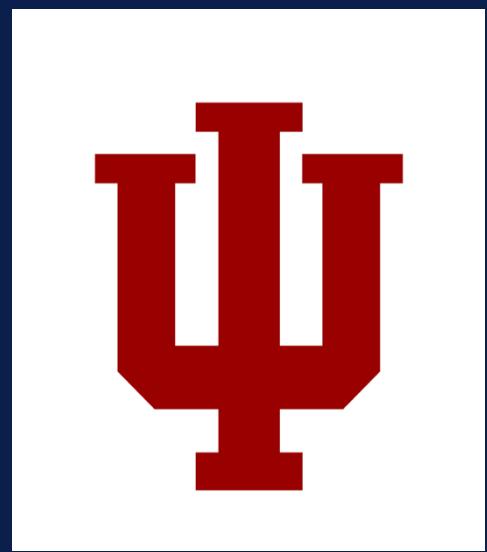




Accelerated brain aging is associated with postsynaptic membrane-related CSF proteins in the Alzheimer's disease continuum

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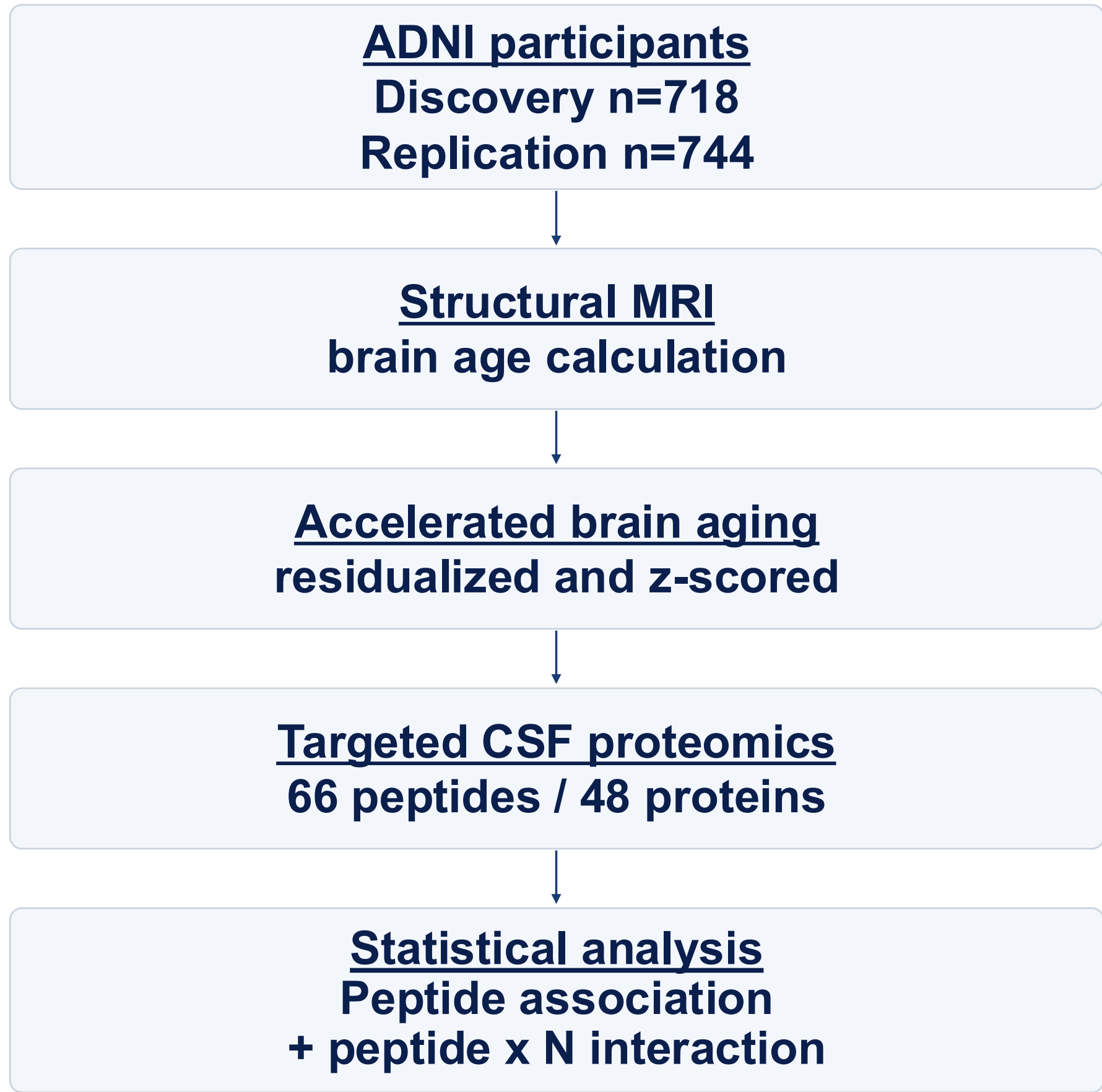
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Background & Objective

- Accelerated brain aging reflects the gap between MRI-calculated brain age and chronological age.
- This biological clock has been linked to Alzheimer's disease (AD) and cognitive decline.
- However, the relationship between CSF proteomic signatures and accelerated brain aging remains understudied in the AD continuum.
- Goal: To identify CSF proteins associated with accelerated brain aging and test whether these associations differ by neurodegeneration biomarker (N) status.

Study design



Key takeaways

- 10 CSF proteins were identified as significantly associated with accelerated brain aging, six of which were replicated.
- Six peptide-by-neurodegeneration (N) biomarker interactions were identified, four of which were replicated.
- CSF proteomics analysis may provide insight into molecular mechanisms underlying brain aging within the AD continuum.

Methods

- Study participants and datasets:** ADNI participants with structural MRI and CSF proteomics data were analyzed after being divided into discovery and replication datasets.
- Accelerated brain aging calculation:** Accelerated brain aging was defined as the z-scored residual of calculated brain age after adjustment for chronological age.
- CSF proteomics analysis:** Peptide-level associations were tested using linear regression and evaluated for reproducibility across datasets.
- AD biomarker-stratified analysis:** The Neurodegeneration biomarker (N) status was defined using CSF total tau or hippocampal atrophy. The Interaction and stratified analyses tested biomarker-dependent effects.
- Statistical significance:** FDR correction was used for multiple testing and replicated peptides were prioritized for interpretation.

Result

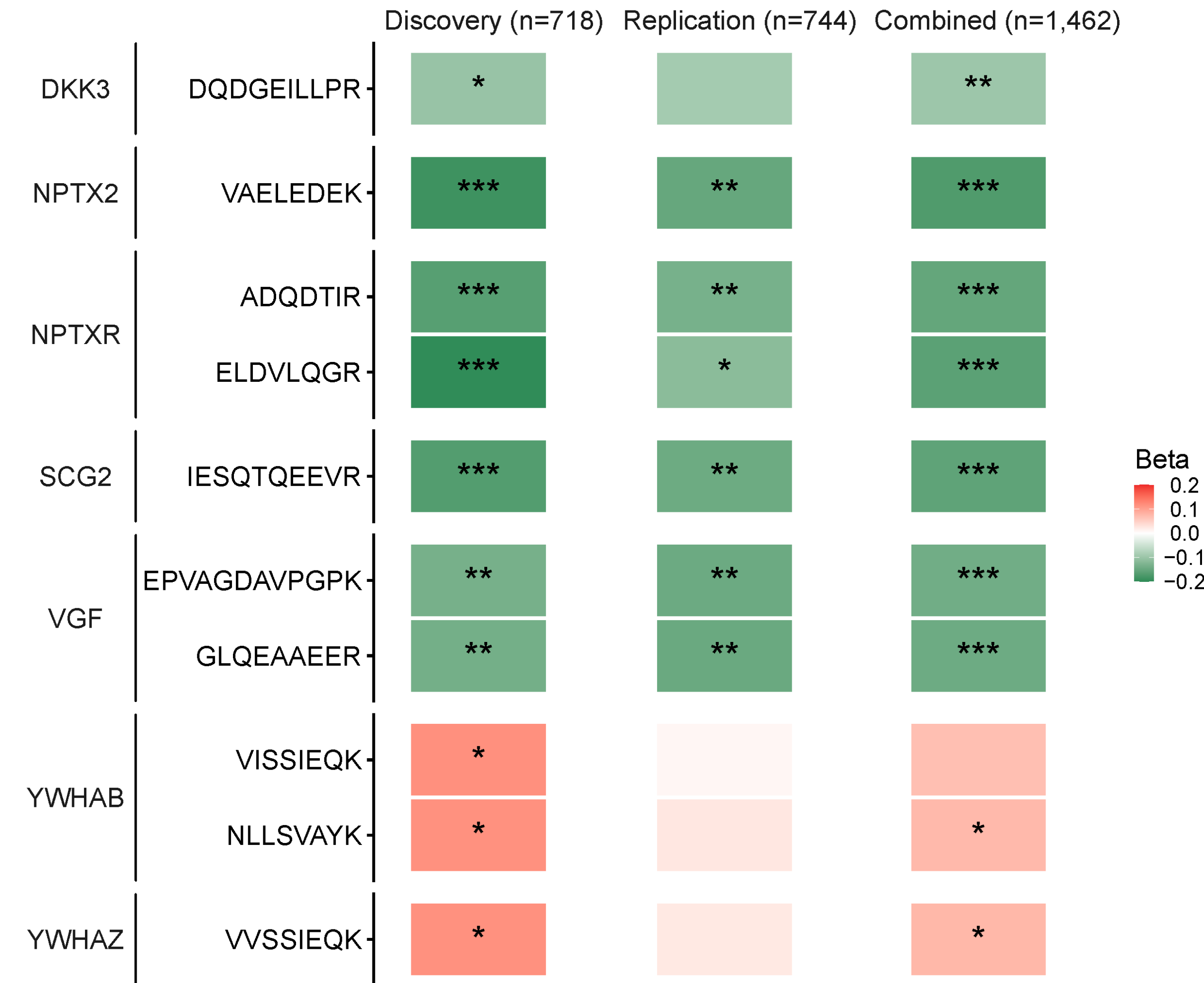


Figure 1. Peptide-level associations with accelerated brain aging. Heatmap summarizing peptide associations with accelerated brain aging in the discovery, replication, and combined datasets. Peptides reaching significance in the discovery dataset (FDR-adjusted $p < 0.05$) are shown, with colors reflecting the corresponding beta coefficients. FDR-adjusted significance is denoted by * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. FDR, false discovery rate.

Result

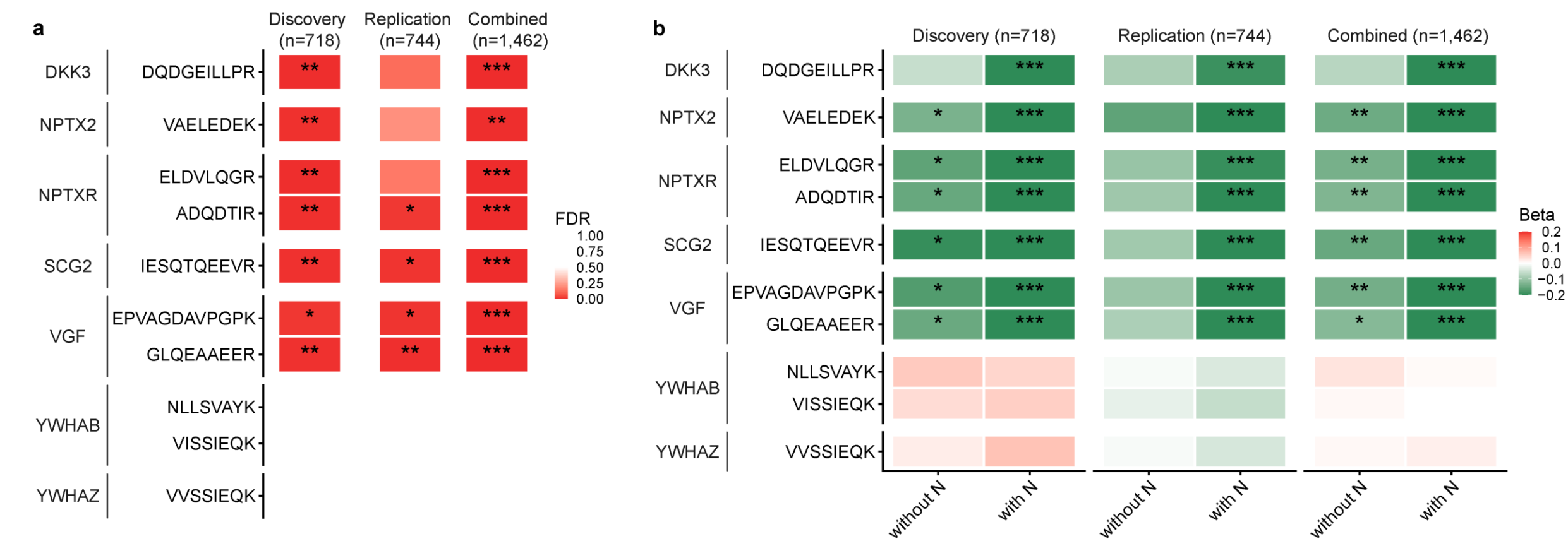


Figure 2. Interaction and stratified association analyses by AD biomarkers.

a, Heatmap summarizing peptide-by-biomarker interaction results for accelerated brain aging across neurodegeneration biomarker (N) status, with colors indicating FDR-adjusted p-values. b, Heatmap showing peptide associations with accelerated brain aging stratified by the neurodegeneration biomarker (N) status, with colors representing beta coefficients. FDR-adjusted significance is denoted by * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. A, A β ; T, tau; N, neurodegeneration biomarker; AD, Alzheimer's disease; FDR, false discovery rate.

Conclusions

- Accelerated brain aging was associated with CSF peptide signatures in two independent ADNI datasets.
- Several peptide associations were replicated in the independent dataset.
- The neurodegeneration biomarker (N) status modified the associations between CSF peptides and accelerated brain aging.

Acknowledgements

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