

Imaging-guided transcriptomic vulnerability distinguishes Alzheimer's, vascular, and Lewy body dementia

Je Ryoung Im, BS^{1,2,†}, Constance A. Zanze, BS^{2,3}, Michel J. Grothe, PhD⁴, David H. Wang^{2,3}, Di Wang, PhD^{2,3}, Mengjin Dong, PhD^{2,3}, Ngoc Huynh Ho, PhD^{2,3},

Nicolas Honnorat, PhD^{2,3}, Derek Archer, PhD⁵, Agustin Ruiz Laza, MD PhD³, Timothy Hohman, PhD⁵, Mohamad Habes, PhD^{2,3}

¹UT Health San Antonio, San Antonio, TX, ²Neuroimage Analytics Laboratory, UT Health San Antonio, ³Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, UT Health San Antonio, ⁴Centre for Research in Neurological Diseases, Madrid, Spain, ⁵Department of Neurology, Vanderbilt University Medical Center, Nashville, TN



Biggs Institute for Alzheimer's & Neurodegenerative Diseases

Introduction

Alzheimer's disease (AD), vascular dementia (VD), and Lewy body dementia (LBD) are major causes of late-life dementia. They exhibit substantial clinical and biological overlap despite distinct neuropathological hallmarks, complicating diagnosis and disease stratification. The transcriptional and molecular mechanisms underlying regionally selective vulnerability across these dementia subtypes remain incompletely understood.

We integrated deep learning-derived, pathology-specific neuroimaging signatures (DeepSPARE) with brain-wide transcriptomic data to identify molecular pathways associated with spatial patterns of disease vulnerability in AD, VD, and LBD.

Materials and Methods

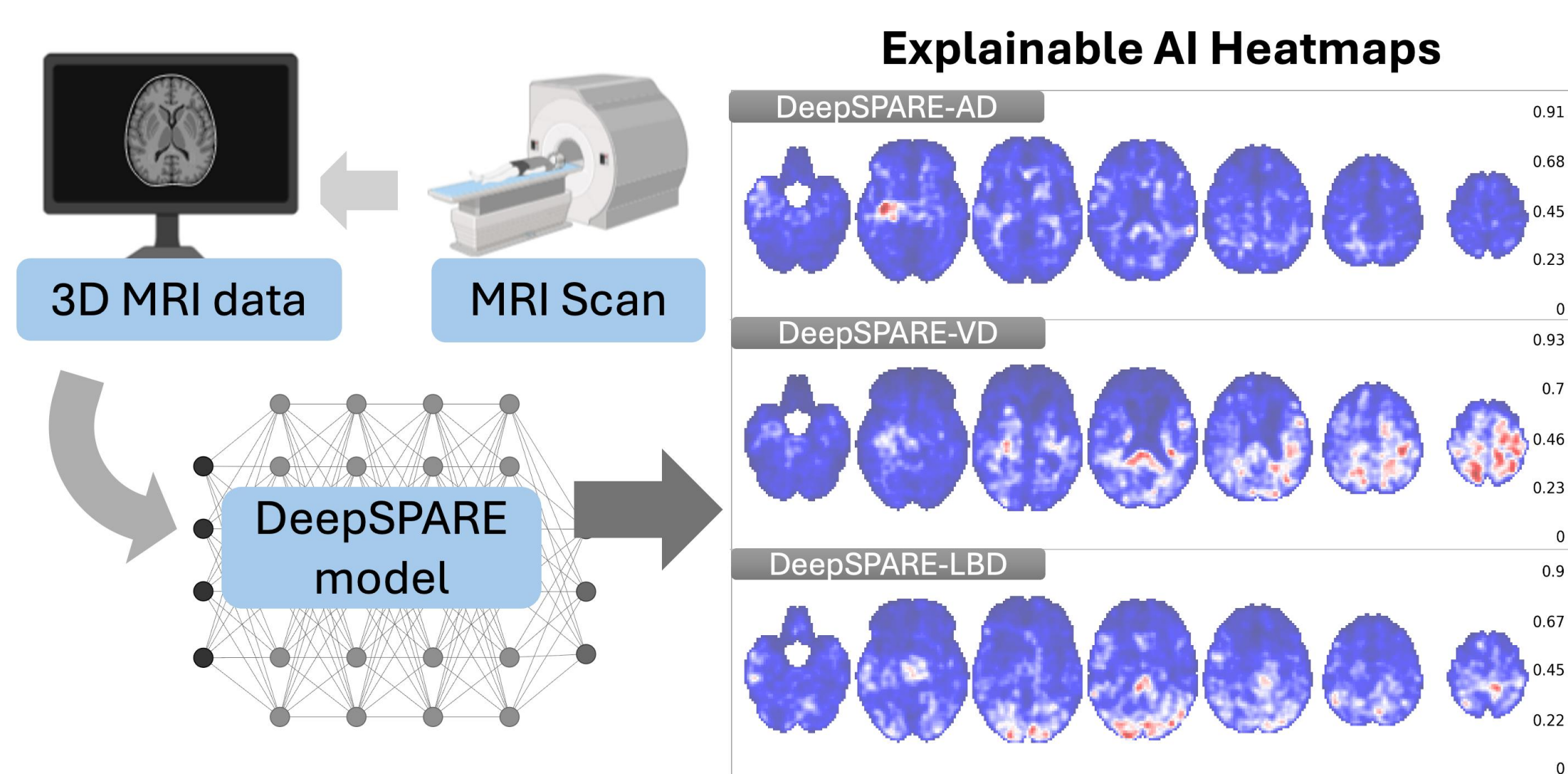


Fig 1. Generation of deep-learning based explainable heatmaps for AD, VD, LBD

- The DeepSPARE model quantifies biomarkers for AD, VD, and LBD using pathology confirmed diagnoses and MRI scans from NACC and ADNI datasets.
- Explainable heatmaps are extracted to visualize regional vulnerability.

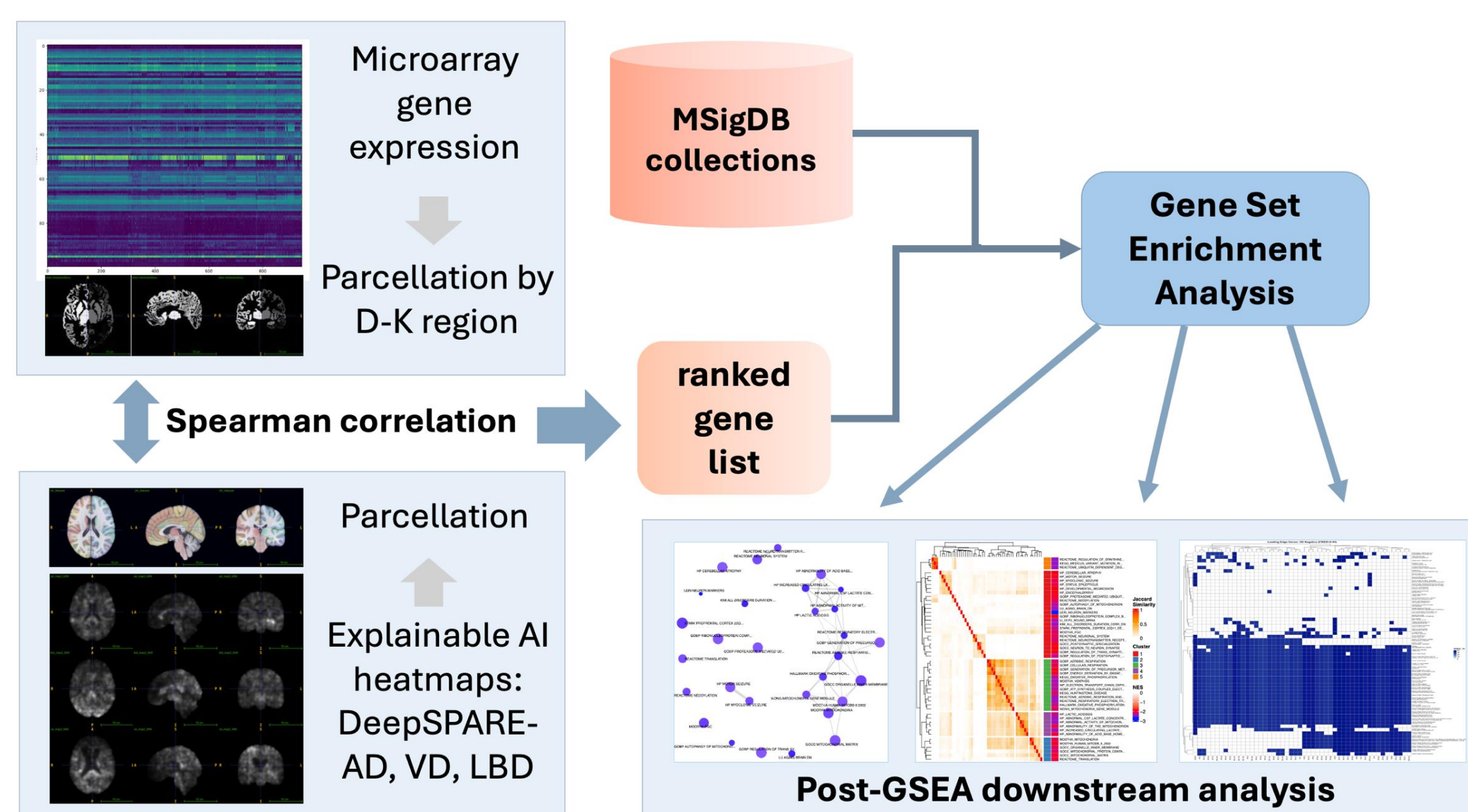


Fig 2. Pipeline for imaging-guided transcriptomic vulnerability mapping.

Results

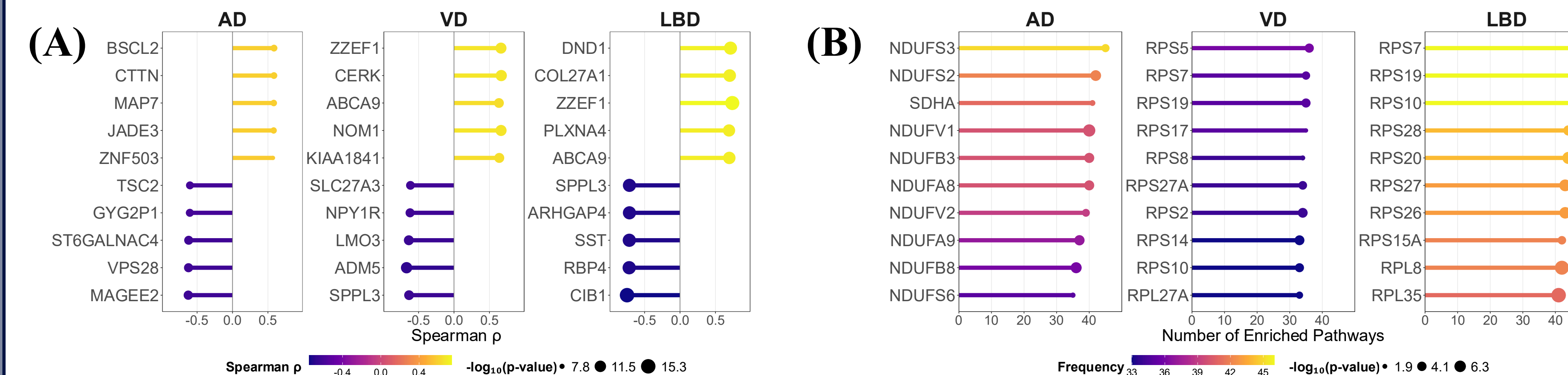


Fig 3. (A) Top 5 positively correlated and negatively correlated genes. (B) Top 10 hub genes.

Hub genes leading multiple enriched pathways reveal that regions vulnerable to AD normally maintain high oxidative phosphorylation activity while VD/LBD vulnerable regions are characterized by high protein synthesis demands.

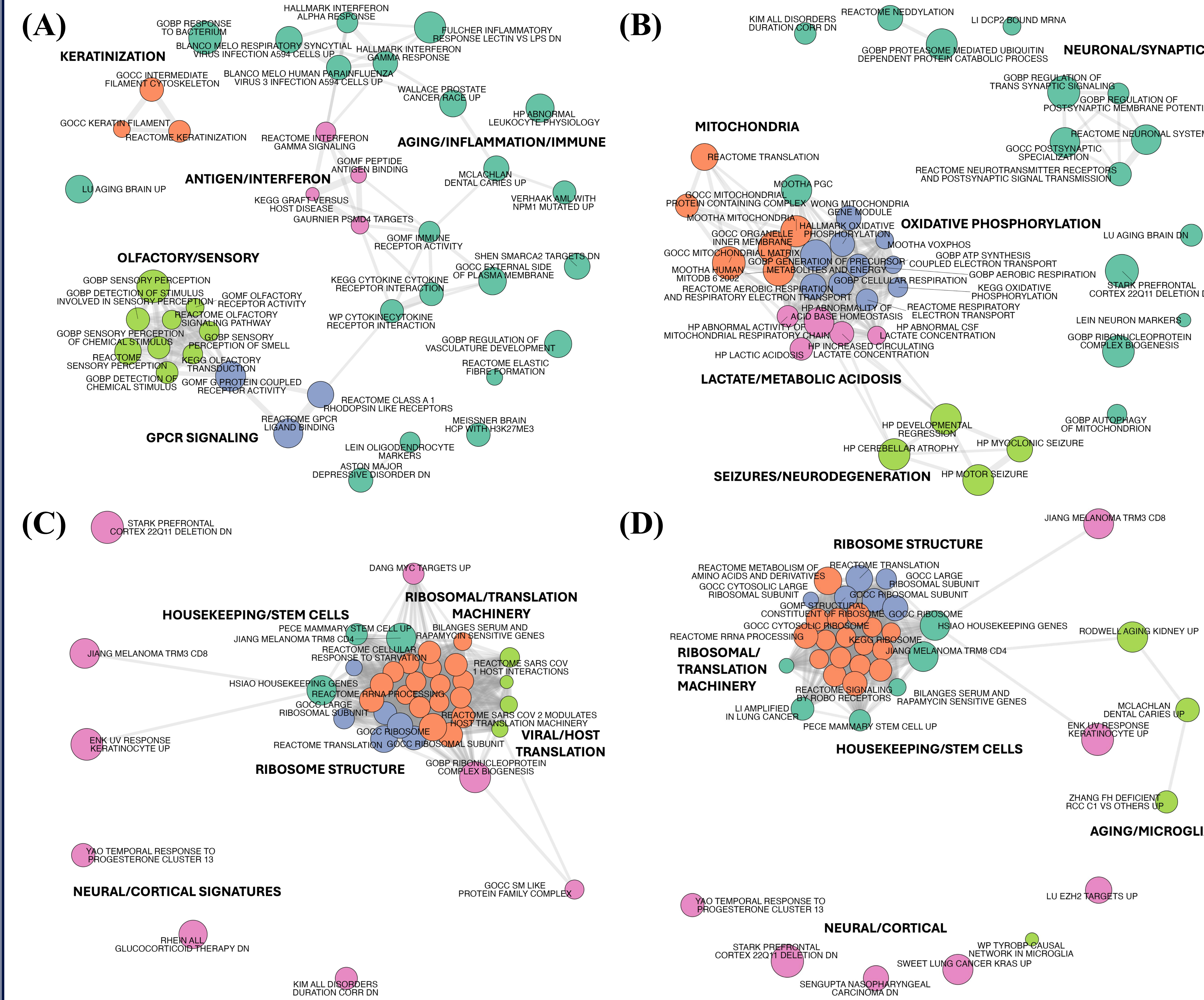


Fig 4. Enrichment maps of top 40 enriched pathways for (A) AD positive, (B) AD negative, (C) VD negative, and (D) LBD negative patterns.

AD regions had distinct positive and negative enrichments related to neuroinflammation, oligodendrocyte function, and mitochondrial function, whereas VD and LBD patterns both exhibited heavily downregulated ribosomal translational machineries.

Results (cont.)

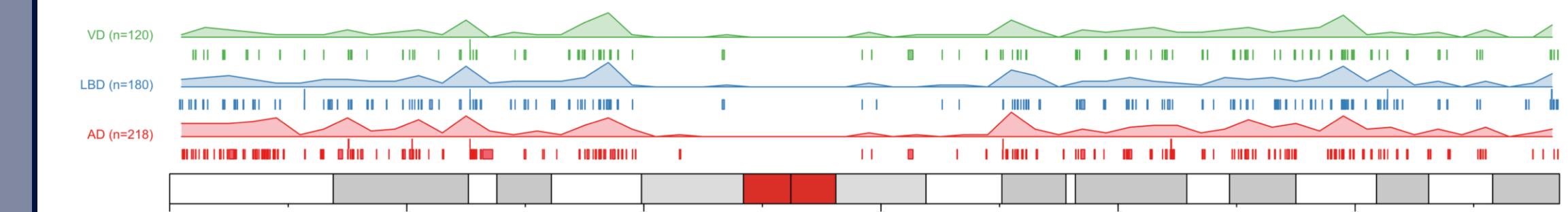


Fig 5. Leading edge genes on chromosome 19

- There was a significant spatial clustering of leading genes across chromosomes, suggesting coordinated regulation or shared regulatory mechanisms.
- Leading edge genes showed significant proximity to known GWAS loci, validating their disease relevance.
- All three pathologies show significant enrichment on chr19, but the specific cytobands differ:
- 19q13.32 (containing APOE, APOC1, APOC2, APOC4, TOMM40) expression increased with AD but decreased with VD/LBD. VD specific 19p13.11 expression contains genes involved in immune response and protein trafficking. 16q13 enrichment in LBD support role of oxidative stress and lipid metabolism.

cytoband	AD	VD	LBD
19p13.11	1.57 (0.563)	3.29 (0.005)**	2.45 (0.026)*
19p13.13	3.06 (0.027)*	3.06 (0.361)	3.72 (0.026)*
19q13.32	1.79 (0.027)*	1.23 (1.)	1.55 (0.707)
19p13.3	2.26 (0.027)*	2.42 (0.342)	2.00 (0.580)

Table 1. Fold enrichment = observed / expected
($p < 0.05^*$, $p < 0.01^{**}$)

Conclusions

Imaging-guided transcriptomic vulnerability mapping reveals convergent and divergent molecular pathways across AD, VD, and LBD. Vulnerable brain regions exhibit distinct baseline transcriptomic signatures with organized chromosomal architecture. Shared features across dementias indicate common biological vulnerability mechanisms, while pathology specific patterns highlight distinct molecular determinants. These findings suggest that deep learning-based neuropathologic imaging signatures can provide noninvasive insight into disease-specific molecular mechanisms, with potential implications for early detection, biological stratification, and individualized therapeutic targeting in dementia.

Acknowledgements

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