



Abstract

Definitive diagnosis of Alzheimer's disease and related dementias relies on post-mortem assessment of protein aggregates, but manual quantification is labor-intensive and subject to inter-rater variability. We developed a multi-target deep learning platform using four independently trained YOLOv11 models to detect TDP-43 inclusions, neurofibrillary tangles, Lewy bodies, and amyloid plaques in neuropathology whole-slide images. Models were optimized with transfer learning, pathology-specific augmentation, and cross-validation. Performance was robust, achieving mAP scores of 93% (TDP-43), 82% (Lewy bodies), 78% (amyloid), and 77% (tangles). Validation in the ART-AD and NACC cohorts demonstrated significant associations between automated pathology burden and cognitive decline, including stepwise increases in TDP-43 burden across normal cognition, MCI, and dementia ($p < 0.0001$). Regional pathology patterns across the amygdala, hippocampus, DLPFC, and pons recapitulated established disease staging, supporting the use of AI-driven pathology quantification for scalable clinicopathological studies.

Methods

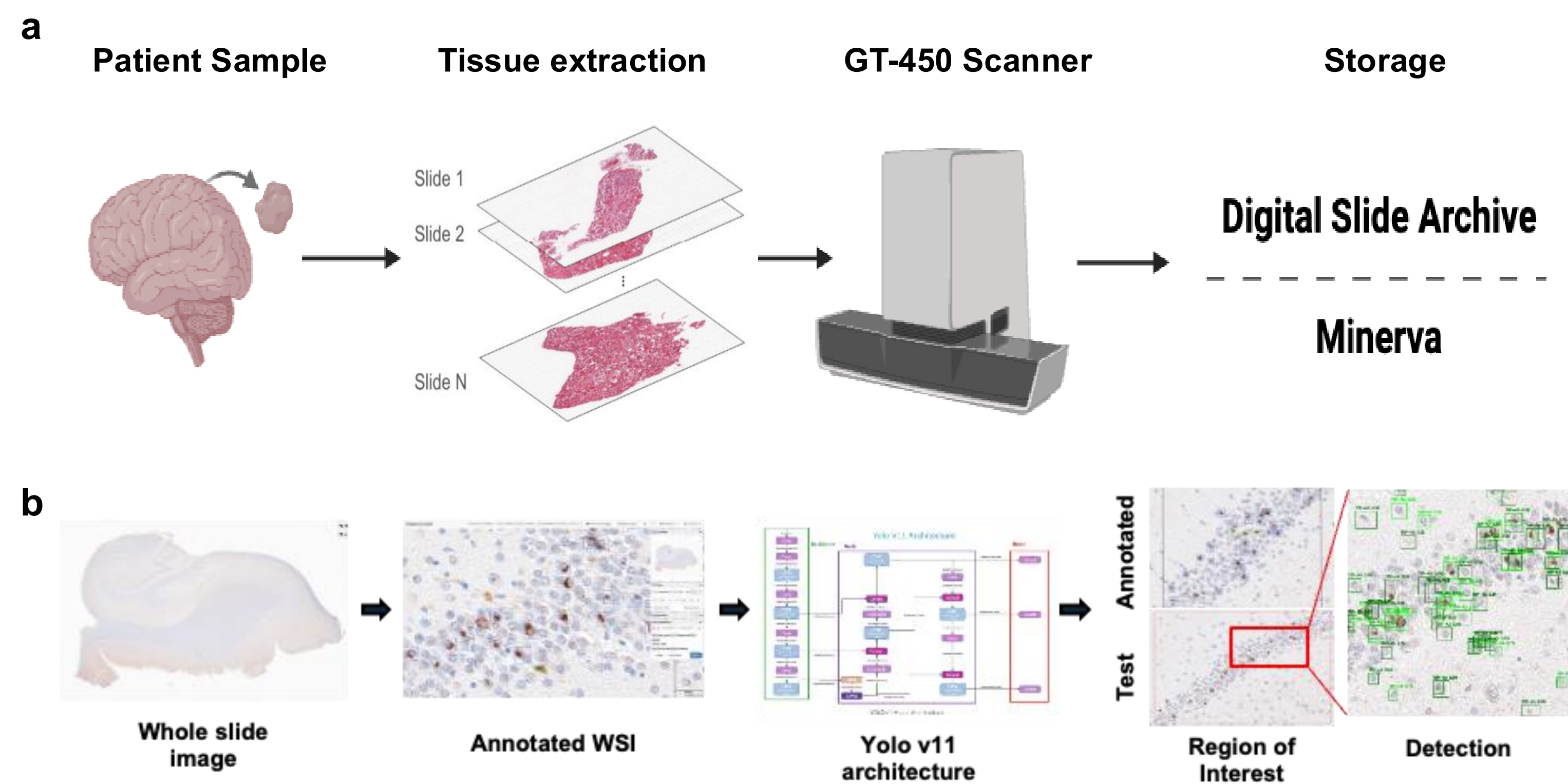


Figure 1. Experimental overview of the automated neuropathological detection pipeline. (a) Patient brain tissue was sectioned, immunostained, digitized using a GT-450 whole slide scanner, and archived within the Digital Slide Archive on the Minerva high-performance computing cluster. (b) Whole-slide images were annotated by expert neuropathologists to train a YOLO-based object detection model, which generates automated bounding box predictions for protein aggregate quantification during inference.

Training Dataset

Characteristic	Overall (n=89)	NFT (n=73)	TDP-43 (n=6)	Amyloid Plaque (n=7)	Lewy Body (n=3)
Age at death, mean $\pm$ SD	85.1 $\pm$ 7.9	85.2 $\pm$ 8.0	85.3 $\pm$ 8.8	83.7 $\pm$ 7.6	84.3 $\pm$ 1.2
Age range	62–98	62–93	74–98	71–96	83–85
Male, n (%)	41 (46)	36 (84)	3 (50)	—	2 (67)
White, n (%)	49 (55)	42 (98)	5 (83)	—	3 (100)
Primary diagnosis	Mixed ND cohort	AD/PART enriched	Mostly AD	—	PD/LBD enriched
Dementia, n (%)	7 (8)	—	4 (67)	—	3 (100)
WSIs	127	73	9	37	8
Annotations	11,710	3,305	448	6,833	1,124

Table 1. Summary of cohort demographics and neuropathological whole-slide imaging dataset characteristics. The dataset included whole-slide images (WSIs) from multiple neurodegenerative pathologies stained with AT8, pTDP-43, AB4G8, and α -synuclein.

Annotation, Model Training & Evaluation

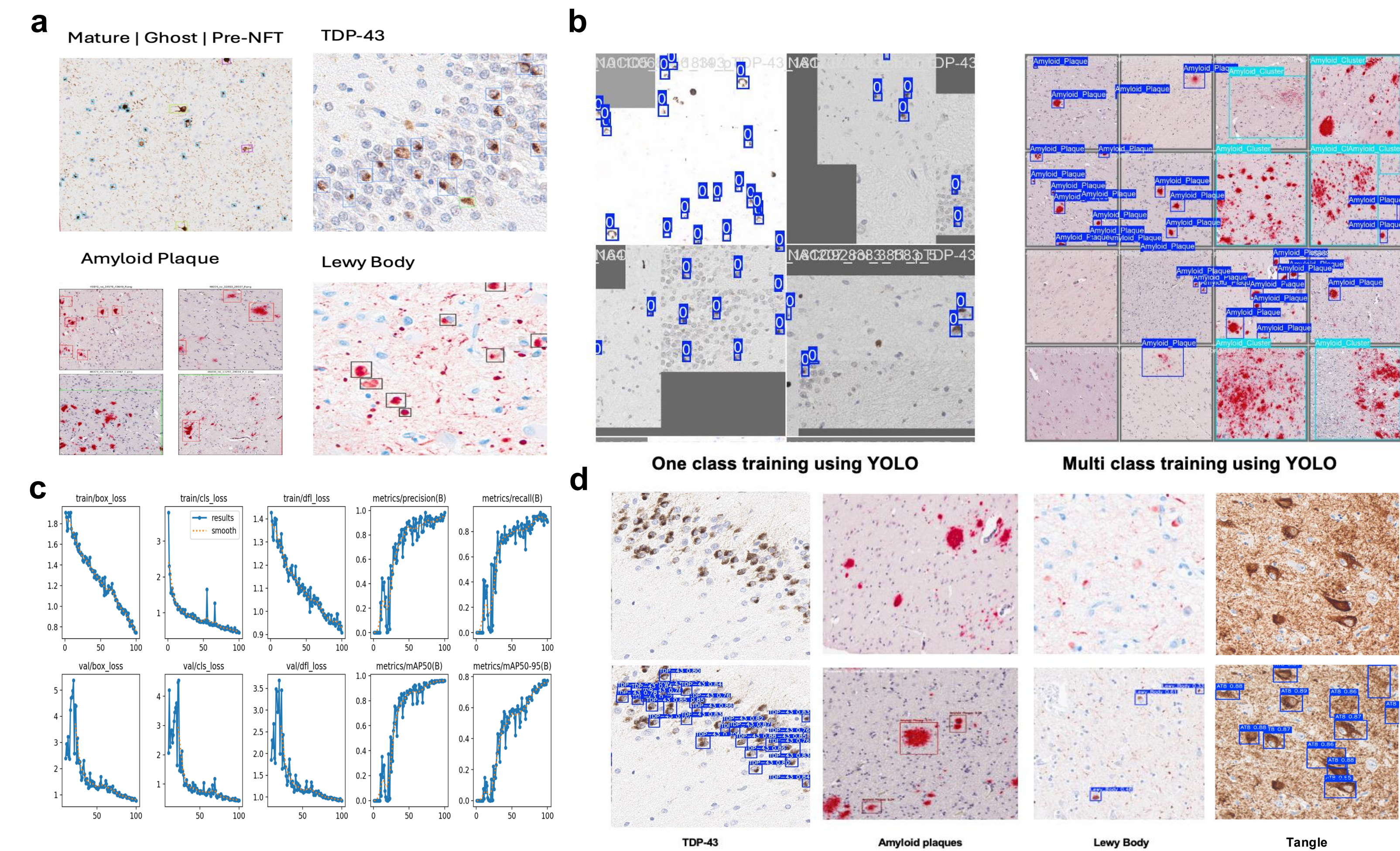


Figure 2. Automated detection model training and performance across neurodegenerative pathology types (a) Representative expert-annotated training regions for NFTs (mature, ghost, and pre-NFT tau pathology), TDP-43 inclusions, amyloid plaques, and Lewy bodies across immunostained whole-slide images. (b) Examples of single-class and multi-class YOLO training outputs demonstrating automated bounding box detection across multiple neuropathological protein aggregate types. (c) YOLOv11 training and validation metrics across epochs, showing progressive improvement in loss, precision, recall, and mean average precision (mAP), consistent with stable model convergence. (d) Representative inference results showing model-predicted detections and confidence scores for TDP-43 inclusions, amyloid plaques, Lewy bodies, and tau tangles on unseen image regions.

Attention Maps

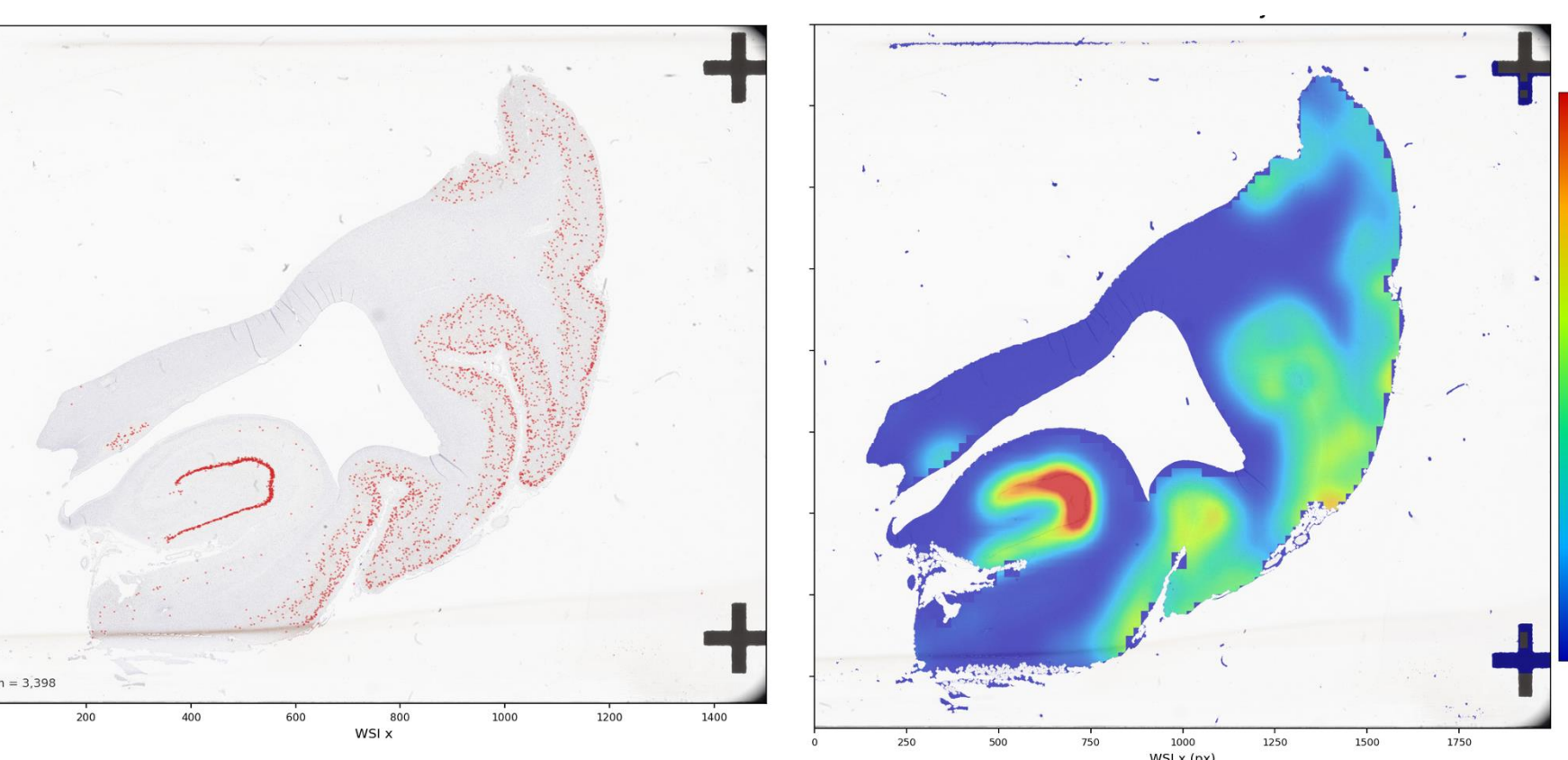


Figure 3. Whole-slide spatial density maps of pTDP-43 pathology generated from YOLOv11 detections. Individual pTDP-43 inclusion coordinates were aggregated and Gaussian-smoothed to visualize regional pathological burden across tissue sections. Heatmaps revealed focal clustering of pTDP-43 inclusions within selectively vulnerable neuroanatomical regions, consistent with known patterns of pTDP-43 proteinopathy. This approach enables quantitative assessment and visualization of pTDP-43 burden across entire whole-slide images.

Results

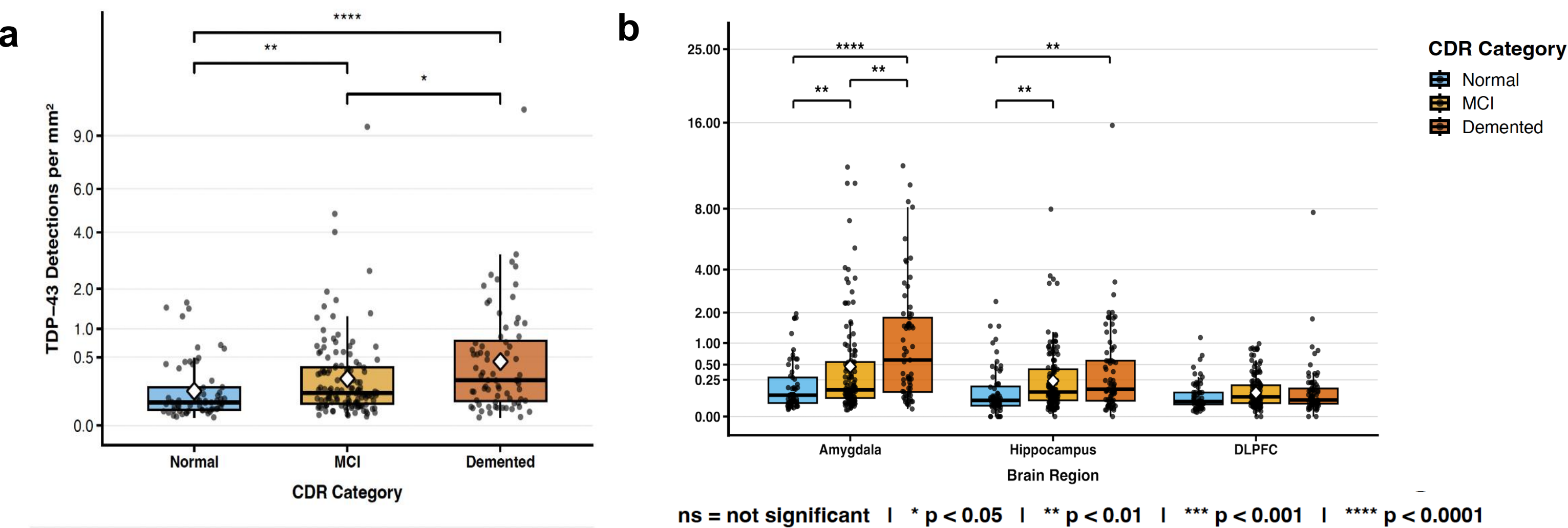


Figure 4. Automated protein aggregate burden stratified by cognitive status and brain region. Violin plots depicting total per-patient detections for TDP-43 inclusions. TDP-43 burden showed significant progressive increase from cognitively normal to MCI to demented cases.

Results

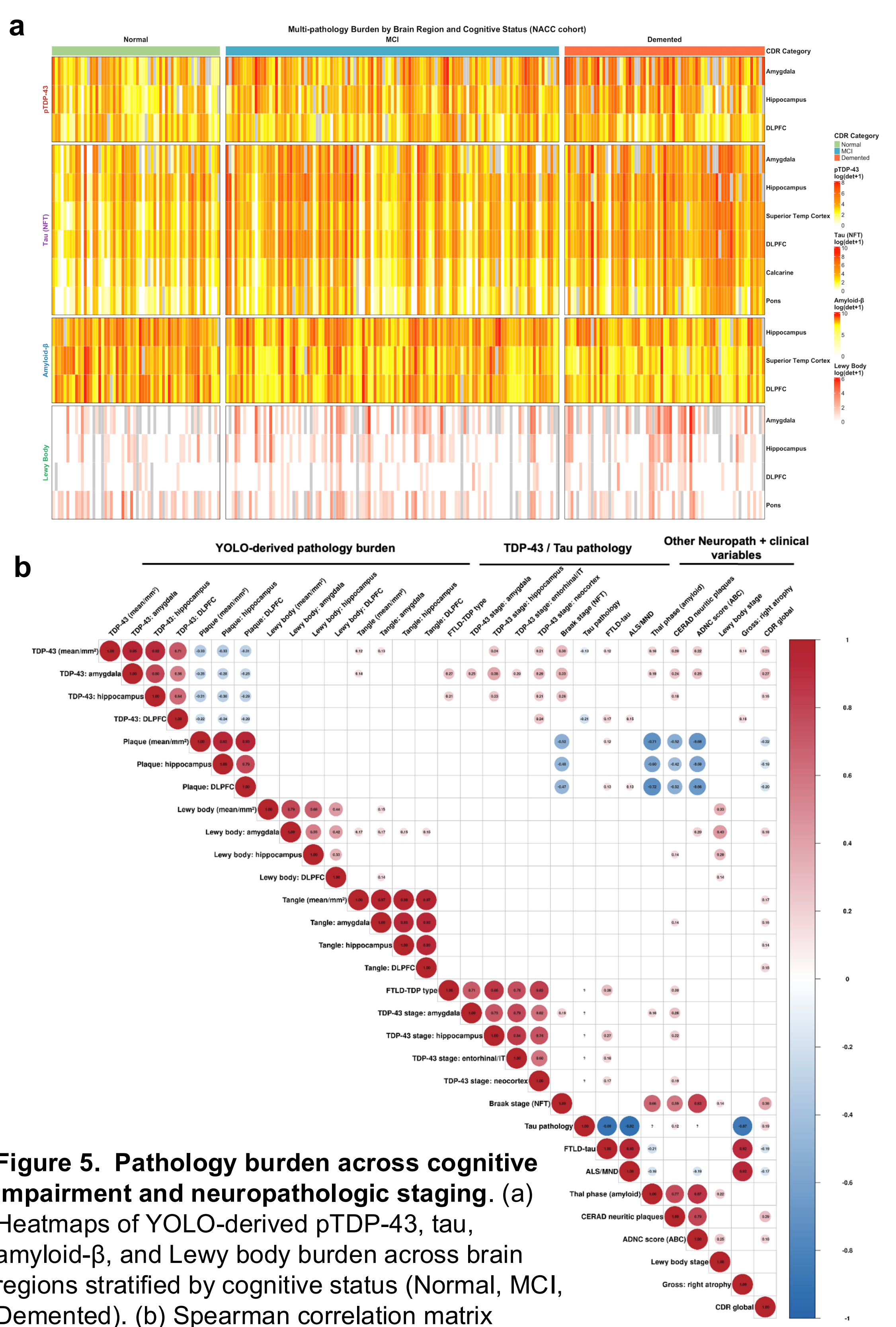


Figure 5. Pathology burden across cognitive impairment and neuropathologic staging. (a) Heatmaps of YOLO-derived pTDP-43, tau, amyloid- β , and Lewy body burden across brain regions stratified by cognitive status (Normal, MCI, Demented). (b) Spearman correlation matrix demonstrating concordance between automated pathology measurements and established neuropathologic and clinical variables.

Conclusion

- YOLOv11-based deep learning models enabled accurate and automated detection of multiple neuropathological protein aggregates across whole-slide histopathology images.
- Automated pathology burden measurements mirrored established neuropathologic staging systems and correlated with cognitive impairment.

Acknowledgement

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