MAYO CLINIC

PRACTICAL APPROACH AND EVALUATION OF COMMON NEURODEGENERATIVE DISEASES

CASE-BASED LEARNING

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AANP Teaching Rounds
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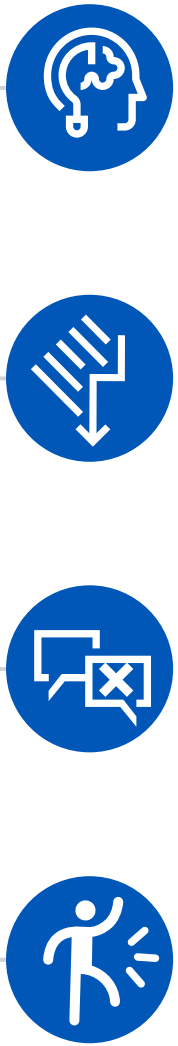
LEARNING OBJECTIVES

1. **Build** a differential diagnosis of neurodegenerative diseases based upon gross pathologic findings

2. **Identify** key histologic sections used to diagnose Alzheimer's disease neuropathologic change (ADNC) and common comorbidities

3. **Apply** harmonized criteria to diagnose ADNC and other neurodegenerative diseases

DEMENTIA



PROGRESSIVE MEMORY DYSFUNCTION

Beta-amyloid plaques

Neurofibrillary tangles

STEPWISE NEUROLOGIC DECLINE

Vascular-mediated brain injury

BEHAVIORAL / PERSONALITY CHANGES

LANGUAGE DYSFUNCTION

TDP-43

Tau

MOVEMENT DISORDER

Lewy Bodies

Lewy Neurites

NEURODEGENERATIVE DISEASE OVERVIEW

DISEASE	LESIONS	COMPONENTS
Alzheimer's Disease	Extracellular plaques Neurofibrillary tangles	Amyloid Tau
Parkinson's Disease Dementia with Lewy Bodies	Lewy bodies Lewy neurites	Alpha-synuclein
Multiple System Atrophy	Glial cytoplasmic inclusions	Alpha-synuclein
FTLD-Tau (e.g., Pick's disease, PSP, CBD)	Neuronal and glial tangles	Tau
FTLD-TDP	Cytoplasmic and nuclear inclusions	TDP-43
Amyotrophic Lateral Sclerosis	Cytoplasmic inclusions	TDP-43
Trinucleotide Repeat Diseases (e.g., Huntington's Disease)	Nuclear and cytoplasmic inclusions	Polyglutamine expansion
Chronic Traumatic Encephalopathy	Neuronal and glial tangles	Tau

CASE #1 CLINICAL HISTORY

- 60-year-old female who died with a seven-year history of cognitive impairment and motor deficits.
- No pertinent family history or additional history.
- She first presented with sporadic jerks, REM sleep disorder, and then developed cognitive changes a few months afterwards.
- Physical exam showed asymmetric rigidity in arms and a slowed gait.
- Brain scans were performed. Eventually, she demonstrated worsening cognitive impairment. She died at home.

GROSS FINDINGS

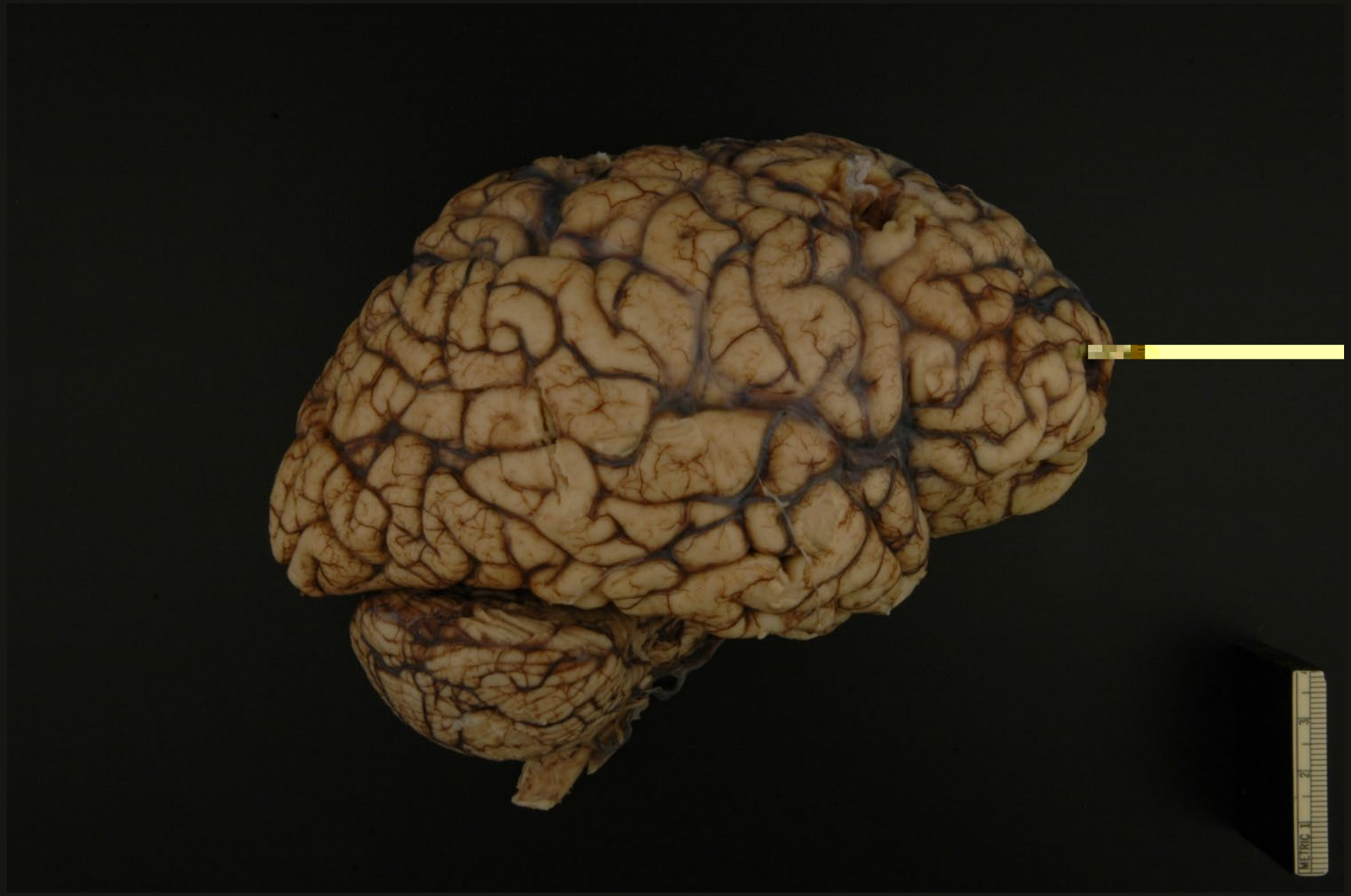
MICROSCOPIC FINDINGS

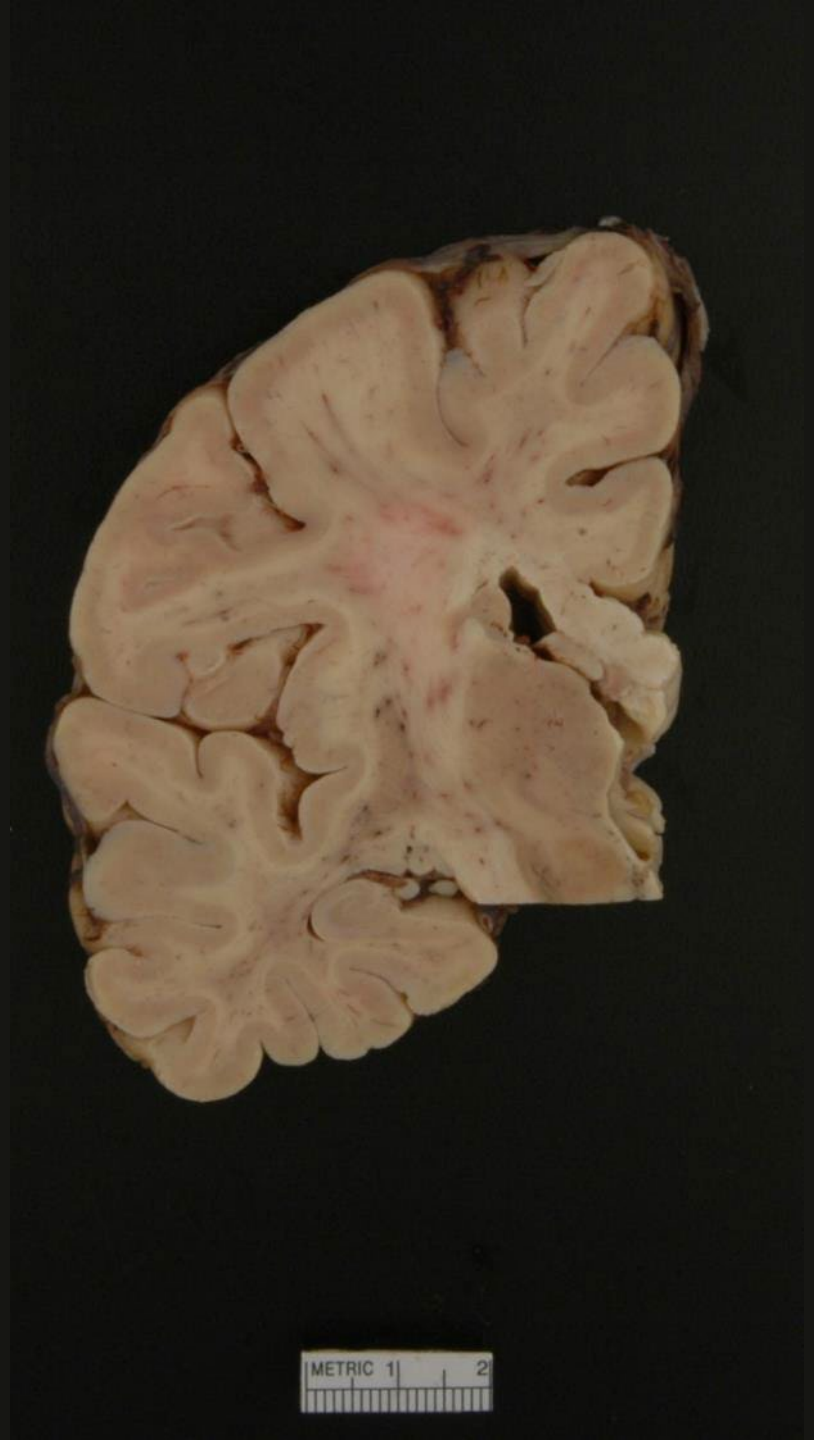
H&E

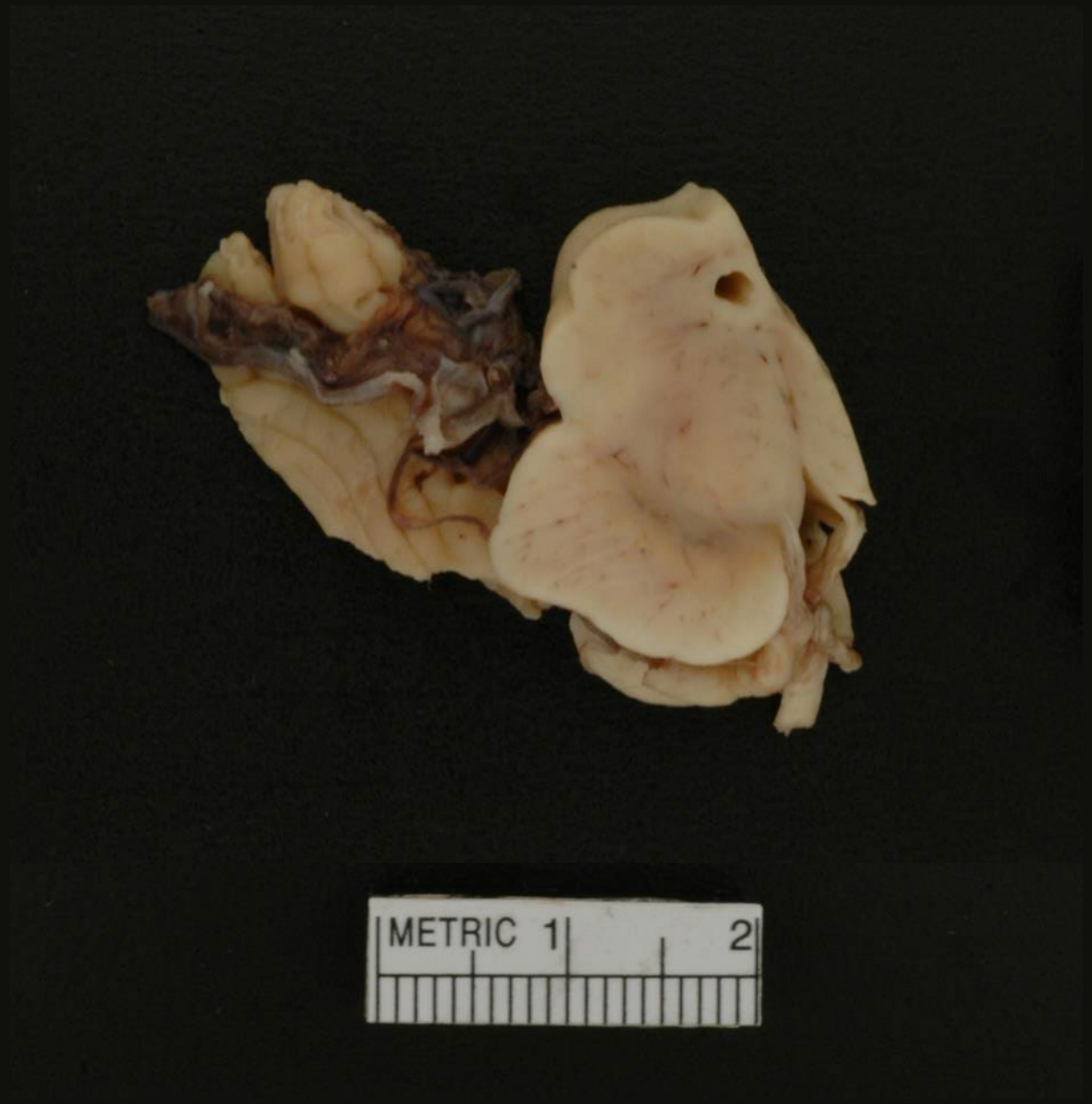
ANCILLARY STUDIES

- Tau
- Beta-amyloid
- Alpha-synuclein
- TDP-43
- Bielschowsky silver stain

NEUROPATH DIAGNOSES



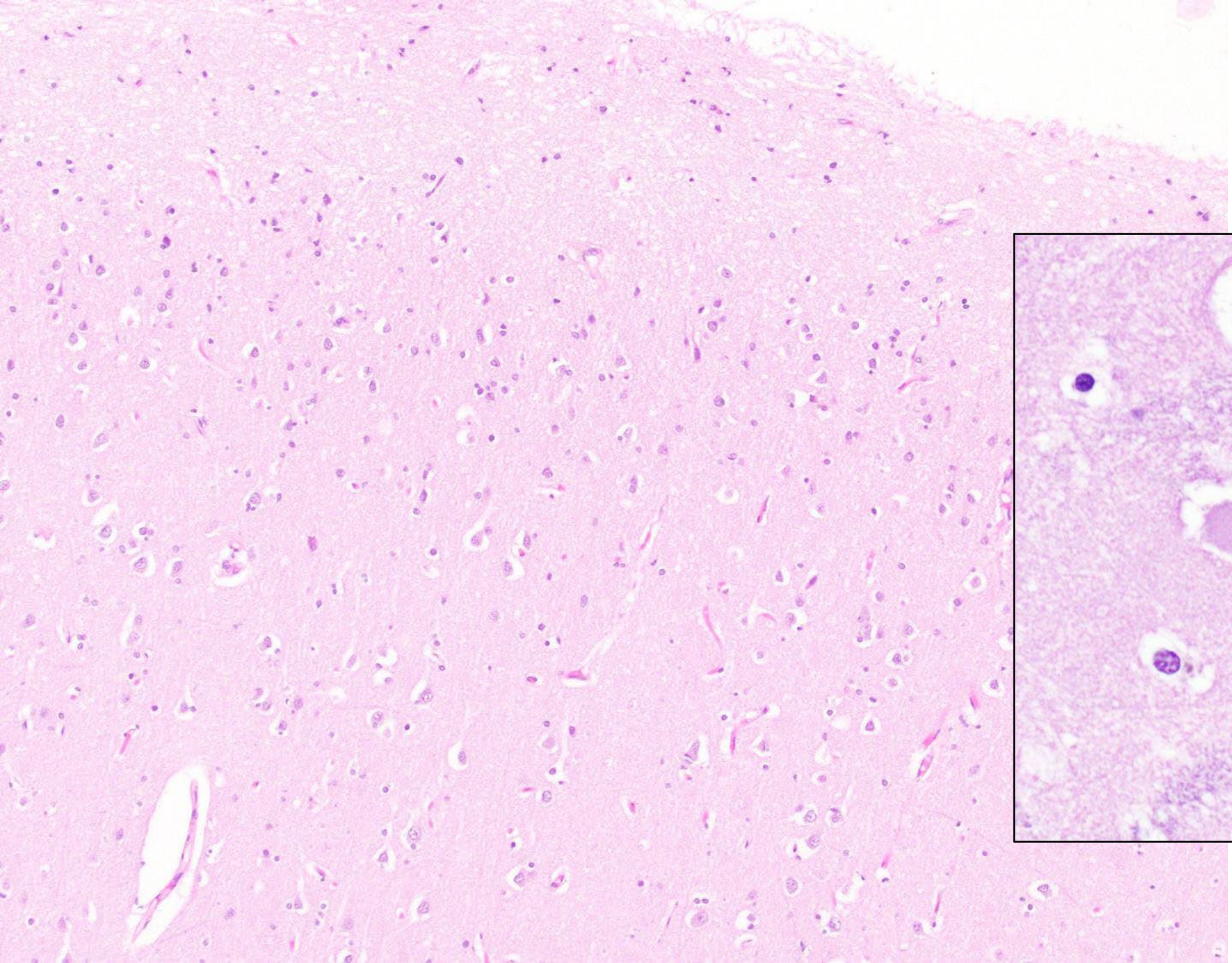


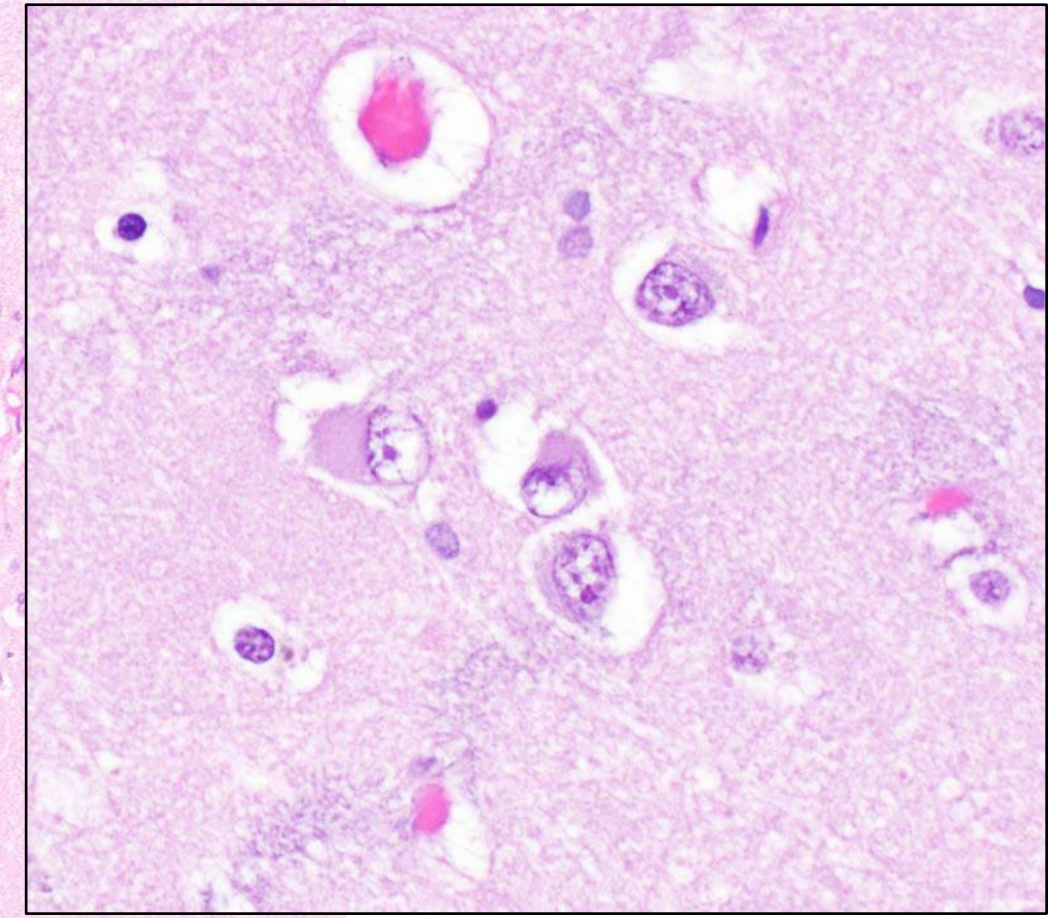


HISTOLOGIC FINDINGS

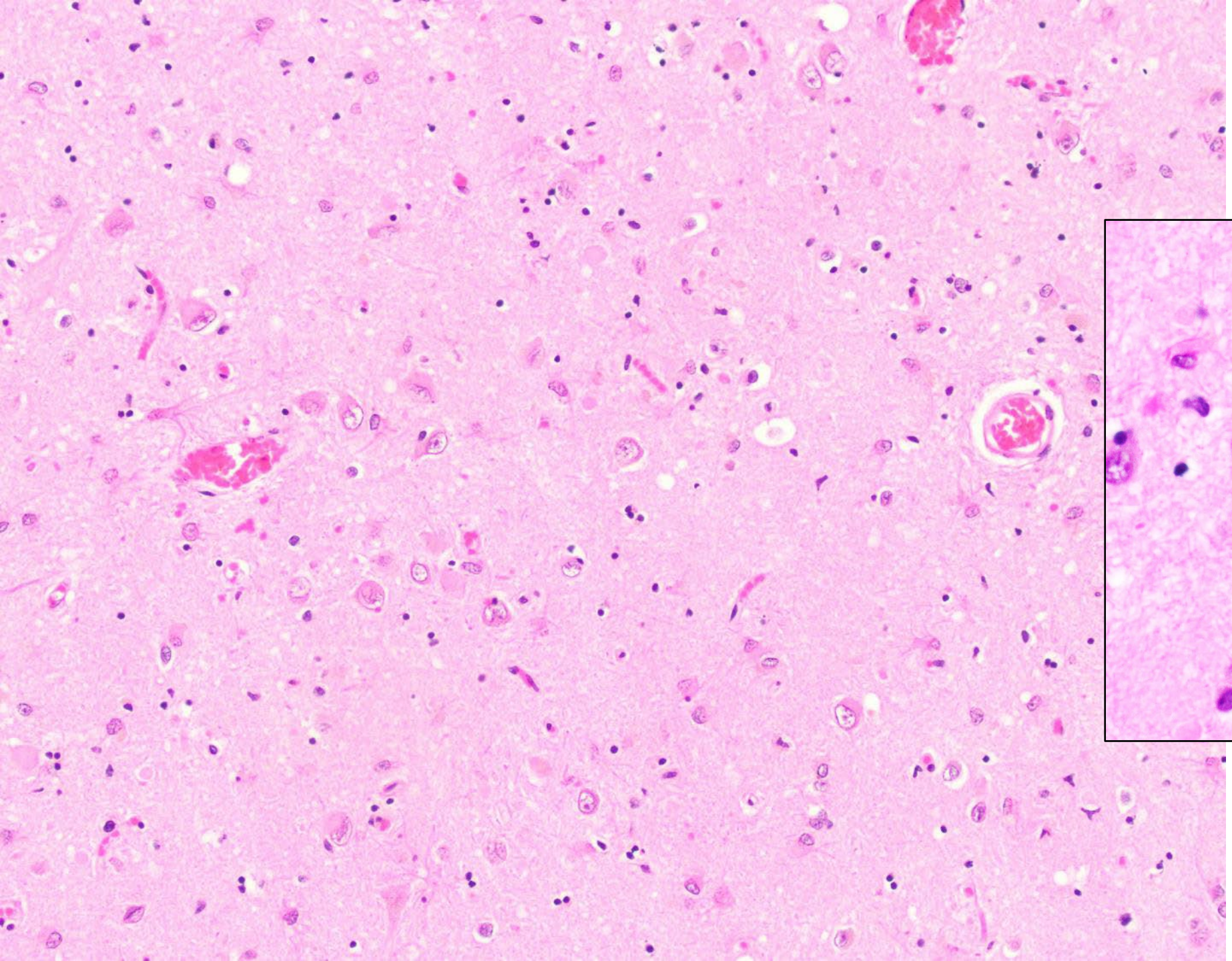
AND ANCILLARY STAINS

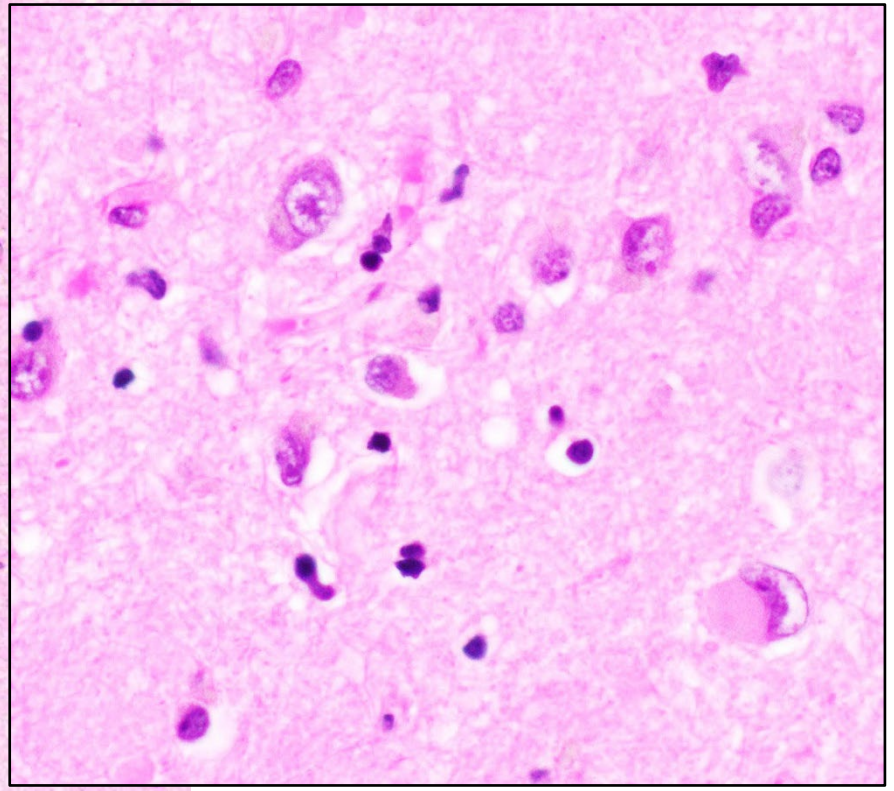
- H&E
- Tau
- Beta-amyloid
- Alpha-synuclein
- TDP-43
- Bielschowsky



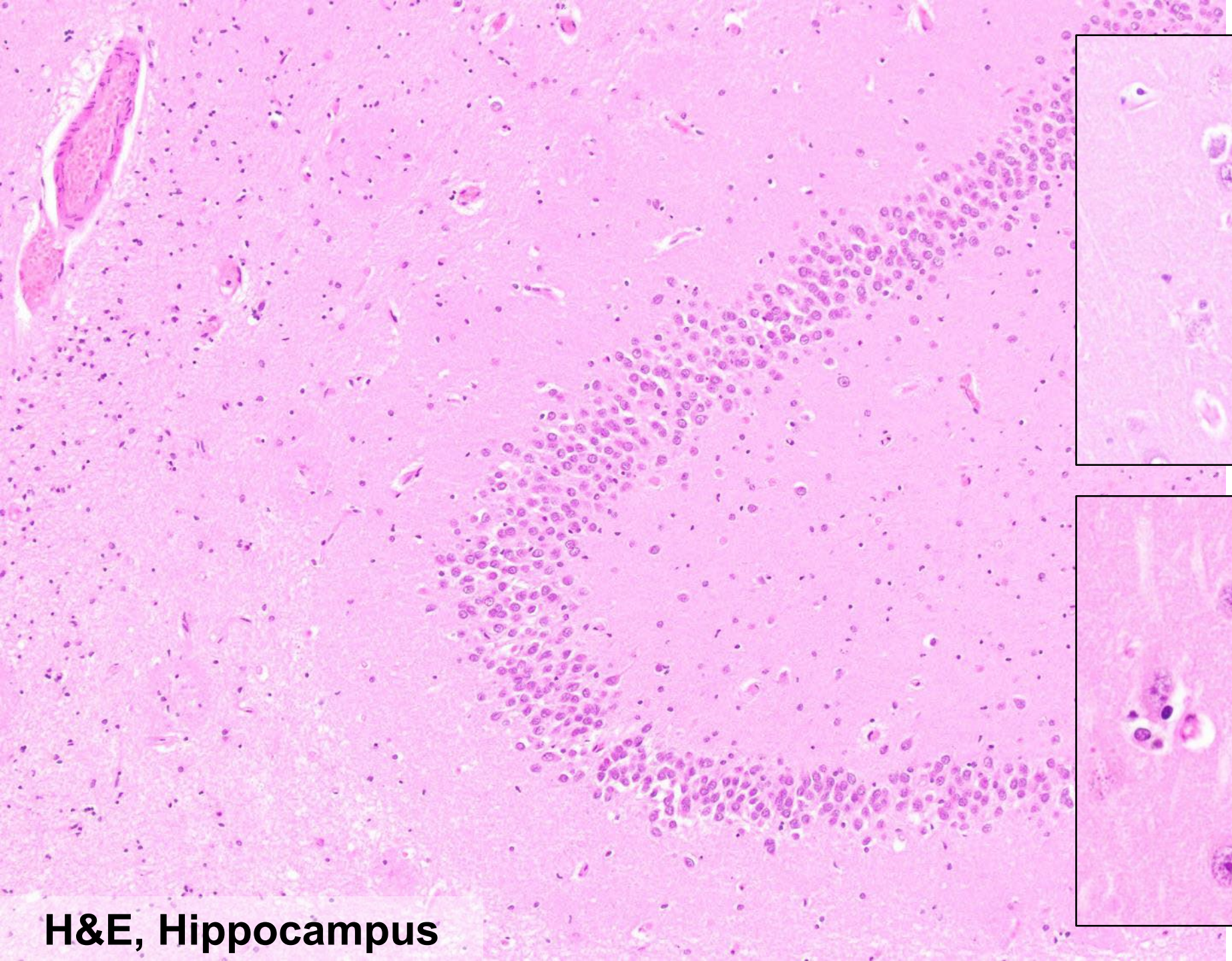


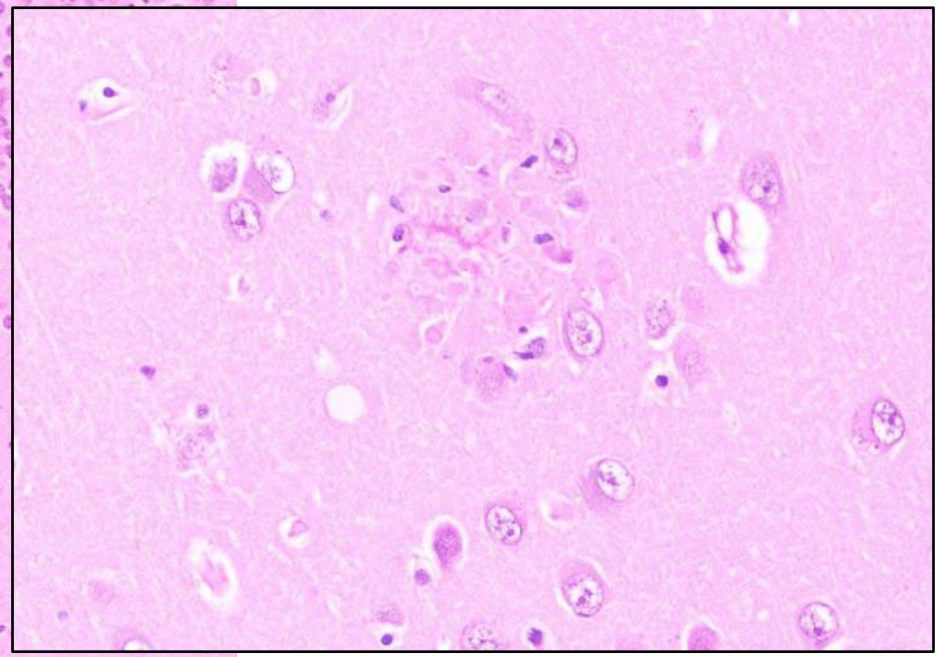
H&E, Frontal lobe

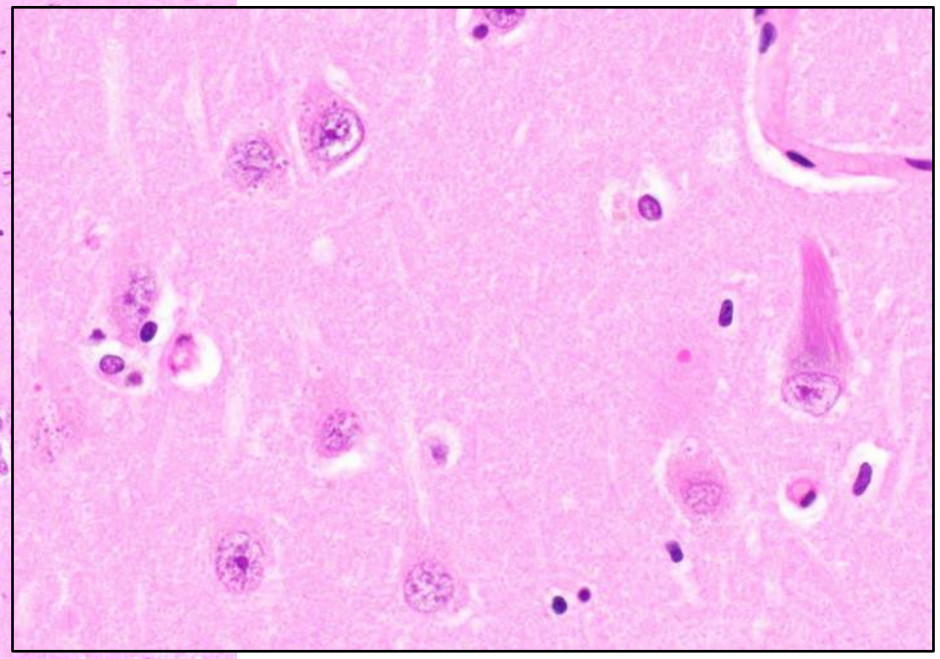




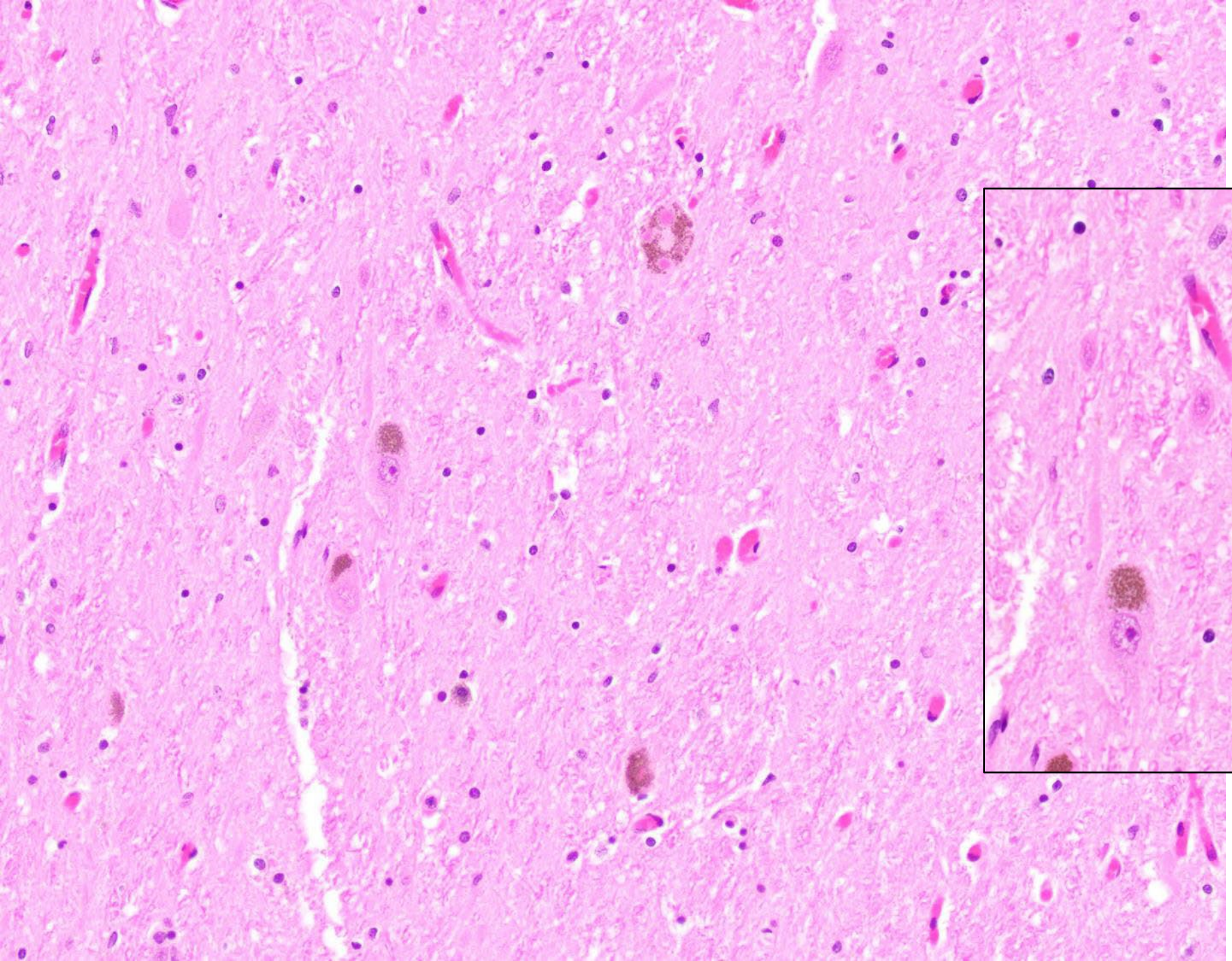
H&E, Amygdala

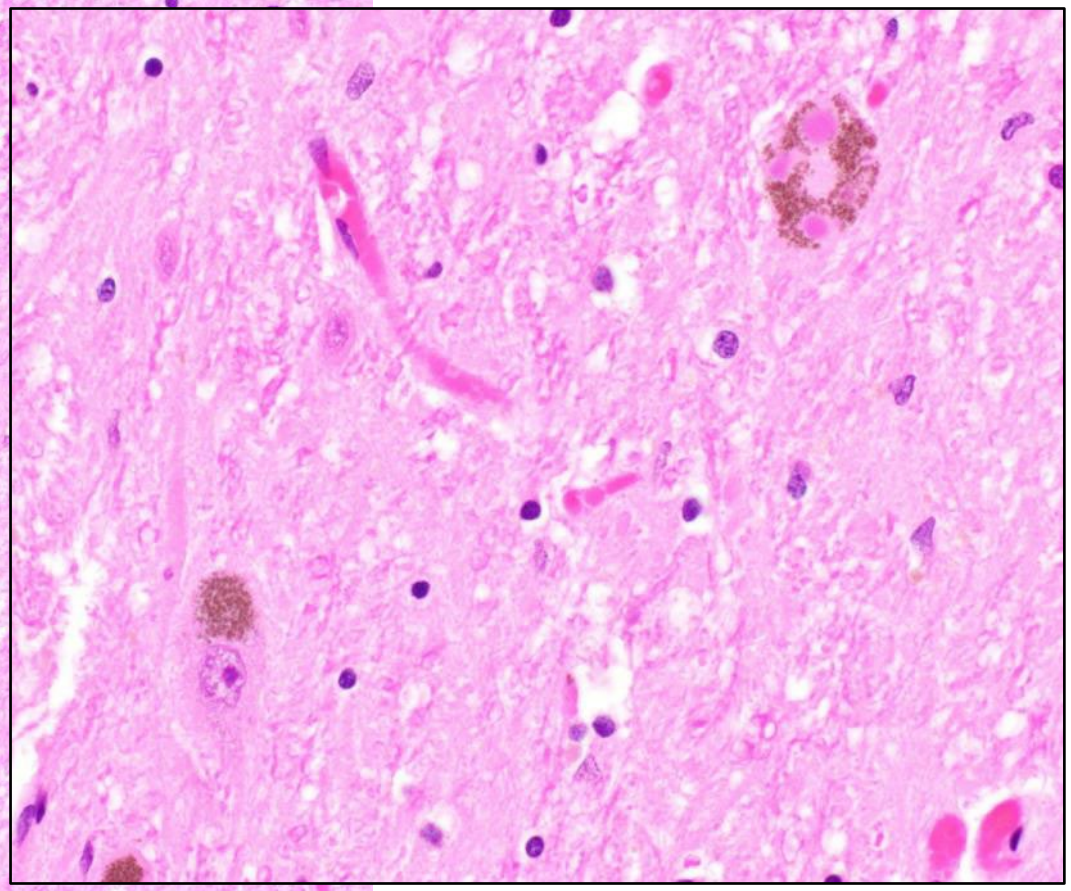






H&E, Hippocampus





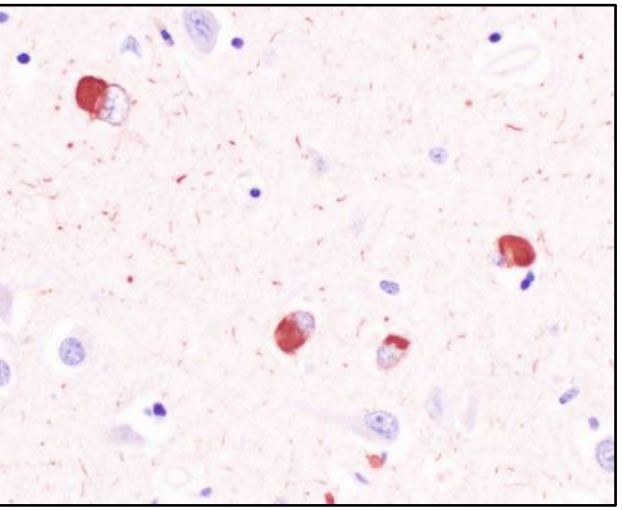
H&E, Substania Nigra

HISTOLOGIC FINDINGS

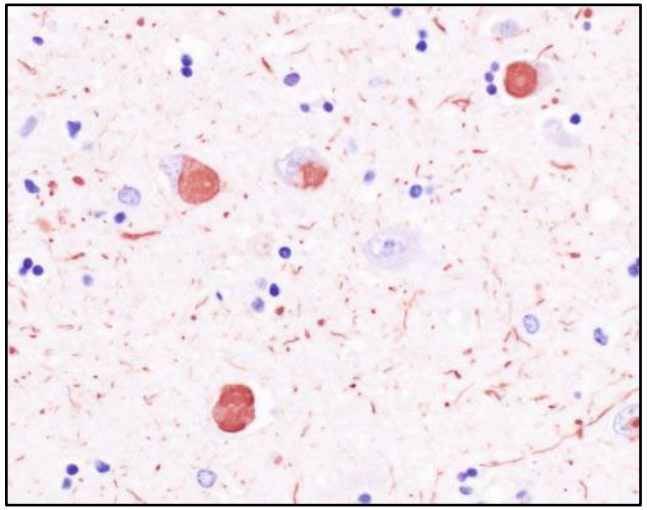
AND ANCILLARY STAINS

- H&E
- Tau
- Beta-amyloid
- Alpha-synuclein
- TDP-43
- Bielschowsky

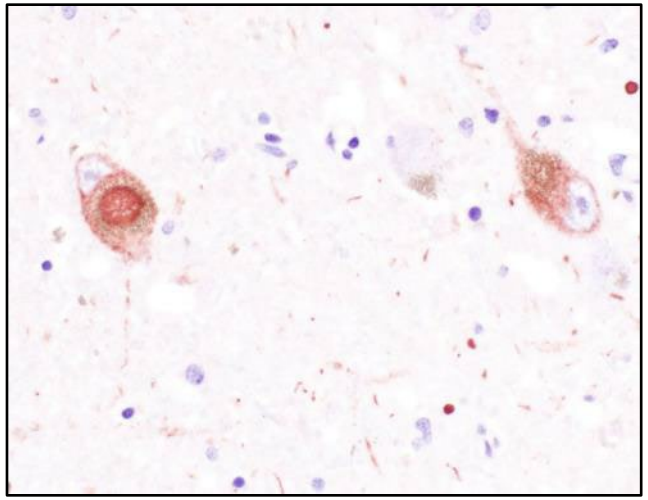
ALPHA-SYNUCLEIN



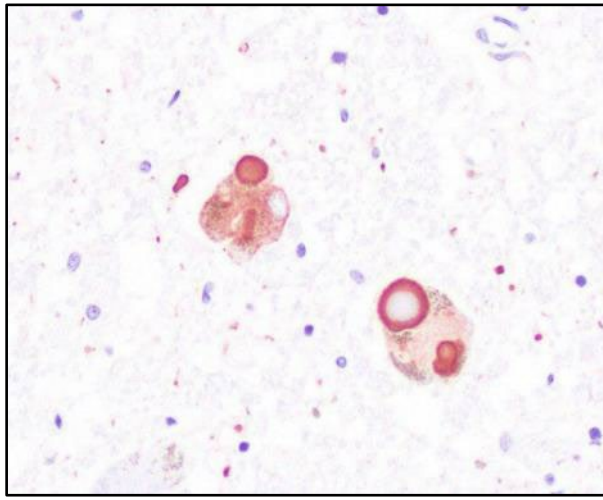
Frontal lobe



Amygdala

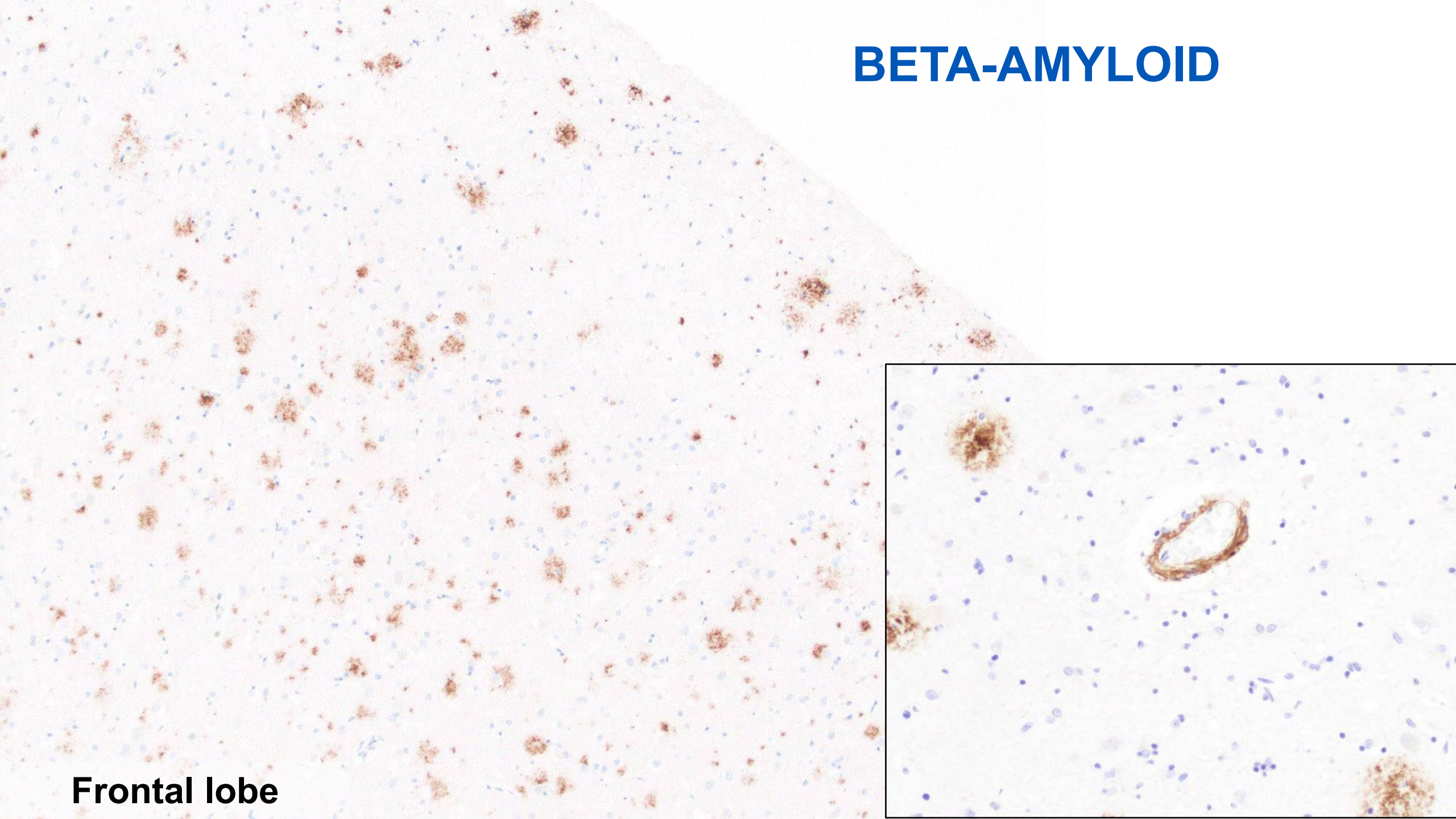


Substantia Nigra



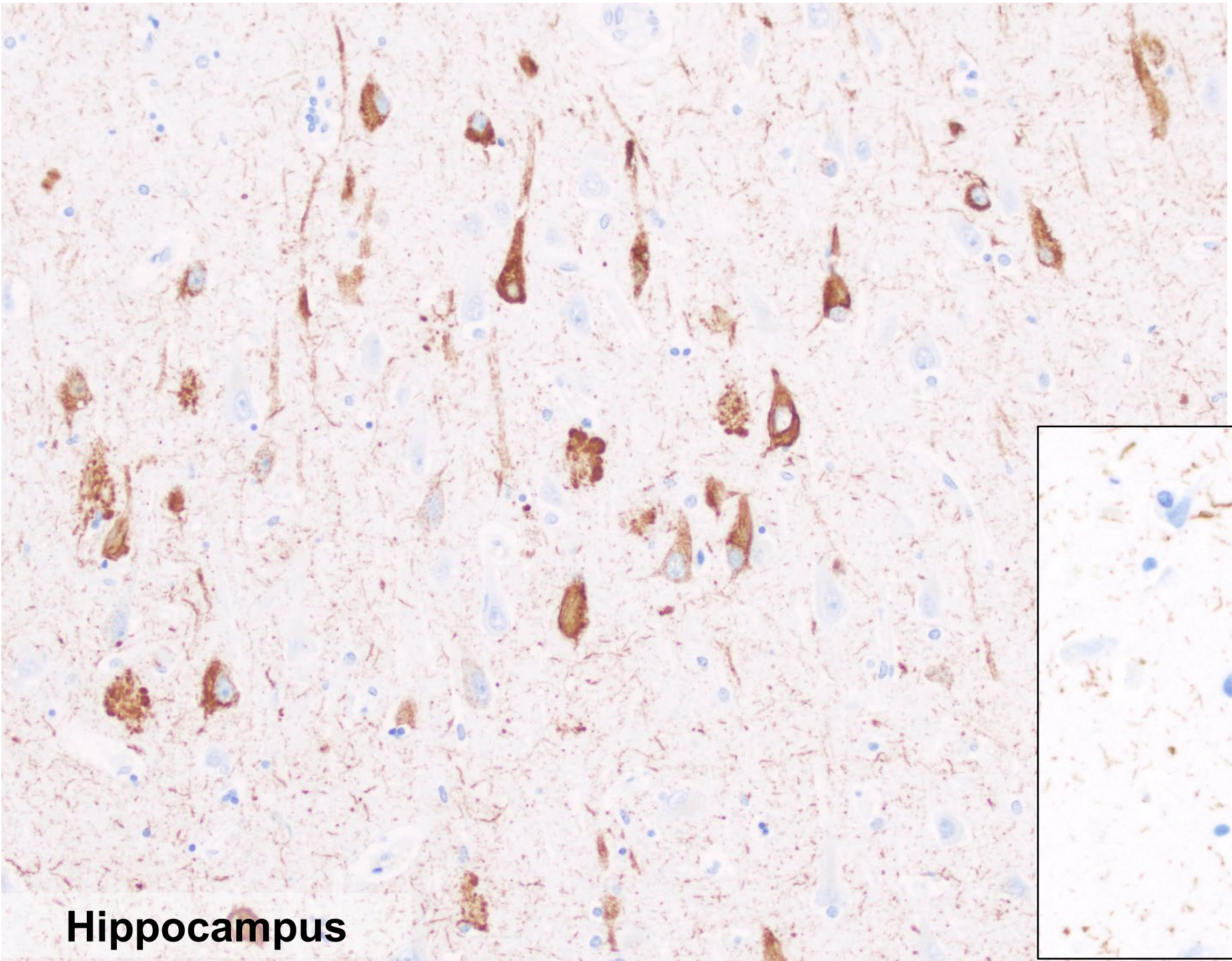
Locus Ceruleus

BETA-AMYLOID

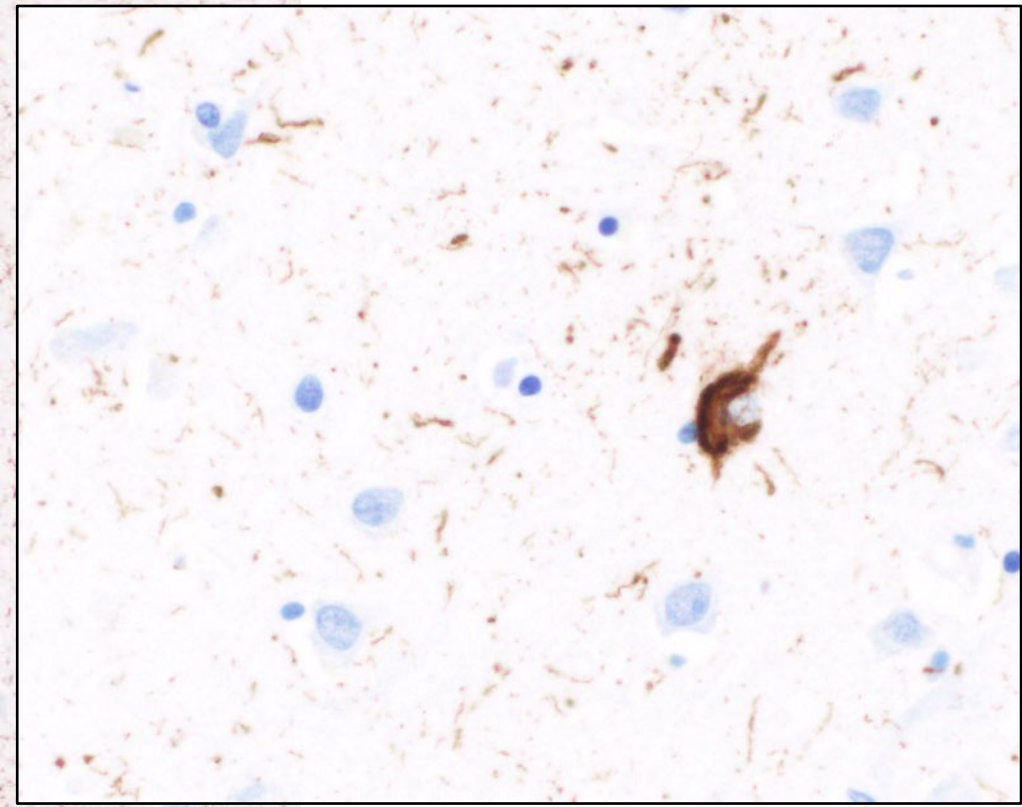


Frontal lobe

TAU

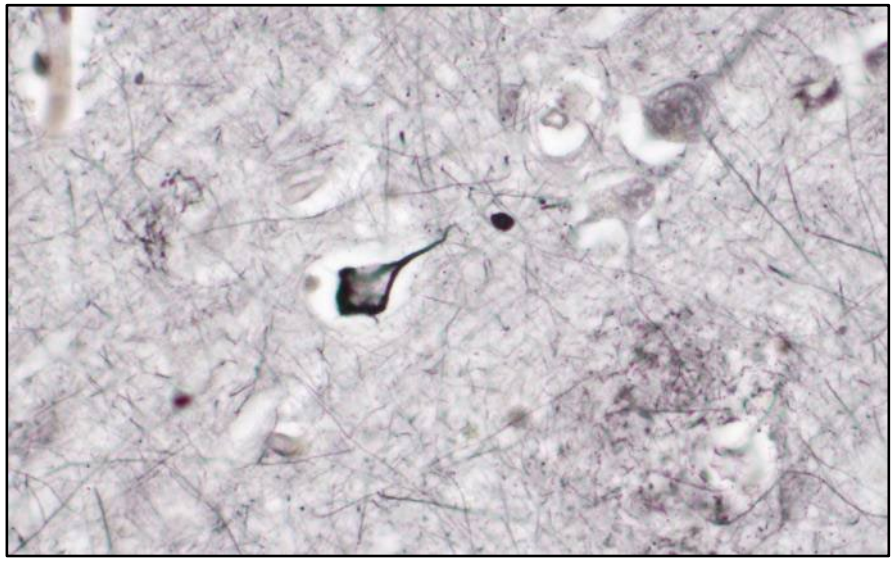


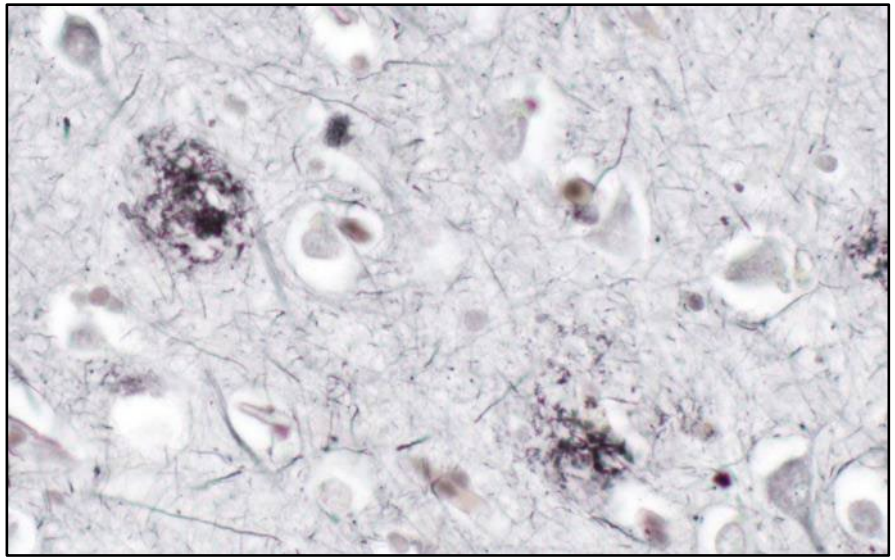
Hippocampus



Temporal lobe

BIELSCHOWSKY STAIN





GROSS FINDINGS

- Mild to moderate cerebral atrophy (global)
- Moderate depigmentation of the substantia nigra

MICROSCOPIC FINDINGS

- Mild to Moderate neuronal loss and concomitant gliosis
- Frequent cytoplasmic inclusions and extracellular plaques

ANCILLARY STUDIES

- Tau: neurofibrillary tangles
- Beta-amyloid: diffuse plaques
- Alpha-synuclein: Lewy bodies and neurites
- TDP-43: absent
- Bielschowsky silver stain: neuritic plaques and neurofibrillary tangles

NEUROPATH DIAGNOSES

FINAL DIAGNOSIS

1. Lewy body disease
2. Alzheimer’s disease neuropathologic change
3. Cerebrovascular disease
4. Vascular brain injury
5. Additional findings

NEURODEGENERATIVE DISEASE OVERVIEW

DISEASE	LESIONS	COMPONENTS
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NEURODEGENERATIVE DISEASE INCLUSIONS

SYNUCLEIN OPATHIES

PD/LBD

Lewy bodies

Lewy Neurites

MSA

Glial cytoplasmic inclusions

ALZHEIMER DISEASE

BETA-AMYLOID

Diffuse plaques

Neuritic plaques

PHOSPHO-TAU

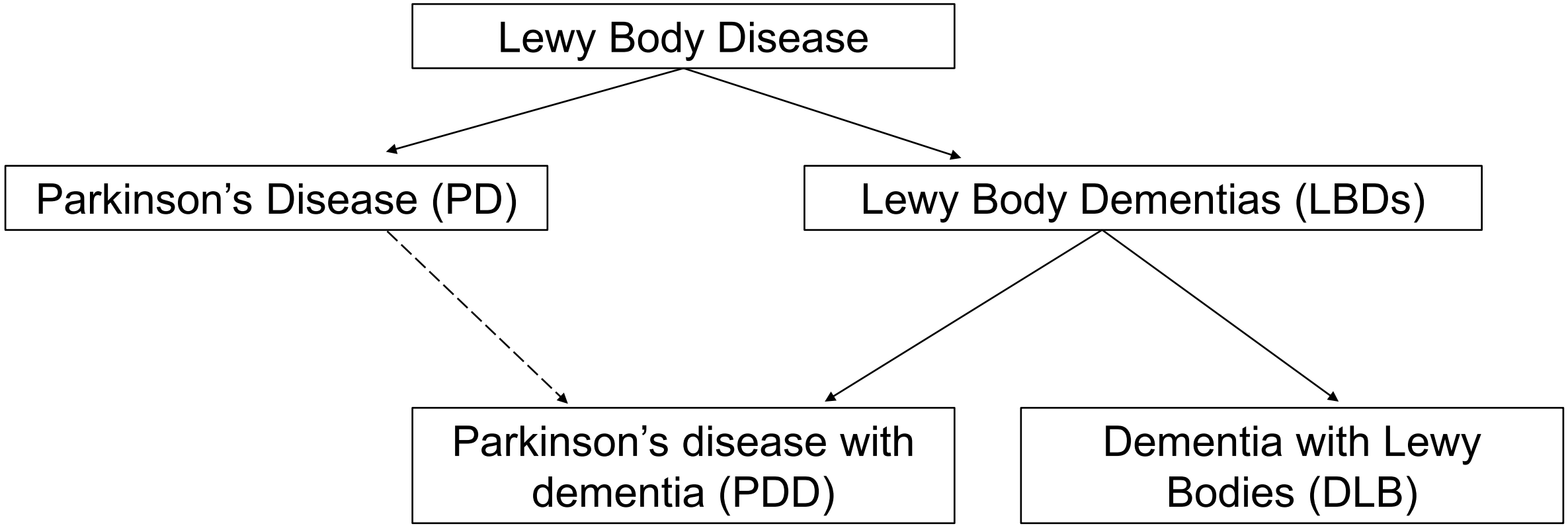
Neurofibrillary tangles

Dystrophic neurites

Neuritic plaques

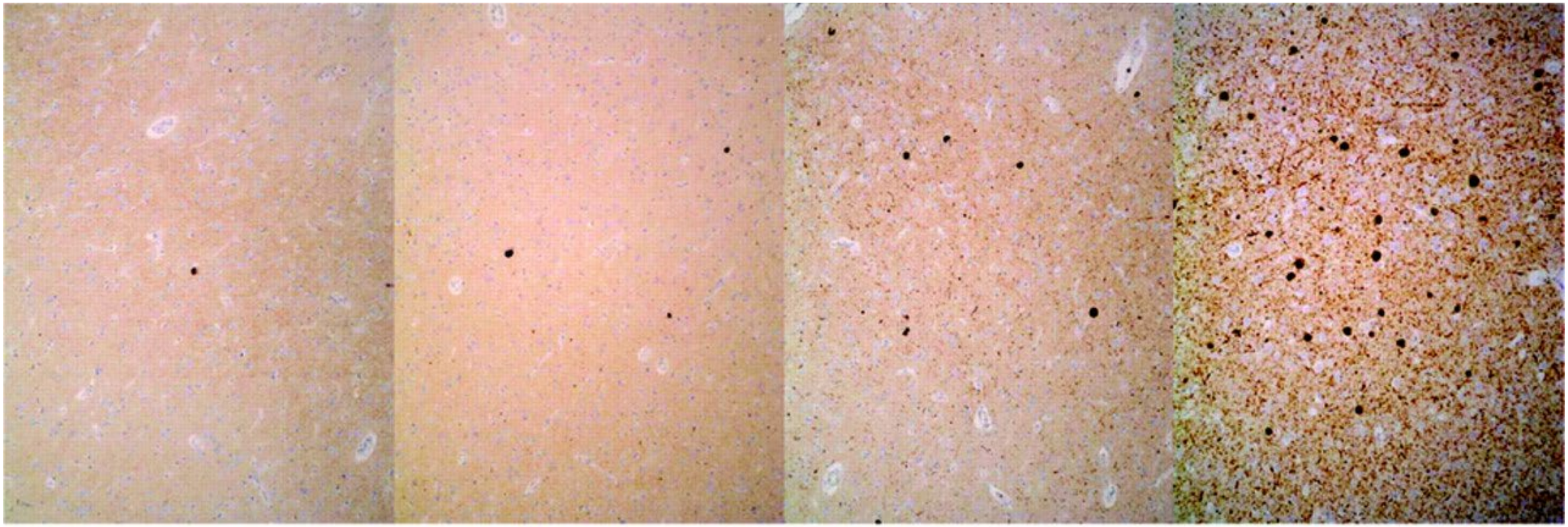
…AND MANY MORE!

LEWY BODY DISEASE



Third consensus report of the DLB Consortium. *Neurology* (2005)

LEWY BODY PATHOLOLOGY GRADING



Third consensus report of the DLB Consortium. *Neurology* (2005)

LEWY BODY DISEASE TYPES

Table 2 *Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

Brain regions are as defined anatomically in the original Consensus report.[1]

IX = 9th cranial nerve nucleus; X = 10th cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert.

Third consensus report of the DLB Consortium. *Neurology* (2005)

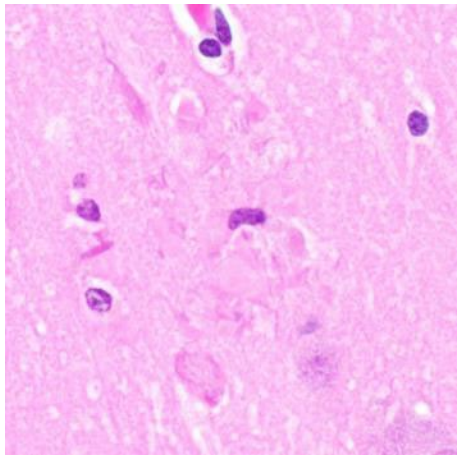
LEWY BODY DISEASE

1. Lewy body disease: Diffuse neocortical; substantia nigra with moderate neuronal cell loss (DLB consortium, 2017)

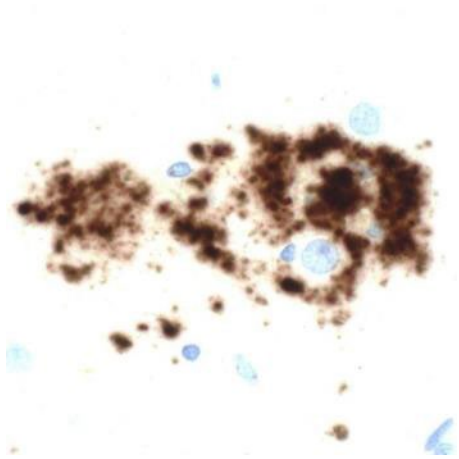
REGION	Severity
Medulla	Severe
Pons	Severe
Midbrain	Very Severe
Amygdala	Very Severe
Anterior cingulate gyrus	Very Severe
Transentorhinal	Very Severe
Temporal lobe	Very Severe
Frontal lobe	Very Severe
Parietal lobe	Very Severe

ALZHEIMER'S DISEASE (AD)

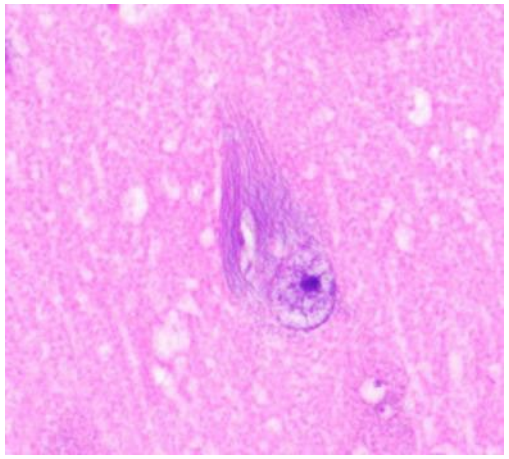
- Progressive and fatal neurodegenerative disease
  - Marked by changes in memory and cognitive functions
  - Language, visuospatial, and executive domains
- Affects more than 40 million people worldwide
- Leading cause of dementia in the elderly worldwide
- Neuropathologic hallmarks include beta-amyloid plaques and neurofibrillary tangles



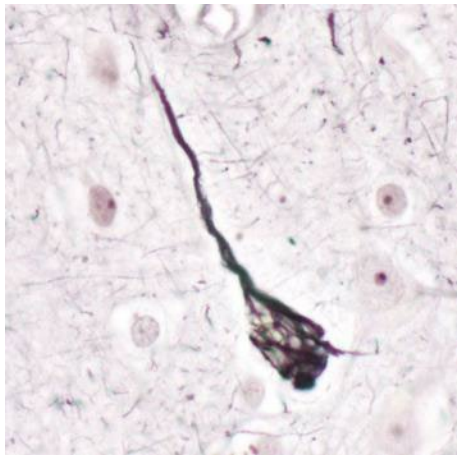
Extracellular plaque



Beta-amyloid IHC



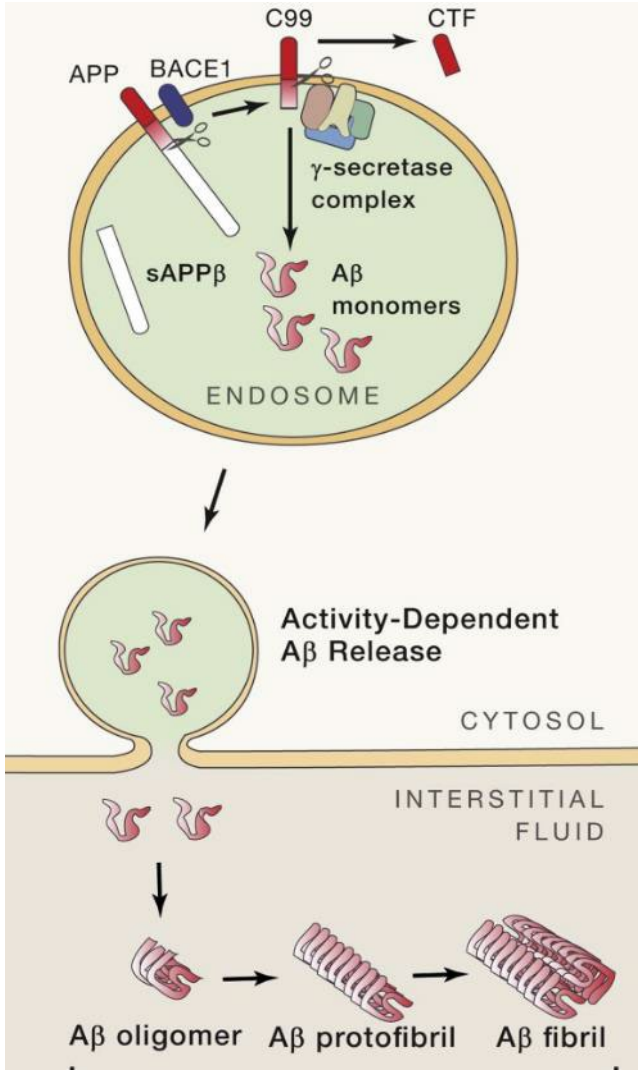
Neurofibrillary tangle

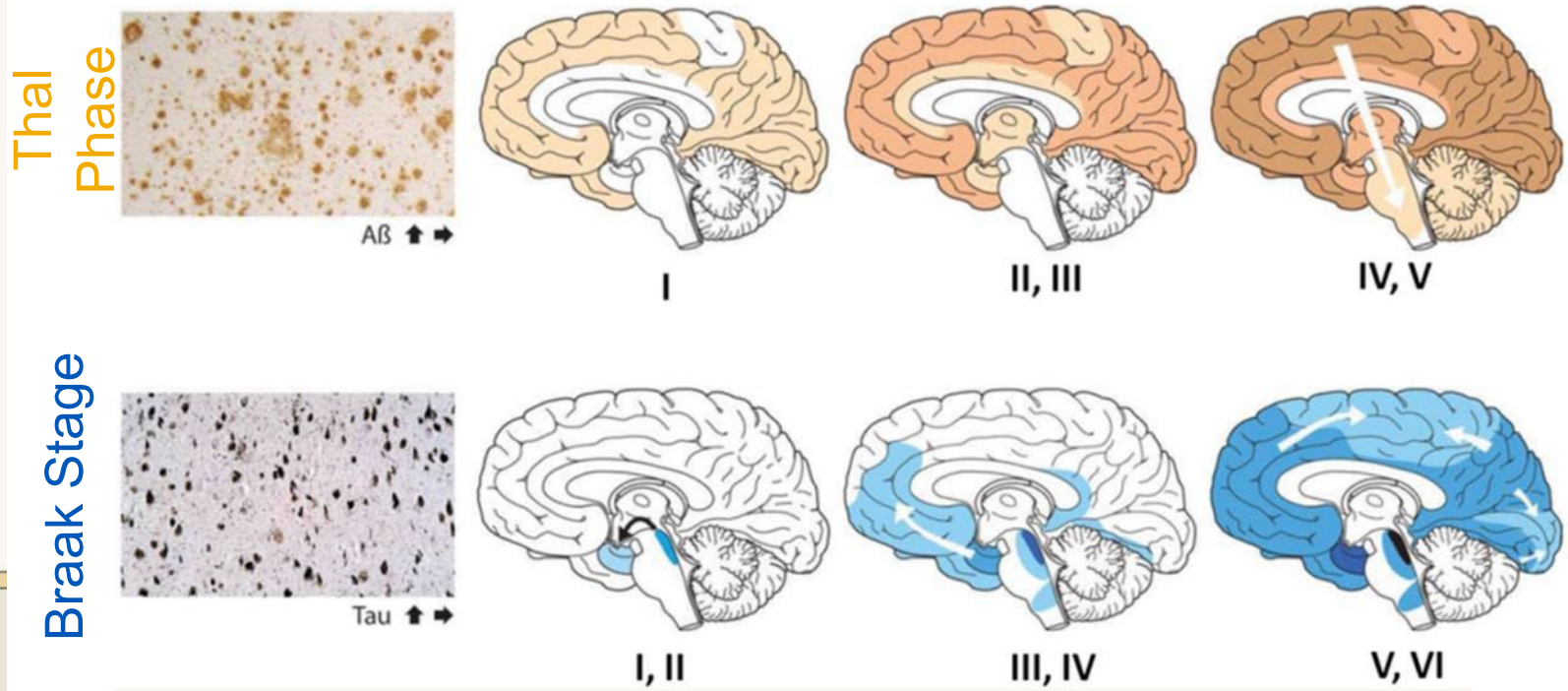


Bielchowsky Stain

Alzheimer's Dement. 2018 (14); 367-429. Acta. Neuropathol. 1991; 239-259. Science. 2002; 353-356.

PATHOBIOLOGY OF AD





Long and Holtzman. Cell. 2019 179(2); 312-339

Jouanne et al. Euro. J of Med Chemistry. 2017. 139; 153-167.

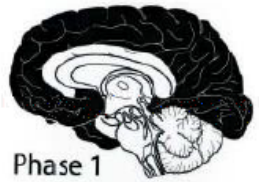
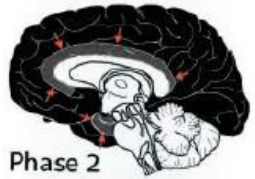
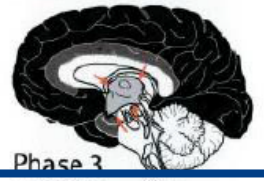
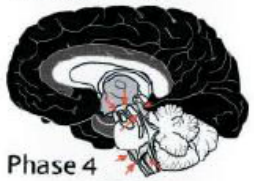
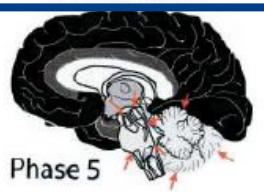
ALZHEIMER'S DISEASE NEUROPATHOLOGIC CHANGE

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

National Institute on Aging-Alzheimer's Association Consensus. *Alzheimers Dement* (2012)

THAL PHASE (A SCORE)

(A)myloid phase

A0		No plaques	
A1	 Phase 1	Neocortical	Middle frontal gyrus, angular gyrus, superior/middle temporal gyrus, occipital cortex
	 Phase 2	Allocortical	Amygdala, hippocampus and dentate gyrus, CA1, entorhinal cortex, cingulate gyrus
A2	 Phase 3	Subcortical	Basal ganglia, globus pallidus, putamen, thalamus
A3	 Phase 4	Brainstem	Mid-brain, substantia nigra, pons, locus ceruleus, medulla
	 Phase 5	Cerebellum	

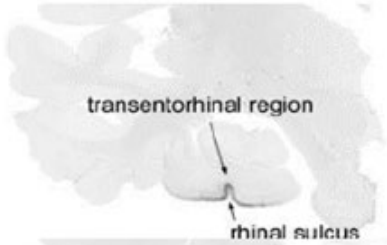
Thal et al. *Neurology* (2002)

BRAAK STAGE (B SCORE)

Notes on Braak Staging of NFTs

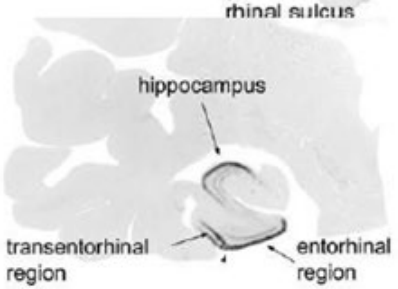
Braak I

Cases with EC NFT pathology only. No other NFTs in the brain including the hippocampal CA regions.



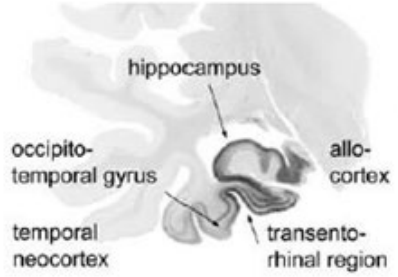
Braak II

Cases with up to 1-2+ in EC and hip CA regions with no NFT pathology in any other area of the brain



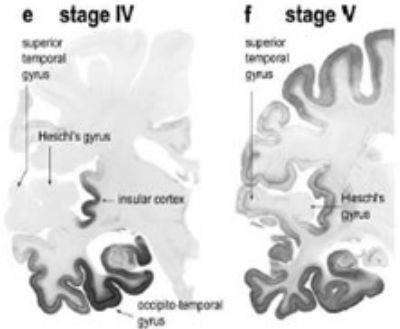
Braak III

Cases with 2+ EC and hip CA regions with NFT pathology continuously from CA3 to subiculum, then Braak and 1+ in occipito-temporal gyrus, but with no NFT pathology in any other area of the brain.



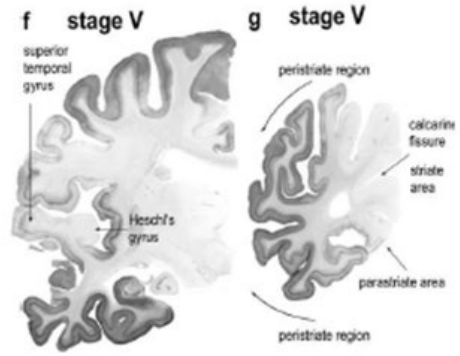
Braak IV

Cases with 2-3+ throughout the hippocampus including the occipito-temporal gyrus. Laterally, the middle temporal gyrus may be affected, but not the superior temporal gyrus. No NFT pathology in any other area of the brain (see examples of this for Braak V in panels e.-f.



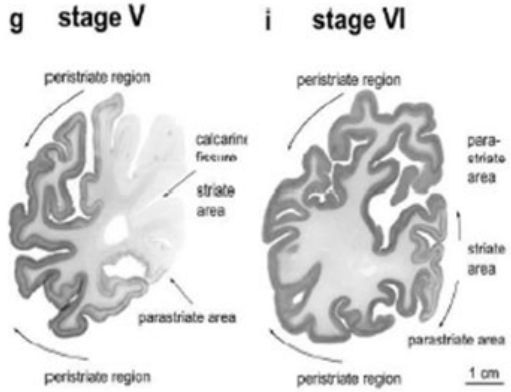
Braak V

Cases with NFTs in the neocortex involving superior temporal gyrus, and beyond to frontal and partietal cortex usually, and also the visual cortex, but not area 17. If the line of Gennari remains unaffected, then it's Braak V. Thus, 2-3+ in the superior temporal and at least one other cortical lobe – either mid frontal or angular gyrus – is also Braak V.



Braak VI

Cases with NFTs throughout the visual cortex which must includie the line of Gennari (area 17). Also, NFTs in most areas of the brain.



Braak Score	Braak Stage
B0	No NFTs
B1	Stage I or II
B2	Stage III or IV
B3	Stage V or VI

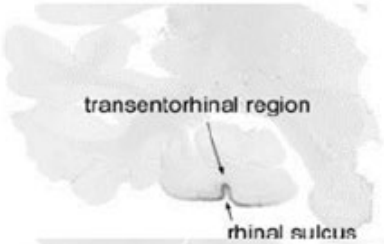
Braak et al. *Acta Neuropathol* (2006, 1991)

BRAAK STAGE (B SCORE)

Notes on Braak Staging of NFTs

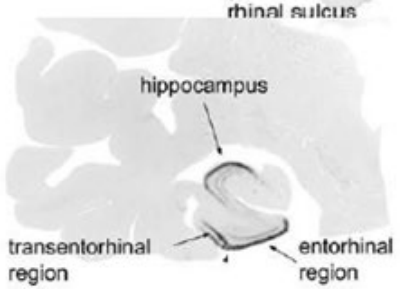
Braak I

Cases with EC NFT pathology only. No other NFTs in the brain including the hippocampal CA regions.



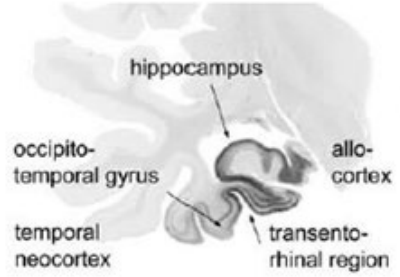
Braak II

Cases with up to 1-2+ in EC and hip CA regions with no NFT pathology in any other area of the brain



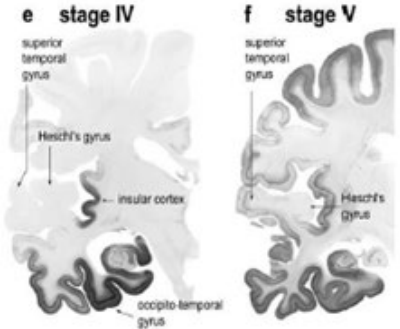
Braak III

Cases with 2+ EC and hip CA regions with NFT pathology continuously from CA3 to subiculum, then Braak and 1+ in occipito-temporal gyrus, but with no NFT pathology in any other area of the brain.



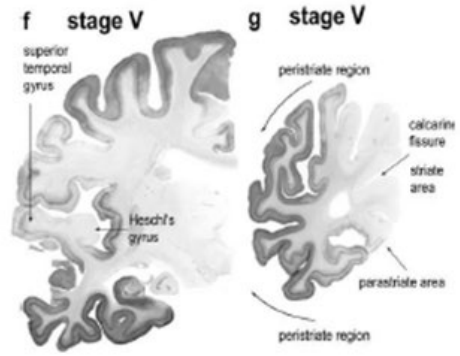
Braak IV

Cases with 2-3+ throughout the hippocampus including the occipito-temporal gyrus. Laterally, the middle temporal gyrus may be affected, but not the superior temporal gyrus. No NFT pathology in any other area of the brain (see examples of this for Braak V in panels e.-f.



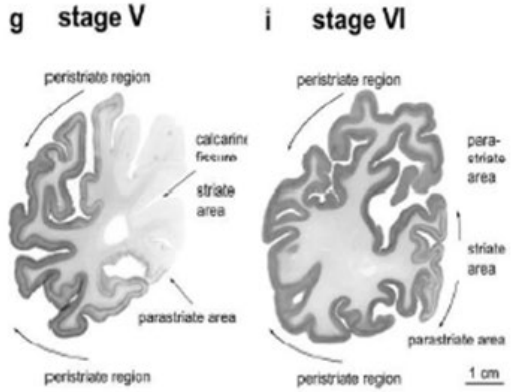
Braak V

Cases with NFTs in the neocortex involving superior temporal gyrus, and beyond to frontal and partietal cortex usually, and also the visual cortex, but not area 17. If the line of Gennari remains unaffected, then it's Braak V. Thus, 2-3+ in the superior temporal and at least one other cortical lobe – either mid frontal or angular gyrus – is also Braak V.



Braak VI

Cases with NFTs throughout the visual cortex which must includie the line of Gennari (area 17). Also, NFTs in most areas of the brain.



Braak Score	Braak Stage
B0	No NFTs
B1	Stage I or II
B2	Stage III or IV
B3	Stage V or VI

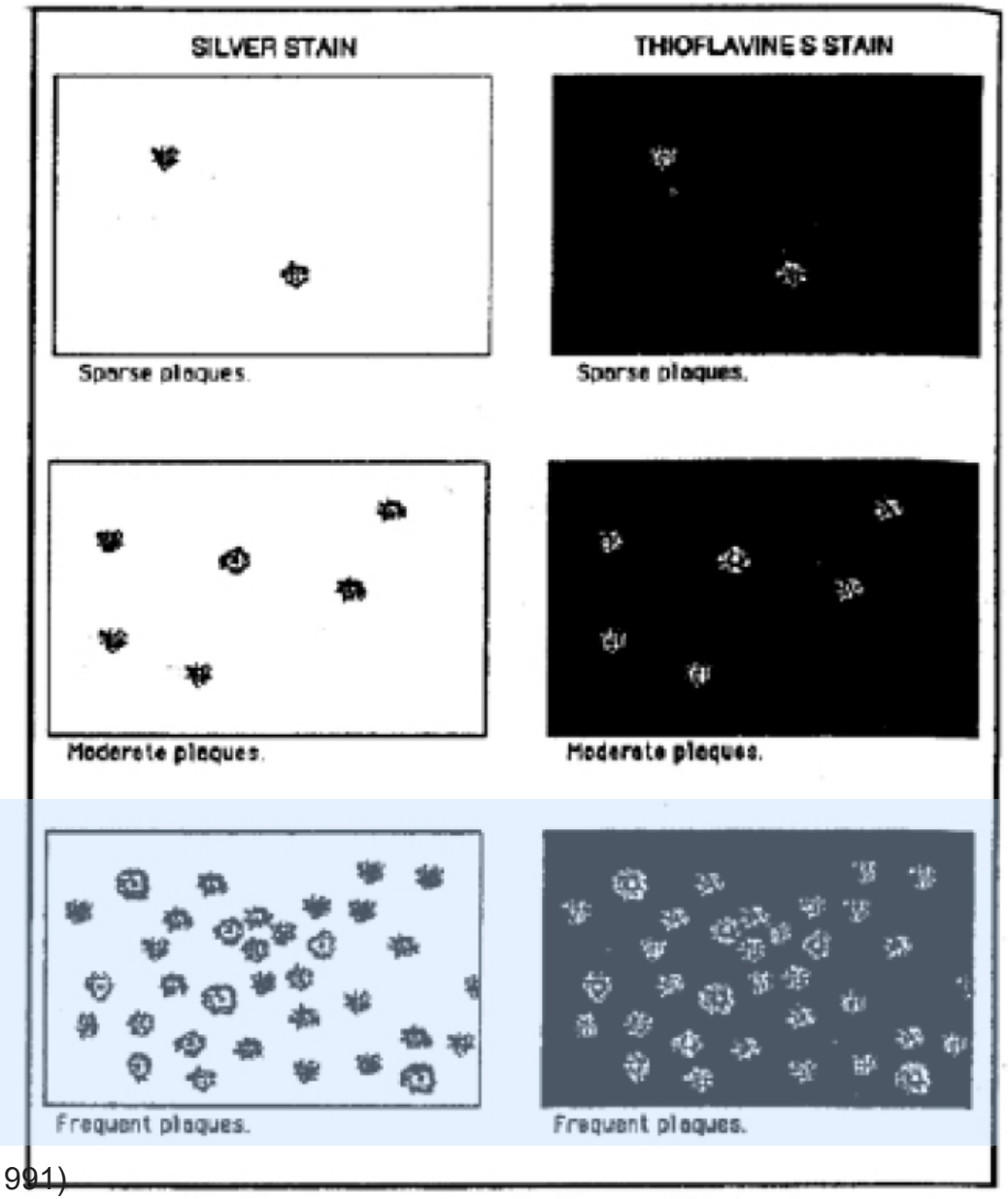
Braak et al. *Acta Neuropathol* (2006, 1991)

CERAD SCORE (C SCORE)

C1

C2

C3



Scoring only for **Neuritic plaques**

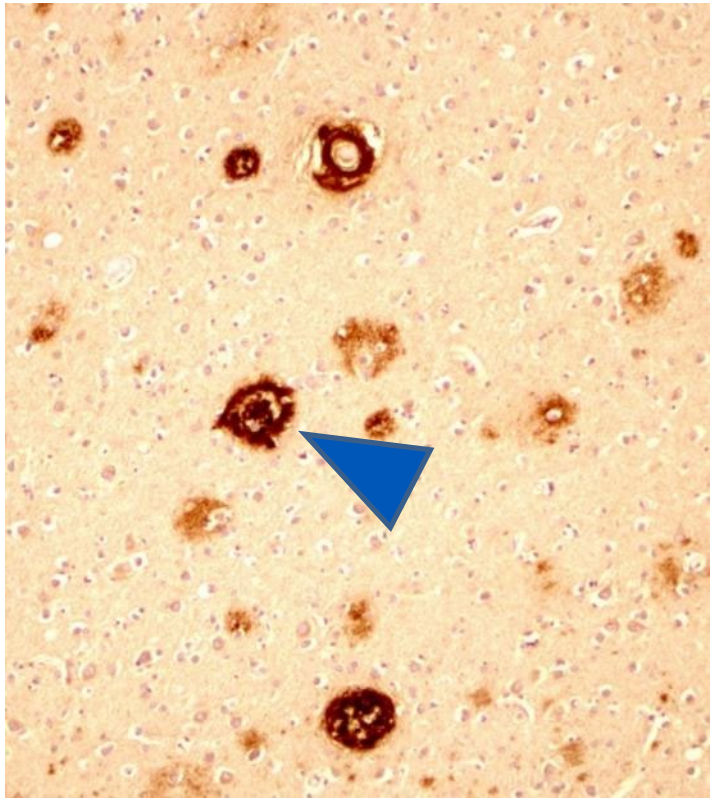


Figure 2. Senile plaques (neuritic) per 100× microscopic field. This cartoon provides a guide to semiquantitative assessment of plaque density per square millimeter.

CERAD *Neurology* (1991)

ALZHEIMER'S DISEASE NEUROPATHOLOGIC CHANGE

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

National Institute on Aging-Alzheimer's Association Consensus. *Alzheimers Dement* (2012)

ALZHEIMER'S DISEASE NEUROPATHOLOGIC CHANGE

2. Alzheimer disease neuropathologic changes: A3, B2, C3; Intermediate likelihood (National Institute on Aging-Alzheimer's Association Consensus, 2012)
   a. β-Amyloid plaque score: Thal phase 4 (of 5), A3
   b. Neuritic plaque score: CERAD Frequent ("C"), C3

REGION	Neuritic Plaques	Diffuse Plaques
Hippocampus	Moderate	Moderate
Entorhinal cortex	Moderate	Frequent
Middle frontal gyrus	Moderate	Frequent
Superior/middle temporal gyri	Moderate	Frequent
Inferior parietal lobule	Moderate	Frequent
Occipital lobe	Frequent	Frequent
Basal ganglia	Sparse	Moderate
Midbrain	N/A	Sparse
Cerebellum	N/A	None

   c. Neurofibrillary tangle stage: Braak stage IV (of VI), B2

REGION	Neurofibrillary Tangles	Pre-Tangles
Hippocampus	Moderate	Frequent
Entorhinal cortex	Moderate	Frequent
Middle frontal gyrus	None	Rare
Superior/middle temporal gyri	Moderate	Sparse
Inferior parietal lobule	None	Sparse
Occipital lobe	None	Rare
Midbrain	N/A	Rare

ADDITIONAL FINDINGS

2. *(contd.)*

   d. Amyloid angiopathy: present, cerebral and cerebellar parenchymal and leptomeningeal vessels, mild to moderate
   e. Hippocampal sclerosis: absent; No TDP-43-immunoreactive lesions
3. Cerebrovascular disease:
   a. Arteriolosclerosis: Mild with perivascular tissue rarefaction
   b. Atherosclerosis: Absent
4. Vascular brain injury: absent
5. Global moderate cerebral atrophy; brain weight (unfixed): 1260 grams

DIFFUSE LEWY BODY PROBABILITY

Table 3 *Assessment of the likelihood that the pathologic findings are associated with a DLB clinical syndrome*

	Alzheimer type pathology		
	NIA-Reagan Low (Braak stage 0–II)	NIA-Reagan Intermediate (Braak stage III–IV)	NIA-Reagan High (Braak stage V–VI)
Lewy body type pathology			
Brainstem-predominant	Low	Low	Low
Limbic (transitional)	High	Intermediate	Low
Diffuse neocortical	High	High	Intermediate

DLB = dementia with Lewy bodies; NIA = National Institute on Aging.

Third consensus report of the DLB Consortium. *Neurology* (2005)

FINAL DIAGNOSIS

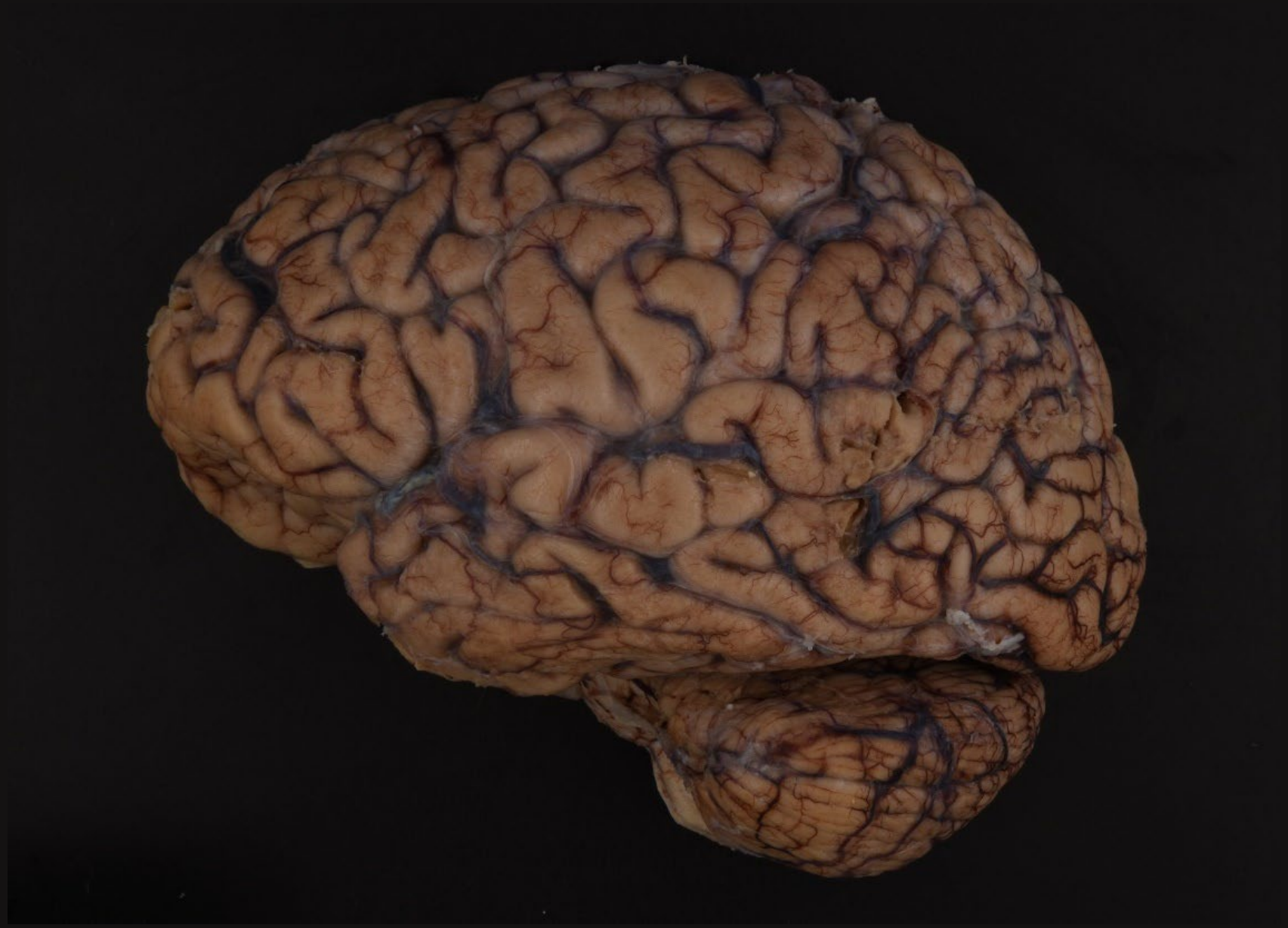
1. Lewy body disease: diffuse neocortical type with moderate substantia nigra neuronal loss and gliosis
2. Alzheimer's disease neuropathologic change: A3, B2, C3; Intermediate likelihood
3. Cerebrovascular disease
    1. Arteriolosclerosis: mild to focally moderate with perivascular tissue rarefaction
    2. Atherosclerosis: none
4. Vascular brain injury: absent
5. Additional findings:
    1. Amyloid angiopathy: present, mild; cerebral and cerebellar parenchyma and leptomeningeal vessels
    2. Hippocampal sclerosis: absent

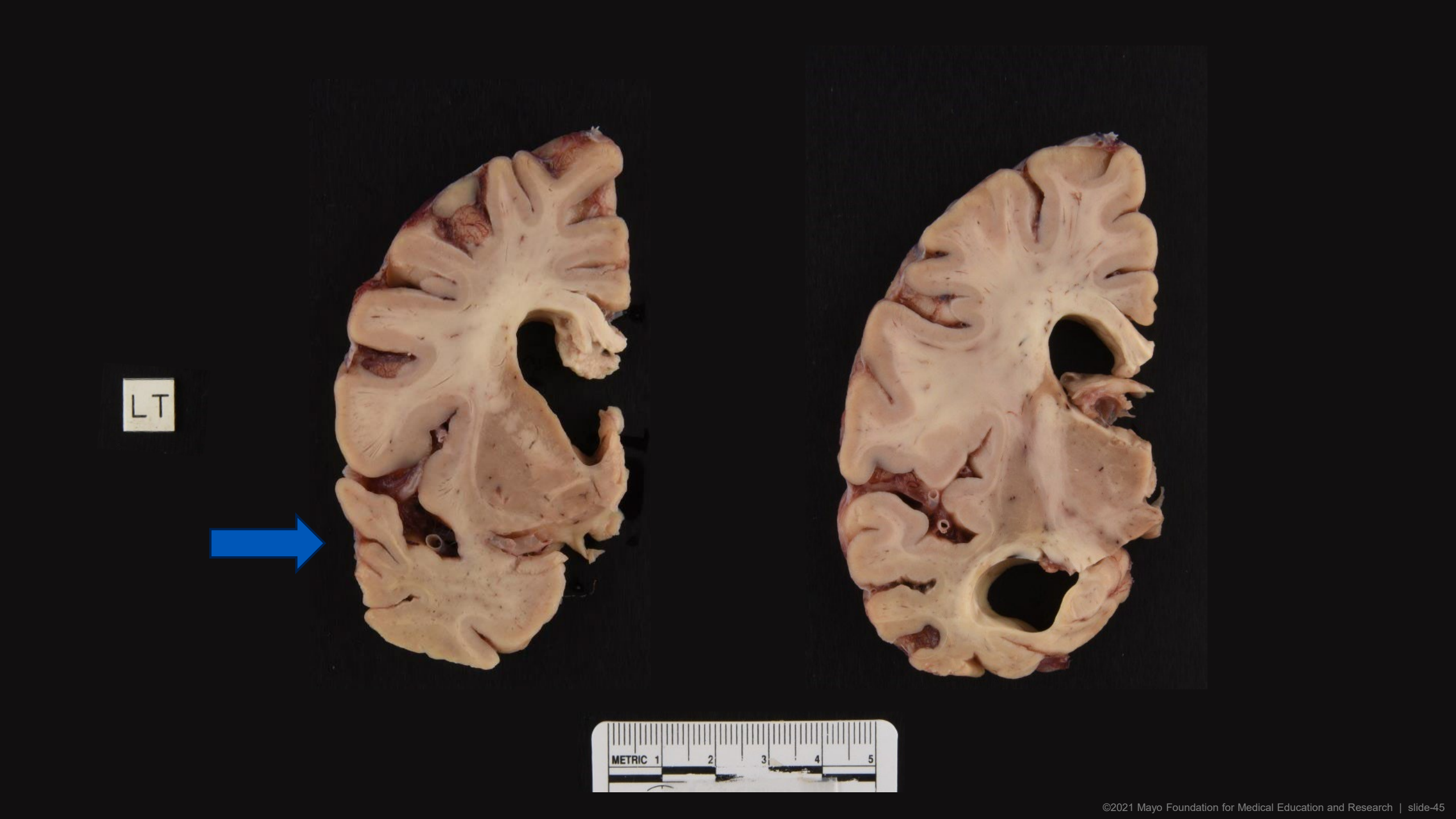
KEY POINTS

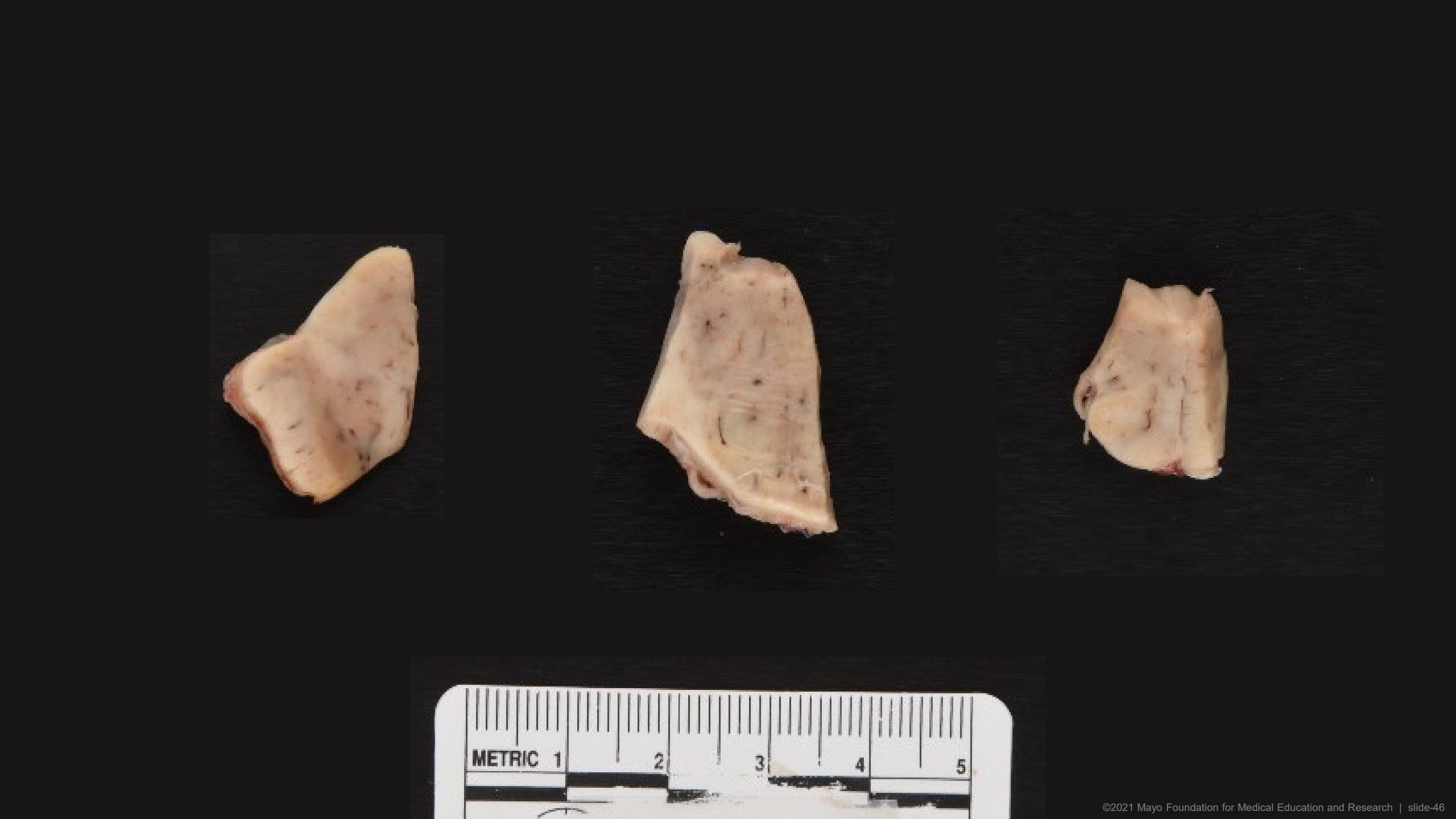
1. Review **neuropathologic approach** to neurodegenerative cases
2. Review **Lewy Body Disease** as a neuropathologic entity
3. Review **Alzheimer's disease neuropathologic change (ADNC)**
4. Understand the importance of **clinicopathologic correlation** in neurodegenerative cases

CASE #2 CLINICAL HISTORY

- 74-year-old male who died with an at least seven-year history of REM sleep disturbance with neurocognitive decline.
- Pertinent **family history** includes a mother and aunt who both had dementia.
- **REM sleep disorder** was first noticed and was characterized by dream enactment and jumping out of bed with resulting injury.
- He was later noted to have **mild motor** (left greater than right upper extremity tremors) and autonomic symptoms.
- He also demonstrated signs of **non-amnestic cognitive impairment** but was overall high functioning.
- Later showed progressive decline in ambulation, increased stiffness, weight loss, decreased speech, and urinary incontinence.



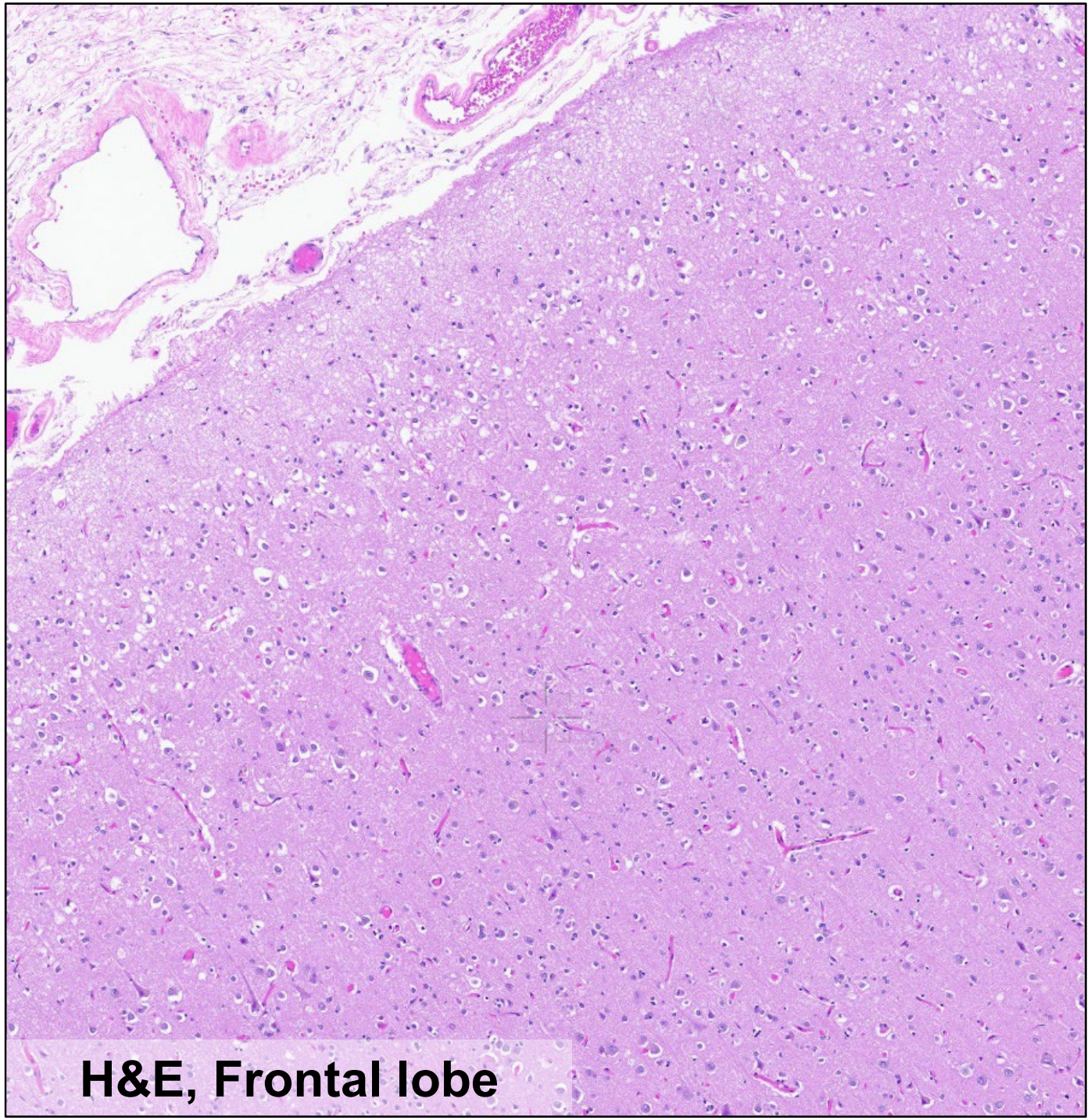




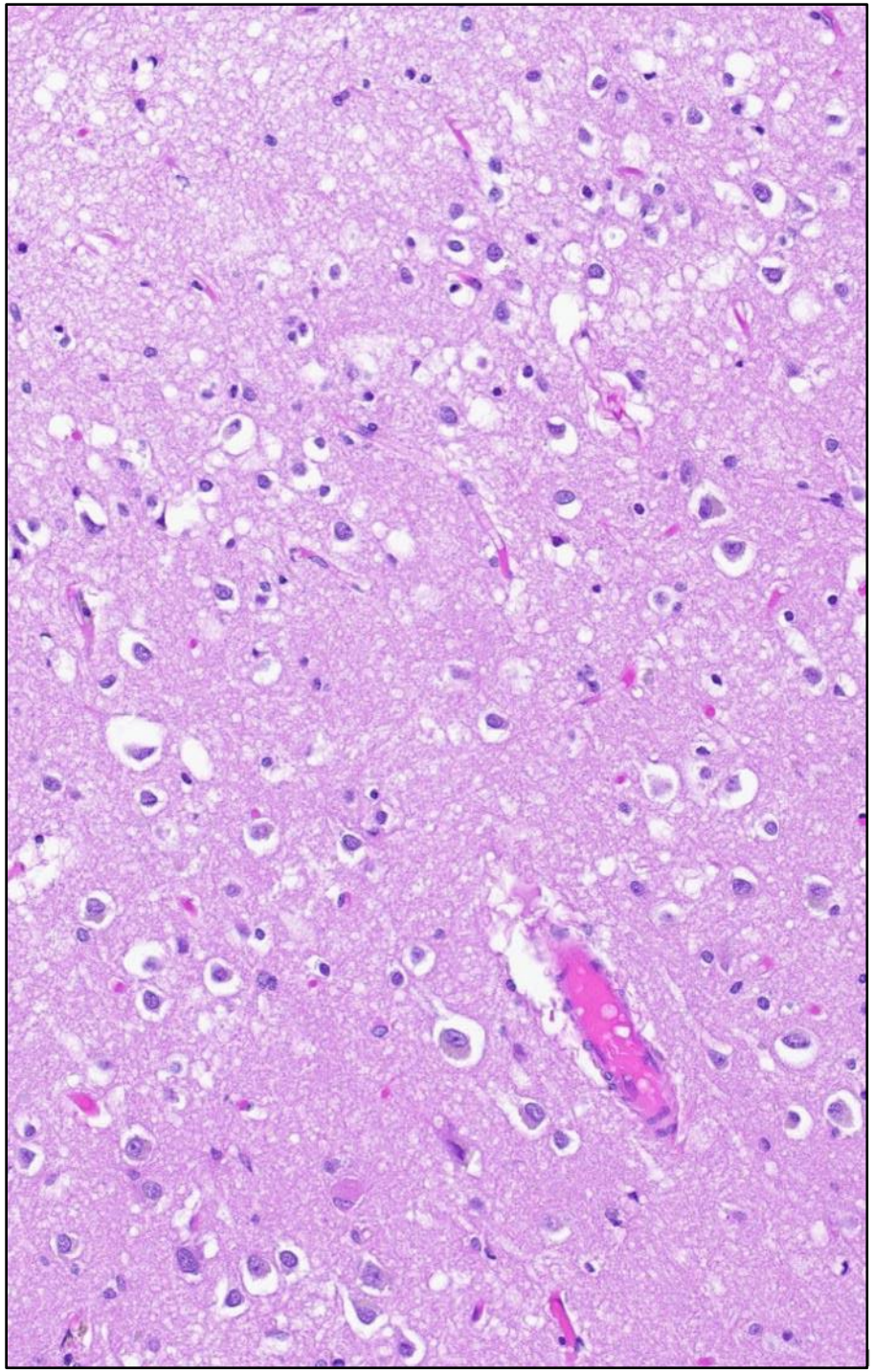
HISTOLOGIC FINDINGS

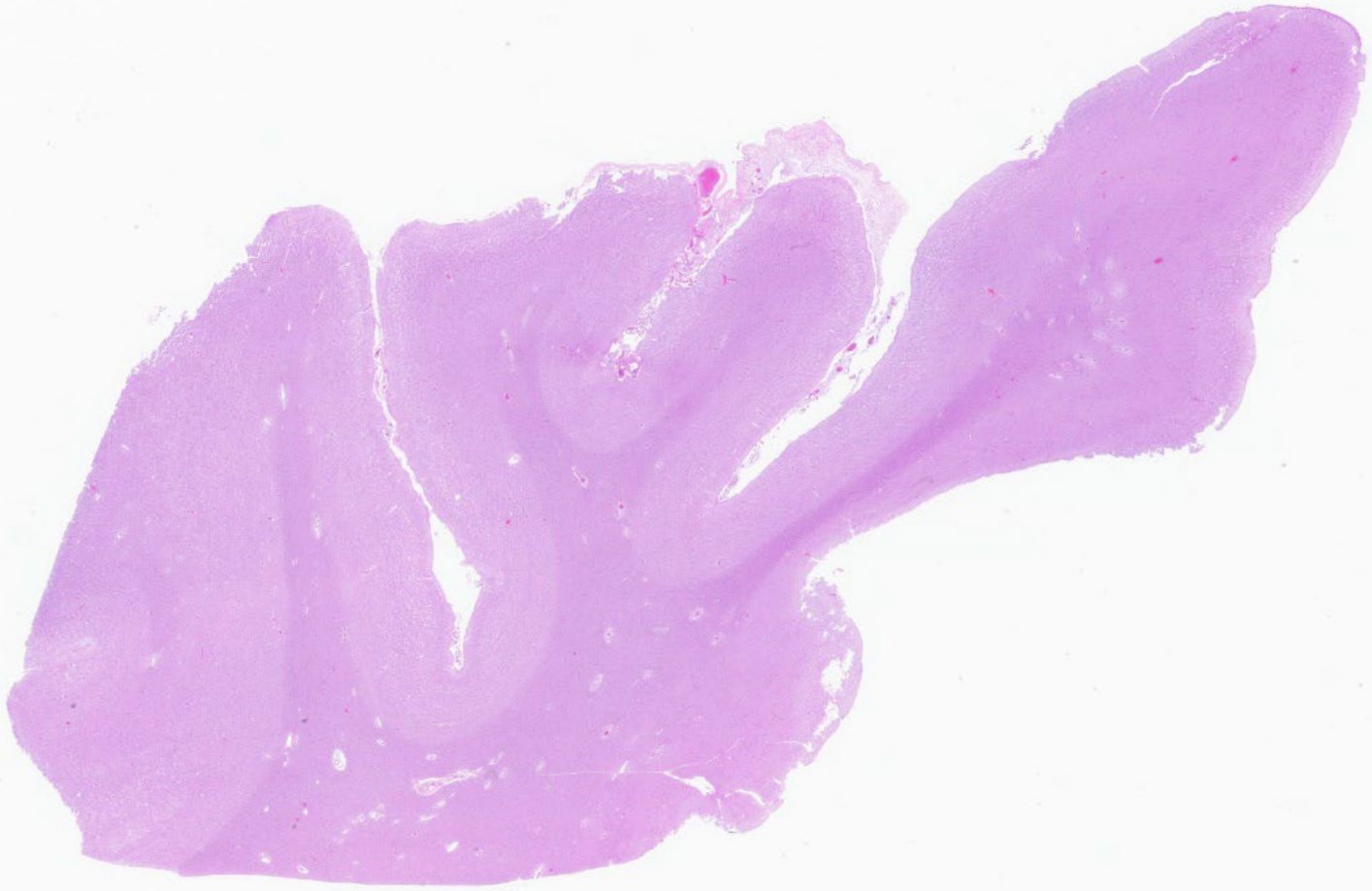
AND ANCILLARY STAINS

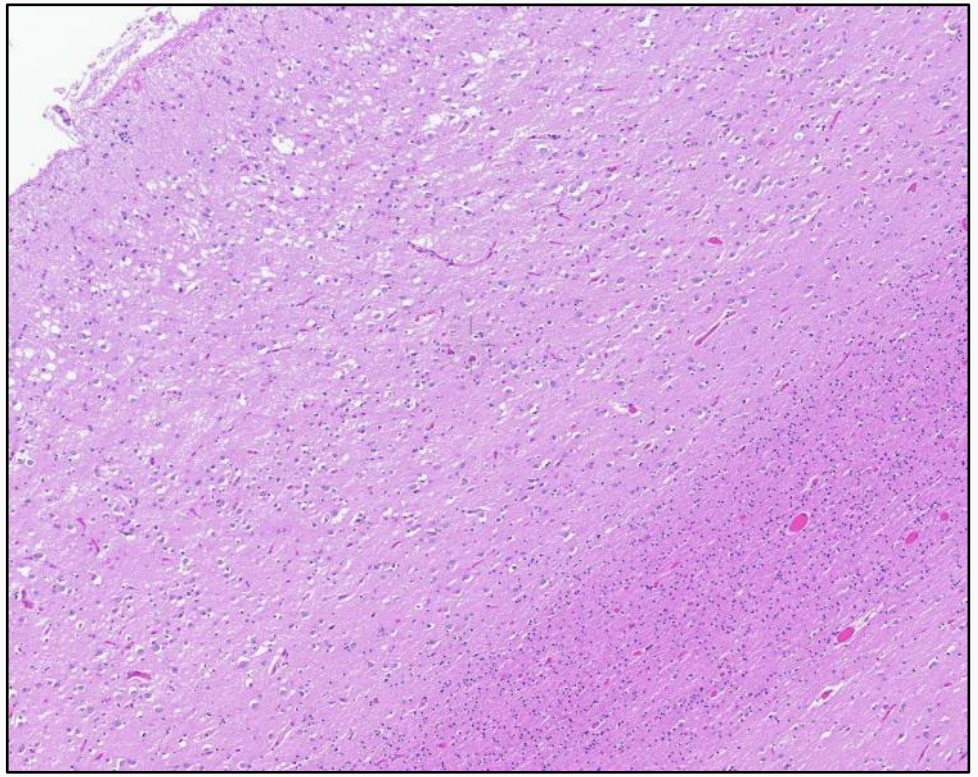
- H&E
- Tau
- Beta-amyloid
- Alpha-synuclein
- TDP-43
- Bielschowsky

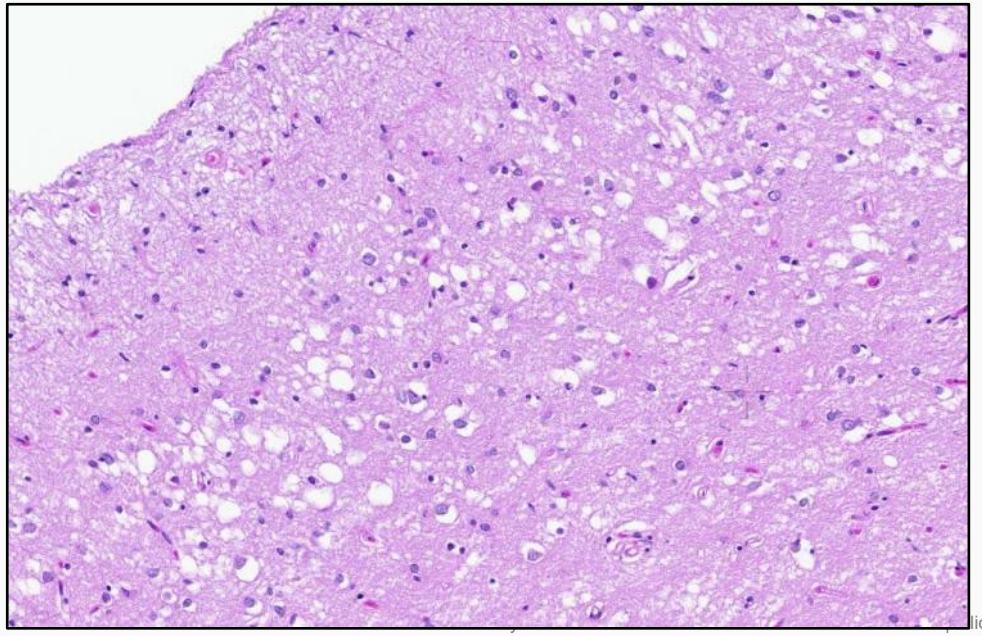


H&E, Frontal lobe

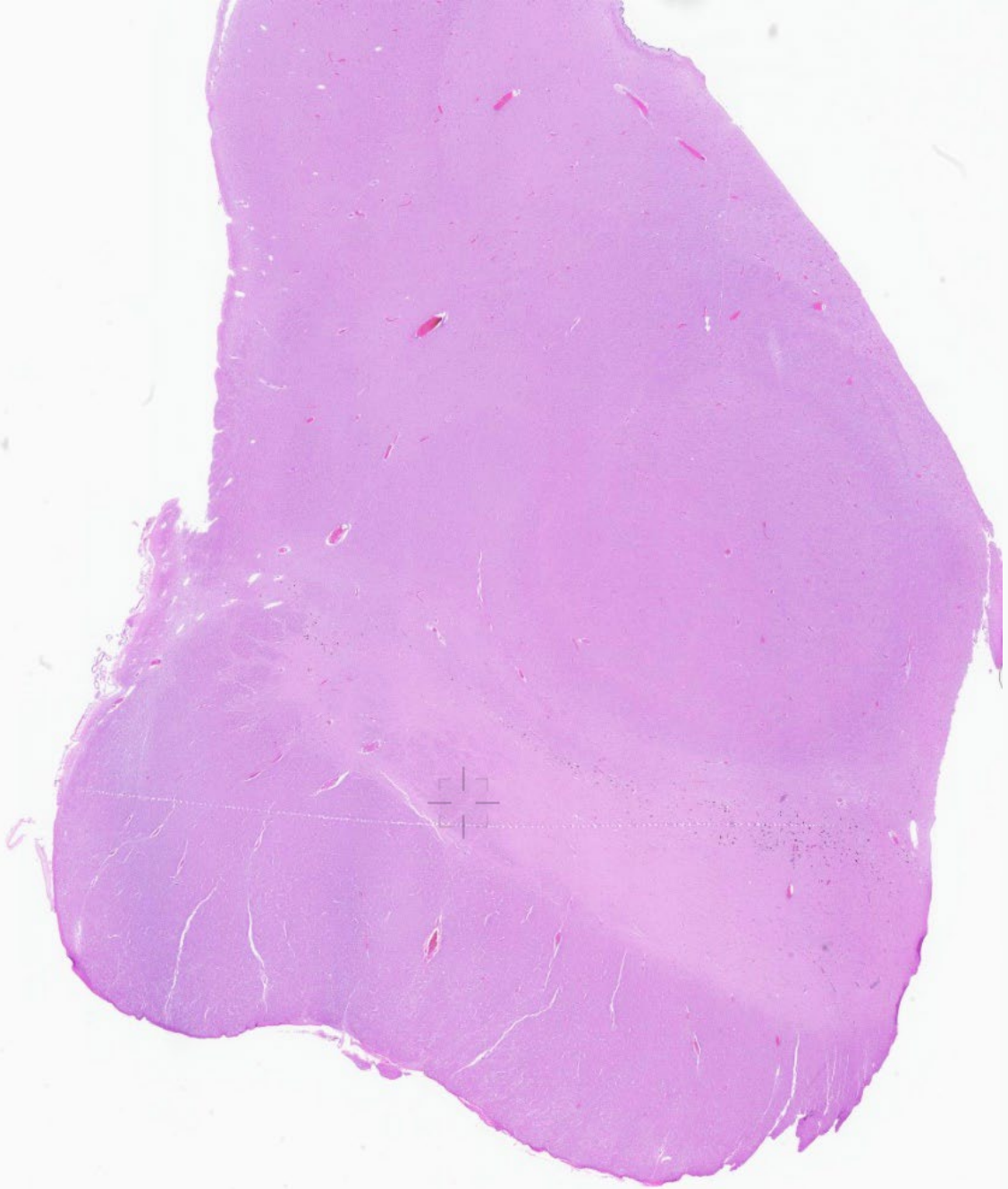


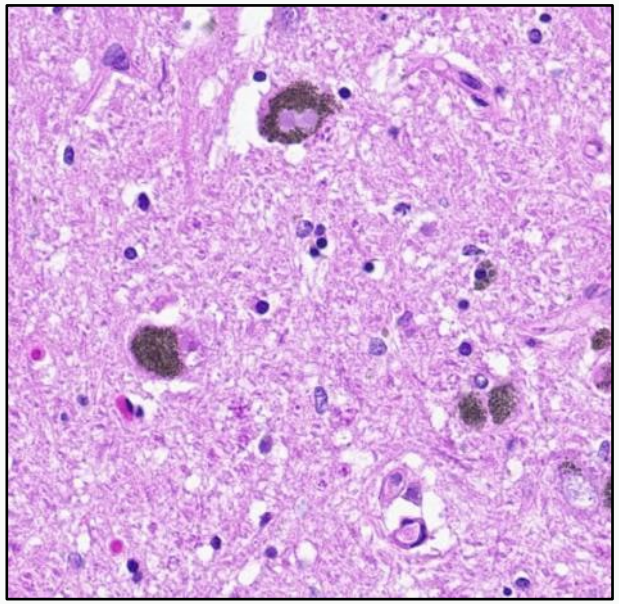


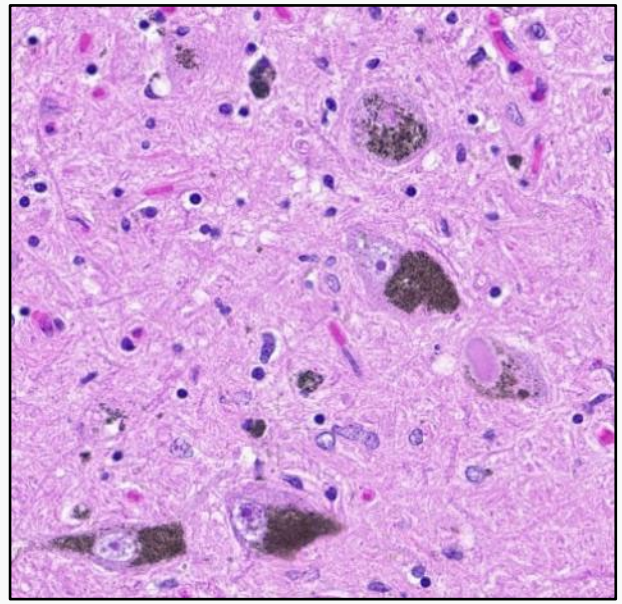


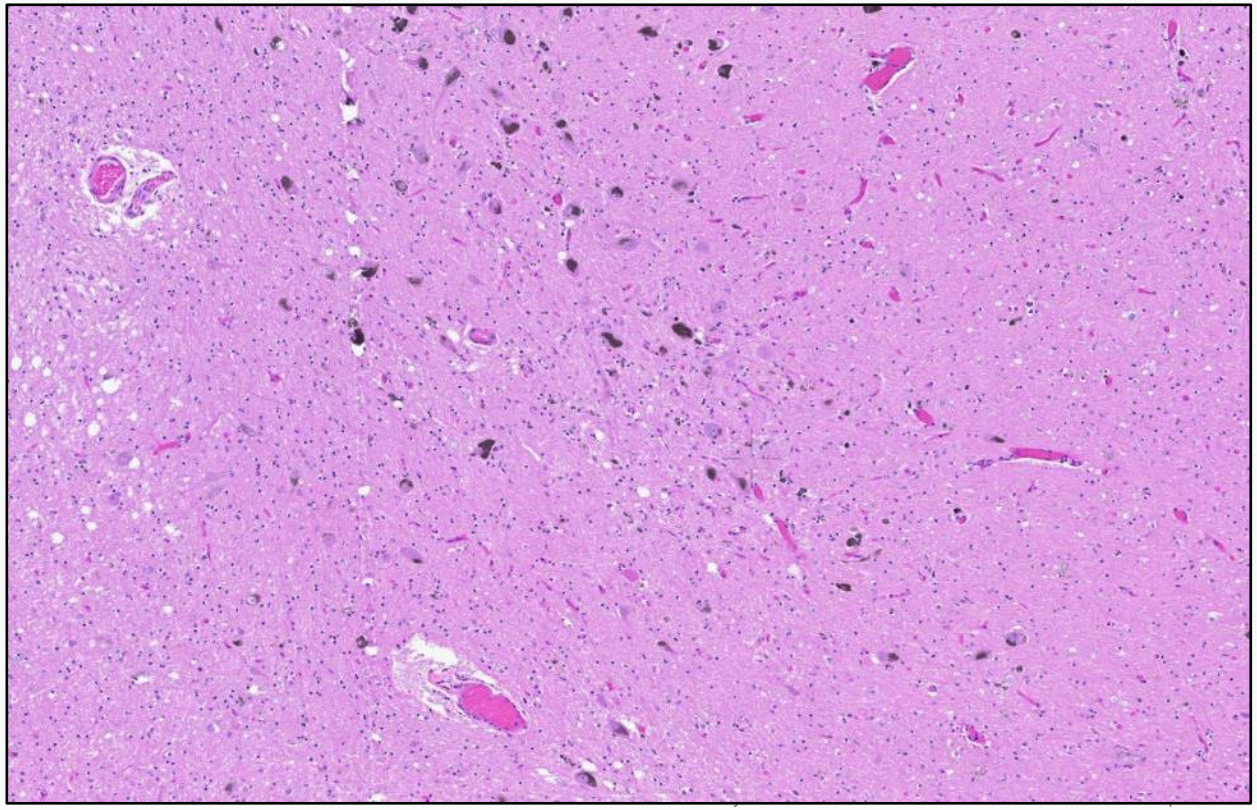


H&E, Temporal lobe





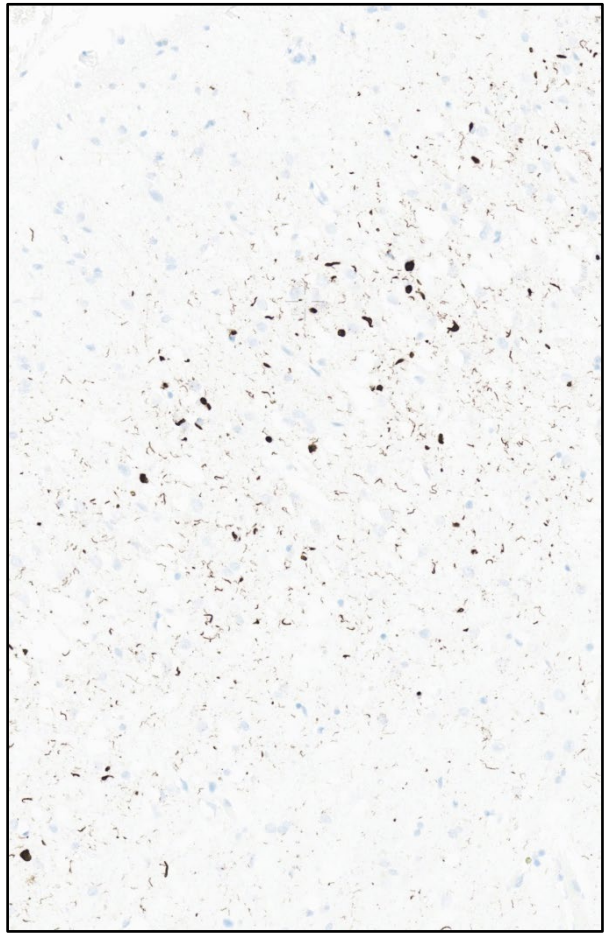




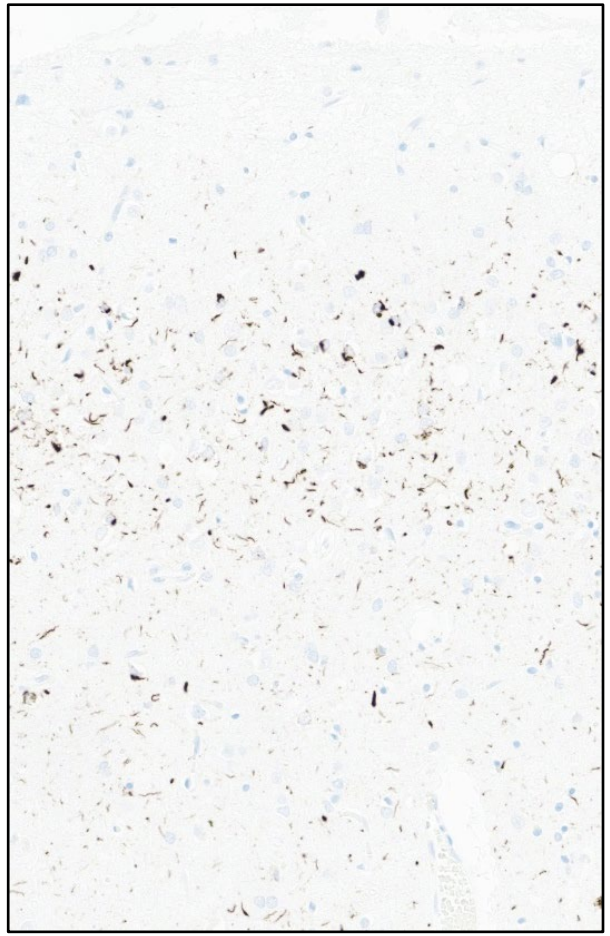
H&E, Midbrain

TDP-43

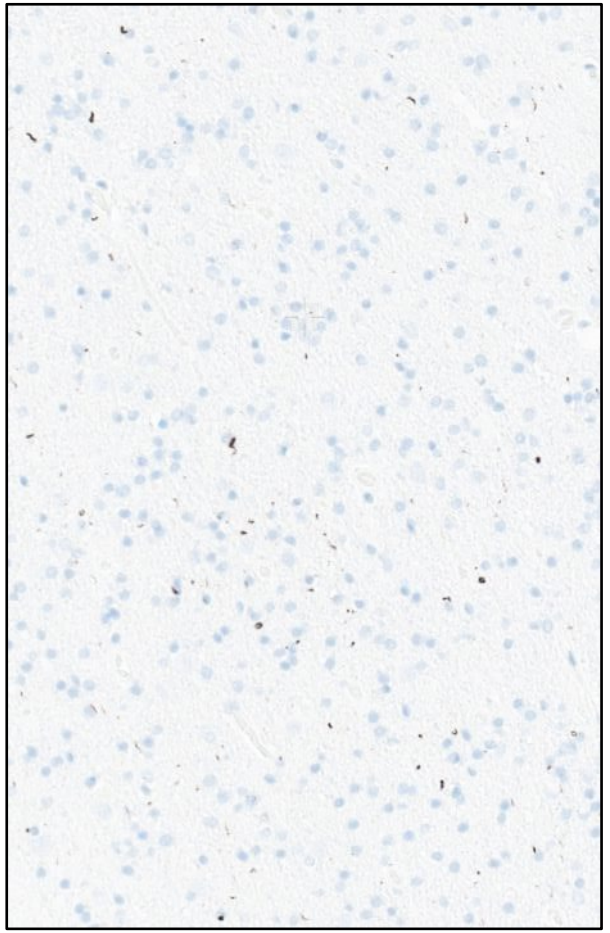
Frontal lobe



Frontal lobe
Grey Matter

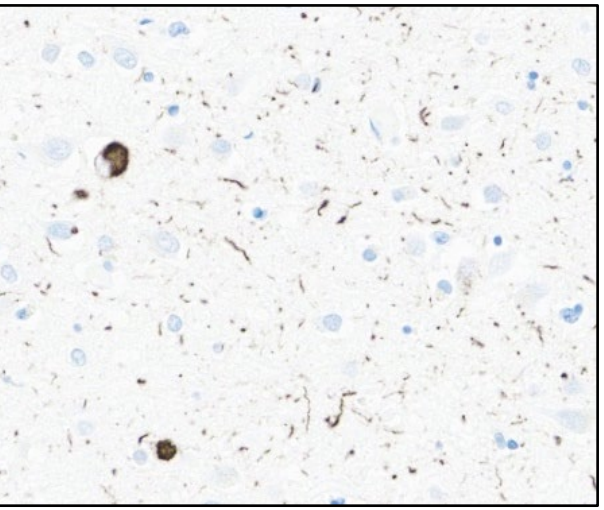


Temporal lobe
Grey Matter

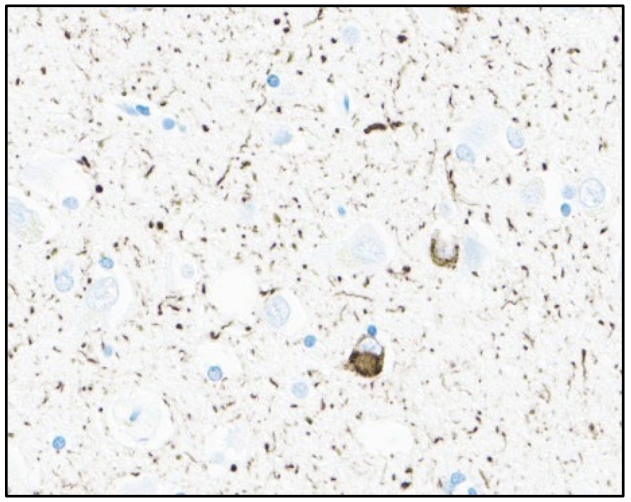


Temporal lobe
White Matter

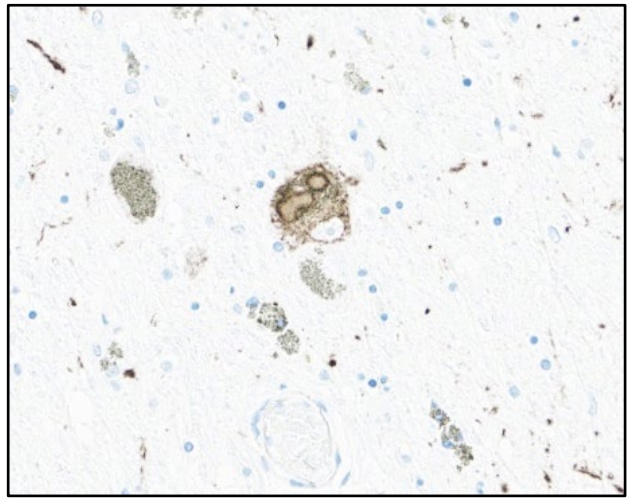
ALPHA-SYNUCLEIN



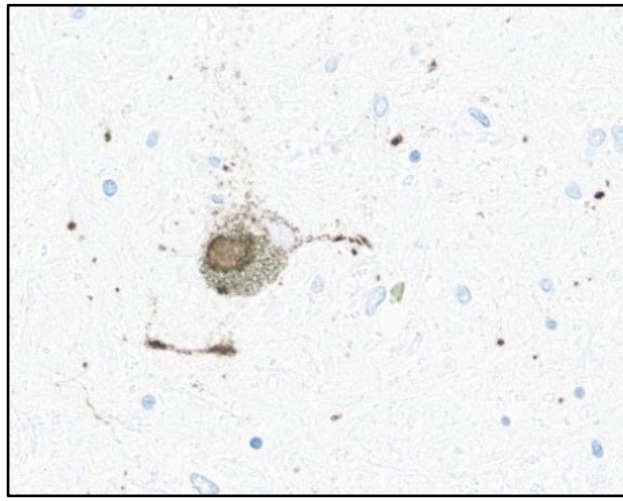
Frontal lobe



Amygdala



Substantia Nigra



Locus Ceruleus

GROSS FINDINGS

- Severe atrophy of temporal lobe
- Severe hydrocephalus ex-vacuo
- Marked depigmentation of the substantia nigra

MICROSCOPIC FINDINGS

- Moderate superficial spongiosis, predominantly involving temporal > frontal lobes

ANCILLARY STUDIES

- Tau
- Beta-amyloid
- **Alpha-synuclein**
- **TDP-43**
- Bielschowsky stain

NEUROPATH DIAGNOSES

FINAL DIAGNOSIS

1. Frontotemporal dementia with TDP-43 inclusions (FTLD-TDP)
2. Lewy body disease
3. Cerebrovascular disease
    1. Arteriolosclerosis: moderate with perivascular tissue rarefaction
    2. Atherosclerosis: none
4. Vascular brain injury: absent

NEURODEGENERATIVE DISEASE OVERVIEW

DISEASE	LESIONS	COMPONENTS
Alzheimer's Disease	Extracellular plaques Neurofibrillary tangles	Amyloid Tau
Parkinson's Disease Dementia with Lewy Bodies	Lewy bodies Lewy neurites	Alpha-synuclein
Multiple System Atrophy	Glial cytoplasmic inclusions	Alpha-synuclein
FTLD-Tau (e.g., Pick's disease, PSP, CBD)	Neuronal and glial tangles	Tau
FTLD-TDP	Cytoplasmic and nuclear inclusions	TDP-43
Amyotrophic Lateral Sclerosis	Cytoplasmic inclusions	TDP-43
Trinucleotide Repeat Diseases (e.g., Huntington's Disease)	Nuclear and cytoplasmic inclusions	Polyglutamine expansion
Chronic Traumatic Encephalopathy	Neuronal and glial tangles	Tau

Adapted from slide originally created by Dr. Edward Lee (UPenn)

NEURODEGENERATIVE DISEASE OVERVIEW

DISEASE	LESIONS	COMPONENTS
Alzheimer's Disease	Extracellular plaques Neurofibrillary tangles	Amyloid Tau
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Multiple System Atrophy	Glial cytoplasmic inclusions	Alpha-synuclein
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FTLD-TDP	Cytoplasmic and nuclear inclusions	TDP-43
Amyotrophic Lateral Sclerosis	Cytoplasmic inclusions	TDP-43
Trinucleotide Repeat Diseases (e.g., Huntington's Disease)	Nuclear and cytoplasmic inclusions	Polyglutamine expansion
Chronic Traumatic Encephalopathy	Neuronal and glial tangles	Tau

Adapted from slide originally created by Dr. Edward Lee (UPenn)

Clinical Subtypes

Behavioral Variant (bvFTD)

Primary Progressive Aphasia

- Primary non-fluent aphasia (PNFA)
- Semantic Dementia (SD)
- Logopenic variant

Pathologic Subtypes

FTLD-Tau

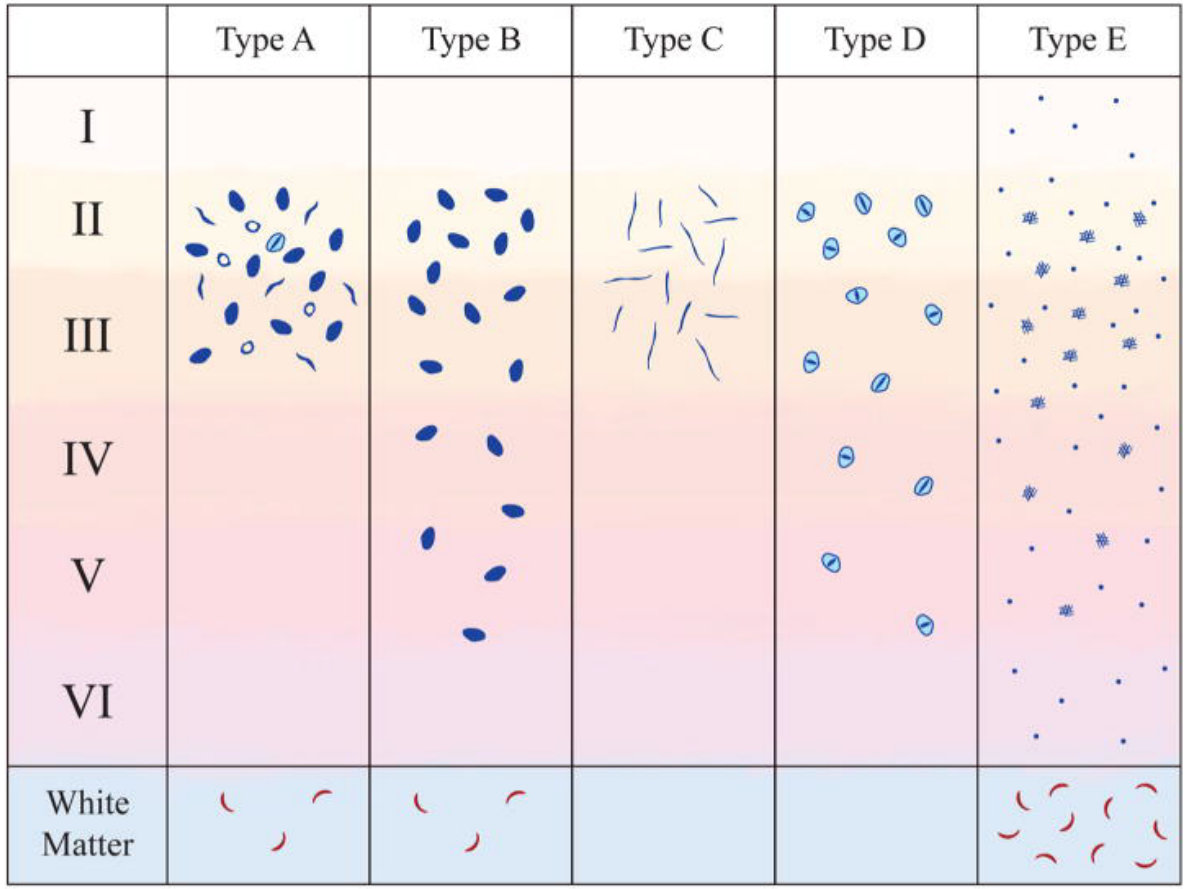
- PSP
- CBD
- Pick's disease
- FTDP-17
- Tauopathy, NOS

FTLD-TDP-43

- A-E subtypes
- ALS-FTLD

Other

- FTLD-FUS
- FTLD-UPS
- FTLD-ni

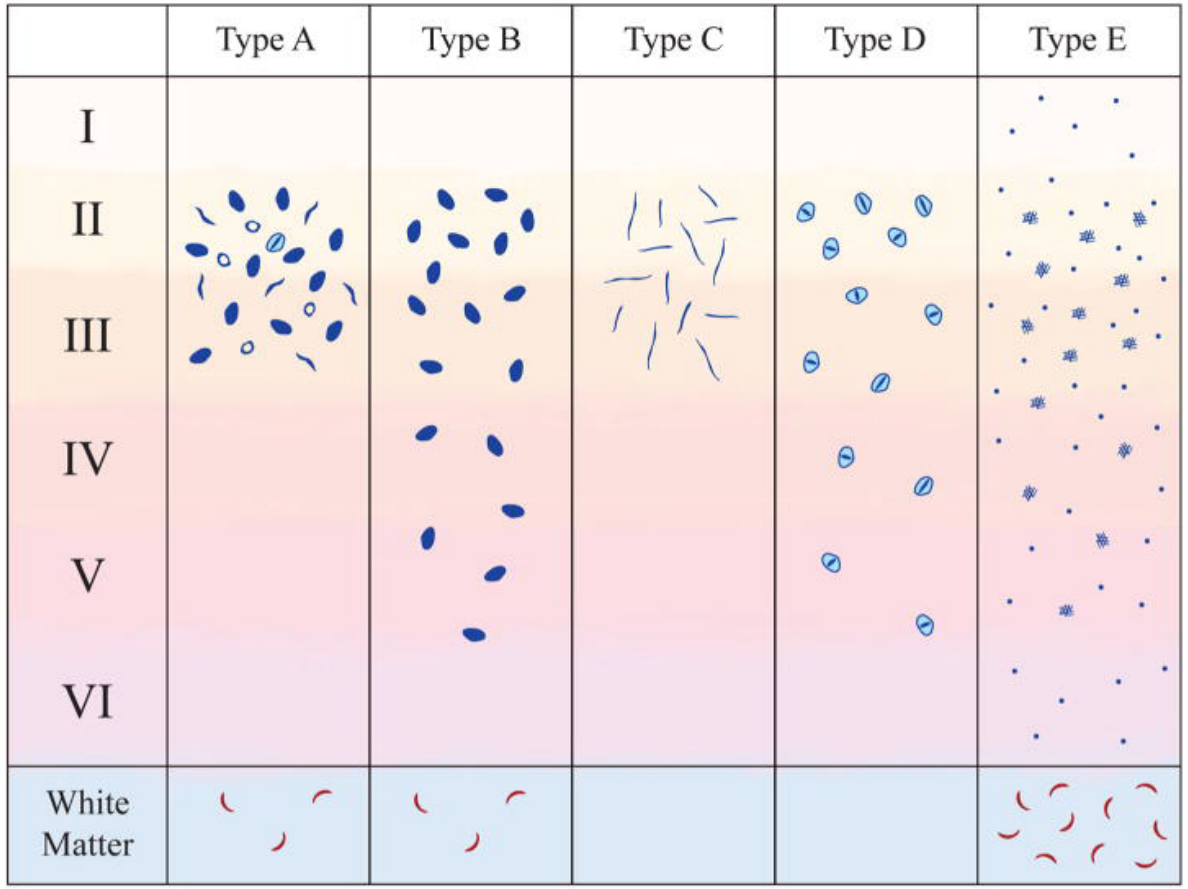


	Type A	Type B	Type C	Type D	Type E
Cortical Pathology	• NCI's including ring inclusions • Short DN's • +/- Lentiform NII's • +/- Oligo inclusions • Superficial	• NCI's • Few DN's • +/- Oligo inclusions • Superficial and deep	• Long DN's • Few NCI's • Superficial	• Lentiform NII's • Few NCI's • Superficial and deep	• GFNI's • Grains • Cuvilinear oligodendroglial inclusions • Superficial and deep
Common Phenotype	bvFTD naPPA	bvFTD +/- MND	svPPA bvFTD	IBMPFD-ALS	bvFTD
Genetic Associations	*GRN* mutations	*C9orf72* mutations	None	*VCP* mutations	Uncertain

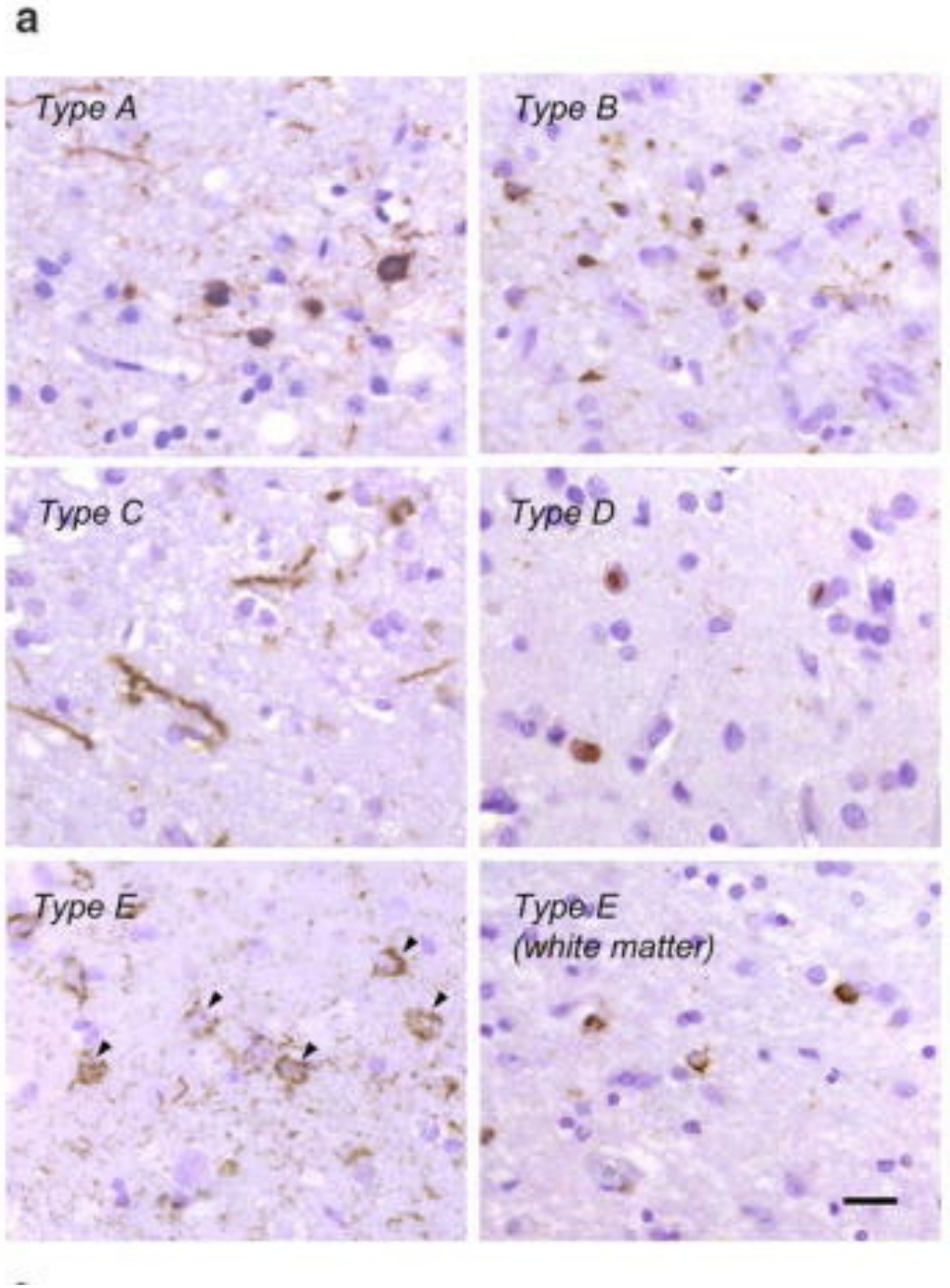
FTLD-TDP TYPES

- Types A-E
- Cortical pathology
  - Evaluate superficial vs. deep
  - Evaluate forms
- White matter pathology
- Commonly associated clinical phenotypes
- Genetic associations

Lee, EB et al. Acta Neuropathol (2017) 134(1):65-78.



	Type A	Type B	Type C	Type D	Type E
Cortical Pathology	• NCI's including ring inclusions • Short DN's • +/- Lentiform NII's • +/- Oligo inclusions • Superficial	• NCI's • Few DN's • +/- Oligo inclusions • Superficial and deep	• Long DN's • Few NCI's • Superficial	• Lentiform NII's • Few NCI's • Superficial and deep	• GFNI's • Grains • Cuvilinear oligodendroglial inclusions • Superficial and deep
Common Phenotype	bvFTD naPPA	bvFTD +/- MND	svPPA bvFTD	IBMPFD-ALS	bvFTD
Genetic Associations	*GRN* mutations	*C9orf72* mutations	None	*VCP* mutations	Uncertain



Lee, EB et al. Acta Neuropathol (2017) 134(1):65-78.

LEWY BODY DISEASE TYPES

Table 2 *Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

Brain regions are as defined anatomically in the original Consensus report.[1]

IX = 9th cranial nerve nucleus; X = 10th cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert.

Third consensus report of the DLB Consortium. *Neurology* (2005)

FINAL DIAGNOSIS

1. Frontotemporal dementia with TDP-43 inclusions (FTLD-TDP)
2. Lewy body disease
3. Cerebrovascular disease
    1. Arteriolosclerosis: moderate with perivascular tissue rarefaction
    2. Atherosclerosis: none
4. Vascular brain injury: absent

FINAL DIAGNOSIS

1. Frontotemporal dementia with TDP-43 inclusions (FTLD-TDP): most consistent with Type A

   Note: the decedent had a GRN mutation

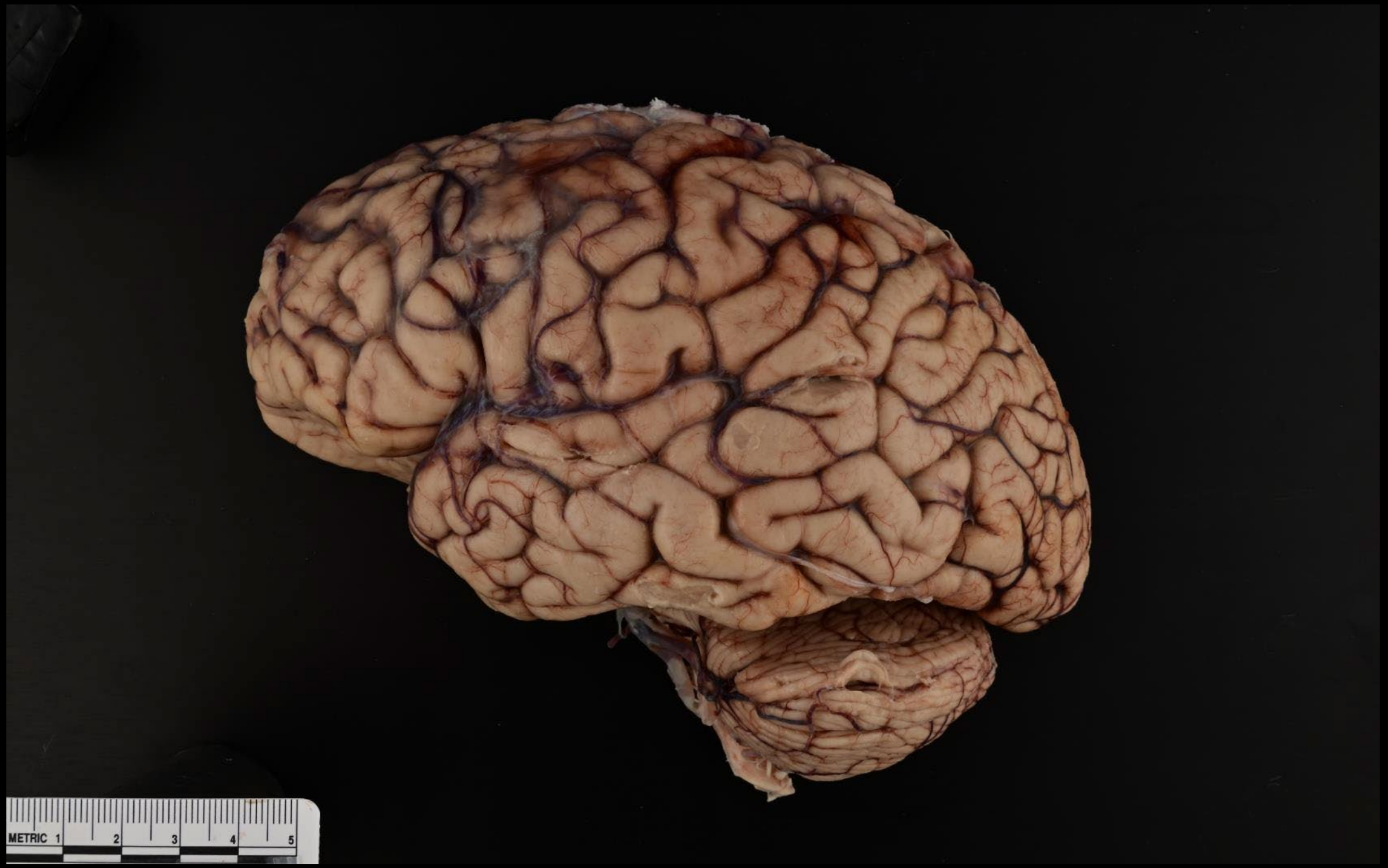
1. Lewy body disease: diffuse neocortical type with moderate substantia nigra neuronal loss and gliosis
2. Cerebrovascular disease
   1. Arteriolosclerosis: moderate with perivascular tissue rarefaction
   2. Atherosclerosis: none
3. Vascular brain injury: absent

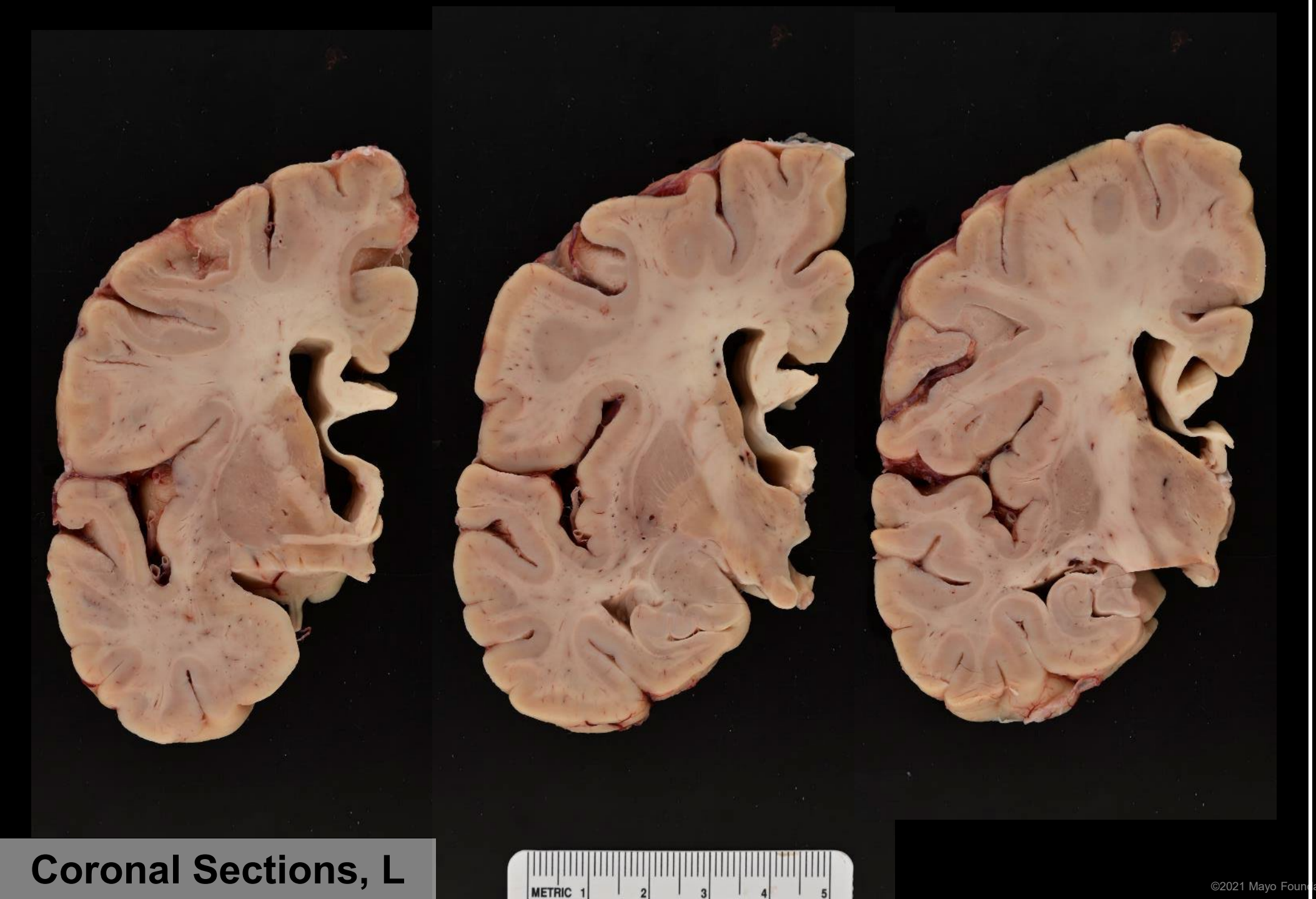
KEY POINTS

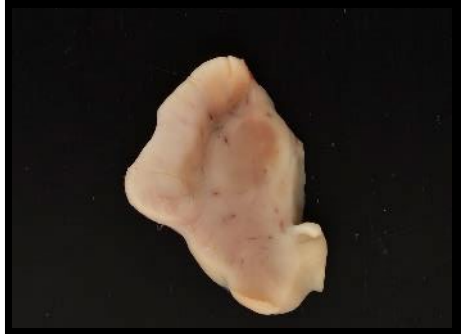
1. Review **neuropathologic approach** to neurodegenerative cases
2. Review **FTLD-TDP** as a neuropathologic entity
3. Understand the importance of **clinicopathologic correlation** in neurodegenerative cases

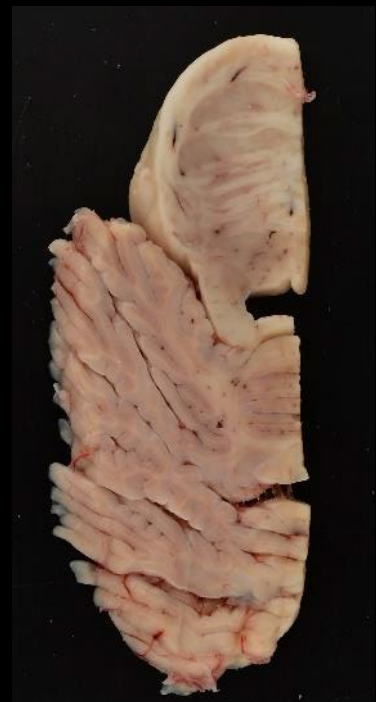
CASE #3 CLINICAL HISTORY

- 73-year-old female first presented with feeling “absent-minded” and “disconnected.” Kokmen short test was unrevealing (36/38), and MRI was within normal limits.
- The following year, she began to develop personality changes (obsessive and compulsive behaviors), predilection for sweet foods, showed little verbal output, and was disoriented to time and place.
- Physical exam revealed marked bradykinesia, slow eye movements but with intact vertical and horizontal gaze, slowed and unsteady gait, and mild rigidity.
- FDG-PET imaging showed severe frontal hypometabolism, most marked in the right superior frontal region.
- Near the end of her life, she demonstrated almost no verbal output.

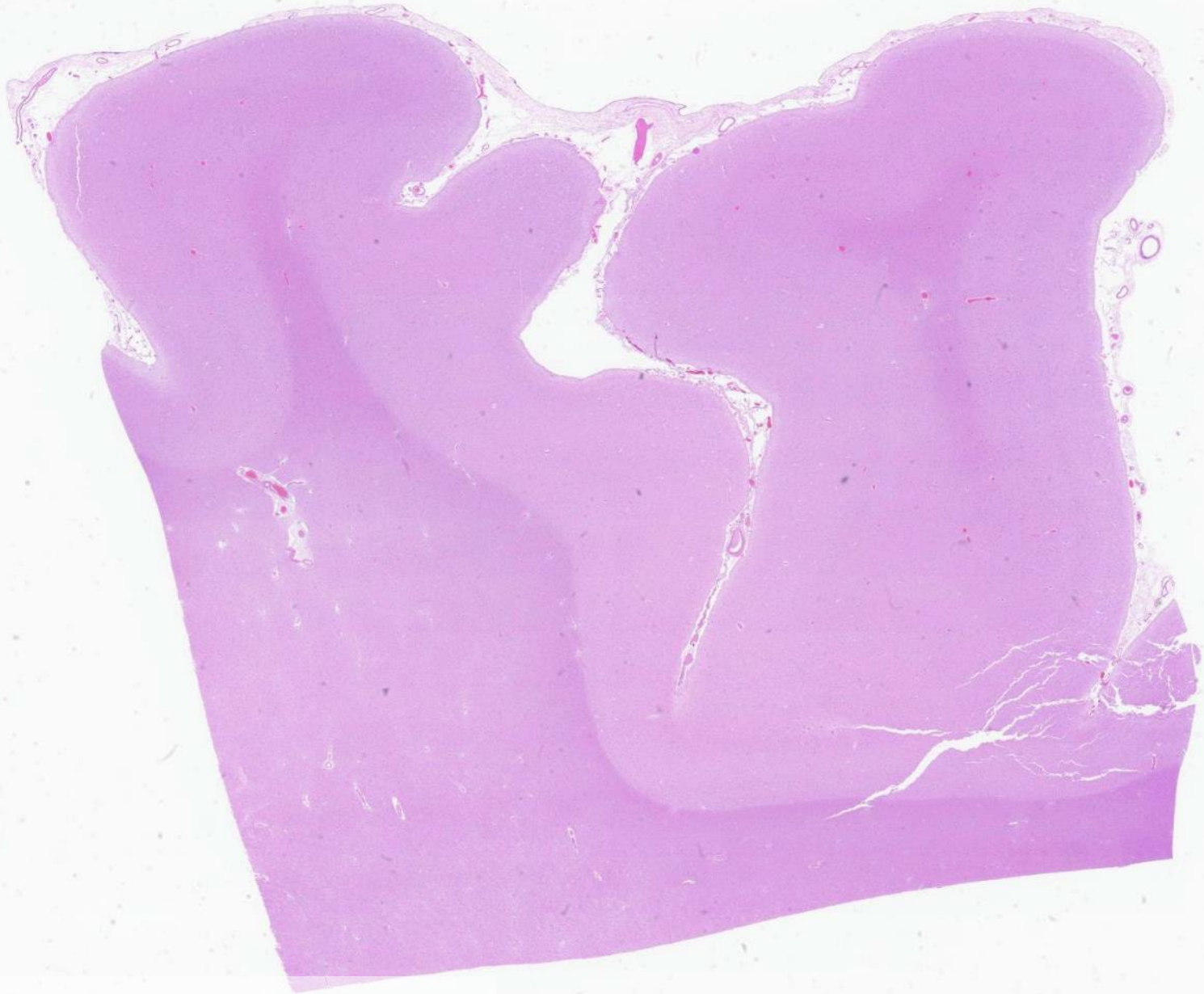


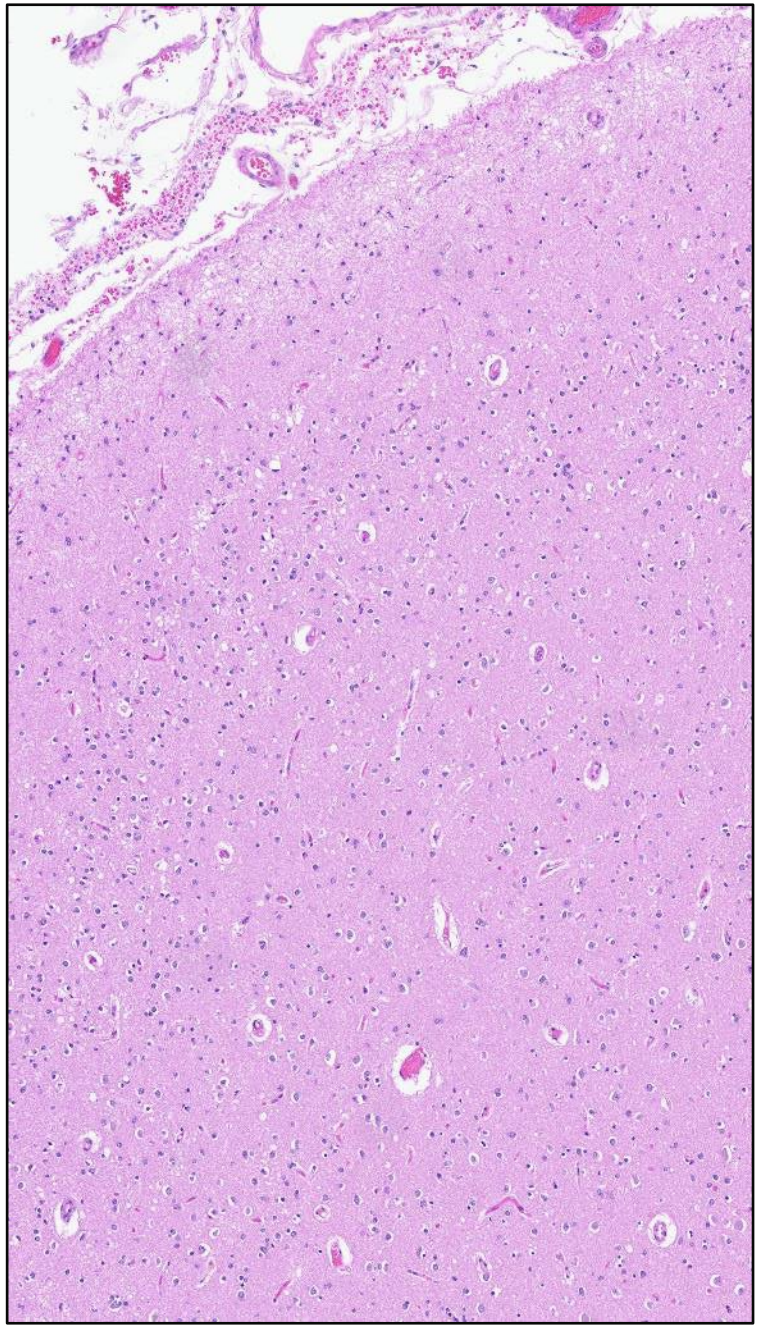




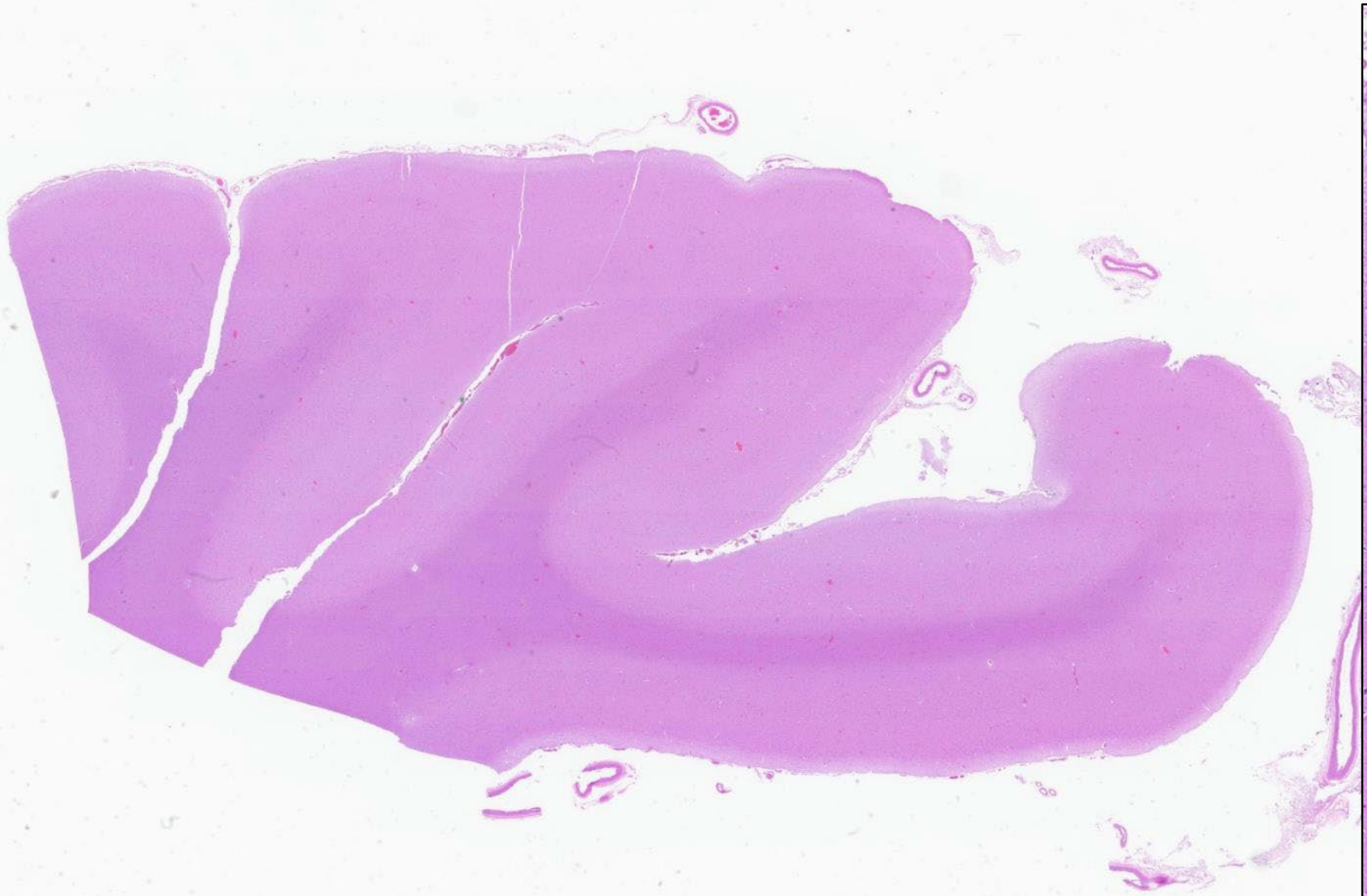


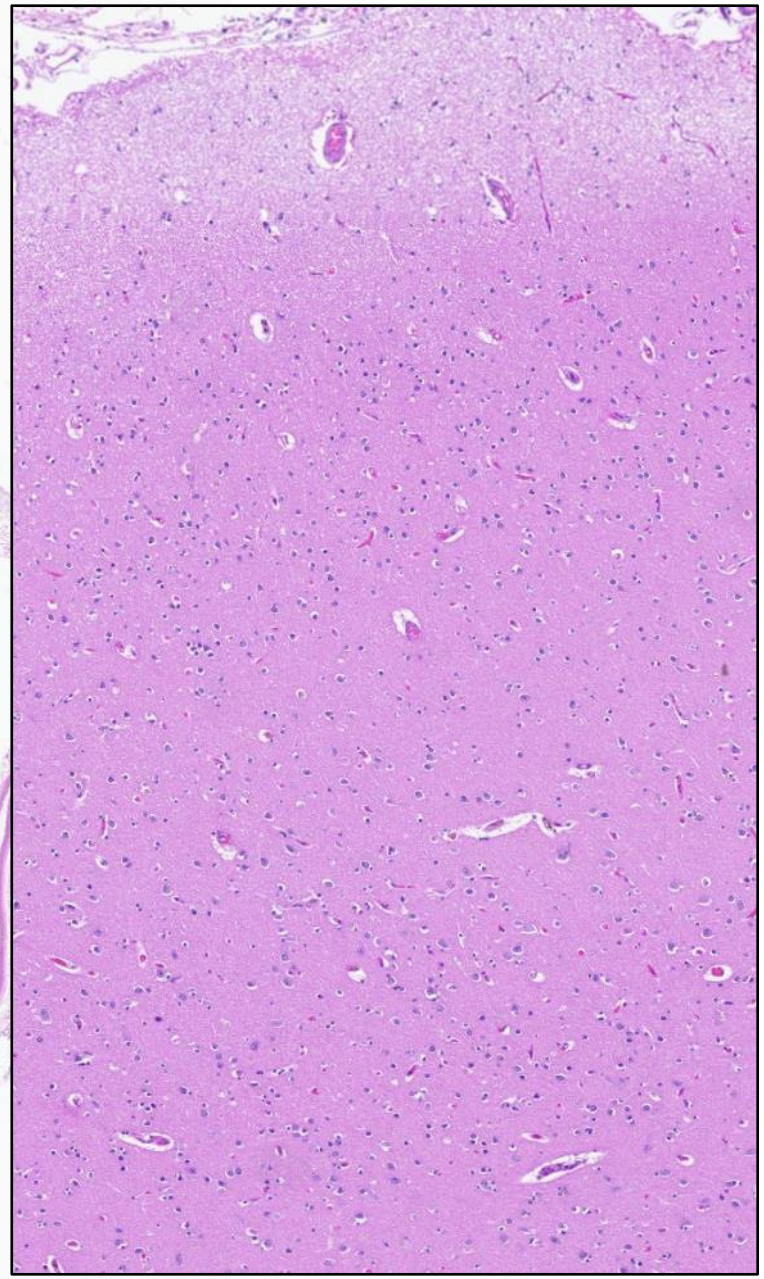
Coronal Sections, L



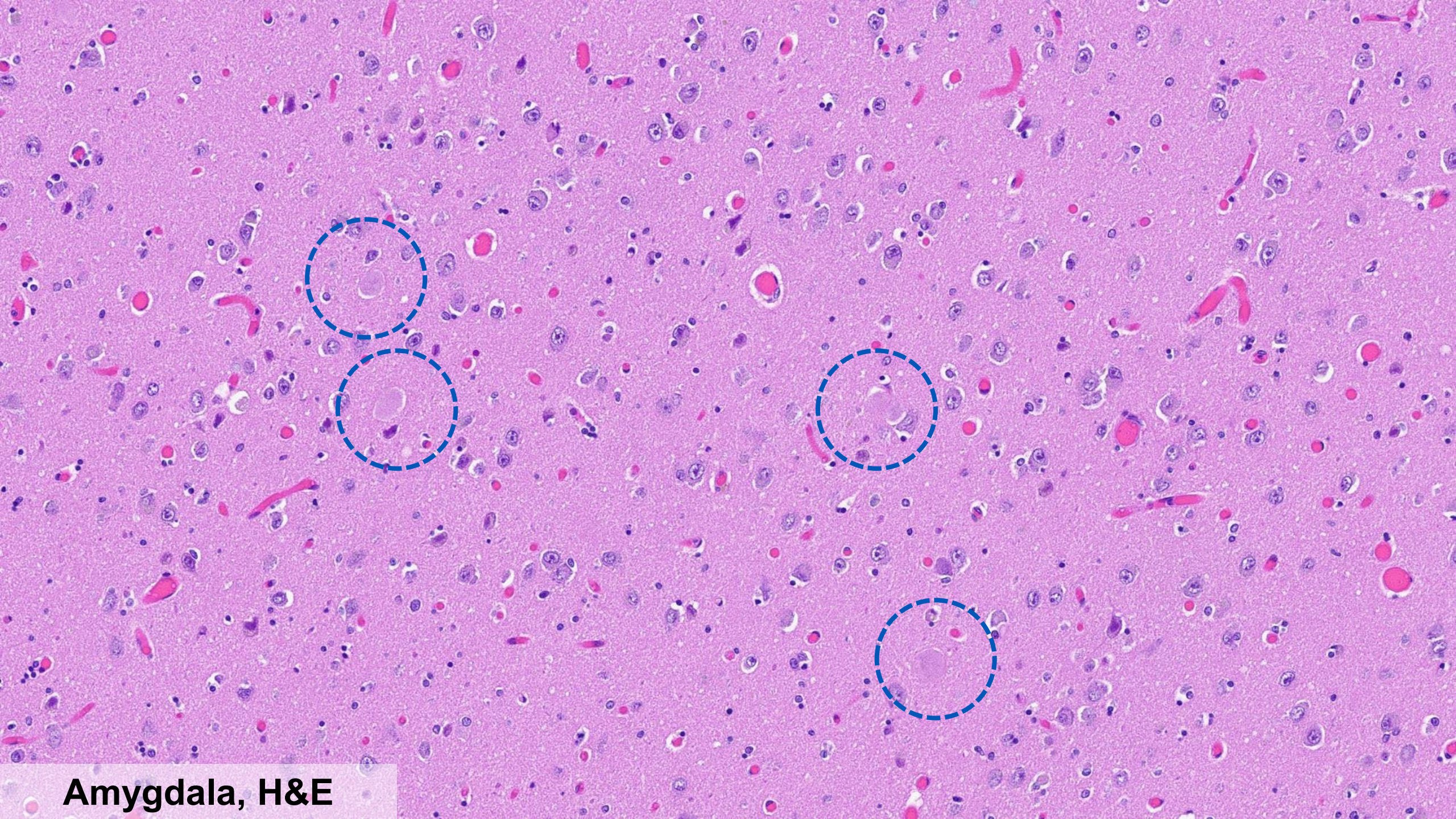


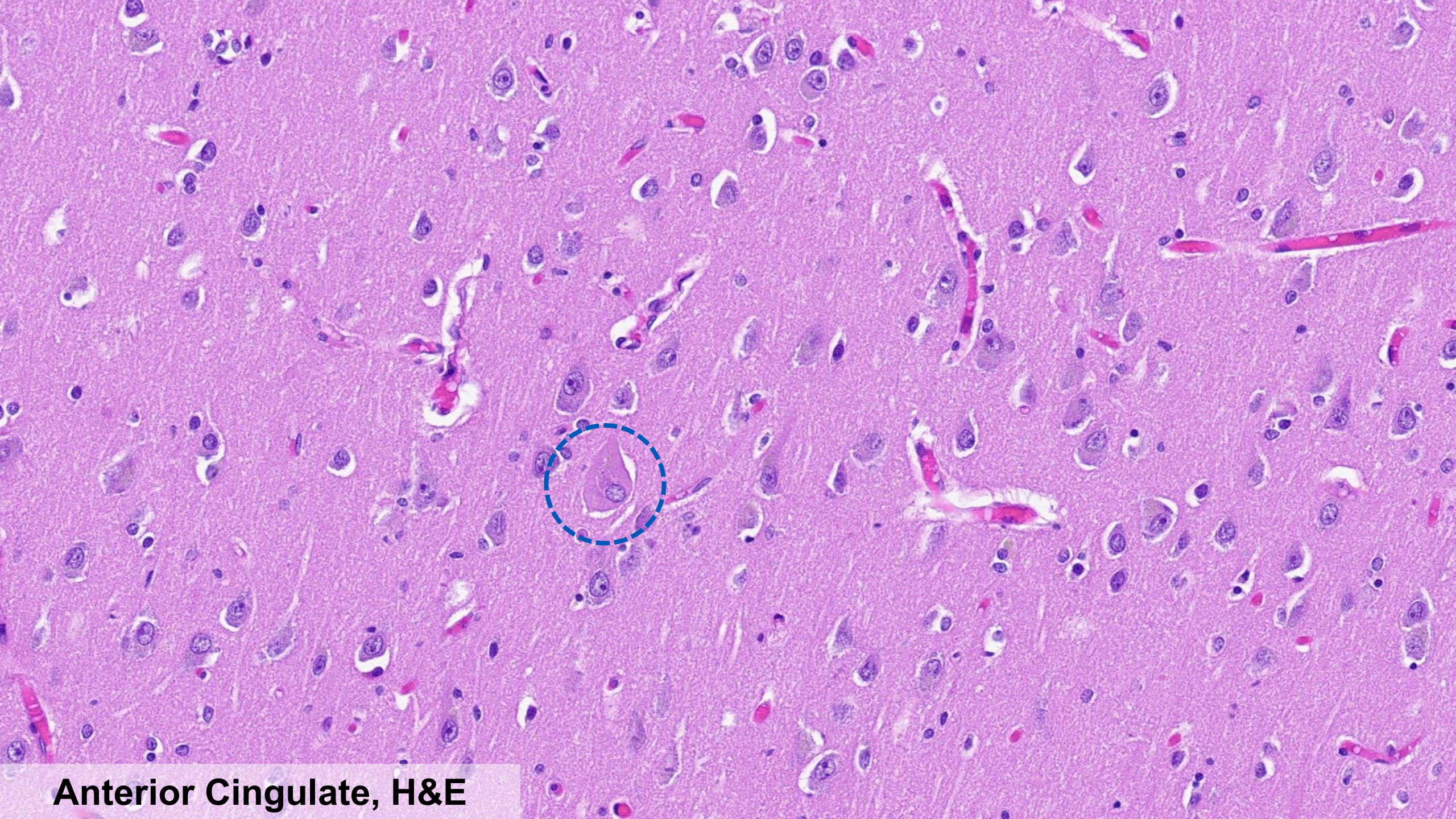
Frontal lobe, H&E



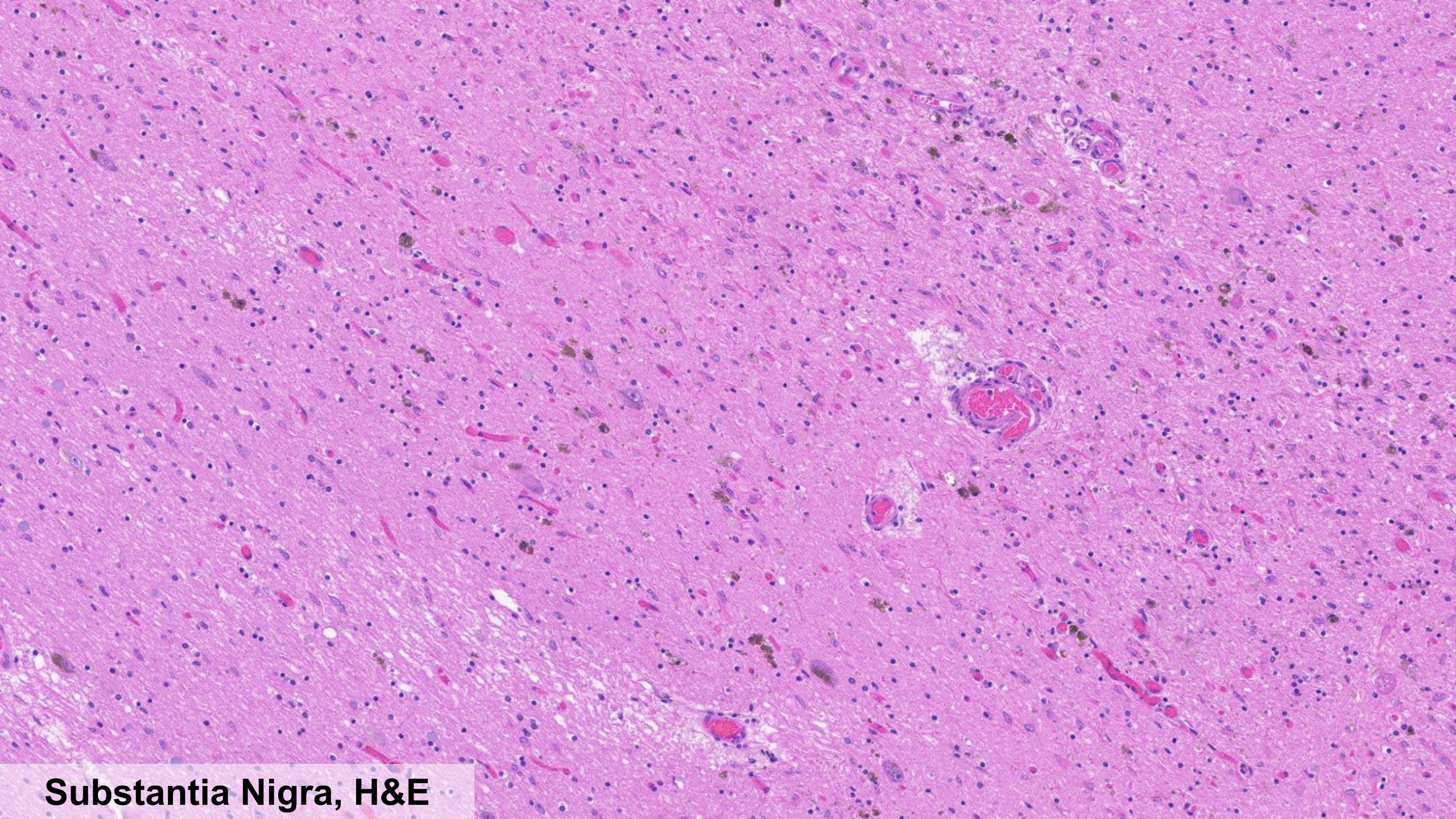


Temporal lobe, H&E

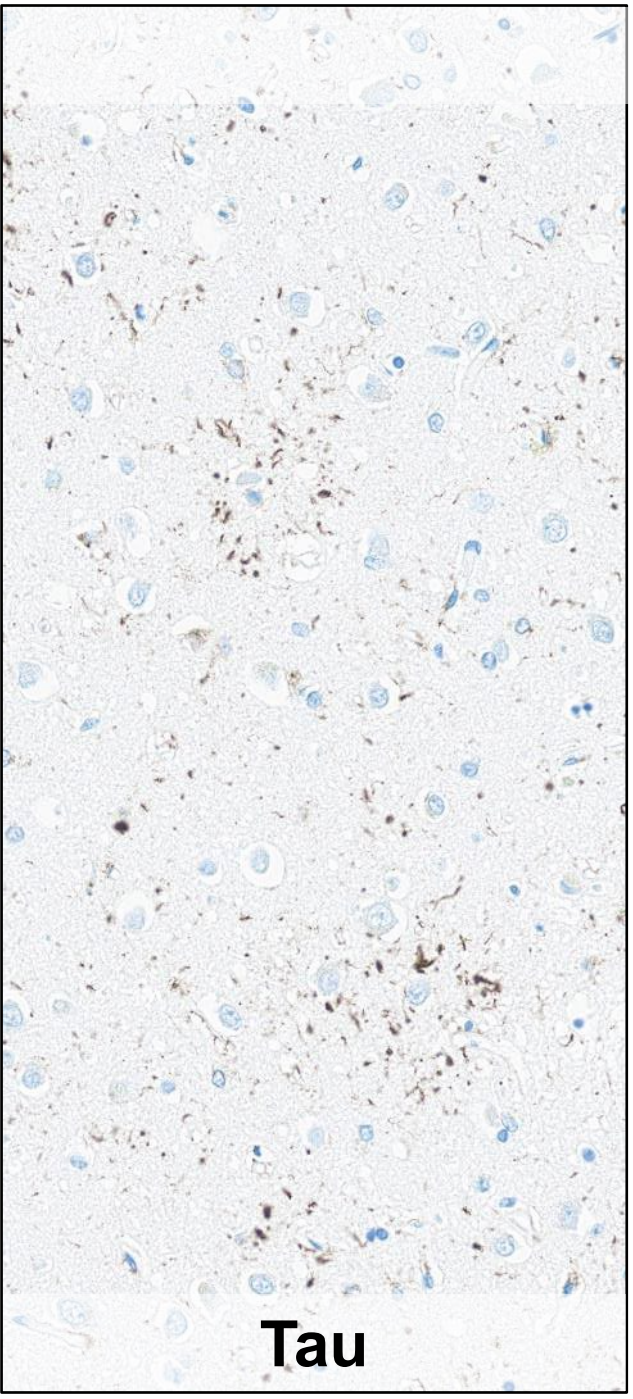

Amygdala, H&E

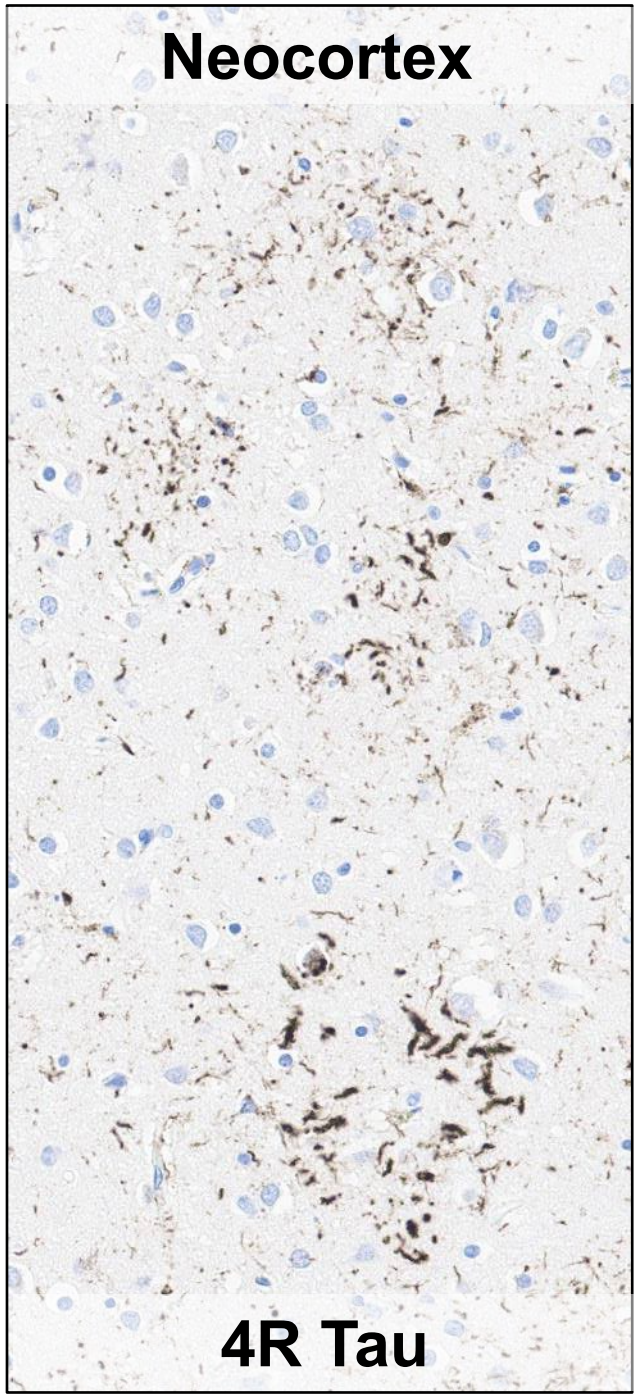


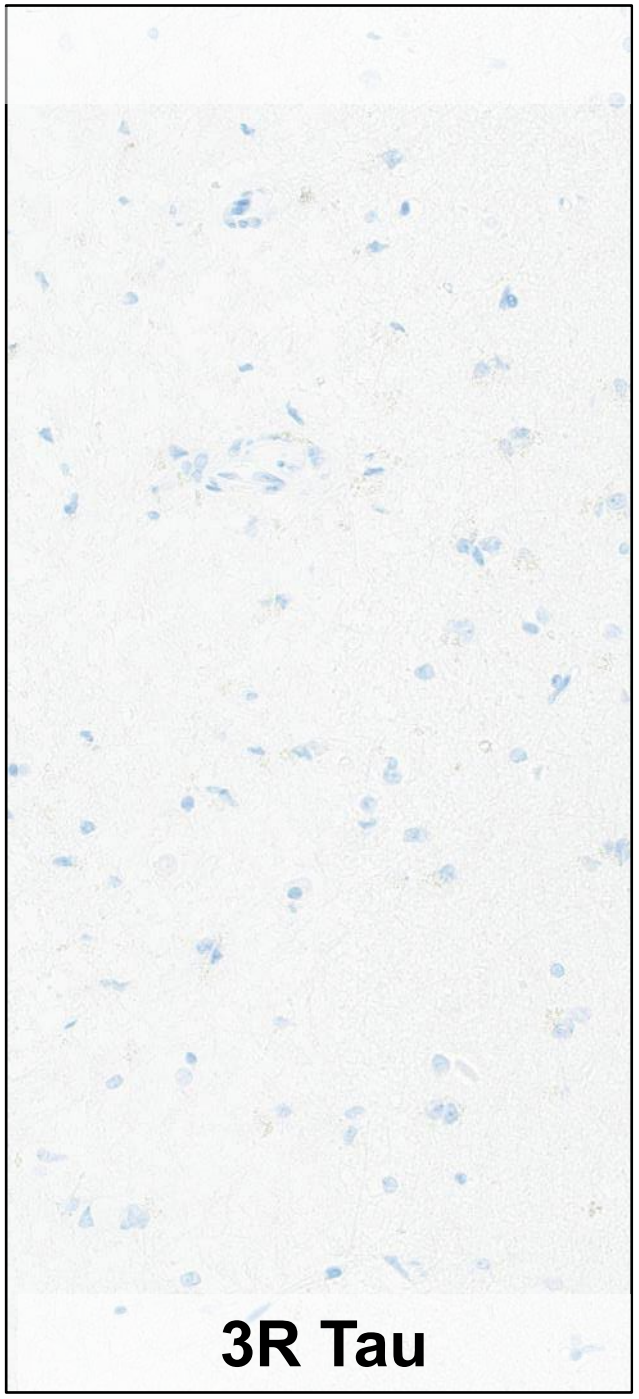
Anterior Cingulate, H&E

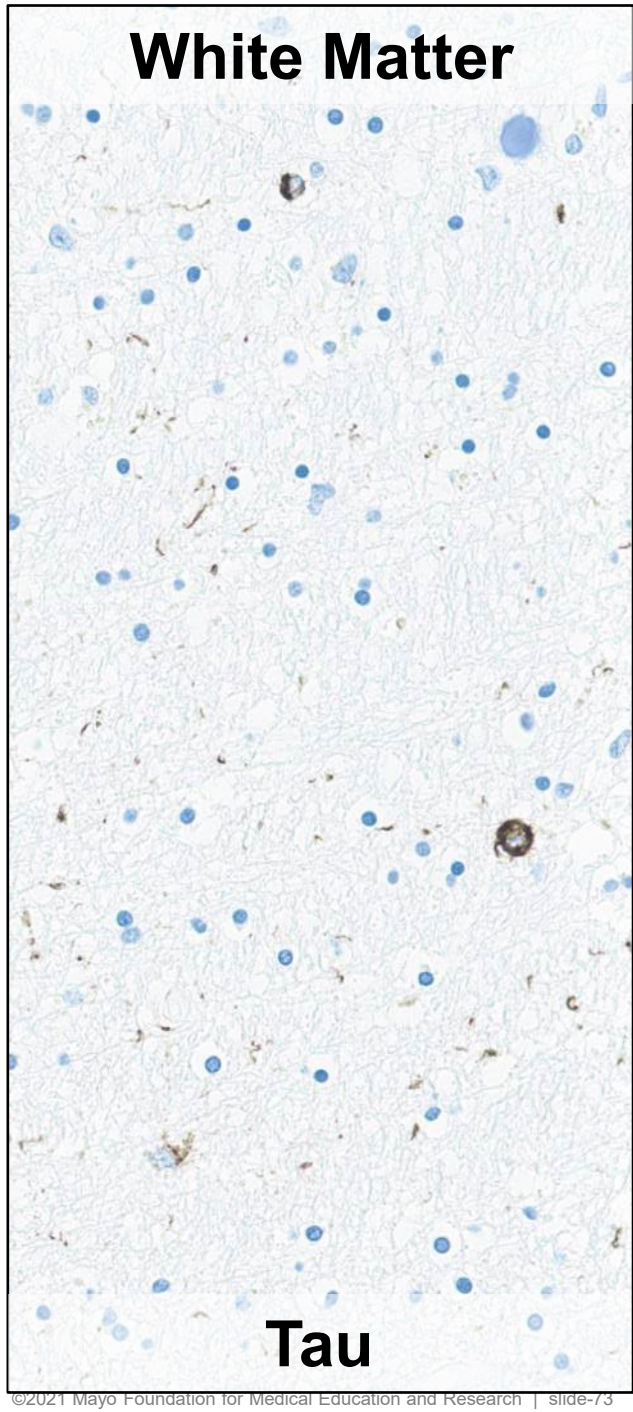


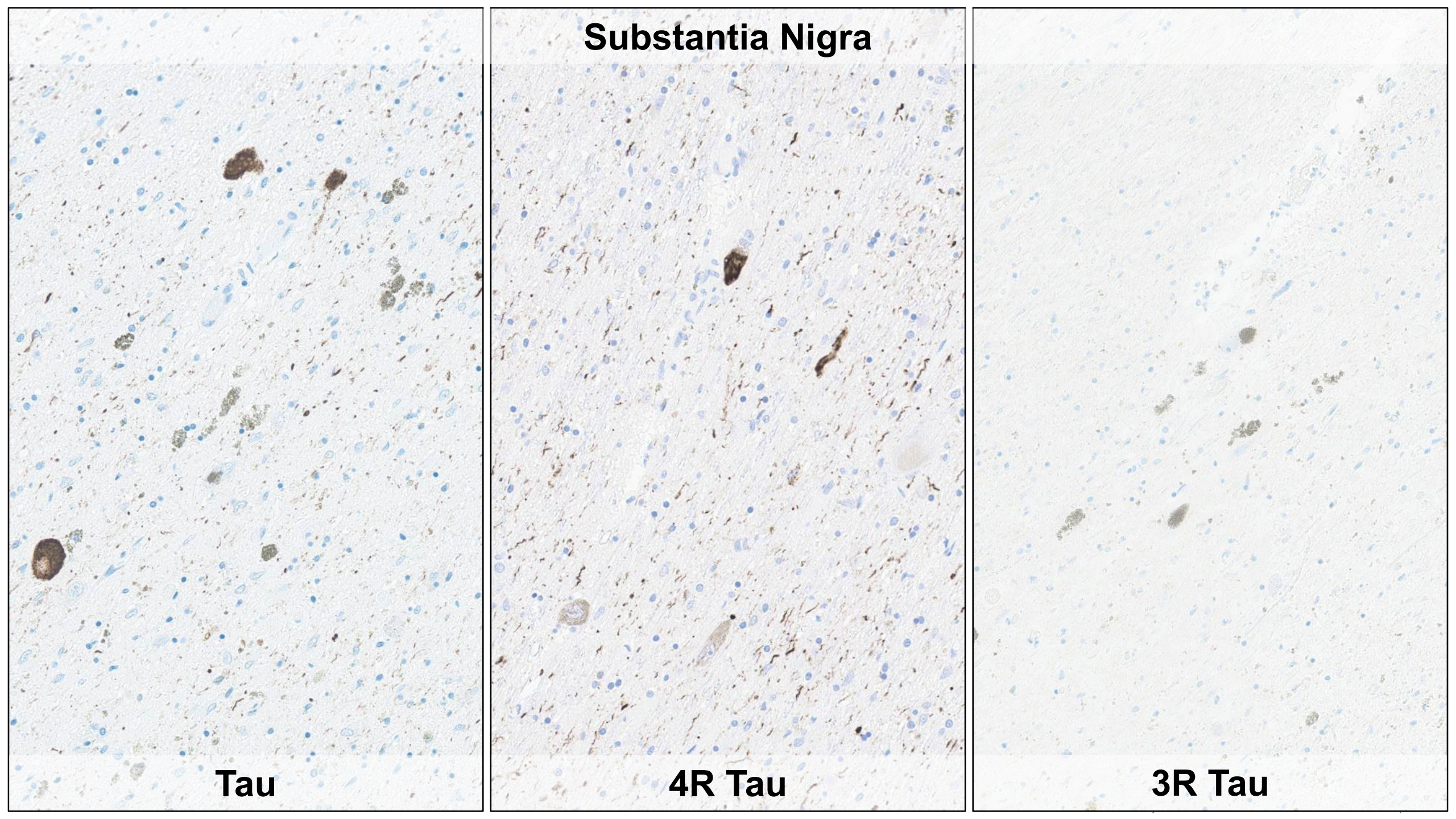
Substantia Nigra, H&E

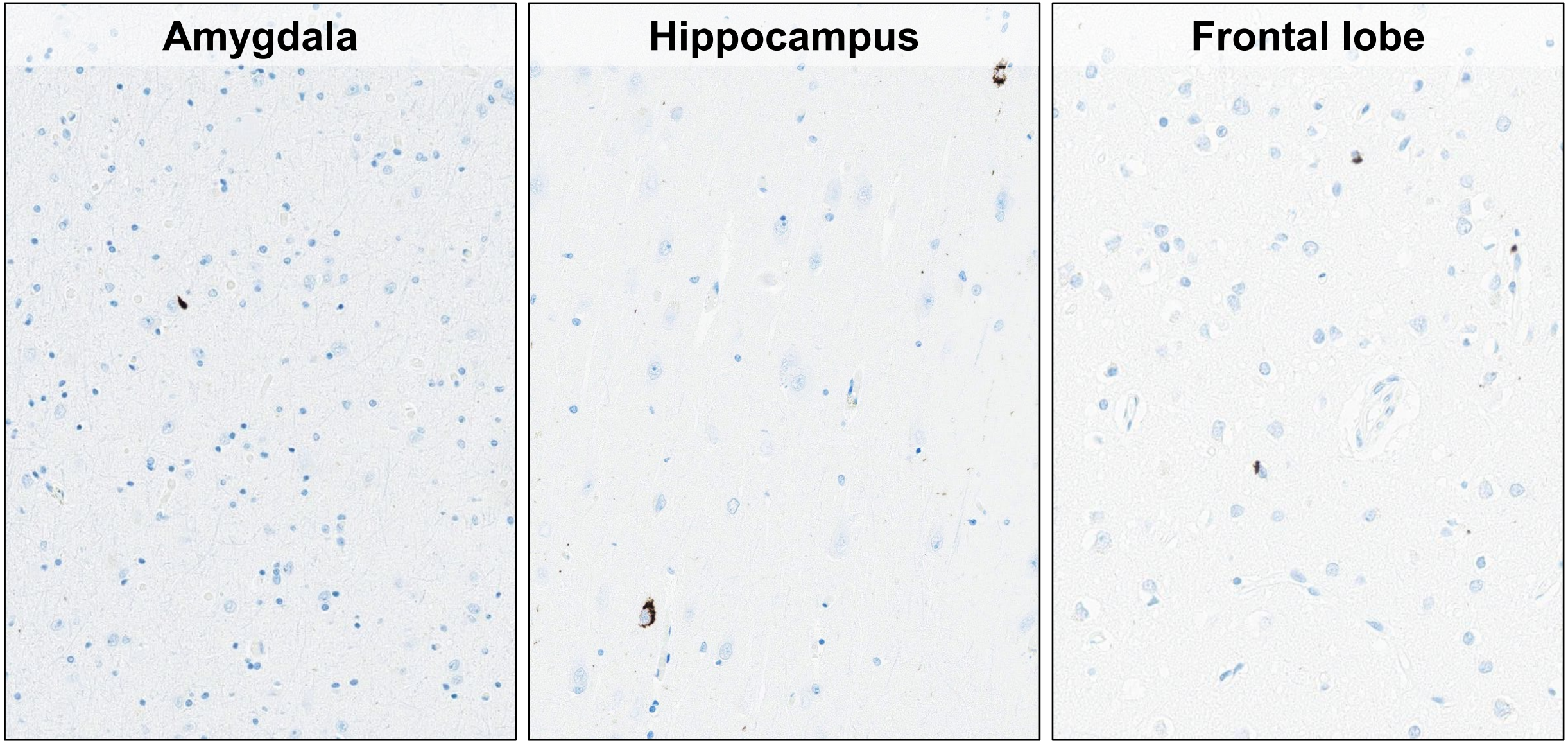









Substantia Nigra
Tau
4R Tau
3R Tau



TDP-43

GROSS FINDINGS

- Mild generalized atrophy
- Mild hydrocephalus ex-vacuo
- Marked depigmentation of the substantia nigra

MICROSCOPIC FINDINGS

- Neuronal loss and concomitant gliosis
- Pronounced and extensive ballooned neurons

ANCILLARY STUDIES

- Tau
- Beta-amyloid
- Alpha-synuclein
- TDP-43
- Bielschowsky stain

NEUROPATH DIAGNOSES

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1. Frontotemporal lobar degeneration tau inclusions (FTLD-Tau), consistent with Corticobasal Degeneration (CBD)
2. Argyrophilic grain disease (AGD)
3. Limbic-predominant age-related TDP-43 encephalopathy-neuropathologic change (LATE-NC)
4. Cerebrovascular disease
    1. Arteriolosclerosis: severe
    2. Atherosclerosis: basilar, grade 1 (of 4); right PCA, 2; bilateral ICAs, 1; left MCA, 1; otherwise, none
5. Vascular brain injury: absent

NEURODEGENERATIVE DISEASE OVERVIEW

DISEASE	LESIONS	COMPONENTS
Alzheimer's Disease	Extracellular plaques Neurofibrillary tangles	Amyloid Tau
Parkinson's Disease Dementia with Lewy Bodies	Lewy bodies Lewy neurites	Alpha-synuclein
Multiple System Atrophy	Glial cytoplasmic inclusions	Alpha-synuclein
FTLD-Tau (e.g., Pick's disease, PSP, CBD)	Neuronal and glial tangles	Tau
FTLD-TDP	Cytoplasmic and nuclear inclusions	TDP-43
Amyotrophic Lateral Sclerosis	Cytoplasmic inclusions	TDP-43
Trinucleotide Repeat Diseases (e.g., Huntington's Disease)	Nuclear and cytoplasmic inclusions	Polyglutamine expansion
Chronic Traumatic Encephalopathy	Neuronal and glial tangles	Tau

Adapted from slide originally created by Dr. Edward Lee (UPenn)

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Adapted from slide originally created by Dr. Edward Lee (UPenn)

Clinical Subtypes

Behavioral Variant (bvFTD)

Primary Progressive Aphasia

- Primary non-fluent aphasia (PNFA)
- Semantic Dementia (SD)
- Logopenic variant

Pathologic Subtypes

FTLD-Tau

- PSP
- CBD
- Pick's disease
- FTDP-17
- Tauopathy, NOS

FTLD-TDP-43

- A-E subtypes
- ALS-FTLD

Other

- FTLD-FUS
- FTLD-UPS
- FTLD-ni

CORTICOBASAL DEGENERATION

- Differentiated from **Corticobasal Syndrome**
- Clinically presents with
  - Motor features
  - Gait abnormalities
  - Alien limb phenomenon
  - Apraxia/ language disturbance
  - Cognitive decline

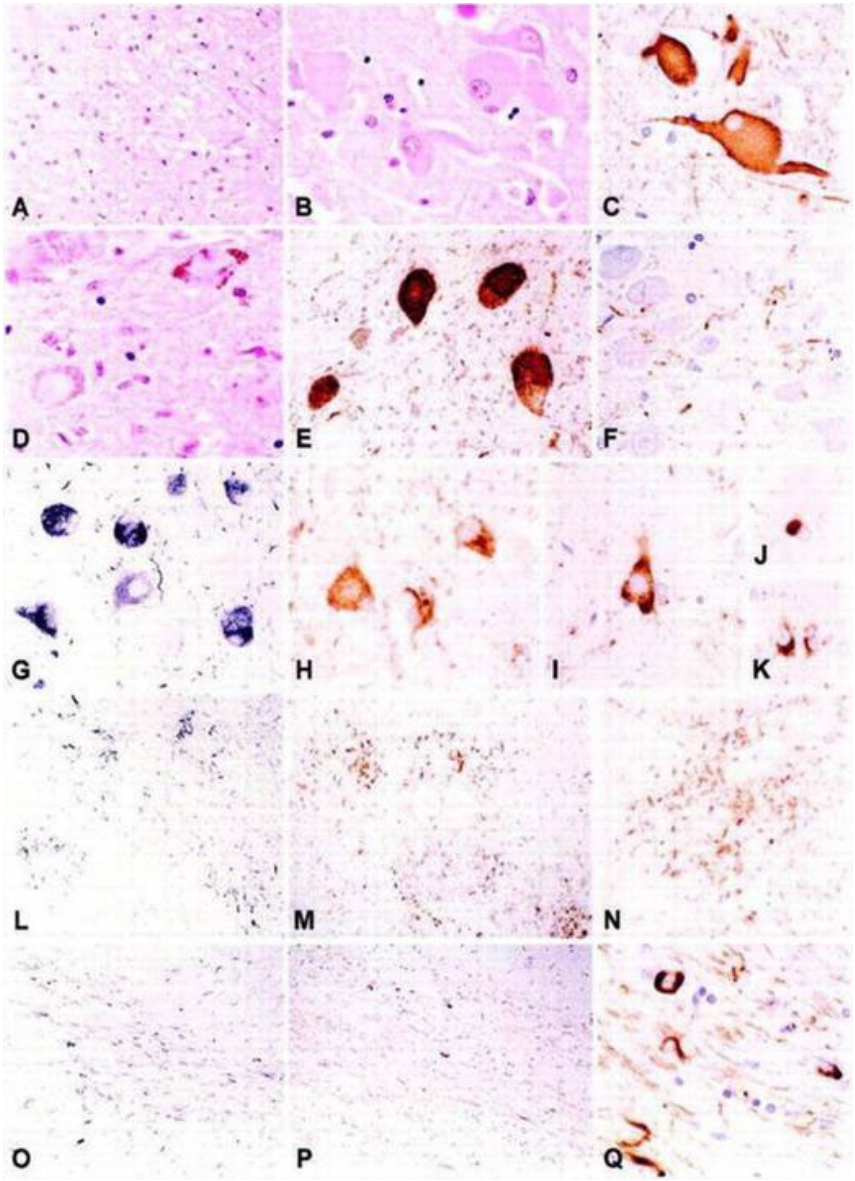
Table 1 Frequency of motor features in available brain banks and studies with ≥5 pathologically confirmed corticobasal degeneration cases[a]

Feature	At presentation, n (%)	During entire course, n (%)
Limb rigidity	65/114 (57)	153/180 (85)
Bradykinesia or clumsy limb	53/111 (48)	126/165 (76)
Postural instability	20/49 (41)	73/94 (78)
Falls	27/76 (36)	83/111 (75)
Abnormal gait	30/92 (33)	102/140 (73)
Axial rigidity	18/67 (27)	68/98 (69)
Tremor[b]	17/83 (20)	50/127 (39)
Limb dystonia	18/91 (20)	47/123 (38)
Myoclonus	14/94 (15)	34/128 (27)

[a] The denominator represents the total number of cases where it was mentioned whether or not the feature in question was present. The total number of cases reviewed was 209, but not all data had information on presenting signs.
[b] This may include some patients with myoclonus; repetitive myoclonic bursts in corticobasal degeneration may be mistaken for tremor.

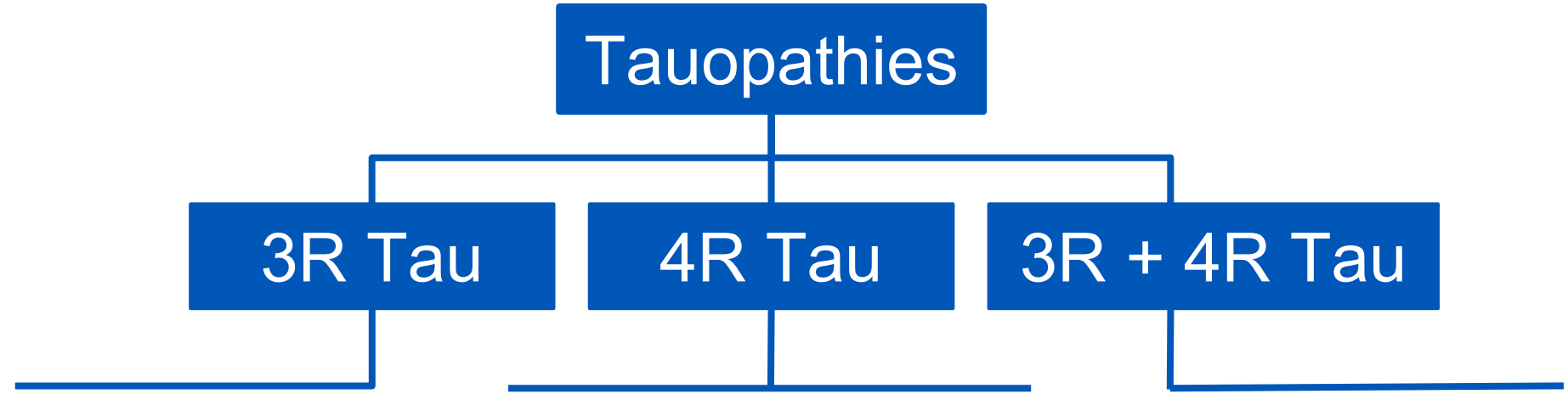
Armstrong et al. Neurology (2013)

CORTICOBASAL DEGENERATION



	Neuronal loss & gliosis	Ballooned neurons	Tau- or Gallyas-positive neurons	Tau- or Gallyas-positive glia	Tau- or Gallyas-positive threads
Cerebral cortex					
Frontal					
Motor (peri-Rolandic)					
Cerebral white matter					
Parietal					
Temporal					
Entorhinal					
Subcortical areas					
Hippocampus					
Amygdala					
Basal nucleus of Meynert					
Caudate & putamen					
Globus pallidus					
Internal capsule					
Thalamus					
Subthalamic nucleus					
Brainstem					
Midbrain tectum (colliculi)					
Red nucleus					
Substantia nigra					
Cerebral peduncle					
Locus ceruleus					
Pontine tegmentum					
Pontine base					
Fibers in pontine base					
Inferior olivary nuclei					
Cerebellum					
Dentate nucleus					
Cerebellar white matter					

Dickson et al. JNEN (2002)



- Pick's Disease (PiD)
- FTDP-17 (*MAPT*)

- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Globular glial tauopathy (GGT)
- Argyrophilic grain disease (AGD)
- Aging-related tau astrogliopathy (ARTAG)
- FTDP-17 (*MAPT*)

- Alzheimer's disease (AD)
- Primary age-related tauopathy (PART)
- Chronic traumatic encephalopathy (CTE)
- FTDP-17 (*MAPT*)
- Anti-IgLON5-related tauopathy

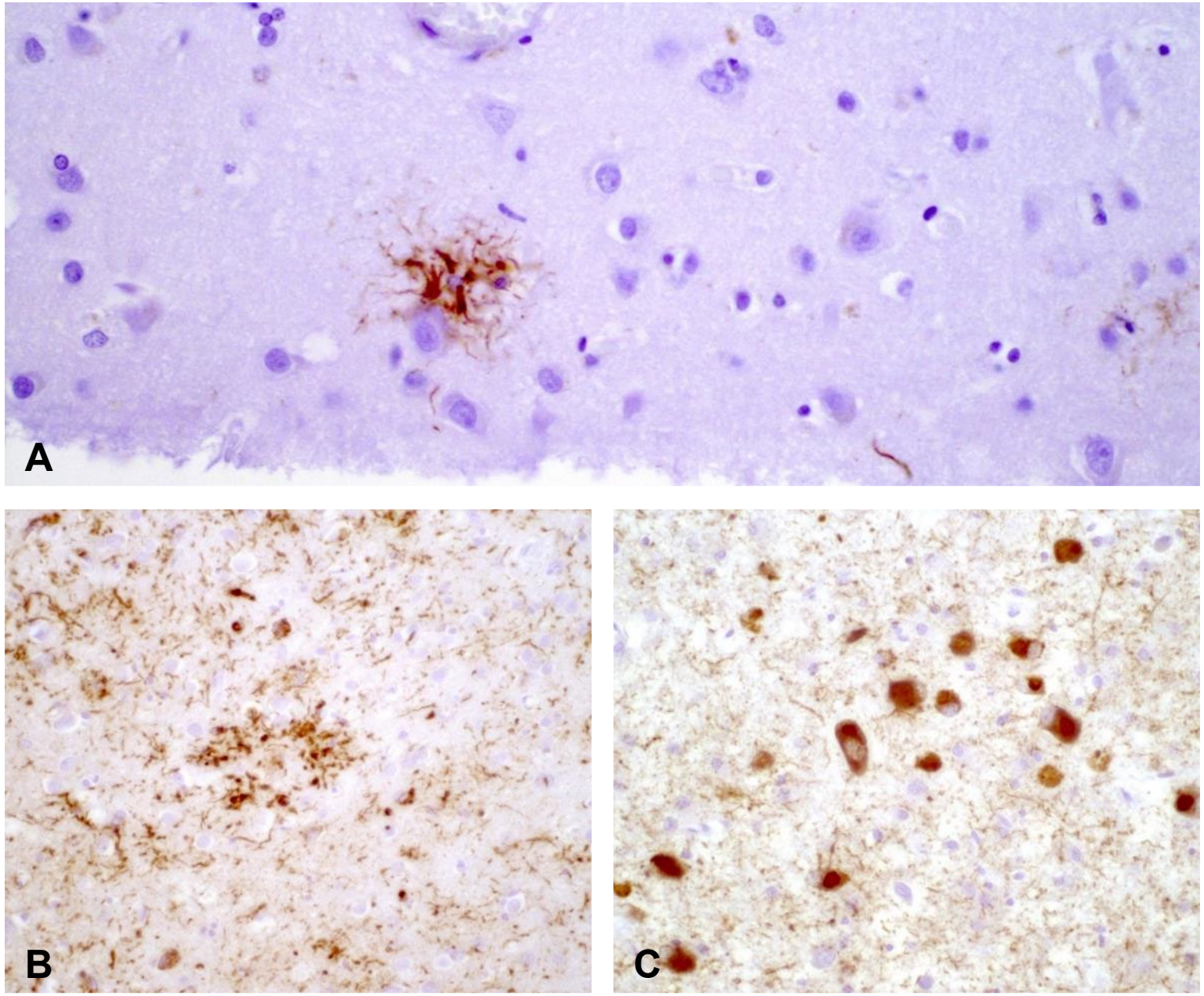
Kovacs GG (2015) Neuropathology of tauopathies: principles and practice. Neuropathology and Applied Neurobiology 41:3 -23.

TAU INCLUSION TYPES

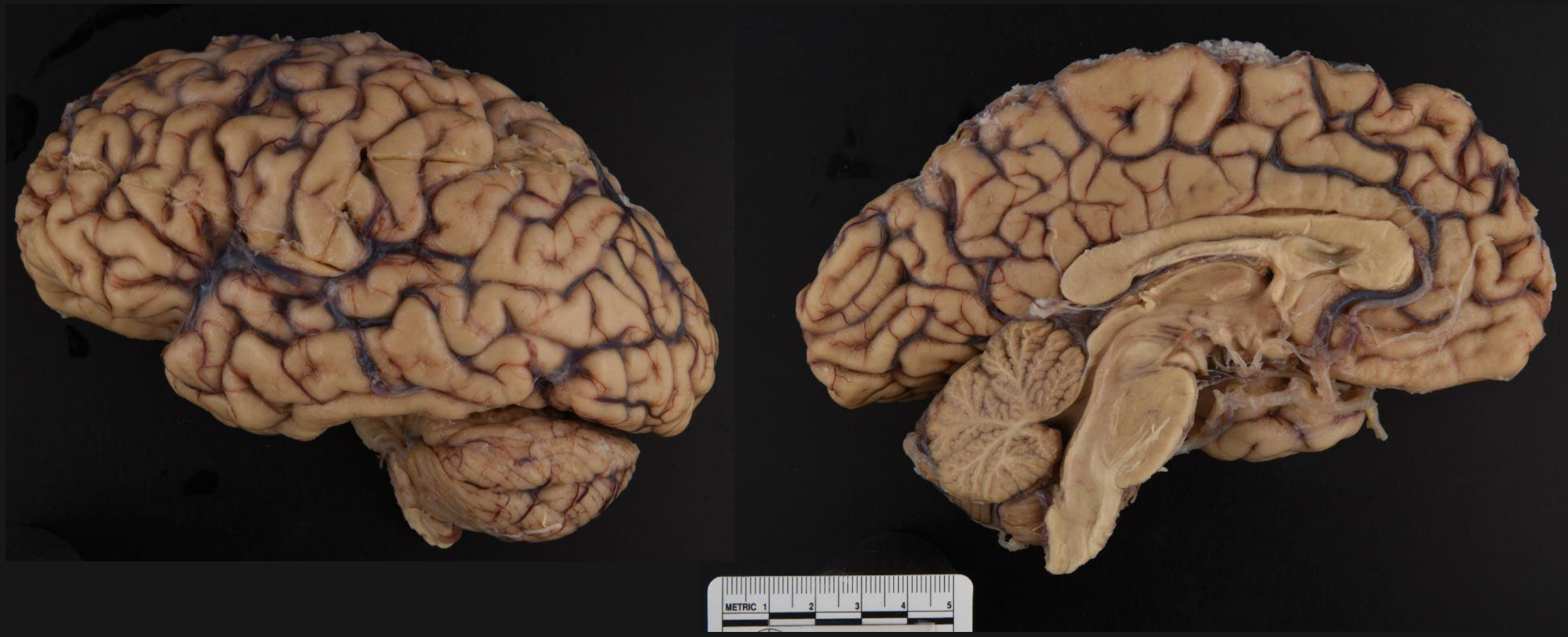
(A)**Tufted Astrocyte**, seen in Progressive Supranuclear Palsy (PSP)

(B)**Astrocytic plaque**, seen in Corticobasal Degeneration

(C)**Pick bodies**, seen in Pick Disease



GROSS PATHOLOGY PROGRESSIVE SUPRANUCLEAR PALSY



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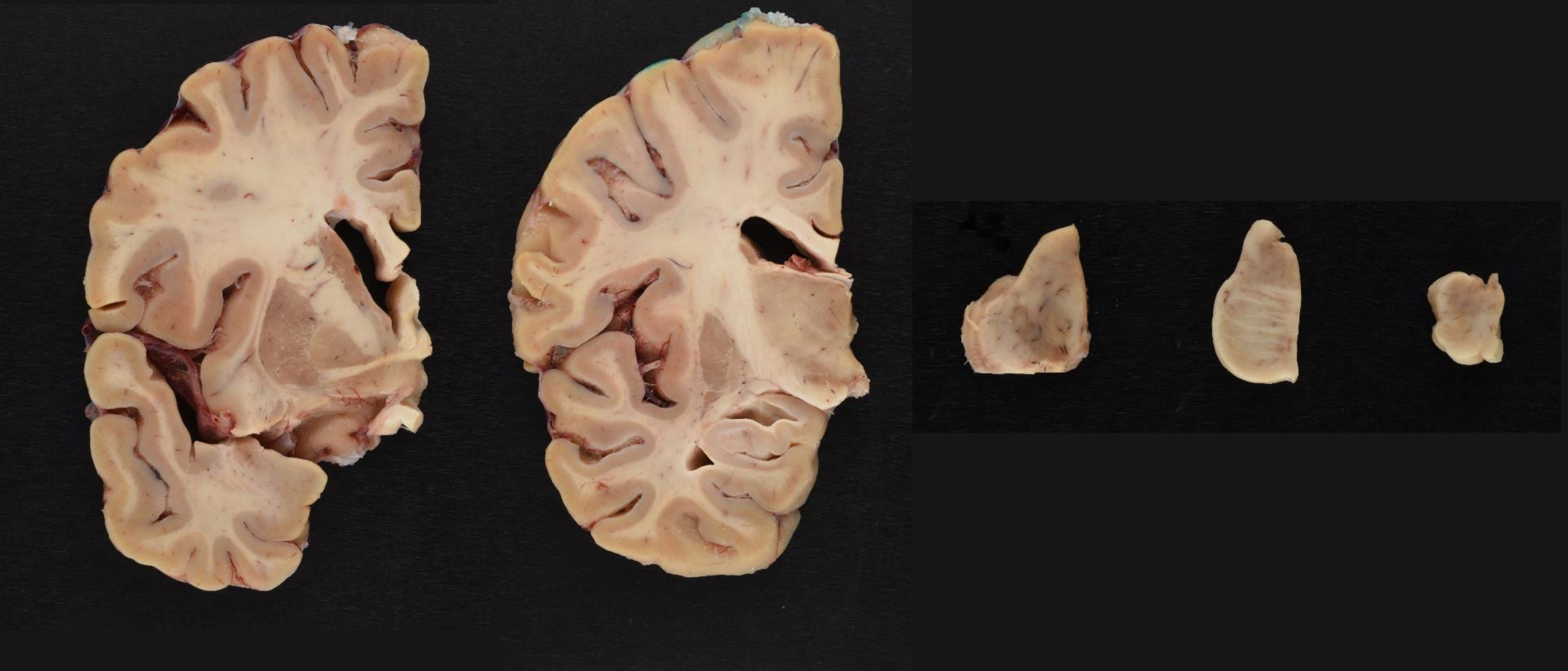
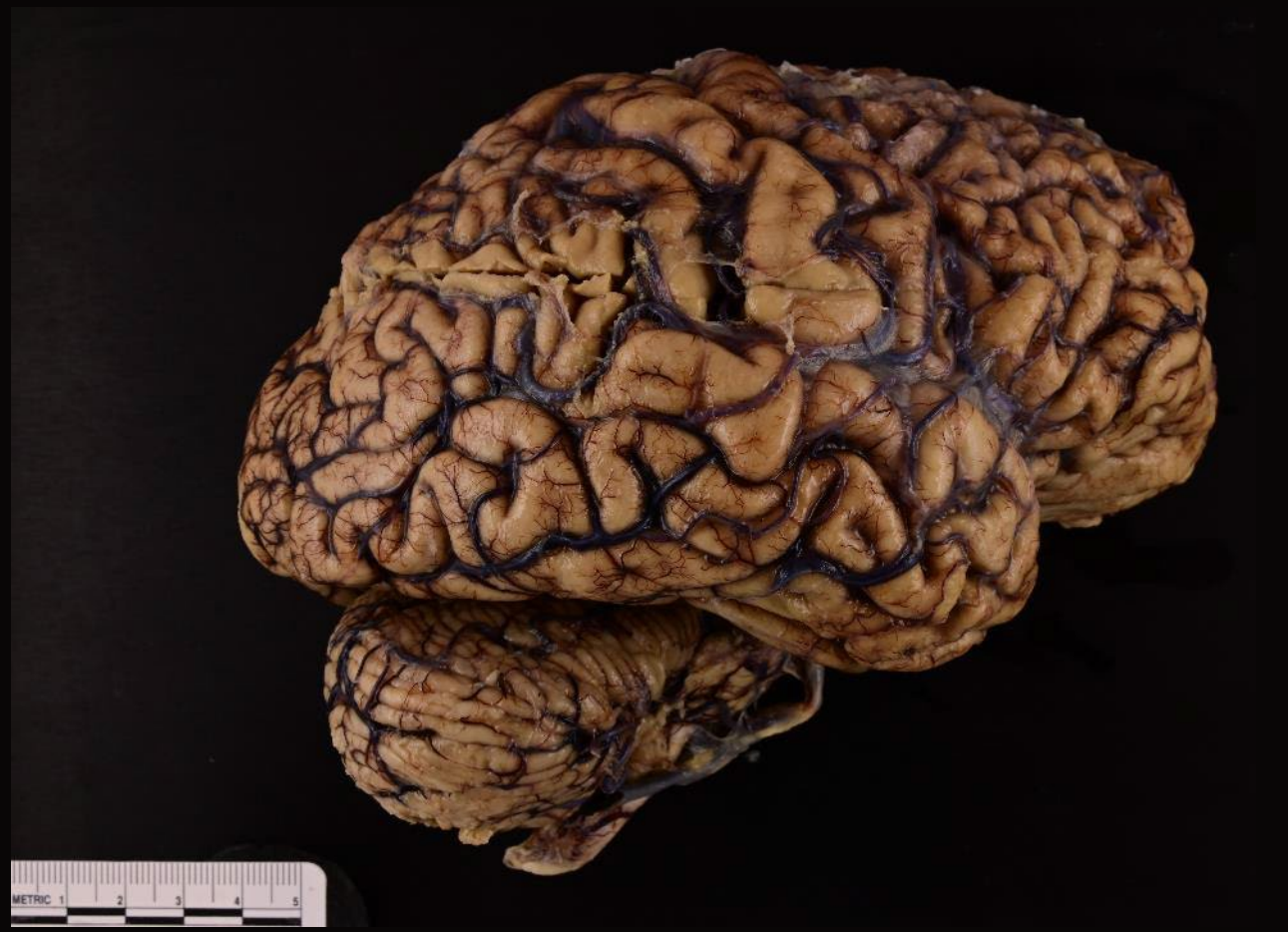
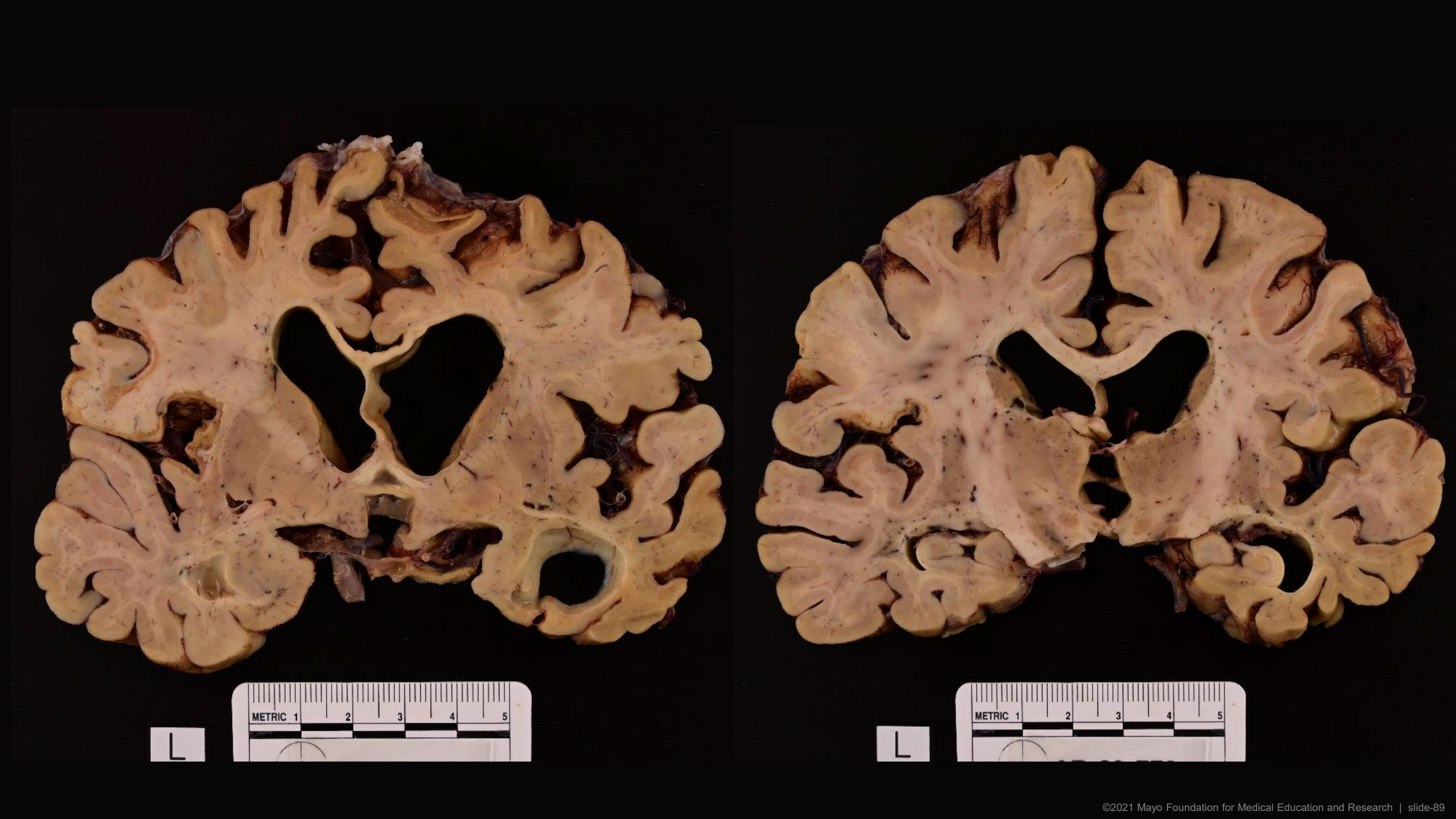


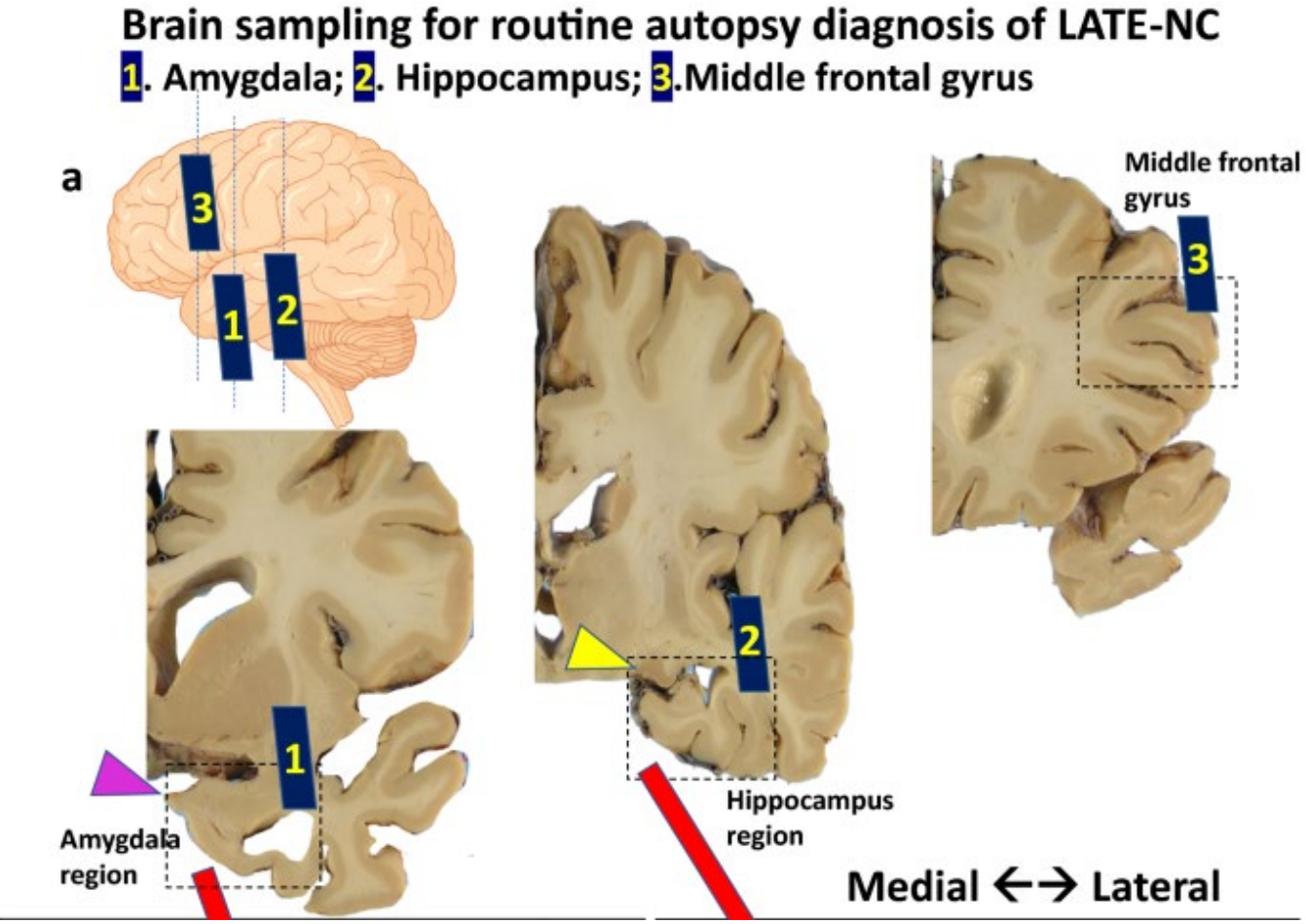
Coronal Sections, L

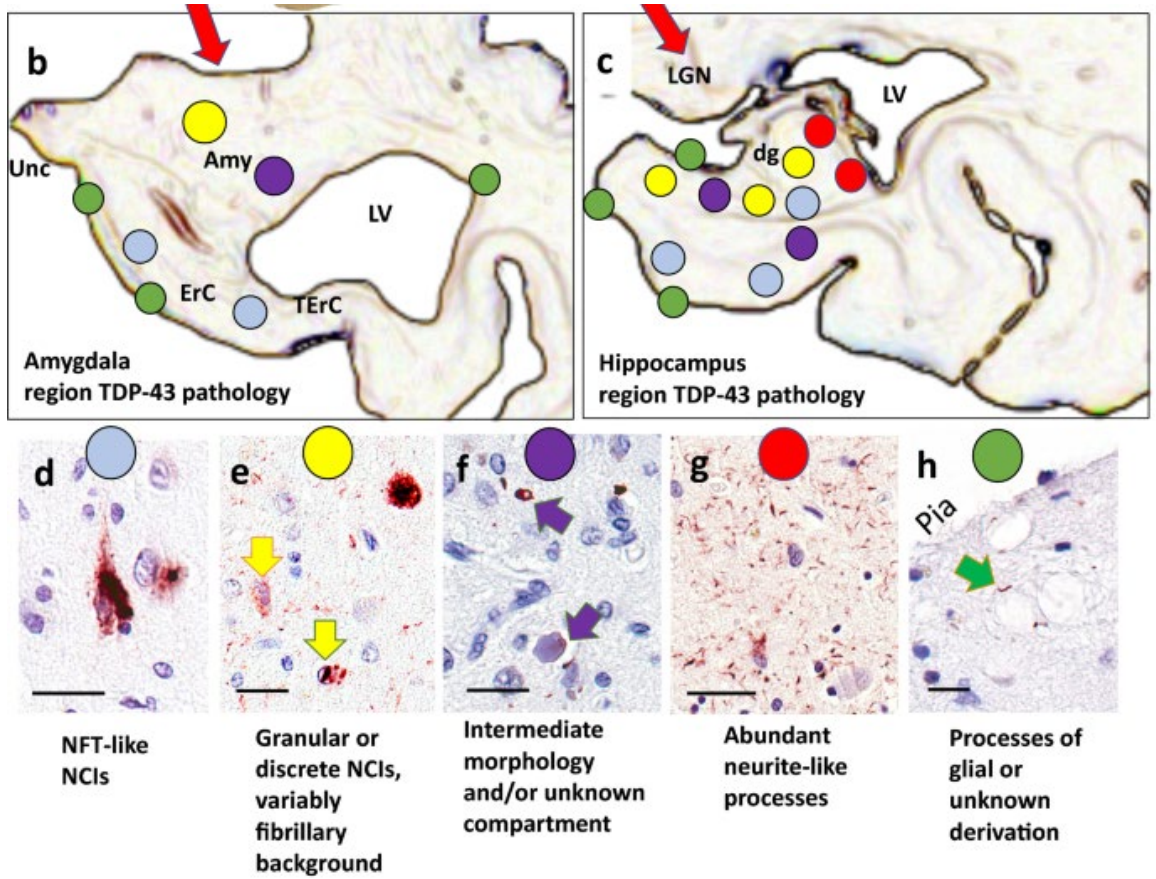
GROSS PATHOLOGY PICK'S DISEASE





LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY: AN UPDATE





Nelson et al. Brain (2019); Nelson et al. Acta Neuropathologica (2022)

INCIDENCE OF TDP-43 PATHOLOGY IN CBD

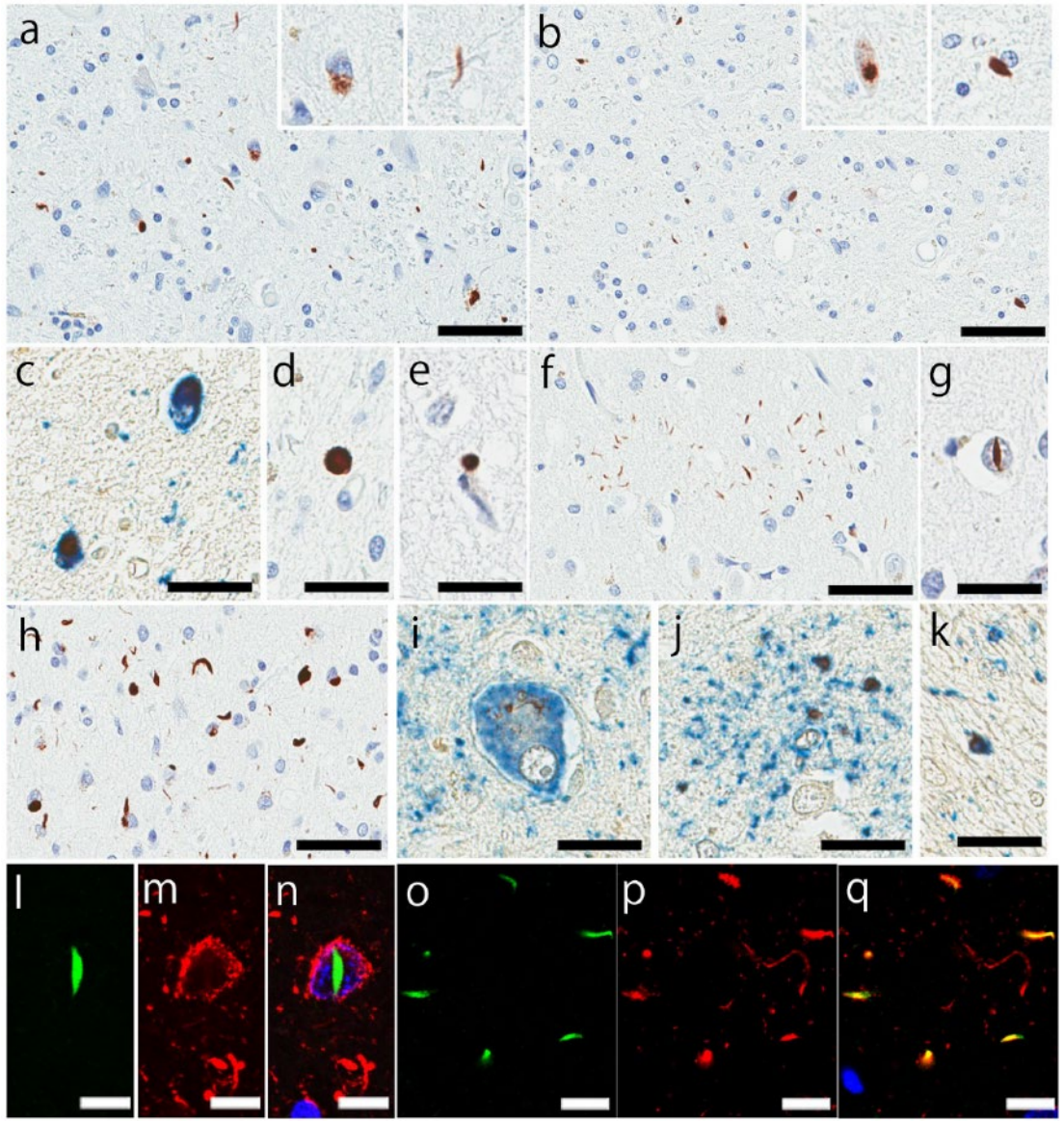
Acta Neuropathologica (2018) 136:389–404
https://doi.org/10.1007/s00401-018-1878-z

ORIGINAL PAPER

CrossMark

Corticobasal degeneration with TDP-43 pathology presenting with progressive supranuclear palsy syndrome: a distinct clinicopathologic subtype

Shunsuke Koga[1] · Naomi Kouri[2] · Ronald L. Walton[1] · Mark T. W. Ebbert[1] · Keith A. Josephs[3] · Irene Litvan[4] · Neill Graff-Radford[5] · J. Eric Ahlskog[3] · Ryan J. Uitti[5] · Jay A. van Gerpen[5] · Bradley F. Boeve[3] · Adam Parks[6] · Owen A. Ross[1] · Dennis W. Dickson[1]



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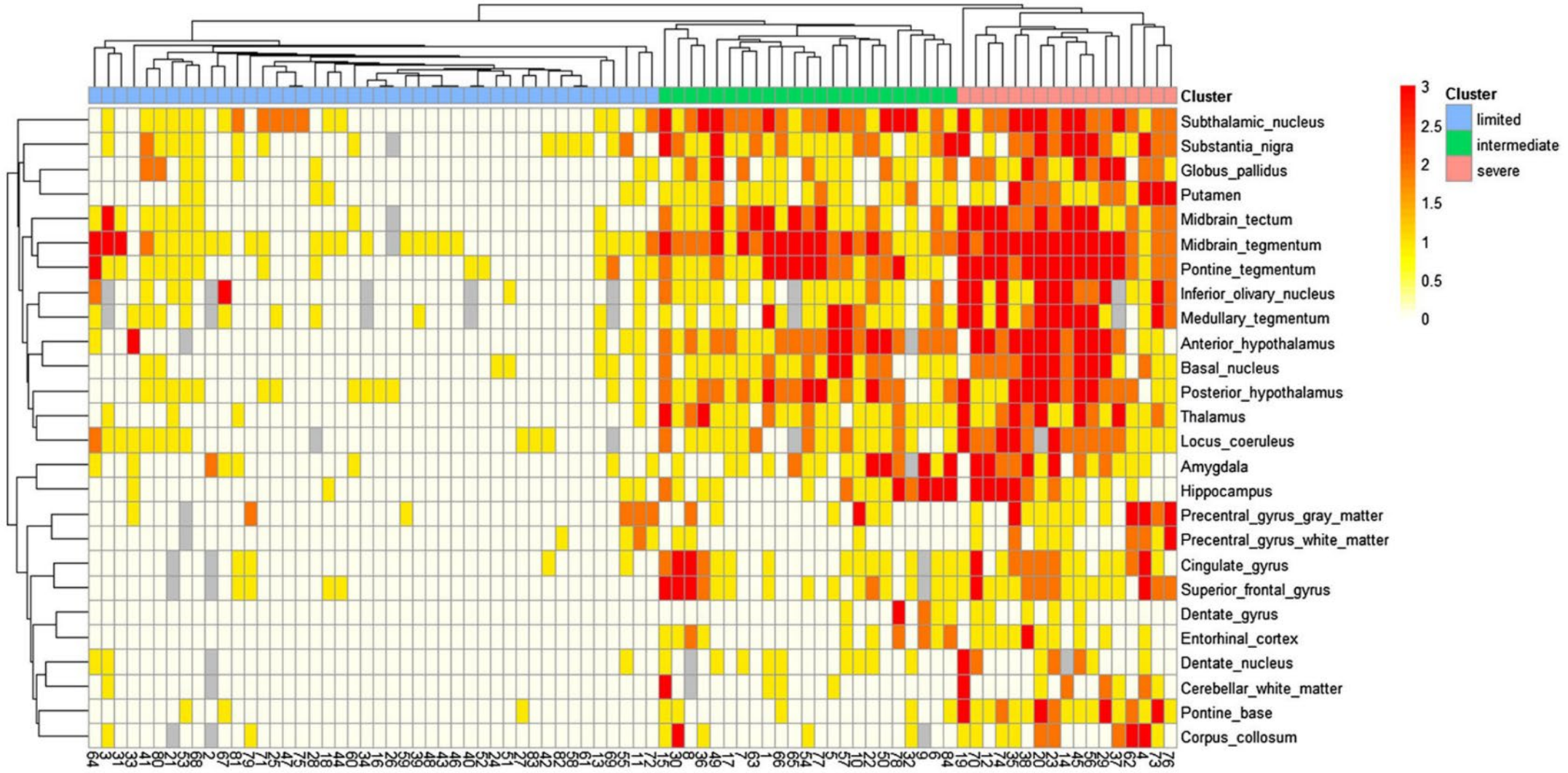

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KEY POINTS

1. Review **neuropathologic approach** to neurodegenerative cases
2. Review **FTLD-Tau** as a neuropathologic entity
3. Understand the importance of **clinicopathologic correlation** in neurodegenerative cases

QUESTIONS & ANSWERS

MAYO CLINIC

THANK YOU

AND MANY THANKS TO THE MAYO CLINIC ADRC AND MCSA

ADDITIONAL REFERENCES

1. McKeith, I.G., Dickson, D.W., Lowe J., *et al.* Diagnosis and management of dementia with Lewy bodies Third report of the DLB consortium. *Neurology* **65,** 12: 1863-1872 (Dec 2005); DOI: 10.1212/01.wnl.0000187889.17253.b1
2. McKeith IG, Boeve BF, Dickson DW *et al.* Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89(1), 88-100 (2017) doi: 10.1212/WNL.0000000000004058. Epub 2017 Jun 7. PMID: 28592453; PMCID: PMC5496518.
3. Montine, T.J., Phelps, C.H., Beach, T.G. *et al.* National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol* **123,** 1–11 (2012). https://doi.org/10.1007/s00401-011-0910-3

