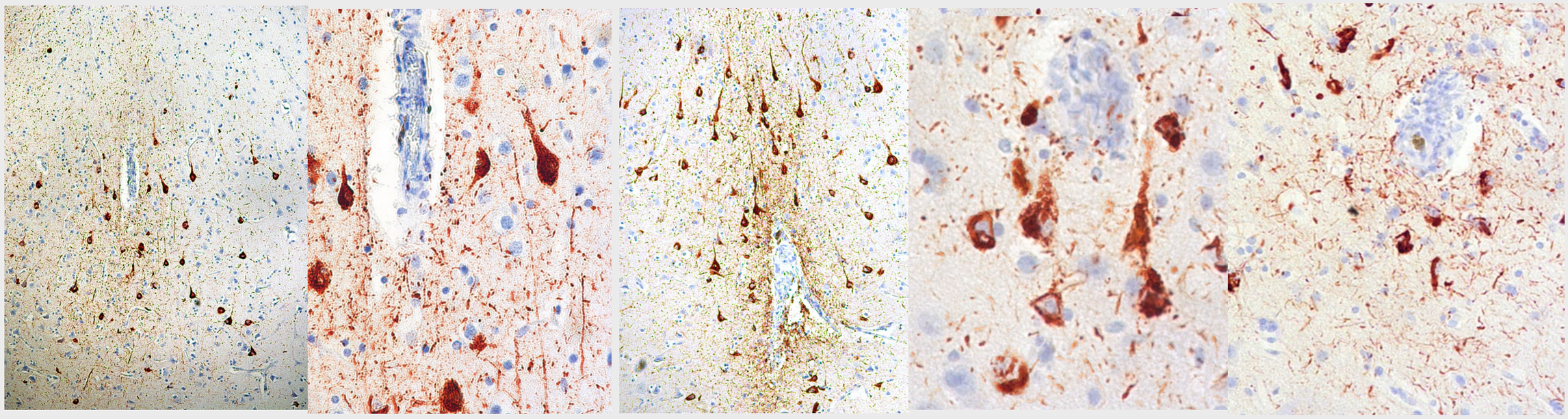
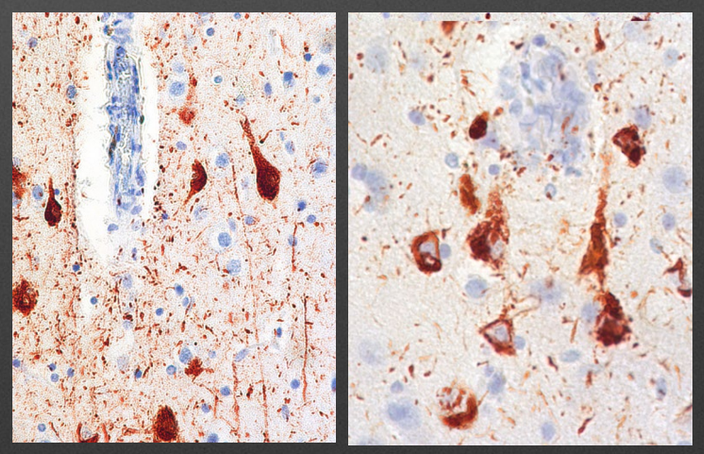


The Diagnosis of CTE

Ann C. McKee M.D.
Neuropathology Core Leader and Associate Director,
BU Alzheimer's Disease Research Center
Director, BU CTE Center

Pathognomonic lesion of CTE

- First NINDS/NIBIB consensus panel (1): “an accumulation of abnormal hyperphosphorylated tau (p-tau) in neurons and astroglia distributed around blood vessels at the depths of the cortical sulci and in an irregular pattern”
- Second NINDS/NIBIB panel (2): a single pathognomonic lesion in the cortex is the minimum threshold for a diagnosis of CTE
- The following features of the pathognomonic lesion are necessary:
  - *p-tau aggregates in neurons*
  - *with or without p-tau in astrocytes*
  - *at the depth of the sulcus*
  - *around blood vessels*
  - *deep in the parenchyma, not in the subpial and superficial region*



(1) McKee et al, Acta NP 2015 (2) Bieniek et al, in prep, 2020

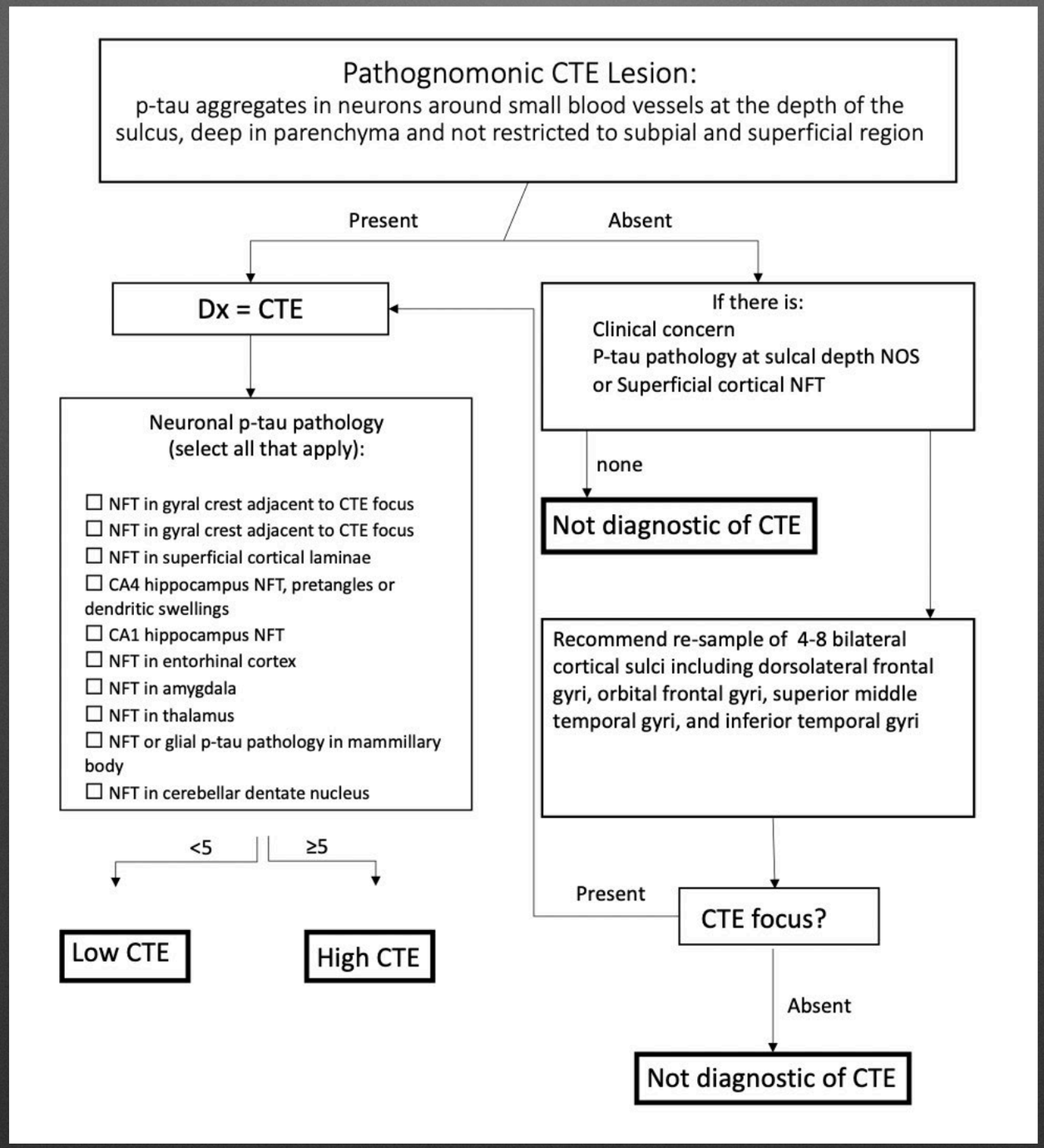
Supportive features of CTE

- 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 NP, 2020

Proposed Working Protocol

The panel also proposed an operational workflow for the diagnosis and binary classification of CTE as “Low CTE” or “High CTE”



Bieniek et al, in prep, 2020

Distinction from ARTAG

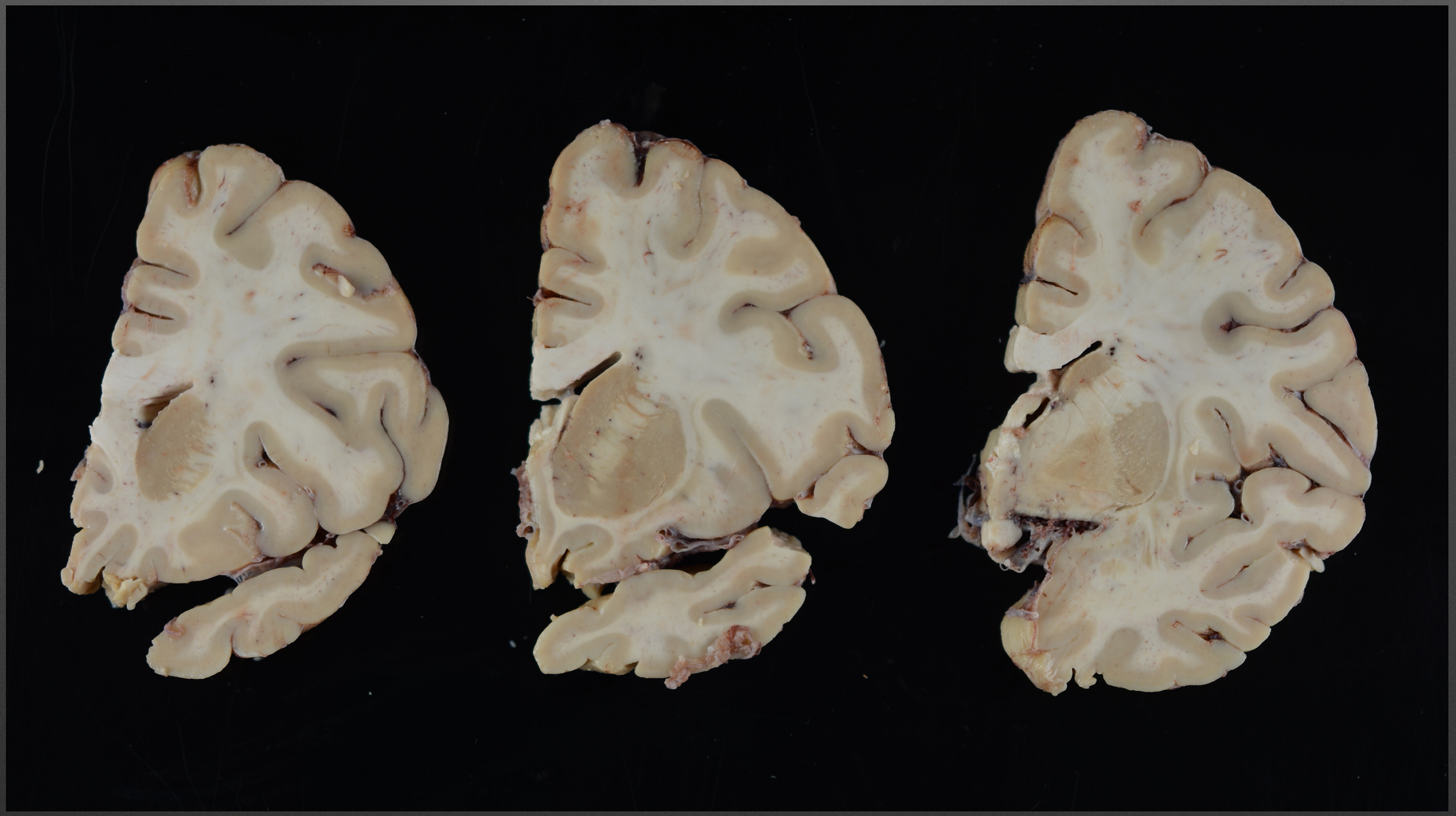
- The consensus panel also confirmed that purely astrocytic perivascular p-tau lesions, including subpial ARTAG, did not meet criteria for CTE.

- Clusters of p-tau astrocytes in the white matter of the frontal and temporal cortex, basal ganglia, and brainstem are considered ARTAG and are not specific features of CTE.

Bieniek et al, in prep, 2020

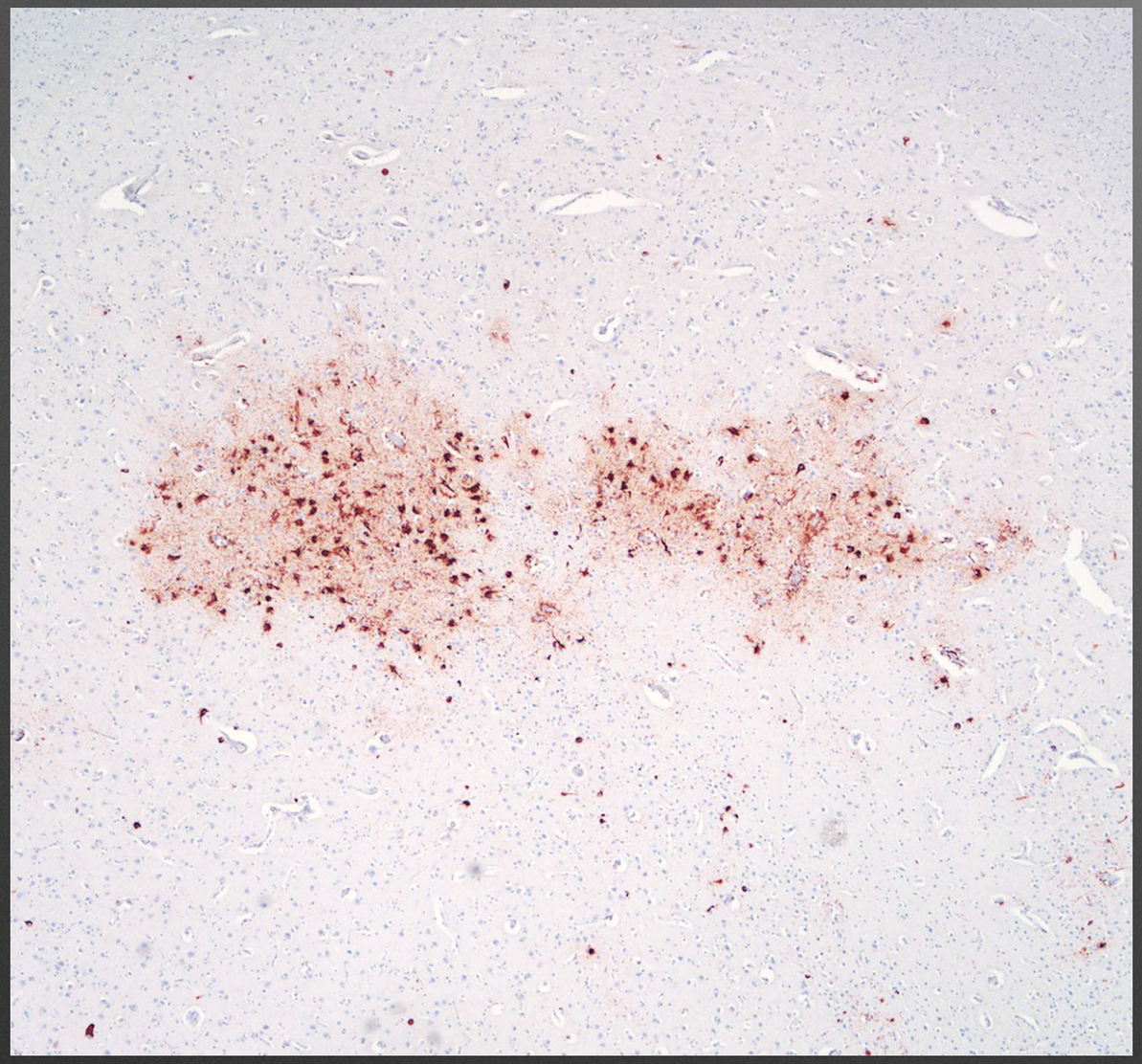
Case 1

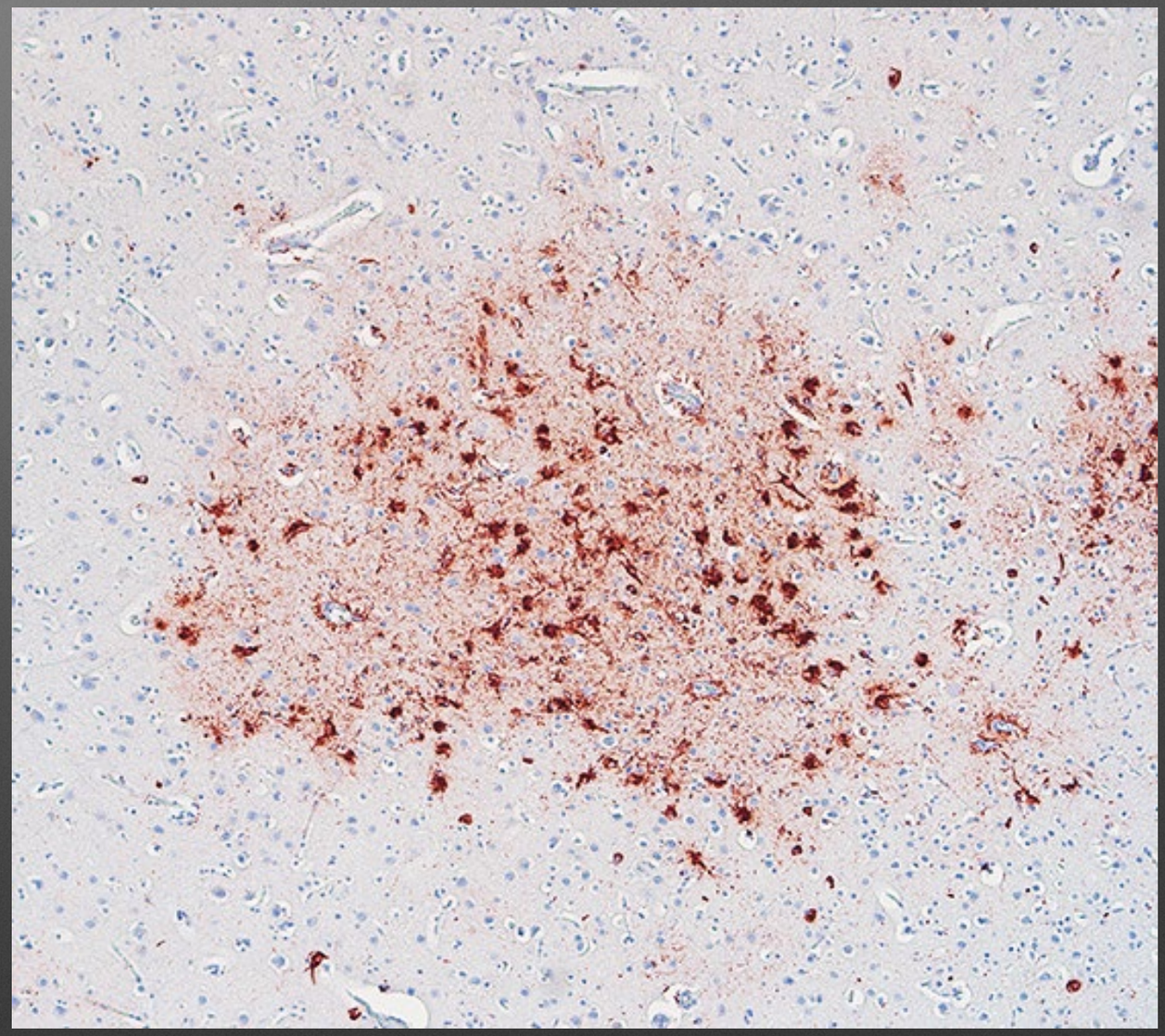
- Played football for 19 years:
  4 years youth, 4 years high school, 4 years college, 7 years NFL.
- Long-standing attention difficulties. Occasional temper outbursts.
- Late 40s: Mild memory complaints
- Early 50s: Forgetful, misplaced objects, word-finding difficulty
  MicroCog assessment: Average to above average
- Late 50s: Repeating himself, getting lost driving
- Age 61: metastatic cancer diagnosis
  Neurological evaluation: Dx: Traumatic Encephalopathy Syndrome (TES), possible
- Age 61: Death



Brain weight: 1453 grams

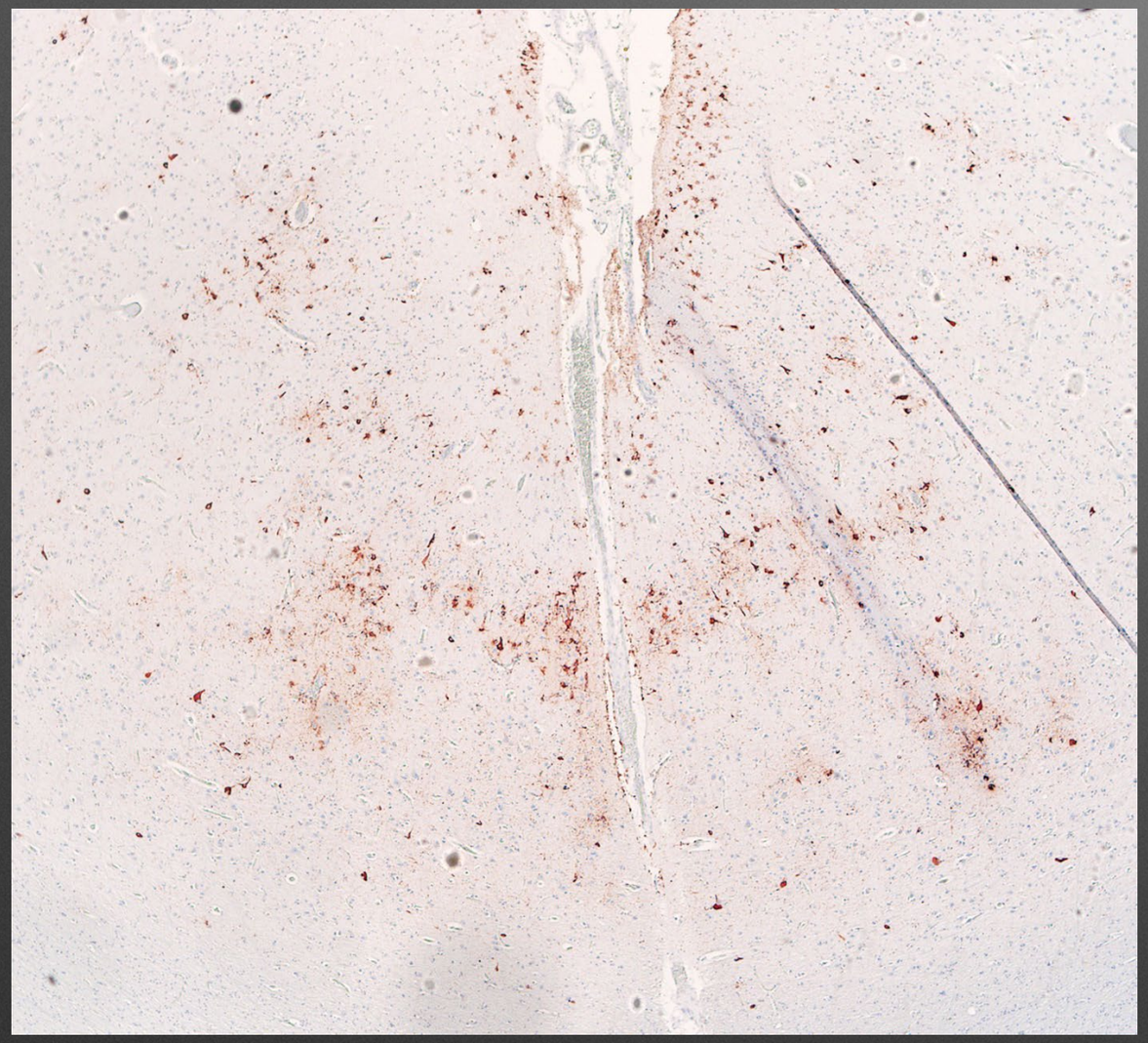
Sulcal depth of superior frontal cortex

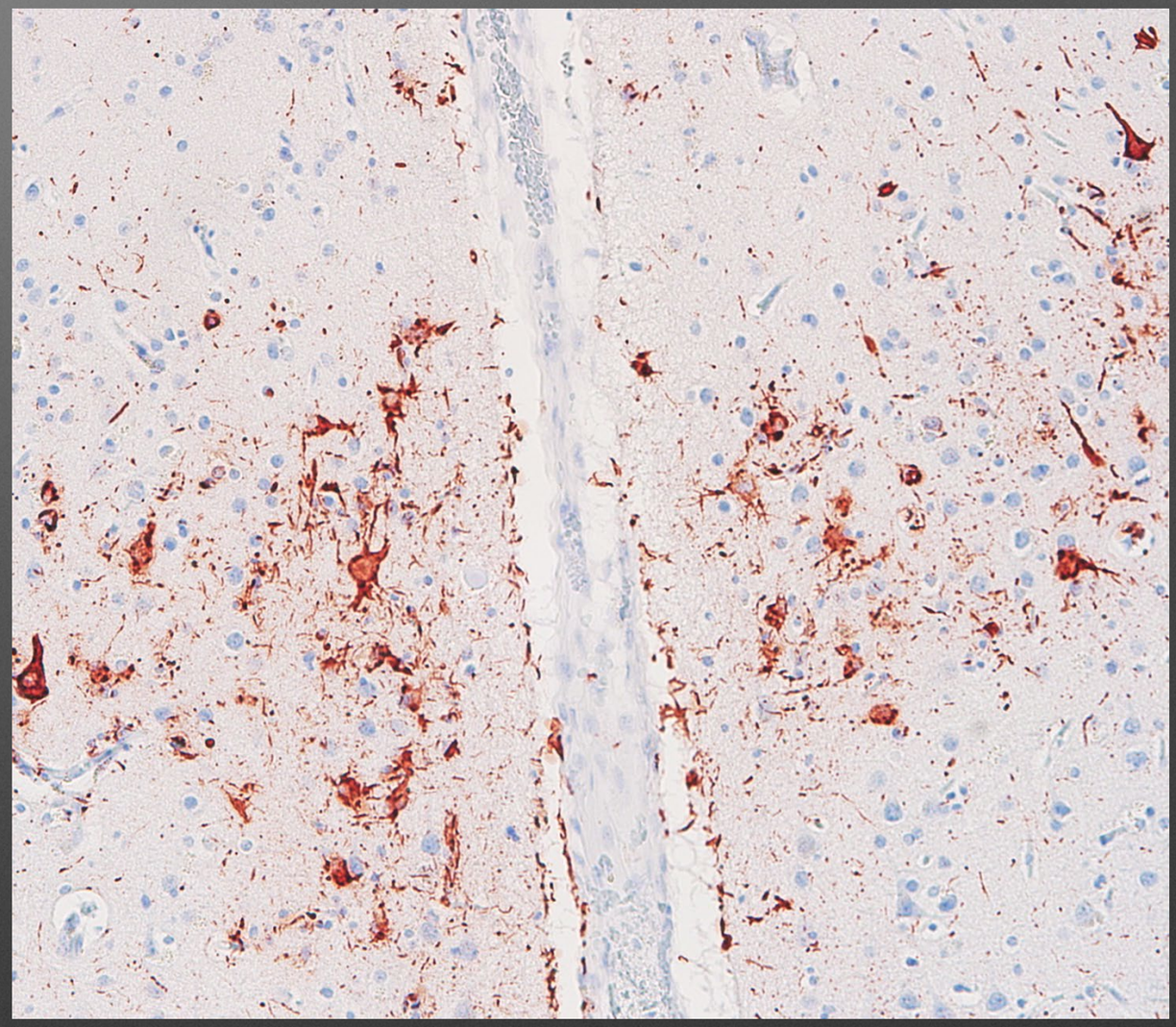




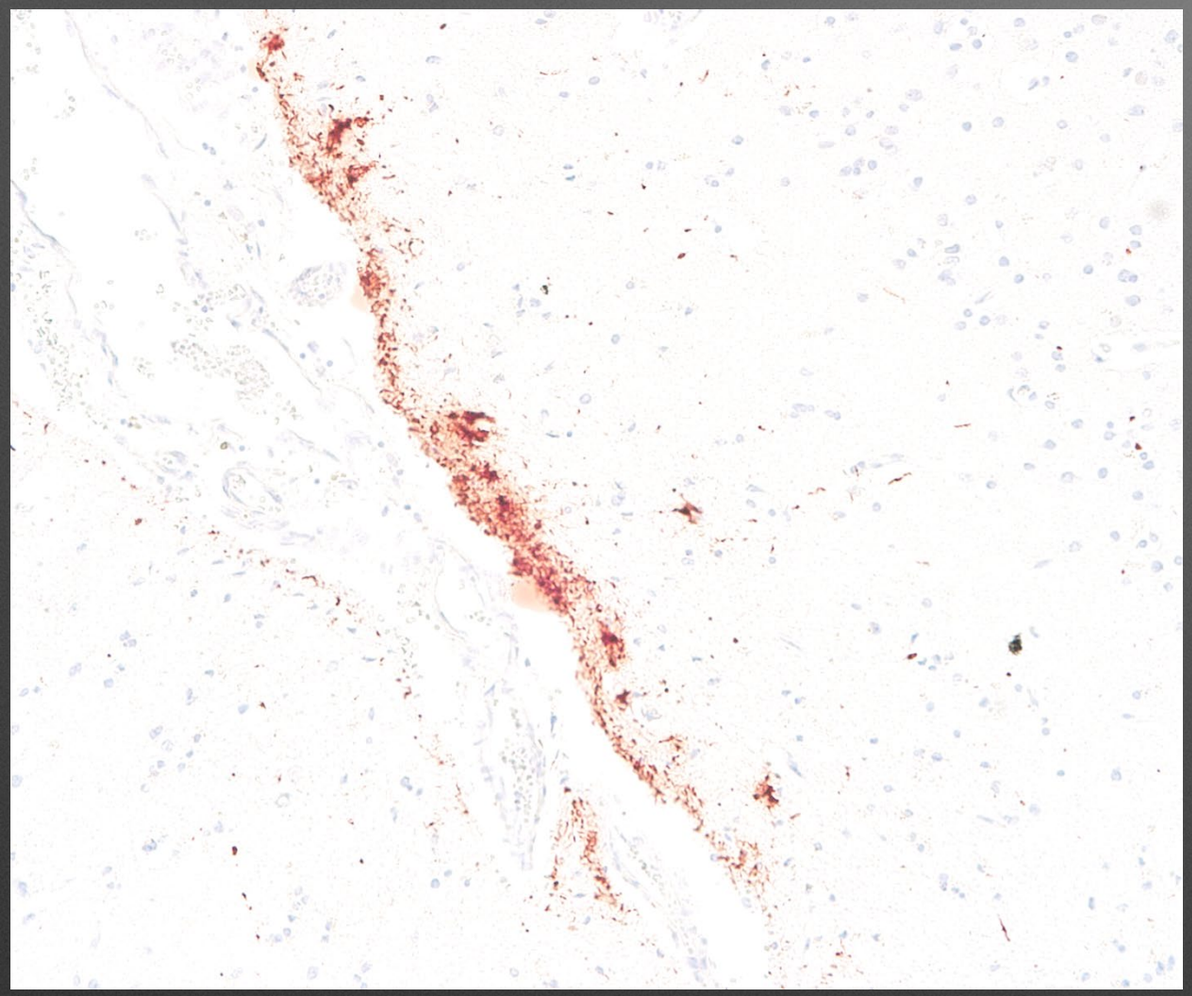
AT8: Pathognomonic lesions of CTE

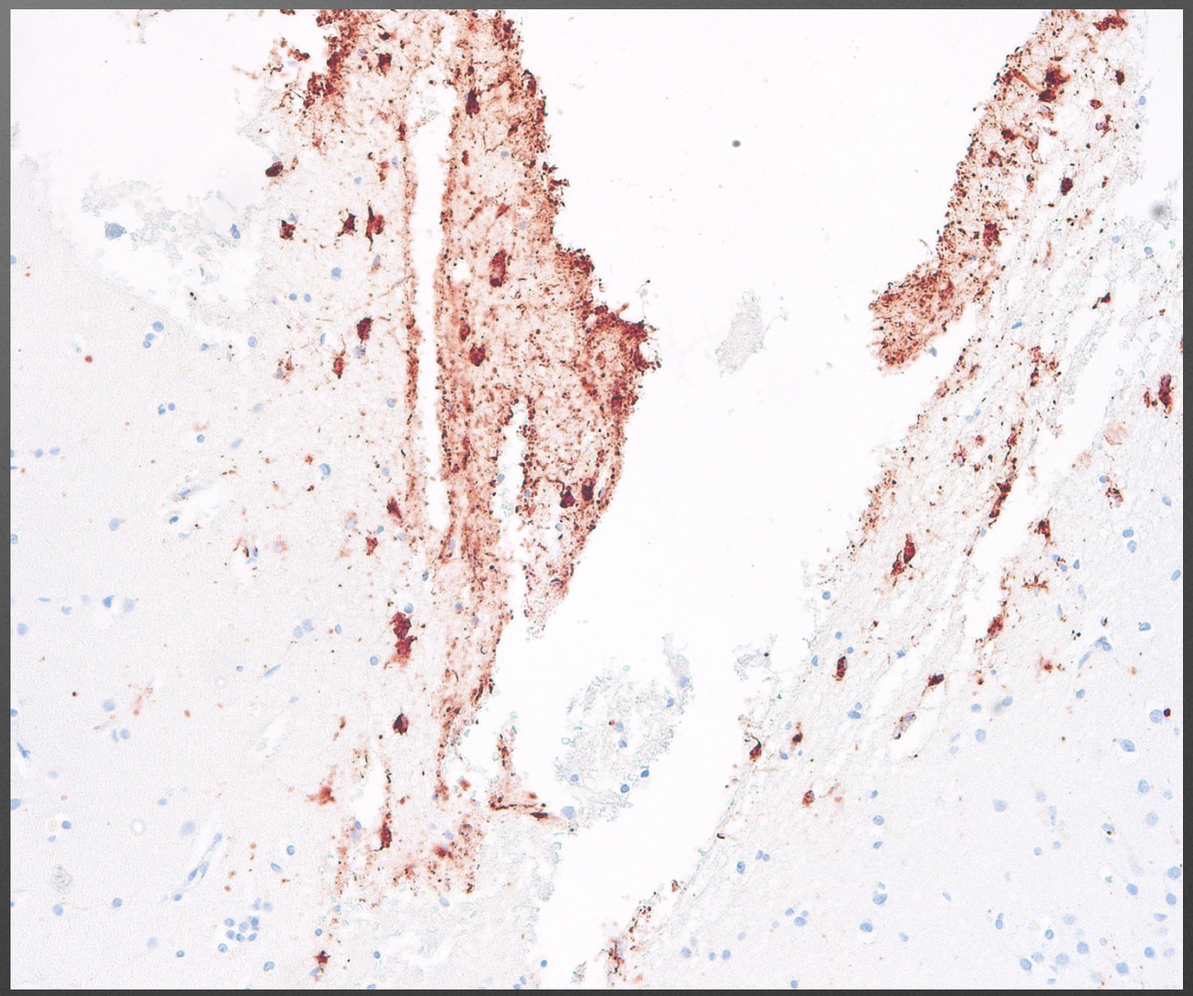
Sulcal depth of dorsolateral frontal cortex



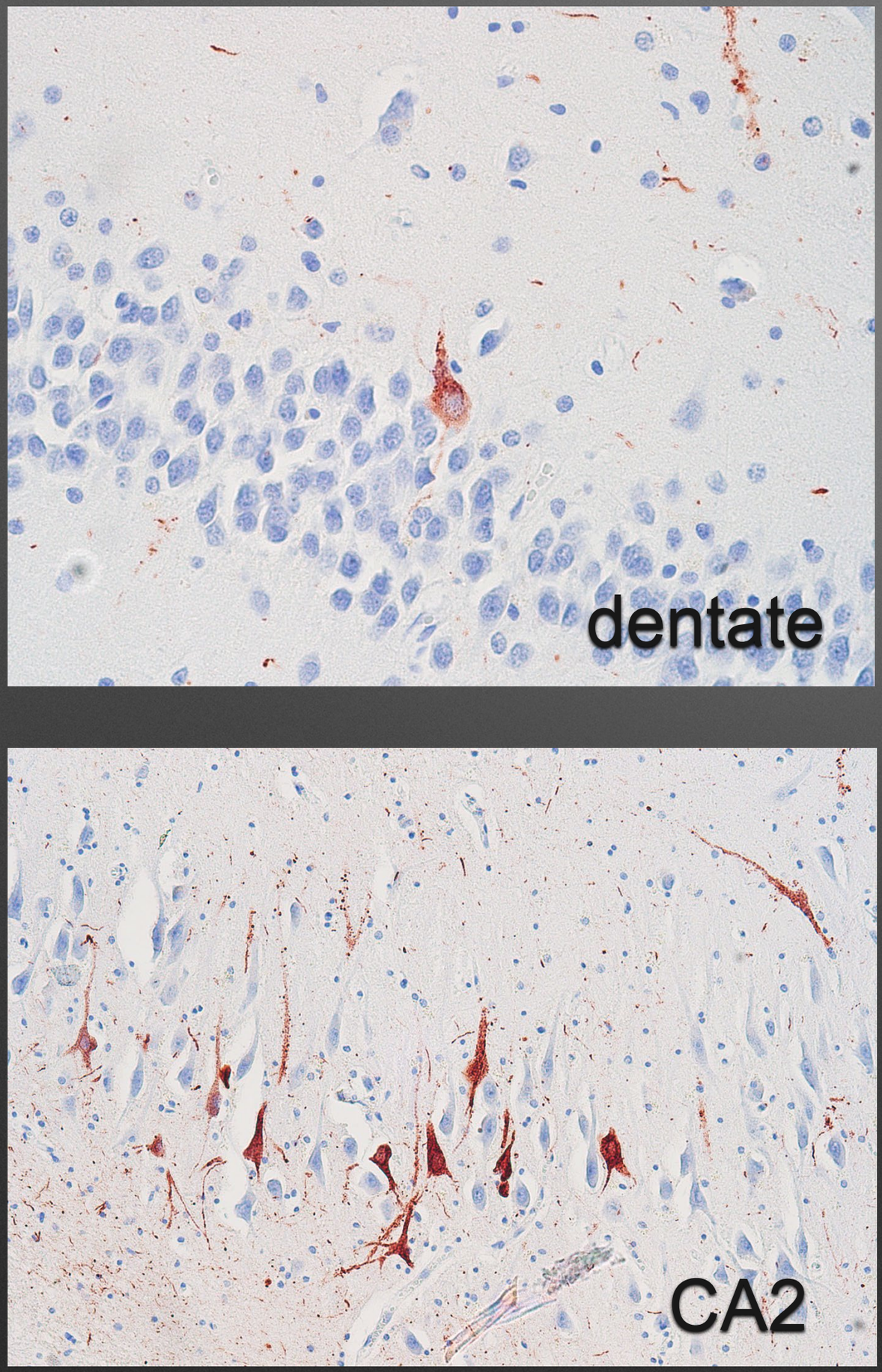


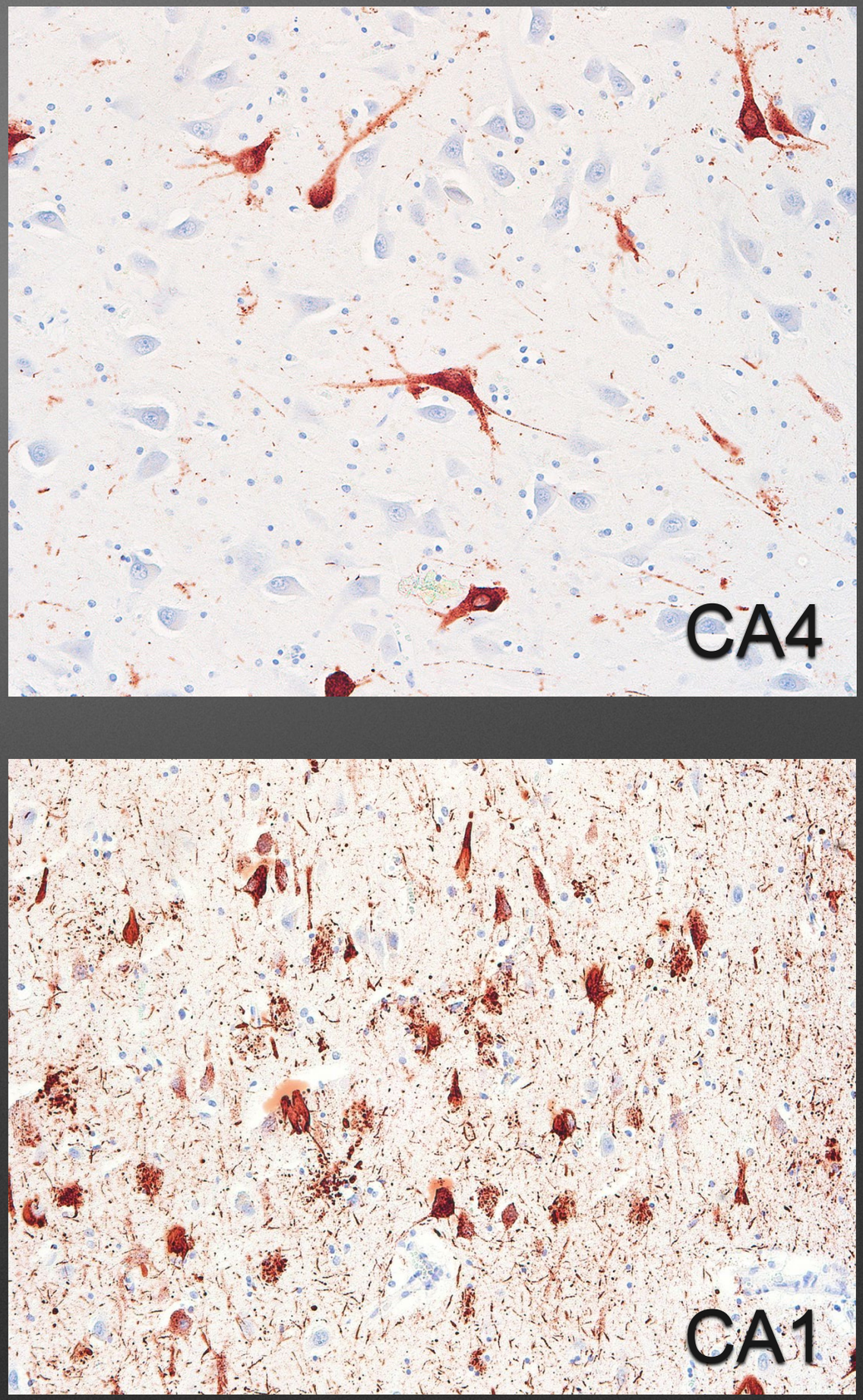
AT8: Pathognomonic lesions of CTE





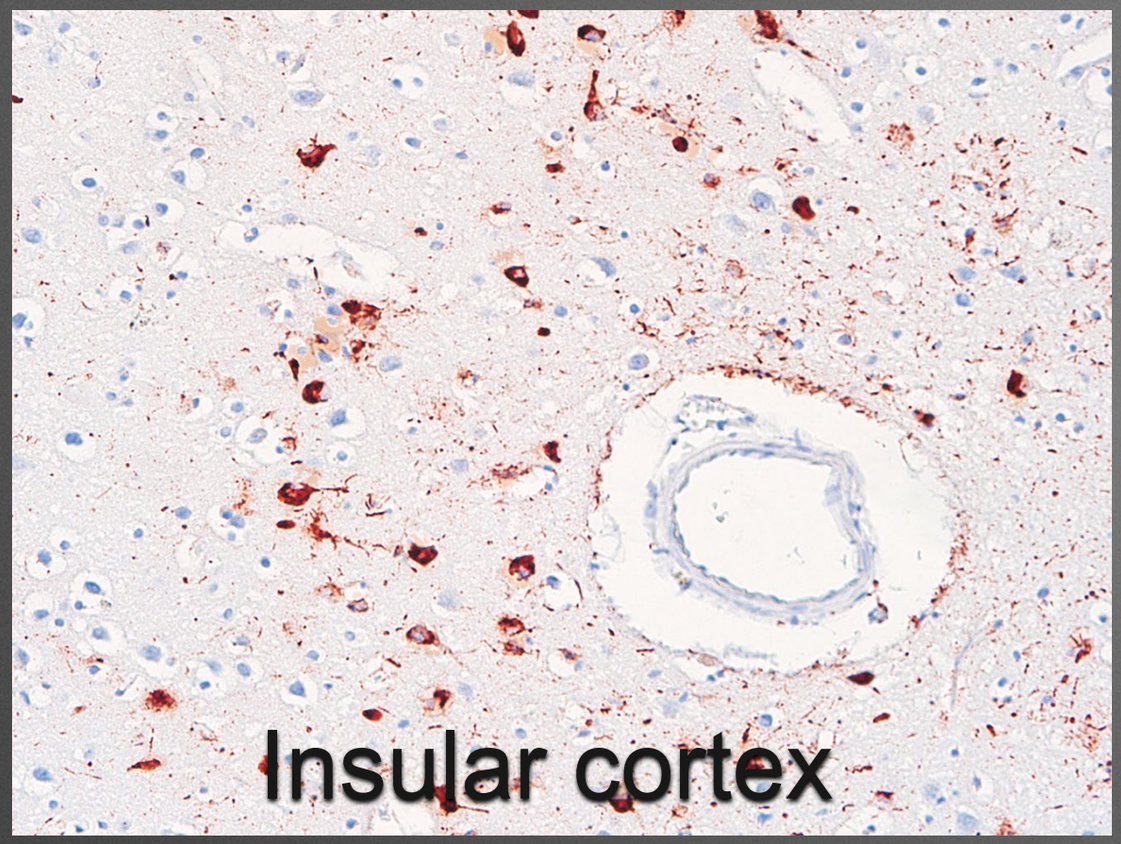
Subpial thorn-shaped astrocytes

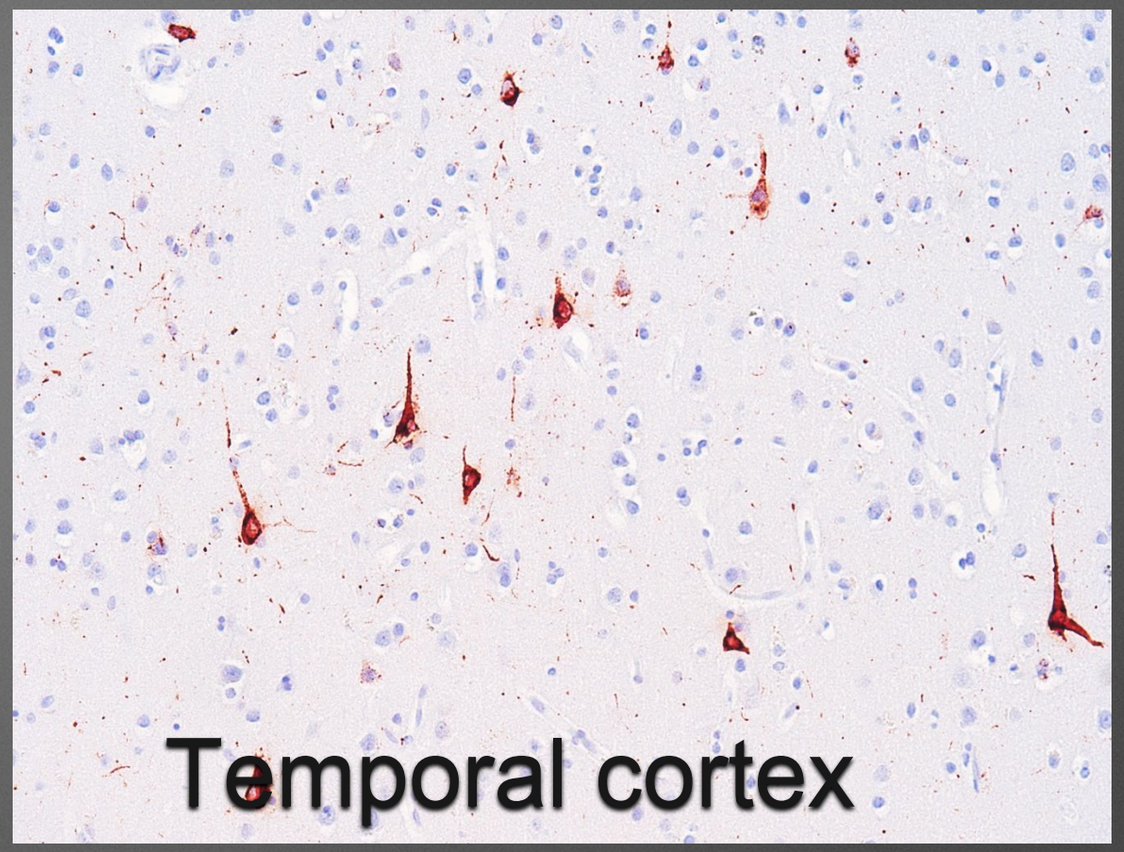

dentate

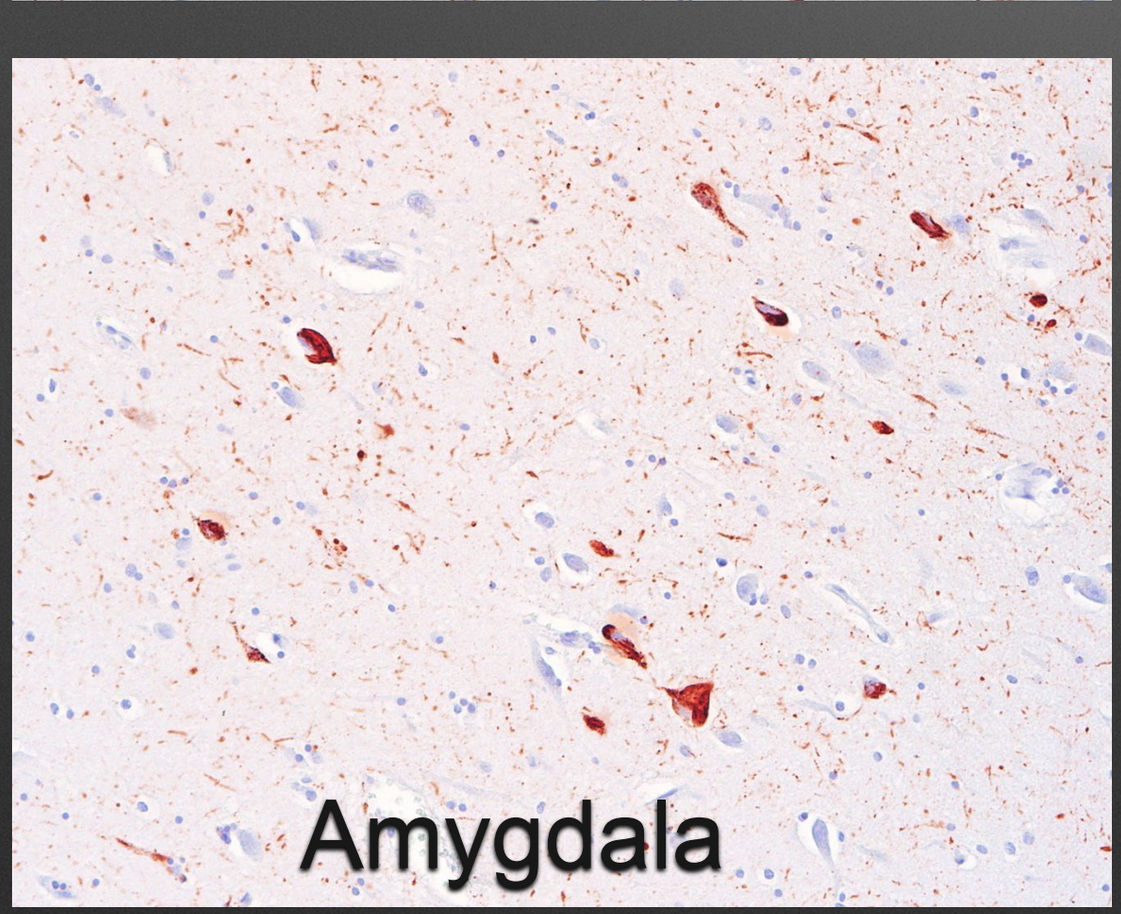

CA4

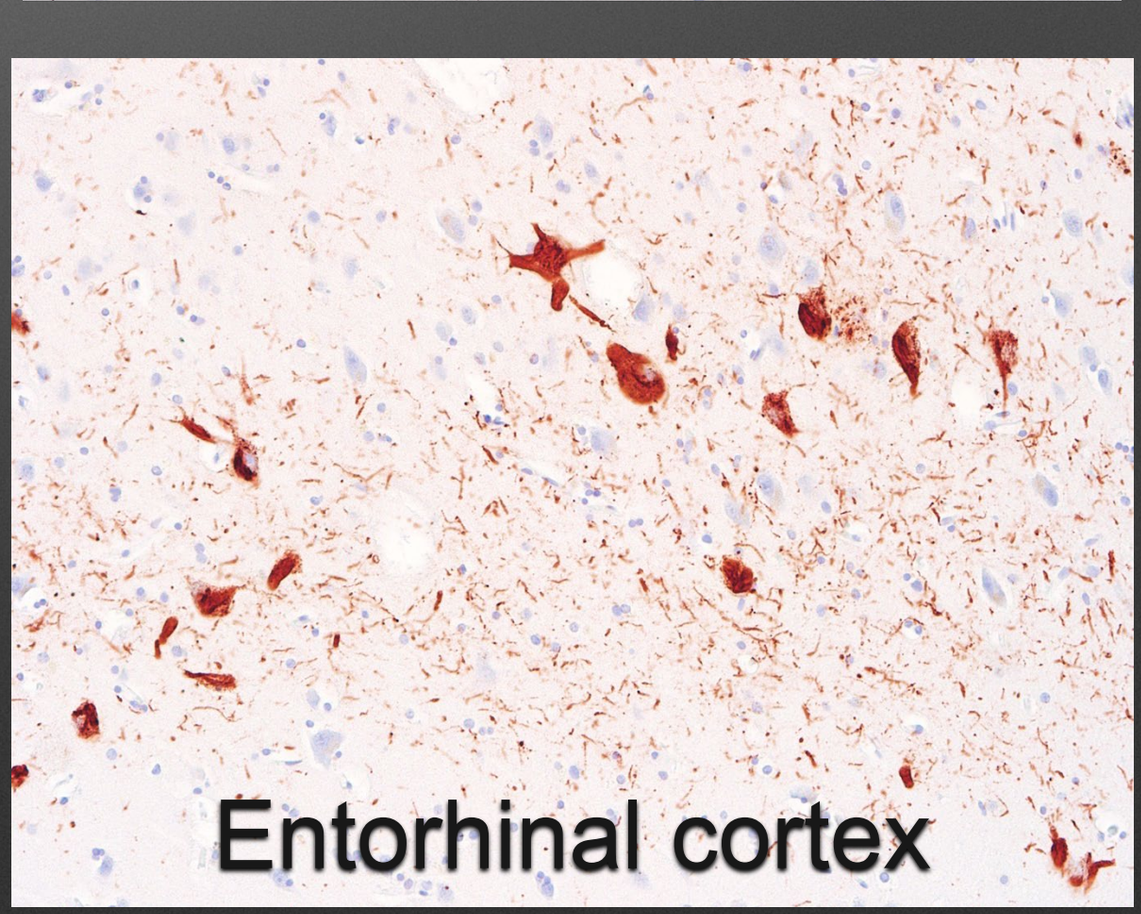
CA2

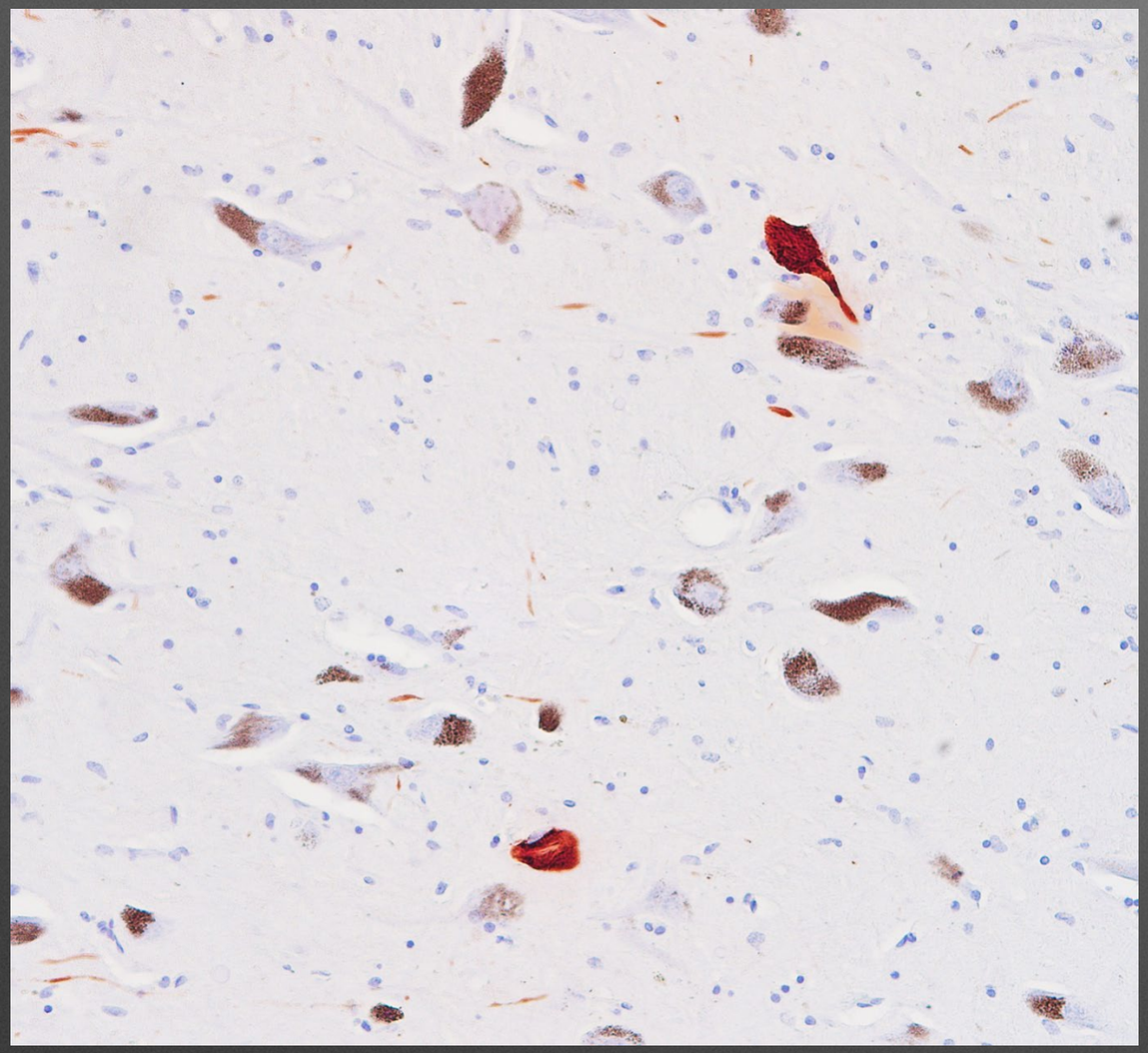
CA1


Insular cortex

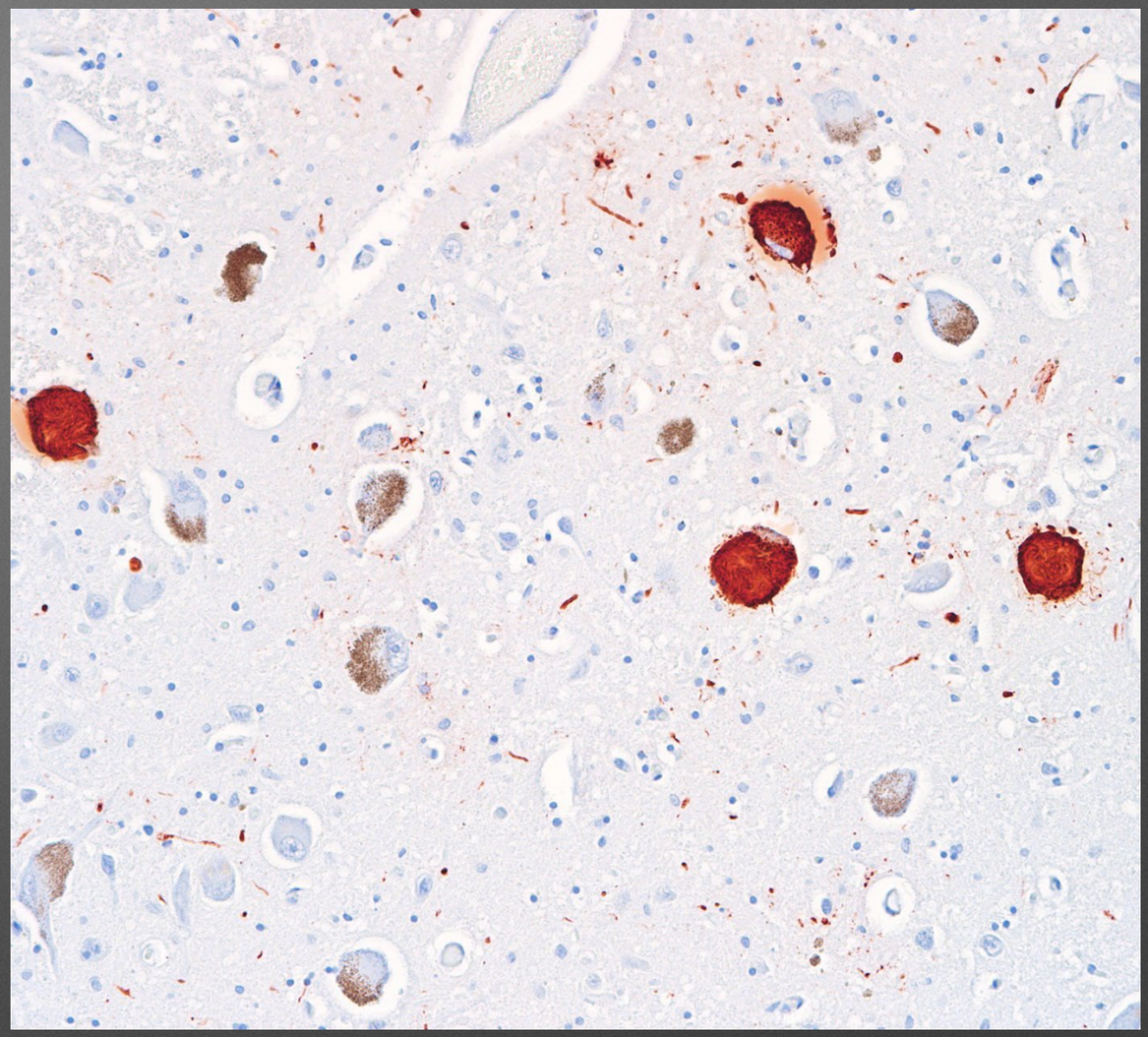

Temporal cortex


Amygdala


Entorhinal cortex



Substantia Nigra



Locus Coeruleus

Diagnoses:

1. Chronic traumatic encephalopathy, High, (Stage III)

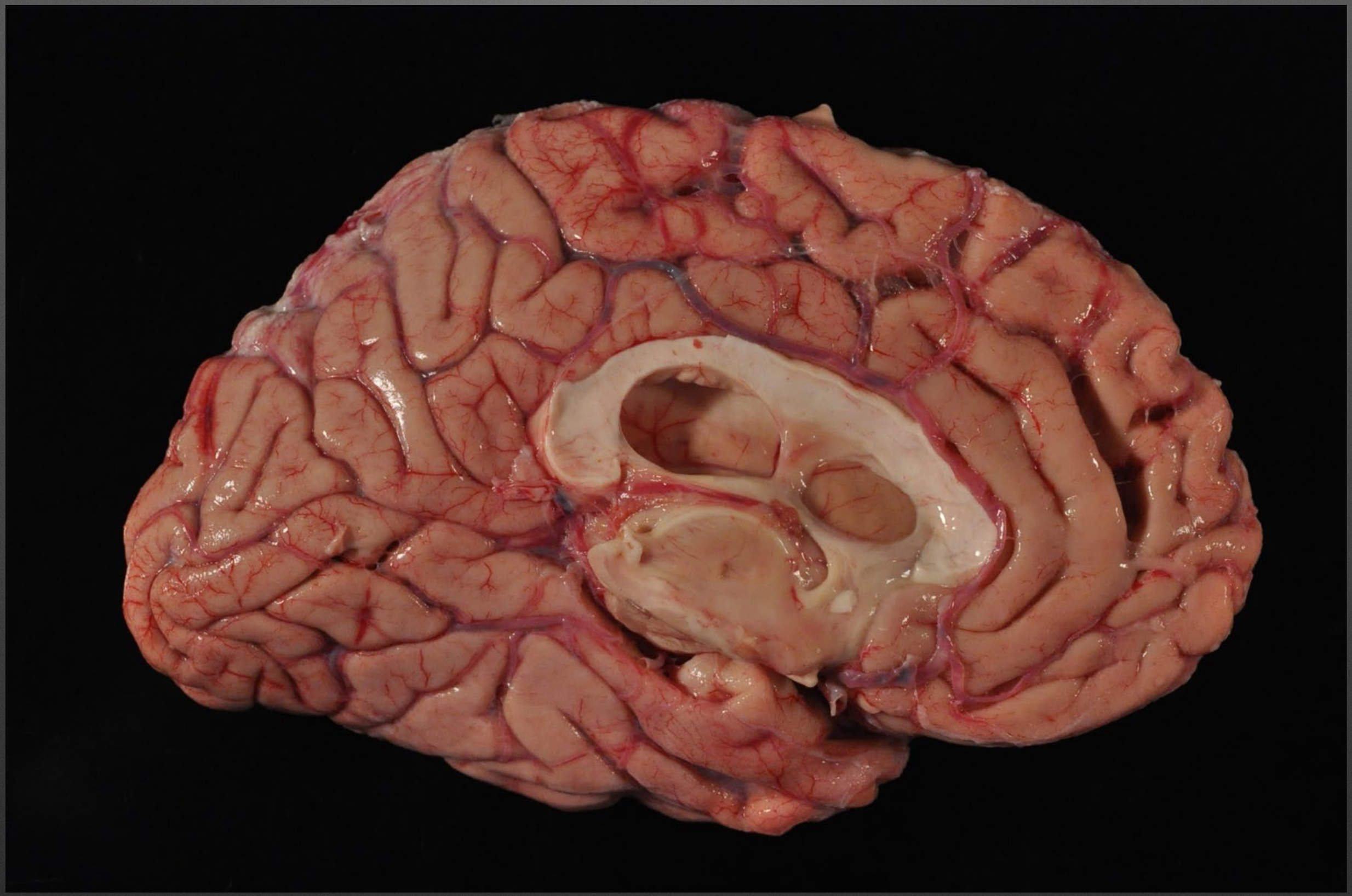
2. Subpial ARTAG

Case 2

- Boxing career: 18 years, amateur and professional, retired at 33 years old
- Stably “irritable”, quick temper, gambling addiction
- Age 66: Left MCA embolic stroke with little residual
- Age 71: accused grandchildren of stealing his keys and money, got lost while driving, retired
- Age 73: diagnosed with: AD, VCID
- Age 74: increasingly impaired orientation, memory, verbal fluency, visuospatial function, judgment, reasoning and problem solving

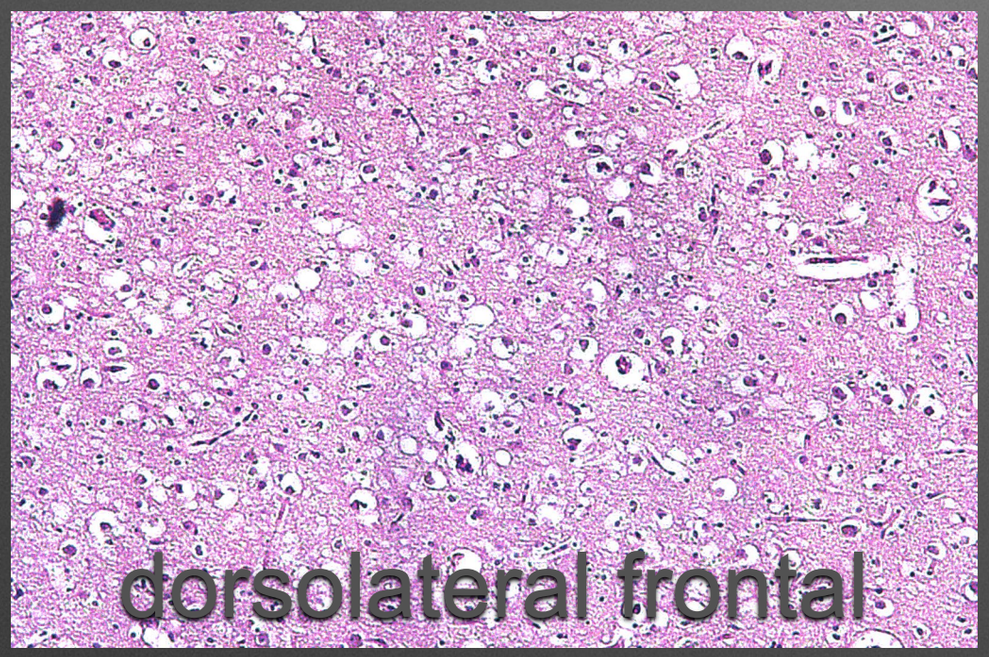
  MOCA: 10/30; started on Aricept and Namenda
- Age 76: Unable to remember children’s names, urinary and fecal incontinence; MOCA: 3/30
- Age 78: Death from congestive heart failure

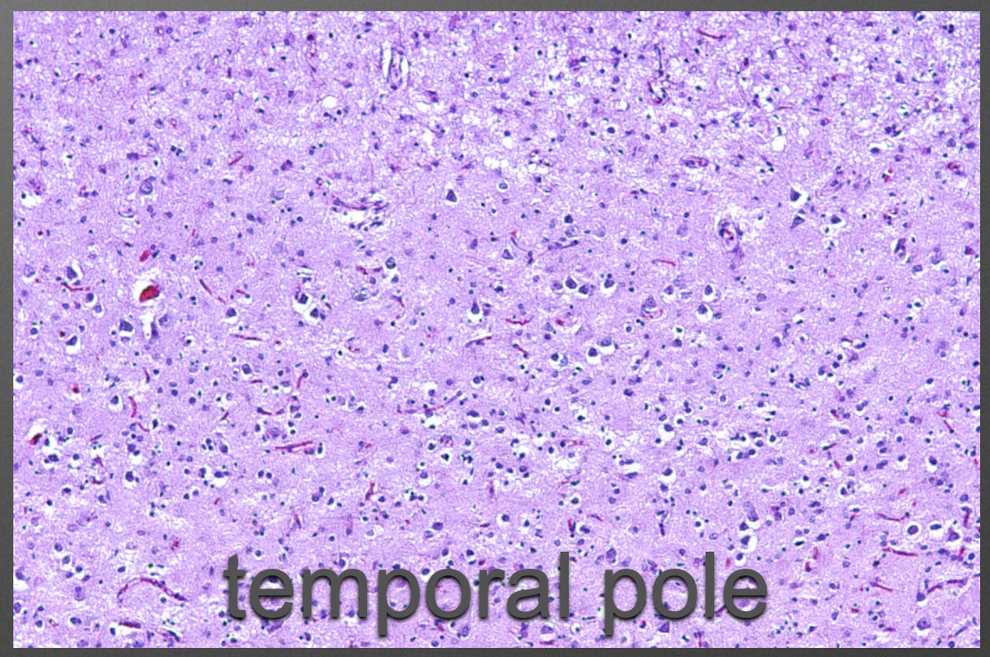
Brain weight: 991 grams

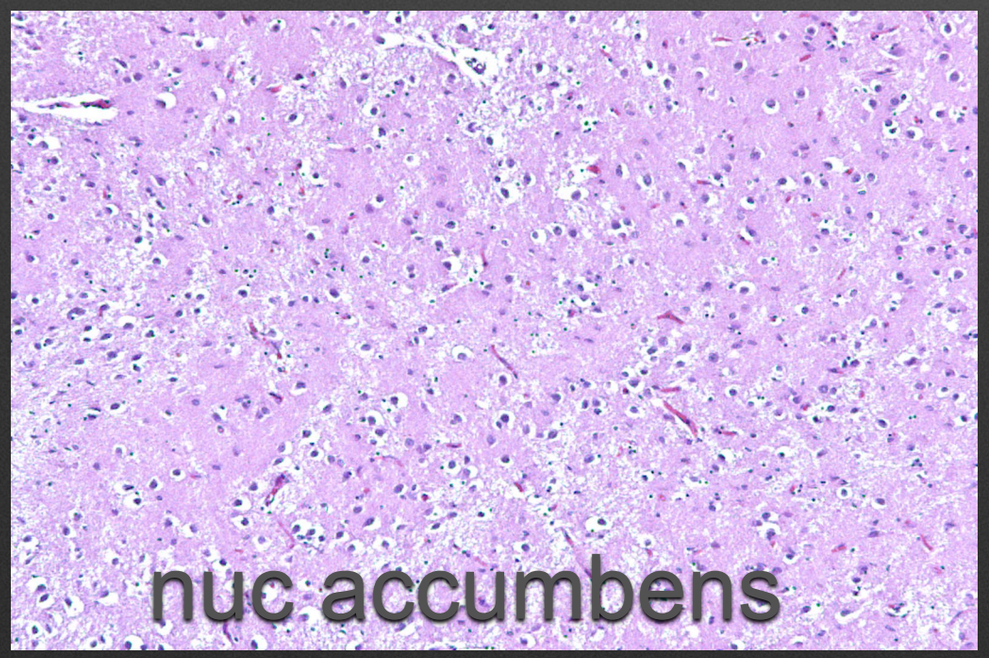


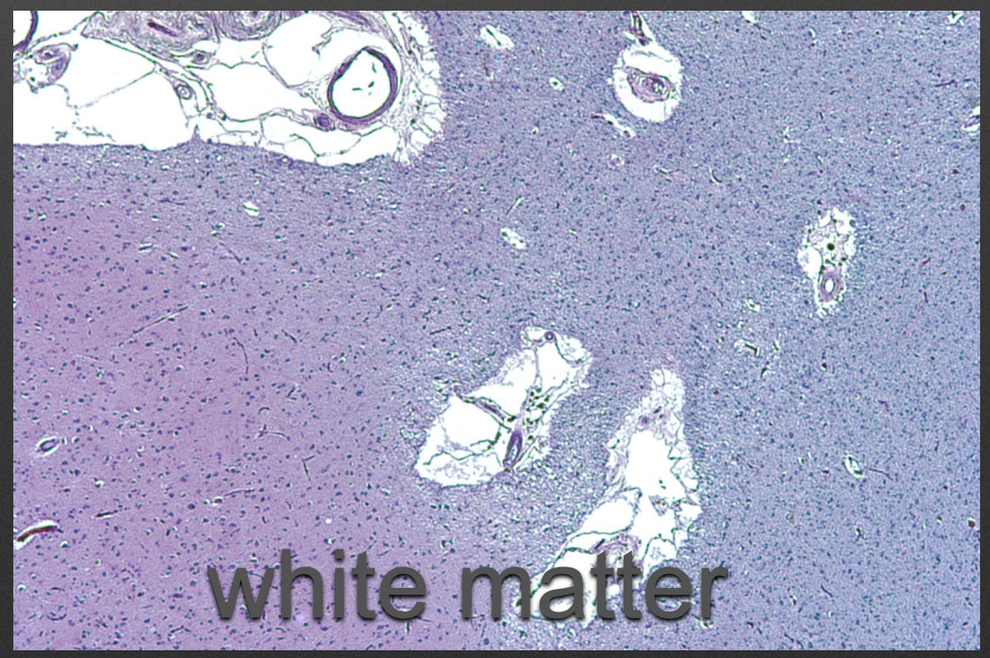
Severe neuronal loss and gliosis:

frontal and temporal lobes, medial temporal lobe, nucleus accumbens, severe white matter rarefaction

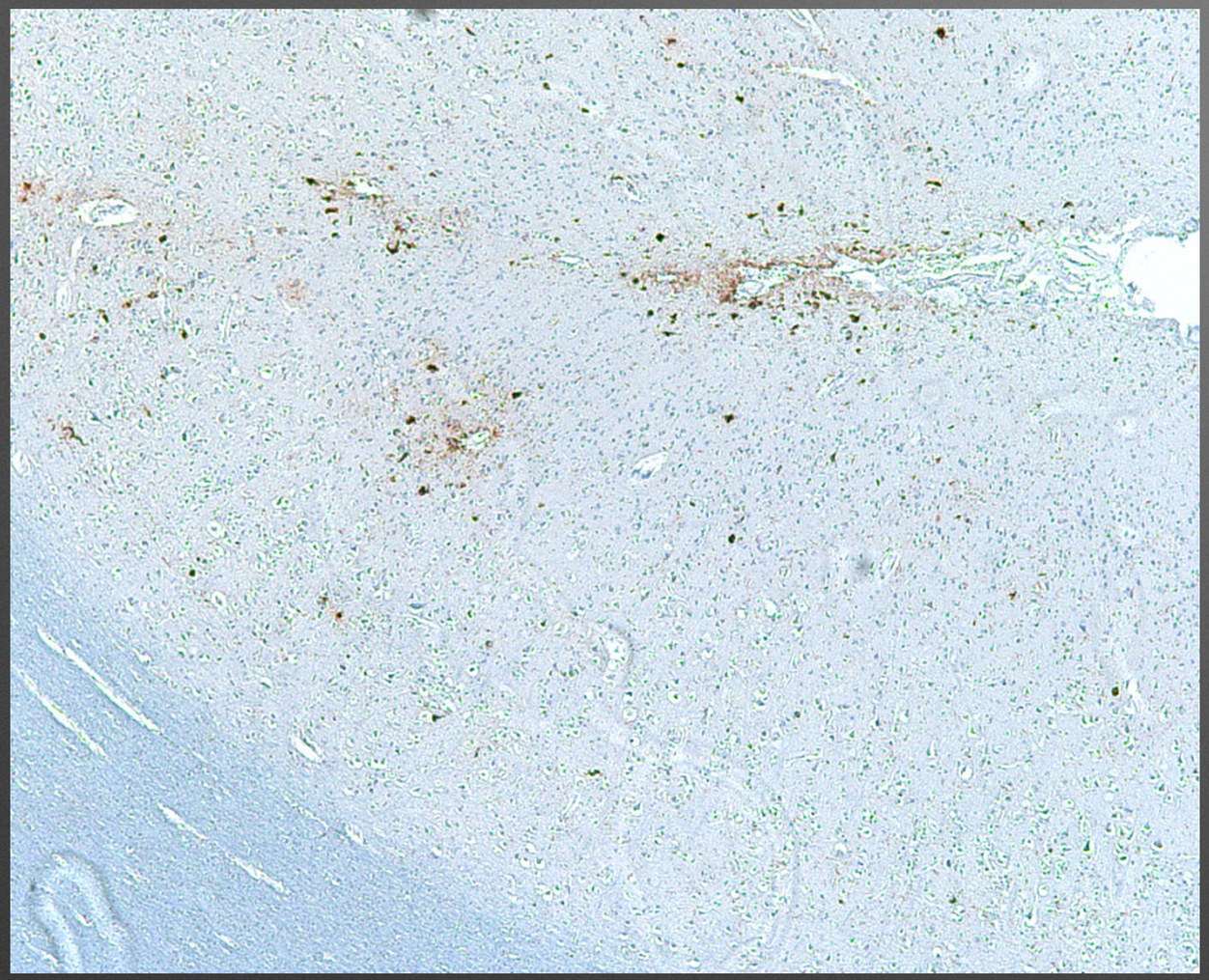




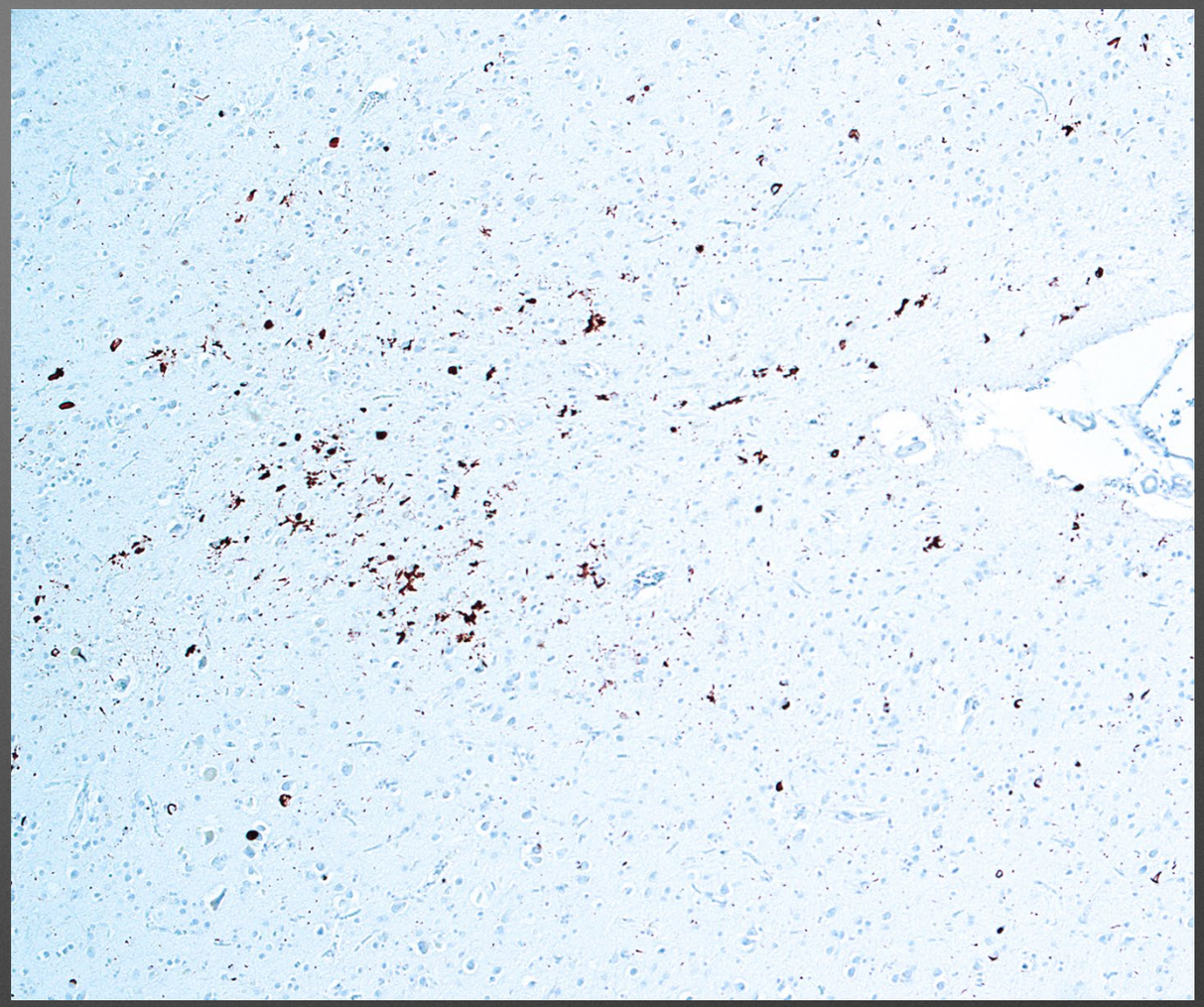




Inferior parietal

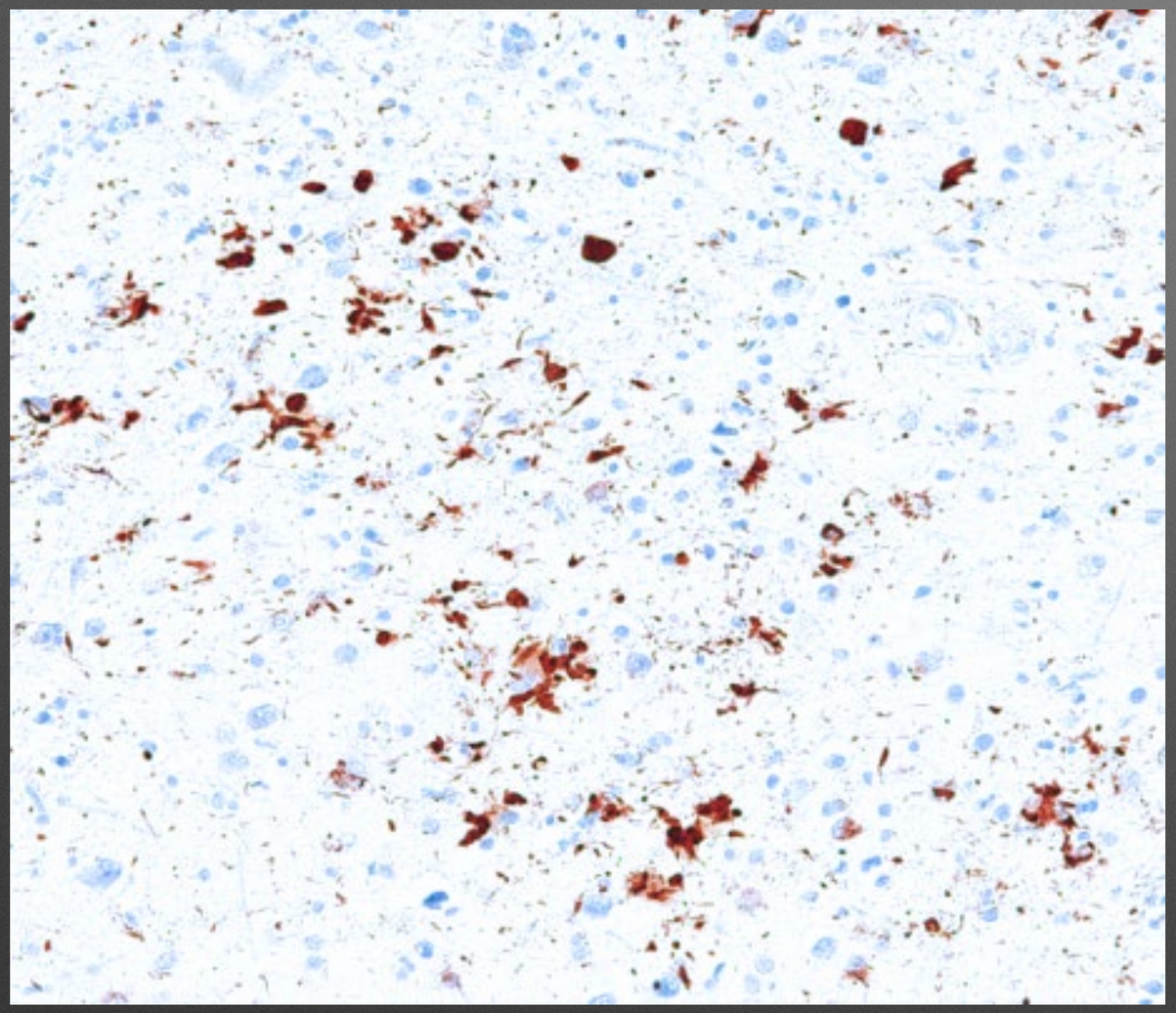


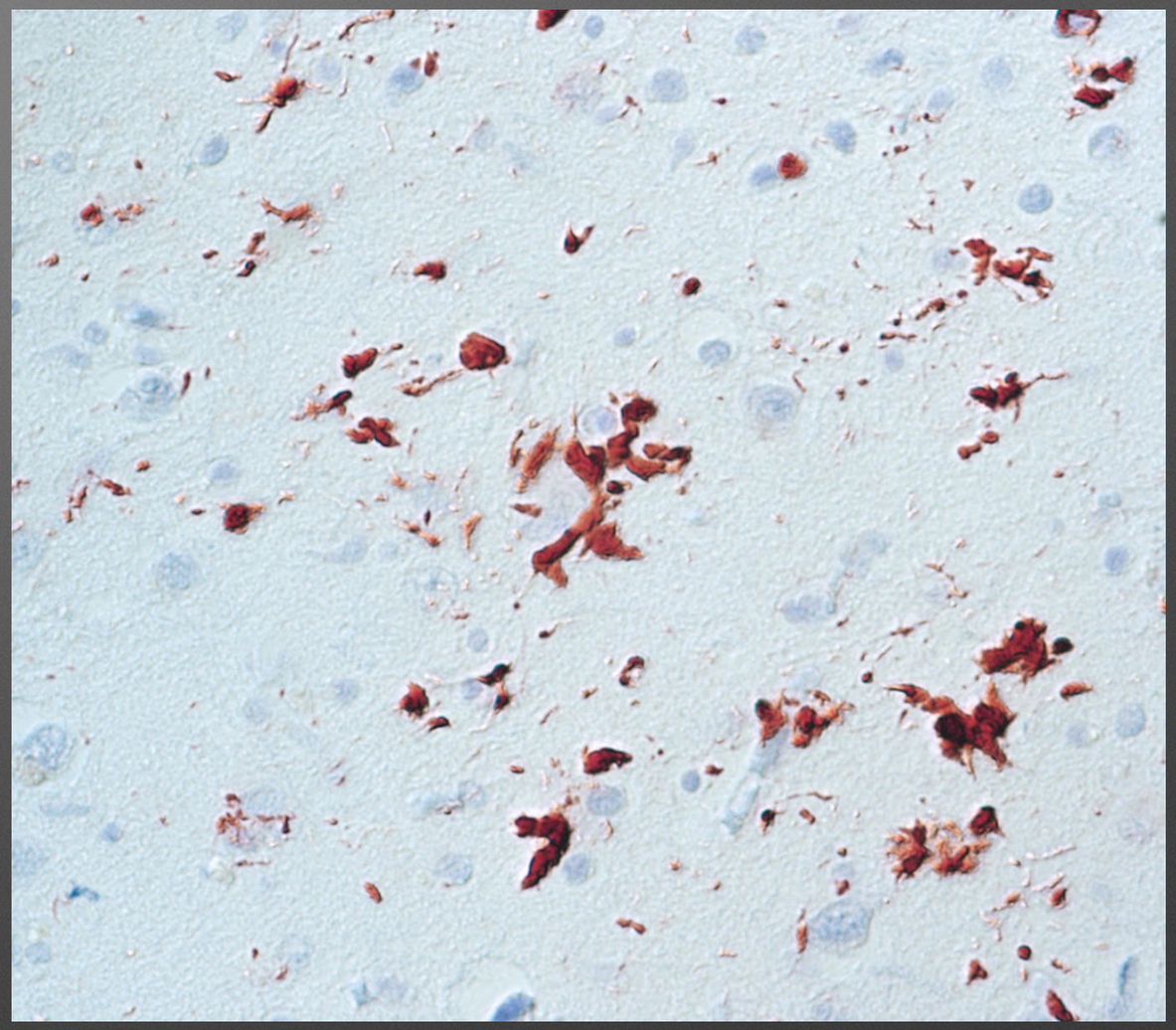
Superior temporal



AT8: pathognomonic lesions

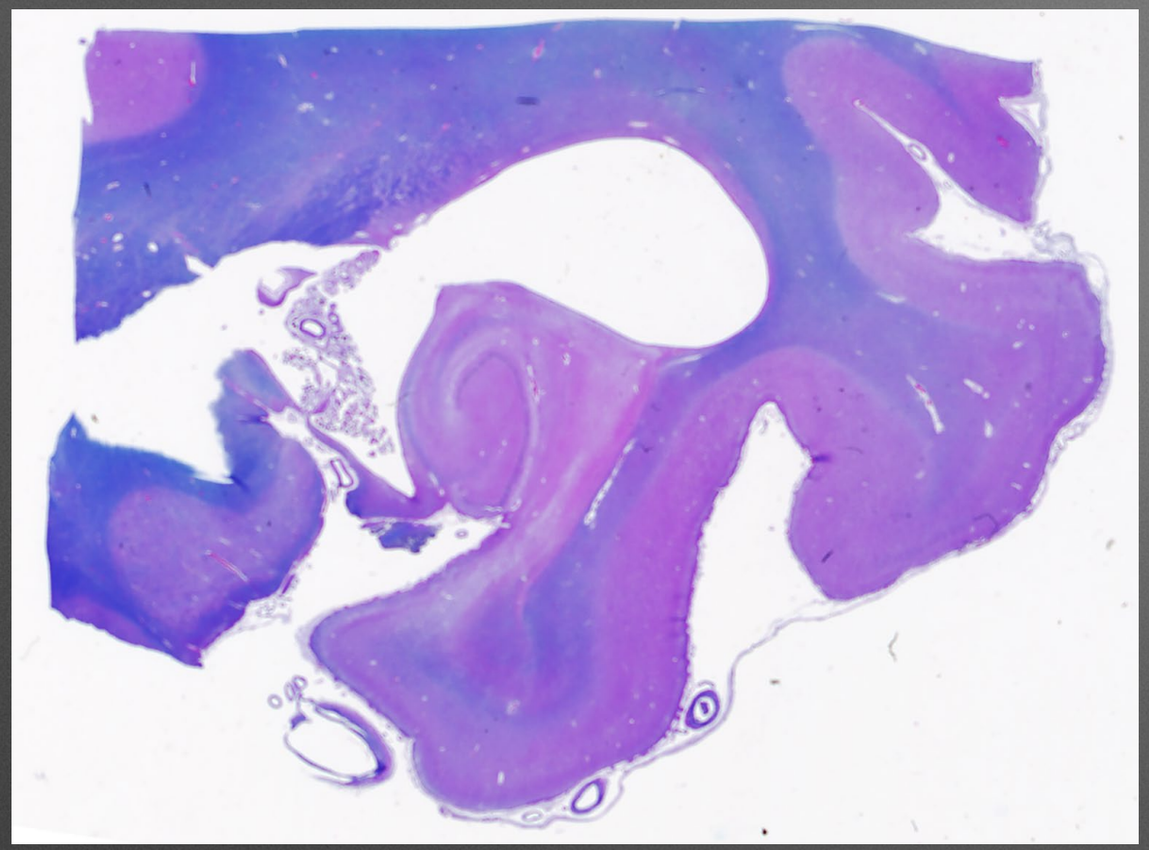
Superior temporal

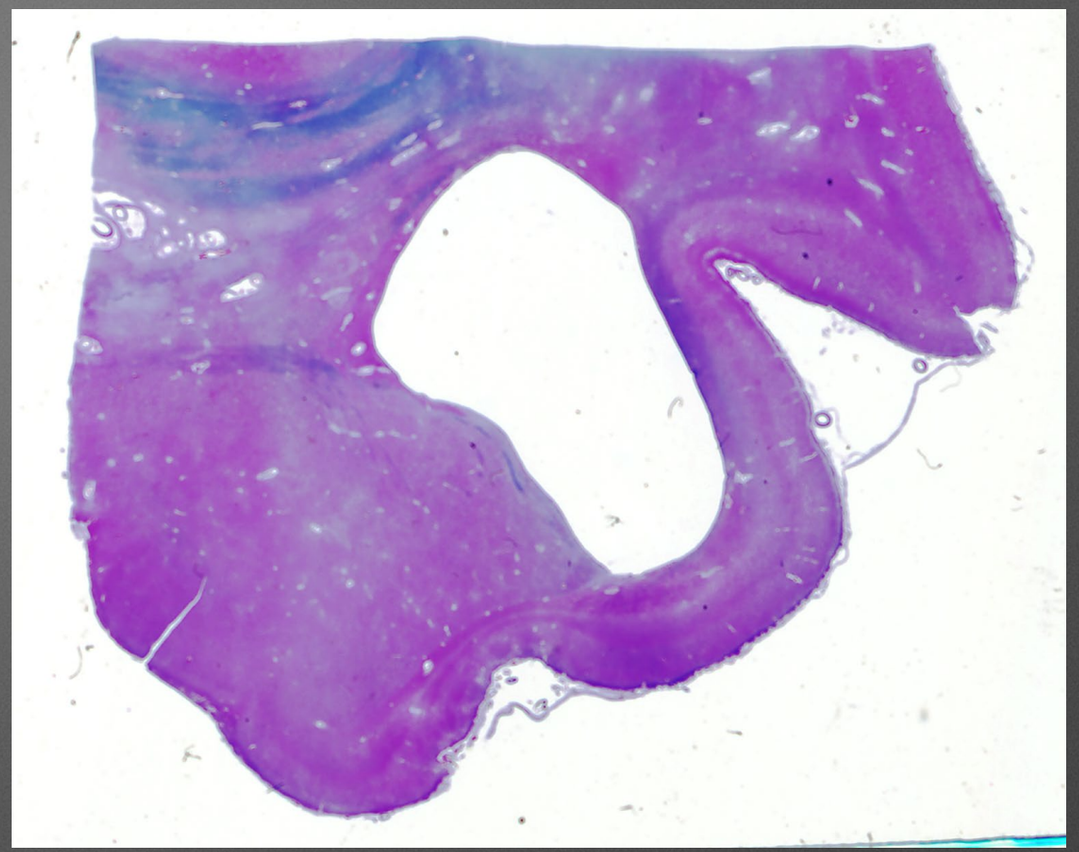


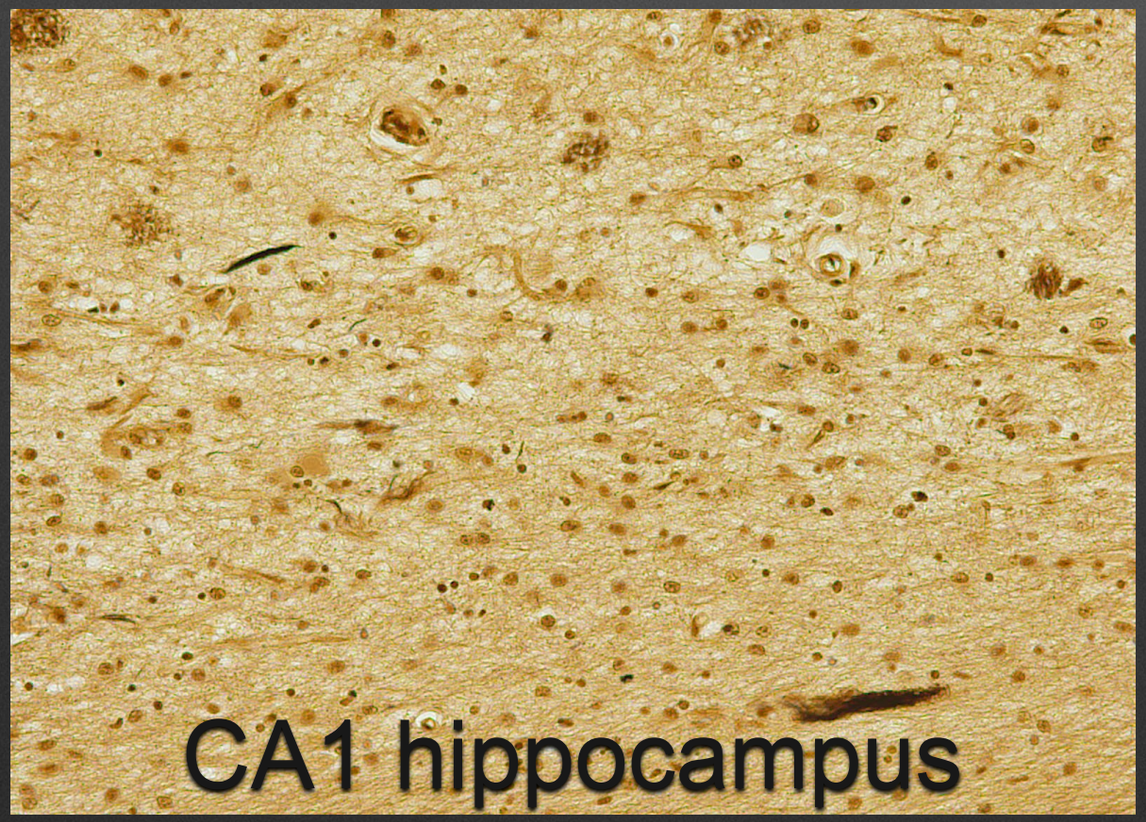


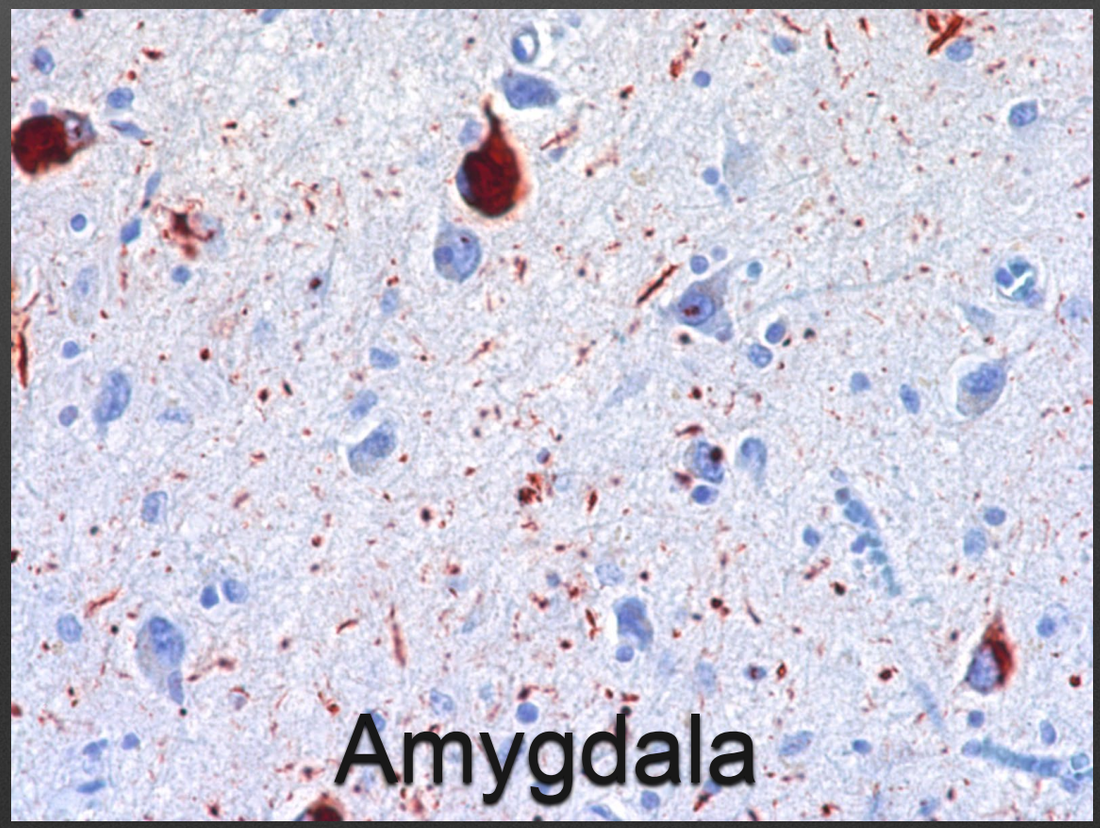
AT8: pathognomonic lesions

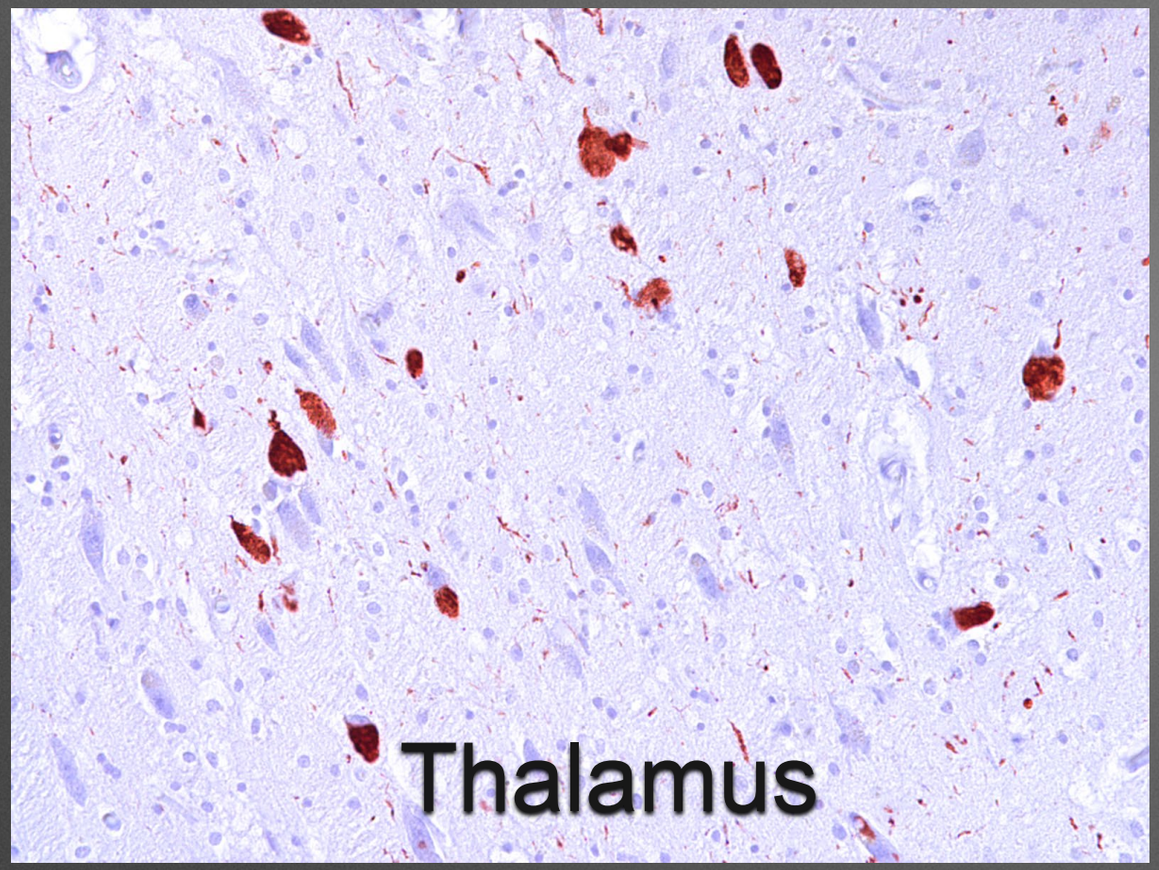
Severe neuronal loss and gliosis: MTL

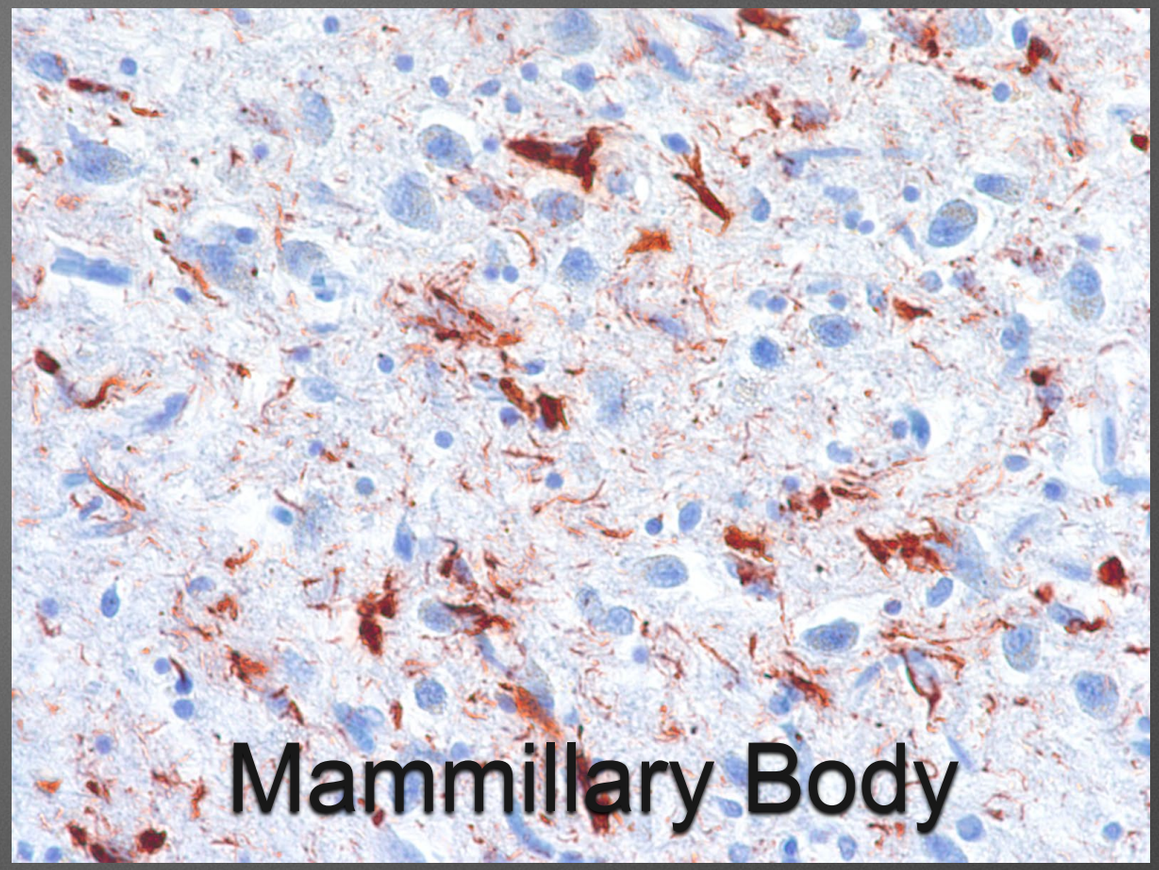


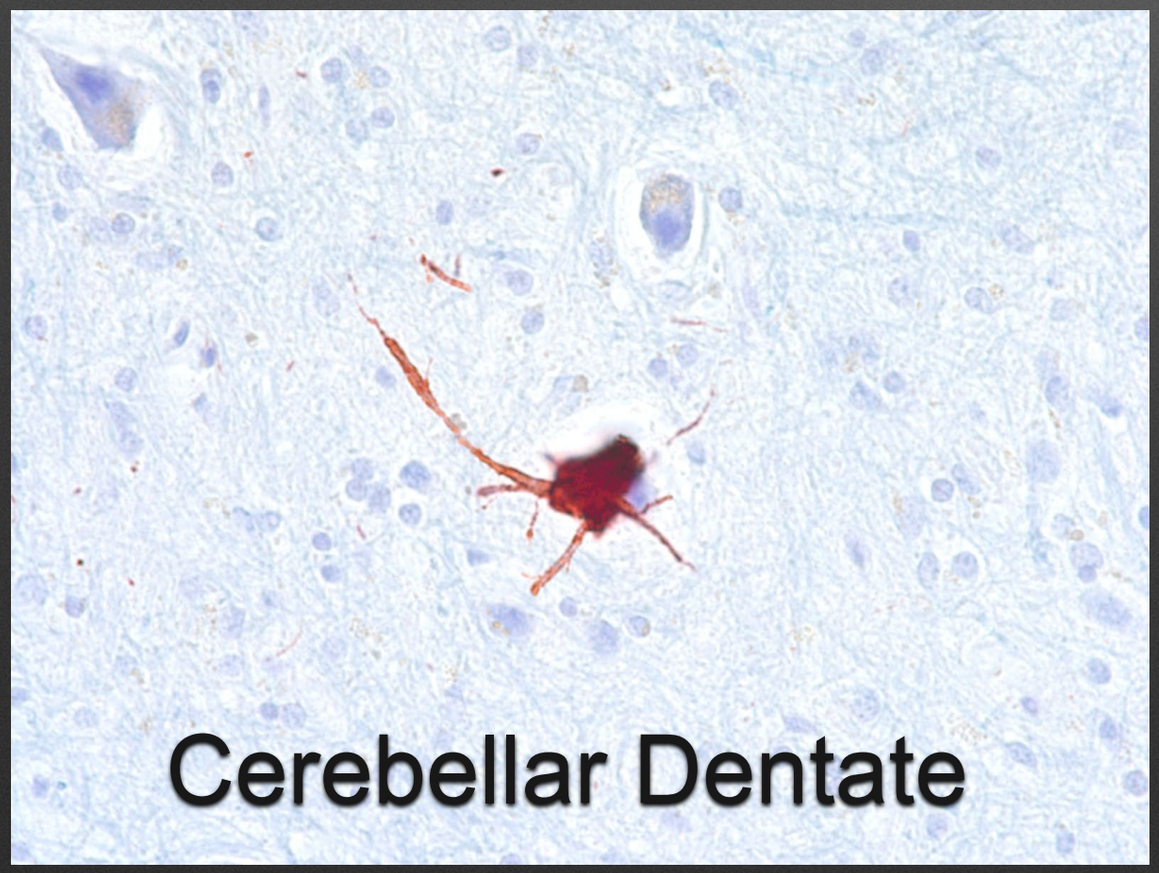


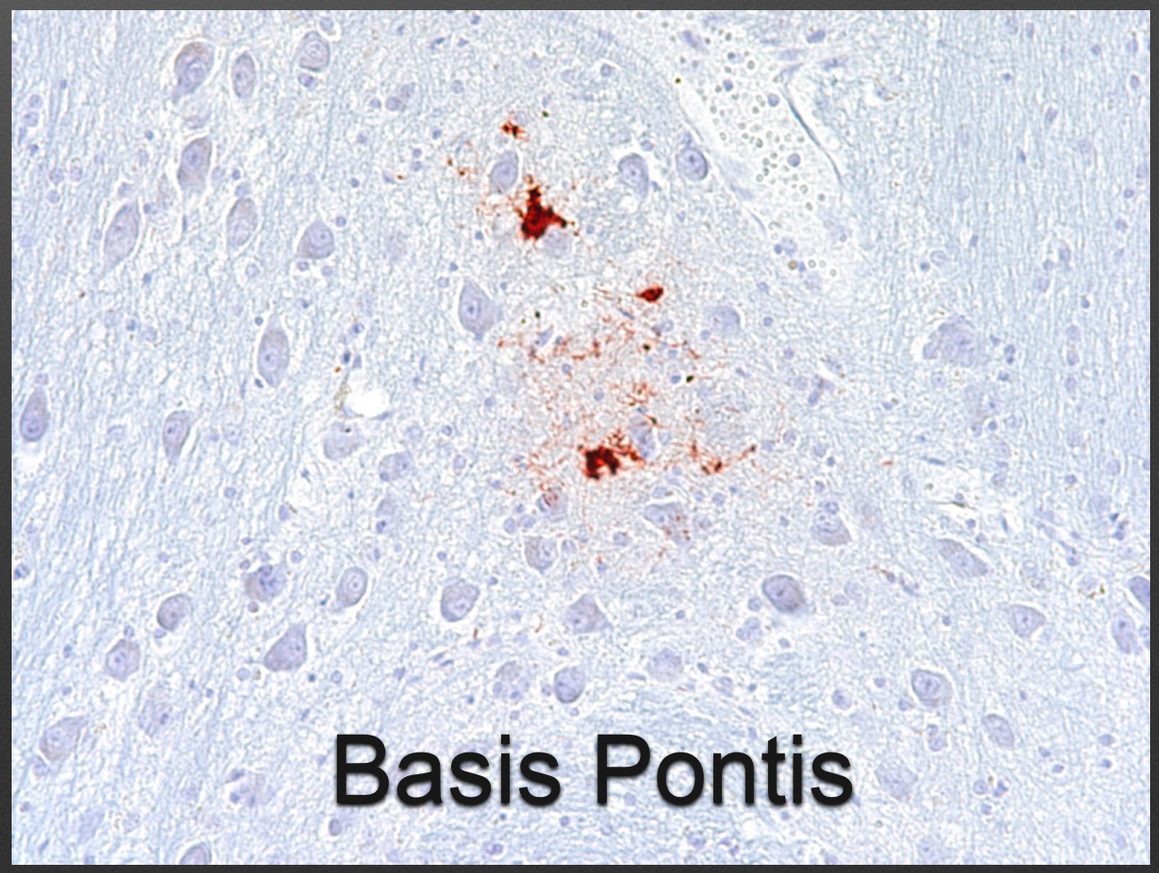




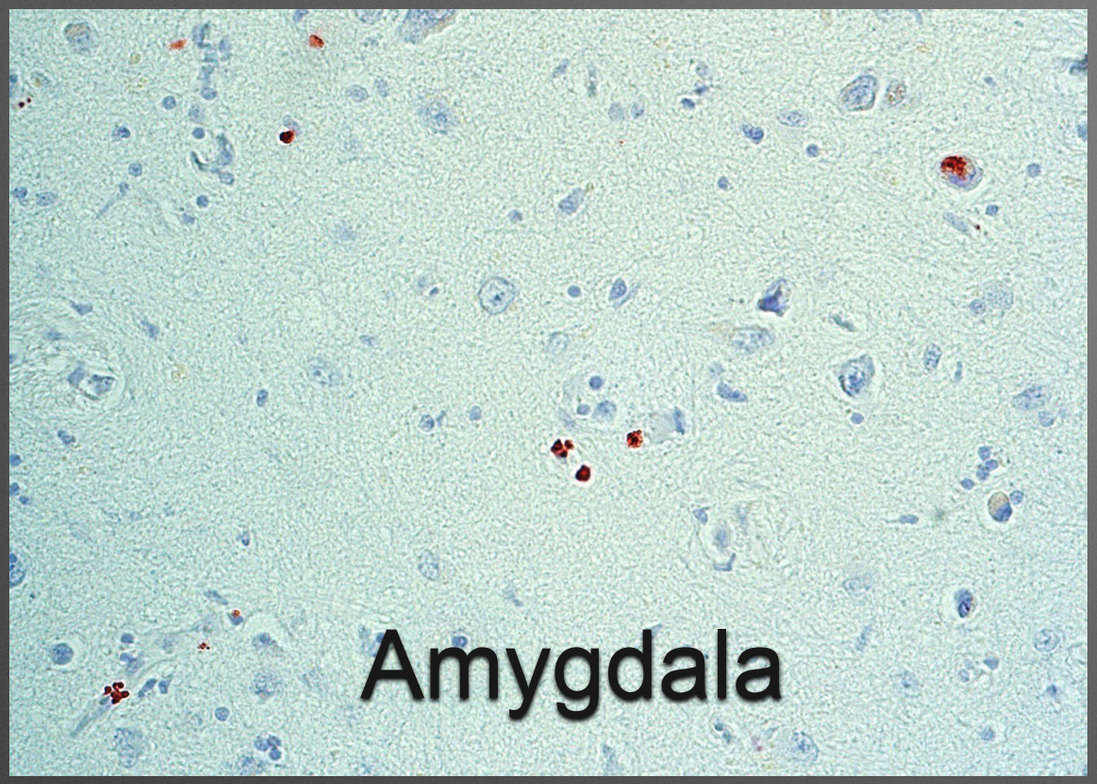

Thalamus

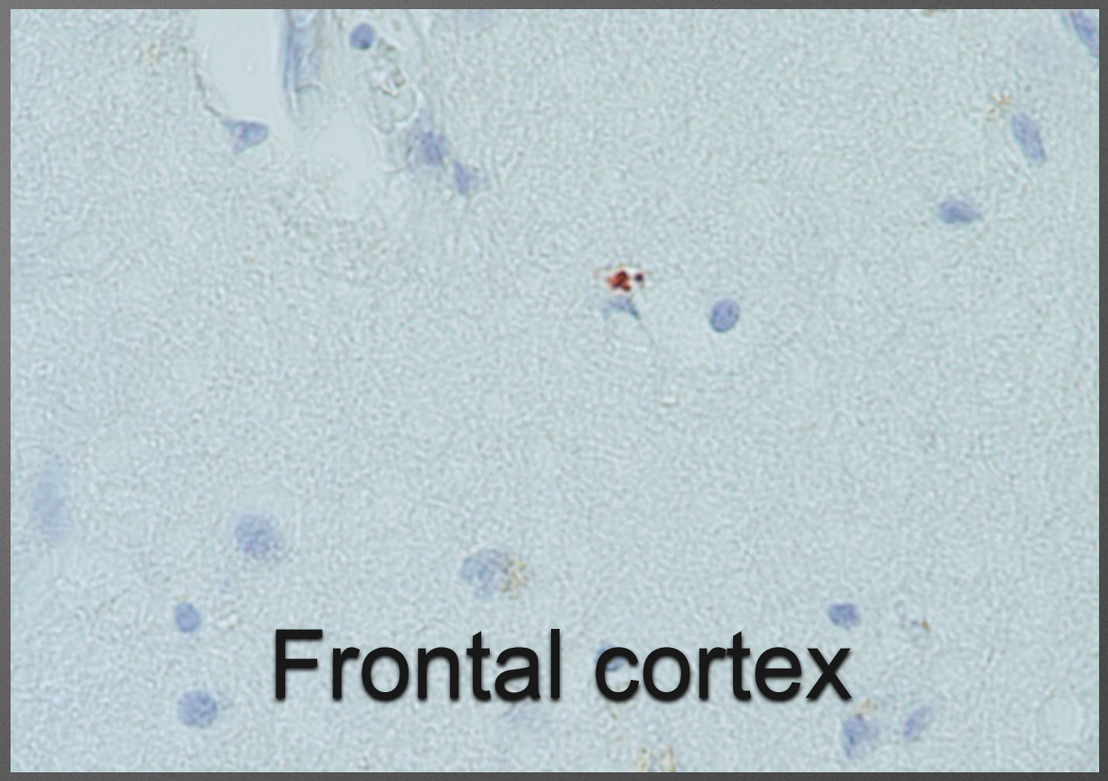

Mammillary Body

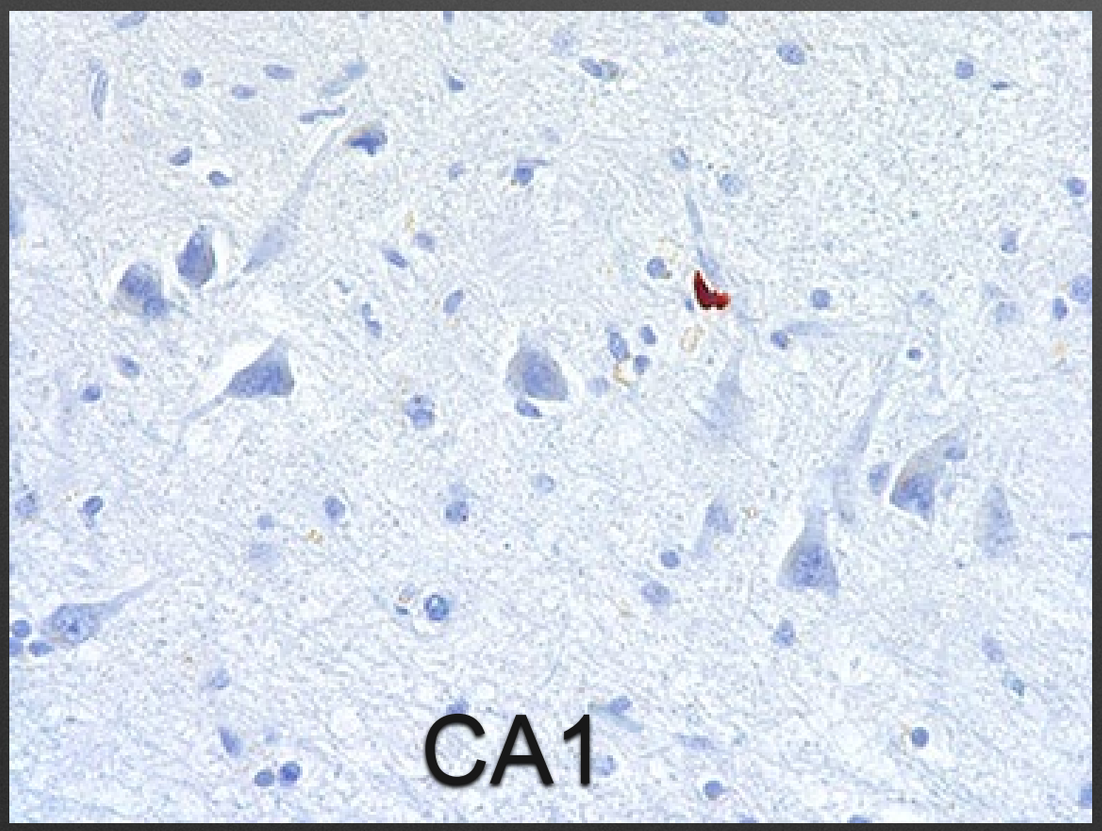

Cerebellar Dentate

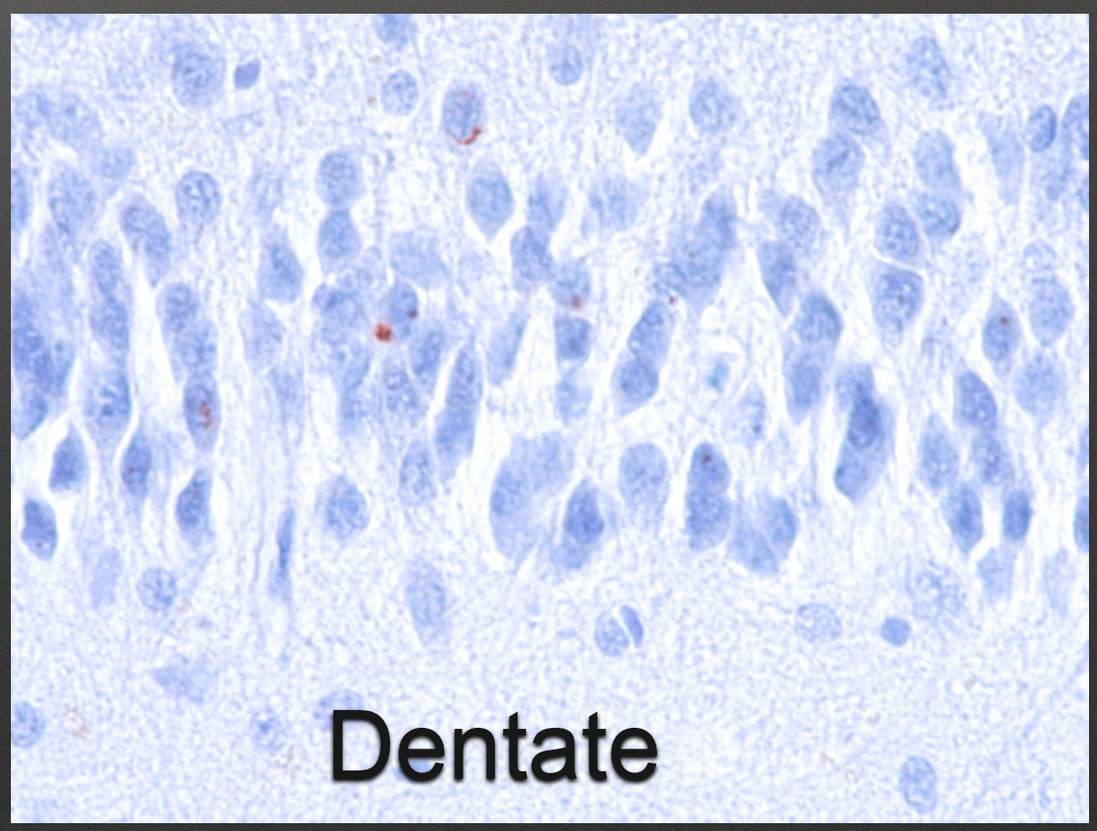

Basis Pontis

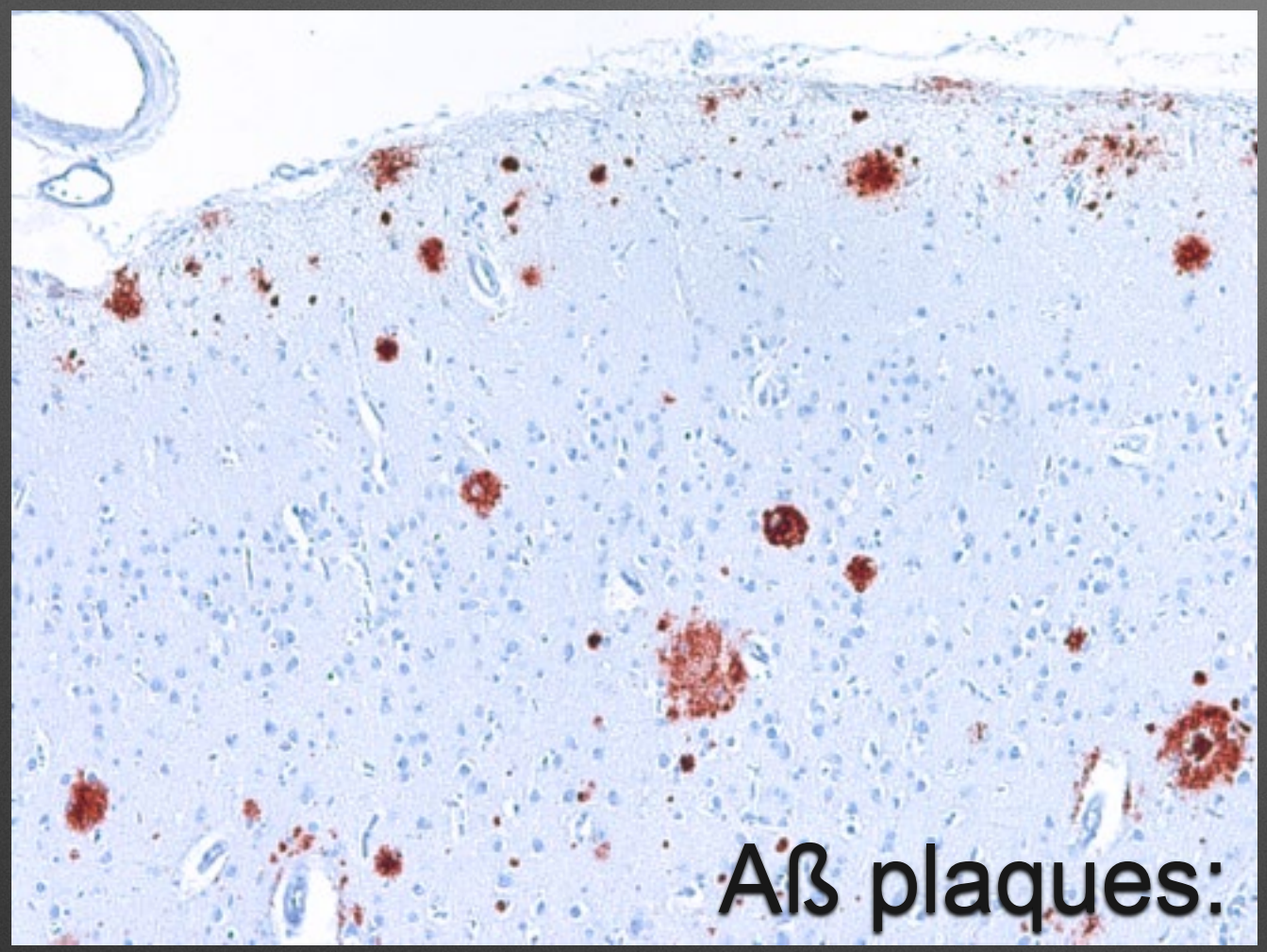
TDP-43



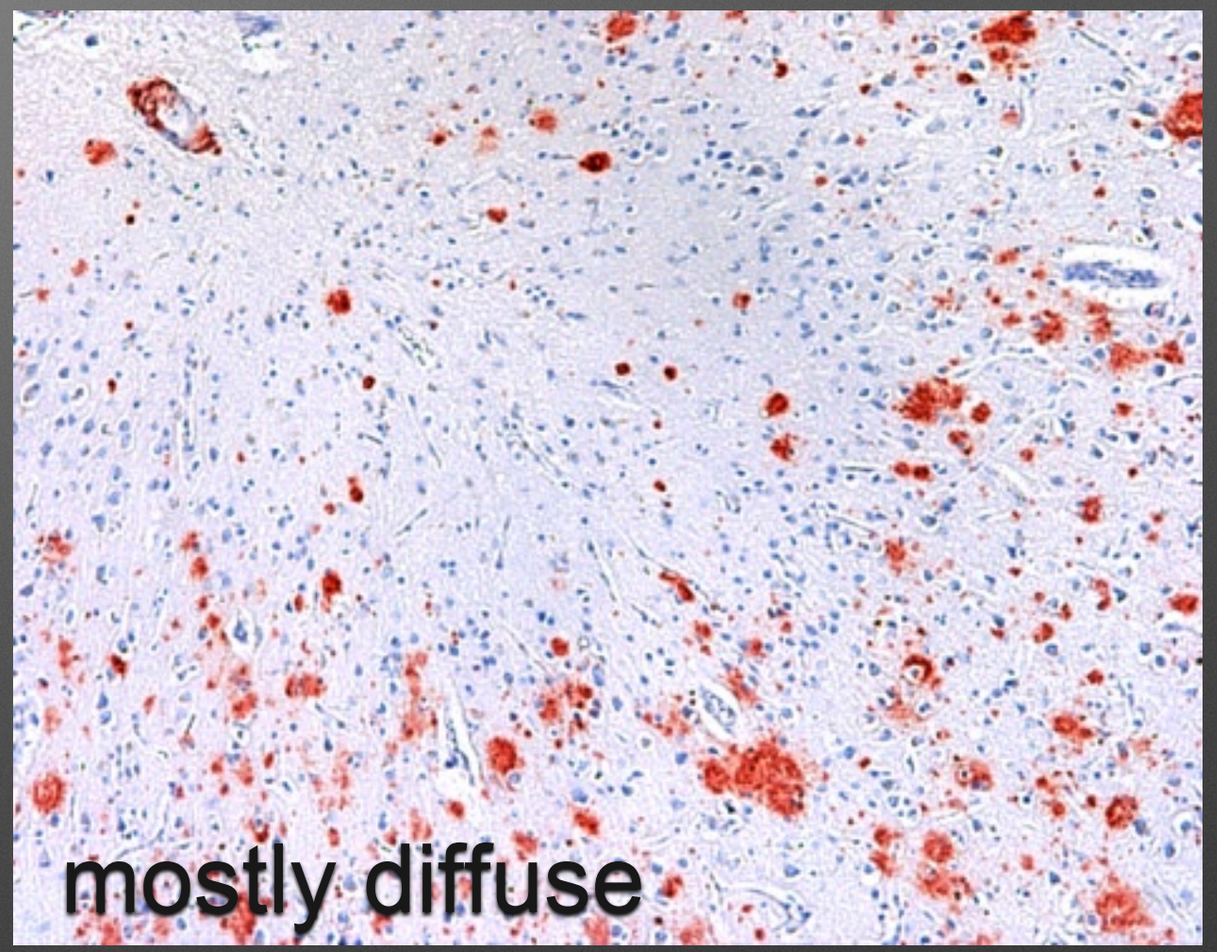




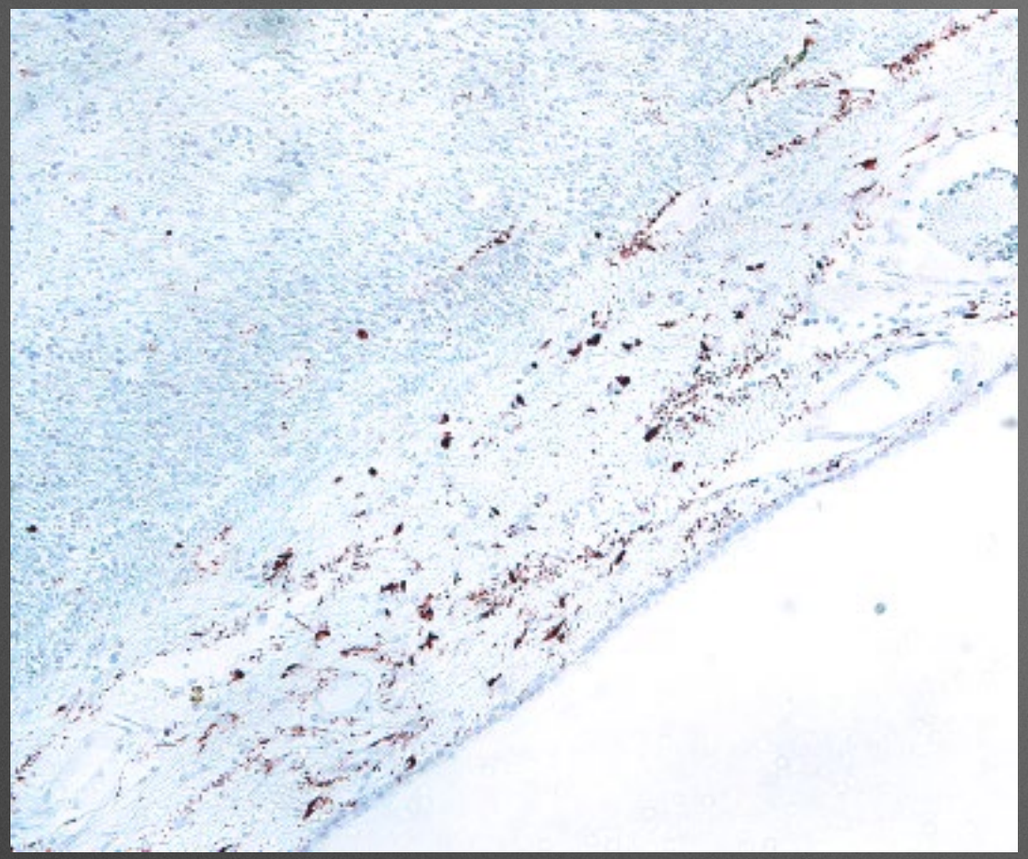


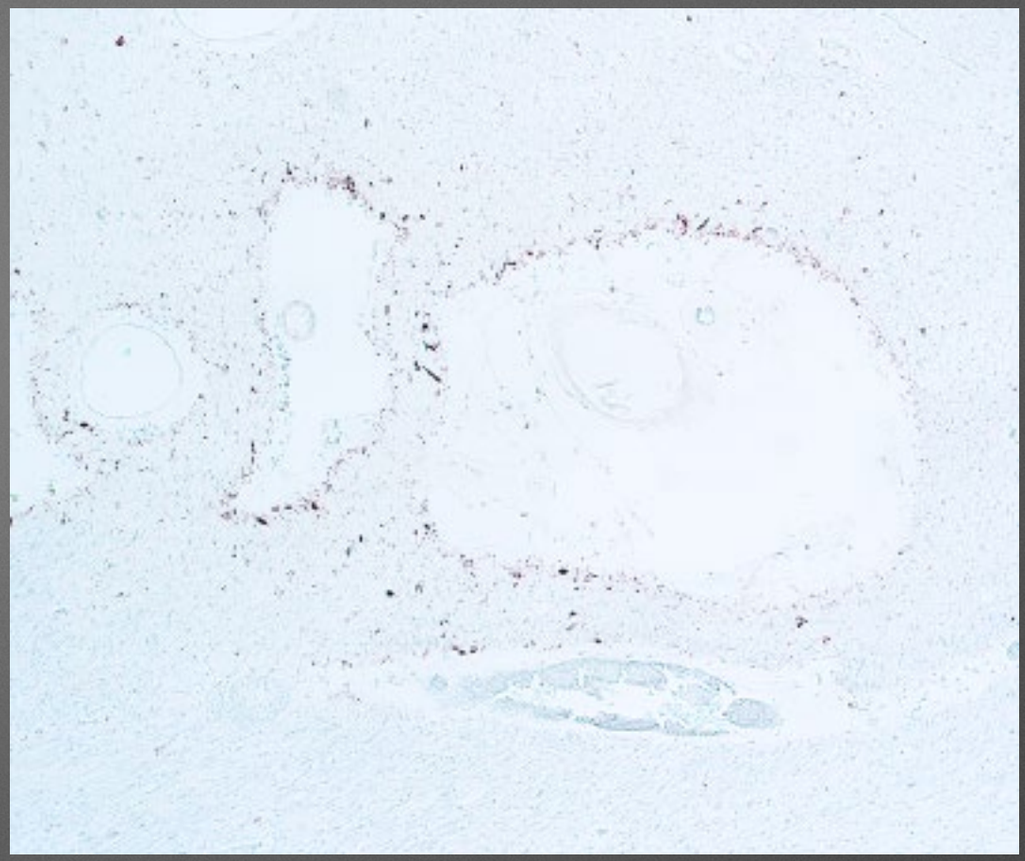


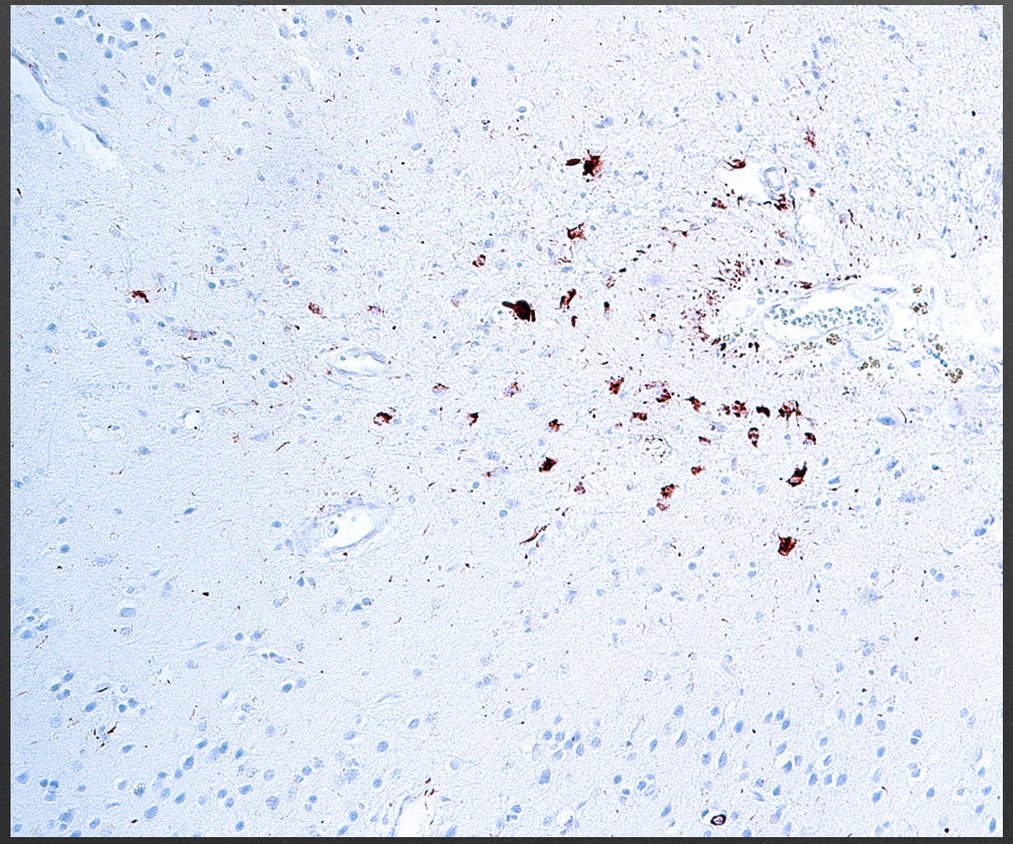
Aß plaques:

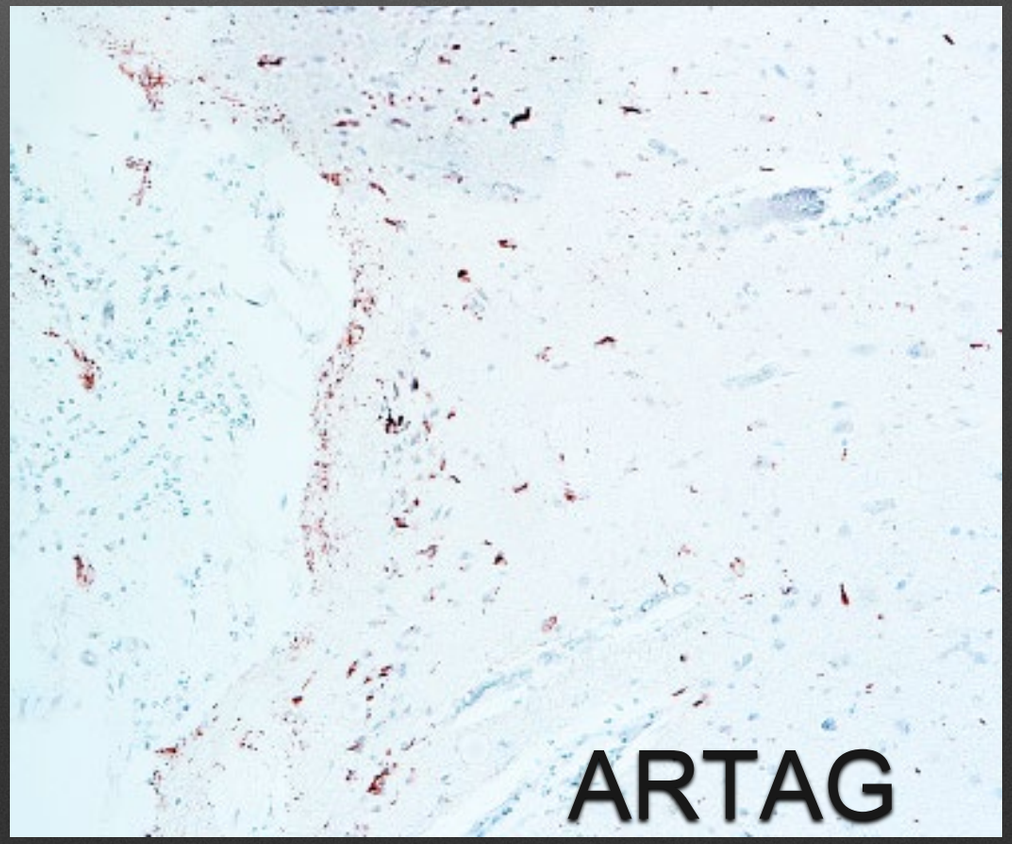


mostly diffuse








ARTAG

Diagnoses:

1. CTE, High (Stage IV)
2. Alzheimer' disease neuropathological change:
   (Thal 4) A3, (Braak 5) B3, CERAD sparse, C1
   NIA Reagan: Intermediate likelihood
3. LATE
4. Vascular disease:
   Atherosclerosis
   Left insular-inferior parietal infarct
5. Cerebellar degeneration
6. ARTAG

References

- *Bieniek K, Cairns N, Crary J, et al. The second NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. In preparation, 2020*

- *Alosco M, Cherry J, Huber B, et al. Characterizing Tau Deposition in Chronic Traumatic Encephalopathy (CTE): Utility of the McKee CTE Staging Scheme, Acta Neuropathol 2020, Oct;140(4):495-512*

- *McKee A, Stein T, Crary J, et al. Practical Considerations in the Diagnosis of Mild Chronic Traumatic Encephalopathy and Distinctions from Age-related Tau Astrogliopathy. J Neuropathol Exp Neurol. 2020 Aug 1;79(8):921-924.*

- *McKee A, Cairns N, Dickson D, et al. The First NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy. Acta Neuropathol 2016 Jan;131(1):75-86.*

Introduction of new ARTAG data entry elements for NACC

18. Aging Related Tau Astrogliopathy (ARTAG)

18. AGING-RELATED TAU ASTROGLIOPATHY (ARTAG)
Evaluation should follow published guidelines. See the Coding Guidebook for the NACC Neuropathology Data Form.

a. Is ARTAG pathology present?	☐ 0 No **(SKIP TO QUESTION 19)** ☐ 1 Yes **(CONTINUE)** ☐ 8 Not assessed **(SKIP TO QUESTION 19)** ☐ 9 Missing/unknown **(SKIP TO QUESTION 19)**
b. Overall severity of ARTAG pathology	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe ☐ 8 Not assessed ☐ 9 Missing/unknown

18 a. Based on review of all slides, not restricted to frontal cortex or amygdala
Not assessed: ARTAG pathology was not evaluated
Missing/unknown: If ARTAG pathology was examined but the data cannot be found

18. Aging Related Tau Astrogliopathy (ARTAG)

b. Overall severity of ARTAG pathology	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe ☐ 8 Not assessed ☐ 9 Missing/unknown

18 b. Provide a semi-quantitative assessment of overall ARTAG pathology as identified using p-tau immunohistochemistry.

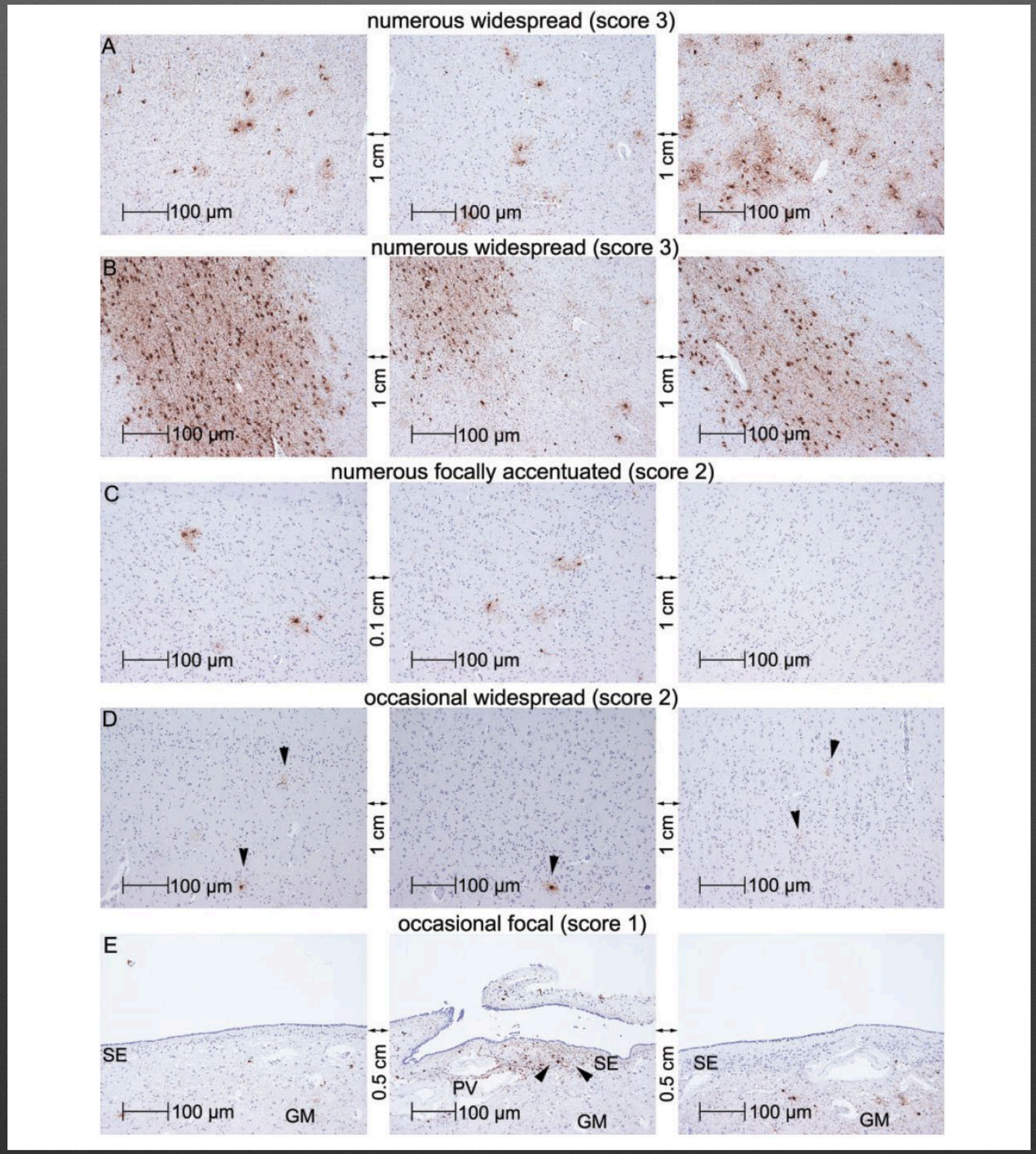
The tau pathology in the frontal cortex and amygdala are the foci of this semi-quantitative measure.

1- Mild: minimal or sporadically distributed ARTAG pathology
2- Moderate: intermediate level of ARTAG pathology
3- Severe: Numerous and widespread ARTAG pathology

Score 3:

Score 2:

Score 1:



Kovacs G, Xie S, Lee E et al. Multisite assessment of ARTAG, JNEN, 2017

18.c. ARTAG in the amygdala

c. Is ARTAG pathology present in the **AMYGDALA?**

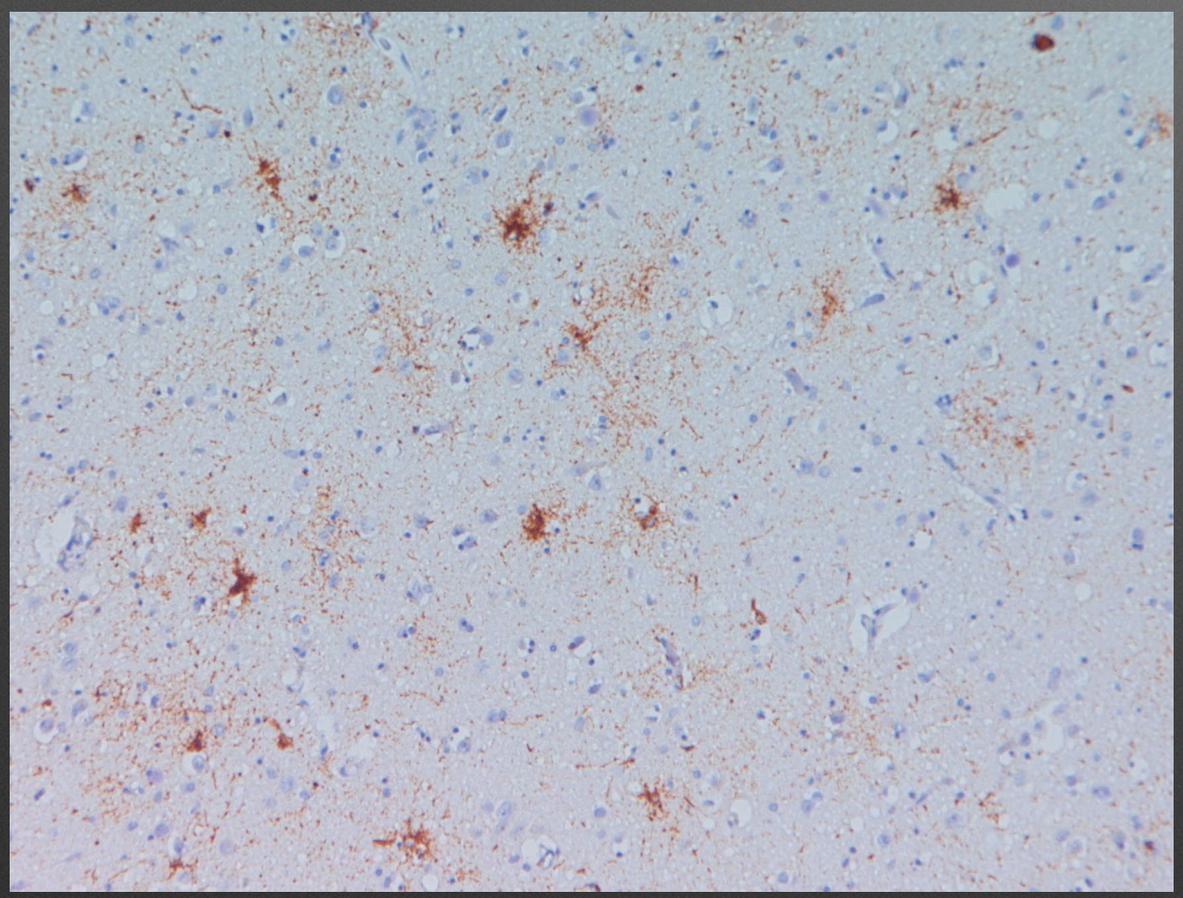
- ☐ 0 No **(SKIP TO QUESTION 18e)**
- ☐ 1 Yes **(CONTINUE)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 18e)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 18e)**

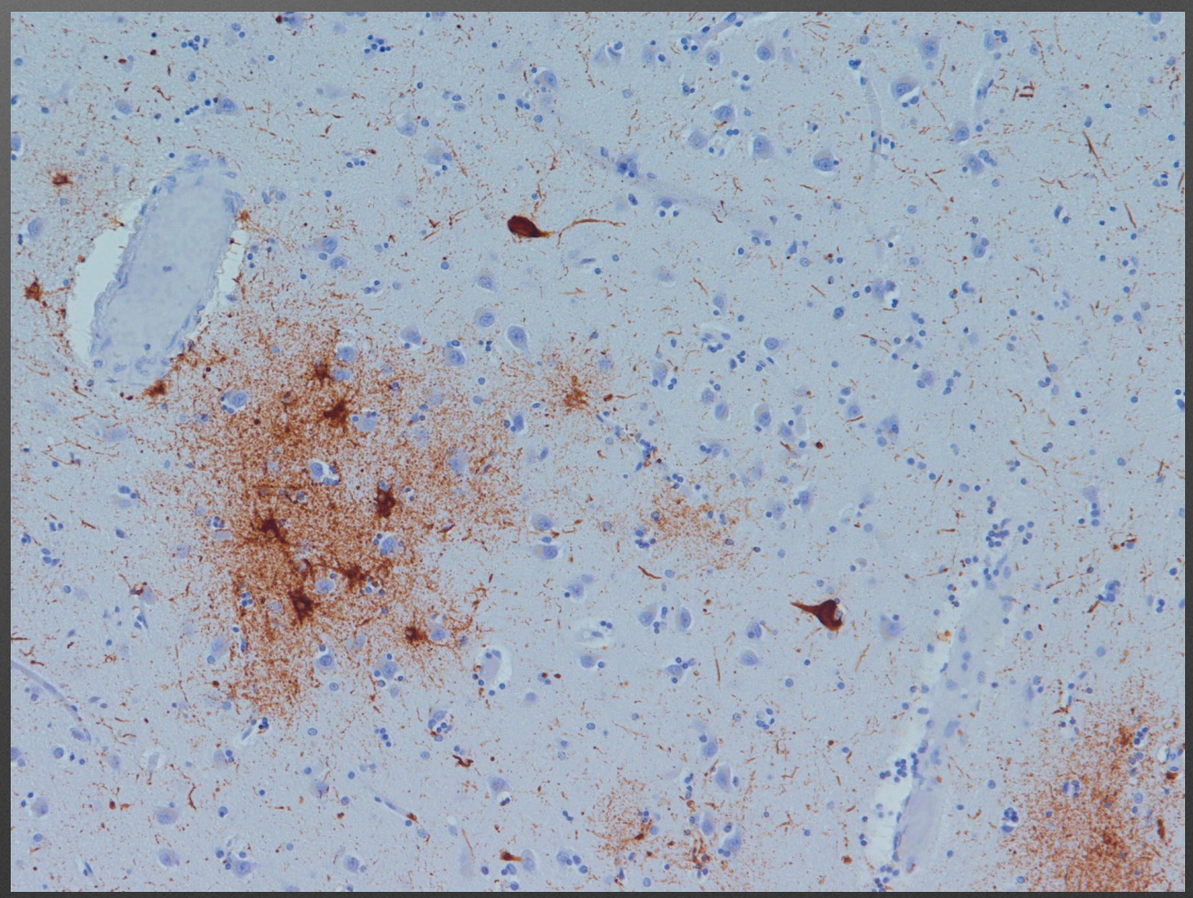
d. Localization of ARTAG pathology in the amygdala:

(CHECK ONE BOX PER ROW)	None	Focal	Widespread	Not assessed	Missing/ unknown
Subpial	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Subependymal	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Gray matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
White matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Perivascular	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐

18.c. Is ARTAG present in the amygdala?

18.d.Amygdala gray matter and perivascular ARTAG





Images Courtesy of Gabor Kovacs, MD, PhD

Amygdala white matter and perivascular ARTAG

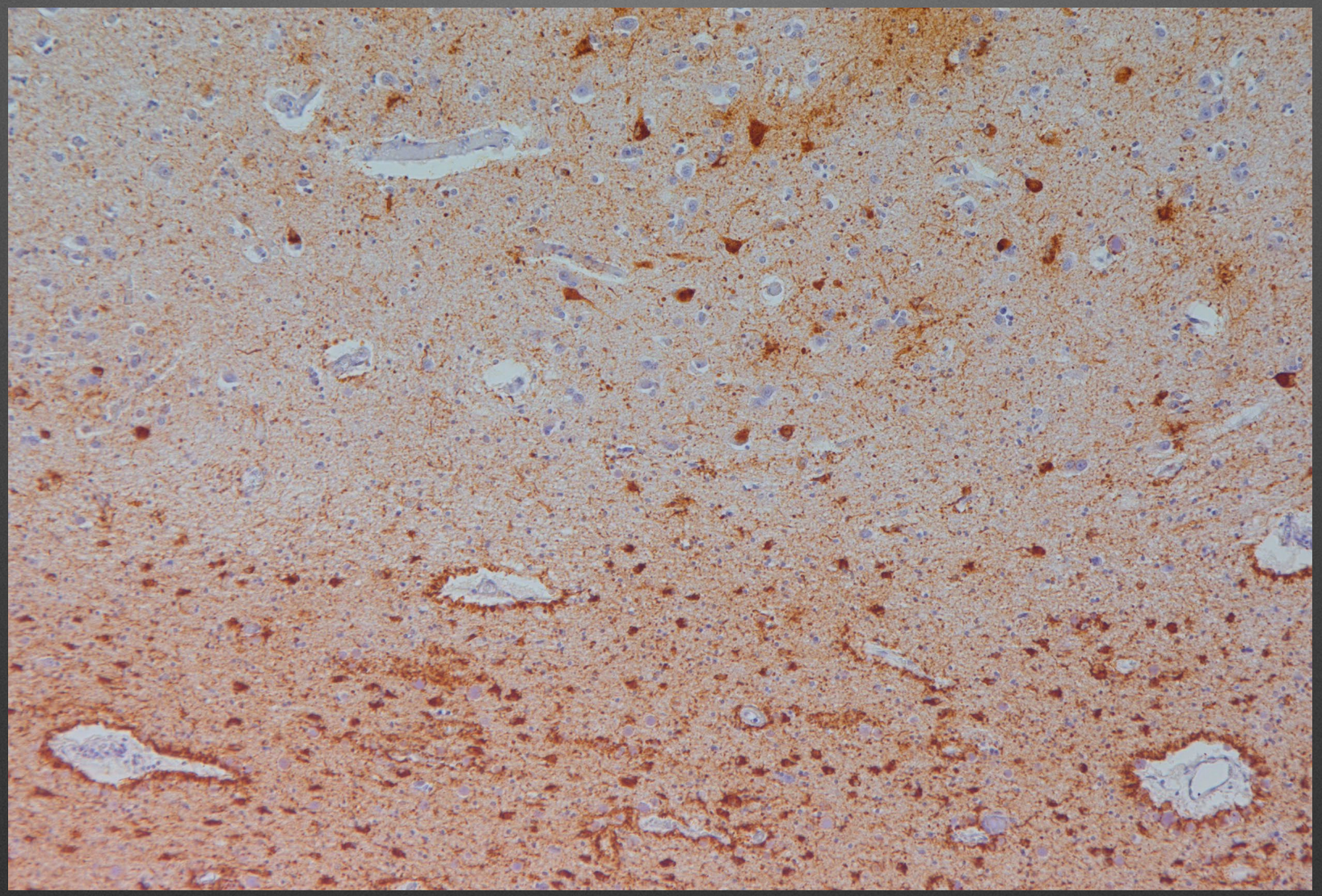
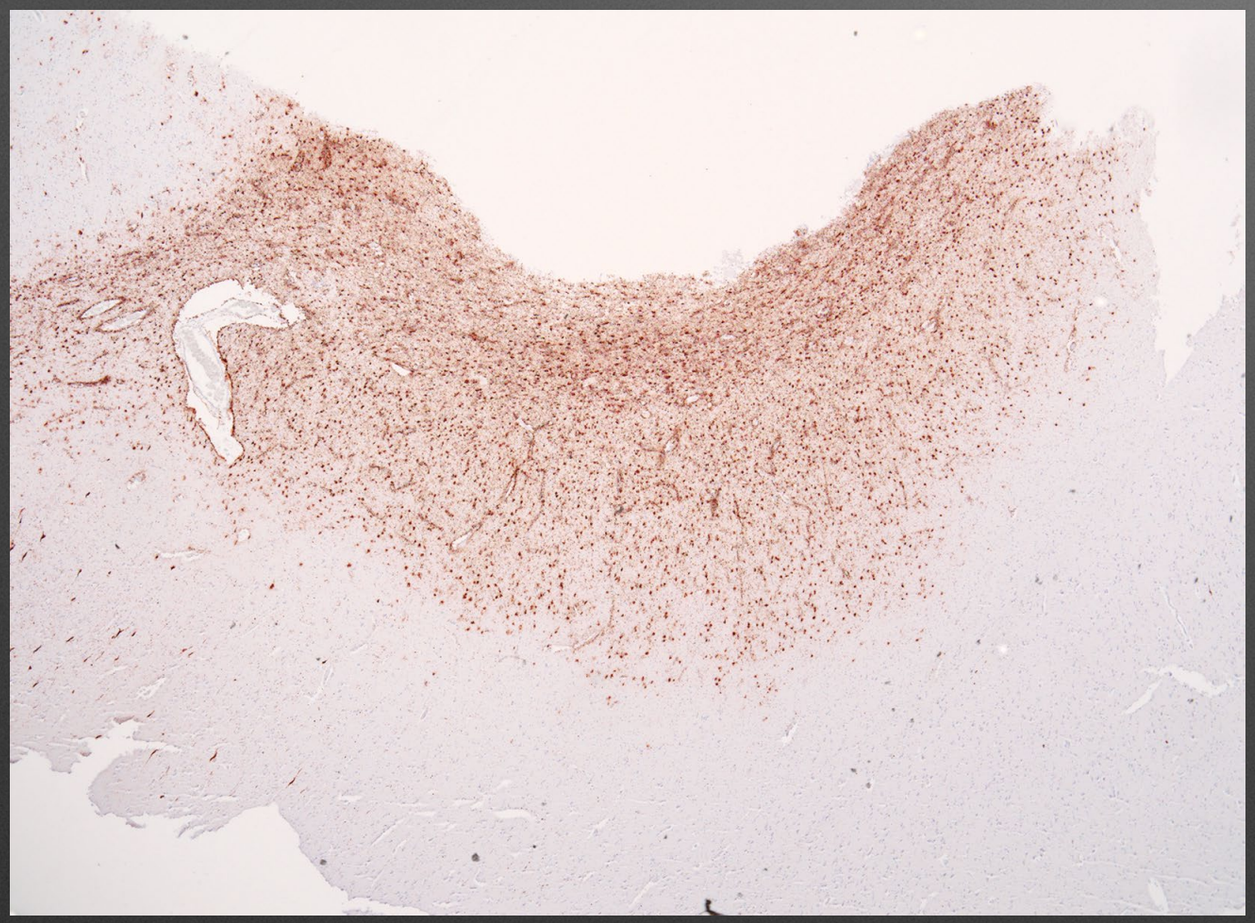
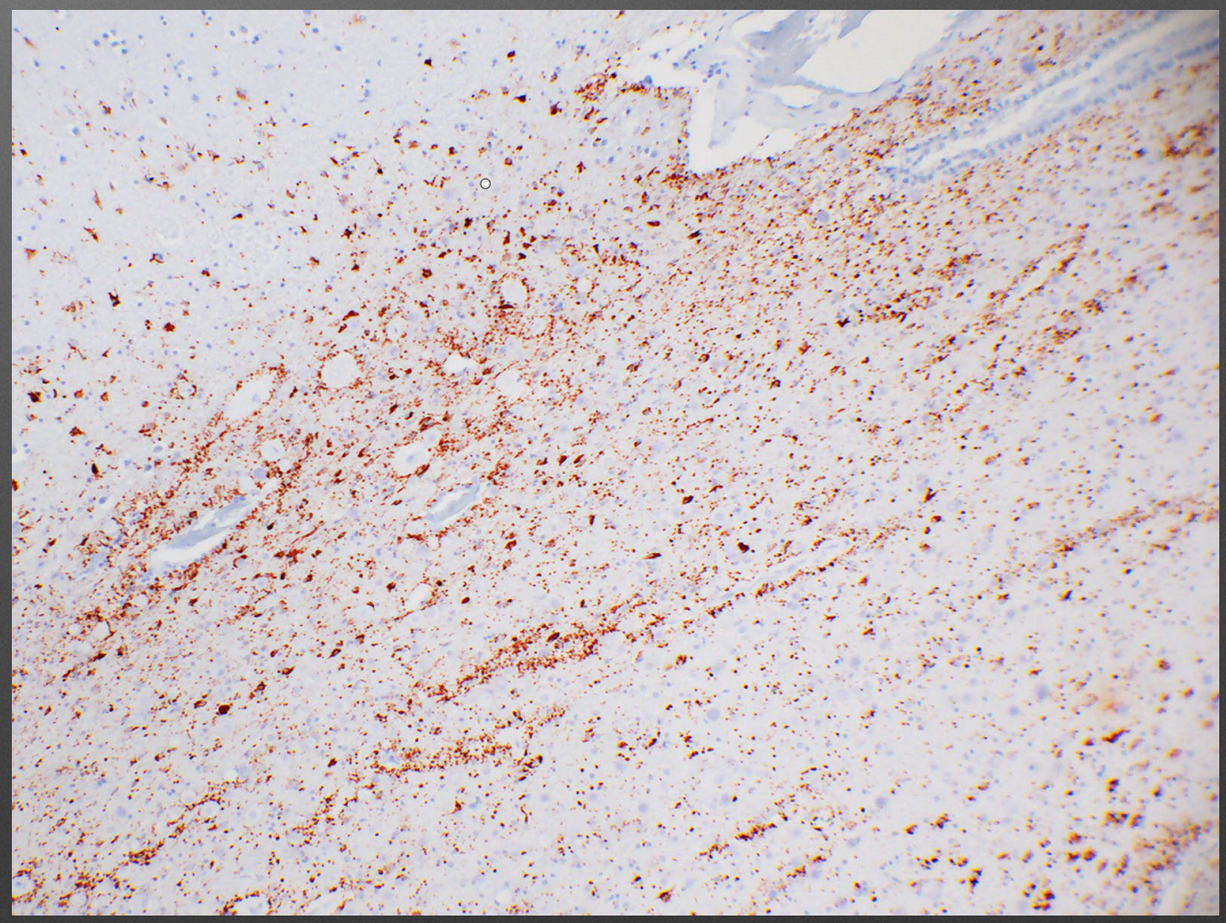


Image Courtesy of Gabor Kovacs, MD, PhD

Amygdala subpial and subependymal





Images Courtesy of Russ Huber, MD, PhD

18.e. ARTAG in the frontal cortex

e. Is ARTAG pathology present in the **FRONTAL NEOCORTEX**?

- ☐ 0 No **(SKIP TO QUESTION 19)**
- ☐ 1 Yes **(CONTINUE)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 19)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 19)**

f. Localization of ARTAG pathology in the frontal neocortex:

(CHECK ONE BOX PER ROW)	None	Focal	Widespread	Not assessed	Missing/ unknown
Subpial	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Gray matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
White matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Perivascular	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐

18.e. Is ARTAG present in the frontal cortex?

Frontal cortex gray matter and perivascular

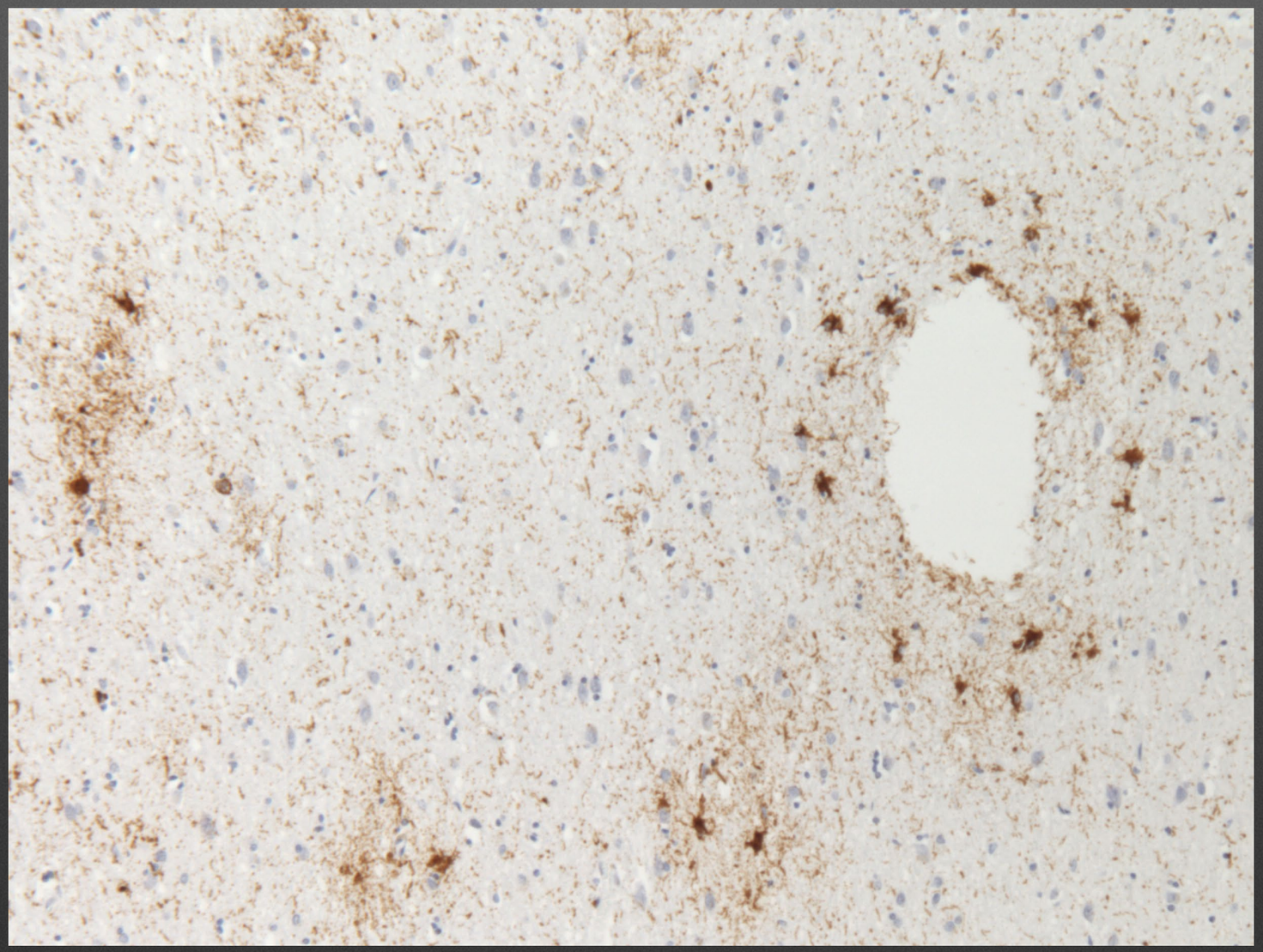


Image Courtesy of Gabor Kovacs, MD, PhD

GFA frontal cortex

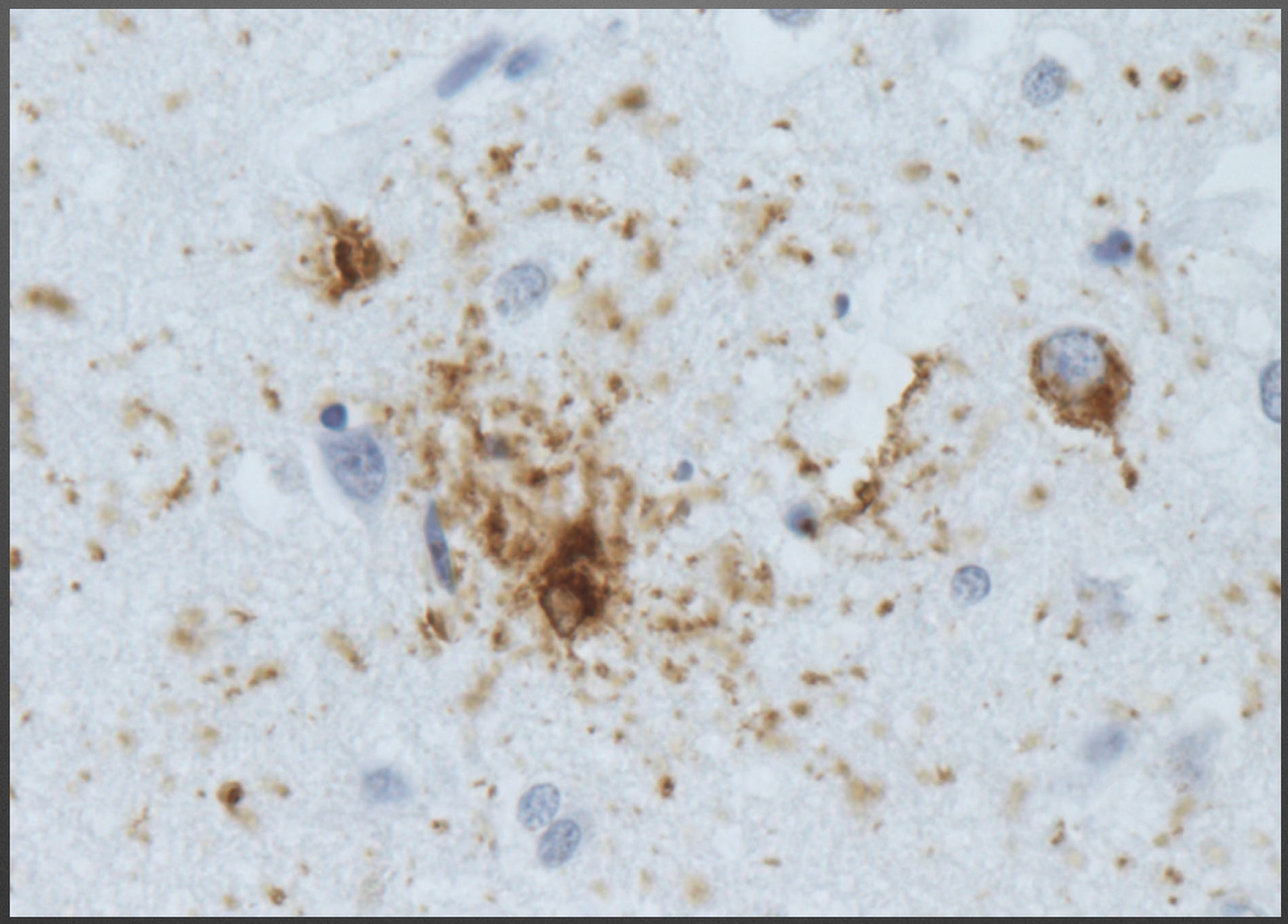
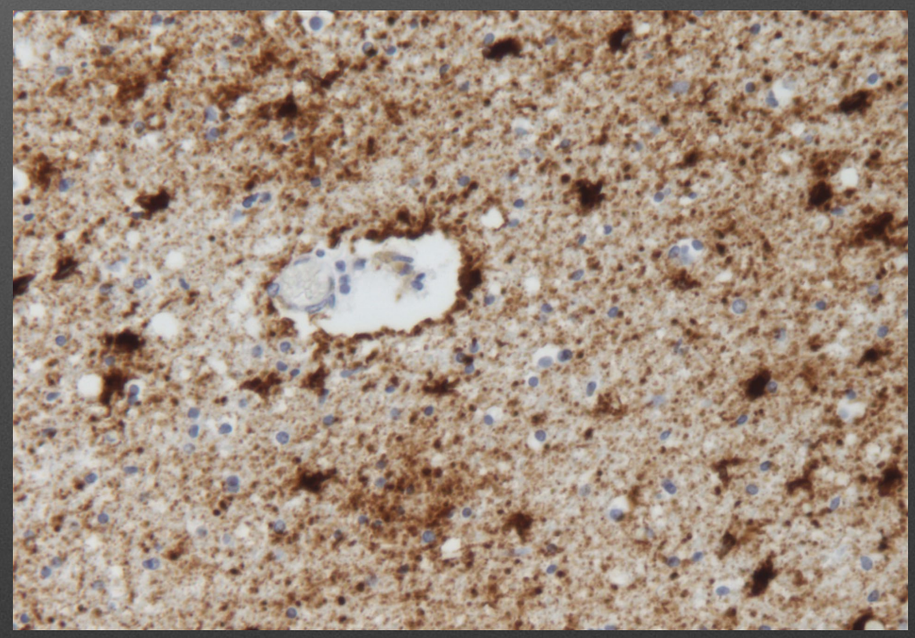


Image Courtesy of Gabor Kovacs, MD, PhD

Frontal lobe white matter and perivascular ARTAG



Images Courtesy of Gabor Kovacs, MD, PhD

Frontal lobe subpial TSA

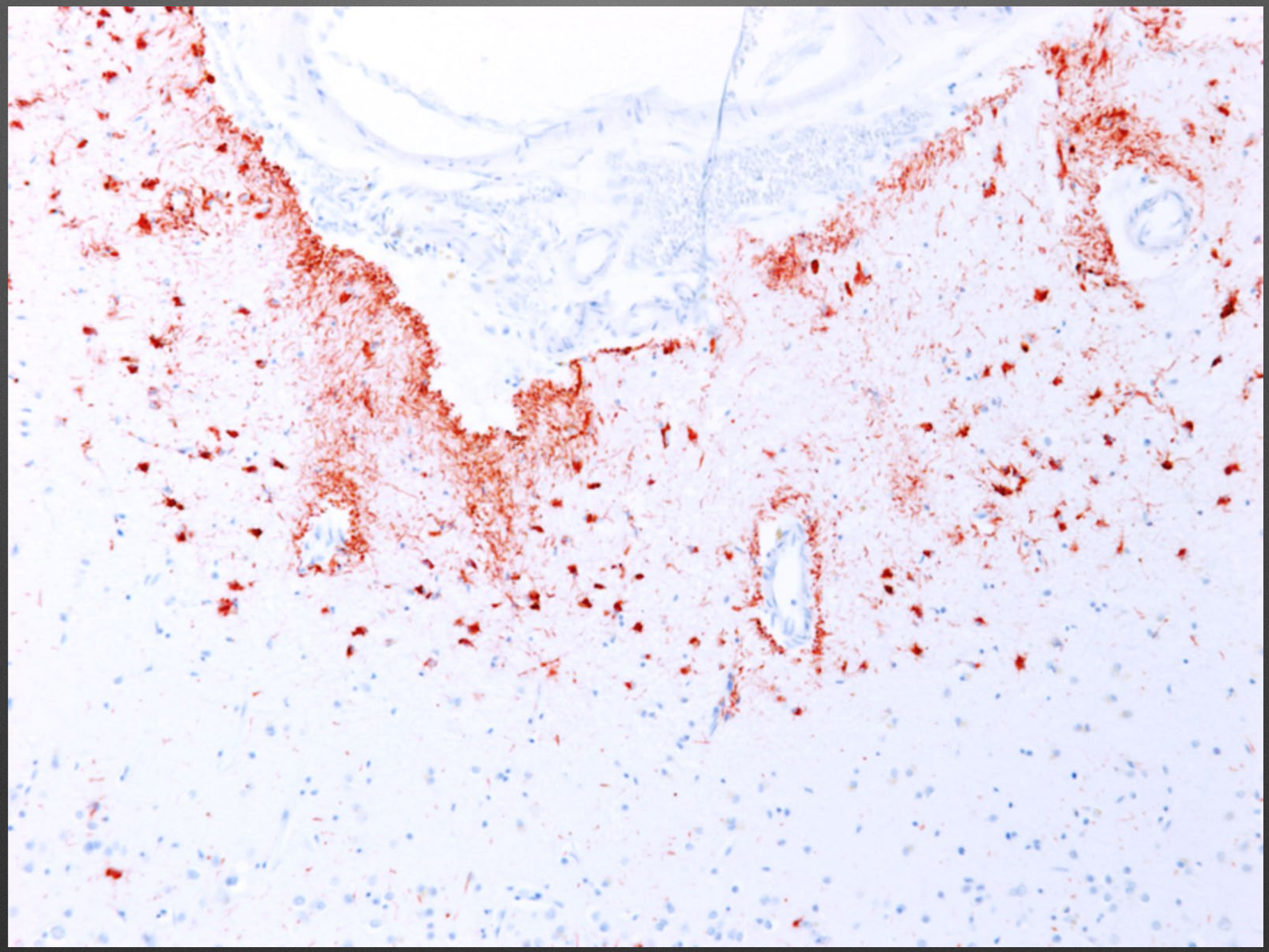


Image Courtesy of Russ Huber, MD, PhD

References

- *Kovacs G et al. ARTAG: harmonized evaluation strategy. Acta Neuropathol. 2016. Jan:131(1):87-100*
- *Kovacs G, Xie S, Lee E et al. Multisite assessment of ARTAG, JNEN, 2017, Jul 1;76(7):605-619*
- *Forrest S, Kril J, Wagner S, et al. CTE is absent from a European community-based aging cohort while ARTAG is highly prevalent. JNEN. 2019 May 1;78(5):398-405.*