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Case 2018-9

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Clinical History

80 year-old male with a 10 year history of cognitive decline

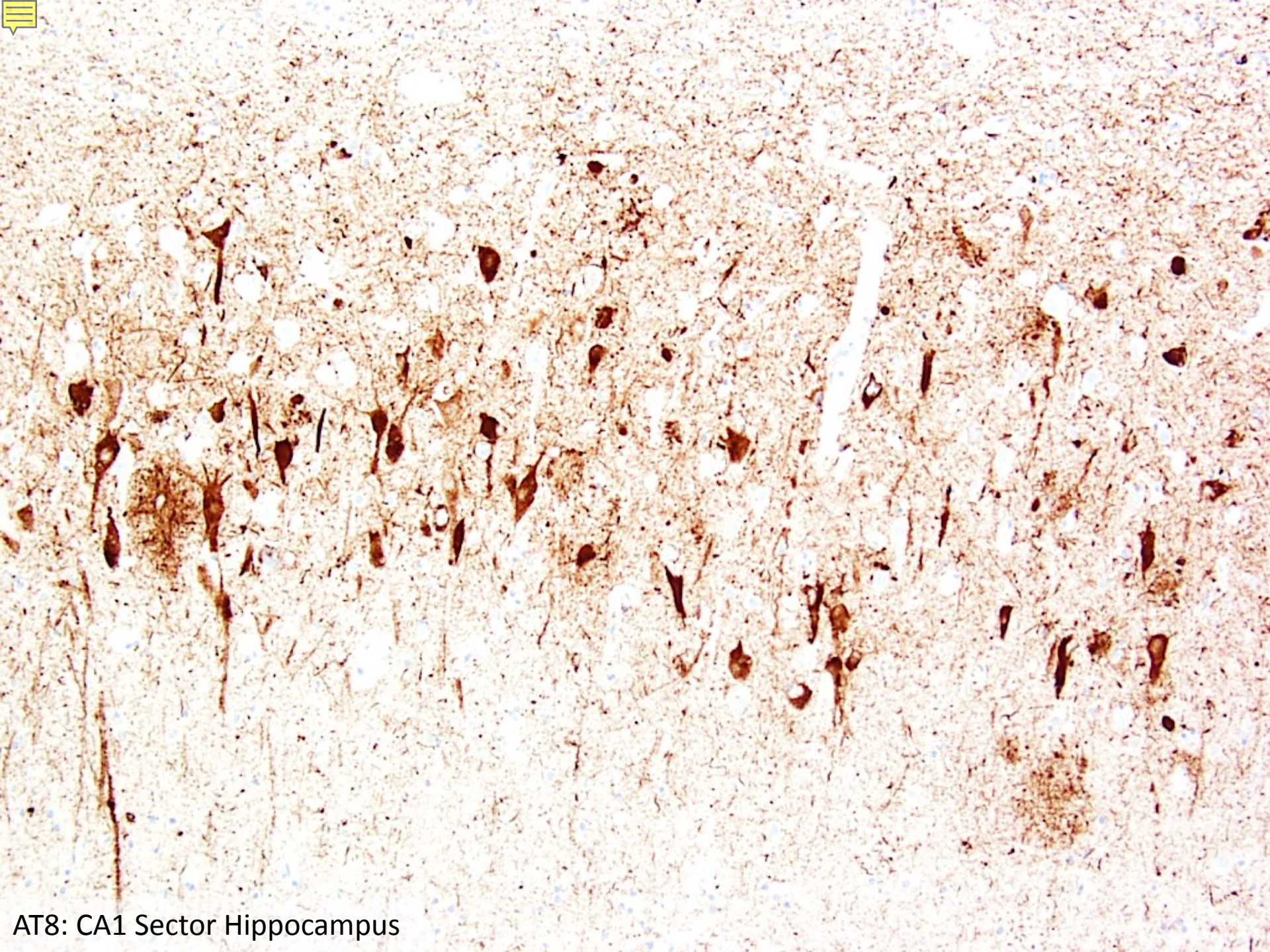
- 2015
  - 6-7 years of progressive cognitive decline and problem solving
  - Difficulties with attention and working memory
  - Still independent in daily functions (driving)
  - Cognitive exam: Amnestic, moderate executive dysfunction
  - APOE 4,4
- 2017
  - Experienced more word finding trouble
  - Hospitalized multiple times for falls and infections
  - Declined quickly and died
- Clinical dx?
  - Probable Alzheimer disease

Gross Description and Radiology

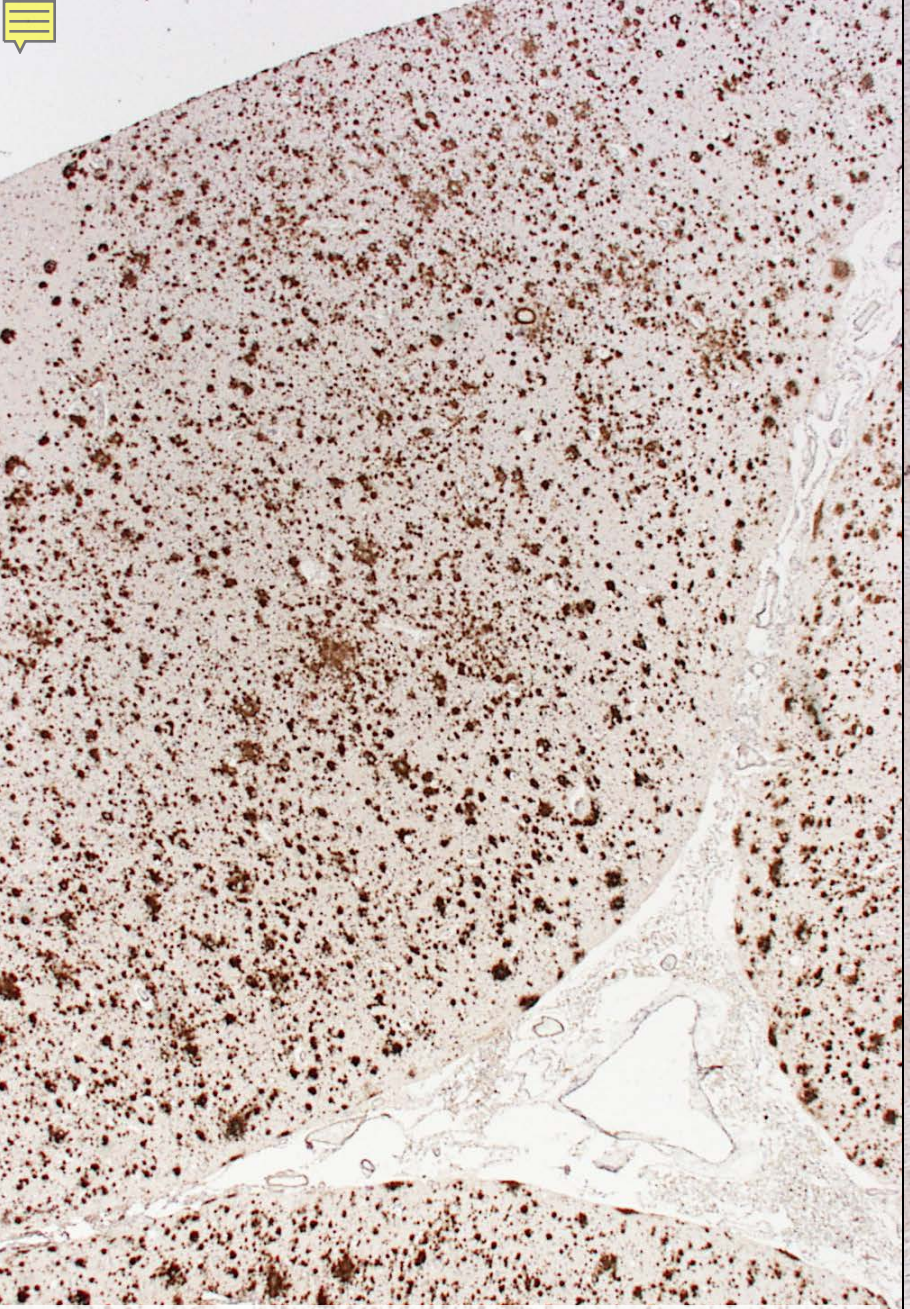
- Brain weight: 1473 g
- Mild atherosclerosis
- Atrophy:
  - Mild: hippocampus
  - Absent: frontal, temporal, parietal, occipital, caudate, brainstem and cerebellum
- Mild ventricular dilatation
- Pallor:
  - Substantia nigra: mild
  - Locus coeruleus: severe

- Radiology: last known MRI in 2009 showed mild global parenchymal volume loss

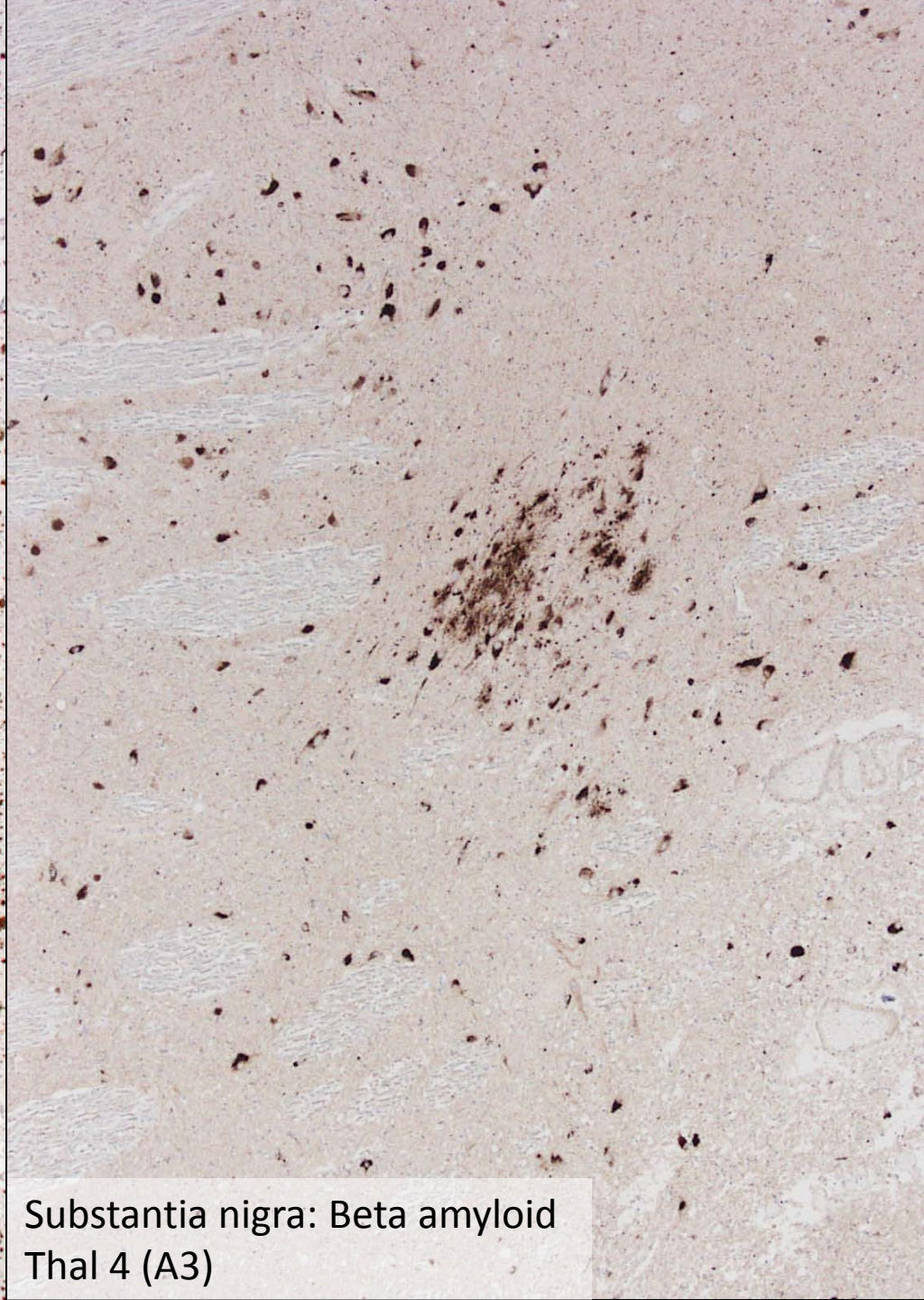

Differential Diagnosis?
or
Further work-up?
CA1 sector Hippocampus



AT8: CA1 Sector Hippocampus



Left frontal: Beta amyloid- frequent plaques, mild cerebral amyloid angiopathy



Substantia nigra: Beta amyloid
Thal 4 (A3)

ABC Score

Table 2 "ABC" score for AD neuropathologic change

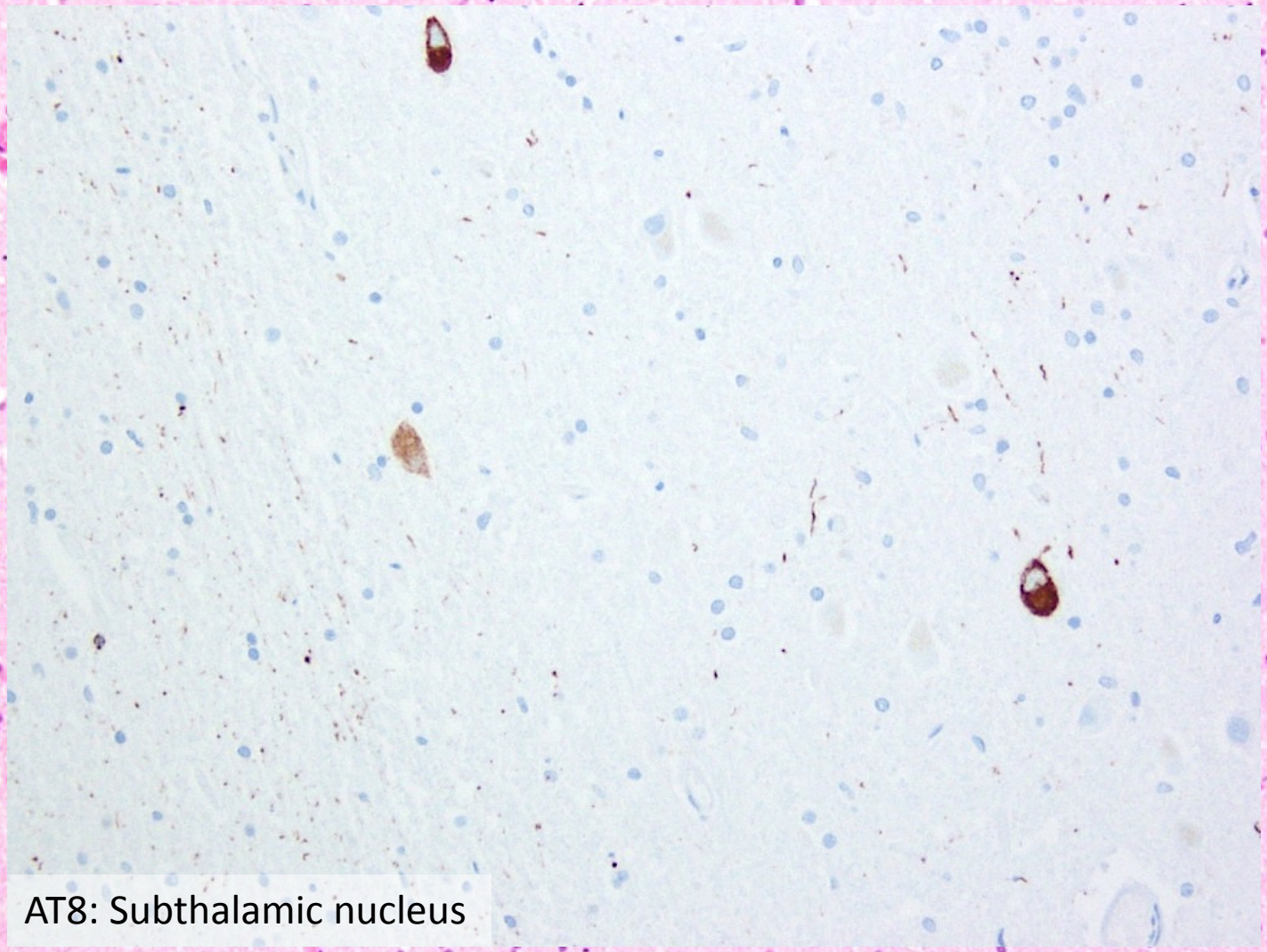
"A"	Thal Phase for Aβ plaques [57]	"B"	Braak and Braak NFT stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

AD neuropathologic change: A3, B3, C3

Level of ADNC

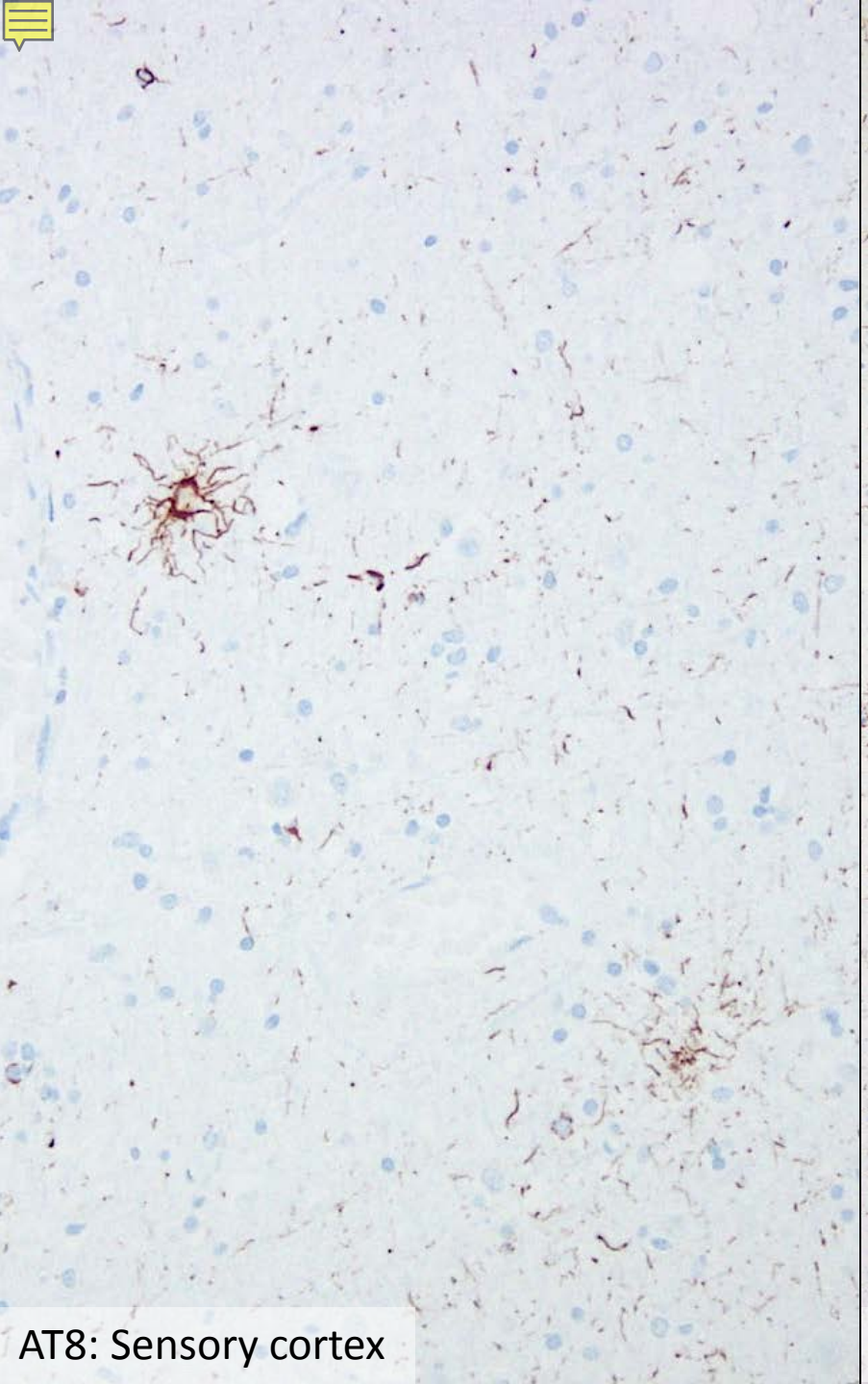
Table 3 "ABC" score for level of AD neuropathologic change

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

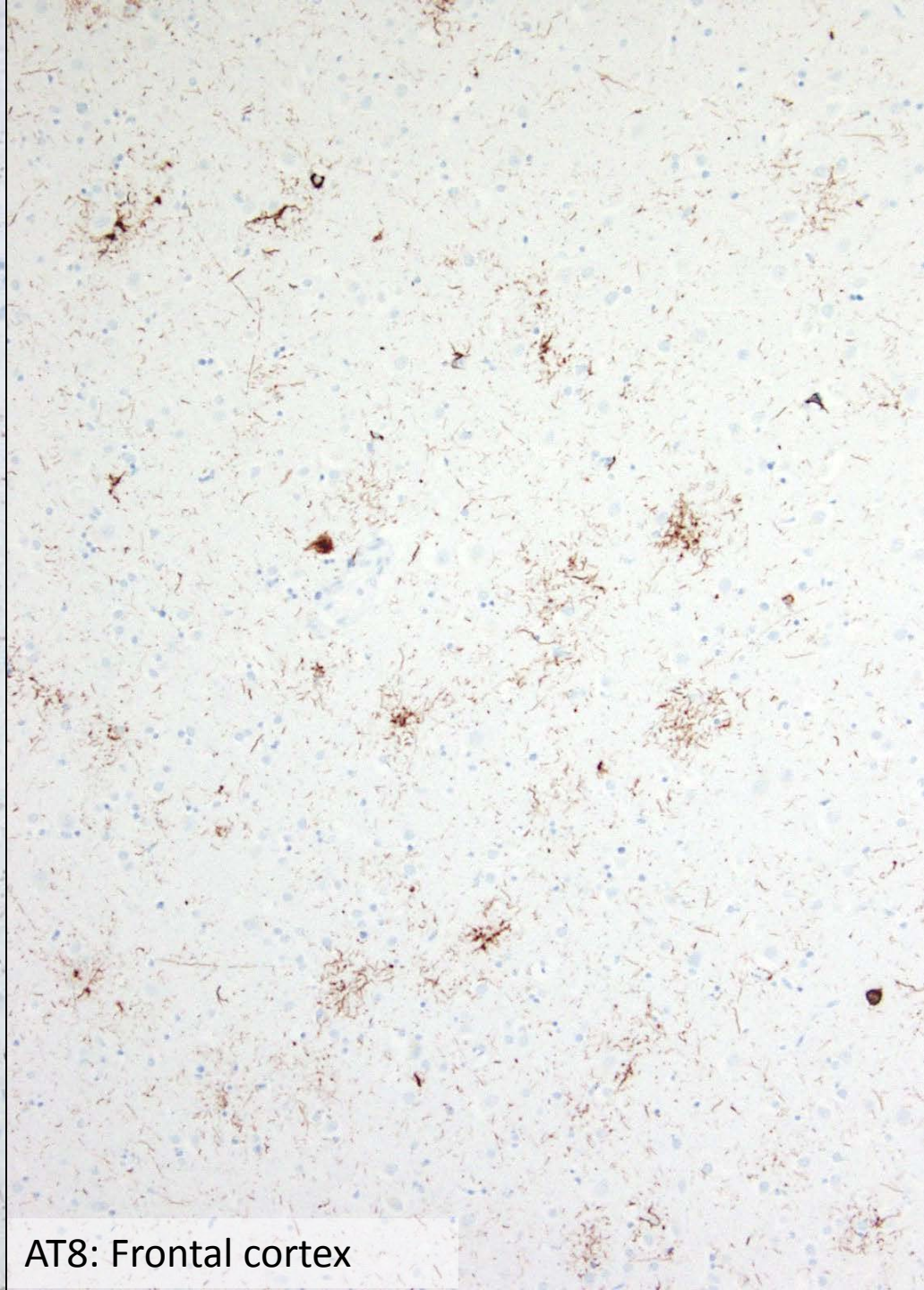


AT8: Subthalamic nucleus

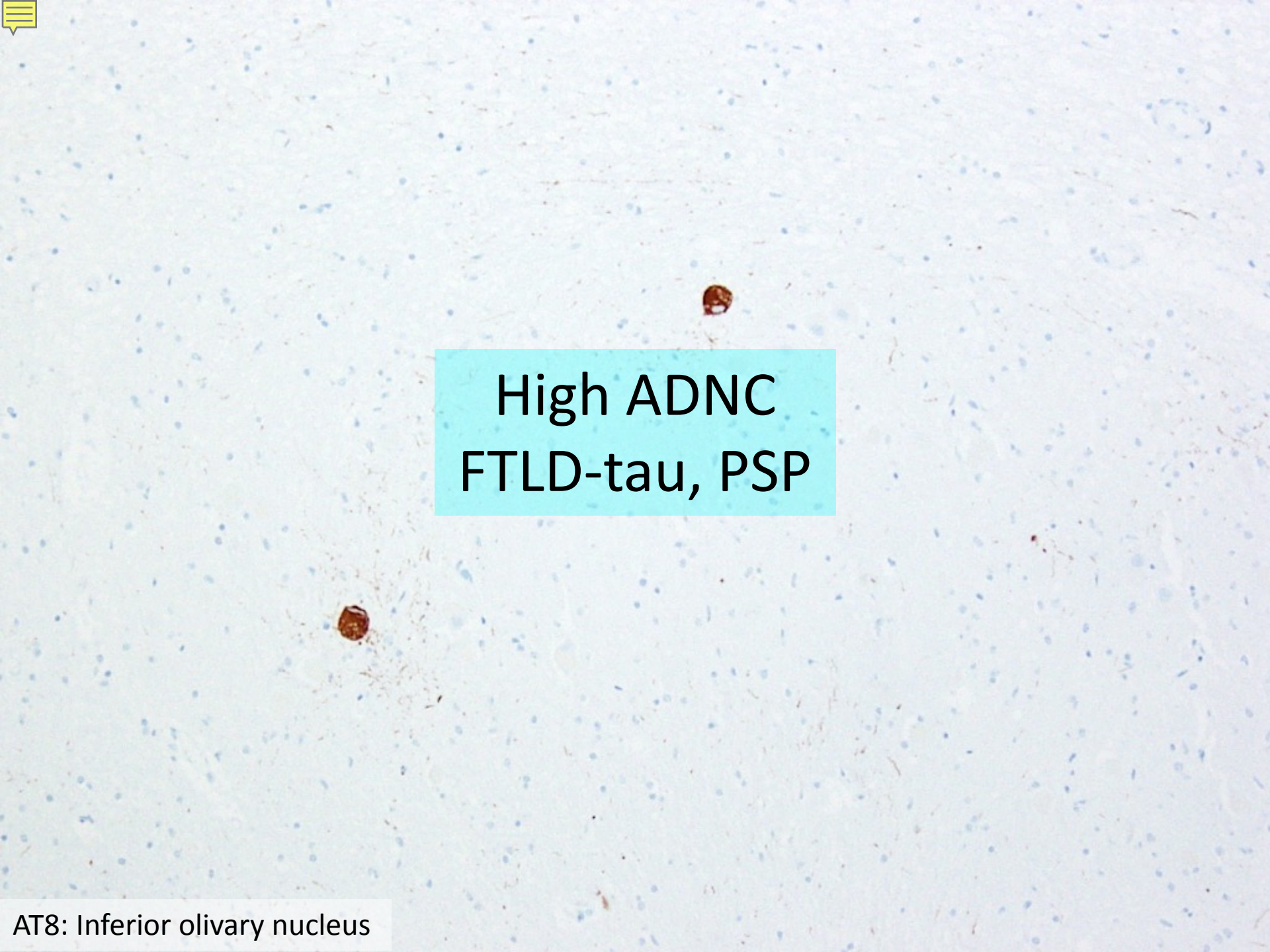
Subthalamic nucleus: moderate NL&G



AT8: Sensory cortex

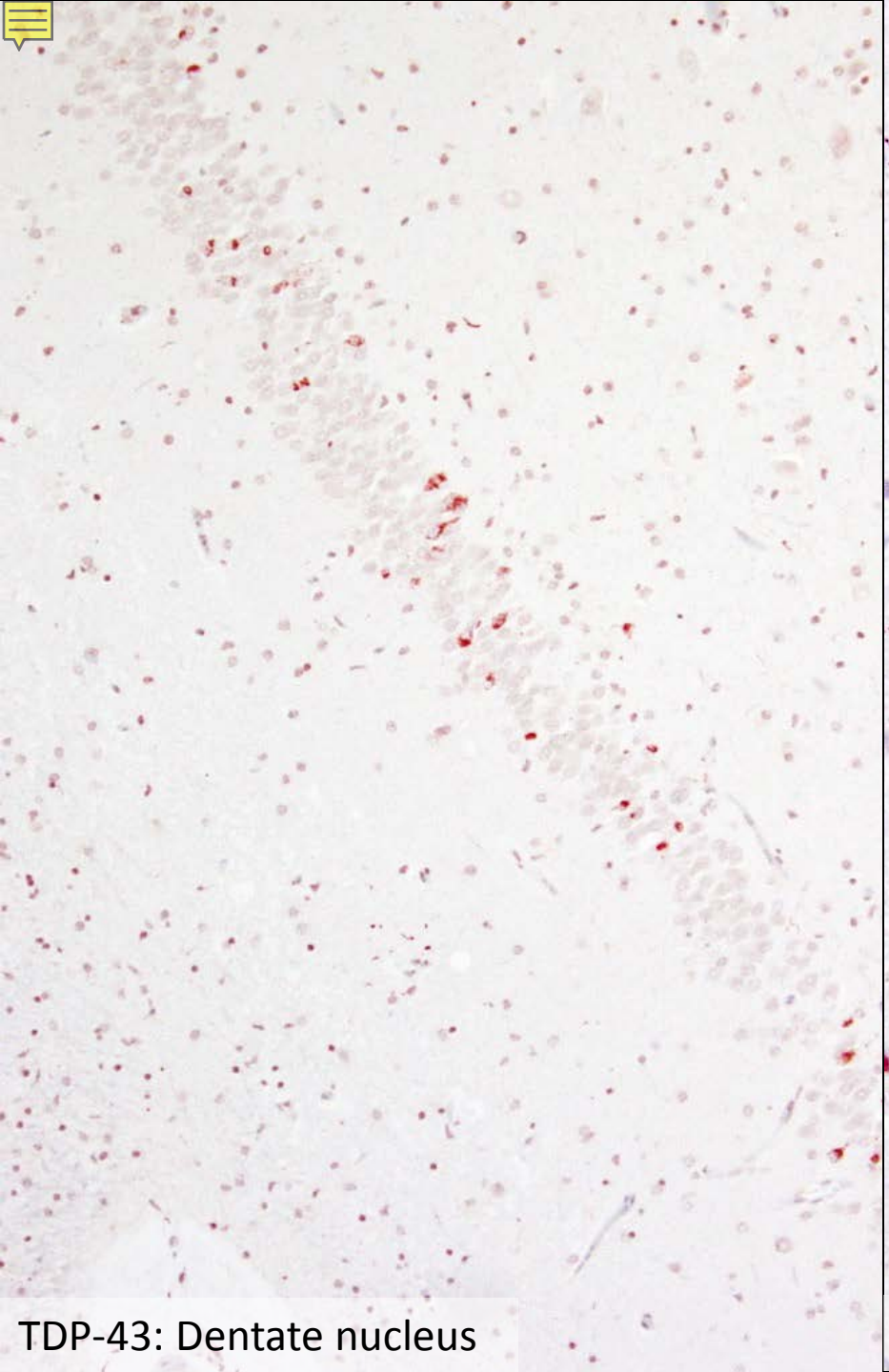


AT8: Frontal cortex

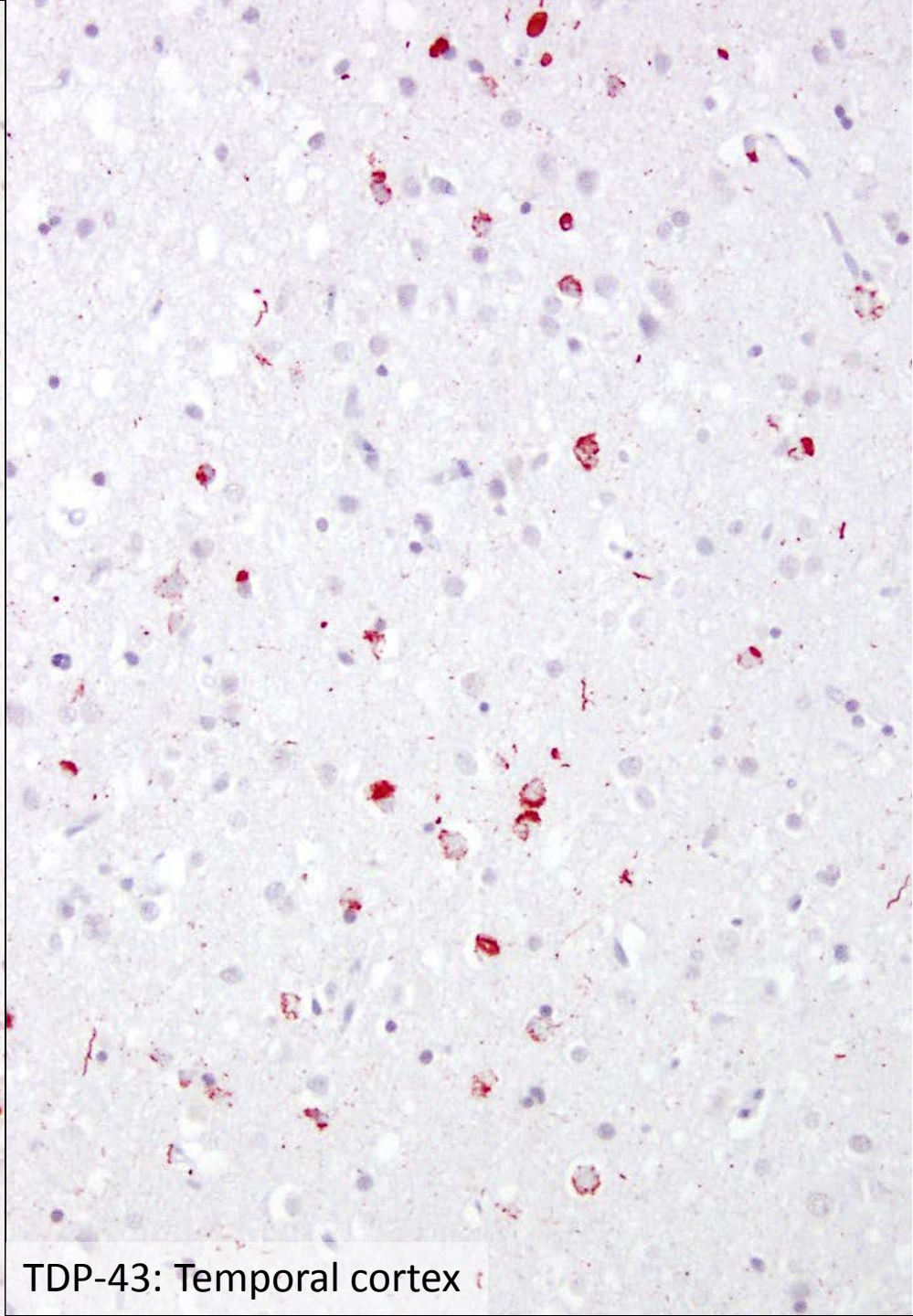


AT8: Inferior olivary nucleus

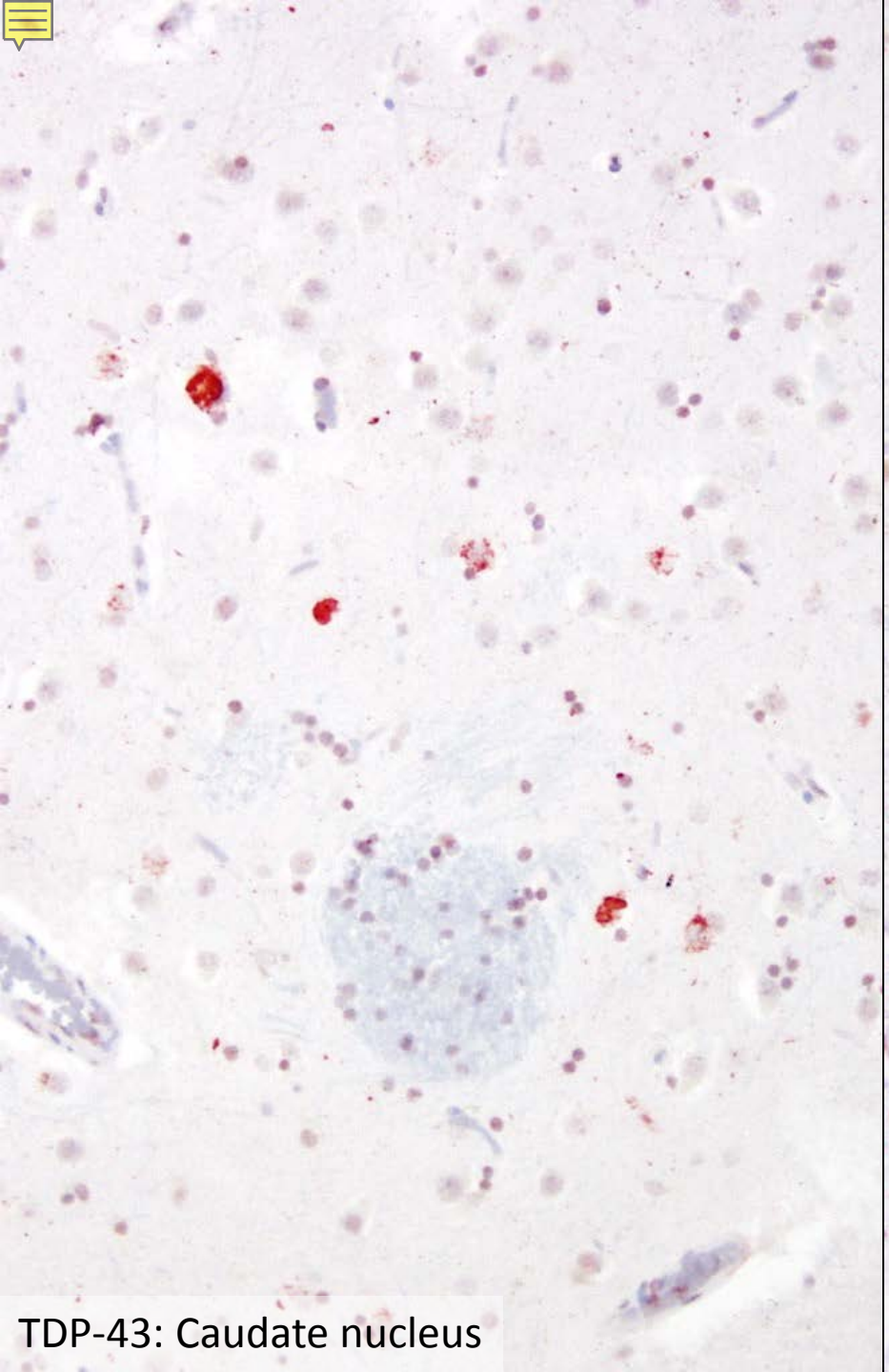

BUT WAIT
THERE'S MORE



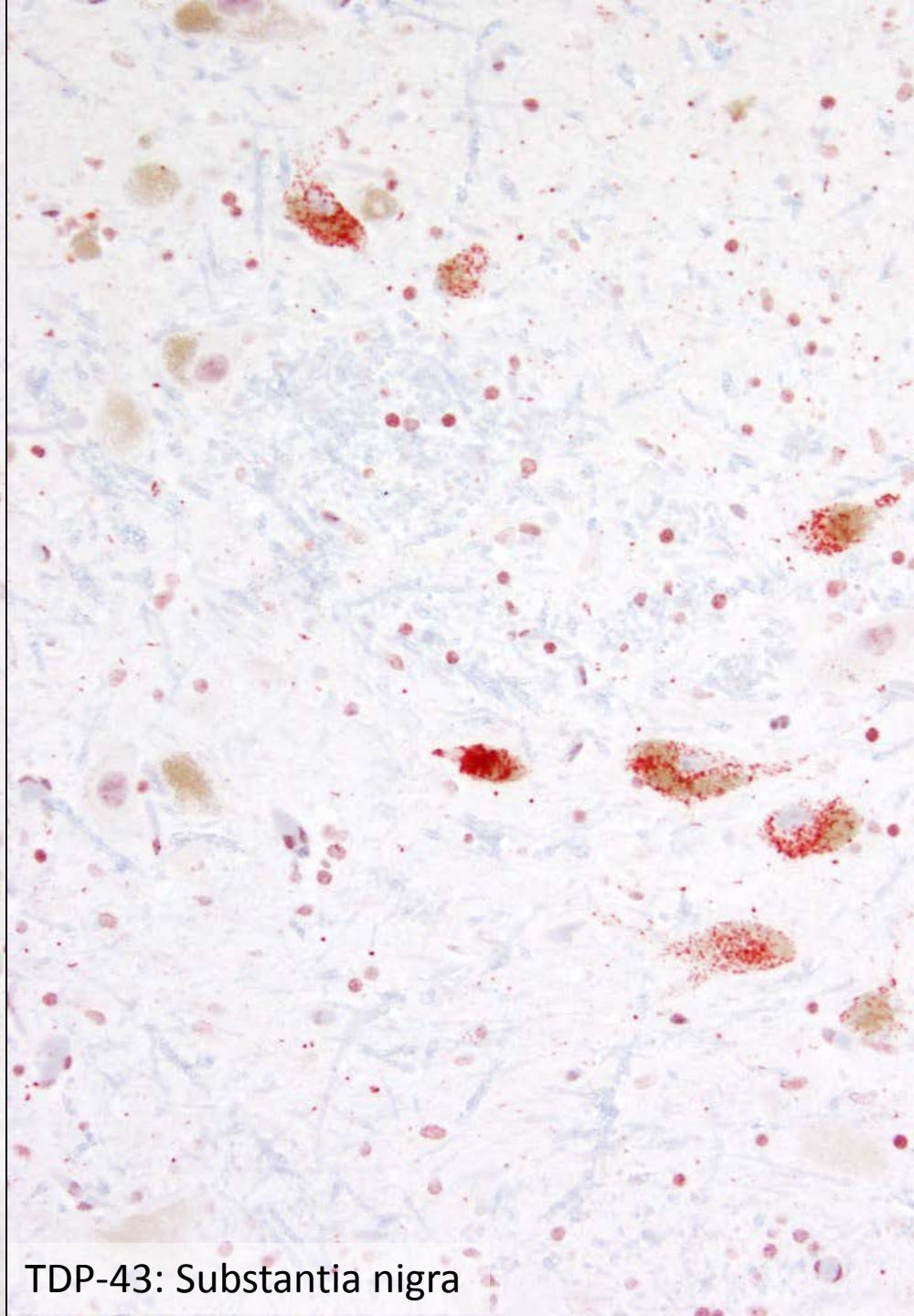
TDP-43: Dentate nucleus



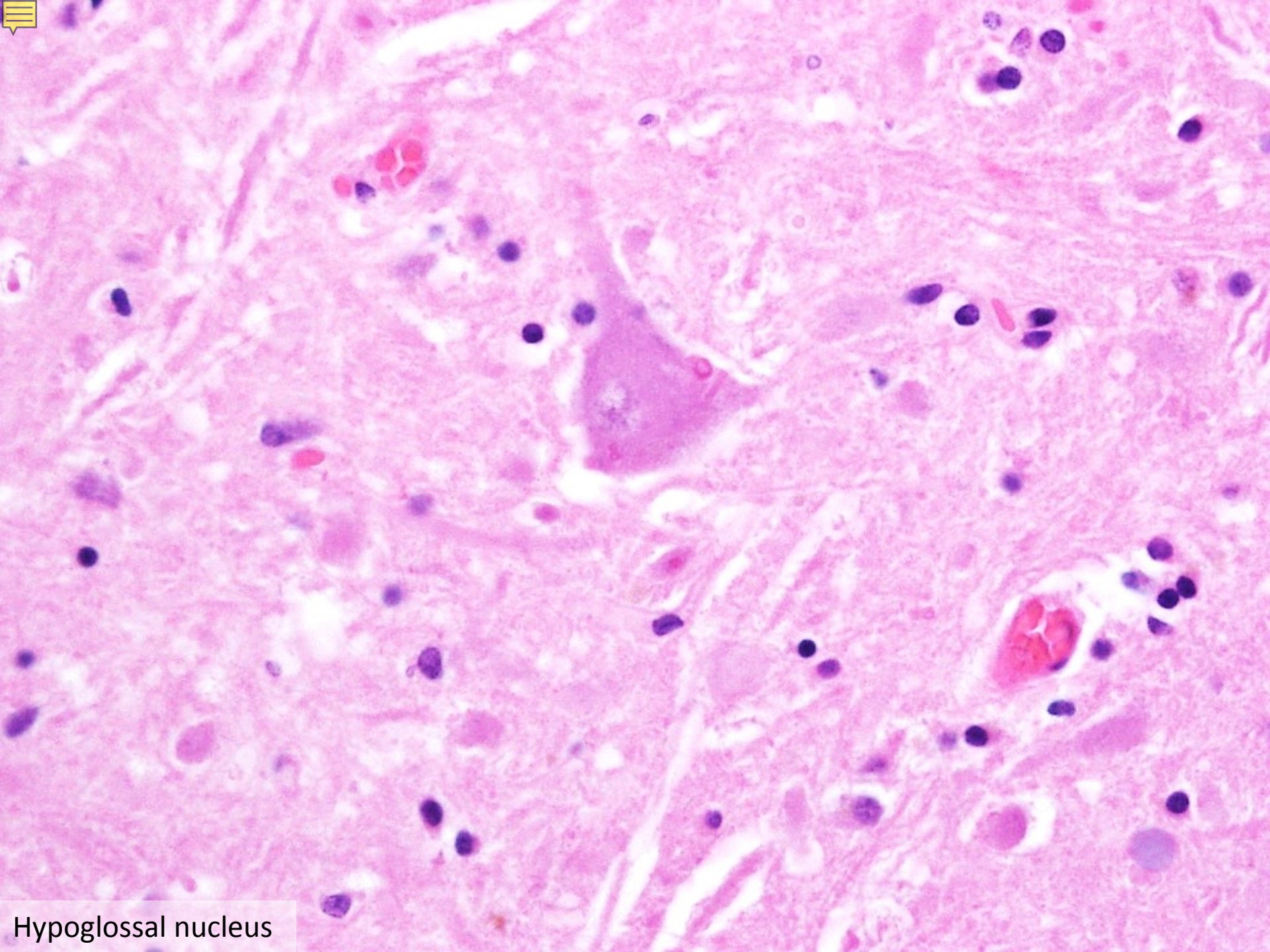
TDP-43: Temporal cortex



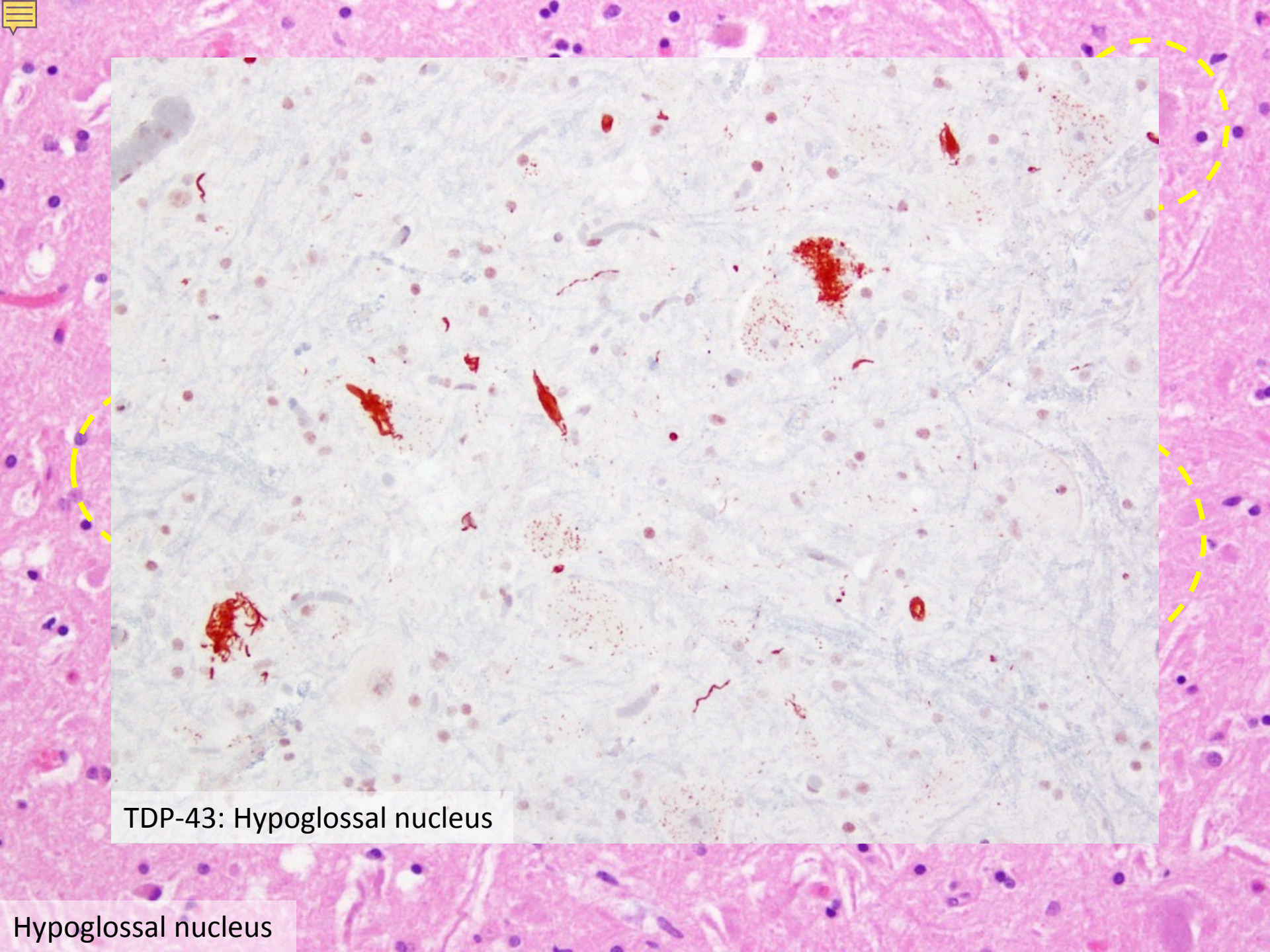
TDP-43: Caudate nucleus



TDP-43: Substantia nigra



Hypoglossal nucleus


TDP-43: Hypoglossal nucleus
Hypoglossal nucleus

FTLD-TDP classification system

Proposed new classification system for FTLD-TDP pathology, compared with existing systems

New system	Mackenzie et al. [7]	Sampathu et al. [11]	Cortical pathology	Common phenotype	Associated genetic defects
Type A	Type 1	Type 3	Many NCI Many short DN Predominantly layer 2	bvFTD PNFA	*GRN* mutations
Type B	Type 3	Type 2	Moderate NCI Few DN All layers	bvFTD MND with FTD	Linkage to chromosome 9p
Type C	Type 2	Type 1	Many long DN Few NCI Predominantly layer 2	SD bvFTD	
Type D	Type 4[a]	Type 4[a]	Many short DN Many lentiform NII Few NCI All layers	Familial IBMPFD	*VCP* mutations

Mackenzie, I. R., et al (2011). A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathologica, 122*(1), 111-113.

Final Diagnoses

- FTLD-tau (PSP)
- FTLD-TDP type B
- ALS-type pathology
- High Alzheimer disease neuropathologic change
- Lewy body disease, limbic stage

Discussion

Query of Northwestern ADC Cohort

- 57/284 (20%) High ADNC
  - DLBD or medial temporal TDP
- 27/195 (14%) FTLDs (FTLD-tau, TDP or FUS)
  - Intermediate or high ADNC
- 2/935 (0.2%) all cases
  - FTLD-tau with FTLD-TDP

Combined Pathologies

- Boyle et al. looked at 1079 cases from 2 aging studies
  - 78% of cases had two or more diagnoses, 58% had three or more diagnoses, 35% had four or more diagnoses
  - Greater than 230 different combinations were observed
- Dr. Nelson - pure AD is not typical, and there are often overlapping neuropathologies, including CARTS
- Dickson PSP cases
  - 46% have PART, 33% have AD pathology, 5% have LBD, 6% have TDP
  - Only 8% are pure PSP
- Many proposed mechanisms for these combined or "mixed" pathologies
  - Misfolded protein aggregation cascade (synergistic aggregation)
  - Proteosome or chaperone malfunction and proteotoxic stress
- "Polyproteinopathies" are going to be more recognized and more relevant in the future
  - Therapy targeting multiple proteins will be necessary
- Questions or comments?

References

- Mackenzie, I. R., Neumann, M., Baborie, A., Sampathu, D. M., Plessis, D. D., Jaros, E., . . . Lee, V. M. (2011). A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathologica, 122*(1), 111-113.
- Boyle et al. Person-specific contribution of neuropathologies to cognitive loss in old age. *Annals of Neurology.* 2017; 83(1):74-83