Cerebrospinal Fluid (CSF) Proteomic Patterns Vary with Neurobehavioral Characteristics

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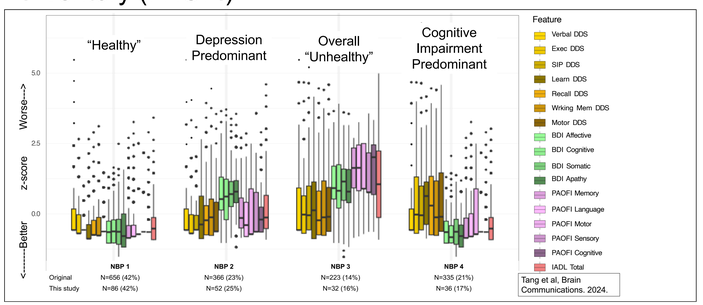
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BACKGROUND

- Neurobehavioral conditions in people with HIV (PWH) are common and have diverse, complex etiologies
- Negative clinical trials for depression and cognitive impairment in PWH suggest that historical classifications may not reflect underlying mechanisms
- Aim: Determine CSF protein profiles linked to historical classifications and four neurobehavioral phenotypes (NBPs) previously identified by machine learning

METHODS

- Cross-sectional analysis of 286 virally suppressed PWH
- Neuropsychiatric outcome measures:
- Global and domain-specific neurocognitive performance
- Beck Depression Inventory (BDI)-II and subscales
- Four NBPs identified by two-stage machine learning based on the above and: instrumental activities of daily living (IADL), Patient's Assessment of Own Functioning Inventory (PAOFI)



- Proteomics Olink Target-96 Inflammation panel. Normalized protein expression (NPX) values.
- Statistical methods:
- Hierarchical clustering for protein patterns.
- Associations tested via linear regression, Benjamini-Hochberg correction, ANOVA, and Tukey HSD.
- Exploratory enrichment analysis.

RESULTS

- Cohort: Mean age 45 years, 21% female, 46.5% Black, 9% Hispanic, median CD4+ 473/μL, nadir CD4+ 118/μL, 35% HCV seropositive, median duration of HIV 11 years
- Proteomics: Hierarchical clustering of the 60 proteins with >25% detectable values identified six clusters

CSF Inflammation Profiles Reveal Biologically Distinct Neurobehavioral Subtypes in PWH

RESULTS (continued)

- Distinct CSF protein profiles were identified across neurobehavioral classifications, with unique and overlapping proteins.
- CD40, FLT3L, and MMP-10 were the most commonly associated proteins.
- Recall and Motor domains linked to multiple proteins; Global performance linked to fewer.
- BDI-II affective subscale associated with 32 proteins (most of any individual feature); total BDI-II showed no associations.
- NBPs 2-4 showed at least one protein association, with NBP3 being the most distinct.
- Key biological processes included: T-cell activation, interferon signaling, chemotaxis, and B-cell, dendritic cell, and monocyte activation/development.

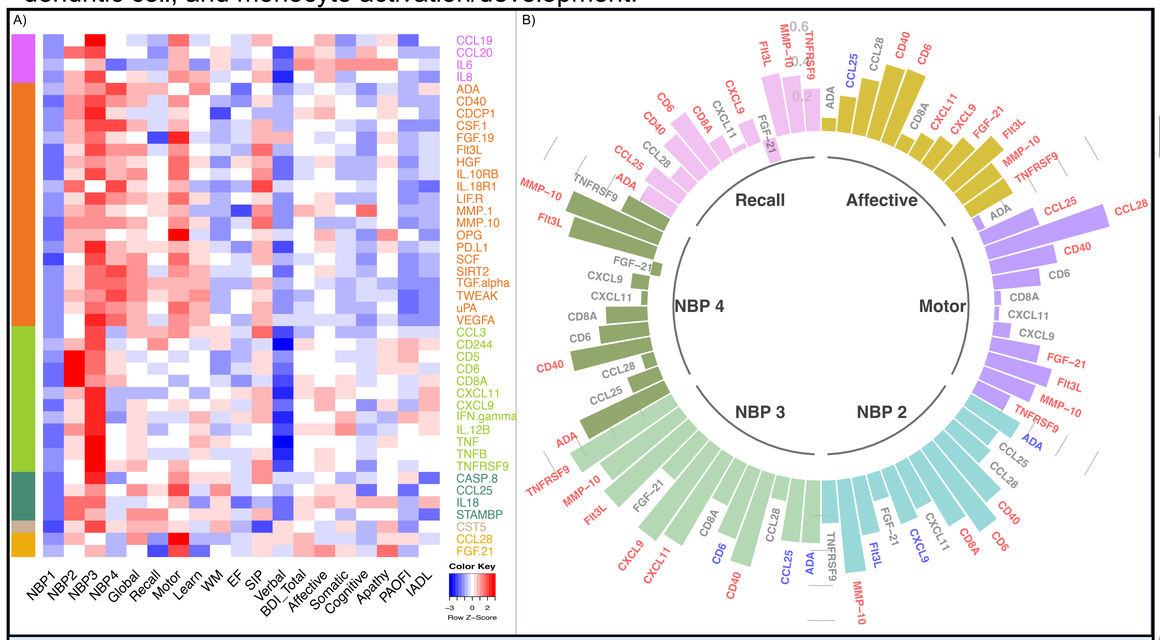


Figure 1. CSF Protein Associations with Neuropsychiatric Outcome Measures
A) Heatmap: Z-score scaled protein levels across neurobehavioral measures. Protein names color-coded by cluster.
B) Circular Bar Graph: Associations for five neurobehavioral outcome measures (NBPs 2-4; Recall and Motor Impairment; BDI Affective subscale) with a subset of 12 proteins show distinct and overlapping patterns. Gray perpendicular lines indicate standardized coefficients (0.2, 0.4, 0.6, and 0.8). Text color indicates significance: Adjusted $p < 0.05$ (red); Unadjusted $p < 0.05$ (blue); Unadjusted $p \geq 0.05$ (gray)

CONCLUSIONS

- Distinct CSF inflammation profiles were identified across neurobehavioral classifications, reinforcing the heterogeneity of these conditions in PWH.
- Novel, biologically plausible targets were identified for validation and future investigation
- Composite scores for individual components (e.g., total BDI-II) had minimal associations with inflammation, while some subscale level metrics and the multidimensional, data-driven NBPs had more.
- NBP3 (unhealthy in all features) and motor performance had the strongest associations.
- NBPs with similar clinical symptoms (e.g., depression-dominant NBP2 vs. NBP3) had distinct inflammation profiles, highlighting how different etiologies can result in similar phenotypes
  - In contrast, total BDI-II score was not significantly associated with any proteins
- Findings support a shift toward data-driven, multidimensional, biologically informed profiles to identify targeted therapies for the right patient.

FUTURE DIRECTIONS

- Validate findings in larger, longitudinal cohorts
- Expand analysis beyond inflammation to other biological pathways.
- Leverage diverse machine learning approaches to refine NP classifications based on underlying mechanisms.
- Further investigation of novel proteins and biological pathways identified in this study (e.g., FGF-21 which appears to have differential effects)
- Long-term goal: Develop streamlined biomarker panels integrated with accessible clinical measures for precision diagnostics and therapeutics in brain health.

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