

Plasma Proteomic Biomarkers of Alzheimer's Disease and Related Dementias in Older Adults with Late-life Depression and Associations with Cognitive Performance

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INTRODUCTION

- Late-life depression (LLD) is associated with persistent cognitive impairment and elevated Alzheimer's and related dementia (ADRD) risk. A combination of depression-related, vascular, and AD pathology contribute to dementia risk in LLD but their relative contributions to cognitive impairment have not been well characterized.

- We examined plasma proteomic profiles of the following five biological domains: 1) Amyloid and tau pathologies, 2) Inflammation, 3) Synuclein and synaptic function, 4) Neurodegeneration, and 5) Vascular; in those with LLD and its association with cognitive performance.

METHODS

- Figure 1A** illustrate the cross-sectional blood analysis and statistical methods. Plasma from 35 sedentary older adults (mean age 67.5 years, 70% female) with recently remitted LLD (52% adjudicated with research diagnosis of Mild Cognitive Impairment (MCI)) were profiled using Nucleic Acid Linked Immuno-Sandwich Assay (NULISeq) CNS 120 Panel.

- Statistical analysis: Plasma proteins were organized into five a priori biological domains (i.e., Amyloid and Tau Pathologies, Inflammation, Neurodegeneration, Synuclein and Synaptic Disorders, and Vascular) and subjected to within-domain principal component analysis (PCA), with retained components determined by Horn's parallel analysis. To assess shared variation, Pearson correlation between all PCs were computed with Benjamini-Hochberg FDR correction; those with FDR-adjusted $p \leq 0.0021$ were considered significant and shown in the cross-domain network (**Figure 3**).

- Pearson correlations were used to examine associations between domain-specific PC and cognitive performance using domain-specific age- and education- corrected normed scores (**Figure 5**). All participants completed cognitive assessment using the Neuropsychological Assessment Battery (NAB).

Table 1. Demographics, Clinical Characteristics, and Cognitive Outcomes by MCI Status

Variable	LLD N = 16 ¹	LLD+MCI N = 17 ¹	p-value ²	Overall N = 33
Age (years)	68.1 ± 5.3	67.0 ± 5.1	0.612	67.5 ± 5.1
Sex			>0.999	
Male	5 (31%)	5 (29%)		10 (30%)
Female	11 (69%)	12 (71%)		23 (70%)
Race			>0.999	
White	15 (94%)	15 (88%)		30 (91%)
Black or African American	1 (6.3%)	2 (12%)		3 (9.1%)
Asian	0 (0%)	0 (0%)		0 (0%)
Education (years)	16.0 ± 1.7	16.8 ± 1.8	0.237	16.4 ± 1.8
Attention	107.5 ± 11.4	85.4 ± 25.4	<0.001	96.4 ± 22.4
Processing Speed 1	53.1 ± 12.9	48.8 ± 11.8	0.266	51.0 ± 12.4
Processing Speed 2	51.6 ± 8.0	44.1 ± 14.5	0.108	47.8 ± 12.1
Executive Function 1	102.2 ± 11.9	97.3 ± 8.5	0.264	99.5 ± 10.3
Executive Function 2	95.5 ± 6.7	93.6 ± 4.8	0.350	94.5 ± 5.7
Learning	50.1 ± 8.5	41.5 ± 12.2	0.029	45.8 ± 11.2
Delayed Memory	53.8 ± 7.0	41.6 ± 18.1	0.027	47.7 ± 14.9

¹ Mean ± SD; n (%)

² Wilcoxon rank sum test; Pearson's Chi-squared test

Mean ± SD for continuous variables; n (%) for categorical variables.

p-values: Wilcoxon rank-sum test (continuous); Pearson Chi-squared test (categorical).

LLD = Late-Life Depression; LLD+MCI = Late-Life Depression with Mild Cognitive Impairment.

RESULTS

Figure 1. Principal component analysis of NULISeq CNS panel in the cross-sectional FitBOLD cohort. A) Overview of the study design and analysis pipeline. B) Correlation heatmap for NULISeq CNS 120 panel plasma proteins. C) Screen plot displaying variance explained by each principal component from Principal Component Analysis (PCA) by domain.

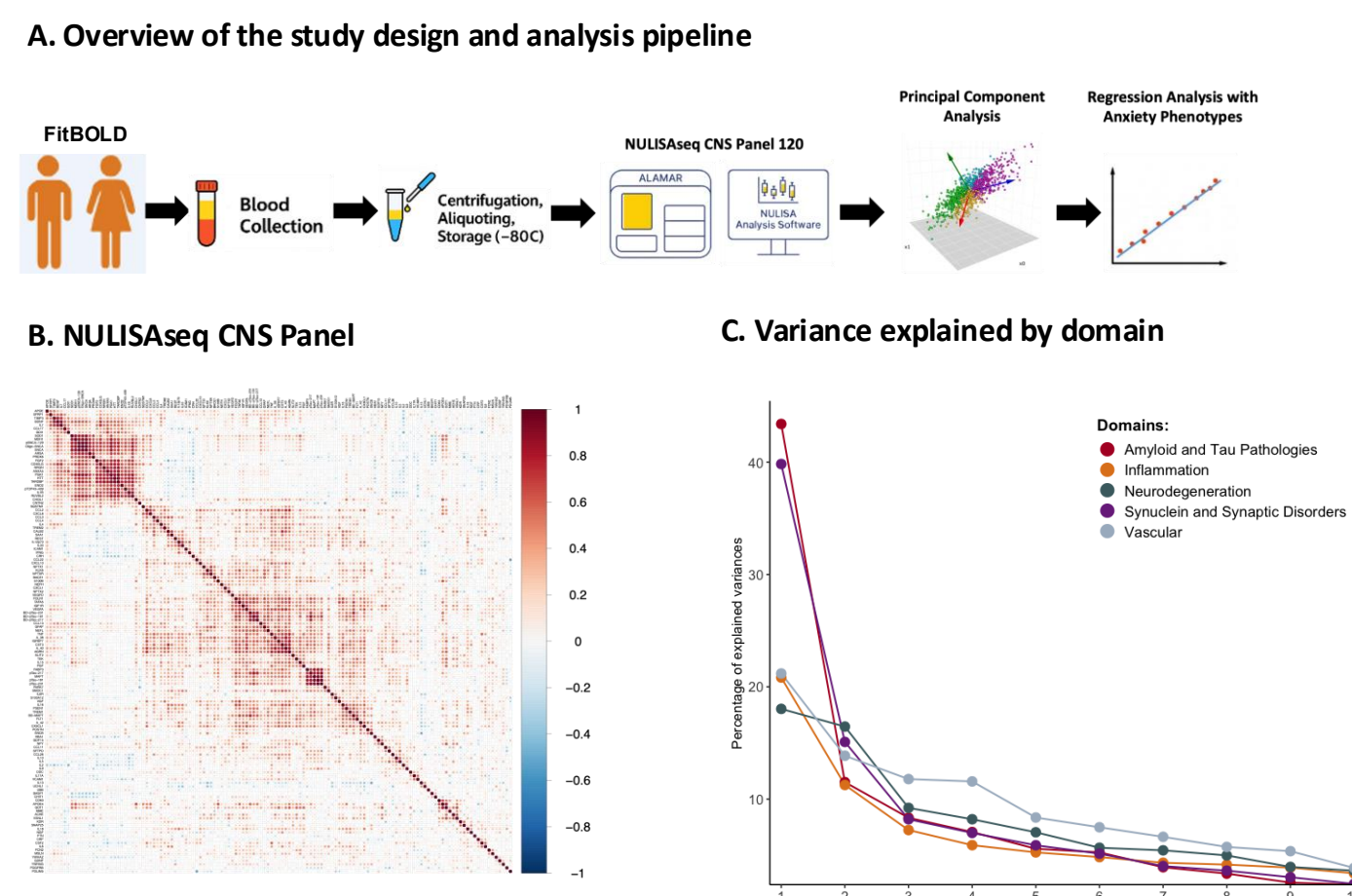


Figure 2. Cross-domain principal component Spearman Correlation Matrix in overall sample (N=35).

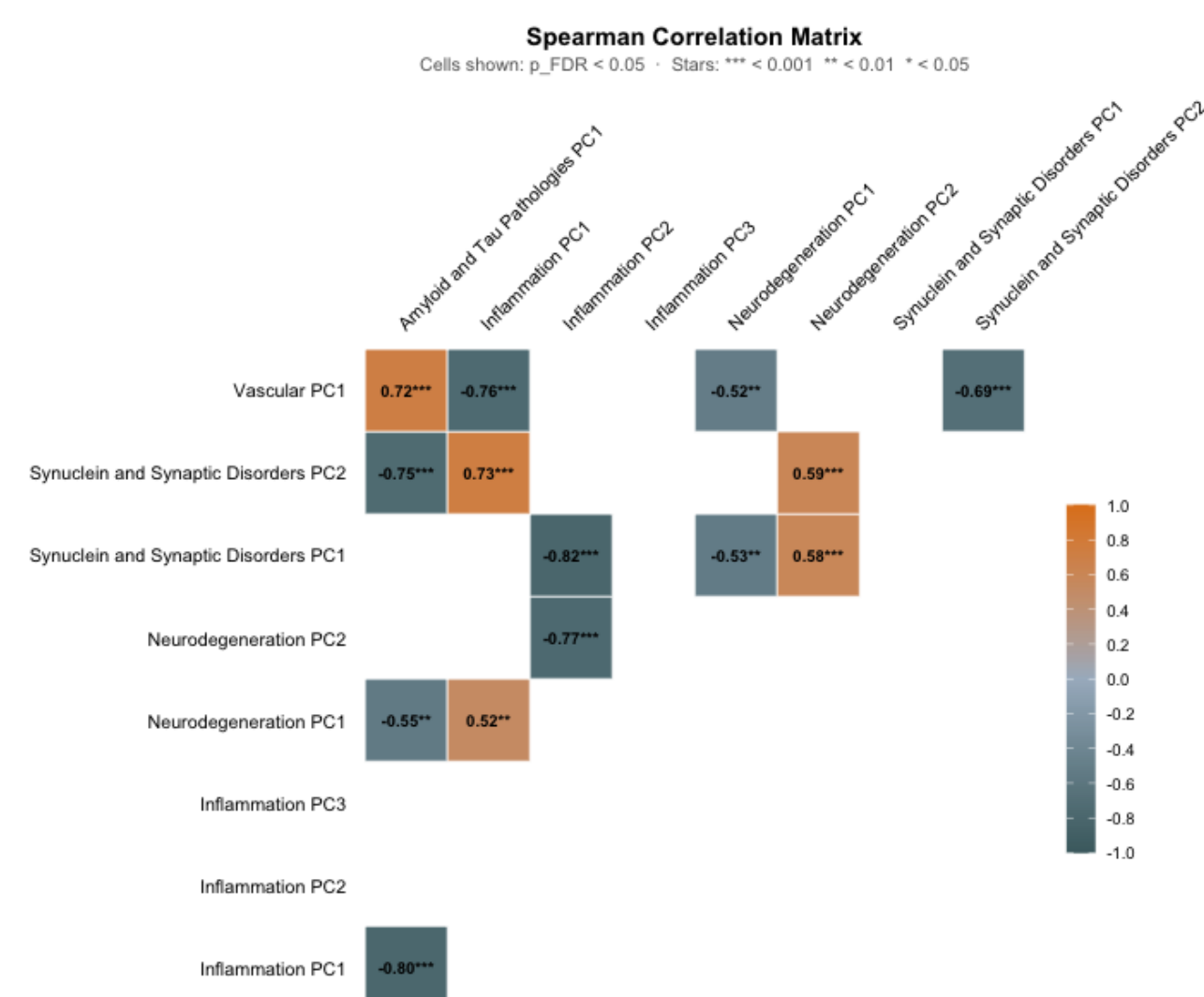
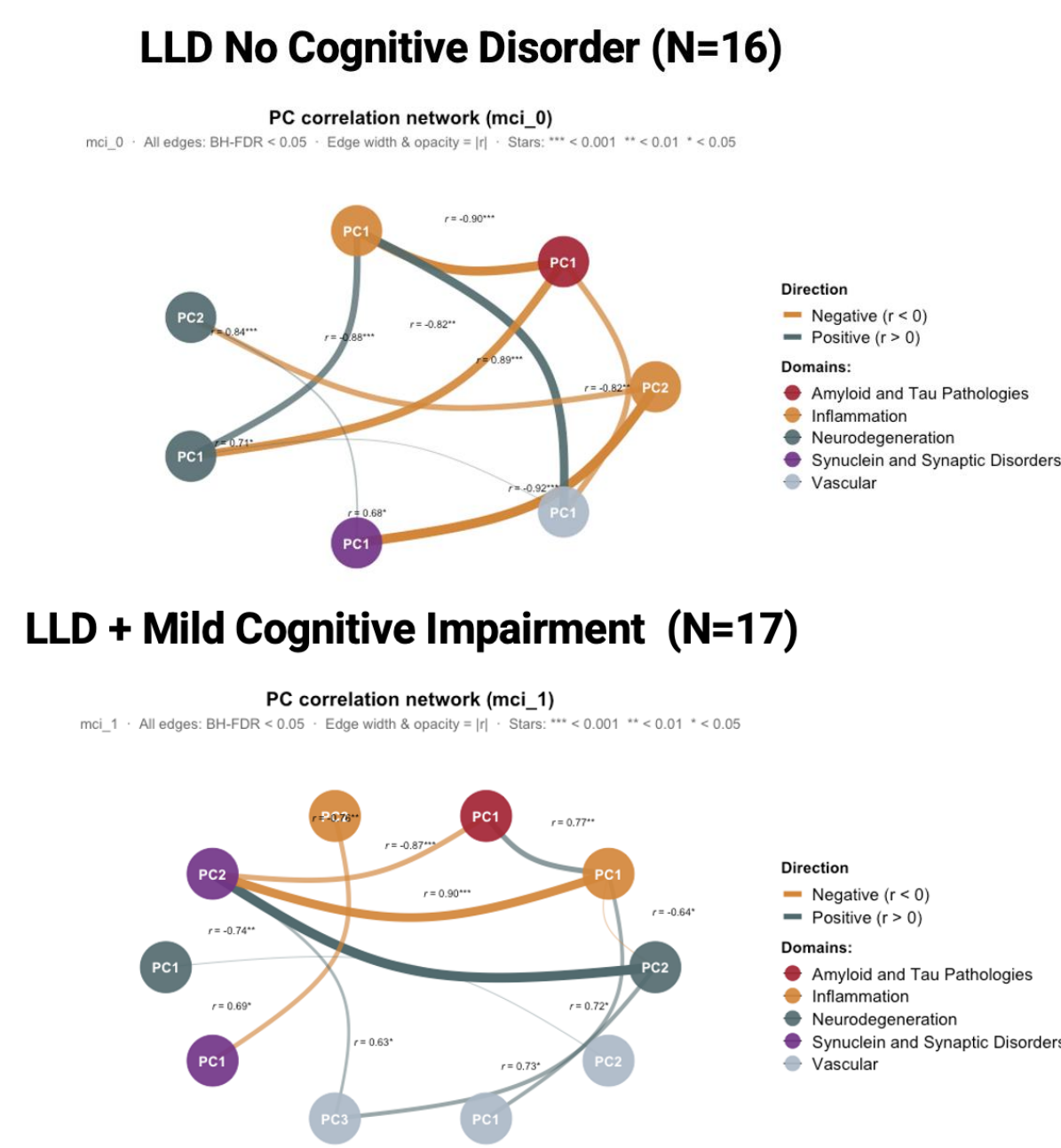


Figure 3. Cross-domain principal component correlation network shown separately for those with LLD with and without MCI. Nodes represent the 8 PCs, colored by domain. Edges are pairwise Pearson correlations significant after Benjamini-Hochberg correction (p-FDR≤0.0021). Edge color denotes direction (teal, positive; orange, negative) and edge width/opacity scale with |r|. FDR-adjusted significance (*p<0.05, **p<0.01, ***p<0.001).



ACKNOWLEDGMENTS



K23MH125074
R03MH136435

Figure 4. Volcano plot of principal component (PC) correlations with cognitive domains. Each point represents linear regression tests (8 PCs × cognitive performance on 7 tests across domains of attention, processing speed, executive function, and learning and memory). The x-axis shows the correlation coefficient, and the y-axis shows statistical significance as $-\log_{10}(\text{BH-FDR-adjusted } p)$. The dashed horizontal line marks the FDR=0.05 threshold; points above it (filled, colored, and labeled with the PC number) are statistically significant.

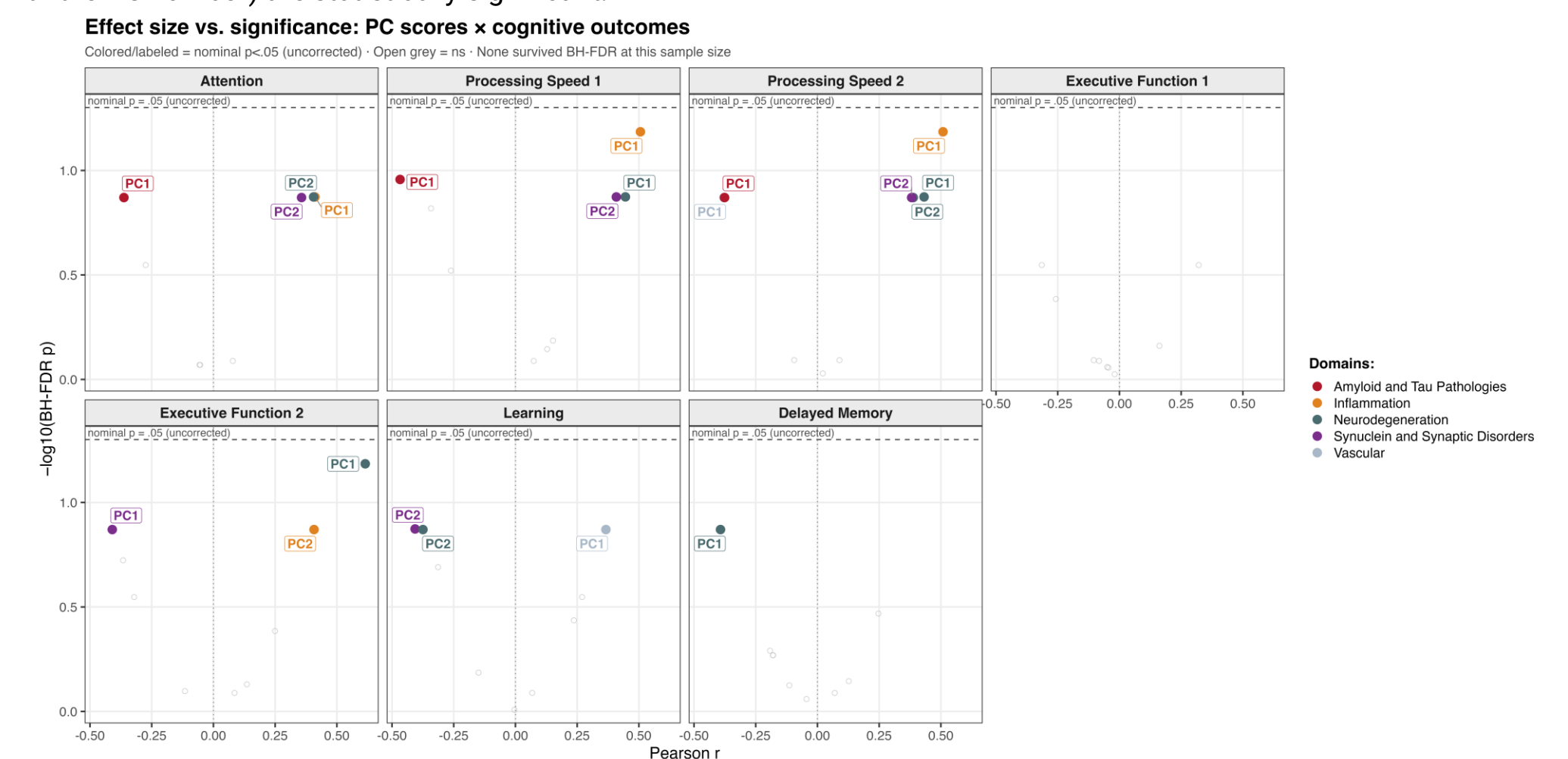


Figure 5. Heatmap of Correlations Between Blood-Based Biomarker PC Scores and Cognitive Performance.

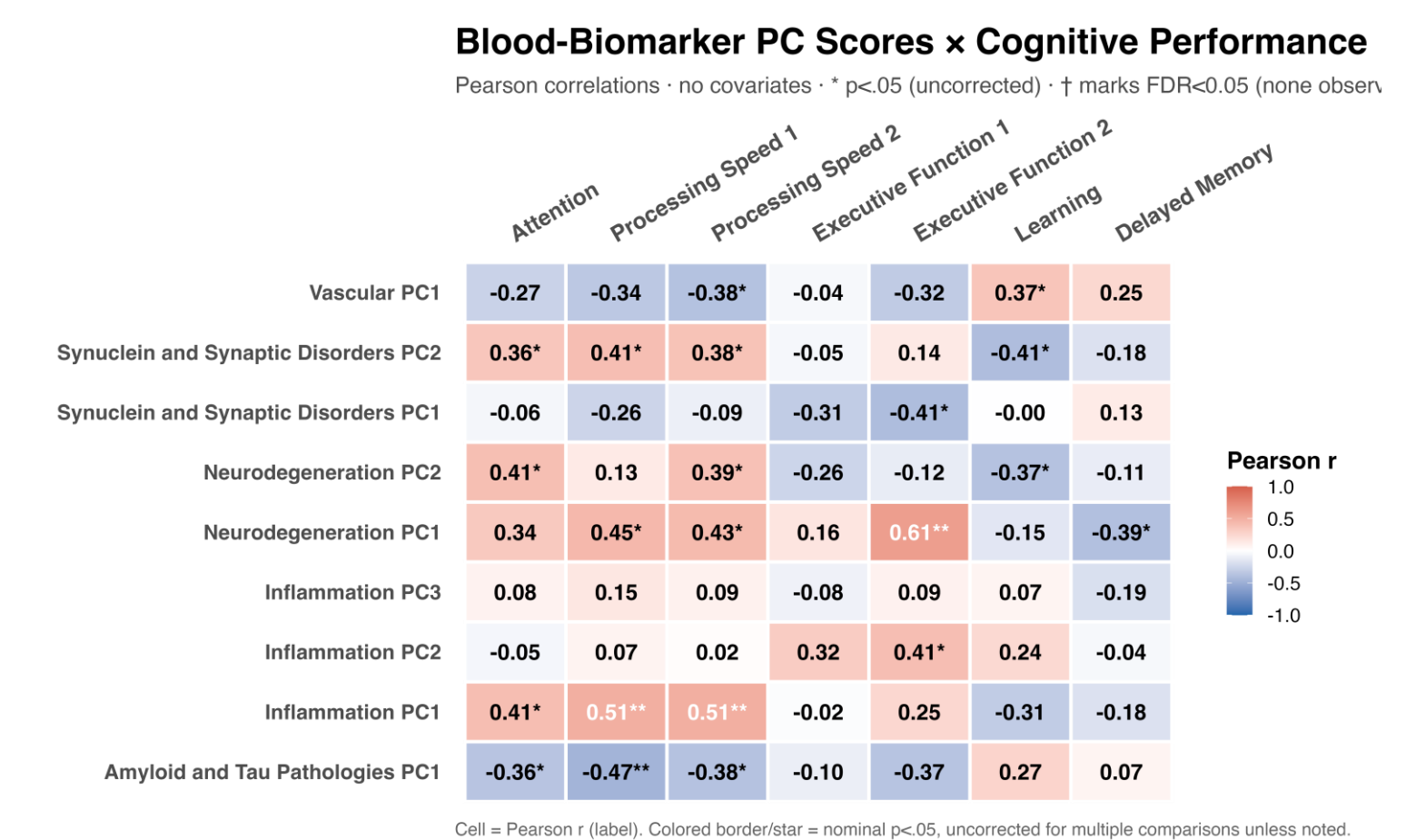
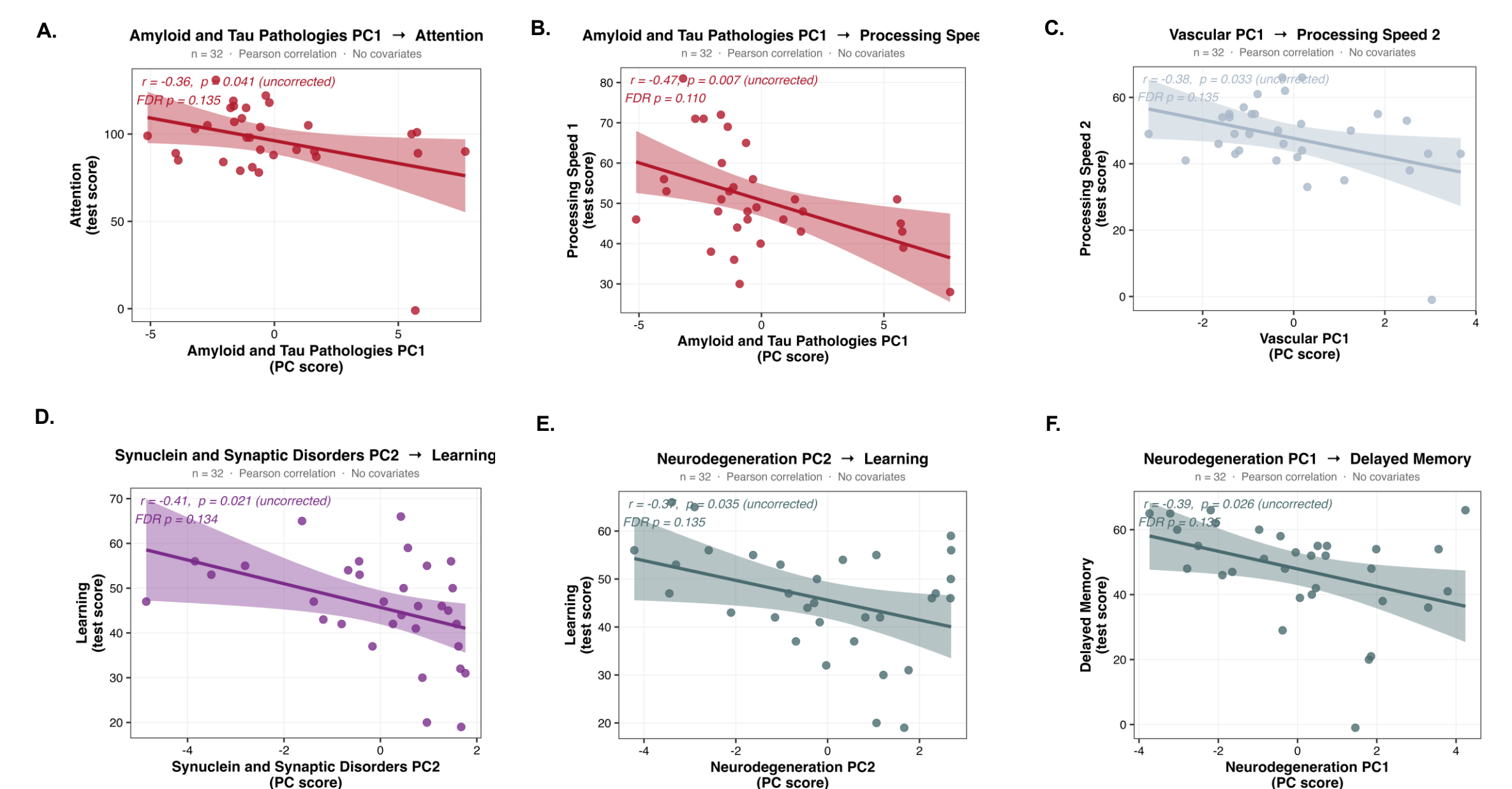


Figure 6. Correlations between Amyloid and Tau Pathologies domain with (A) Attention, and (B) Processing Speed; Vascular Pathology with (C) Processing Speed; Synuclein and Synaptic Damage with (D) Learning; and Neurodegeneration markers with (E) Learning and (F) Memory.



CONCLUSIONS

- In those with LLD+MCI, components across brain health domains were tightly coupled.
- The amyloid and tau components reflected AD-related pathological burden and were closely linked to neurodegenerative components.
- Inflammatory and vascular components were also strongly linked to amyloid and neurodegenerative components, suggesting these components may modify/accelerate pathological progression.
- These preliminary results characterize proteomic profiles linked to worse cognition in those with LLD.
- Further, in those with LLD+MCI, depression-related inflammatory and vascular pathology appear to interact with AD pathology, shaping neurodegenerative expression and clinical risk for dementia.