Chronic Traumatic Encephalopathy:

A Distinct Pathologic Entity Associated with Repeated Brain Injuries

What we've learned from athletes

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Center for the Study of Traumatic Encephalopathy

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Goal: To study the long-term effects of sports-related brain trauma

CSTE Brain Bank – pathological research is the bedrock of the study of disease. We study brain and spinal cord tissue of former athletes to better understand the cause, progression, and characteristics of the disease

Brain Donation Registry – a registry of current and former athletes who are willing to participate in longitudinal research and donate their brains and spinal cords after death

Clinical Studies – CSTE will conduct and support research designed to identify genetic and environmental risk factors, diagnostic tests, and treatment

CSTE Brain Bank

2008-2010

Number of brains	Sport	Age range
32	football, boxing, wrestling, hockey, other	17 – 87 years
26	CTE	
12	CTE - NFL football	38 – 87 years
12 NFL /13 analyzed		12 /13 with CTE
Same time period		321 NFL deaths

Lifetime Prevalence of CTE

	# cases with CTE	# cases without CTE	age range	mean :	Lifetime Prevalence
12 = number of former NFL players' brains analyzed at autopsy 2008-2010	12	0	38 – 85 years	60.5 years	
308 = number of former NFL player deaths without autopsy 2008-2010 (NFL families who declined autopsy or could not be contacted)	(0*)	(308*)			
321§ = number of former NFL player deaths 2008-2010					12/321 = at least 3.7% among former NFL players who died between 2008-2010

§ http://www.freewebs.com/oldestlivingnfl/2009200necrology.htm

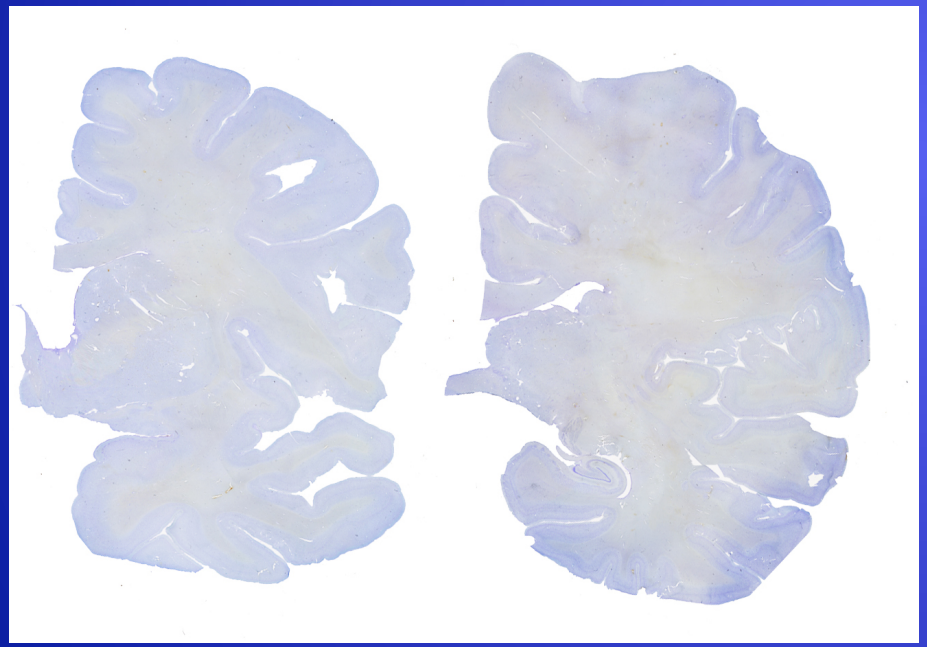
* assumption

variables affecting lifetime prevalence include life expectancy, head trauma exposure, genetic susceptibility

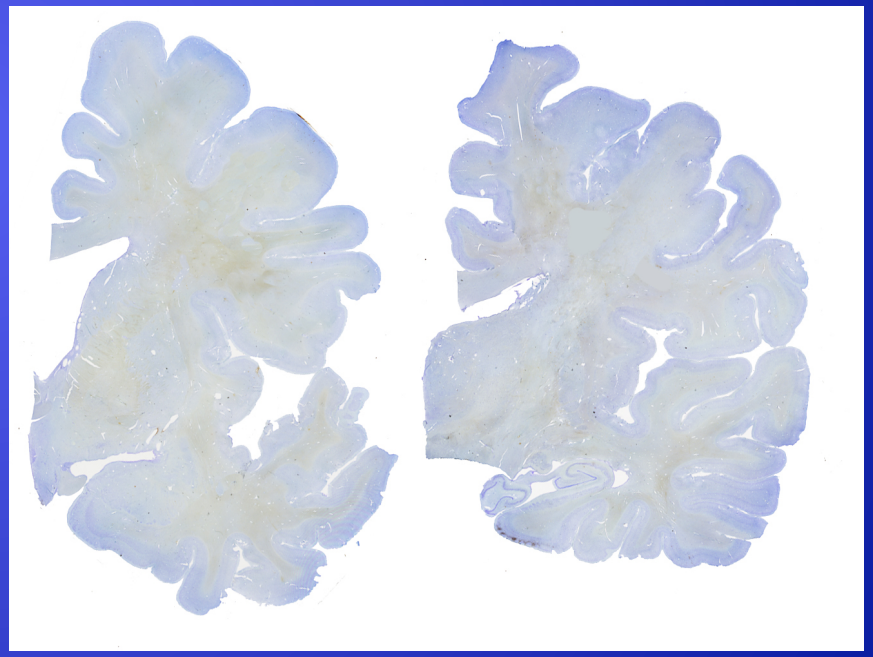
Framingham Heart Study

>140 subjects; >70 cognitively intact Longitudinally assessed since 1948

Immunostained for hyperphosphorylated tau



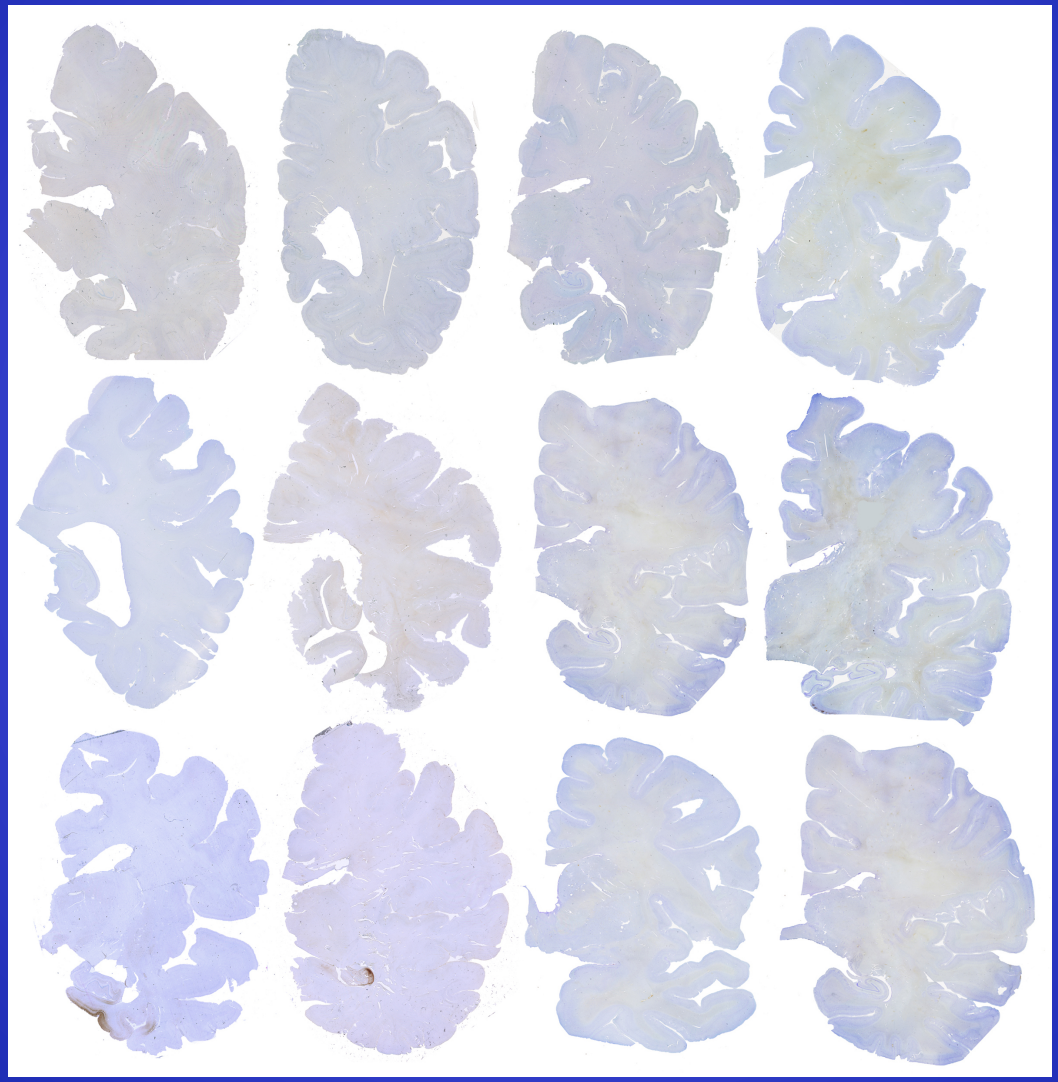
61 year old man



68 year old man

Age-matched controls

12 cognitively normal men, ranging in age from 53 – 85, mean 65 years



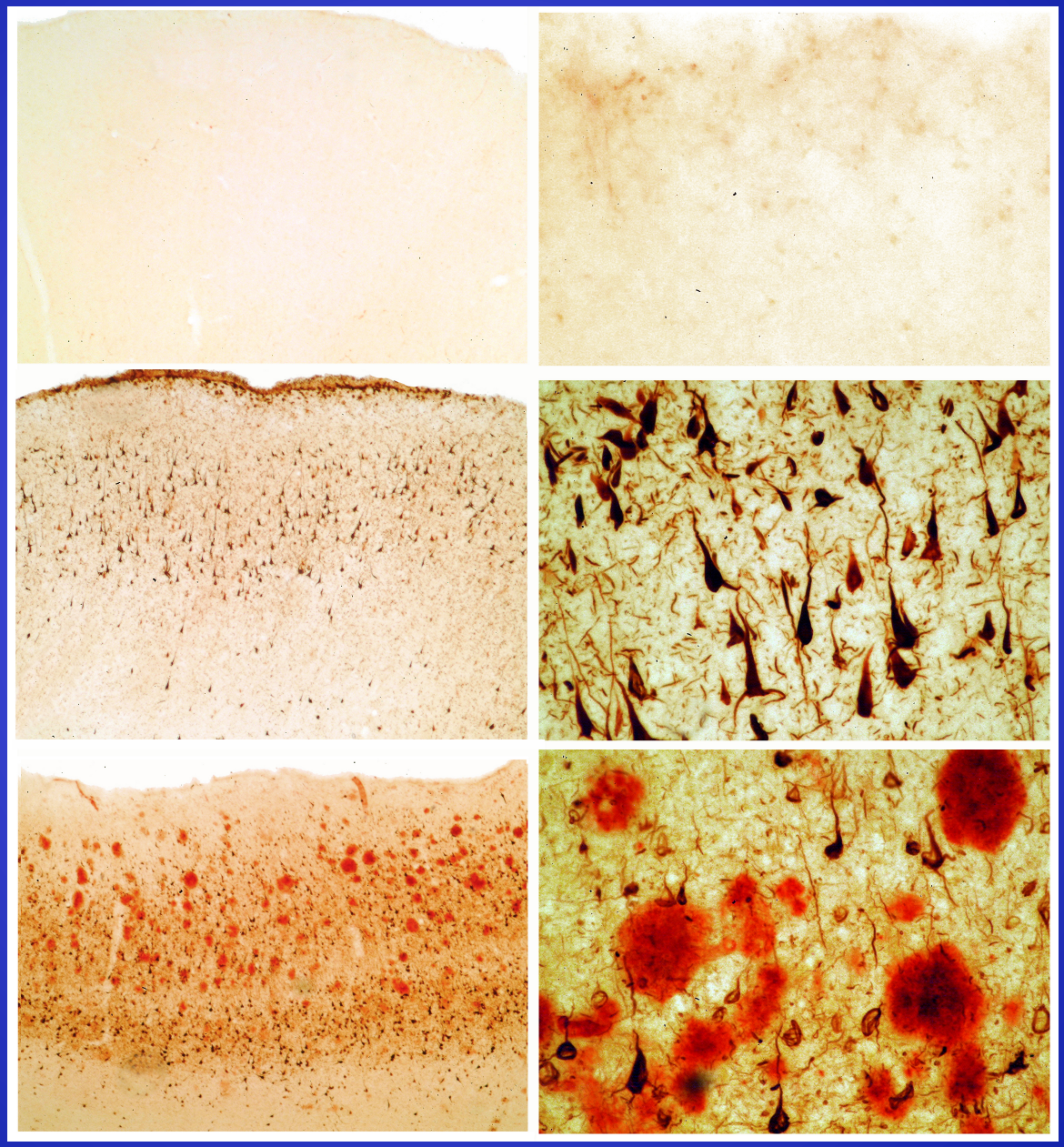
Hyperphosphorylated tau

CTE is entirely distinct from Alzheimer's disease

Normal

CTE

Alzheimer's disease



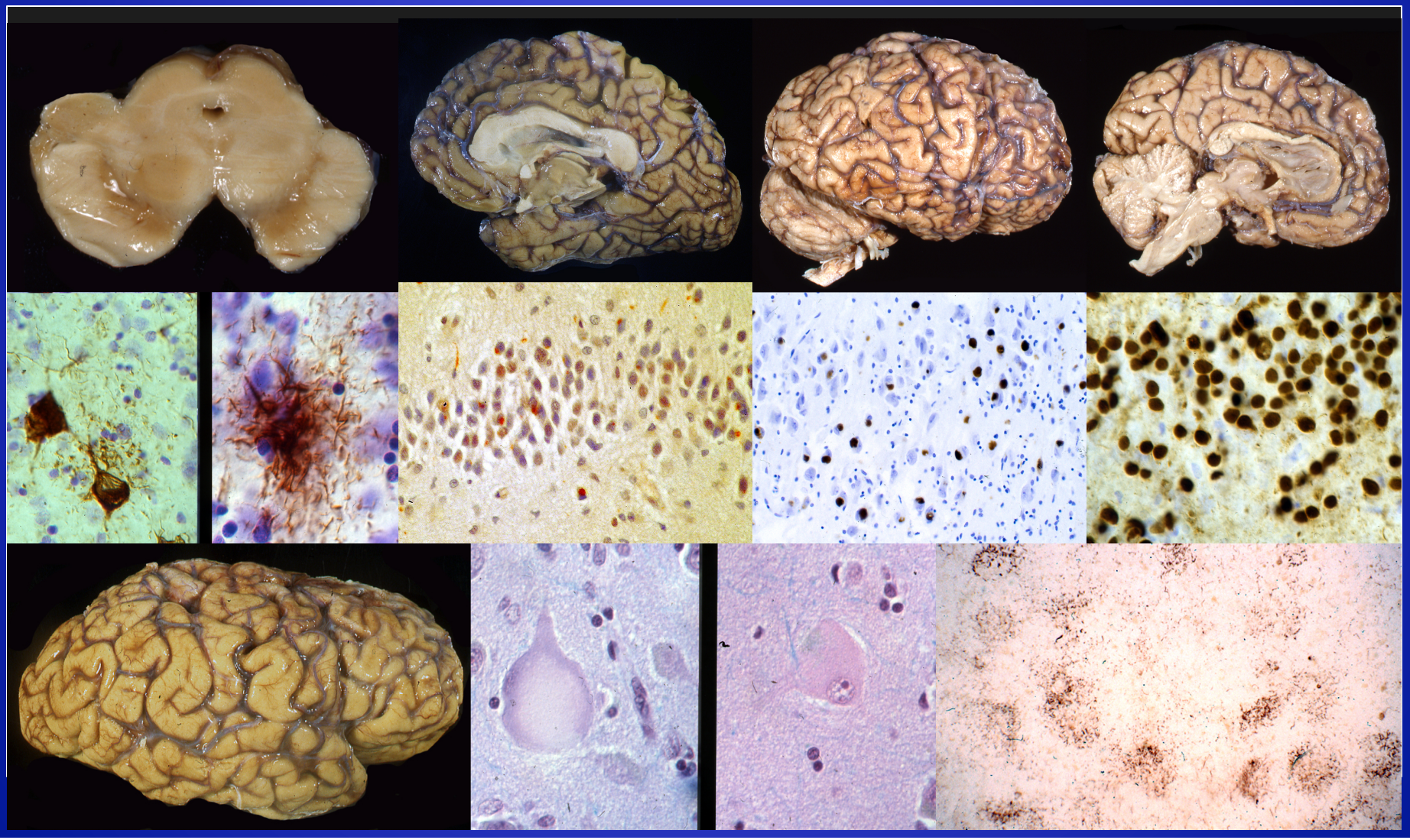
no Aß, no tau

P-tau no Aß

P-tau and Aß

CTE is a distinct disease, not to be confused with any other tauopathy

psp ftld-u picks cbd



CTE is characterized by the accumulation of hyperphosphorylated tau protein

There is no evidence that steroid use, such as corticosteroids administered to treat rheumatological or autoimmune disease, produces any neuropathological abnormalities in tau protein in human brain

There is no evidence that alcohol, marijuana, cocaine, or other recreational drugs alone produce neuropathological abnormalities in tau protein

The players who developed CTE had no history of anabolic steroid use - 40% played in the 1950s and 1960s - before the use of performance enhancing drugs or anabolic steroids

Chronic Traumatic Encephalopathy or Dementia Pugilistica

First described in boxers by Martland in 1928

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

*Prevalence in boxers: at least 17% **

* Roberts GW, Allsop D, Bruton C. The occult aftermath of boxing. J Neurol Neurosurg Psychiatry 1990;53:373-378

Harrison S. Martland

(1883-1954)
First full time paid pathologist
Newark city Hospital, 1909-1927
Chief Medical examiner Essex county

73 year old boxer

Died in the Bedford VA Hospital after 20 years of progressive dementia

World champion boxer for 13 years, retired at the age of 33
In his late 50s, became forgetful with mood swings and restlessness.
Developed apathy, paranoia, irritability, violent agitation, anxiety, aggression
Hospitalized with severe dementia and parkinsonism in his late 60s
Death at age 73

73 year old boxer

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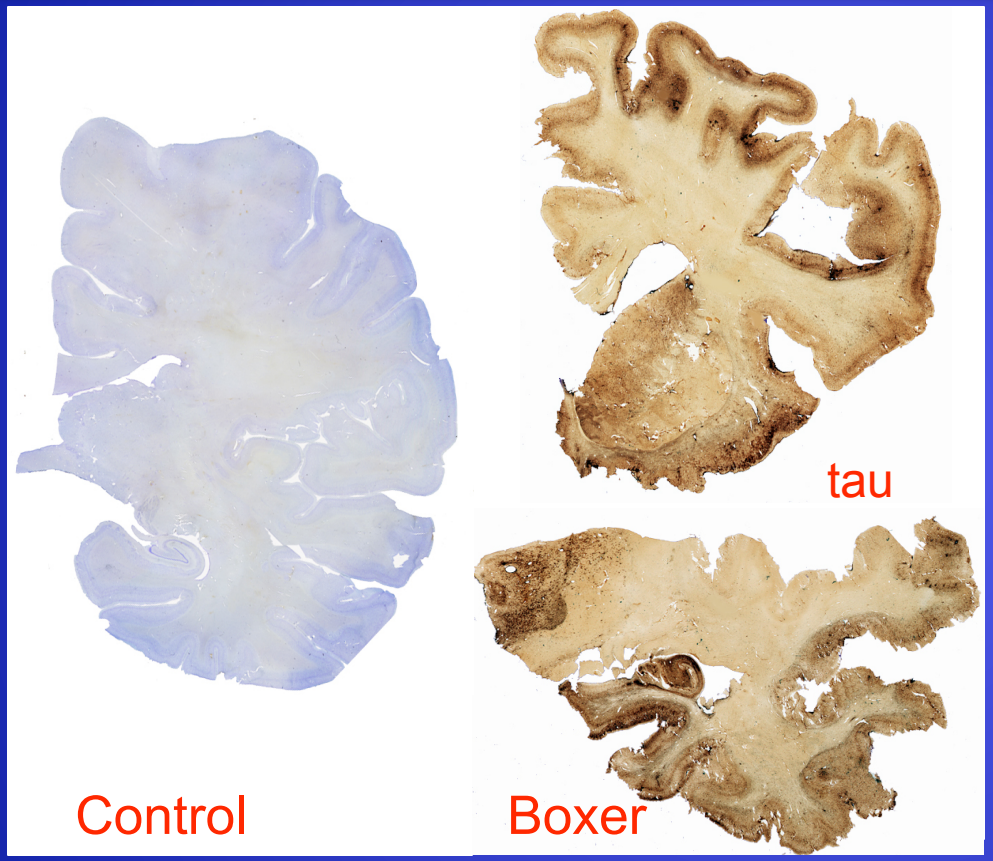
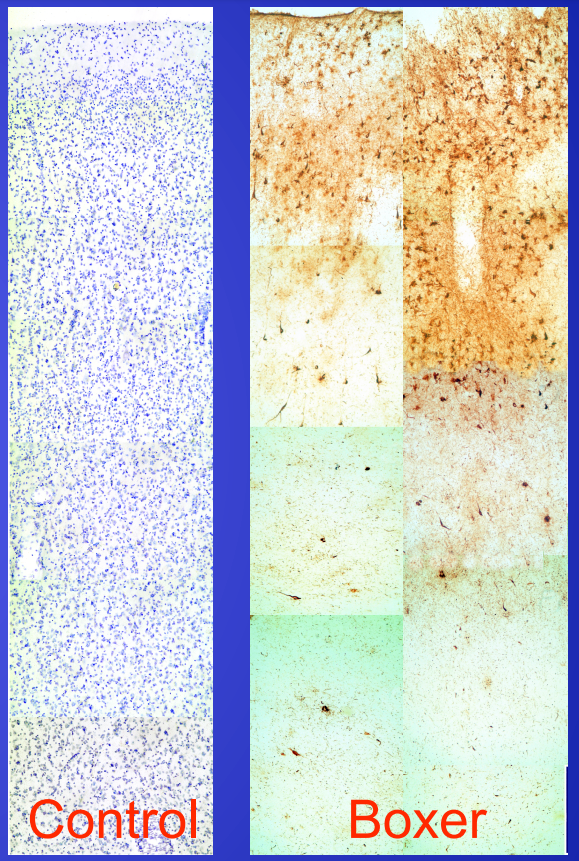
Died in the Bedford VA Hospital after 20 years of progressive dementia





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Death at age 73

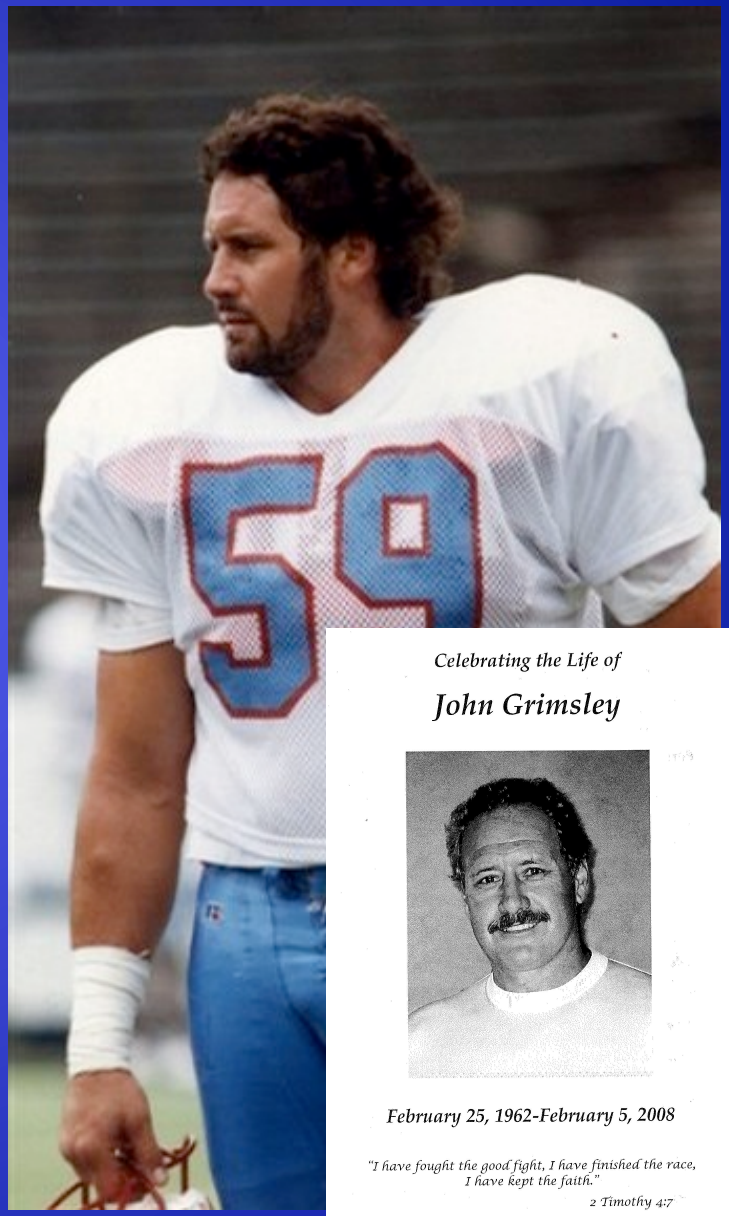
John Grimsley

Linebacker, played professionally for 9 years

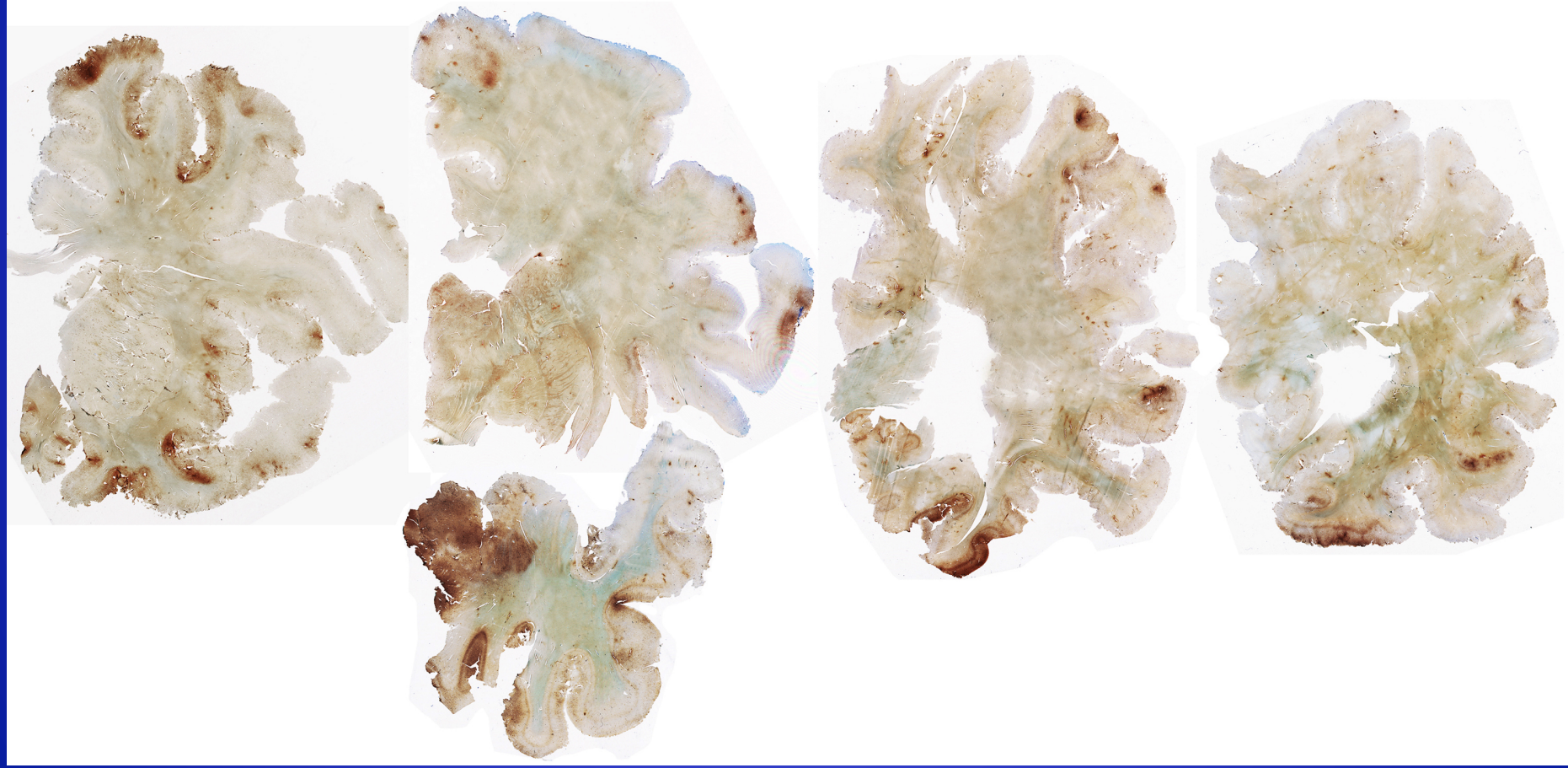
Houston Oilers 1984-1990
Miami Dolphins 1991-1993

Pro-Bowl, 1988
Married, father of 2 sons

- Retired from football at the age of 32
- Age 40: problems with short-term memory, attention, concentration, judgment, and ability to juggle more than one task at one time.
- Age 45: death from accidental self-inflicted gunshot wound

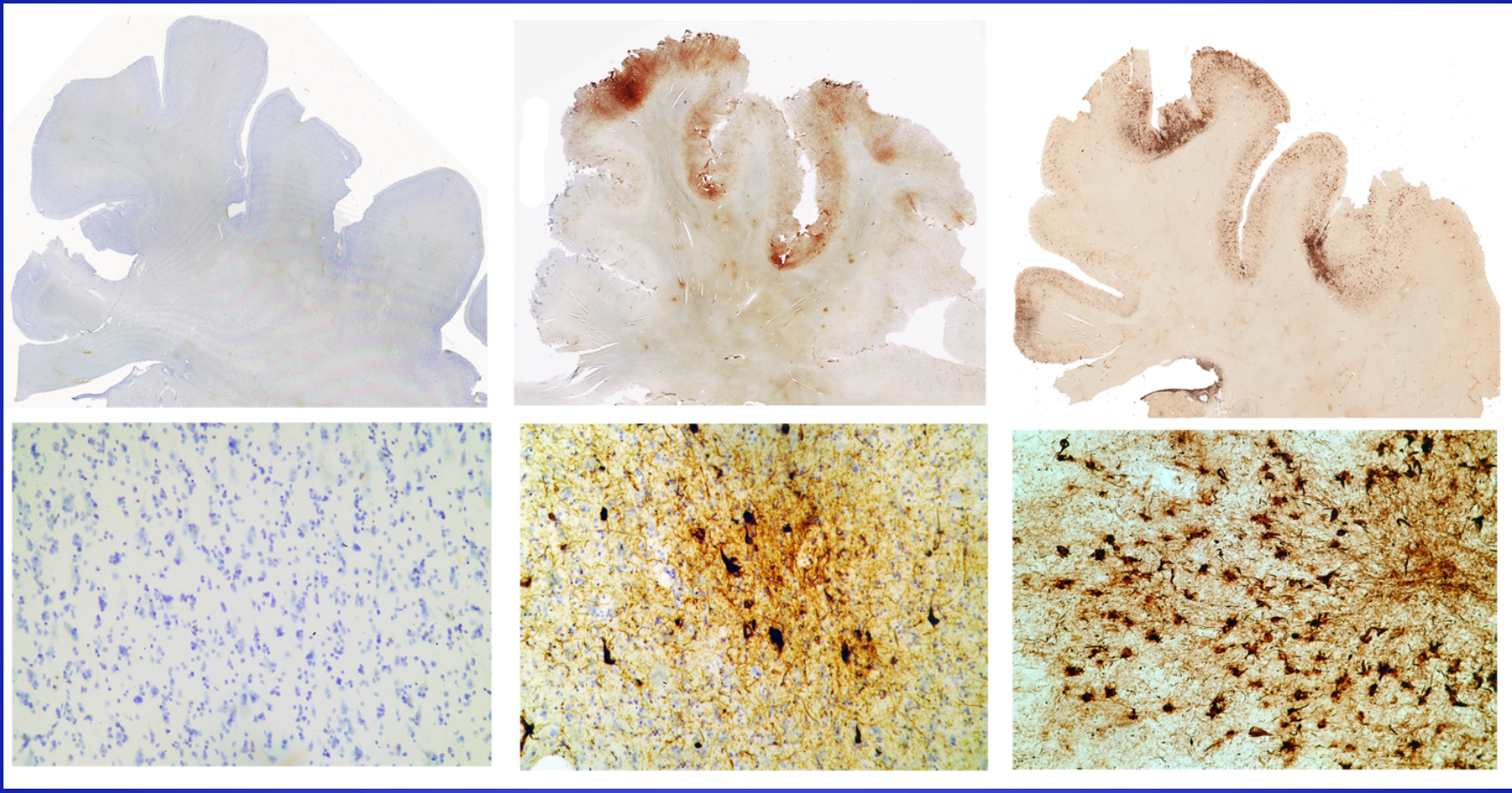


John Grimsley



Hyperphosphorylated Tau Immunohistochemistry

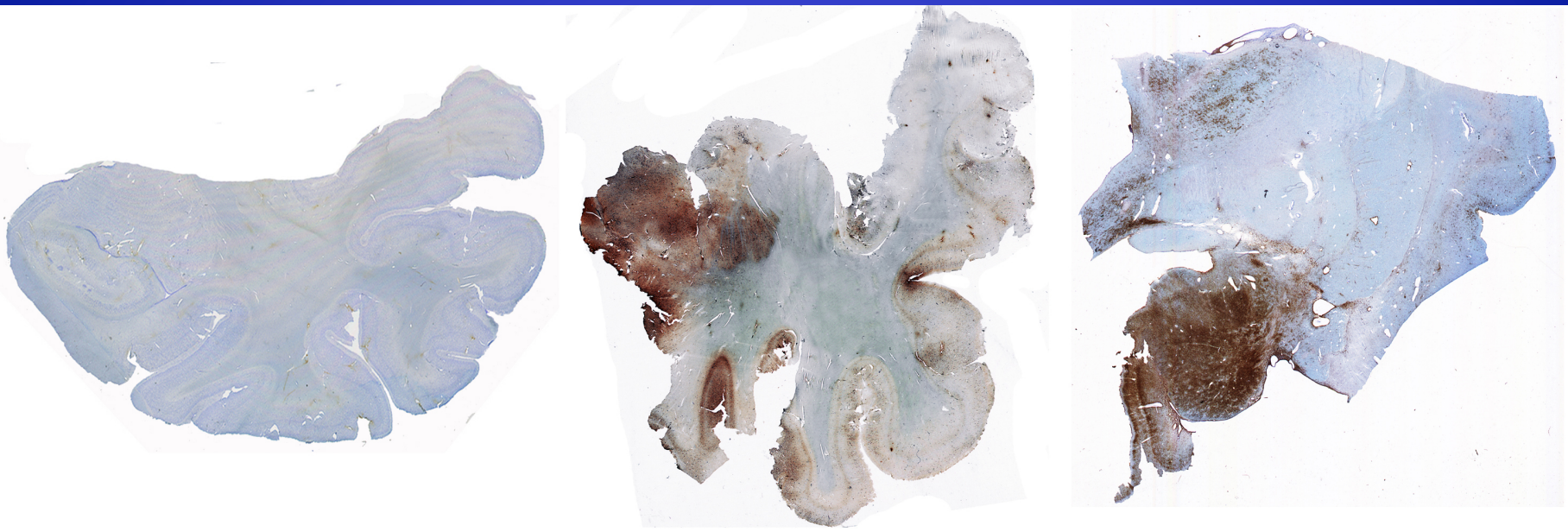
Frontal cortex



65 y.o. control 45 y.o. John Grimsley 80 y.o. prof boxer

Hyperphosphorylated Tau Immunohistochemistry

Amygdala



65 y.o. control 45 y.o. NFL football 73 y.o. prof boxer

Hyperphosphorylated Tau Immunohistochemistry

What is Chronic Traumatic Encephalopathy?

also known as Dementia Pugilistica

52 neuropathologically verified cases in the world's literature

McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, Santini VE, Lee H-Y, Kubilus CA, Stern RA.

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

J Neuropath Exp Neurol, 2009 68(7): 709-735

Chronic Traumatic Encephalopathy

Of the 52 neuropathologically confirmed cases of CTE, 47 (90%) occurred in athletes:

- 41 boxers (2 from BU) (76%)
- 5 football players (1 from BU) (10%)
- 1 professional wrestler (2%)
- 1 soccer player (2%)

10% non-athletes

- 1 physical abuse (2%)
- 2 head banging behavior (4%)
- 1 circus clown (2%)
- 1 epilepsy (2%)

First symptoms of CTE are insidious

CTE commonly begins as a personality change, behavioral and mood disturbance in midlife

- First symptoms of CTE — age 25-76 years; m = 43 yrs
- Long latent period between stopping the sport and onset of symptoms:
  - mean onset of symptoms = 8 years after stopping (range: 0-37 yrs)

Chronic Traumatic Encephalopathy

Long latent period

- Athletes began their sport at young ages — 11-20 yrs; mean 16
- Played for varying lengths of time — 14-23 yrs; mean 18

Much longer, slower course than most dementing conditions such as Alzheimer's disease

- Interval between onset of symptoms and death: — 2-46 yrs, mean 18
- Age at death: — 23-91 yrs, mean 55

Symptoms of CTE

- Cognitive changes: 69%
  - Memory loss
  - Dementia
- Personality/ Behavioral changes 65%
  - Aggressive or violent behavior
  - Confusion
  - Mood changes, usually depression
  - Paranoia
  - Irritability
- Movement abnormalities 41%
  - Gait problems
  - Parkinsonism
  - Speech abnormalities

Chronic Traumatic Encephalopathy in 5 football players

Symptom onset ranged from 40 - 56 years of age (M = 46.8, SD = 7.3 years).

The most common difficulties:

- short-term memory loss (4/5 cases)
- outbursts of anger and aggression (4/5 cases)
- inattention (4/5 cases)
- worsening organization and planning skills (4/5 cases)
- executive dysfunction (4/5)
- depression (2/5 cases)
- profound apathy (2/5)
- dementia (1/5)

High functionality:

- significant functional dependence only in the player with dementia (1/5)
- difficulty preparing taxes, shopping alone, and paying attention to and understanding television programs (2/5)

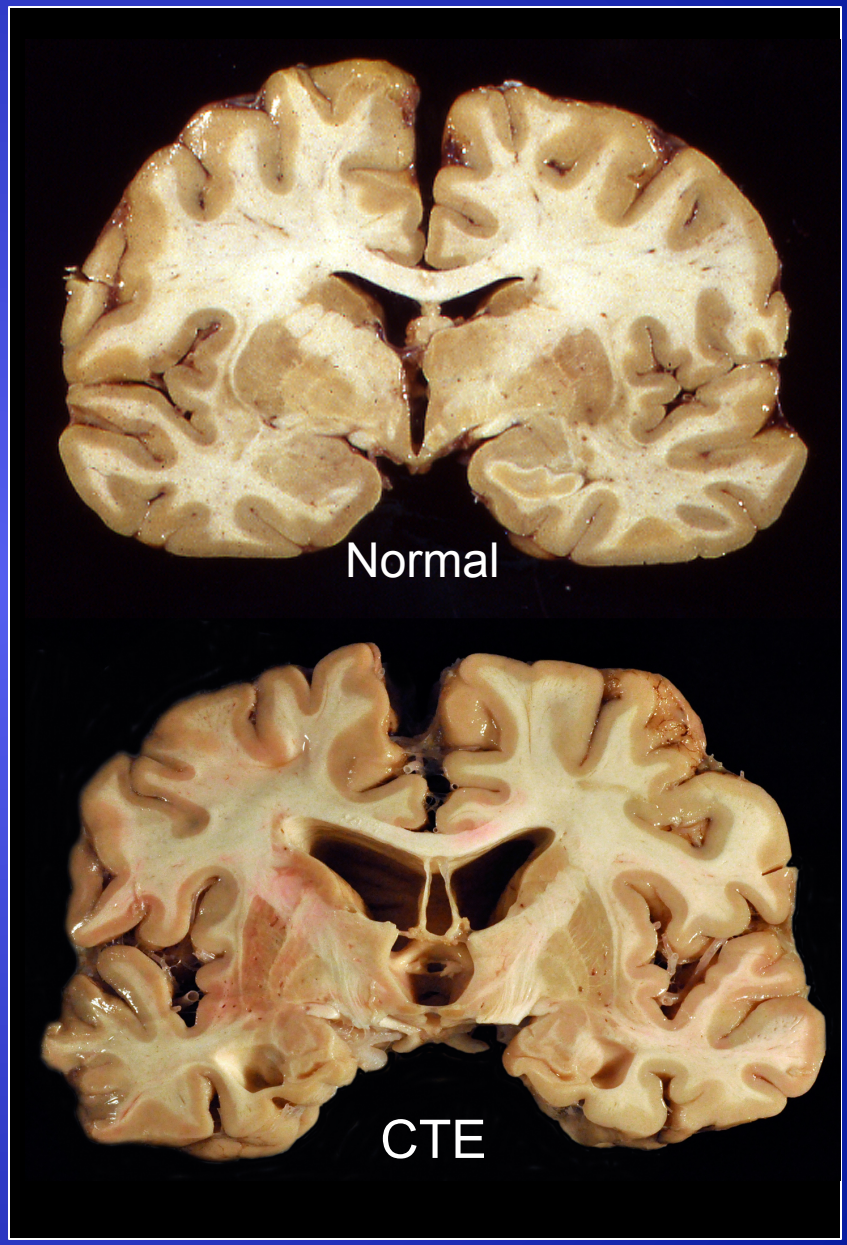
All 5 showed irritability and a quick temper; more pronounced several years before death

Most severely affected player developed significant dysarthria, followed by gait disturbances and parkinsonian features in his final years.

Pathology of CTE

Gross changes of:

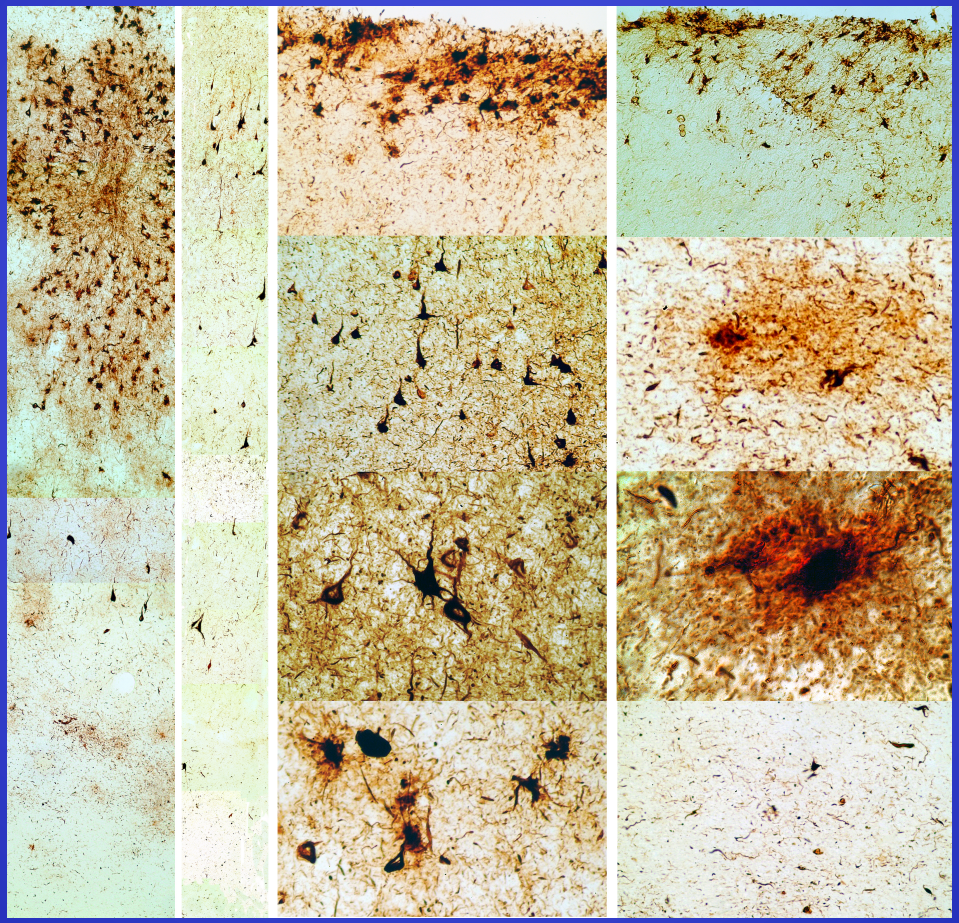
- Cerebral atrophy
- Medial temporal lobe atrophy
- Mammillary body atrophy
- Thinning of the hypothalamic floor
- Marked dilation of II and III ventricles
- Cavum septum pellucidum with fenestrations
- Pallor of the substantia nigra



Microscopic Pathology of CTE

Hyperphosphorylated tau protein

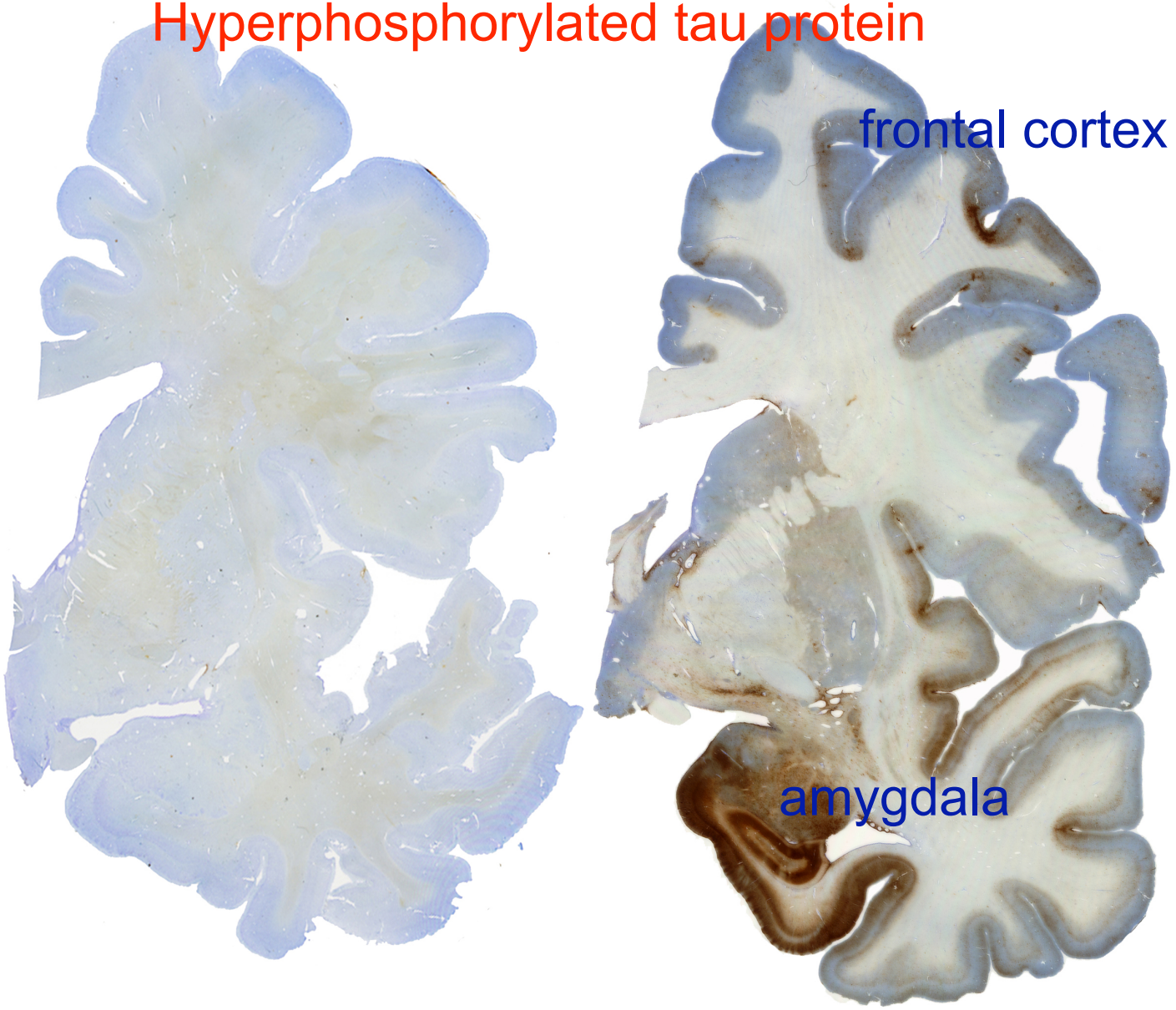
Neurofibrillary tangles



Widespread distribution throughout the central nervous system

Unique pattern of involvement – not found in any other disease

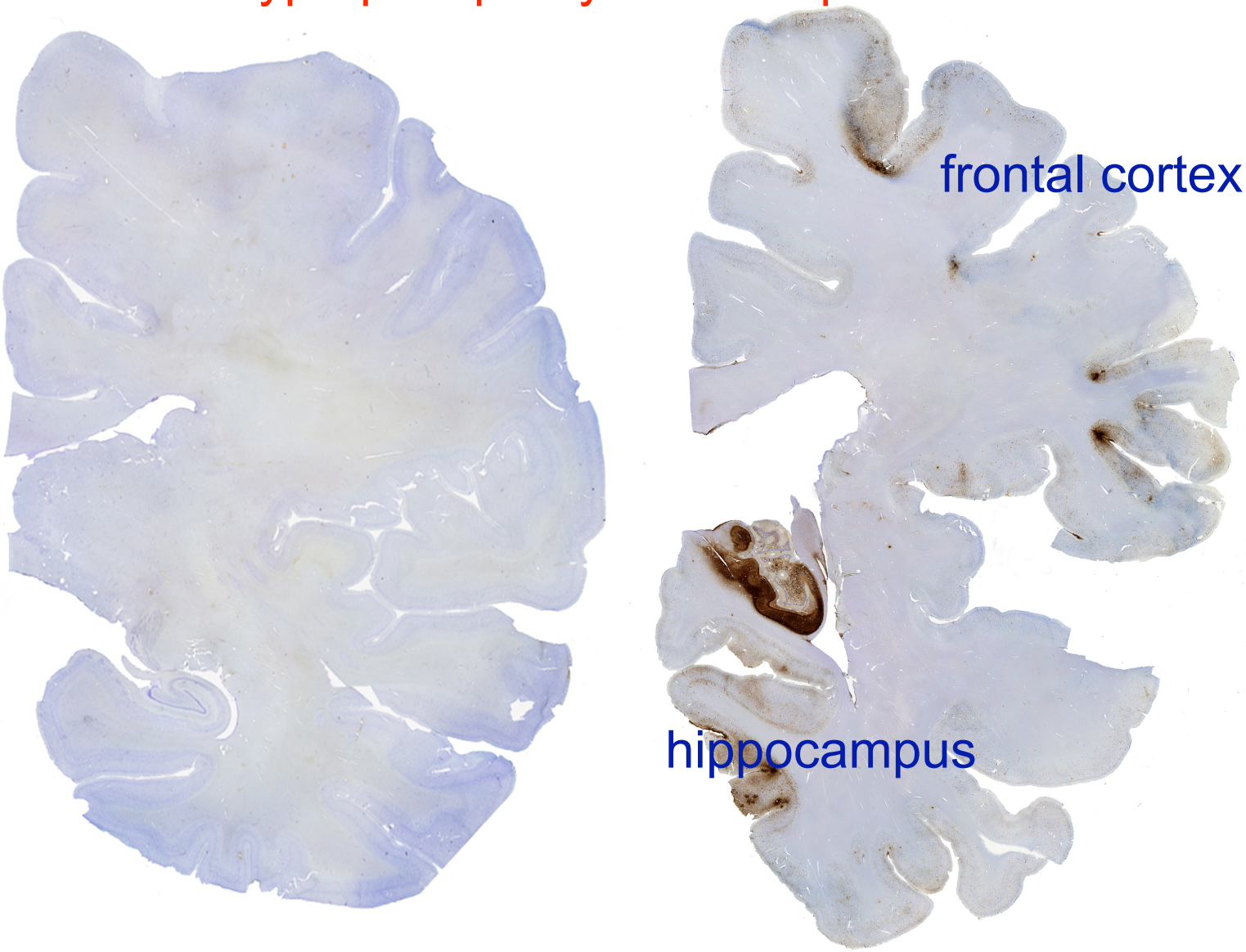
Hyperphosphorylated tau protein



Normal Control

CTE

Hyperphosphorylated tau protein

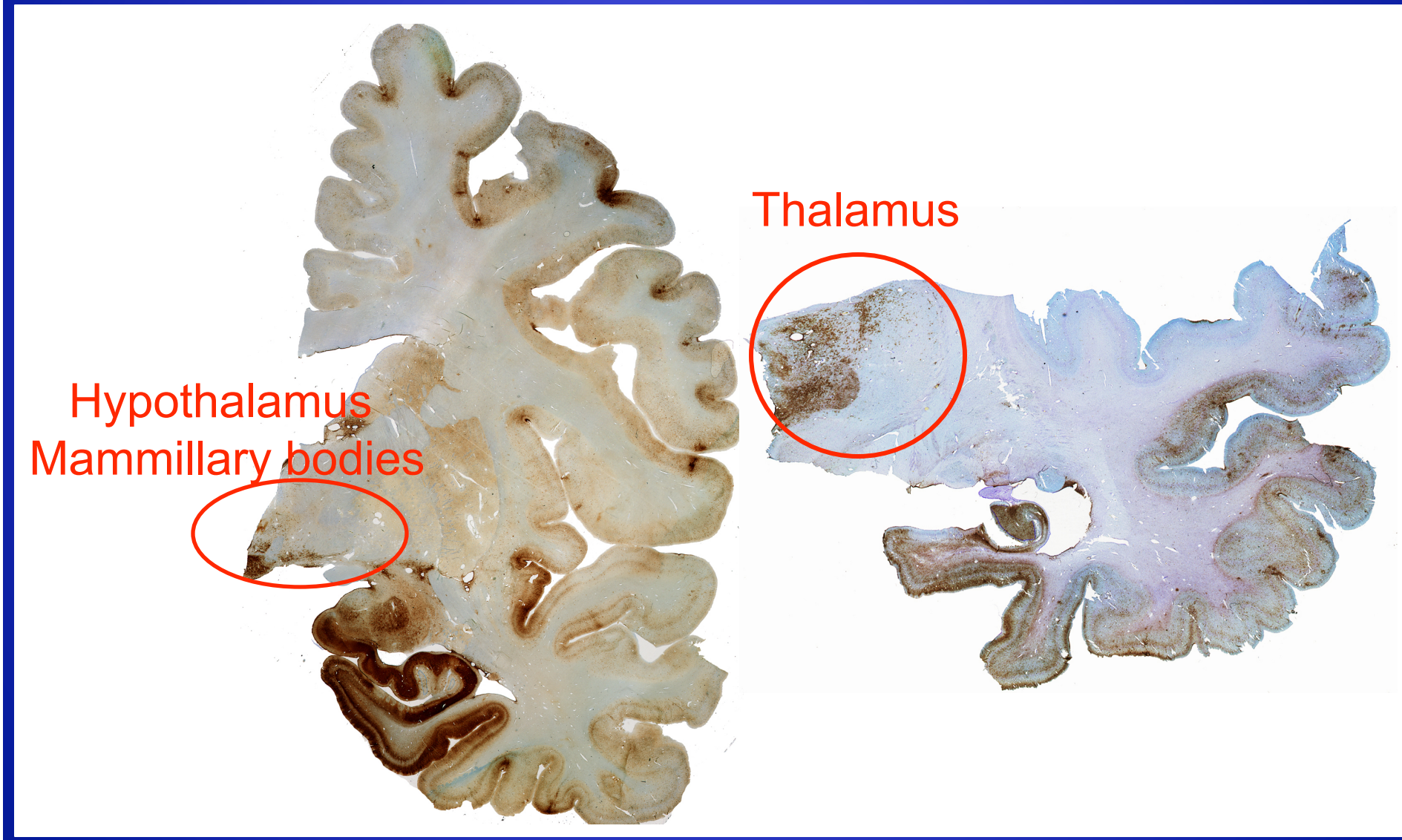


Normal Control

CTE

CTE: Hyperphosphorylated Tau in NFTs

Subcortical Nuclei



CTE: Hyperphosphorylated Tau in NFTs

Brainstem and Spinal cord

Substantia Nigra

Locus ceruleus

Midbrain

Pons

Medulla

Cord

Tom McHale

Defensive lineman at Cornell

Offensive lineman in NFL 1987-1995

Operated multiple successful restaurants after retiring from NFL at age 32

Age 40: his business failed due to poor business decisions

Began experiencing problems with drugs, initially using painkillers to treat a back problem.

During the last year of his life he was in and out of rehab.

Problems with short-term memory, depression, irritability, and poor judgment

Died at age 45 from substance abuse

Football player: 9 years in NFL

death at age 45 years: depression, poor decision making, substance abuse

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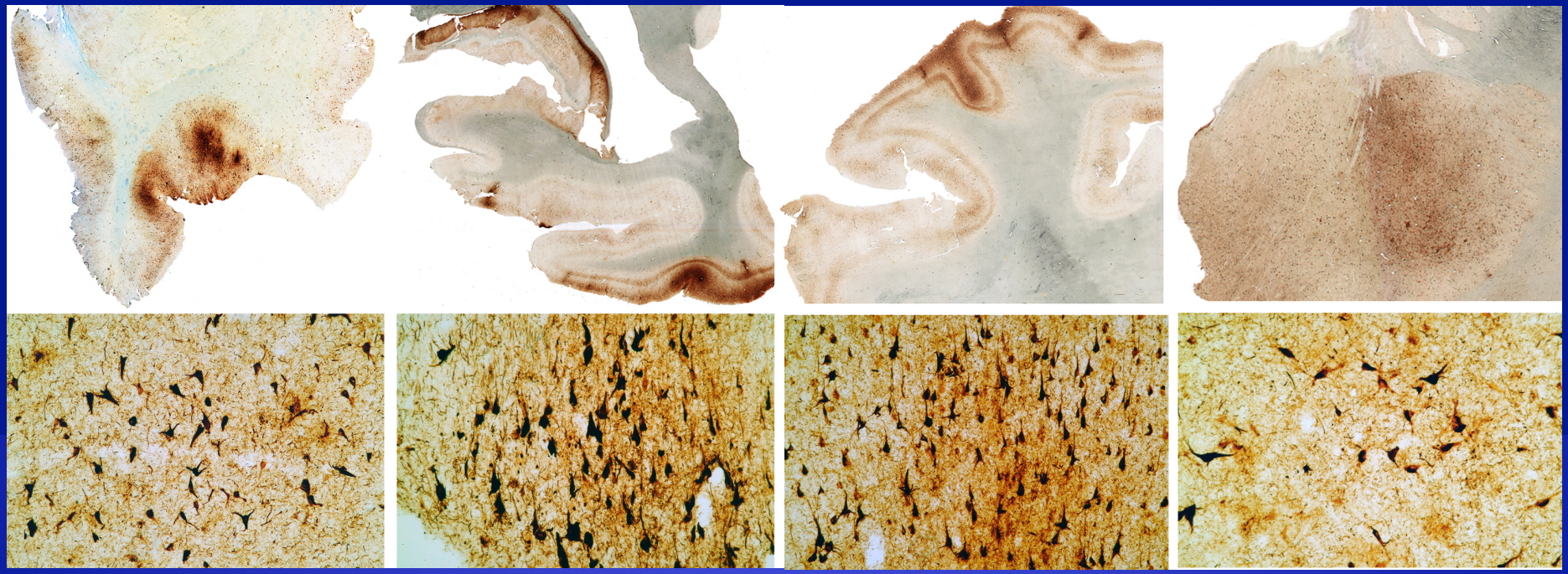
Orbital frontal | Hippocampus | Temporal | Amygdala



Hyperphosphorylated Tau Immunohistochemistry

Aß: rare diffuse plaques

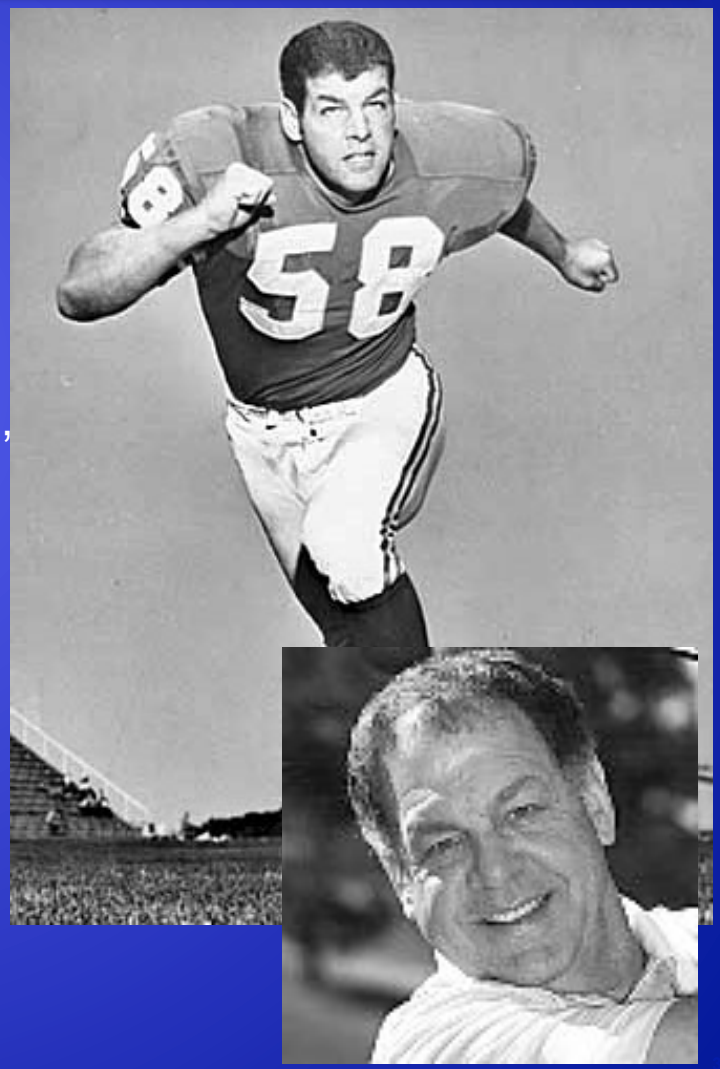
Walter Hilgenberg

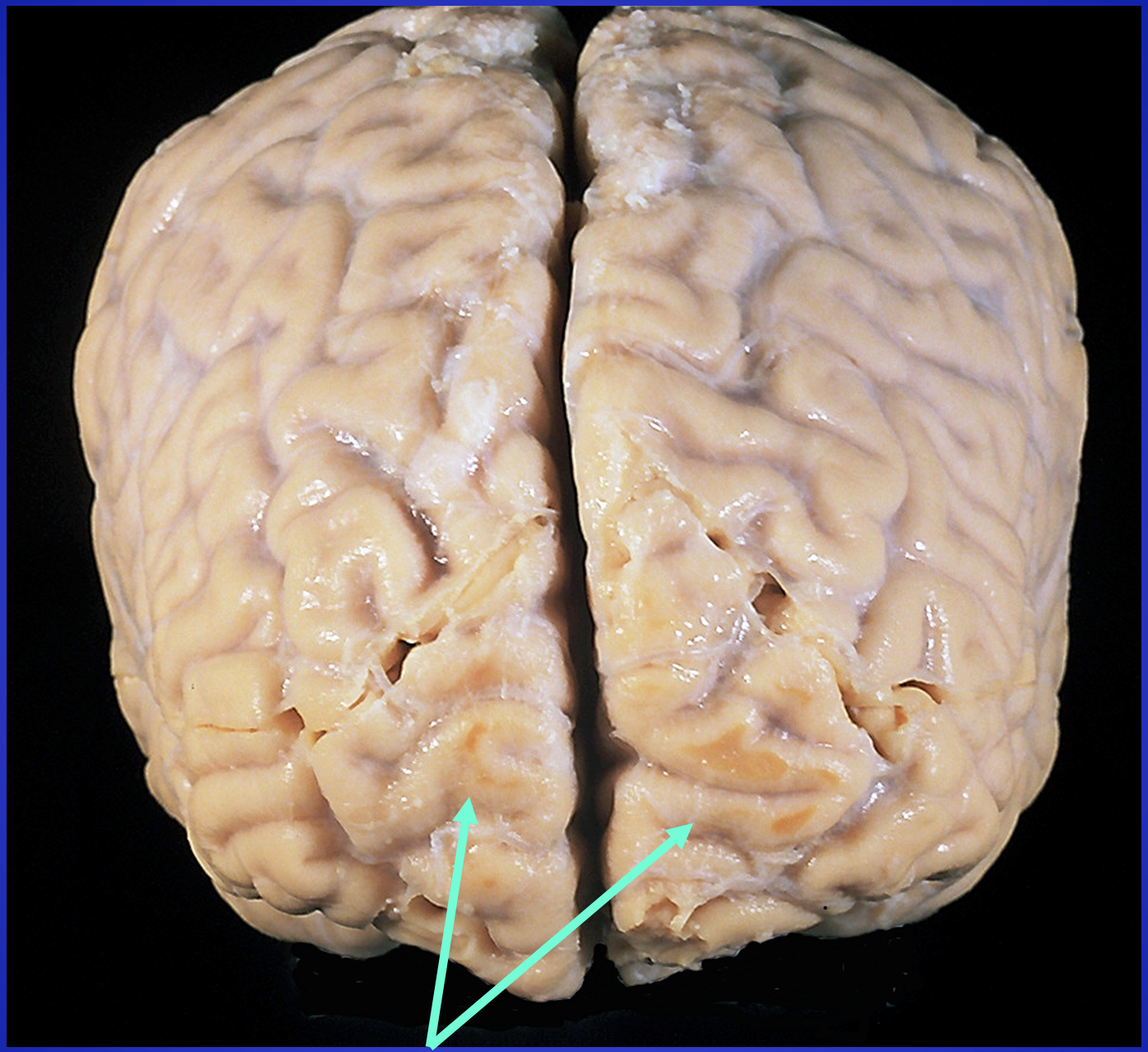
Death at age 66 years

- Played 16 years as a linebacker for the
•Minnesota Vikings

  •>10 concussions

- Age 56: Slow and steady cognitive decline
- Difficulty understanding things at a “deeper level”
- Worsening planning and organization skills
- Memory loss
- Apathy
- Death at age 66 with cognitive impairment and severe apathy





Frontal Contusions

16 years of professional football

Death at age 66 years with apathy, MCI

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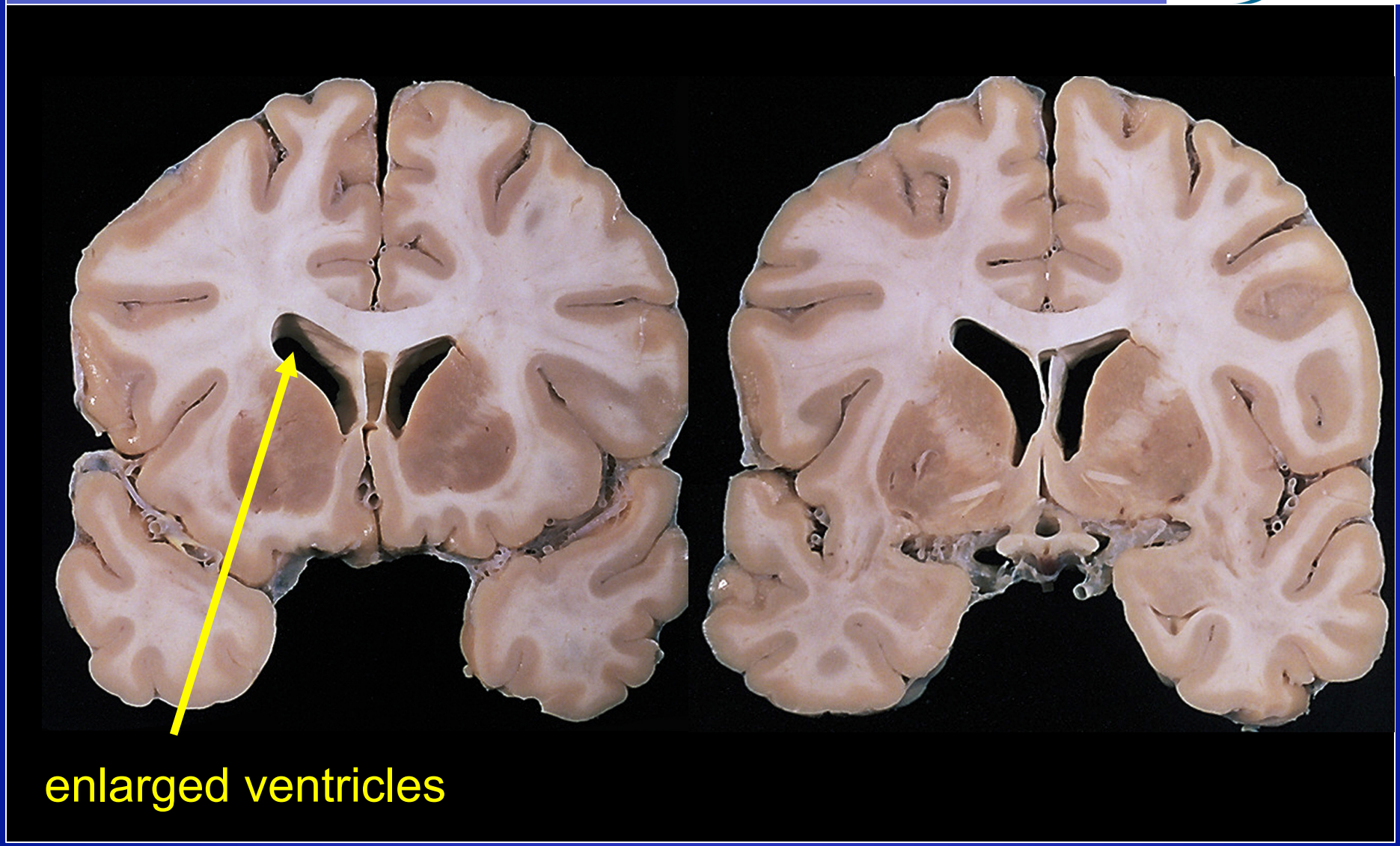

16 years of professional football

Death at age 66 years with apathy, MCI

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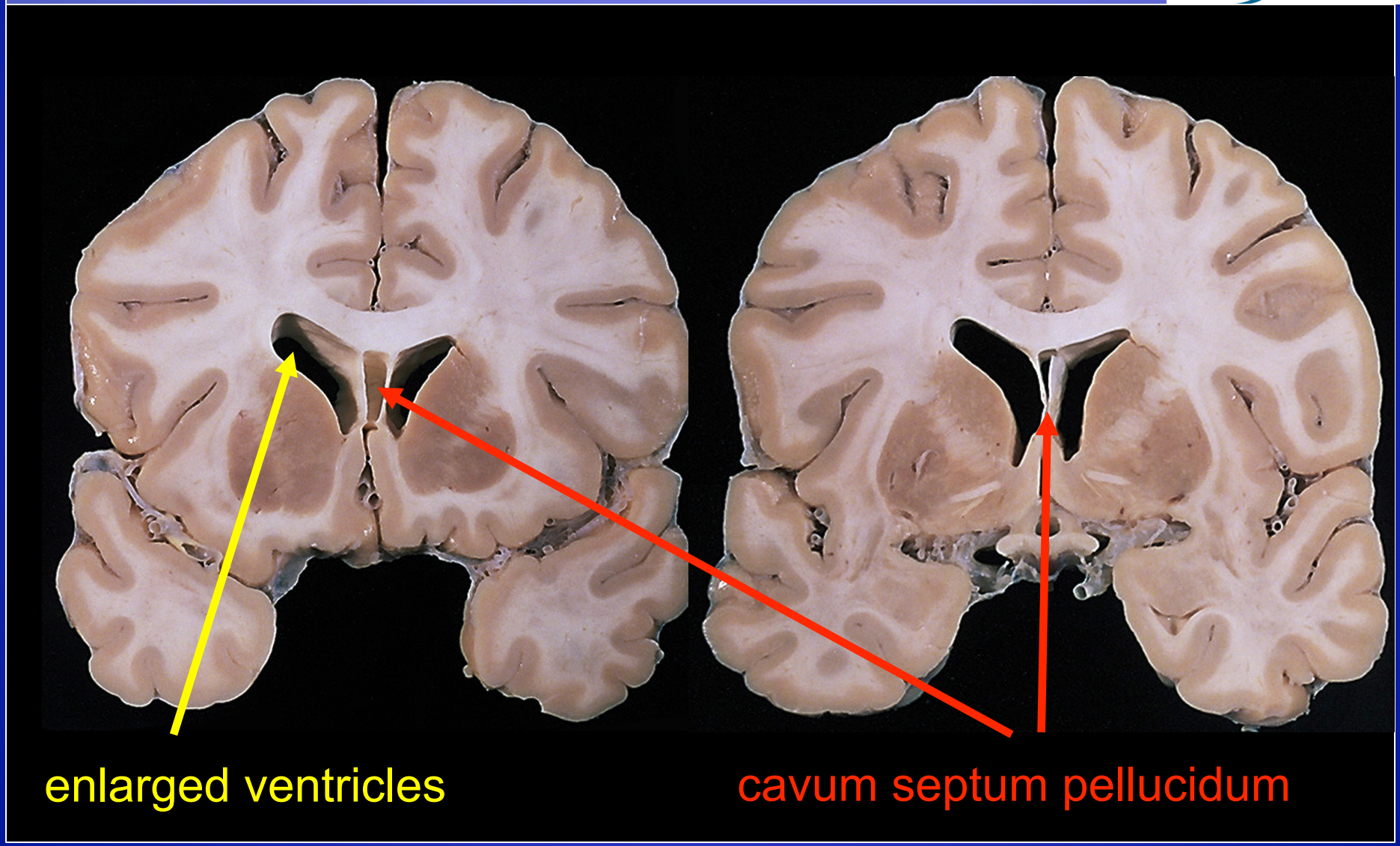

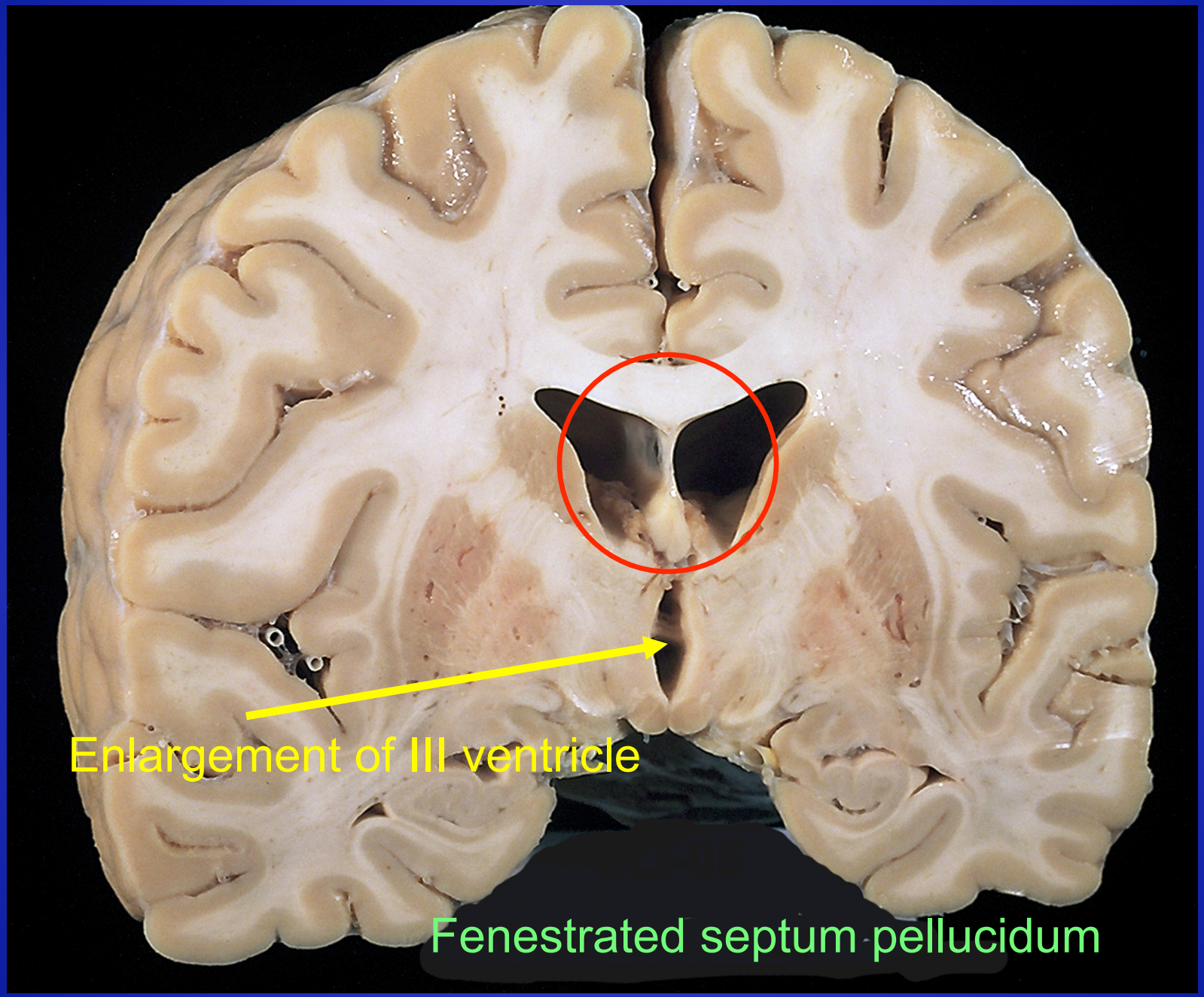
Enlargement of III ventricle
Fenestrated septum pellucidum

Football player: 16 years in NFL

death at age 66 years: memory loss, confusion, executive dysfunction, profound apathy

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Hyperphosphorylated Tau Immunostaining

No Aß

Football player: 16 years in NFL

death at age 66 years: memory loss, confusion, executive dysfunction, profound apathy

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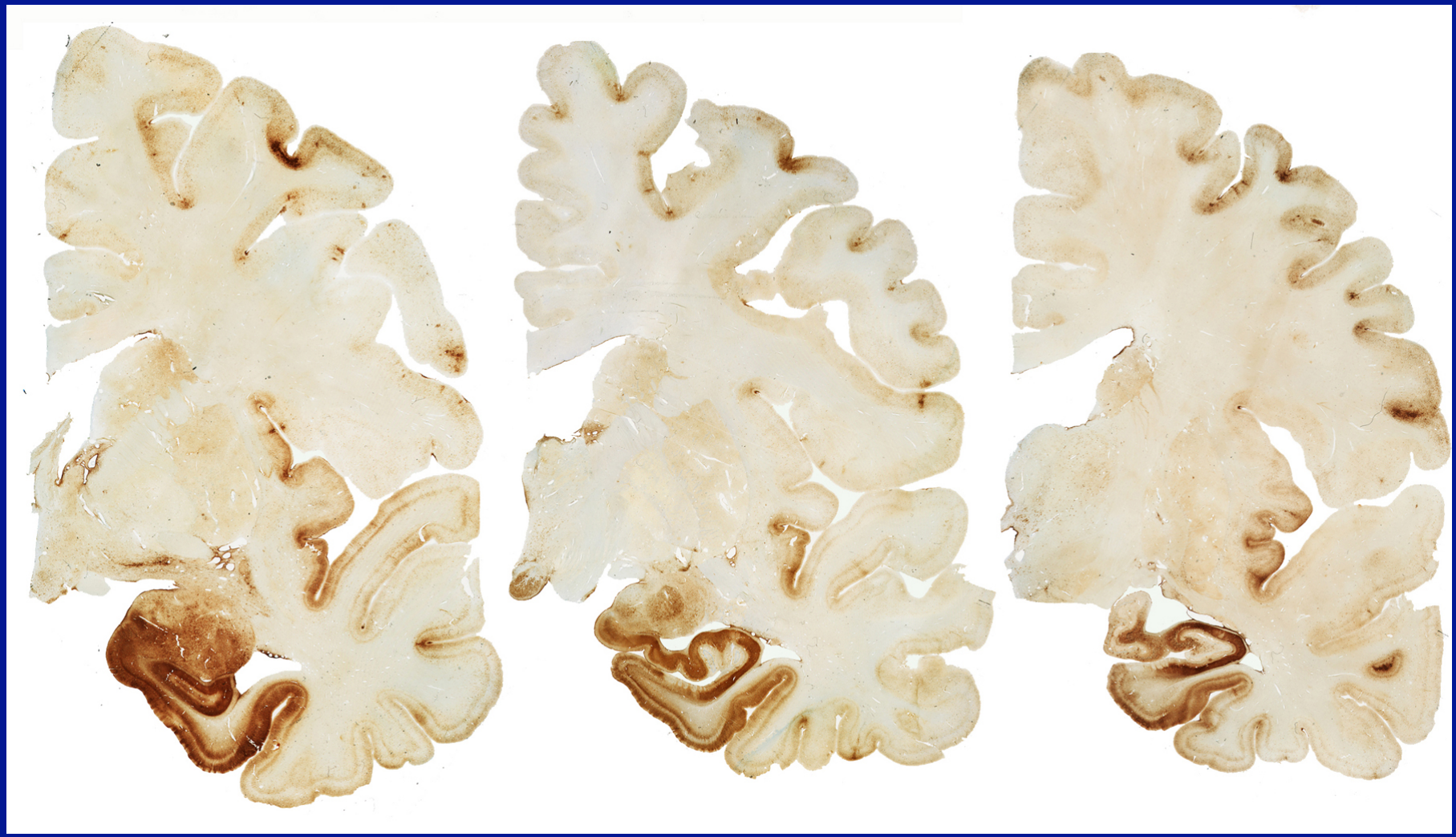

No Aß

Football player: 16 years in NFL

Death at age 66. Cognitively impaired, severe apathy

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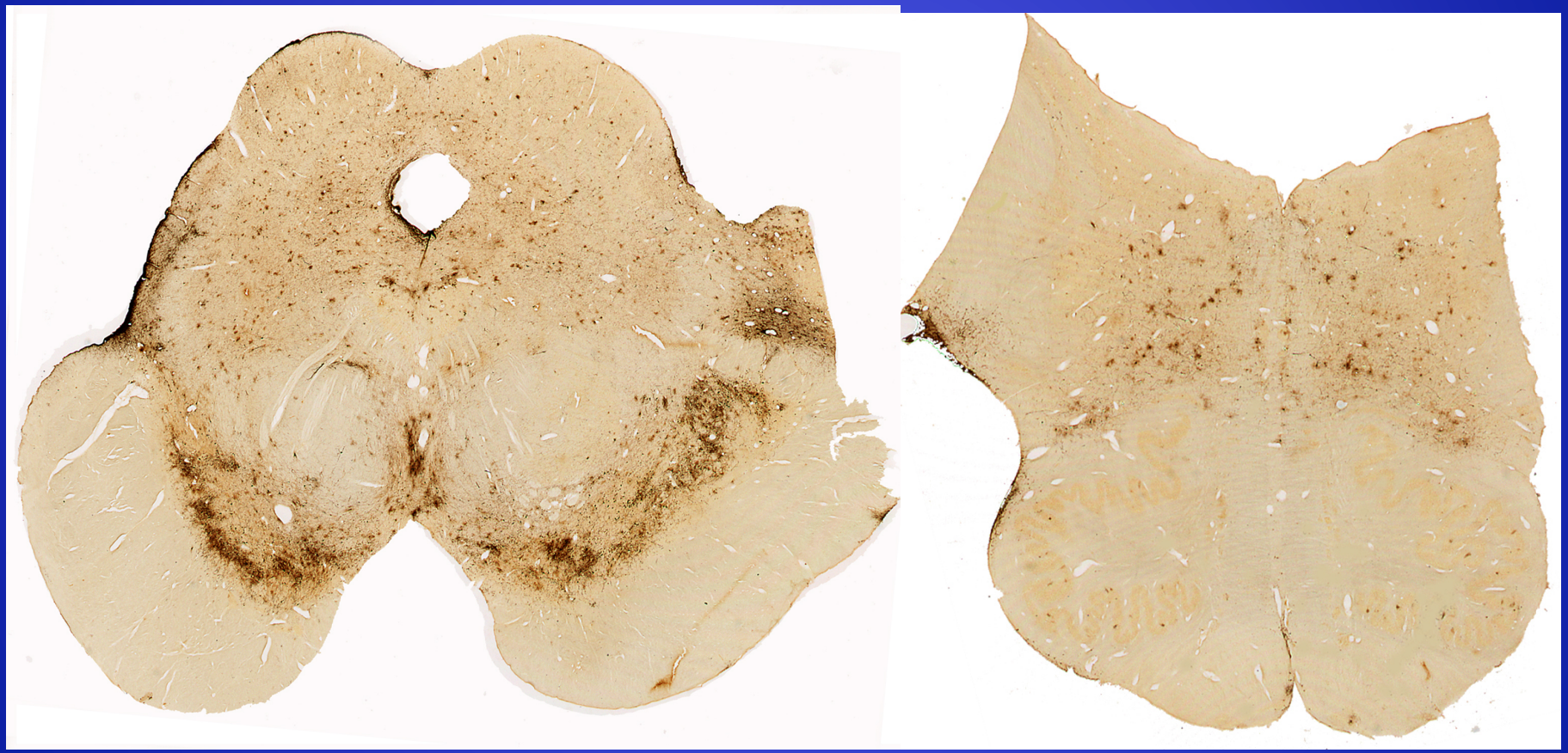


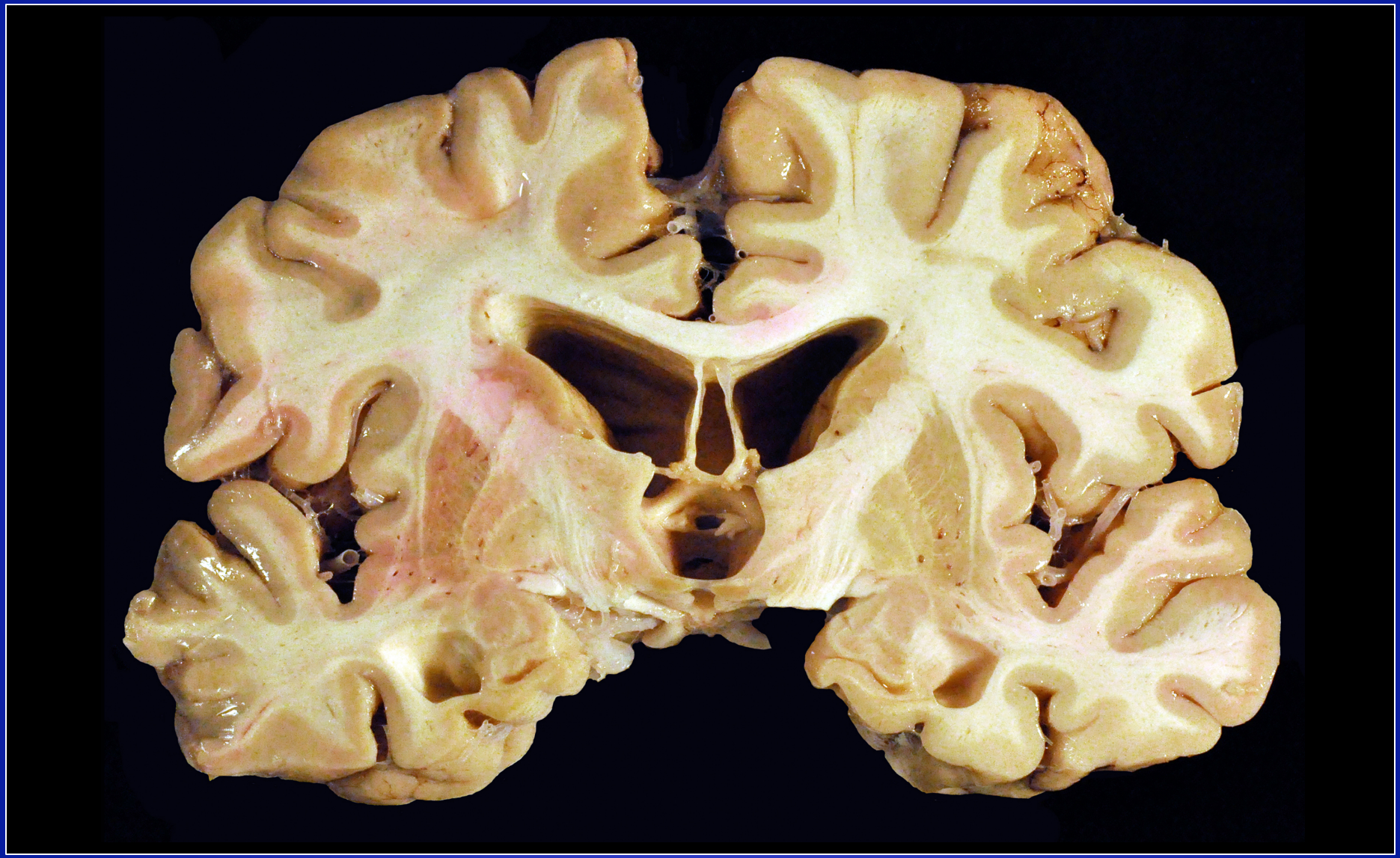
Midbrain

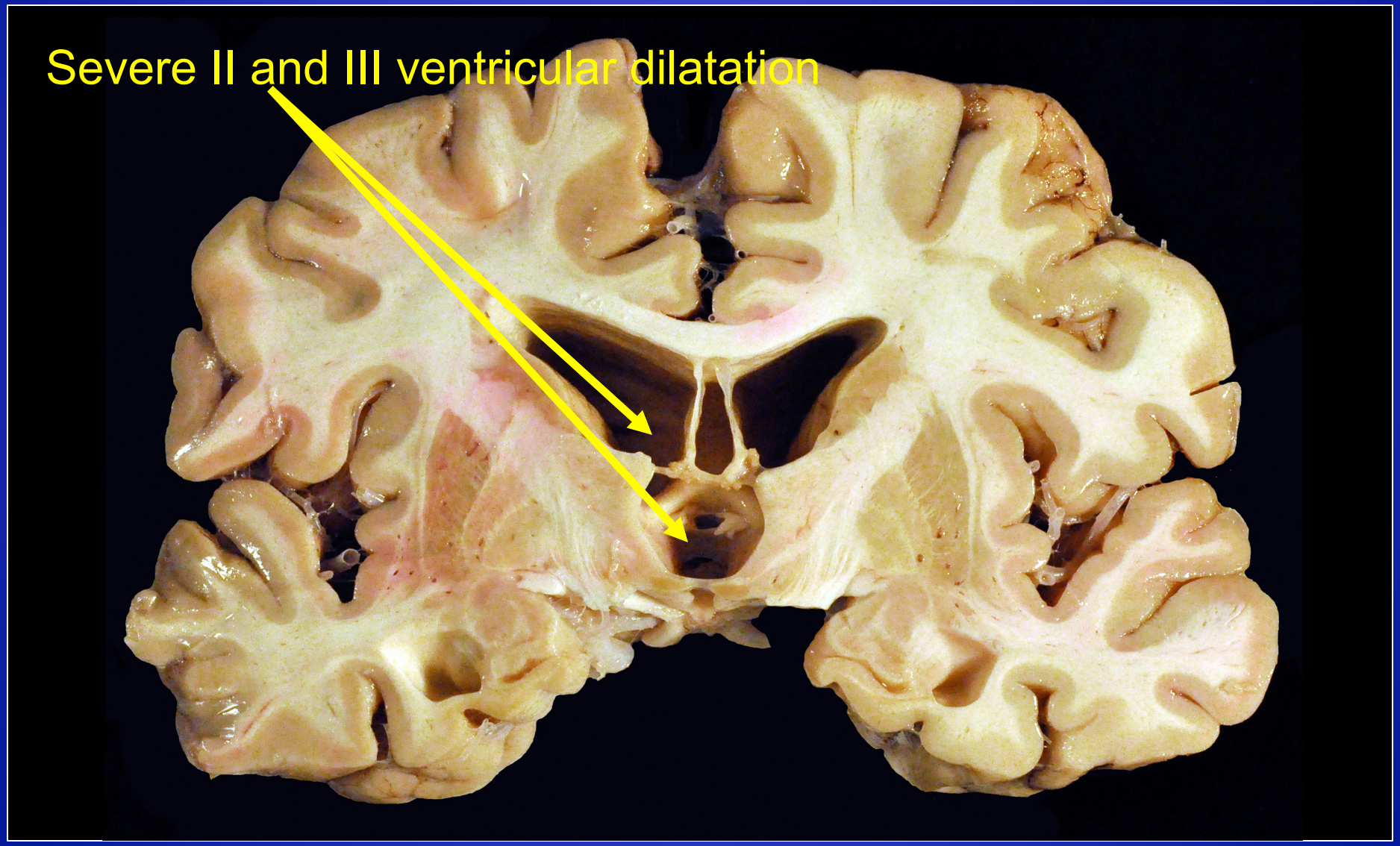
Medulla

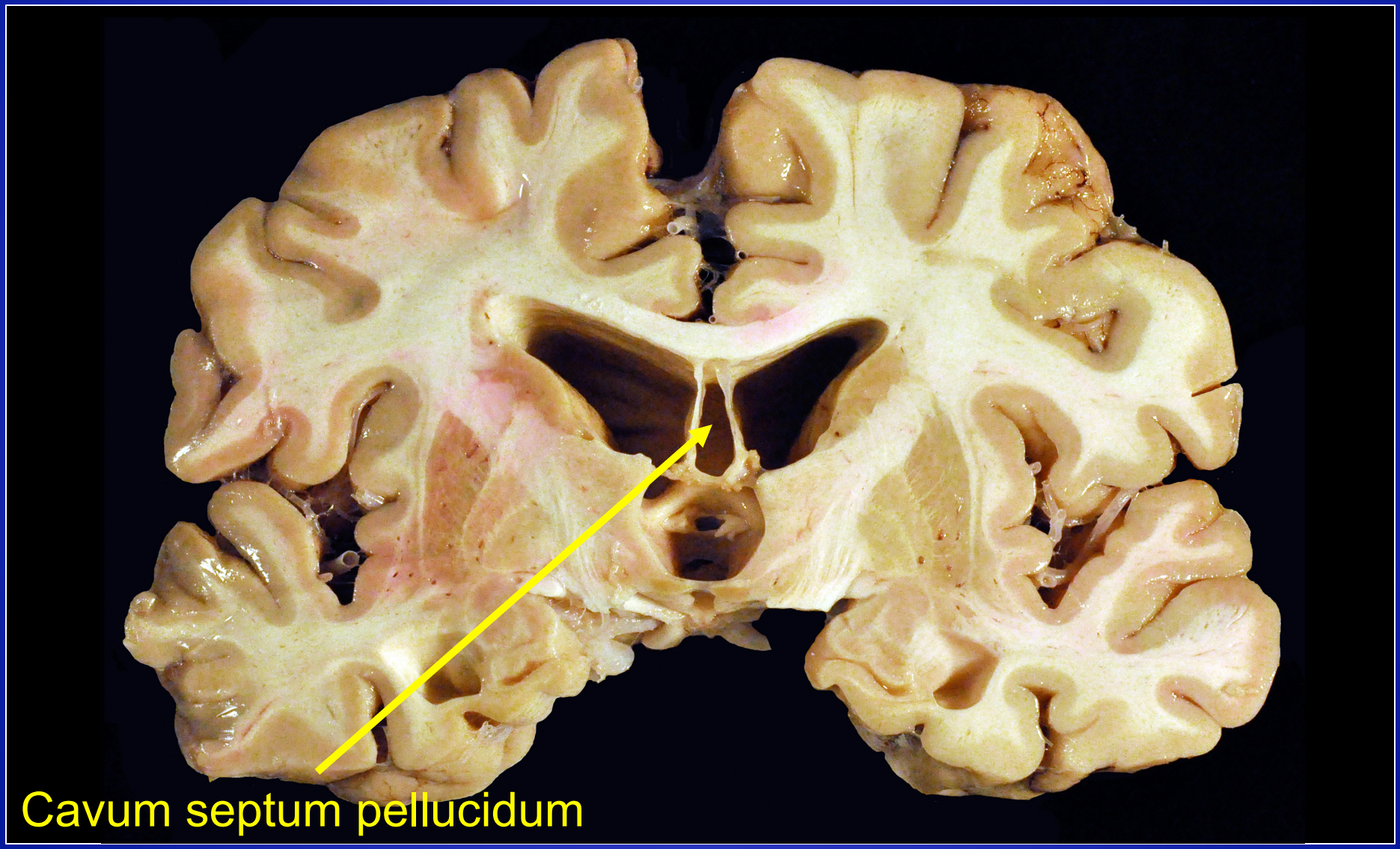
Louis Creekmur

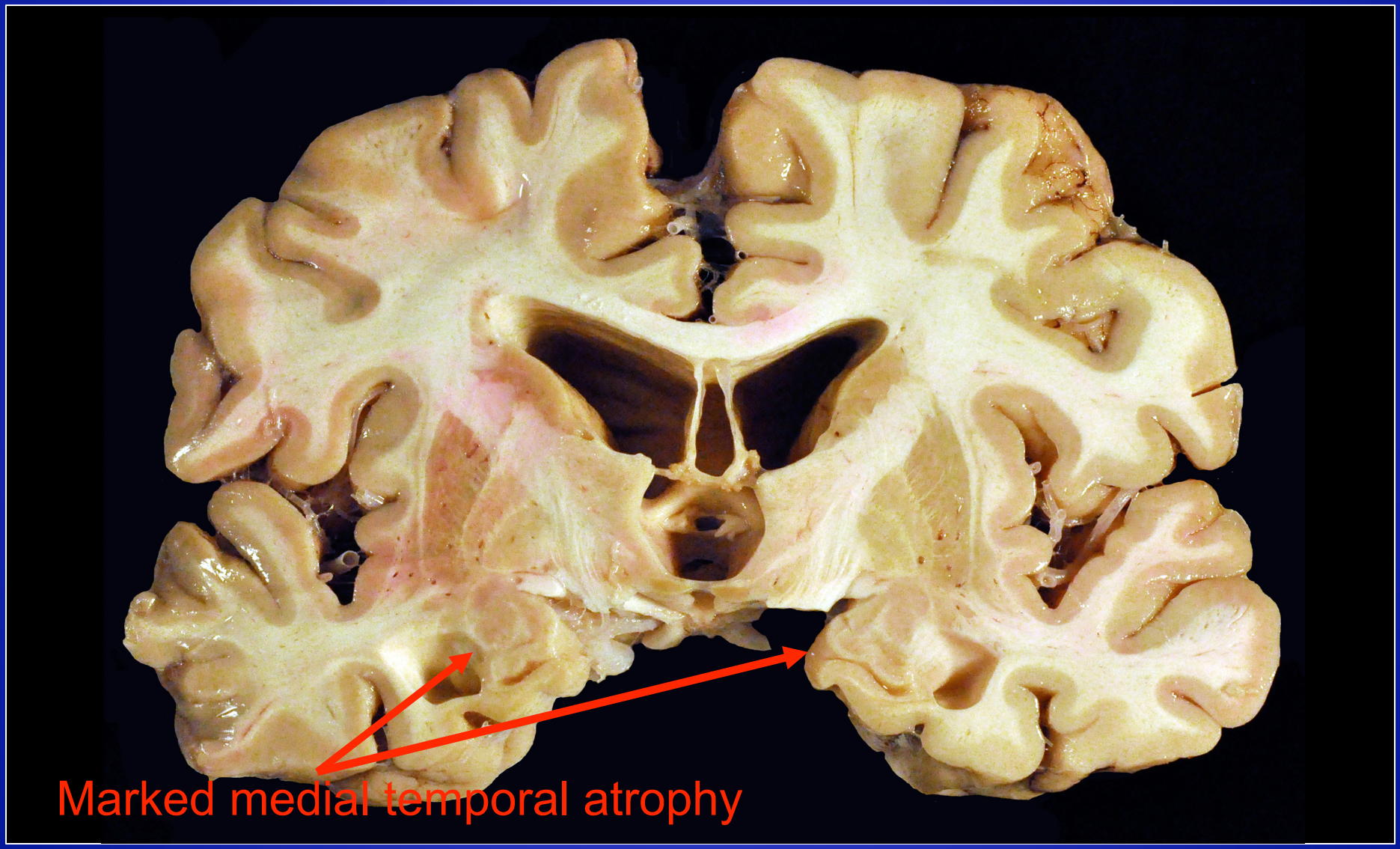
82 years old

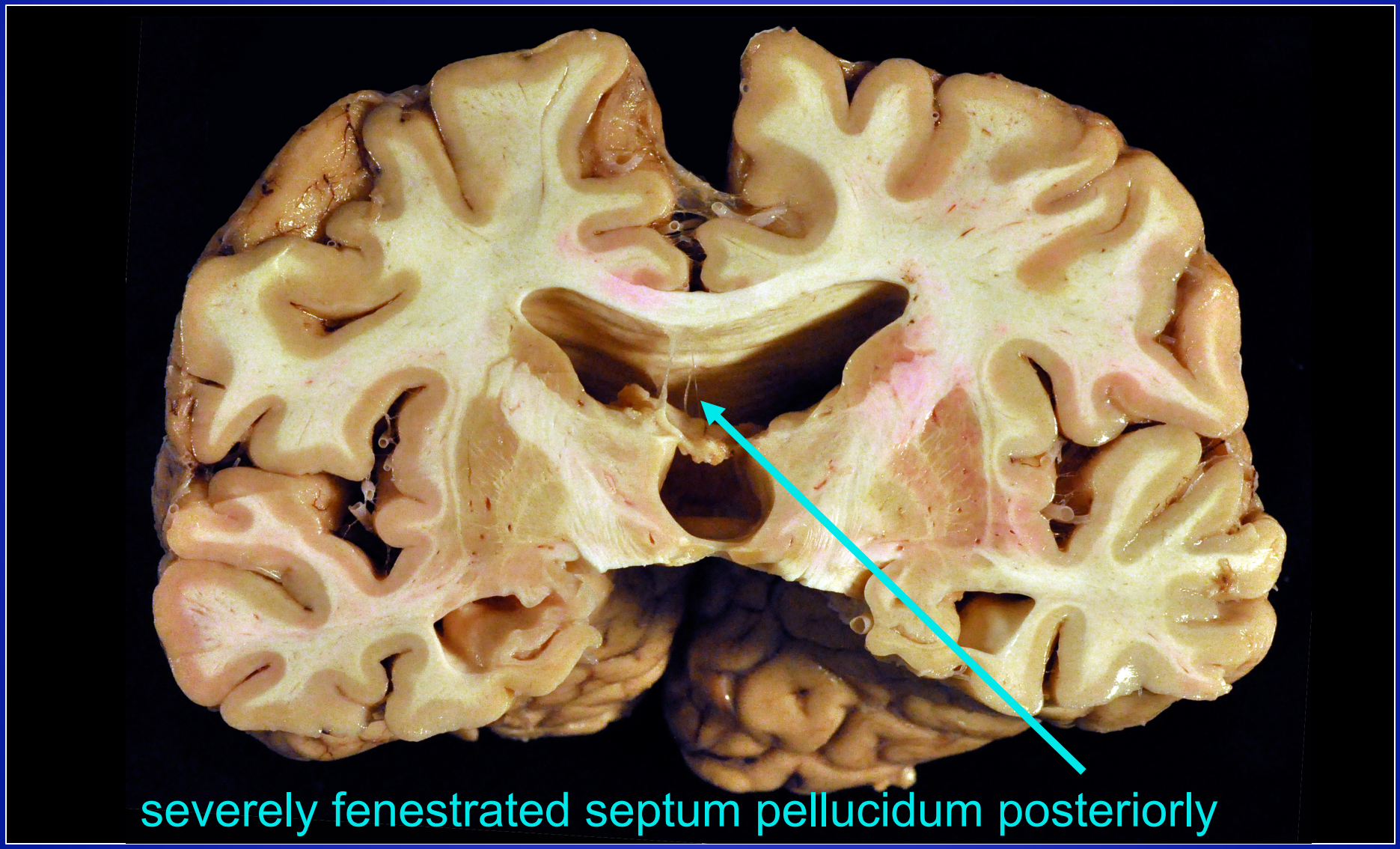
- Offensive lineman for the Detroit Lions (1950-1959)
  8-time Pro Bowl
  Hall of Fame
- 16-17 concussions; 13 broken noses
- Retired from football at age 31
- Age 49: “Punchy”, occasional angry aggressive outbursts
- Inattention, memory loss, disorganization, depression
- Developed difficulties walking, slurred speech, parkinsonism, and eventually dementia
- Participant in the 88 plan

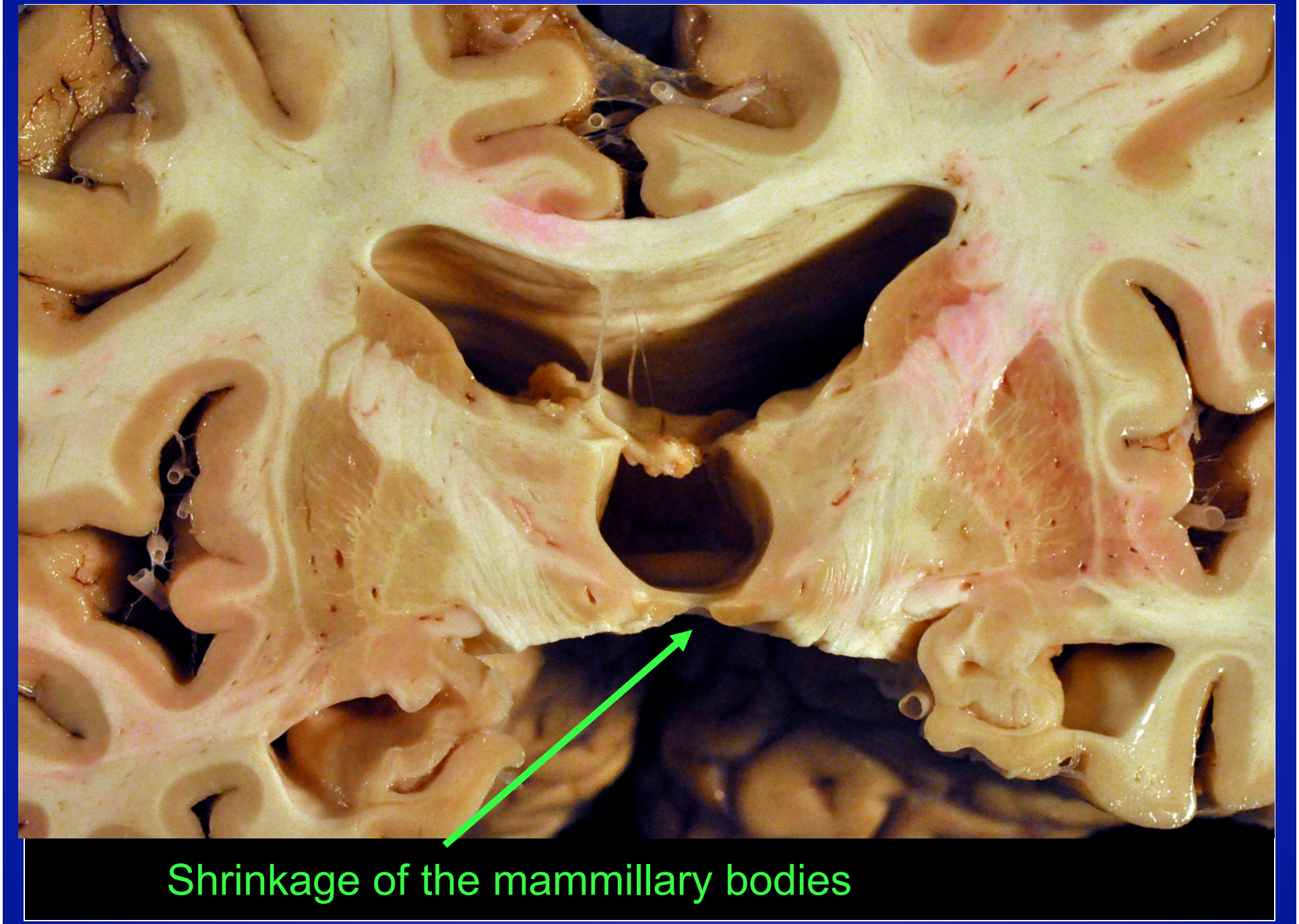


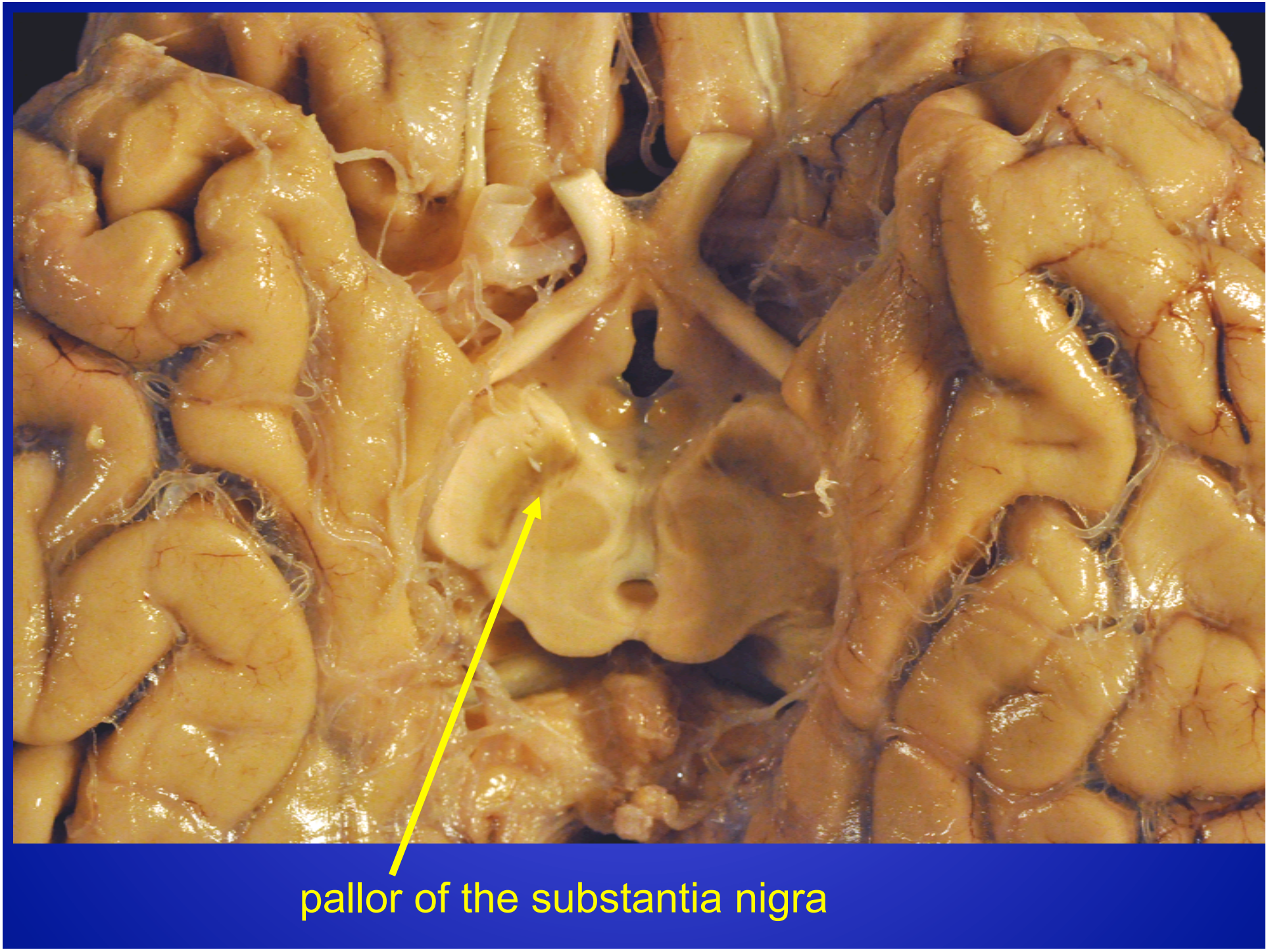

Severe II and III ventricular dilatation


Cavum septum pellucidum


Marked medial temporal atrophy


severely fenestrated septum pellucidum posteriorly


Shrinkage of the mammillary bodies


pallor of the substantia nigra

Football player: 10 years in NFL

Death in his 80s: dementia

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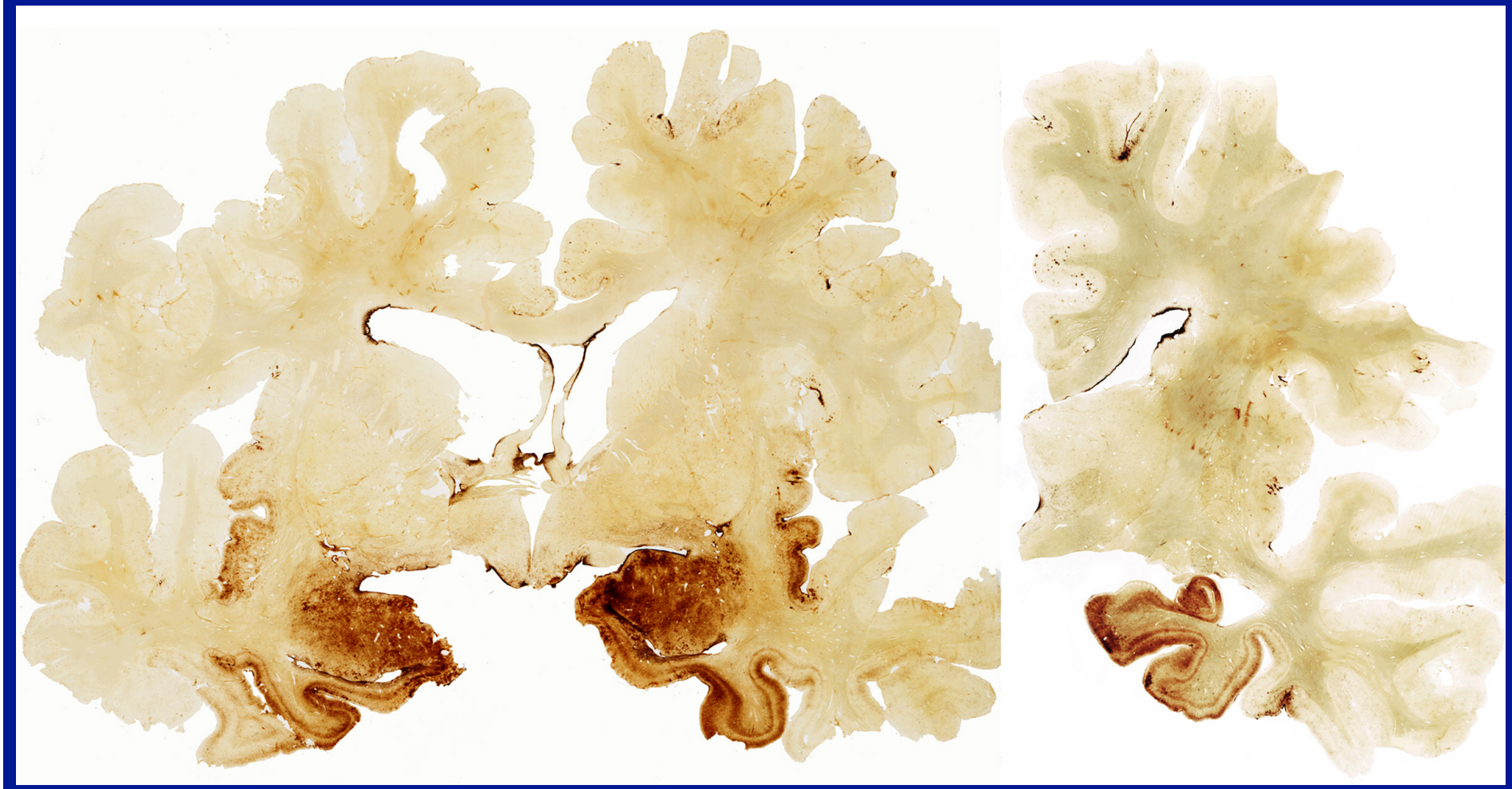

Hyperphosphorylated Tau Immunohistochemistry

Football player: 10 years in NFL

Death at age 82 with dementia

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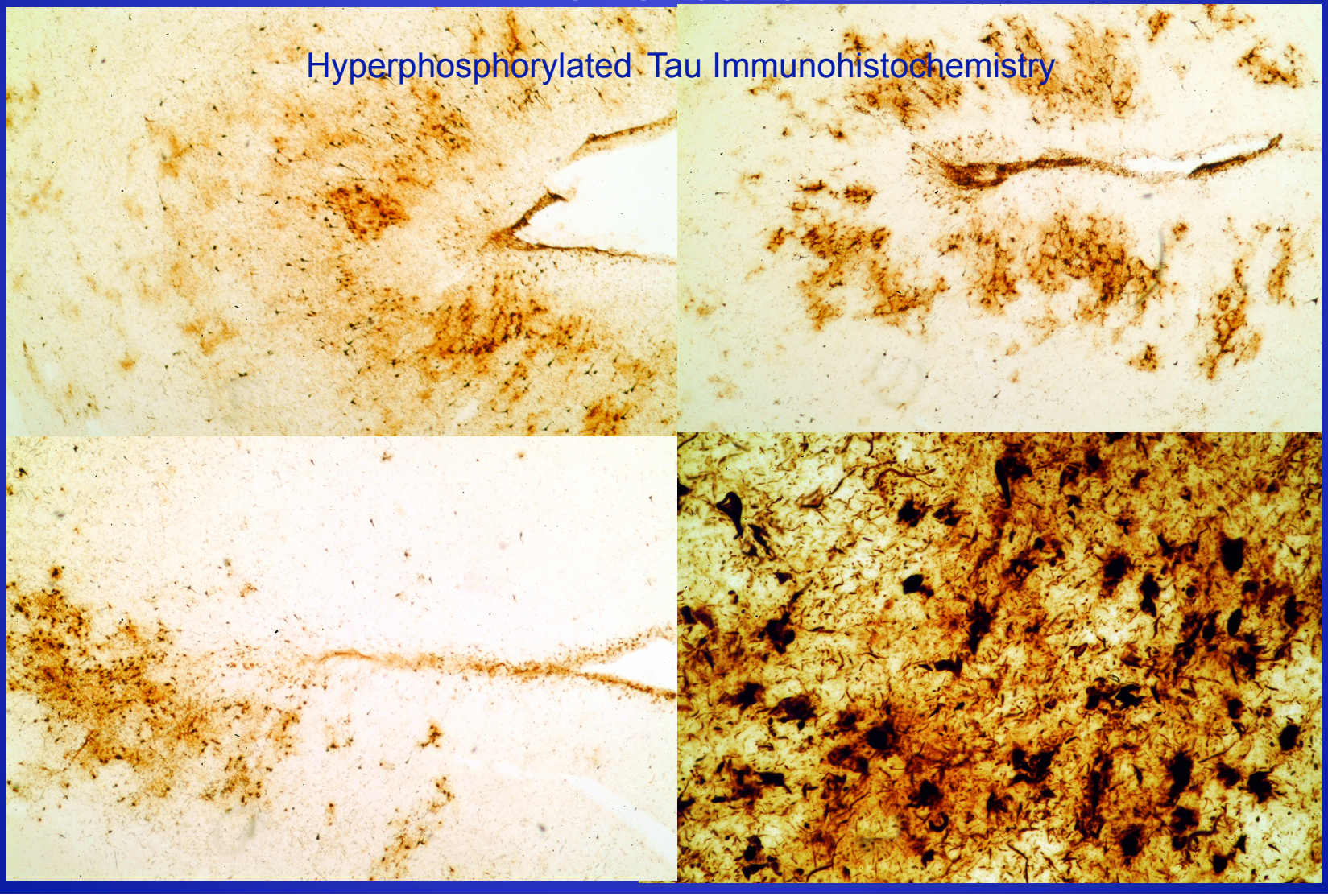
Frontal cortex



Football player: 10 years in NFL

Death at age 82 with dementia

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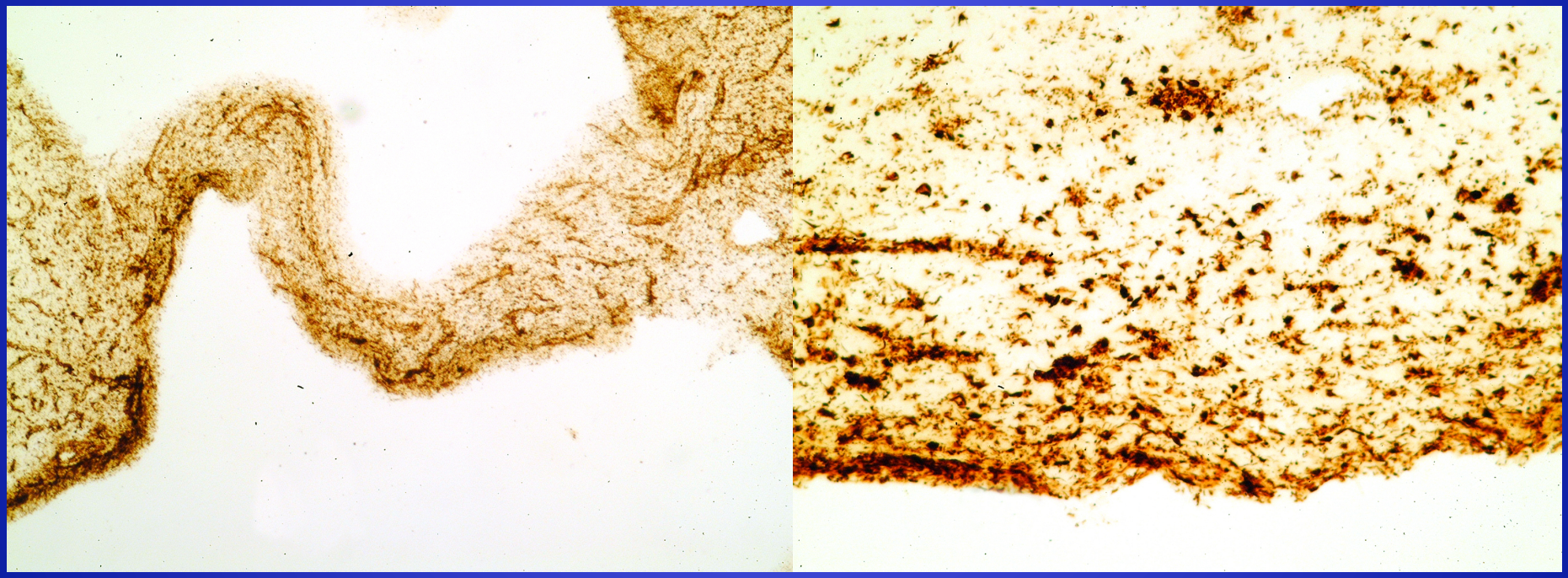
Fornix



Hyperphosphorylated Tau Immunohistochemistry

Normal gross appearance

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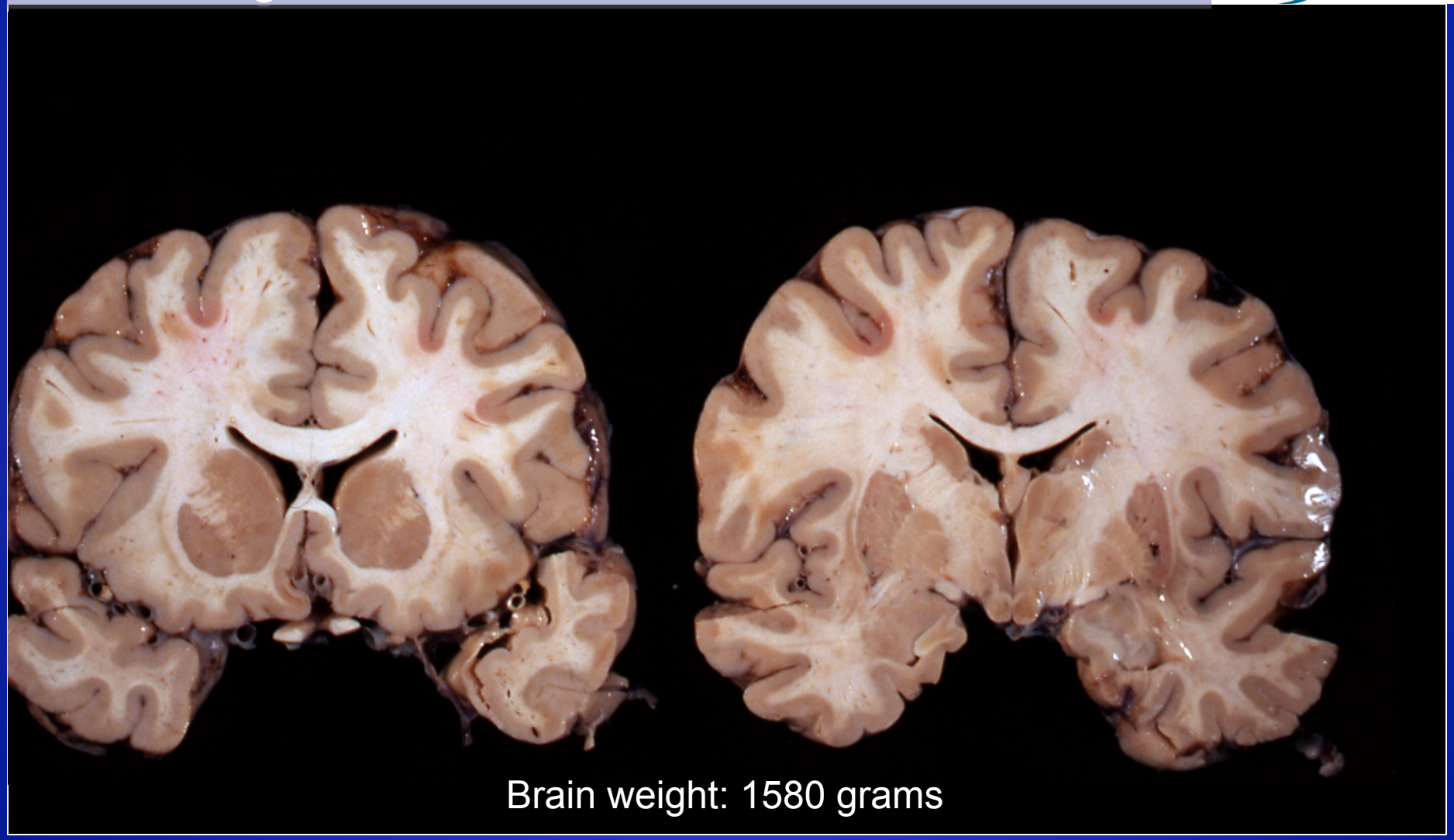
3 years of professional football. Cognitively intact. Death at age 49.



Brain weight: 1580 grams

Football player: 3 years in USFL, NFL

Death at age 49. Cognitively intact

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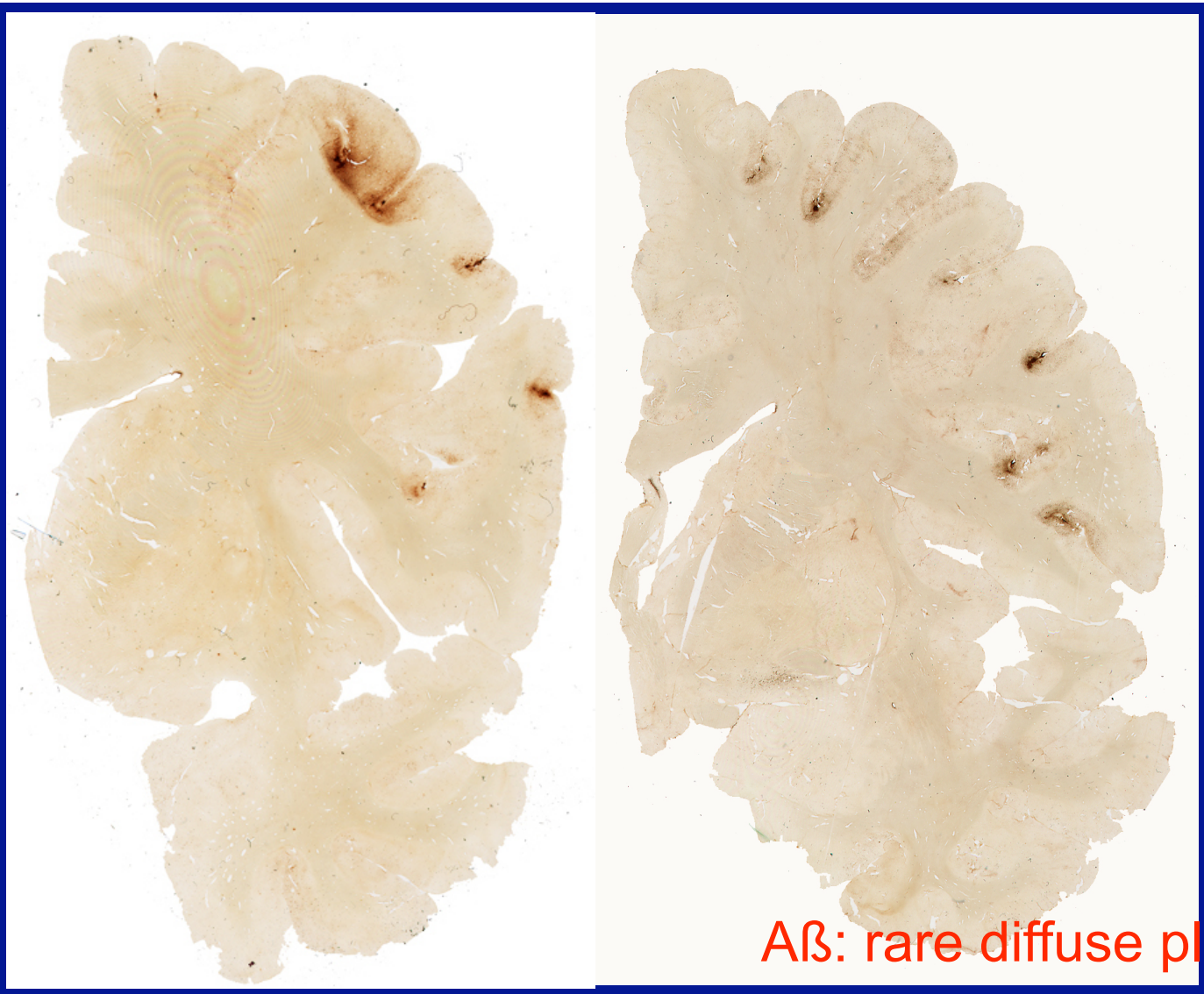


Aß: rare diffuse plaques

Mike Borich

Age 42

- Wide receiver for Snow College and Western Illinois University

  Total football playing years = 8

  9-10 concussions (> 5 in college, 4 in HS)

- Assistant coach for Brigham and Young University

- Beginning at age 38, developed increasing irritability, aggressive and violent outbursts

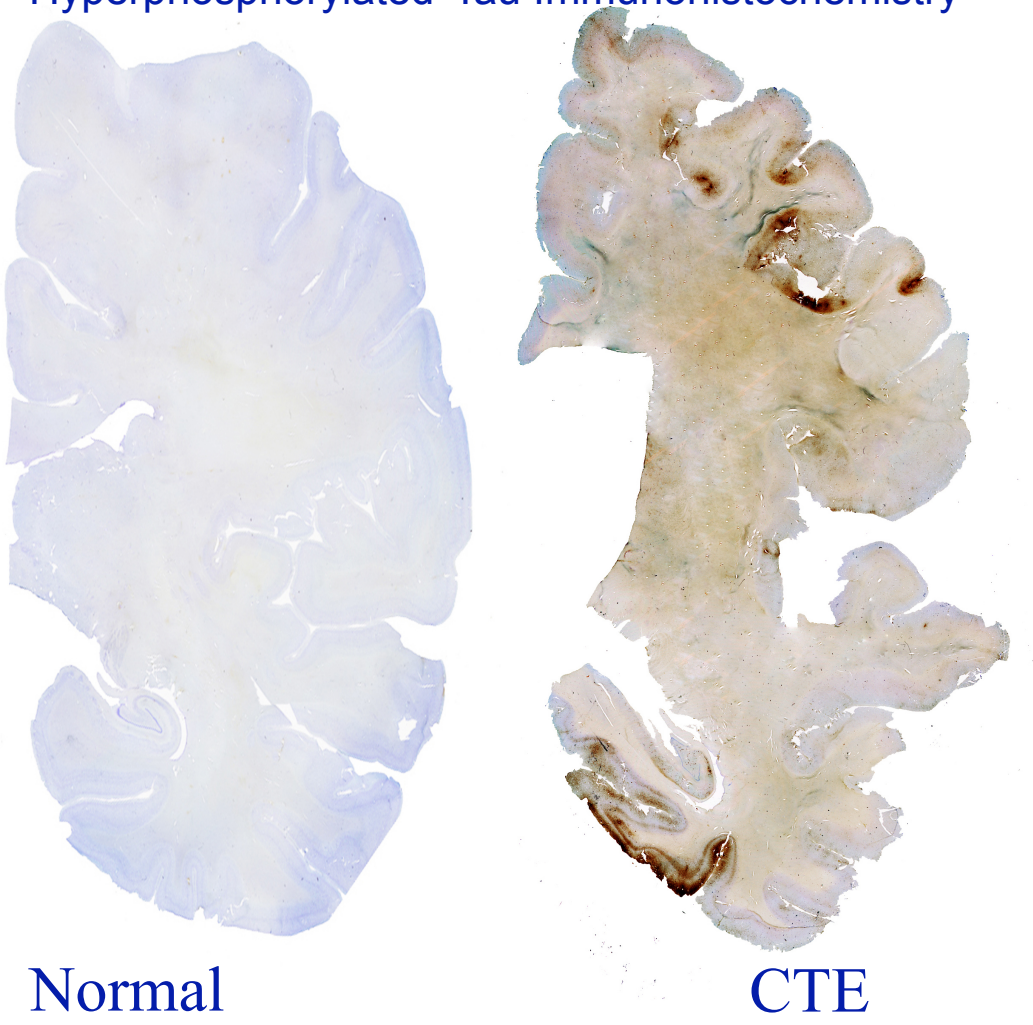
- Drug and alcohol abuse

- Marriage dissolved, lost his job as coach

Mike Borich

Death at age 42 with confusion, depression, erratic behavior, and substance abuse

Hyperphosphorylated Tau Immunohistochemistry



Normal

CTE

No Aß

Reggie Fleming

Death at 72 | Professional Hockey Player

Defensemen and forward: 1959 to 1971.

Remembered for hard-nosed play /combative style

108 NHL goals, 1468 penalty minutes, Stanley Cup

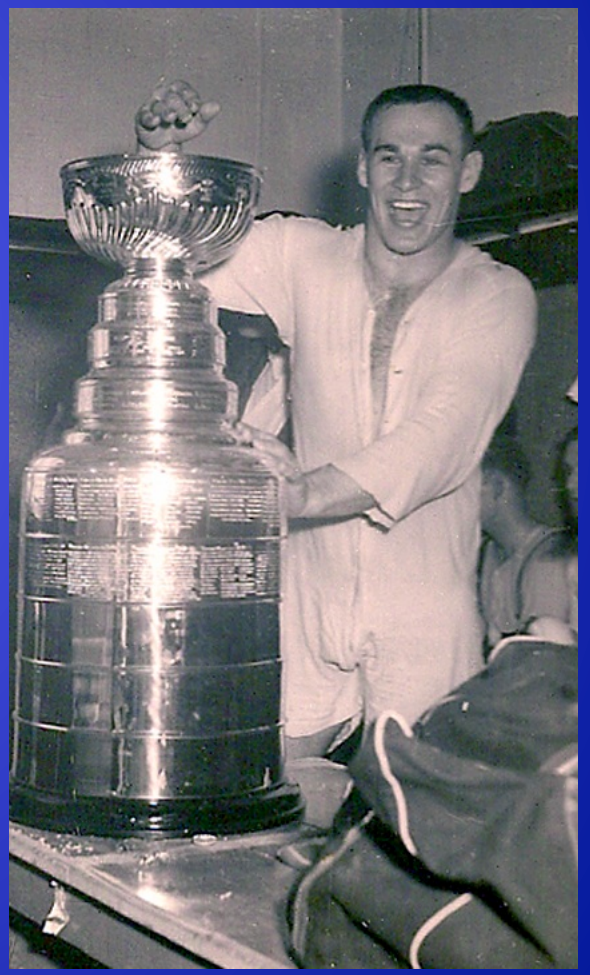
>20 concussions

Early 40's: "manic depression" with frequent extreme behavioral outbursts

Problems controlling his eating, drinking, gambling, and temper : "out of control"

Impairments in attention, concentration, memory, executive impairment

Overt dementia final two years



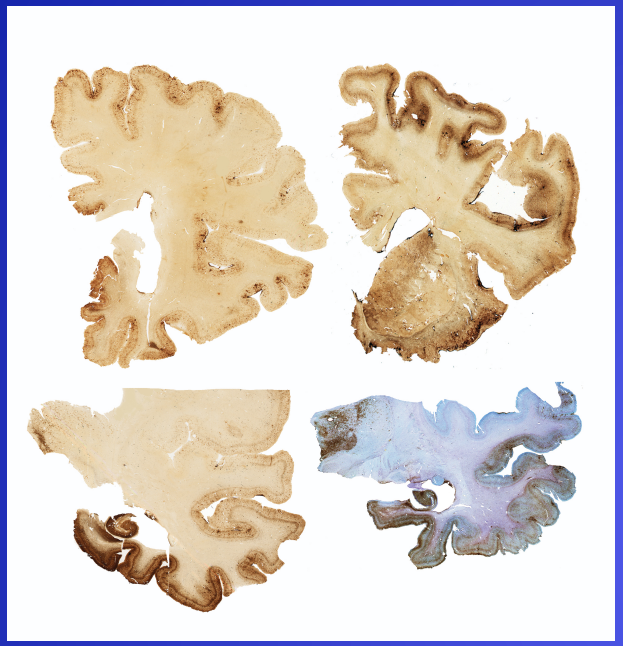
Reggie Fleming

Death at age 72 with dementia after decades of manic-depression, out of control behavior

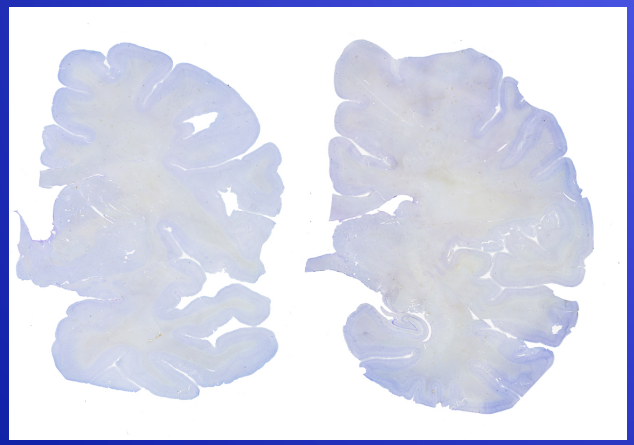
Hyperphosphorylated Tau Immunohistochemistry

CTE: Unique, predictable pattern of tau neurofibrillary change very distinct from Alzheimer's disease or any other tauopathy

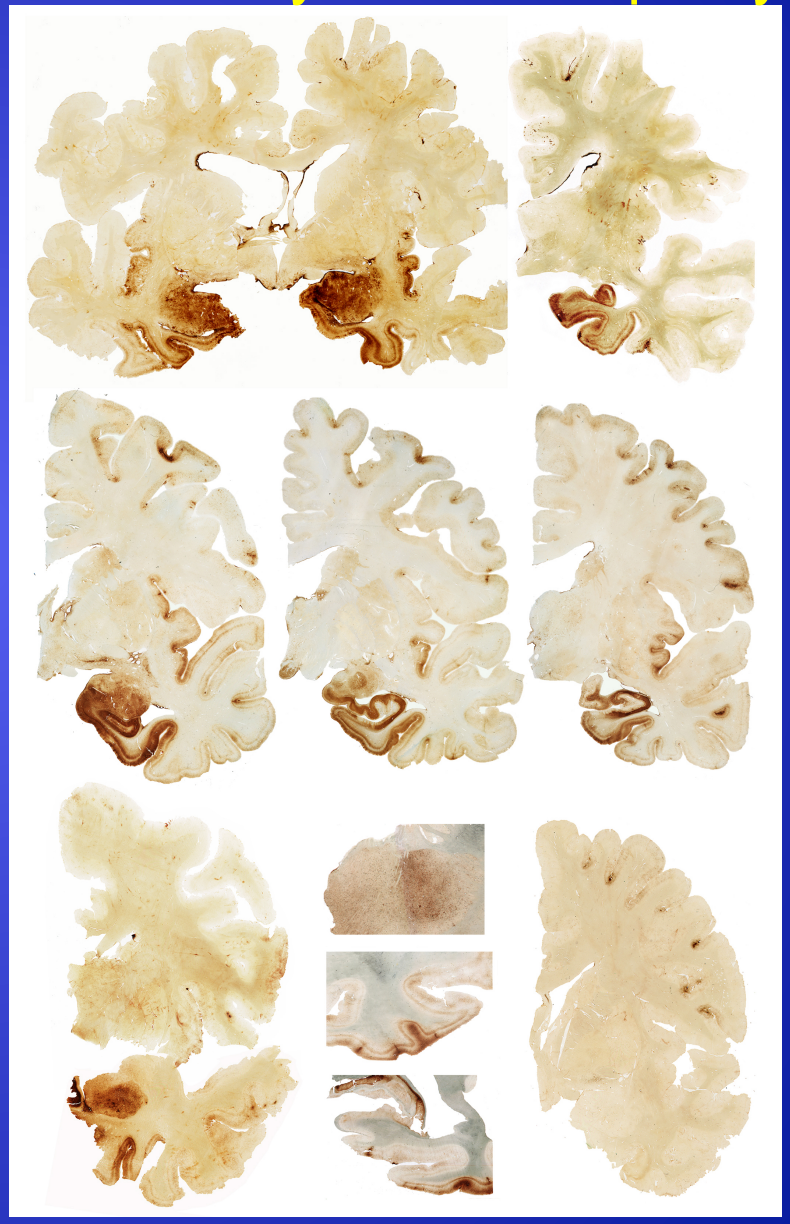
Boxers



Controls



Football players



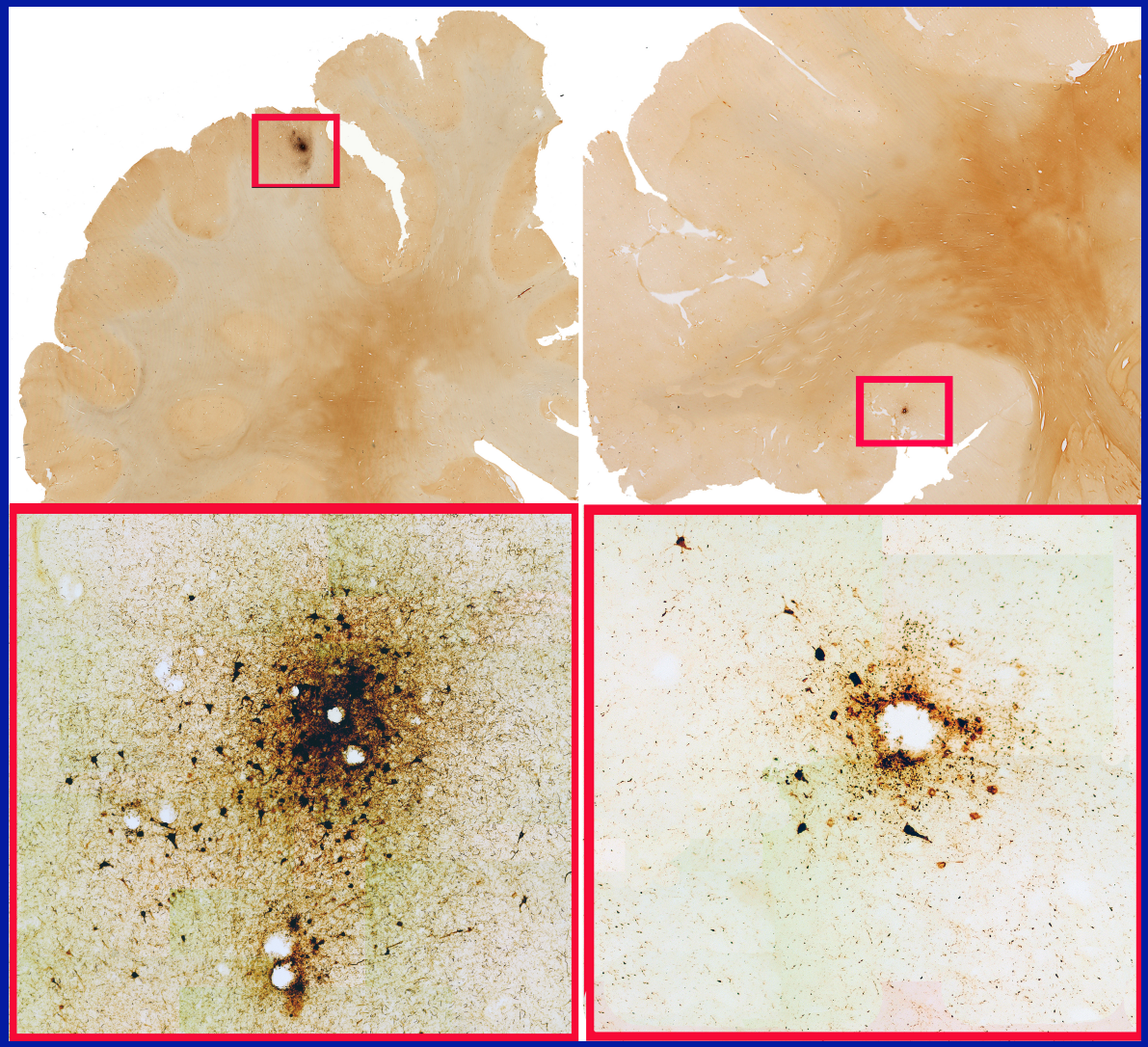
High school football player

Death at age 18. Cognitively intact. Focal evidence of perivascular tau

BOSTON UNIVERSITY

sportslegacy INSTITUTE

P-Tau immunohistochemistry



Chronic Traumatic Encephalopathy

So what do we know?

- The evidence suggests that CTE is associated with repeated sublethal brain trauma that most commonly occurs in an individual's teens and early twenties.
- There is characteristically a long latent period (m=8 years, range 0-37 years) between stopping play of the sport and the onset of symptoms
- Once triggered, the neurodegeneration progresses slowly, with an mean survival of 18 years after the onset of symptoms (range 2-46 years).
- The symptoms of CTE are often insidious and begin in mid-life with prominent early personality and behavioral changes and memory loss.
- There is a slow deterioration that progresses to include dementia, Parkinsonism, gait and speech disorders.
- In the advanced cases, the dementia make be clinically misdiagnosed as AD or FTD

So What Do We Need to Know?

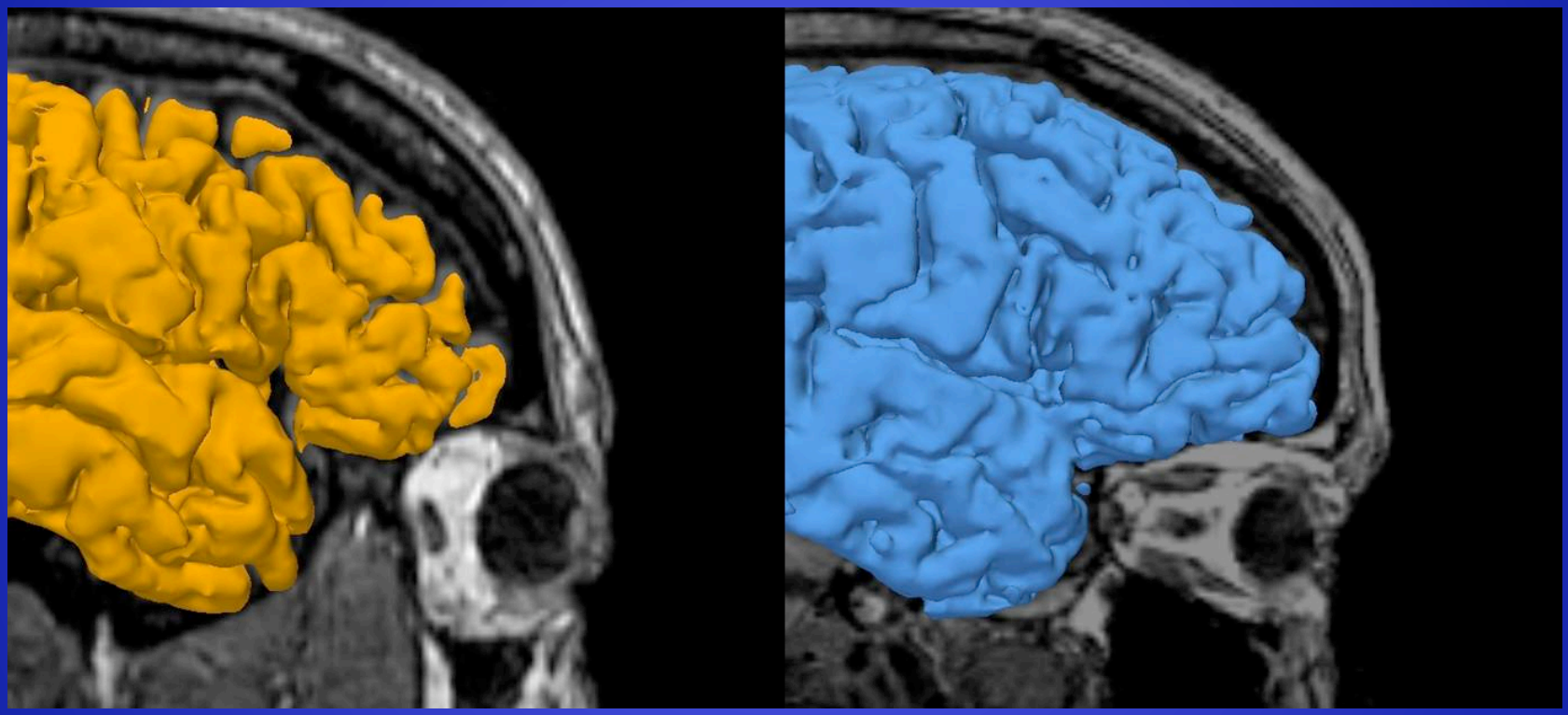
- How do we diagnose CTE?
- How do we treat CTE?
- How do we prevent CTE?

- What is the clinical course of CTE?
- What is the prevalence of CTE?
- What are the risk factors of CTE?
  - Genetic risk factors (ApoE4)
  - Severity of trauma
  - Type of trauma (LOC, grade of concussion, subconcussive blow)
  - Frequency and time interval between successive head traumas
  - Age of individual at time of injury and duration of exposure
  - Positions played and and type of sport

- Through our contact registry, we are beginning to make progress identifying CTE in living athletes

Pilot Imaging Data on 5 Retired Pro Athletes

Structural MRI with 3D Reconstruction



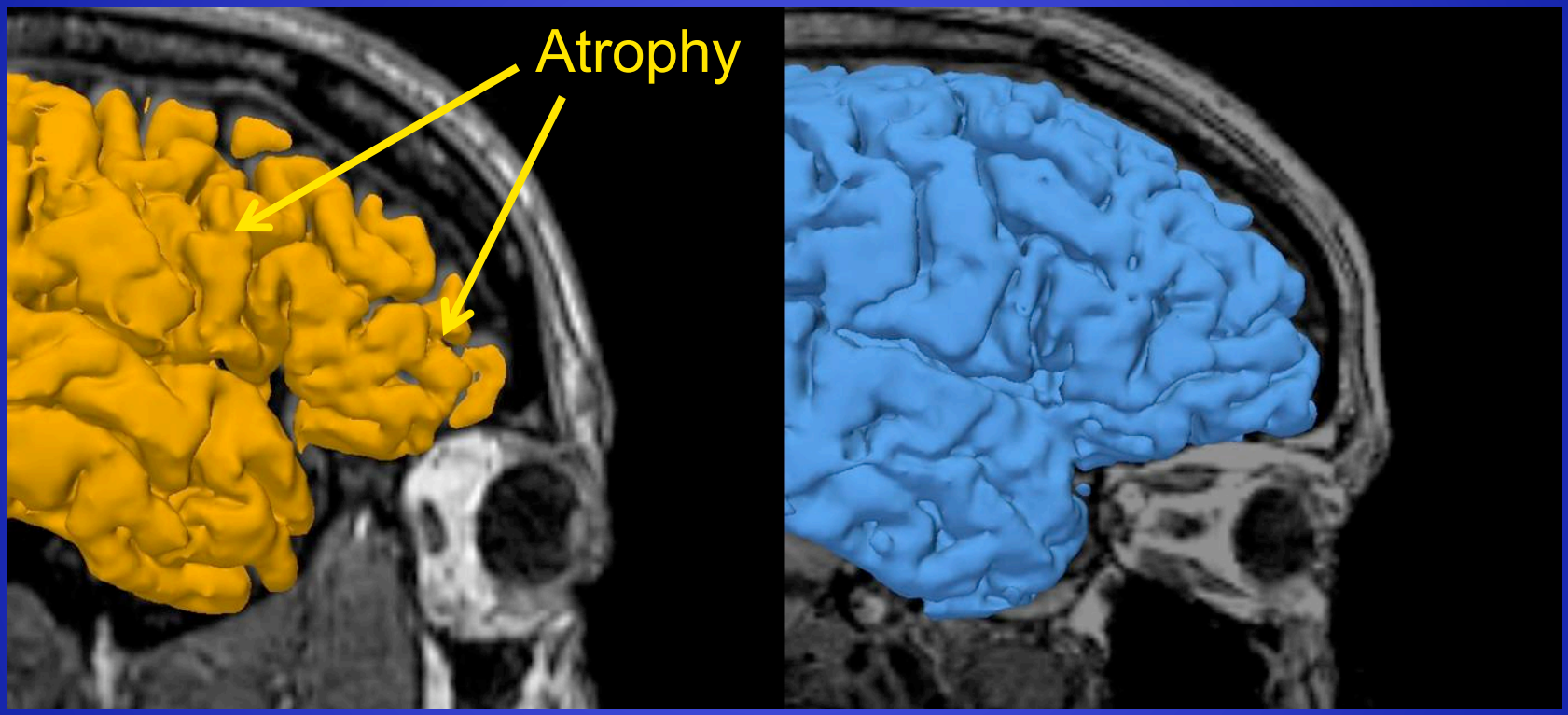
Athlete

Healthy Volunteer

Brigham and Women's Hospital: Martha Shenton, Jorge Alvarado, Marek Kubicki, Alex Linn, Carolyn Mountford, David Tate, Rayna Zacks

Pilot Imaging Data on 5 Retired Pro Athletes

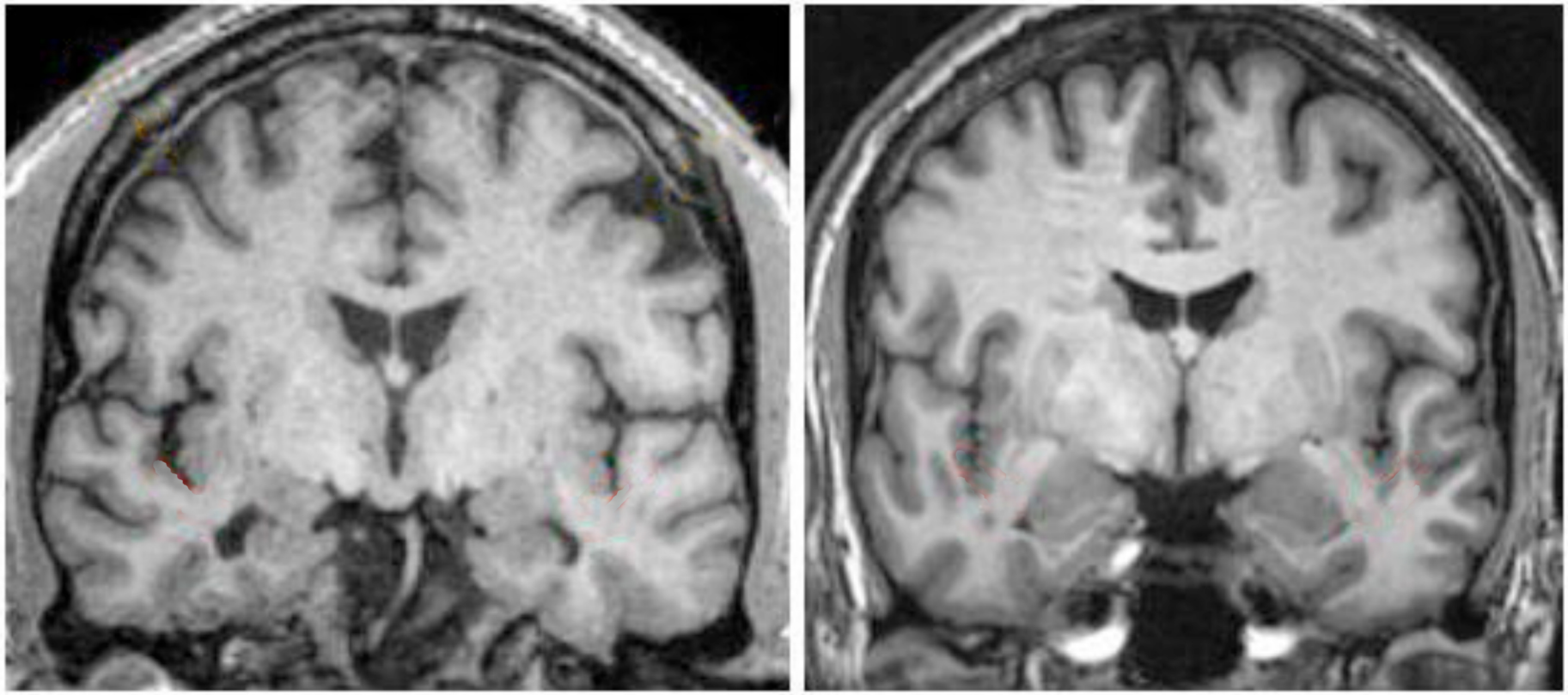
Structural MRI with 3D Reconstruction



Athlete

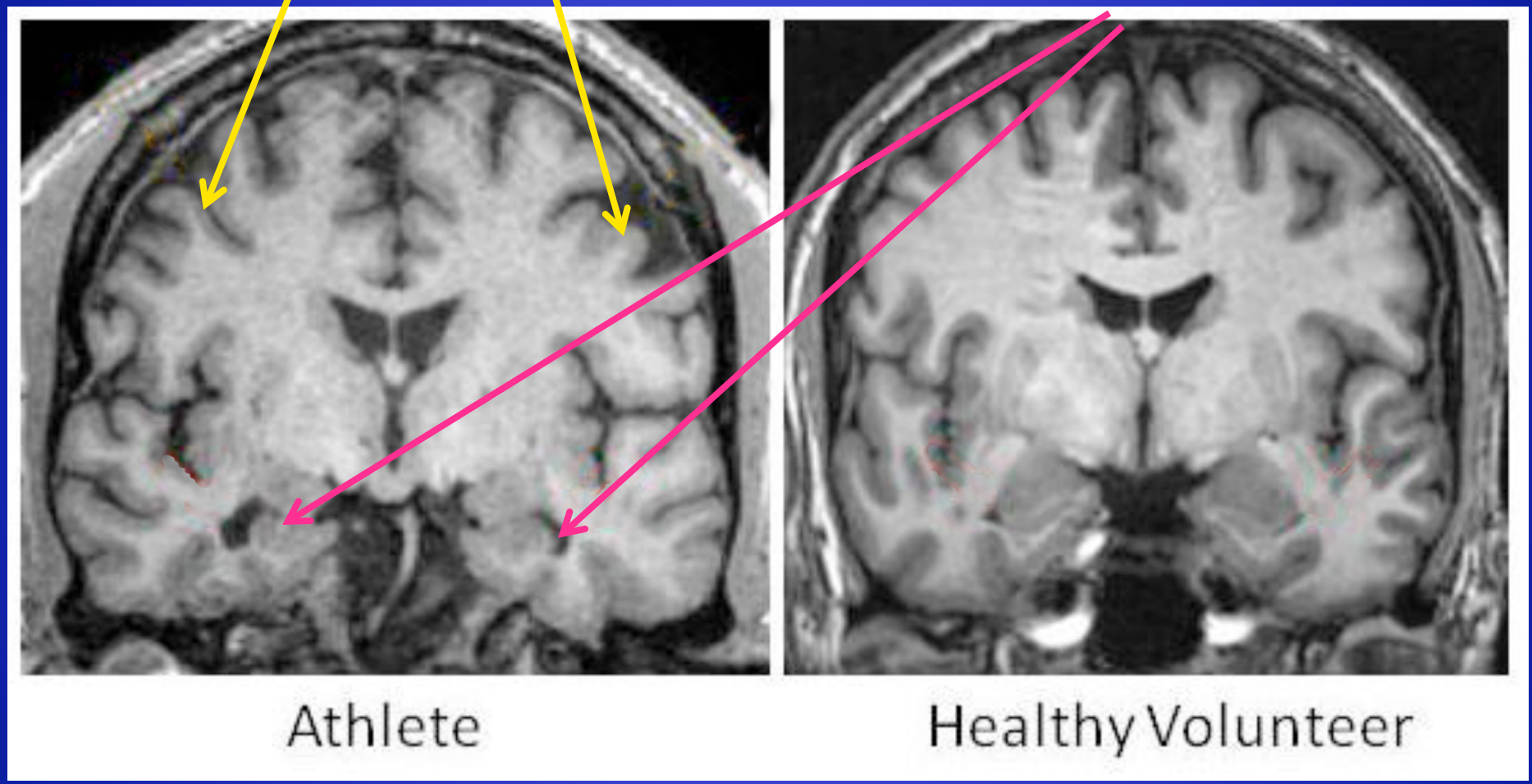
Healthy Volunteer

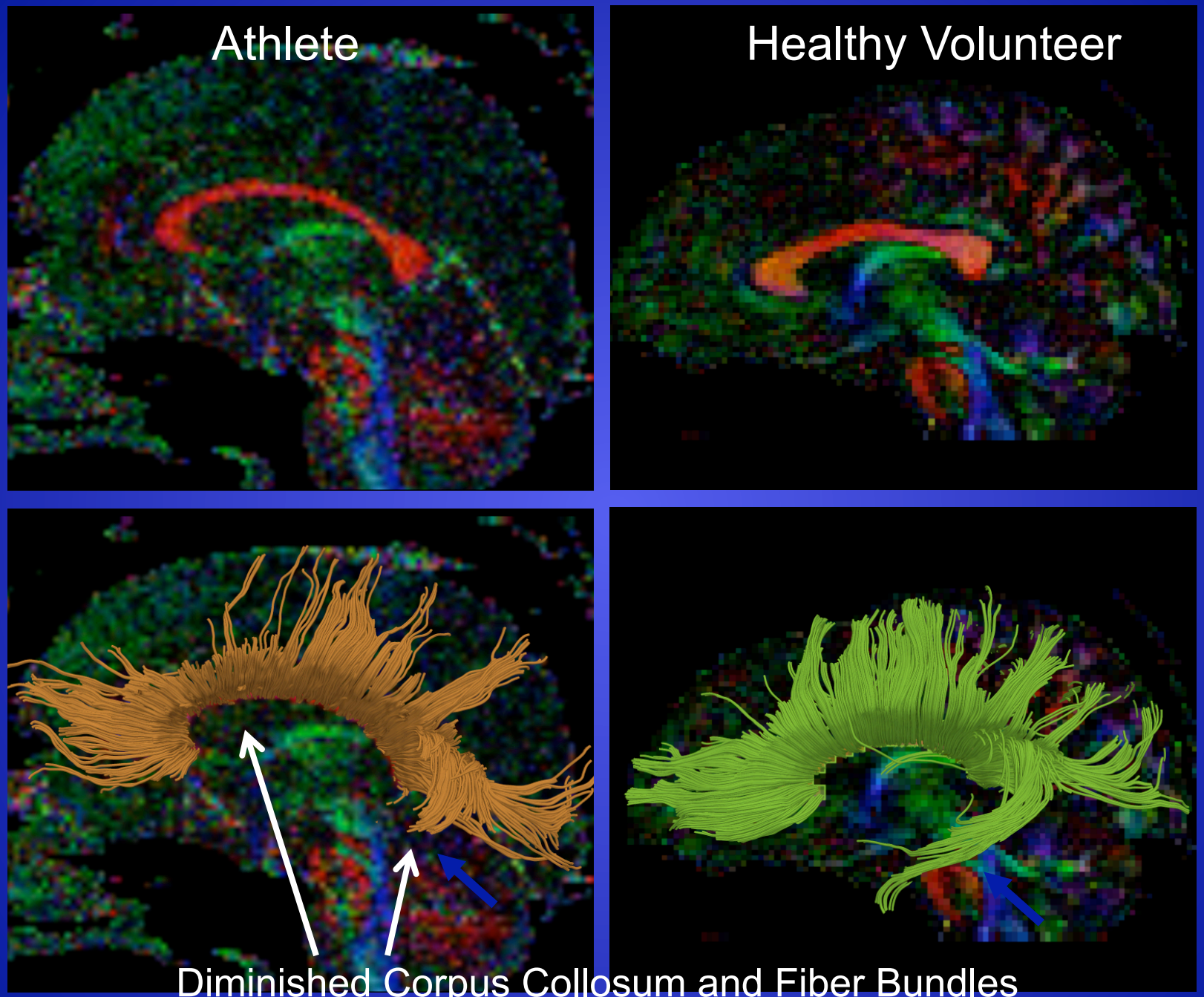
Brigham and Women's Hospital: Martha Shenton, Jorge Alvarado, Marek Kubicki, Alex Linn, Carolyn Mountford, David Tate, Rayna Zacks



Athlete

Healthy Volunteer


Cortical atrophy
Medial temporal lobe atrophy
Athlete
Healthy Volunteer


Athlete
Healthy Volunteer
Diminished Corpus Collosum and Fiber Bundles

How do you treat CTE?

Presently there is no therapy for CTE except for symptomatic treatment

Anti-tau therapies are on the horizon, a few are currently in clinical trials and may be only a few years away:

NAP (NAPVSIPQ, generic name, davunetide) (Allon Therapeutics Inc.)

Rember (methylene blue) TauRx

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