

Plasma Proteomics Reveals Continuous, Region-Specific Vulnerability Axes in Alzheimer's Disease

Plasma proteomics supports continuous regional vulnerability gradients rather than discrete Alzheimer's disease subtypes

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BACKGROUND

- Alzheimer's disease (AD) is clinically and biologically heterogeneous.
- Many analytical approaches assume discrete molecular subtypes, but this assumption may be overly simplistic.
- Neuropathology, imaging, and transcriptomic data suggest individuals may vary along continuous axes of regional vulnerability.
- Plasma proteomics offers a scalable, minimally invasive window into AD biology.

OBJECTIVE

- To test whether AD heterogeneity is better captured by continuous, biologically interpretable brain-region vulnerability gradients rather than discrete subtypes.
- To develop a region-informed plasma proteomic framework anchored in brain-region-specific biology.

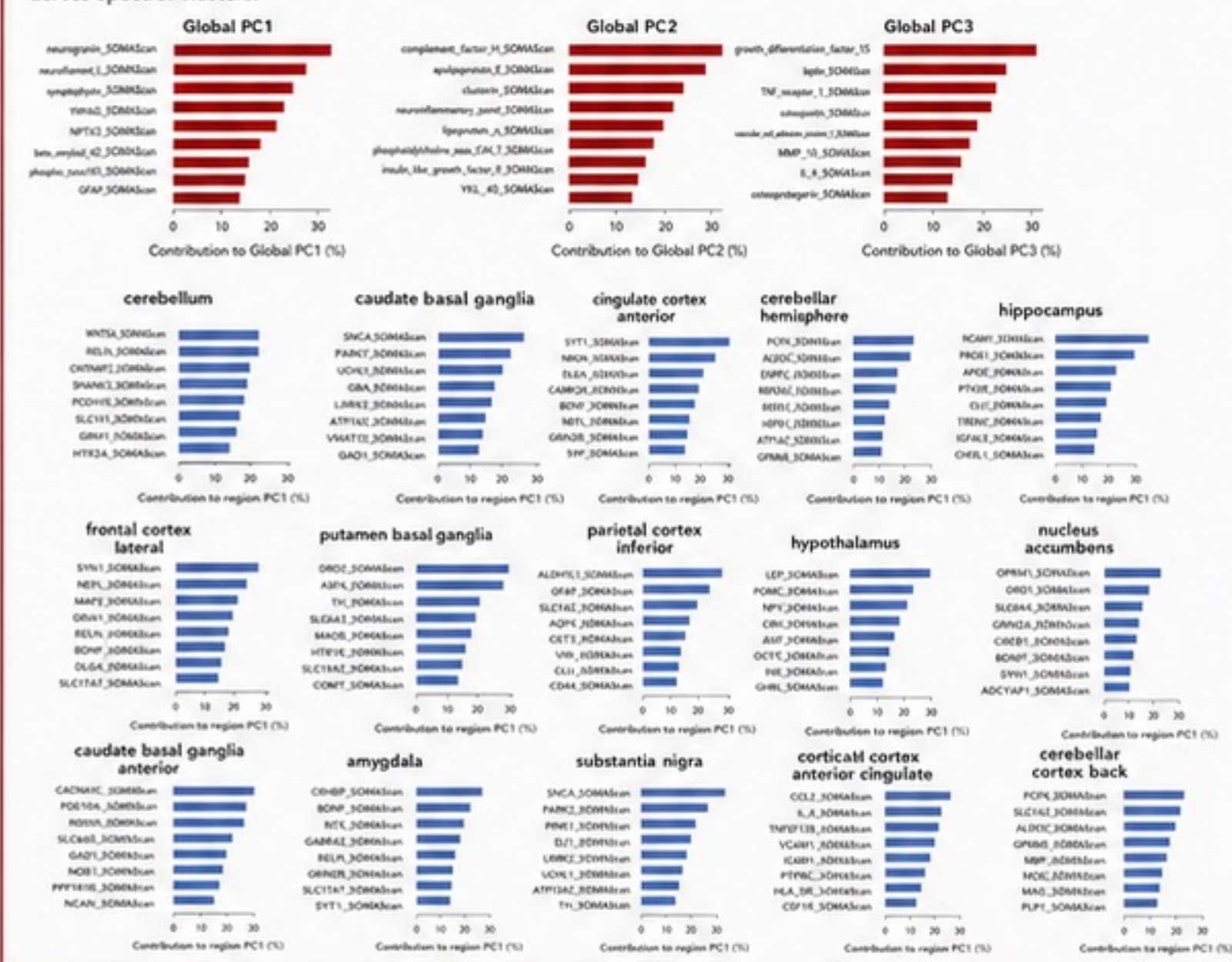
METHODS

- Brain-region-specific gene sets were defined from GTEx v10 across 13 brain regions.
- Region-enriched genes were mapped to GNPC SomaScan plasma proteins.
- Protein abundances were residualized for global plasma PC1, age, and sex.
- Residualized regional protein sets were summarized with regional PCA and then integrated with global PCA.
- Spectral clustering and related unsupervised methods were used post hoc to assess whether AD samples formed discrete groups.
- Heatmaps and embeddings emphasized low-dimensional structure and continuity across individuals.

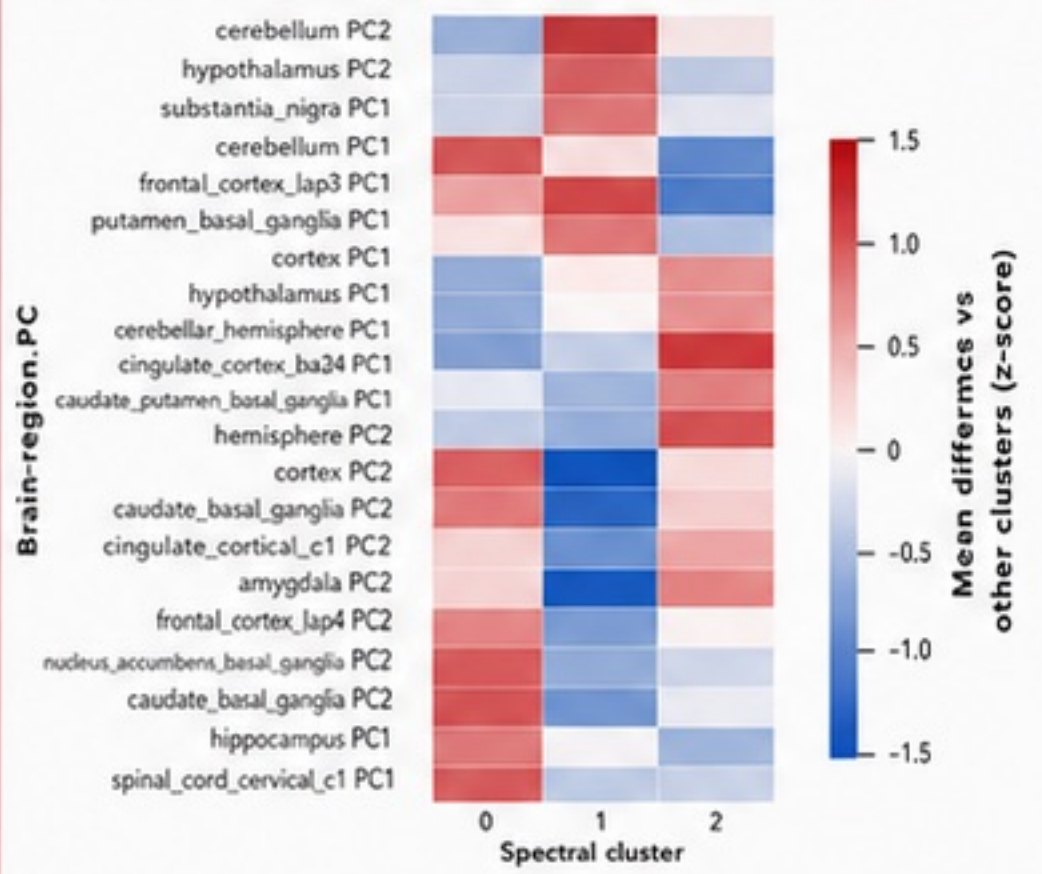
RESULTS

Figure 1. Continuous brain-region vulnerability axes in Alzheimer's disease revealed by proteomic principal components.

Left: Global and region-specific PC loadings and protein drivers. Right: Distribution of regional vulnerability axes across spectral clusters.



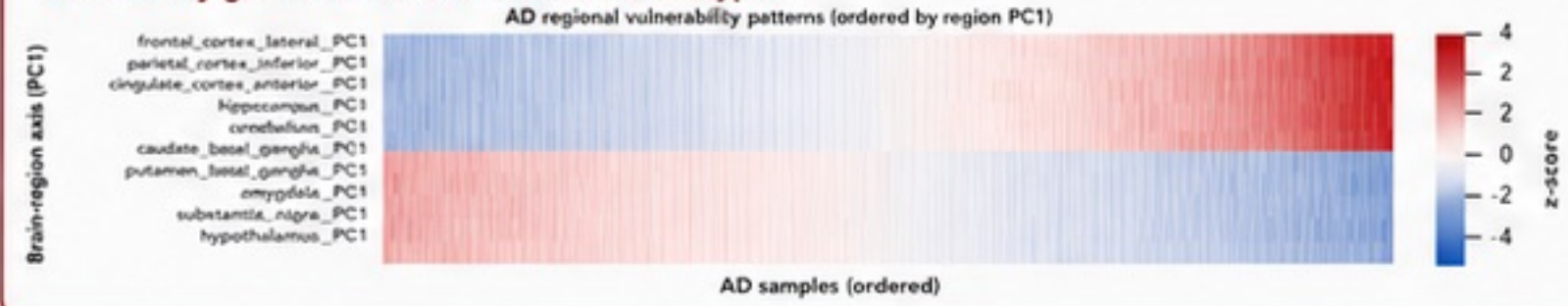
Distribution of regional vulnerability axes across spectral clusters



KEY FINDINGS

- Global PC1 captured a primary cortical-limbic vulnerability gradient.
- Global PC2 emphasized cerebellar and hypothalamic involvement.
- Global PC3 captured additional region-specific structure.
- Spectral clusters differed mainly by position along continuous axes rather than by sharply separated subtypes.

Figure 2. Alzheimer's disease heterogeneity reflects continuous regional vulnerability gradients rather than discrete subtypes.



INTERPRETATION

- Ordered heatmaps showed smooth transitions across individuals rather than discrete subtype blocks.
- Cortical and cerebellar vulnerability patterns were anti-correlated with several limbic and subcortical regions.
- Region-specific protein drivers differed across regions, supporting multiple molecular programs underlying vulnerability.

CONCLUSION / TAKE-HOME MESSAGES

- AD heterogeneity is best represented by continuous regional vulnerability axes.
- Region-informed plasma proteomics yields biologically interpretable patient-level embeddings linked to neuroanatomical systems.
- This framework provides a scalable alternative to subtype-based models and may improve stratification in neurodegenerative disease.

FUTURE DIRECTIONS

- Validate plasma-derived vulnerability axes against imaging, regional atrophy, and CSF biomarkers.
- Test generalizability in BioFINDER and large population-scale cohorts such as UK Biobank.



Scan to view our proteomic vulnerability analysis resources and code repository.