Chronic Traumatic Encephalopathy (CTE):
Neuropathology

Ann C. McKee M.D.
William Fairfield Warren Distinguished Professor
of Neurology and Pathology
Boston University School of Medicine
Director, Neuropathology, VA Boston Healthcare
Director, BU CTE Center
Associate Director and Neuropathology
Core Leader, BU Alzheimer's Disease Center

AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose

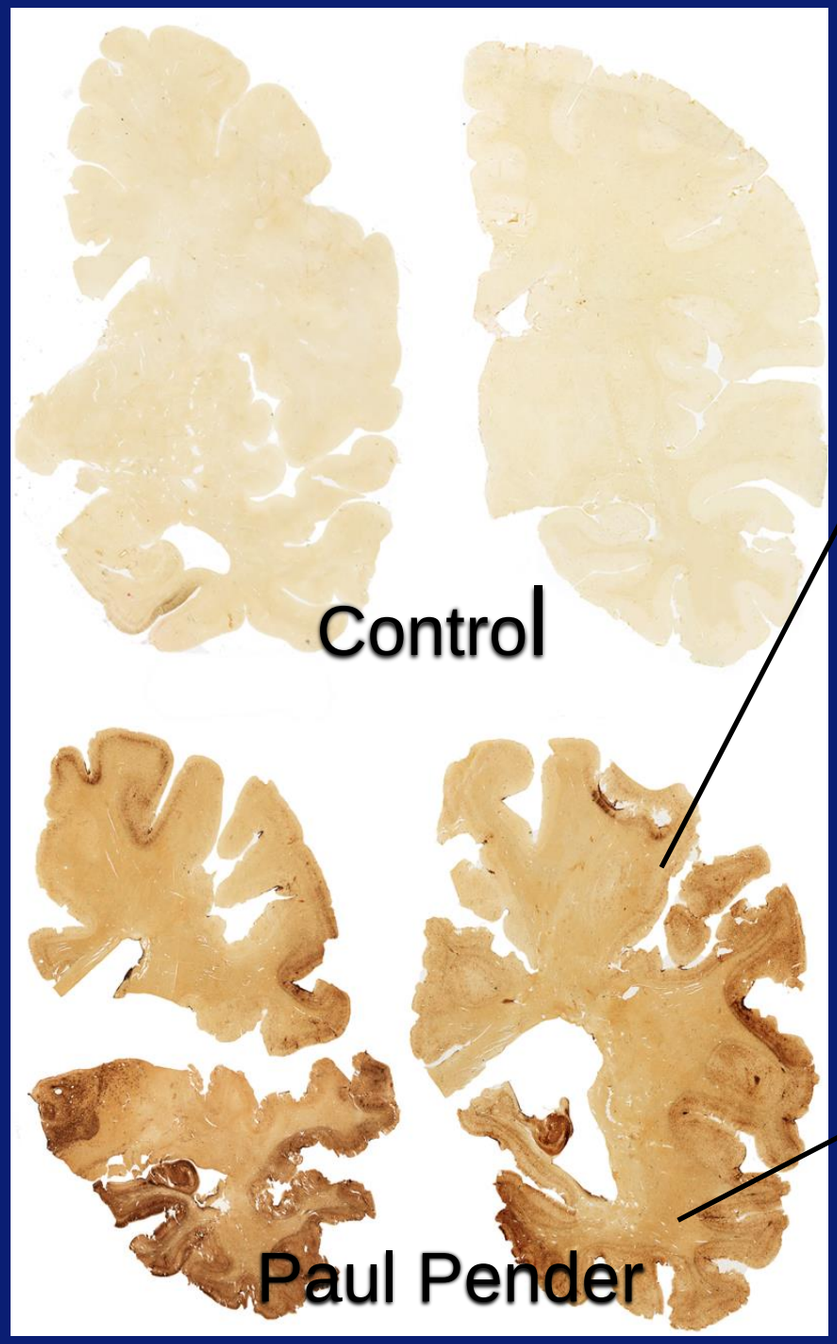
Learning Objectives

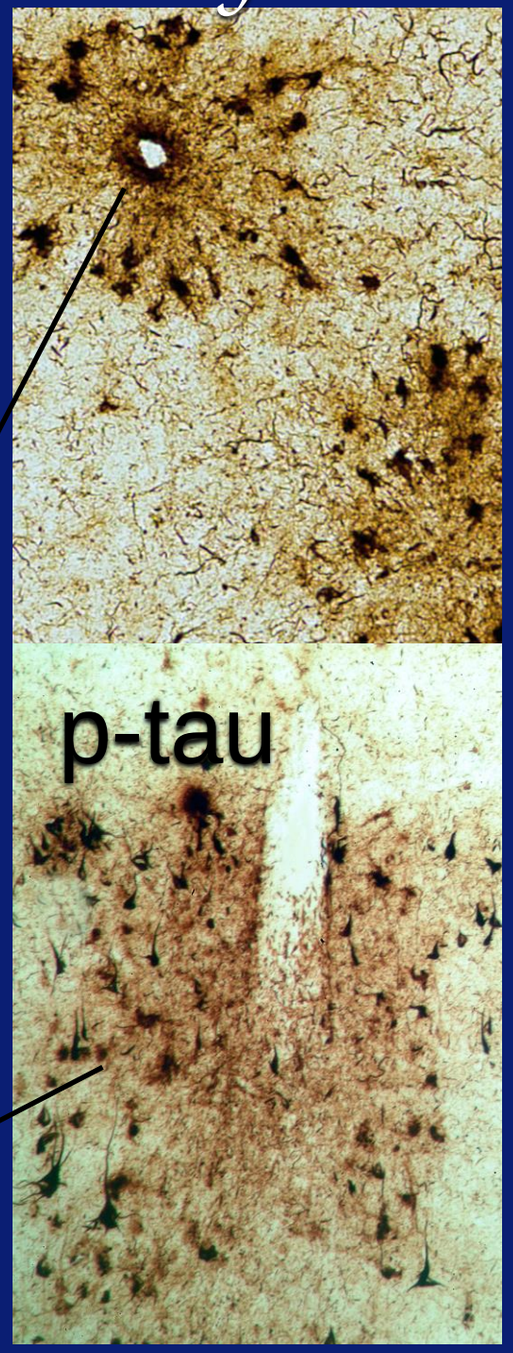
- Identify the key features of the pathognomonic lesion of CTE
- Distinguish CTE from other age-related tauopathies
- List common co-morbidities of CTE

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

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

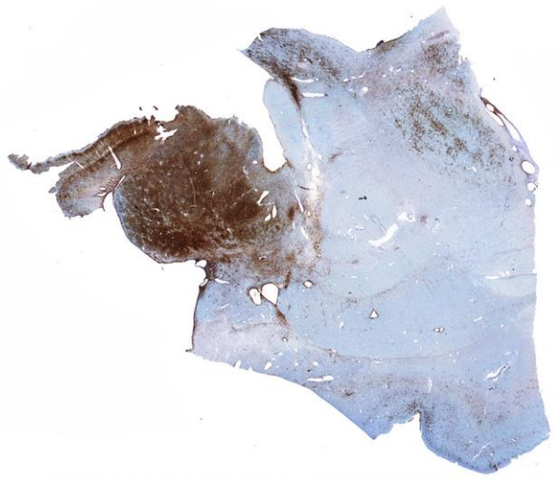
45 year old ex-NFL players

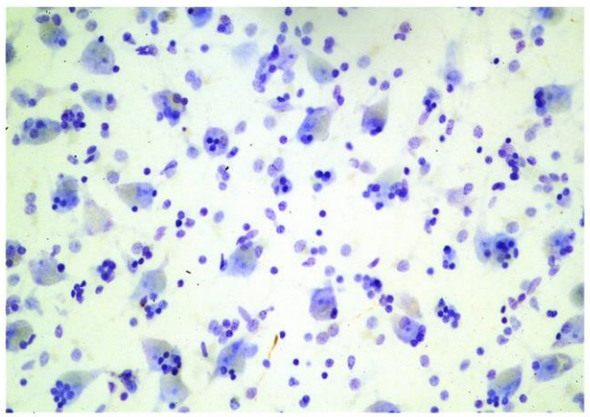
Tom McHale

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

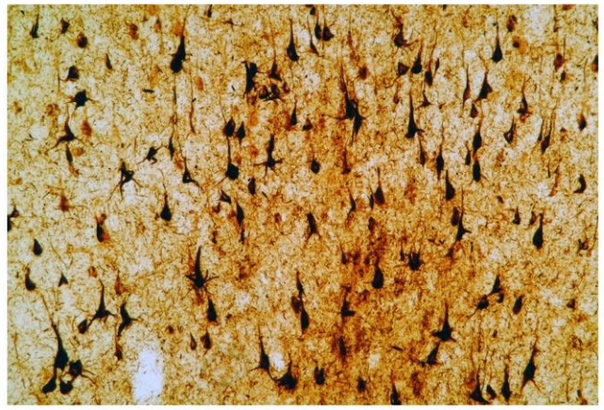
John Grimsley

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

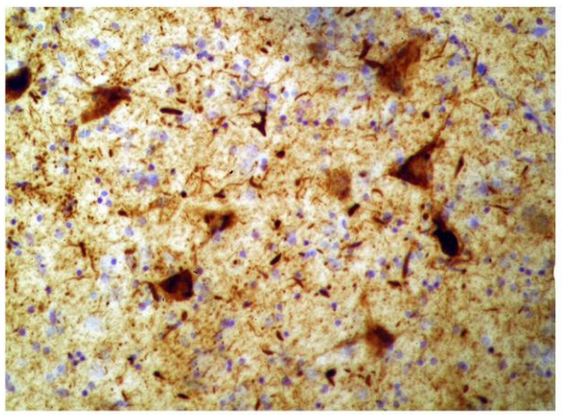




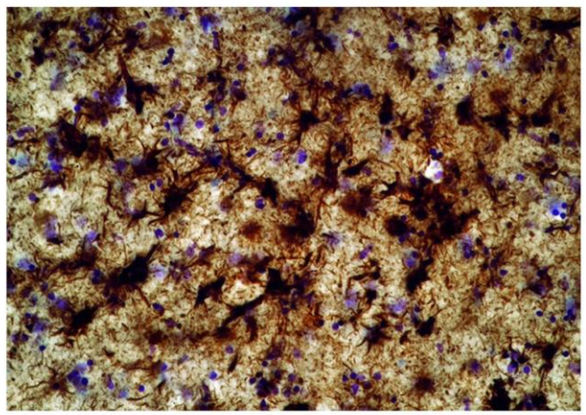
Control



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

VA-BU-CLF Brain Bank, 2008-present

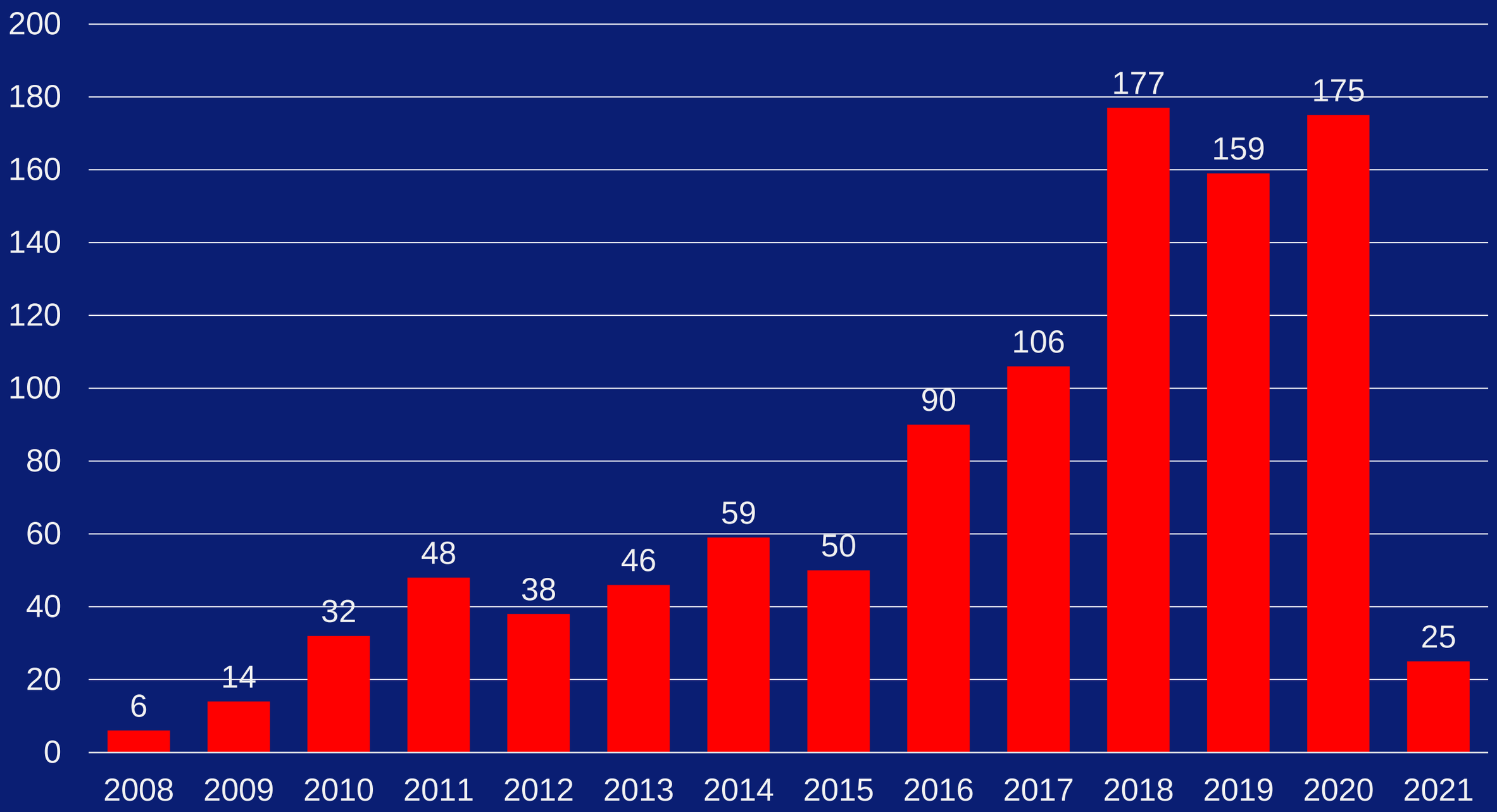
To investigate the long-term consequences of TBI





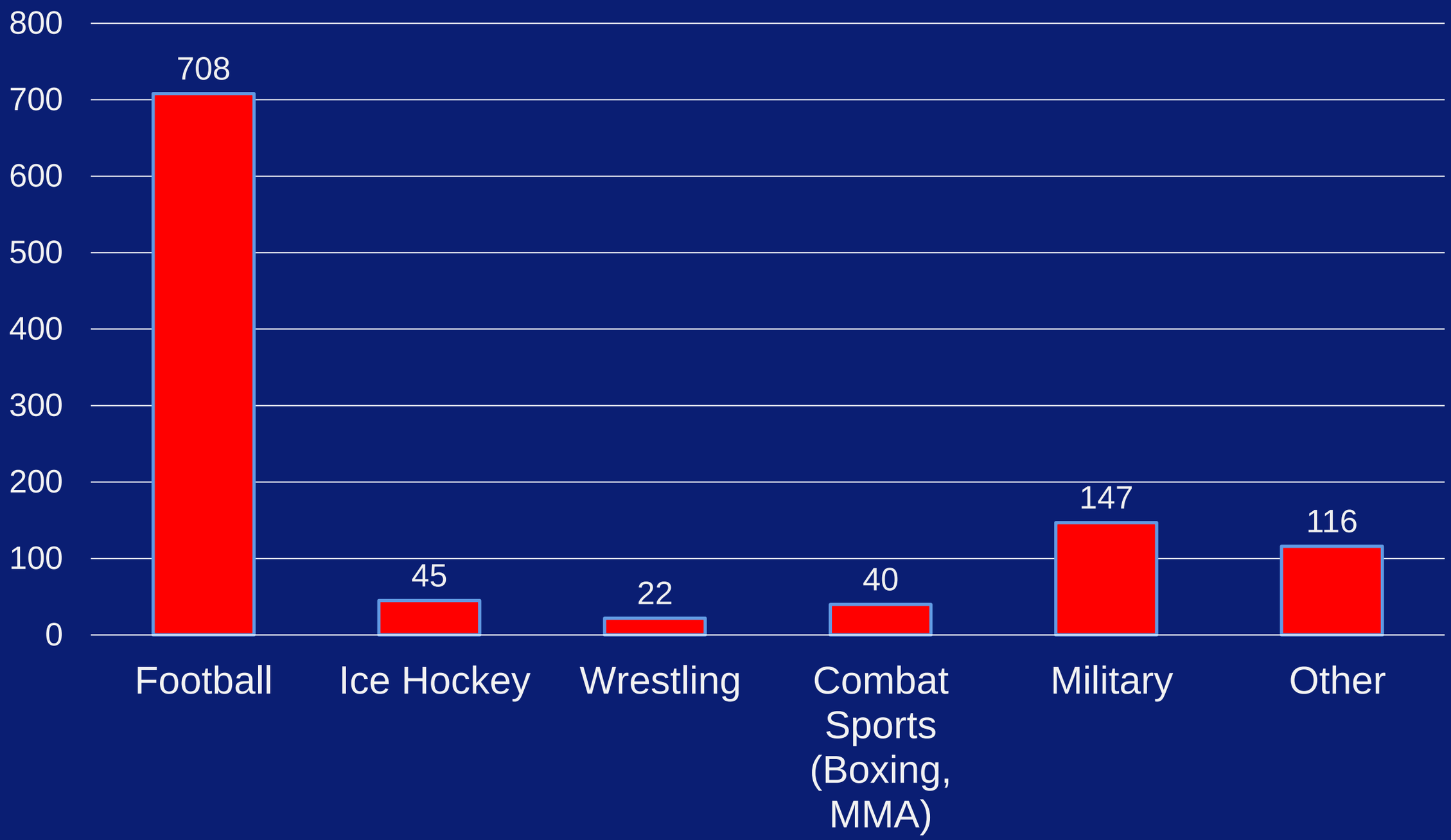



Brain donations to the UNITE Brain Bank per year

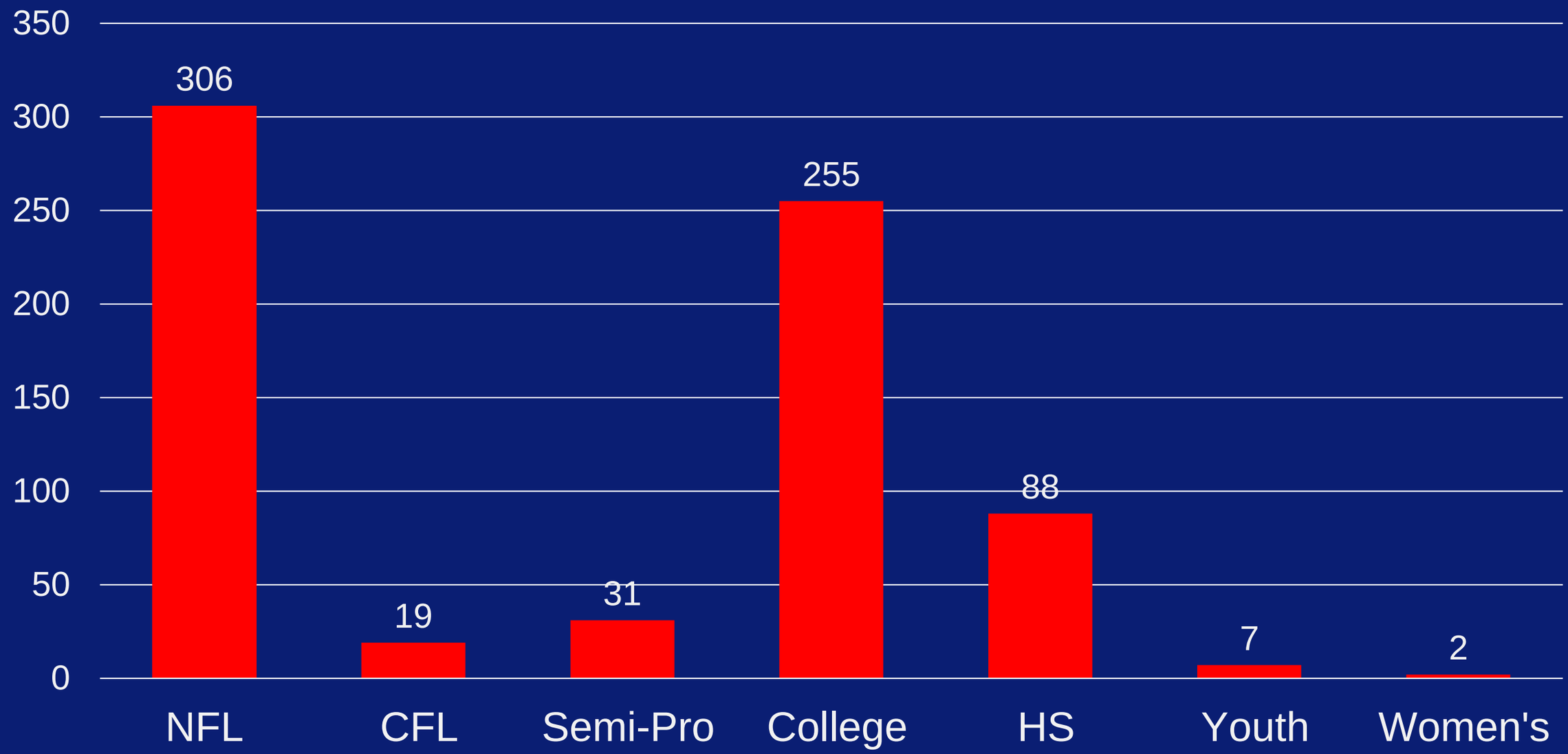


N = 1025

Brain donations to the UNITE (VA-BU-CLF) Brain Bank by primary exposure source

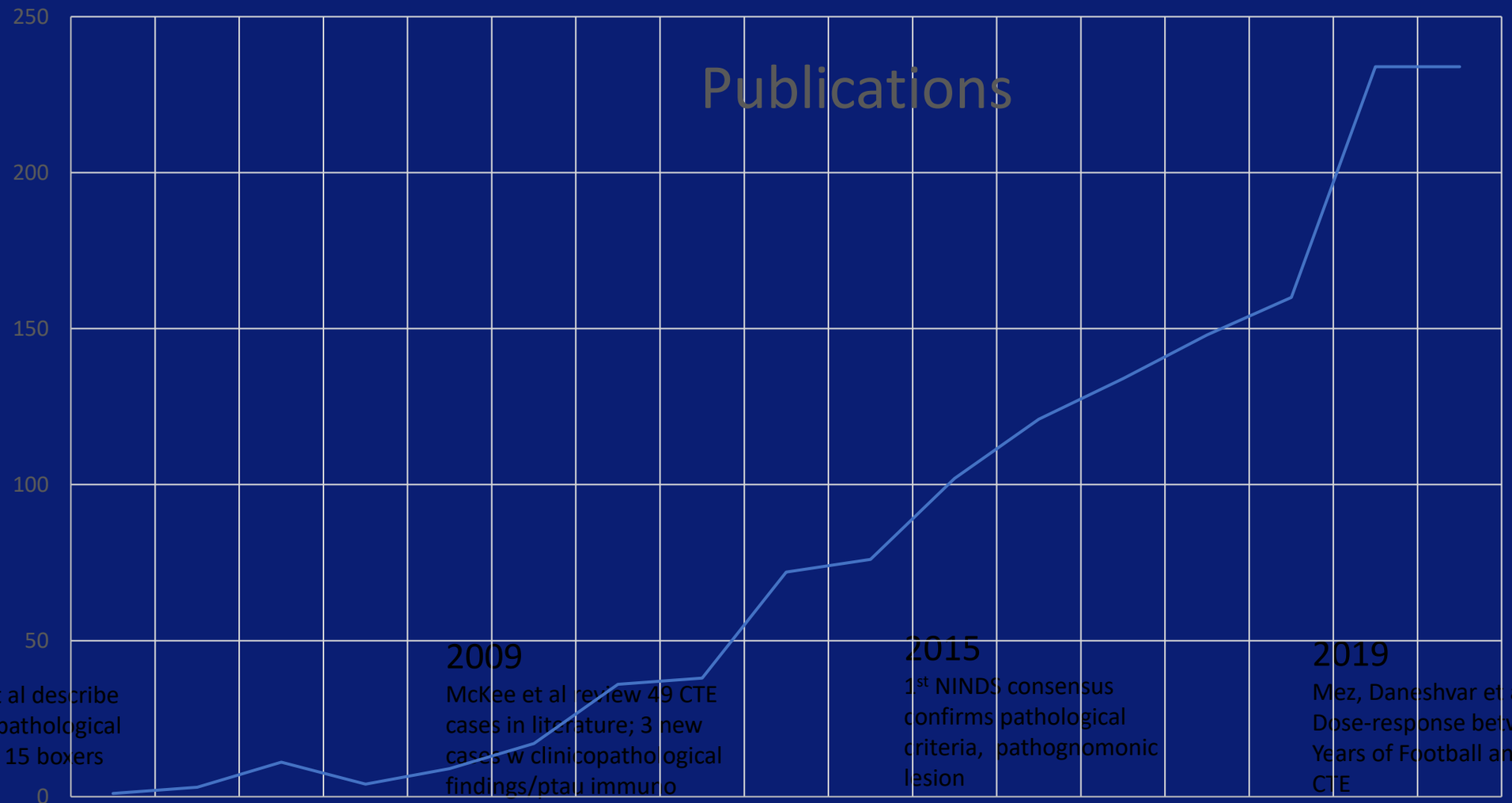


Brain donations from American football players to the UNITE (VA-BU-CLF) Brain Bank



N = 708

Timeline of CTE



1928
Martland describes the clinical syndrome of "punch drunk" in boxers

1949
Critchley introduces the term "chronic traumatic encephalopathy"

1973
Corsellis et al describe the clinicopathological features in 15 boxers

2005, 2006
Omalu et al describe CTE in 2 NFL players

2009
McKee et al review 49 CTE cases in literature; 3 new cases w clinicopathological findings/ptau immuno

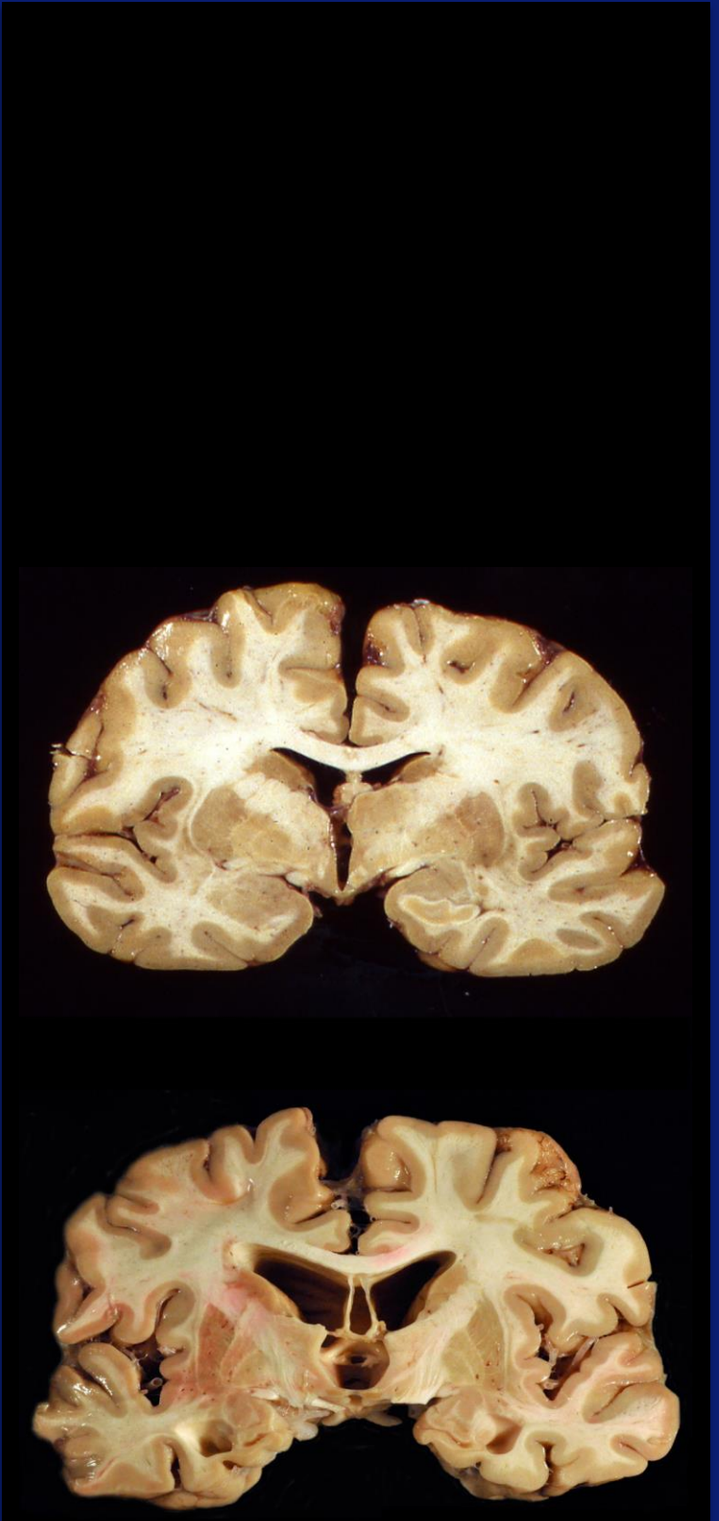
2013
McKee et al criteria for pathological diagnosis of CTE and a staging scheme

2015
1st NINDS consensus confirms pathological criteria, pathognomonic lesion

2017
Mez, Daneshvar et al JAMA CPC study of 202 football players, 99% NFL players with CTE

2019
Mez, Daneshvar et al. Dose-response between Years of Football and CTE

2020
Quantitative validation of McKee staging scheme

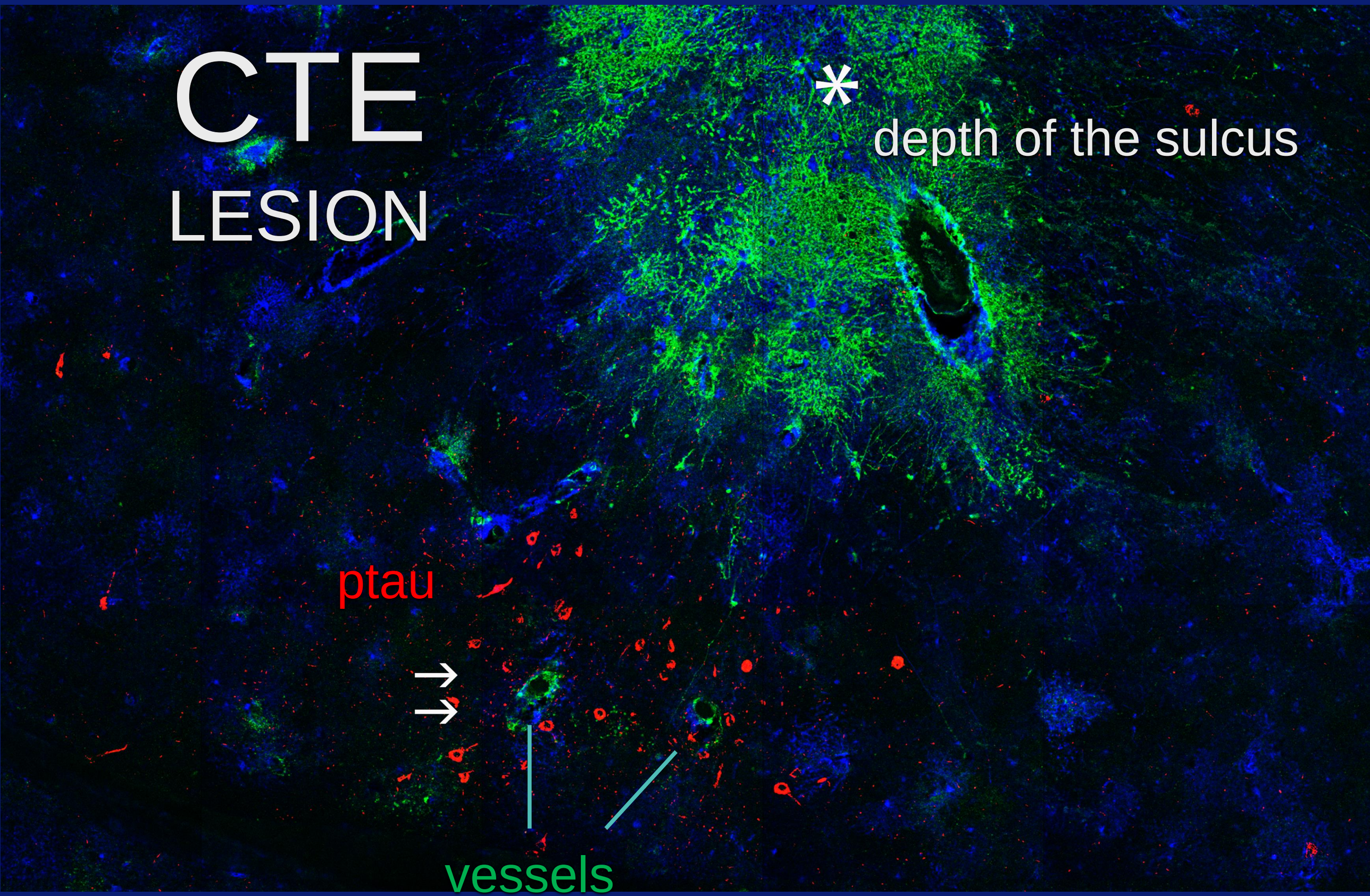


What is CTE?

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI), including symptomatic concussions and asymptomatic subconcussive injuries, often incurred during contact sports.

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

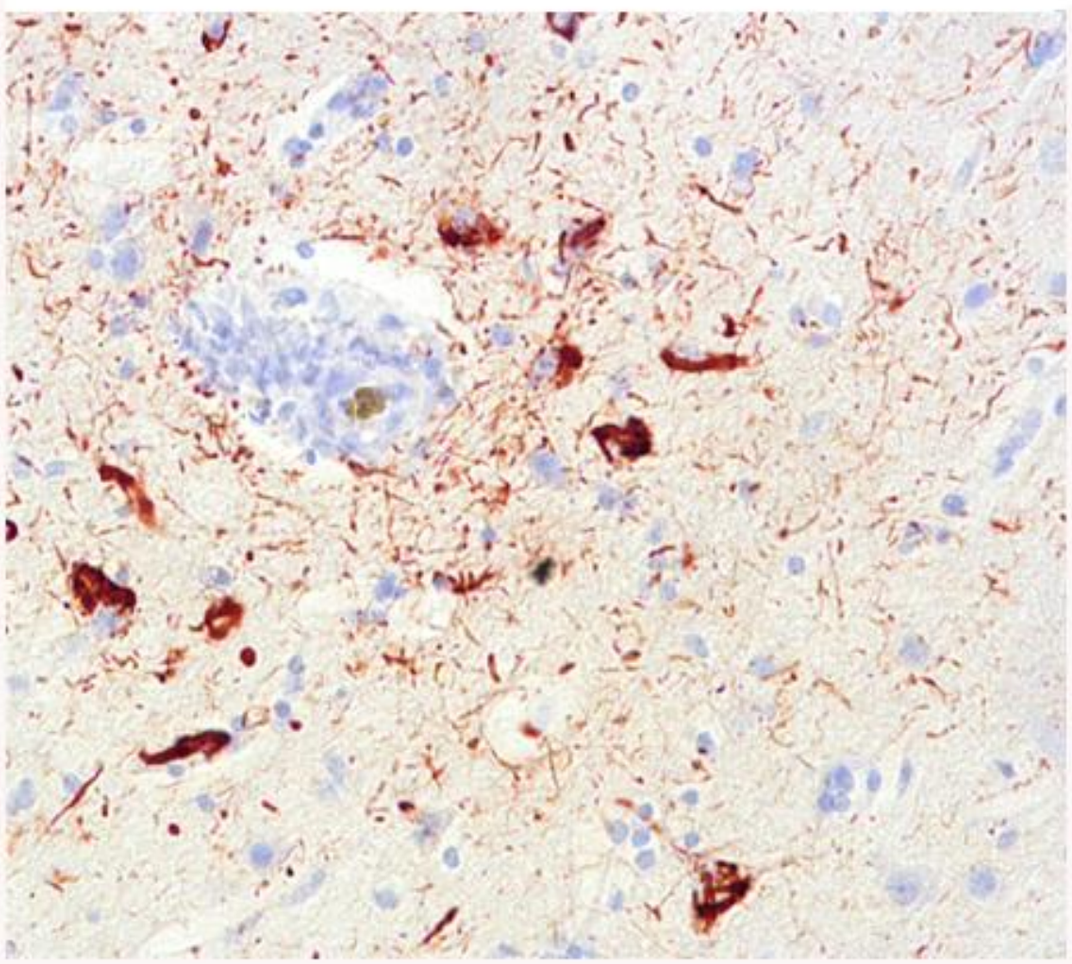
CTE can only be diagnosed after death by post-mortem examination. It cannot be diagnosed with certainty during life.

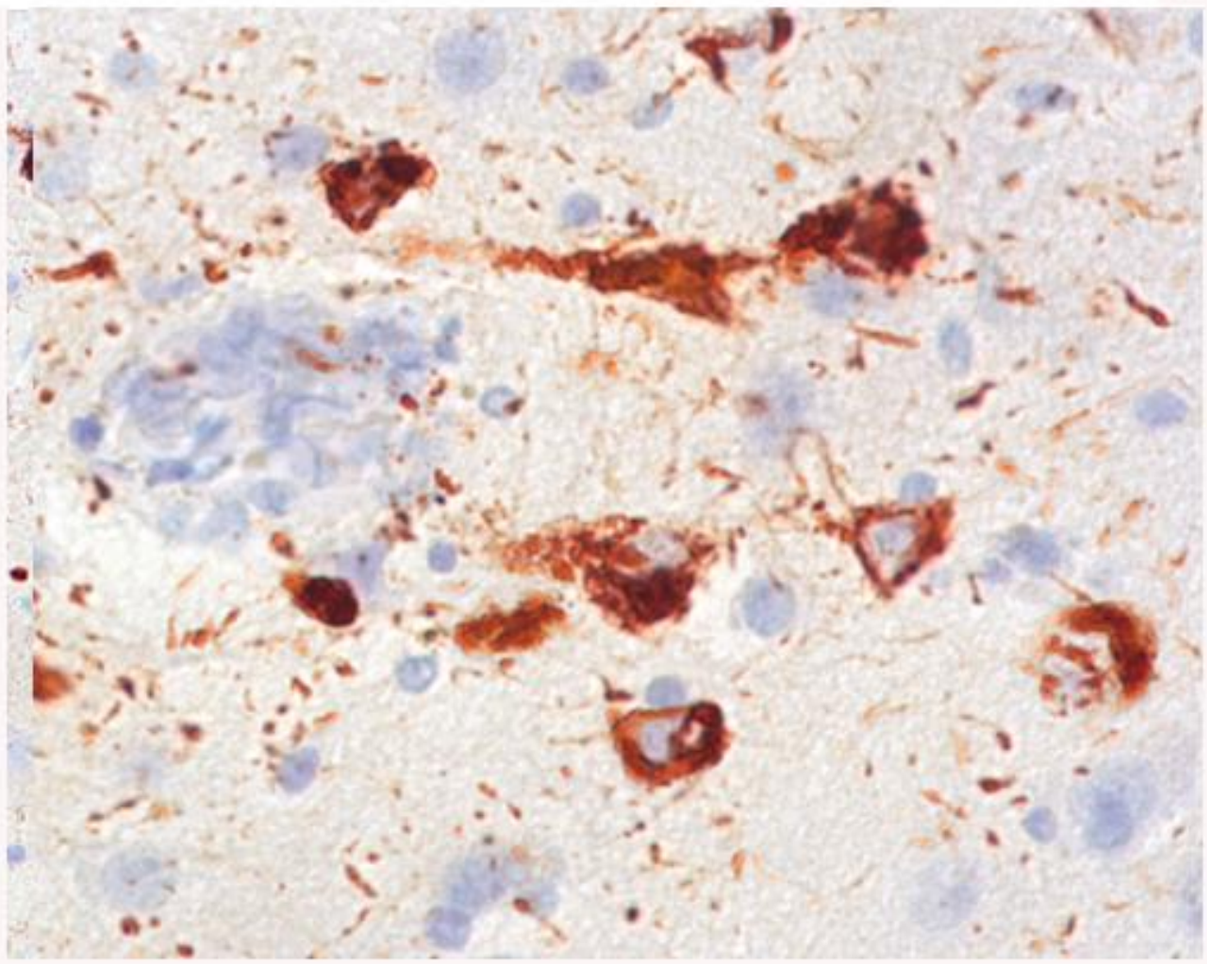

CTE
LESION
* depth of the sulcus
ptau
vessels

McKee et al, The spectrum of disease in CTE, Brain 2013

Diagnostic features of CTE:

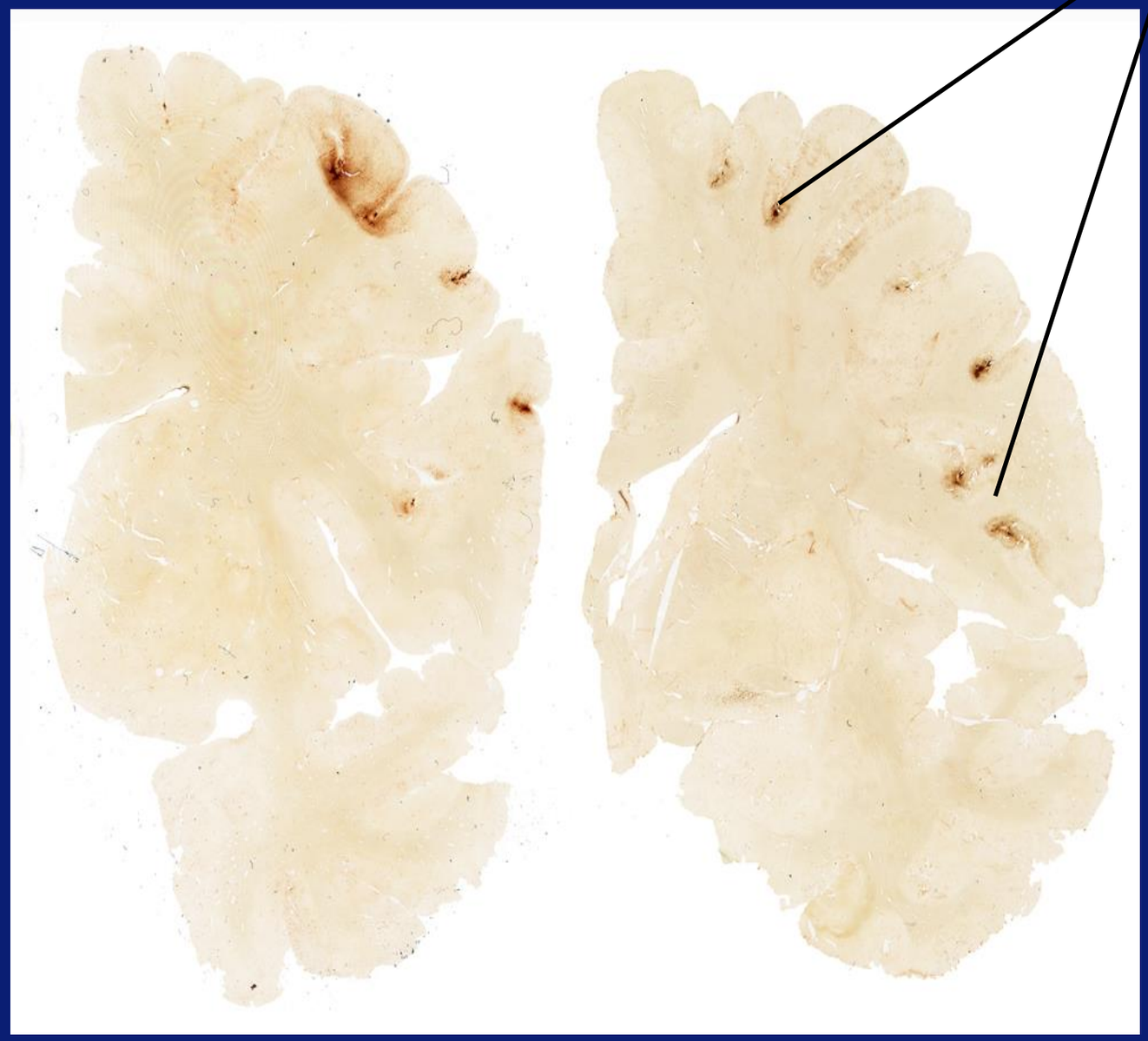
1. Perivascular p-tau lesion (CTE lesion)





Diagnostic features of CTE:

2. CTE lesions are found at the sulcal depths



Stages of Tau Pathology Age at Death

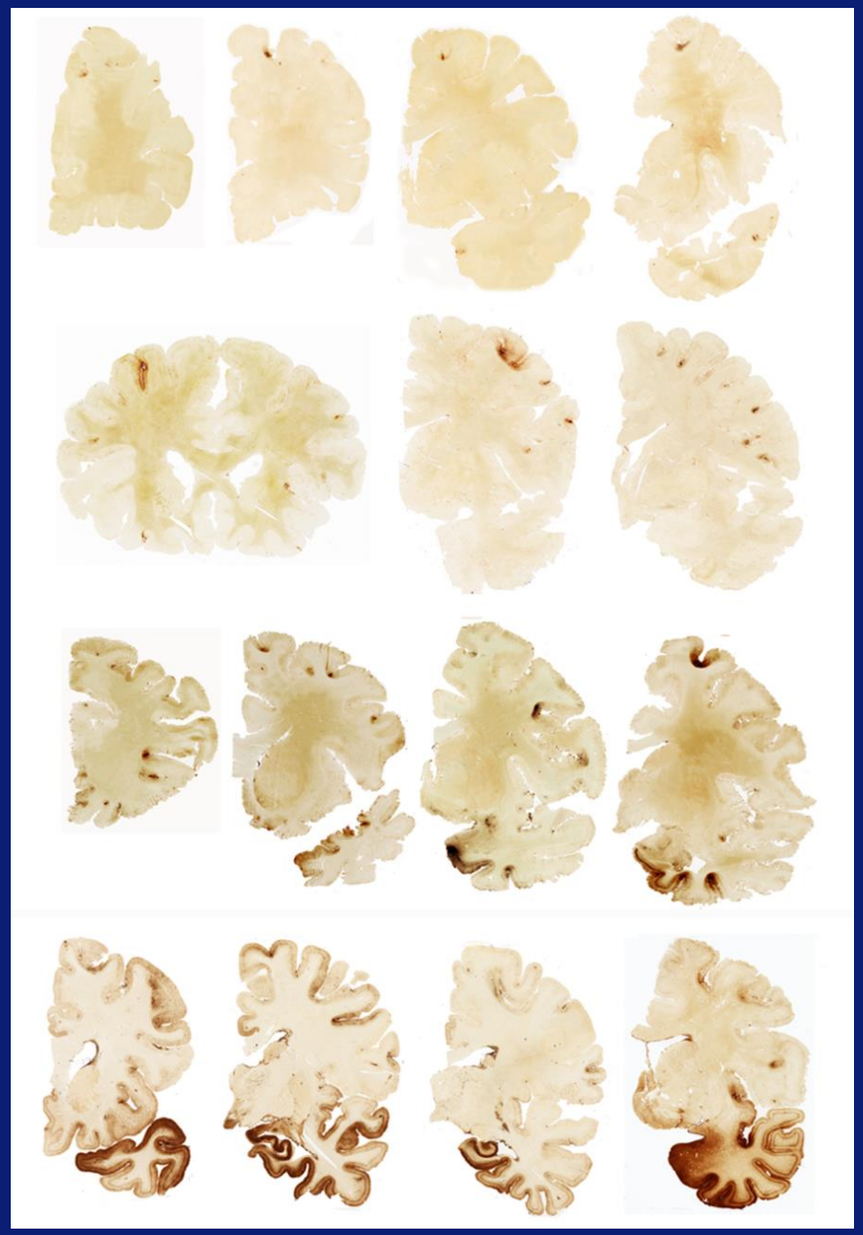
The method of staging CTE ptau pathology was based on large hemispheric 50-mm-thick slides immunostained as free-floating sections for p-tau

Stage I

m age: 28.3 + 13 yrs

Stage II

m age: 44.3 + 16 yrs



Stage III

m age: 56.0 + 14 yrs

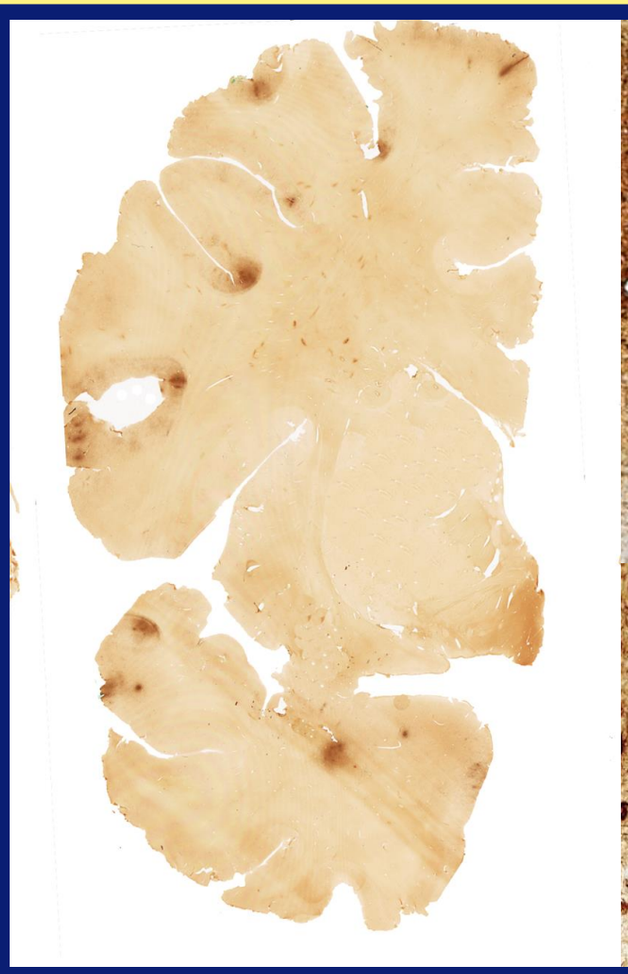
Stage IV

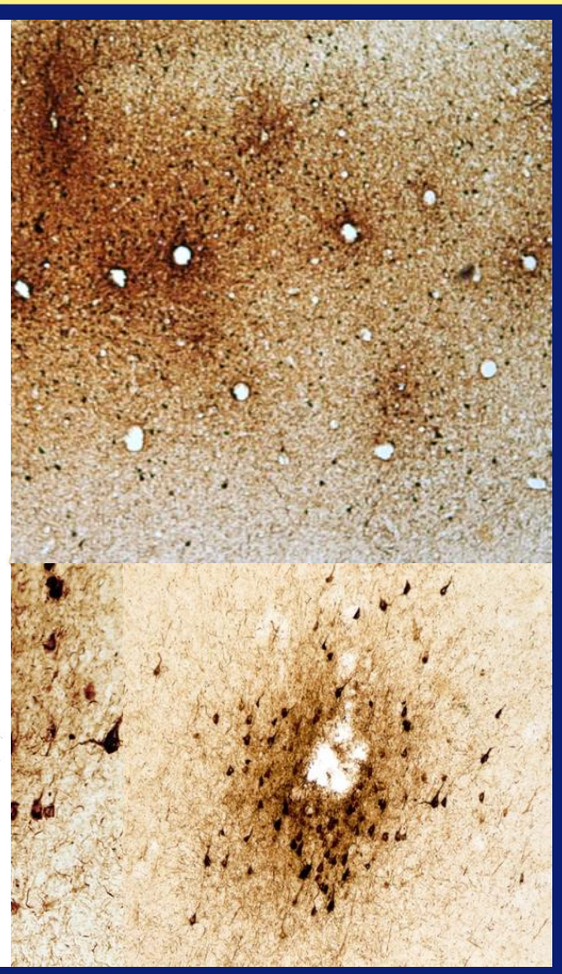
m age: 77.4 + 12 yrs

CTE stage significantly correlates with age at death and total number of years playing football *McKee et al, 2013, Brain*

Pathognomonic Lesion of CTE

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





Based on blinded review of 25 cases of **t**auopathies, a panel of 7 neuropathologists determined that CTE could be distinguished from AD, PSP, argyrophilic grain disease, CBD, PART, and Parkinson's dementia complex of Guam.

The panel defined a pathognomonic lesion of CTE, defined supportive but non-diagnostic features, and recommended a minimum blocking and staining scheme

"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

Supportive features of CTE

- 1) superficial NFTs
- (2) p–tau in CA2 and CA4 hippocampus
- (3) p-tau in: mammillary bodies, hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus.
- (4) p-tau thorn-shaped astrocytes (TSA) in the subpial region
- (5) p-tau dot-like neurites

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

Kevin F. Bieniek, PhD, Nigel J. Cairns, PhD, FRCPath, John F. Crary, MD, PhD, Dennis W. Dickson, MD, Rebecca D. Folkerth, MD, C. Dirk Keene, MD, PhD, Irene Litvan, MD, Daniel P. Perl, MD, Thor D. Stein, MD, PhD, Jean-Paul Vonsattel, MD, William Stewart, PhD, FRCPath, Kristen Dams-O'Connor, PhD, Wayne A. Gordon, PhD, Yorghos Tripodis, PhD, Victor E. Alvarez, MD, Jesse Mez, MD, Michael L. Alosco, PhD, Ann C. McKee, MD, and the TBI/CTE group

8 neuropathologists evaluated 27 cases of tauopathies, including 17 CTE cases, using the 2016 NINDS criteria, blinded to all clinical and demographic information.

Bieniek et al, JNEN 2021

Findings of the Second NINDS/NIBIB Consensus

- The panel confirmed the robustness of the 2016 NINDS criteria with the clarification that the pathognomonic lesion must include ptau in neurons to distinguish CTE from ARTAG

- Purely astrocytic perivascular p-tau pathology represents ARTAG and does not meet the criteria for CTE

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

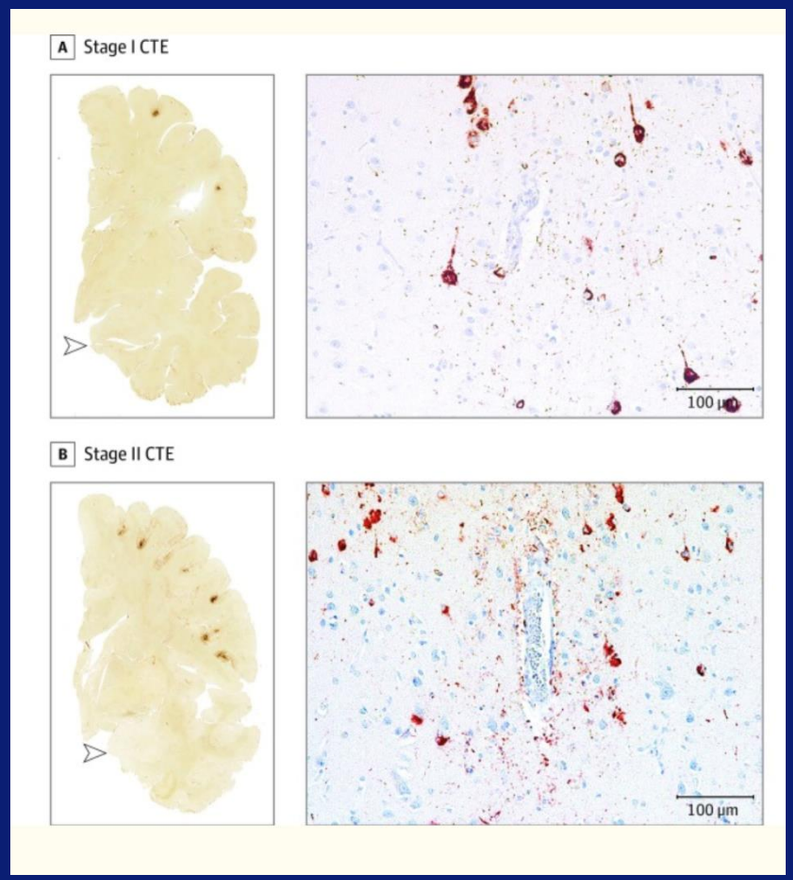
Bieniek et al, JNEN 2021

Findings of the Second NINDS/NIBIB Consensus

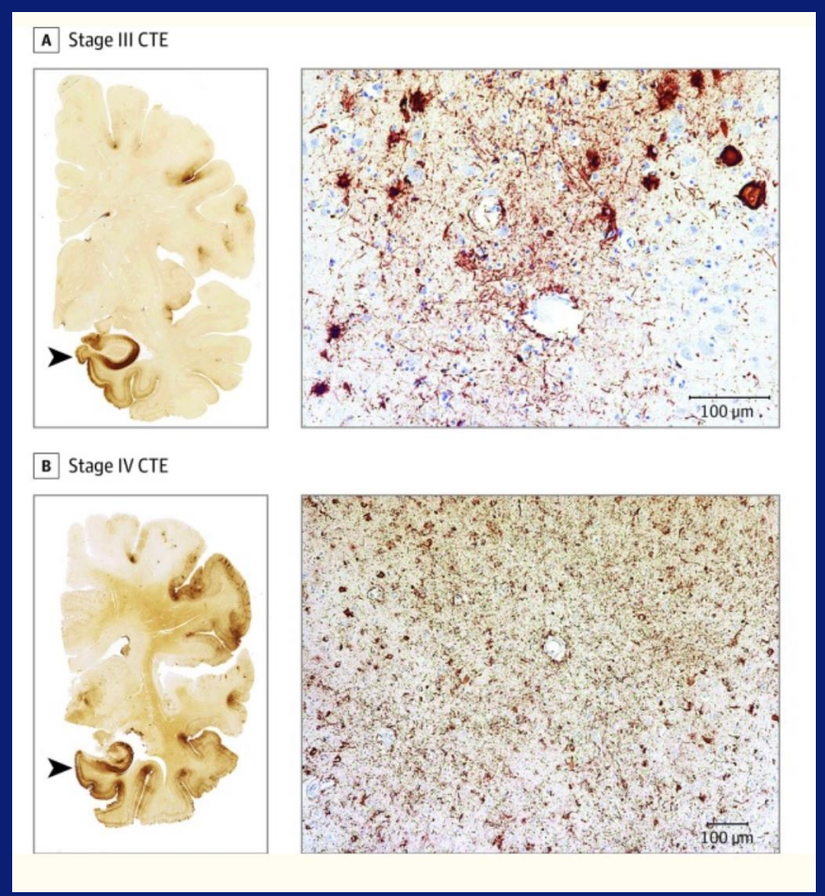
- When only a limited number of standard paraffin slides is available, the McKee staging scheme is inconsistent, *therefore, when only a limited number of slides are available for evaluation*, the panel suggested an algorithm for classifying CTE as low and high stage.

Bieniek et al, JNEN 2021

LOW (I-II)



HIGH (III-IV)



Pathognomonic CTE Lesion:

p-tau aggregates in neurons, with or without thorn-shaped astrocytes, at the depth of a cortical sulcus around a small blood vessel, deep in the parenchyma, and not restricted to the subpial and superficial region of the sulcus.

Present

Diagnostic of CTE

Neuronal p-tau pathology (select all that apply):

- ☐ NFT in gyral side adjacent to CTE lesion
- ☐ NFT in gyral crest adjacent to CTE lesion
- ☐ NFT in superficial cortical laminae (layer II)
- ☐ NFT in CA4 of hippocampus (with dendritic swellings)
- ☐ NFT in CA2 of hippocampus
- ☐ NFT in entorhinal cortex
- ☐ NFT in amygdala
- ☐ NFT in thalamus
- ☐ NFT in mammillary body
- ☐ NFT in cerebellar dentate nucleus

<5 → Low CTE

≥5 → High CTE

Absent

Suggestive features (select all that apply):

- ☐ Clinical concern
- ☐ Tau pathology at sulcal depth NOS
- ☐ Superficial cortical NFT without amyloid-β

none → Not Diagnostic of CTE

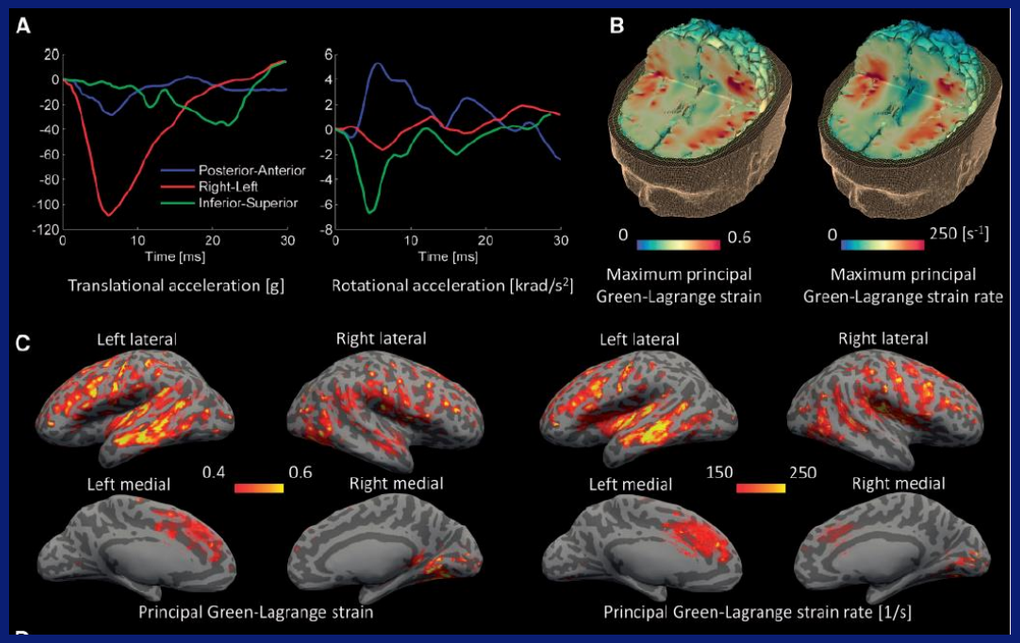
≥1 → Recommend resampling of 4-8 bilateral cortical sulci including dorsolateral frontal, orbital frontal, superior middle temporal & inferior temporal gyri

→ CTE Lesion?

Present → Diagnostic of CTE

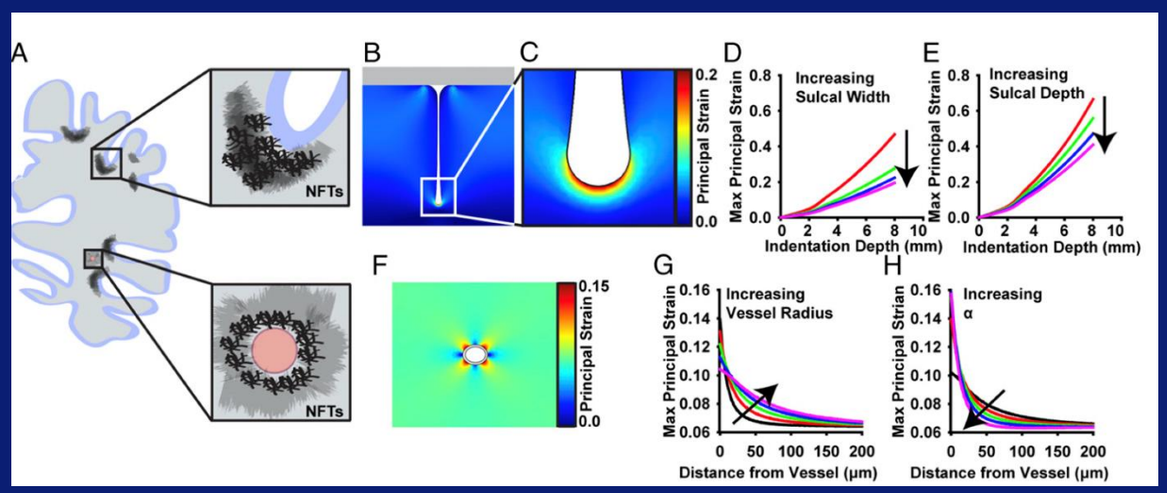
Absent → Not Diagnostic of CTE

Multiple studies modeling head impact injury show greatest tissue strain, strain rate, mechanical deformation 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 of a sulcus and perivascular region during impact injury: greatest mechanical deformation in depth of sulcus and perivascular region.

Liao et al. PNAS 2021

Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules

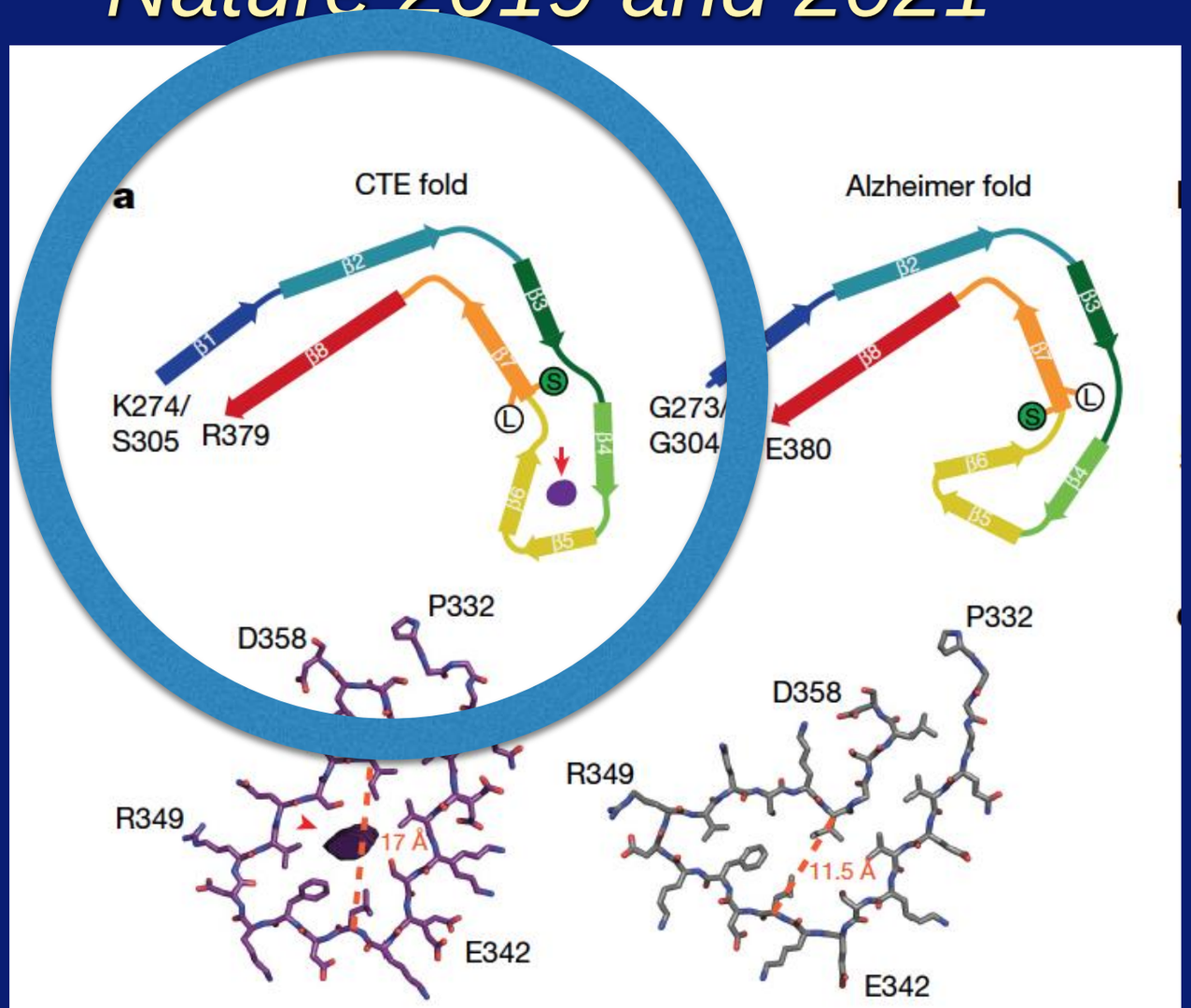
Benjamin Falcon[1], Jasenko Zivanov[1], Wenjuan Zhang[1], Alexey G. Murzin[1], Holly J. Garringer[2], Ruben Vidal[2], R. Anthony Crowther[1], Kathy L. Newell[3], Bernardino Ghetti[2], Michel Goedert[1,4]* & Sjors H. W. Scheres[1,4]*

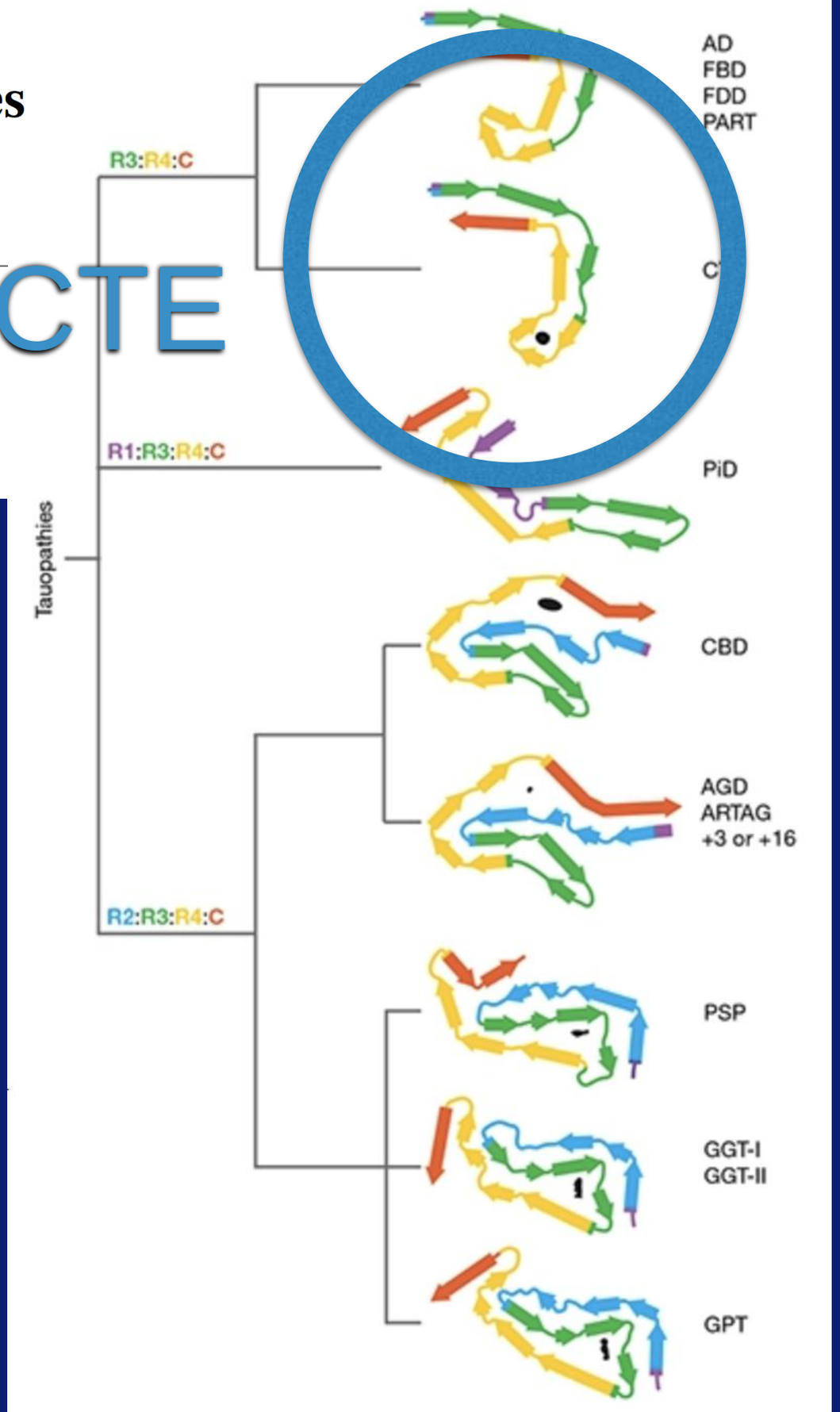
Article

Structure-based classification of tauopathies

CTE

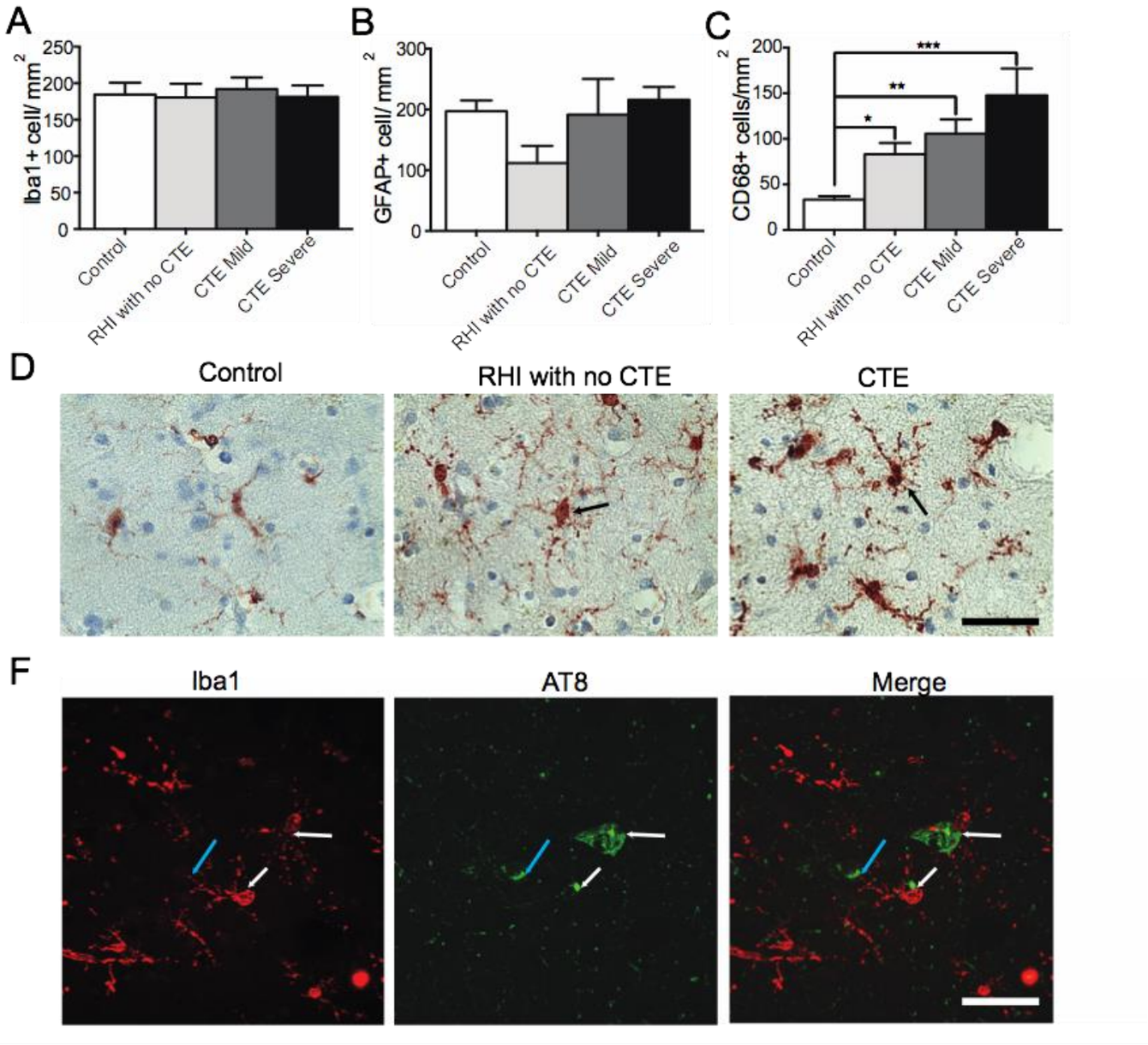
Nature 2019 and 2021





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 greater increase in CTE.



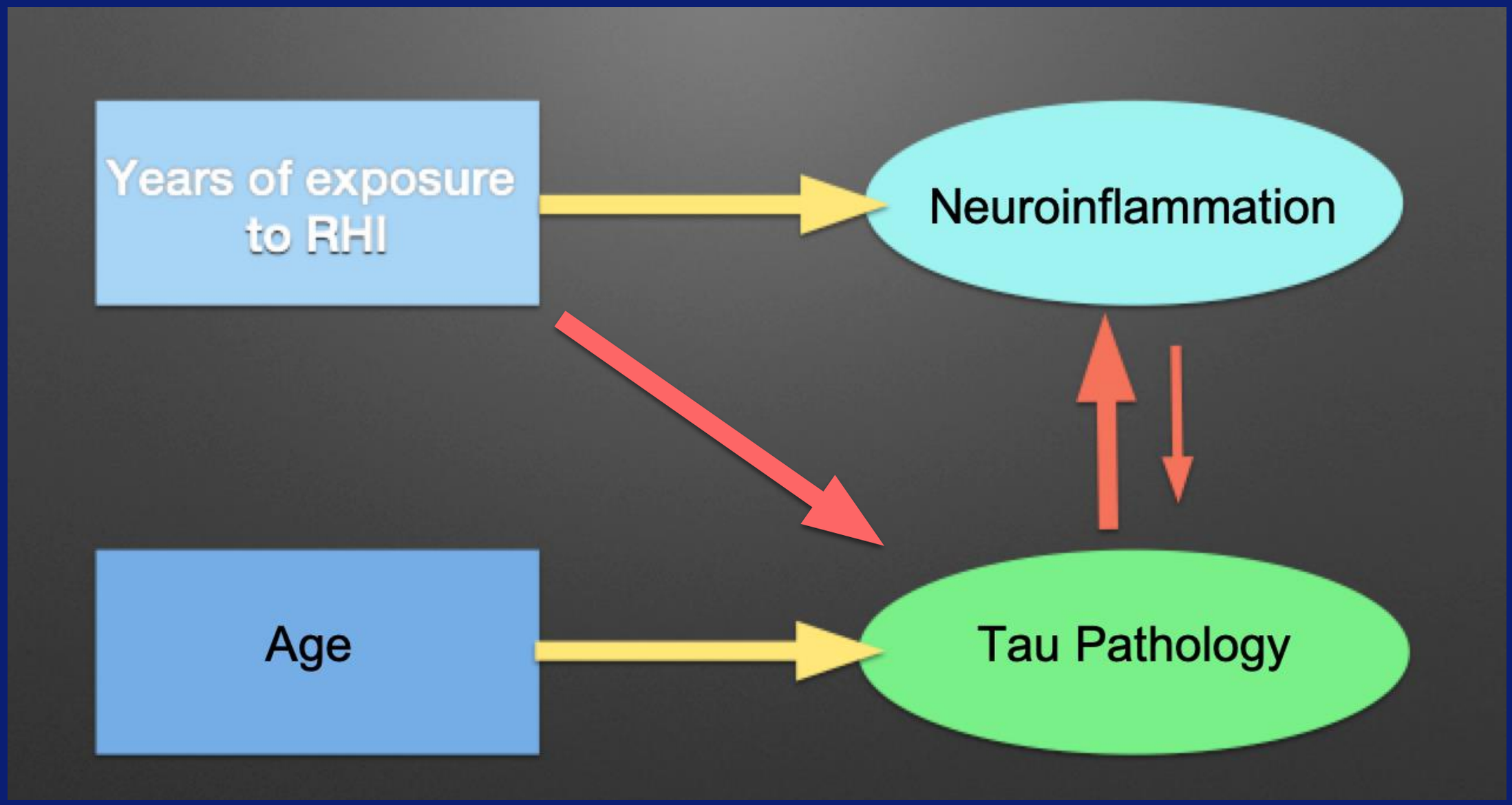
Increased neuroinflammation associated with increased AT8 pathology

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

Cherry J et al,, Acta Neuropathol Comm, 2016

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 NFTs
- White matter rarefaction and 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, JAMA Ny, 2019

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]

366 individuals neuropathologically diagnosed with CTE evaluated to determine the association between CTE stage and:

1. Semi-quantitative assessments of AT8 pathology from 14 brain regions
2. Quantitative digital assessment of AT8 pathology 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

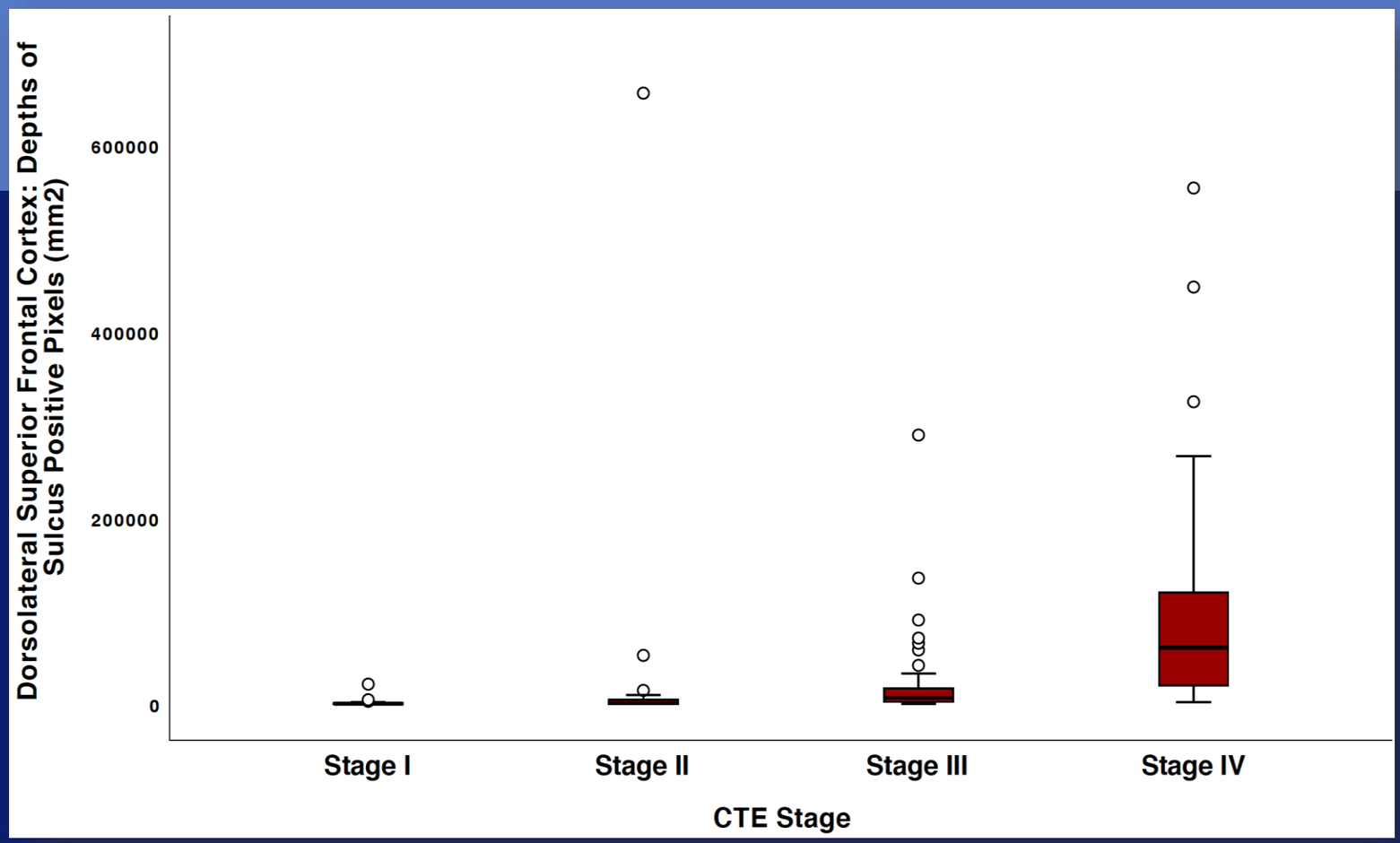
Statistically significant across all 14 brain regions:

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

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

Statistically significant across all brain regions:

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



3. Stages of CTE Correlate with Age at Death

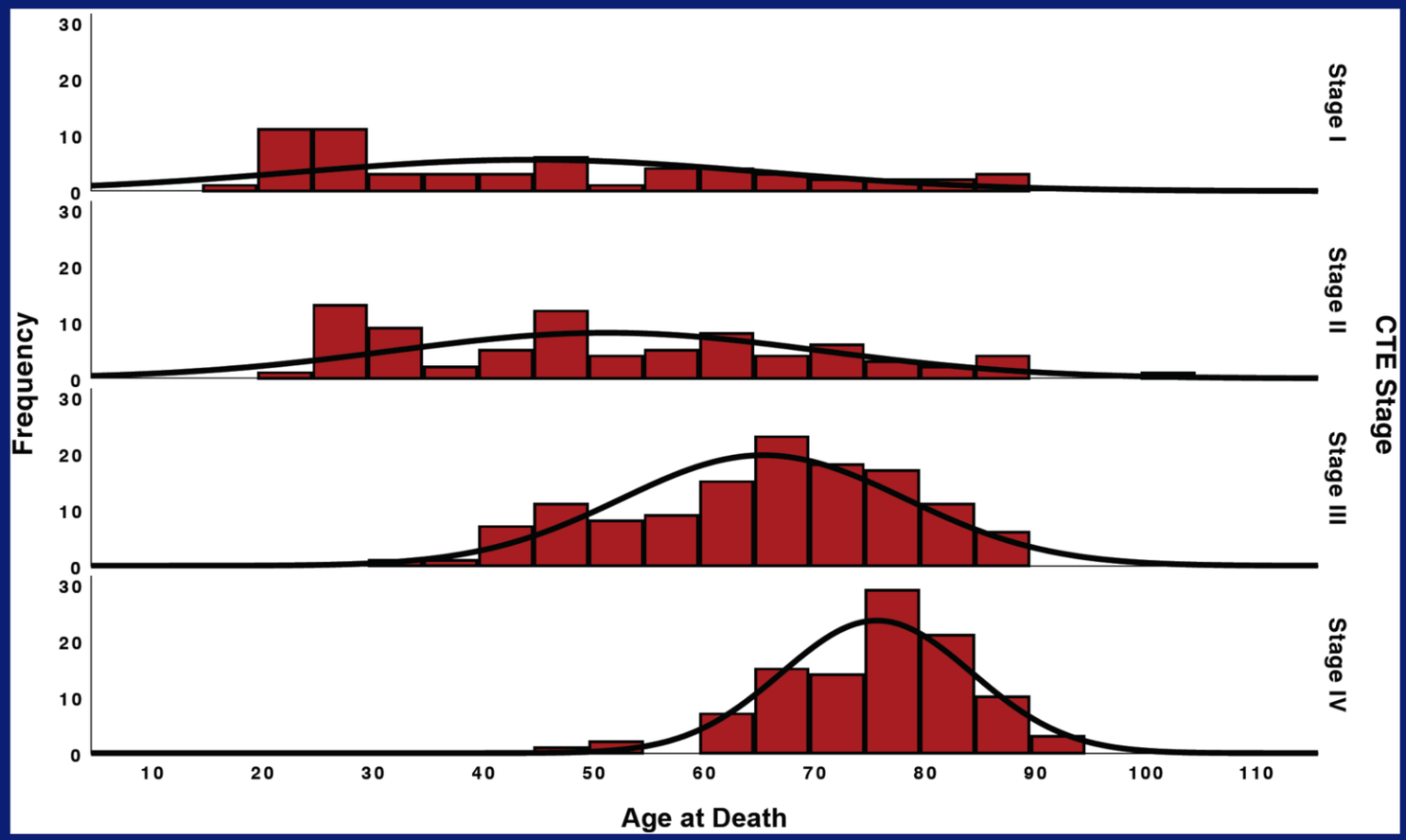
The nature, severity and distribution of CTE-related ptau pathology followed an age-dependent progression

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)

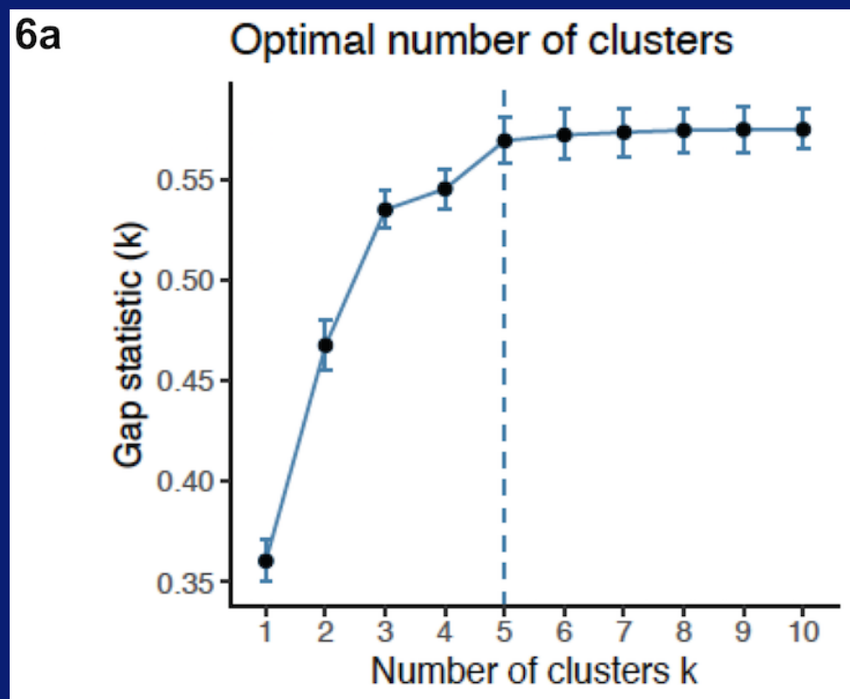
- 216 (60%) determined by consensus panel to have had ante-mortem dementia
- Binary logistic regression controlling for age showed higher CTE stage was associated with increased odds for having dementia (OR = 1.64, 95% CI = 1.19-2.27, p = 0.003); remained after controlling for neurodegenerative and vascular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

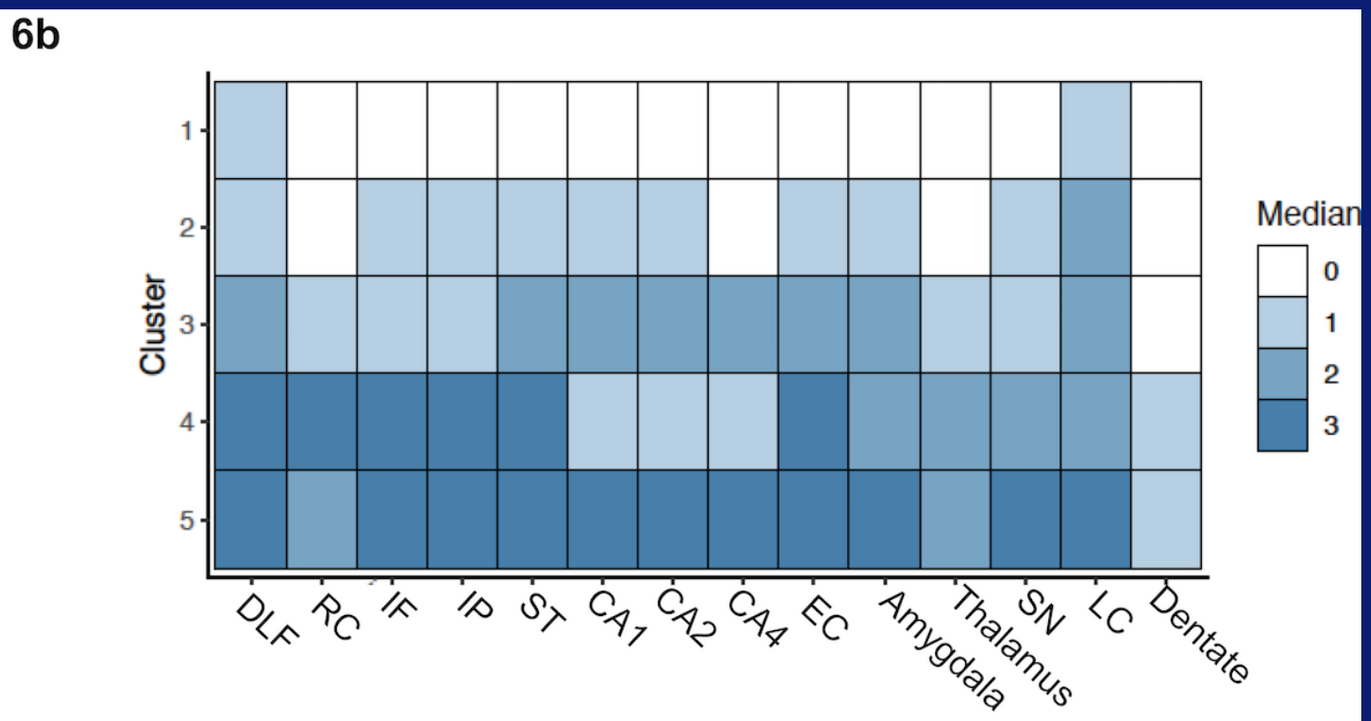
5. Stages of CTE Correlate with Years of American Football Play

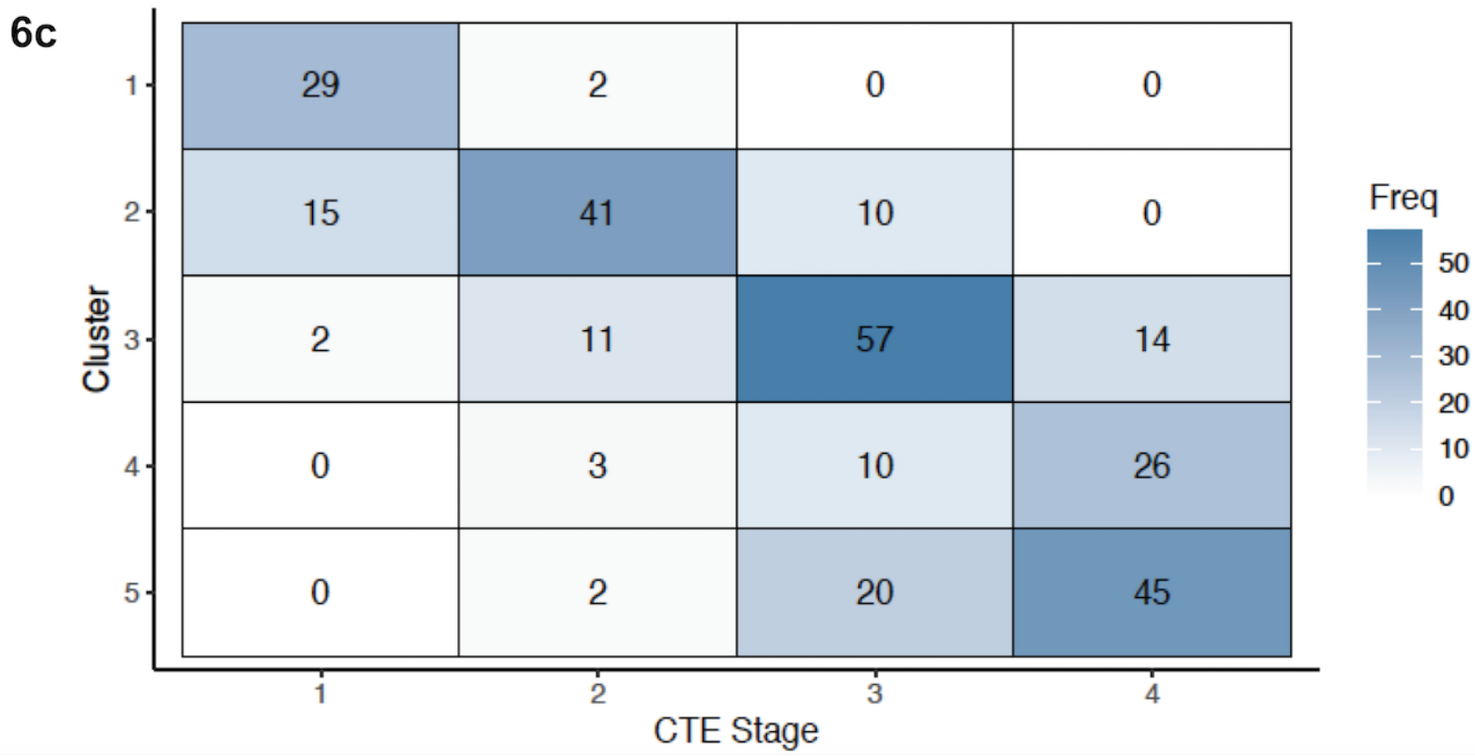
Replicated our past work in this larger sample:

- 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.

K-medoid cluster analysis of the semiquantitative scales of p-tau across 14 regions identified 5 clusters of p-tau that conformed to increasing CTE stage (stage 4 had 2 slightly different clusters), age at death, dementia, and years of American football play.







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,*]

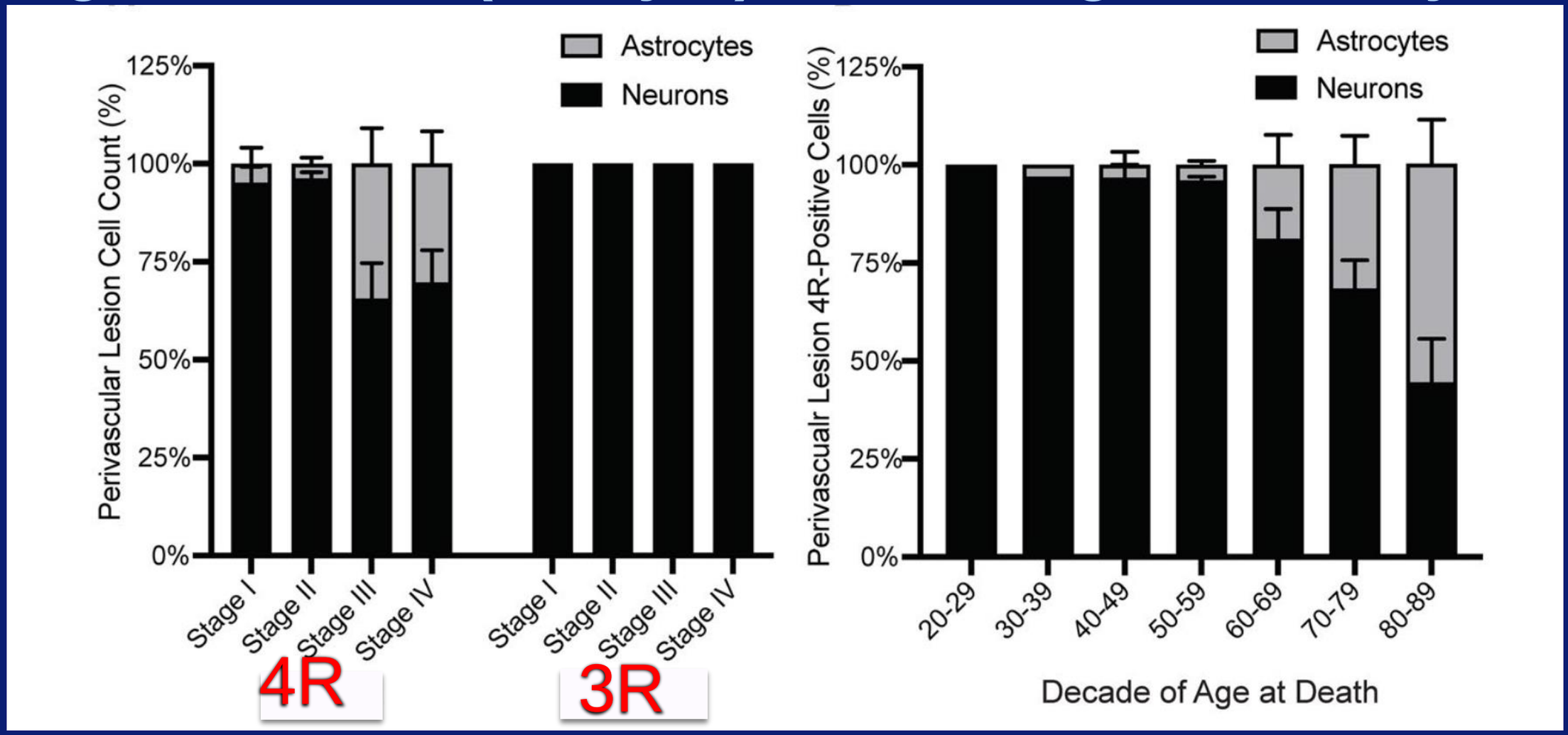
99 male athletes with CTE
range of age at death (20-90 years)
range of disease severity (CTE I-IV)

Quantitative morphologic assessment and multiplex immunofluorescence were used to determine:

- ratio of 4R and 3R tau-containing neurons and astrocytes within the pathognomonic CTE lesion
  at various stages and ages at death.

Cherry et al, Brain Pathology, 2020

The early CTE lesion: 3R and 4R in neurons, 4R predominates.
As age increases (> 60 yrs), increasing 4R astrocytes



- 4R tau cells: CTE stage I 95.8% neurons, stage II 96.1% neurons, stage III 65.6% neurons, CTE IV 69.7% neurons
- 3R was detected only in neurons.
- At age 60–69 years and increasing in each subsequent decade, there is a trend toward increased astrocytes in the CTE lesion

Evolution of tau pathology in CTE

- *CTE tau consists of 3R and 4R*
- *P-tau neurons predominate in early CTE*
- *4R neuronal tau predominates in early CTE*
- *P-tau astrocytes only contain 4R tau*
- *There is a shift from 4R toward 3R tau as the severity of CTE increases*
- *P-tau astrocytes increase with age (not disease severity)*
- *Large increase in astrocytic ptau after age 60*

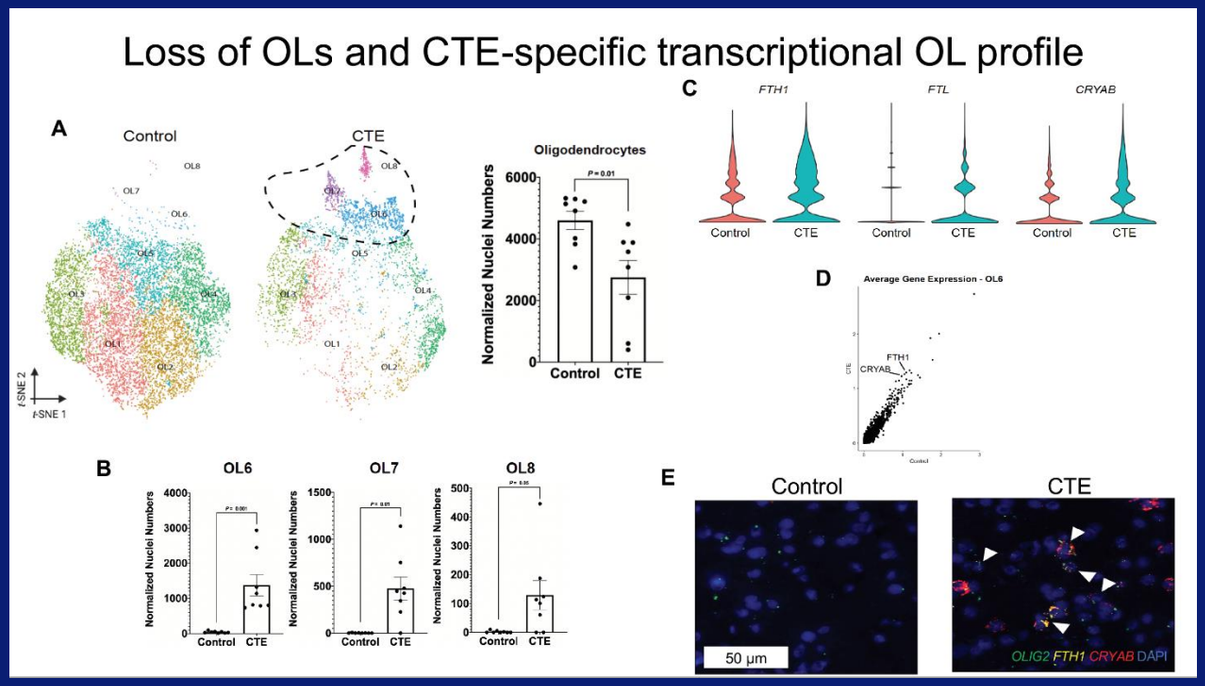
Cherry et al, Brain Pathology, 2020

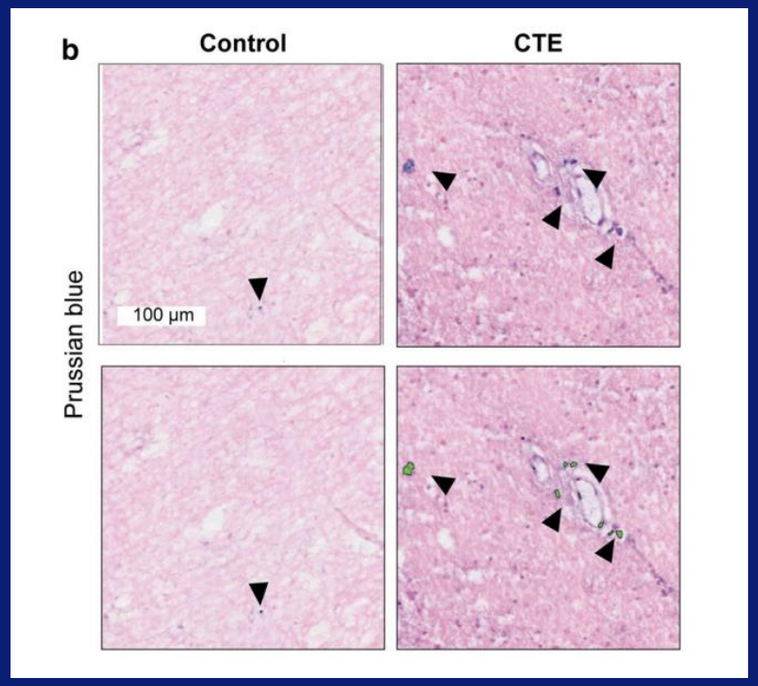
Altered oligodendroglia and astroglia in chronic traumatic encephalopathy

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



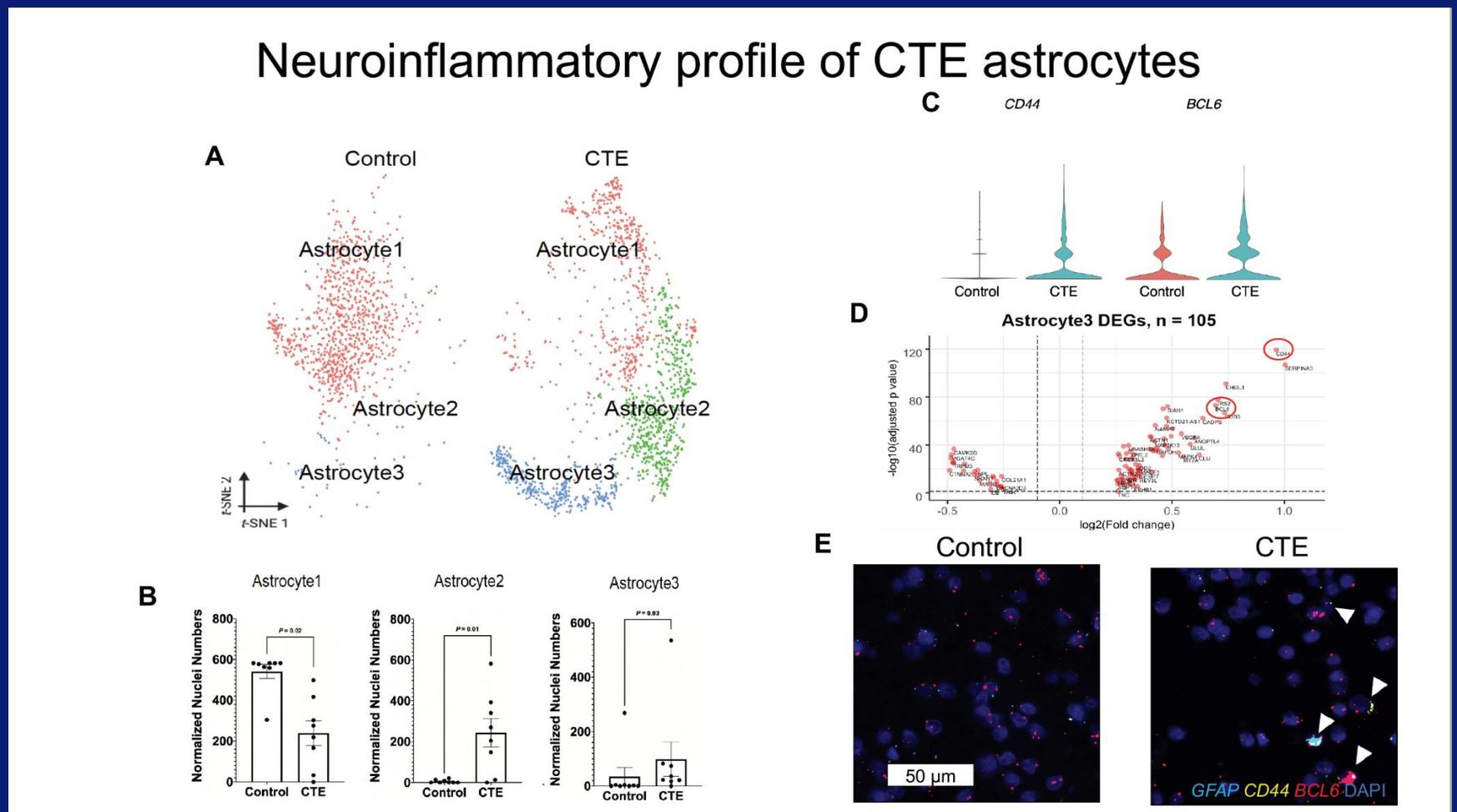


Chancellor et al, Acta Neuropath 2021

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]

- Total astrocyte number indistinguishable between CTE and control samples, but transcripts associated with neuroinflammation were elevated in CTE astrocytes compared to controls.



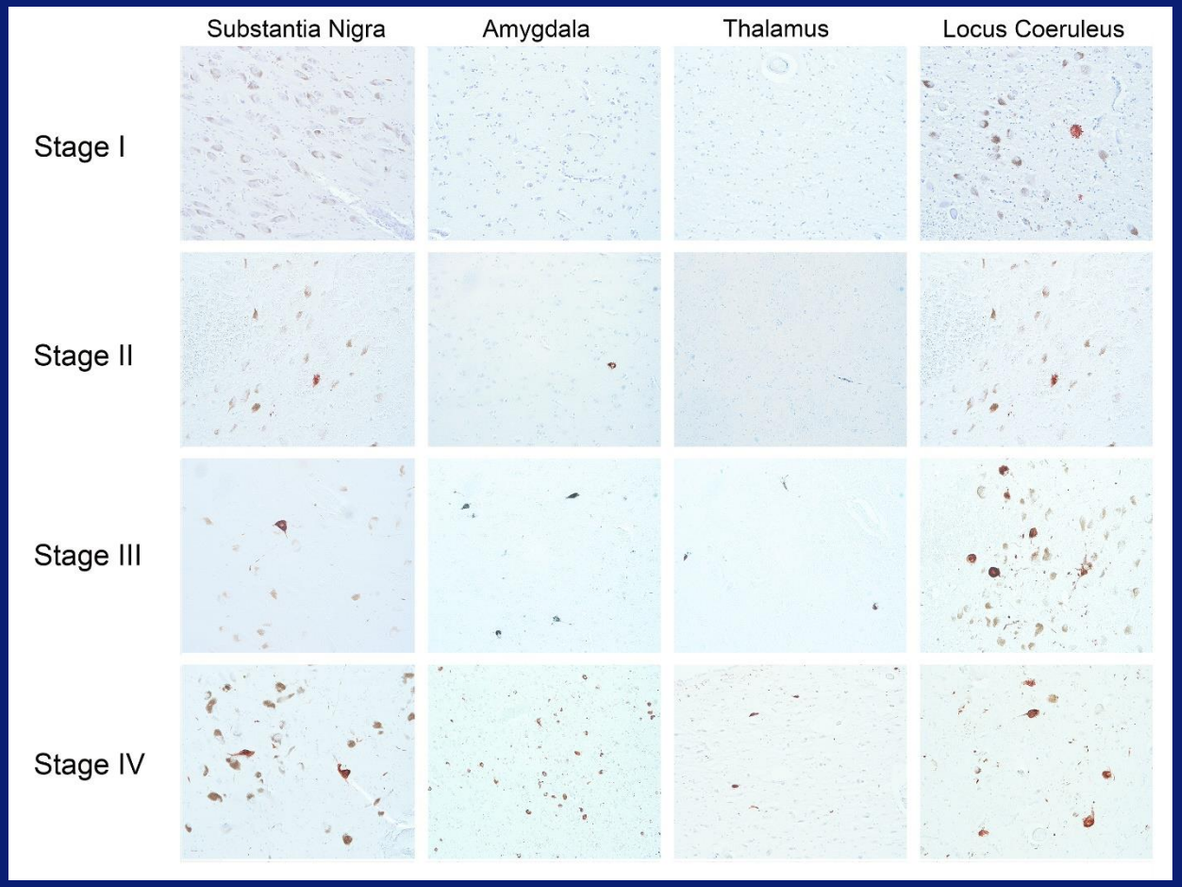
Chancellor et al, Acta Neuropath 2021

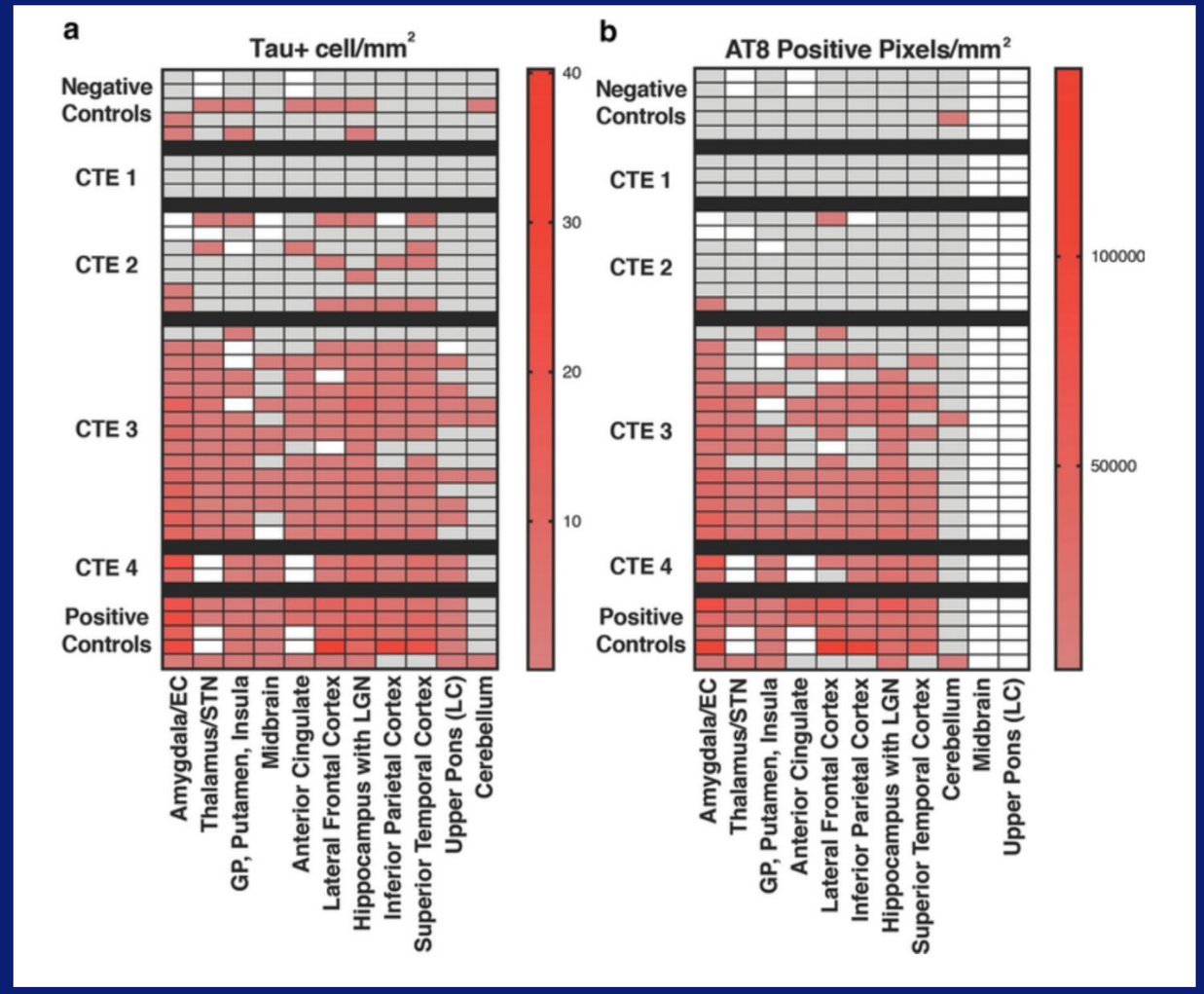
Tau seeding in chronic traumatic encephalopathy parallels disease severity

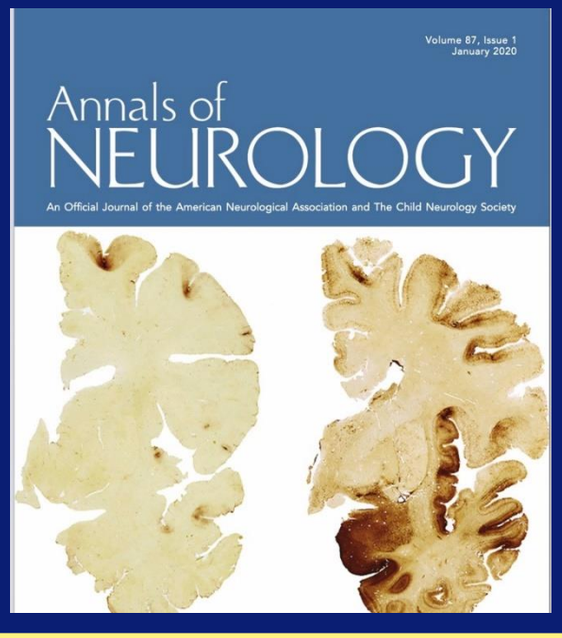
S Kaufman, S Svirsky, J Cherry, A McKee, M Diamond.

Acta Neuropathologica 2021, in press

Using a biosensor assay to independently quantify tau seeding compared to AT8 phospho-tau pathology in 11 brain regions from 27 patients with CTE, 5 with other tauopathies, and 5 negative controls, tau seeding was detected primarily in CTE stage III and IV and restricted to the amygdala, thalamus, and basal ganglia.
The relationship of seeding to the staging of the disease remains unclear.







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]

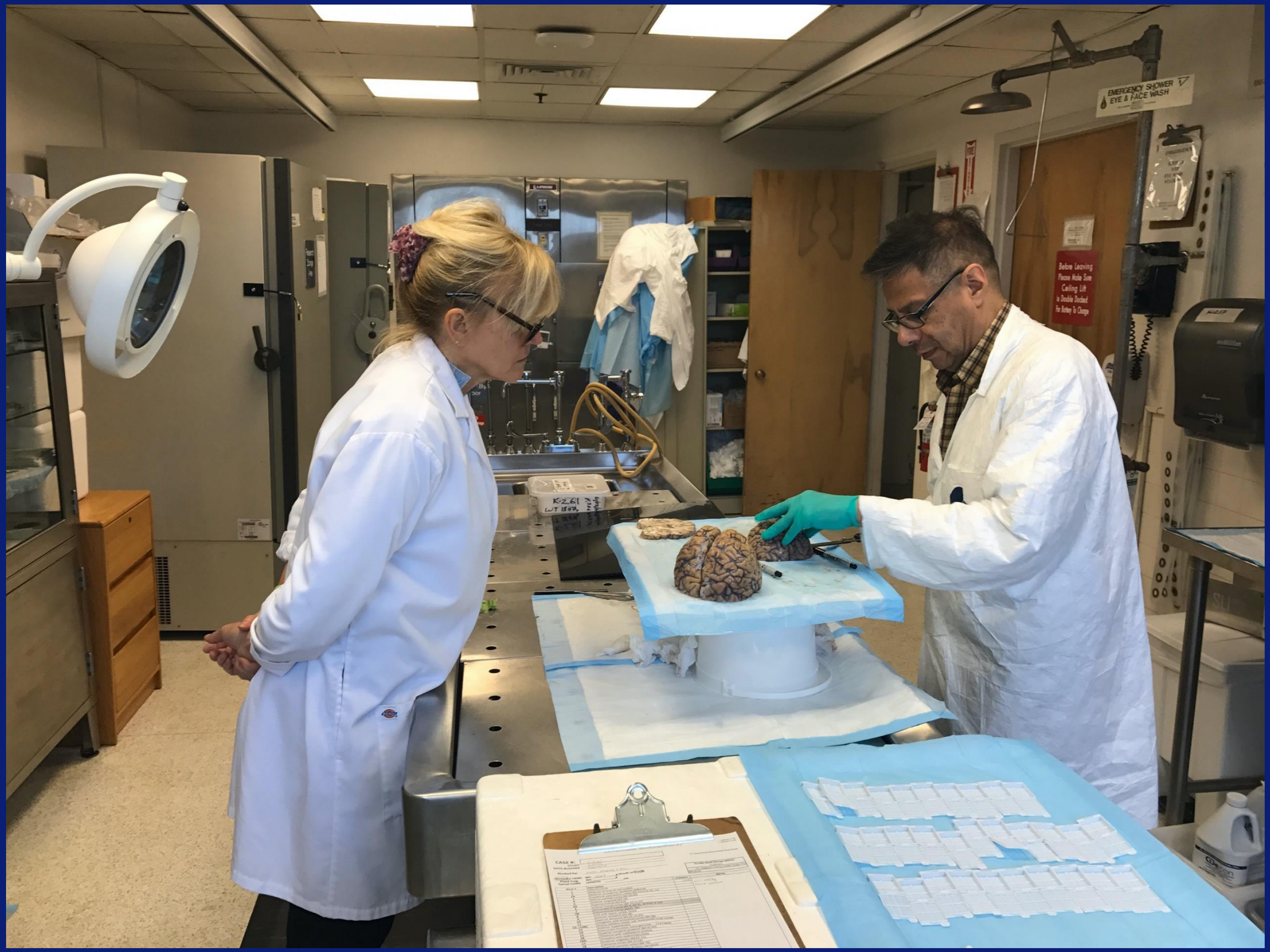
Among 266 football players:

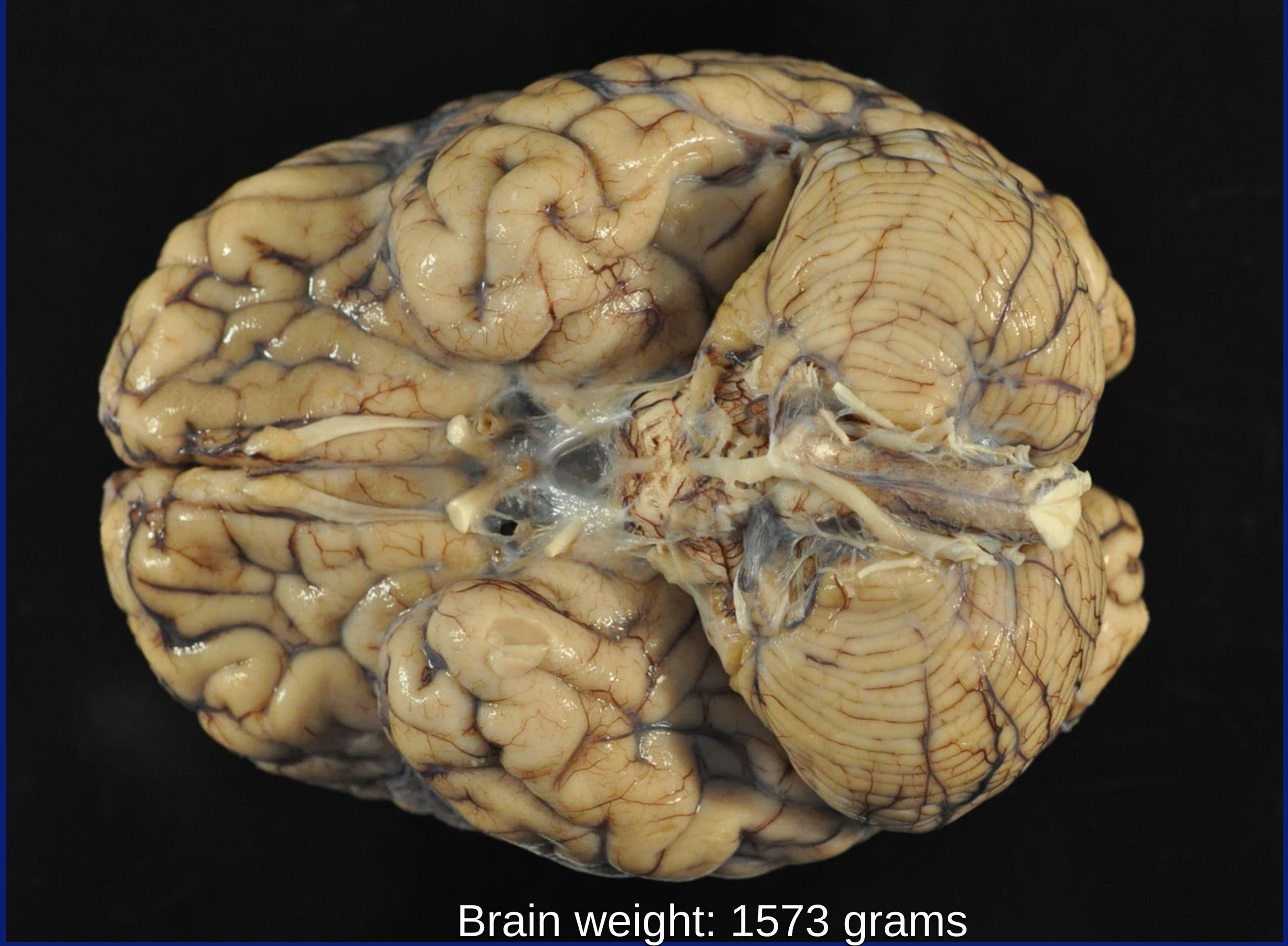
- Risk of developing CTE increased by 30 percent per year played
- For each 2.6 additional years of football, odds of developing CTE doubled
- Among those w CTE, for each additional 5.3 yrs, the odds for severe CTE doubled
- Those who played < 4.5 yrs were 10 X less likely to develop CTE than those who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

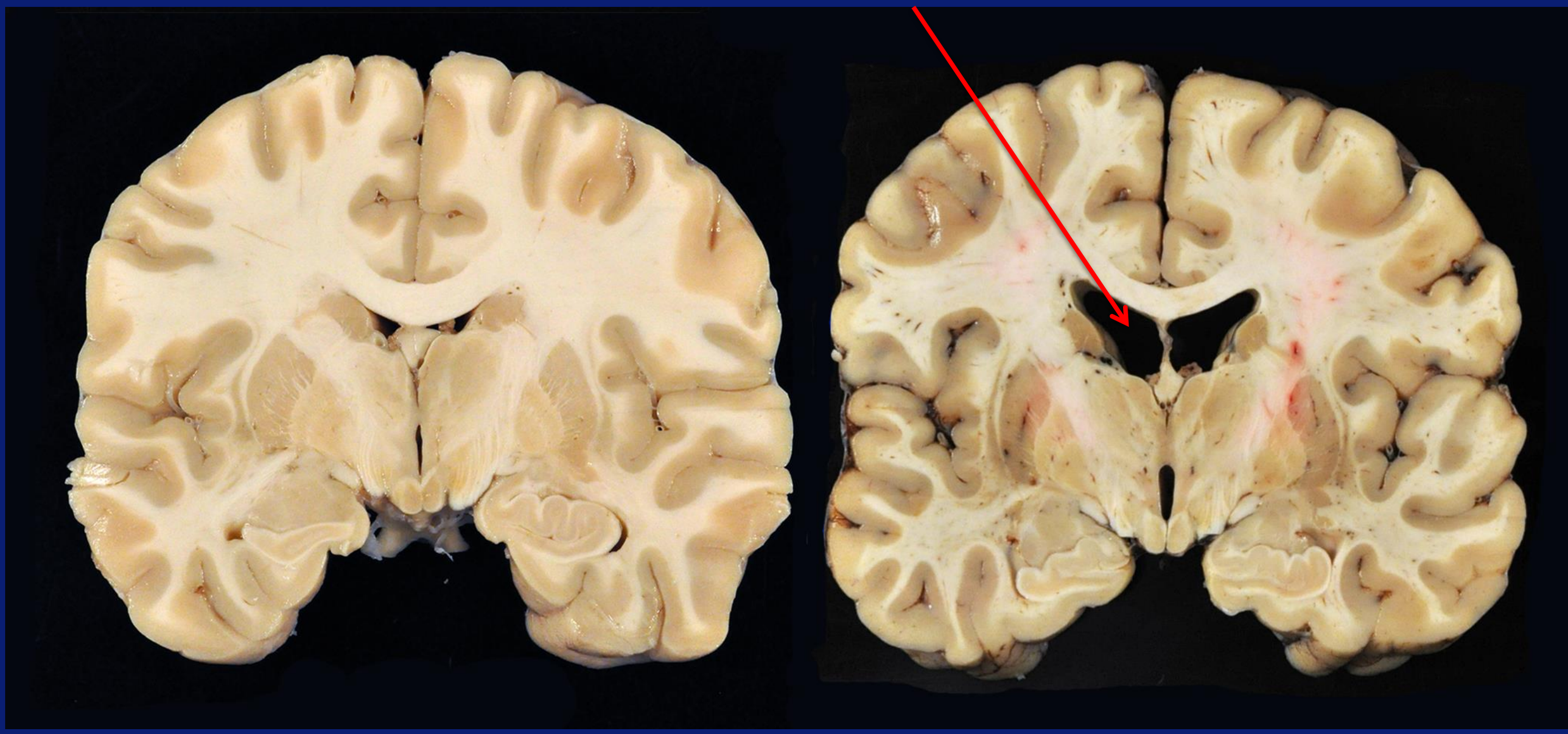
Aaron Hernandez:
27 year old NFL player


EMERGENCY SHOWER
EYE & FACE WASH
Before Leaving
Please Make Sure
Ceiling Lift
is Double Docked
for Battery To Charge



Brain weight: 1573 grams

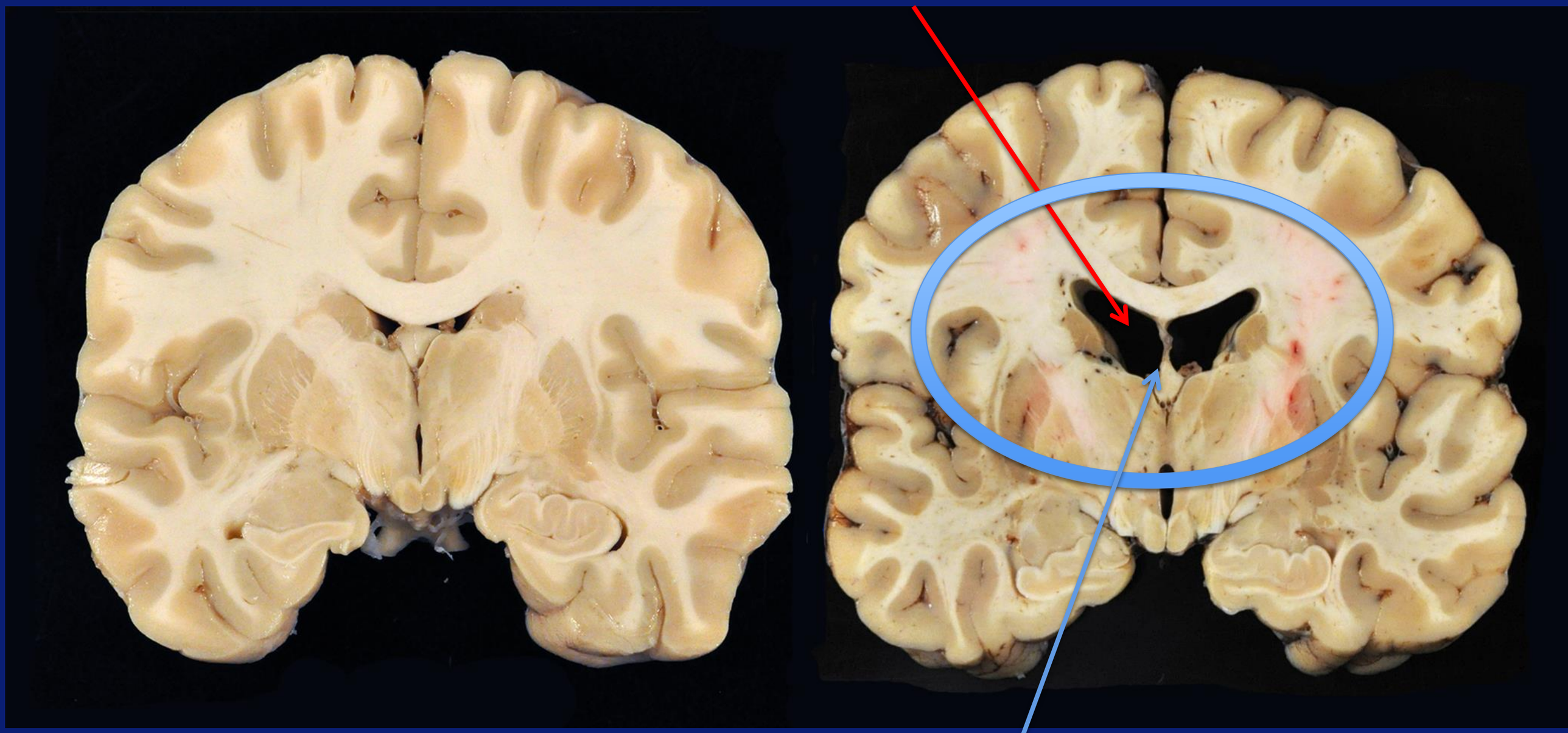
Ventricular enlargement



Normal 27 year old

Aaron Hernandez

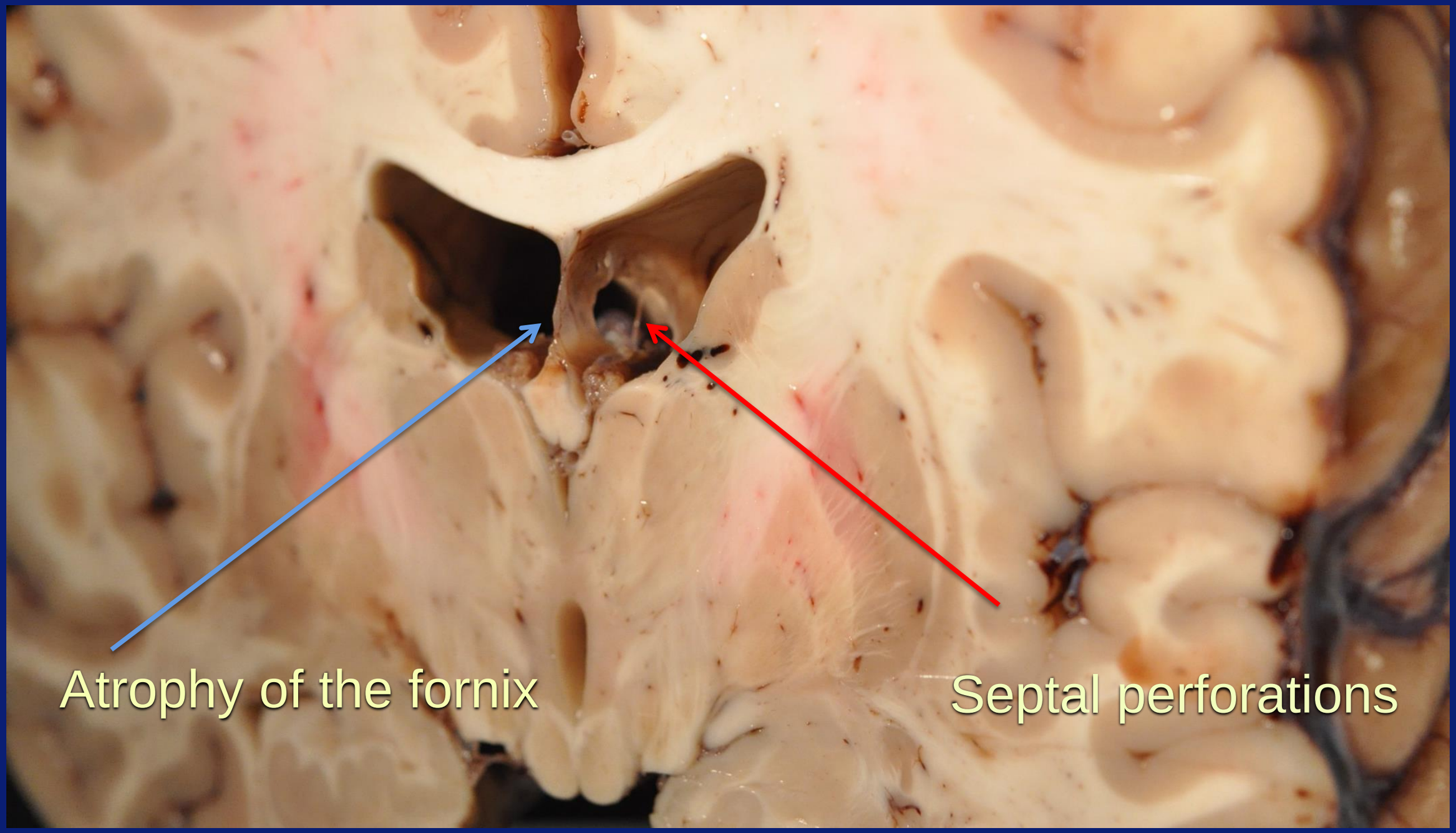
Ventricular enlargement



Normal 27 year old

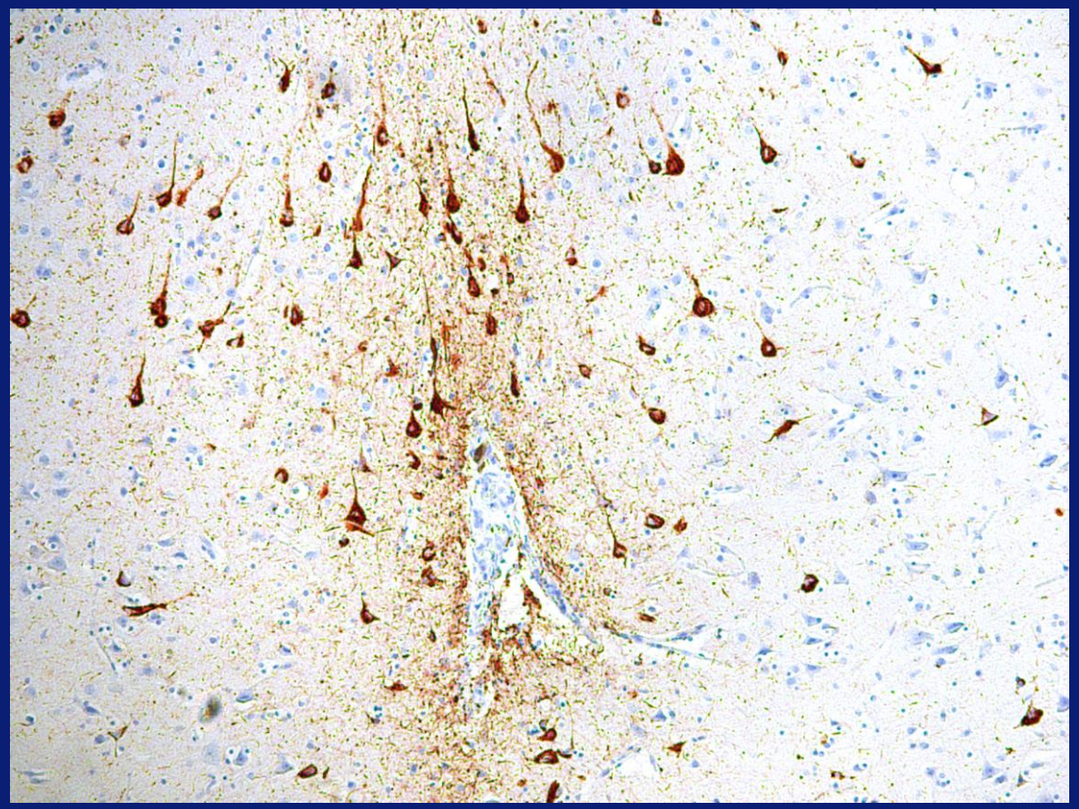
Aaron Hernandez

Atrophy of the fornix

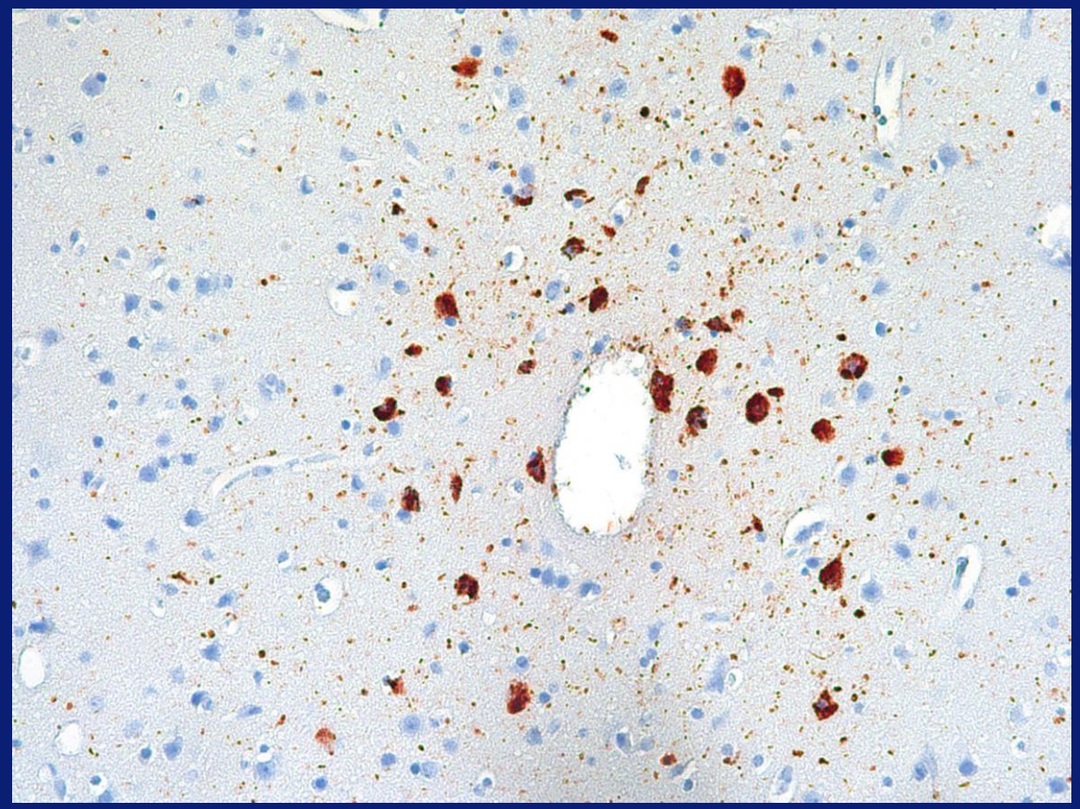


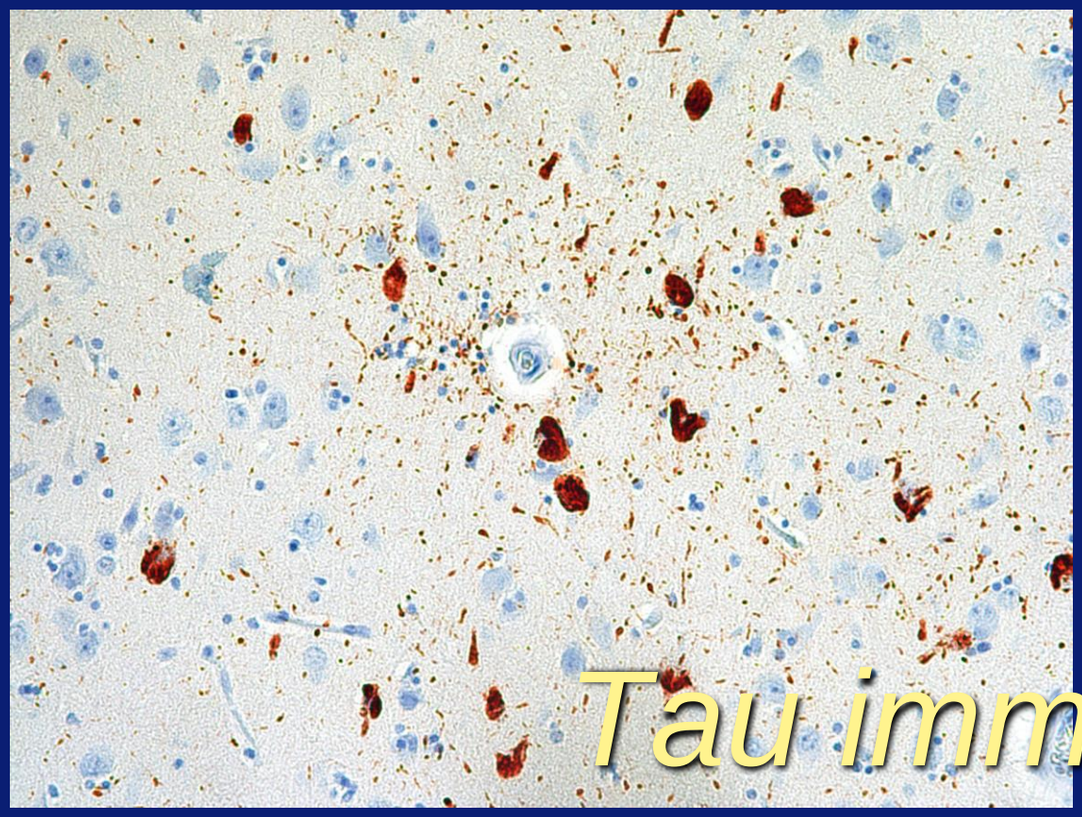
- Neuropathological abnormalities of this magnitude are unusual in young individuals with CTE.
- Among 348 donors neuropathologically diagnosed with CTE in the UNITE Brain Bank with recorded ratings for septal fenestrations, approximately 30% had evidence of septal fenestrations.
- This case demonstrates the first instance of CTE with septal fenestrations under the age of 40 in our experience.

Superior frontal cortex

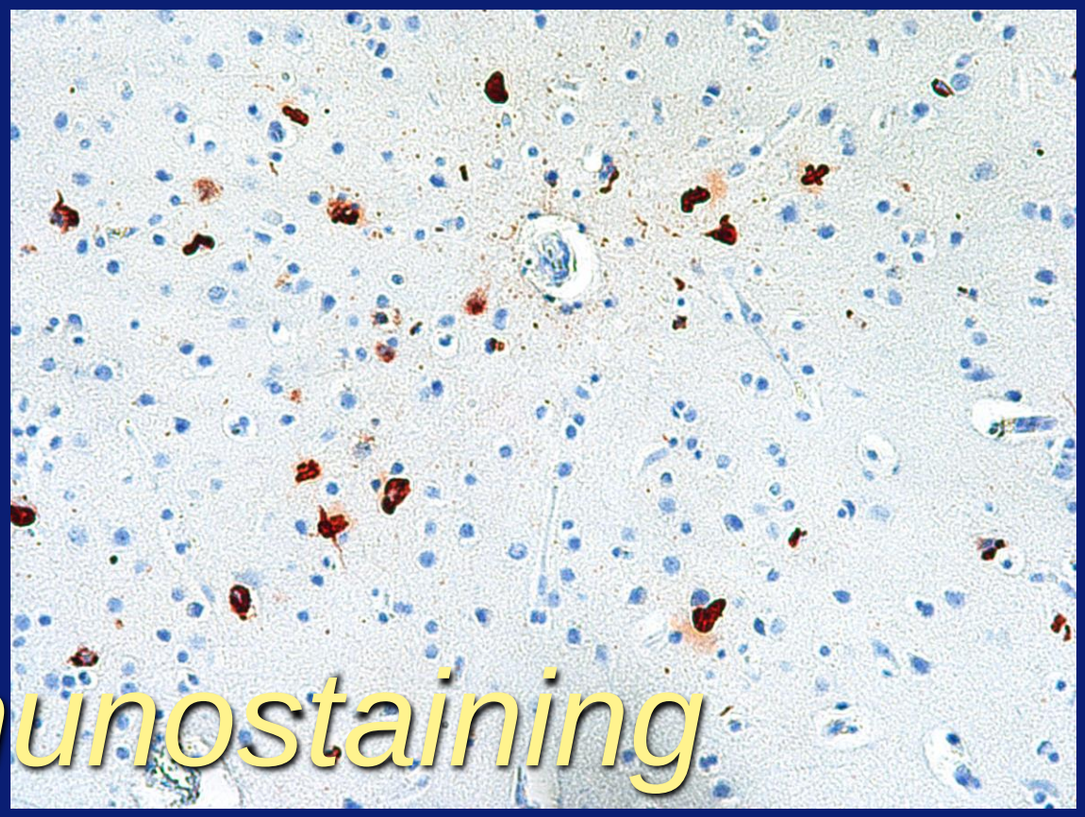


Temporal cortex





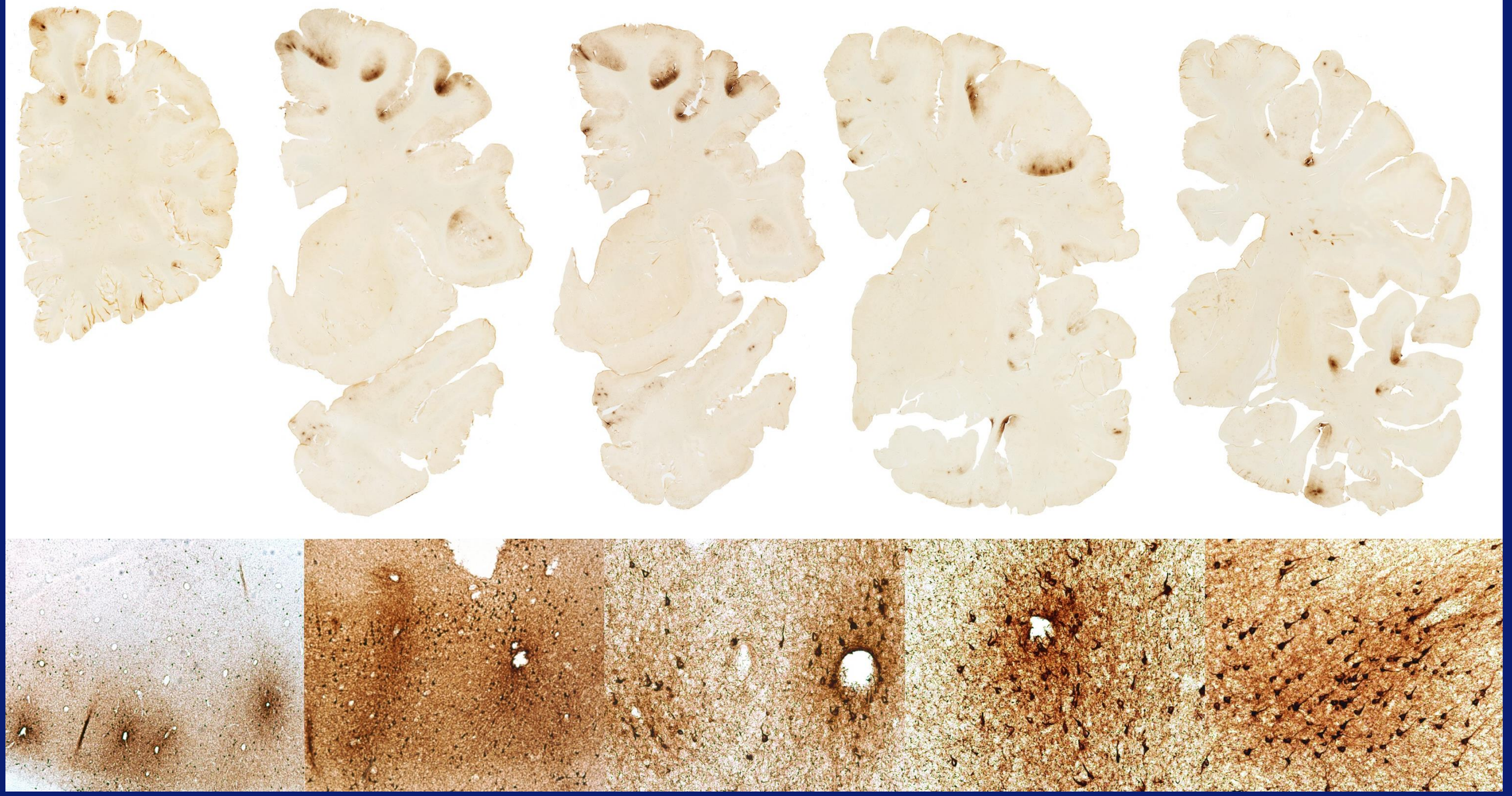
Tau immunostaining



Amygdala

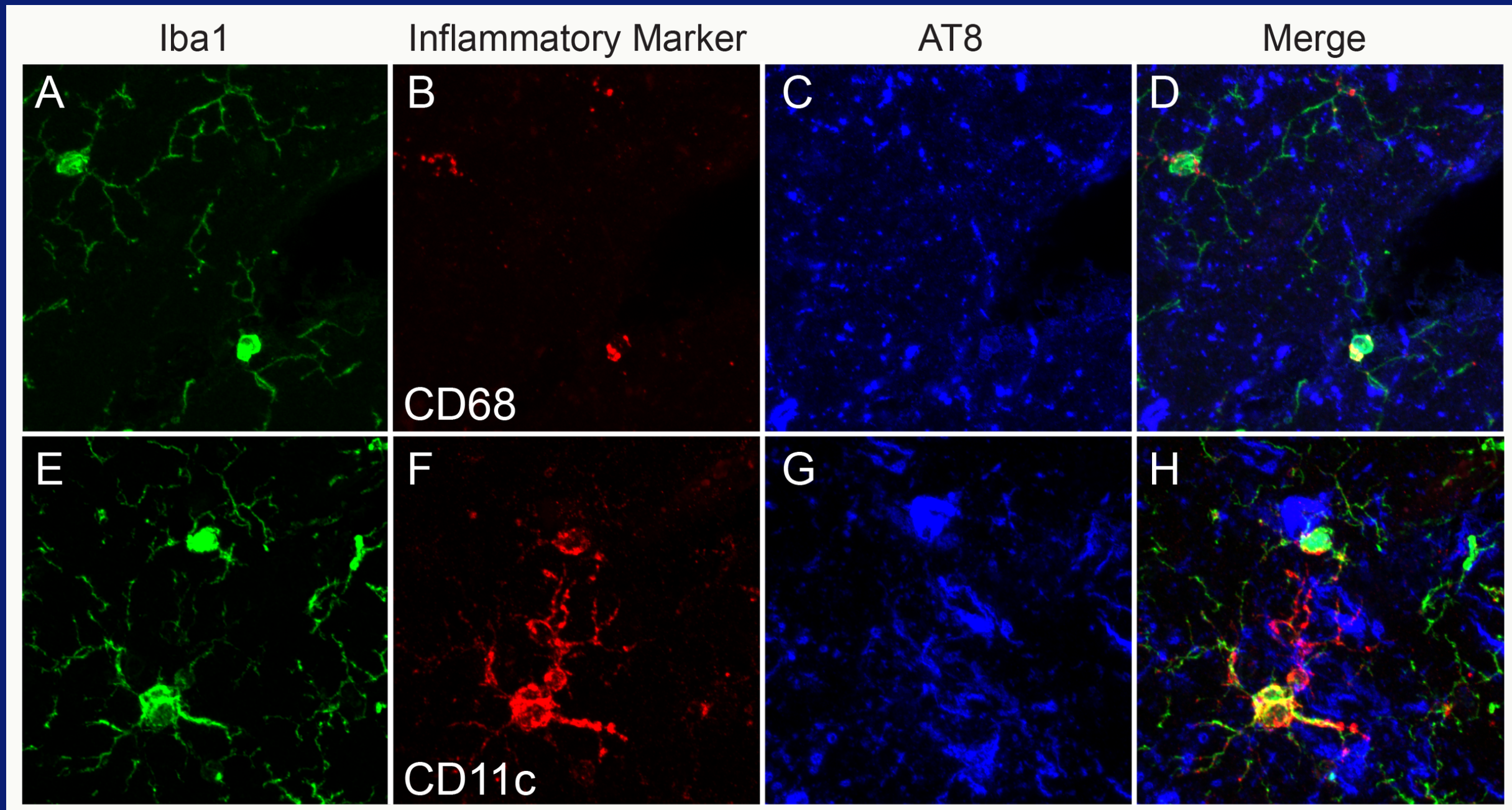
Inferior parietal

Aaron Hernandez

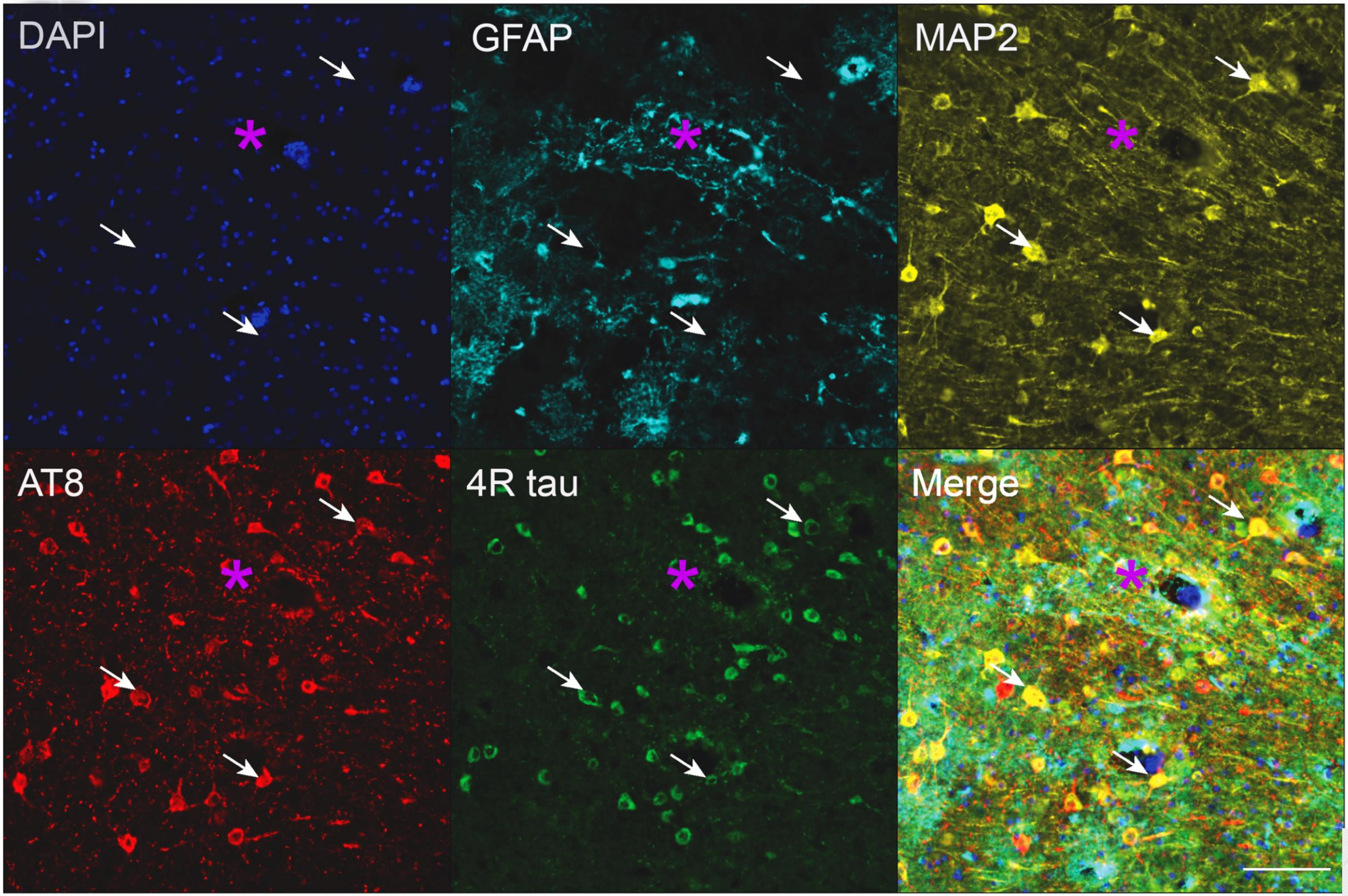


CTE, stage III:
with severe frontal lobe involvement
moderate involvement of temporal lobe and amygdala

Inflammatory microglia are present within the CTE lesion



P-tau aggregates in neurons and neuronal processes in CTE lesions in young individuals
4R tau is the predominant isoform



Clinicopathological case series: 158 brain donors ≤ age 34 years

- 158 brains from contact sport athletes 34 years or younger at the time of death, mean 24.6 years

- 78 (49%) diagnosed with CTE:
  Stage 1 n = 43 (55.1%)
  Stage 2 n = 32 (41.0%)
  Stage 3 n = 3 (3.8%)

  80 negative for CTE

-

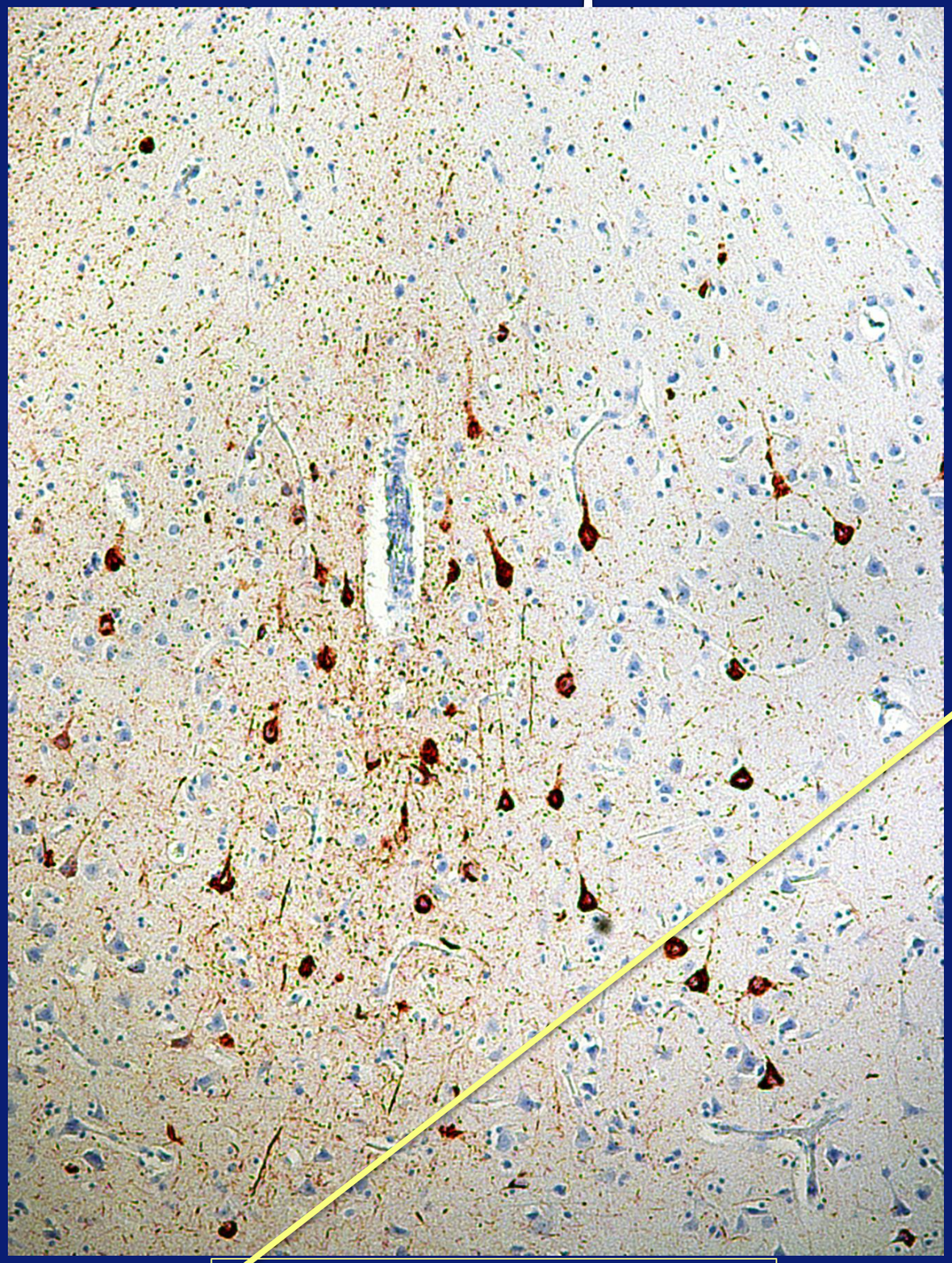
Young CTE

Demographics	Total sample (n=158)		No CTE (n=80)		CTE (n=78)	
Age of death	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years	24.63	5.33	22.11	5.44	27.19	3.80
Sex	**n**	**%**	**n**	**%**	**n**	**%**
Female	6	3.8	6	7.5	0	0
Primary cause of death	**n**	**%**	**n**	**%**	**n**	**%**
Suicide	71	44.9	40	50	31	39.7
Accidental Overdose	17	10.8	9	11.3	8	10.3
Injury	14	8.9	6	7.5	8	10.3
Cardiovascular disease	4	2.5	2	2.5	2	2.6
Infection	3	1.9	0	0	3	3.8

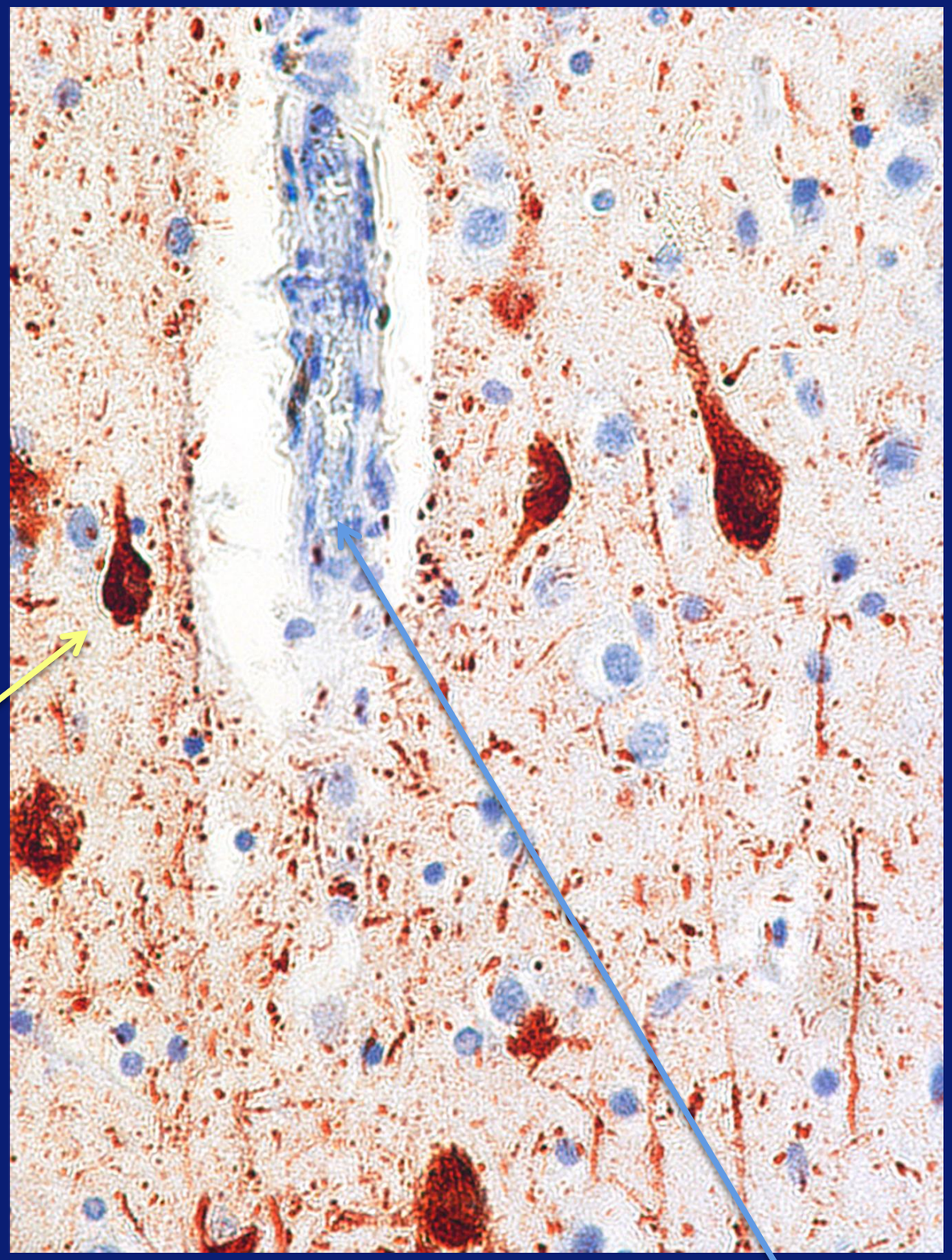
Young CTE

Demographics	Total sample (n=158)		No CTE (n=80)		CTE (n=78)	
Athletic History						
Primary sport played	**n**	**%**	**n**	**%**	**n**	**%**
American football	107	68	45	56	62	80
Ice Hockey	20	13	10	13	10	13
Soccer	12	8	9	11	3	4
Wrestling	7	4	6	8	1	1
Rugby	2	1	2	3	0	0
Other exposure	3	2	2	3	1	1
Duration of American Football play	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years	9.77	4.70	7.97	4.17	11.18	4.64
Highest level of sport play	**n**	**%**	**n**	**%**	**n**	**%**
Professional	25	16	3	4	22	28
Semi-professional/Juniors	10	6	7	9	3	4
College	38	24	9	11	29	37
High school	65	41	45	56	20	26
Youth	16	10	12	15	4	5

Superior frontal cortex



Ptau tangles



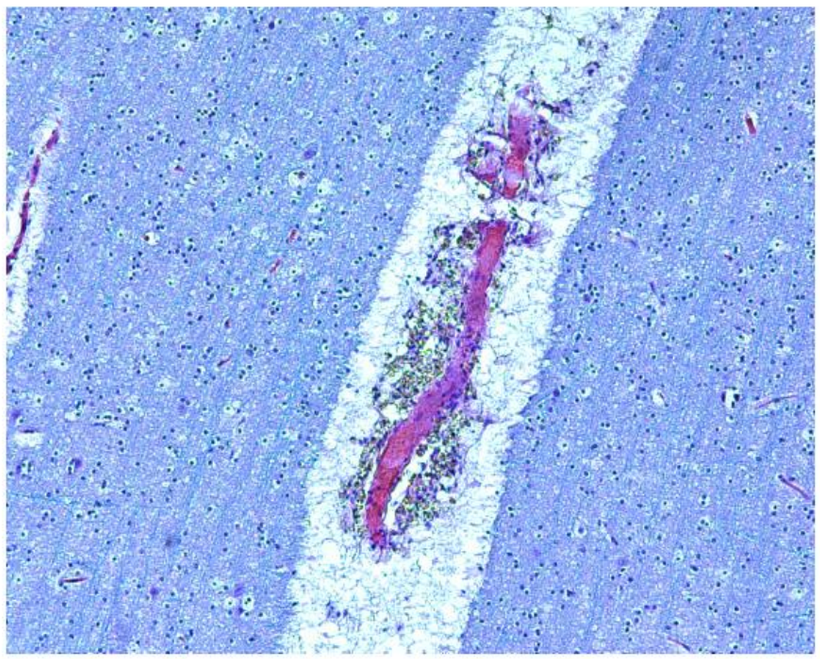
blood vessel

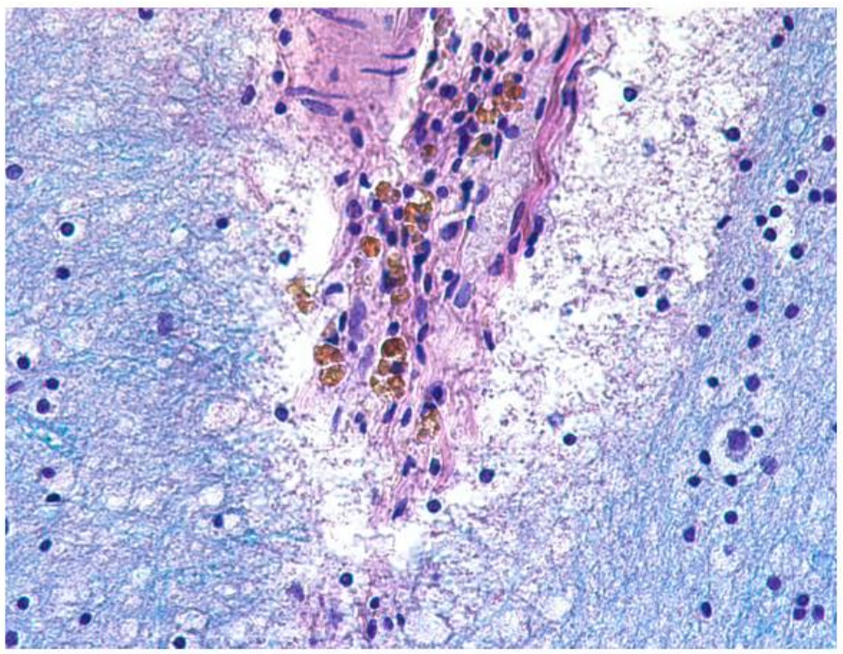
Fig. Association Between CTE Stage and Regional P-tau Progression. Heat map of semi-quantitative p-tau pathology (0 to 3, 3 most severe) for 14 brain regions

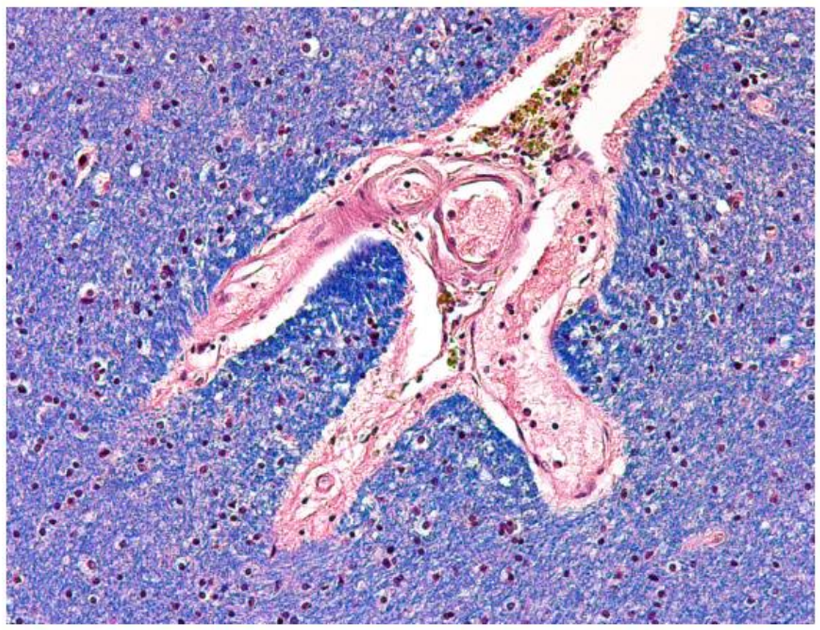
CTE Stage	N (%)	DLF	RC	IF	IP	ST	CA1	CA2	CA4	EC	Amygdala	Thalamus	SN	LC	Dentate
0	79 (55.6)	0.09	0.00	0.03	0.03	0.03	0.03	0.00	0.00	0.08	0.05	0.00	0.00	0.16	0.00
I	35 (24.6)	1.06	0.23	0.28	0.50	0.48	0.14	0.03	0.07	0.29	0.17	0.06	0.03	0.64	0.00
II	25 (17.6)	1.88	1.04	1.18	1.35	1.74	0.68	0.21	0.52	1.33	1.23	0.63	0.54	1.73	0.04
III	3 (2.1)	3.00	2.00	1.00	2.00	2.33	2.00	0.33	1.33	1.67	2.33	1.00	1.33	2.33	0.00
Total	142	0.77	0.28	0.31	0.40	0.50	0.23	0.06	0.15	0.41	0.34	0.16	0.13	0.62	0.01

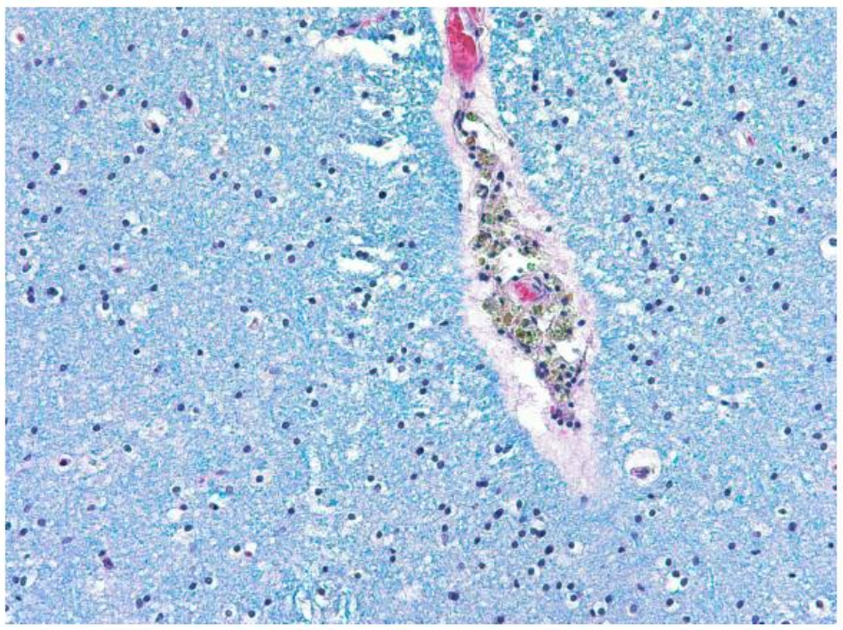
CTE in subjects ≤ 34 years

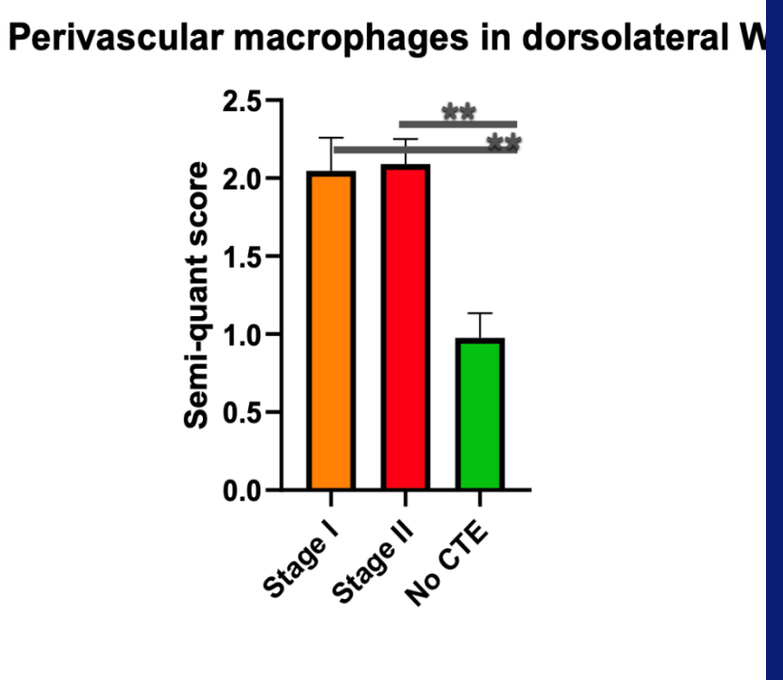
- Pre**lim**inary results show that there are significantly more perivascular hemosiderin-laden macrophages in the frontal and temporal white matter in CTE compared to non-CTE

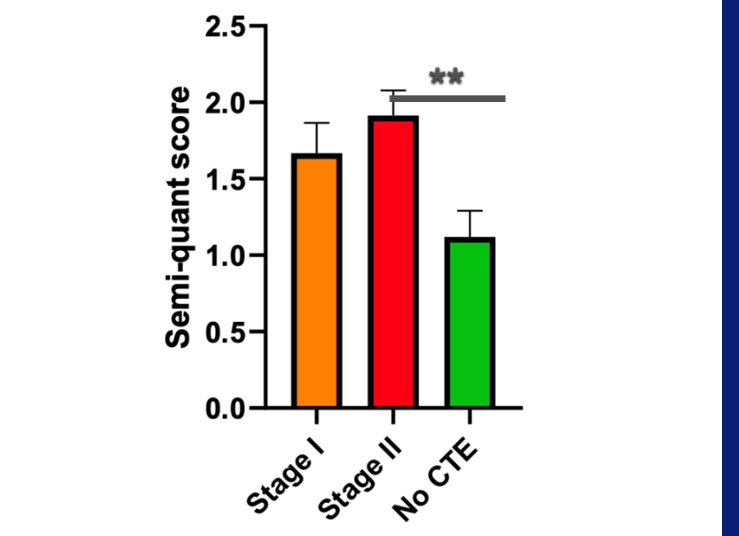






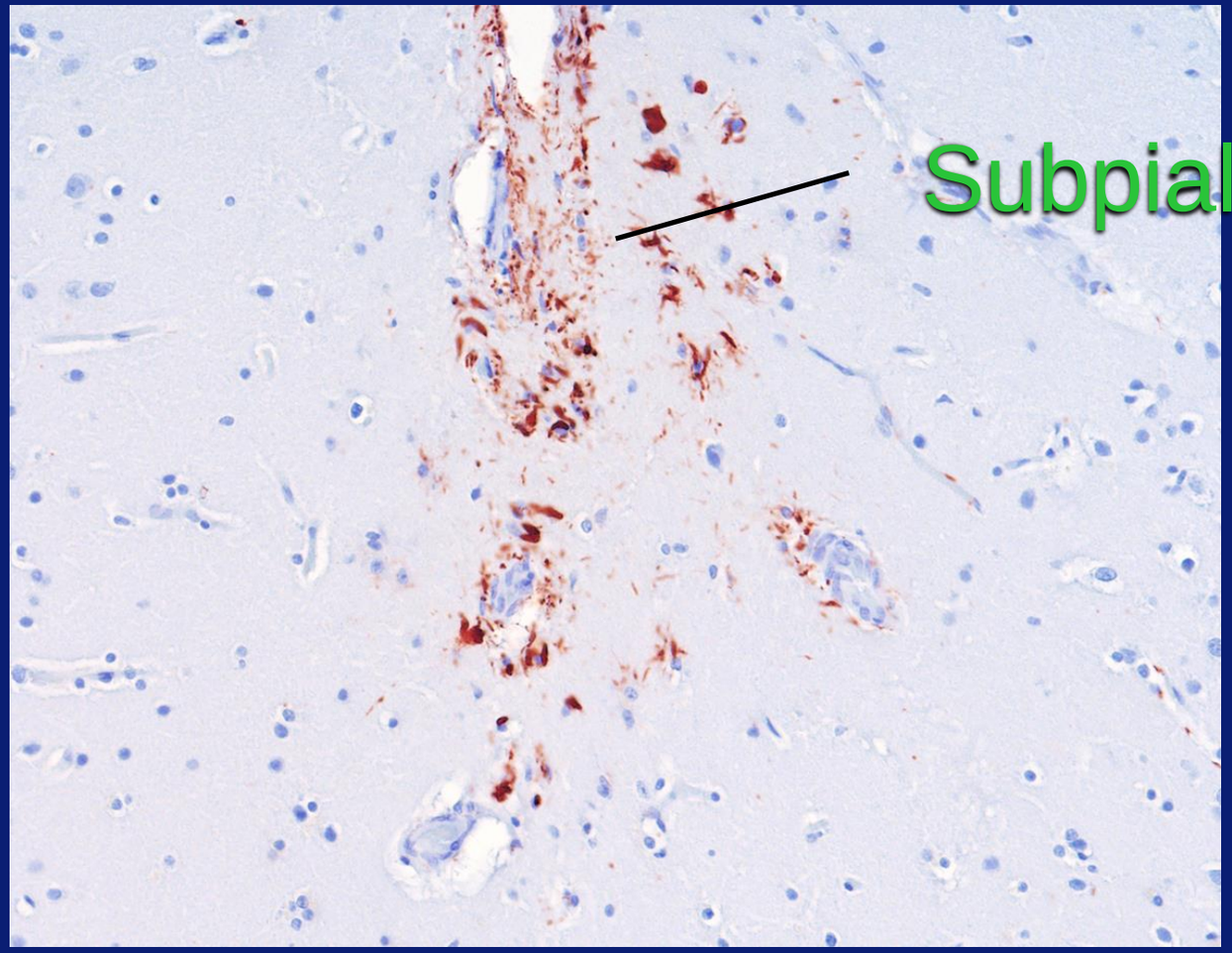






Subpial TSA at sulcal depths

- Only 19% of the young subjects with CTE had p-tau thorn-shaped astrocytes (TSA) in the glial limitans at the depth of the sulcus; subpial TSA were not found in non-CTE subjects



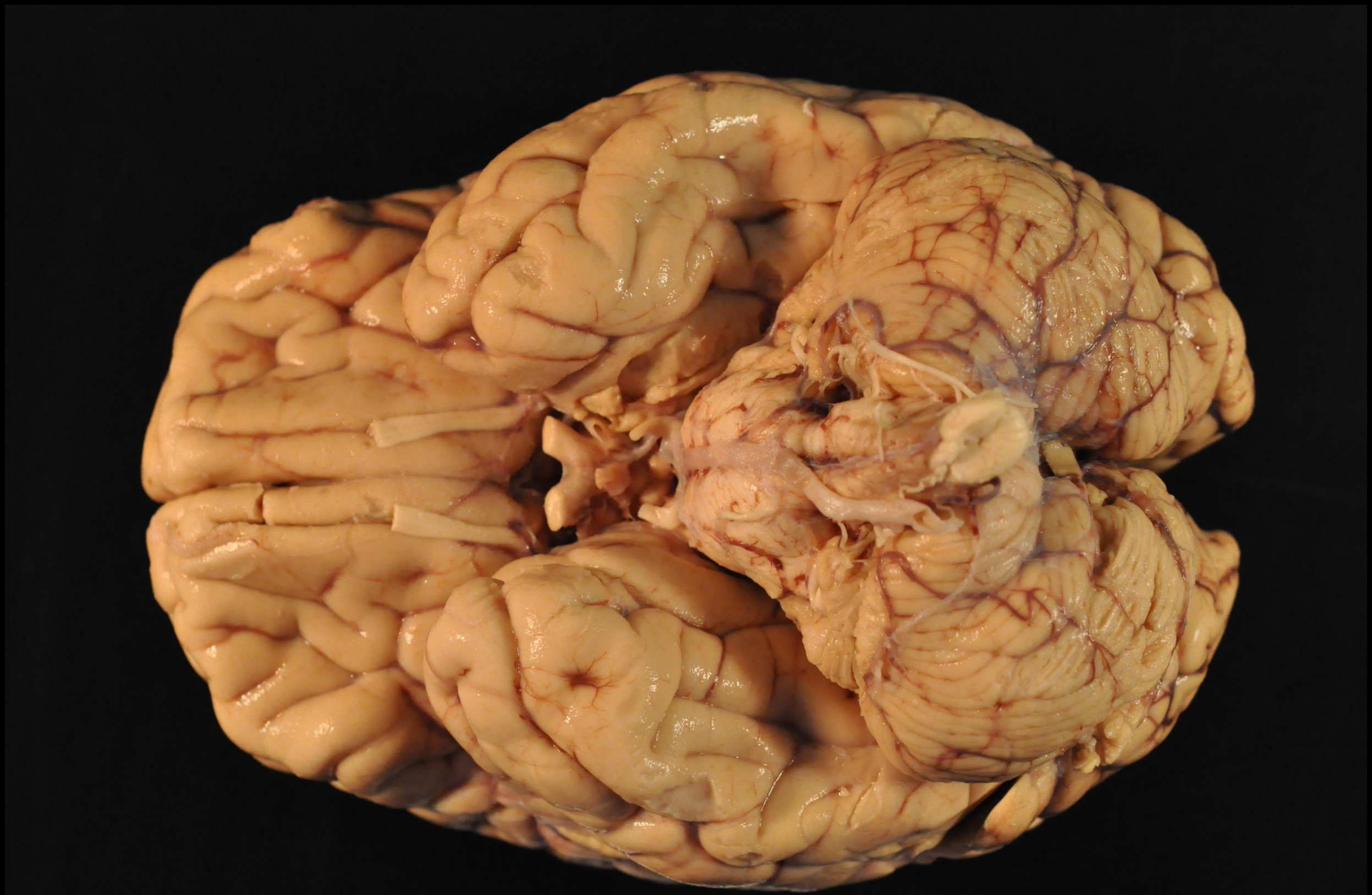
CTE is a Primary Tauopathy

- None of the 158 young subjects, with or without CTE, showed any immunopositivity for Aß, either as plaques or amyloid angiopathy.

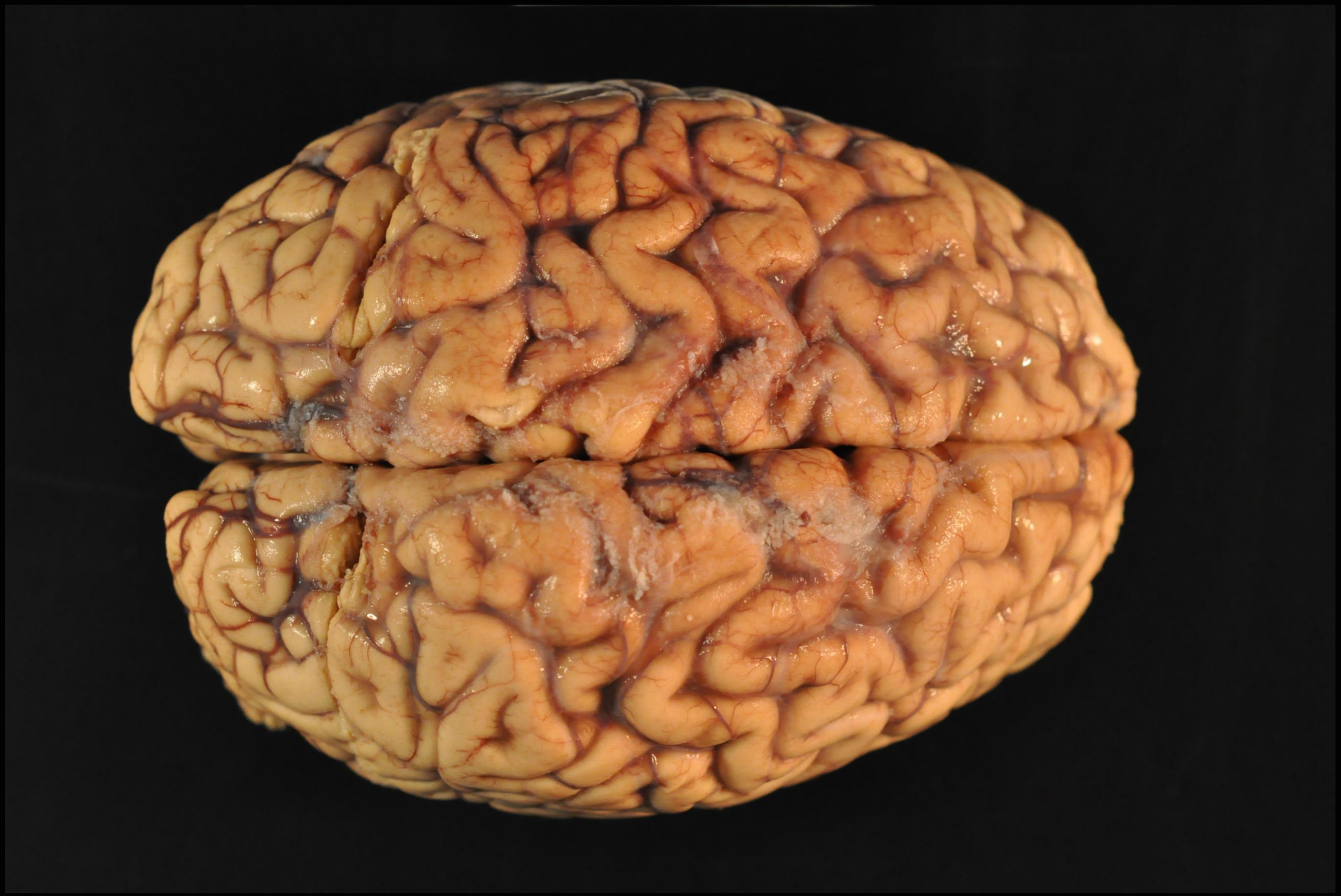
- One subject had a-synuclein Lewy bodies: 27-year-old with Stage 2 CTE - rare LB in the medulla

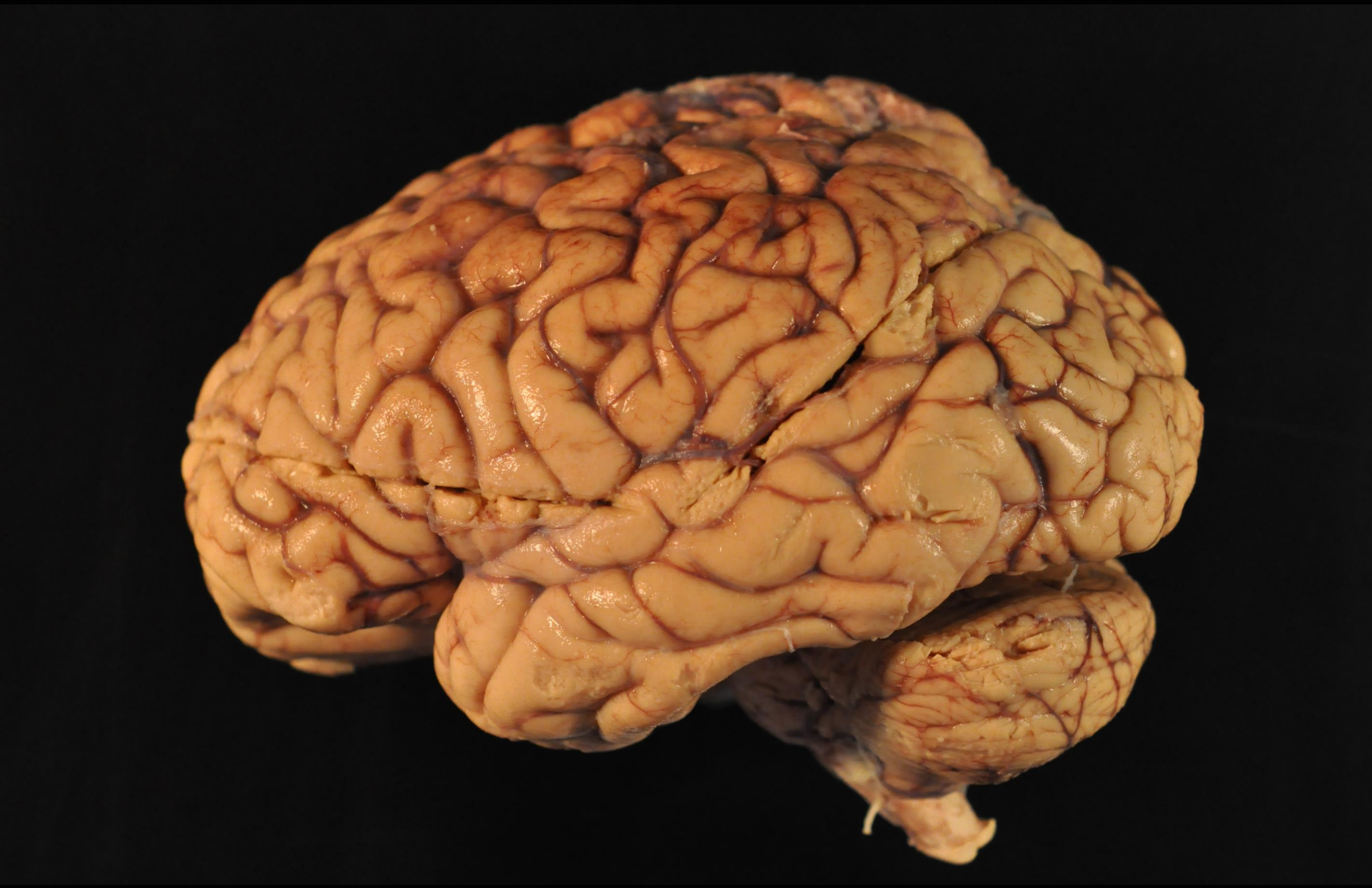
- 9 of the 78 with CTE (12%) had immunopositivity for phosphorylated TDP-43, primarily as neurites; 3 were diagnosed with motor neuron disease

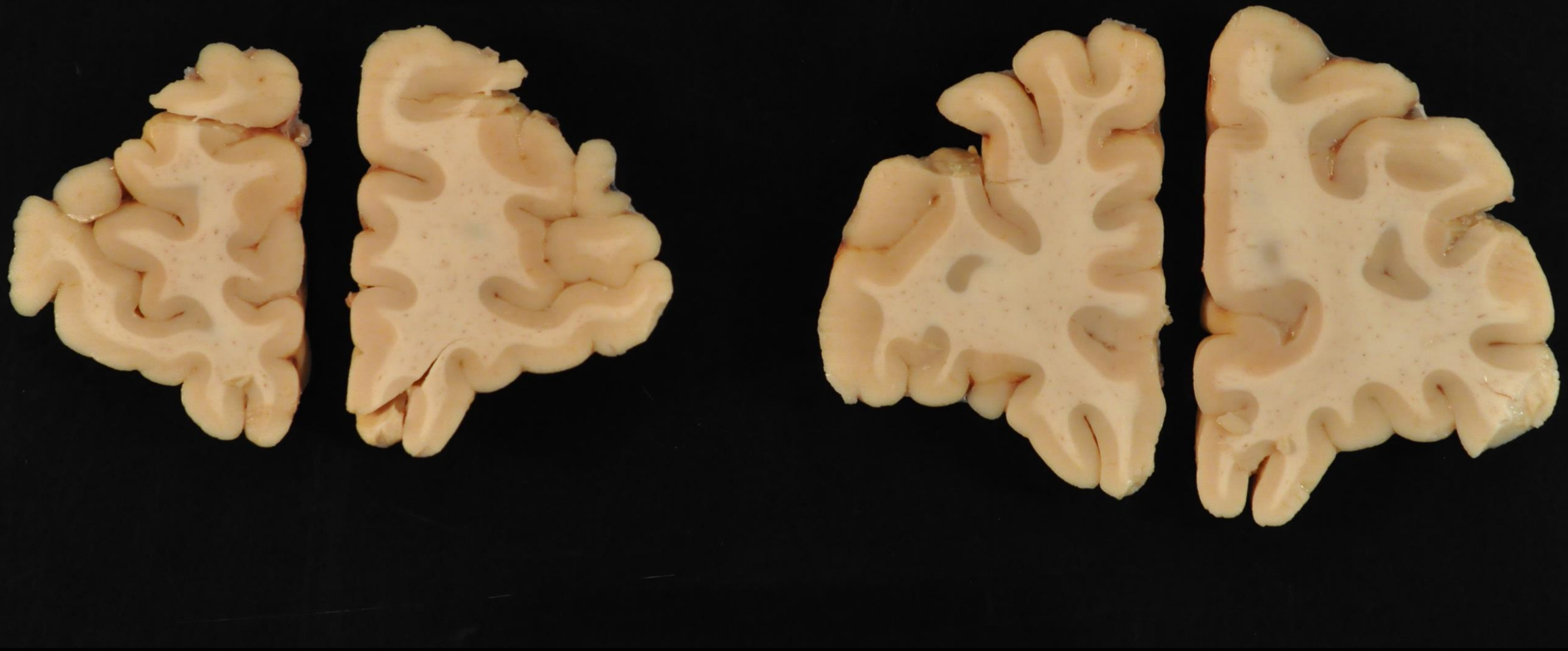
Case 1:

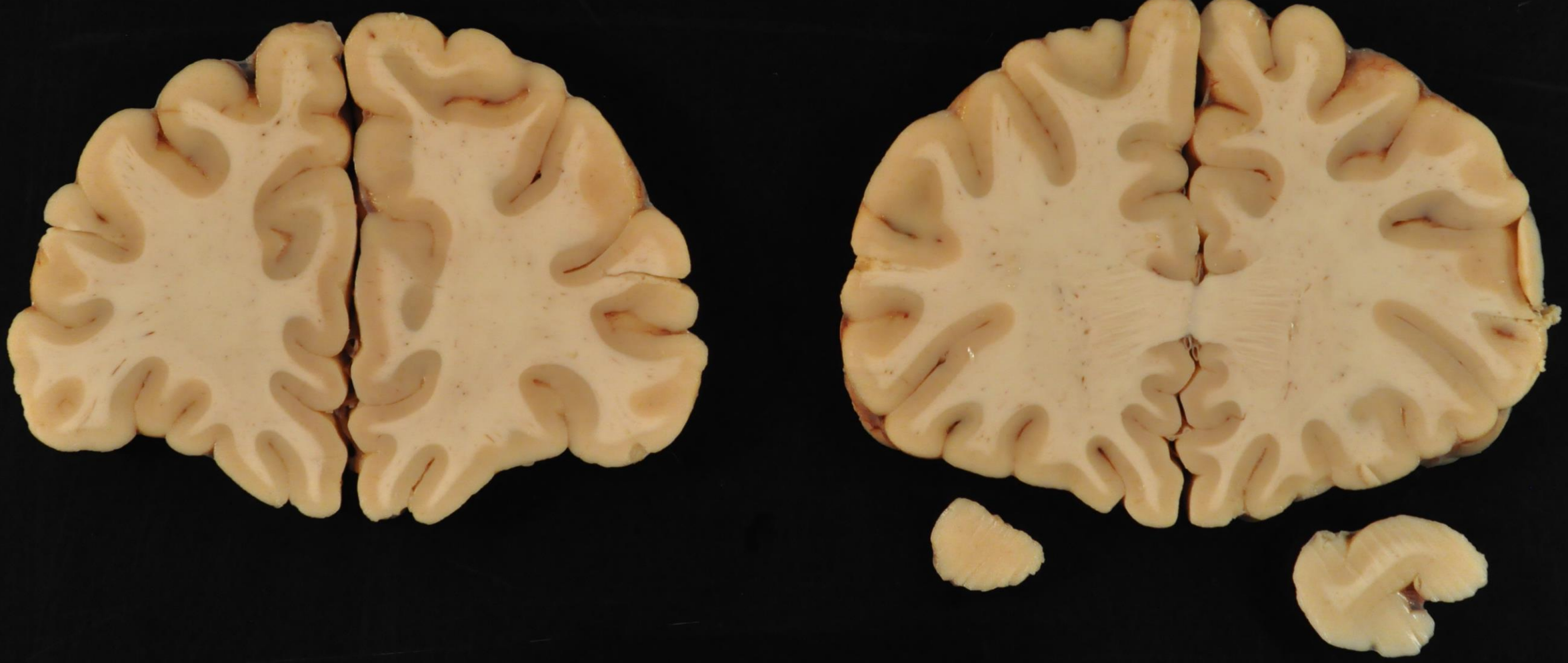


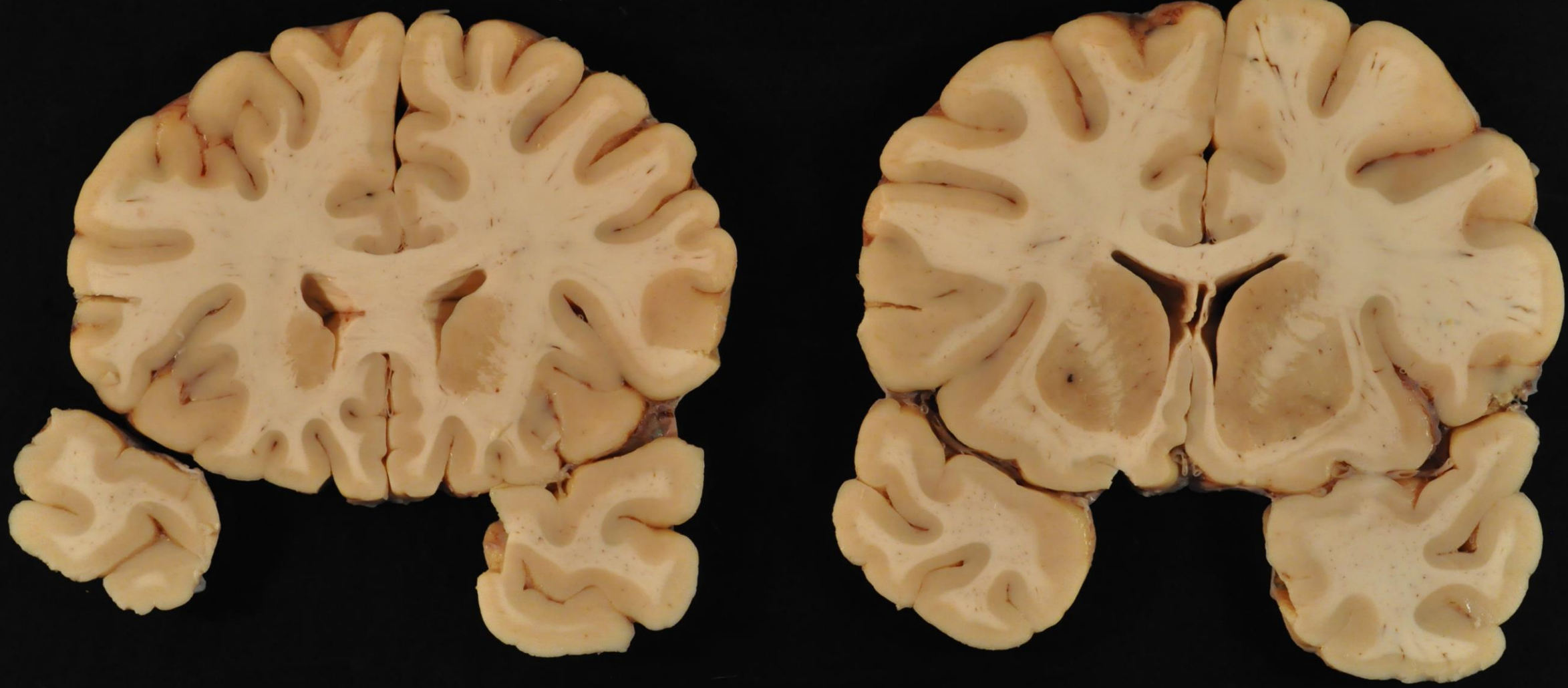
Brain weight: 1374 grams

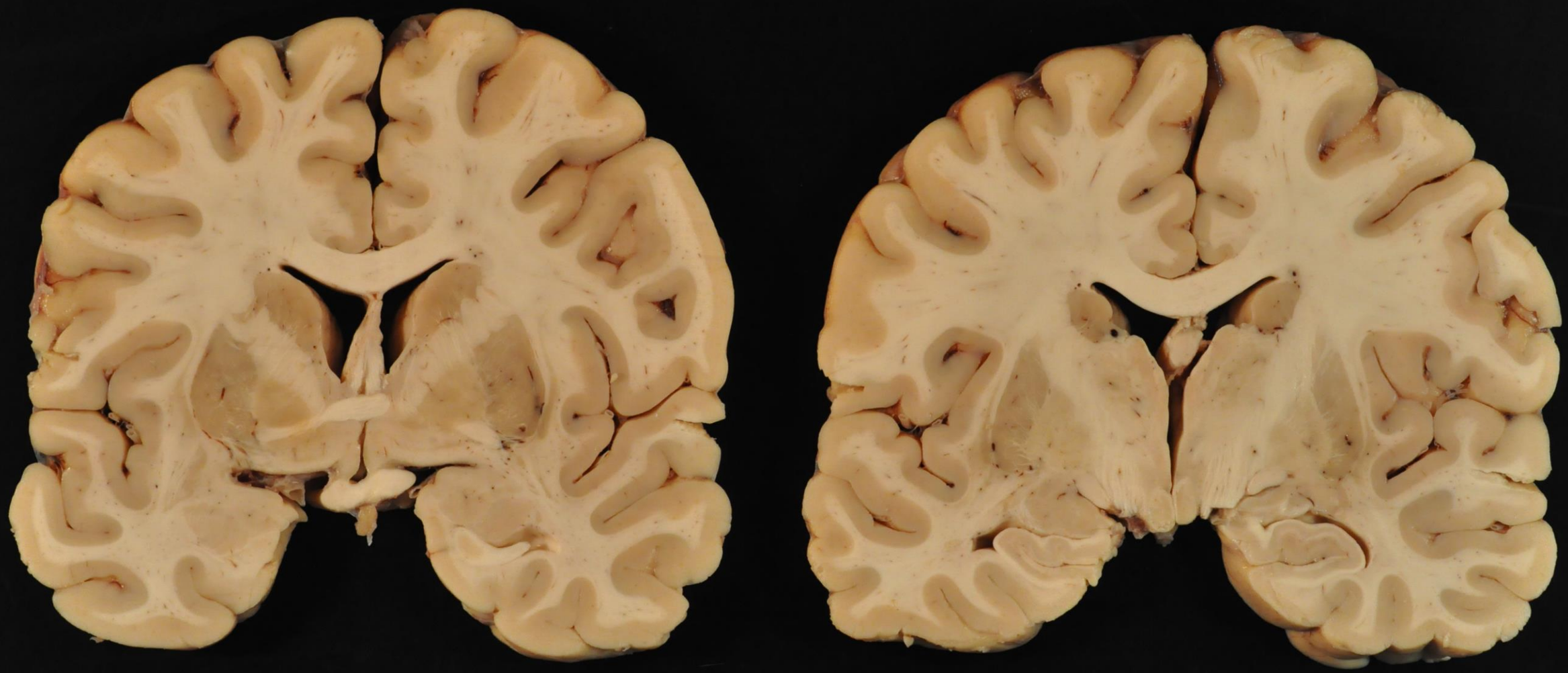


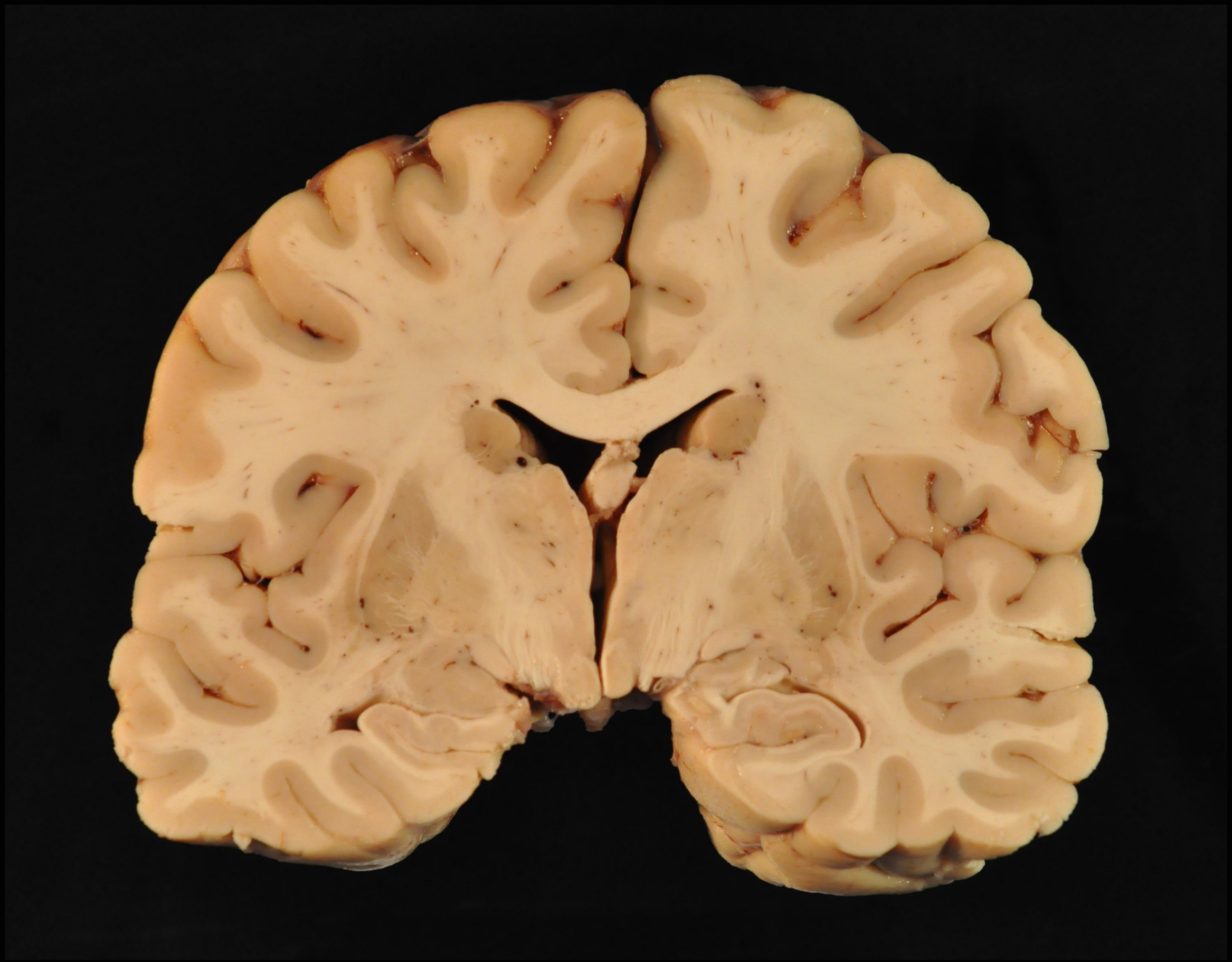


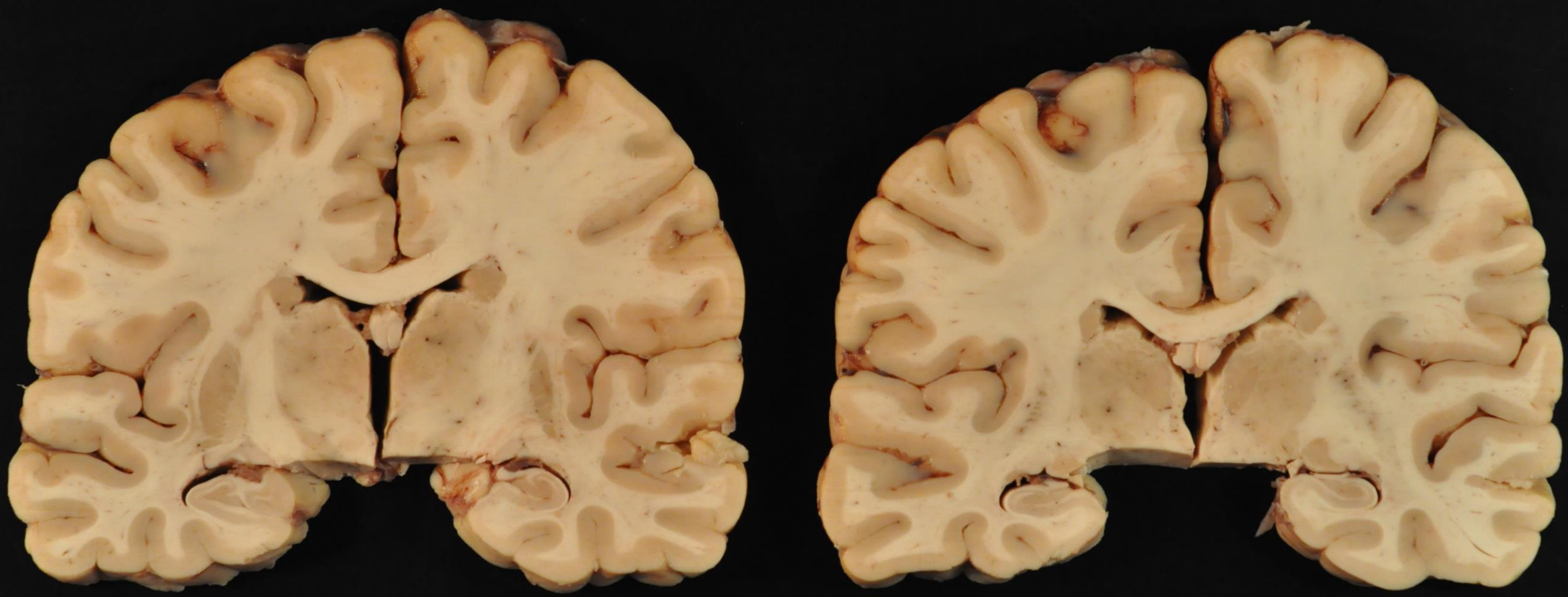


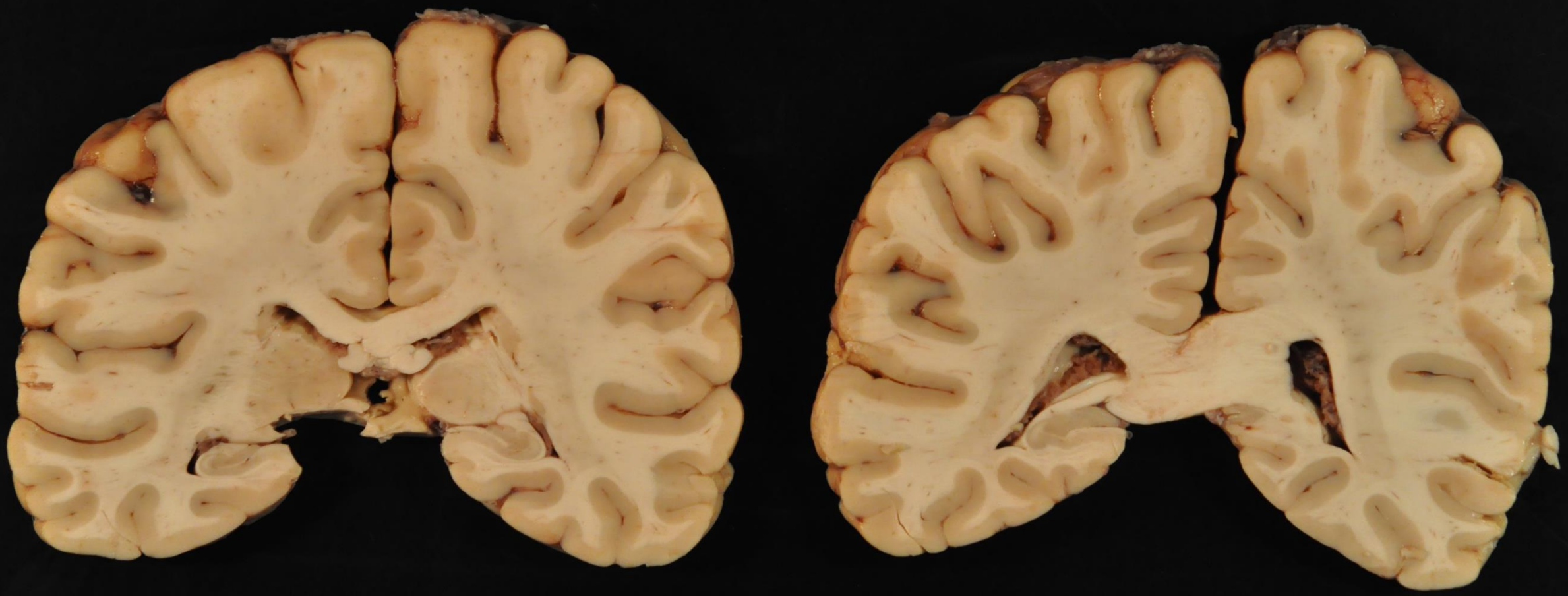




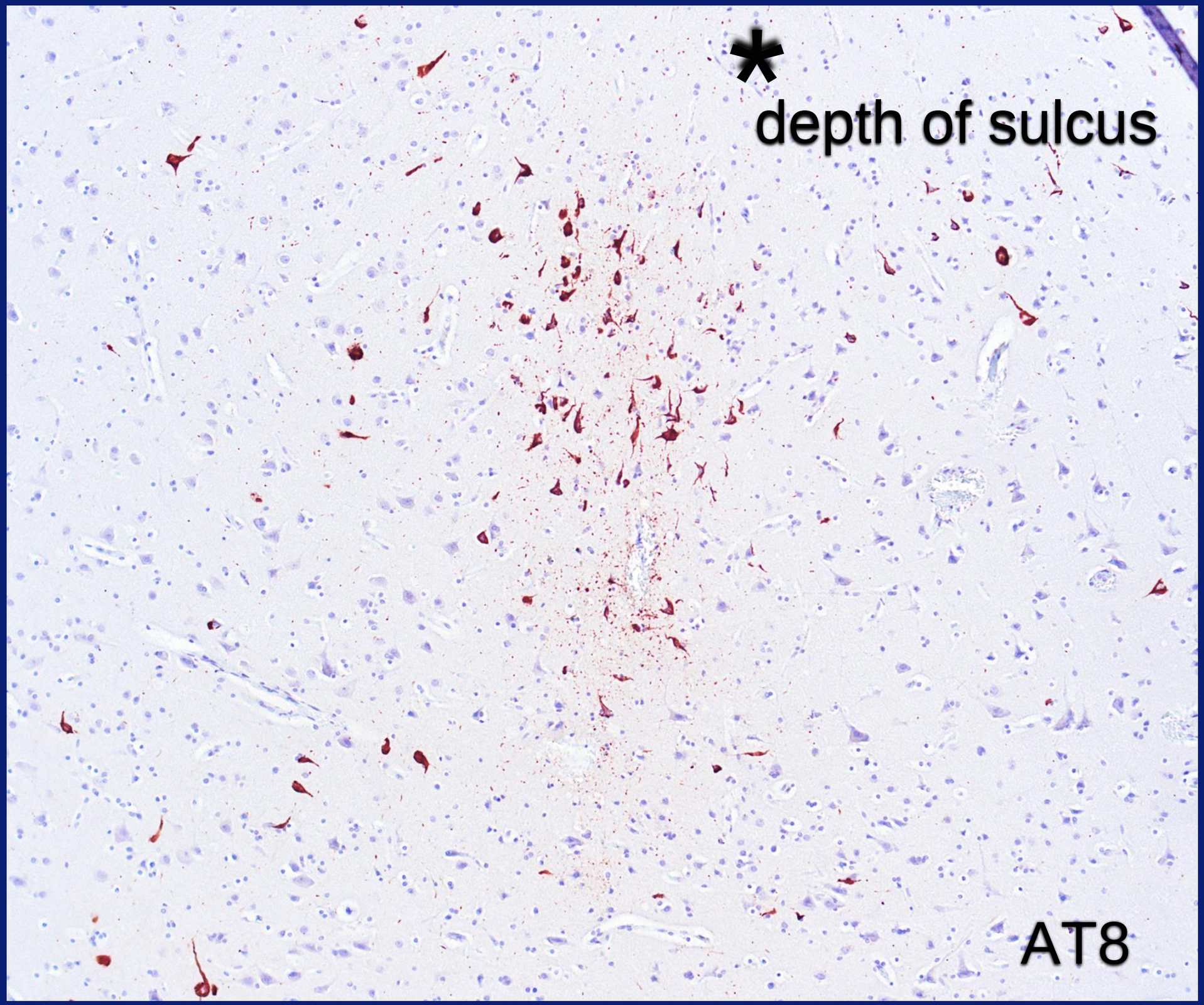




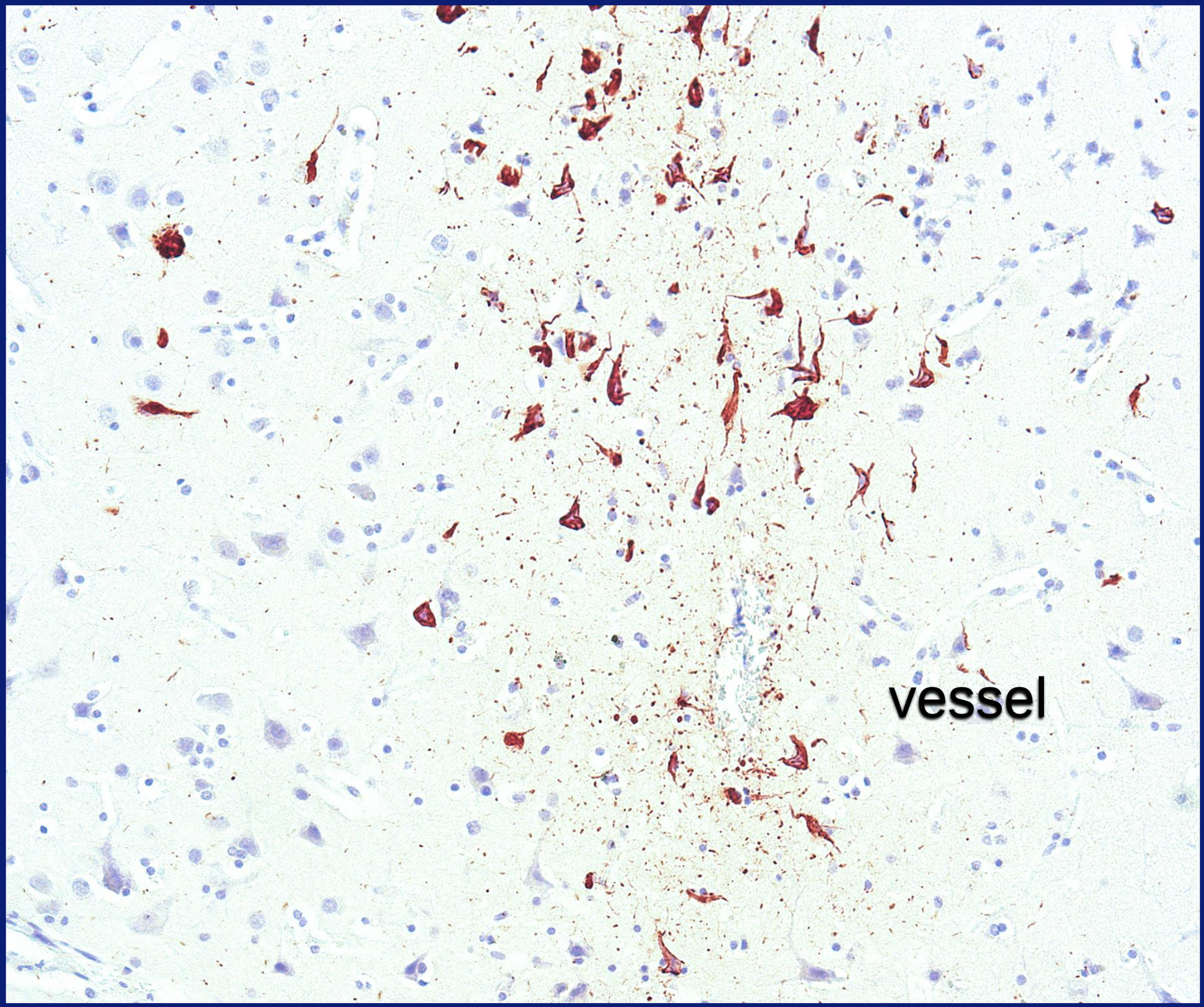




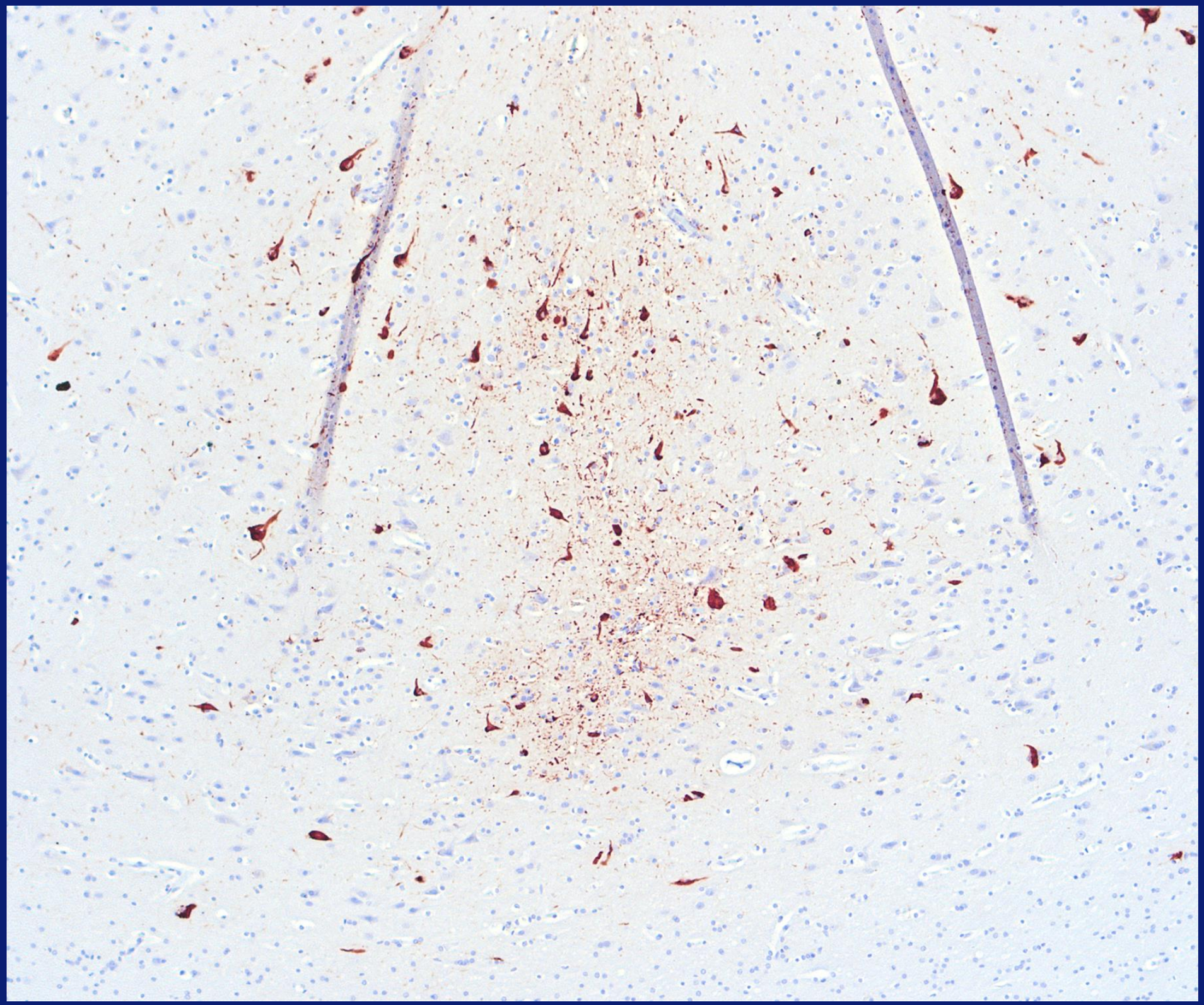
Superior frontal cortex



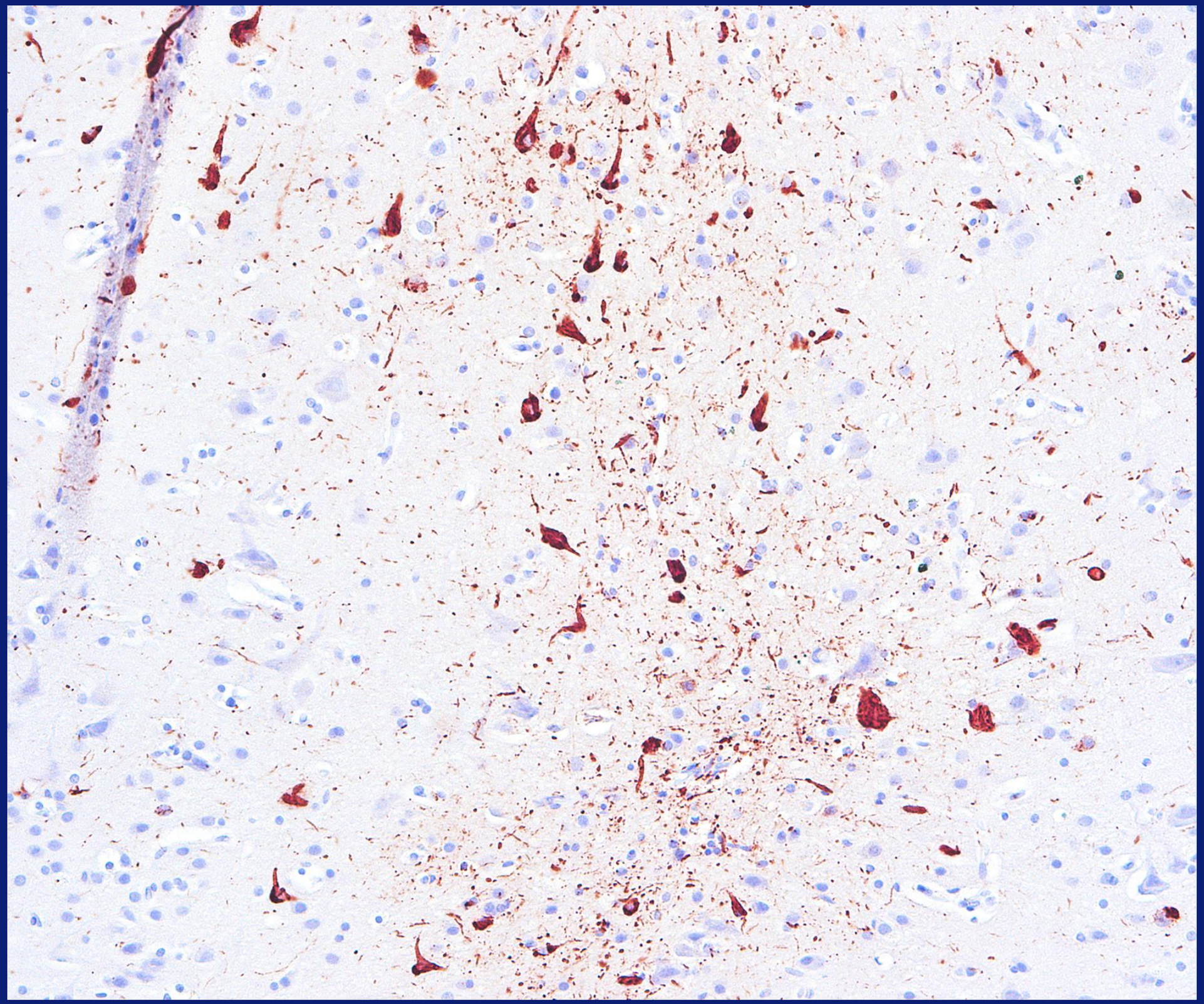
Superior frontal cortex



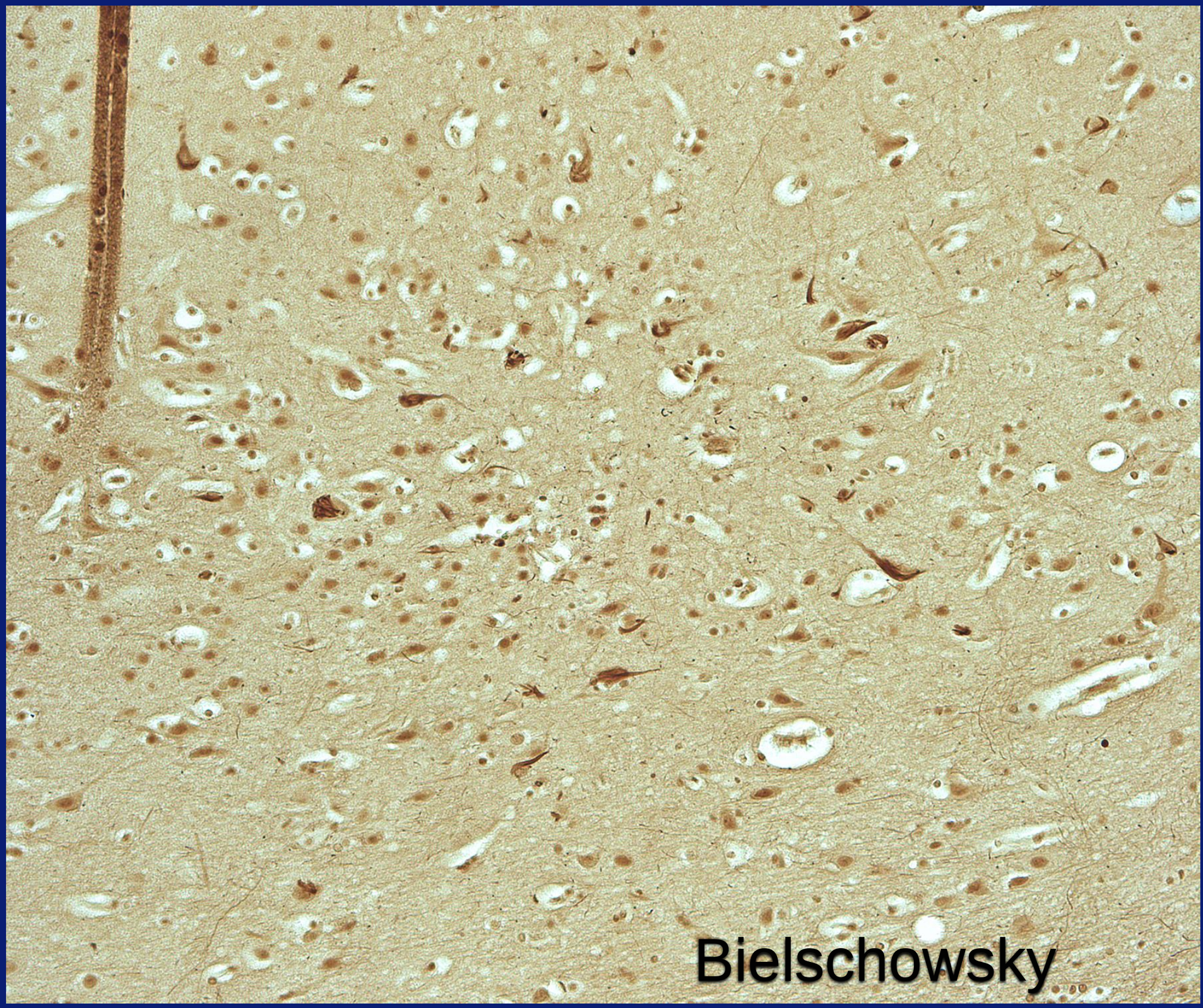
Inferior parietal



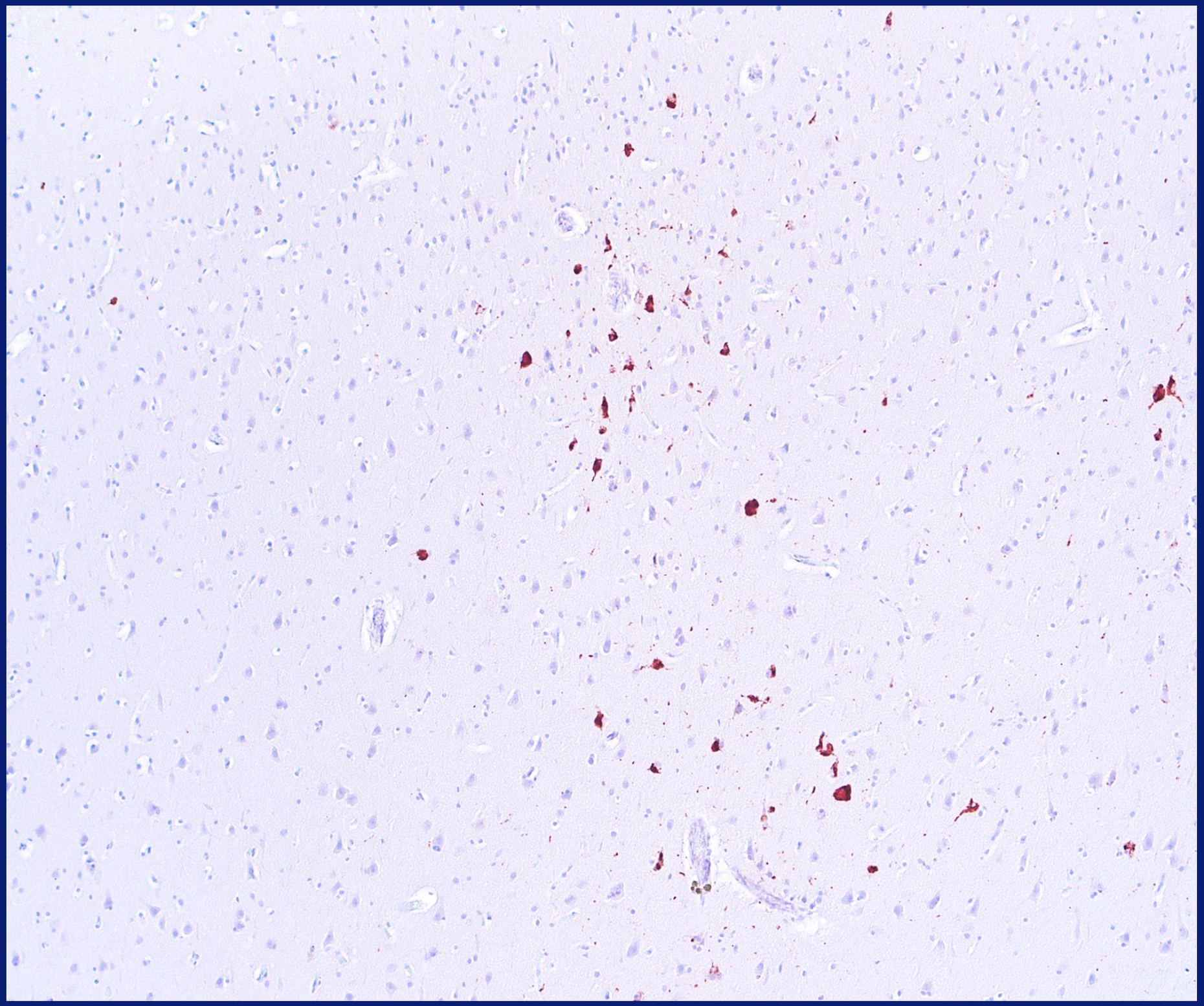
Inferior parietal



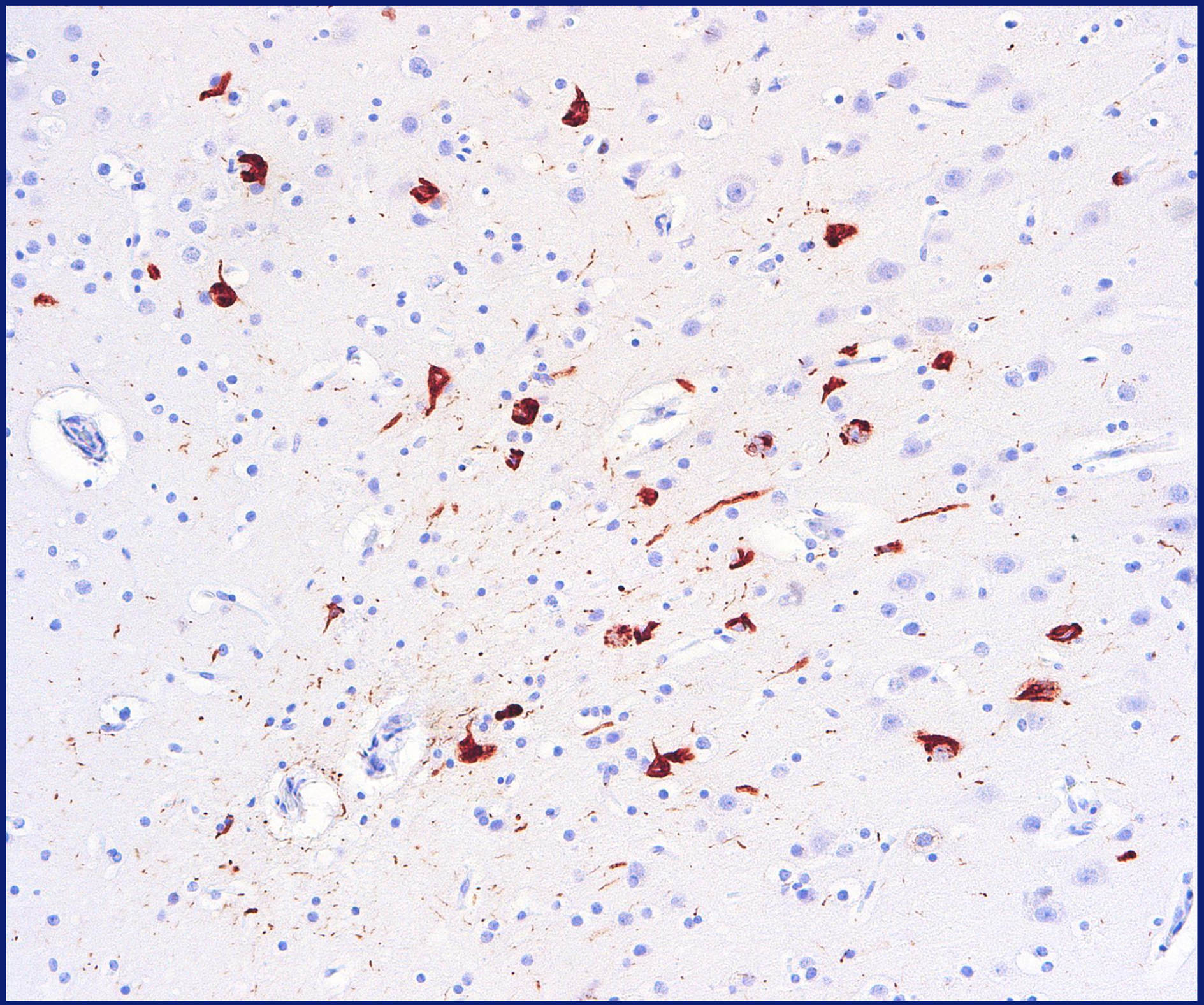
Inferior parietal cortex

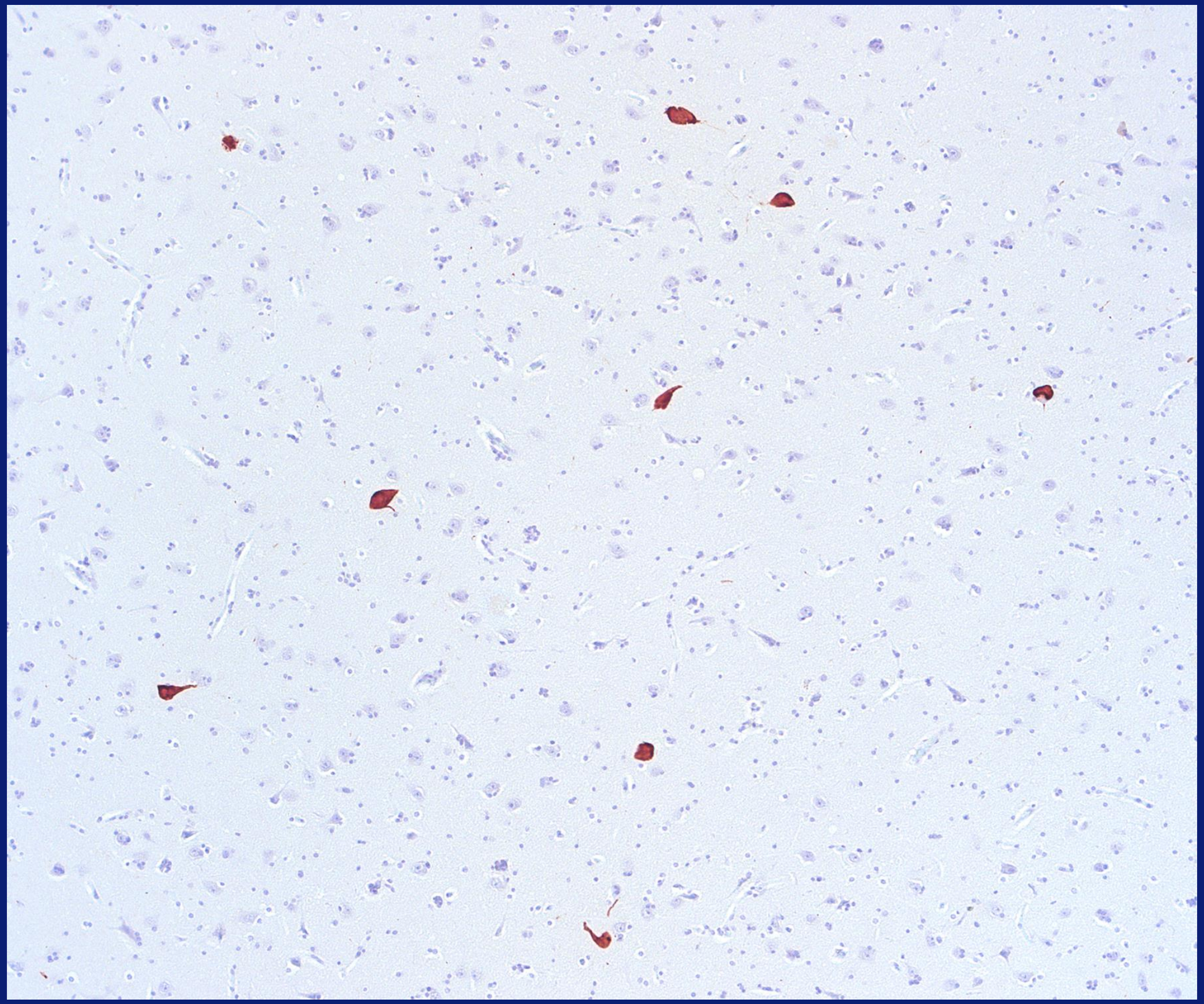


Inferior temporal cortex

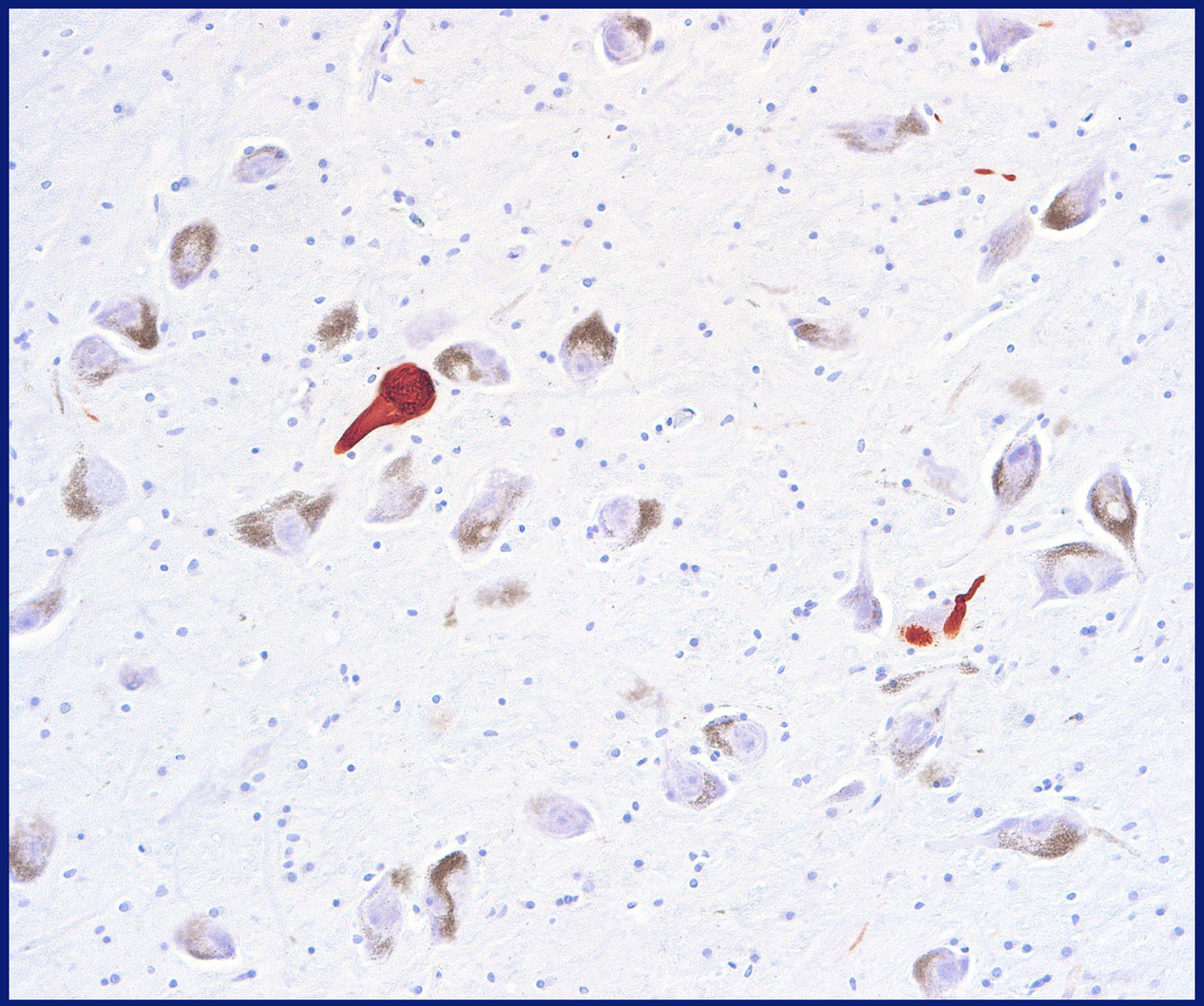


Rolandic

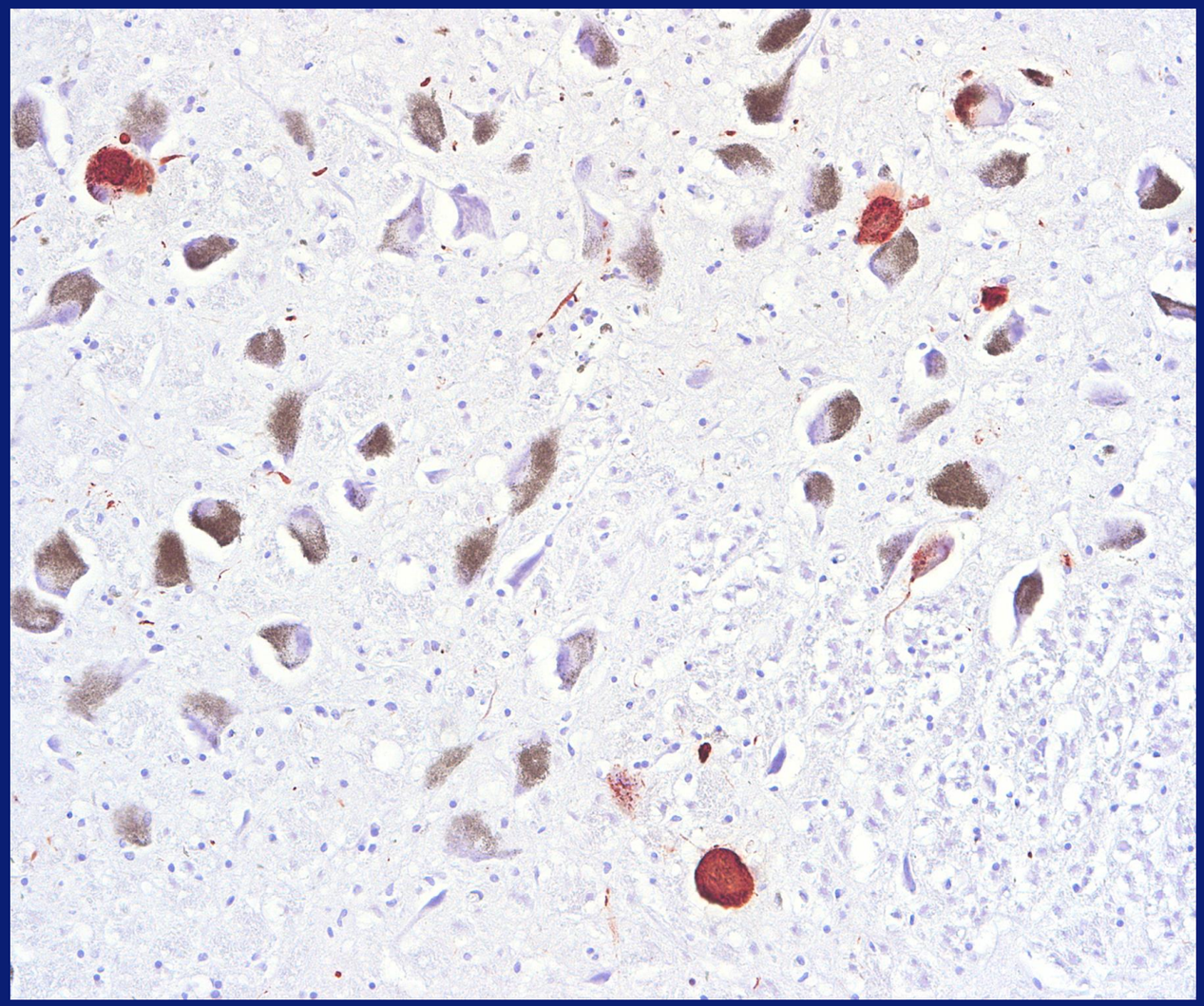




amygdala



Substantia Nigra



Locus Coeruleus

Case 1:
Diagnosis?

Case 1

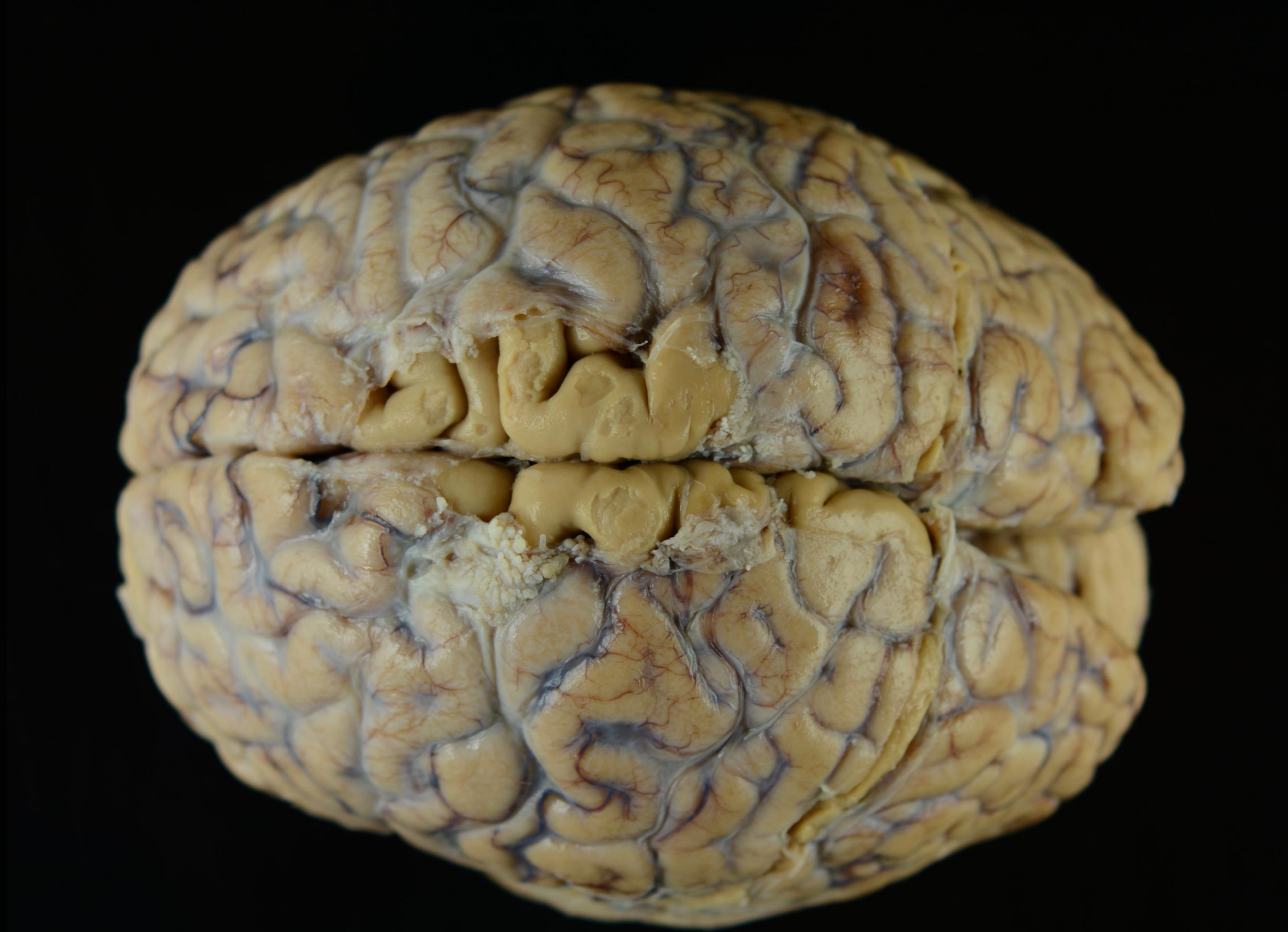
CTE Stage II:

- mild frontal atrophy
- small cavum septum pellucidum
- perivascular lesions in superior frontal, dorsolateral frontal, Rolandic, inferior parietal and inferior temporal cortices.
- Moderate neurofibrillary degeneration - locus coeruleus
- Mild neurofibrillary degeneration - substantia nigra and amygdala

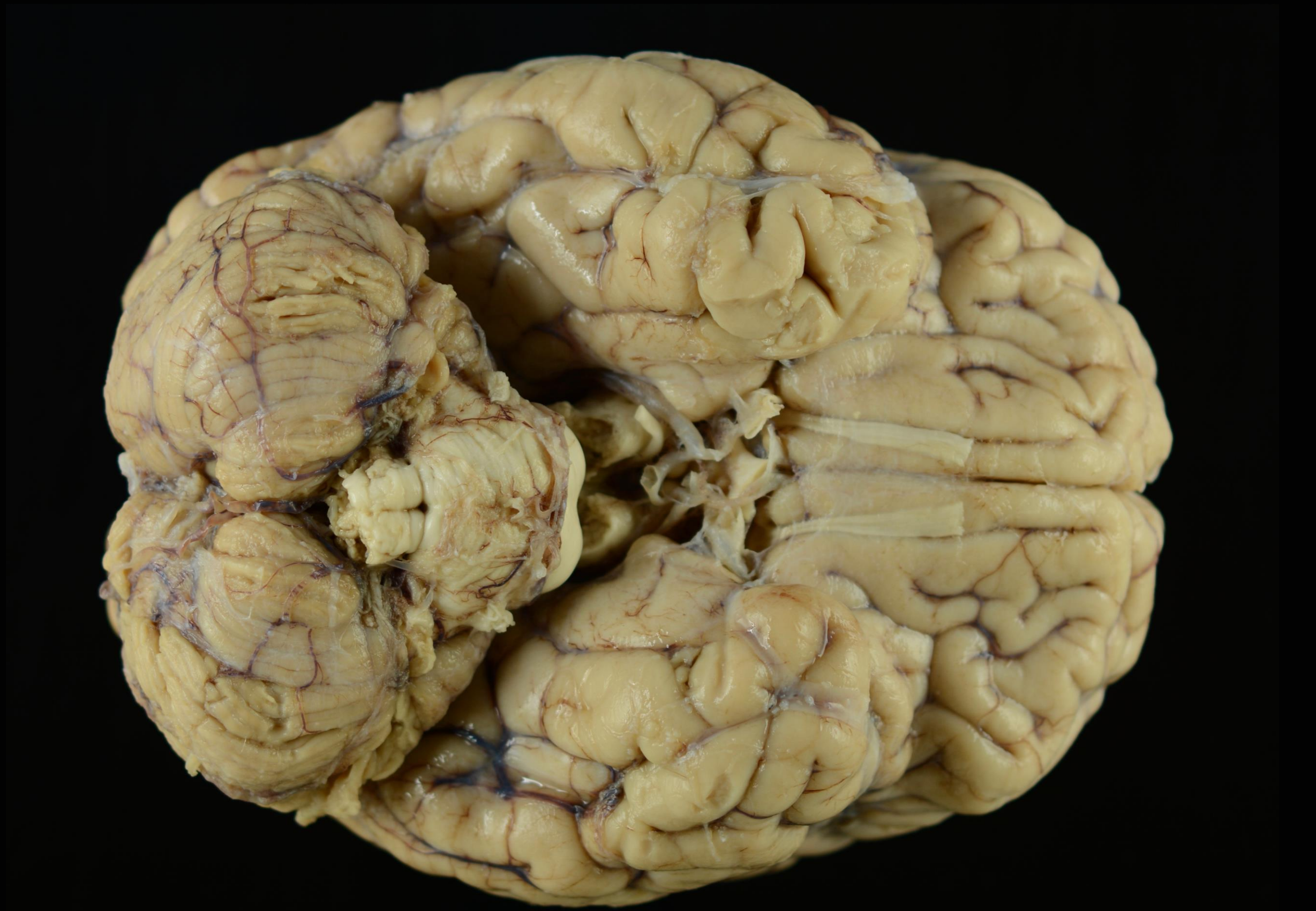
Case 1

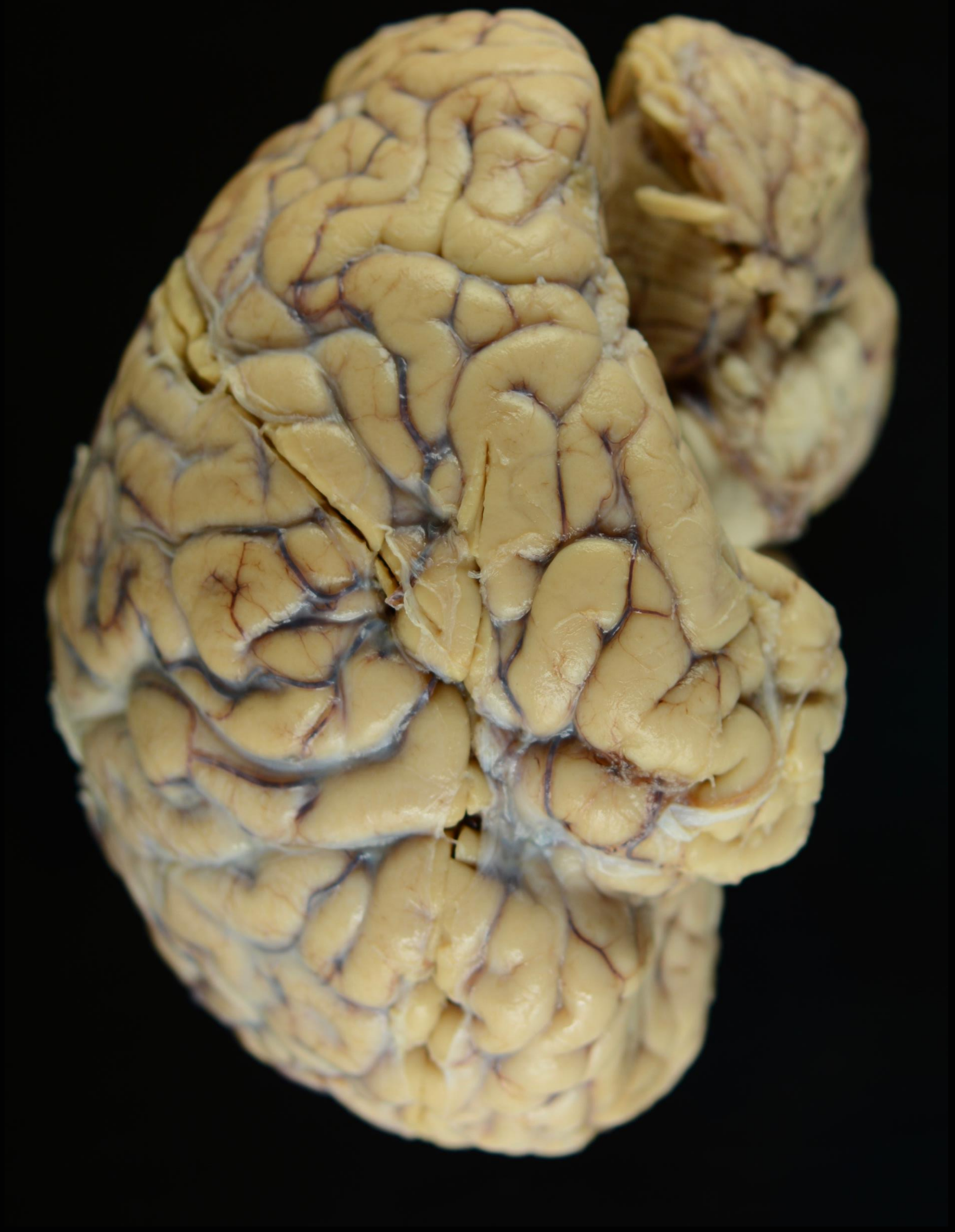
- 31 years old
- Football for 20 years as a safety:
  started at age 6, including 2 years AFL and 2 years NFL.
- At 21, knee surgery and prescribed hydrocodone-acetaminophen, became dependent.
- At 24, memory problems
- At 25, progressive attentional difficulties, anxiety, depression.
- Dxd as bipolar vs. schizoffective. Delusions and hallucinations, manic episodes.
- At 26, daily headaches
- Death age 31 from MVA

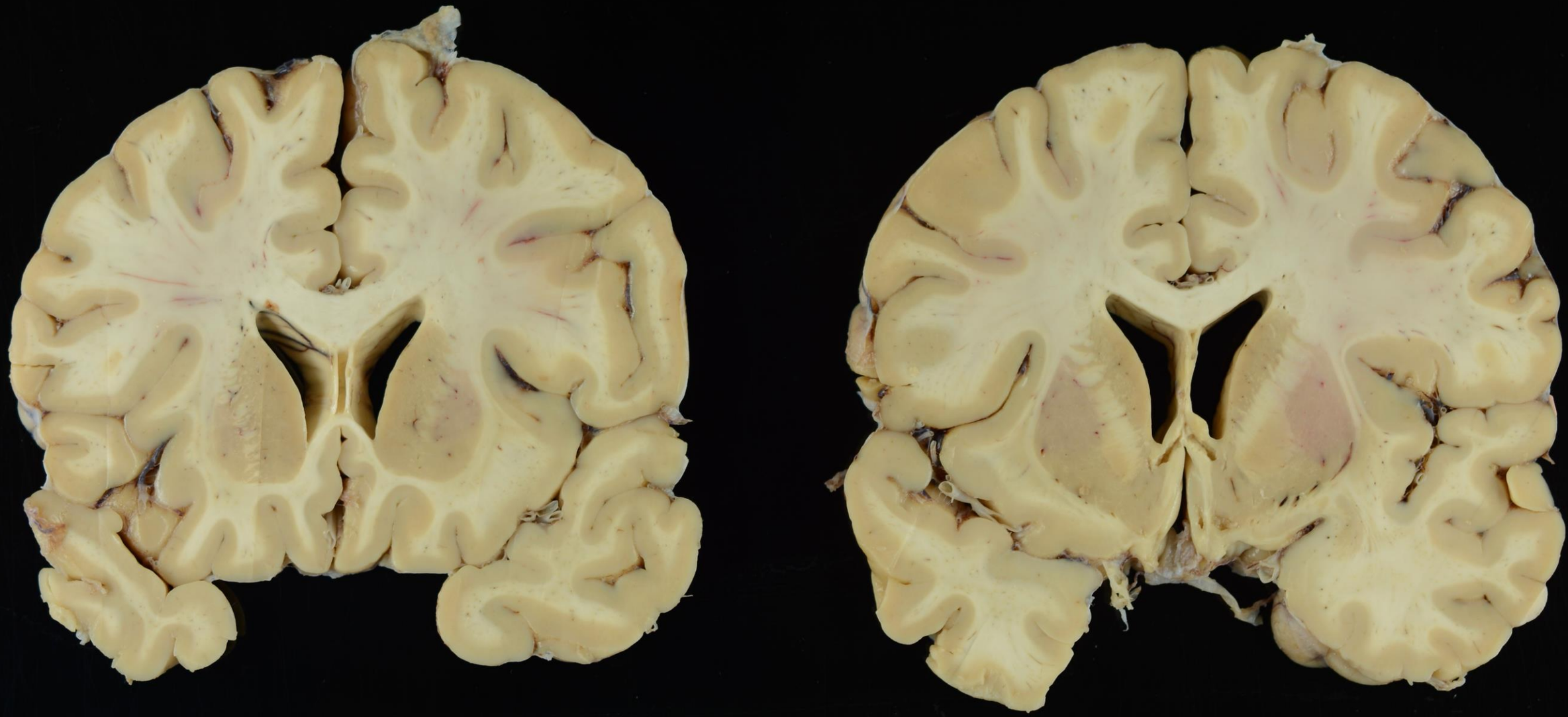
Case 2

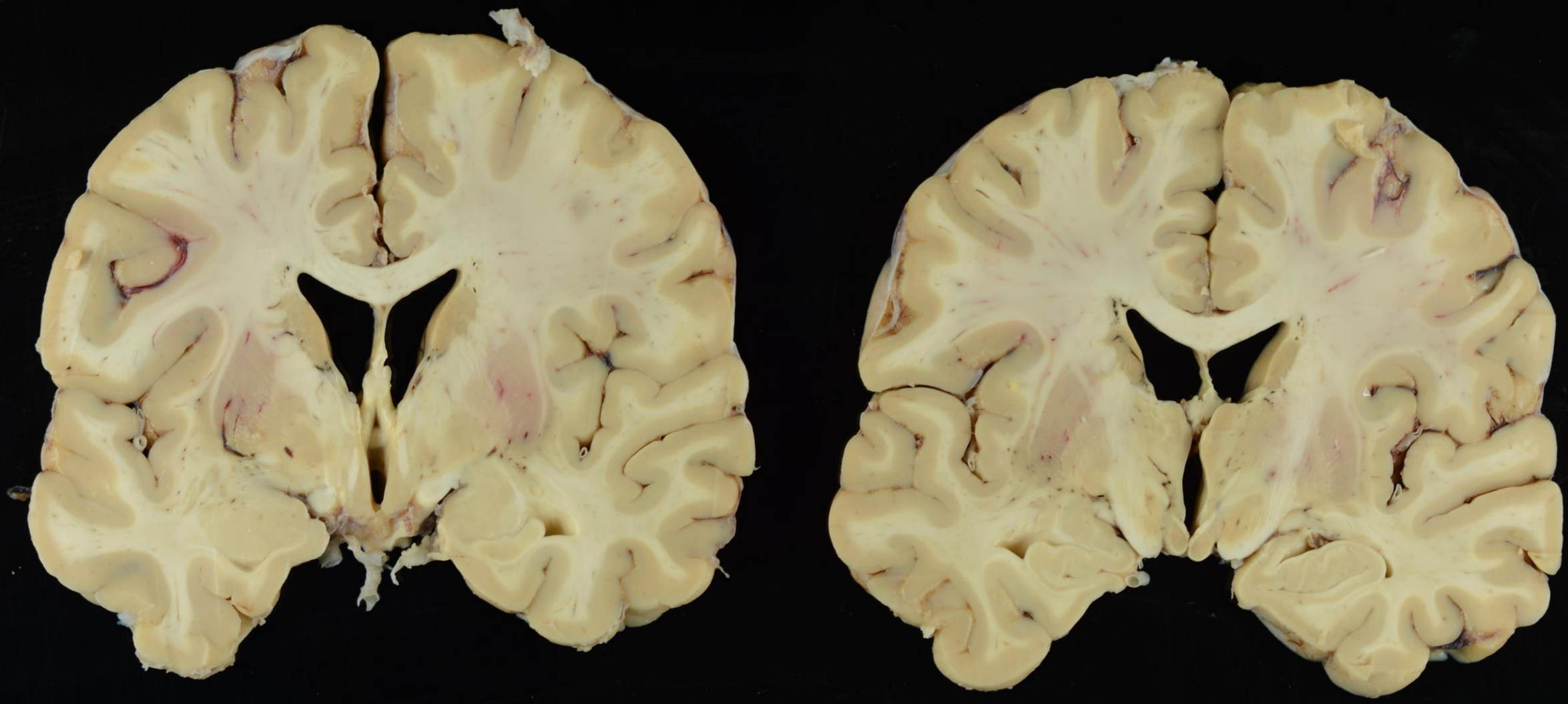


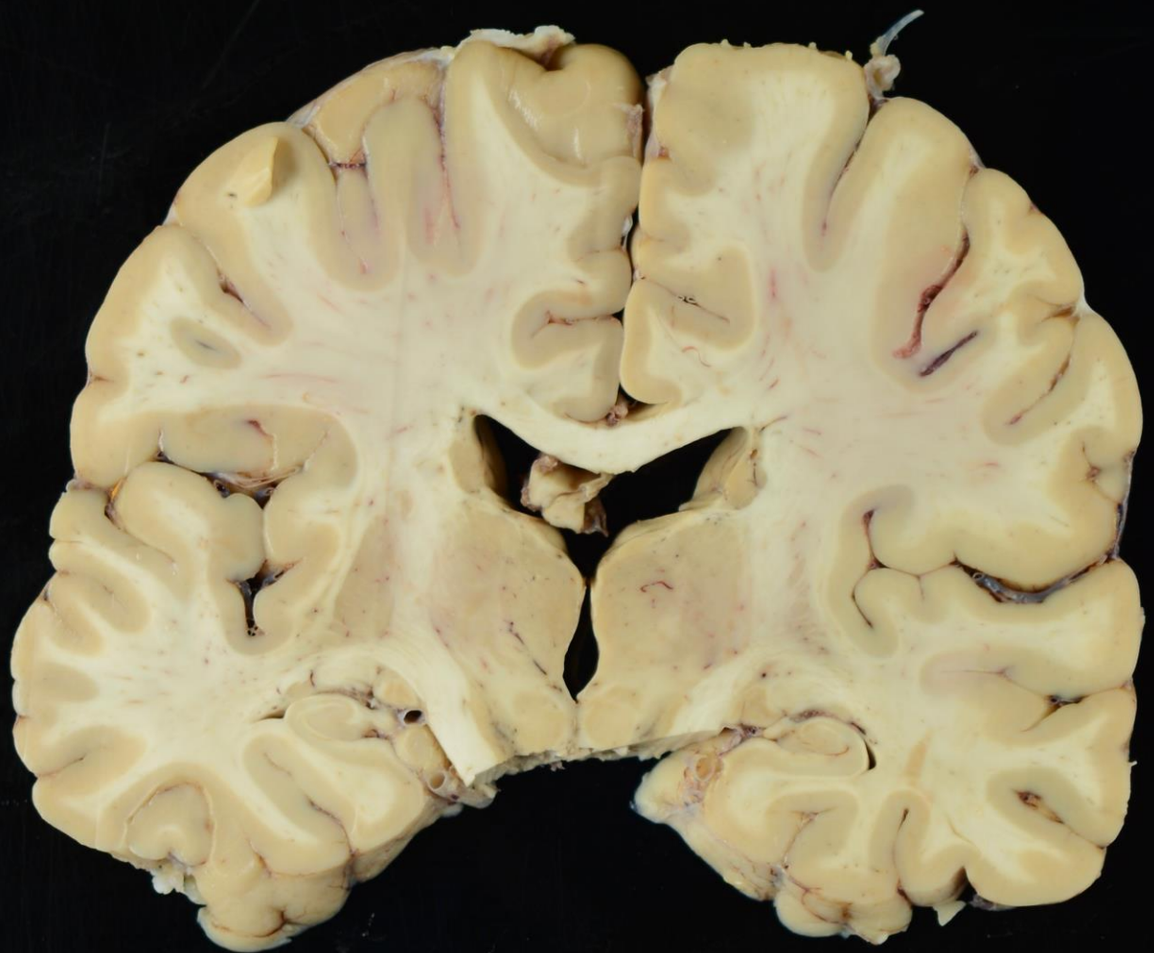
Brain weight: 1475 grams

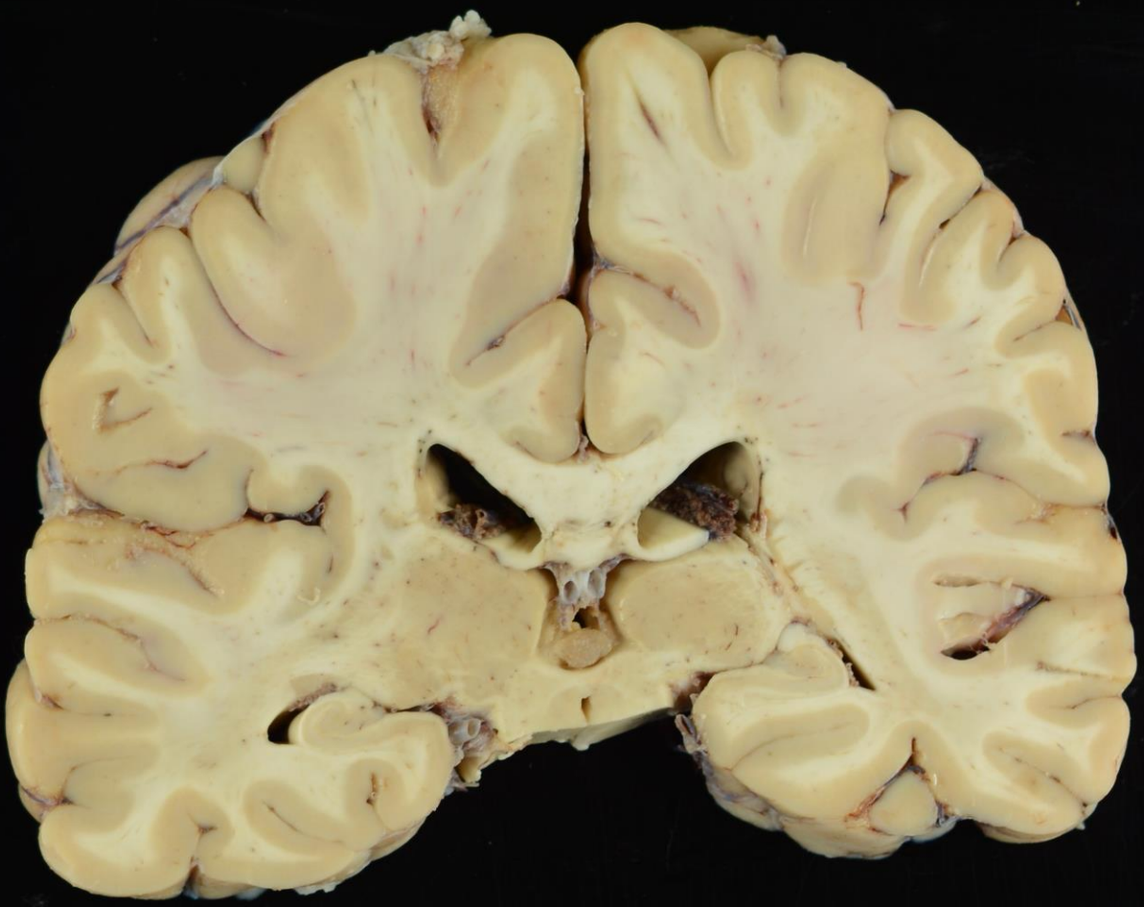




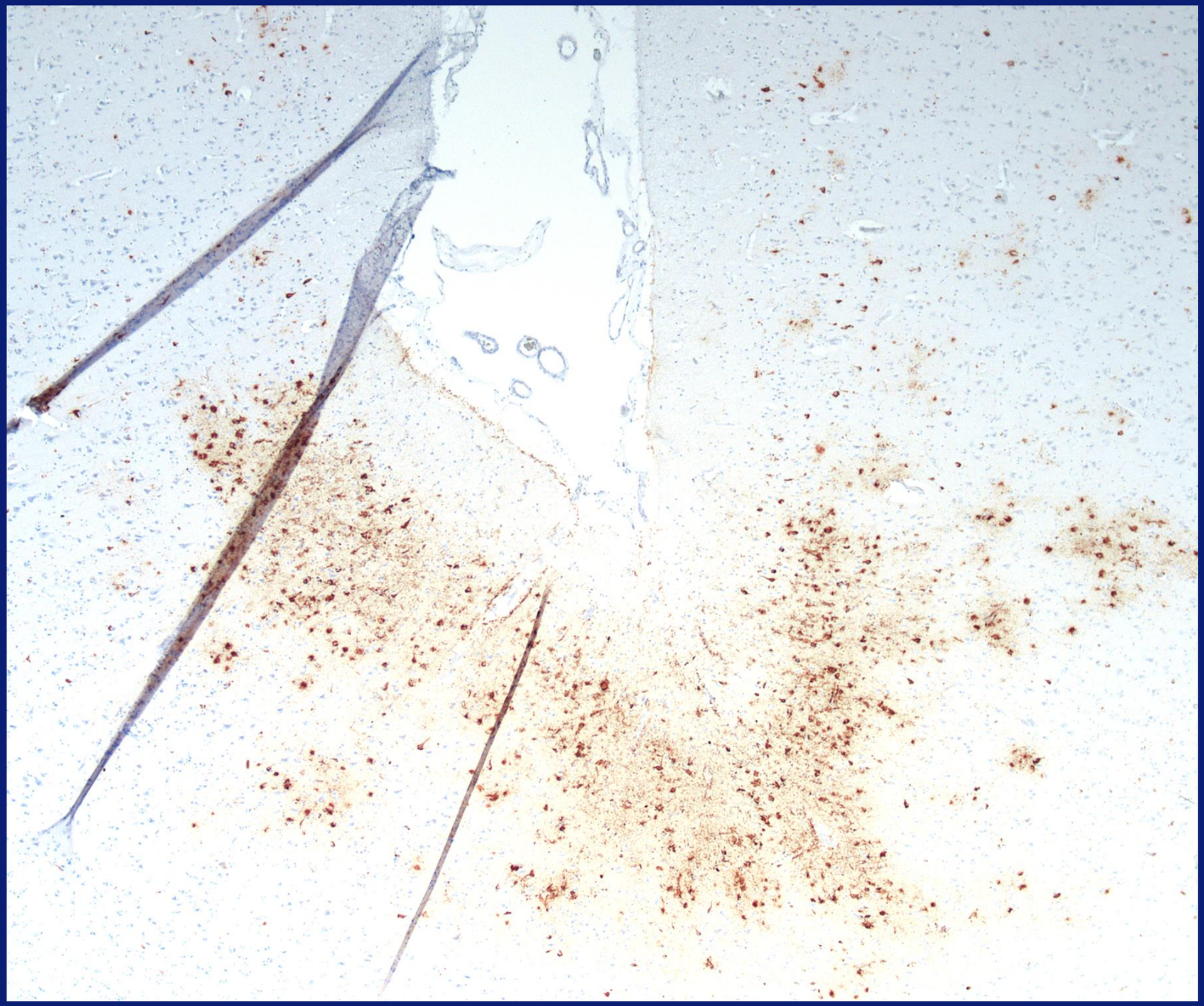




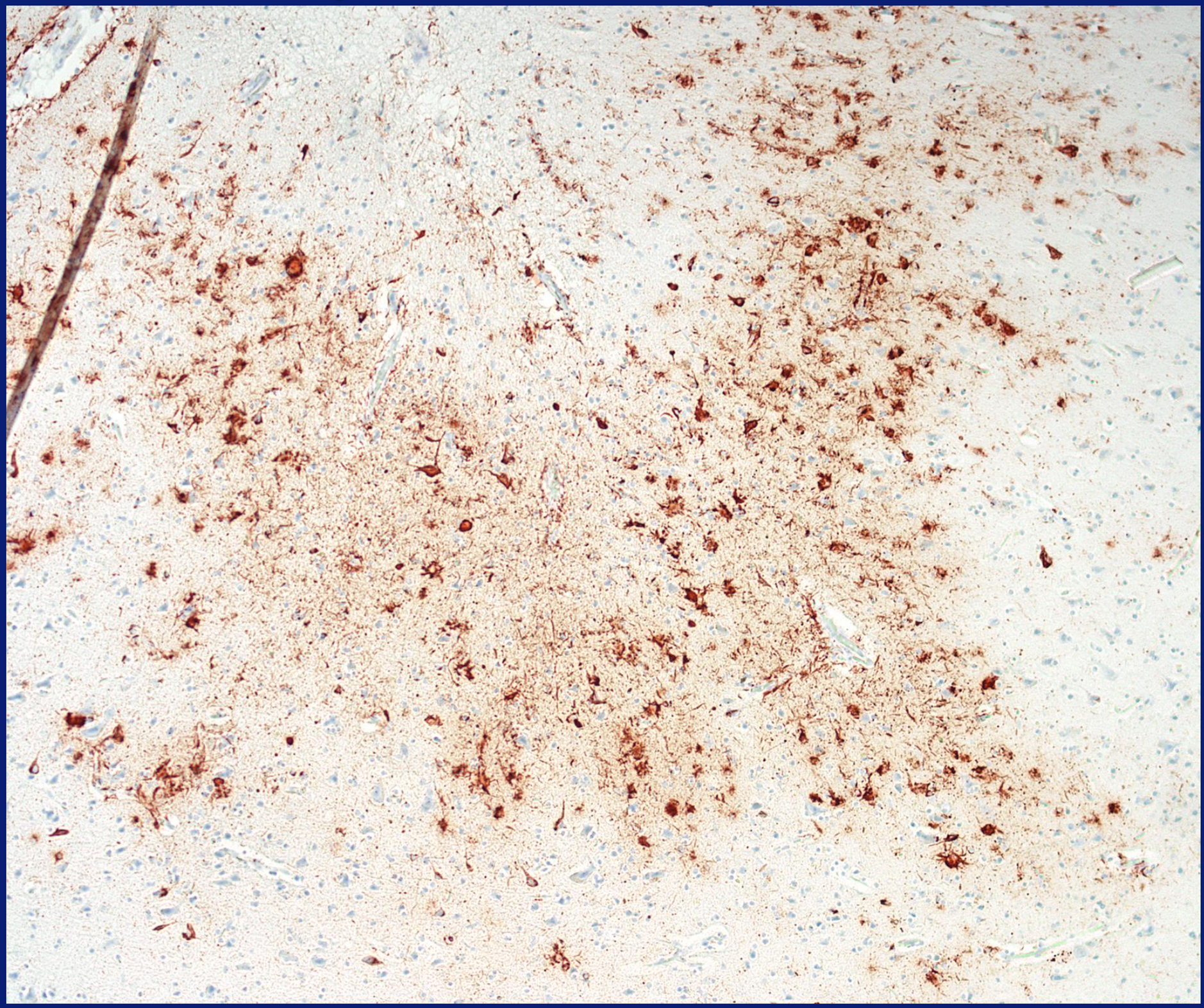




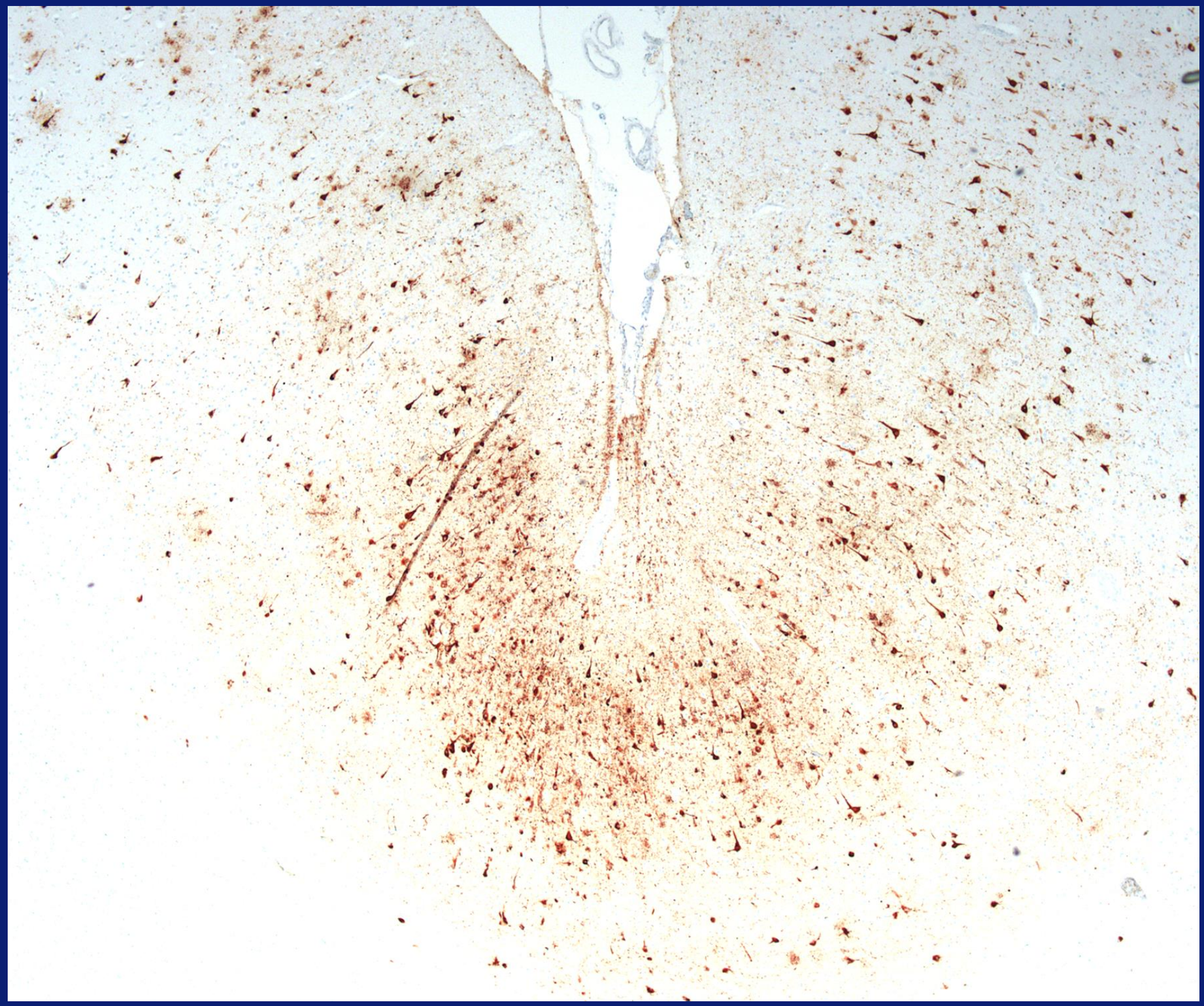
Superior frontal cortex



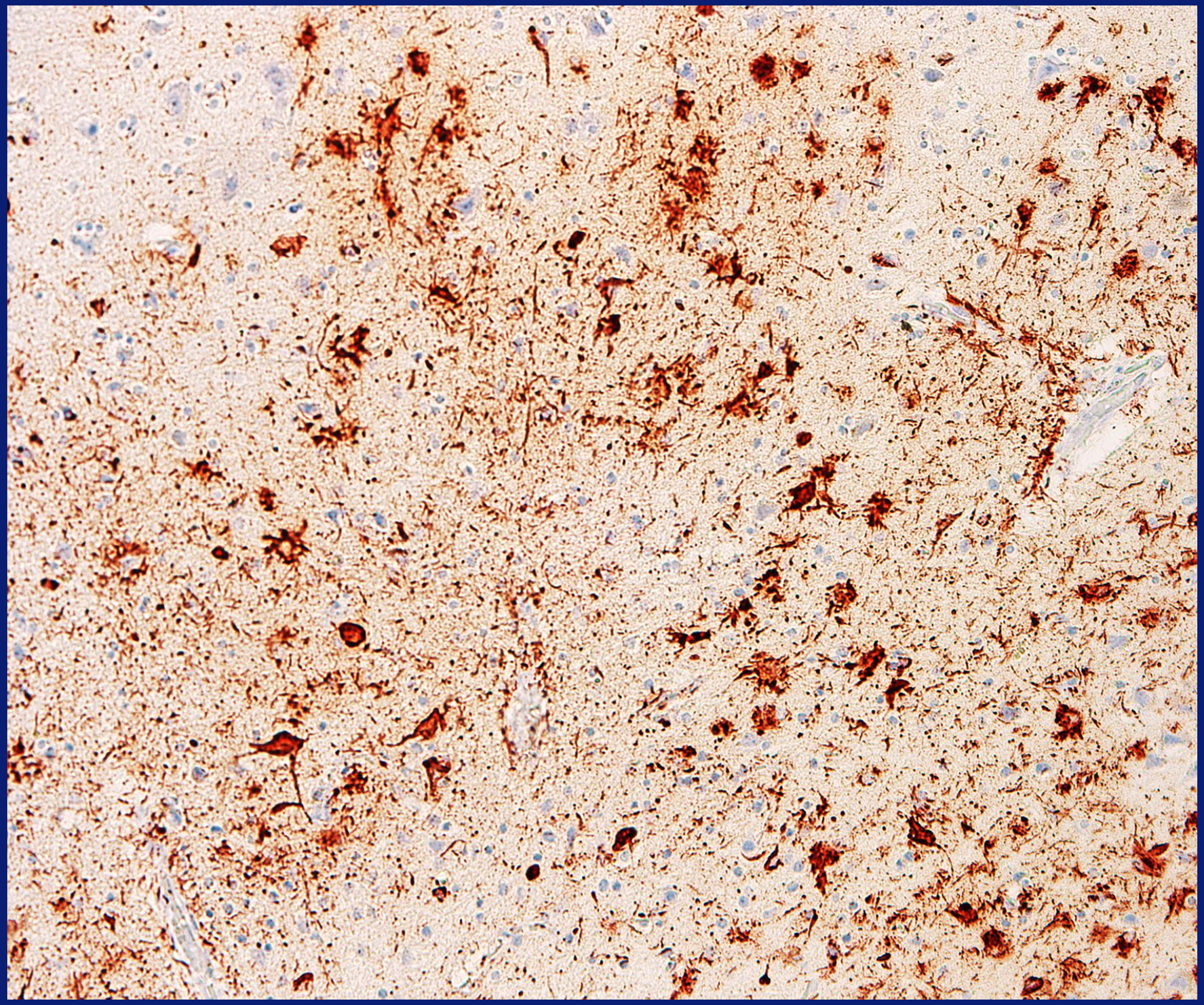
Superior frontal cortex



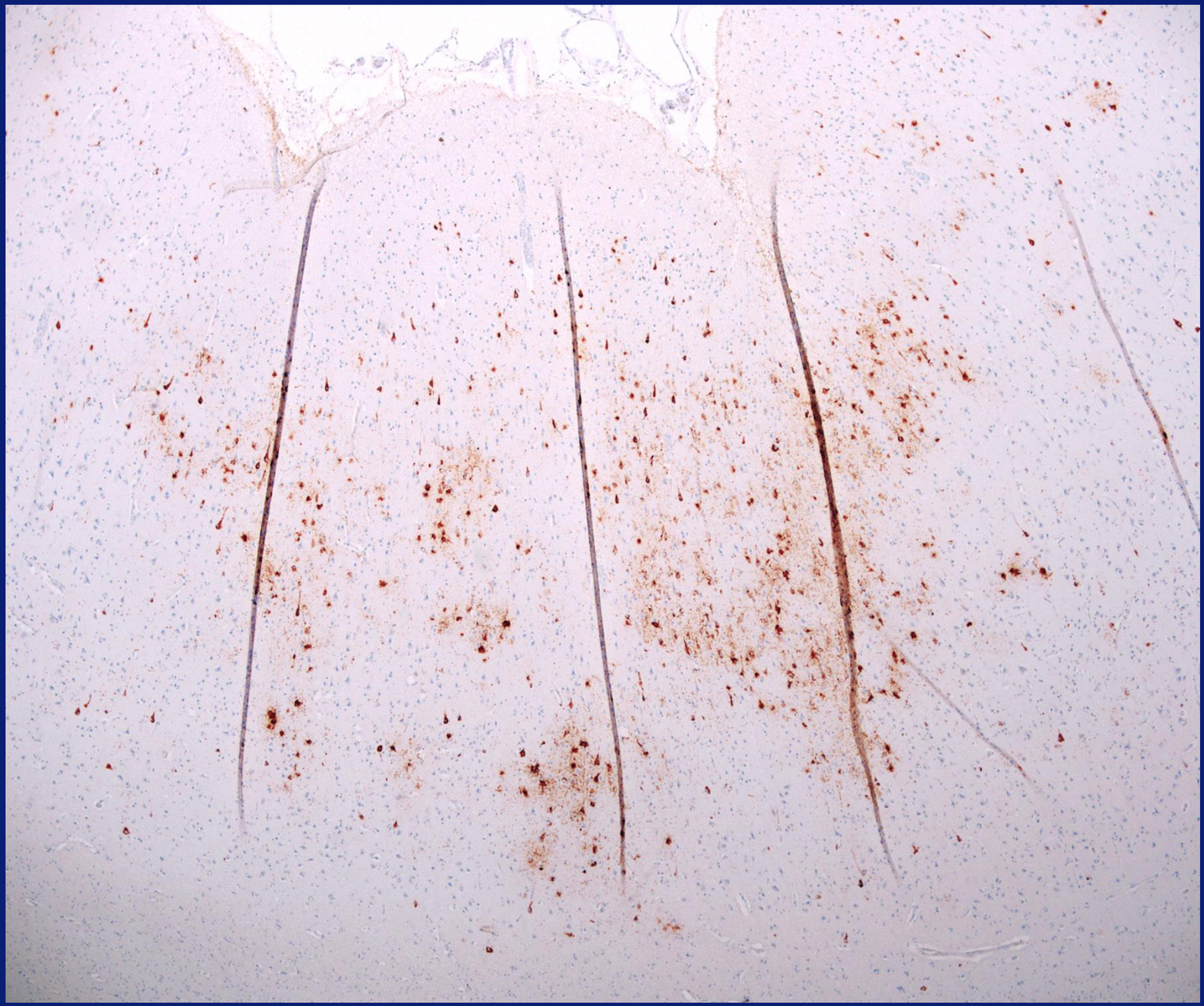
Superior Temporal Cortex



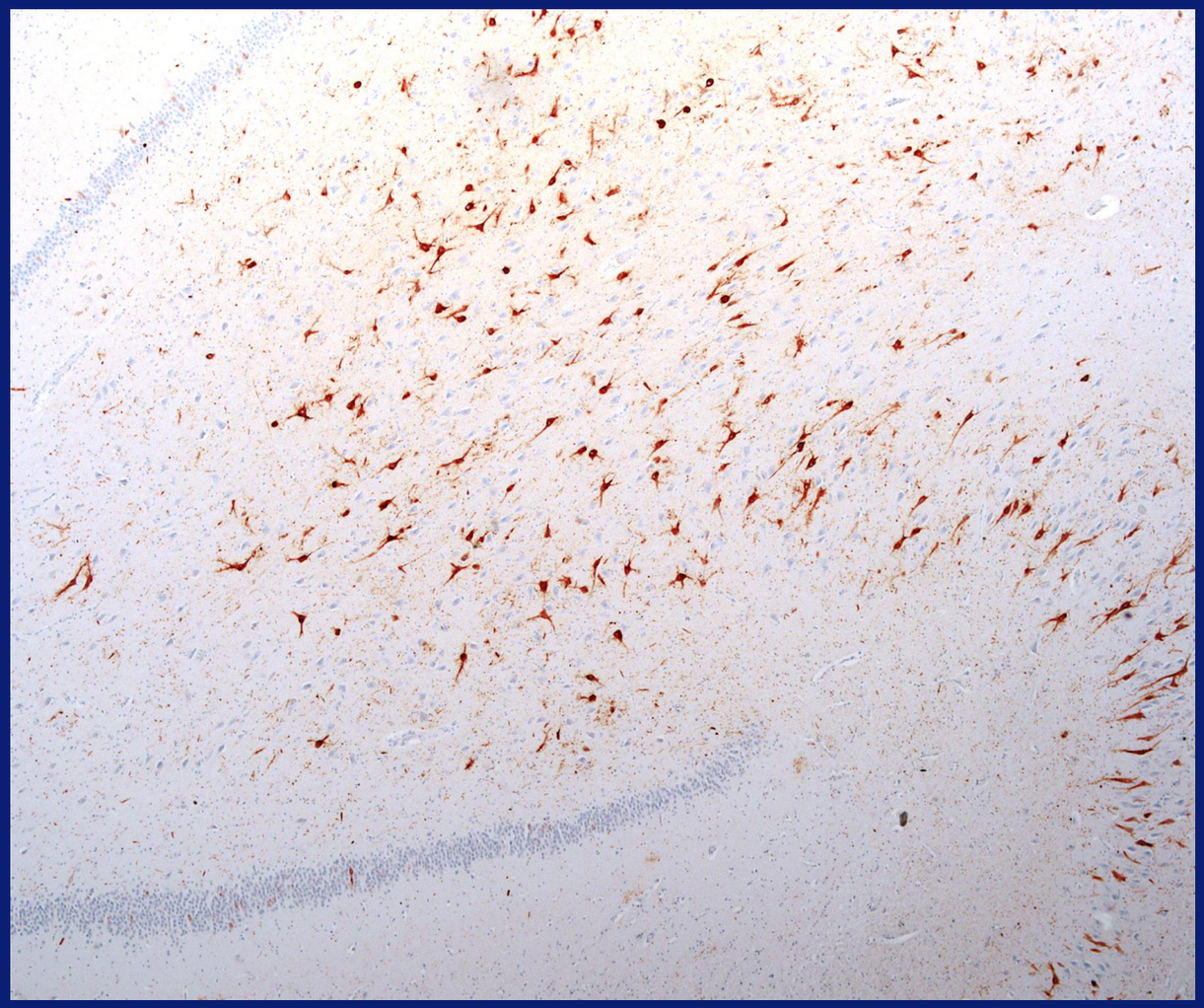
Superior Temporal Cortex



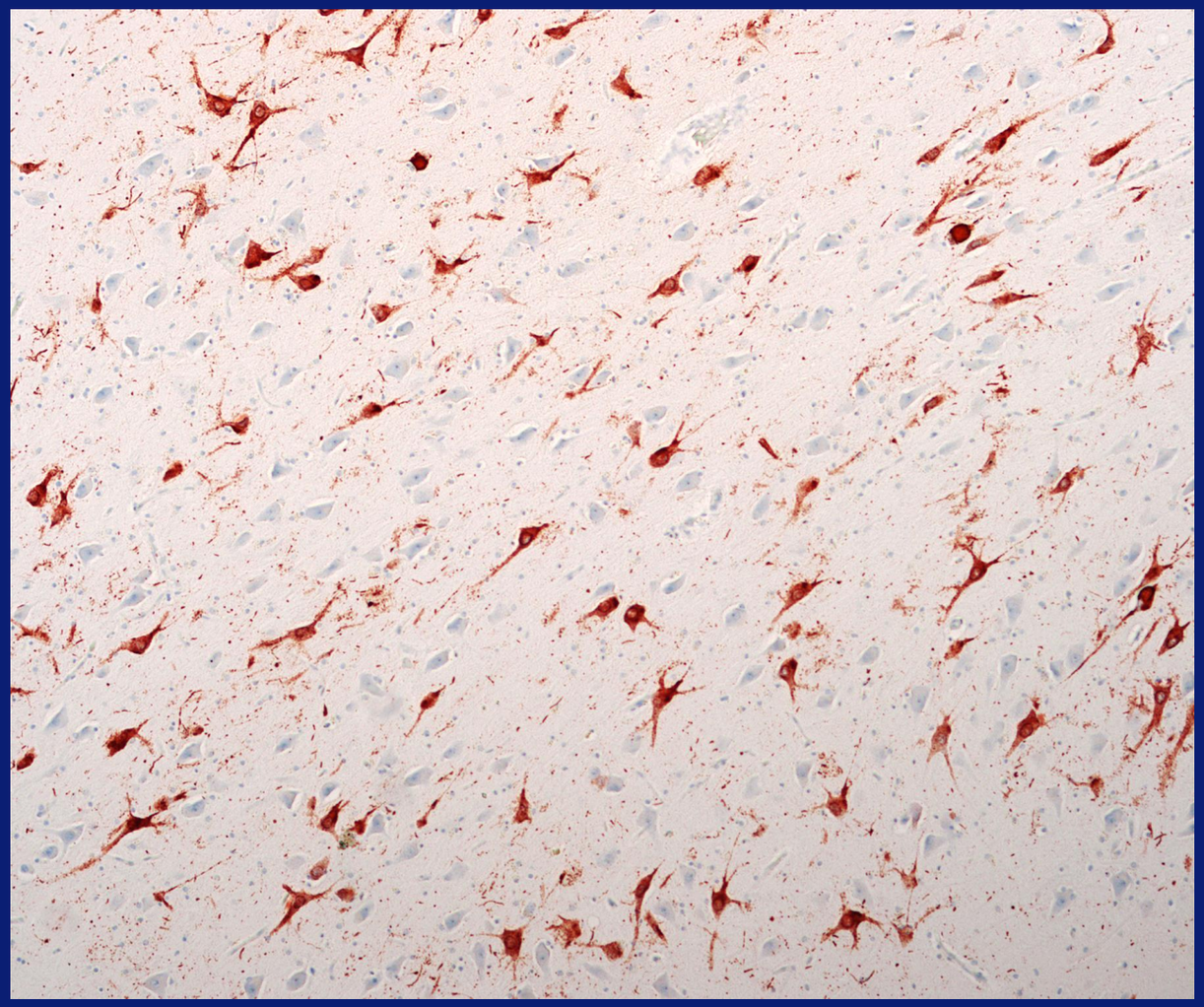
Inferior Frontal Cortex



Hippocampus

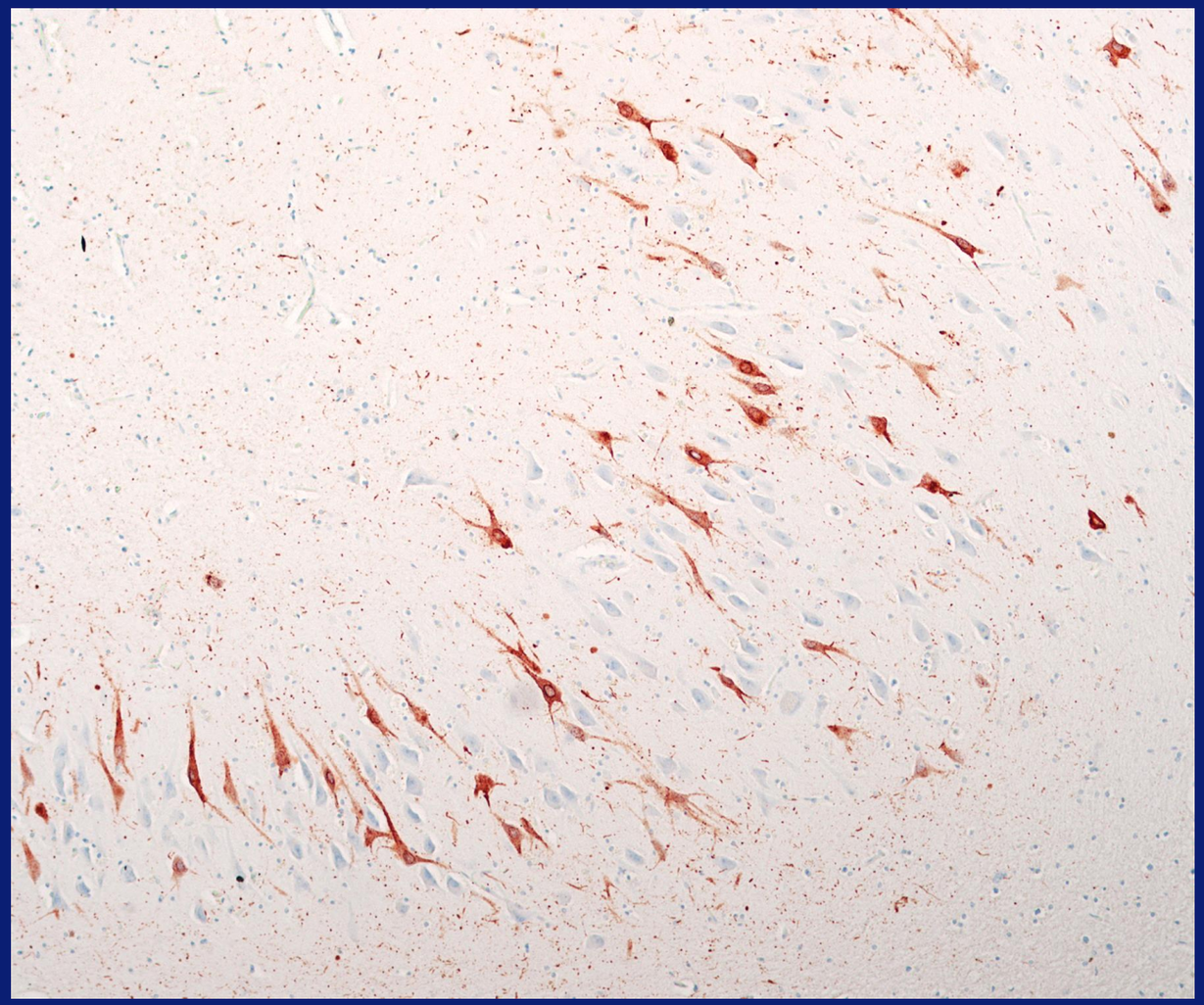


CA4/CA3

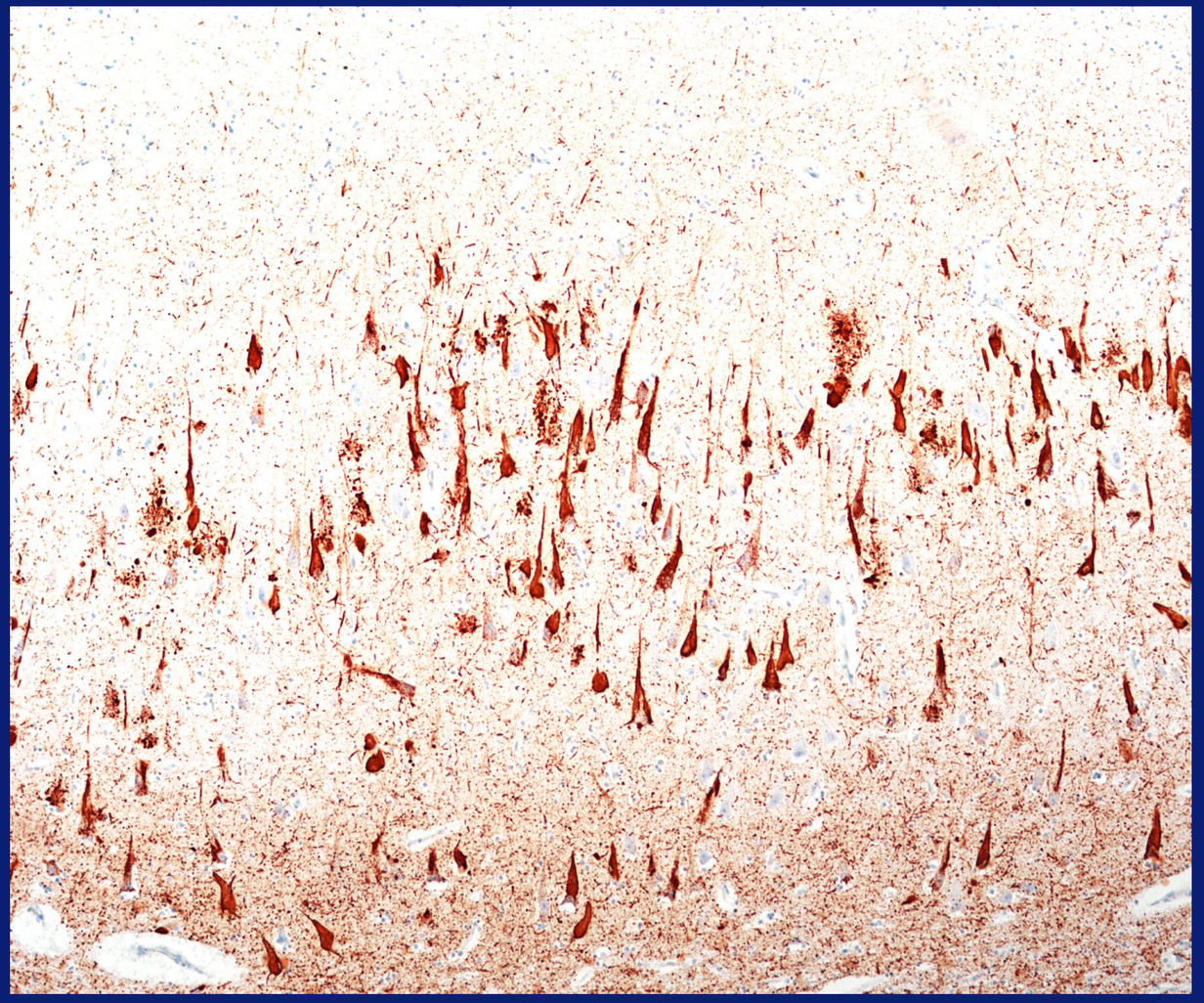


CA4

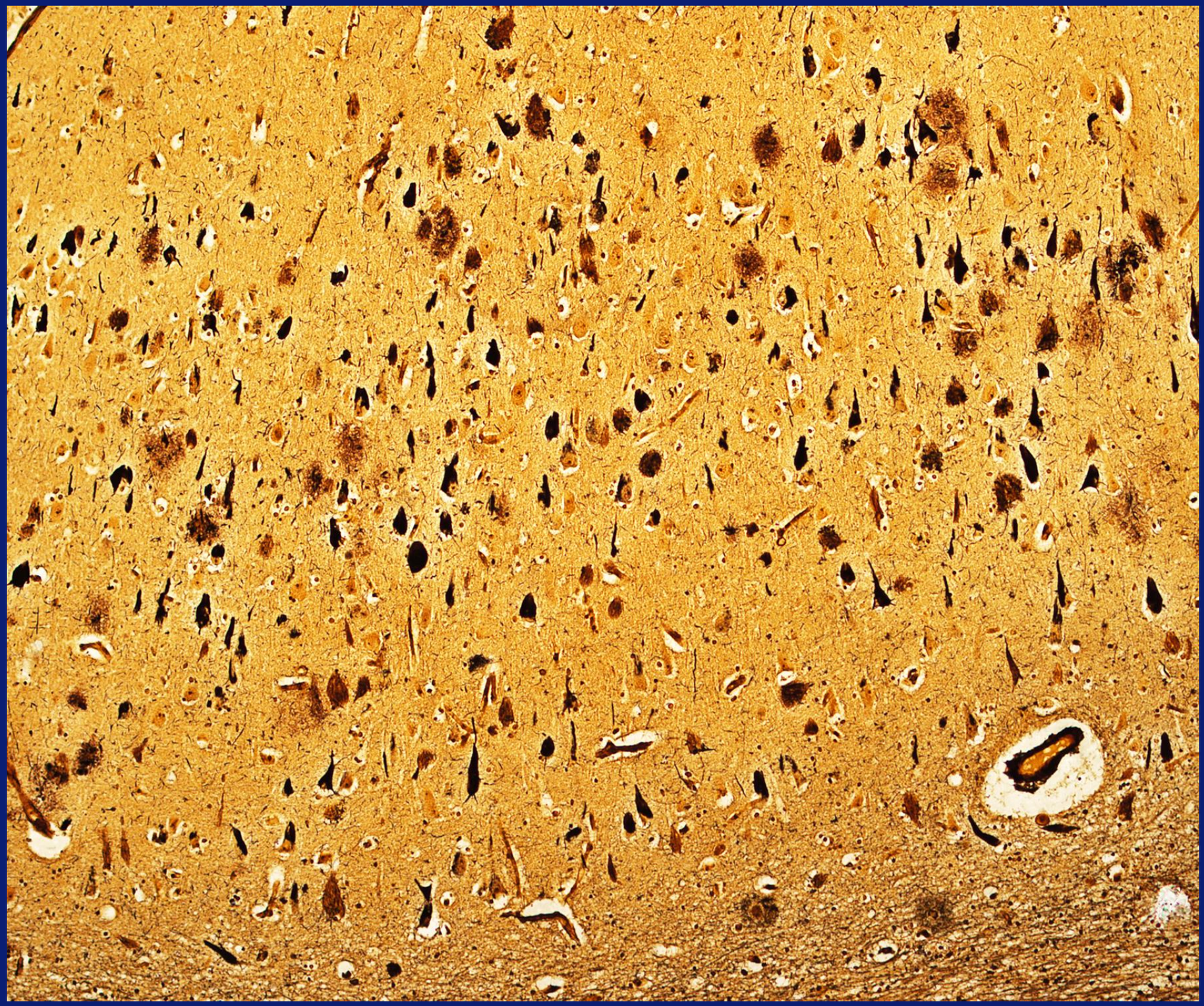
Hippocampus



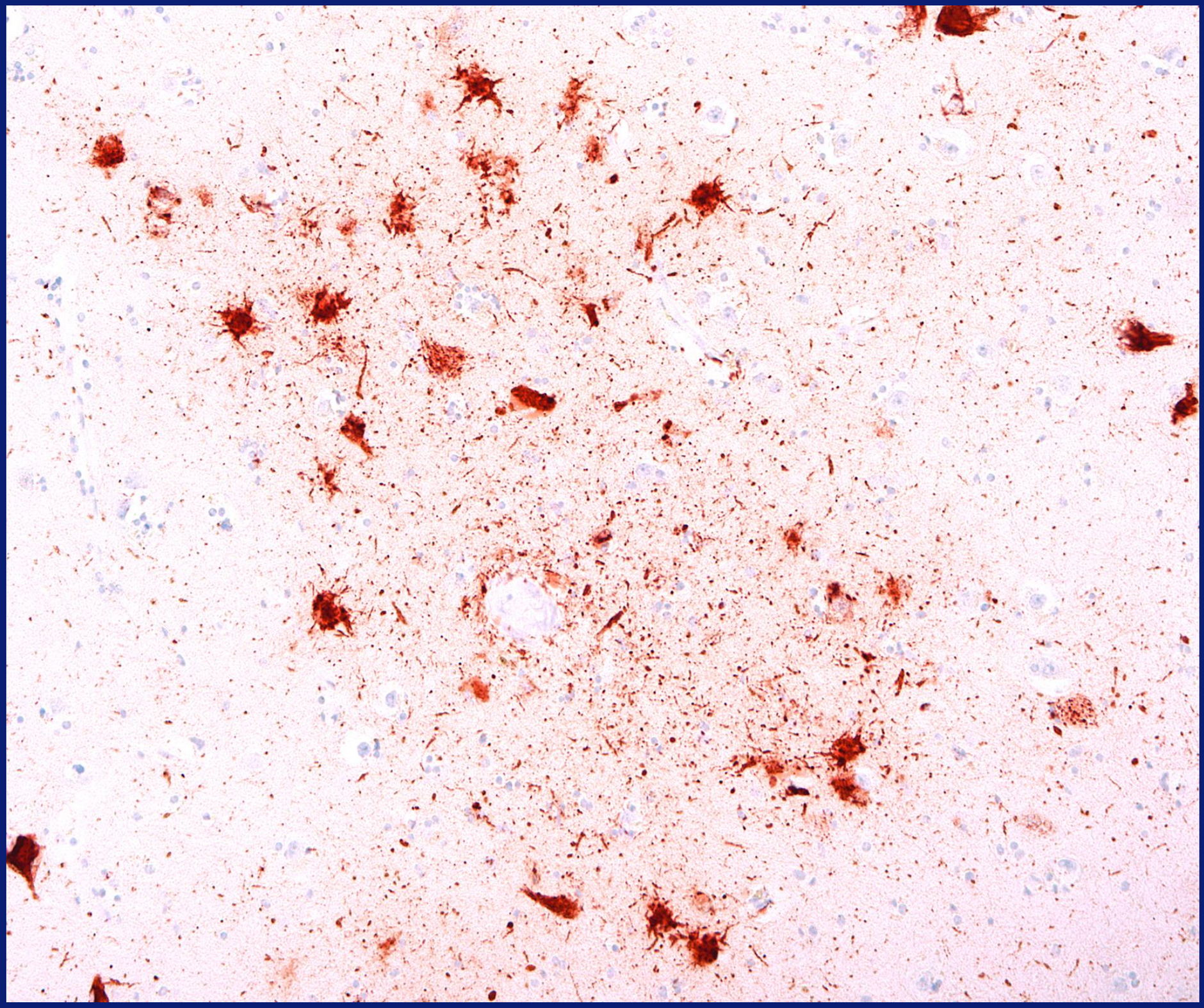
CA2



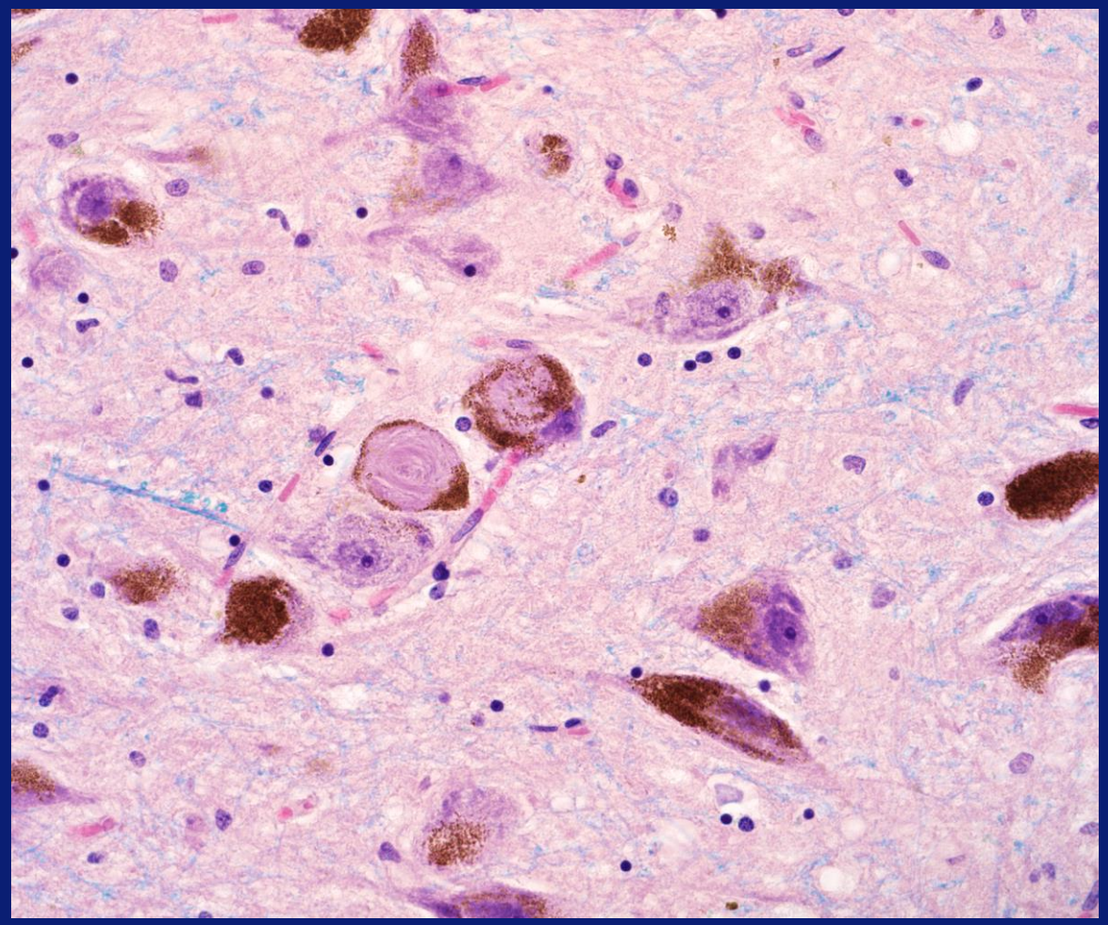
CA1

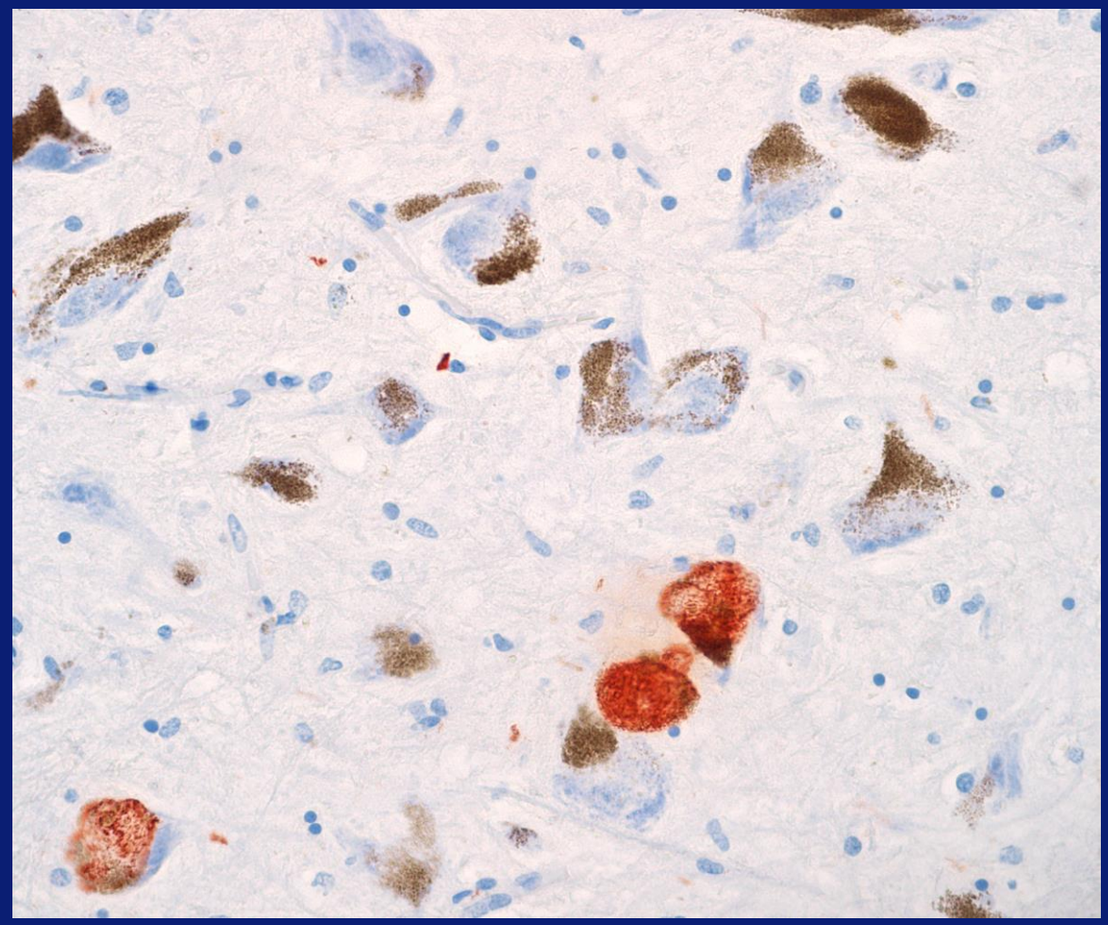


CA1 Bielschowsky

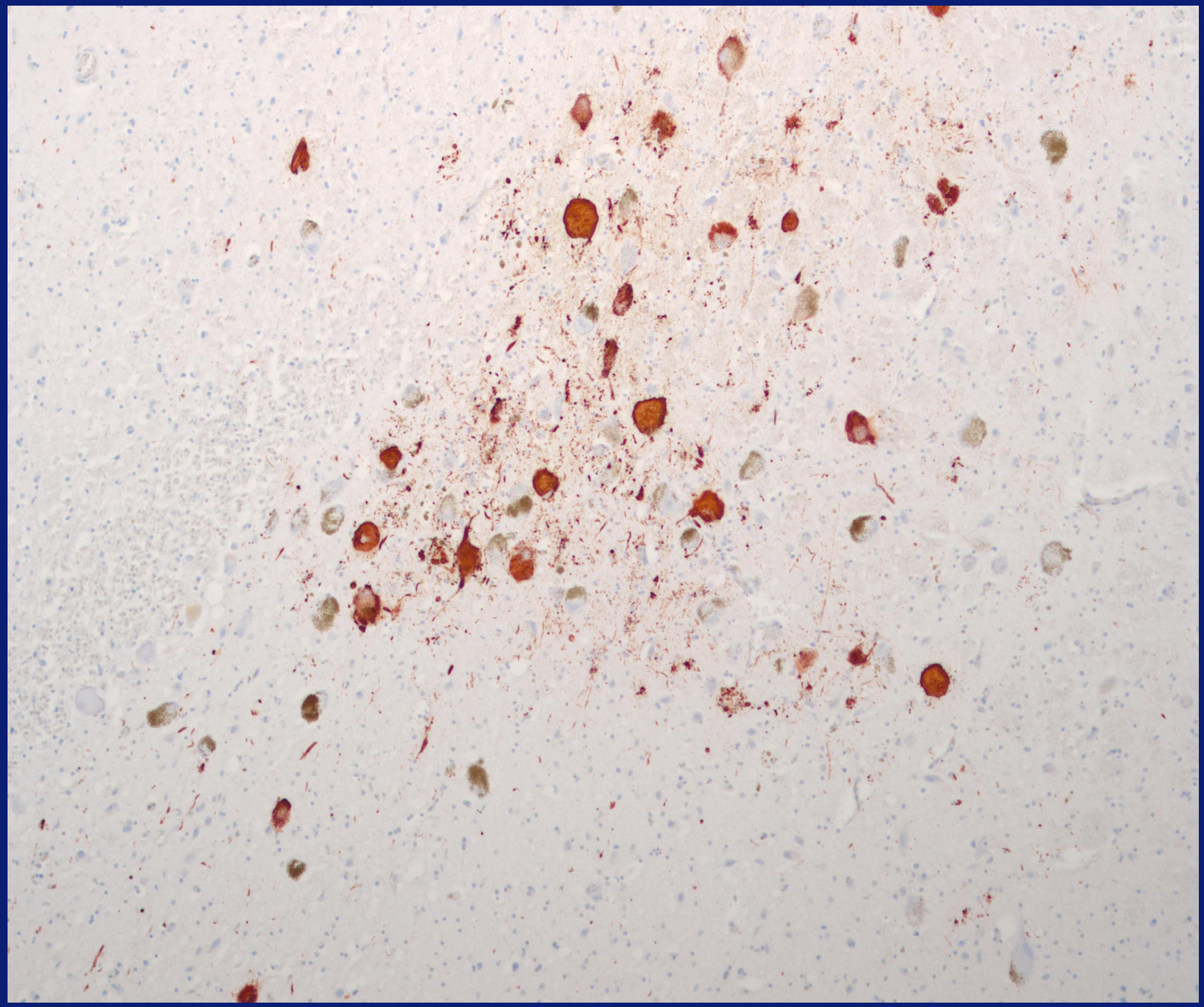


Amygdala

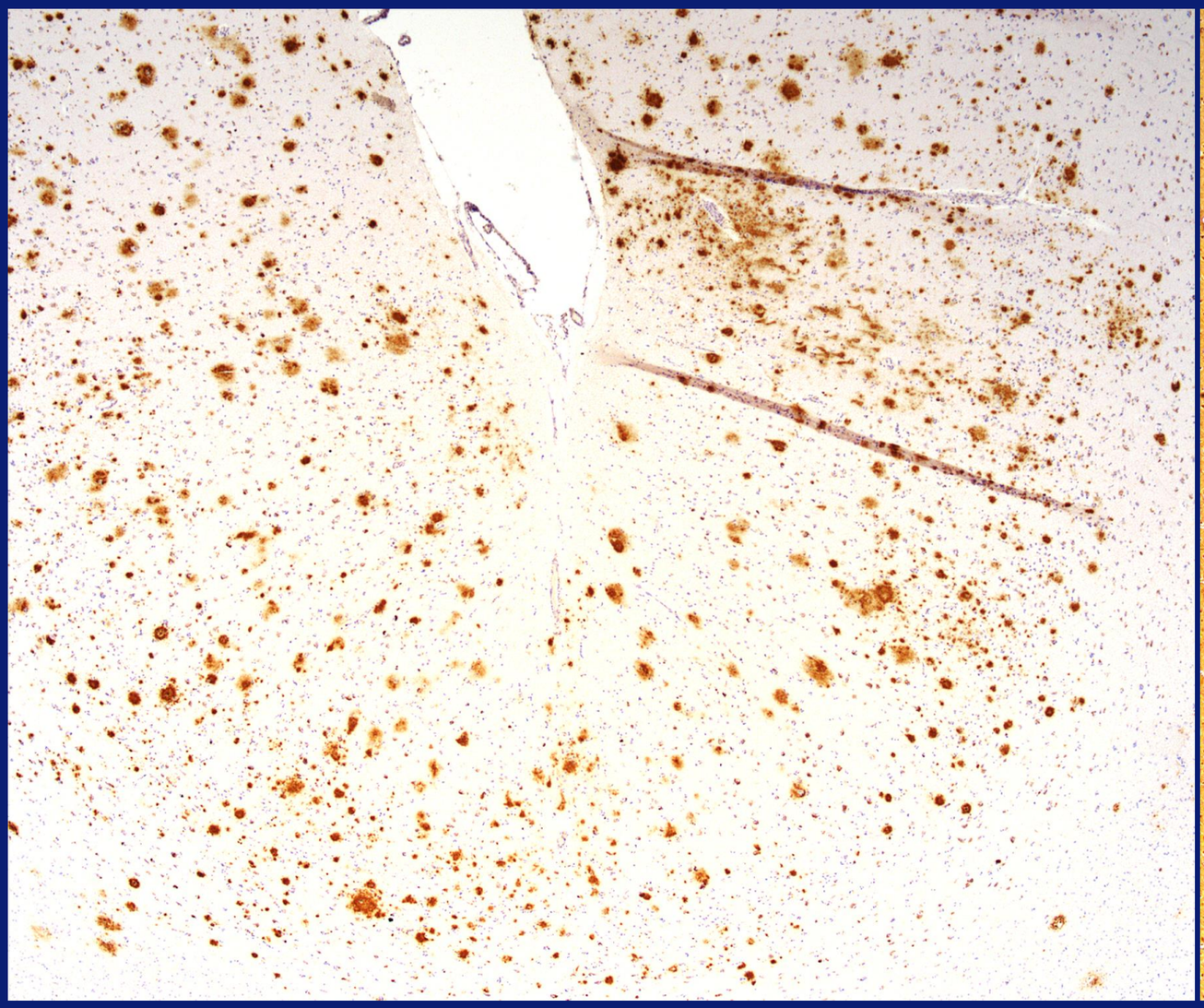




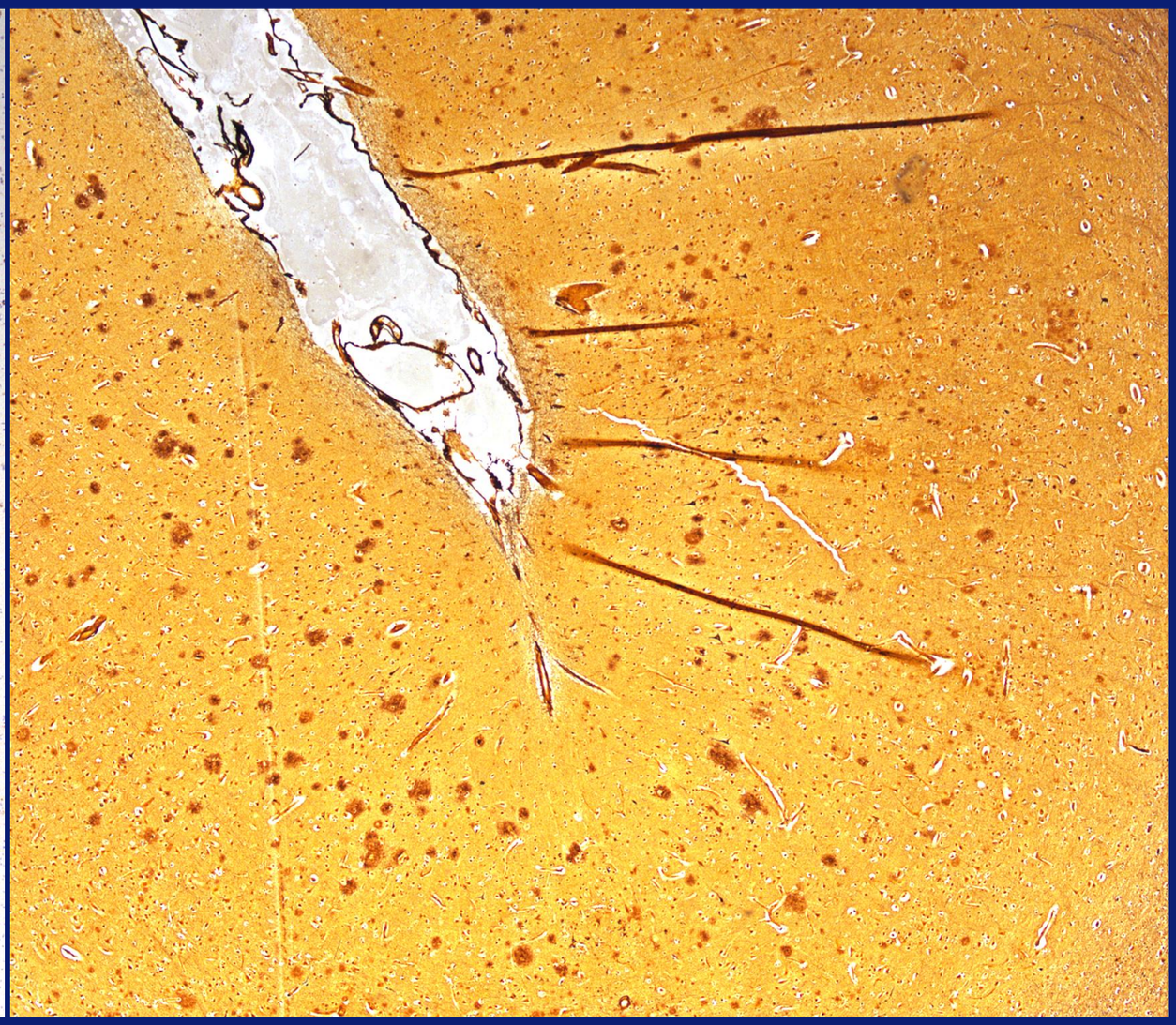
Substantia nigra



Locus Coeruleus

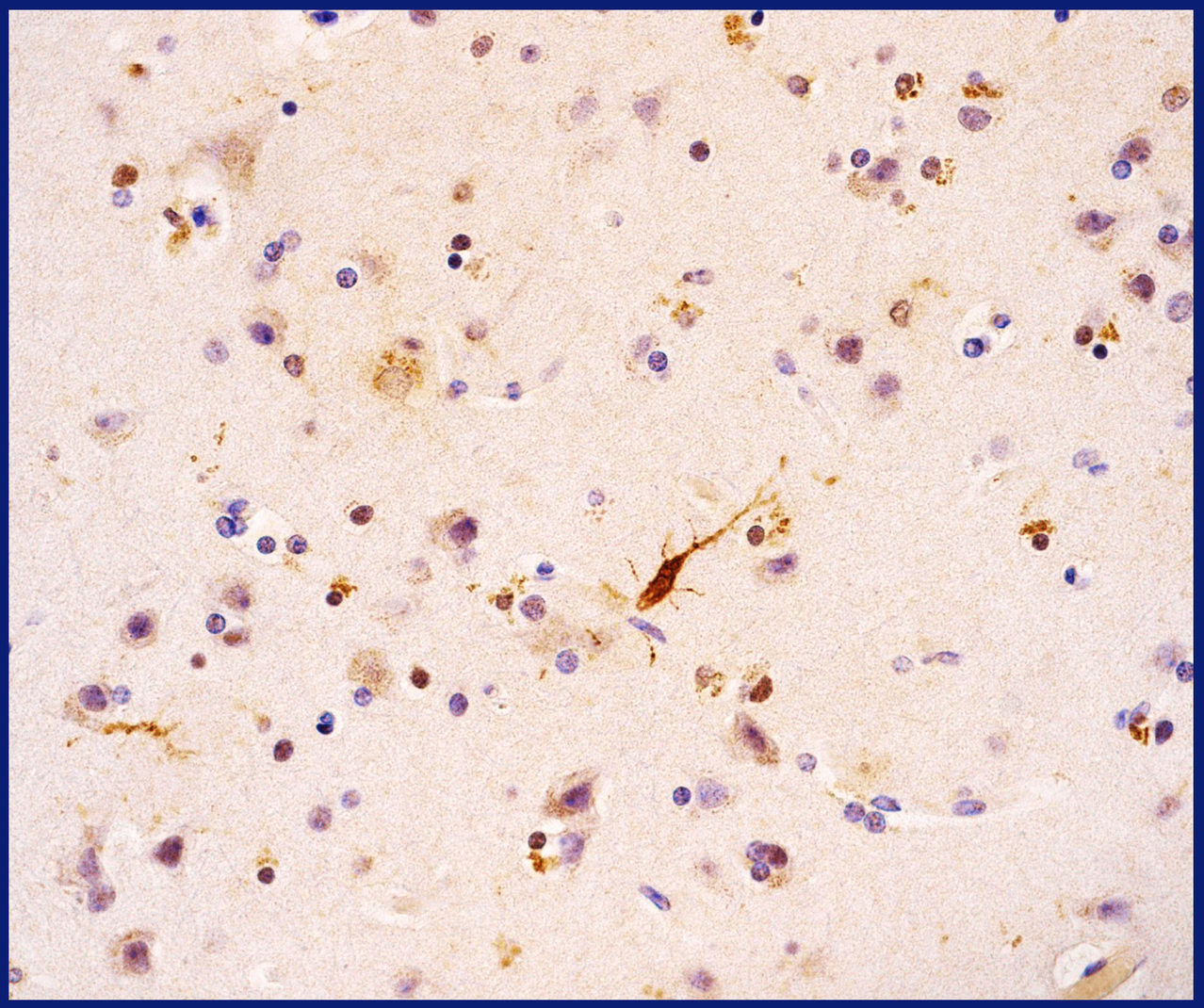


Aß

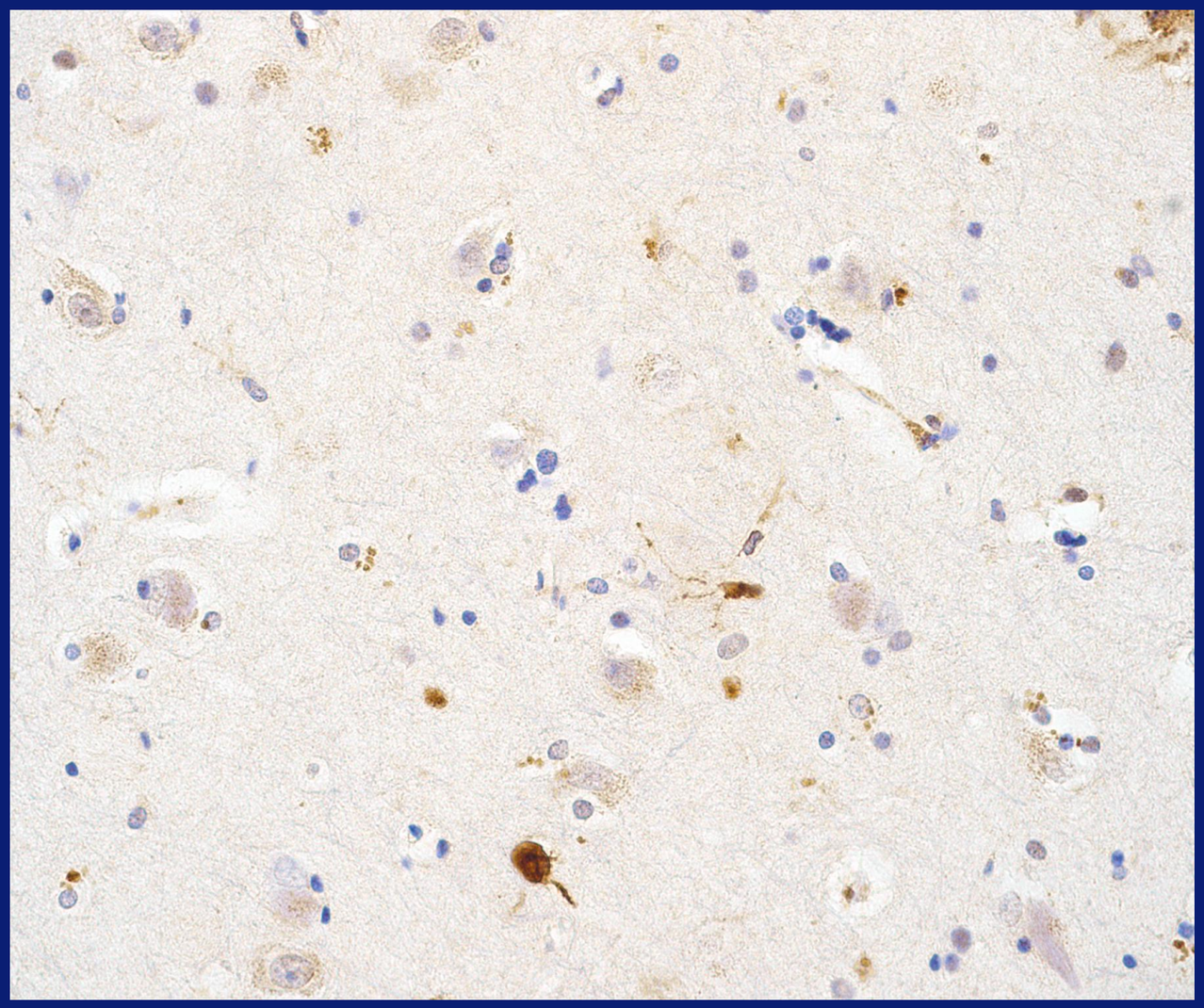


Bielschowsky

Thal Stage 4, Sparse Neuritic Plaques



Frontal cortex



Amygdala

TDP-43

Case 2:
Diagnosis?

Case 2:

CTE Stage III:

- Mild frontal, parietal, temporal atrophy
- Cavum septum pellucidum
- Multiple pathognomonic lesions cerebral cortex
- Widespread p-tau lesions: bank and crest of cerebral cortex, dense NFTs in CA4, CA1, entorhinal cortex, amygdala, substantia nigra, locus coeruleus

Without prominent neuronal loss

Without involvement of basis pontis, dentate nucleus cerebellum

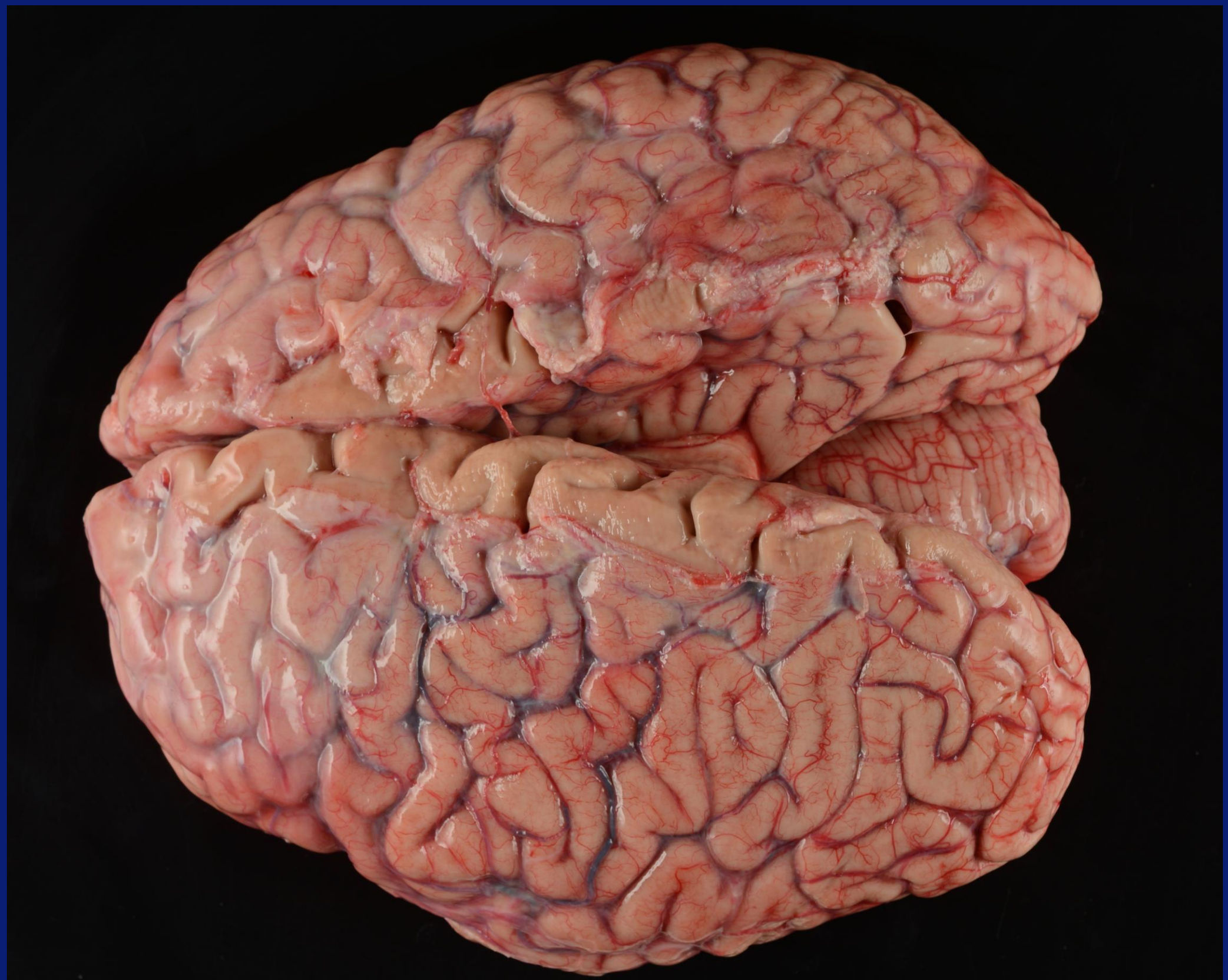
Case 2:

1. CTE Stage III
2. **Alzheimer's Disease Neuropathological Change: NIA/Reagan: Intermediate likelihood Thal 4, A3; Braak 5, B2; CERAD 1, C1**
3. **LATE Stage 3**
4. **White Matter Rarefaction, moderate**
5. **Arteriolosclerosis**

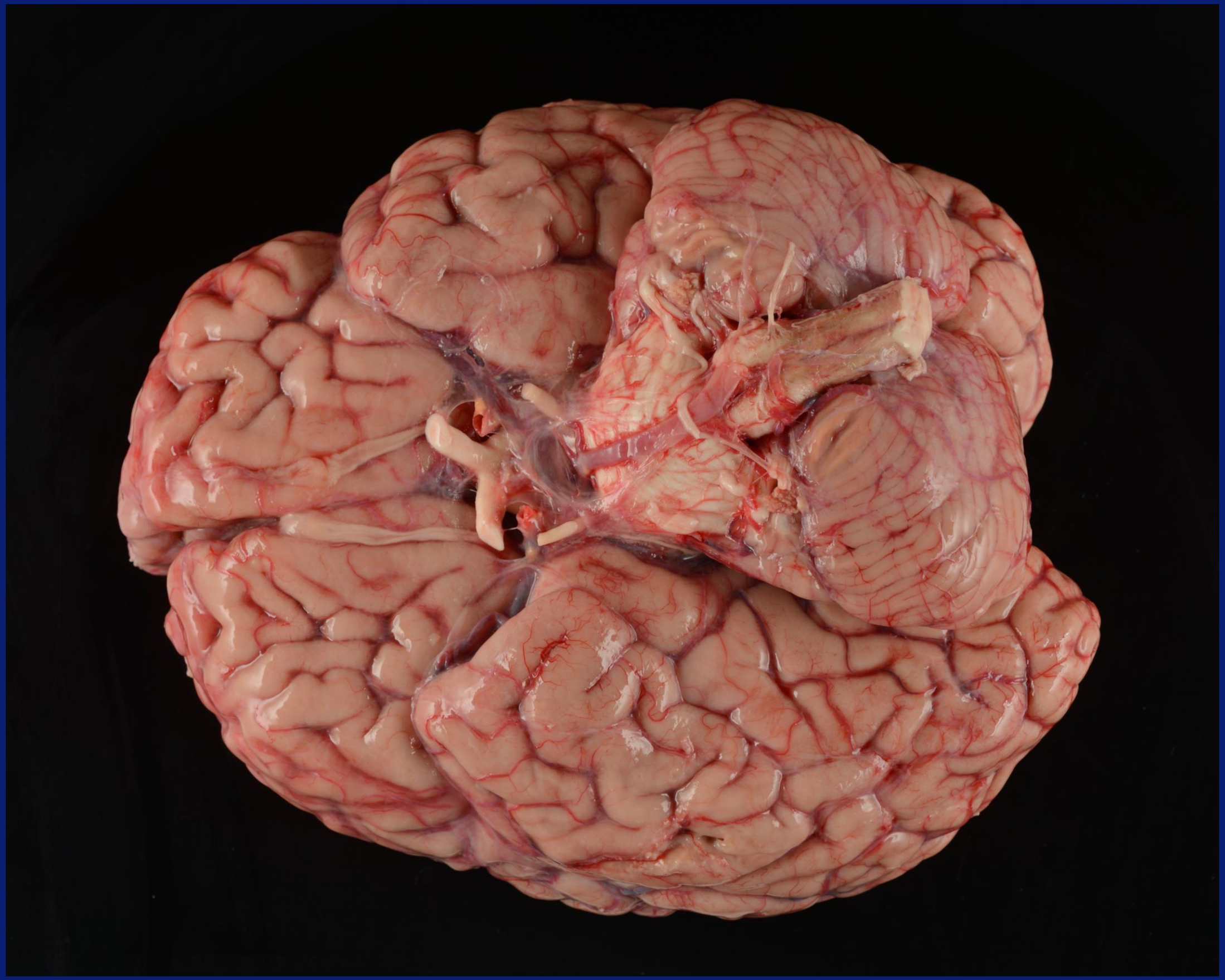
Case 2:

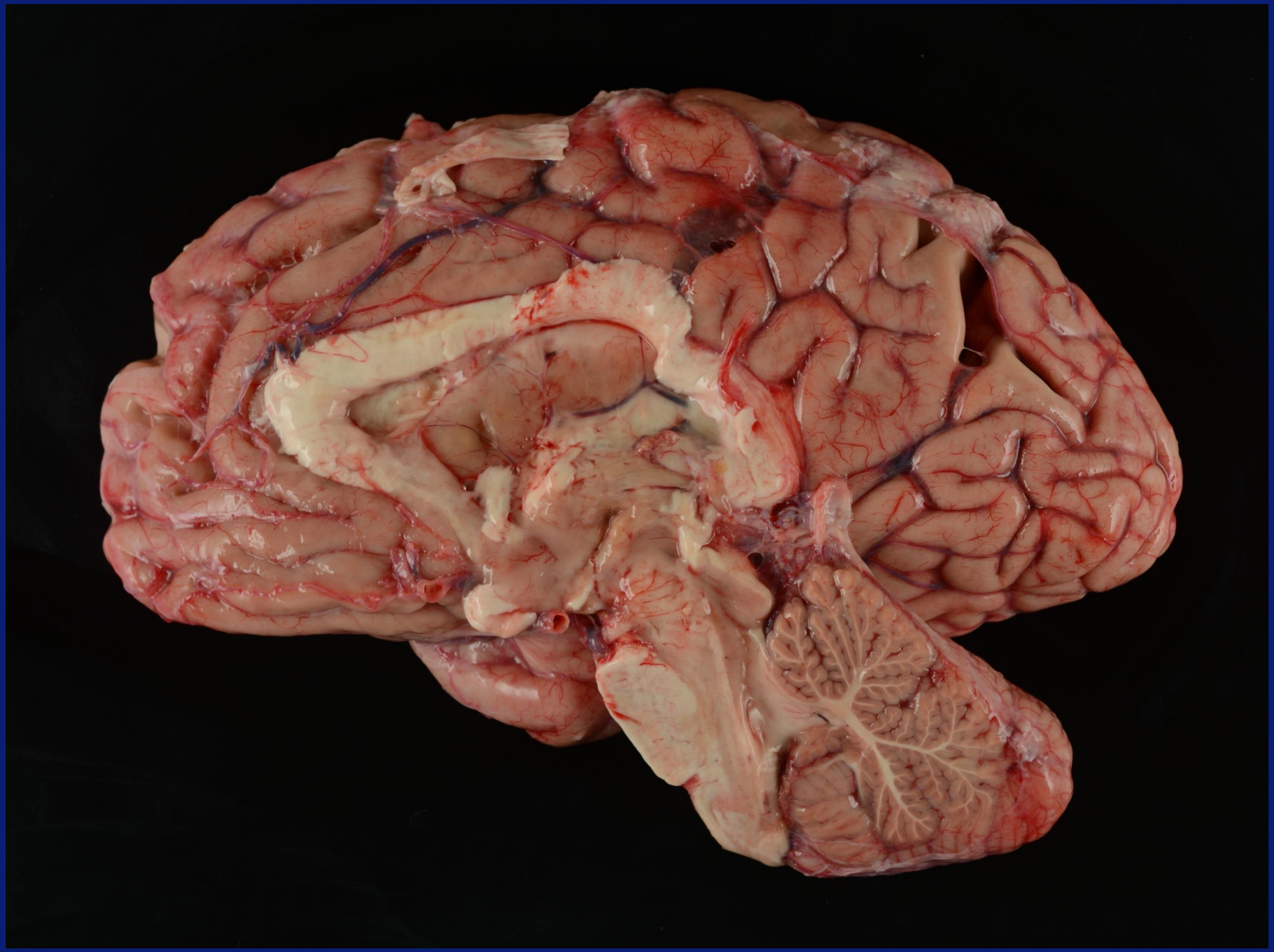
63 years old
Football for 21 years as a middle linebacker
    4 years in the NFL
    3 years in the USFL
At 56, increasingly short fuse
Late 50s, lost interest in his hobbies
Sleep difficulties and sleepwalking episodes
Worsening depressed mood and mood lability
At age 61, memory problems and mild cognitive impairment
At age 62-63, more isolated, childlike and immature
Death by suicide

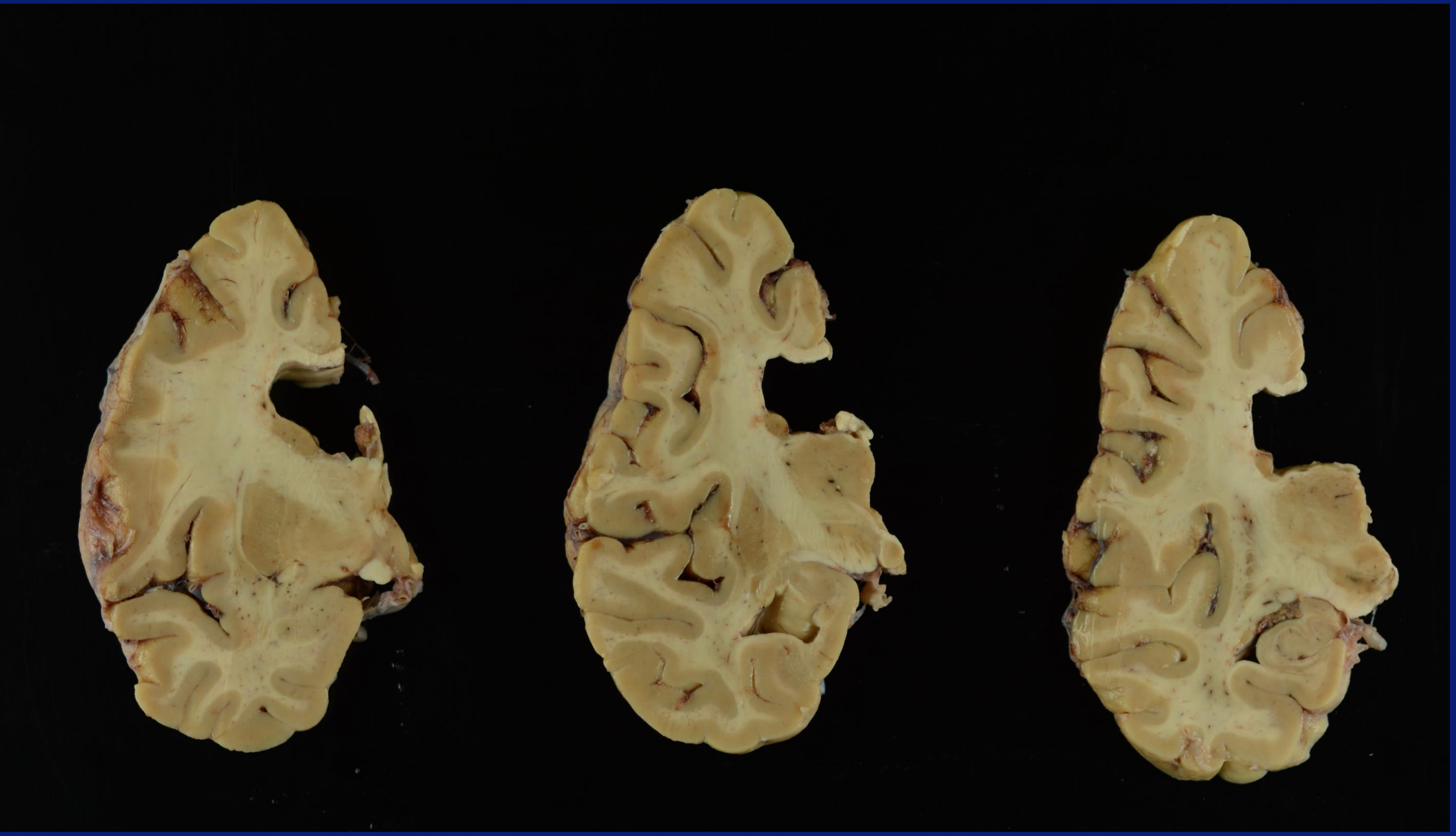
Case 3



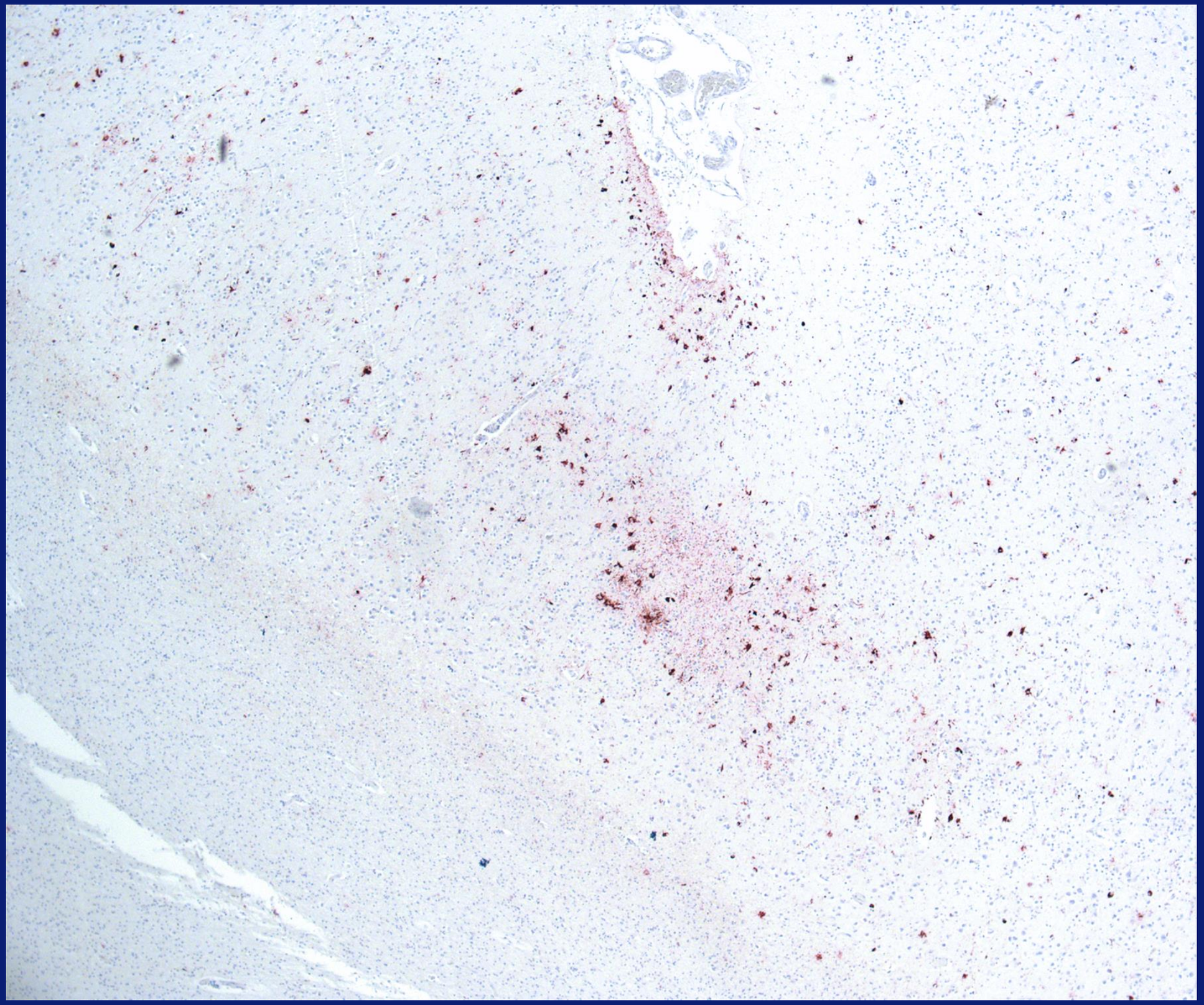
Brain weight: 1092 grams



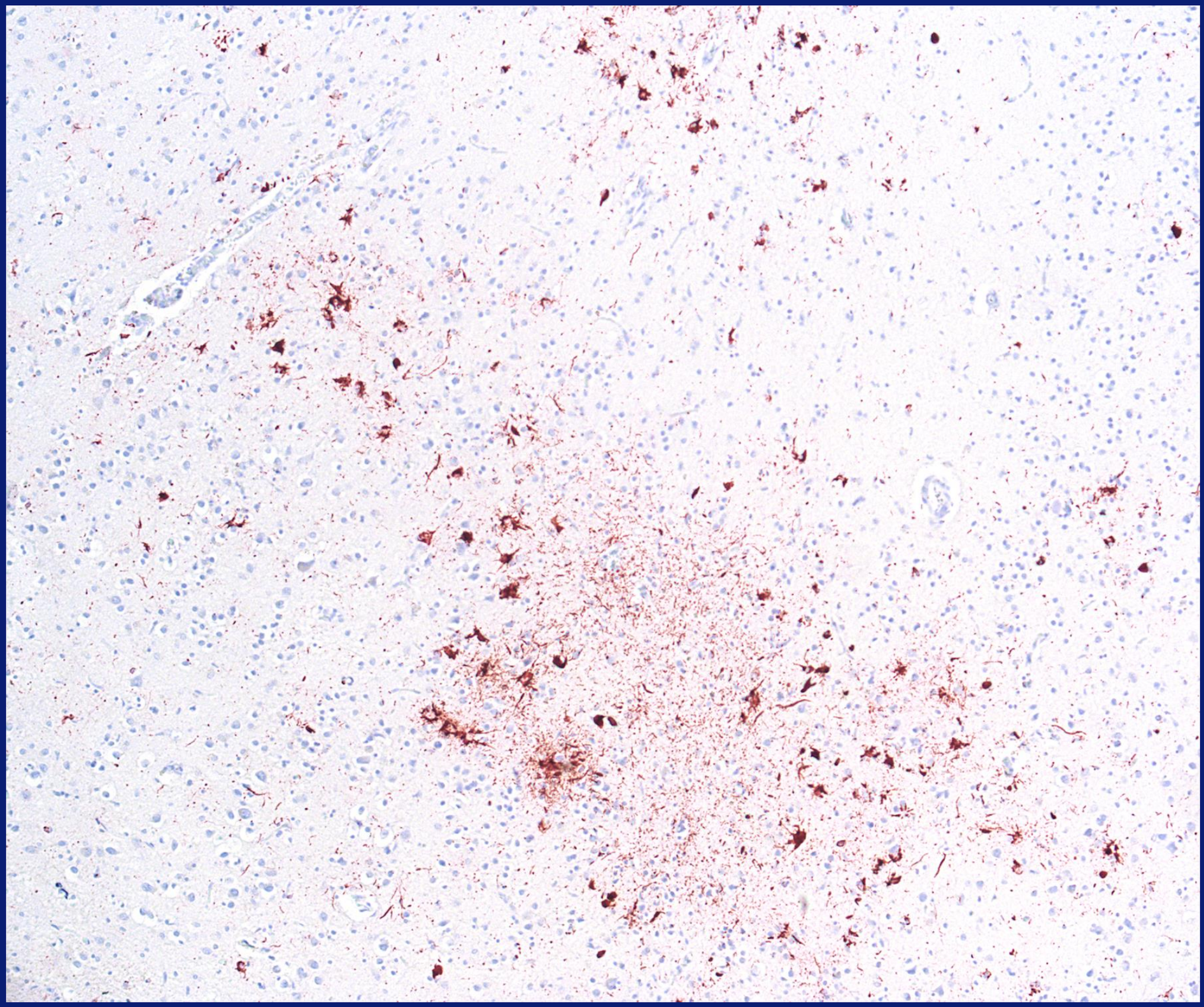




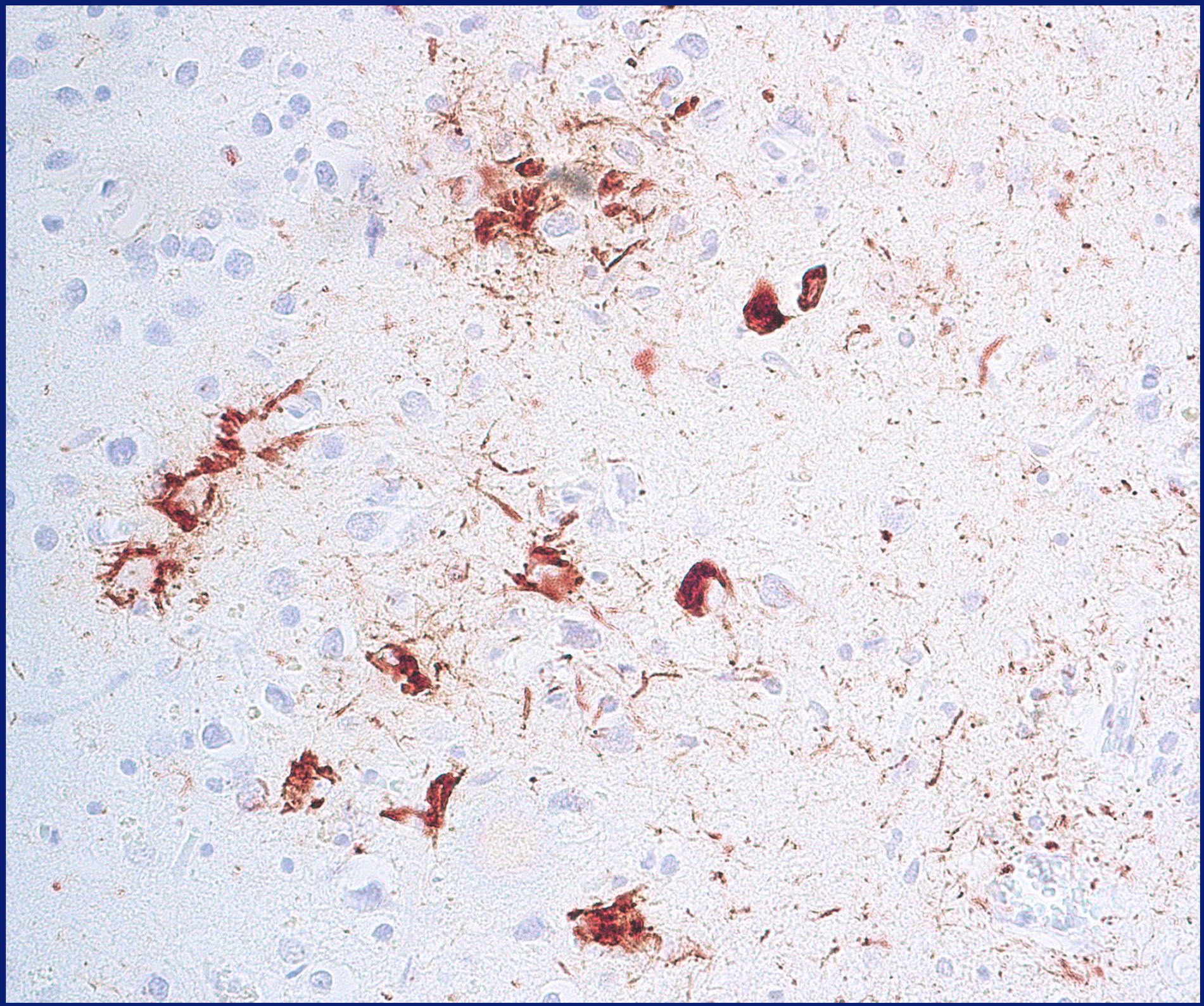
Rolandic cortex



Rolandic cortex



Rolandic cortex



Case 3:
Diagnosis?

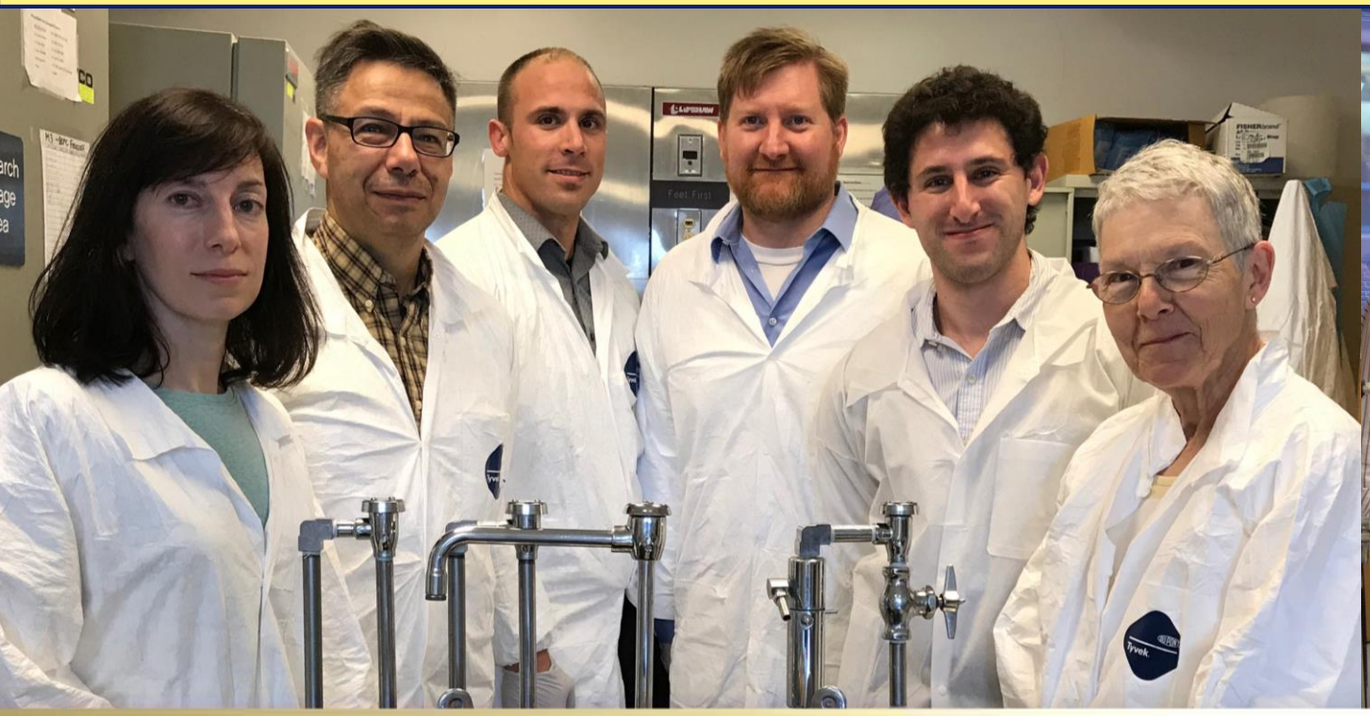
Case 3:

1. **Chronic Traumatic Encephalopathy, stage IV**
2. **Features of PSP:**
   Dense NFT in motor nuclei: basis pontis, red nucleus, subthalamic nucleus, dentate nucleus, globus pallidus, inferior olives, spinal cord
   Unclassifiable astrocytic inclusions
3. **LATE**

Case 3:

75 year old
Football for 28 years including 12 years as linebacker in NFL
At age 69, his driving declined, hesitations in making turns
Age 70, slowed, effortful movements
Age 71, anxious and occasional falls
Asymmetric poor functioning of the left side while walking
Impulsive changes in position triggered falls
Severe apraxia
By 73, he could not button a shirt or put a letter into an envelope
Word-finding difficulty, angered easily with perseveration
Impulsivity, poor insight.
By 75, episodes of festination, occasional choking
Hypophonic with mild masking of left face, bilateral tremor,
Severe apraxia on the left
Difficulty initiating voluntary eye movements
Increased axial and appendicular tone L>R
Frontal release signs present.
Gait was wide-based and unsteady
Cognitive impairment with relatively preserved memory
Death from aspiration pneumonia

Boston University CTE Program
BU Alzheimer's Disease Research Center
VA Boston



Thank you!

BU/VA CTE Program

Bobby Abdolmohammadi
Jason Adams, MD
Mike Alosco, PhD
Victor Alvarez MD
Kathryn Babcock
Alexandra Bourlas
Christine Baugh
Andrew Budson MD
Kerry Cormier
Dan Daneshvar, MD, PhD
Brian Frye, MD
Matthew Jacobs
Lee Goldstein MD PhD
Bertrand R. Huber, MD, PhD
Doug Katz, MD
Patrick Kiernan
Neil Kowall, MD
Carol Kubilus
Ian Mahar
Jesse Mez, MD
Jason Miller
Phillip Montenigro, MD PhD
Lauren Murphy
David Riley, MD
Cliff Robbins
Jon Cherry, PhD
Hyo Soon-Lee MD
Todd Solomon, PhD
Thor Stein, MD, PhD
Robert Stern PhD
Sarah Svirsky
Prince Williams
Rhoda Au, PhD

BU Goldstein Lab

Andrew Fisher, PhD
Chad Tagge, PhD
Juliet Montcaster, PhD
Mark Wojnarowicz

CLF

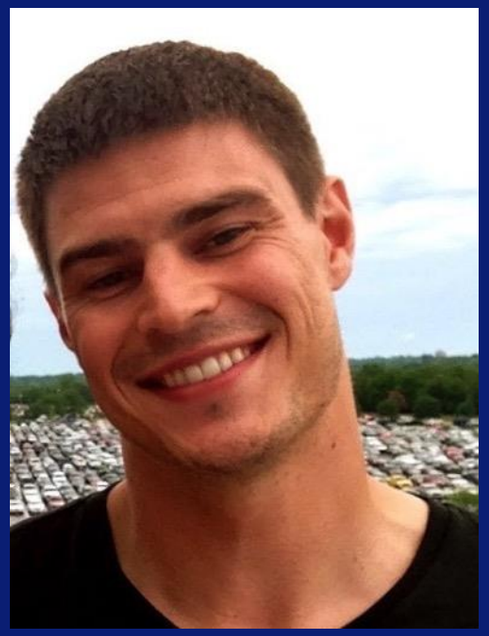
Robert Cantu, MD FACS
Chris Nowinski PhD
Lisa McHale

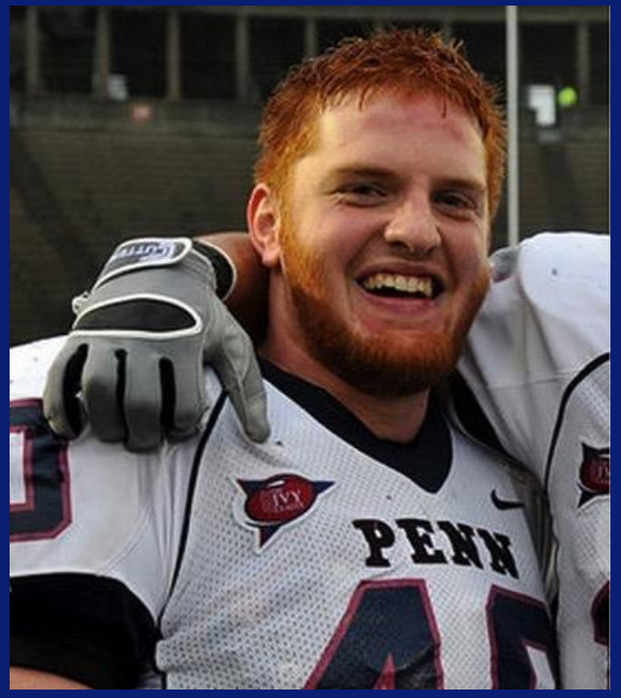
BU/VA CTE Program

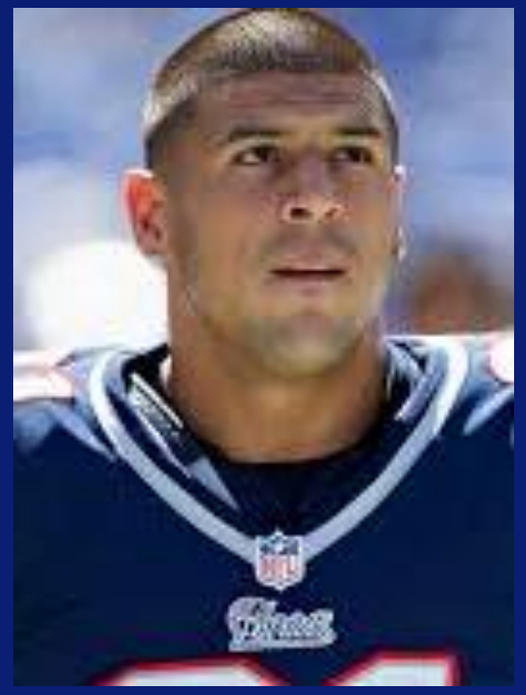
Sarah Chancellor
Ern Dixon
Racheal Downes
Camille Esnault
Lucas Fishbein
Sarah Horowitz
Hunter Kelley
Daniel Kirsch
Rebecca Mathias
Robert McCormack
Evan Nair
Ray Nicks
Nicole Saltiel
Arsal Shah
Madeline Uretsky

Other Institutions

Kevin Bieniek, UT San Antonio
John Crary, MD, PhD ISMMS
Dennis Dickson, MD Mayo Clinic
Kristin Dams O'Connor PhD ISMMS
Kurt Farrell, PhD ISMMS
Michael Strong, MD Western
Amanda Woerman, PhD U Mass Amherst







All the families who participated in our research

Funding sources:

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

Q and A?