Poster 596

Plasma Proteomics Identifies Variable Patterns of Association with Neuropsychiatric Dimensions

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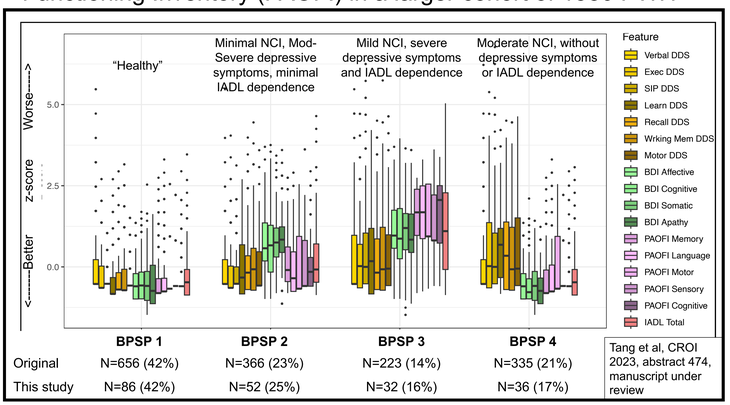
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BACKGROUND

- Neuropsychiatric (NP) conditions have complex etiologies, especially in people with HIV (PWH)
- Traditional diagnostic classification methods may not reflect underlying mechanisms
- Aim: Determine proteomic signatures of traditional NP classifications and 4 biopsychosocial phenotypes (BPSPs) previously identified by machine learning

METHODS

- Cross-sectional analysis of 206 virally suppressed PWH
- Neuropsychiatric classifications/ outcome measures:
- Global and domain-specific neurocognitive impairment (NCI)
- Beck Depression Inventory (BDI)-II and subscales
- Four BPSPs identified by two-stage unsupervised machine learning based on the above measures, instrumental activities of daily living (IADL) dependence, and Patient's Assessment of Own Functioning Inventory (PAOFI) in a larger cohort of 1580 PWH

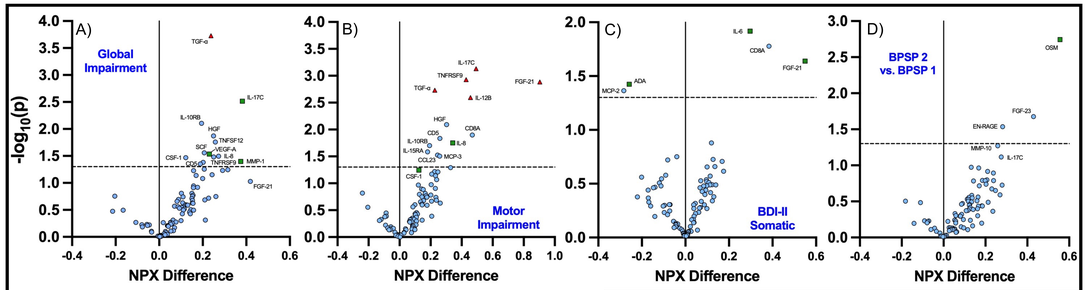


- Proteomics Olink Target-96 Inflammation panel. Normalized protein expression (NPX) values on log2 scale.
- Analysis. Group differences were analyzed by linear regression. Proteins with unadjusted p<0.10 were analyzed by multivariable regression adjusting for demographic, disease, and treatment characteristics. Benjamini-Hochberg (BH) adjustment for multiple comparisons was performed. Discrimination analysis determined

RESULTS

- Cohort: Mean age 45 years, 23% women, 52% Black, 9% Hispanic, median CD4+ 480/μL, nadir CD4+ 114 /μL, 35% HCV seropositive, median duration of HIV 11 years

Data-driven, cross-sectional analyses identified distinct patterns of inflammation related proteins associated with different neuropsychiatric classification methods



E)

	Global	Motor	Recall	BDI-II	Somatic	BPSP 2	BPSP 3	BPSP 4
TGF-alpha	▲	▲	▲					
IL-17C	▲	▲	▲			▲		▲
IL-8	▲	▲	▲					
FGF-21	▲	▲		▲	▲			
CD8A	▲	▲		▲	▲		▲	▲
IL-12B	▲	▲		▲				
TNFRSF9	▲	▲		▲				
VEGFA	▲	▲						
CSF-1	▲	▲						
IL-10RB	▲	▲						
HGF	▲	▲						
CCL23	▲	▲						
CD5	▲	▲					▲	
FGF-23	▲		▲	▲		▲		
MMP-1	▲		▲					
TNFSF12	▲		▲					▲
CCL11	▲		▲					
CD244	▲		▲					
SCF	▲							▲
IL-6		▲		▲	▲			
MMP-10		▲		▲		▲		
OSM		▲				▲		
CXCL6			▲					
CXCL11			▲					
CCL20				▲				
MCP-2				▲	▲			
ADA					▼			
EN-RAGE						▲		
DNER							▼	
CCL19							▲	
TNFSF11								▲
CCL3								▼
IL33								▼
Analytes	4	4	3	4	3	1	2	5
Model R^2	**0.154**	**0.221**	0.087	0.142	**0.162**	**0.183**	**0.227**	**0.266**
Model p	1.36E-04	6.78E-06	4.04E-02	2.75E-04	1.59E-05	4.83E-04	1.90E-03	6.11E-04
Discriminant Analysis								
Unhealthy	71.3%	73.5%	60.6%	65.9%	67.4%	63.5%	**75.0%**	**80.6%**
Healthy	68.4%	69.9%	68.7%	68.4%	69.1%	74.1%	**78.8%**	70.6%

Red: BH adjusted p-value<0.05, Green: unadjusted p<0.10 selected in multivariable model, Blue: unadjusted p<0.10 not selected in multivariable models

Figure 1:

- Different NP classifications had patterns that included distinct and overlapping proteins
- The NP outcome measures that had proteins with adjusted p values < 0.05 were global (Figure 1A) and motor (Figure 1B) impairment
- Across all analyses, the most frequently associated proteins were CD8 antigen, IL-17C, FGF-21, and FGF-23.
- Adjusted multivariable models with R^2>0.15 were found for global NCI, motor function impairment, BDI-II somatic subscale, and all BPSPs
- BPSPs 3 and 4 performed best in the discriminant analyses despite having less power

CONCLUSIONS

- Cross-sectional analyses revealed overlapping yet distinct patterns of inflammation-associated plasma proteins across different NP classifications
  - Suggests diverse inflammatory pathways contribute to NP condition heterogeneity
  - May indicate differential response to treatments
- Motor impairment, a prevalent NP complication in PWH, showed the strongest association with inflammation-associated proteins
- The data-driven, multidimensional BPSPs *may* better represent distinct underlying mechanisms since plasma protein profiles explained more variance in multivariable models and better discriminated between BPSP groups, despite reduced power
- Our findings reinforce the complexity of NP complications, and identified novel, biologically plausible targets for validation and future investigation
- This provides a step toward identifying NP biotypes

FUTURE DIRECTIONS

- Validate findings in larger, longitudinal cohorts
- Investigation of biological pathways beyond inflammation
- Comparisons of different machine learning approaches to improve classification of NP disorders to better reflect underlying mechanisms
- Further investigation of novel or underinvestigated proteins and biological pathways identified in this study. For example:
  - Oncostatin M (OSM) is in the IL-6, STAT3 pathway and may promote glutamate mediated neurotoxicity and depression. OSM was upregulated in BPSP2 with prominent depression symptoms but not associated with BDI scores or BPSP3
    - If validated, perhaps individuals with the BPSP2 profile could be more likely to respond to newer glutamatergic modulatory antidepressants

AUTHOR CONTACT AND ACKNOWLEDGEMENTS

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