Title

Biopsychosocial phenotypes in people with HIV in the CHARTER cohort.

Journal

Brain Communications, 6(4)

Authors

Tang, Bin

Ellis, Ronald

Vaida, Florin

et al.

Publication Date

2024

DOI

10.1093/braincomms/fcae224

Peer reviewed

BRAIN COMMUNICATIONS

Biopsychosocial phenotypes in people with HIV in the CHARTER cohort

Bin Tang,[1] Ronald J. Ellis,[1,2] Florin Vaida,[1] Anya Umlauf,[1] Donald R. Franklin,[1] Raha Dastgheyb,[3] Leah H. Rubin,[3] Patricia K. Riggs,[4] Jennifer E. Iudicello,[1] David B. Clifford,[5] David J. Moore,[1] Robert K. Heaton[1] and Scott L. Letendre[1,4]

Neuropsychiatric complications such as neurocognitive impairment and depression are common in people with HIV despite viral suppression on antiretroviral therapy, but these conditions are heterogeneous in their clinical presentations and associated disability. Identifying novel biopsychosocial phenotypes that account for neurocognitive performance and depressive and functional symptoms will better reflect the complexities encountered in clinical practice and may have pathological and therapeutic implications. We classified 1580 people with HIV based on 17 features, including 7 cognitive domains, 4 subscales of the Beck depression inventory-II, 5 components of the patient's assessment of own functioning inventory, and dependence in instrumental and basic activities of daily living. A two-stage clustering procedure consisting of dimension reduction with self-organizing maps and Mahalanobis distance-based *k*-means clustering algorithms was applied to cross-sectional data. Baseline demographic and clinical characteristics were compared between the phenotypes, and their prediction on the biopsychosocial phenotypes was evaluated using multinomial logistic regression. Four distinct phenotypes were identified. Participants in Phenotype 1 overall did well in all domains. Phenotype 2 had mild-to-moderate depressive symptoms and the most substance use disorders. Phenotype 3 had mild-to-moderate cognitive impairment, moderate depressive symptoms, and the worst daily functioning; they also had the highest proportion of females and non-HIV conditions that could affect cognition. Phenotype 4 had mild-to-moderate cognitive impairment but with relatively good mood, and daily functioning. Multivariable analysis showed that demographic characteristics, medical conditions, lifetime cocaine use disorder, triglycerides, and non-antiretroviral therapy medications were important variables associated with biopsychosocial phenotype. We found complex, multidimensional biopsychosocial profiles in people with HIV that were associated with different risk patterns. Future longitudinal work should determine the stability of these phenotypes, assess factors that influence transitions from one phenotype to another, and characterize their biological associations.

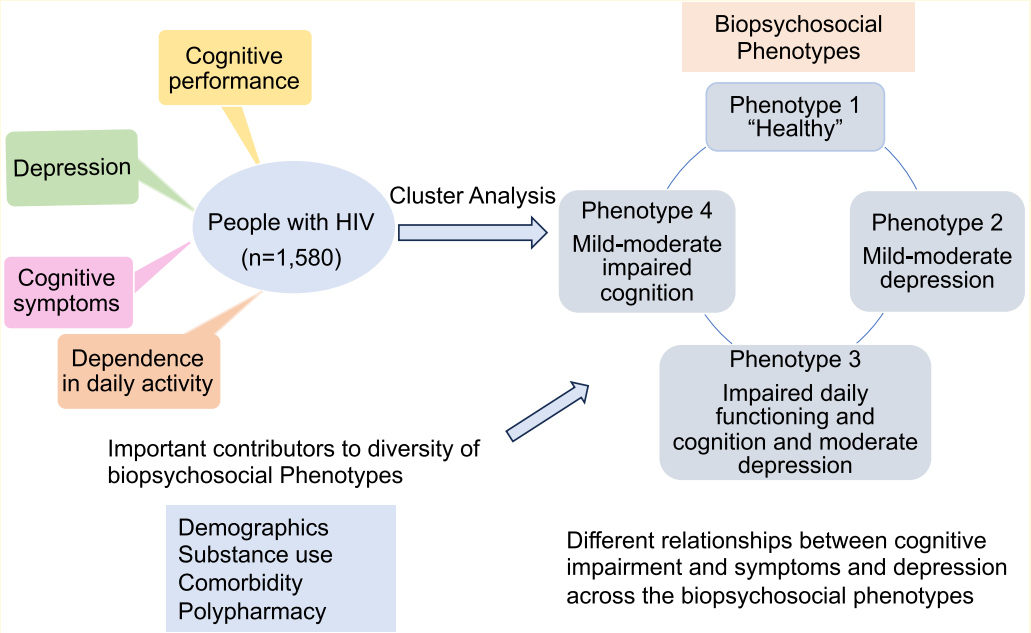
1 Department of Psychiatry, University of California San Diego, San Diego, CA 92093, USA
2 Department of Neurosciences, University of California San Diego, San Diego, CA 92093, USA
3 Department of Neurology, Johns Hopkins University, Baltimore, MD 21218, USA
4 Department of Medicine, University of California San Diego, San Diego, CA 92093, USA
5 Department of Neurology, Washington University at St. Louis, St. Louis, MO 63110, USA

Correspondence to: Scott L. Letendre
University of California, San Diego, Departments of Medicine and Psychiatry, 220 Dickinson Street
Suite B, San Diego, CA 92103, USA
E-mail: sletendre@ucsd.edu

Keywords: HIV; cluster analysis; cognition; depression; daily functioning

Received November 17, 2023. Revised May 22, 2024. Accepted July 23, 2024. Advance access publication July 29, 2024
Published by Oxford University Press on behalf of the Guarantors of Brain 2024.

Graphical Abstract



Introduction

With the advent of potent antiretroviral therapy (ART), the life expectancy of people with HIV (PWH) has been extended, but a high prevalence of neurocognitive (NC) and psychiatric disturbances persists and is associated with worse functional and medical outcomes as well as reduced quality of life. Most prior work in this area has focused on either NC[1,2] or mood disorders ,[3-6] which are among the most common central nervous system[7] diseases, but these often co-occur[8,9] and may have complex, interacting effects. Studies have shown that PWH with depressive symptoms may experience increased cognitive and functional difficulties in their everyday lives, regardless of objective evidence of NC impairment (NCI).[10,11]

Categorizing cognitive and mood disorders in PWH in a biologically meaningful manner has long been challenging. In the early 2000s, combination ART fundamentally shifted the landscape in multiple ways, including nearly eliminating many of the most severe CNS complications of HIV. In recognition of these changes, experts devised a systematic research approach in 2007 that defined mild asymptomatic and two levels of symptomatic disorders, broadly categorizing them as HIV-associated NC disorders, or HAND. Now more than a decade old, this nosology advanced the field but is also a source of debate. While many analyses identified biological associations with HAND, criticisms have included that the method is overly sensitive, particularly regarding asymptomatic individuals; that the approach does not adequately account for other important CNS conditions (e.g. depression); and that common conditions that can adversely affect cognition in PWH also occur in people without HIV (e.g. substance use, cardiovascular disease), and that these alternative conditions may explain impairment rather than HIV itself. Perhaps most importantly, clinical trials have not consistently identified a therapeutic intervention for HAND, which has raised questions about whether the HAND nosology adequately reflects convergent, underlying pathology. Together, the debate has led to a movement within the field to devise a new approach for understanding 'CNS biotypes' that will incorporate other aspects of the brain injuries that can occur in PWH and that will better reflect the biological mechanisms that drive disease.

Machine learning approaches are a powerful tool in characterizing the heterogeneity in cognitive complications among PWH and in systematically investigating the complex and interrelated factors that place PWH at risk for cognitive deficits.[12] Prior publications that applied machine learning to high-dimensional, health-related data among PWH have demonstrated novel and important findings. Paul *et al.*[13] applied gradient-boosted multivariate regression to demographic, clinical, medical history, cognitive and neuroimaging data to identify risk factors of frailty among 105 older PWH and found that psychomotor speed, CD4+ T-cell count, and neuroimaging alterations in motor and visual brain systems, differentiated frail from non-frail PWH. Dastgheyb *et al.*[14] used self-organizing maps (SOM) followed by model-based clustering to identify cognitive profiles in 929 virally suppressed women with HIV and 717 HIV-uninfected women using 17 NC measures and found that the two cohorts differed in the patterns and predictors of cognitive function. In another study of 1666 PWH

(201 women with HIV and 1465 men with HIV) and data from 13 cognitive tests, machine learning (SOM followed by model-based clustering) revealed different cognitive profiles by sex and supported the finding that women with HIV had greater cognitive impairment than men with HIV.[15] These studies exemplify the utility of multimodal data and machine learning methods.

New classifications of CNS disorders in PWH using machine learning to categorize high-dimensional data, such as those which have been collected in the CNS HIV ART Effects Research (CHARTER) study, would yield not just cognitive phenotypes but biopsychosocial (BPS) phenotypes that could identify new mechanisms that lead to clinically useful diagnostic assessments, new therapies, and better management of CNS disorders in PWH. The present study aimed to address the interplay between cognition, depressive symptoms, and self-reported daily functioning in PWH by using machine learning algorithms to identify distinct phenotypes based on 17 BPS features. We sought to characterize these phenotypes by comparing participants' demographic characteristics, HIV disease and treatment history, and history of neuromedical and psychiatric disorders between the phenotypes. Finally, we assessed the relationship between objective and subjective cognitive problems and depression in each phenotype.

Materials and methods

Participants

Analyses used baseline data from 1580 CHARTER participants who enrolled between 2003 and 2010 and were assessed at six university-based medical centres in the United States (University of California San Diego, Johns Hopkins University, Washington University, St. Louis, Mount Sinai School of Medicine, University of Texas, Galveston, University of Washington, Seattle).[1] All participants had HIV-1 infection and enrolled without regard to comorbidities or other exclusions, to obtain a sample that was as representative as possible of the US population of adult PWH. The local Institutional Review Boards approved the study procedures and all participants provided written informed consent.

Neuromedical assessments

Comprehensive neuromedical assessments were performed by centrally trained investigators and staff using standardized case report forms and included medical and treatment history, physical examination, phlebotomy, and collection of cerebrospinal fluid (CSF) by lumbar puncture. Details can be found on the CHARTER study website (https://www.nntc.org/content/relationship-charter) and in prior publications.[1] ART adherence was assessed using the AIDS Clinical Trials Group method, which considers good adherence to be no fewer than 95% of doses in the 4 days before the assessment. HIV infection was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Routine clinical chemistry panels, complete blood counts, hepatitis C virus antibody, and CD4+ T-cells (flow cytometry) were performed at each site's Clinical Laboratory Improvement Amendments (CLIA)–certified, or CLIA equivalent, medical center laboratory. HIV RNA was quantified by commercial RT-PCR (Amplicor version 1.5, Roche Diagnostics, Indianapolis, IN, USA; lower limit of quantification 50 copies per mL). Nadir CD4+ T-cell count was defined as the lowest value of either self-reported count or study measurement. We calculated the Veterans Aging Cohort Study Index,[16] a composite risk indicator that combines age with clinical HIV biomarkers (i.e. HIV-1 plasma RNA and CD4+ T-cell count) and measures of anaemia, and renal and liver function.[17-19] The distal sensory polyneuropathy (DSP) evaluations included self-reported neuropathy symptoms (pain, numbness and paresthesias) and a clinical examination for neuropathy signs (bilateral distal vibration, sharp and touch loss).

Biopsychosocial feature assessments

NC performance was measured using a comprehensive NC test battery that assessed seven cognitive domains (multiple tests per domain)[20]: verbal fluency (controlled oral word association test: F–A–S, category fluency: animals/actions), speed of information processing [stroop colour trial, Wechsler Adult Intelligence (WAIS)-III: digit symbol, WAIS-III: symbol search, trail making test: part A], learning (Hopkins Verbal Learning Test—Revised: immediate recall, Brief Visuospatial Memory Test—Revised: immediate recall), delayed recall (Hopkins Verbal Learning Test-Revised: delayed recall, Brief Visuospatial Memory Test-Revised: delayed recall), executive function (stroop colour-word trial, Wisconsin Card Sorting Test: computerized 64-card version, trail making test: part B), working memory (Paced Auditory Serial Addition Task: 50-item single-trial version, WAIS-III: letter-number sequencing), and motor skills (grooved pegboard test for both dominant and non-dominant hand). Raw scores of each test were converted first to demographically uncorrected, normally distributed scaled scores by generating normalized quantiles of the raw scores and scaling them to have a mean of 10 and standard deviation (SD) of 3, such that higher values always correspond to better performance on the test. Second, the scaled scores were predicted by regressing on age, education, sex, race and ethnicity. Residuals, calculated as differences between the observed and predicted scaled scores, were standardized and scaled (mean of 50 and SD of 10).[21,22] These values were termed demographically corrected *T*-scores and then converted to deficit scores using a five-point scale (0 = normal cognition to 5 = severe impairment) and averaged within each NC domain to generate a domain deficit score (DDS).[23,24] These seven domain deficit scores were then used in the machine learning analysis described below. A global deficit score (GDS) was calculated by averaging all individual test deficit scores and NCI was defined as a GDS $\geq$ 0.5.[23]

Neuromedical and psychiatric history information was used to classify comorbid neuropsychiatric conditions that would confound the attribution of NCI to HIV according to the published criteria.[1,20]

Current mood symptoms were evaluated with the Beck Depression Inventory-II (BDI-II), which is a 21-item self-report instrument. Each item is rated on a 4-point Likert scale from 0 to 3 (worst).[25] BDI-II total score ranges from 0 to 63, and clinically significant levels of depressive symptoms are conventionally defined as none to minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63). Component BDI-II subscales capture cognitive, somatic, affective, and apathy symptoms.[26]

Daily functioning was evaluated using the Patient's Assessment of Own Functioning Inventory (PAOFI)[27] for NC difficulties in everyday life and an adaptation of the Lawton–Brody instrumental activities of daily living (ADLs) scale.[28] The PAOFI assesses five components about difficulties with higher/more complex NC functions (range, 0–9), language and communication (0–10), episodic memory (0–10), motor (0–2) and sensory-perceptual (0–3) functions.[27] PAOFI total scores range from 0 to 34. Component scores of 3 or above are considered to indicate significant experiences of cognitive difficulties in daily life (i.e. PAOFI total score $\geq$ 3).[7,29] The ADL instrument assessed possible changes in levels of independence in performing 16 everyday tasks such as doing laundry and financial management, which are rated with respect to whether the participant requires more assistance now than in the past. Each task of the ADL is scored as 0 (no change from best functioning) or 1 (more dependent now). The ADL total score ranges from 0 to16 and is categorized overall as ADL independence (0–2) and ADL dependence (3–16), which signifies a need for help in accomplishing ADLs (ADL impaired).

Data analysis

Data from the 17 BPS features (7 NC domain deficit scores, 4 BDI-II subscales, 5 PAOFI symptom domains, and 1 ADL total score) were entered into a two-stage clustering procedure, consisting of dimension reduction with SOM followed by *k*-means clustering. Prior to performing the clustering procedure, the data were standardized.

SOM is an unsupervised machine learning technique used for data reduction, data visualization and computation efficiency.[30] SOM produces a low-dimensional nonlinear approximation of a high-dimensional data by grouping individual observations (input level) into a set of nodes in a rectangular grid with a given size (output level) based on similarities of input data, so that we can visualize complex high-dimensional data in a 2D map (SOM map). At the first stage of the clustering procedure, SOM transformed the standard scores (*z*-scores) of raw data into nodes, to reduce dimensionality using the *Kohonen* packages[31,32] in R. Those with similar input features were mapped to the nodes close together on the grid, and each node had values for all 17 features. The SOM map size was determined based on Kohonen's advice that the optimal number of nodes is $5\sqrt{N}$, where N is the number of observations.[33] We started with $5\sqrt{N}$ as an initial number of nodes (the maximum size) and then decreased the size until each node had at least one participant. A set of nodes (smaller than 1580) produced from the SOM algorithm was used as input data in the next step of *k*-means clustering, which partitioned all the SOM nodes into k distinct groupings. The optimal number of clusters for *k*-means clustering was selected from a range of cluster numbers ($k = 2$ to 8) based on cluster stability, which was assessed by resampling the data[34,35]: data were randomly split in half into training and test sets, and the SOM followed by *k*-means clustering (the *k*-means function in R) was carried out on training and test sets separately. The trained clustering solutions were used to predict clusters on test-set with K-nearest-neighbours classifier. The agreement of the predicted test-set clusters with the test-set clusters generated directly by the SOM/*k*-means algorithms was measured using adjusted Rand index[36] and Cramer's V[37]. These values were compared between cluster numbers from $k = 3$ to $k = 5$ using ANOVA. Multiple comparisons of $k = 4$ versus $k = 2$ and $k = 6$–8 were performed in a linear regression, and their *P*-values were adjusted with the Benjamini–Hochberg method. Higher values on Adjusted Rand Index (ARI) and Cramer's V indicate higher stability. The variance and intercorrelation of the features supported use of Mahalanobis distance,[38-40] instead of Euclidean distance for clustering.

Demographics, HIV disease characteristics, psychiatric and substance use, medical comorbidities, NC performance, and daily life functioning were summarized for each phenotype. Numeric variables were compared between phenotypes using a one-way analysis of variance. Categorical variables were compared using Pearson's χ^2 test. The variables significantly differing between the BPS phenotypes in the univariable analysis were included in a multinomial logistic regression model and were retained in the model if they remained associated with the BPS phenotype at $P < 0.10$. Multiple comparisons were performed between Phenotype 1 and other phenotypes and were adjusted using the Benjamini–Hochberg procedure.

To explore the relationships between objectively assessed NCI and self-reported cognitive symptoms (RCI), participants were also categorized into four subgroups: Participants who had both NCI (GDS $\geq$ 0.5) and RCI (PAOFI total score $\geq$ 3[7,29]) (NCI+/RCI+); those who had only NCI but without symptoms (NCI+/RCI−); those who reported only cognitive symptoms but without NCI (NCII–/RCI+); and those who had neither NCI nor symptoms (NCII–/RCII-). Fisher's exact test was used to determine whether the percentage of participants who had at least mild depression (BDI-II > 13) in each phenotype differed between subgroups, and multiple logistic regression was applied to evaluate the association of depression with NCI and RCI. Statistical analyses were performed using R version 3.6.3 (R Core Team, 2020). The significance level was set to $\alpha = 0.05$.

Results

Participants

This study included 1580 participants who enrolled between 2003 and 2010. Most [1212 (76.7%)] were male, and 368 (23.3%) were female. Mean age was 43.0 years (SD = 8.54), and the mean education was 12.6 years (SD = 2.61). Approximately half were Black (48.1%), followed by non-Hispanic White (39.9%), Hispanic (9.49%), Asian (0.063%) and other races (2.47%). Consistent with treatment practices at the time of enrolment, most participants (70.0%) took ART, and of those, 68.2% were virally suppressed (HIV RNA ≤ 200 copies/mL) in plasma. The most common ART regimens were (i) atazanavir, ritonavir (RTV), tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), (ii) efavirenz (EFV), TDF, and FTC, (iii) lopinavir, RTV, TDF and FTC, and (iv) EFV, zidovudine and lamivudine.

Biopsychosocial profile identification

About 100 nodes generated from the SOM algorithm in a 10×10 grid were used as input data for the k-means clustering. To determine an optimal number of clusters, we assessed cluster stability. The values on ARI and Cramer's V for $k = 2$ to 8 cluster solutions were visualized in boxplots (Supplementary Fig. 1). The similar median ARI and Cramer's V for the clustering solutions of $k = 3$, 4 and 5 indicated that they had similar stability (ARI, $F = 0.75$ and $P = 0.48$; Cramer's V, $F = 0.25$ and $P = 0.78$), which was more stable than the clustering solutions of $k = 6$–8 (e.g. $k = 4$ versus $k = 6$, ARI $t = 2.31$, $P = 0.023$; Cramer's V $t = 3.67$, $P < 0.001$) but less stable than $k = 2$ (e.g. $k = 4$ versus $k = 2$ ARI, $t = -6.03$ and $P < 0.001$; Cramer's V, $t = -12.6$ and $P < 0.001$). We selected $k = 4$ as the optimal number of clusters and then used Mahalanobis distance-based k-means clustering algorithm to generate 4 clusters, which assigned 41.5% ($n = 656$) participants to phenotype 1, 23.2% ($n = 366$) to phenotype 2, 14.1% ($n = 223$) to phenotype 3, and 21.2% ($n = 335$) to phenotype 4. Figure 1 shows the pattern of the 17 features for each phenotype: (i) Phenotype 1 had the best overall combined performance in cognition, depression, and daily functioning; (ii) Phenotype 2 had evidence of mild-to-moderate depression and mild problems with cognition and daily functioning; (iii) Phenotype 3 also had moderate depression, but worse cognitive impairment than Phenotype 2, and very impaired daily functioning; and (iv) Phenotype 4 had mild-to-moderate impaired cognitive performances but with relatively good mood, and daily functioning.

Clinical and demographic characteristics by phenotype

Participant characteristics by phenotype are summarized and compared in Table 1 (statistically significant differences between phenotypes) and Supplementary Table 1 (statistically non-significant differences). The four phenotypes had only marginal differences in age, body mass index and ART adherence and were comparable in ethnicity, current CD4+ T-cells, CSF HIV RNA, CNS penetration effectiveness rating,[41,42] haematocrit and serum aspartate aminotransferase (AST), total protein, albumin, total cholesterol, hypertension, hyperlipidaemia, head injury, total Veterans Aging Cohort Study Index, and lifetime alcohol, methamphetamine, cannabis, and opioid use disorders. Participants in Phenotype 1 had the highest mean education (13.0 years) and estimated premorbid intelligence [Wide Range Achievement Test (WRAT)-III 95.2], the highest proportions of employment (35.7%), mostly unimpaired objective NC performance, and the lowest proportion of Frascati-defined non-HIV conditions that would preclude attributing NCI or functional difficulties to HIV (6.1%).[1,20] Those in Phenotype 1 also had the lowest prevalence of DSP signs (32.6%), the fewest number of ART drugs ever used (mean, 5.32) and number of current non-ART medications (mean, 1.77), the lowest proportions of diabetes (6.86%), chronic pulmonary disease (CPD, 4.58%), and current nicotine use (33.2%). Participants in Phenotype 2 (mild-to-moderate depression and mild cognitive impairment and impairments in daily functioning) had the highest proportions of CPD (12.2%), lifetime cocaine use disorder (50.1%) and any substance use disorder (78.7%). Participants in Phenotype 3 (moderate depression and the worst self-reported symptoms and daily functioning) had the highest proportions of females (32.7%) and DSP signs (47.6%), the highest mean triglyceride levels (225 mg/dL), the lowest rate of current employment (13.9%), the largest number of current non-ART medications (mean, 3.26) and the most current nicotine use (43.1%). Phenotype 4 (mild-to-moderately impaired cognition) had the longest duration of HIV infection (mean, 61.0 months), the lowest mean WRAT-III score (87.6), the highest alkaline phosphatase level (mean, 103.9 IU/L) and the highest proportion of participants with AIDS (69.0%) and NCI (77.3%), but the lowest proportions of lifetime major depressive disorder (34.6%) and lifetime cocaine use disorder (36.8%) and any substance use disorder (67.5%).

Multivariable analysis determined that 10 variables significantly or marginally significantly associated with the BPS phenotype (Fig. 2). Participants who took more non-ART medications or had neuropsychiatric comorbidity were more likely to belong to the phenotypes having depression, or impairment in cognition or daily functioning (Phenotypes 2–4); females tended to be in Phenotype 3 more than male (OR = 1.92, $P = 0.004$); those who had lifetime cocaine use disorder or higher WRAT-III score were less likely to be in Phenotypes 3 or 4; those with CPD tended to be in Phenotypes 2 or 4; those having higher education were less likely to be in Phenotype 2 (OR = 0.92, $P = 0.029$); unemployed status was most frequent in Phenotypes 2 or 3. Those having longer ART exposure had a trend towards being in Phenotype 4 (OR = 1.04, $P = 0.11$). The P-values were adjusted for multiple comparisons with the Benjamini–Hochberg procedure.

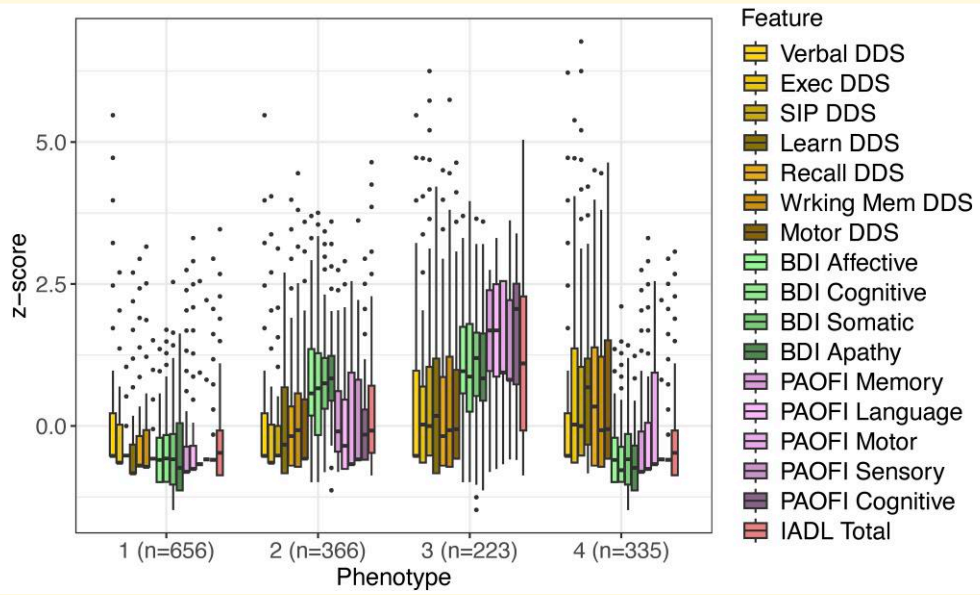


Figure 1 Boxplots representing the pattern of the 17 features for each phenotype. Four phenotypes were generated using SOM and *k*-means clustering algorithms with Mahalanobis distance. Higher z-score indicated worse outcome. DDS, domain deficit score; SIP, speed of information processing; Exec, executive function; Wrking Mem, working memory; BDI, the Beck depression inventory-II; PAOFI, the patient's assessment of own functioning inventory; ADL, instrumental activities of daily living.

NCI, cognitive symptoms, and depression

We were next interested in how the relationships between objective and subjective cognitive findings related to the phenotypes, specifically to depression. The distributions of NCI and cognitive symptoms by phenotype and the distributions of at least mild depressive symptoms (BDI-II > 13) by subgroup in each phenotype are displayed in the bar plots (Fig. 3). Most participants (58.5%) in Phenotype 1 were in the NCII−/RCII− group, which had more than 2-fold lower proportion of at least mild depression than the NCII−/RCI+ group (12.5 versus 29.9%, $P < 0.001$) and a marginally lower proportion of depression than the NCI+/RCI+ group (12.5 versus 22.5%, $P = 0.088$), but did not differ in the proportion of depression from the NCI+/RCI− group (12.5 versus 17.8%, $P = 0.35$). Multiple logistic regression determined people with RCI were more likely to be depressed (BDI-II > 13) than those without symptoms [OR (95% CI) = 2.68 (1.79, 4.01), $P < 0.001$], while mood symptoms did not differ between those with and without cognitive impairment [0.97 (0.54, 1.75)]. The results showed that RCI, but not objective cognitive impairment, were associated with at least mild depression in participants in Phenotype 1.

In Phenotype 2, most of the participants reported cognitive symptoms (36.6% in NCI+/RCI+ group and 43.2% in NCI−/RCI+ group), and all four groups had high proportions of depression (BDI-II > 13), from 83 to 88%. We found participants with concordant impairment (NCI+/RCI+) were more likely to be females than those with discordant impairment (NCI+/RCI−) or those with neither NCI nor symptoms [NCI−/RCI− (35.1 versus 20.8% and 22.3%, $P = 0.028$ and.073, respectively); Supplementary Table 2).

All participants in Phenotype 3 reported cognitive symptoms, yet only 59% had objective NCI. Both the NCI+/RCI+ and NCI−/RCI+ groups had high proportions of depression (≥88%), while participants with discordant impairment (NCI−/RCI+) reported lower mean education (11.6 versus 12.6 years, $P = 0.014$) but a higher proportion of lifetime substance use disorder (83.3 versus 69.3%, $P = 0.025$) than those with concordant impairment [NCI+/RCI+ (Supplementary Table 2)].

In Phenotype 4, one-third of the participants (32.5%) had both NCI and RCI (NCI+/RCI+), and 44.8% had NCI without symptoms (NCI+/RCI−). Approximately 30% of participants in the NCI+/RCI+ group reported depression compared to 12.0, 3.7 and 4.1% of those in the other three groups ($ps < 0.05$), indicating that the participants with concordant cognitive problems in Phenotype 4 were more likely to have depressed mood compared to those who had discordant or no impairment. Multiple logistic regression showed that both NCI and RCI were associated with depression in Phenotype 4 [OR (95% CI) = 5.65 (1.70, 18.8), $P = 0.0048$ and 2.80 (1.51, 5.18), $P = 0.0010$, respectively].

Discussion

Machine learning methods have been successfully applied to improve phenotypic and biological understanding of cognitive and mental health disorders in the general population,[43] including Alzheimer's Disease,[44] depression,[45]

Table 1 Participant characteristics that differ by phenotype

Characteristics	Phenotype 1 ($n = 656$)	Phenotype 2 ($n = 366$)	Phenotype 3 ($n = 223$)	Phenotype 4 ($n = 335$)	Overall *P*-value	Comparison[d]
Demographics						
Education (years)	13.0 (2.65)	12.2 (2.42)	12.2 (2.79)	12.7 (2.49)	<0.001	1 > 2, 3
Male	539 (82.2%)	268 (73.2%)	150 (67.3%)	255 (76.1%)	<0.001	1 > 2, 3, 4
WRAT-III reading score	95.2 (14.9)	91 (16.0)	88.4 (17.0)	87.6 (17.1)	<0.001	1 > 2, 3, 4
Employment	234 (35.7%)	74 (20.2%)	31 (13.9%)	87 (26.0%)	<0.001	1 > 2, 3, 4
Socioeconomic status[c]	40.7 (11.9)	44.1 (11.3)	45.2 (13.4)	43.0 (12.1)	<0.001	2, 3, 4 > 1
HIV disease characteristics						
AIDS diagnosis	368 (56.1%)	237 (65.5%)	144 (65.2%)	231 (69.0%)	<0.001	2, 3, 4 > 1
Duration of HIV (months)	50.4 (50.1)	56.6 (49.8)	58.3 (50.3)	61.0 (52.1)	0.002	2, 3, 4 > 1
Nadir CD4+ T-cells (/μL)	186 [41.8, 324]	170 [43.3, 294]	171 [50, 299]	133 [33.5, 256]	0.026	1 > 4
On ART	429 (65.4%)	261 (72.1%)	160 (72.1%)	256 (76.4%)	0.002	2, 4 > 1
Plasma HIV RNA ≤ 200 copies/mL	301 (46.8%)	176 (49.2%)	114 (52.5%)	183 (56.0%)	0.048	4 > 1
Number of ART drugs used ever	5.32 (3.97)	6.1 (3.88)	6.14 (3.84)	5.92 (3.89)	0.003	2, 3, 4 > 1
Number of non-ART medications	1.77 (2.18)	2.59 (2.5)	3.26 (2.49)	2.22 (2.25)	<0.001	2, 3, 4 > 1
Psychiatric and substance use						
BDI-II total score[a]	8.09 (6.03)	22.8 (8.17)	26.5 (10.2)	7.34 (5.52)	<0.001	2, 3 > 1
Lifetime major depressive disorder	276 (42.1%)	259 (71.8%)	155 (71.4%)	115 (34.6%)	<0.001	2, 3, 4 > 1
Lifetime cocaine use disorder	291 (44.4%)	181 (50.1%)	92 (42.4%)	122 (36.8%)	0.005	2 > 4
Lifetime any substance use disorder	479 (73.1%)	284 (78.7%)	163 (75.1%)	224 (67.5%)	0.009	2 > 4
Current nicotine use	218 (33.2%)	153 (41.9%)	96 (43.1%)	126 (37.8%)	0.011	2, 3 > 1
Medical comorbidities						
Diabetes	45 (6.86%)	31 (8.56%)	31 (14.0%)	26 (7.76%)	0.011	3 > 1
Chronic pulmonary disease	30 (4.58%)	44 (12.2%)	19 (8.56%)	32 (9.55%)	<0.001	2, 3, 4 > 1
DSP signs (≥2)	154 (32.6%)	95 (38.2%)	78 (47.6%)	101 (44.5%)	0.001	3, 4 > 1
Neuropsychiatric comorbidity (confounding)	40 (6.1%)	57 (15.6%)	64 (28.7%)	82 (24.5%)	<0.001	2, 3, 4 > 1; 3, 4 > 2[e]
Clinical chemistry						
Alkaline phosphatase[b] (IU/L)	91.6 (38.6)	100.5 (48.7)	102.3 (70.3)	103.9 (61.8)	0.001	2, 3, 4 > 1
Serum sodium (mEq/L)	139.1 (2.72)	139.0 (2.84)	139.0 (3.27)	138.5 (3.02)	0.037	1 > 4
Triglycerides[b] (mg/dL)	182.8 (143.7)	201.5 (166.3)	225.0 (158.5)	187.9 (131.6)	0.002	3 > 1
Serum glucose[b] (mg/dL)	96.9 (34.6)	100.7 (44.1)	106.8 (56.5)	103.5 (43.4)	0.005	3, 4 > 1; 3, 4 > 2[e]
Cognition						
Global scaled score	9.38 (1.85)	8.33 (1.72)	7.37 (1.83)	7.32 (1.72)	<0.001	1 > 2, 3, 4
GDS[a]	0.23 (0.27)	0.49 (0.38)	0.85 (0.74)	0.93 (0.59)	<0.001	2, 3, 4 > 1
Neurocognitive impairment	85 (13.0%)	160 (43.7%)	132 (59.2%)	259 (77.3%)	<0.001	2, 3, 4 > 1
Global *T*-score	49.7 (5.16)	46.0 (5.41)	42.3 (7.05)	41.7 (5.67)	<0.001	1 > 2, 3, 4
Domains' *T*-score						
Verbal fluency	50.1 (9.35)	49.1 (8.05)	44.9 (9.44)	47.2 (8.94)	<0.001	1 > 3, 4
Speed of information processing	52.7 (7.45)	48.7 (7.74)	44.1 (9.61)	43.5 (8.57)	<0.001	1 > 2, 3, 4
Learning	46.1 (7.31)	41.5 (7.69)	38.0 (8.54)	36.8 (8.0)	<0.001	1 > 2, 3, 4
Recall	49.4 (6.82)	44.7 (8.89)	41.9 (9.74)	39.6 (9.17)	<0.001	1 > 2, 3, 4
Working memory	48.8 (8.37)	44.8 (8.32)	41.6 (8.47)	41.8 (8.28)	<0.001	1 > 2, 3, 4
Executive function	49.5 (7.6)	46.7 (7.68)	43.3 (9.11)	41.8 (8.59)	<0.001	1 > 2, 3, 4
Motor	50.0 (8.78)	45.2 (8.85)	41.2 (10.7)	40.4 (11.4)	<0.001	1 > 2, 3, 4
Daily functioning						
Total PAOFI score[a]	2.77 (3.83)	6.86 (4.72)	20.3 (6.44)	3.38 (4.47)	<0.001	2, 3, 4 > 1
PAOFI complaints (total score ≥3)	227 (34.6%)	292 (79.8%)	223 (100%)	136 (40.6%)	<0.001	2, 3 > 1
Total ADL score[a]	1.18 (1.45)	2.82 (2.42)	5.18 (3.47)	1.56 (1.78)	<0.001	2, 3, 4 > 1
ADL dependence (total score ≥2)	191 (29.1%)	243 (66.4%)	192 (86.1%)	123 (36.7%)	<0.001	2, 3, 4 > 1

Variables with *P*-value > 0.05 not included in Table 1 are in Supplemental Table 1. ART, antiretroviral therapy; BDI-II, beck depression inventory-II; DSP, distal symmetric polyneuropathy; GDS, neurocognitive global deficit score; ADL, activities of daily living; IU, international units; PAOFI, assessment of own functioning inventory; WRAT, wide range achievement test; values are mean (SD) or number of cases (%). [a]Square root; [b]$\log_{10}$ transformations prior to comparative analysis; [c]a composite that is based on each participant's education and job of highest responsibility; [d]Three pairs comparisons (2, 3, and 4 versus 1, where 1 = Phenotype 1; 2 = Phenotype 2; 3 = Phenotype 3; 4 = Phenotype 4) were performed and adjusted using the Benjamini–Hochberg procedure for multiple comparisons ($k = 3$); [e]Adding a comparison between Phenotype 2 and Phenotype 4 ($k = 4$).

schizophrenia, and bipolar disorder.[46] Using machine learning, we identified four distinct, clinically meaningful, and complex BPS phenotypes among PWH, characterized by differences in NC performance, depressive mood symptoms, cognitive symptoms, and dependence on daily activities that are important in PWH, such as medication management. We demonstrated that 41.5% of the participants scored well across the 17 features, 23.2% had predominantly mild-to-moderate depression, 14.1% had multidimensional problems (mild-to-moderate cognitive impairment, moderate-to-severe depression, and very impaired daily functioning), and 21.2% had isolated mild-to-moderate cognitive impairment. The identification of a large group with preserved cognition, mood and daily activities is particularly

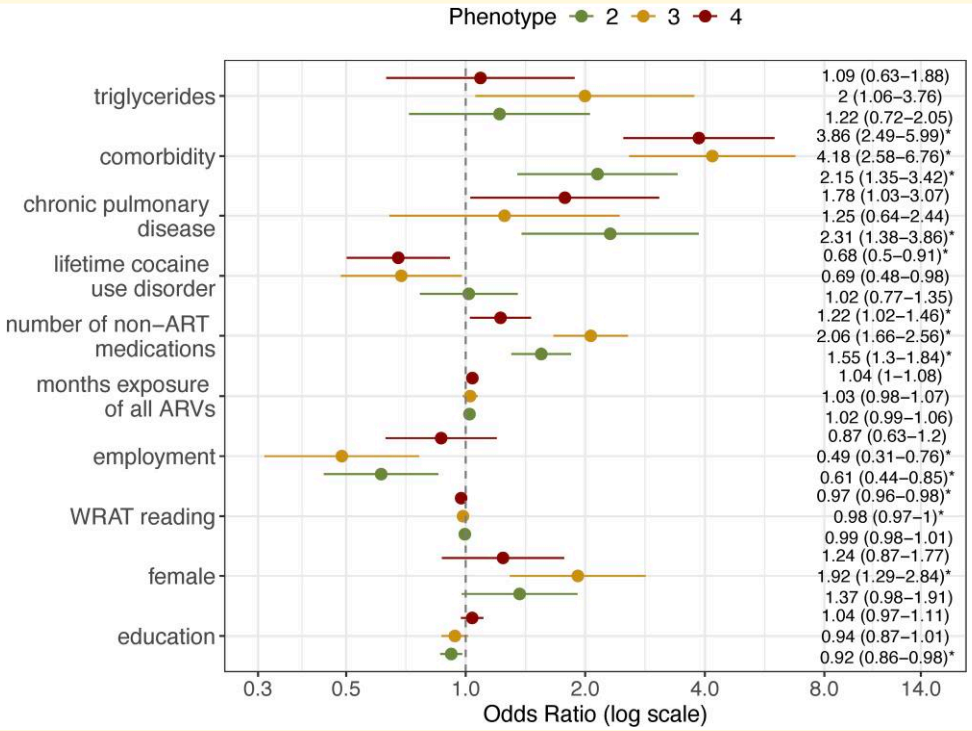


Figure 2 Odds ratios of a multinomial logistic regression model. Summary of the effects of demographics, HIV disease characteristics, medical comorbidities, substance use and clinical chemistry on the BPS phenotypes. Odds ratio ranges were calculated relative to Phenotype 1. The number of participants in Phenotypes 1–4 was 656, 366, 223 and 335, respectively. Error bar represents 95% confidence interval and * denotes $P < 0.05$ after multiple comparison correction using the Benjamini Hochberg procedure. LT, lifetime; CPD, chronic pulmonary disease; Dx, diagnosis; ART, antiretroviral therapy; ARVs, antiretroviral drugs; WRAT, wide range achievement test.

important, as it may facilitate the future discovery of interventions to optimize these domains of functioning in the other groups.

The study also aimed to investigate the relationship between objective and subjective cognitive problems and depression. Participants were categorized into four subgroups based on objectively assessed NCI and RCI: NCI–/RCI–, NCI+/RCI–, NCI–/RCI+, and NCI+/RCI+. The results showed that RCI, but not cognitive impairment, were associated with at least mild depression in participants of Phenotype 1. Participants in Phenotype 2 with concordant impairment (NCI+/RCI+; objective and self-reported cognitive impairment) were more likely to be females than those with discordant impairment (NCI+/RCI–) or those with neither objective nor self-reported cognitive difficulties. This suggests that females may have more accurate self-perceptions than males. Participants in Phenotype 3, on average, had self-reported cognitive difficulties, yet only 59% had objective NCI. This harmonizes with previous studies demonstrating that individuals with depression tend to have an unrealistically negative self-perception of their abilities.

In many past analyses, characteristic features of HIV infection have been found to differentiate groups. For example, Rubin *et al.*[15] demonstrated HIV disease variables as strong determinants of cognitive profiles in both women and men. In our study, however, demographics (e.g. sex, employment), number of non-ART medications, and medical and substance use comorbidities showed stronger relationships to cluster membership than did HIV disease characteristics such as viral suppression and total duration of ART exposure, indicating that HIV characteristics may be minor contributors in the diversity of the BPS phenotypes. We did find differences across the BPS phenotypes in education and estimated premorbid intelligence, which are commonly used as proxies of cognitive reserve. Cognitive reserve is defined as the ability to maintain optimal NC function.[47] A study found that higher educational attainment was associated with a lower proportion of NCI, defined using Frascati criteria, in a cohort of virologically suppressed older PWH (≥60 years old) and suggested a protective role of cognitive reserve against cognitive decline.[48] Similarly, better-estimated premorbid intelligence was protective against a decline in processing speed in women who exposed to chemotherapy for breast cancer.[49] Our analyses showed that PWH in Phenotype 1 had better-estimated premorbid intelligence than those in the other phenotypes. In addition, previous studies report that sex is a contributor to the heterogeneity in cognitive function among PWH and that women with HIV are more likely to demonstrate cognitive deficits than males with HIV.[15,50] We observed that participants having either depression or cognitive impairment (Phenotypes 2–4),

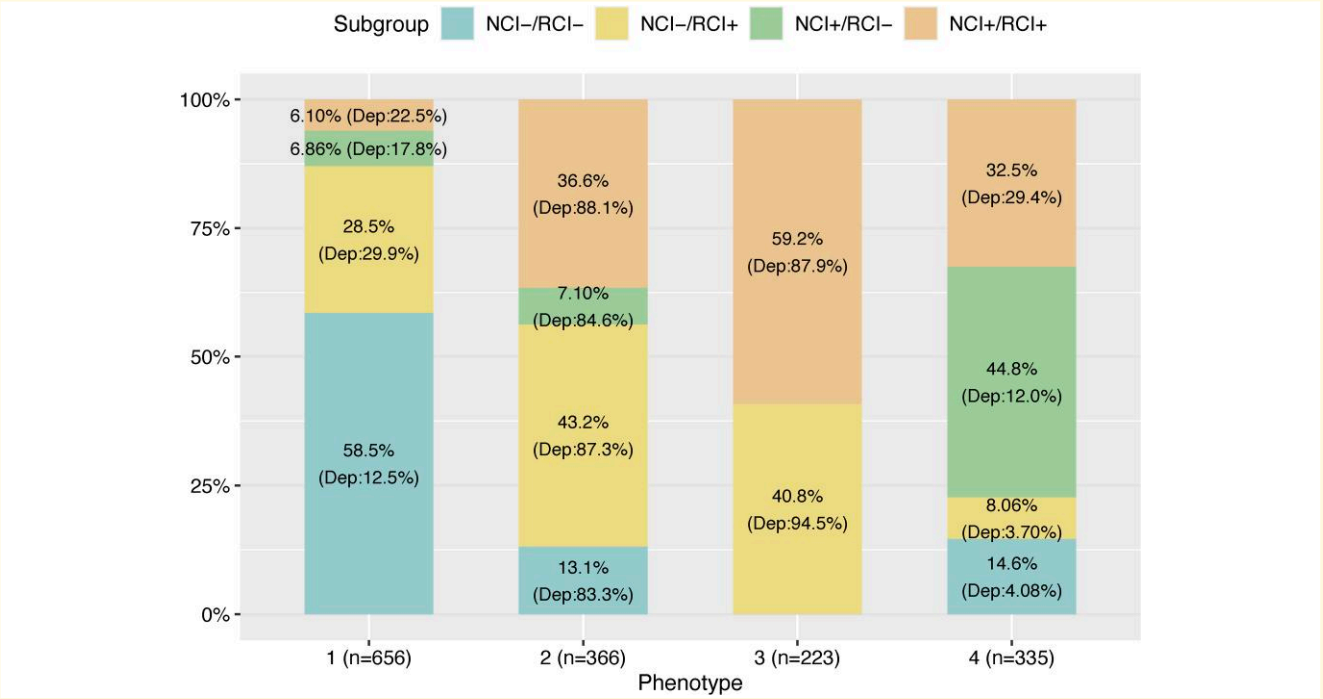


Figure 3 Barplots showing distributions of cognition and depression (in parenthesis; Dep, depression) by phenotype. Relationship of depression with concordant and discordant impairments was determined. NCI+/RCI+, both NCI and RCI; NCI+/RCI−, only NCI but without symptoms; NCI−/RCI+, only cognitive symptoms but without NCI; NCI−/RCI−, neither NCI nor symptoms; a BDI-II score of > 13 indicates depression. Proportions of depression between the subgroups were compared in each phenotype using Fisher's exact test: for Phenotype 1, the NCI−/RCI+ group reported more frequent depression than the NCI−/RCI− group (29.9 versus 12.5%, $P < 0.001$); for Phenotype 2, proportions of depression in all groups were high (from 83% to 88%, $P = 0.66$); for Phenotype 3, the NCI−/RCI+ (94.5%) and NCI+/RCI + (87.9%) groups had high proportions of depression ($P = 0.11$); for Phenotype 4, the NCI+/RCI+ group (29.4%) had higher proportion of depression than the other three groups (12.0, 3.70 and 4.08%; *p*s < 0.05). NCI, neurocognitive impairment; RCI, self-reported cognitive symptoms.

especially having both and impaired daily functioning, were more likely to be women than those in Phenotype 1, suggesting that depression and cognitive impairment are more common in women with HIV than men with HIV.

The potential value of identifying these phenotypes lies in the possibility that they reflect different underlying pathogenic mechanisms, which could influence response to therapies. Past clinical trials, for example, likely would have enrolled people in both Phenotypes 3 and 4 but they might respond very differently to the intervention: those in Phenotype 3 might respond best to antidepressant medications and cognitive behavioural therapy, whereas those with more isolated NC impairment in Phenotype 4 might benefit most from neuroprotective medications (e.g. intranasal insulin, iptakalim, antibody to interferon alpha and beta receptor subunit 2, letermovir, physical exercise and ketogenic diet).[51] The groups that differed in medical and neuropsychiatric conditions might also benefit from optimization of general clinical management (beyond managing only their HIV disease). While the current analyses focus on defining these phenotypes, future analyses will focus on validating them in independent cohorts and better understanding their biological distinctions.

The relative independence of the identified phenotypes from HIV disease and treatment characteristics (except for very disparate Phenotypes 1 and 4) indicates that these clinically important outcomes in PWH are probably significantly influenced by host factors apart from HIV itself. Whether these factors are genetic, environmental, or otherwise is an important consideration. For example, if molecular pathways underlying genetic vulnerabilities to these phenotypes can be identified, perhaps those associated with persistent inflammation, then interventions to manipulate these pathways, such as anti-inflammatory medications or probiotics, could be leveraged to treat or prevent adverse outcomes. Emerging evidence suggests that comorbidities such as diabetes mellitus, DSP and CPD, rather than HIV and treatment factors, by themselves, increasingly drive poor outcomes.[52-54]

The strengths of this study include the focus on multiple factors in the determination of the phenotypes, large size of the cohort, its racial, ethnic, and geographic diversity, and the comprehensive, multidimensional clinical and laboratory assessments. The multicentre design enhances the generalizability of the findings. While other investigators have evaluated changing clinical phenotypes in the modern ART era,[55,56] previous studies have not benefitted from the rich dataset analysed here. In addition, we used Mahalanobis distance instead of Euclidean distance to generate better clustering performances. The *k*-means clustering algorithm with Mahalanobis distance took account of variance and intercorrelation of the features.

This study has several limitations. The number of female participants was relatively small, though it approximated the proportion of women with HIV in the United States. The data are from the baseline assessments in CHARTER, which were performed between 2003 and 2010. For this reason, a substantial proportion of participants had not achieved viral suppression. While this may reduce generalizability to PWH in care today, we found that viral suppression was not associated with the BPS phenotypes in multivariable models, which suggests that the BPS phenotypes are not driven by HIV replication. In the present study, although a two-stage procedure (including both SOM and *k*-means algorithms) was used for clustering, we should compare this procedure with other algorithms such as hierarchical clustering and model-based clustering (latent profile analysis) on principal components, to find out the most appropriate algorithm and number of clusters in CHARTER data via assessing stability of clustering. In addition, when validating clustering stability, we used the nearest-neighbours classifier to transfer clustering solutions generated in the training set to the test-set. Based on the least-cost-increase strategy proposed,[35] the nearest centroid classifier would produce better prediction results for the *k*-means algorithm; hence we might underestimate the stability values. The phenotypes should be validated in independent samples and be strengthened by analyses of longitudinal trajectories. Even with these limitations, the findings advance work in understanding neuropsychiatric phenotypes in PWH. If these novel phenotypes do have distinct underlying biological mechanisms, then their identification may lead to better therapies that improve the burden of these complications on PWH and better maintain functional capacity and life quality.

Supplementary material

Supplementary material is available at *Brain Communications* online.

Acknowledgements

Thank Dr Raha Dastgheyb and Dr Leah Rubin for sharing their work with us about cluster analysis using machine learning methods. The CNS HIV Anti-Retroviral Therapy Effects Research (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, PhD, Scott L. Letendre, MD, Ronald J. Ellis, MD, PhD, Christine Fennema-Notestine, PhD, Rebecca Theilmann, PhD, Amanda Bischoff-Grethe, Bin Tang, Clint Cushman, Debra Cookson, Matthew Dawson and Donald Franklin, Jr; Johns Hopkins University Site: Leah Rubin, PhD (P.I.); Icahn School of Medicine at Mount Sinai Site: Susan Morgello, MD (P.I.), Letty Mintz, N.P.; University of California, San Diego Site: J. Allen McCutchan, MD (P.I.); University of Washington, Seattle Site: Christina Marra, MD (P.I.); University of Texas, Galveston Site: Benjamin Gelman, MD, PhD (P.I.), Eleanor Head, R.N., B.S.N.; and Washington University, St. Louis Site: David Clifford, MD (P.I.), Beau Ances, MD, PhD, Muhammad Al-Lozi, MD, Mengesha Teshome, MD.

Funding

This study was supported by grants from the National Institutes of Health (R01 MH107345, R01 MH125720, R24 MH129166, and N01 MH22005).

Competing interests

The authors report no competing interests.

Data availability

The data that were analysed are available from the National NeuroAIDS Tissue Consortium-CHARTER Data Coordinating Center (https://www.nntc.org/content/relationship-charter) upon request. The code supporting the findings of this study is available upon reasonable request to the authors.

References

1. Heaton RK, Clifford DB, Franklin DR Jr, *et al.* HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology*. 2010;75:2087-2096.
2. Song MK, Ward SE, Bair E, *et al.* Patient-reported cognitive functioning and daily functioning in chronic dialysis patients. *Hemodial Int*. 2015;19:90-99.
3. Gokhale RH, Weiser J, Sullivan PS, Luo Q, Shu F, Bradley H. Depression prevalence, antidepressant treatment status, and association with sustained HIV viral suppression among adults living with HIV in care in the United States, 2009–2014. *AIDS Behav*. 2019;23:3452-3459.
4. Bing EG, Burnam MA, Longshore D, *et al.* Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Arch Gen Psychiatry*. 2001;58:721-728.
5. Orlando M, Burnam MA, Beckman R, *et al.* Re-estimating the prevalence of psychiatric disorders in a nationally representative sample of persons receiving care for HIV: Results from the HIV cost and services utilization study. *Int J Methods Psychiatr Res*. 2002;11:75-82.
6. Basu S, Chwastiak LA, Bruce RD. Clinical management of depression and anxiety in HIV-infected adults. *AIDS*. 2005;19:2057-2067.
7. Blackstone K, Moore DJ, Heaton RK, *et al.* Diagnosing symptomatic HIV-associated neurocognitive disorders: Self-report versus performance-based assessment of everyday functioning. *J Int Neuropsychol Soc*. 2012;18:79-88.
8. Channon S, Green PS. Executive function in depression: The role of performance strategies in aiding depressed and non-depressed participants. *J Neurol Neurosurg Psychiatry*. 1999;66:162-171.
9. Joormann J, Gotlib IH. Emotion regulation in depression: Relation to cognitive inhibition. *Cogn Emot*. 2010;24:281-298.
10. Rourke SB, Halman MH, Bassel C. Neurocognitive complaints in HIV-infection and their relationship to depressive symptoms and

neuropsychological functioning. *J Clin Exp Neuropsychol*. 1999; 21:737-756.
11. Thames AD, Kim MS, Becker BW, *et al*. Medication and finance management among HIV-infected adults: The impact of age and cognition. *J Clin Exp Neuropsychol*. 2011;33:200-209.
12. Mukerji SS, Petersen KJ, Pohl KM, *et al*. Machine learning approaches to understand cognitive phenotypes in people with HIV. *J Infect Dis*. 2023;227(Suppl 1):S48-S57.
13. Paul RH, Cho KS, Luckett P, *et al*. Machine learning analysis reveals novel neuroimaging and clinical signatures of frailty in HIV. *J Acquir Immune Defic Syndr*. 2020;84:414-421.
14. Dastgheyb RM, Buchholz AS, Fitzgerald KC, *et al*. Patterns and predictors of cognitive function among virally suppressed women with HIV. *Front Neurol*. 2021;12:604984.
15. Rubin LH, Sundermann EE, Dastgheyb R, *et al*. Sex differences in the patterns and predictors of cognitive function in HIV. *Front Neurol*. 2020;11:551921.
16. Justice AC. HIV and aging: Time for a new paradigm. *Curr HIV/AIDS Rep*. 2010;7:69-76.
17. Marquine MJ, Montoya JL, Umlauf A, *et al*. The veterans aging cohort study (VACS) Index and neurocognitive change: A longitudinal study. *Clin Infect Dis*. 2016;63:694-702.
18. Marquine MJ, Sakamoto M, Dufour C, *et al*. The impact of ethnicity/race on the association between the veterans aging cohort study (VACS) index and neurocognitive function among HIV-infected persons. *J Neurovirol*. 2016;22:442-454.
19. Marquine MJ, Umlauf A, Rooney AS, *et al*. The veterans aging cohort study index is associated with concurrent risk for neurocognitive impairment. *J Acquir Immune Defic Syndr*. 2014;65:190-197.
20. Antinori A, Arendt G, Becker JT, *et al*. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69: 1789-1799.
21. Heaton RK, Miller SW, Taylor JT, Grant I. *Revised comprehensive norms for an expanded halstead-reitan battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults*. Psychological Assessment Resources; 2004.
22. Norman MA, Moore DJ, Taylor M, *et al*. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, brief visuospatial memory test-revised, stroop color and word test, and wisconsin card sorting test 64-card version. *J Clin Exp Neuropsychol*. 2011;33: 793-804.
23. Carey CL, Woods SP, Gonzalez R, *et al*. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *J Clin Exp Neuropsychol*. 2004;26:307-319.
24. Blackstone K, Moore DJ, Franklin DR, *et al*. Defining neurocognitive impairment in HIV: Deficit scores versus clinical ratings. *Clin Neuropsychol*. 2012;26:894-908.
25. Beck AT, Steer RA, Brown OK. *Beck depression inventory manual*, 2nd edn. Psychological Corporation; 1996.
26. Castellon SA, Hardy DJ, Hinkin CH, *et al*. Components of depression in HIV-1 infection: Their differential relationship to neurocognitive performance. *J Clin Exp Neuropsychol*. 2006;28:420-437.
27. Chelune GJ, Heaton RK, Lehman RAW. Neuropsychological and personality correlates of patients' complaints of disability. In: Goldstein G, Tarter RE, eds. *Advances in clinical neuropsychology*. Plenum Press; 1986:95-118.
28. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179-186.
29. Woods SP, Rippeth JD, Frol AB, *et al*. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. *J Clin Exp Neuropsychol*. 2004;26:759-778.
30. Vesanto J, Alhoniemi E. Clustering of the self-organizing map. *IEEE Trans Neural Netw*. 2000;11:586-600.
31. Wehrens R, Buydens LMC. Self- and super-organizing maps in R: The kohonen package. *J Stat Softw*. 2007;21:1-19.
32. Wehrens R, Kruisselbrink J. Flexible self-organizing maps in kohonen 3.0. *J Stat Softw*. 2018;87:1-18.
33. Kohonen T. *Self-organizing maps*. 3rd ed. *Springer series in information sciences*. Springer; 2001:501.
34. Breckenridge JN. Replicating cluster analysis: Method, consistency, and validity. *Multivariate Behav Res*. 1989;24:147-161.
35. Lange T, Roth V, Braun ML, Buhmann JM. Stability-based validation of clustering solutions. *Neural Comput*. 2004;16:1299-1323.
36. Hubert LaA P. Comparing partitions. *J Classif*. 1985;2:26.
37. Agresti A. *An introduction to categorical data analysis. Wiley series in probability and statistics*. Wiley; 1996:xi:290 pages: illustrations.
38. Nelson JD. On k-means clustering using Mahalanobis distance. MS thesis, NDSU, USA. 2012:47.
39. Lahav A, Talmon R, Kluger Y. Mahalanobis distance informed by clustering. *Inform Inference J IMA*. 2019;8:377-406.
40. Brown PO, Chiang MC, Guo SQ, *et al*. Mahalanobis distance based K-means clustering. *Big Data Anal Knowl Discovery, Dawak 2022*. 2022;13428:256-262.
41. Letendre S, Marquie-Beck J, Capparelli E, *et al*. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008; 65:65-70.
42. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic complications of HIV disease and their treatment. *Top HIV Med*. 2010; 18:45-55.
43. Iyortsuun NK, Kim SH, Jhon M, Yang HJ, Pant S. A review of machine learning and deep learning approaches on mental health diagnosis. *Healthcare (Basel)*. 2023;11:285.
44. Wang Y, Gao R, Wei T, *et al*. Predicting long-term progression of Alzheimer's disease using a multimodal deep learning model incorporating interaction effects. *J Transl Med*. 2024;22:265.
45. Lee KS, Ham BJ. Machine learning on early diagnosis of depression. *Psychiatry Investig*. 2022;19:597-605.
46. Montazeri M, Montazeri M, Bahaadinbeigy K, Montazeri M, Afraz A. Application of machine learning methods in predicting schizophrenia and bipolar disorders: A systematic review. *Health Sci Rep*. 2023;6:e962.
47. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8:448-460.
48. Milanini B, Ciccarelli N, Fabbiani M, *et al*. Cognitive reserve and neuropsychological functioning in older HIV-infected people. *J Neurovirol*. 2016;22:575-583.
49. Ahles TA, Saykin AJ, McDonald BC, *et al*. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: Impact of age and cognitive reserve. *J Clin Oncol*. 2010; 28:4434-4440.
50. Rubin LH, Neigh GN, Sundermann EE, Xu Y, Scully EP, Maki PM. Sex differences in neurocognitive function in adults with HIV: Patterns, predictors, and mechanisms. *Curr Psychiatry Rep*. 2019;21:94.
51. Ellis RJ, Marquine MJ, Kaul M, Fields JA, Schlachetzki JCM. Mechanisms underlying HIV-associated cognitive impairment and emerging therapies for its management. *Nat Rev Neurol*. 2023;19: 668-687.
52. Ellis RJ, Paolillo E, Saloner R, Heaton RK. Higher comorbidity burden predicts worsening neurocognitive trajectories in people with human immunodeficiency virus. *Clin Infect Dis*. 2022;74:1323-1328.
53. Cysique LA, Brew BJ. Vascular cognitive impairment and HIV-associated neurocognitive disorder: A new paradigm. *J Neurovirol*. 2019;25:710-721.
54. Yu B, Pasipanodya E, Montoya JL, *et al*. Metabolic syndrome and neurocognitive deficits in HIV infection. *J Acquir Immune Defic Syndr*. 2019;81:95-101.
55. De Francesco D, Underwood J, Bagkeris E, *et al*. Depression, lifestyle factors and cognitive function in people living with HIV and comparable HIV-negative controls. *HIV Med*. 2019;20:274-285.
56. Sacktor N. Changing clinical phenotypes of HIV-associated neurocognitive disorders. *J Neurovirol*. 2018;24:141-145.