

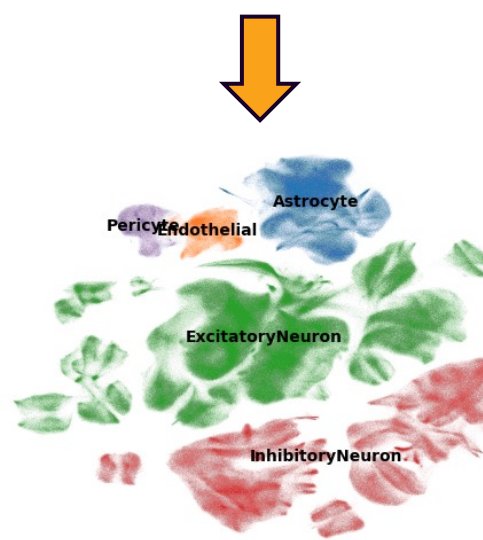
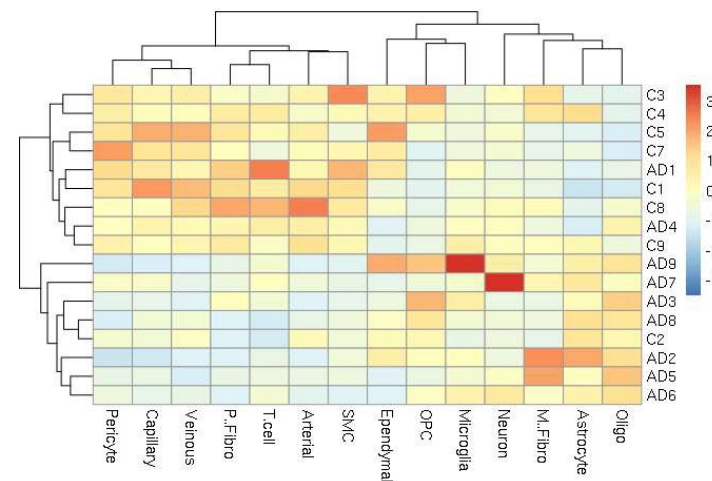
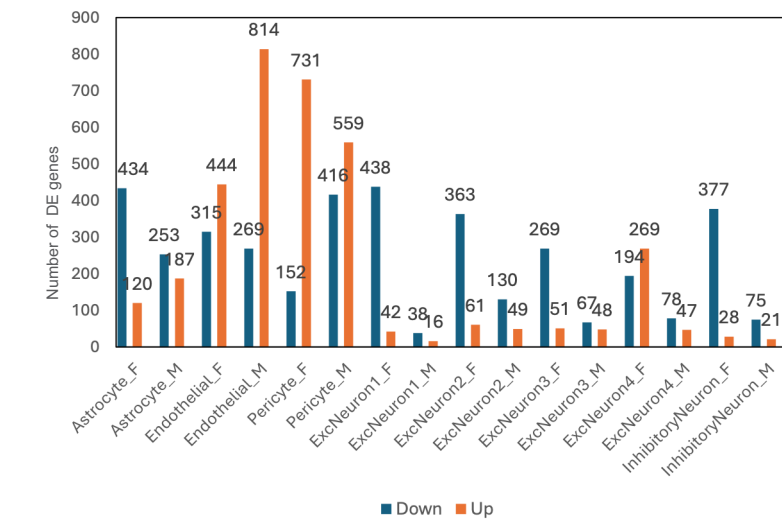
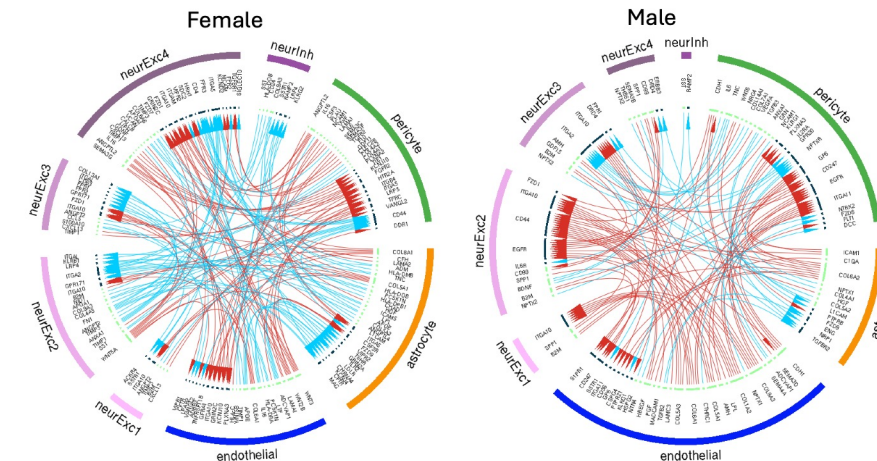
Development Of Human Neurovascular Unit Atlas For Alzheimer's Patients

P2-03

Douglas A Nelson¹, Xiaojia Tang², Mikel Hernaez³, Karunya K Kandimalla^{1*}, Krishna R Kalari²

¹Department of Pharmaceutics and Brain Barriers Research Center, University of 6 Minnesota, College of Pharmacy, Minneapolis, MN, USA
²Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA
³Centro de Investigación Médica Aplicada (CIMA), Universidad de Navarra, Spain.

The NVUAtlas reveals extensive disruption of vascular homeostasis, sex-specific molecular responses, and altered intercellular signaling across the neurovascular unit in Alzheimer’s patients. This integrated atlas leverages existing datasets to support systematic investigation of neurovascular unit dysfunction in the pathogenesis of Alzheimer’s disease.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																																																																		
The neurovascular unit (NVU) includes endothelial cells, pericytes, astrocytes, and neurons. The endothelial cells lining the capillary lumen form the blood-brain barrier (BBB), which drives neurovascular coupling and regulates molecular exchange between the circulation and brain. The uncoupling of NVU is being recognized as an early contributor to Alzheimer’s disease (AD), with BBB dysfunction often preceding neurodegeneration^{1,2}. The human NVU Atlas leverages existing datasets to advance systematic investigation of the NVU dysfunction and intercellular interactions in AD.	Prefrontal cortex 11 snRNA-seq cohorts 748 donors, 4.25M nuclei  scVI³ integration Consensus annotation (KNN, SVM, scANVI, scGPT)  DE (NEBULA⁴) Pathway enrichment Ligand-receptor inference	Vascular cells show the most extensive changes  Sex-specific changes in NVU intercellular signaling  <table><tr><th>Cell</th><th>Sex</th><th>Pathway</th><th>P.value</th><th>Dir</th><th>Genes</th></tr><tr><td>End</td><td>F</td><td>Mineral absorption</td><td>2.1E-03</td><td>up</td><td>MT2A; MT1A; MT1M; MT1X; ATP1B3; SLC39A4</td></tr><tr><td>End</td><td>F</td><td>ECM-receptor</td><td>1.4E-02</td><td>up</td><td>LAMA1; ITGA10; COL6A1; FREM2; THBS4; THBS3</td></tr><tr><td>End</td><td>M</td><td>Focal adhesion</td><td>1.8E-02</td><td>up</td><td>VASP; PDGFRB; LAMC3; MYL12A; VAV1; PGF; MYLK4; THBS3; MYLPP; COL1A2; ITGA11; COL6A1; BCL2; AKT1; COL9A3</td></tr><tr><td>End</td><td>M</td><td>Mineral absorption</td><td>2.9E-03</td><td>up</td><td>MT2A; MT1A; MT1M; MT1F; MT1X; CLCN2; SLC39A4; MT1E</td></tr><tr><td>Per</td><td>F</td><td>ECM-receptor</td><td>3.0E-02</td><td>dn</td><td>COL4A2; COL4A1; CD44</td></tr><tr><td>Per</td><td>M</td><td>Smooth muscle contraction</td><td>1.9E-03</td><td>dn</td><td>ADORA2B; PLA2G4C; ADCY3; MYH11; ADCY2; AVPR1A; MYL9; ACTG2; MYLK</td></tr><tr><td>Ast</td><td>F</td><td>Ferroptosis</td><td>1.9E-03</td><td>dn</td><td>MAP1LC3A; TFRC; FTH1; MAP1LC3B2; SLC39A14</td></tr><tr><td>Ast</td><td>F</td><td>WNT signaling</td><td>3.3E-03</td><td>up</td><td>FOSL1; TLE2; FZD9; NOTUM; LGR6</td></tr><tr><td>Ast</td><td>M</td><td>NF-kappa B</td><td>1.6E-02</td><td>up</td><td>NFKBIA; ICAM1; GADD45G; TNFSF13B</td></tr><tr><td>Ast</td><td>M</td><td>WNT signaling</td><td>2.0E-02</td><td>up</td><td>TLE2; FZD9; WNT7A; NOTUM; LGR6</td></tr></table>	Cell	Sex	Pathway	P.value	Dir	Genes	End	F	Mineral absorption	2.1E-03	up	MT2A; MT1A; MT1M; MT1X; ATP1B3; SLC39A4	End	F	ECM-receptor	1.4E-02	up	LAMA1; ITGA10; COL6A1; FREM2; THBS4; THBS3	End	M	Focal adhesion	1.8E-02	up	VASP; PDGFRB; LAMC3; MYL12A; VAV1; PGF; MYLK4; THBS3; MYLPP; COL1A2; ITGA11; COL6A1; BCL2; AKT1; COL9A3	End	M	Mineral absorption	2.9E-03	up	MT2A; MT1A; MT1M; MT1F; MT1X; CLCN2; SLC39A4; MT1E	Per	F	ECM-receptor	3.0E-02	dn	COL4A2; COL4A1; CD44	Per	M	Smooth muscle contraction	1.9E-03	dn	ADORA2B; PLA2G4C; ADCY3; MYH11; ADCY2; AVPR1A; MYL9; ACTG2; MYLK	Ast	F	Ferroptosis	1.9E-03	dn	MAP1LC3A; TFRC; FTH1; MAP1LC3B2; SLC39A14	Ast	F	WNT signaling	3.3E-03	up	FOSL1; TLE2; FZD9; NOTUM; LGR6	Ast	M	NF-kappa B	1.6E-02	up	NFKBIA; ICAM1; GADD45G; TNFSF13B	Ast	M	WNT signaling	2.0E-02	up	TLE2; FZD9; WNT7A; NOTUM; LGR6	➤Extensive vascular changes support central role for NVU dysfunction in AD. ➤Vascular remodeling involves basement membrane changes. ➤ Altered calcium and contractile signaling suggest impaired neurovascular coupling. ➤Suppression of canonical WNT signaling in astrocytes. ➤Semaphorin–plexin emerges as a potential mediator of vascular remodeling.	1. Soto-Rojas, L. O. <i>et al.</i> The Neurovascular Unit Dysfunction in Alzheimer's Disease. <i>Int. J. Mol. Sci.</i> 22, 2022 (2021). 2. van de Haar, H. J. <i>et al.</i> Neurovascular unit impairment in early Alzheimer's disease measured with magnetic resonance imaging. <i>Neurobiol. Aging</i> 45, 190–196 (2016). 3. Lopez, R., Regier, J., Cole, M. B., Jordan, M. I. & Yosef, N. Deep generative modeling for single-cell transcriptomics. <i>Nat. Methods</i> 15, 1053–1058 (2018). 4. He, L. <i>et al.</i> NEBULA is a fast negative binomial mixed model for differential or co-expression analysis of large-scale multi-subject single-cell data. <i>Commun. Biol.</i> 4, 1–17 (2021). CONTACT Karunya K. Kandimalla: kkandima@umn.edu Krishna R. Kalari Kalari.Krishna@mayo.edu ALZHEIMER'S ASSOCIATION AAIC>26
Cell	Sex	Pathway	P.value	Dir	Genes																																																																	
End	F	Mineral absorption	2.1E-03	up	MT2A; MT1A; MT1M; MT1X; ATP1B3; SLC39A4																																																																	
End	F	ECM-receptor	1.4E-02	up	LAMA1; ITGA10; COL6A1; FREM2; THBS4; THBS3																																																																	
End	M	Focal adhesion	1.8E-02	up	VASP; PDGFRB; LAMC3; MYL12A; VAV1; PGF; MYLK4; THBS3; MYLPP; COL1A2; ITGA11; COL6A1; BCL2; AKT1; COL9A3																																																																	
End	M	Mineral absorption	2.9E-03	up	MT2A; MT1A; MT1M; MT1F; MT1X; CLCN2; SLC39A4; MT1E																																																																	
Per	F	ECM-receptor	3.0E-02	dn	COL4A2; COL4A1; CD44																																																																	
Per	M	Smooth muscle contraction	1.9E-03	dn	ADORA2B; PLA2G4C; ADCY3; MYH11; ADCY2; AVPR1A; MYL9; ACTG2; MYLK																																																																	
Ast	F	Ferroptosis	1.9E-03	dn	MAP1LC3A; TFRC; FTH1; MAP1LC3B2; SLC39A14																																																																	
Ast	F	WNT signaling	3.3E-03	up	FOSL1; TLE2; FZD9; NOTUM; LGR6																																																																	
Ast	M	NF-kappa B	1.6E-02	up	NFKBIA; ICAM1; GADD45G; TNFSF13B																																																																	
Ast	M	WNT signaling	2.0E-02	up	TLE2; FZD9; WNT7A; NOTUM; LGR6																																																																	