Chronic traumatic encephalopathy:
Emerging Concepts

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Boston University School of Medicine
Director of the CTE Center
Boston University Alzheimer's Disease Center

What is Chronic Traumatic Encephalopathy?

"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*.

Chronic Traumatic Encephalopathy 1957

Clinical symptoms typically present years - decades after the trauma, but not always

Diverse clinical symptoms:
Emotional liability, slowness of thought & speech, memory problems and dementia.

Other symptoms: mood swings, irritability, violent behavior, depression & paranoia.

Common motor features: tremor & dysarthria

(Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. Br Med J 1957; 1: 357

Chronic Traumatic Encephalopathy 2009

REVIEW ARTICLE

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

Ann C. McKee, MD, Robert C. Cantu, MD, Christopher J. Nowinski, AB, E. Tessa Hedley-Whyte, MD, Brandon E. Gavett, PhD, Andrew E. Budson, MD, Veronica E. Santini, MD, Hyo-Soon Lee, MD, Caroline A. Kubilus, and Robert A. Stern, PhD

2009: 51 cases in the worlds literature

3 at BU/ VA Boston

39 boxers (76%)

5 Am football players (10%)

Chronic Traumatic Encephalopathy 2015

	WORLD	BU	BU
	2009	2009	2015
Boxing	37	2	12
American Football	4	1	113
Ice Hockey	0		5
Wrestling	1		2
Rugby	0		2
Military Veterans*	0		23
Soccer	1		1
Other: physical abuse, poorly controlled epilepsy, head banging	5		3
TOTAL	48	3	143

McKee et al 2013, McKee et al 2014

McKee et al 2009 ; McKee et al 2010; McKee et al 2014

Clinical Presentations of CTE

36 athletes with pathologically confirmed pure CTE:

Behavioral and/or mood	*Cognitive*
Younger age at onset (m 35 yrs)	Older age at onset (m 59 yrs) Indistinguishable from AD

Most subjects (86%) who present with behavioral/ mood symptoms progress to have cognitive symptoms (m age death: 51 yrs)

Behavioral or mood symptoms less likely to develop (46%) in subjects who present initially as cognitive impairment (m age death: 69 yrs)

Stern et al. Neurology 2013

Systematic review of the clinical features in 83 confirmed CTE cases:

An additional subtype, the "mixed subtype" was identified

Mixed subtype cases presented with a combination of behavioral, mood and cognitive features without dementia

68% cases were found to have a progressive clinical course

Younger subjects were found to have a higher degree of stability

Montenigro et al. Alzheimers Res Ther 2014

Most common clinical features

(>70% of CTE cases)

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	

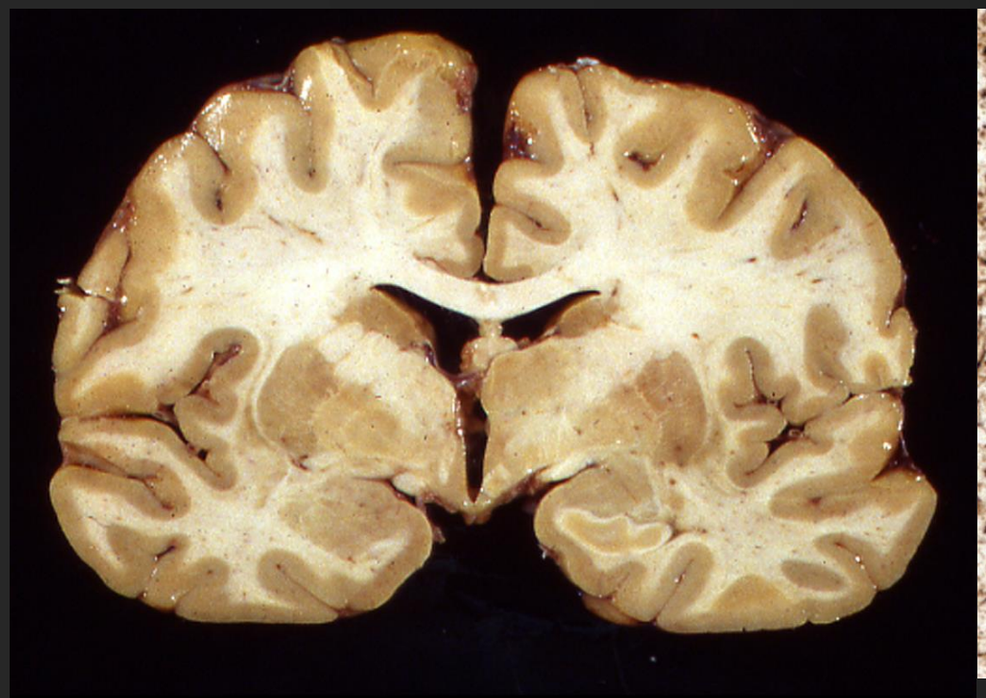
Montenigro et al. Alzheimers Res Ther 2014

Pathology of CTE

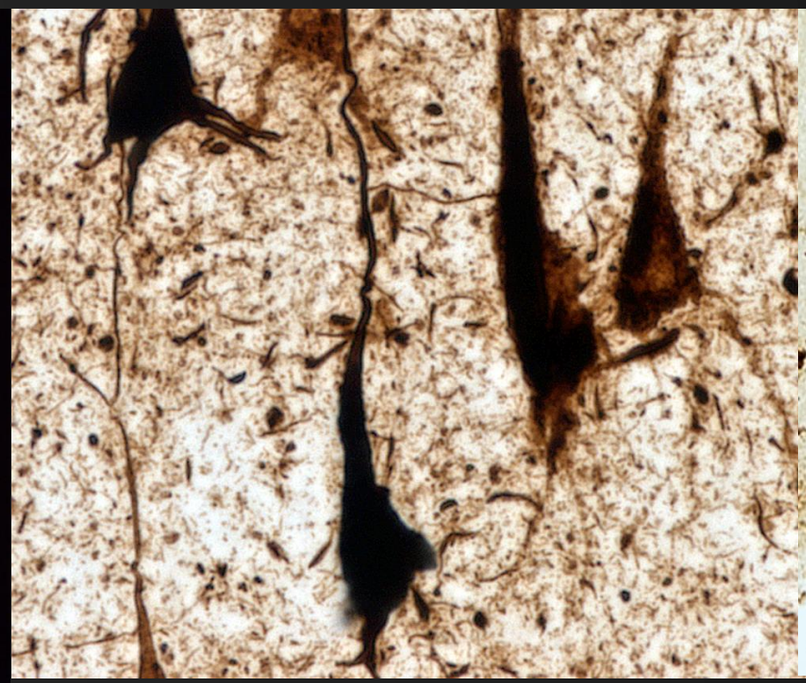
Brain Atrophy

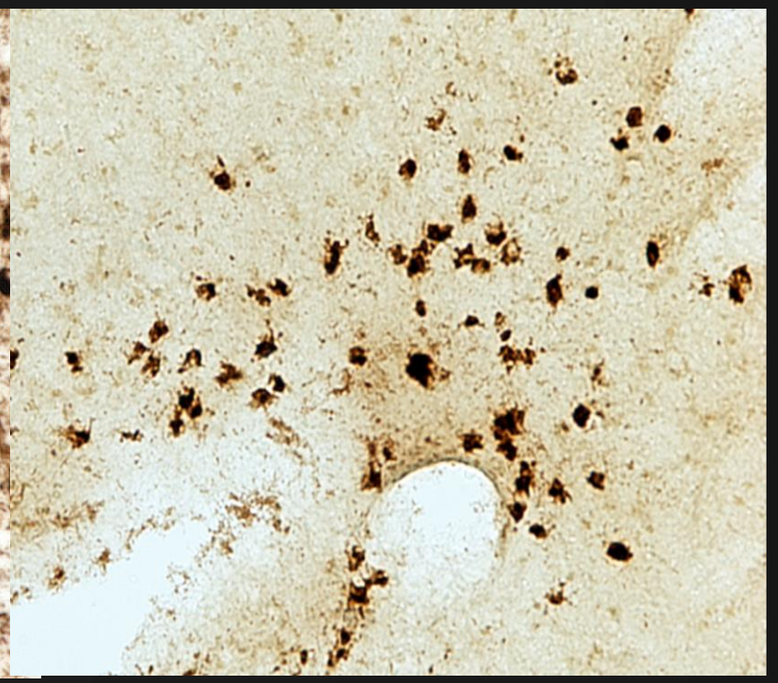
P- Tau

P-TDP-43

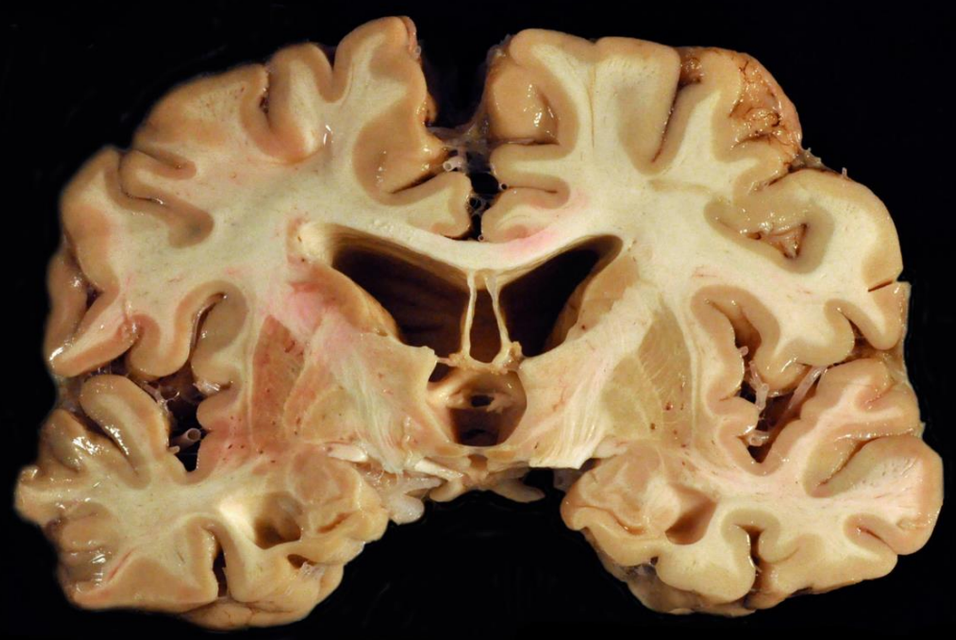


Normal

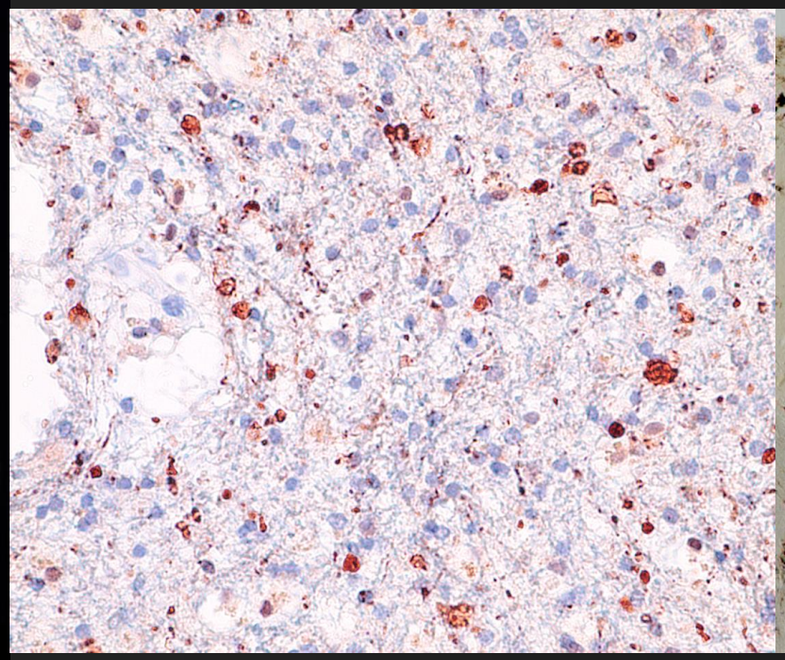




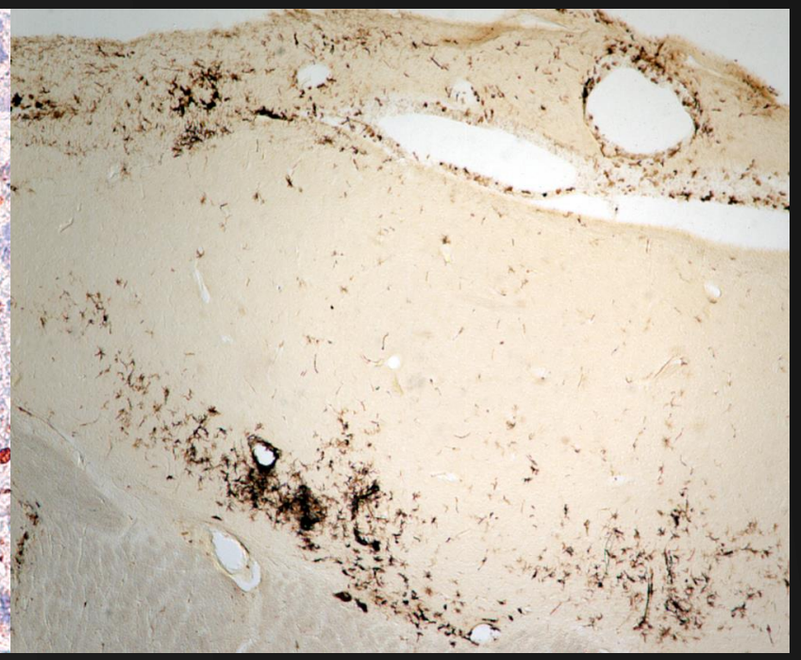
Aggregation of Abnormal Proteins



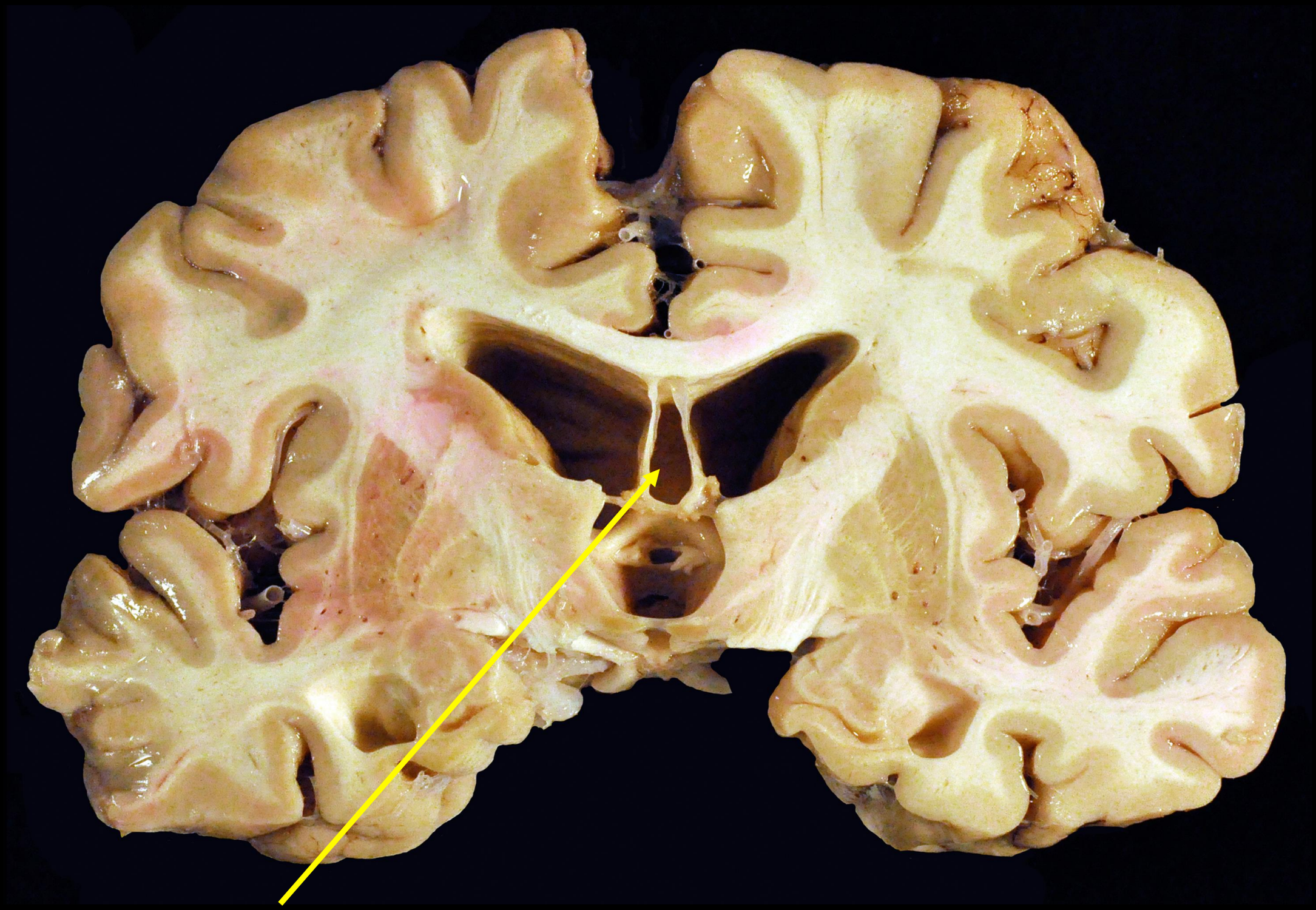
CTE



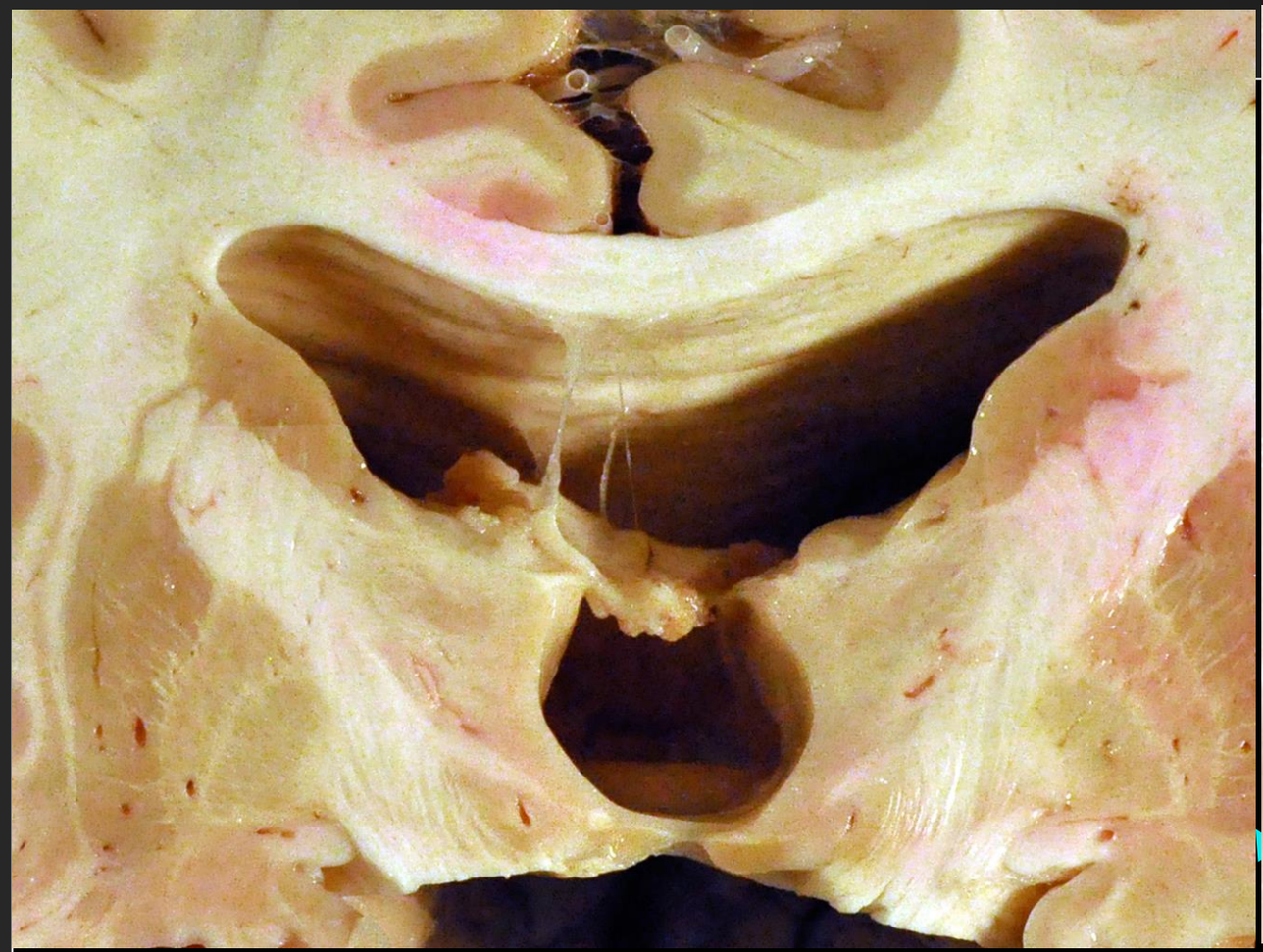
Axonal injury & loss



Neuroinflammation

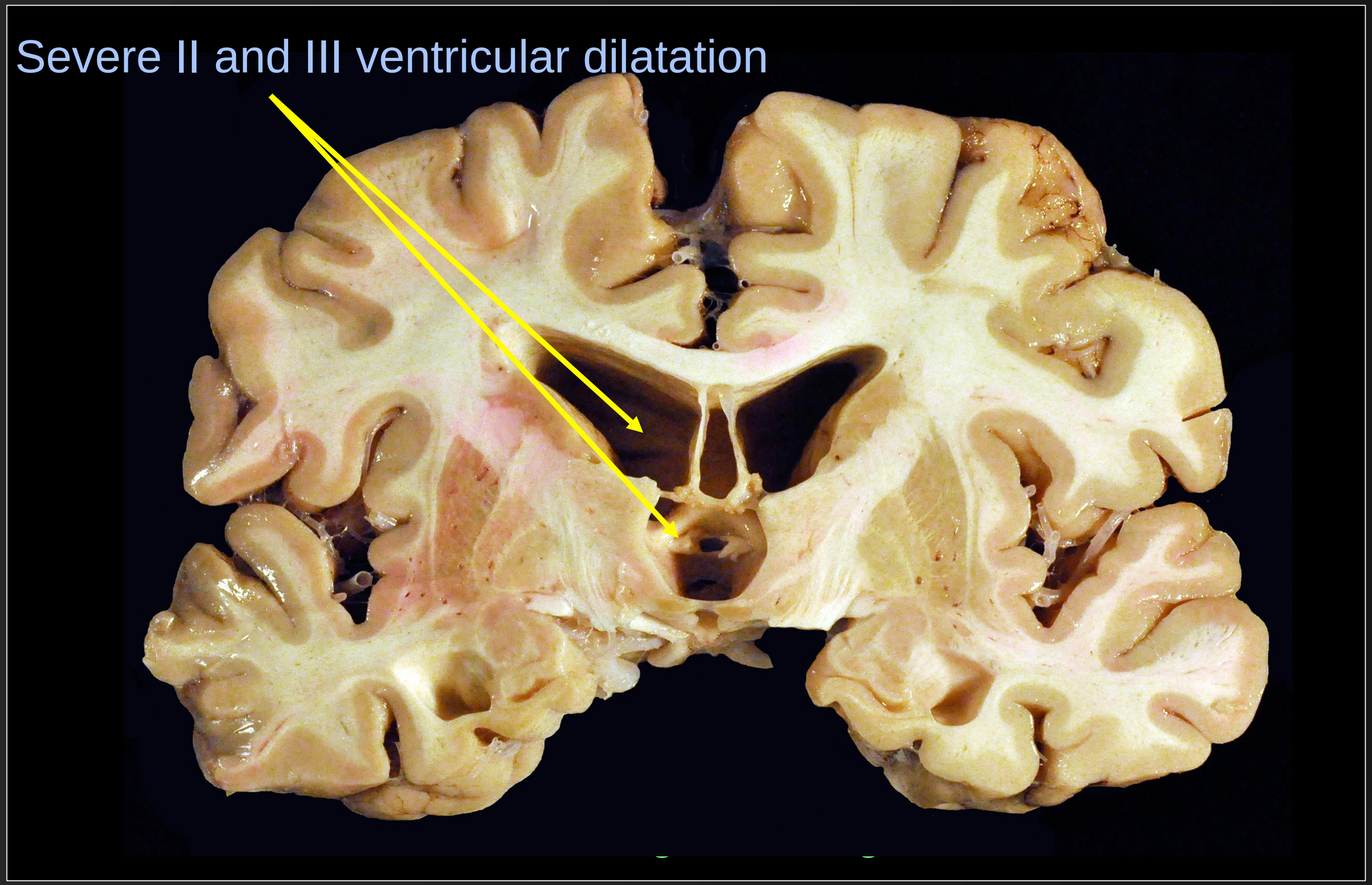


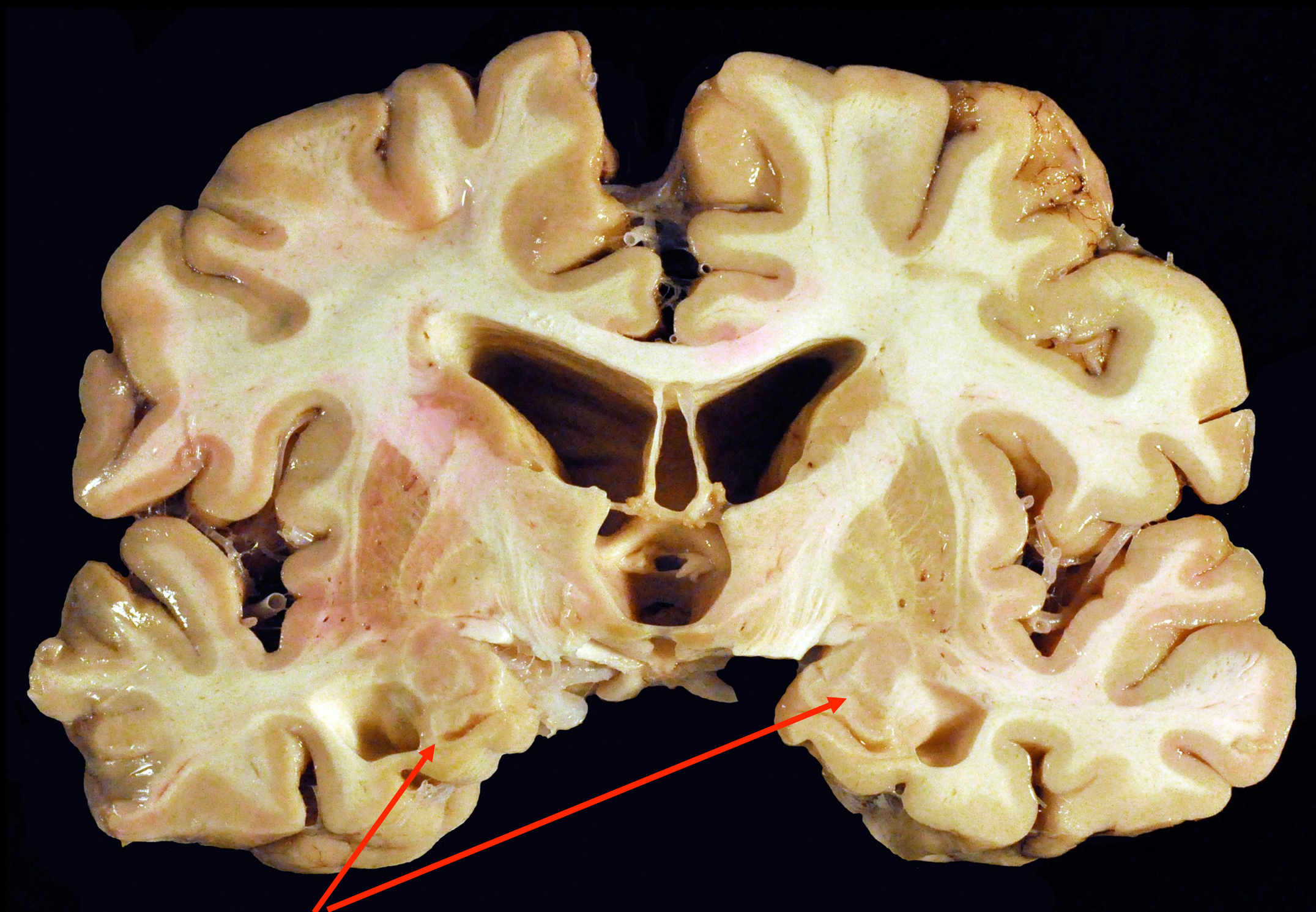
Cavum septum pellucidum



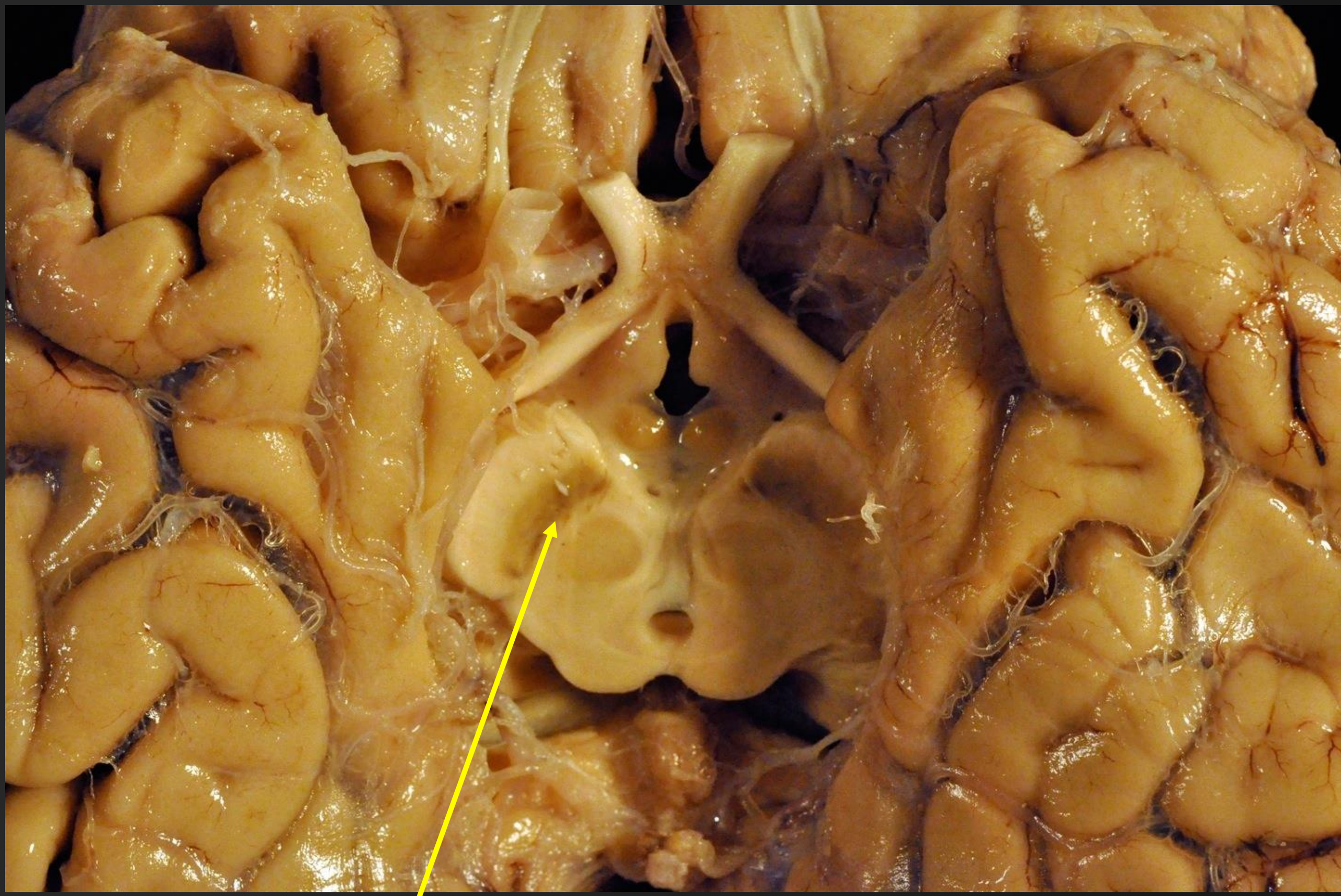
Abnormalities of posterior septum pellucidum

Gross Characteristics: Cerebral Atrophy

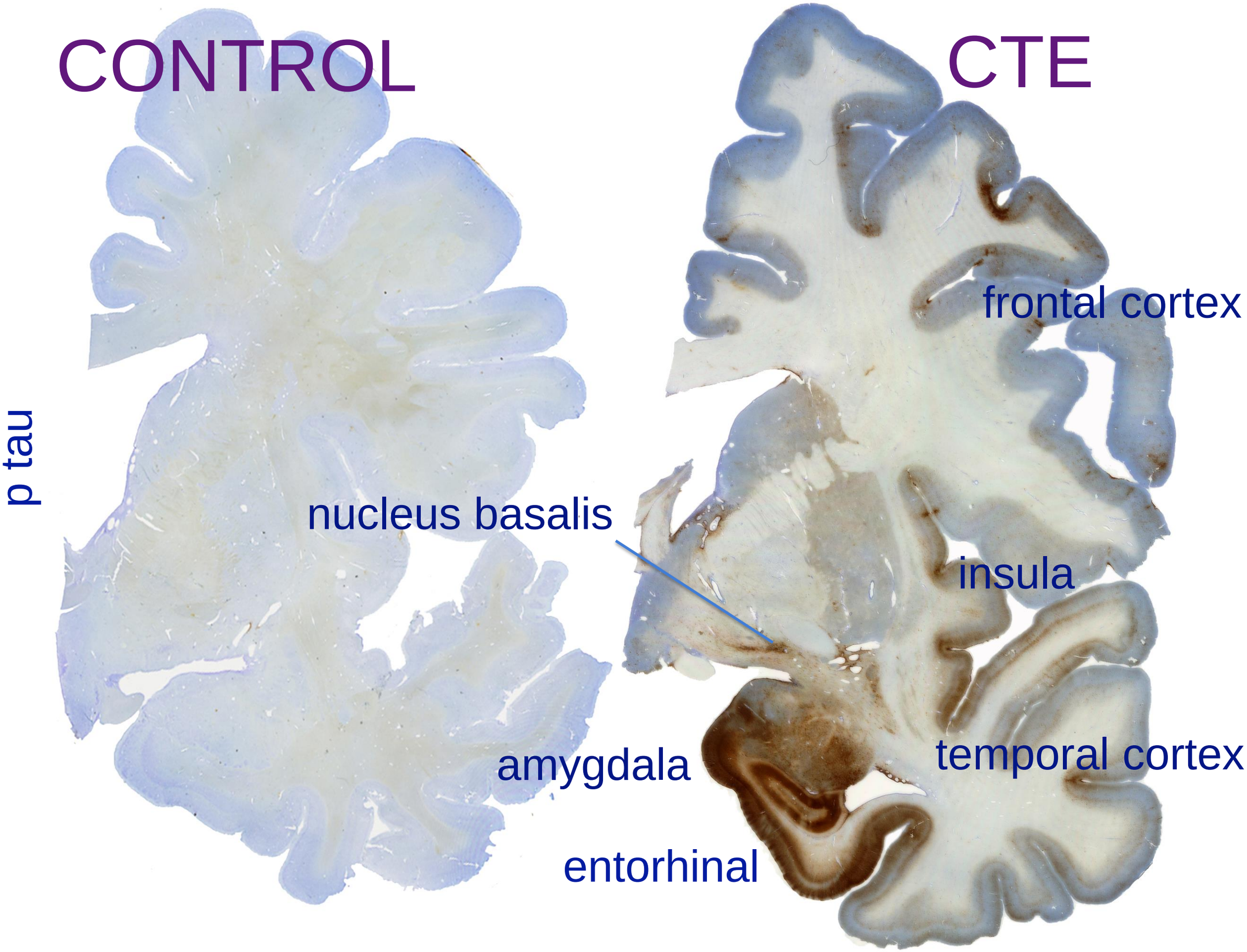




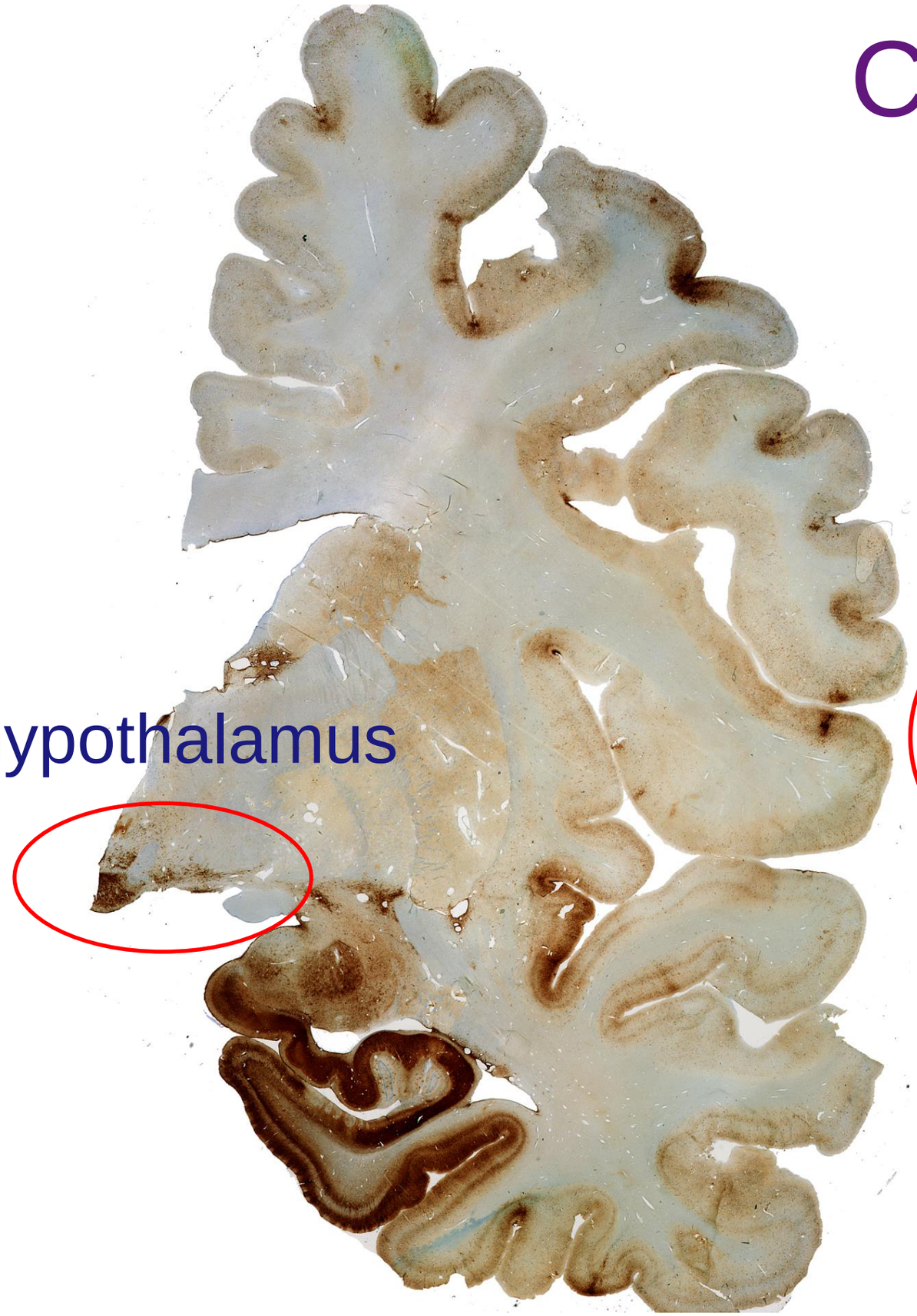
Marked medial temporal atrophy

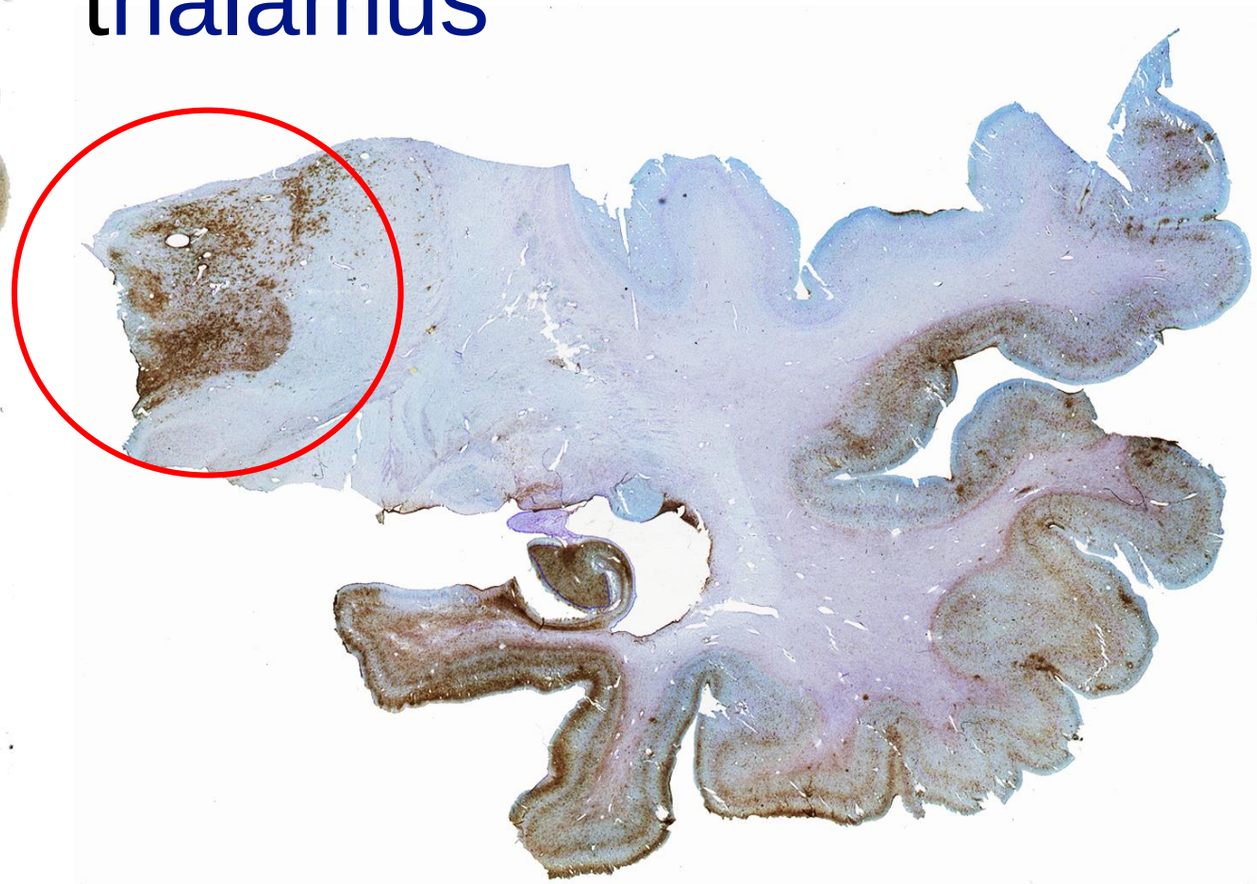


pallor of the substantia nigra


CONTROL
CTE
p tau
frontal cortex
nucleus basalis
insula
amygdala
temporal cortex
entorhinal

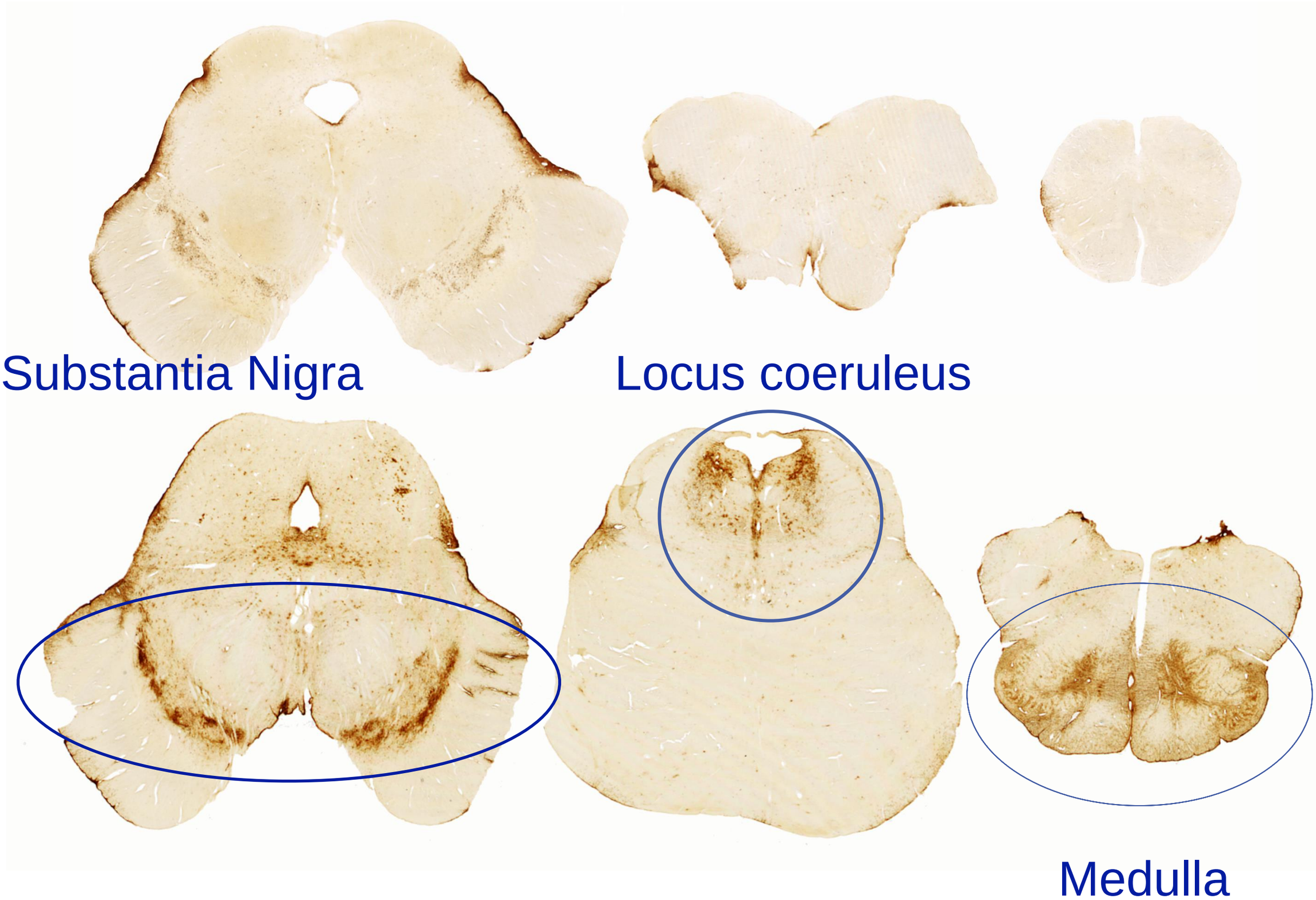
CTE





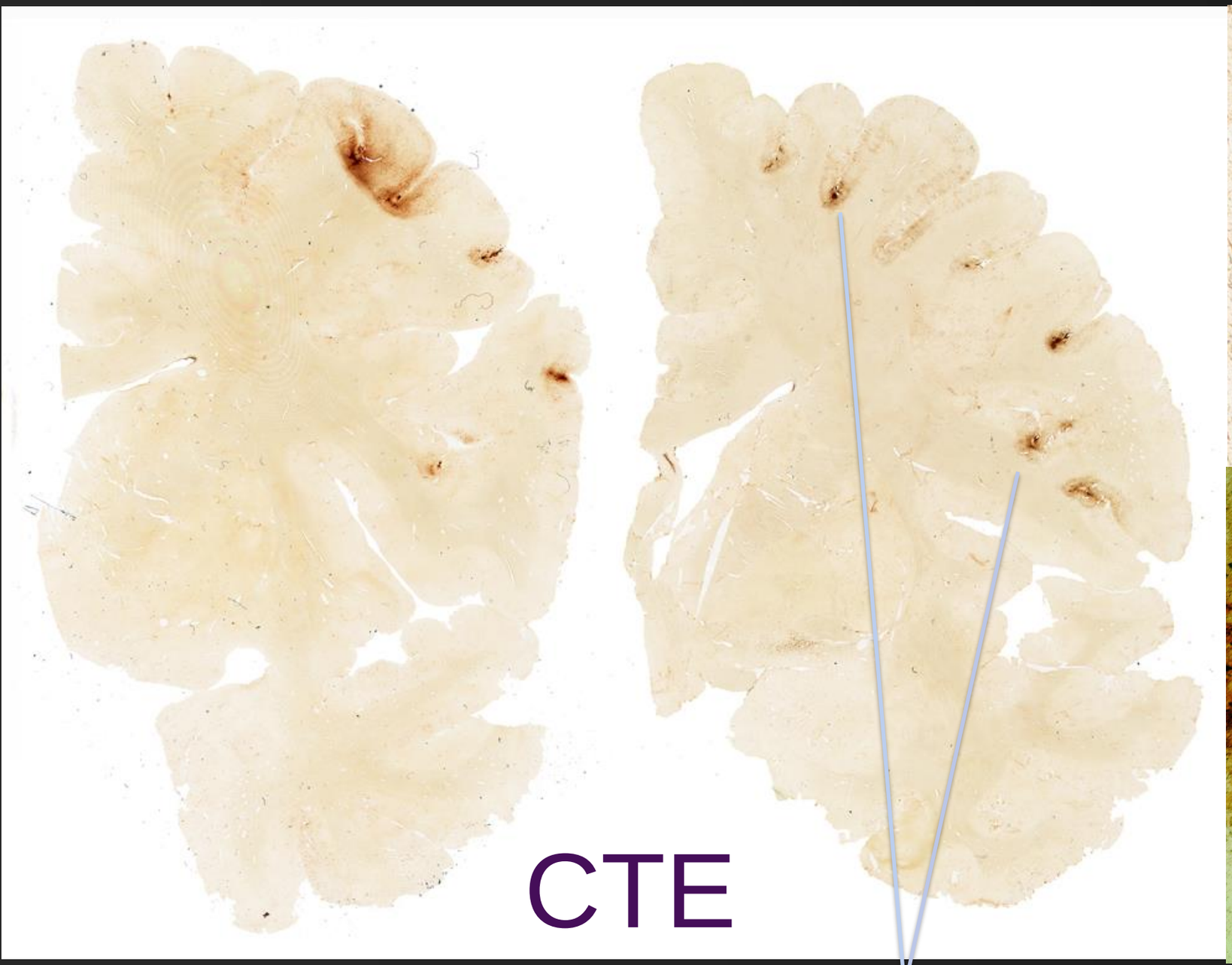
p tau

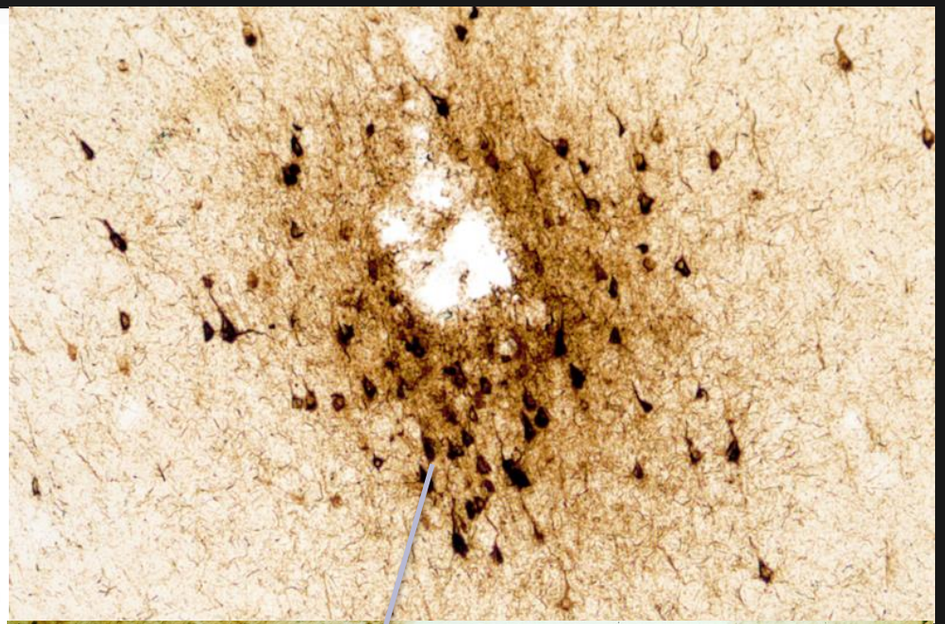
CTE

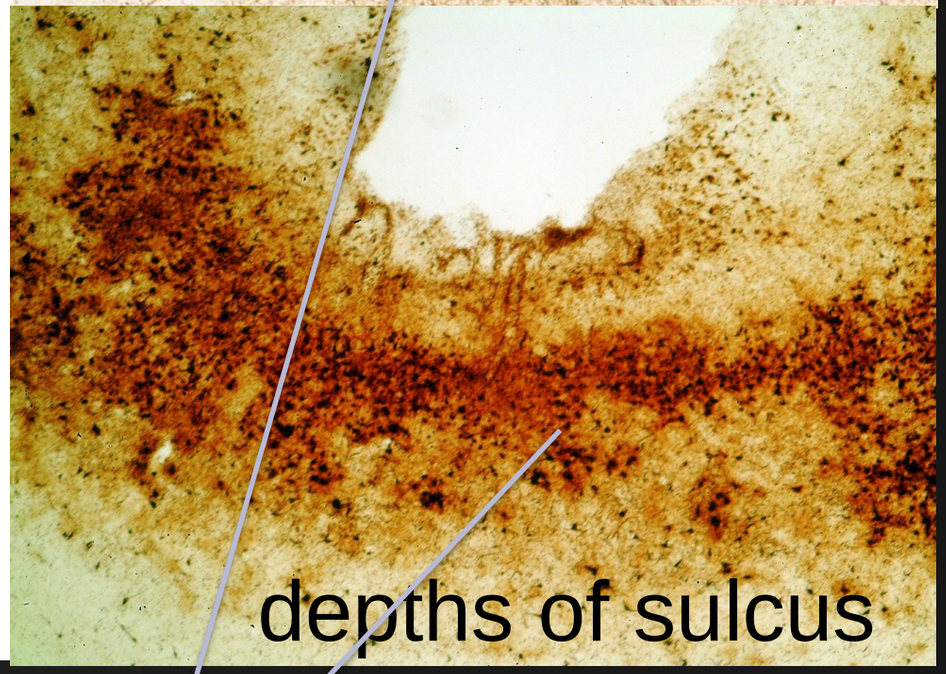


Hallmarks of CTE Pathology

PHF-tau neuronal & glial pathology





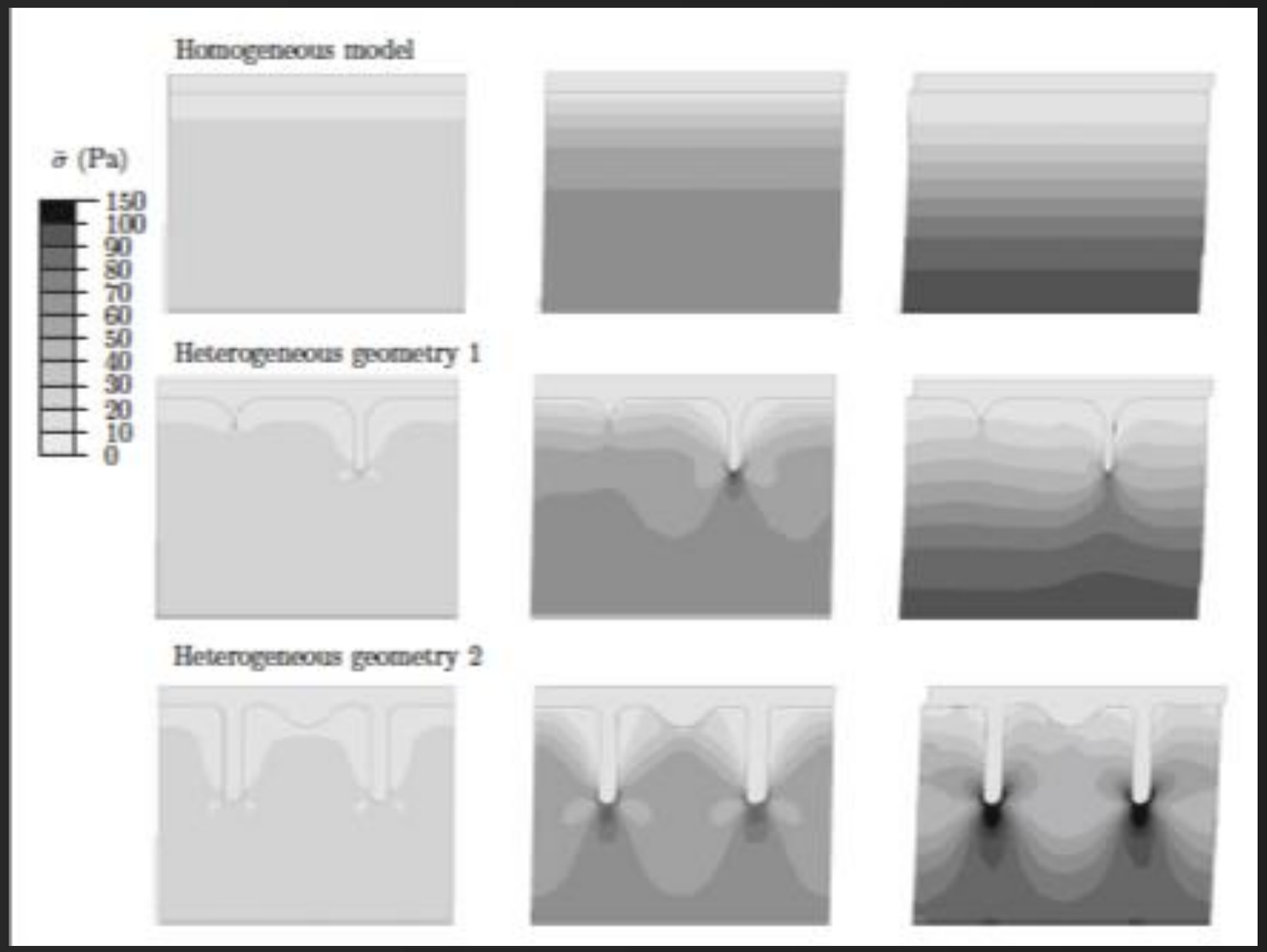


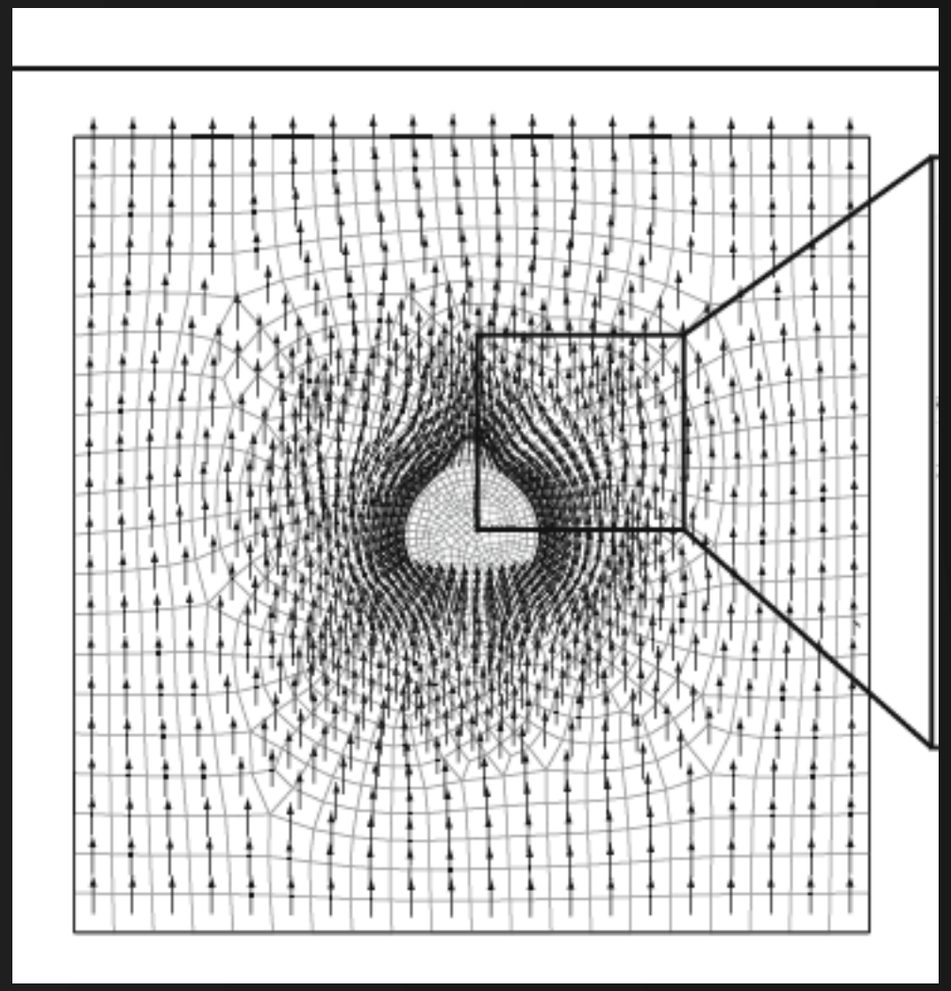
1. Focal epicenters in neocortex at depth of sulci

2. Perivascular

Why is tau protein deposited in those brain regions?

Depth of sulcus and perivascular area are regions of physical stress concentration





Cloots et al Annals of Biomedical Engineering, Vol. 36, No. 7, July 2008
Cloots et al.J Mechanical Behavioral Biomedical Materials 2012 (41-52)

Hammer injury to brain

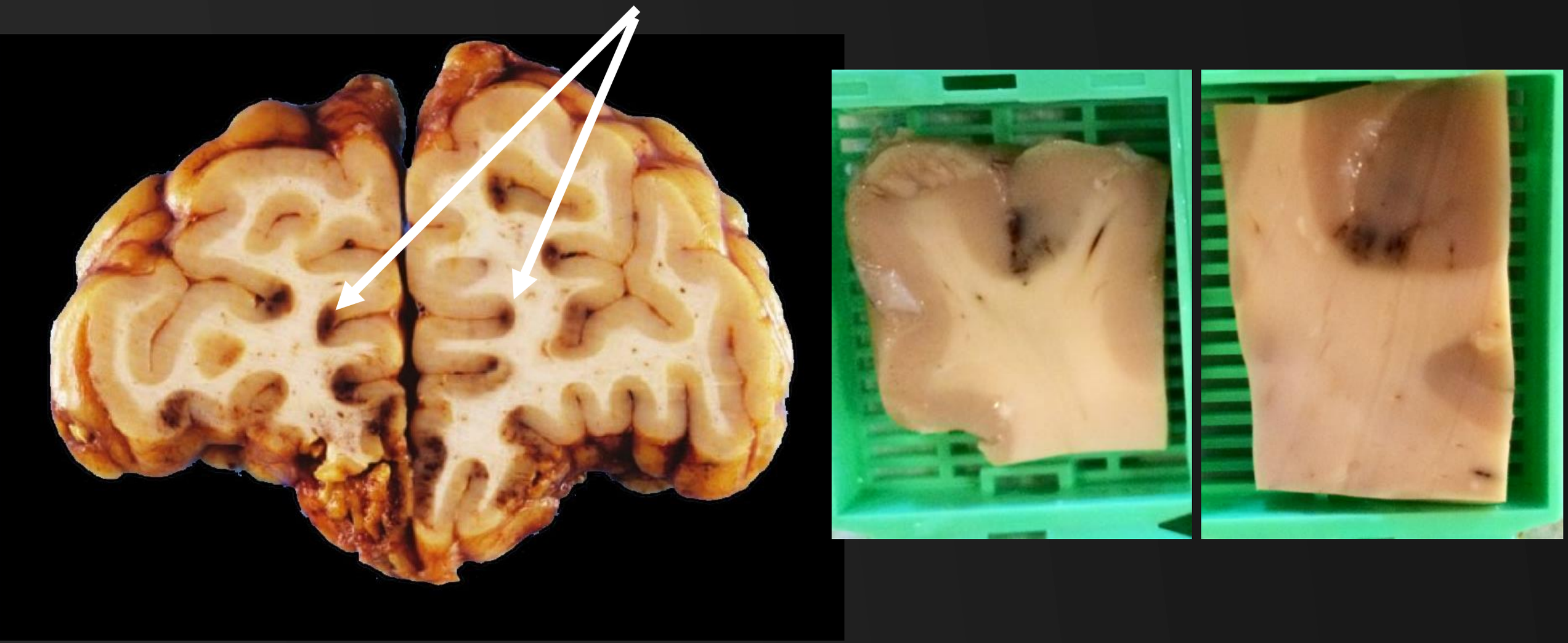
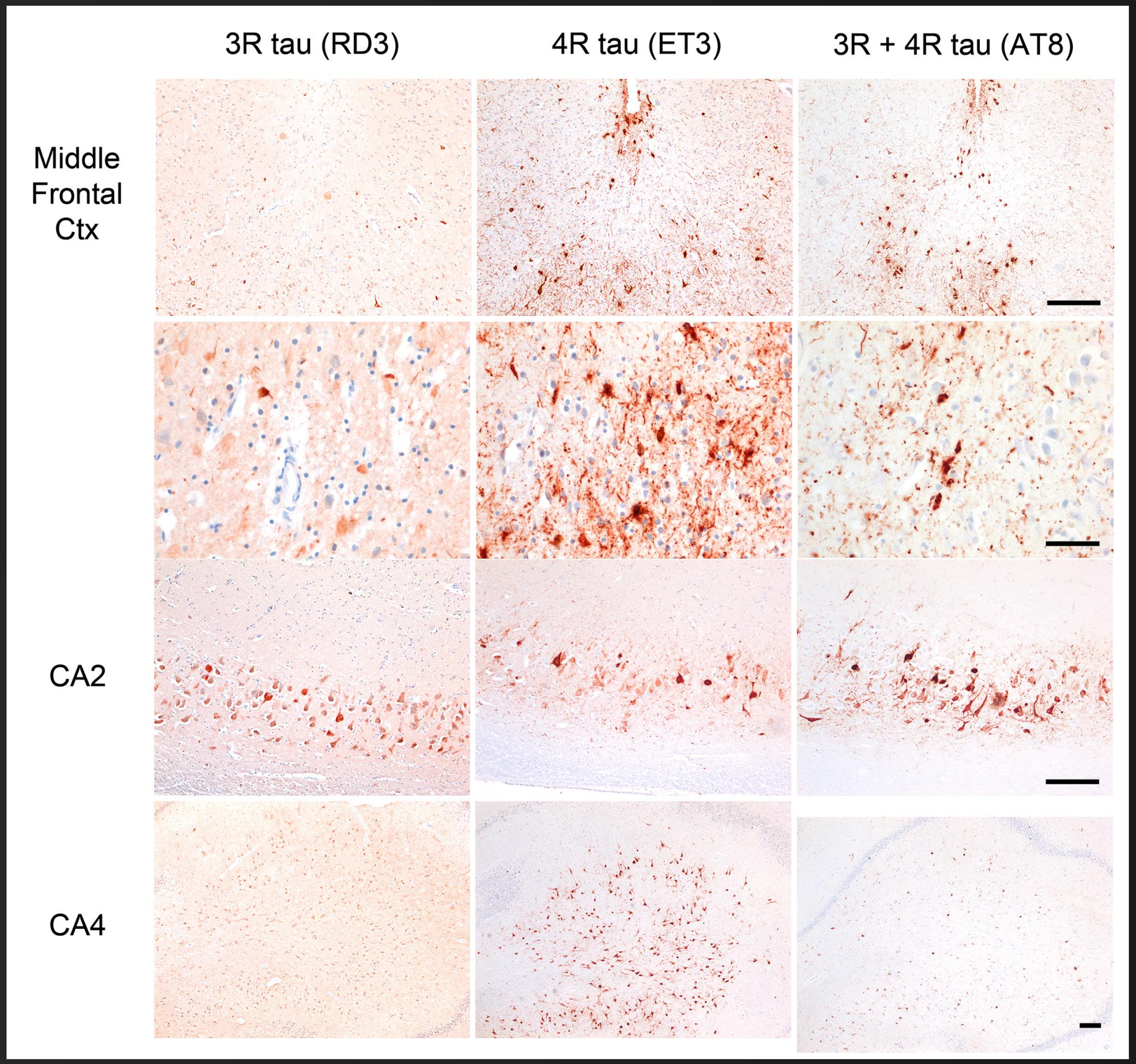


Figure 6.57 Coronal frontal section of the brain from the victim of a homicidal beating with a hammer that shattered the frontal skull, illustrating a peculiar pattern of contusions that

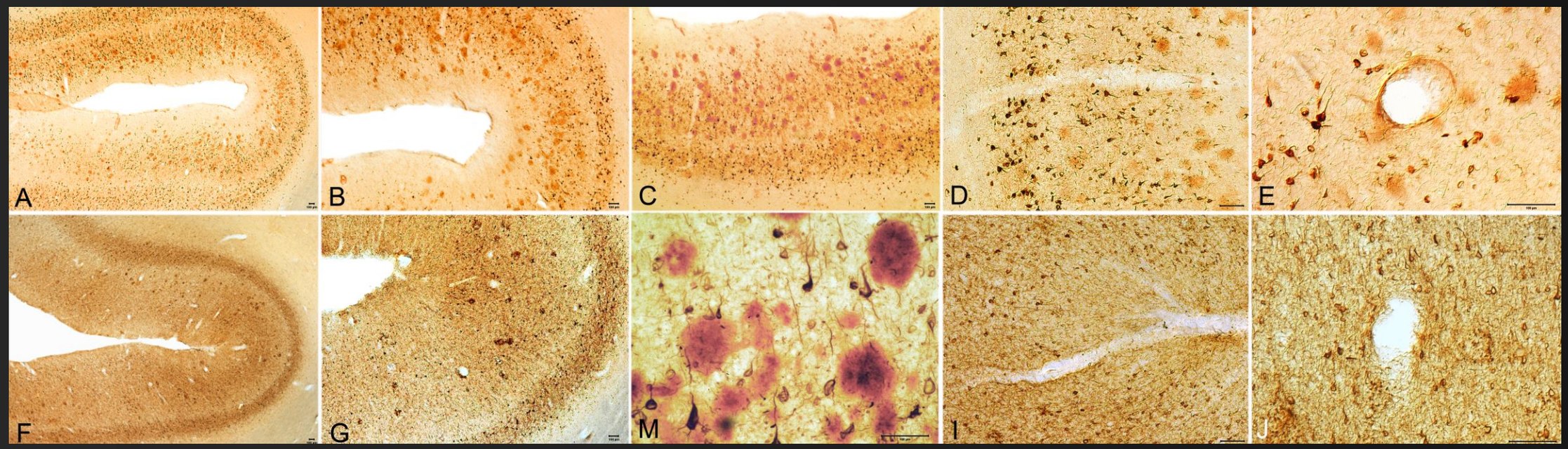
Leestma, Forensic Pathology, 2008, second edition

3 repeat (3R) and 4 repeat (4R) tau are present in CTE



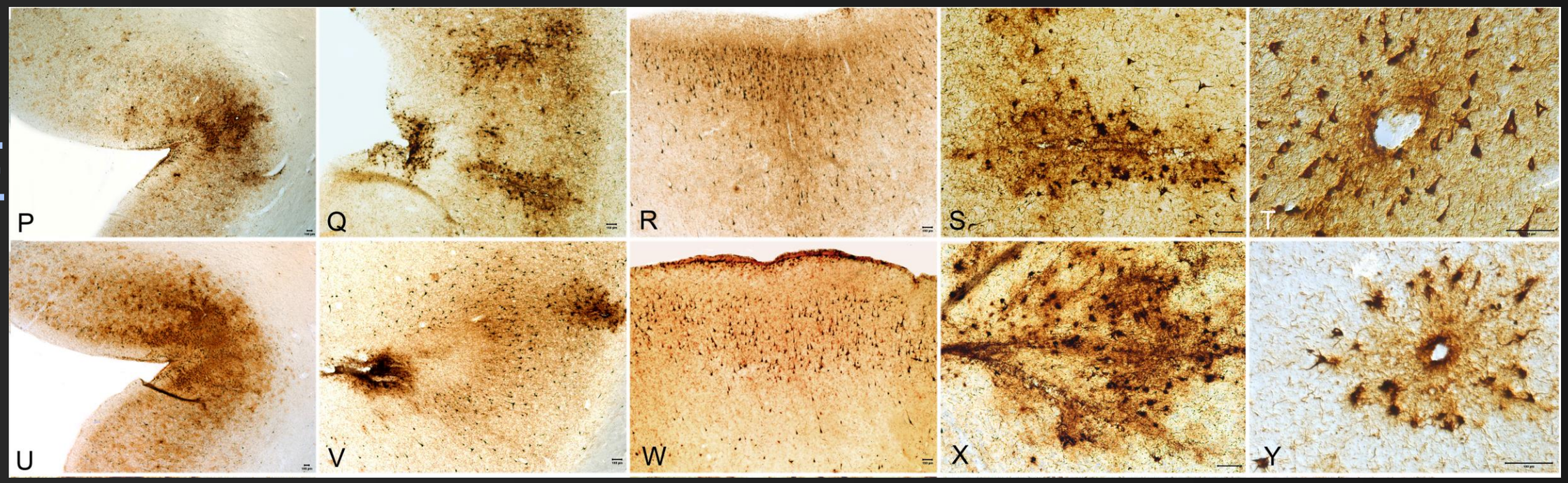
Distinctions between AD and CTE TAU pathology

AD



Aß is always present (100%) as neuritic plaques

CTE



McKee et al, Brain 2013

Aß is sometimes present (43%) as diffuse plaques; never in early stage disease

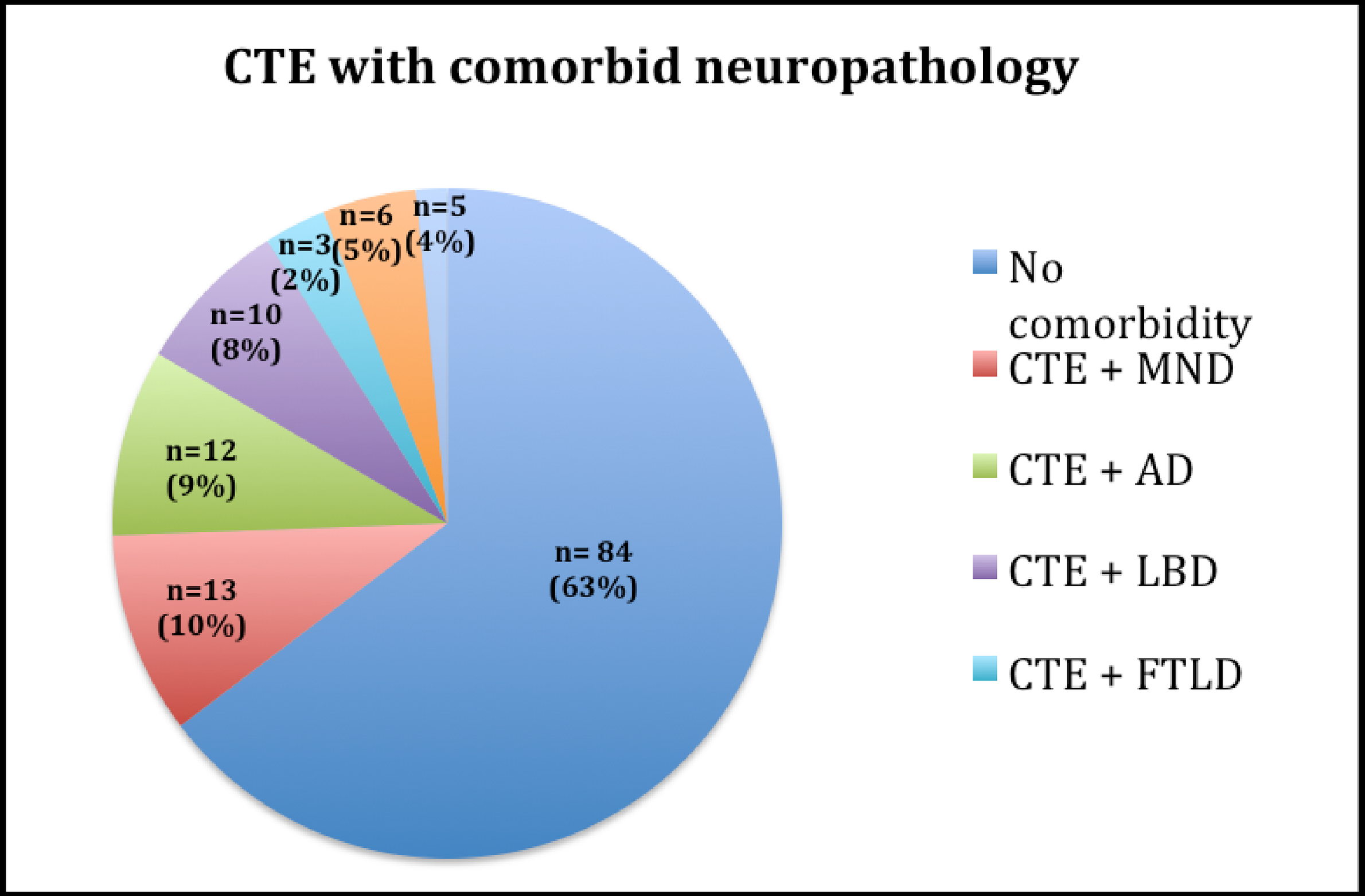
Neuropathological Dx: CTE

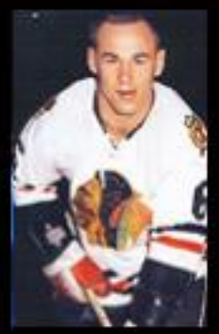
Athletes

	Boxing		Football					Hockey		Soccer	Rugby		MLB	WWE	MMA	Total
	Pro	Am	NFL	CFL	SP	Coll	HS	NHL	Am	SP	Pro	Am				
#CTE	11	1	77	4	2	15	4	4	1	1	1	1	1	0	1	128
# evaluated	11	2	80	4	3	23	19	4	2	1	1	1	1	1	2	158
			96 %													80%

McKee et al. 2009 ; McKee et al, 2010; McKee et al 2013a, McKee et al. 2013b

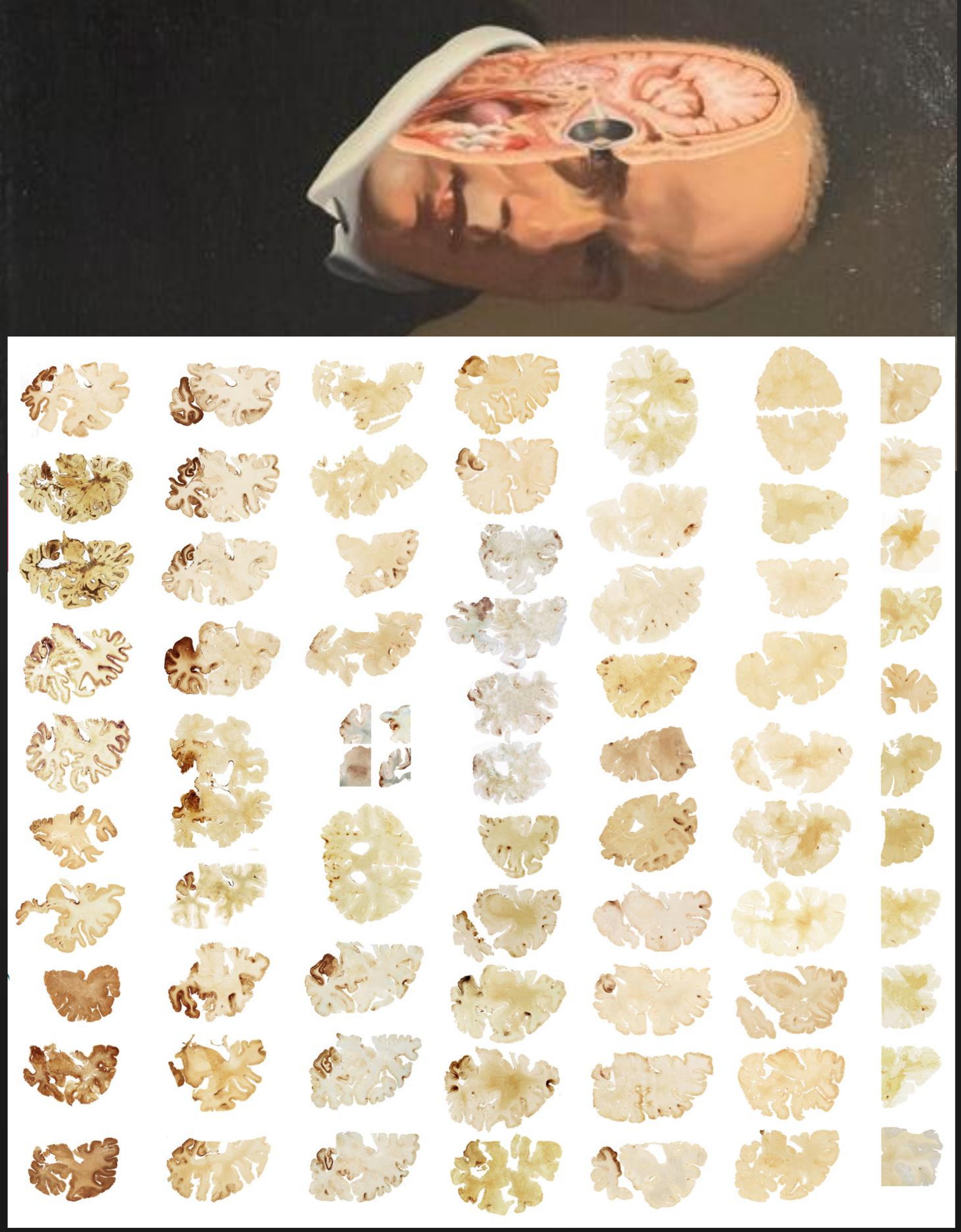
128 cases of CTE





N MEMORIAM
AVE DUERSON

Sports
Illustrate
JUNIOR
SEAU



McKee et al, 2013, Brain

Stages of Tau Pathology

Age at Death

Stage I

mean age: 28.3 ± 13 years

Stage II

mean age: 44.3 ± 16 years

Stage III

mean age: 56.0 ± 14 years

Stage IV

mean age: 77.4 ± 12 years

McKee et al, 2013, Brain

For American football players: number years played, years since retirement, and age at death significantly correlated with pathological stage of CTE

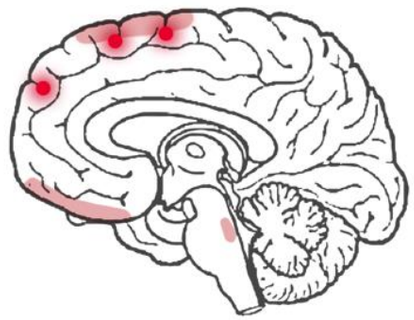
McKee et al.'s (2013)
CTE Tau Staging

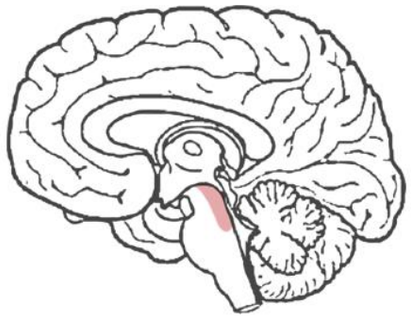
CTE

AD

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

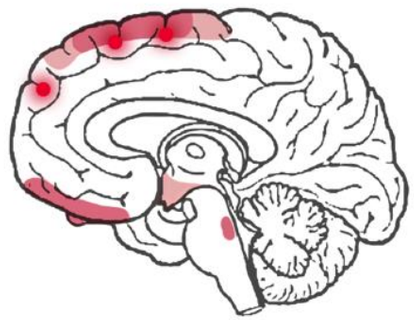
STAGE I
- Isolated perivascular epicenters
- Predilection for depths of sulci
- Neocortex: superior, dorsolateral and inferior frontal
- Locus coeruleus (66% of cases)

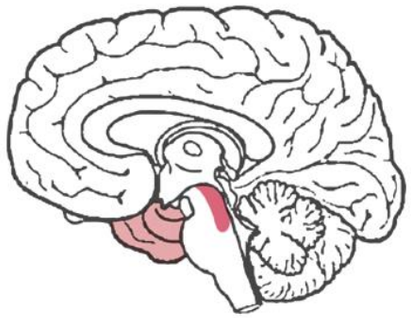




STAGE a-c
- Locus coeruleus
- Upper raphe nuclei
- Magnocellular nuclei

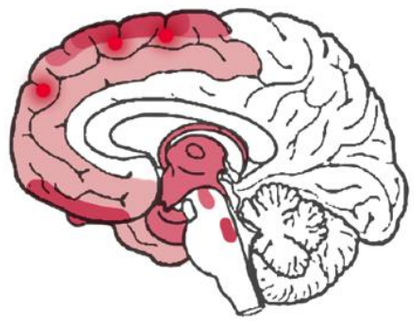
STAGE II
- Multiple epicenters in frontal, temporal cortex, and parietal neocortices
- Diencephalon

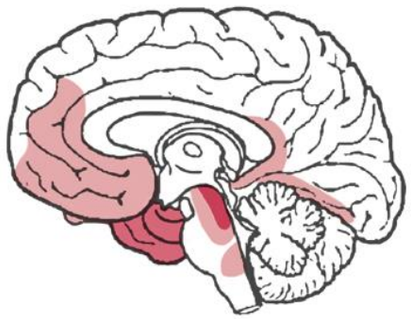




STAGE 1a, 1b, I-II
- Transentorhinal cortex
- Entorhinal cortex

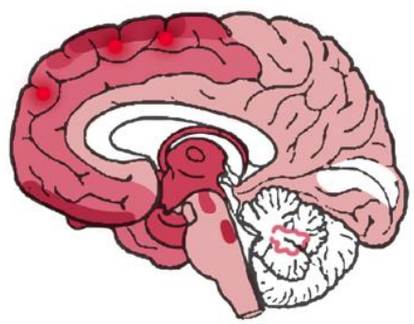
STAGE III
- Widespread neocortical involvement
- Hippocampus
- Entorhinal cortex
- Amygdala
- Nucleus basalis of Meynert

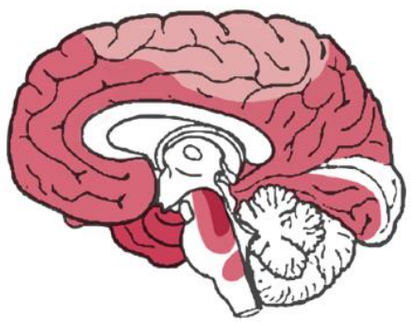




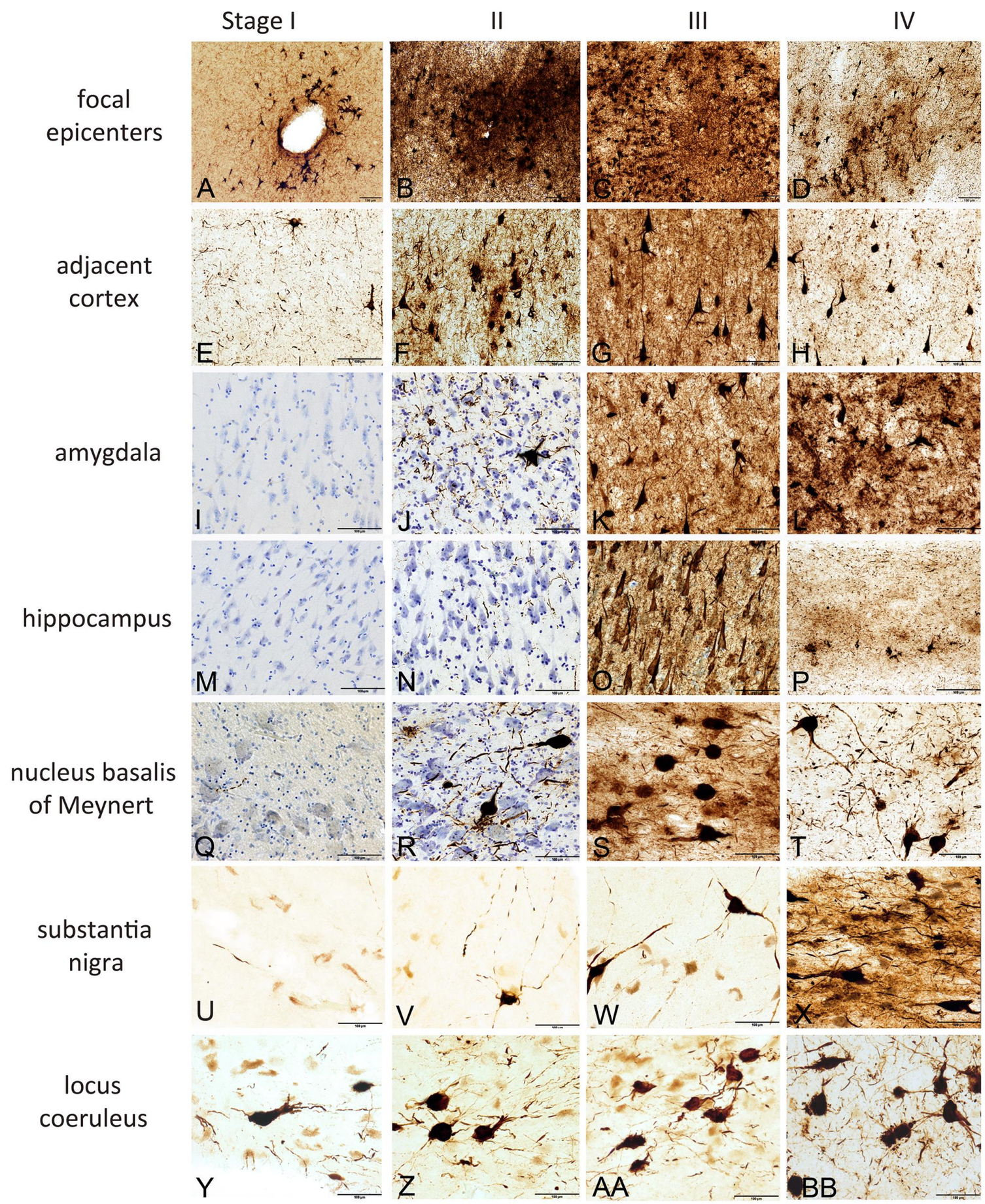
STAGE III-IV
- Hipppocampus
- Amygdala
- Basal temporal
- Insular
- Basal frontal

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



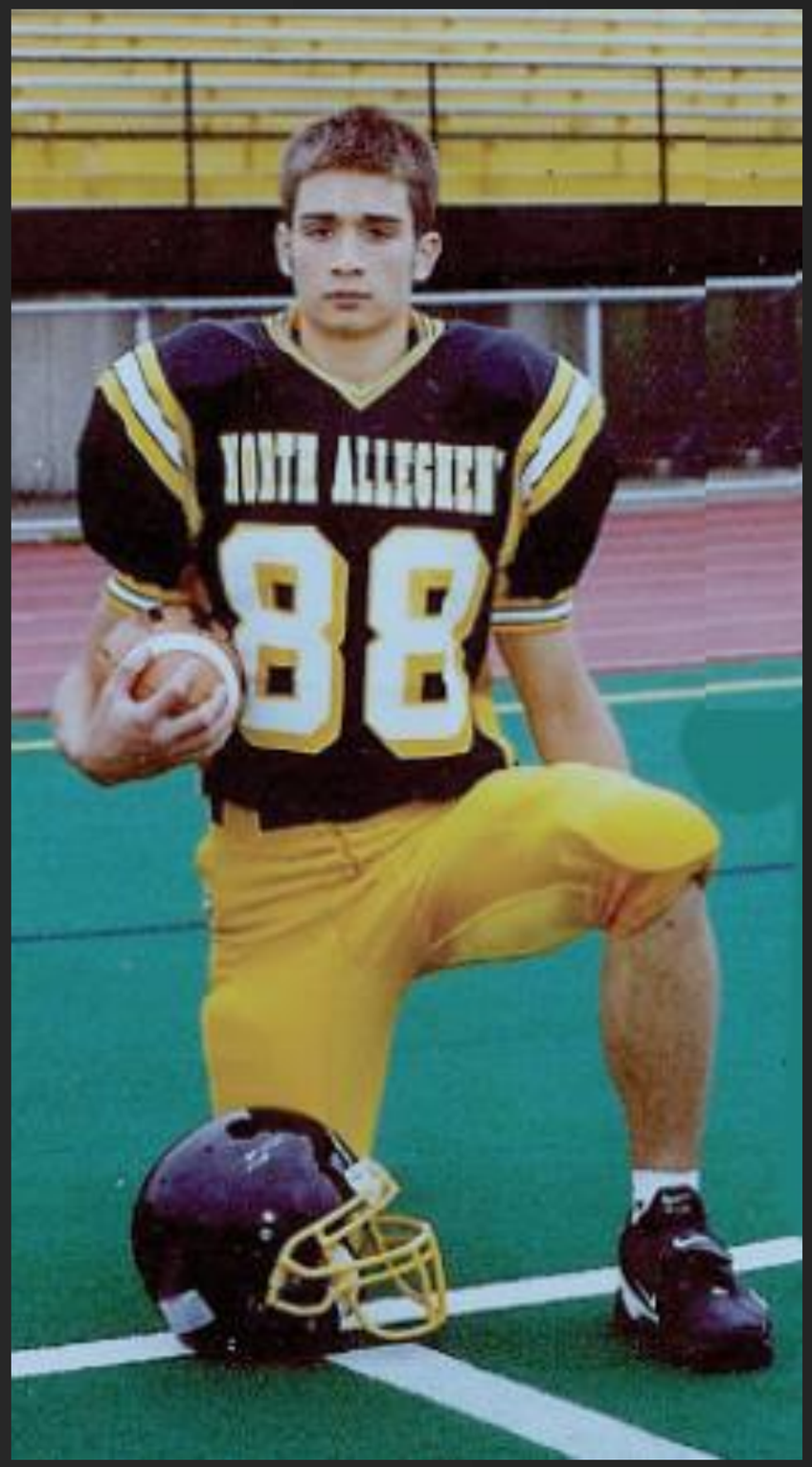


STAGE V-VI
- Widespread neocortical involvement
- Sparing of cerebellum

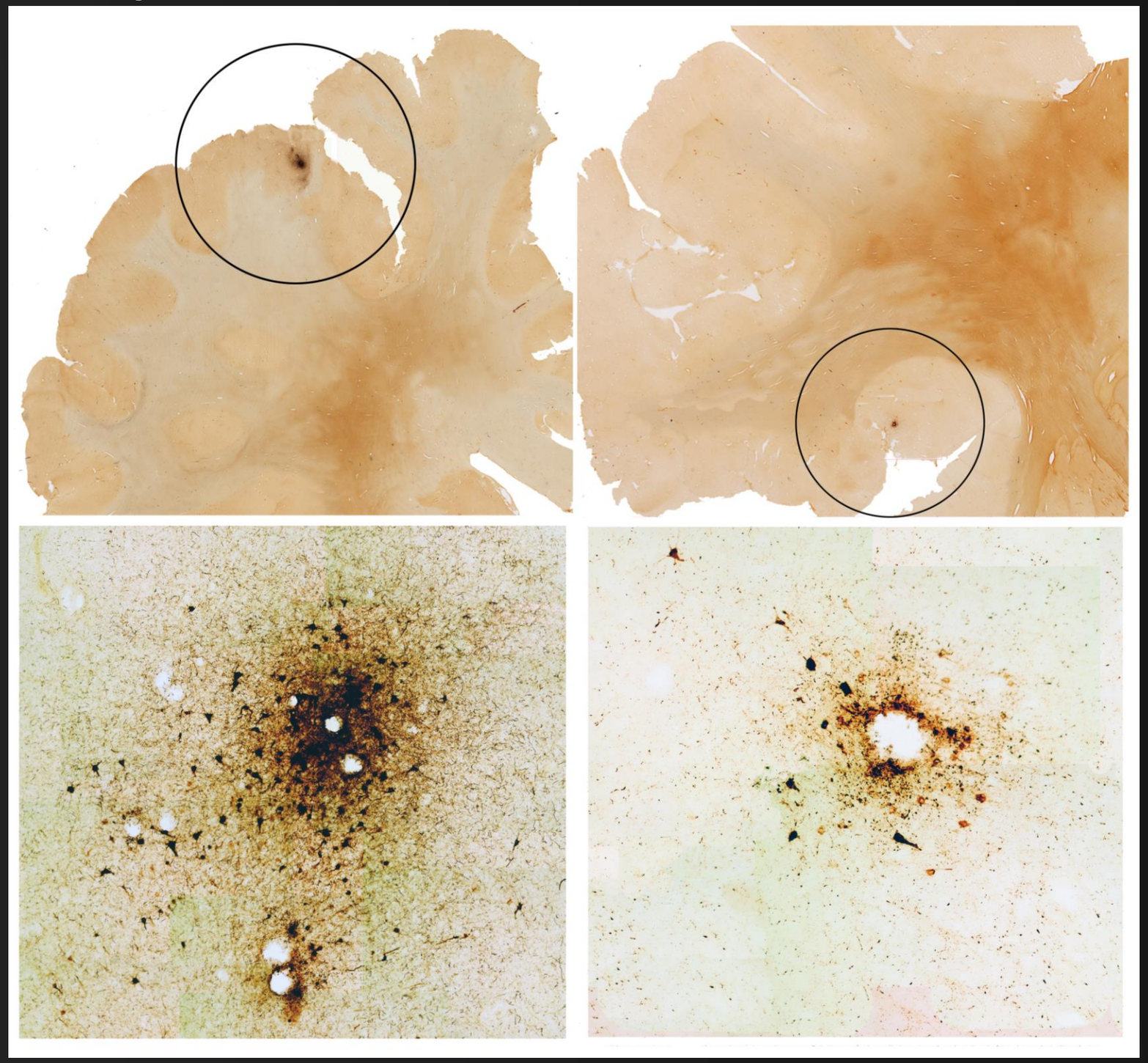

Stage I
II
III
IV
focal epicenters
adjacent cortex
amygdala
hippocampus
nucleus basalis of Meynert
substantia nigra
locus coeruleus
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
S
T
U
V
W
X
Y
Z
AA
BB

Eric Pelly:18 yo high school football & rugby player

Death 10 days after 4th concussion



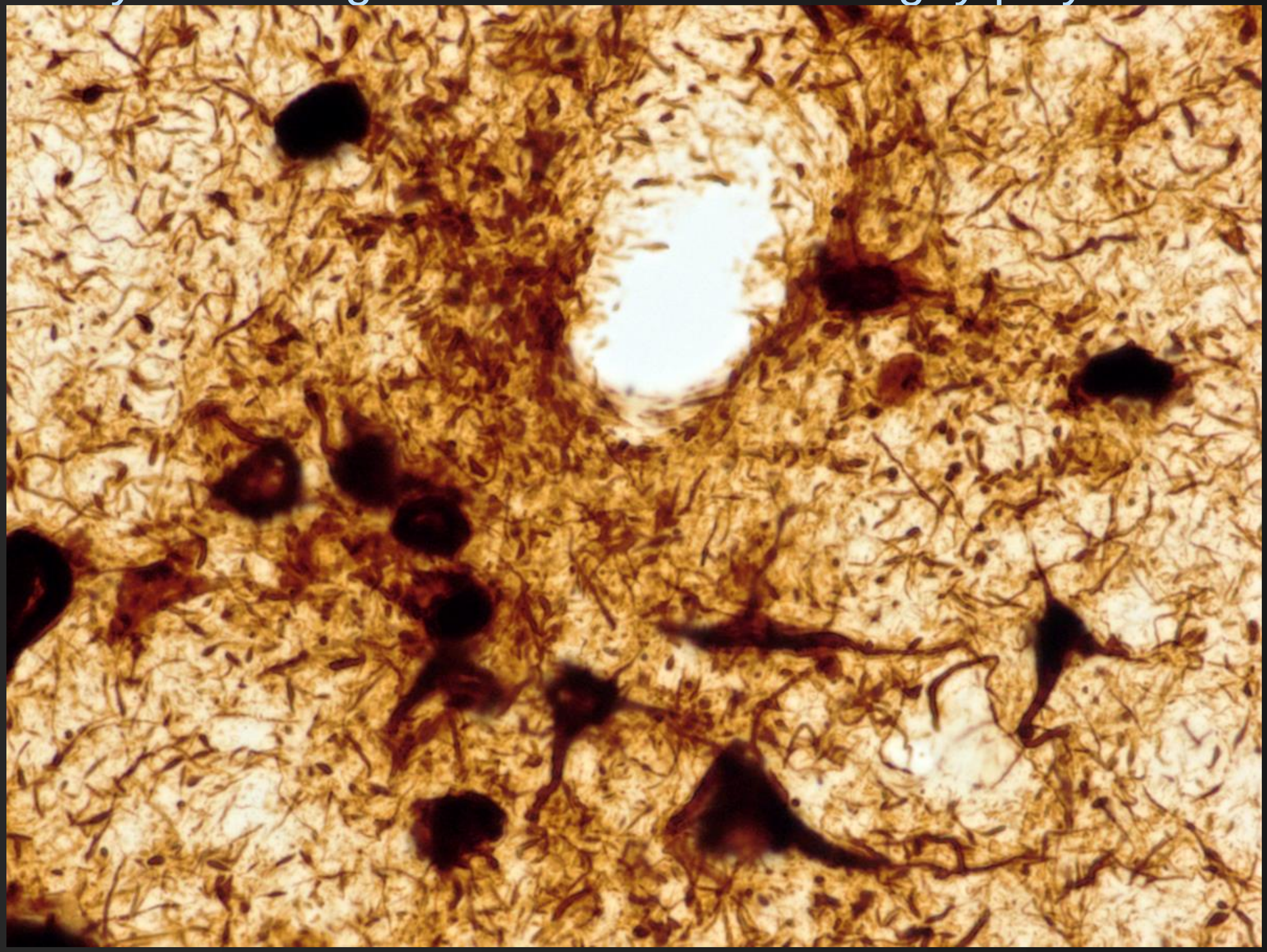
P-Tau



Stage I CTE

18 year old high school football and rugby player

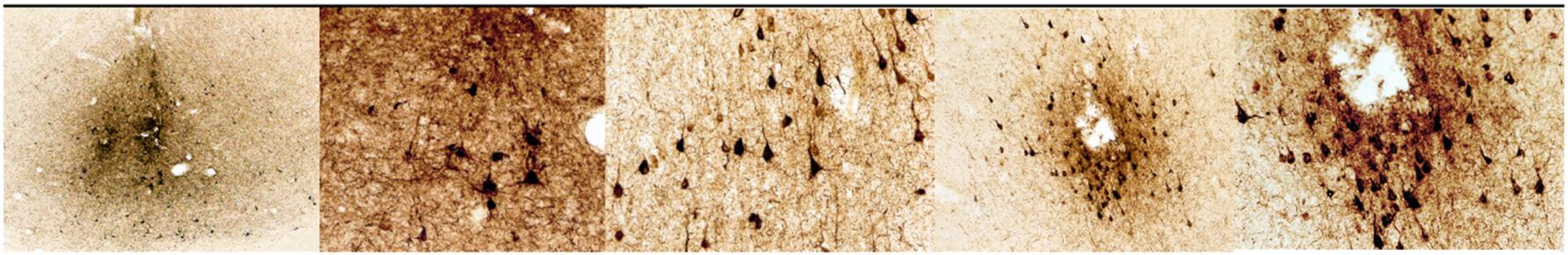
P-Tau



Stage I CTE

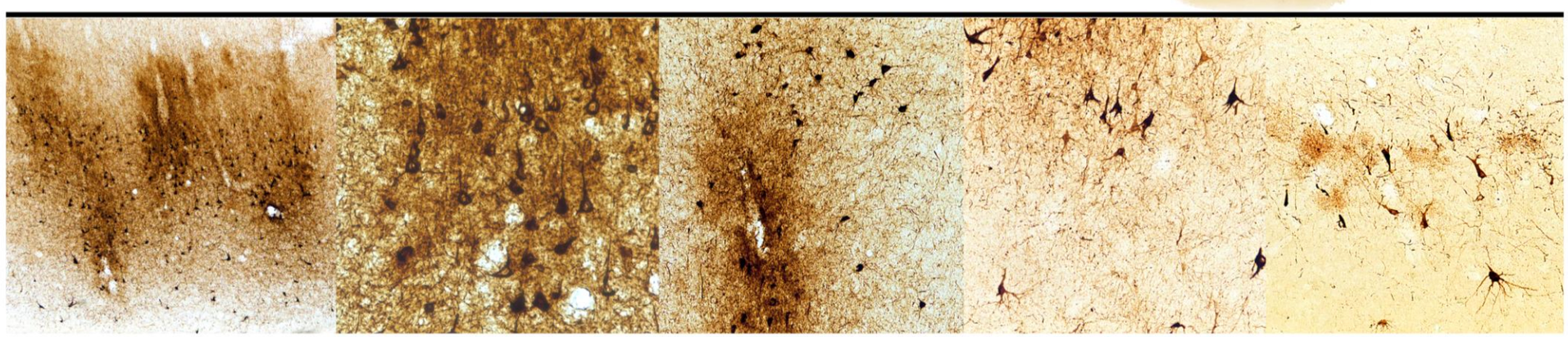
Owen Thomas
21 year old
U Penn football player
Death from suicide

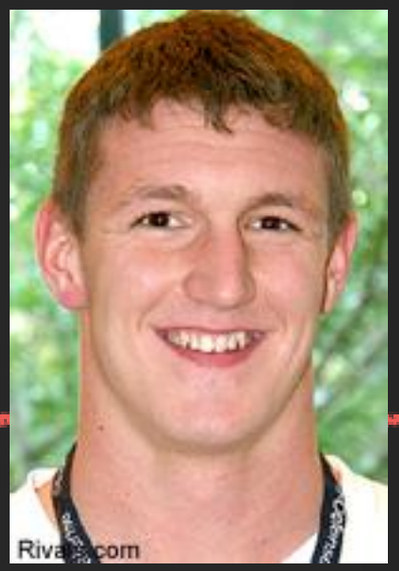
Stage II CTE



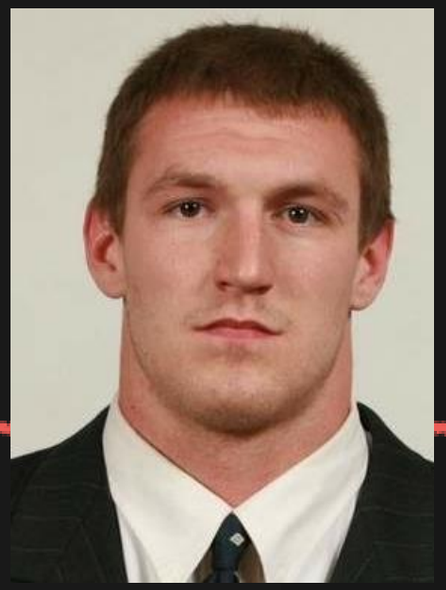
Derek Boogaard
28 year old
NHL player
Death from overdose oxycontin and alcohol

Stage II CTE



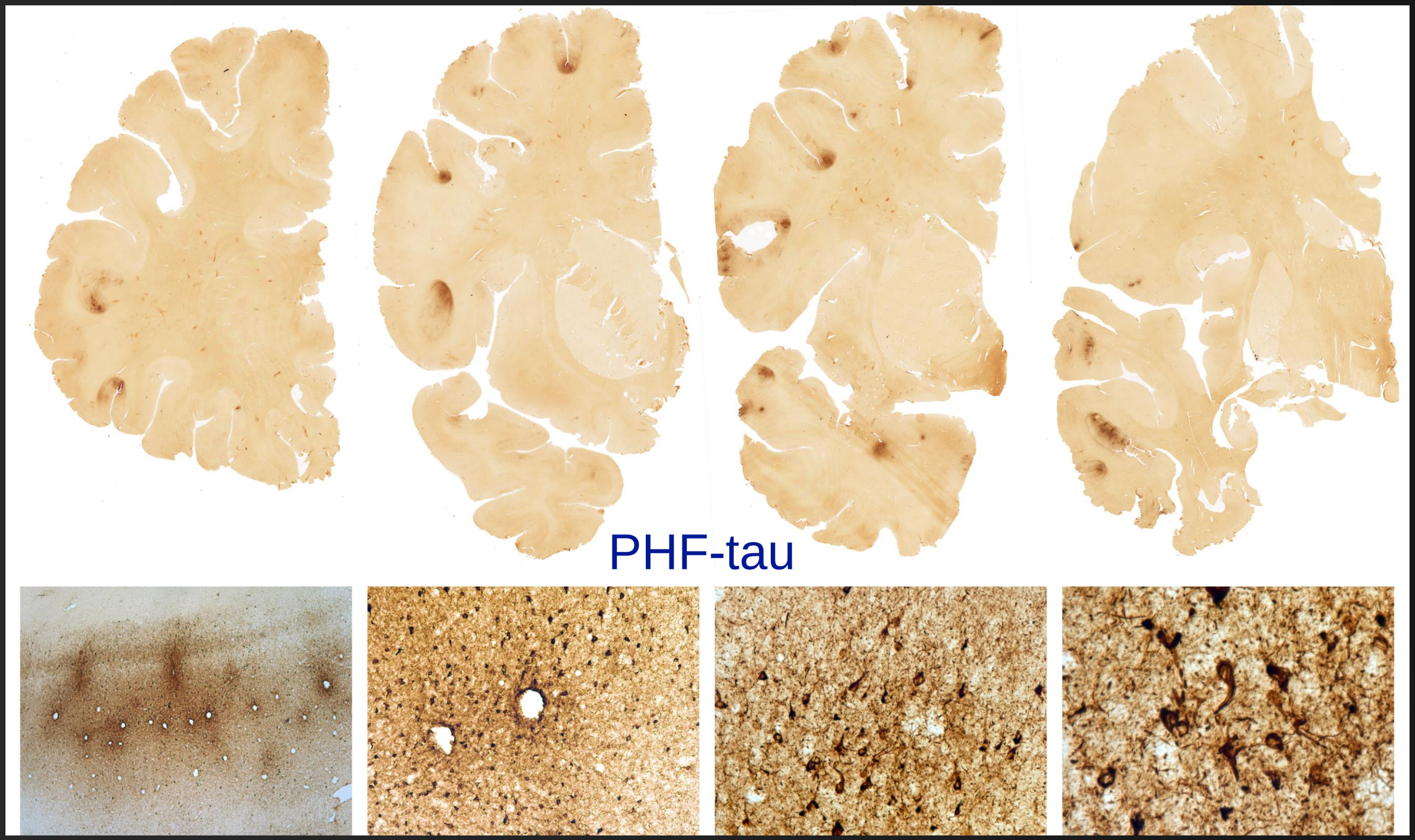


25 yo college football player

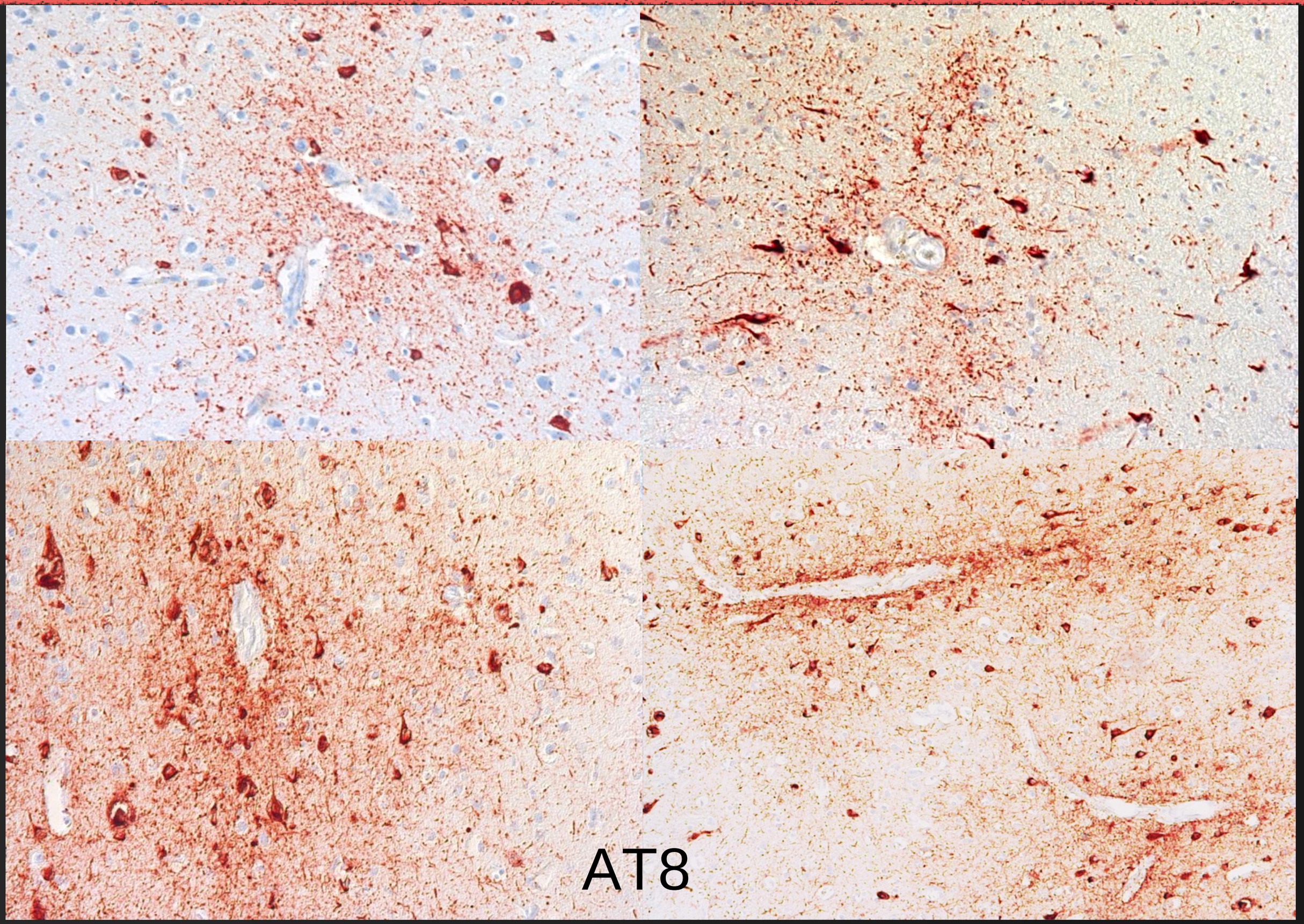


- 16 year exposure to football, 3 years division I college FB Linebacker and special teams
- Several severe concussions during college with persistent vision changes, memory problems, confusion, difficulty sleeping and debilitating headaches.
- Quit football after 3 yrs. Continued to experience episodic memory loss, disorientation, difficulty with attention and concentration and word finding, progressively worsened over the last 18-24 months of his life.
- Also experienced depression, bouts of impulsivity and severe anger.
- He died at age 25 following a staph infection.

Stage II CTE
25 yo College Football Player

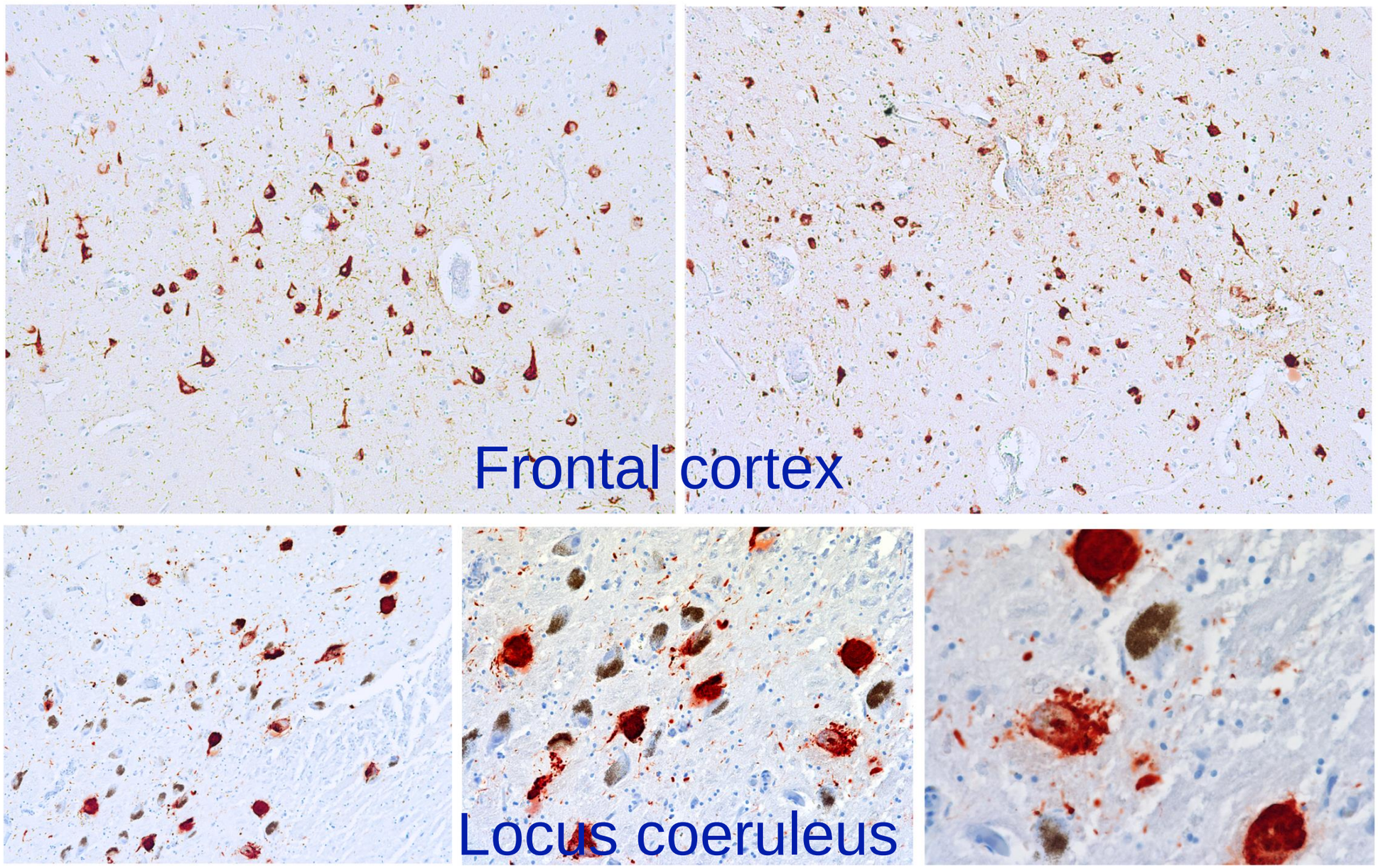


Stage II CTE: 25 yo College Football Player



Stage II CTE

Joseph Chernach
25 year old
Former HS football player, pole vaulter, wrestler
Death from suicide



Dave Duerson

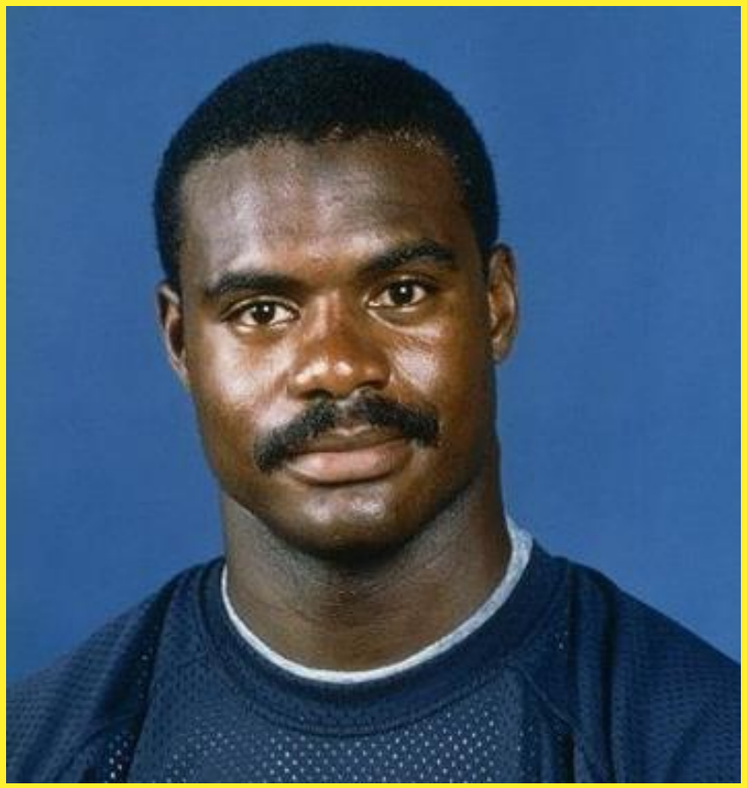
Death at age 50 years

Football since at age 8 - 11-year NFL career

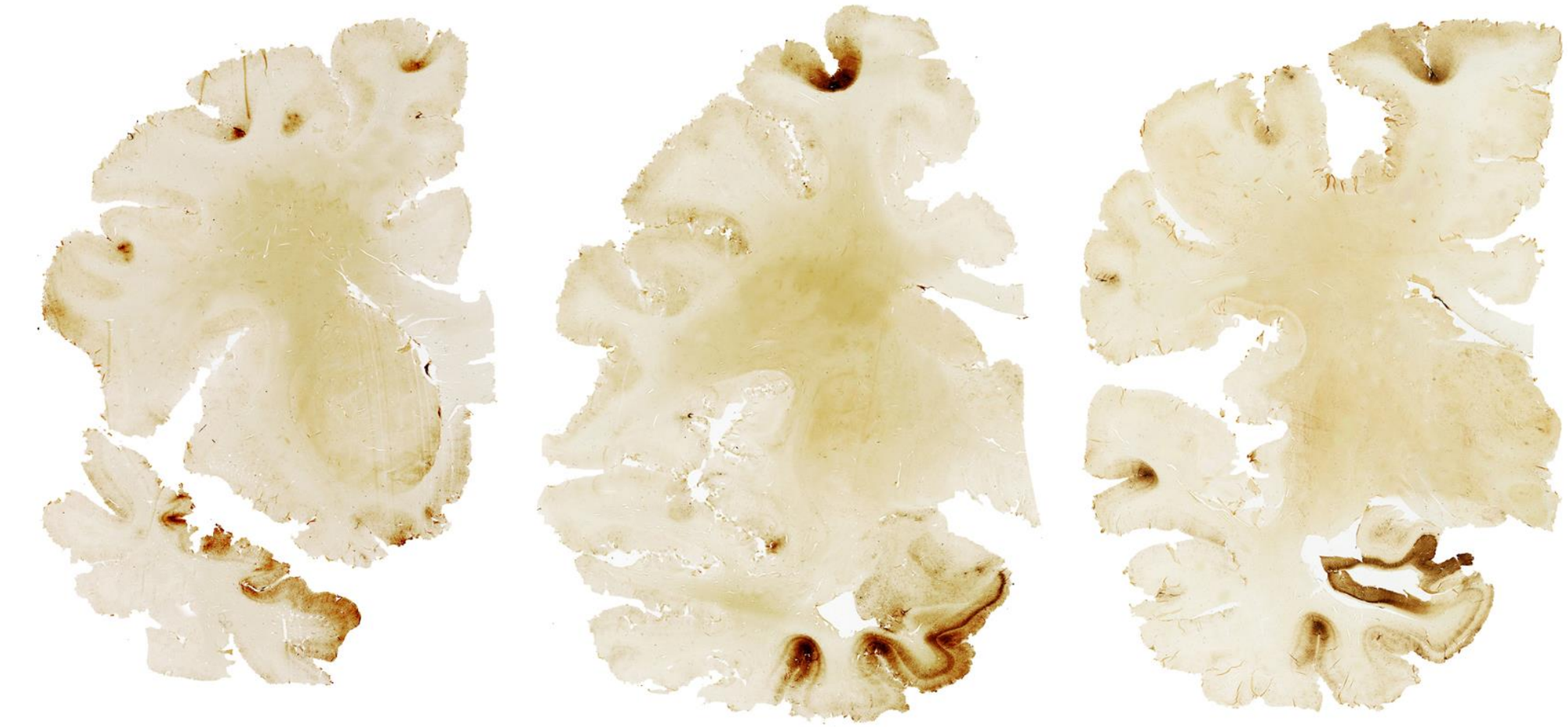
Post-NFL, successful businessman
Active in NFLPA; Benefits Board
Business and financial difficulties began in 2007

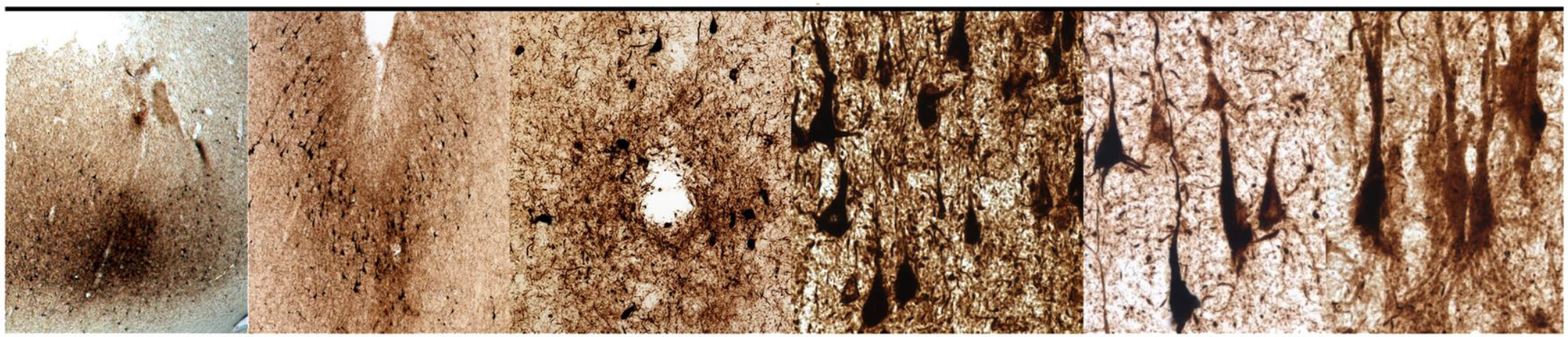
Personal difficulties in 2007
Increasingly out of control:
Short fuse, hot temper, physically and verbally abusive
Long-standing complaint of headaches since retirement NFL
Worsening short-term memory, word-finding and vision difficulties

Self-inflicted gunshot wound, texted family to donate brain to NFL brain bank



Stage III CTE





Dave Duerson

BOSTON UNIVERSITY

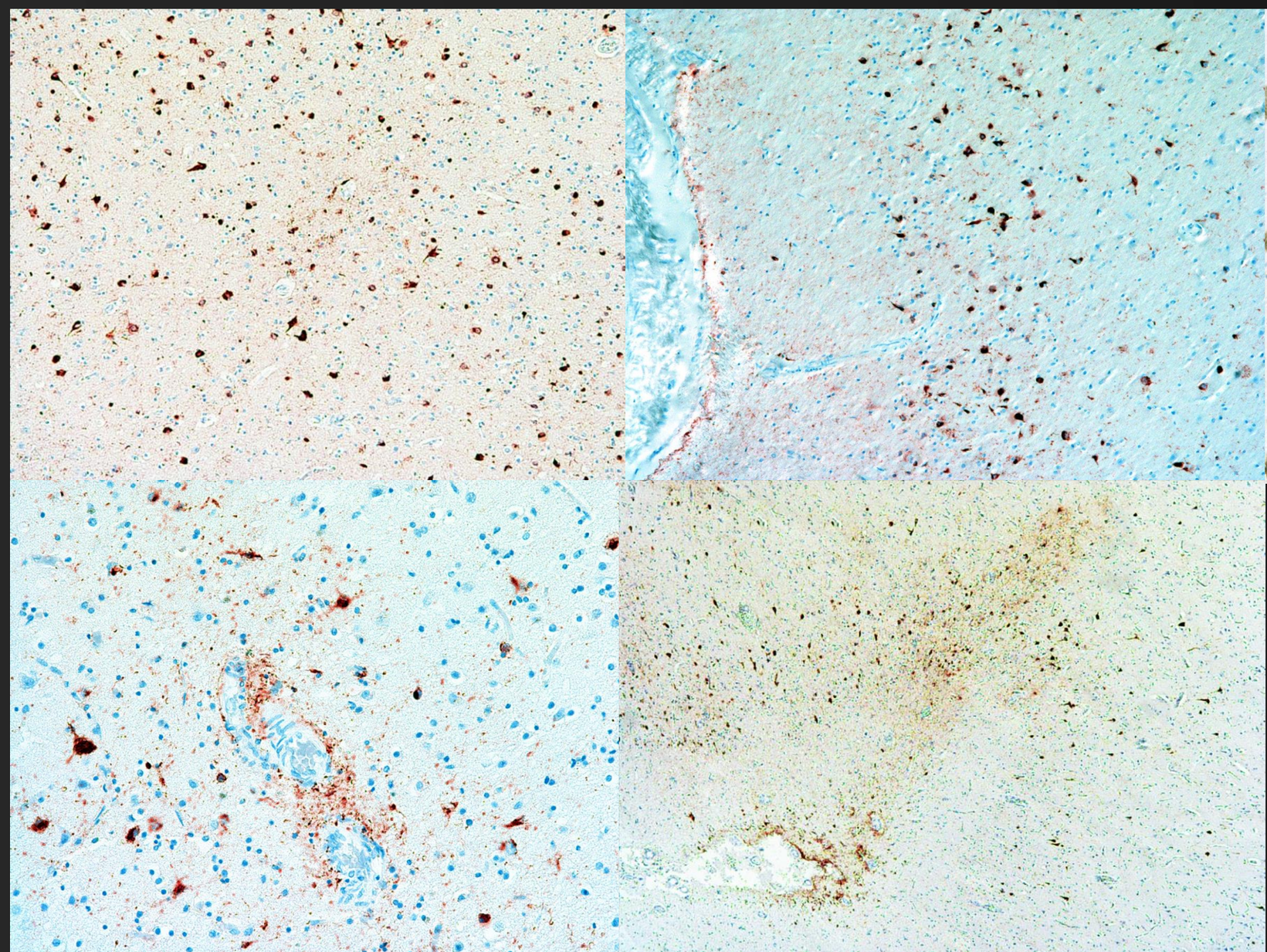
Department of Veterans Affairs

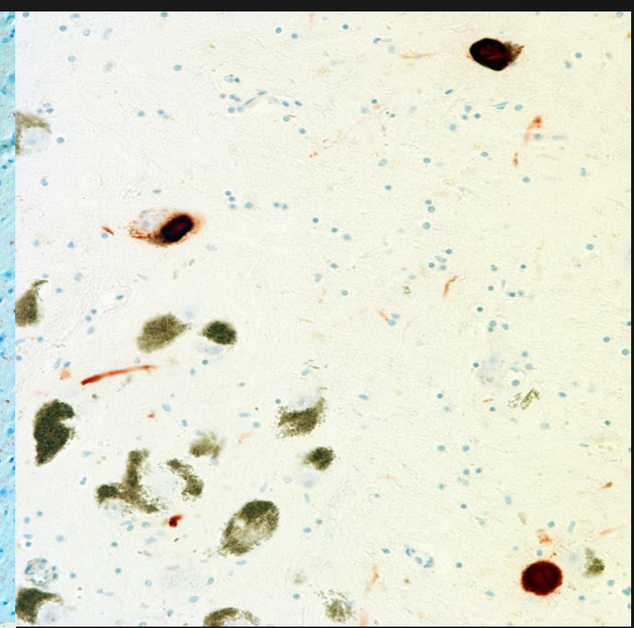
sportslegacy INSTITUTE

Stage III CTE

52 year old former NFL player
24 years football, 14 in NFL
memory problems occurred intermittently in college and NFL
at end of his NFL career, memory loss, depression, short fuse, angry outbursts
gambling, drinking excessively, irresponsible behaviors
Decreased facial expression
Death from MI

AT8





Alpha-synuclein

77 yo Australian Rugby Player

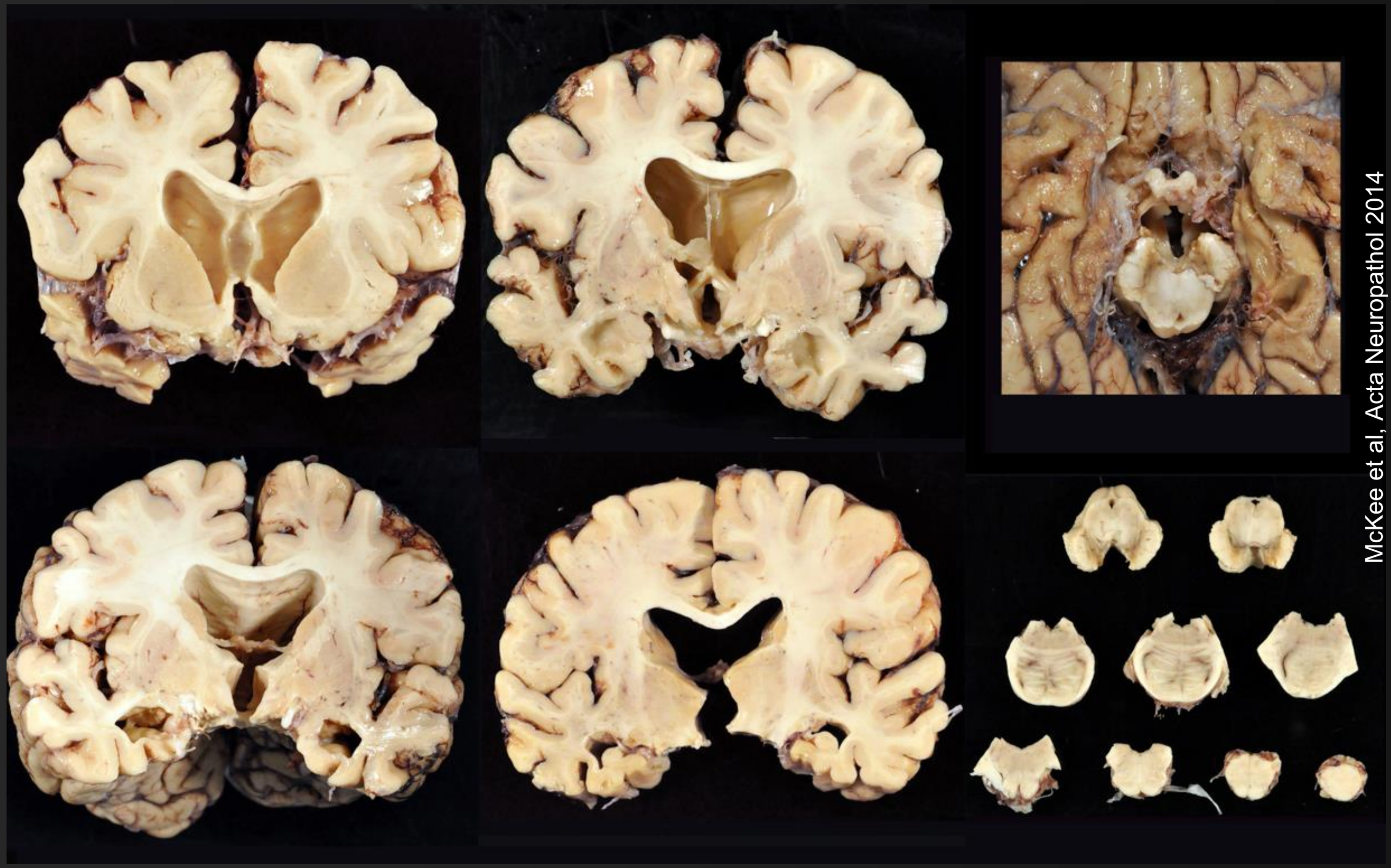
- Began playing rugby at age 13, played 6 years of U21 rugby, and 10 years of senior rugby as flanker and breakaway (18 years).

- Age 54: Cognitive problems, memory loss, attention difficulties, executive dysfunction, followed by depression and anxiety, worsening explosivity and impulsivity.

- Age 65: physically and verbally abusive, with paranoia, disinhibition and severe dementia

- Died at age 77 from myocardial infarction

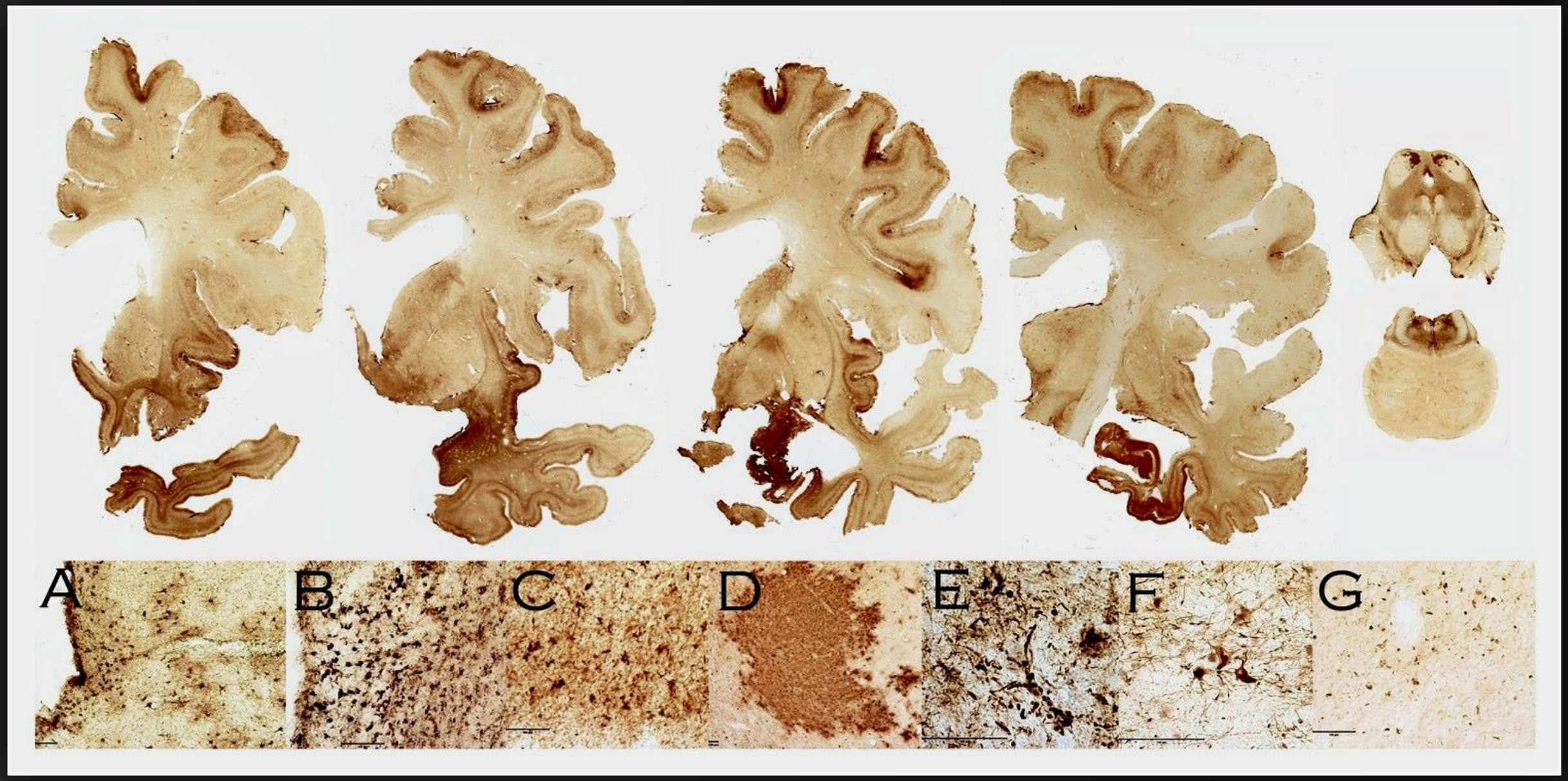
77 yo Australian Rugby Player



McKee et al, Acta Neuropathol 2014

Brain weight : 1030 grams

Barry “Tizza” Taylor
Stage IV CTE



McKee et al, Acta Neuropathol 2014

PHF-tau

pTDP-43

SOCCER

Brain Trauma Extends Reach Into Soccer

Researchers Find Bellini, Star for Brazil, Had Brain Disease C.T.E.

By SAM BORDEN SEPT. 23, 2014

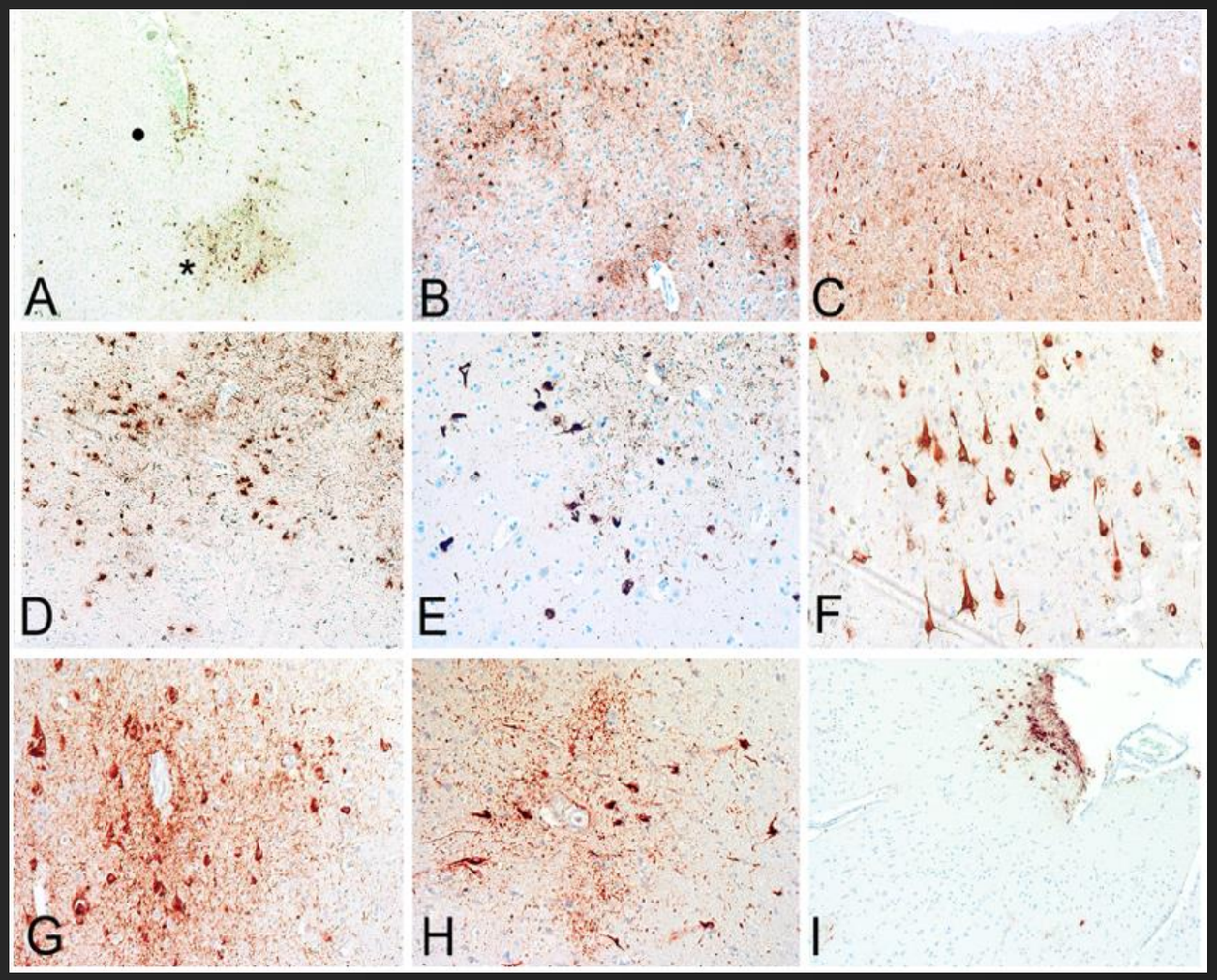
Bellini, right, as Brazil's captain in the 1958 World Cup. He died in March and was found to have had chronic traumatic encephalopathy. Associated Press

Stage IV CTE

NINDS/NIBIB Consensus Conference

February 25-27, 2015

Validation of neuropathological criteria for CTE:



VS.

AD
PSP
CBD
PART
AGD
GPDC

Ann McKee, M.D., Nigel Cairns, Ph.D., John Crary, M.D.,, Rebecca Folkerth, MD,
C. Dirk Keene, M.D., Thomas Montine, M.D., Ph.D., Daniel Perl, M.D.,
Thor Stein M.D., Ph.D., William Stewart, M.D., Jean Paul Vonsattel, M.D.,
Dennis Dickson, M.D

CTE: where are we now?

- CTE can only be diagnosed at autopsy; however, promising efforts to develop neuroimaging, CSF & blood biomarkers are underway

- Future therapeutic efforts in mTBI will need to address management of acute mTBI as well as identification and monitoring of the long-term progressive neurodegeneration that follows.

- Currently, prevention of trauma and continued public education regarding proper detection and management of acute mTBI are our best strategies to lessen to reduce the development of CTE.

CTE:
What are the unresolved questions?

- Incidence and prevalence of CTE
- Diagnosis of CTE during life with validated biomarkers
  - Blood, CSF, saliva assays
  - Neuroimaging: DTI, SWI, PET tau, TDP43 and inflammatory ligands
- Validated animal models: to understand the pathogenetic mechanisms
- Other factors: genetic risk factors, other environmental risk factors
- Treatment, comprehensive care, rehabilitation strategies

Boston University CTE Program
Boston University Alzheimer's Disease Center

VA Boston/ Boston University/ SLI
Chronic Traumatic Encephalopathy Program

BU/VA CTE Program

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All the families who participated in our research

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Mark Wojnarowicz

SLI

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WWE