

Age and phenotype shape thalamic subnuclear tau vulnerability in progressive supranuclear palsy

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Introduction

The thalamus is a critical structure in the brain, directing the flow of limbic, sensory, and motor information to widespread cortical regions. Anatomically complex, it contains numerous subnuclei, each projecting to distinct cortical areas.

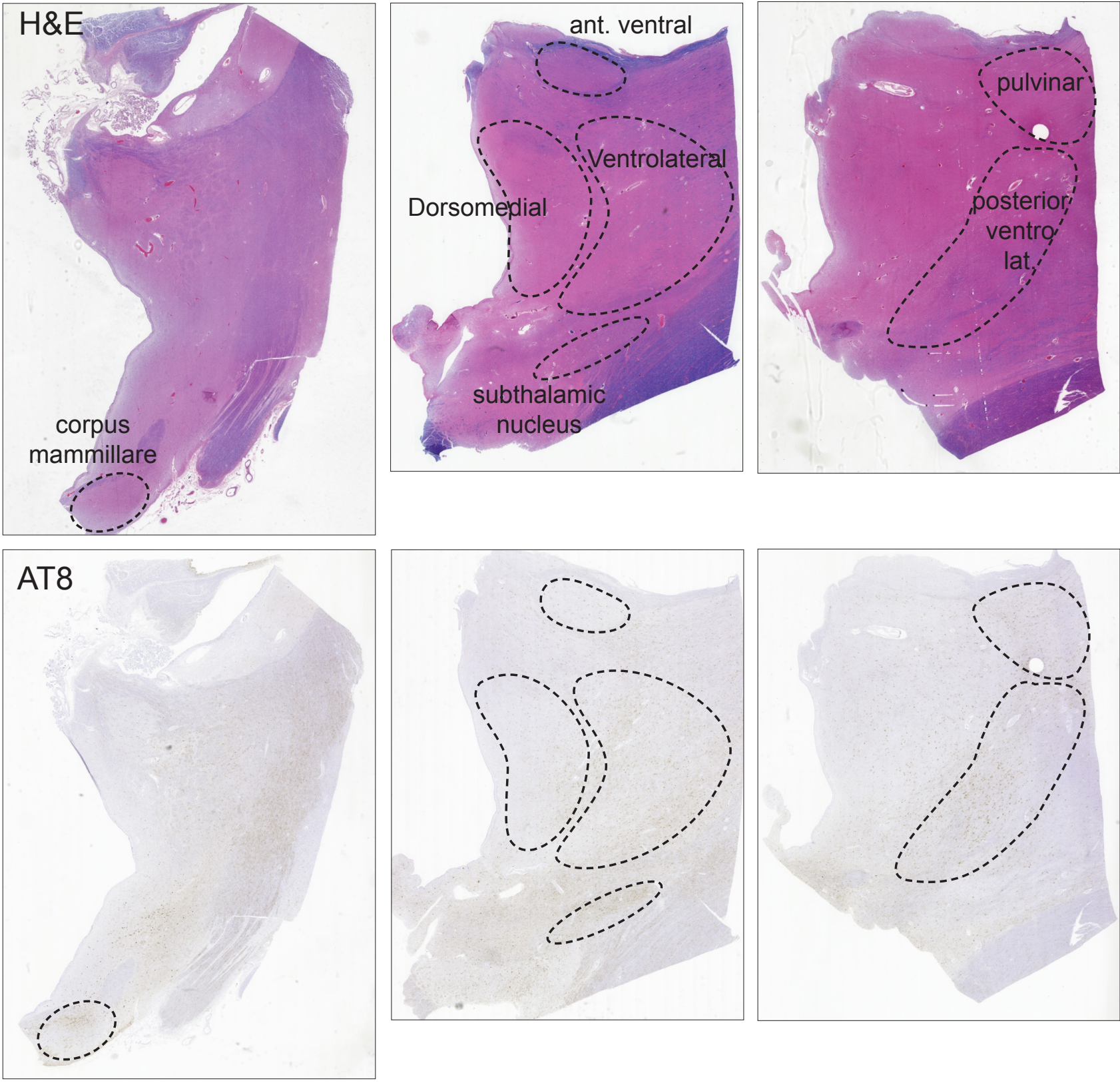
Progressive Supranuclear Palsy (PSP) shows clinical and neuropathological heterogeneity, and the early major vulnerable areas include the pallido-nigro-Luysian axis. The subthalamic nucleus (STN) is a hallmark brain region that is affected early in PSP and shows severe tau pathology. The characteristic pathological features of PSP include neurofibrillary tangles in neurons in subcortical and brainstem regions in combination with tau-immunopositive tufted astrocytes. Tau-immunopositive oligodendroglial coiled bodies are also a common and widespread neuropathological features of PSP.

Objective: Our aim to study thalamic subnuclei is based on the hypothesis that thalamic subnuclei show differential vulnerability across clinical and neuropathological PSP subtypes.

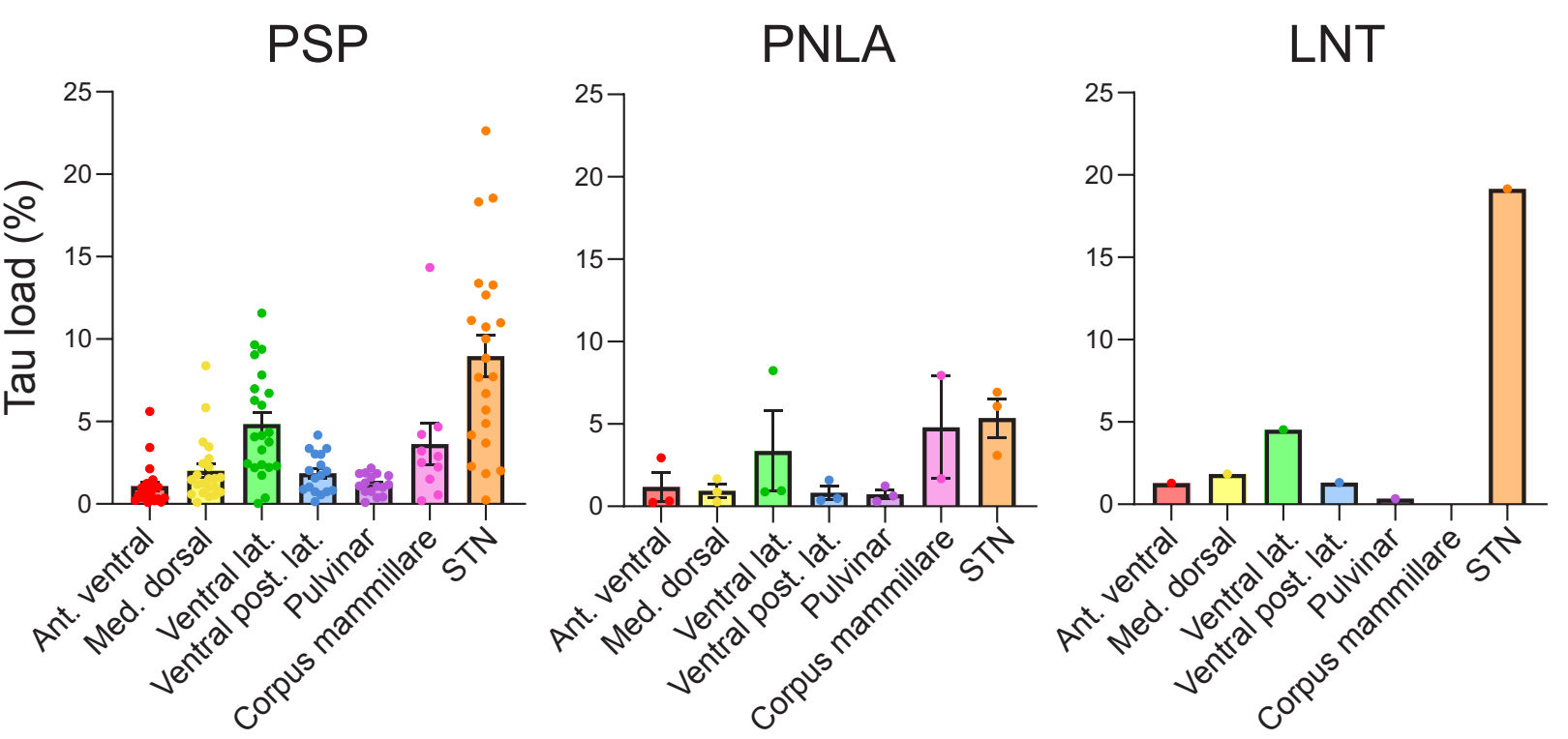
Methods: 27 cases showing classical neuropathological features of PSP (n=21), Pallido-nigro-Luysian atrophy (PNLA; n=5) and limbic predominant 4R tauopathy (LNT) were included in this study representing the following clinical subtypes: Richardson syndrome (RS), Parkinsonism, and corticobasal syndrome (CBS).

Three thalamic levels, including different subnuclei and the subthalamic nucleus and corpus mammillare, were evaluated using immunostaining for pTau (AT8). Total Tau load was evaluated using computer-based morphometry and complemented by semiquantitative scores of different cytopathologies including neuronal, astrocytic, and oligodendrocytic.

Thalamic levels included:

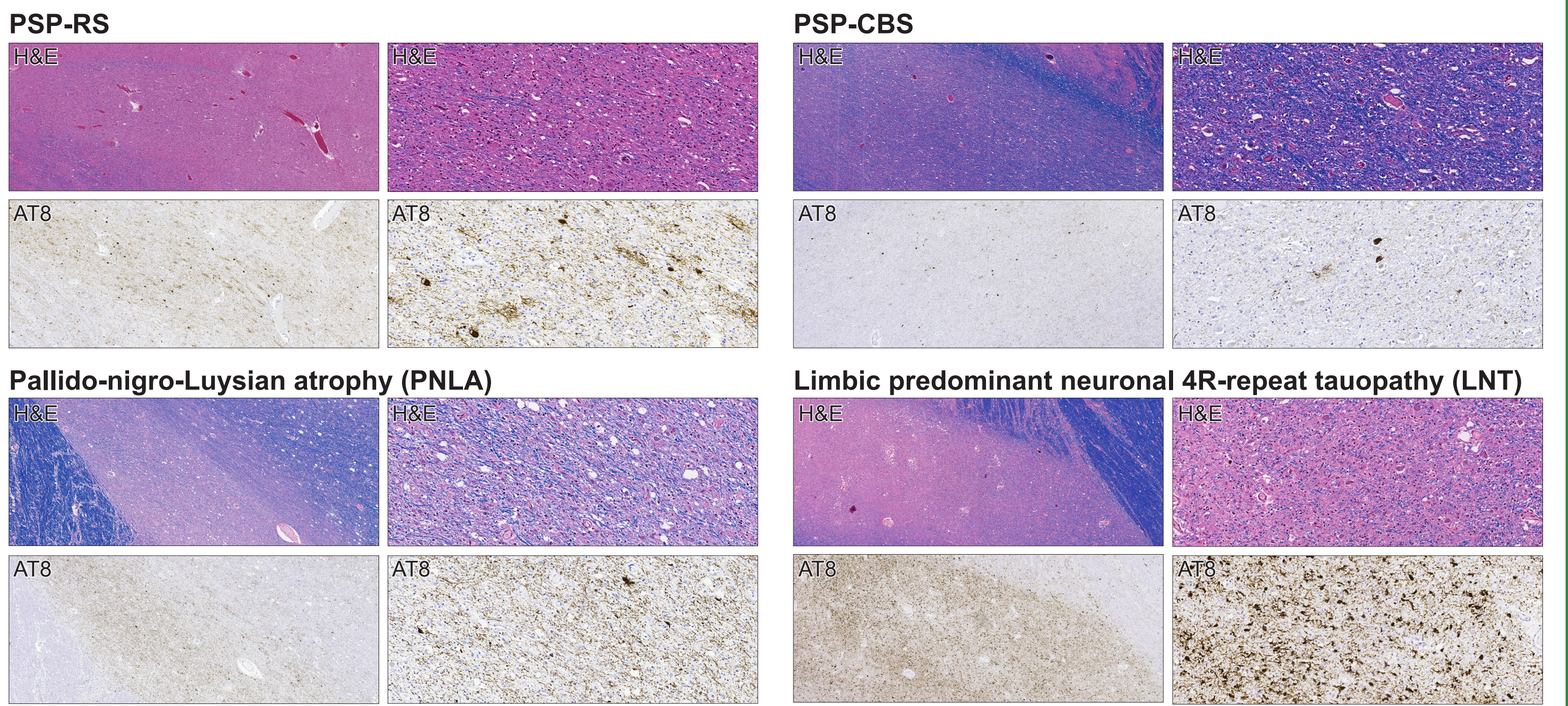


RESULTS-1: Tau load varies between thalamic nuclei

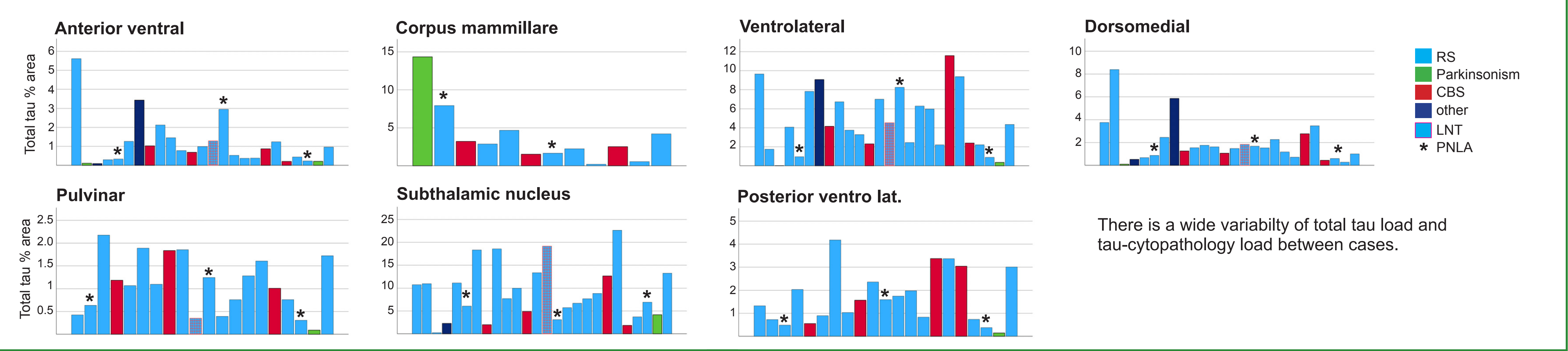


1. Total tau burden varied widely across cases and subnuclei.
2. The subthalamic nucleus (STN) showed the highest tau load, followed by the ventrolateral (VL) nucleus and mammillary body.
3. Neuronal and oligodendroglial tau pathologies predominated in these regions, while diverse astrocytic tau morphologies were most prominent in the VL and ventral posterolateral nuclei.

RESULTS-2: Tau load and cytopathology varies between cases



RESULTS-3: Graphic summary of Tau load and cytopathology variations



There is a wide variability of total tau load and tau-cytopathology load between cases.

SUMMARY OF RESULTS

Variable tested for effect:	Which has an effect?				
	Region	Age	Clinical subtype	Neuropath subtype	PSP stage
Neuropath variable					
Total Tau	+	+	-	+	+
Gliosis	+	+	+	+	+
Tau: NCI's	+	+	+	+	-
Tau: neurophil threads	+	+	-	+	+
Tau: tufted astrocytes	+	+	-	-	-
Tau: granular fuzzy astrocytes	+	+	+	+	-
Tau: thorn-shaped astrocytes	-	-	-	-	-
Tau: all astrocytic	+	+	+	+	-
Tau: all oligodendrocytic	+	+	+	+	-

1. Involvement of thalamic nuclei is different in cases with corticobasal syndrome versus Richardson syndrome.
2. Neuropathological subtypes, such as PNLA or LNT compared to PSP, also show difference.
3. Regression models indicate that age is the most consistent variable that determines the vulnerability patterns in addition to clinical and neuropathological phenotypes.

TAKE HOME MESSAGE

1. Our study reveals heterogeneity of cytopathologies and tau accumulation in a relatively small brain area with diverse anatomical relationships.
2. Our observations support the notion that tau pathology is most likely initiated in the STN and distinct involvement of micro-circuitries lead to selective vulnerability patterns that are well reflected in the involvement of thalamic nuclei that differ in different clinical and pathological phenotypes.
3. In addition to clinical phenotype and neuropathological subtype, aging is the most significant contributor to the variability.

