UCI University of California, Irvine

UCI MIND Institute for Memory Impairments and Neurological Disorders

Not too early for LATE: a case report of a younger ADRC and A4 participant

NACC LATE Webinar Series
February 17, 2026

Presented on behalf of the UCI ADRC CPC Team:
Davis C. Woodworth, Michelle McDonnell, Jerry Lou, Beatriz Vides, Maria Corona, Craig E.L. Stark, William H. Yong, David L. Sultzer, Elizabeth Head, S. Ahmad Sajjadi

Summary Slide

- Participant enrolled in ADRC at age 54, cognitively normal.
- Significant family history of Alzheimer's disease.
  - Mother diagnosed clinically with AD at 73; ADNC confirmed at autopsy at 78
- Enrolled in A4 trial at age 67.
- Fairly rapid cognitive decline from age 68 to age 75.
  - Diagnosed with MCI at age 69, dementia at age 72
- Some atrophy on MRIs at age 68, but subsequent rapid decline.
- Fairly high amyloid PET at age 68 (centiloid~120).
- Died at age 76.
- ADNC: Intermediate (A1/B3/C2).
- LATE-NC stage 2 (with HS-A).

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Clinical Report:
Visits from age 54 to 75

Michelle McDonnell, PhD
Maria Corona, PhD
David Sultzer, MD

Demographics

Age

- Age at Enrollment – 54
- Age at Final In-Person evaluation – 75
- Age at Death – 76

Basic Demographics

- White Female, Left-handed

Education/Employment

- 16 years of education
- Employed as an editor

Family History

- Mother: Diagnosed AD at age 73 and passed at 78
  - Was also a participant in our clinic with AD confirmed on pathology
- Father: Diagnosed with AD at 80 and died at 89 (no neuropath)

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Progression of cognitive symptoms

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54yo (Baseline) - 67yo	68 - 70yo	71yo	72-76yo

• **54-66** – Intermittent reports of sleep concerns and depression
• **66** – "Benign memory difficulties" "less precise with names"
• **67** – Increased concerns related to memory, depression and sleep
	• **Cognition**
	  • Declines in memory (misplacing objects, names, notes)
	  • Word-finding difficulties
	  • Getting lost
	  • Received negative feedback at work
		• **Cognition**
		  • Declines in memory
		  • Language (WF, hesitant speech)
		  • Distractible
		  • Increased depression
		• **Behavior**
		  • Irritability, depression, sleep concerns
			• **Cognition**
			  • Continued declines in cognition
			  • Disoriented outside of familiar locations
			  • Placed in assisted living
			• **Behavior**
			  • Continued depression and irritability
			  • Disinhibited

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Neurological and Psychiatric symptoms

Age	Neurological exam	Psychiatric symptoms	Neurotropic meds
	No prior history of neurologic or psychiatric symptoms or syndromes		
54-67	Normal neuro exam. UPDRS 0.	Mild – moderate intermittent depression Mild insomnia	Diphenhydramine 25mg prn sleep
68-70	Mild ↓ sensation, B legs (intermittent) Mild ↓ ankle reflex, B (intermittent)	Mild – moderate depression, generally increasing over time Mild insomnia	Diphenhydramine 38mg prn sleep (68) Melatonin 0.5mg qhs (69 →)
71	Normal neuro exam. UPDRS 0.	Moderate depression Insomnia Irritability	Melatonin 0.5mg qhs
72-75	Mild ↓ ankle reflex, B (intermittent) Poor tandem gait	Mild-moderate depression Irritable; disinhibited, impulsive Paranoid delusions Agitation - stubborn	None
76	N/A	Mild agitation (upset; pacing) Awake and pacing at night	Valproate 250mg BID (“behavior”; 76) Melatonin 3mg qhs

Medical History and ADLs

Condition	Year	Status
Osteoarthritis	2012	recent/active
Appendectomy	1968	remote/inactive
Fall	2013	remote/inactive
Insomnia	2006	recent/active

Medication	Dose	Number	Frequency
Solanezumab vs Placebo (A4)	1600mg	OLE(41)	qmo (monthly)
Tylenol	325mg	1	prn (as needed)
Diphenhydramine HCl	25mg	1	prn (as needed)

Change in Functional Ability Scores									
Functional Scale	R19 75yo	R18 73yo	R17 72yo	R16 71yo	R15 70yo	R14 69yo	R13 68Yo	Normal Range	Max/Worst Scores
FAQ	30	27	23	1	0	0	0	0-6	30
BADLS	13	11	13	0	0	0	0	0-4	60

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A4 Data

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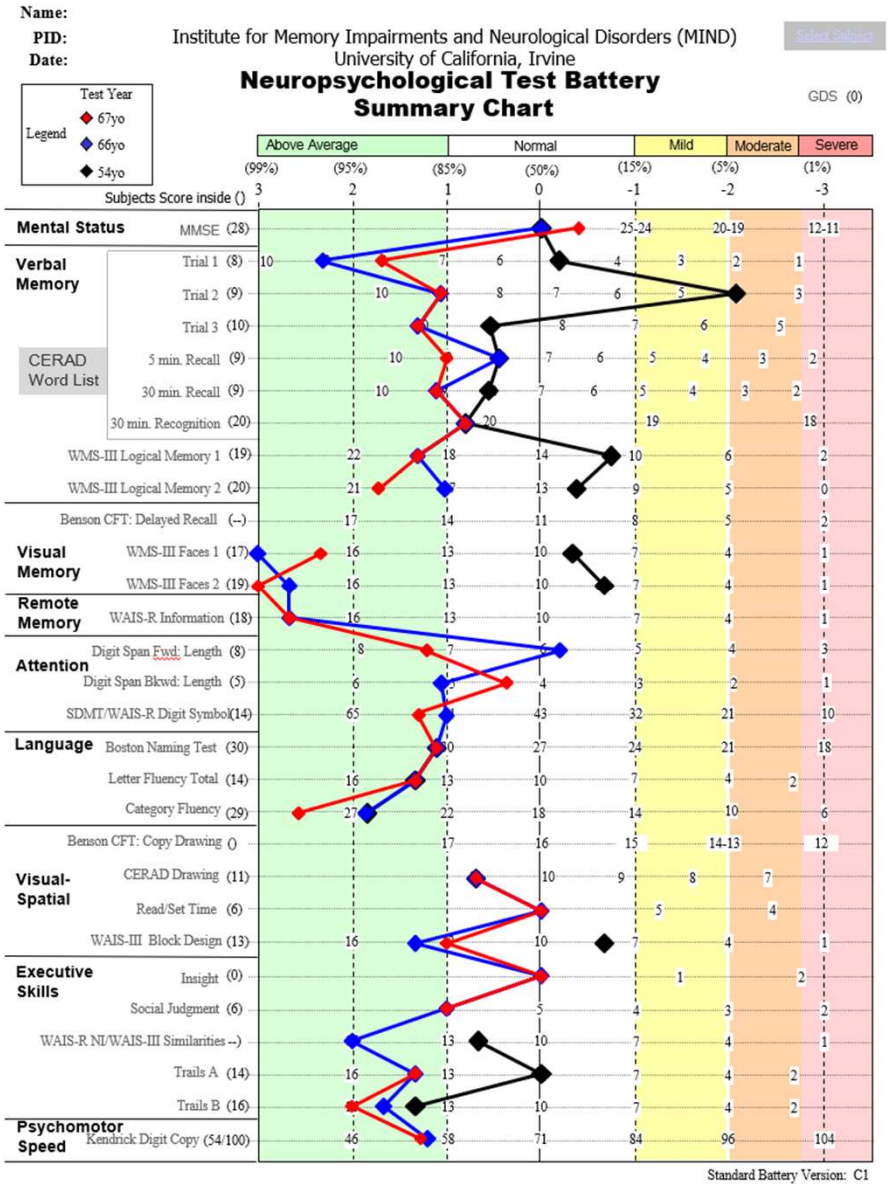
- Participant enrolled in A4 trial (Solanezumab) at age 67 (minimum was 65).
- Was on placebo for trial, but on Solanezumab for OLE (41 months).

	67yo	68yo	70yo	71yo	72yo	73yo	74yo	75yo
MMSE	30	30	28	27	25	17	12	3
LM I	12	7	13	4	3	1	0	0
LM II	13	6	12	4	0	0	1	0
DSST	50	54	52	52	47	32	31	0
CDR Global	0	0	--	0.5	0.5	2.0	2.0	2.0
CDR SOB	0	0	--	1.0	4.0	11.0	12.0	14.0

LM = Logical Memory
DSST = Digit Symbol Substitution Test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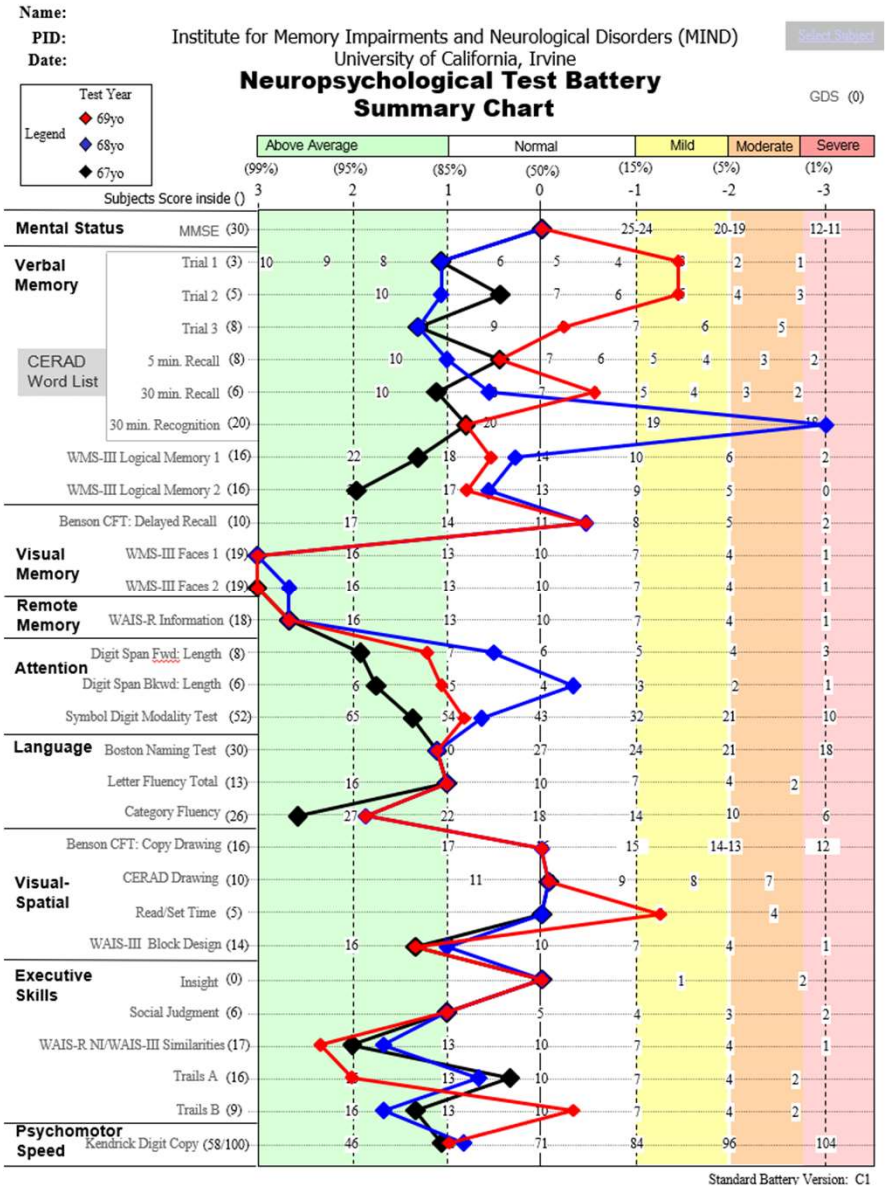
PID:
Date:
Institute for Memory Impairments and Neurological Disorders (MIND)
University of California, Irvine
Neuropsychological Test Battery
Summary Chart
GDS (0)
Legend
Test Year
67yo
66yo
54yo
Above Average
Normal
Mild
Moderate
Severe
(99%)
(95%)
(85%)
(50%)
(15%)
(5%)
(1%)
Subjects Score inside ()
Mental Status
MMSE (28)
Verbal Memory
CERAD Word List
Trial 1 (8)
Trial 2 (9)
Trial 3 (10)
5 min. Recall (9)
30 min. Recall (9)
30 min. Recognition (20)
WMS-III Logical Memory 1 (19)
WMS-III Logical Memory 2 (20)
Benson CFT: Delayed Recall (--)
Visual Memory
WMS-III Faces 1 (17)
WMS-III Faces 2 (19)
Remote Memory
WAIS-R Information (18)
Attention
Digit Span Fwd: Length (8)
Digit Span Bkwd: Length (5)
SDMT/WAIS-R Digit Symbol(14)
Language
Boston Naming Test (30)
Letter Fluency Total (14)
Category Fluency (29)
Benson CFT: Copy Drawing ()
Visual-Spatial
CERAD Drawing (11)
Read/Set Time (6)
WAIS-III Block Design (13)
Executive Skills
Insight (0)
Social Judgment (6)
WAIS-R NI/WAIS-III Similarities --)
Trails A (14)
Trails B (16)
Psychomotor Speed
Kendrick Digit Copy (54/100)
Standard Battery Version: C1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Date:
Institute for Memory Impairments and Neurological Disorders (MIND)
University of California, Irvine
Neuropsychological Test Battery
Summary Chart
GDS (0)
Legend
Test Year
69yo
68yo
67yo
Above Average
Normal
Mild
Moderate
Severe
(99%)
(95%)
(85%)
(50%)
(15%)
(5%)
(1%)
Subjects Score inside ()
Mental Status
MMSE (30)
Verbal Memory
CERAD Word List
Trial 1 (3)
Trial 2 (5)
Trial 3 (8)
5 min. Recall (8)
30 min. Recall (6)
30 min. Recognition (20)
WMS-III Logical Memory 1 (16)
WMS-III Logical Memory 2 (16)
Benson CFT: Delayed Recall (10)
Visual Memory
WMS-III Faces 1 (19)
WMS-III Faces 2 (19)
Remote Memory
WAIS-R Information (18)
Attention
Digit Span Fwd: Length (8)
Digit Span Bkwd: Length (6)
Symbol Digit Modality Test (52)
Language
Boston Naming Test (30)
Letter Fluency Total (13)
Category Fluency (26)
Visual-Spatial
Benson CFT: Copy Drawing (16)
CERAD Drawing (10)
Read/Set Time (5)
WAIS-III Block Design (14)
Executive Skills
Insight (0)
Social Judgment (6)
WAIS-R NI/WAIS-III Similarities (17)
Trails A (16)
Trails B (9)
Psychomotor Speed
Kendrick Digit Copy (58/100)
Standard Battery Version: C1

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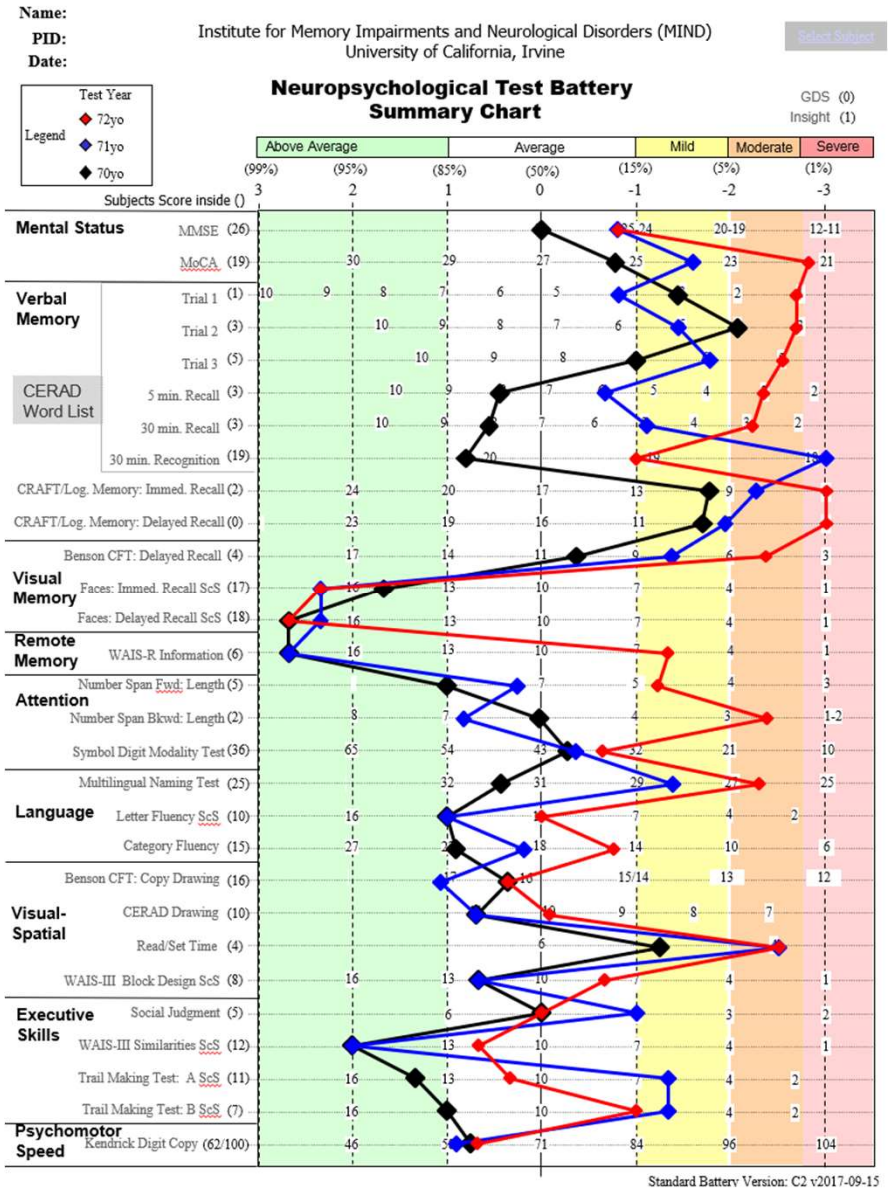
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Date:
Institute for Memory Impairments and Neurological Disorders (MIND)
University of California, Irvine
Neuropsychological Test Battery
Summary Chart
Legend
Test Year
72yo
71yo
70yo
GDS (0)
Insight (1)
Above Average
Average
Mild
Moderate
Severe
(99%) (95%) (85%) (50%) (15%) (5%) (1%)
3 2 1 0 -1 -2 -3
Subjects Score inside ()
Mental Status
MMSE (26)
MoCA (19)
Verbal Memory
CERAD Word List
Trial 1 (1)
Trial 2 (3)
Trial 3 (5)
5 min. Recall (3)
30 min. Recall (3)
30 min. Recognition (19)
CRAFT/Log. Memory: Immed. Recall (2)
CRAFT/Log. Memory: Delayed Recall (0)
Visual Memory
Benson CFT: Delayed Recall (4)
Faces: Immed. Recall ScS (17)
Faces: Delayed Recall ScS (18)
Remote Memory
WAIS-R Information (6)
Attention
Number Span Fwd: Length (5)
Number Span Bkwd: Length (2)
Symbol Digit Modality Test (36)
Language
Multilingual Naming Test (25)
Letter Fluency ScS (10)
Category Fluency (15)
Visual-Spatial
Benson CFT: Copy Drawing (16)
CERAD Drawing (10)
Read/Set Time (4)
WAIS-III Block Design ScS (8)
Executive Skills
Social Judgment (5)
WAIS-III Similarities ScS (12)
Trail Making Test: A ScS (11)
Trail Making Test: B ScS (7)
Psychomotor Speed
Kendrick Digit Copy (62/100)
Standard Battery Version: C2 v2017-09-15

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Clinical Summary Table

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Summary	R19 75yo	R18 73yo	R17 72yo	R16 71yo	R15 70yo	R14 69yo	R13 68yo	R12 67yo	R11 67yo	R0 54yo
MMSE	11	--	26	26	30	30	30	30	28	30
MoCA	5	10	19	22	24	--	--	--	--	--
UDSD		[Dem]	[Dem]	[MCI]	[MCI]	[MCI]	[QCI]	[Norm]	[Norm]	[Norm]
Etiology		[AD_P]	[AD_P] [Dep]	[AD_P] [Dep]	[AD_P]	[AD_P]	[AD_P]	[None]	[None]	[None]

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Imaging Report:
MRI at 68 - 73
Amyloid PET at 68

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David Sultzer, MD
S. Ahmad Sajjadi, MD PhD

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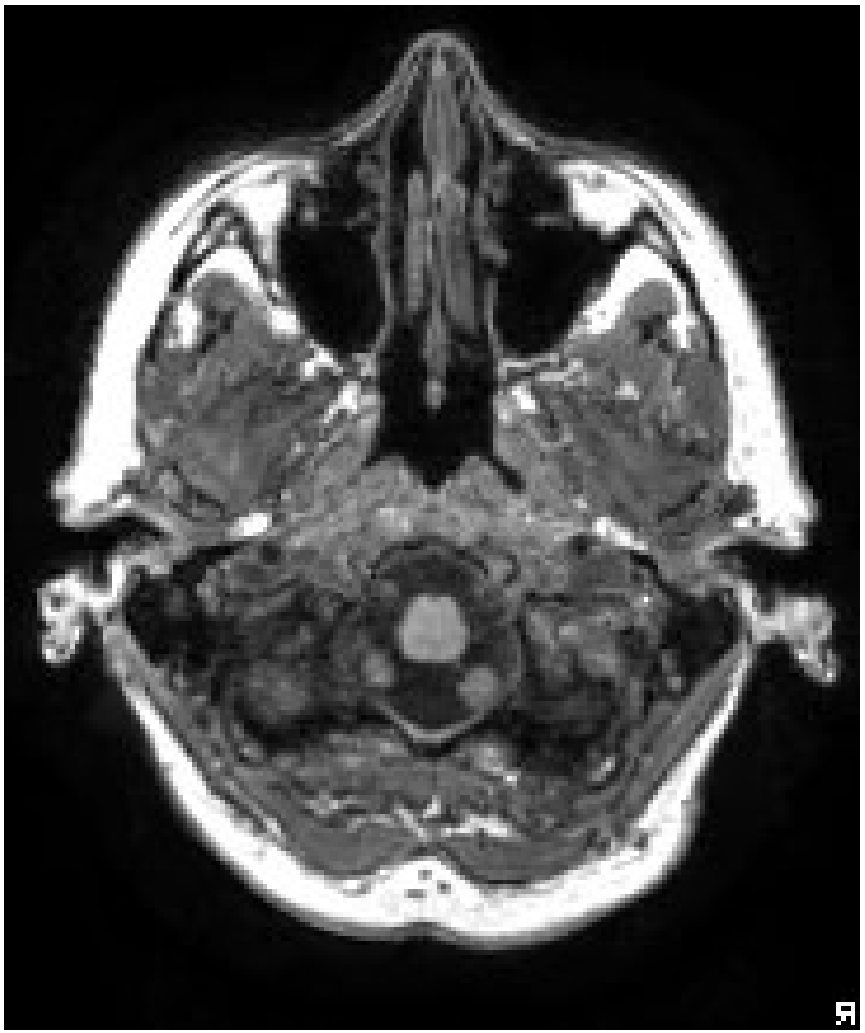
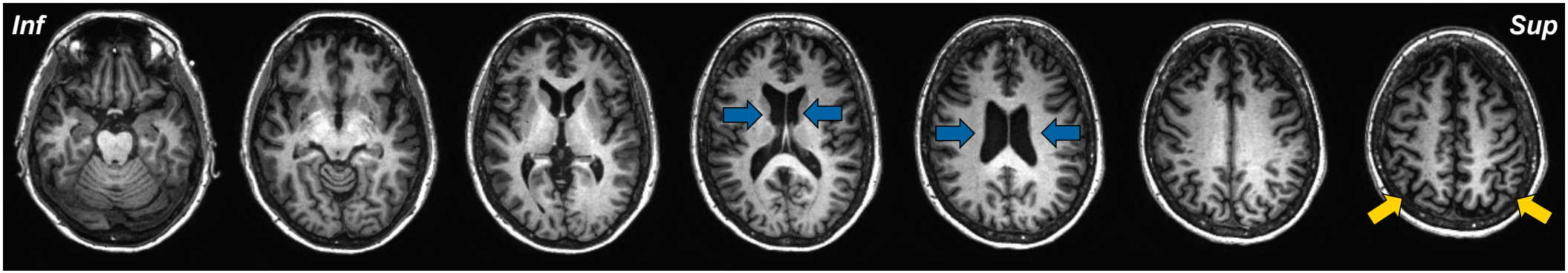
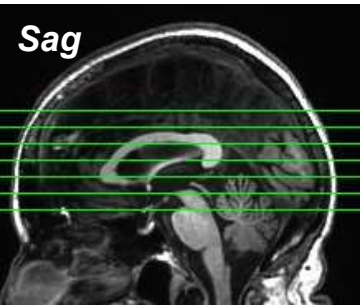
MRI at 68: T1w



MRI at 68: T1w - Atrophy

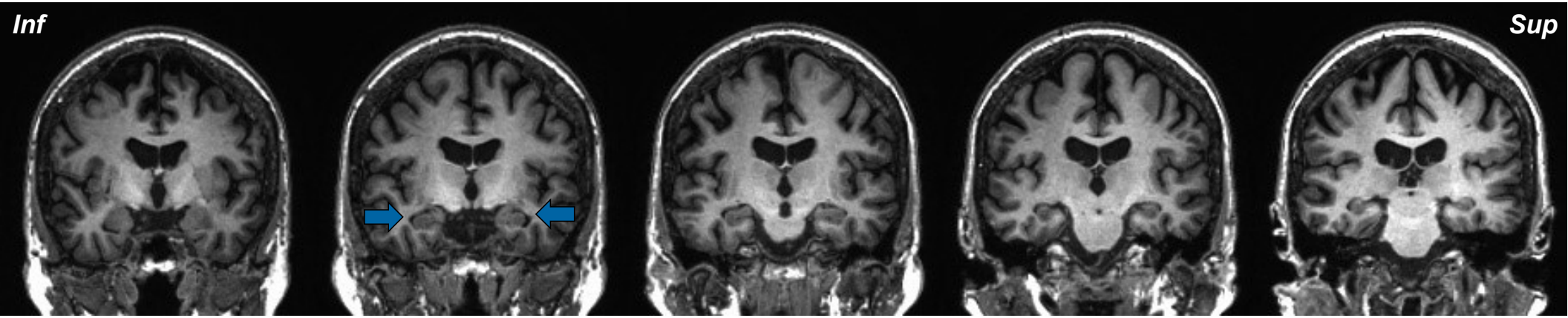
- Participant presented with mild global atrophy:
  - Moderate ventricular enlargement (**blue** arrows)
  - Mild cortical atrophy (**gold** arrows)

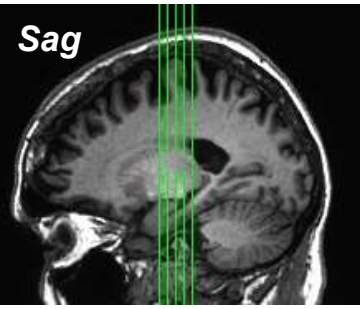




MRI at 68: T1w - Hippocampus

- Mild degree of hippocampal atrophy.
  - Inferior lateral ventricles slightly visible anteriorly (**blue** arrows)





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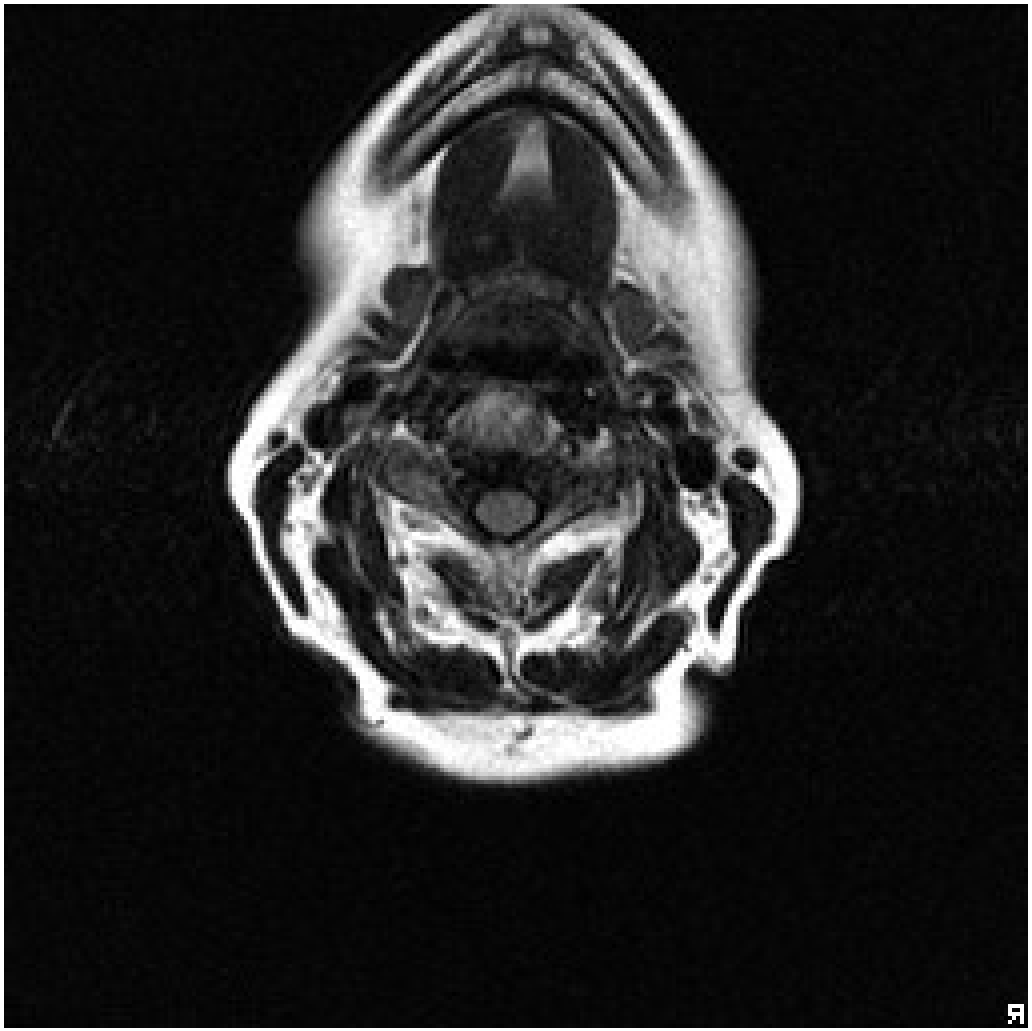
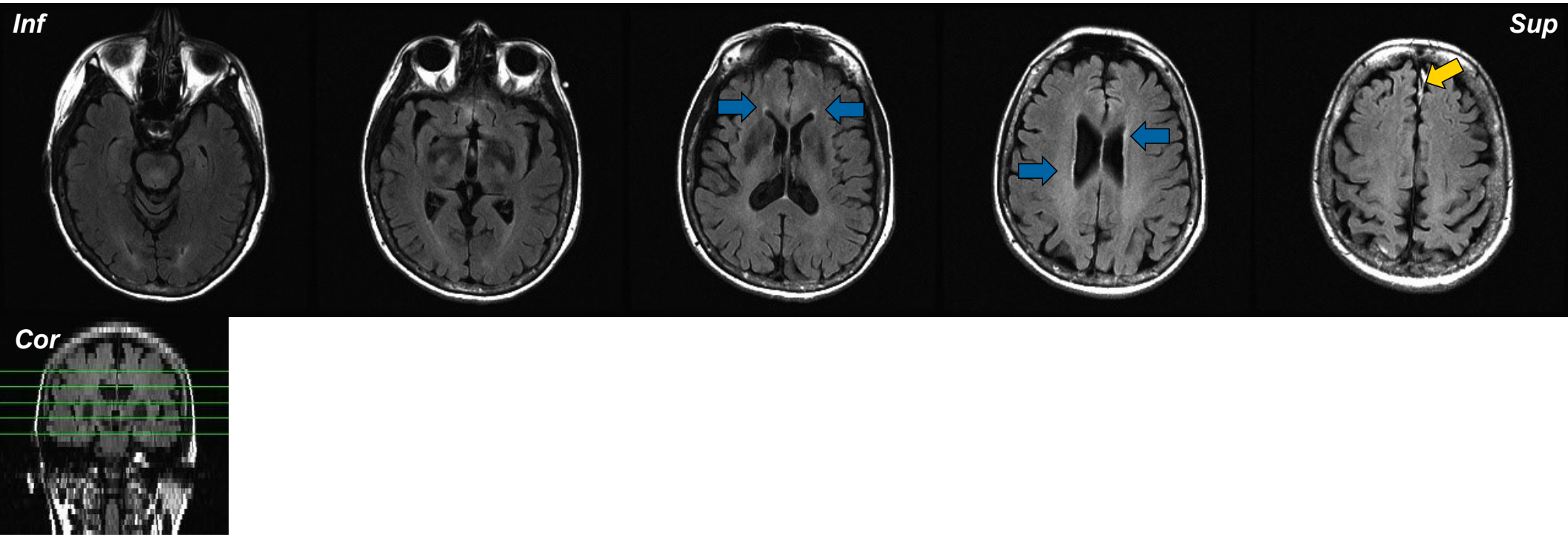
MRI at 68: FLAIR



MRI at 68: FLAIR - WMH

- Participant presented with a mild degree of WMH:
  - Some periventricular WMH (**blue** arrows)
  - Midline hyperintensity (**gold** arrow)



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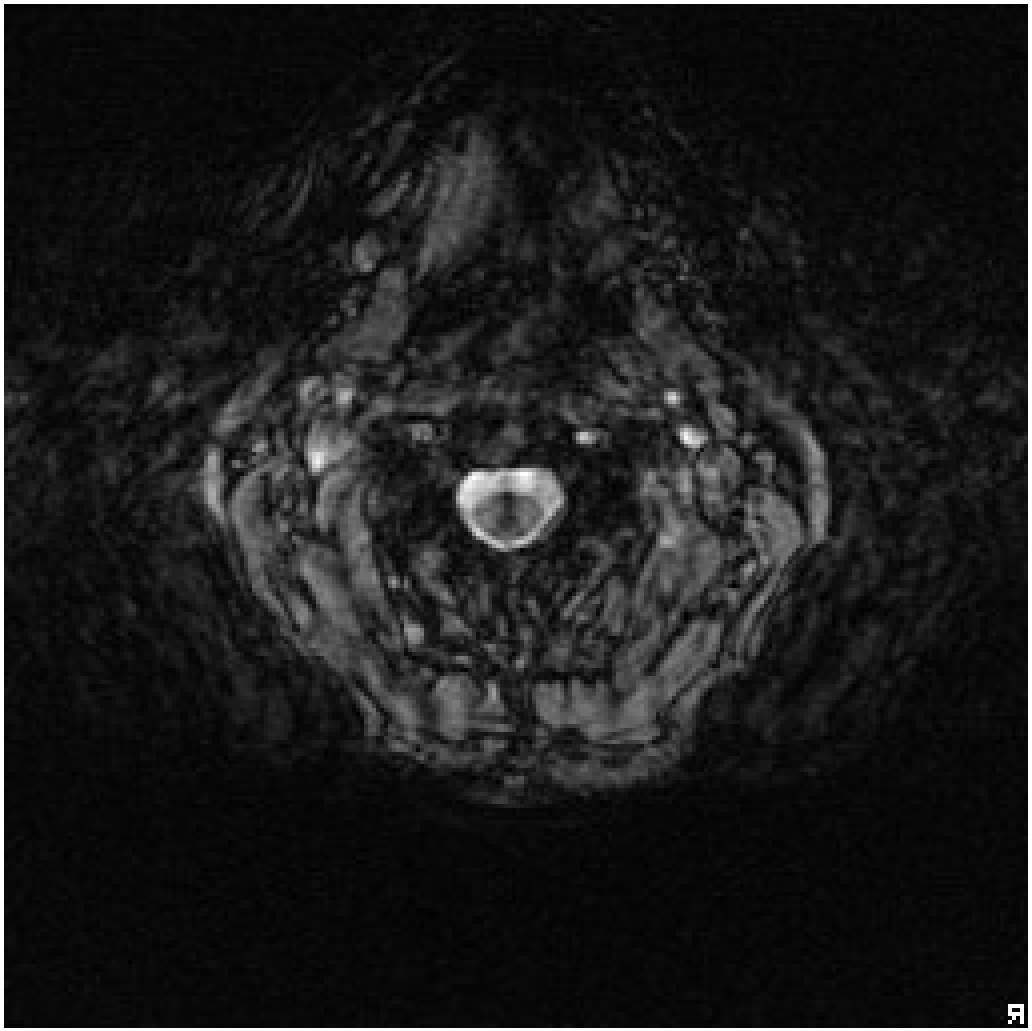
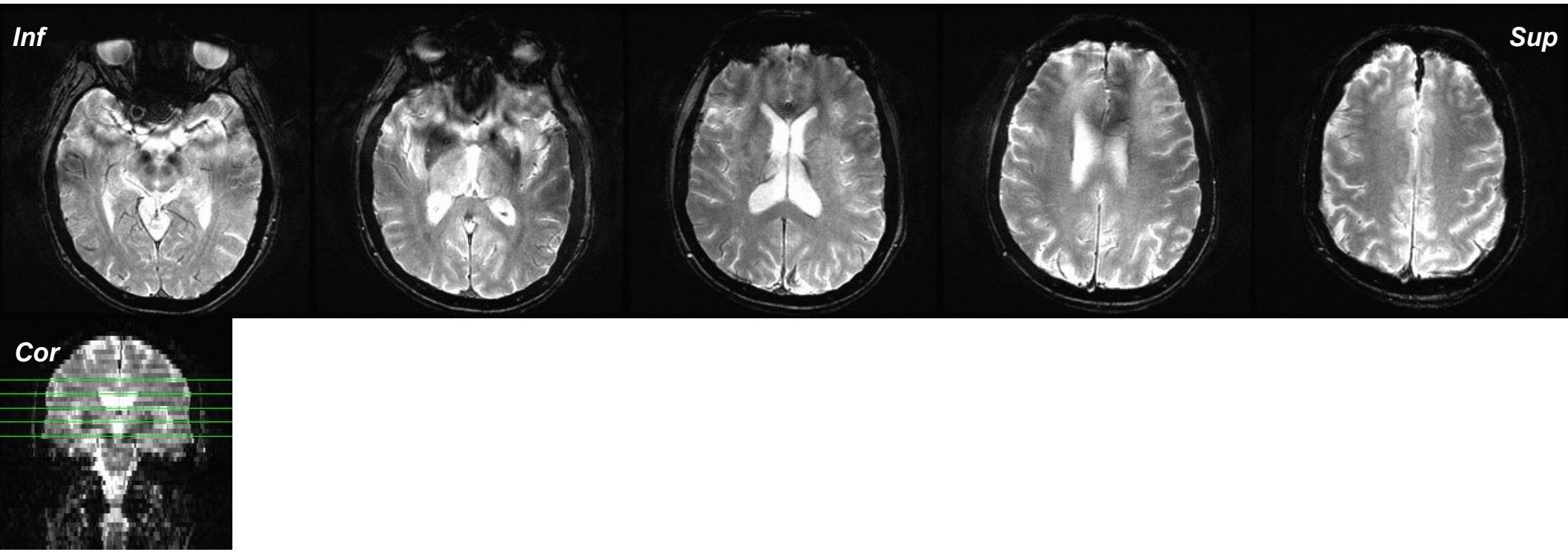
*MRI at 68: T2**



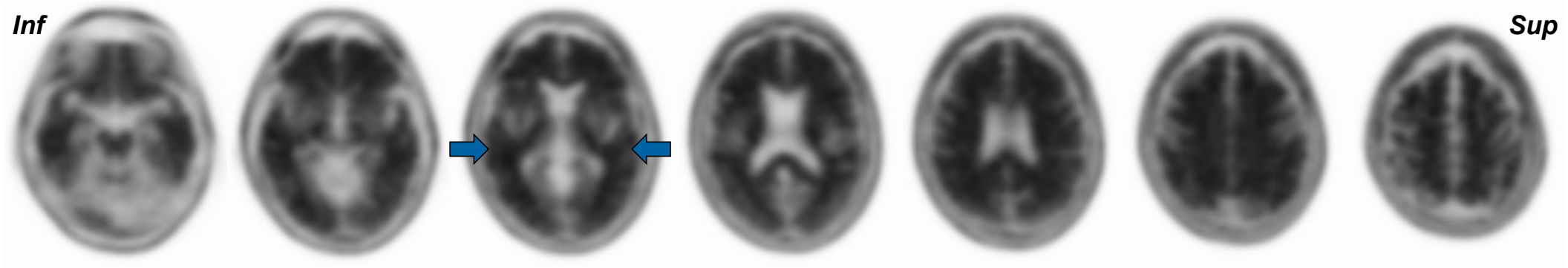
*MRI at 68: T2**

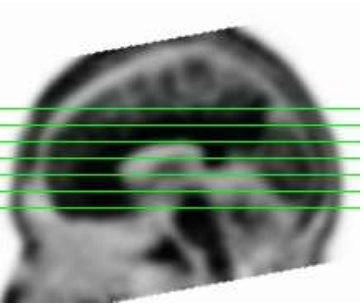
- No findings noted.



Amyloid PET at 68

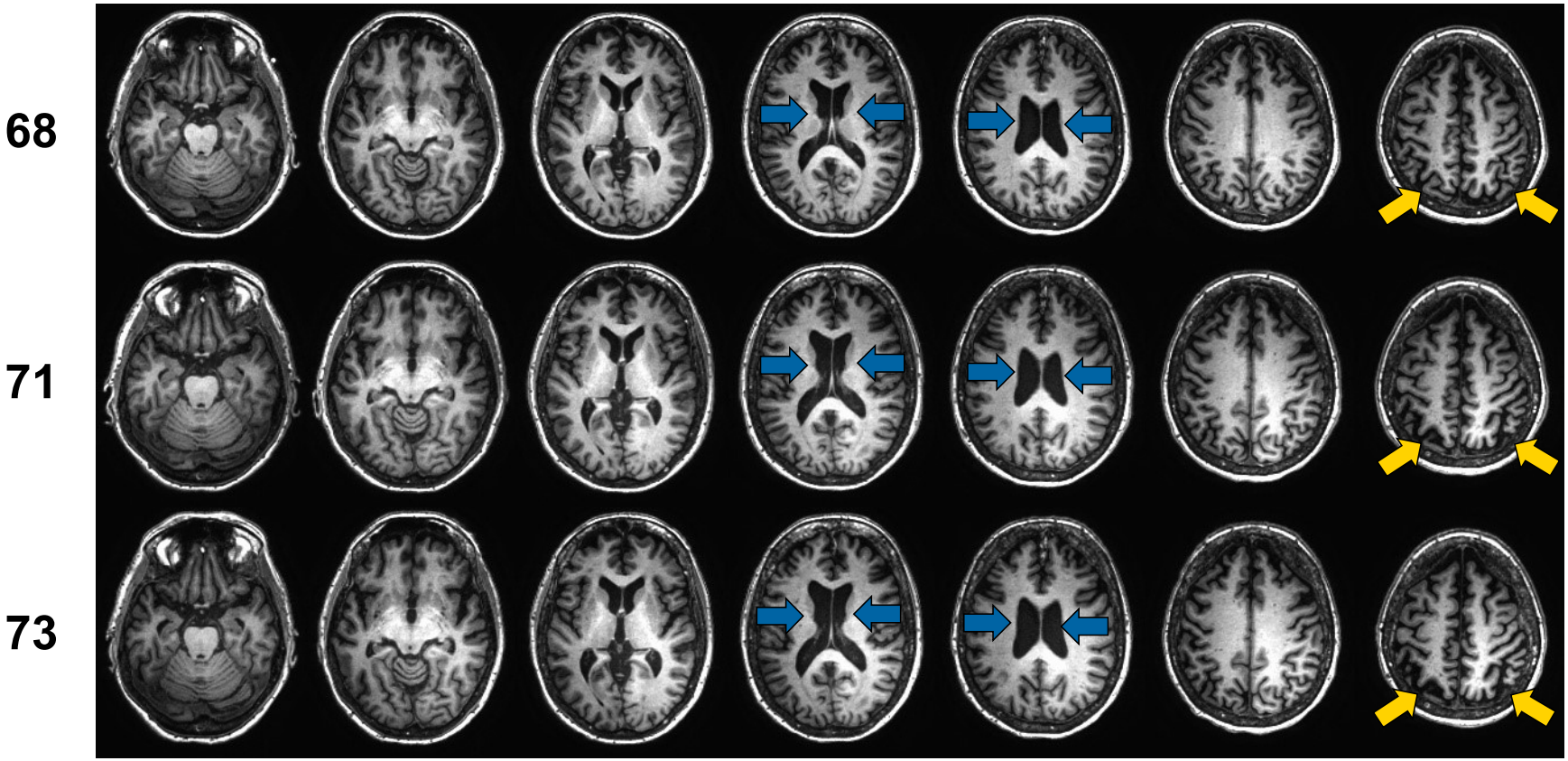
- Amyloid positive:
  - WM only somewhat discernible at mid-axial levels (**blue** arrows)
  - SUVr: 1.68 (landau cortical target/cerebellum reference, approx. equivalent to centiloid of ~120)





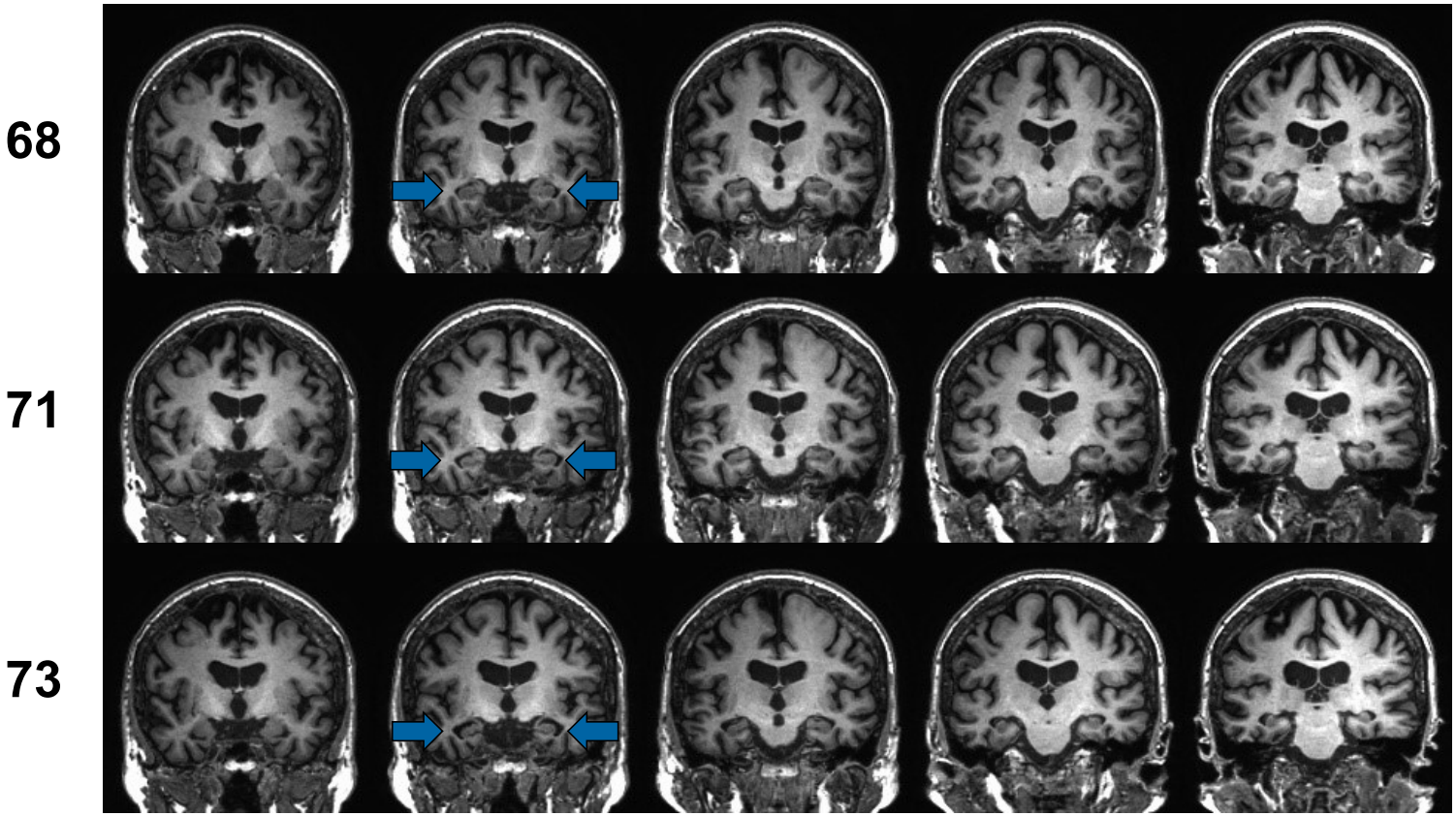
T1w – Global atrophy from 68 to 73

- Progressive atrophy:
  - Ventricular enlargement (**blue** arrows) cortical atrophy (**gold** arrows)



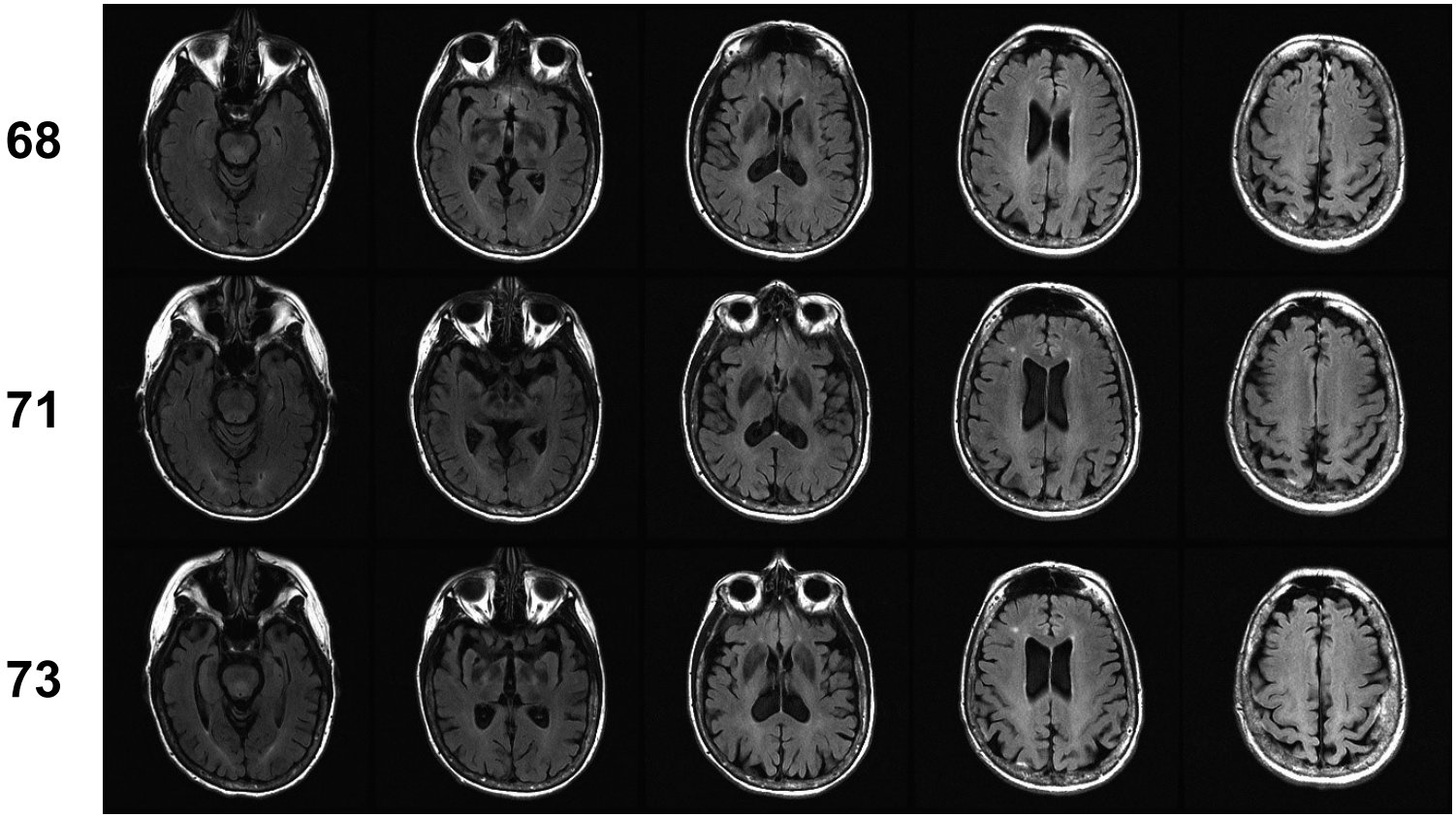
T1w – Hippocampal atrophy from 68 to 73

- Progressive atrophy:
  - Inferior lateral ventricles more visible over time (**blue** arrows)



FLAIR – WMH from 68 to 73

- Minimal increase in WMH.



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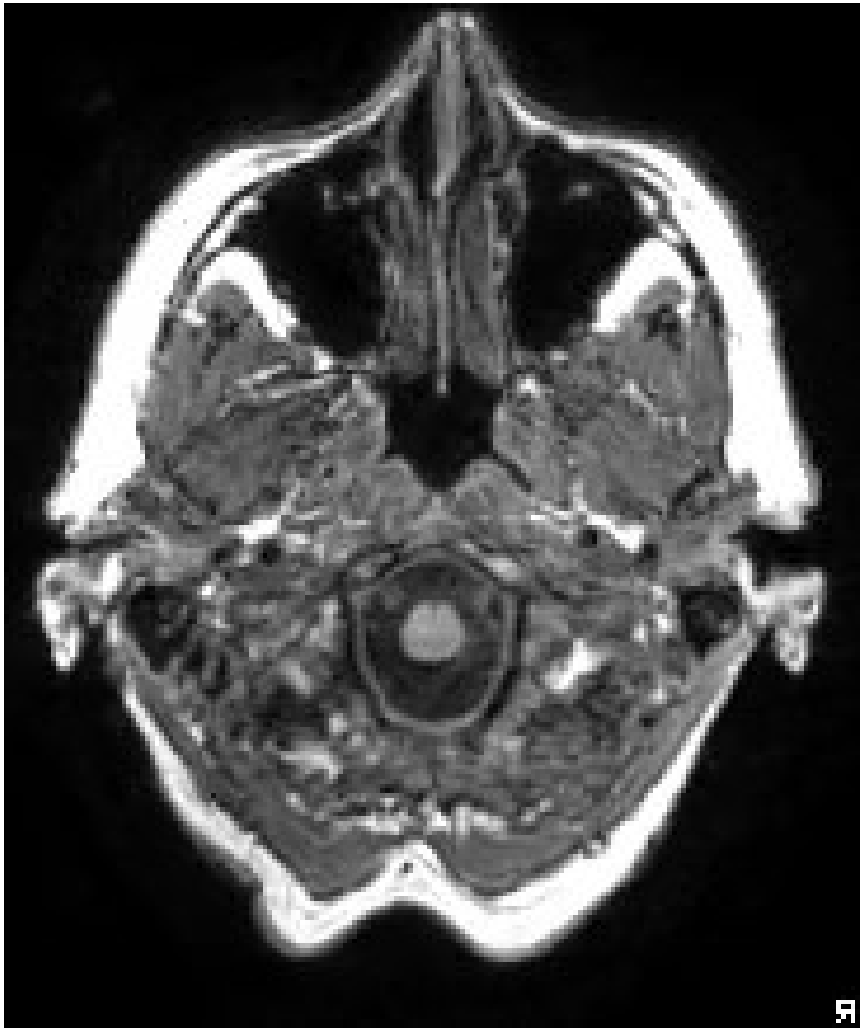
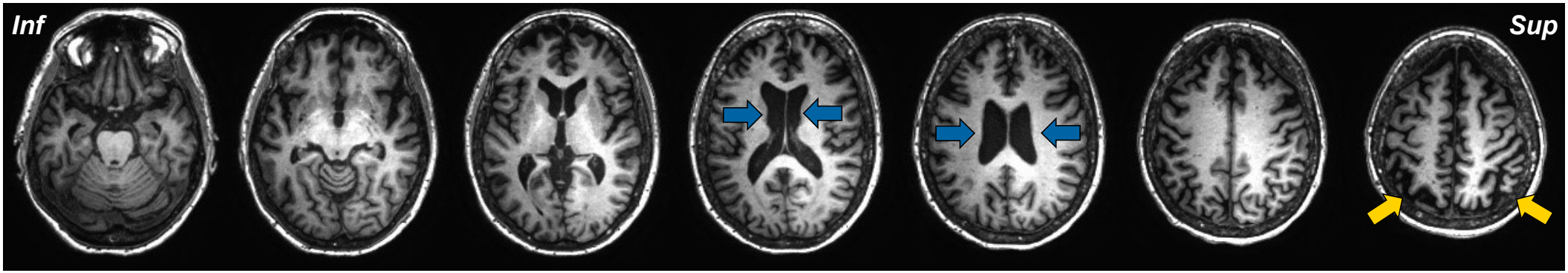
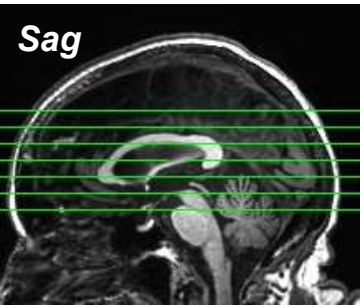
MRI at 73: T1w



MRI at 73: T1w - Atrophy

- Participant presented more moderate global atrophy:
  - Moderate ventricular enlargement (**blue** arrows)
  - Mild cortical atrophy (**gold** arrows)





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MRI at 73: T1w - Hippocampus

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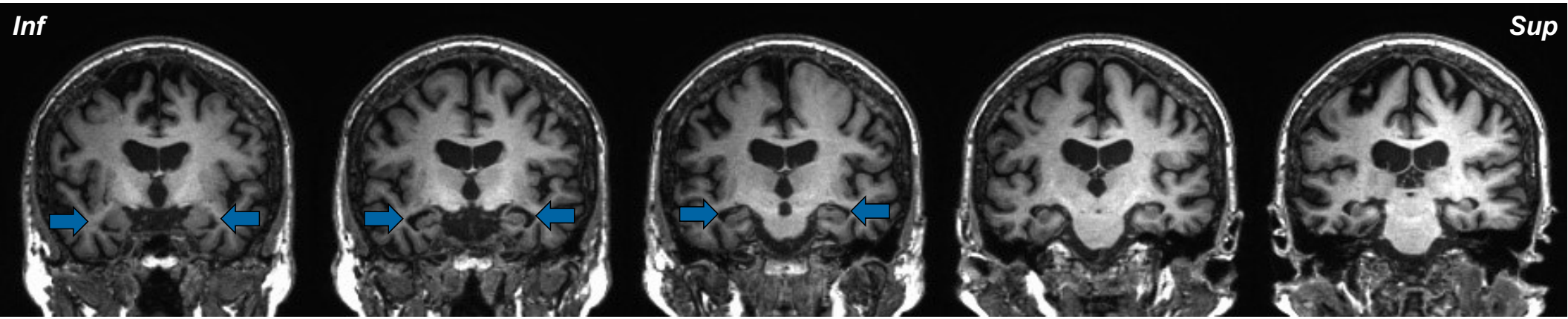
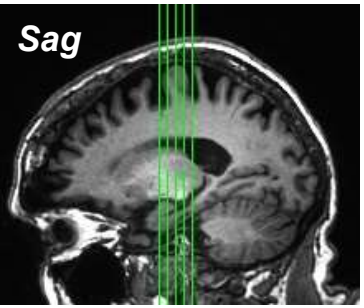
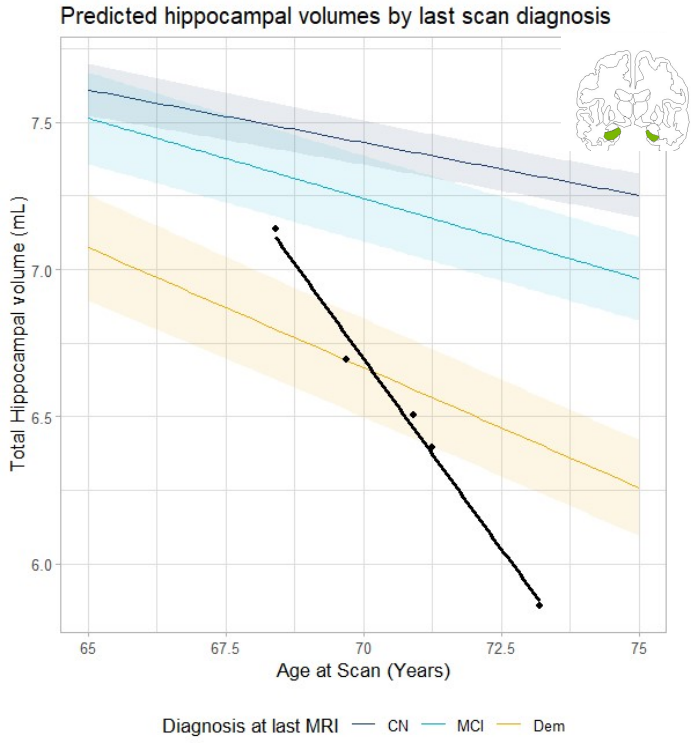
- Moderate degree of hippocampal atrophy.
  - Inferior lateral ventricles visible anteriorly (**blue** arrows)

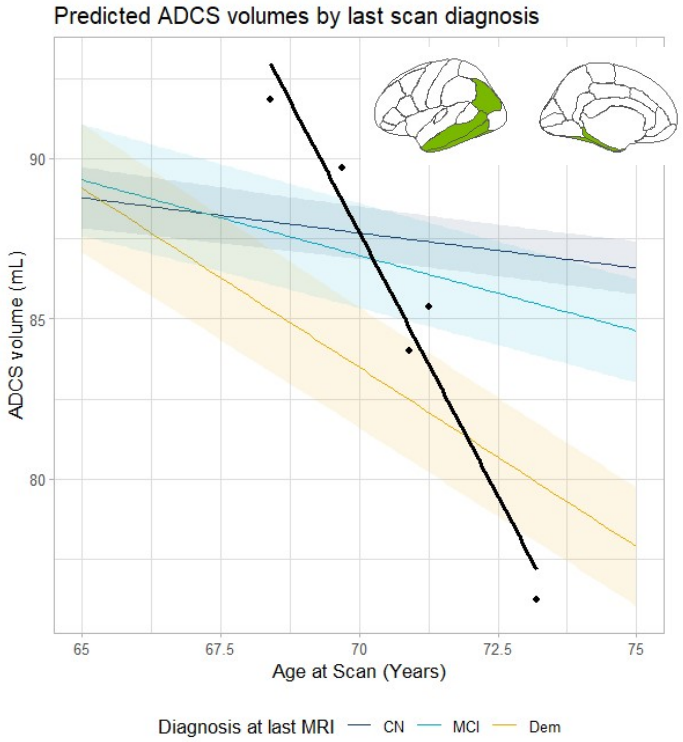


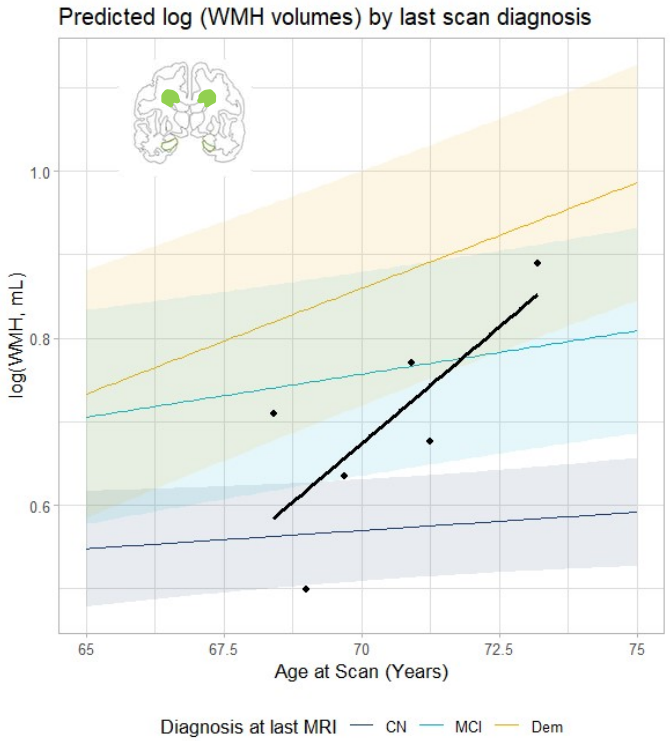


Distributions of Volumes: Comparison to ADNI ADSP

- Predictions (from ADNI ADSP) for participant (colored lines and shades) with observed volumes (non-harmonized)







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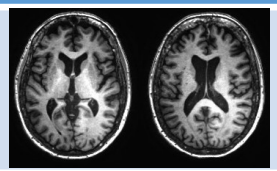
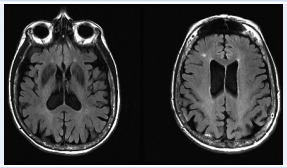
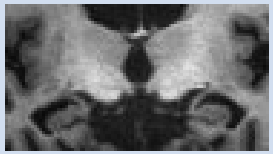
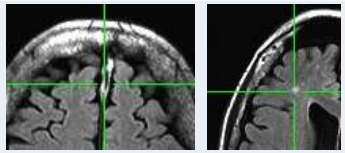
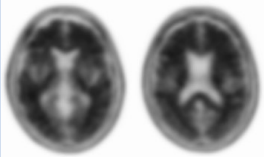
Imaging Summary Table

Region	Findings	Representative Image
Gross Findings	Moderate global atrophy, more central than cortical.	
White Matter Lesions	Mild degree of WMH.	
Hippocampus	Moderate visual hippocampal atrophy. Low hippocampal volume.	
Lesions, infarcts, PVS, etc	Falx ossification with fat. Lesion in left frontal WM.	
Amyloid PET	Positive by both visual read and SUVr.	

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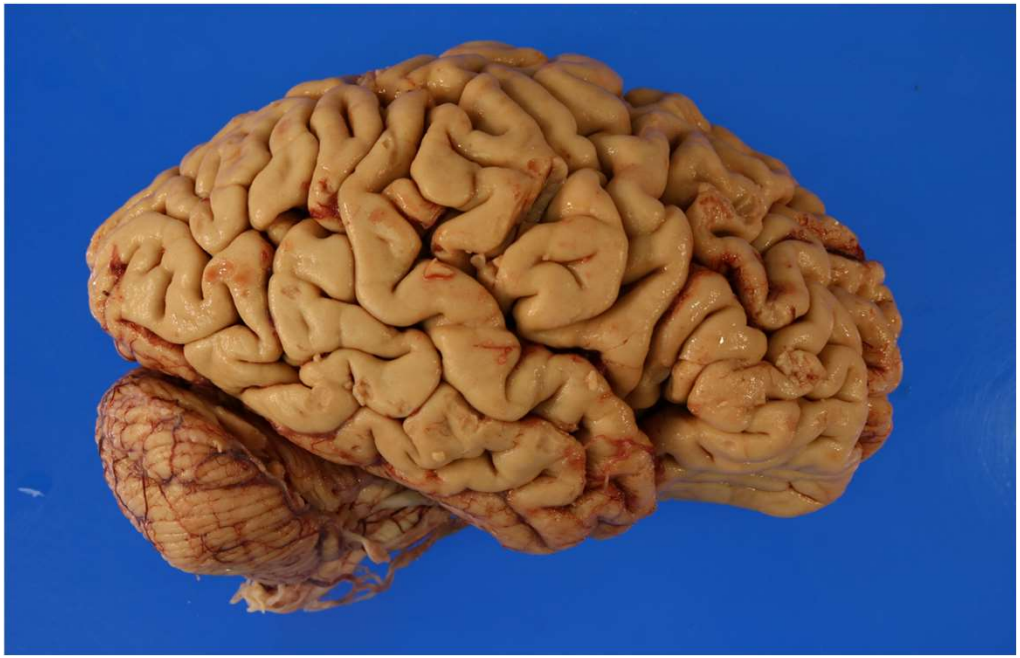
Neuropathology Report:
Age at death of 76

Jerry Lou, MD
William Yong, MD

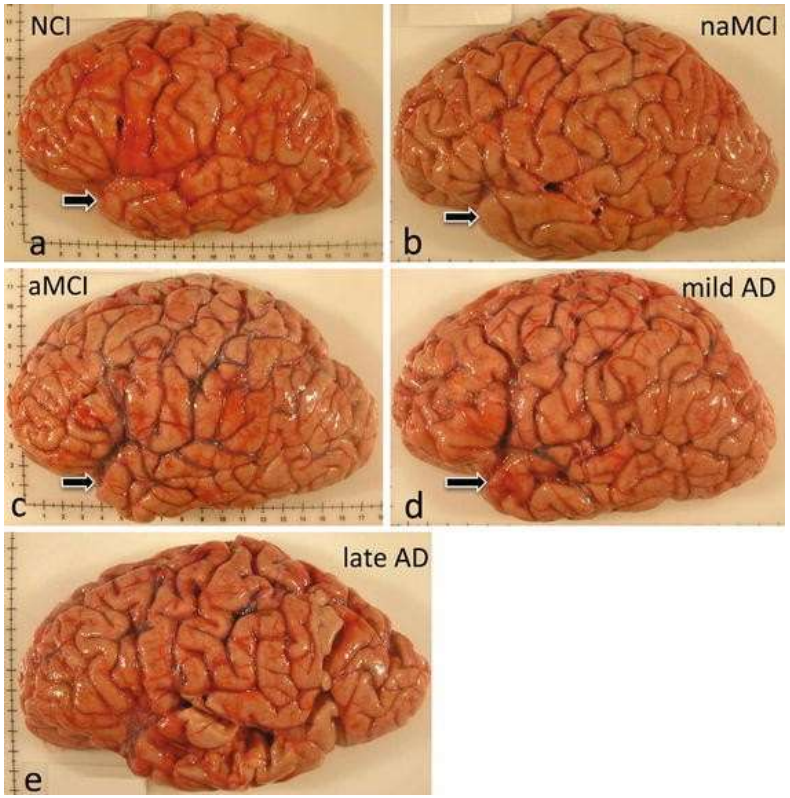
Cortical Atrophy

Participant



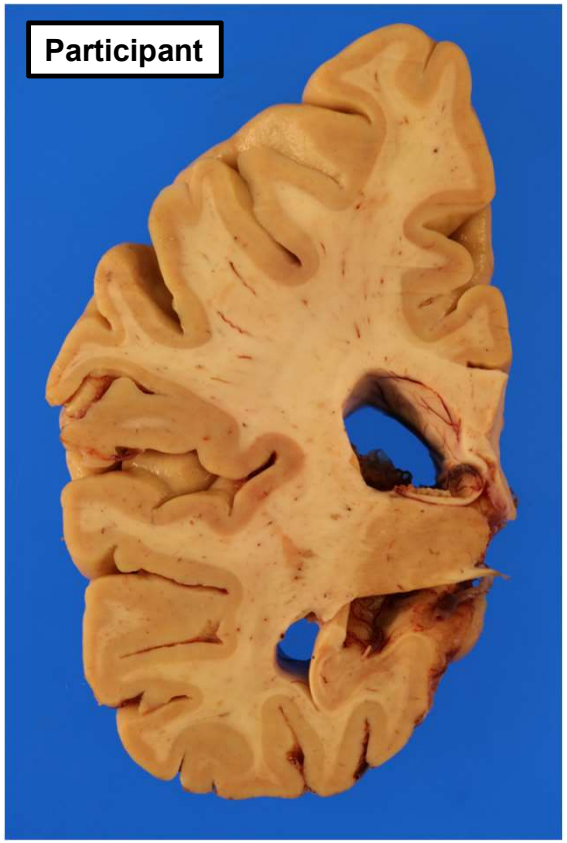
Moderate cortical atrophy

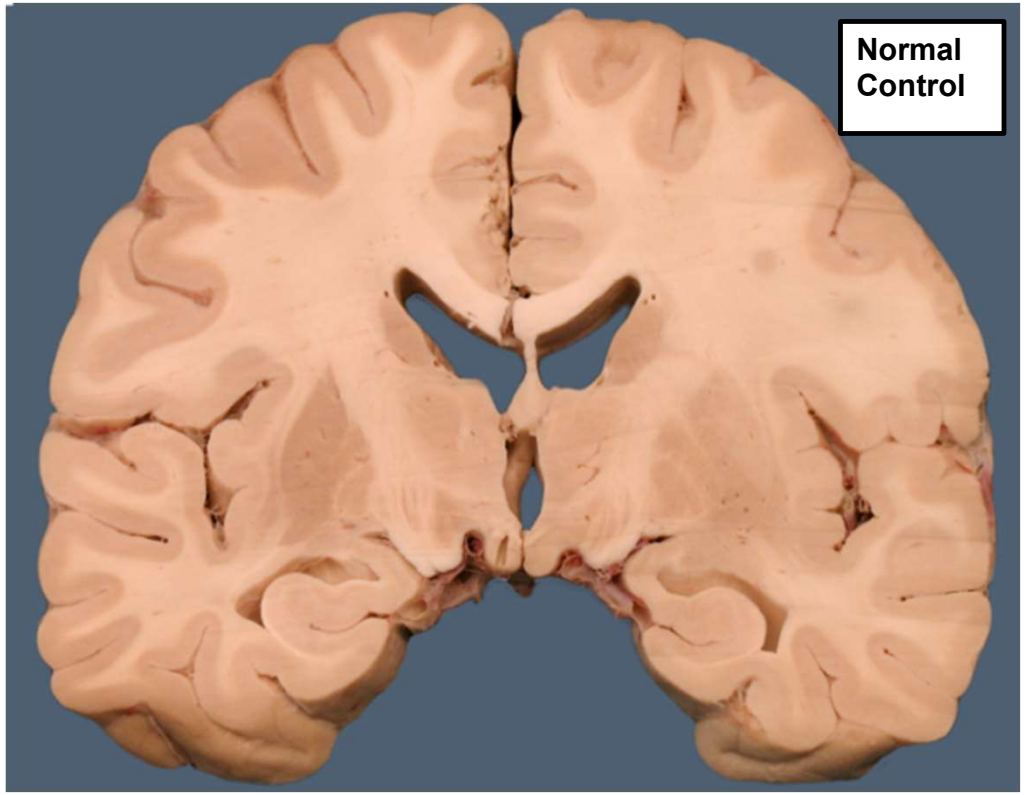
Normal Control



Mufson, E.J., Binder, L., Counts, S.E. et al. Mild cognitive impairment: pathology and mechanisms. Acta Neuropathol 123, 13–30 (2012).

Hippocampal Atrophy



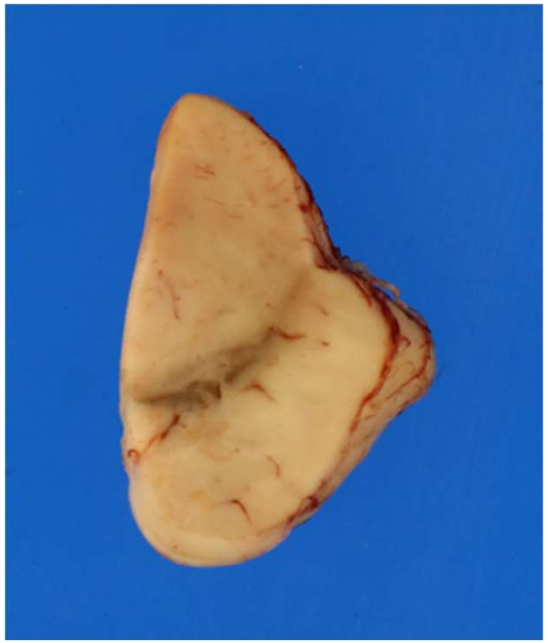


Mild-Moderate hippocampal atrophy

Kurian KM, Moss TH, Camelo-Piragua S. **Atlas of Gross Neuropathology: A Practical Approach**. Cambridge University Press; 2014.

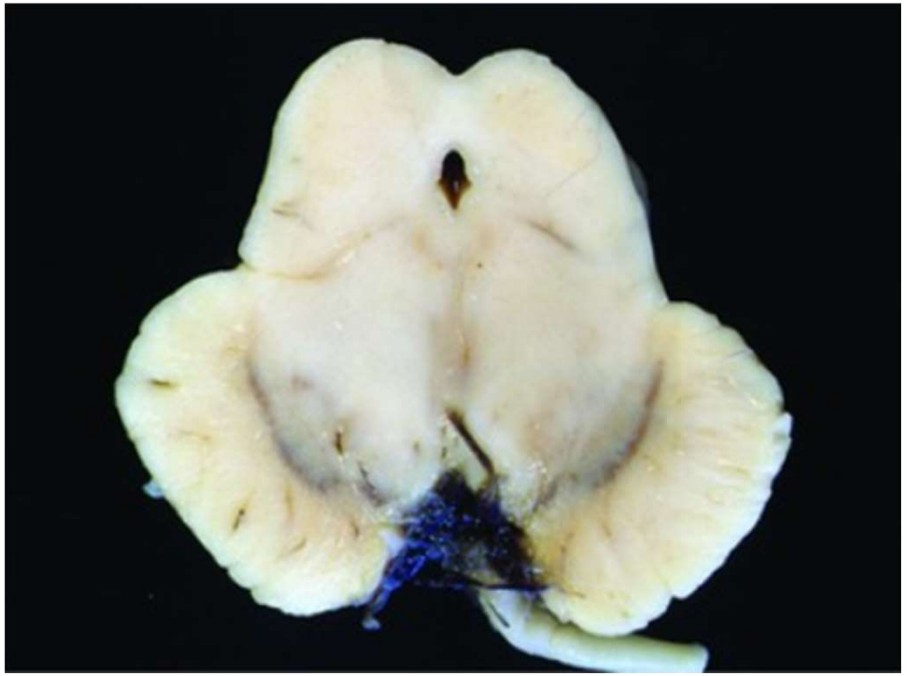
Substantia Nigra Pallor

Participant



Mild pallor of substantia nigra

Normal Control



Kurian, K. M., Moss, T. H., & Camelo-Piragua, S. (2014). Neurodegenerative disease. Atlas of Gross Neuropathology, 146–168. https://doi.org/10.1017/CBO9781139680783.010

Locus Coeruleus Pallor

Participant

Inconspicuous locus coeruleus

Normal Control

Kurian, K. M., Moss, T. H., & Camelo-Piragua, S. (2014). Neurodegenerative disease. Atlas of Gross Neuropathology, 146–168. https://doi.org/10.1017/CBO9781139680783.010

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ADNC: A score

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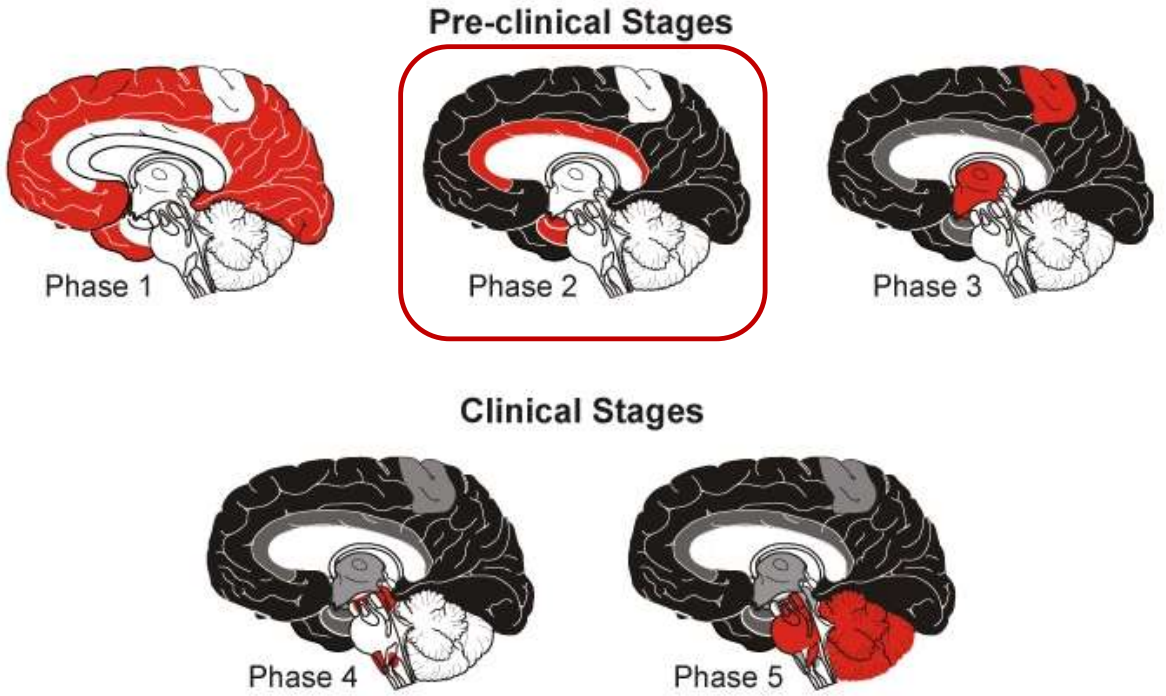
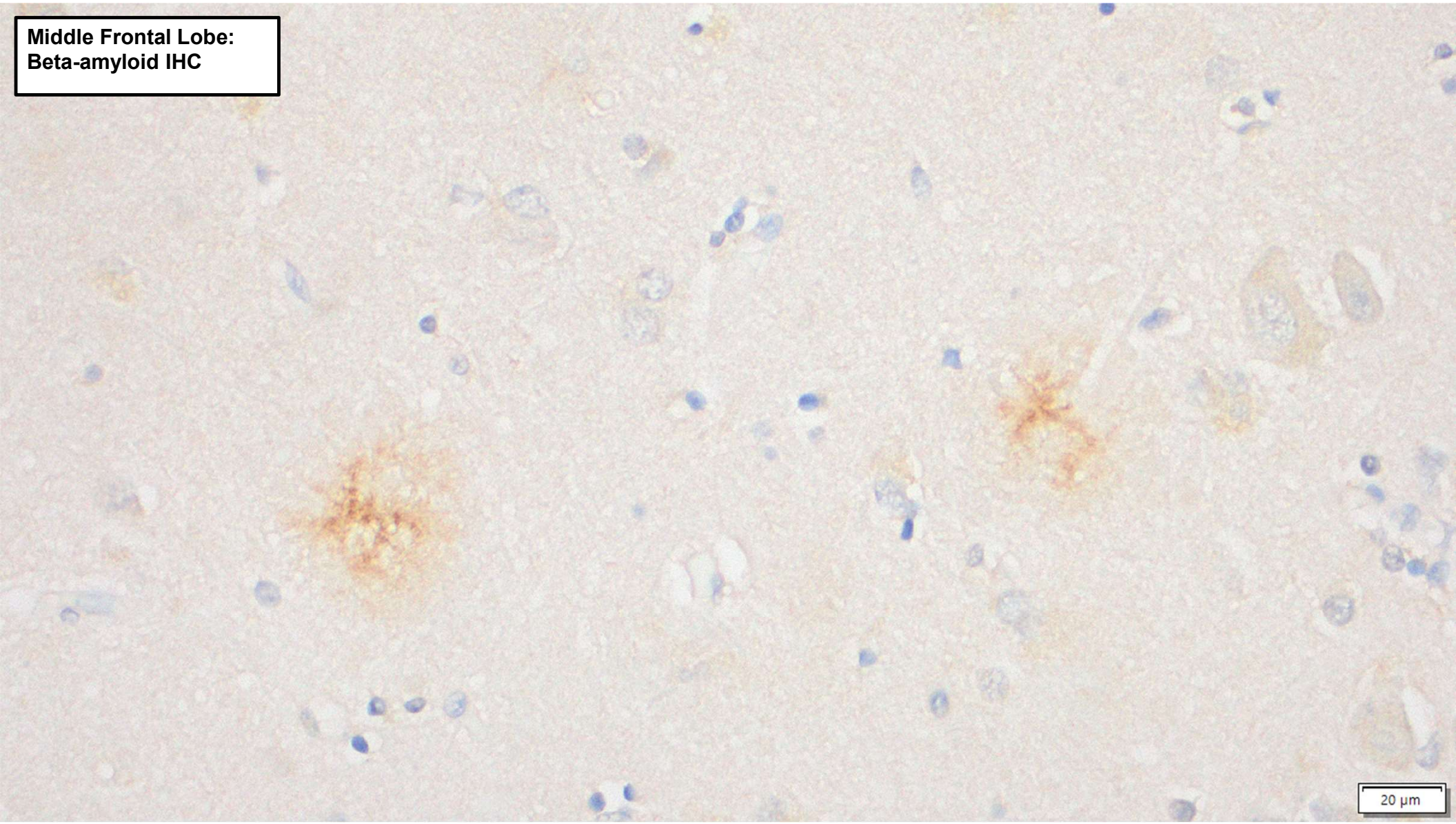
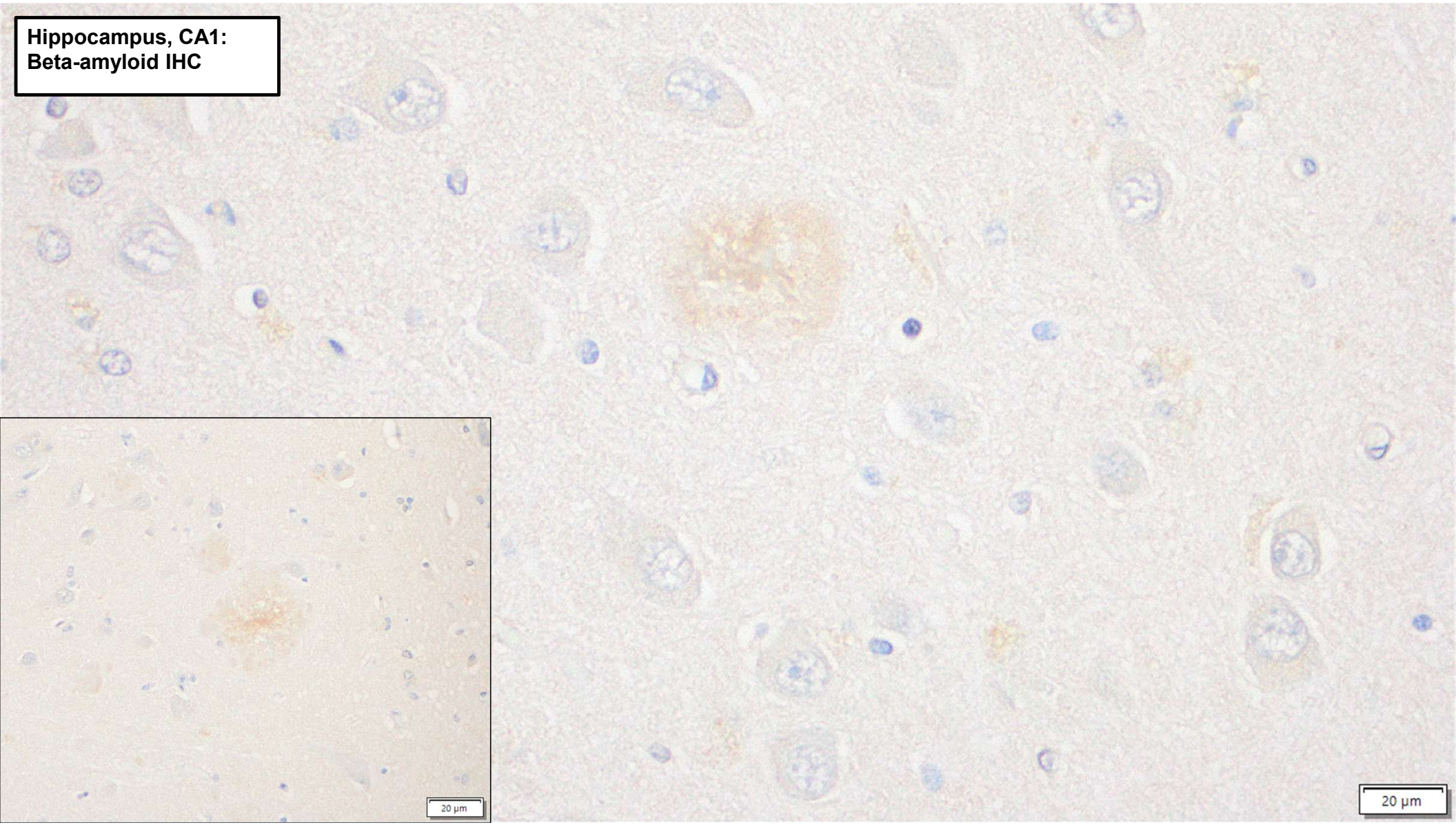
Thal Phase **2 (A1)**



A=0: Thal phase 0.
A=1: Thal phase 1 or 2.
A=2: Thal phase 3.
A=3: Thal phases 4 or 5.


Middle Frontal Lobe:
Beta-amyloid IHC
20 µm


Hippocampus, CA1:
Beta-amyloid IHC
20 µm
20 µm

Amyloid Plaques

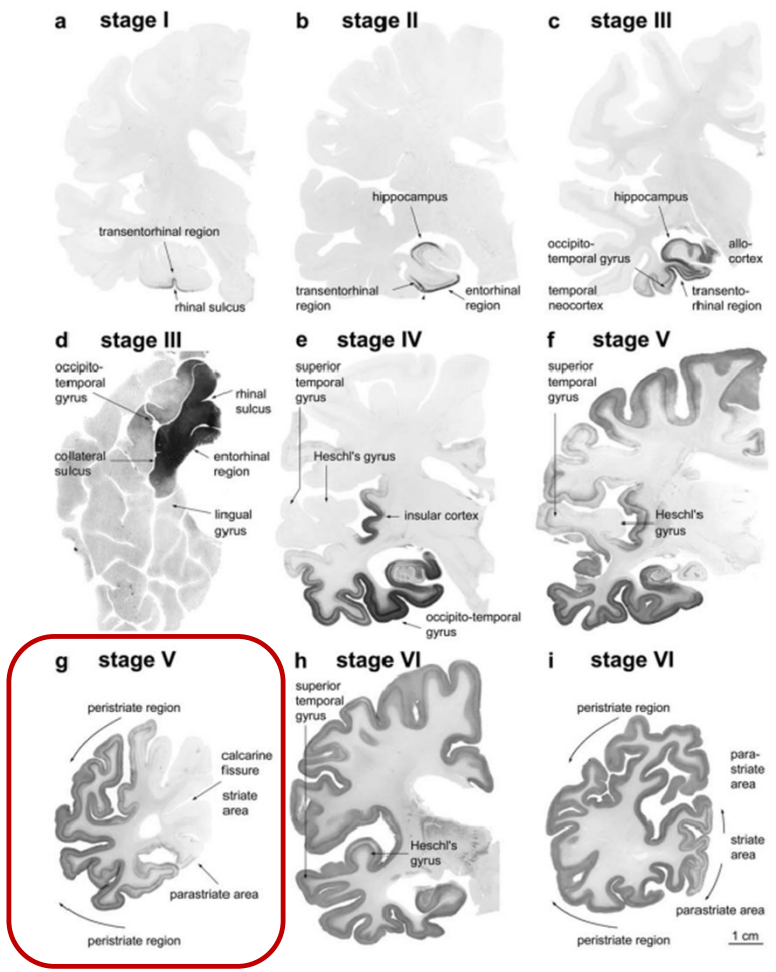
Present:
middle frontal, hippocampus.

Thal Phase: 2

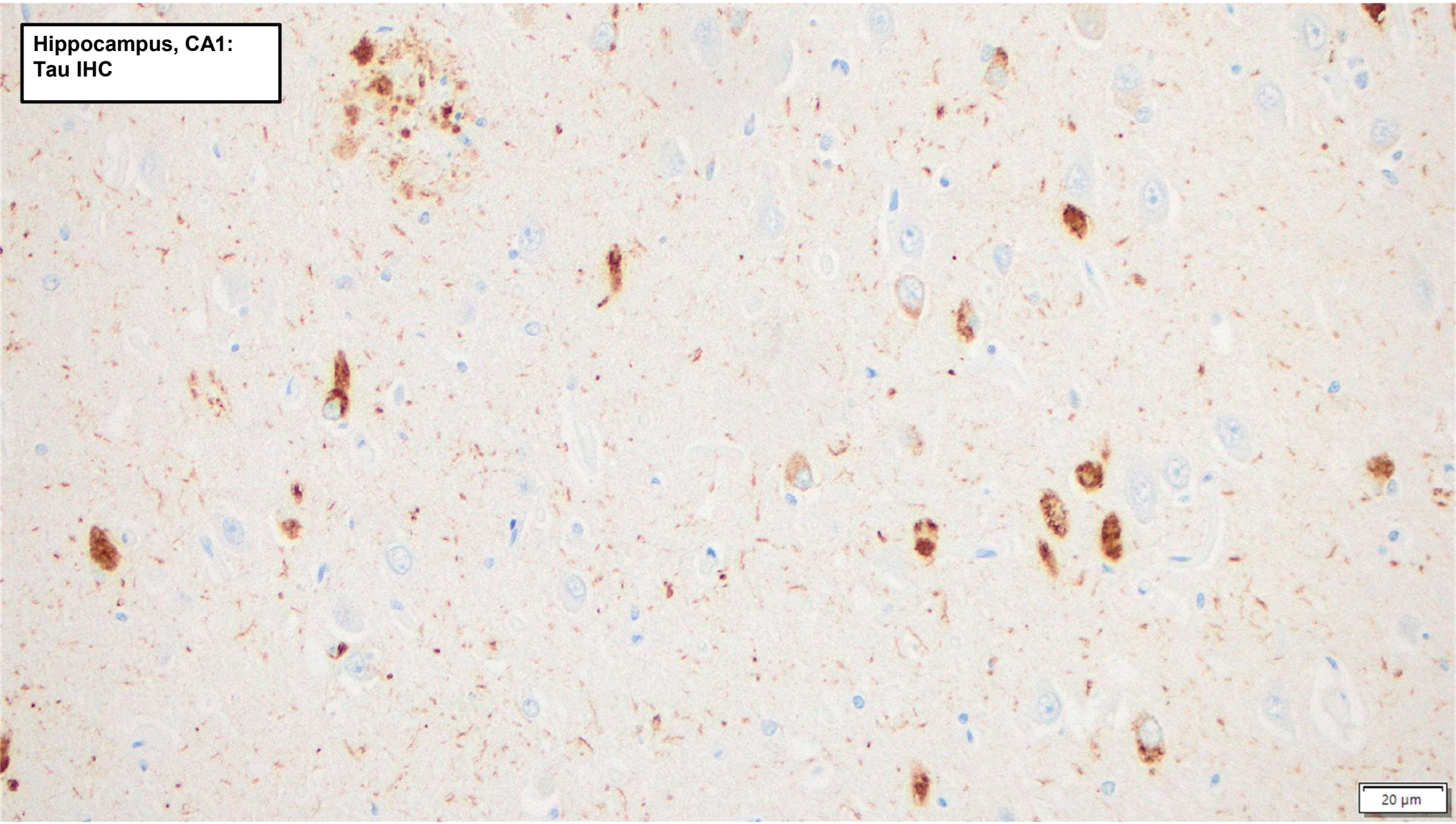
A Score: 1

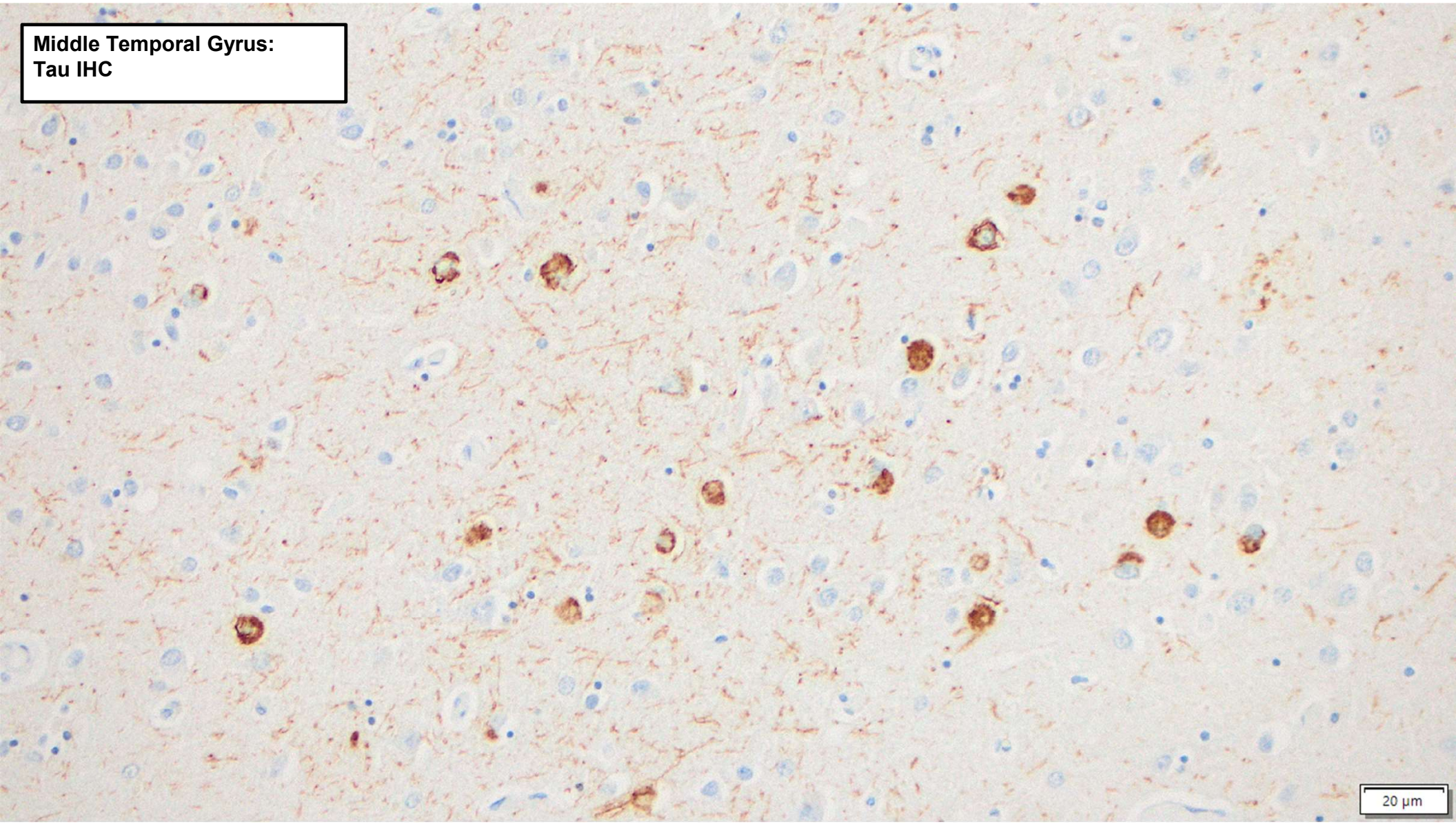
ADNC: B score

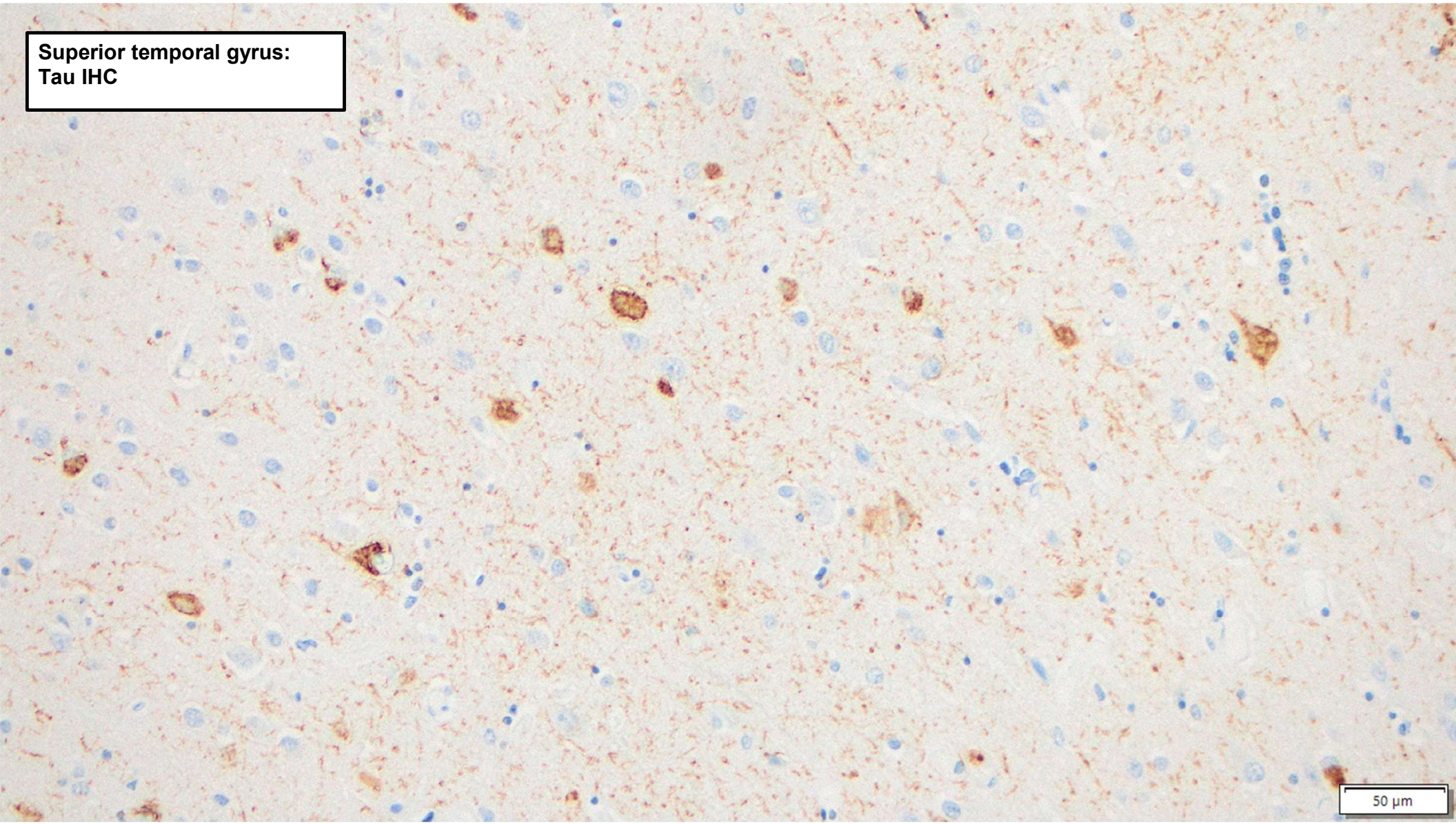
Braak stage **V** for neurofibrillary degeneration **(B3)**

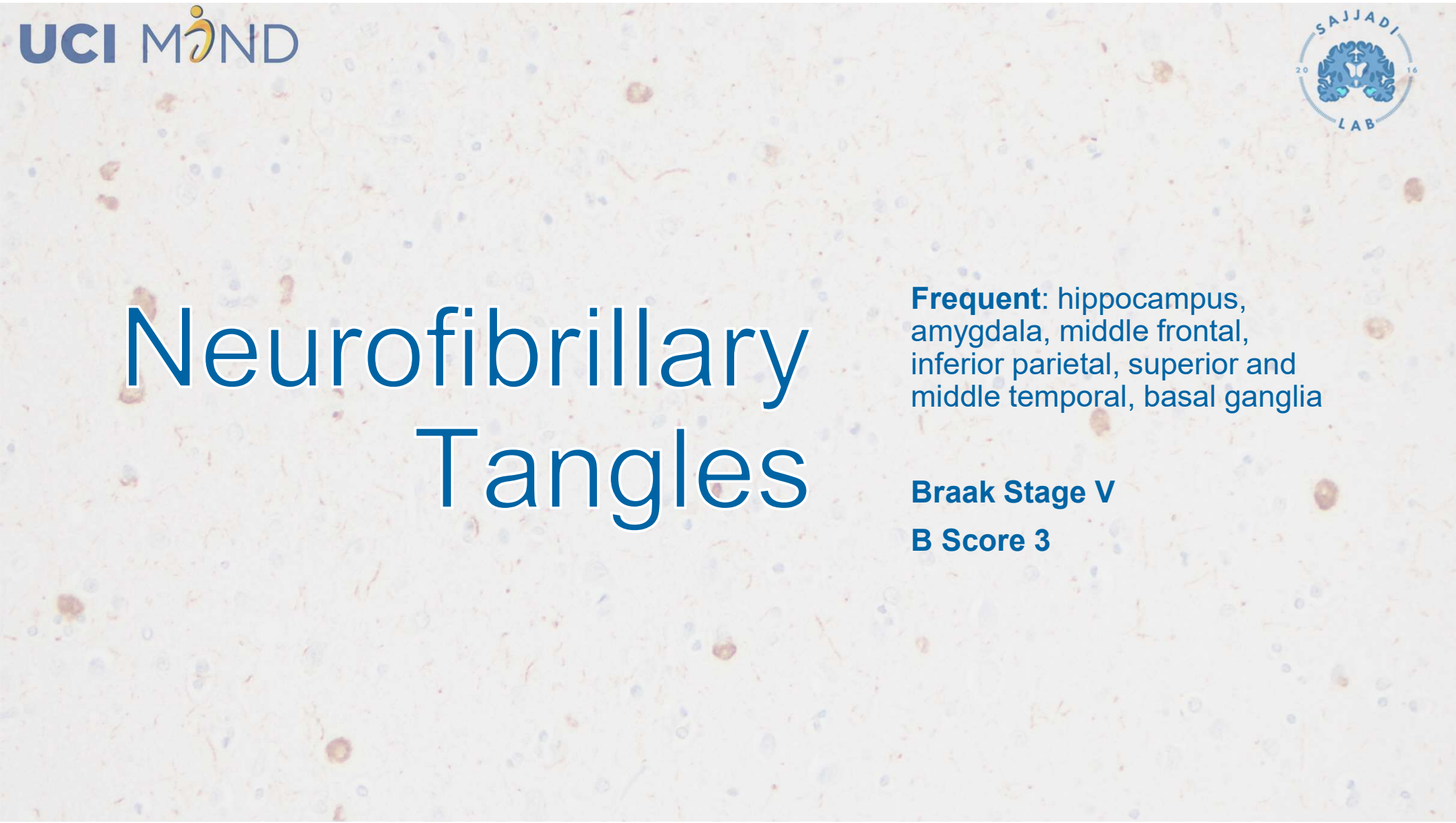


- ☐ 0 Stage 0: AD-type neurofibrillary degeneration not present (B0)
- ☐ 1 Stage I (B1)
- ☐ 2 Stage II (B1)
- ☐ 3 Stage III (B2)
- ☐ 4 Stage IV (B2)
- ☐ 5 Stage V (B3)
- ☐ 6 Stage VI (B3)


Hippocampus, CA1:
Tau IHC
20 µm


Middle Temporal Gyrus:
Tau IHC
20 µm


Superior temporal gyrus:
Tau IHC
50 µm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2016
LAB
Neurofibrillary Tangles
Frequent: hippocampus, amygdala, middle frontal, inferior parietal, superior and middle temporal, basal ganglia
Braak Stage V
B Score 3

ADNC: C score

CERAD score for density of neocortical neuritic plaques – **Moderate (C2)**

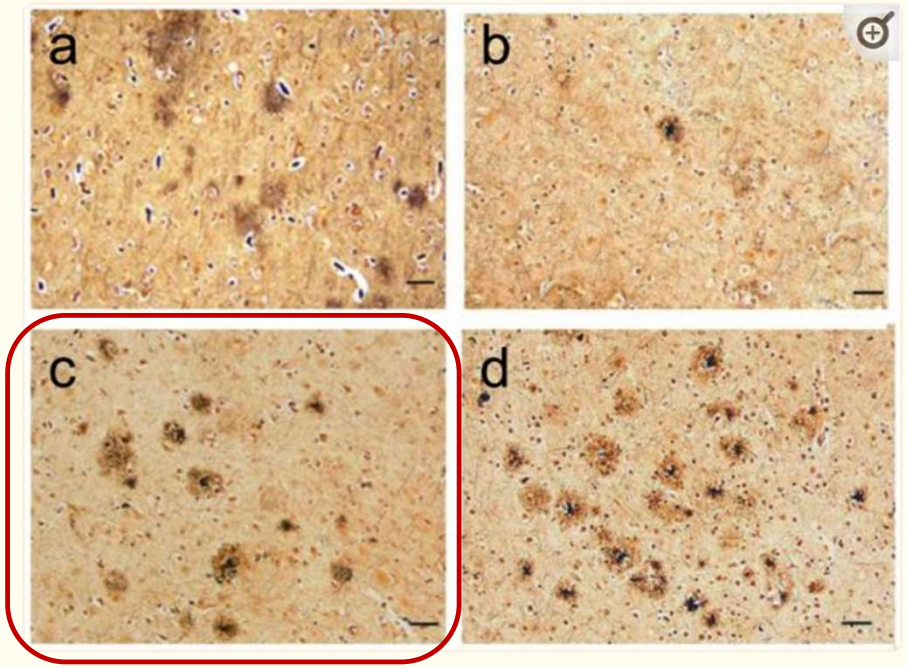
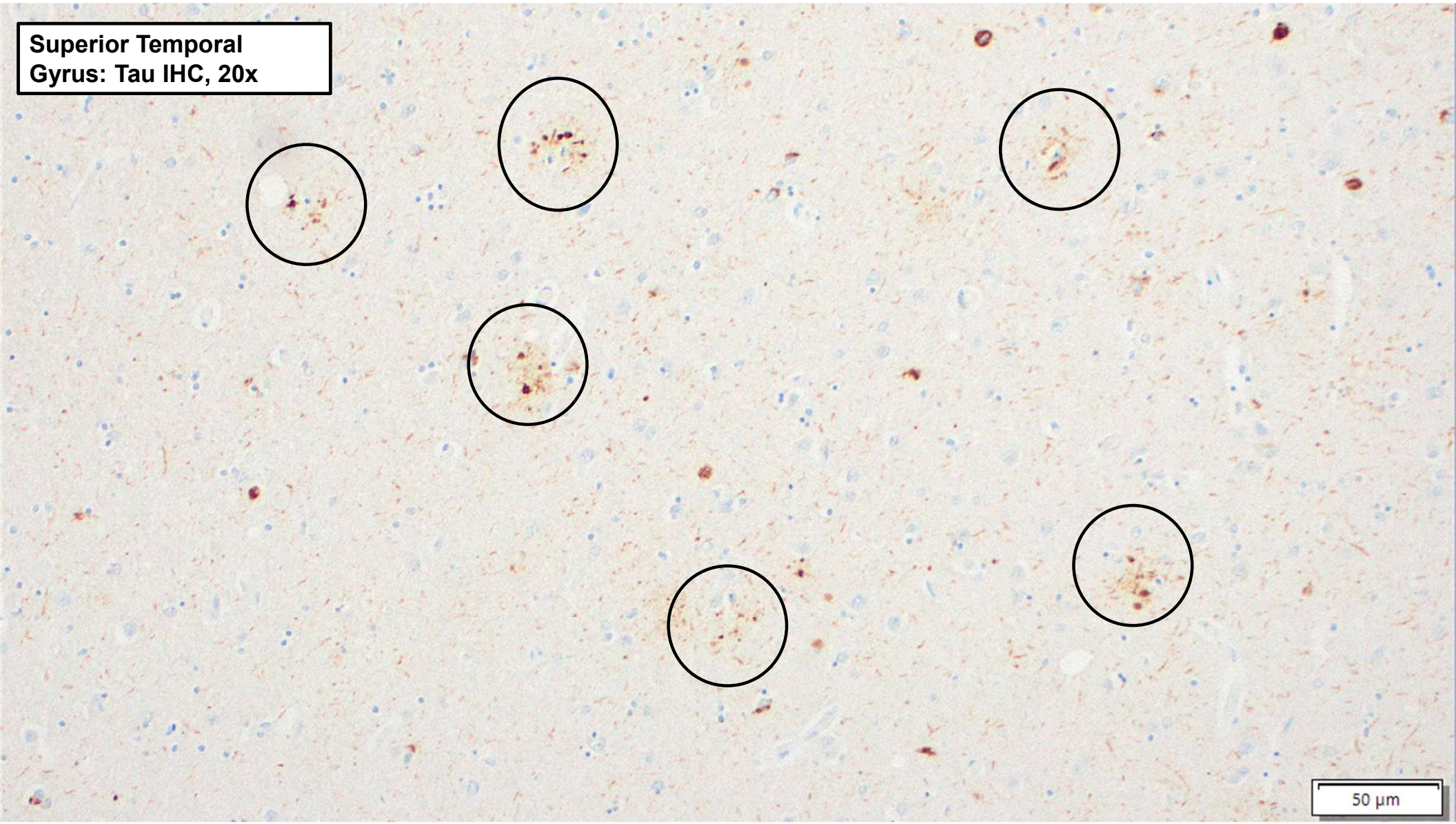
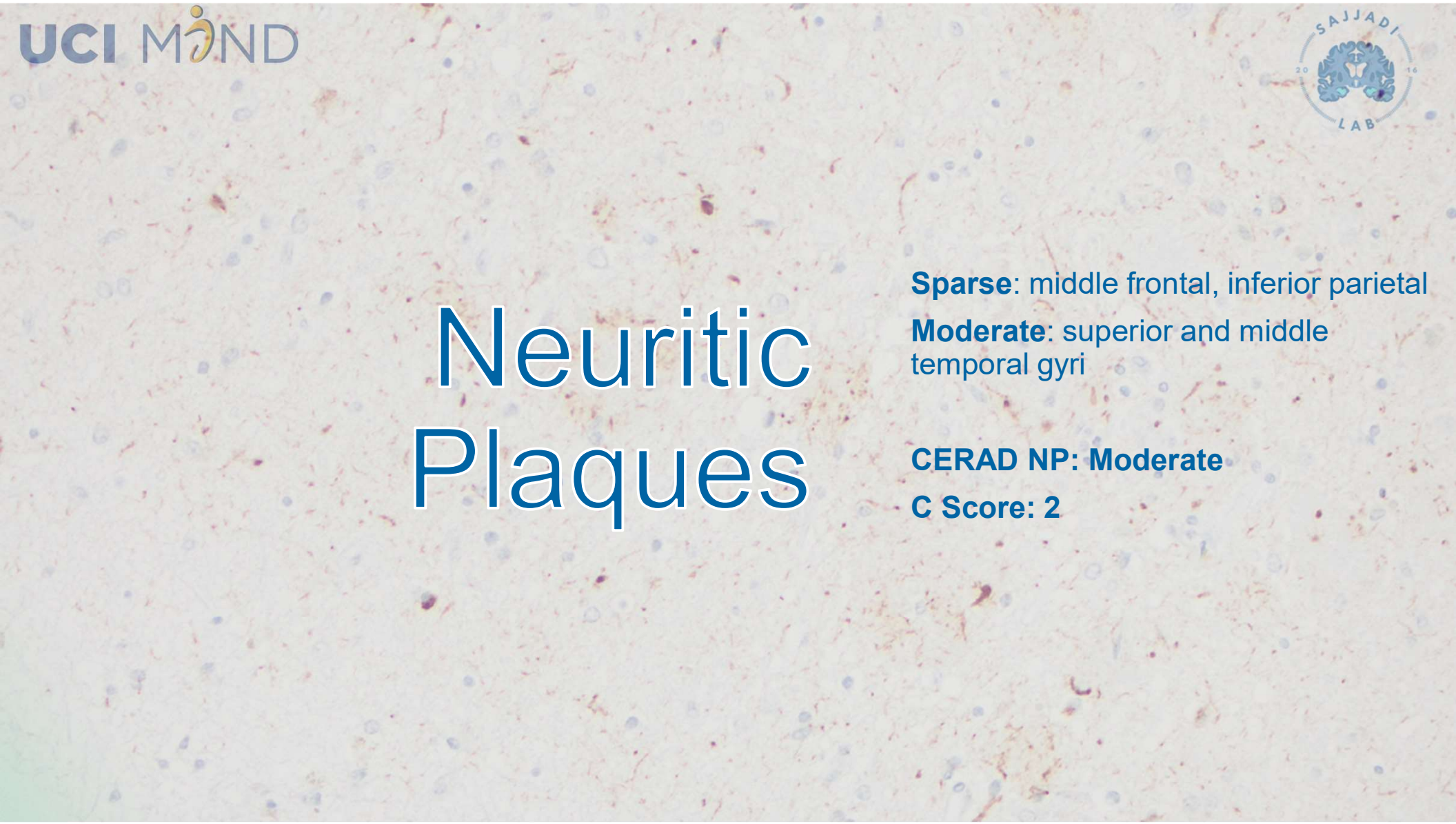


Figure 3

"ABC" Score for Alzheimer's Disease Neuropathologic Change

Bielschowsky stain of neocortex shows (a) diffuse plaques but not neuritic plaques as an example of "C0", and increasing density of neuritic plaques as examples of (b) "C1" (1 to 5 neuritic plaques per 1 mm^2), (c) "C2" (> 6 but < 20 neuritic plaques per 1 mm^2), and (d) "C3" (> 20 neuritic plaques per 1 mm^2). Scale bars equal 100 microns.


Superior Temporal Gyrus: Tau IHC, 20x
50 µm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Neuritic Plaques
Sparse: middle frontal, inferior parietal
Moderate: superior and middle temporal gyri
CERAD NP: Moderate
C Score: 2

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ADNC Likelihood

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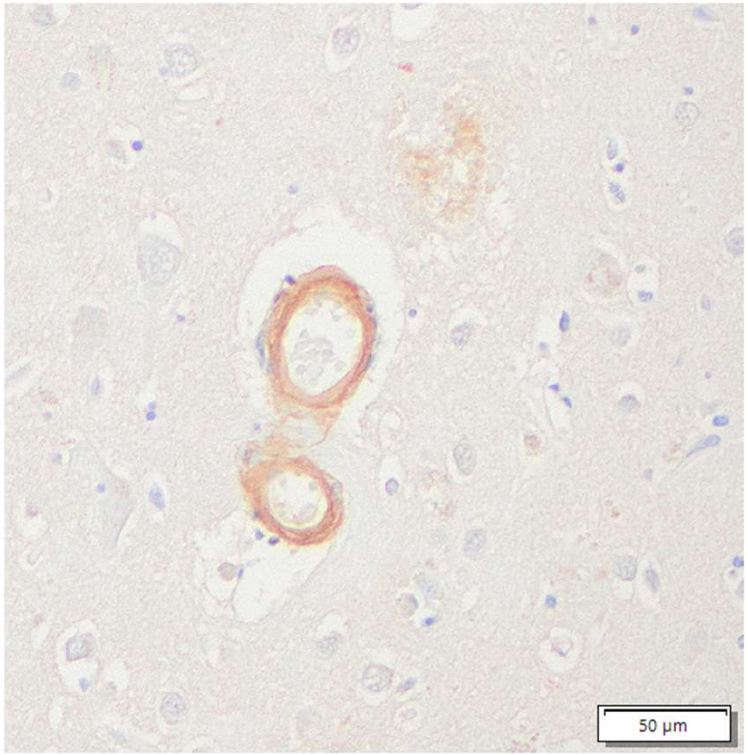
Montine et al. (2012)[1]

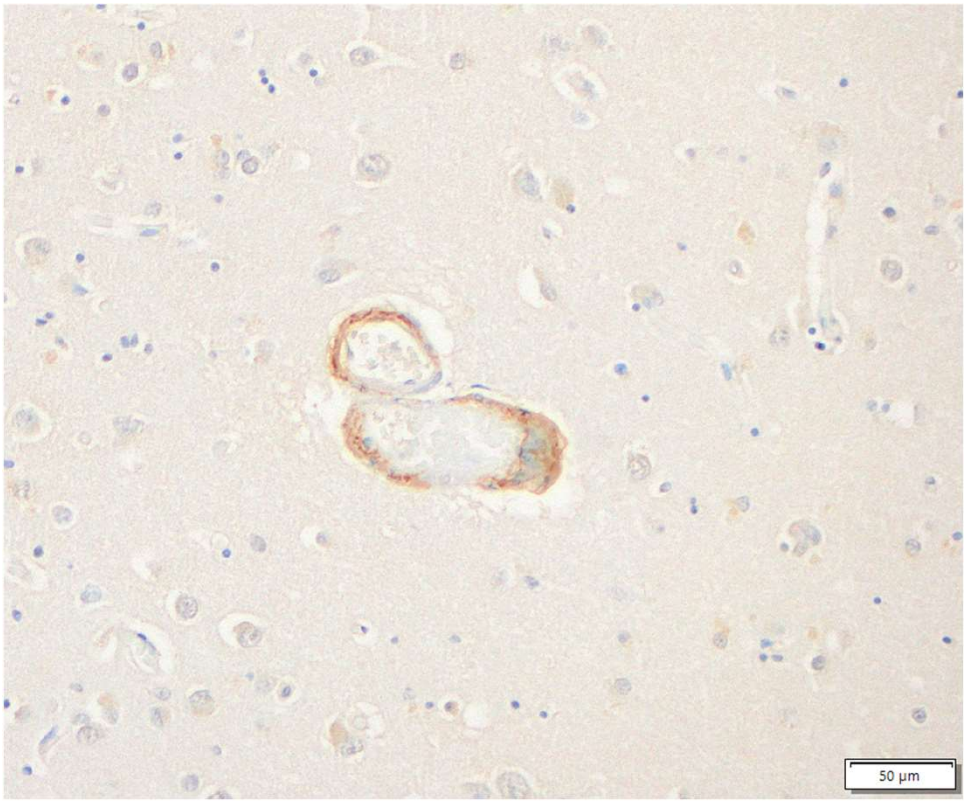
AD Neuropathologic Change		B (Braak/Neurofibrillary Score; See 11b)		
A (Amyloid; see 11a)	C (CERAD; see 11c)	0 or 1	2	3
0	0	Not	Not	Not
1	0 or 1	Low	Low	Low
	2 or 3	Low	Intermediate	Intermediate
2	Any C	Low	Intermediate	Intermediate
3	0 or 1	Low	Intermediate	Intermediate
	2 or 3	Low	Intermediate	High

CAA

Middle frontal lobe: Beta-amyloid IHC



Superior Temporal: Beta-amyloid IHC



Cerebral Amyloid Angiopathy

Scattered positivity in grey matter cortical vessels

CAA: Mild

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LATE-NC

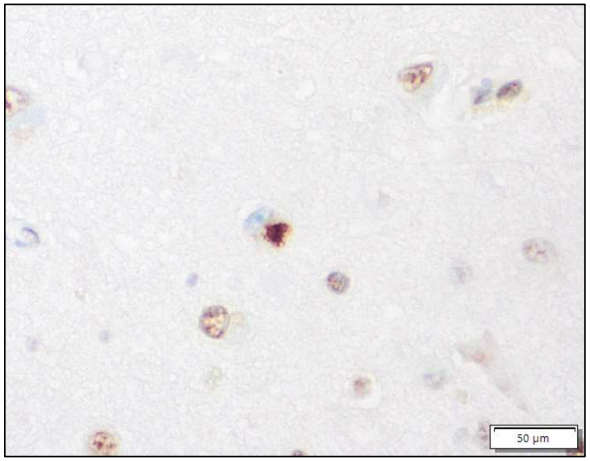
A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy

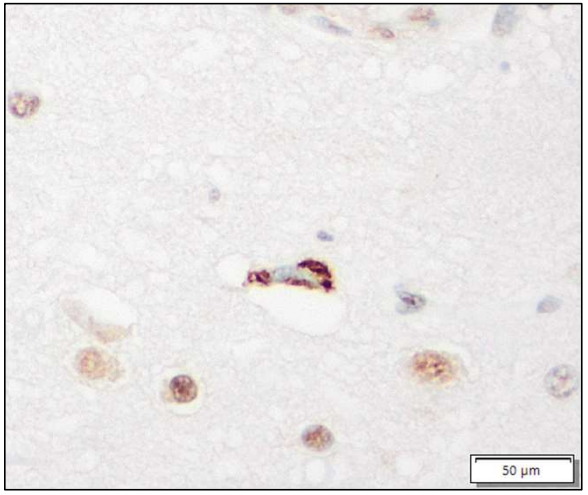
- Stage 1: amygdala only
- Stage 2: +hippocampus
- Stage 3: +middle frontal gyrus

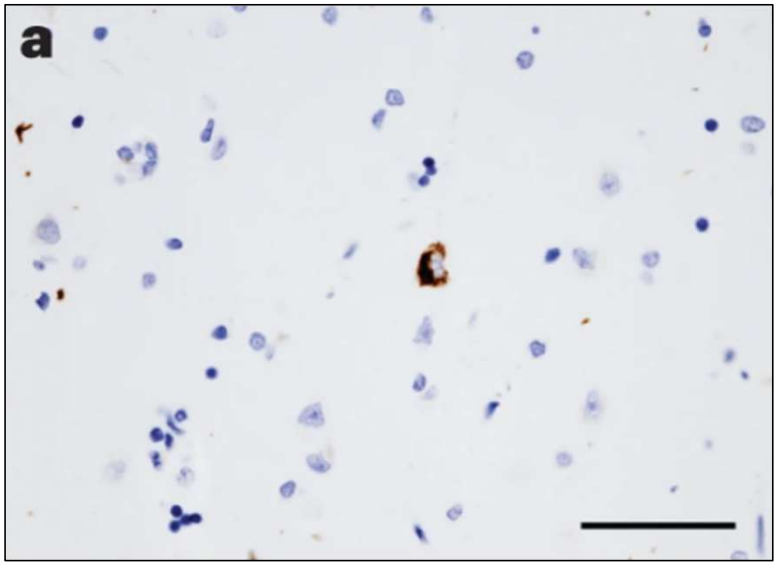
LATE-NC

Participant

Amygdala: Non-phospho TDP-43 IHC





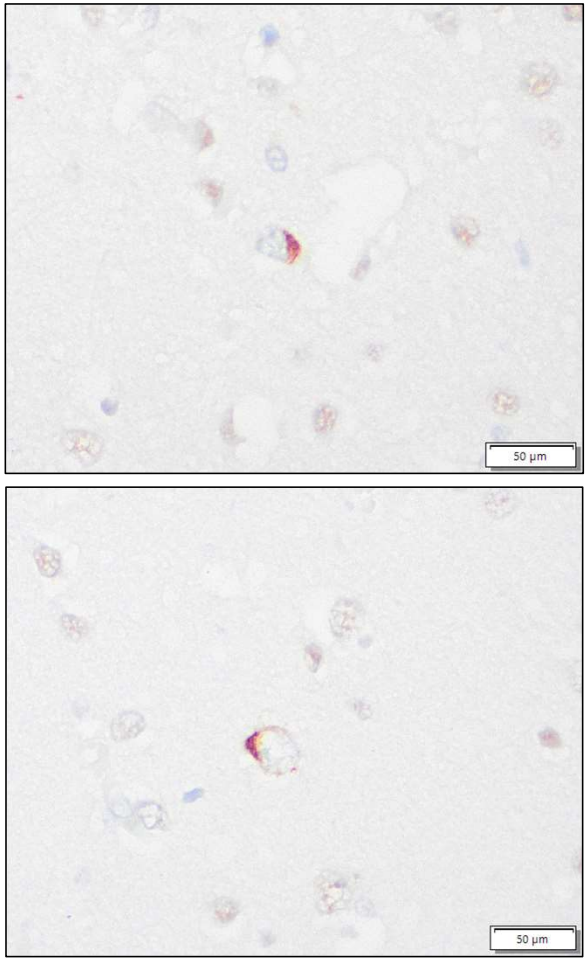


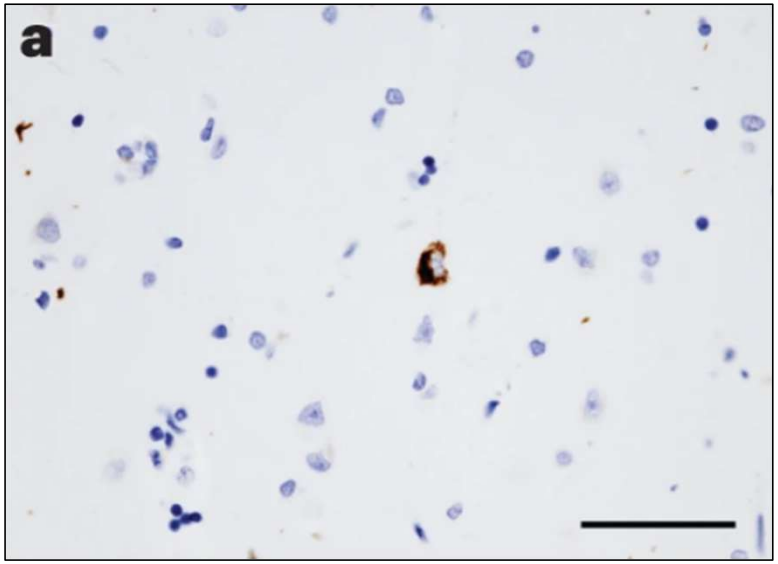
Nag, S., Schneider, J.A. Limbic-predominant age-related TDP43 encephalopathy (LATE) neuropathological change in neurodegenerative diseases. *Nat Rev Neurol* **19**, 525–541 (2023).

LATE-NC

Participant

Hippocampus: Non-phospho TDP-43 IHC





Nag, S., Schneider, J.A. Limbic-predominant age-related TDP43 encephalopathy (LATE) neuropathological change in neurodegenerative diseases. *Nat Rev Neurol* **19**, 525–541 (2023).

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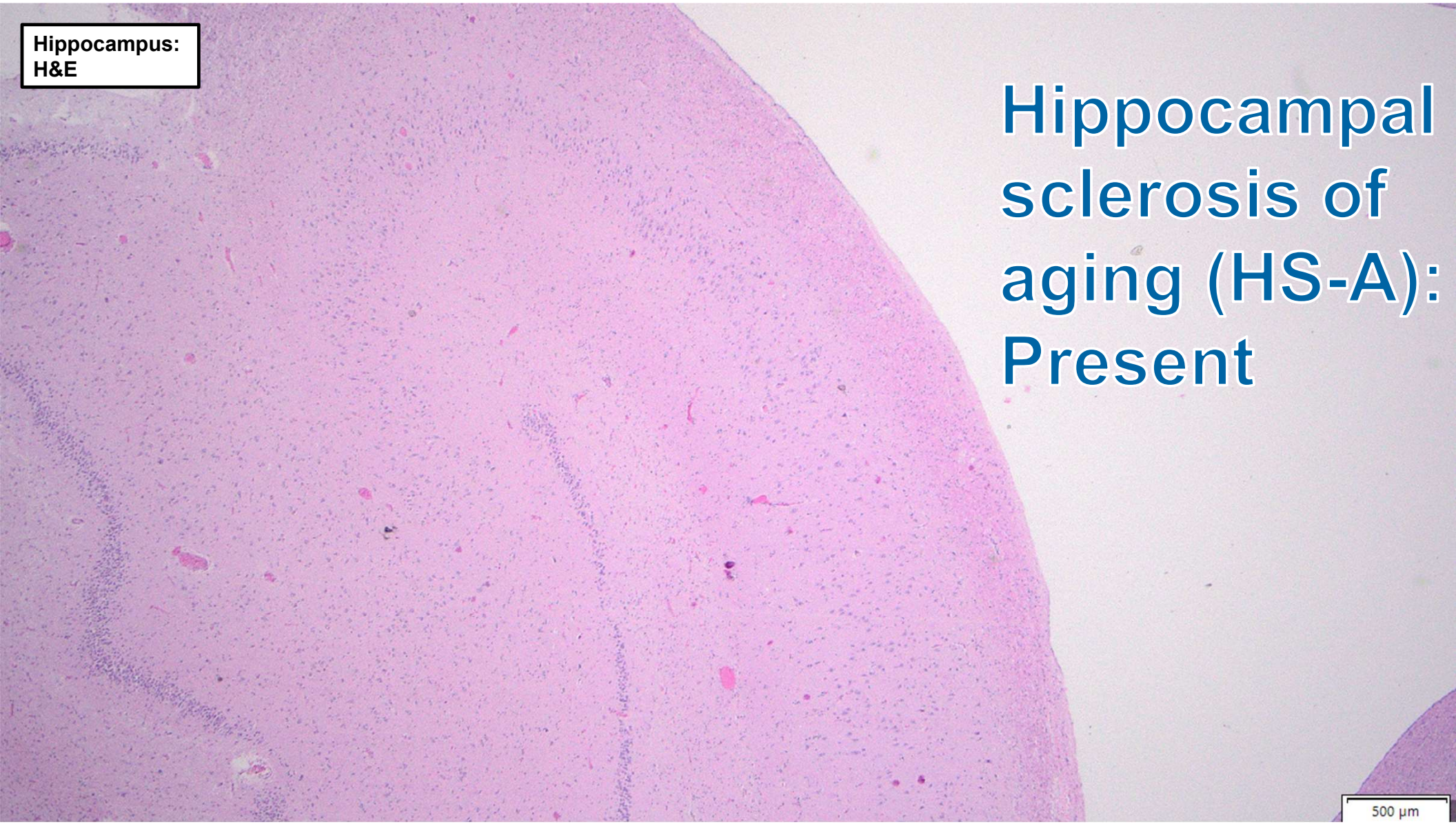
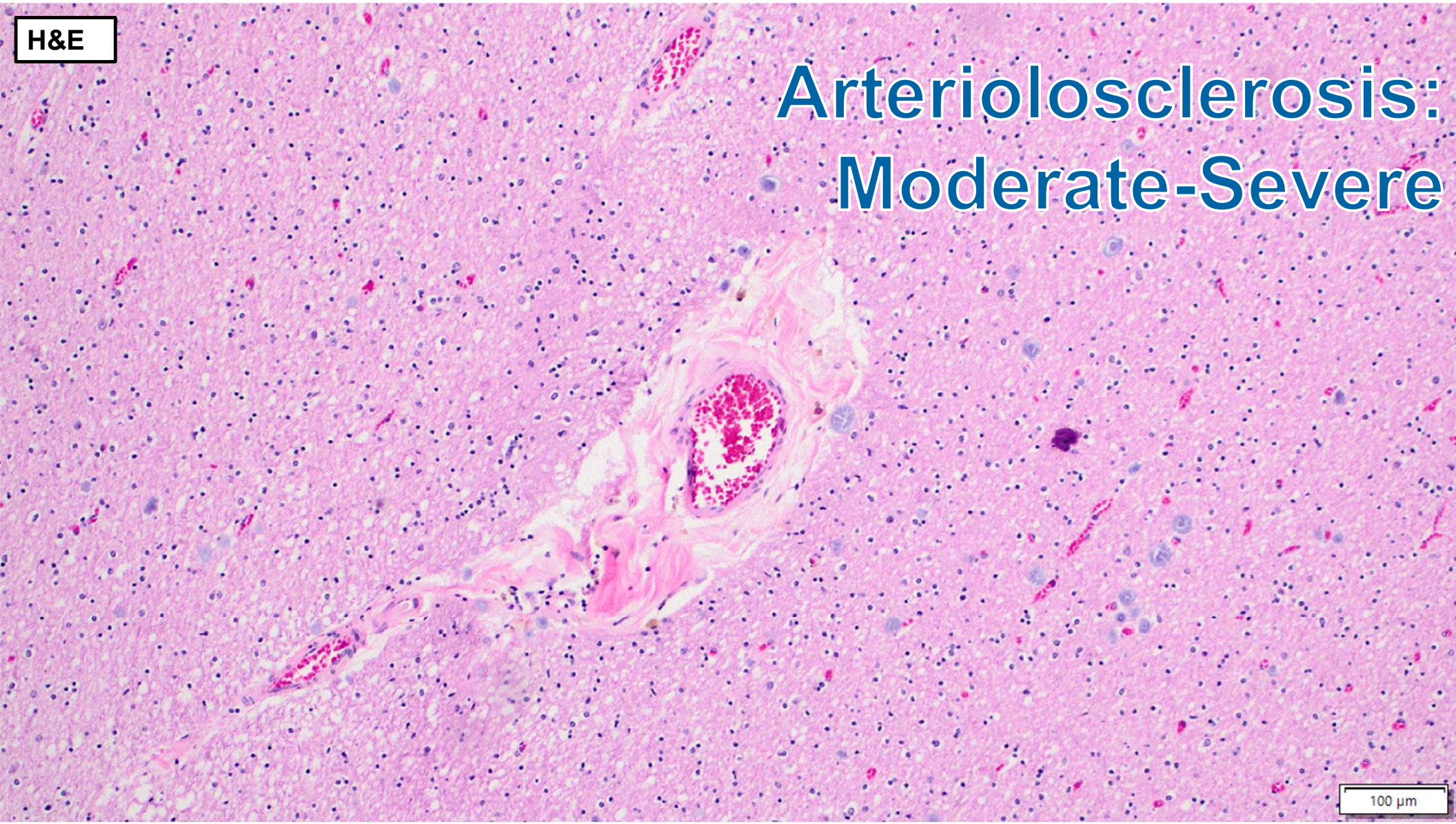
LATE-NC

A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy

- Stage 1: amygdala only
- Stage 2: +hippocampus
- Stage 3: +middle frontal gyrus


Hippocampus:
H&E
Hippocampal sclerosis of aging (HS-A): Present
500 µm


H&E
Arteriolosclerosis:
Moderate-Severe
100 µm

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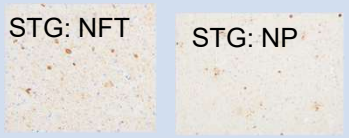
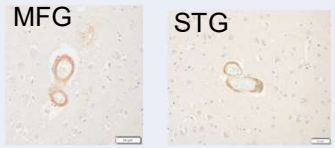
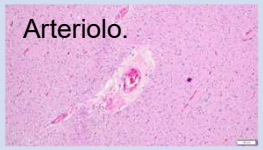
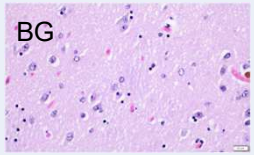
Neuropathology Summary Table

NC	Findings	Representative Image
ADNC	Intermediate A1/B3/C2	
LATE-NC	Stage 2	
HS-A	Present	
CAA	Mild	
Cerebrovascular	Arteriolo.: Moderate-Severe WMR: Moderate Enlarged PVS BG Calcification	
Other	Alzheimer's type II astrocytes	

Summary Slide

- Participant enrolled in ADRC at age 54, cognitively normal.
- Significant family history of Alzheimer's disease.
  - Mother diagnosed clinically with AD at 73; ADNC confirmed at autopsy at 78
- Enrolled in A4 trial at age 67.
- Fairly rapid cognitive decline from age 68 to age 75.
  - Diagnosed with MCI at age 69, dementia at age 72
- Some atrophy on MRIs at age 68, but subsequent rapid decline.
- Fairly high amyloid PET at age 68 (centiloid~120).
- Died at age 76.
- ADNC: Intermediate (A1/B3/C2).
- LATE-NC stage 2 (with HS-A).

Discussion

- Fairly young participant.
  - Young for A4 trial (67 at enrollment)
  - Somewhat young age at death (76)
- ADNC present.
  - High amyloid PET at age 68
- However, (stage 2) LATE-NC (and HS-A) was also present.
  - Likely contributed to rapid decline on neuropsych and imaging
- Implications of co-occurring pathologies for targeted therapies:
  - Other pathologies likely affect effectiveness of ADNC-specific therapies
  - Highlights the need for biomarkers specific for LATE-NC (and other NCs)
  - LATE-NC in “younger” individuals may happen mostly in the context of significant co-occurring ADNC

Thank you!

- ADRC research participants
- UCI ADRC CPC Team
  - UCI ADRC CPC Attendees
- NACC
- LATE PIA (ISTAART)
  - LATE-Neurodegeneration WG
- TRC-LATE
  - UCI, OHSU, USC, UCSD, UW

Contact: dwoodwort@hs.uci.edu

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Extra Slides

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Additional Imaging Findings

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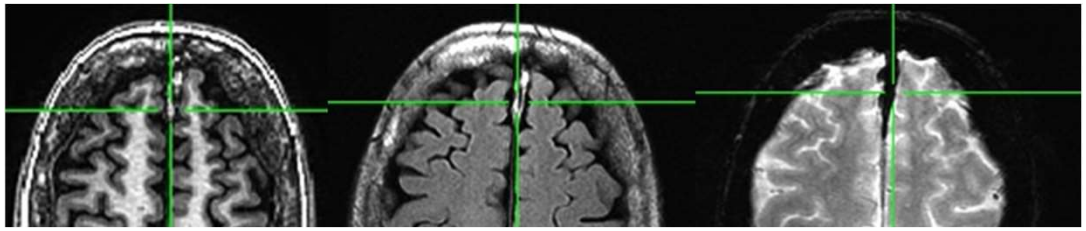
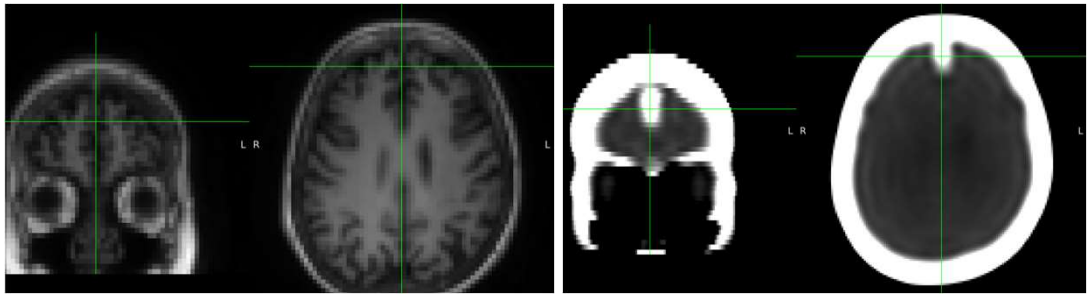
- “Ossification of cerebral falx with fatty marrow.”
- Lesion in left frontal WM.

Ossification of cerebral falx

T1w **FLAIR** **T2***

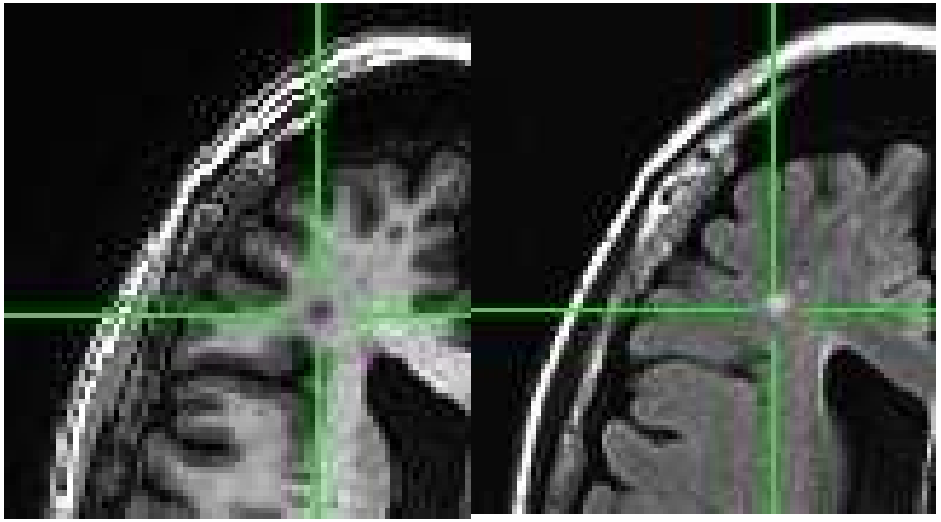


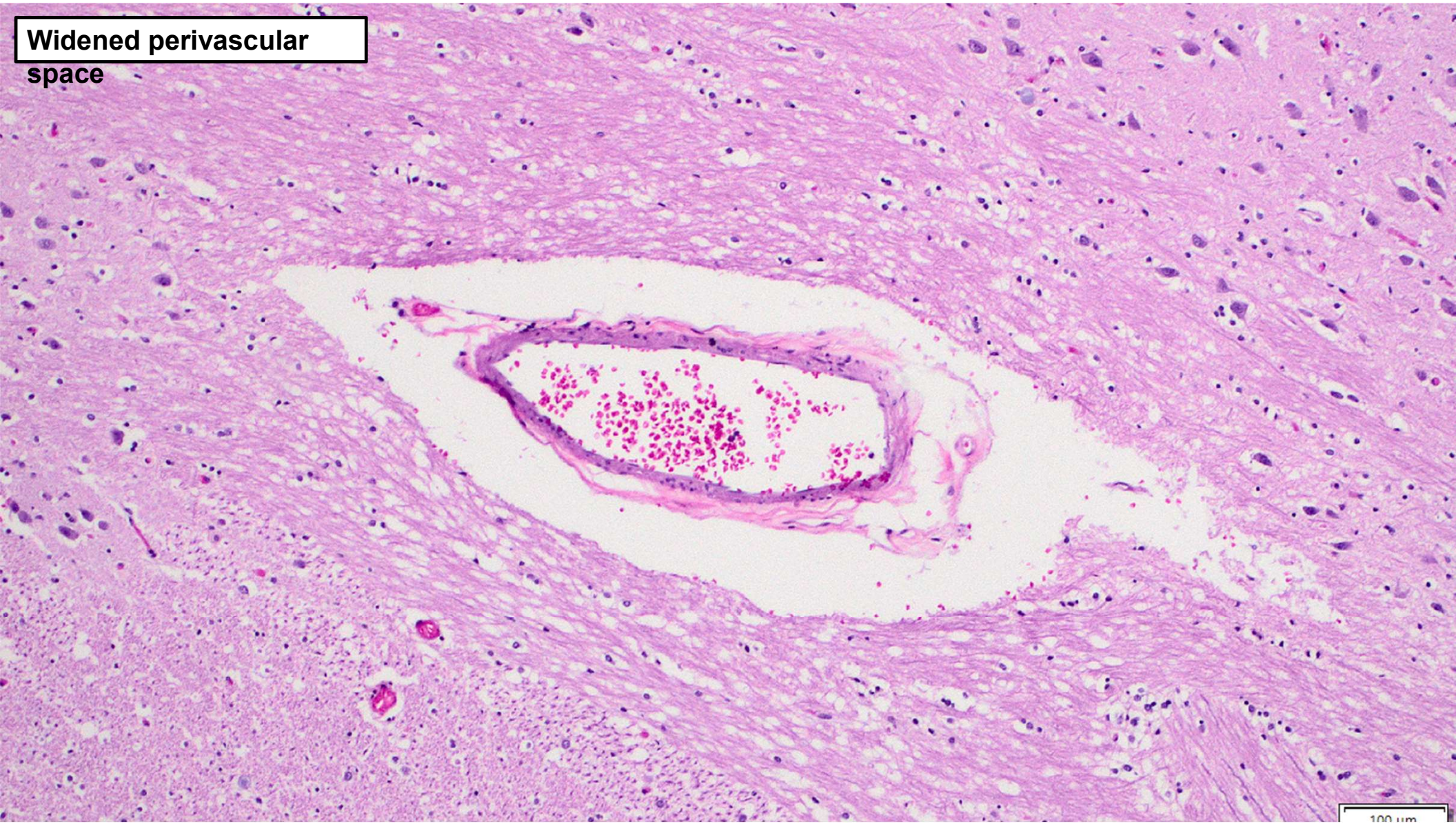
T1w (resampled to CT) **Low-res CT (att. corr. PET)**

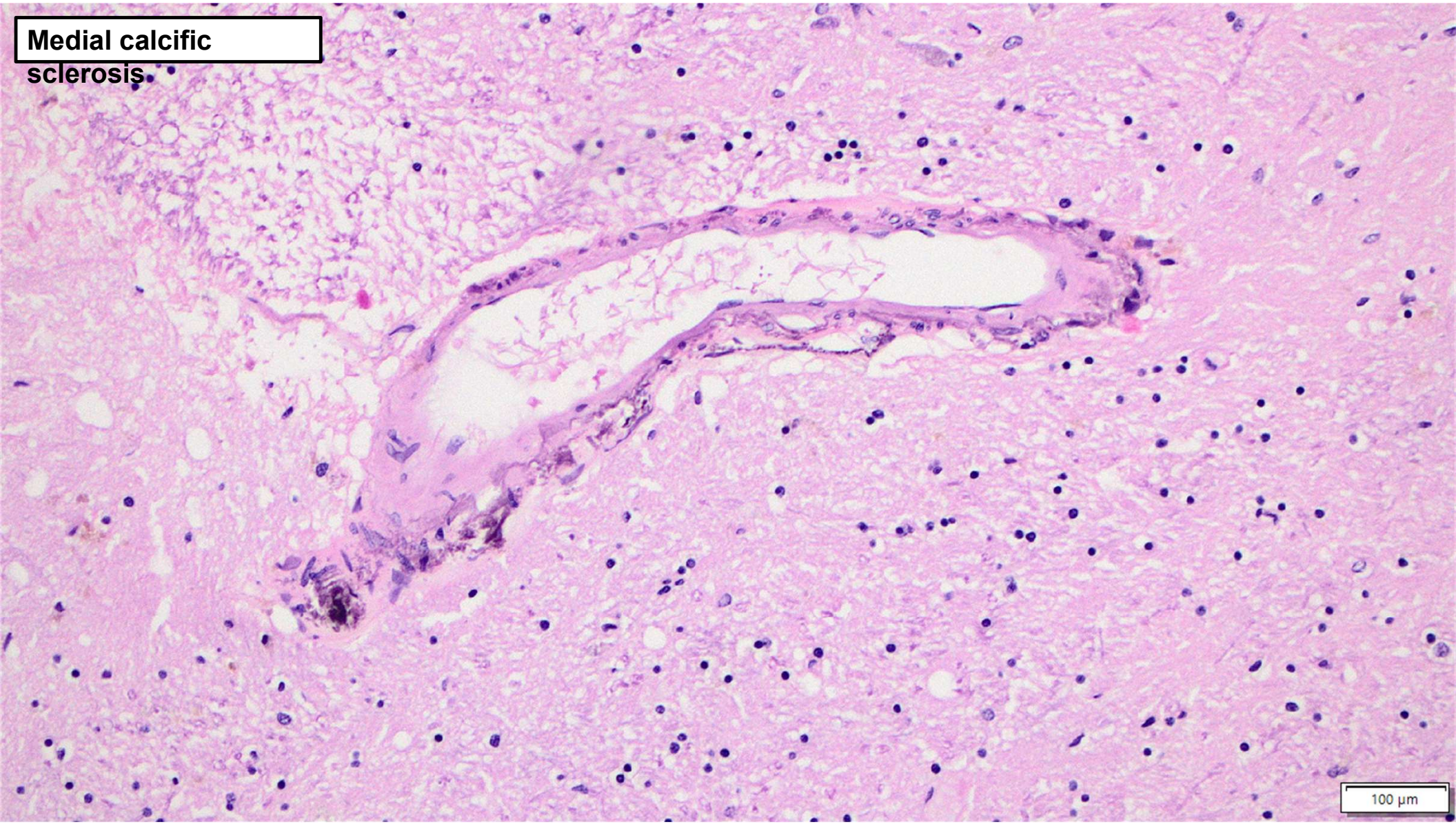


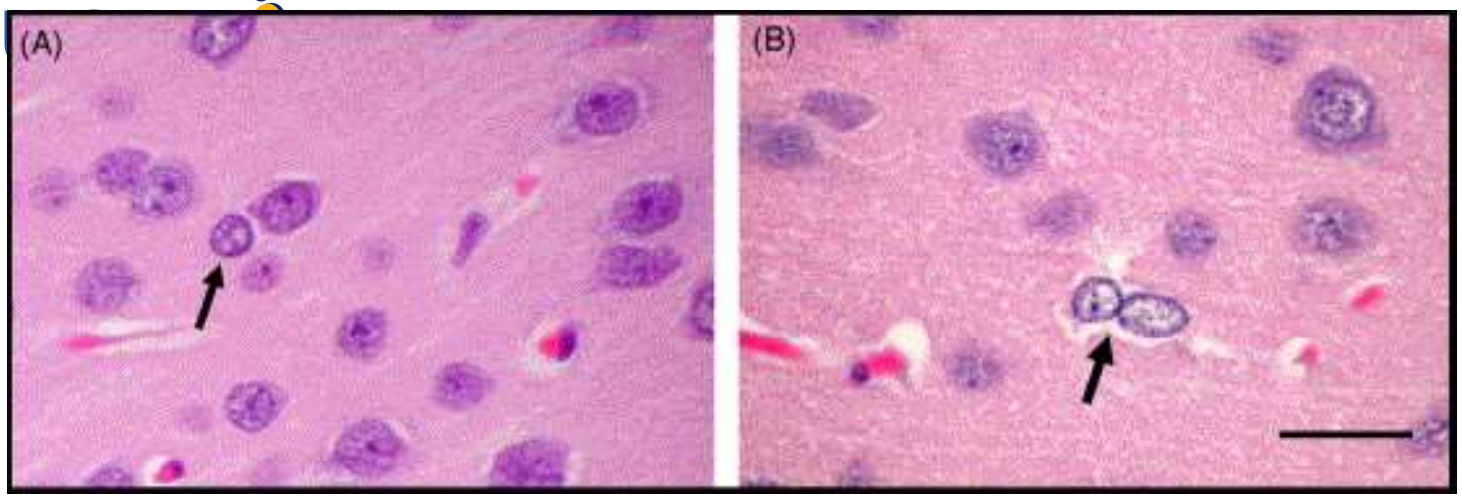
Lesion in left frontal WM

T1w **FLAIR**



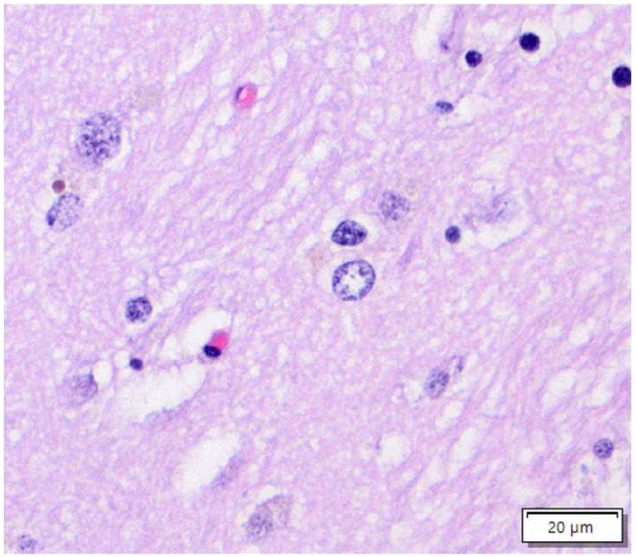

Widened perivascular space
100 µm

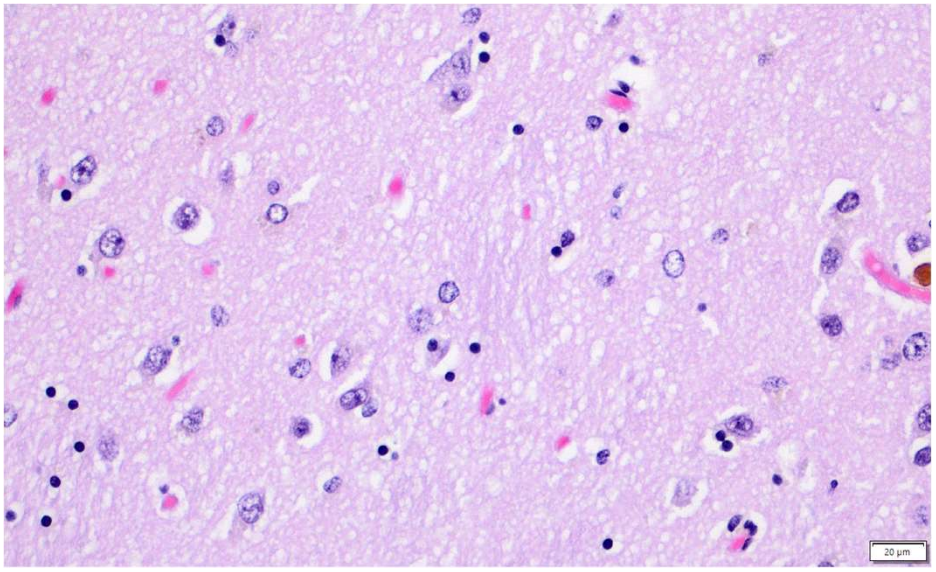

Medial calcific sclerosis
100 µm



Hazell AS, Normandin L, Norenberg MD, Kennedy G, Yi JH. Alzheimer type II astrocytic changes following sub-acute exposure to manganese and its prevention by antioxidant treatment. Neurosci Lett. 2006 Apr 3;396(3):167-71. doi: 10.1016/j.neulet.2005.11.064. Epub 2005 Dec 27. PMID: 16384640.

Case:
Basal Ganglia





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Neuropathology Summary

- Alzheimer Disease Neuropathologic Change (ADNC), Intermediate ADNC
  - Thal phase 2 (A1)
  - Braak stage V (B3)
  - CERAD moderate (C2)
- Cerebral amyloid angiopathy
  - Mild
- Limbic-Predominant Age-Related TDP-43 Encephalopathy Neuropathological Change
  - Stage 2 (Hippocampus)
- Hippocampal Sclerosis (CA1)
- Cerebrovascular Disease
  - Arteriolosclerosis, moderate to severe, widespread involvement of white matter
  - Widened perivascular spaces and white matter rarefaction, extensive
  - Medial calcific sclerosis, mild, basal ganglia
  - Alzheimer Type 2 astrocytosis, basal ganglia
  - Pigment incontinence, moderate, locus ceruleus

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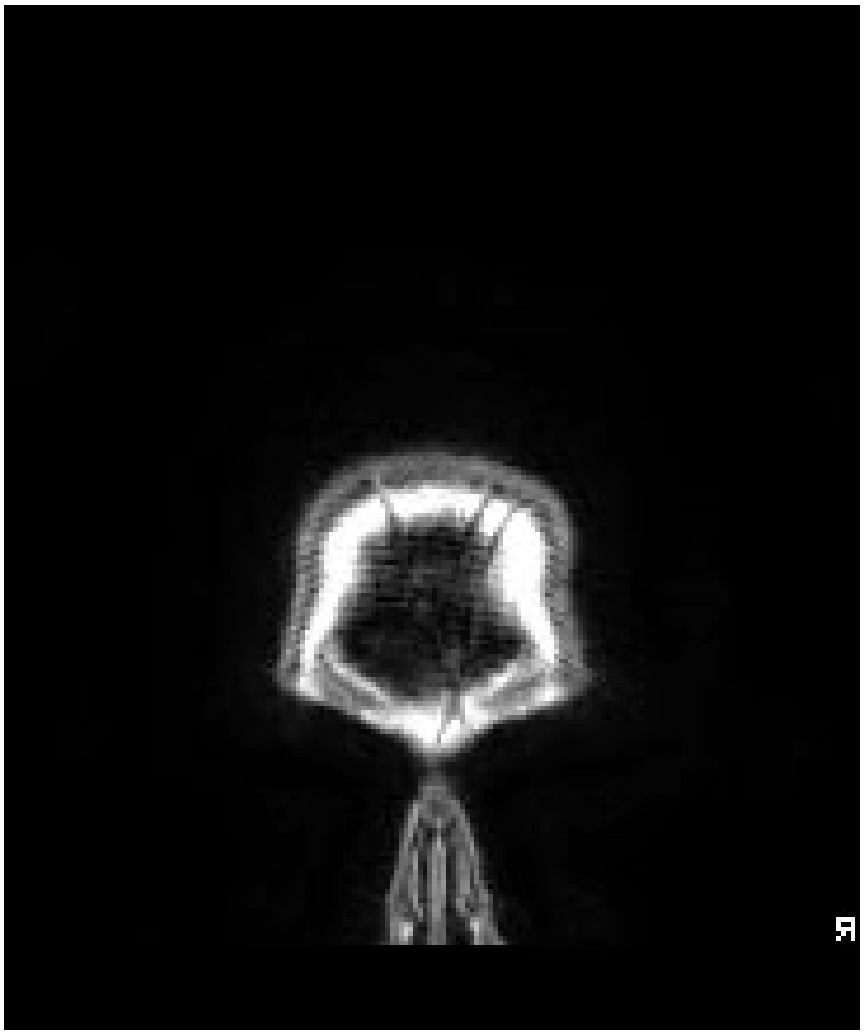
MRI at 68: T1w Coronal



MRI at 73: T1w Coronal