MAYO CLINIC

The Spectrum of Age-Associated Astroglial Tauopathies

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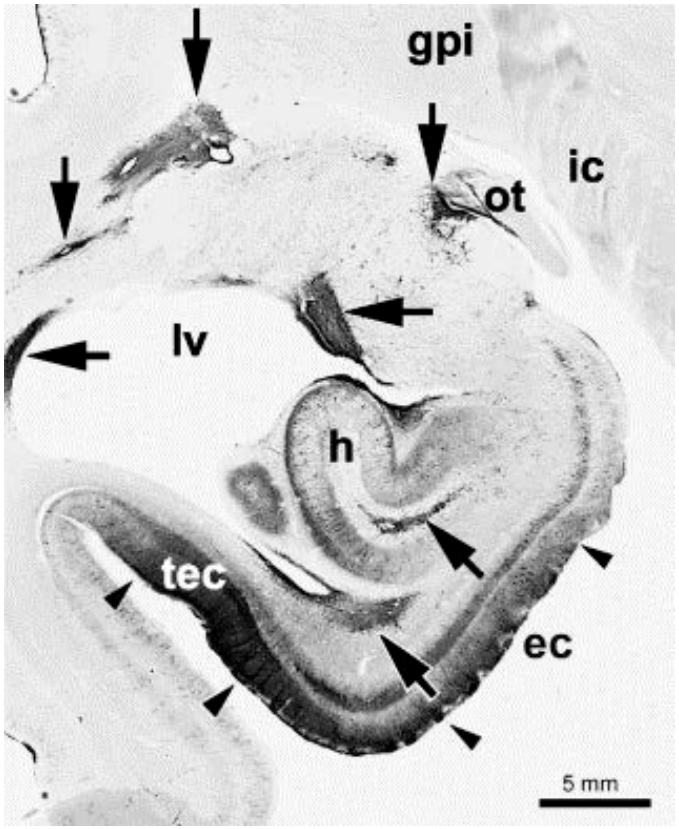
Thorn-shaped astrocytes

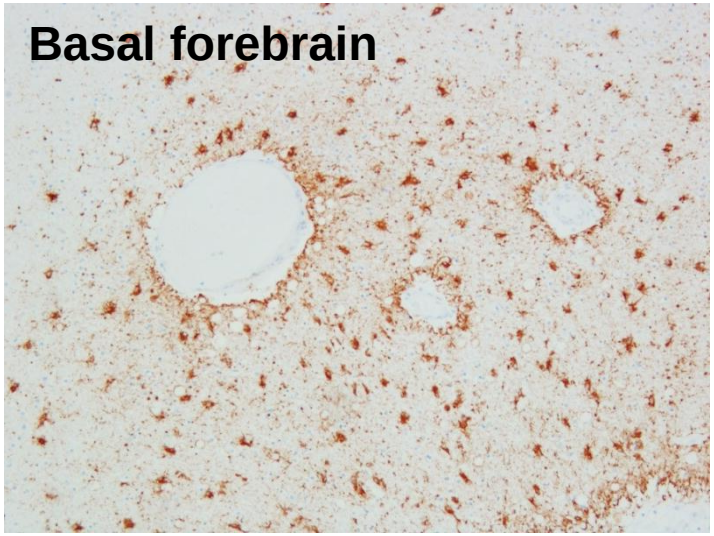
- TSA were first reported by Ikeda (1995), as tau-positive astrocytes in various neurodegenerative disorders.
- TSA are found most often in subpial and perivascular spaces of the medial temporal lobe, as well as in the subependymal region.
- Recent studies have shown that TSA increase in frequency with age.
- Frequency with age (Schulz 2004).
  - 40-74 y/o = 10/48 (21%)
  - 75-100 y/0 = 24/52 (46%)

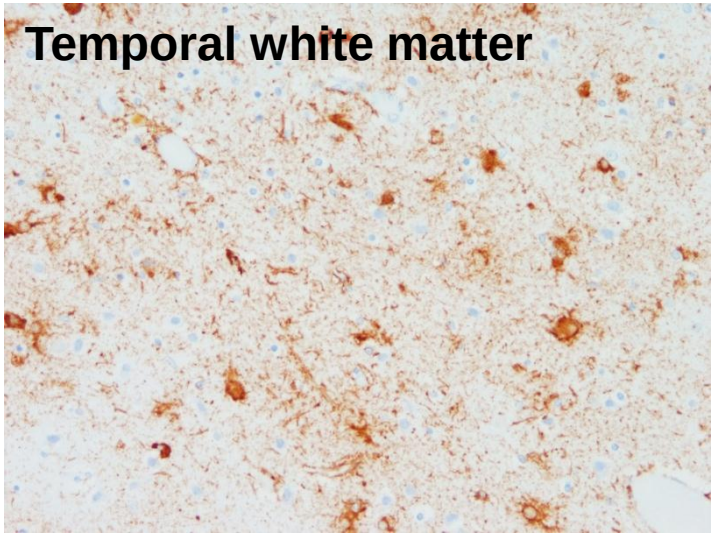


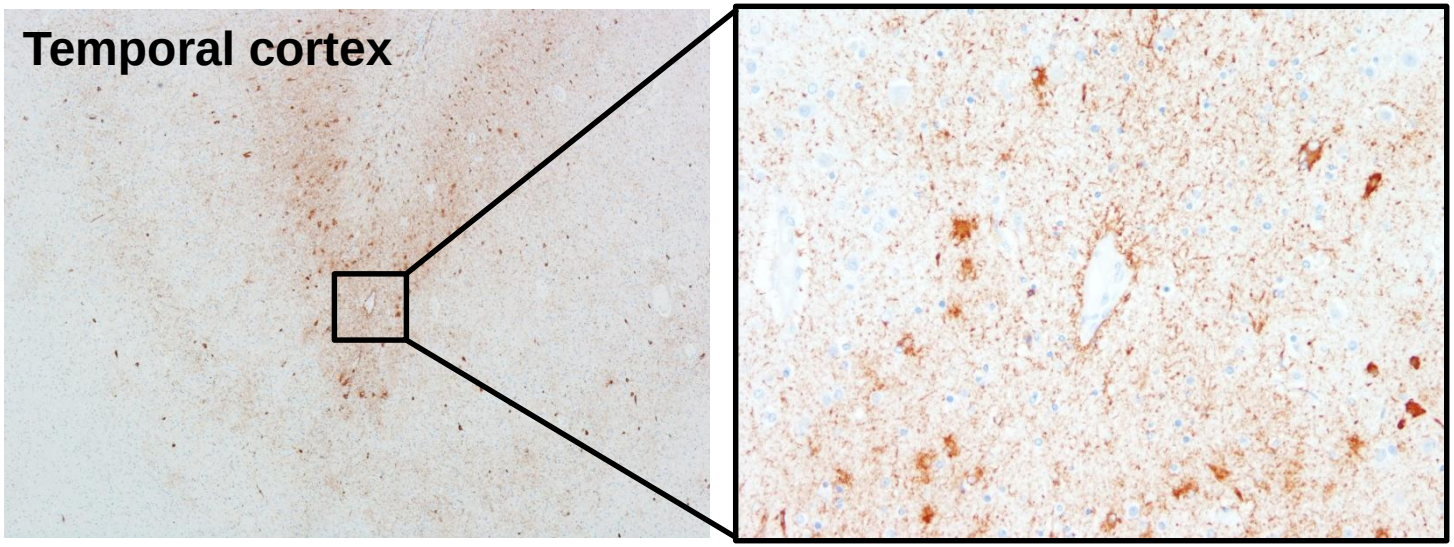
Ikeda K, Akiyama H, Kondo H, et al. Thorn-shaped astrocytes: possibly secondarily induced tau-positive glial fibrillary tangles. *Acta Neuropathol* 1995;90:620-625.

Schultz C, Ghebremedhin E, Del Tredici K, Rüb U, Braak H. High prevalence of thorn-shaped astrocytes in the aged human medial temporal lobe. *Neurobiol Aging* 2004;25:397-405.

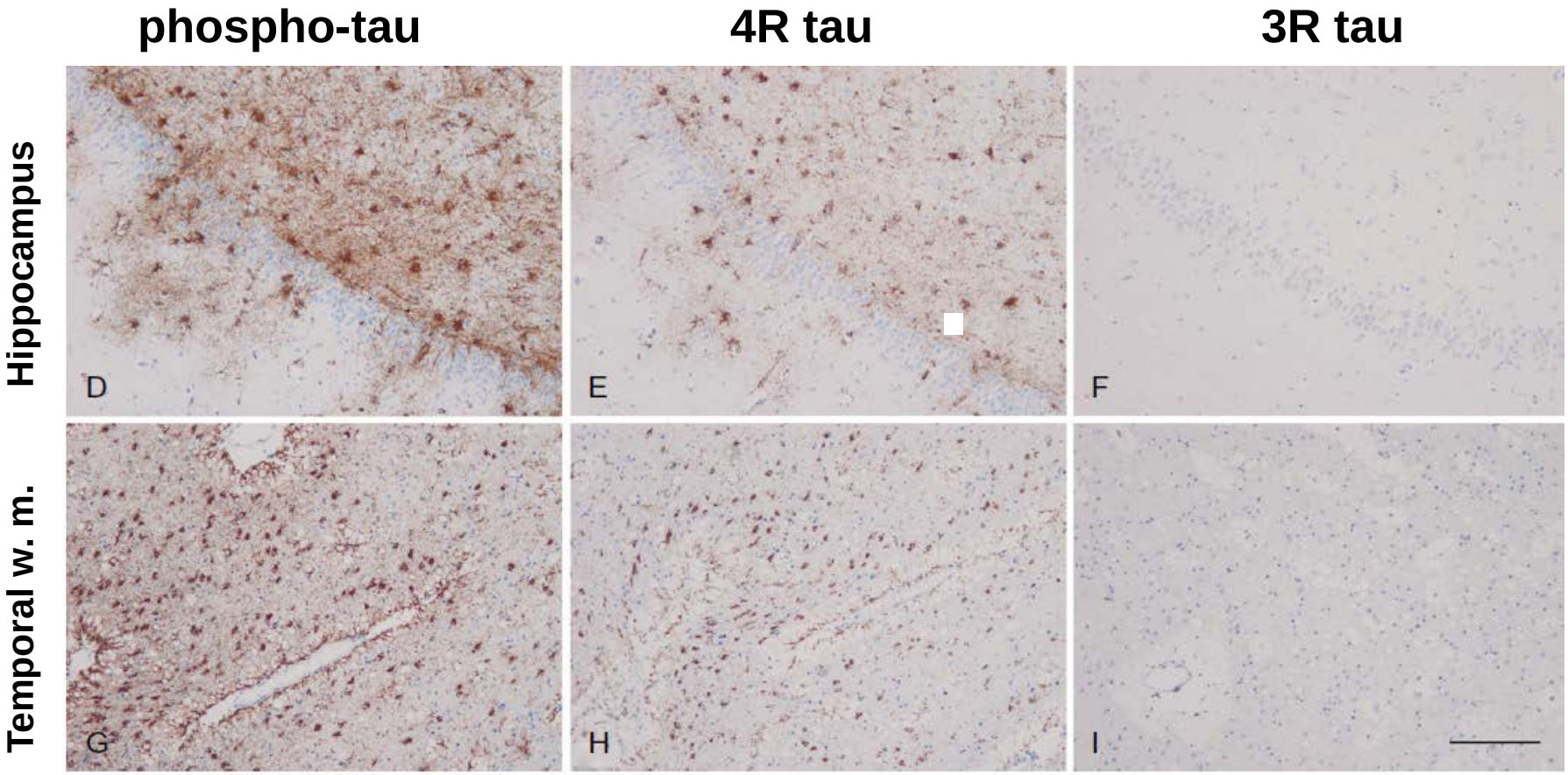
Thorn-shaped astrocytes (TSA)







TSA are composed of 4R tau

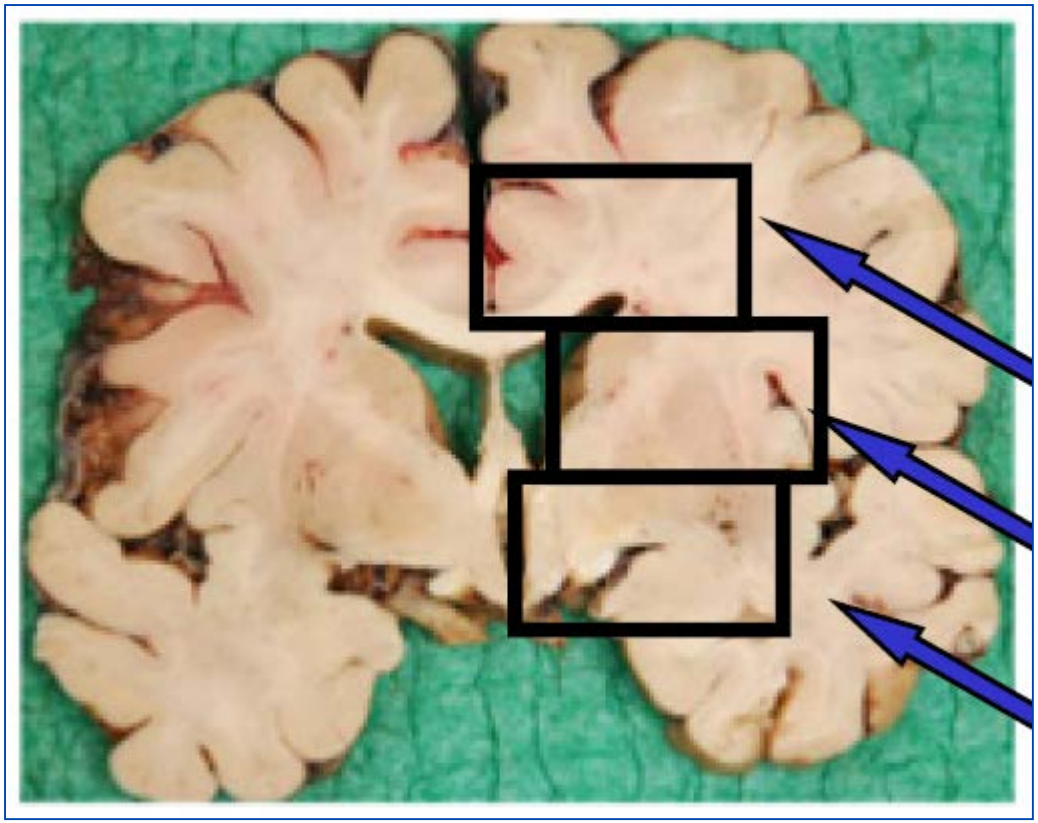


López-González I, Carmona M, Blanco R, Luna-Muñoz J, Martínez-Mandonado A, Mena R, Ferrer I. Characterization of thorn-shaped astrocytes in white matter of temporal lobe in Alzheimer's disease brains. *Brain Pathol* 2013;23:144-153.

Frequency of TSA and AGD in AD

- Investigate frequency and relationship of AGD and TSA in Mayo Clinic brain bank.
- Medial temporal lobe sections from 239 cases of pathologically-confirmed AD (109 men, 130 women; 55-102 years of age)
- Immunohistochemistry with antibodies to phospho-tau (CP13) and 4R-tau (ET3) (from Petr Davies, PhD)
- Double immunostaining & immuno-EM

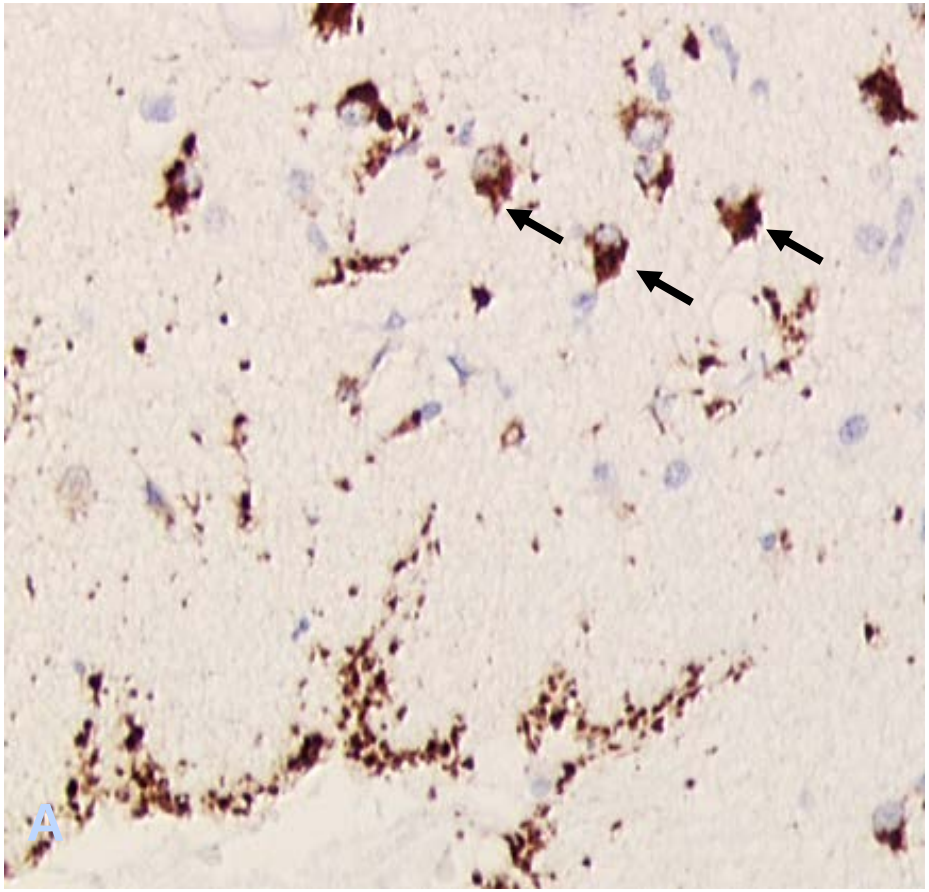
Basal forebrain section



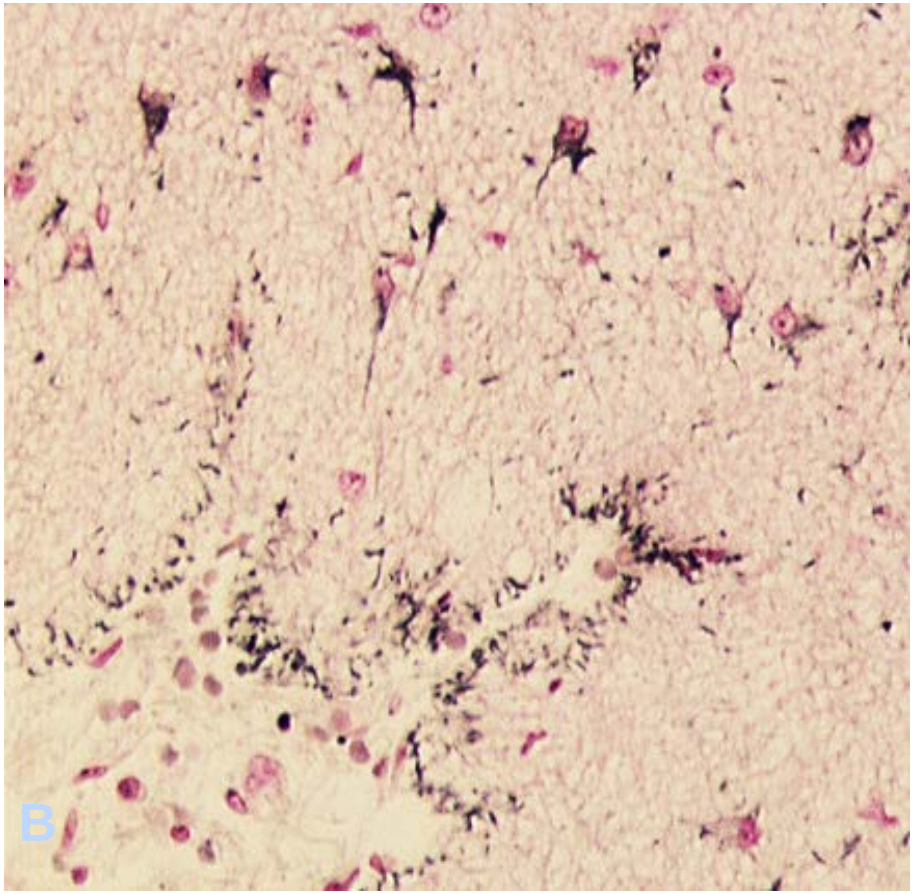
Alafuzoff I, et al. The need to unify neuropathological assessments of vascular alterations in the ageing brain: Multicentre survey by the BrainNet Europe consortium. *Exp Gerontol* 2012;47:825-833.

*
- **Lentiform nucleus**
- **Substantia innominata (basal nucleus of Meynert)**
- **Hypothalamus (infundibulum)**
- **Optic tract**
- **Amygdala**

Thorn-shaped astrocytes

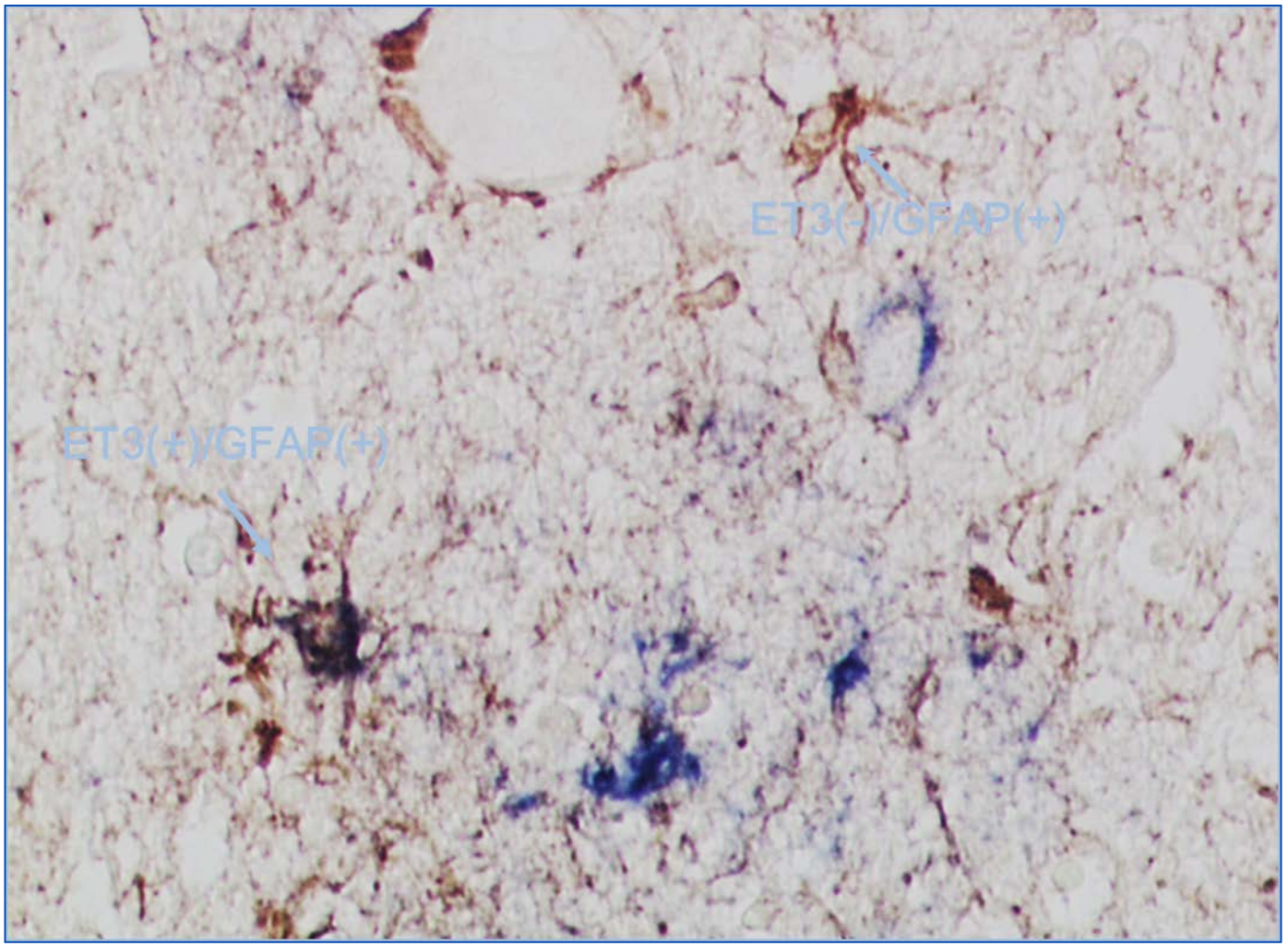


4R tau (ET3) immunostain



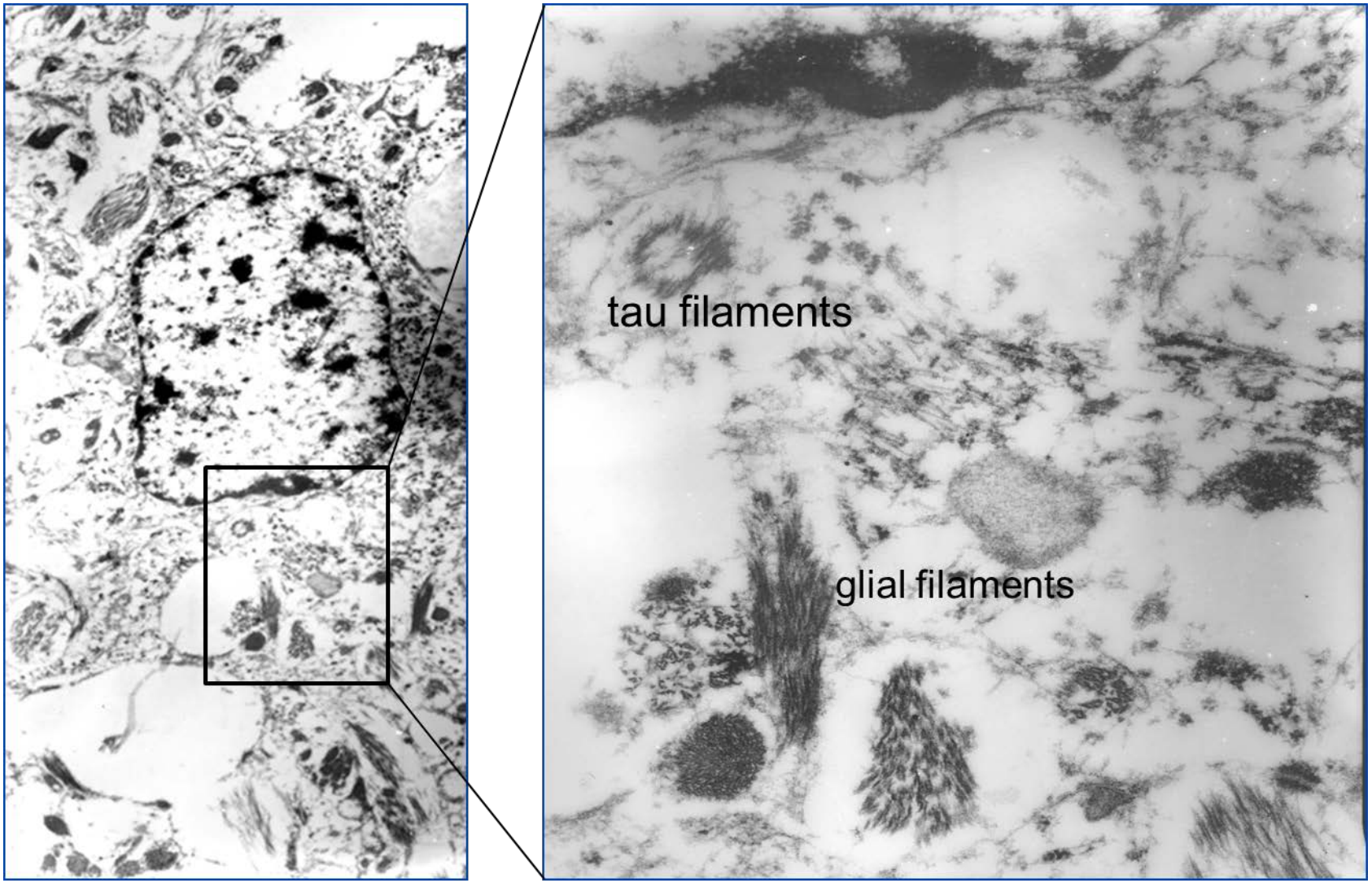
Gallyas silver stain

Double immunostain for 4R tau and GFAP

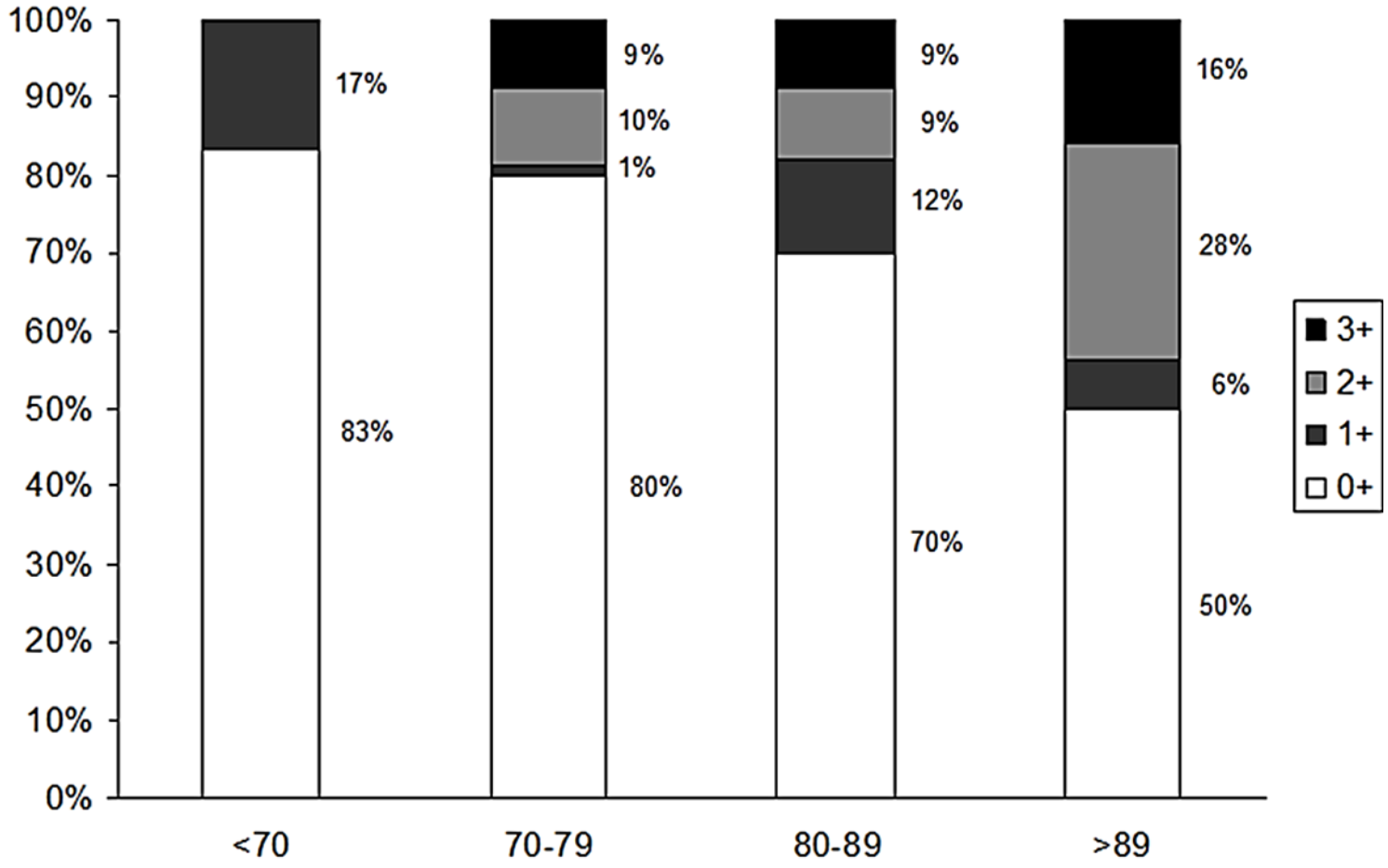


ET3 (BCIP-blue) / GFAP (DAB-brown)

EM of thorn-shaped astrocytes

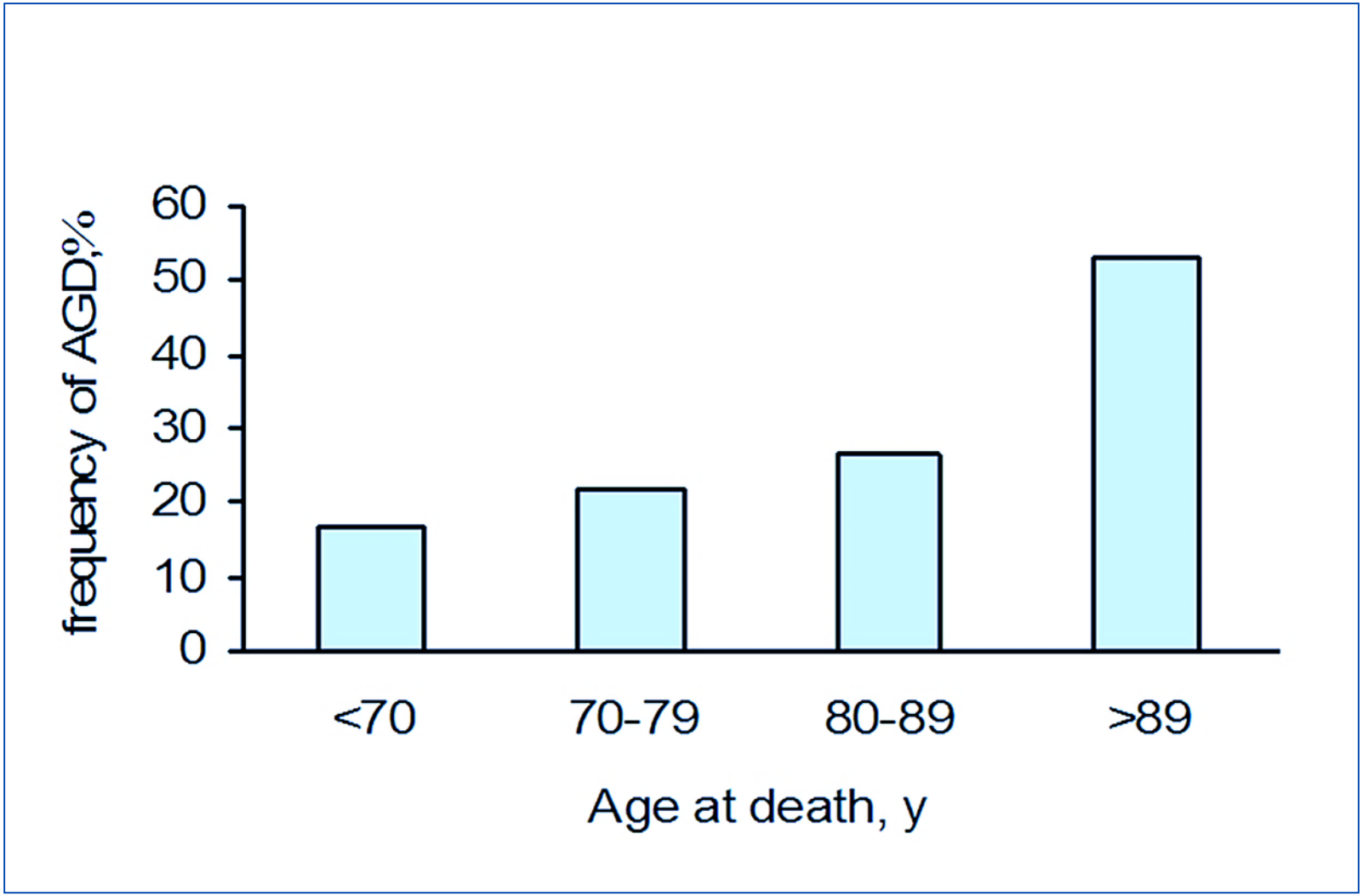


TSA increases in frequency & severity with age



TSA scores as none (0), mild (1+), moderate (2+) and marked (3+).

AGD increases with age



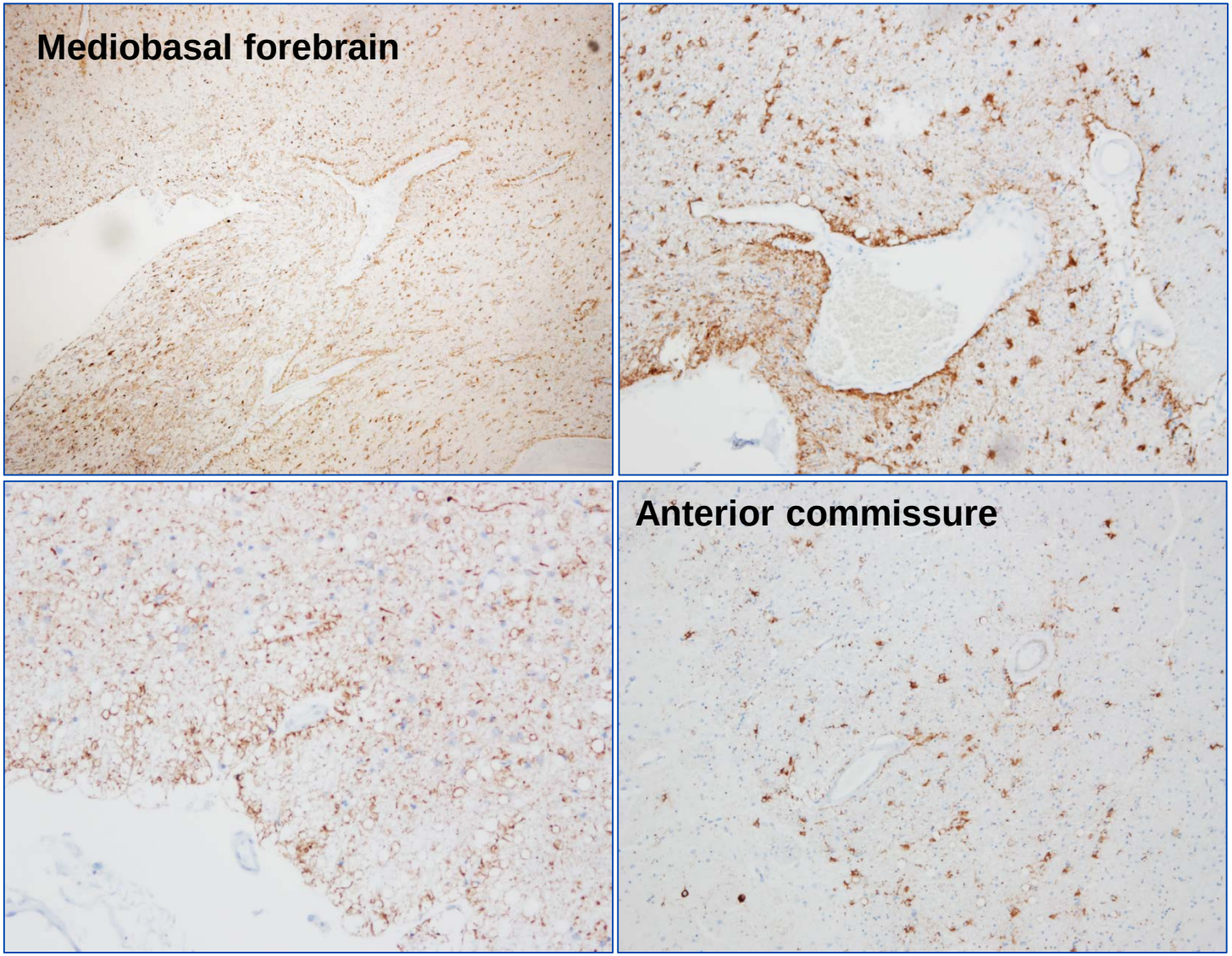
4R tauopathy in AD

- AGD & TSA were found in ~30% of AD.
- AGD & TSA both increased with age.
- Neither not correlate with AD pathology.
- AGD & TSA are distinctive and independent medial temporal 4R tauopathies.

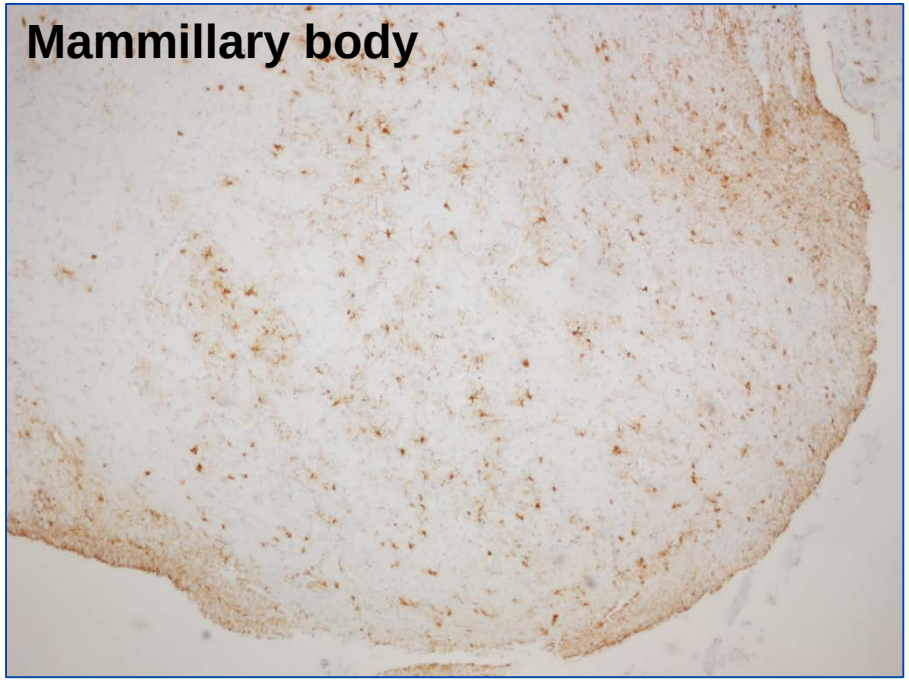
Age-associated astrogliopathy in non-demented elderly from Einstein Aging Study

- Prospective cohort (P01 AG003949-30)
- Minimal or no Alzheimer type pathology
  - Median Braak stage: III
  - Median Thal phase: 1
- Old age (range: 74 to 105 years)
- Median age: 88 years (25%-tile 84 y, 75%-tile 97 y)
- Sex: 13 men & 31 women
- Racially mixed: 40 White & 4 Black
- Screening section – basal forebrain

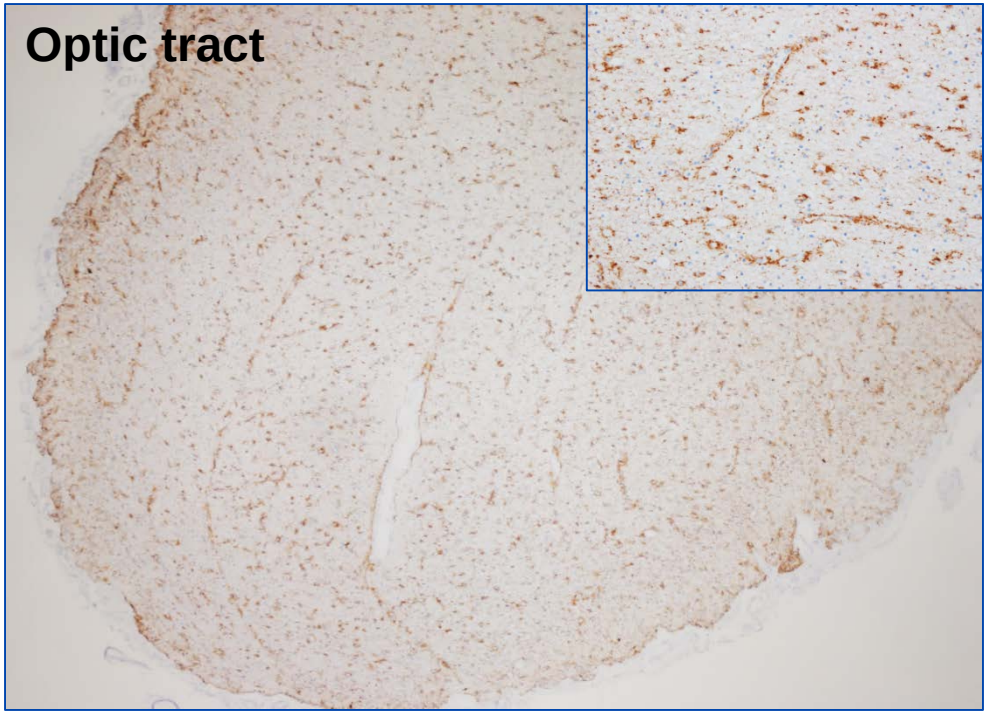
Thorn-shaped astrocytes



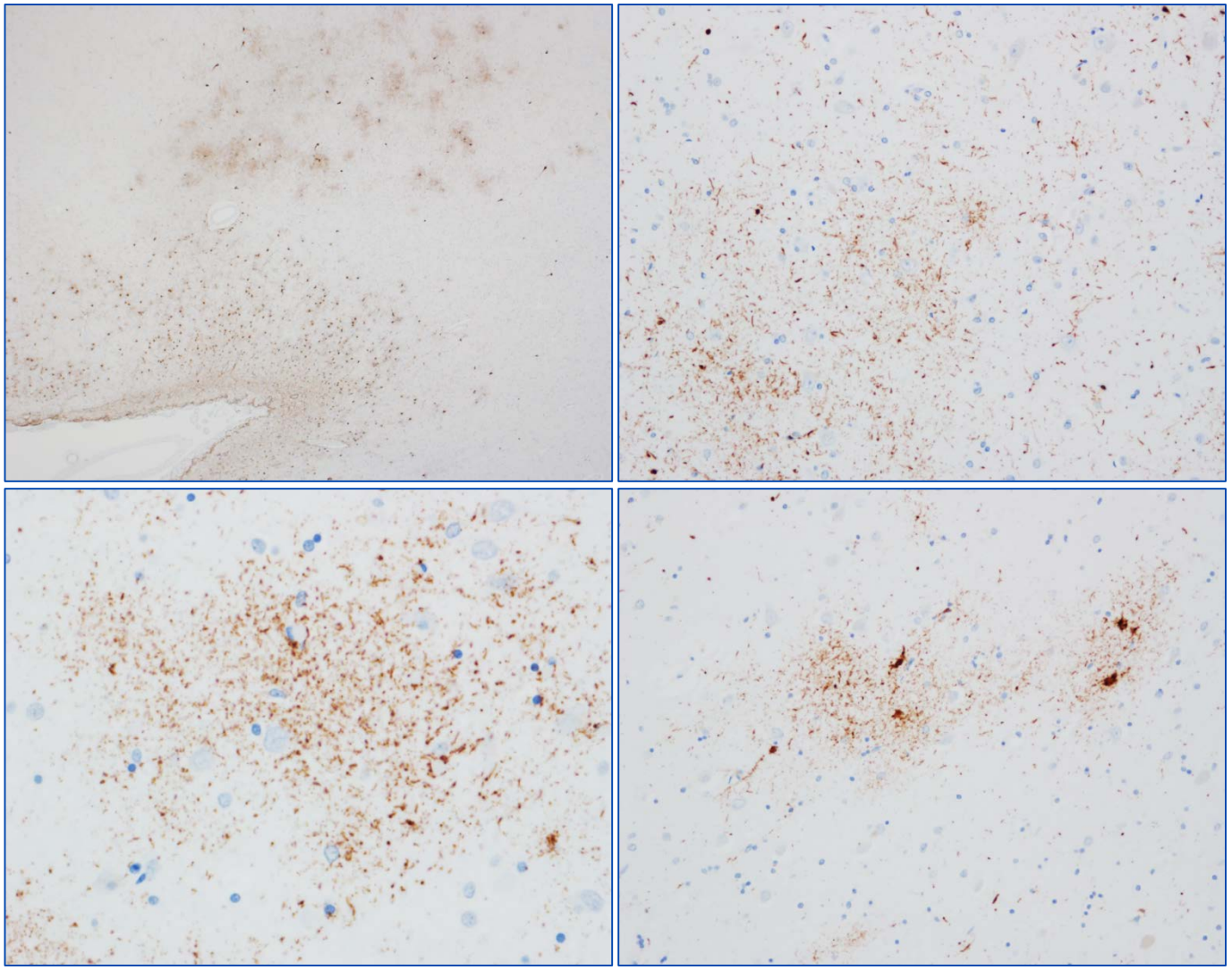
Thorn-shaped astrocytes



Less common sites for TSA in aging



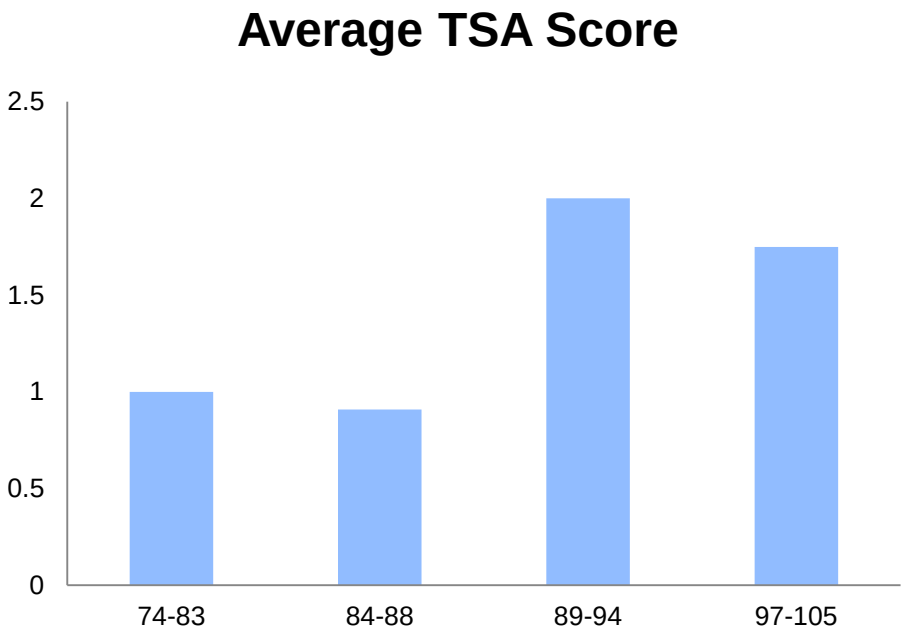
Ramified or bushy astrocytes (gray matter)



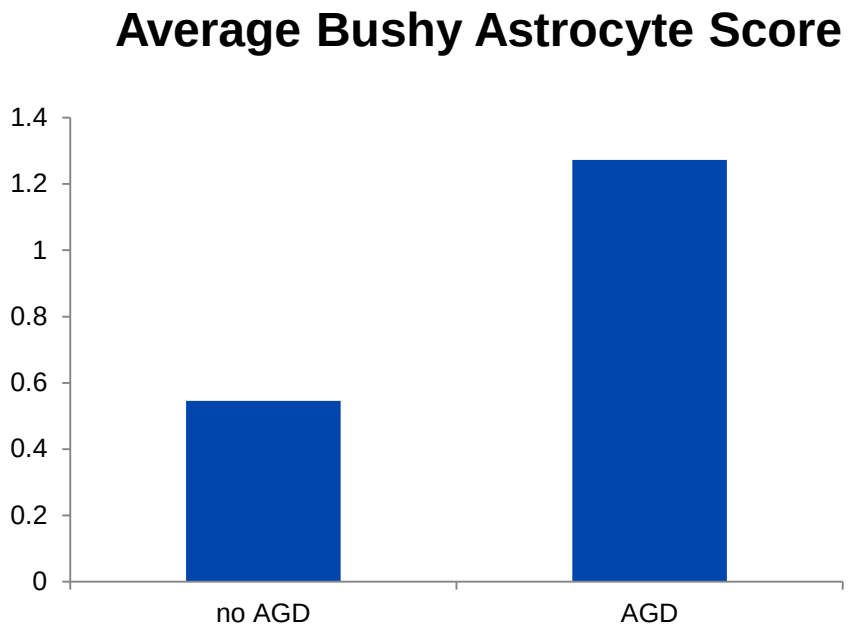
Spearman Correlations

	Age	Brain weight	Braak NFT stage	Thal Amyloid Phase	AGD
Thorn shaped astrocytes	r = 0.28 p = 0.06	r = -0.04 ns	r = 0.43 p < 0.01	r = 0.14 ns	r = 0.07 ns
Bushy astrocytes	r = 0.07 ns	r < -0.01 ns	r < 0.01 ns	r = 0.22 ns	r = 0.43 p < 0.01

- TSA score increases with age.
- Ramified (bushy) astrocyte more frequent in AGD.

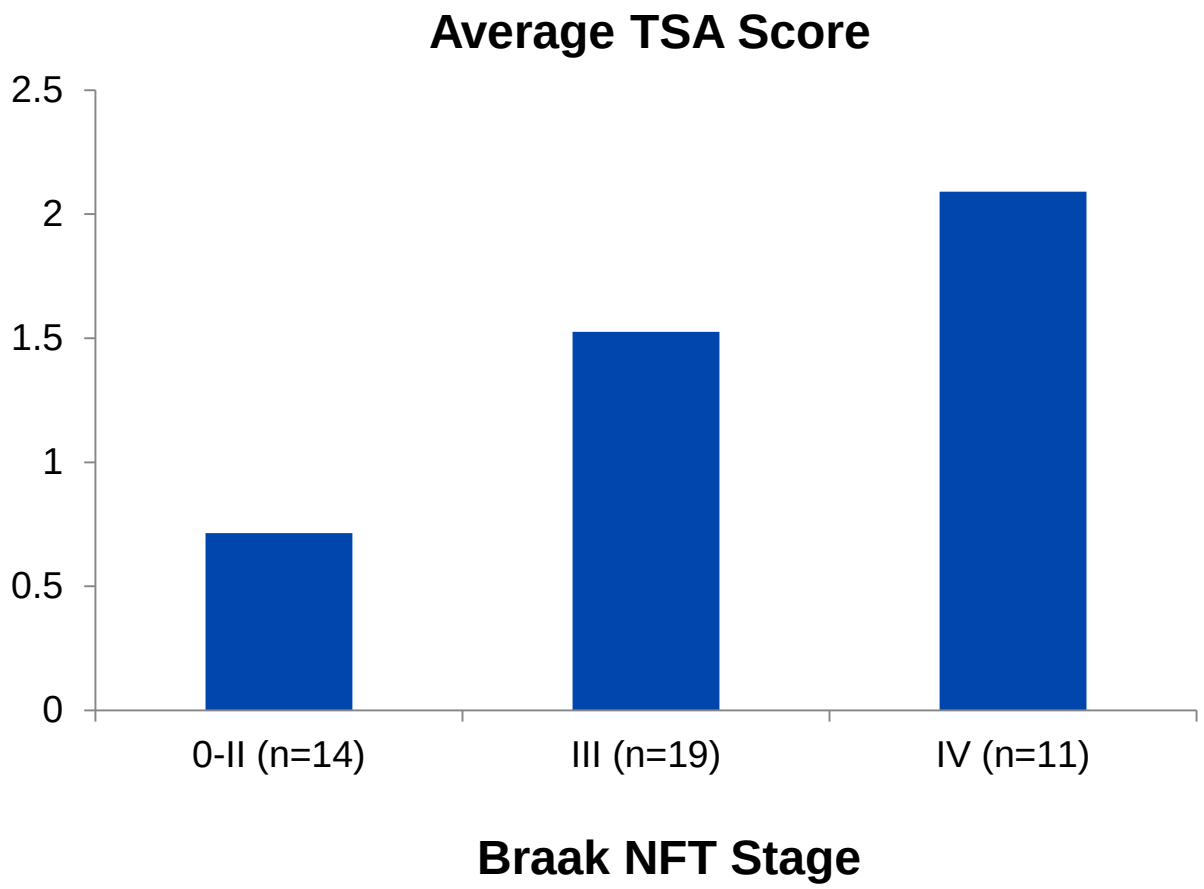


Age Quartiles vs. TSA score

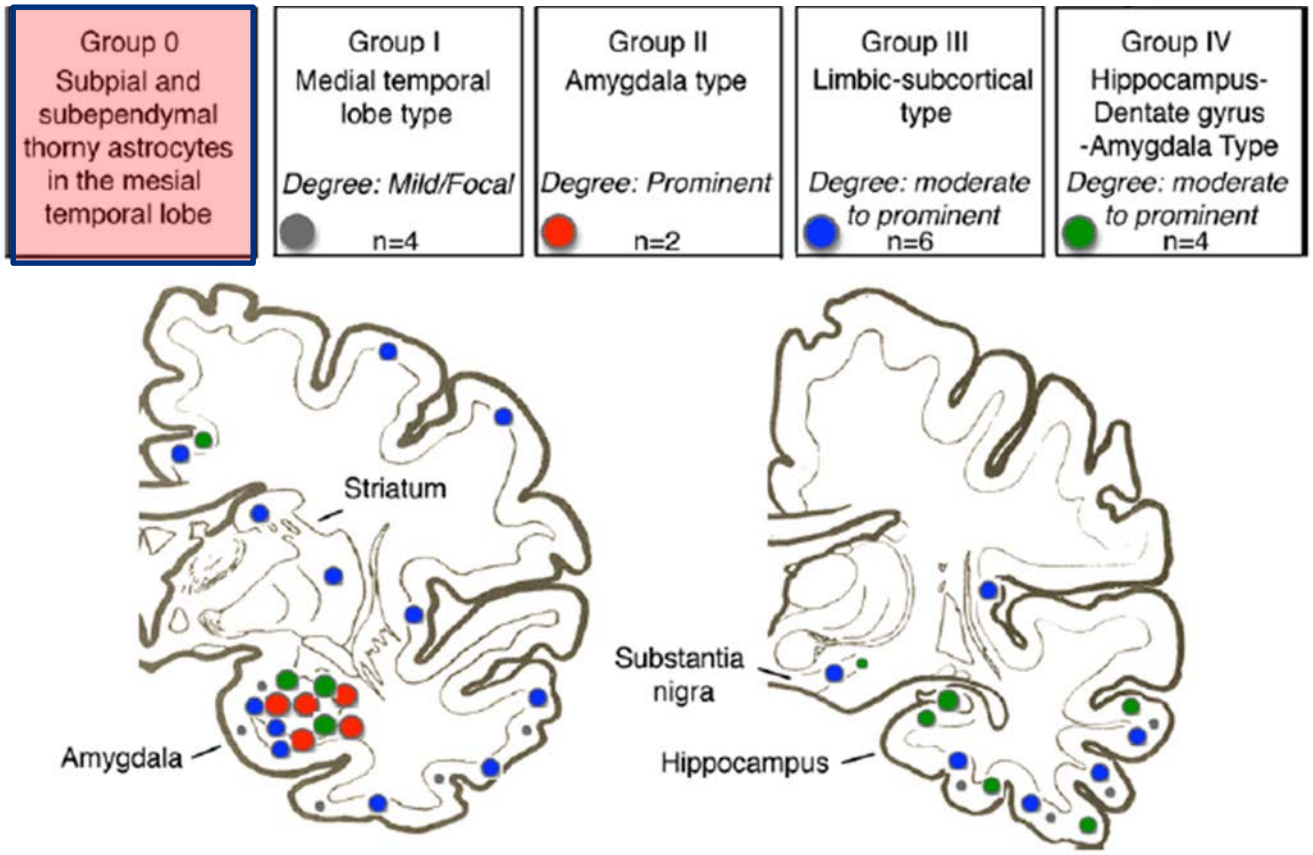


Ramified astrocyte score vs. AGD

TSA score increases with Braak stage

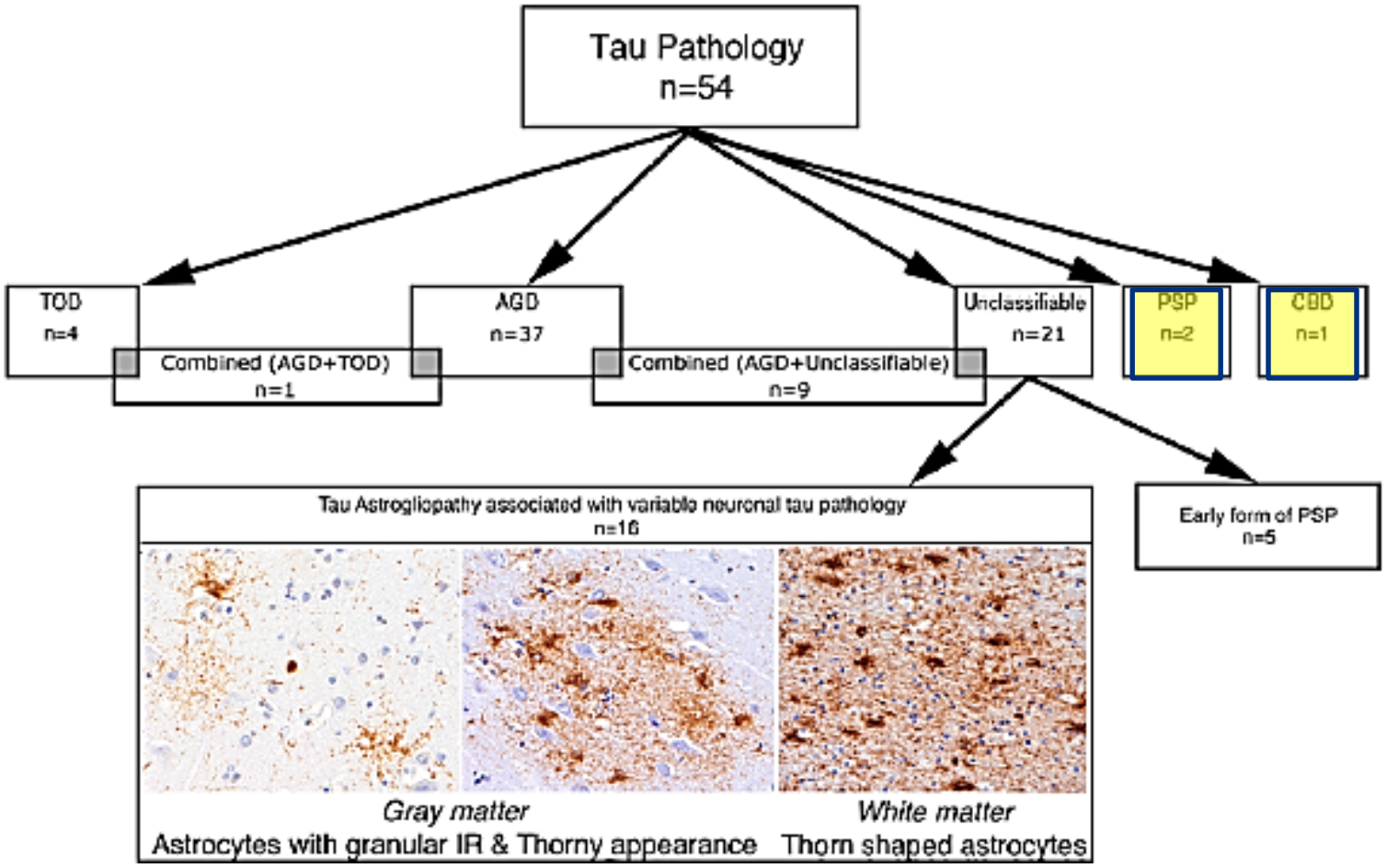


Astrocytic tauopathy in aging



Kovacs GG, Milenkovic I, Wöhrer A, et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol* 2013;126:365-384.

Age associated neuronal tauopathies



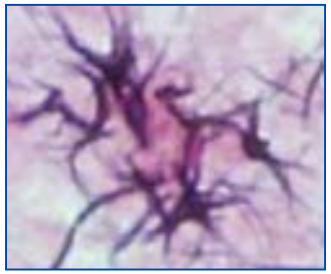
Kovacs GG, Milenkovic I, Wöhrer A, et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol* 2013;126:365-384.

Preclinical PSP in prospectively studied elderly

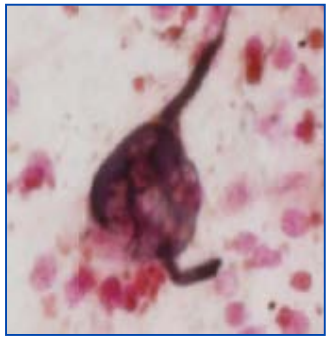
- 87 subjects clinically normal at death
- 33 had extensive AD pathology (preclinical AD)
- 17 had incidental Lewy bodies (preclinical PD)
- 4 had pathology consistent with PSP (preclinical PSP); one with parkinsonism

Case #	9	30	55
Clinical Features	n/a	n/a	n/a
Pathologic Features			
Frontal cortex	NFT, Tft, Thrn, CB	NFT, Tft, Thrn, CB	NFT, Tft, Thrn, CB
Temporal cortex	NFT, Tft, Thrn, CB	NFT, Tft, Thrn, CB	NFT
Parietal cortex	NFT, Tft, Thrn, CB	NFT, Tft, Thrn, CB	—
Putamen	NFT, Tft, Thrn, CB	NFT, Tft, Thrn, CB	—
Subthalamic nucleus	NFT	NFT, Tft, Thrn, CB	—
Globus pallidus	NFT, Tft, Thrn, CB	NFT, Tft, Thrn, CB	—
Thalamus	—	NFT, Tft, Thrn, CB	—
Substantia nigra	NFT	NFT, Tft, Thrn, CB	NFT
Substantia nigra pigment loss	Moderate	Mild	Mild
Pons	NFT	NFT, Tft, Thrn, CB	NFT
Dentate nucleus	NFT, Tft	NFT, Tft, Thrn, CB	NFT

Gallyas silver stain



Tufted astrocyte in basal ganglia



Globose NFT in S. nigra

Dugger BN, Hentz JG, Adler CH, et al. Clinicopathological outcomes of prospectively followed normal elderly brain bank volunteers. *J Neuropathol Exp Neurol* 2014;73:244-252.

Preclinical CBD

- Neurologically normal woman.
- Morphology and distribution of tau pathology consistent with CBD.

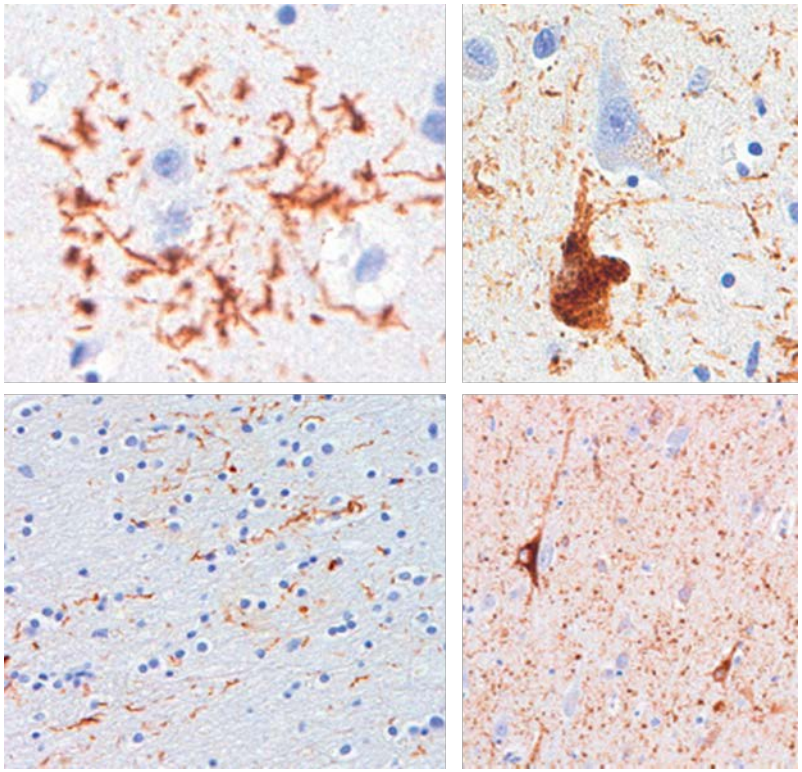


Table 1. Anatomical distribution of τ-pathology.

				τ-pathology		
Region	Neuronal loss/ Gliosis	Threads		DNC-IR	CB	Astrocytic IR
		WM	Cx			
Frontal Cx/WM	–	+	+	++	+	++
Temporal Cx/WM	+	+	+	+	–	+
Parietal Cx/WM	+	+	+	+	–	+
Occipital Cx/WM	–	–	–	–	–	–
Caudate nucleus	++	+		++	–	–
Putamen	+	+		++	+	+
Globus pallidus	+	+		+	+	–
Claustrum	–	+		+	+	+
Thalamus	–	+		+	+	+
Subthalamic nucleus	–	+		+	–	+*
Substantia nigra	+	+		++	–	+
Amygdala	+	+		+	+	+
DG	–	–		++	–	+
CA1	–	++		++	–	+
CA2/3	–	++		++	–	+
CA4	–	+		+	–	–
Subiculum	–	++		++	–	+
Entorhinal Cx	+	+		+	–	+
Pontine base	–	+		–	–	+
Locus coeruleus	–	–		+	–	–
Cerebellar Cx/WM		–		–	–	–

Ivan Milenkovic I, Kovacs GG. Incidental corticobasal degeneration in a 76-yearold woman. *Clin Neuropathol* 2013;32:69-72.

Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy. Kovacs GG, et al.

- Subtype of ARTAG
  - Subpial type (most often mediobasal)
    - Note if pronounced at sulcal depths of convexity cortices (CTE)
  - Subependymal type (most often temporal horn, third ventricle)
  - Gray matter type - fine granular tau immunoreactivity in cytoplasmic processes (most often medial temporal lobe)
  - White matter type – thorn-shaped astrocytes in subcortical white matter
- Anatomical regions affected by ARTAG
  - Mediobasal
  - Lobar
  - Subcortical
  - Brainstem

Summary

- With advancing age, the brain is susceptible to glial, as well as neuronal tauopathies.
- Glial tauopathies affect oligodendroglia and astrocytes
- Oligodendroglial “coiled bodies” - most often seen in association with AGD
- Astrocytic lesions
  - Thorn-shaped (tauopathy of “fibrous astrocytes” – glia limitans, subpial, perivascular subependymal; white matter)
  - Ramified or bushy astrocytes (tauopathy of protoplasmic astrocytes – gray matter, especially amygdala)
- As antemortem biomarkers are developed to detect tau, non-Alzheimer age-associated pathologies need to be taken into consideration.

Acknowledgements

- Brain bank coordinators
  - Deann Gibson and Beth Marten
- Neuropathology – histology & immunohistochemistry
  - Monica Casey-Castanedes, Virginia Phillips, Linda Rousseau
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  - P50 NS072187 – Udall Center for Excellence in Parkinson's Disease Research
  - P01 AG003949 – Einstein Aging Study
  - Florida DOEA – Alzheimer Disease Initiative Brain Bank