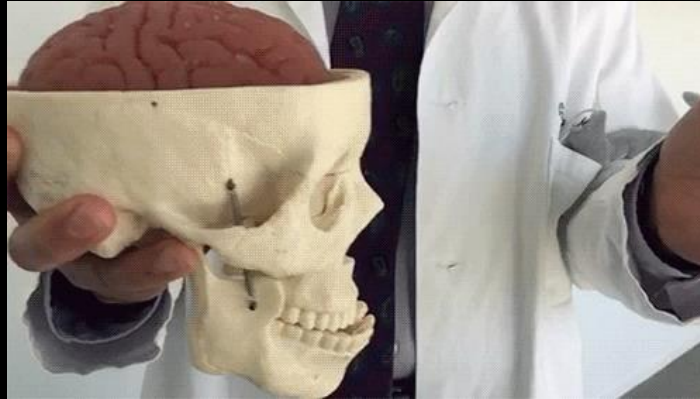
Michael L. Alosco, PhD

Associate Professor of Neurology
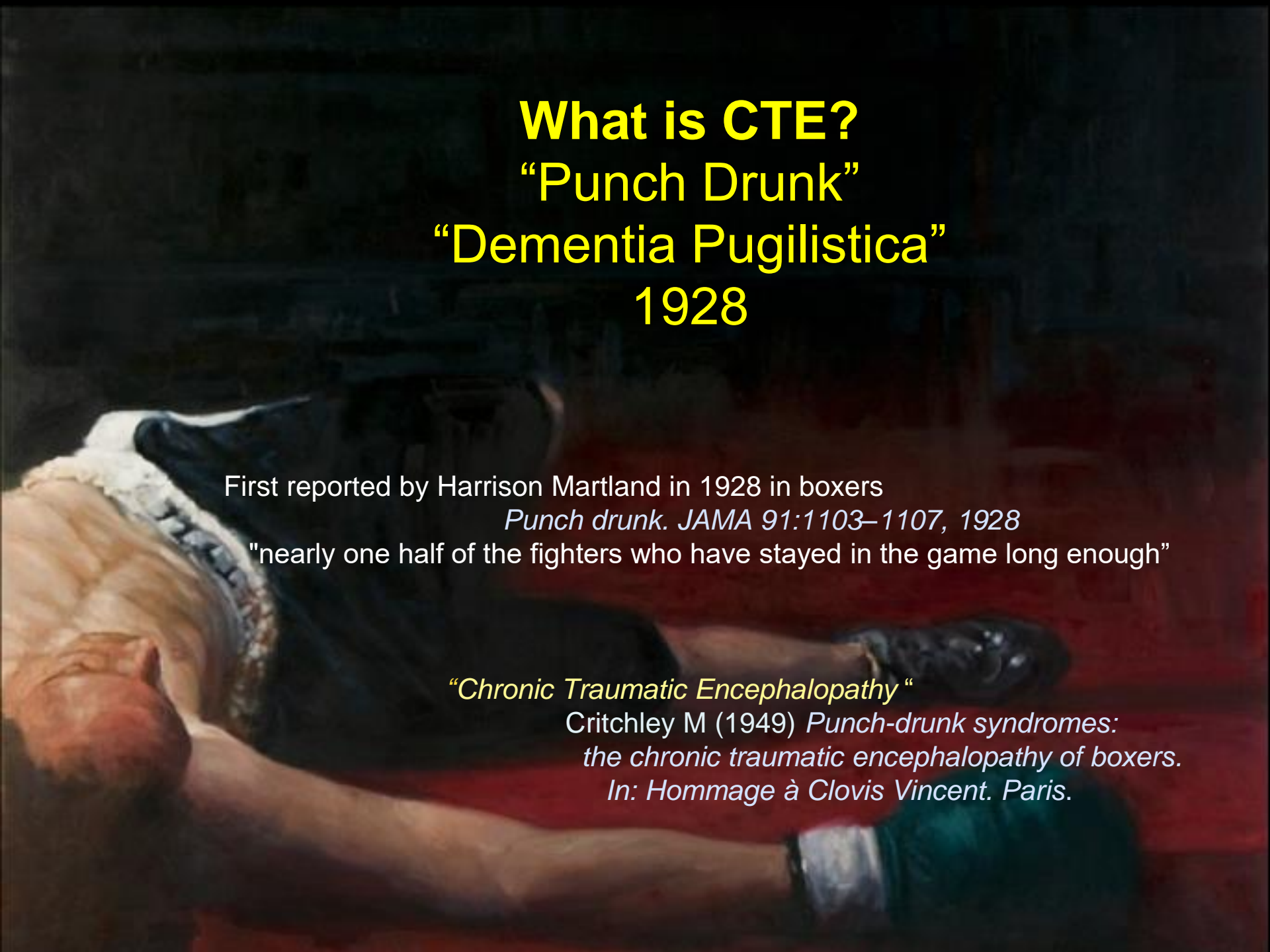Research Vice Chair

Co-Director, Clinical Research, Boston University CTE Center

Boston University Chobanian & Avedisian School of Medicine

BU | Alzheimer's Disease Center

BU | CTE Center

RHI: Repetitive head impacts

- RHI = RHI

- RHI include symptomatic concussions and the much more frequent non-concussive injuries – no universal definition

- **Exposure to RHI is the primary risk factor for chronic traumatic encephalopathy (CTE) – more next**

What is CTE?
"Punch Drunk"
"Dementia Pugilistica"
1928

First reported by Harrison Martland in 1928 in boxers
Punch drunk. JAMA 91:1103–1107, 1928
"nearly one half of the fighters who have stayed in the game long enough"

"Chronic Traumatic Encephalopathy "
Critchley M (1949) *Punch-drunk syndromes:*
the chronic traumatic encephalopathy of boxers.
In: Hommage à Clovis Vincent. Paris.

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy McKee et al.
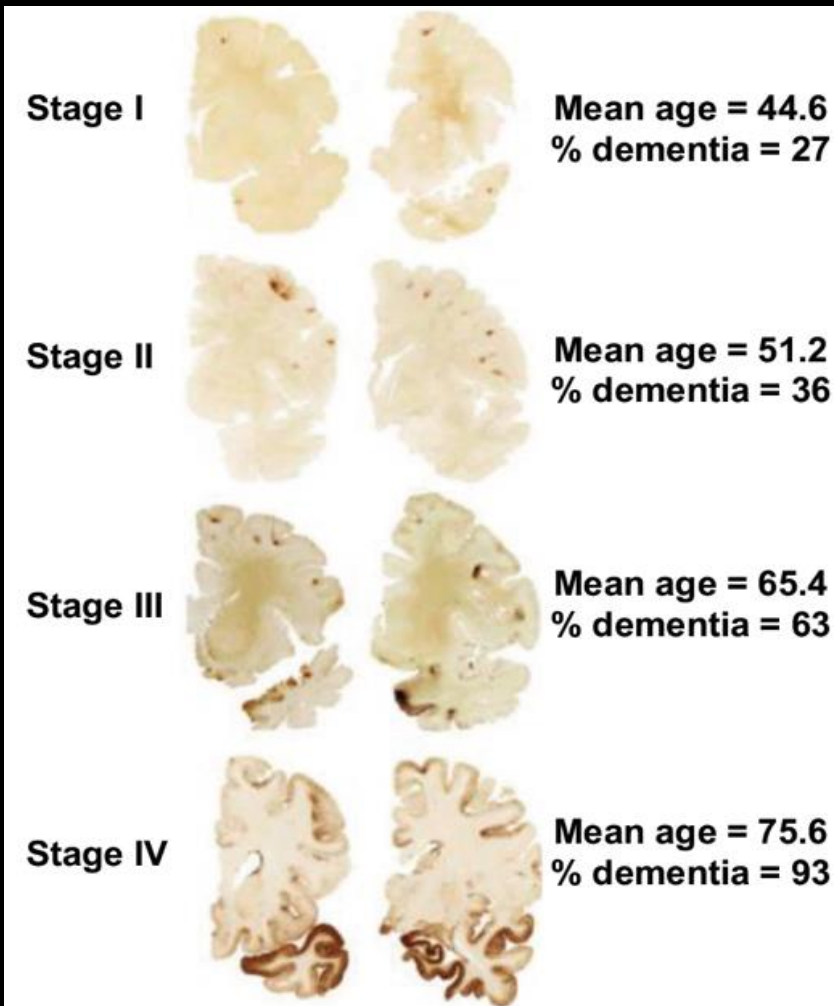
THE PATHOGNOMONIC LESION

Alosco et al 2020, Acta Neuropathologica
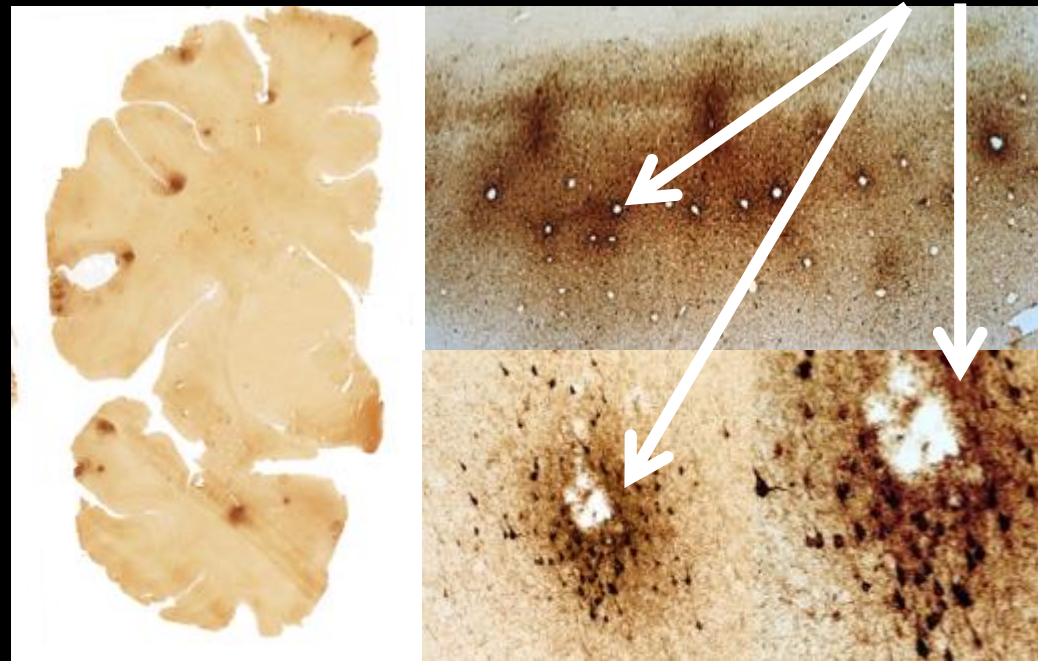
**McKee et al.'s (2013)
CTE Tau Staging**

CTE

AD

**Braak et al.'s (2011)
Aging/AD Tau Staging**

STAGE I
- Isolated perivascular epicenters
- Predilection for depths of sulci
- Neocortex: superior, dorsolateral and inferior frontal
- Locus coeruleus (66% of cases)

STAGE a-c
- Locus coeruleus
- Upper raphe nuclei
- Magnocellular nuclei

STAGE II
- Multiple epicenters in frontal, temporal cortex, and parietal neocortices
- Diencephalon

STAGE 1a, 1b, I-II
- Transentorhinal cortex
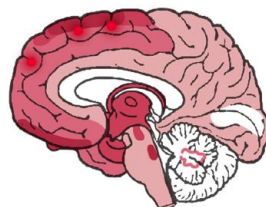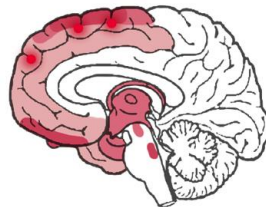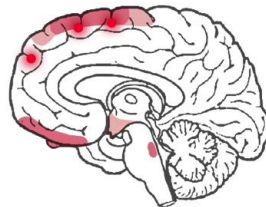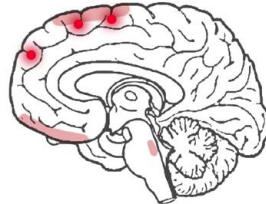- Entorhinal cortex

STAGE III
- Widespread neocortical involvement
- Hippocampus
- Entorhinal cortex
- Amygdala
- Nucleus basalis of Meynert

STAGE III-IV
- Hipppocampus
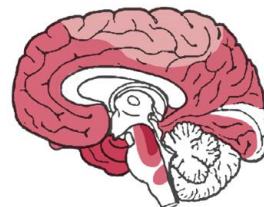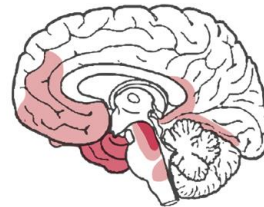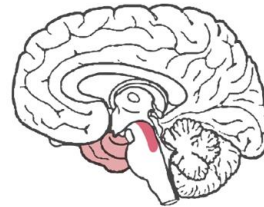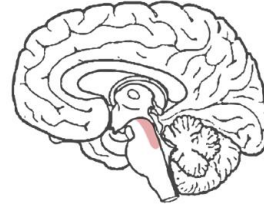- Amygdala
- Basal temporal
- Insular
- Basal frontal

STAGE IV
- Thalamus
- Basal ganglia
- Brain stem
- Cerebellum

STAGE V-VI
- Widespread neocortical involvement
- Sparing of cerebellum

Stein et al 2015

Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules

Benjamin Falcon, Jasenko Zivanov, Wenjuan Zhang, Alexey G. Murzin, Holly J. Garringer, Ruben Vidal, R. Anthony Crowther, Kathy L. Newell, Bernardino Ghetti, Michel Goedert ✉ & Sjors H. W. Scheres ✉
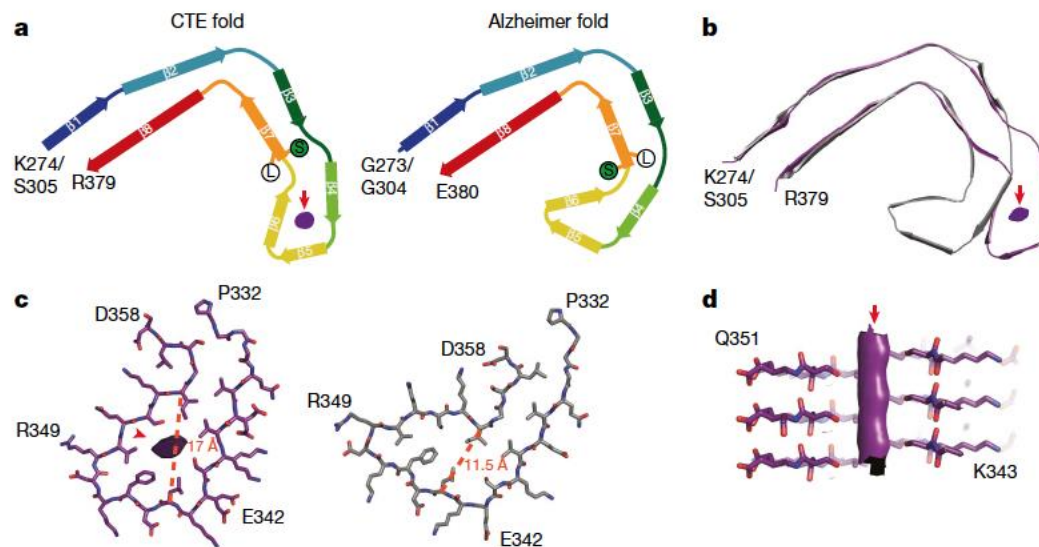
Fig. 3 | Comparison of the CTE and Alzheimer tau filament folds.
a, Schematic of the secondary structure elements in the CTE and Alzheimer folds, depicted as a single rung. The positions of S356 (S in green circle) and L357 (L in white circle) in the two folds are highlighted. In all panels, the extra density is depicted in purple and marked by a red arrow. **b,** Overlay of the CTE fold (purple) and the Alzheimer fold (grey), shown as a single rung. **c,** The β-helices of the CTE fold (purple) and the Alzheimer fold (grey), depicted as a single rung. The distances between the C_α atoms of L344 and I354 are shown as orange dashed lines. **d,** View normal to the helical axis of the CTE fold β-helix, depicted as three rungs and shown as a cross-section through S341 and S352.

Current Challenges

- CTE = neuropathological diagnosis

- **Problem:** CTE can only be accurately diagnosed after death via brain examination

Constellation of Symptoms
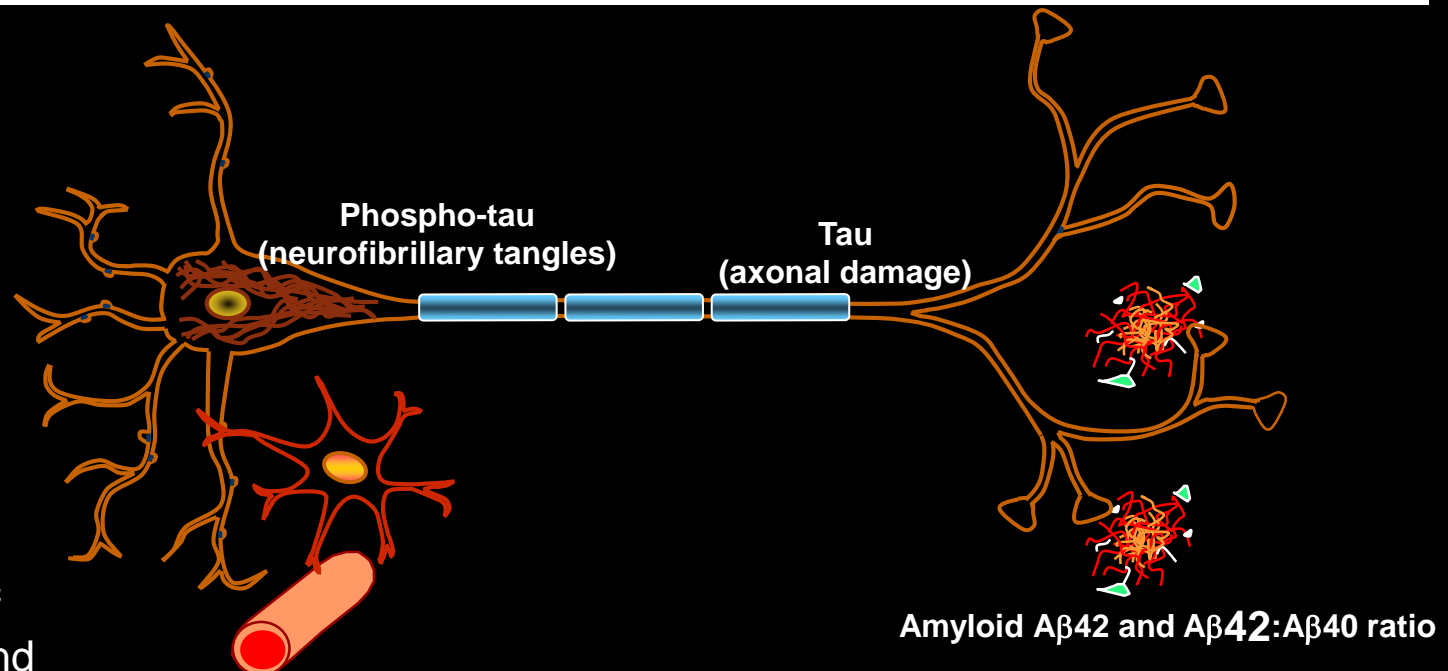## 2021 NINDS TES Research Diagnostic Criteria
Katz et al. 2021, *Neurology*

- **<u>Substantial</u>** exposure to RHI
- **<u>Cognitive Impairment:</u>** Episodic memory, executive function
- **<u>Neurobehavioral Dysregulation:</u>** Emotional dysregulation, explosiveness, impulsivity, rage, violent outbursts, short fuse
- **<u>Progressive course</u>** and **<u>not fully accounted</u>** for by another condition
- **Not for use in clinic - research diagnostic criteria**
- **Developed without biomarkers**

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION
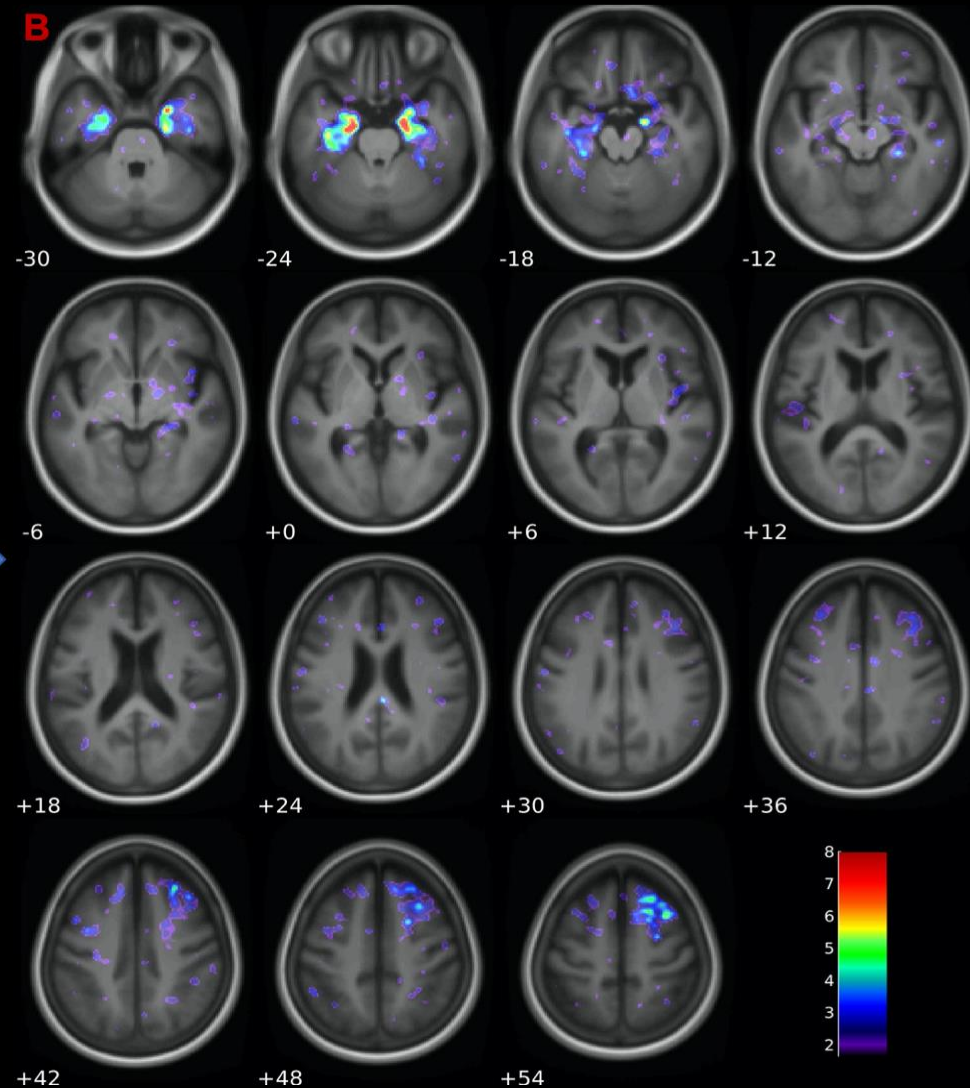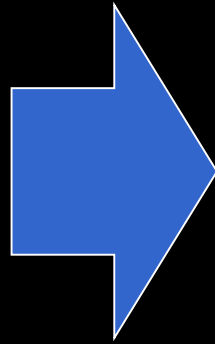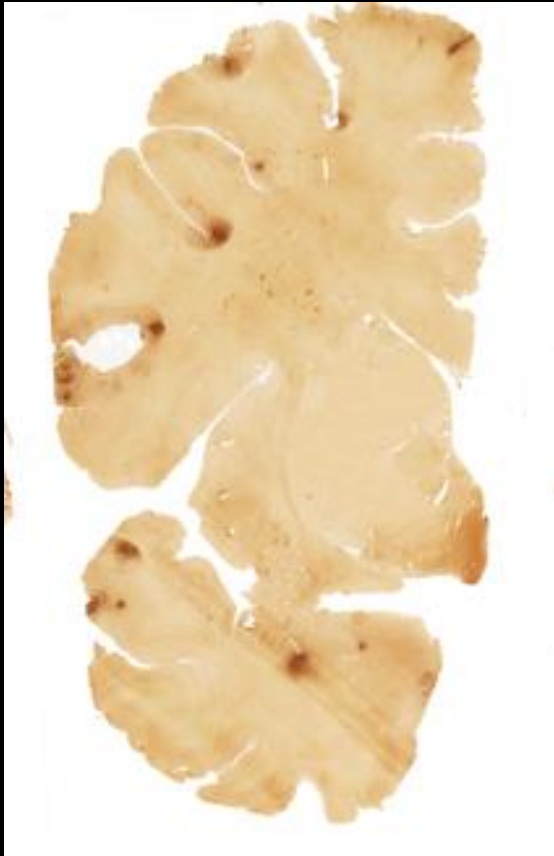
RESEARCH ARTICLE

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr.[1] | J. Scott Andrews[2] | Thomas G. Beach[3] | Teresa Buracchio[4] | Billy Dunn[5] | Ana Graf[6] | Oskar Hansson[7,8] | Carole Ho[9] | William Jagust[10] | Eric McDade[11] | Jose Luis Molinuevo[12] | Ozioma C. Okonkwo[13] | Luca Pani[14] | Michael S. Rafii[15] | Philip Scheltens[16] | Eric Siemers[17] | Heather M. Snyder[18] | Reisa Sperling[19] | Charlotte E. Teunissen[20] | Maria C. Carrillo[18]

Phospho-tau
(neurofibrillary tangles)

Tau
(axonal damage)

Amyloid Aβ42 and Aβ42:Aβ40 ratio

Slide courtesy of
Dr. Elaine Peskind

# Tau PET and CTE
BU-UCSF collaborations

Tau PET Ligands

- First generation tau radiotracers include 18F-FDDNP, 18F-FTP, and others (11CPBB3, THK compounds)—developed to detect AD tau

- FTP has highest affinity to mixed 3R/4R tau in AD—approved by the FDA to detect p-tau in patients who have cognitive impairment due to AD

- FTP has low binding affinity to non-AD neurodegenerative diseases

- 18FMK-6240 and PI-2620 developed to improve binding selectivity and pharmacokinetics
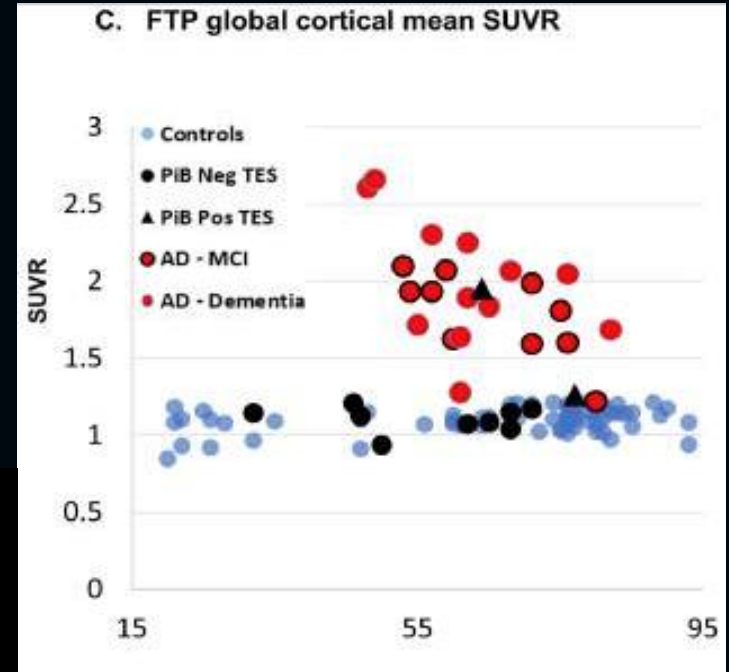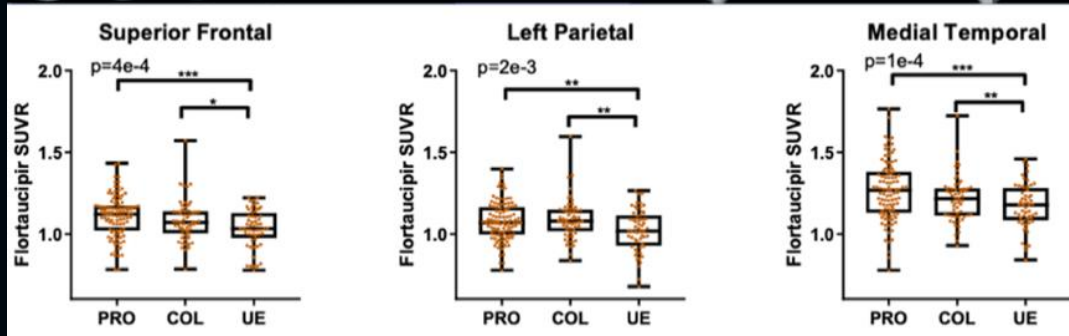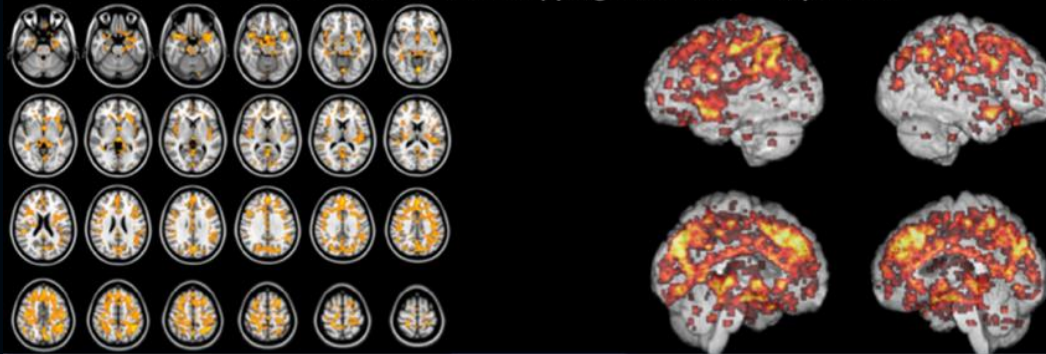
Flortaucipir (TAUVID)

Soleimani-Meigooni et al 2020
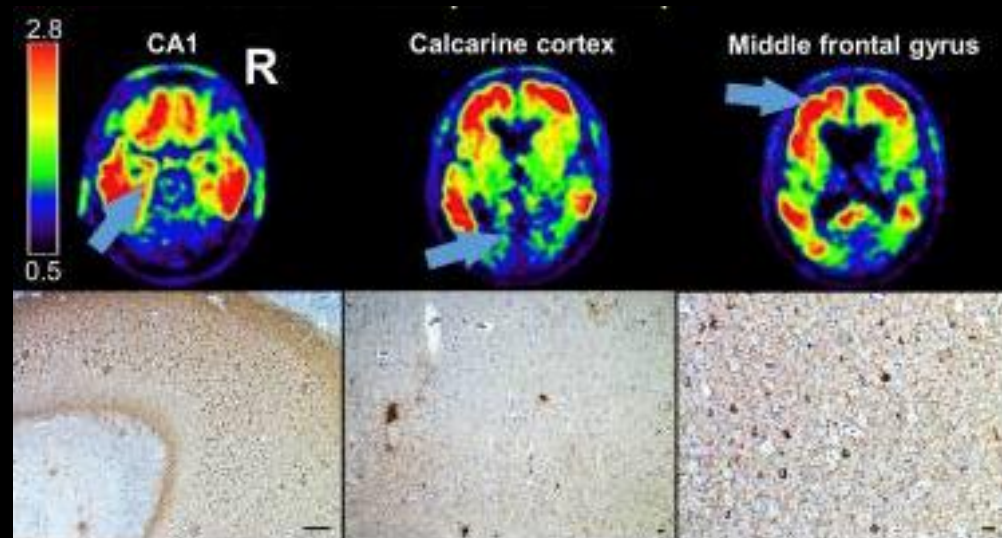
18F-Flortaucipir: Summary
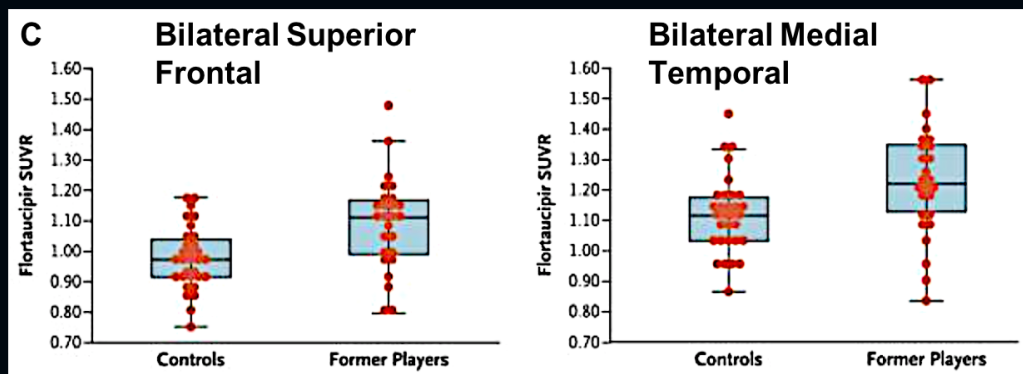
Stern et al 2019, NEJM

Lesman-Segev et al 2019, Neuroimage Clin

Su et al 2023, Alzheimers Dement

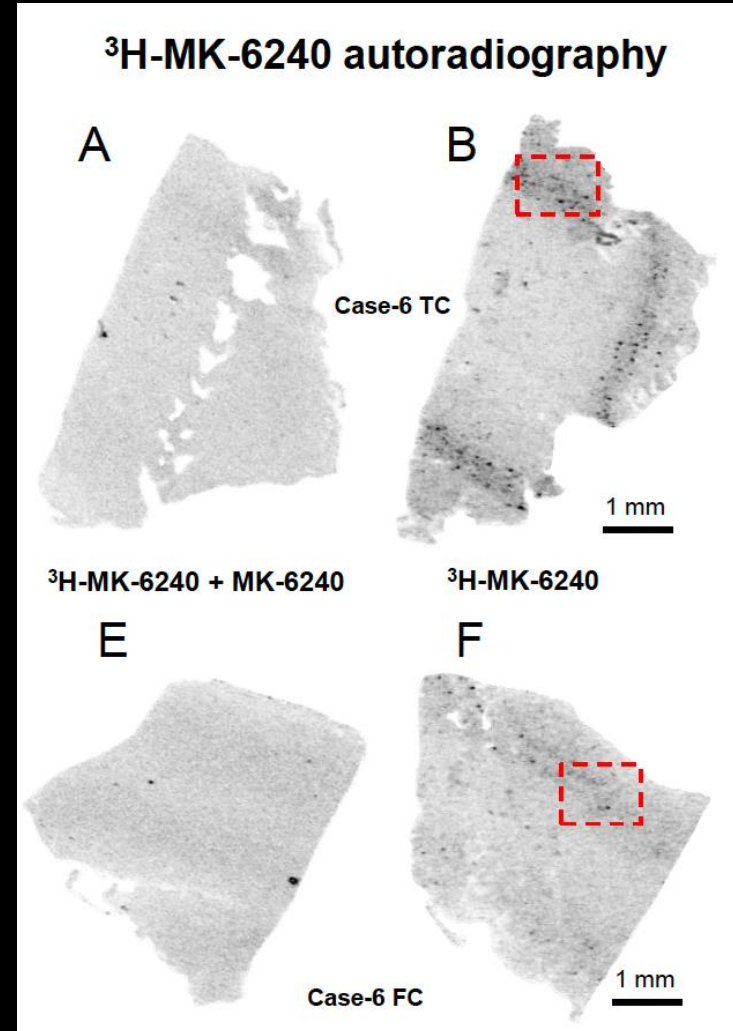# FIND-CTE: [^{18}F]-MK-6240

- **<u>Objective</u>**: To determine the usefulness of MK-6240 as an in vivo biomarker for CTE

- NINDS-funded proof-of-concept R21: UCSF and BU ADRC collaboration

[¹⁸F]MK6240 in CTE

Second generation tracer with improved imaging and binding properties

- Six cases with CTE stage III

- 1 had a laminar pattern of MK ARG signal that corresponded to AT8-immunoreactivity

- Kd=2.0+/-0.9 nM, Bmax=97+/-24 nM, n=3 compared with AD Kd of 0.46 +/- 0.12 nM

³H-MK-6240 autoradiography

A   B   Case-6 TC   1 mm

³H-MK-6240 + MK-6240   ³H-MK-6240

E   F   Case-6 FC   1 mm

Methods

- 30 symptomatic (AD8=2+) former NFL players

- Same-age cognitively unimpaired males without TBI from the Wisconsin Registry for Alzheimer's Prevention

- Enroll in UCSF or BU ADRC

- Complete amyloid (florbetapir) PET and tau (MK-6240) PET

Demographics	Former NFL Players N= 30	Controls N=40
Age, mean (SD) years	58.9 (7.8)	65.7 (6.3)
Education, mean (SD) years	16.6 (1.8)	17.3 (3.0)
Sex, n (%) male	100	100
Race, n (%) Black		
Black, n (%)	13 (43.3)	1 (2.5)
White, n (%)	17 (56.7)	39 (97.5)
Diagnosis		
Traumatic Encephalopathy Syndrome, n (%)	22 (73.3)	--
Level of CTE certainty		--
Suggestive, n (%)	5 (16.7)	--
Possible, n (%)	6 (20.0)	--
Probable, n (%)	11 (36.7)	--
Cognitive Diagnosis		
Cognitively normal, n (%)	9 (30.0)	100
MCI Amnestic, single domain, n (%)	4 (13.3)	0
MCI Amnestic, multiple domains, n (%)	5 (16.7)	0
MCI Non-amnestic, single domain, n (%)	1 (3.3)	0
MCI Non-amnestic, multiple domains, n (%)	3 (10.0)	0
Cognitively impaired, not MCI, n (%)	3 (10.0)	0
Dementia, n (%)	5 (16.7)	0
Elevated 18F-Florbetapir, n (%)	0	1 (2.5)

Individual Level

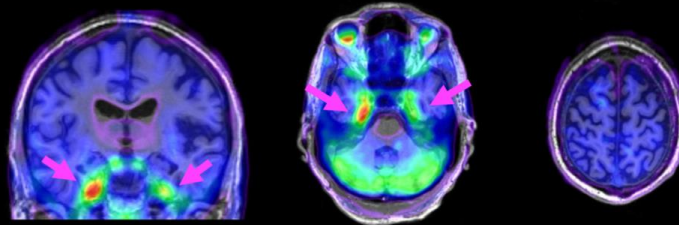**Alosco et al (2025), Molecular Neurodegeneration**

^{18}F-MK-6240 SUVr (inf cbl GM ref)
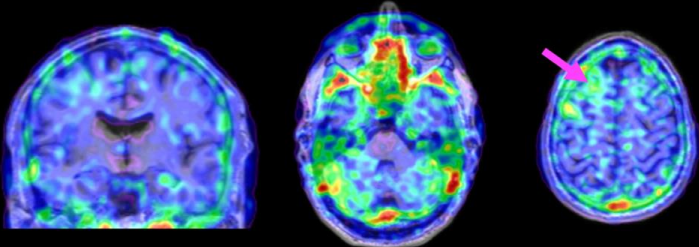
0.5 1 1.5 2

L R
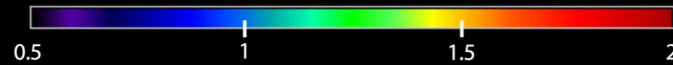
NFL 1
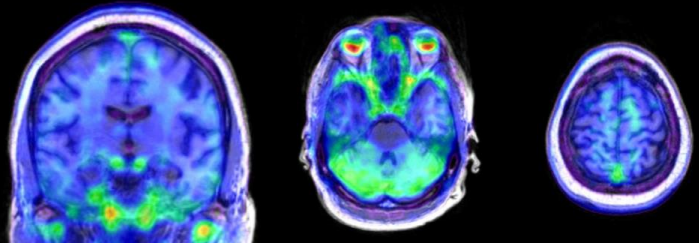MTL & Frontal
65-69 yo

N = 4
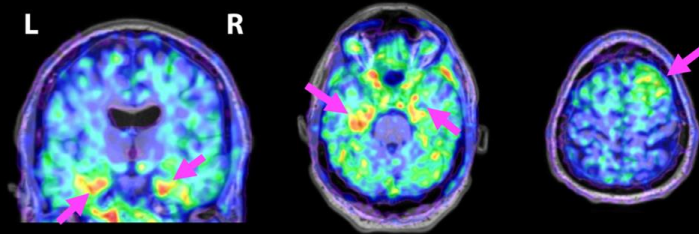
NFL 2
MTL only
75-79 yo

N = 7

NFL 3
Frontal only
60-64 yo

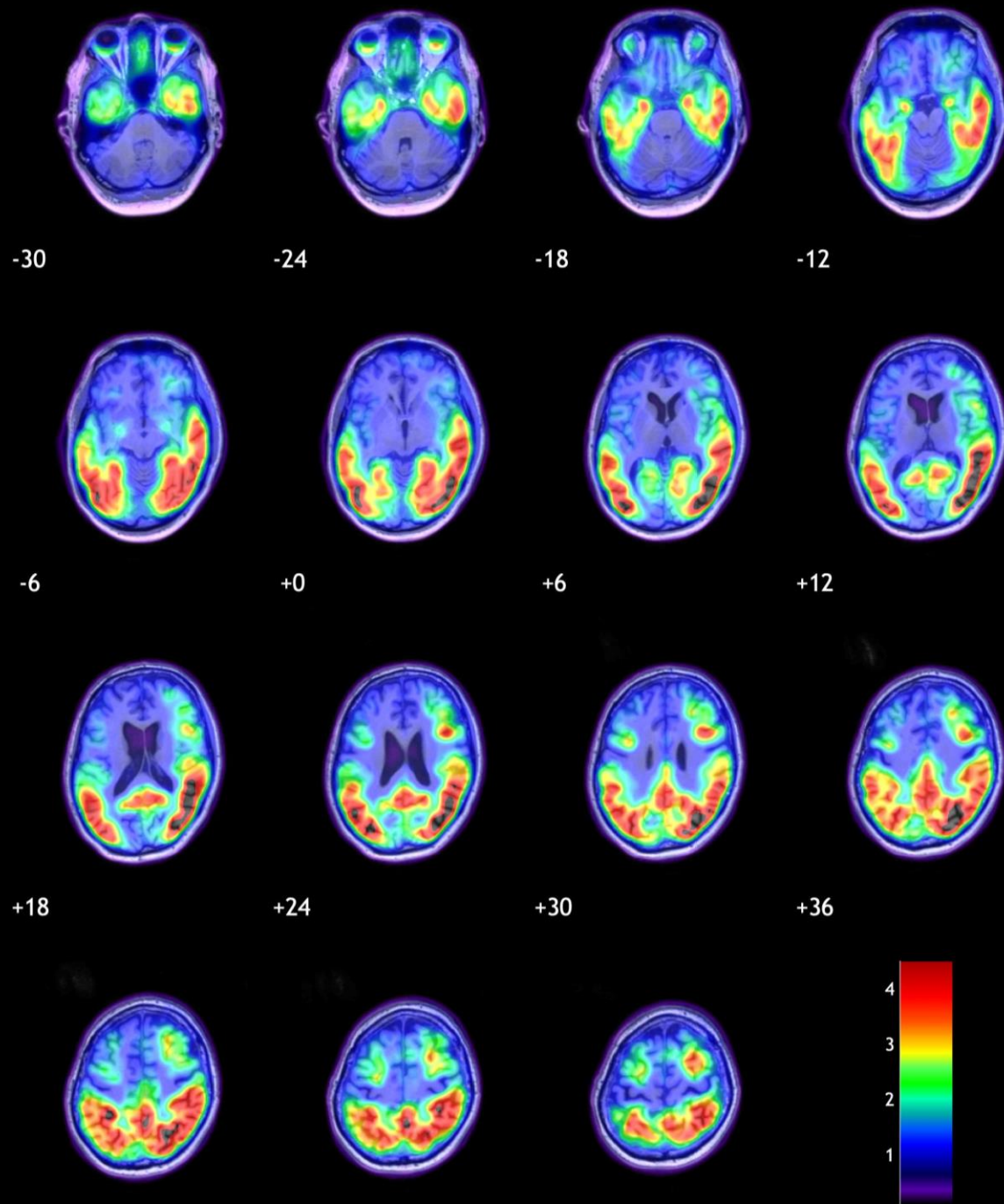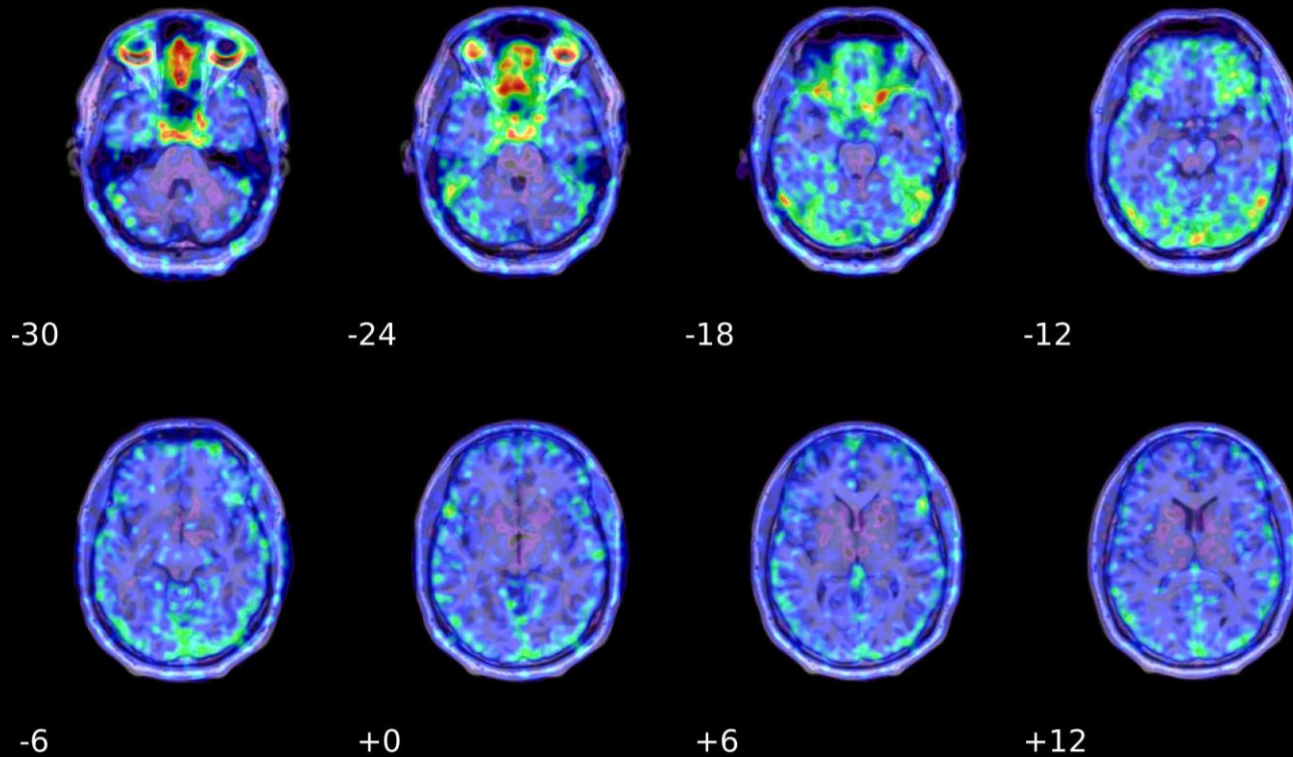N = 2

NFL 4
None
60-64 yo

N = 16

MK-6240
Tau PET in
Alzheimer's
disease

Off Target Meningeal Binding

- Cortical binding complicated by contamination from off-target meningeal binding
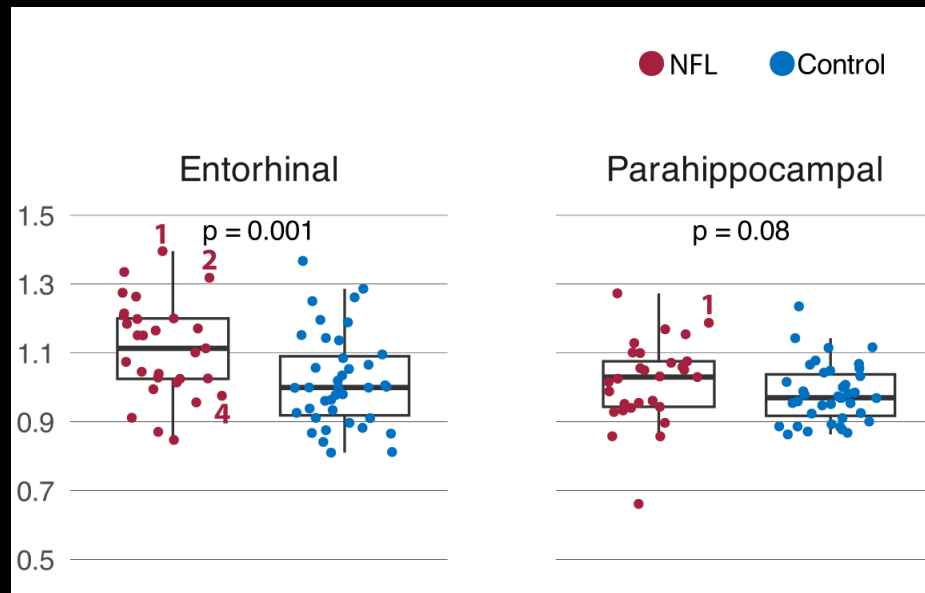

-30   -24   -18   -12

-6   +0   +6   +12

Group Level

B
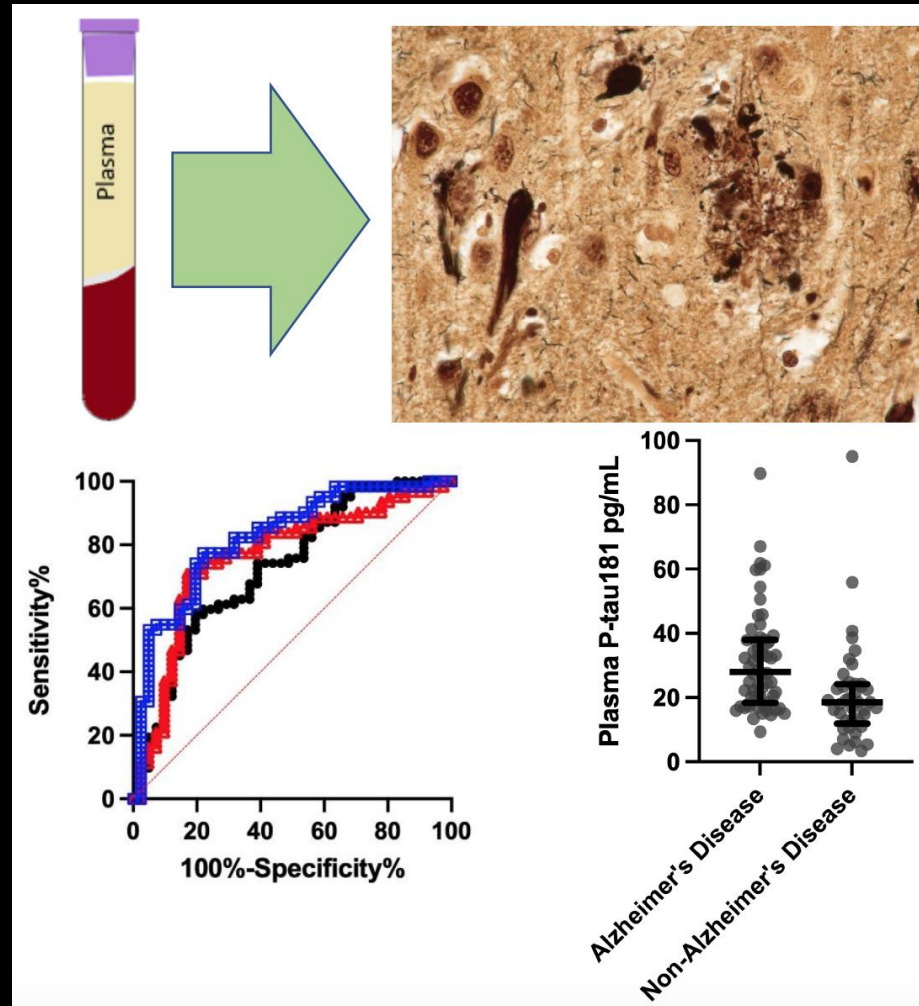
NFL > Control
Voxelwise comparison controlling for age

MK: Still not at diagnostic level, but useful for MTL pathology detection

● NFL   ● Control

Entorhinal   Parahippocampal

p = 0.001   p = 0.08

Can we detect CTE in the blood?

- We can now detect those small proteins in the blood
- Works great for Alzheimer's disease

Morrison et al 2022, Brain

RESEARCH ARTICLE

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

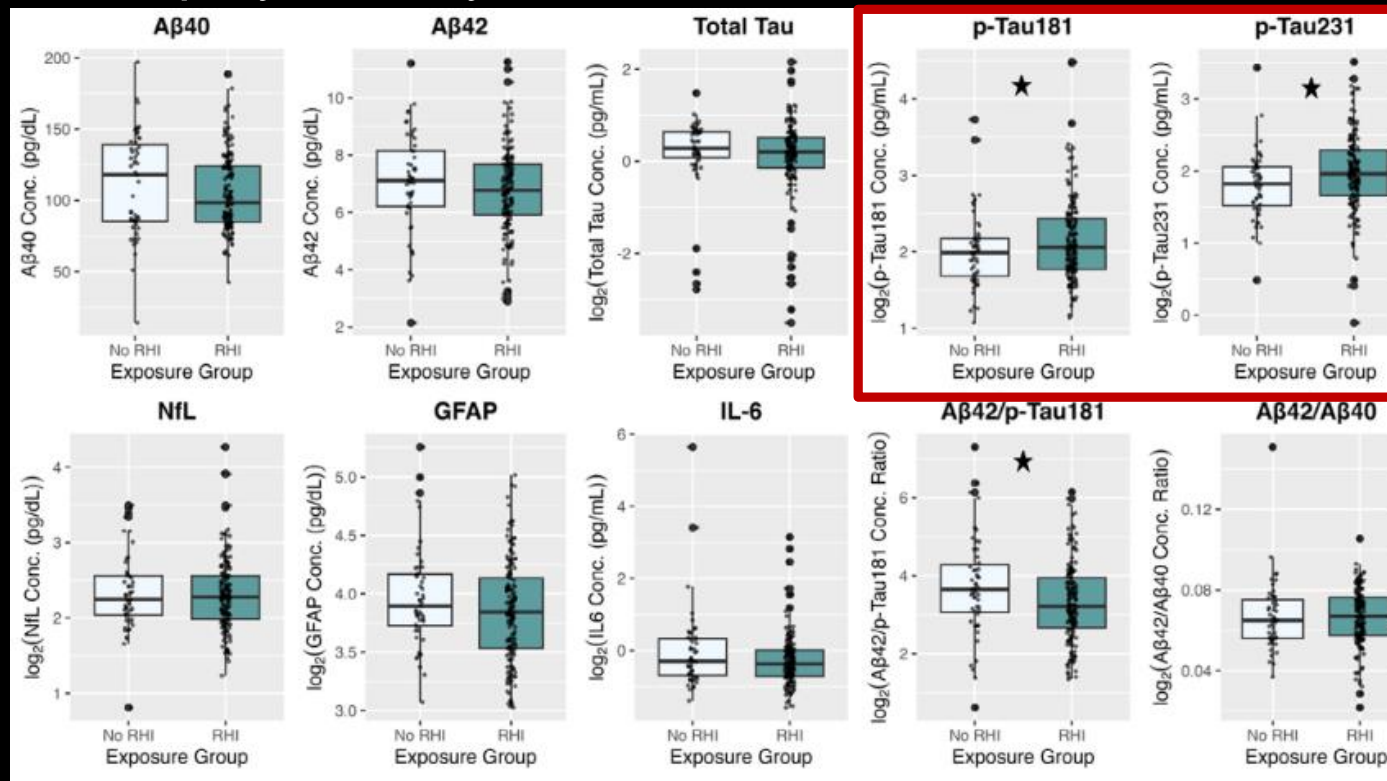## Examination of plasma biomarkers of amyloid, tau, neurodegeneration, and neuroinflammation in former elite American football players

Miner et al (2024)

- 166 symptomatic former football players (45-75 years) compared with 51 asymptomatic unexposed men
- 17 football players amyloid PET elevated

Plasma P-tau181 and P-tau217 in Patients With Traumatic Encephalopathy Syndrome With and Without Evidence of Alzheimer Disease Pathology

Breton M. Asken, PhD, ATC, Jeremy A. Tanner, MD, Lawren VandeVrede, MD, PhD, William G. Mantyh, MD, Kaitlin B. Casaletto, PhD, Adam M. Staffaroni, PhD, Renaud La Joie, PhD, Leonardo Iaccarino, PhD, David Soleimani-Meigooni, MD, Julio C. Rojas, MD, PhD, Raquel C. Gardner, MD, Bruce L. Miller, MD, Lea T. Grinberg, MD, PhD, Adam L. Boxer, MD, PhD, Joel H. Kramer, PsyD, and Gil D. Rabinovici, MD

Correspondence
Dr. Asken
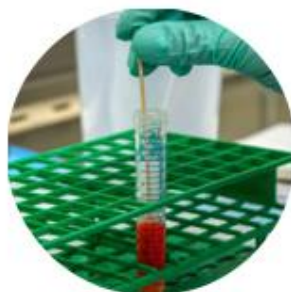breton.asken@ucsf.edu
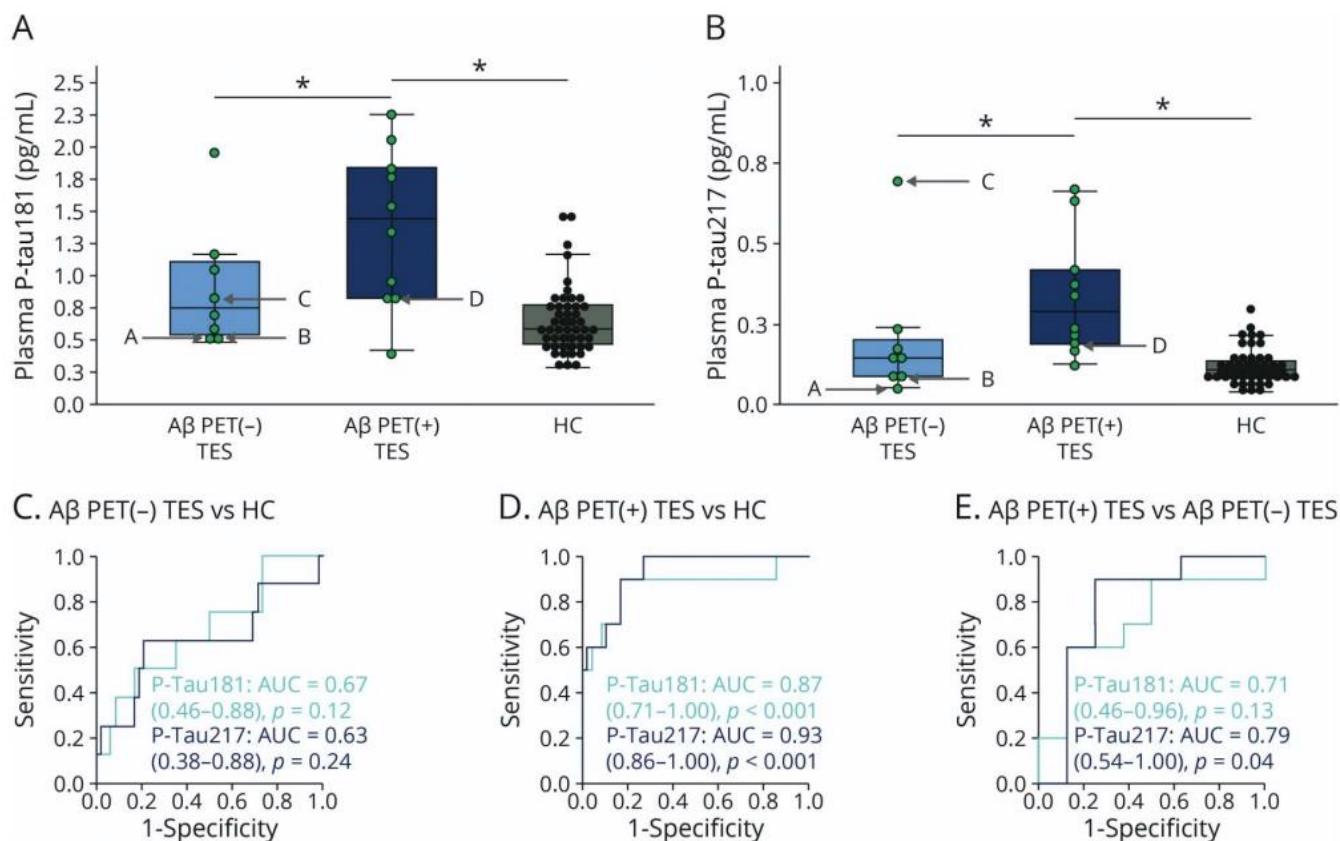
BANK CTE

- Combines three critical elements needed to discover ways to detect and diagnose disease during life

Online Survey
Assess signs & symptoms

Single Blood Draw
Biomarkers using practical methods

Brain Donation Pledge
Validate against gold standard

Structural Magnetic Resonance Imaging

- Integral component of the clinical evaluation of neurodegenerative diseases.
  - Atrophy patterns support diagnosis and monitoring
  - Atrophy rates serve as outcomes for large-scale multi-center clinical trials of disease-modifying therapies.
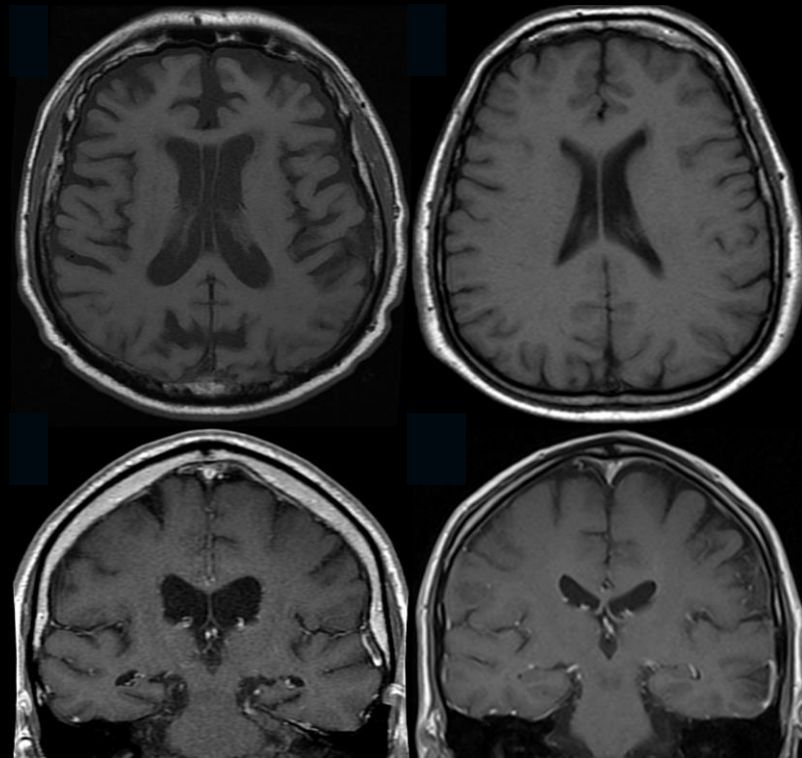
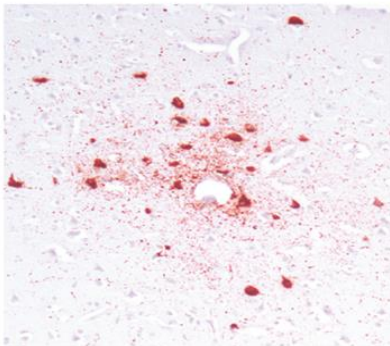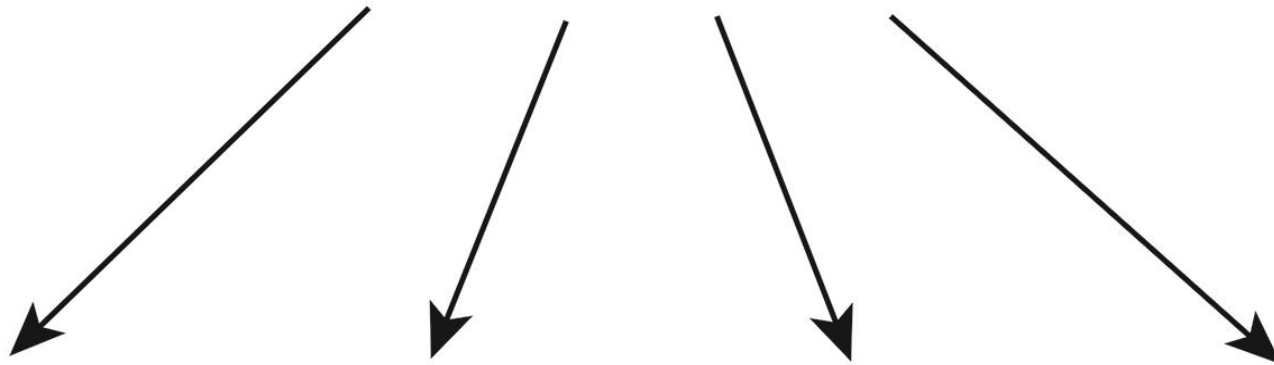# Structural MRI profiles and tau correlates of atrophy in autopsy-confirmed CTE

More frontal atrophy

More temporal atrophy

6.7X higher
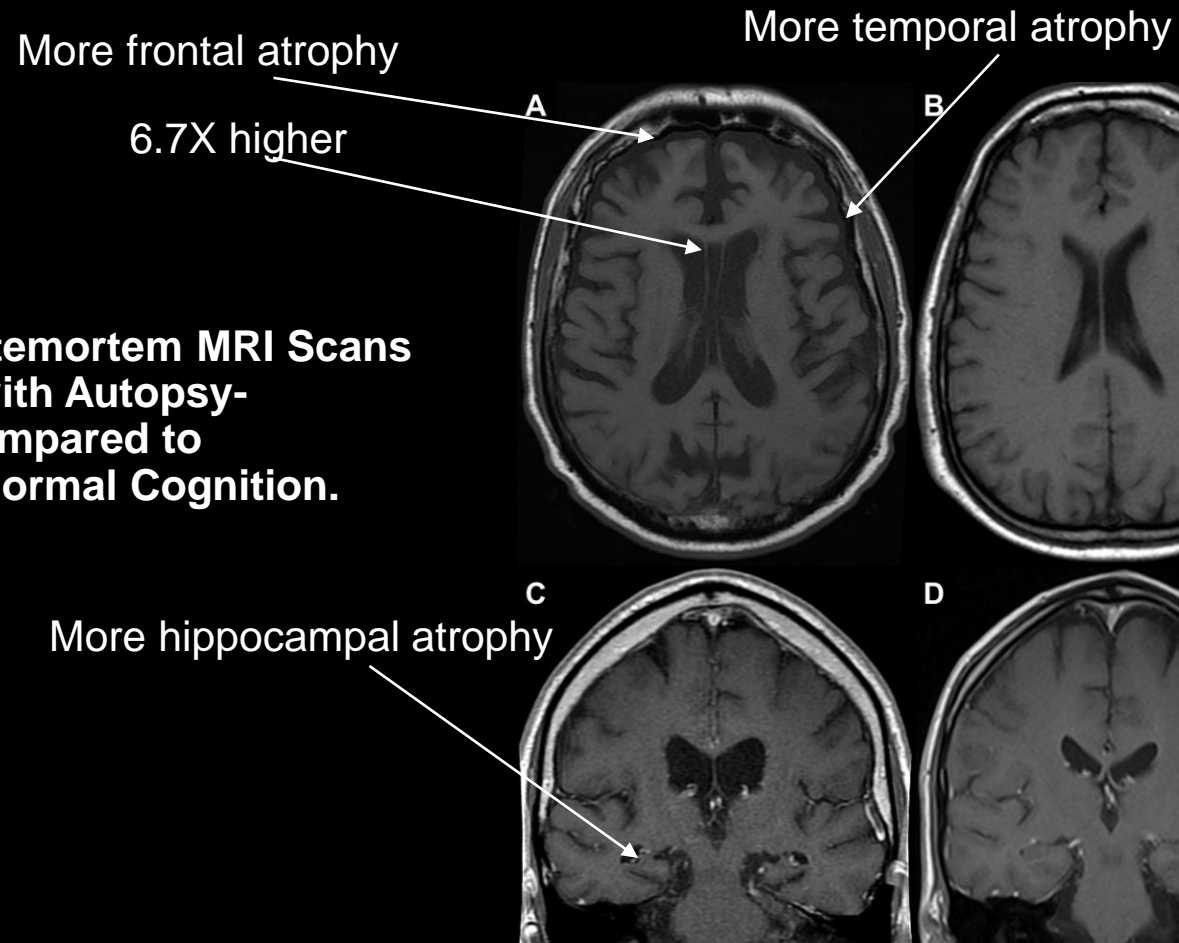
Representative Antemortem MRI Scans for Brain Donors with Autopsy-Confirmed CTE Compared to Participants with Normal Cognition.
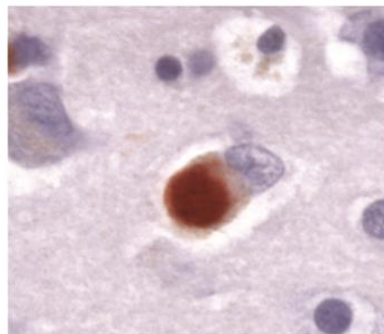
More hippocampal atrophy
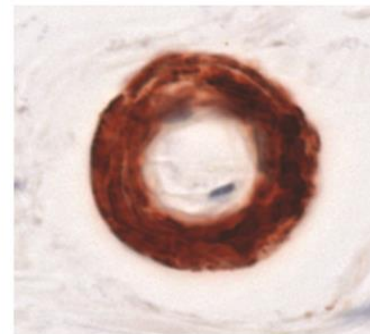
Co-Pathologies
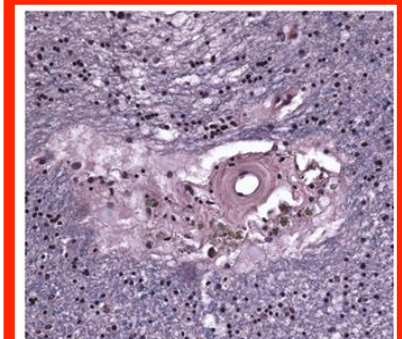

Exposure to repetitive head impacts

Chronic traumatic encephalopathy

Neocortical Lewy body disease

Cerebral amyloid angiopathy

White matter rarefaction

ARTICLE

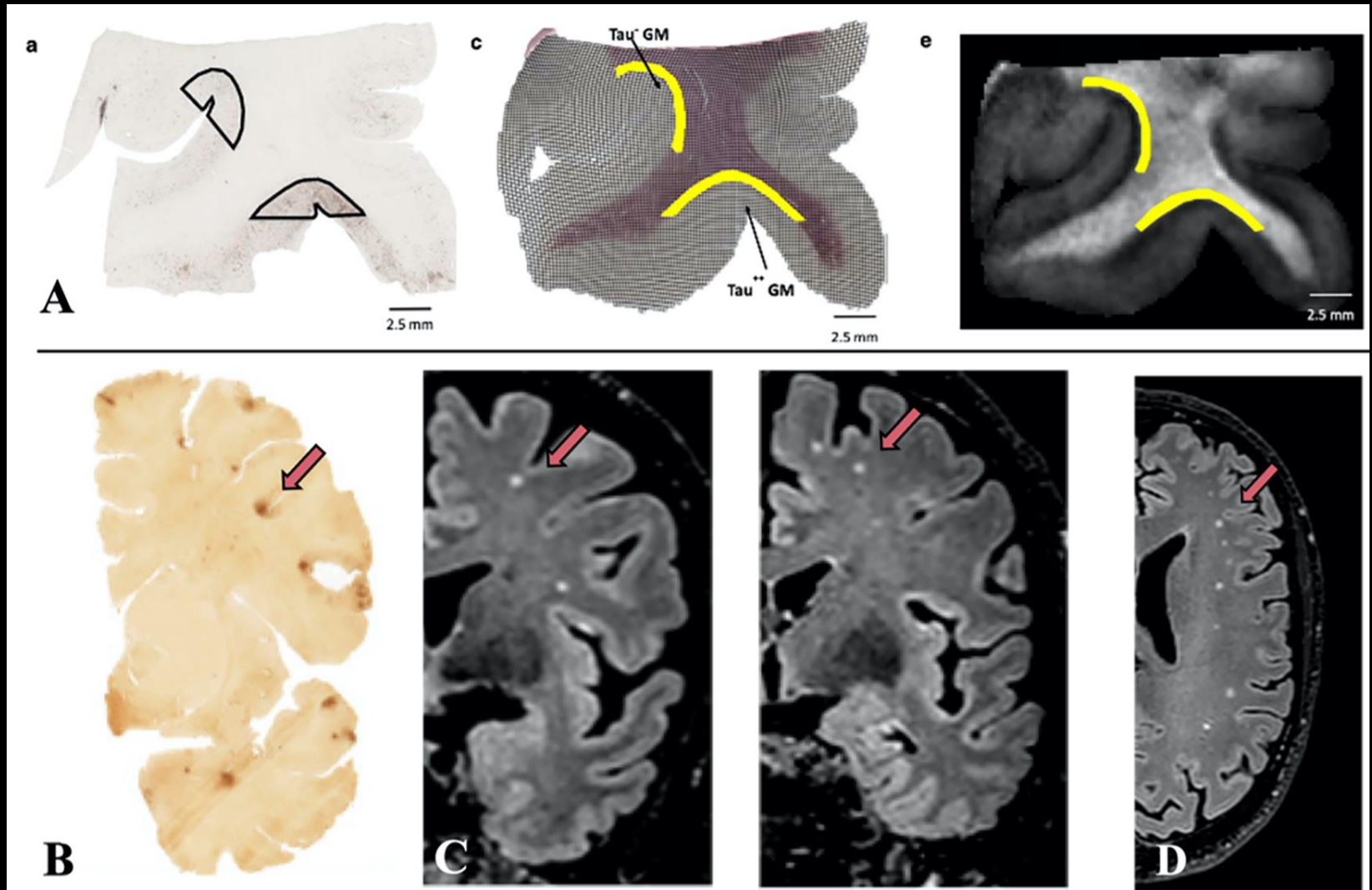## Does white matter and vascular injury from repetitive head impacts lead to a novel pattern on T2 FLAIR MRI? A hypothesis proposal and call for research

RHI-WMH

Small, punctate lesions close to the folds of the brain
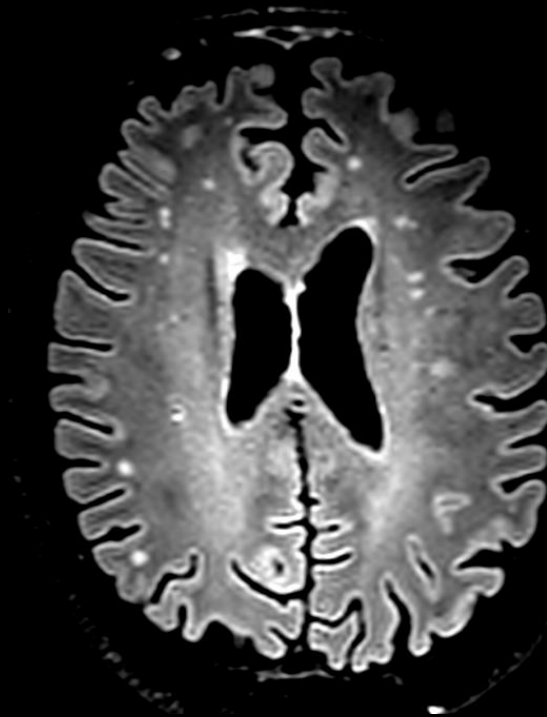
Location Susceptible to Head Trauma: RHI-WMH

Miner et al., 2025

Amyloid PET: Best (negative) biomarker

Alzheimer's
Research & Therapy

RESEARCH   **Open Access**

Amyloid PET across the cognitive spectrum in former professional and college American football players: findings from the DIAGNOSE CTE Research Project

Robert A. Stern[1,2,3,4*†], Diana Trujillo-Rodriguez[1,5†], Yorghos Tripodis[1,2,6], Surya V. Pulukuri[1], Michael L. Alosco[1,2,3], Charles H. Adler[7], Laura J. Balcer[8], Charles Bernick[9], Zachary Baucom[6], Kenneth L. Marek[10], Michael D. McClean[11], Keith A. Johnson[12], Ann C. McKee[1,2,3,13], Thor D. Stein[1,2,13,14], Jesse Mez[1,2,3,15], Joseph N. Palmisano[16], Jeffrey L. Cummings[17], Martha E. Shenton[18], Eric M. Reiman[19] and for the DIAGNOSE CTE Research Project Investigators
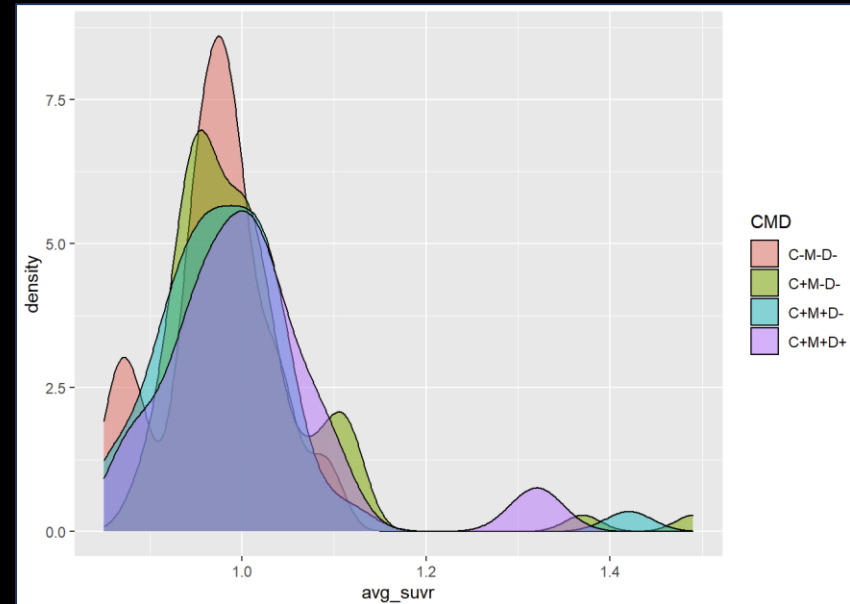
Conclusions Cognitive impairment in former American football players is not associated with PET imaging of neuritic Aβ plaque deposition. These findings are inconsistent with a neuropathological diagnosis of AD in individuals with substantial RHI exposure and have both clinical and medico-legal implications.

- Age 45-74 and 17 of the 179 former college and professional football players had a Florbetapir SUVR of 1.10 or higher.

- 44 had MCI (2+), 18 had dementia (2+), and 70 with subjective concerns (9+)

Conclusions and More Questions

- Neuropsychology + biomarkers = accurate diagnosis of AD/ADRD including CTE

- Substantial exposure + cognitive impairment + young onset + negative amyloid biomarker + frontotemporal atrophy = likely underlying CTE
  - Game of exclusions

- Differences from AD and FTLD?

- Current tau tracers developed for Alzheimer's disease might be able to detect high stage disease
  - Limited diagnostic usefulness, however

Thank you
for further discussion, malosco@bu.edu

Funders (NINDS/NIA), participants, and families who participate in our research

BU Alzheimer's Disease Research Center **BU** CTE Center