

A Specific Oligodendrocyte Population Coordinates Amyloid, Tau, and Cerebrovascular Pathology in Alzheimer's Disease



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Introduction

Methods

- Amyloid burden (A β) and tau co-pathology synergistically accelerates neurodegeneration beyond the contribution of either lesion alone in Alzheimer's disease (AD).
- A β burden drives oligodendrocyte (OLs) dysfunction, myelin breakdown, and impaired microglial A β clearance.
- Disease-associated OLs states show altered myelination, lipid metabolism, and inflammatory gene programs in AD
- The cellular substrate bridging A β and tau pathology in the human brain remains unidentified with limited investigation on pathology-related mechanisms in OLs
- Moreover, no framework has linked OLs subtype dysfunction to multi-domain AD neuropathology simultaneously

To determine whether the disrupted OL biological function observed in AD are linked to more specific features of the neuropathology observed in the disease

Discovery cohort (Omics)

ADRC (n=26)
Entorhinal cortex



	A-/Braak 0-2 (n=9)	A-/Braak 3-4 (n=5)	A+/Braak 1-4 (n=12)
Age, mean (SD)	71 (18.3)	90 (6.12)	81 (10.5)
Female, n (%)	3 (33.3%)	3 (60%)	6 (50%)
A β -plaques*/CERAD score**, mean (SD)	-	-	2.83 (1.11)*
NFTs*/Braak stage**, mean (SD)	0.89 (0.78)*	3.6 (0.54)*	2.75* (1.75)*

Validation cohort (Omics)

ROSMAP (n=62)
Entorhinal cortex & Hippocampus



	A-/Braak 0-2 (n=29)	A-/Braak 3-4 (n=4)	A+/Braak 4-5 (n=29)
Age, mean (SD)	84.1 (5.7)	84.2 (5.4)	85.4 (3.9)
Female, n (%)	14 (48.3%)	1 (25%)	13 (44.8%)
A β -plaques*/CERAD score**, mean (SD)	4.0 (0.0)**	4.0 (0.0)**	1.6 (0.5)**
NFTs*/Braak stage**, mean (SD)	1.4 (0.60)**	3.3 (0.54)**	4.3 (0.90)**

late-severe AD cohort (IHCs)

McGill (n=3)
Entorhinal cortex



	A+/Braak 6 (n=3)
Age, mean (SD)	73.7 (13.0)
Female, n (%)	1 (33.3%)
A β + (4G8+)	Yes (ENT+JFP+; ACTH)
NFTs, mean (SD)	31.3 (22.3)

Methods & Statistical Analysis: 10x Chromium snRNA-seq data processed through ambient RNA removal, doublet filtering, normalization, and Harmony batch integration. Cell types annotated via Azimuth. Clustering subtypes resolved by iNMF (rigger), DEGs calculated via edgeR (adjusted by age and sex, $p \leq 0.05$). Cross-compartmental associations tested using residualized linear models, Stouffer's Z, and LOO-AUC (R & Python; 10,000 permutations).

Neuropathological metrics: All specimens were screened for A β plaques (4G8+) and NFTs (AT8+) across all Braak-stages regions *Entorhinal cortex, Inferior Parietal cortex, Anterior cingulate cortex* via immunohistochemistry. Subjects from McGill cohort presented co-pathologies including Cerebral amyloid angiopathy; Vasculopathy; Terminal acute anoxic- ischemic encephalopathy, Arteriosclerosis, *one individual with TDP-43 proteinopathy.*

Results

Entorhinal cortex snRNA-seq resolves six transcriptionally distinct oligodendrocyte subtypes.

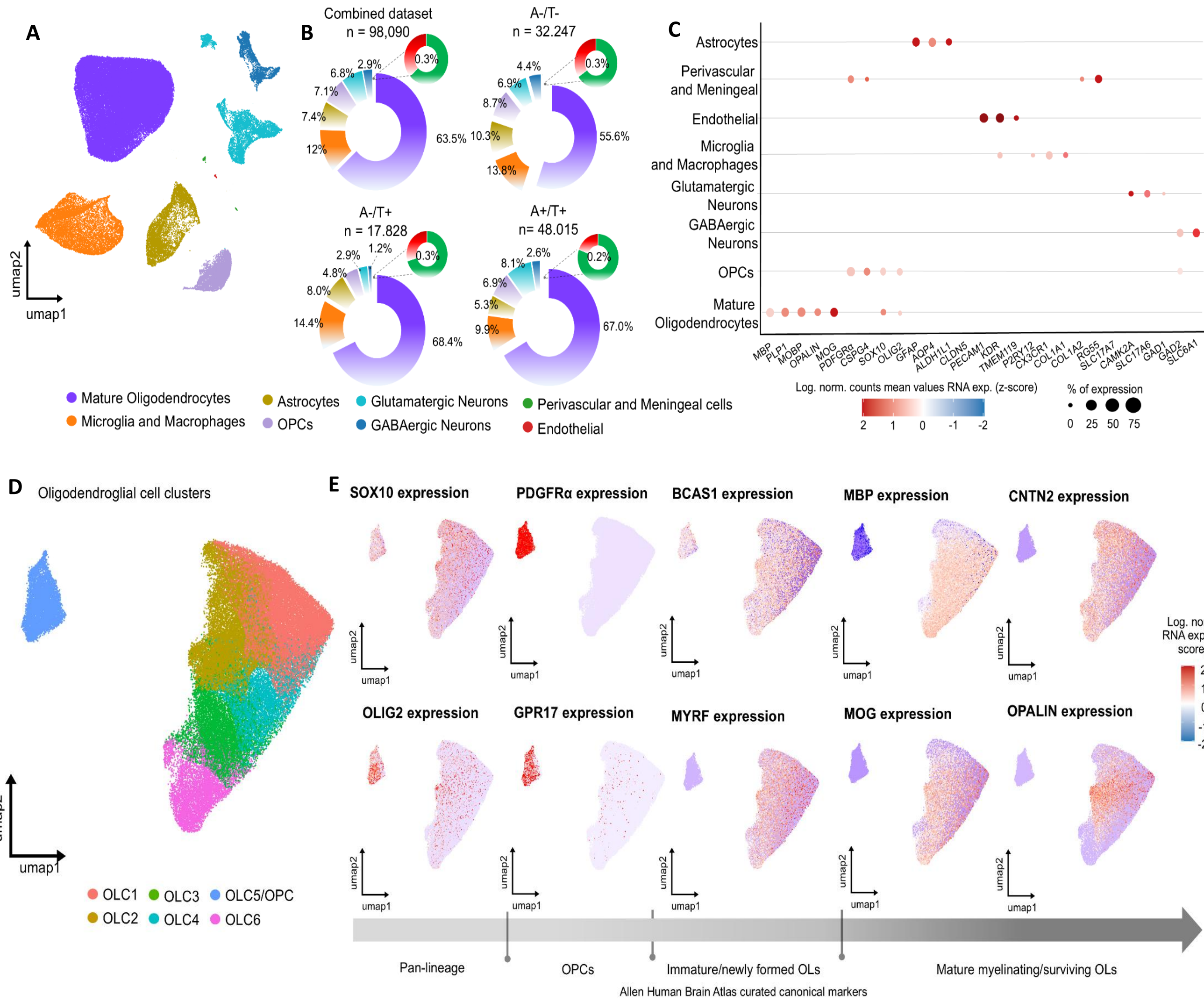


Figure 1. Single-nucleus RNAseq & transcriptional landscape of human entorhinal cortex. snRNA-seq of 98,090 nuclei from 26 ADRC donors and identified major cell types (A-C) following resolved OL lineage subtypes (OLCs = 69,251 nuclei) along maturation continuum from precursors through immature to myelinating states (D-E).

OLC subtype abundance coordinates with multi-domain pathology gene signature in A β + donors.

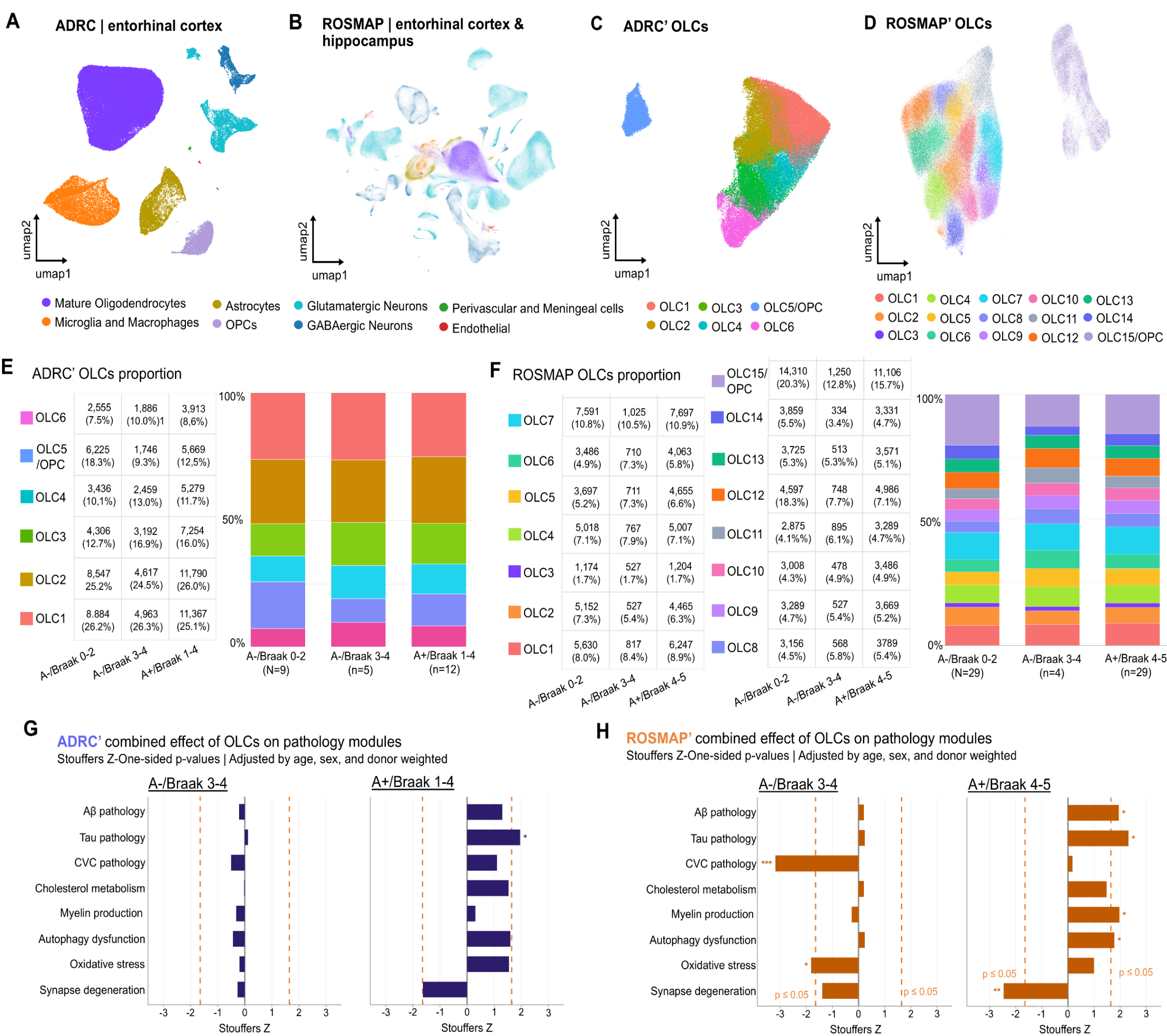


Figure 2. OLC subtype composition and cross-compartmental pathology coordination across cohorts. iNMF (rLIGER) integration of ADRC and ROSMAP (568,170 nuclei) identifies consistent OLC subtype (ROSMAP: 150,683) proportional shifts across neuropathological groups (A-F). Stouffer Z analyses demonstrating pathology module across cohorts (G-H).

Oligodendrocytes bridges a plurality of neuropathology factors in AD.

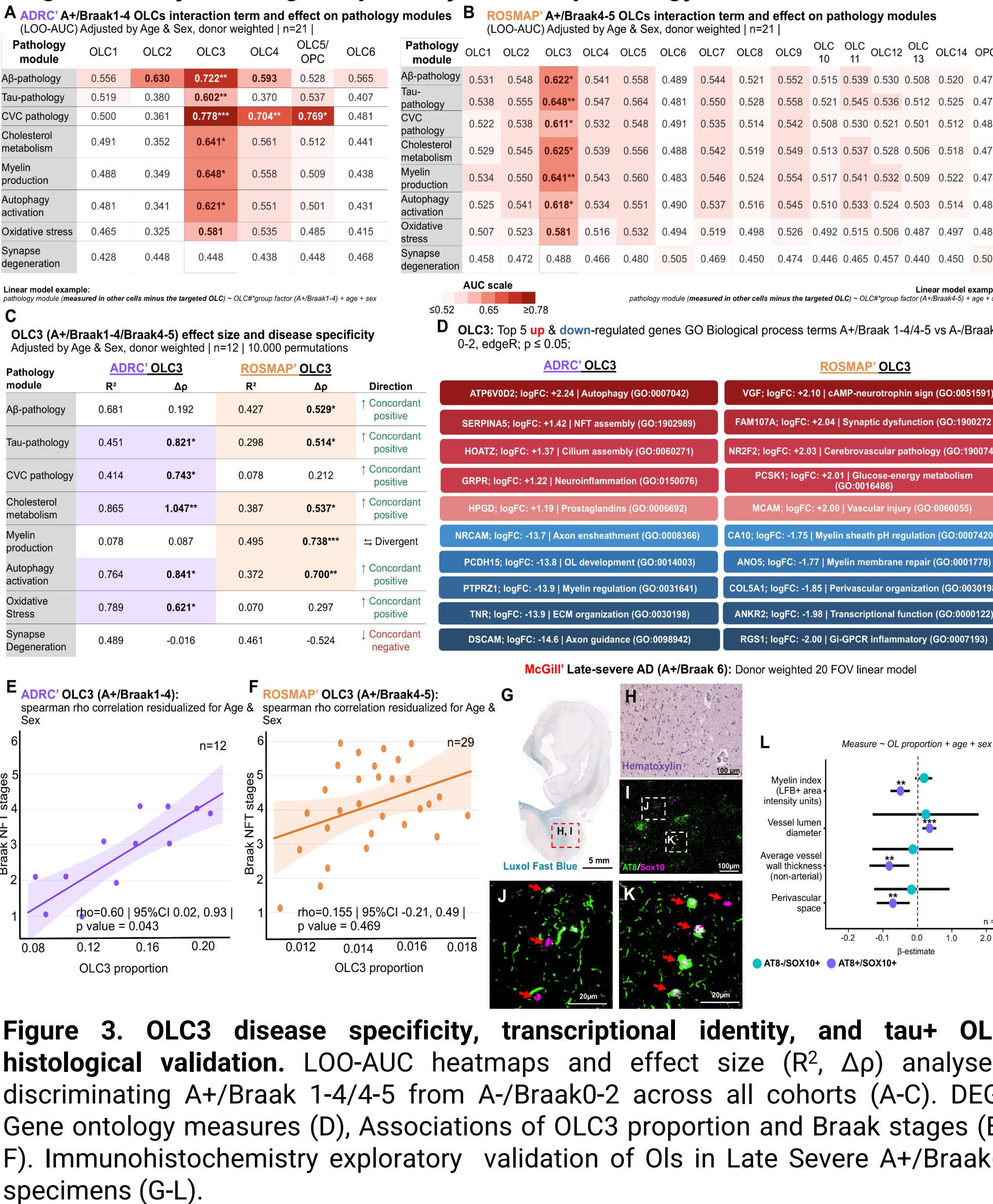


Figure 3. OLC3 disease specificity, transcriptional identity, and tau+ OLs histological validation. LOO-AUC heatmaps and effect size (R^2 , Δp) analyses discriminating A+/Braak 1-4/4-5 from A-/Braak0-2 across all cohorts (A-C). DEG, Gene ontology measures (D), Associations of OLC3 proportion and Braak stages (E, F). Immunohistochemistry exploratory validation of OLs in Late Severe A+/Braak6 specimens (G-L).

Discussion & Conclusion

Using cross-compartmental snRNA-seq analysis across two independent cohorts, we identify OLC3, a transcriptionally distinct, inflammatory OL subtype, as the cellular bridge linking A β , tau, and cerebrovascular pathology exclusively in AD. *Histological exploratory validation* in specimens with late-severe AD (High NFT accumulation) suggests that in late stages of the disease OLs accumulate tau and are linked to demyelination and cerebrovascular changes in AD. Together, these findings redefine OLs as active disease integrators, opening avenues for OLC3-derived biomarkers, myelin-targeted therapeutics, and a mechanistic framework orchestrating AD's converging pathological hallmarks.

Contact & Funding



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