Biopsychosocial Phenotypes in People with HIV in the CHARTER Cohort

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OBJECTIVE

- Aim: To identify novel, multidimensional, biopsychosocial (BPS) phenotypes in people with HIV (PWH) that account for neurocognitive performance, self-reported neurocognitive symptoms and depressed mood, and daily functioning

BACKGROUND

- Neuropsychiatric complications such as neurocognitive impairment (NCI) and depression are common in PWH despite viral suppression on antiretroviral therapy (ART), but these conditions are heterogeneous in their clinical presentations and associated disability
- Most prior investigations focused on narrow phenotypes, such as cognitive impairment or mood disorders
- Specific phenotypes may have pathophysiological and treatment implications
- Machine learning is a powerful tool to characterize the heterogeneity in cognitive and mood complications among PWH and to systematically investigate the complex and interrelated factors that place PWH at risk for cognitive deficits.

METHODS

CHARTER participants

- 1,580 PWH at six university-based medical centers in the U.S., 2003-2010 (NOTE: ART initiation guidelines: CD4 <350 cell/uL)
- Minimal comorbidity exclusions

Biopsychosocial (BPSP) Features:

- 7 cognitive domains (domain deficit scores, DDS)
- 4 subscales of the Beck Depression Inventory-II (BDI-II)
- 5 components of self-reported symptoms according to the Patient's Assessment of Own Functioning Inventory (PAOFI)
- 1 total score of dependence in instrumental activities of daily living (IADLs)

Each feature were mapped to same scale using a z-score transformation

Two-stage unsupervised machine learning clustering approach:

- **Self-organizing maps (SOM)** – for data reduction, increased computational efficiency and easier matrix visualization
- **K-means clustering** using Mahalanobis distance

Statistical analyses: one-way ANOVAs and chi-square tests for continuous and categorical data respectively

RESULTS 1

- SOM: 1,580 participants reduced into 100 "nodes" (**Figure 2**)
- 100 x 17 matrix generated from the SOM partitioned into 4 distinct groups using k-means clustering (**Figure 1**)
  - **Phenotype 1: Healthy** (low z-scores on all 17 features)
  - **Phenotype 2: Very mild NCI + mod-severe depression + mild symptoms/IADL impairment**
  - **Phenotype 3: Mild NCI with severe depression, cognitive symptoms and IADL impairment**
  - **Phenotype 4: Mild-moderate NCI, no depression, cognitive symptoms and IADLs**

Figure 1. K-means clustering Boxplots of 17 features by phenotype

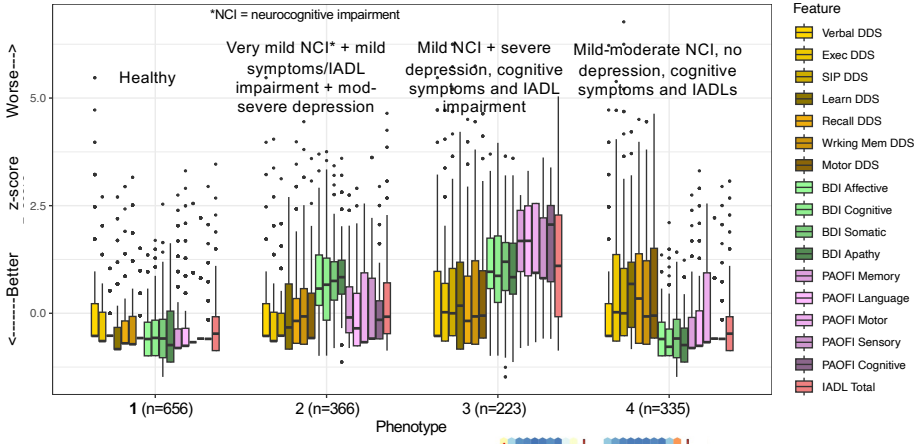


Figure 2. Self-organizing maps

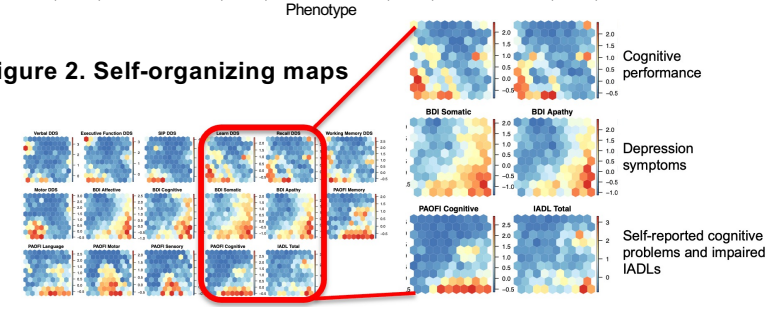


Table 1. Demographics and disease characteristics by phenotype

Variable	Phenotype 1 (n=608)	Phenotype 2 (n=270)	Phenotype 3 (n=205)	Phenotype 4 (n=497)	p-value	Pairwise
	Mean (SD), Median [IQR], or n (%)					
Demographics						
Age (yr)	42.6 (8.81)	42.6 (8.6)	43.9 (7.61)	43.8 (8.48)	0.013	--
Education (yr)	13.0 (2.65)	12.22 (2.42)	12.2 (2.79)	12.7 (2.49)	0.009	1>2
Male N (%)	539 (82.16%)	268 (73.22%)	150 (67.26%)	255 (76.12%)	<0.001	2,3,4<1
Black N (%)	327 (49.92%)	176 (48.09%)	100 (44.84%)	157 (46.87%)	0.57	--
HIV disease and treatment characteristics						
Duration of infection (Mo)	50.41 (50.06)	56.56 (49.84)	58.26 (50.33)	61.03 (52.1)	<0.001	2,3,4>1
Current CD4 median [IQR]	422 [268, 609]	408 [254, 599]	465 [293, 667]	405 [249, 570]	0.69	--
Nadir CD4 median [IQR]	187 [42, 324]	170 [43, 294]	171 [50, 299]	133 [34, 256]	0.006	--
On ART, N (%)	429 (65.4%)	261 (72.1%)	160 (72.1%)	256 (76.4%)	0.002	--
Plasma HIV RNA < 50 c/mL	263 (40.1%)	154 (42.1%)	99 (44.4%)	146 (43.6%)	0.66	--

CONCLUSIONS, IMPLICATIONS

- We identified four distinct, clinically plausible, and complex BPS phenotypes among PWH, characterized by differences in NC performance, depressive mood symptoms, cognitive symptoms, and IADL dependence.
- Characterizing specific multi-dimensional phenotypes and associated risk factors might facilitate identification of interventions.
  - For example, whereas a person with depression but without cognitive impairment might respond best to a combination of psychotherapy and a traditional daily anti-depressant medication, someone who has both depression and cognitive impairment (ie, risk factors for poor adherence) might respond best to a long-acting antiretroviral regimen and a neuroprotective agent to address both components of their disability and to facilitate adherence to the interventions.

Future Directions & Limitations

- The phenotypes should be validated in other study samples, and longitudinal studies should clarify the clusters' stabilities over time and factors that may influence transition from one cluster to another
- If specific biomarker and comorbidity associations of the phenotypes are found, these may provide clues to underlying pathophysiology that could influence treatment approaches
- The number of female participants was relatively small, though it approximated the proportion of females with HIV in the United States
- Characteristics not assessed here, such as HIV reservoir size, might prove to be important drivers of clinical phenotypes

ADDITIONAL KEY INFORMATION

- The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) phenotypes project is funded by NIH award R01MH125720

- The CHARTER group is affiliated with Johns Hopkins University; the Icahn School of Medicine at Mount Sinai; University of California, San Diego; University of Texas, Galveston; University of Washington, Seattle; Washington University, St. Louis; and is headquartered at the University of California, San Diego and includes: Robert K. Heaton, Ph.D., Scott L. Letendre, M.D., Ronald J. Ellis, M.D., Ph.D., Christine Fennema-Notestine, Ph.D., Rebecca Theilmann, Ph.D., Amanda Bischoff-Grethe, Bin Tang, Clint Cushman, Debra Cookson, Matthew Dawson, and Donald Franklin, Jr.; Johns Hopkins University Site: Leah Rubin, Ph.D. (P.I.); Icahn School of Medicine at Mount Sinai Site: Susan Morgello, M.D. (P.I.), Letty Mintz, N.P.; University of California, San Diego Site: J. Allen McCutchan, M.D. (P.I.); University of Washington, Seattle Site: Christina Marra, M.D. (P.I.); University of Texas, Galveston Site: Benjamin Gelman, M.D., Ph.D. (P.I.), Eleanor Head, R.N., B.S.N.; and Washington University, St. Louis Site: David Clifford, M.D. (P.I.), Beau Ances, M.D., Ph.D., Muhammad Al-Lozi, M.D., Mengesha Teshome, M.D.