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ABSTRACT

Objective: Cognitive deficits are common among people with HIV (PWH), even when virally-suppressed. We identified cognitive profiles among virally suppressed PWH and determined how socio-demographic, clinical/behavioral, and HIV disease characteristics distinguish profile membership.

Methods: Participants included 704 virally-suppressed PWH (mean age=43.9 [SD=10.2], 88% male, 58.9% non-Hispanic White) from the HIV Neurobehavioral Research Program. Demographically-adjusted T-scores were derived from a neuropsychological evaluation comprised of 13 tests. We implemented a pipeline involving dimension reduction and clustering to identify profiles of cognitive performance. Random forest models on a 70/30 training/testing set with internal cross-validation were used to identify sociodemographic, clinical/behavioral, and HIV disease correlates of profile membership.

Results: Six cognitive profiles were identified: (1) "unimpaired" (19.9%); (2) weakness in verbal learning and memory (15.5%); (3) weakness in executive function and learning (25.8%); (4) weakness in motor, processing speed, and executive function (8.1%); (5) impaired learning and recall with weak-to-impaired motor, processing speed and executive function (13.1%); (6) global deficits (17.6%). The most discriminative sociodemographic, clinical/behavioral, and HIV disease characteristics varied by profile with self-reported mood symptoms and cognitive/functional difficulties (e.g., language/communication, memory and overall everyday function complaints) most consistently associated with profile membership.

Conclusions: Cognitive profiles and their associated factors among PWH are heterogeneous, but learning/memory deficits were most common and self-reported mood and cognitive/functional difficulties most consistently related to profile membership. This heterogeneity in cognitive profiles and their correlates in PWH suggests that differing mechanisms contribute to cognitive deficits and, thus, underscores the need for personalized risk reduction and therapeutic strategies among PWH.

Key words: HIV, cognitive profiles, mood symptoms, cognitive difficulties

KEY POINTS

- Are there common profiles of cognitive impairment among virally-suppressed PWH and what are their sociodemographic and health-related correlates?
- We found that profiles of cognitive impairment were heterogeneous among PWH although learning/memory deficits were most common and self-reported mood and cognitive/functional difficulties most consistently related to profile membership.
- Findings suggest that differing mechanisms contribute to cognitive deficits among PWH and, thus, personalized approaches are needed for risk reduction and therapeutic strategies for cognitive impairment.
- Future research should examine cognitive profiles in relation to biomarkers to inform mechanism and test the trajectory of the profile groups over time.

INTRODUCTION

Degrees of cognitive impairment (CI) short of frank dementia are common among people with HIV (PWH) despite viral suppression on combination antiretroviral therapy (cART); however, milder forms of CI persist in nearly half of PWH (Grant, 2008; Heaton et al., 2011; Wang et al., 2020; Woods et al., 2009). Although the specific cognitive domains affected in PWH are highly variable (Heaton et al., 1995, 2011), the predominant impairments also shifted in the cART era from attention/working memory, motor, and processing speed to that of learning, memory (delayed recall) and executive dysfunction in both cortical and subcortical networks (Cysique et al., 2004; Dawes et al., 2008; Heaton et al., 2011; Plessis et al., 2014; Sacktor, 2018). This heterogeneity suggests that the CI is inadequately characterized as a single syndrome, but rather as multiple syndromes, each with distinct risk factors, biological mechanisms, and outcomes. Despite this observed variability in CI, the bulk of our research regarding CI in PWH uses diagnostic approaches that do not account for the patterns of CI, but instead rely on the presence of any CI in at least two cognitive domains (i.e., Frascati Criteria for HIV-Associated Neurocognitive Disorders, HAND; (Antinori et al., 2007). Sole reliance on HAND diagnoses, without exploration of CI patterns, may limit our understanding of the risk factors, biological mechanisms, and outcomes of CI among PWH and, ultimately, our ability to appropriately and effectively intervene.

Prior studies have described the complexity of CI among PWH by employing cluster techniques to identify patterns of CI and their correlates among PWH (Dawes et al., 2008; Fazeli et al., 2014; Gomez et al., 2019; Lojek & Bornstein, 2005; Pasipanodya et al., 2021; van Gorp et al., 1993). Almost all these studies identified multiple CI subtypes that differed with respect to the specific cognitive domains impaired and the CI severity, and the specific clusters tended to be highly variable across studies. Most (Gomez et al., 2019; Lojek & Bornstein, 2005; May et al., 2020; Pasipanodya et al., 2021; van Gorp et al., 1993), but not all (Dawes et al., 2008) detected a cluster with impairment across all or most domains reflecting global impairment. Most studies also demonstrated a cluster with unimpaired cognitive performance (Lojek & Bornstein, 2005; Pasipanodya et al., 2021; Rubin, Sundermann, et al., 2020; van Gorp et al., 1993) or strengths in certain domains based on normative data from a cognitively healthy, sample without HIV (Dawes et al., 2008; Rubin, Sundermann, et al., 2020). Studies examining correlates of each subtype found unique correlates, including sociodemographic, clinical comorbidities and HIV disease variables (Fazeli et al., 2014; Gomez et al., 2019; Lojek & Bornstein, 2005; Pasipanodya et al., 2021)

Although these prior studies have improved our understanding of the complexity of CI among PWH, several important knowledge gaps remain. The characterization of cognitive profiles strictly among

PWH who have suppressed plasma HIV RNA remains unclear as prior cognitive profiling studies included PWH with and without viral suppression (VS). This is important as the risk factors and mechanisms of CI differ between those with poorly-treated HIV and those with well-treated HIV. Additionally, recent studies show that the correlates of CI among PWH may be more strongly tied to chronic comorbidities, long-term ART effects and psychosocial risk factors than HIV disease variables (Milanini & Valcour, 2017; Nightingale et al., 2014). VS PWH also face the challenges of risk for age-associated comorbidities (including neurodegenenerative diseases), which may further complicate CI profiles and their correlates. The mechanisms of persistent inflammation, metabolic dysregulation, oxidative stress, and cerebrovascular disease are characteristic of both chronic HIV infection and aging without HIV and are risk factors for Alzheimer's disease (AD) (Alisky, 2007; Cohen et al., 2015; Cruse et al., 2012; Deeks, 2011). Finally, there is the challenge of distinguishing early symptoms of progressive neurodegenerative diseases amid the typically mild and stable CI among PWH. Data-driven cognitive profiling analyses in adult VS PWH may help to identify age-associated contributions to CI and in distinguishing symptoms more reflective of a neurodegenerative disease trajectory. For example, AD and its precursor, amnestic mild cognitive impairment (aMCI), tend to have a more hippocampal-based, cortical pattern of memory impairment (e.g., encoding and retention deficits) (Hyman et al., 1984; R. C. Petersen et al., 1999; Sperling et al., 2010) compared to the more frontal/subcortical pattern typically observed in PWH with CI (retrieval deficit with normal or near normal retention) (Becker et al., 1995; Peavy et al., 1994; White et al., 1997).

In the present study, we used machine learning methods to identify different cognitive profiles in a large cohort of adult PWH who had VS. All participants had comprehensive neuropsychological evaluations conducted at the HIV Neurobehavioral Research Program (HNRP) at the University of California, San Diego. To differentiate memory impairment subtypes, and because they may have different impairment profiles among different neurodegenerative diseases, the memory outcomes of learning, delayed recall and recognition were individually entered into the model. Next, we determined how sociodemographic (e.g., age, education, race/ethnicity), clinical/behavioral (e.g., daily functioning status, mood symptoms and diagnoses, comorbid conditions, substance use disorders) and HIV disease (e.g., CD4 count, nadir CD4, estimated duration of HIV disease) factors related to cognitive profiles. Based on prior literature (Dawes et al., 2008; Gomez et al., 2019; Lojek & Bornstein, 2005; Pasipanodya et al., 2021; van Gorp et al., 1993), we hypothesized that the machine learning approach would identify distinct subgroups of individuals with normal cognitive functioning, global CI across all cognitive domains, and cognitive impairment in subsets of cognitive domains, and that sociodemographic and non-HIV clinical/behavioral factors would discriminate cognitive profiles, beyond risks related to HIV disease severity variables. We hypothesized further that, among those with memory impairment, clusters of distinct cortical and

frontal/subcortical memory impairment profiles would be identified and that the cortical memory impairment profile (i.e., deficits in encoding, recall and recognition) will be more strongly associated with AD-related risk factors (e.g., older age, female sex, diabetes, hypertension) as compared to the frontal/subcortical memory profile (i.e., better recognition relative to recall).

MATERIALS AND METHODS

Participants

We analyzed the baseline data of 704 virally-suppressed PWH enrolled in various NIH-funded research studies at the University of California San Diego's HNRP, https://hnrp.hivresearch.ucsd.edu/. All baseline visits were complete between 1999 and 2018. Exclusion criteria for the parent studies were history of non-HIV-related neurological, medical, or psychiatric disorders that affect brain functioning (e.g., seizure, stroke, psychosis), learning disabilities, and a first language that was not English. Inclusion criteria for the current study were VS and completion of all neuropsychological tests; however, participants were allowed to have missing data for the sociodemographic, clinical/behavioral and HIV disease factors examined in relation to cognitive profiles. VS was defined as plasma HIV-1 RNA below the lower limit of quantification of 50 copies/mL as measured by RT-PCR (Amplicor, Roche Diagnostic System). An additional exclusion criterion for the current study was detection of drugs with addictive potential (excluding marijuana) via urine testing or a positive alcohol Breathalyzer test at the study visit. [BLINDED] approved all studies that provided data for analysis. Participants provided written informed consent and were compensated for their participation.

Neuropsychological (NP) Test Battery

Cognitive performance was evaluated through a comprehensive standardized NP test battery. Complex motor skills were assessed by the Grooved Pegboard (GPEG) Dominant and Non-dominant Hand tests (Kløve, 1963). Executive functioning was assessed by the Trail Making Test (TMT)-Part B (cognitive flexibility) (Reitan & Wolfson, 1985), the Paced Auditory Serial Addition Task (PASAT-50; working memory) (Diehr et al., 2003; Gronwall, 1977), and Controlled Oral Word Association Test (COWAT; verbal fluency) (Borkowski et al., 1967). Verbal learning, memory and recognition was assessed by the the Hopkins Verbal Learning Test Revised (HVLT) Total Learning, Delayed Recall and Delayed Recognition scores, respectively (Brandt & Benedict, 2001). Visual learning, memory and recognition was assessed by the Brief Visuospatial Memory Test Revised (BVMT) Total Learning, Delayed Recall and Delayed Recognition scores, respectively (Benedict, 1997). Information processing speed was assessed by the WAIS-III Digit Symbol Test (Wechsler, 2008) and the TMT-Part A. Raw test scores were converted into age-, education-, sex-, and race/ethnicity-adjusted T-scores based on normative

data from a HIV-uninfected sample (Heaton et al., 2004; Norman et al., 2011). By using demographically-adjusted T-scores, we controlled for the effects of demographic characteristics on cognition that are typically observed in the general population in order to examine how these demographic characteristics related to cognition specifically in the context of HIV. *Impairment* on a NP test outcome was defined as greater than one standard deviation (SD) below the normative mean (T-score<40) and *weakness* on an NP test was defined as a 0.5-1 SD below the normative mean (T-score=40-44).

Socio-demographic, clinical, and HIV disease characteristics

We examined sociodemographic, clinical/behavioral, and HIV disease characteristics that have been previously associated with cognition and were available in enough participants to allow for adequately powered analyses.

Sociodemographic characteristics: Age, sex at birth, years of education, and race/ethnicity were self-reported and reading level (a proxy for cognitive reserve) is based on the Wide Range Achievement Test-4 Reading subtest (WRAT4) (Wilkinson & Robertson, 2006).

Clinical/Behavioral characteristics: Self-reported daily functioning was assessed by the Patients Assessment of Own Functioning Inventory (PAOFI) (Chelune et al., 1986), which included the subscales of cognitive function, language and communication and memory and the total score across subscales. Higher PAOFI scores reflect poorer functioning. The estimated number of daily activities with decreased independence was assessed from the Instrumental Activities of Daily Living questionnaire (IADL) from the modified version of the Lawton and Brody Activities of Daily Living Questionnaire (Lawton & Brody, 1969). Higher IADL scores reflect better everyday function. Depressive symptoms were assessed by the Beck Depression Inventory versions I (BDI-I) or II (BDI-II) (Beck et al., 1996), with higher scores reflecting greater depressive symptoms. Mood symptoms were assessed by the Profile of Mood States (POMS) (McNair, D.M., Lorr, M., Droppleman, 1981), which included the dimensions of tension and anxiety, confusion and bewilderment, anger or hostility, depression or dejection, fatigue or inertia, vigor or activity and a total score across dimensions. Higher POMS scores reflect greater mood disturbance, respectively. The diagnosis of lifetime and current major depressive disorder (MDD) as based on the Composite International Diagnostic Interview (CIDI version 2.1) (Wittchen, 1994) using Diagnostic Statistical Manual IV (DSM-IV) criteria. Current and lifetime substance use disorders based on DSM–IV criteria for alcohol, cannabis amphetamine, cocaine, hallucinogen, inhalant, sedative, opioid, and phencyclidine were provided by the CIDI and collapsed across abuse and dependence diagnoses. A structured clinical interview assessed the clinical

comorbidities of hypertension, hyperlipidemia, diabetes, cancer, chronic pulmonary disease, and the use of anticholinergic medications, which are known to adversely affect cognition (Andre et al., 2019; Rubin et al., 2018). Body mass index (BMI) was calculated from measured height and weight.

HIV disease characteristics: HIV disease characteristics were determined via a combination of self-report (e.g., estimated duration of HIV disease) and laboratory tests (e.g., CD4+ T-cell count). Nadir CD4+ T-cell count was the lowest lifetime value by self-report, study-obtained CD4+ T-cell count, or released medical records. CD4+ T-cell count was measured by flow cytometry. Hepatitis C serostatus was determined by MedMira Multiplo rapid test (MedMira Inc.). ART use was self-reported and confirmed via review of medical regimen records if available. Distribution of ART drugs into the CNS was estimated using the CNS penetration effectiveness (CPE) value (Arentoft et al., 2022; Letendre et al., 2008).

Statistical analyses

The NP tests were used to find groups of similar cognitive profiles using a dimension reduction and clustering pipeline as previously described (Dastgheyb et al., 2021; Rubin, Sundermann, et al., 2020). For this clustering analysis, the input data consisted of continuous T-Scores for each of the NP tests. Dimension reduction was achieved with Kohonen self-organizing maps (SOM) from the Kohonen package in R (Wehrens & Buydens, 2007) and followed by clustering using gaussian mixture models via the MClust package in R (Fraley et al., 2014). By using SOM and MClust in sequence, we were able to achieve fine-tuned clustering based on patterns of performance on the NP tests. After clustering was completed, the identified profiles were manually assigned descriptive names based on patterns observed in each profile, taking into account categorical descriptives of weakness and impairment as well as cognitive domains typically associated with the NP tests.

An ”unimpaired” profile was named based on having average T-Scores for each test that were not considered weak or impaired (T-Score >45). This is the profile to which all the other profiles were compared. Factors predicting profile membership between each impaired profile and the unimpaired profile were investigated in two ways – using both traditional statistical methods as well as machine learning ensemble models. Tables reflecting univariate differences variables were calculated using ANOVA’s on the available unimputed data. Using machine learning models to further investigate potential non-linear interactions we created a predictive Random Forest (RF) modeling using the Caret (Kuhn, 2008) package in R and then extracted variable importance (Kuhn, 2012). Random Forest models are ensemble models that use non-linear combinations of input variables to best separate the outcome classes. They are well-suited for datasets with missing data and multi-collinearity, and studies

using data simulations have shown that predictive power and variable importance metrics are maintained even in the presence of highly correlated variables[1,2]. Prior to model creation, variables were removed as predictors if they had low variance or if they had greater than 50% missing data (Supplementary Table 1). To address unbalanced data sets, Synthetic Minority Over-sampling Technique (SMOTE) was implemented with the DMwR (Torgo, 2013) package. Any missing data in the remaining variables was imputed using the Multivariate Imputation by Chained Equations (Buuren & Groothuis-Oudshoorn, 2011) (MICE) package in R using random forest imputations and ridge regression (size of 0.0001 for a compromise between stability and unbiasedness). RF models were created using 5 separate internal 10x cross-validations as a resampling scheme. They were evaluated based on accuracy and F1 scores which represent the harmonic mean of precision and recall and are more representative of performance than the accuracy metric in the case of unbalanced datasets. After model creation, all predictor variables were plotted by relative variable importance, and attention was given to the top ten variables in each profile. While the machine learning approach is advantageous in identifying the strongest predictors among a large set of correlated variables, it does not provide information on the directionality of the relationship between the predictor and the outcome. Univariate analyses were conducted to indicate the directionality of the relationship between each of the top ten predictor variables and the outcome.

RESULTS

Sample

Participants included 704 VS-PWH with 83% reporting ART use (**Table 1**). The most common ART regimens were efavirenz/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (10%), ritonavir-boosted atazanavir (ATV+RTV)+FTC/TDF (5%), and cobicistat-boosted elvitegravir+FTC+tenofovir alafenamide (5%). On average, participants were 43.9 ± 10.2 years of age with 13.8 ± 2.7 years of education. Eighty-eight percent were male and 59% were non-Hispanic White. The prevalence of current alcohol (4%) and substance use disorders (16%) was low, whereas the prevalence of lifetime alcohol (33%) and substance use (64%) disorders was high, with cannabis, cocaine and methamphetamine being the most common substances reported. Forty-seven percent of the sample reported a history of MDD and 16% reported current MDD. Medical comorbidities were also common including hypertension (27%) and hyperlipidemia (20%) and hepatitis C seropositivity (19%). With respect to cognition, the average T-score for all NP tests fell in the below average to average range (between 42 and 48) (**Table 2**). HVLT Total Learning and Delayed Recall scores were the lowest observed average scores.

Cognitive Profiles among VS-PWH

Profiling of the 704 VS-PWH resulted in six profiles using an ellipsoidal multivariate mixture model with equal orientation (VVE) with an entropy of 0.98. The profiles are depicted in **Figure 1** and univariable differences between the profiles on NP outcomes are provided in **Table 3**. Six profiles were identified. For each profile we describe the top important predictor variables from the machine learning models and where applicable we include the *P*-values from the univariate statistical tests to enhance interpretation and directionality.

- **Profile 1 (n=140): Normal/unimpaired** was indicated by a majority of mean T-scores for each NP test falling into the normal/average range between 45 and 55 (averaged across all participants assigned to this profile). Mean TMT-A and TMT-B T-scores were >55 suggesting relative strengths in processing speed and executive function.
- **Profile 2 (n=109): Weaknesses in auditory verbal learning and memory** was indicated by weaknesses on the HVLT Total Learning and Delayed Recall scores. All other NP outcomes were preserved.
- **Profile 3 (n=182): Weaknesses in executive function and learning** was indicated by weaknesses on executive function outcome measures (PASAT-50 and COWAT) and on both measures of learning (HVLT and BVMT). All other NP outcomes were preserved.
- **Profile 4 (n=57): Weaknesses in motor, processing speed, and executive function was** indicated by weaknesses on complex motor skills (GPEG), processing speed (TMT-A, Digit Symbol), and executive function (PASAT-50, COWAT, TMT-B). All learning and memory outcomes were preserved.
- **Profile 5 (n=92): Impaired learning, memory (spared recognition) and motor function with weak processing speed and executive function** was indicated by performance in the impaired range on all learning and memory outcomes (HVLT and BVMT) and performance in the weak-to-impaired range on motor (GPEG), processing speed (TMT-A, Digit Symbol), and executive function outcomes (PASAT-50, COWAT, TMT-B). All recognition outcomes and verbal fluency were preserved.
- **Profile 6 (n=124): Global deficits defined by impaired learning, memory and recognition and weak motor, processing speed, and executive function** was indicated by impairment in learning, memory, and recognition on the HVLT and BVMT as well as weaknesses on motor (GPEG), processing speed (TMT-A, Digit Symbol), and executive function outcomes (PASAT-50, COWAT, TMT-B).

Factors Distinguishing Cognitively Unimpaired and Other Profiles.

RF models were created to identify variables that distinguished each profile from the unimpaired profile without needing to assume a linear relationship. Variable importance was calculated and those that ranked as the top ten variables were identified and are depicted in **Figure 2**. None of the top 10 predictor variables were missing more than 15% of their cases prior to imputation except for disease duration, which was missing in 25% of the population. The top variables distinguishing impaired profiles from the normal/unimpaired profile were education, age, WRAT4, race/ethnicity, subjective ratings of difficulties with cognition and everyday function (PAOFI and Lawton), mental health complaints (POMS, BDI), BMI and the HIV disease *variables* of CD4+ T-cell count, estimated duration of HIV infection, and CPE.

- **Profile 2 (n=109): Weaknesses in auditory verbal learning and memory** (Accuracy = 0.97, F1 = 0.97): Compared to persons in Profile 1, those in Profile 2 were more educated (14.5 vs. 13.6 years, *P*=0.004), reported more overall cognitive difficulties (*P*=0.001) particularly in memory (*P*=0.001) as well as overall IADL losses of independence (*P*=0.004). Members of Profile 2 were also more likely to report greater confusion/bewilderment (*P*=0.002), depression/dejection (*P*=0.03), and tension/anxiety (*P*=0.058) as well as less vigor/activation (*P*=0.03) on the POMS than Profile 1. BDI scores were also marginally higher in persons in Profile 2 versus 1 (*P*=0.14).
- **Profile 3 (n=182): weaknesses in executive function and learning** (Accuracy = 0.92, F1 = 0.92): Compared to persons in Profile 1, those in Profile 3 were younger (42 vs. 45 years old, *P*=0.01), had lower WRAT4 reading scores (98 vs. 104, *P*<0.001) and higher CPE scores (*P*=0.12), and self-rated more overall cognitive difficulties (*P*<0.001), particularly in higher level cognitive and intellectual function (*P*<0.001) on the PAOFI as well as more overall IADL independence losses (*P*=0.005). Members of Profile 3 were also more likely to report greater anger/hostility (*P*=0.007) and tension/anxiety (*P*=0.01), and less vigor/activation (*P*=0.05) on the POMS.
- **Profile 4 (n=57): Weaknesses in motor, processing speed, and executive function** (Accuracy = 0.86, F1 = 0.89): Compared to persons in Profile 1, those in Profile 4 were more likely to be Hispanic/Latinx (25% vs. 11%, *P*=0.05) and less educated (12.5 vs. 13.5 years, *P*=0.002), had lower WRAT4 reading scores (101 vs. 104, *P*=0.08), and self-rated more memory difficulties on the PAOFI (*P*<0.001). Members of Profile 4 were also more likely to report anger/hostility (*P*=0.03) and less vigor/activation (*P*=0.04) on the POMS than members of Profile 1.
- **Profile 5 (n=92): impaired learning, memory (spared recognition) and motor function with weak processing speed and executive function** (Accuracy = 0.96, F1 = 0.97): Compared to

persons in Profile 1, those in Profile 5 self-rated more overall cognitive difficulties (P<0.001) particularly on in higher level cognitive and intellectual function (P<0.001) and language and communication on the PAOFI (P<0.001) as well as more overall IADL dependence (P<0.001). Members of profile 5 also reported more mood disturbances overall (P=0.001) and in particular anger/hostility on the POMS (P=0.005) as well as greater depressive symptoms on the BDI (P=0.01) versus those in Profile 1. Those in profile 5 also had lower CD4+ T-cell counts (nadir and at the time of assessment, P's<0.05) than those in Profile 1. No socio-demographic factors differed between these profiles.

- **Profile 6 (n=124): global deficits defined by impaired learning, memory and recognition and weak motor, processing speed, and executive function** (Accuracy = 0.99, F1 = 0.99): Compared to persons in Profile 1, those in Profile 6 had lower WRAT4 reading scores (98 vs. 104, P<0.001) and greater self-rated language and communication difficulties on the PAOFI (P<0.001). Members in Profile 6 also reported greater overall mood disturbances (P<0.001) particularly in tension/anxiety (P<0.001), depression/dejection (P<0.001), confusion/bewilderment (P<0.001), and anger/hostility (P=0.003) and less vigor/activation on the POMS (P=0.009) compared to those in Profile 1. Members in Profile 6 also reported more depressive symptoms on the BDI versus those in Profile 1 (P<0.001).

Discussion

In this large-scale cross-sectional study, we applied our novel pipeline combination of machine learning methods to provide additional evidence in support of heterogeneity in cognition in VS-PWH. As expected, we were able to identify distinct cognitive profiles (in our case six) that included a normal/unimpaired cognitive profile and five profiles demonstrating domain-specific cognitive impairments and/or weaknesses. Although these six clusters differed in terms of the combination of cognitive domains with deficits and the degree of deficits, there were also some similarities or overlap across the clusters. In general, deficits in learning, memory, and executive function were most commonly observed across profiles, which is consistent with the shift in the most common deficits in HAND from the pre- to post-cART era with learning, memory and executive function deficits replacing motor and psychomotor deficits as the most common manifestations (Cysique et al., 2004; Dawes et al., 2008; Heaton et al., 2011; Plessis et al., 2014; Sacktor, 2018). Additionally, the most common impairment/weakness profile was one indicating weaknesses in learning and executive function (Profile 3, n=183) whereas the least common impairment/weakness profile indicated weaknesses in motor, processing speed, and executive function with preserved learning and memory (Profile 4, n=57). Although Profile 6 showed performance in the weak to impaired range across domains, it is notable that

a globally impaired profile did not emerge that may be due to our focus on VS rather than mixed samples of virally suppressed and not suppressed PWH.

Identification of six distinct cognitive profiles among VS-PWH is consistent with some, but not all, studies in PWH with others demonstrating three or four profiles. Clustering approaches are data driven and the ideal number of profiles will differ depending on the sample size, the relationships between the input data variables, and the chosen evaluation metric. Differences in the number of cognitive profiles across studies also is not surprising given differences including participants' age, years of education, race/ethnicity (e.g., range for percent White, non-Hispanic was 14% to 79% across studies), biological sex (range for percent male was 0 to 100%), viral suppression status (range 42% to 100%), as well as the prevalence and severity of global cognitive impairment and medical and psychiatric comorbidities. Additional differences are likely due to the number/type of NP tests administered, normative standards employed, and the number of NP outcomes included in the clustering algorithm. The sample size (range 144 to 1666) as well as the type of clustering approach also differed across studies (e.g., SOM + mClust, k-means, latent class analysis, hierarchical clustering + k-means). Despite the differences in the number of cognitive profiles identified across studies, there were some similarities in the types of cognitive profiles. For example, we identified a normal/unimpaired profile that is consistently seen across studies. We identified a profile of weaknesses in auditory learning and memory that was previously demonstrated in three other studies, (Lojek & Bornstein, 2005; Pasipanodya et al., 2021), and one of which focused on VS-PWH where all participants were female (Dastgheyb et al., 2021). However, in contrast to most studies, we did not identify a profile indicative of global impairment/weaknesses.

By including individual outcomes from our learning/memory tests (i.e., learning, delayed recall, recognition), we were able to identify more subtle differences in memory impairment profiles across clusters. The pattern of learning and recall impairment with spared recognition performance in Profile 5 reflects a more retrieval-based frontal/subcortical memory impairment profile that has been previously characterized in PWH, likely due to the preponderance of subcortical neuropathological changes associated with HIV infection (Aili et al., 2022; Becker et al., 1995; Doyle et al., 2019; Peavy et al., 1994; White et al., 1997). In support of this, HIV-related disease variables related more to Profile 5 than any other Profile, whereas sociodemographic factors did not relate. This suggests that the cognitive deficits in Profile 5 may be due, in part, to legacy (or other) effects of HIV disease (irreversible brain injury) despite successful VS or to brain insult that may have occurred in the pre-cART era. In contrast, the learning, recall and recognition impairment in Profile 6 reflects encoding, retrieval and retention

deficits that are typical of cortical-based 'rapid forgetting' memory impairment profile in HIV-uninfected patients on the AD trajectory (R. C. Petersen et al., 1999). The possibility stands that the cortically-based memory impairment in Profile 6 may be driven by a subset of PWH experiencing a pathogenesis similar to AD or AD-related dementias.

In prior work, we exploited the difference in retention deficits between cortical versus subcortical dementia by adapting the actuarial Jak/Bondi criteria for aMCI (Bondi et al., 2014) to require recognition impairment (more common in aMCI/AD) to identify potential aMCI cases among PWH. In support for this adapted diagnostic method, we found that aMCI classification related to a higher likelihood of amyloid-β (Aβ) plaque deposition in the frontal cortex in a postmortem sample of older (age 50+) PWH (Sundermann et al., 2021). While the well-established AD risk factors of older age, female sex, hypertension and diabetes did not relate to Profile 6 membership, interpretation of this should be considered in light of the low prevalence of older PWH, females and diabetes in our total sample. Profile 2 showed weakness limited to auditory learning and memory, which is characteristic of single-domain aMCI, often a precursor to AD dementia, again raising the question of whether age-associated neuropathogenic pathways may contribute to the heterogeneity in cognitive profiles among VS-PWH. The reason why the learning/memory weakness was specific to auditory (not visual) memory is unclear. Such discrepancy between impaired or weak auditory-verbal memory and intact visual or visuospatial is a common finding in left temporal pathologies, particularly those targeting the hippocampus, such as left mesial temporal sclerosis, which is a common cause of temporal lobe epilepsy (Hermann et al., 1987). Prodromal neurodegenerative disorders can initially present unilaterally (e.g., Parkinsonian movement disorder symptoms; primary progressive aphasia), and our finding of weaker verbal vs. visual memory may be consistent with the notion of unilateral pathogeneity. It is also true that measures of auditory-verbal memory are more sensitive to language dominant (typically left) temporal dysfunction than their visuospatial counterparts are to non-dominant (typically right) temporal dysfunction. Follow-up studies including brain MRI scanning could be helpful in identifying underlying temporal lobe pathology in this subgroup. Future longitudinal studies with biomarker data would have immense value in identifying stability versus change trajectories of these clusters and determining potential biological mechanisms underlying profiles including age-associated neurodegenerative disease pathways.

With respect to the correlates of cognitive profiles in VS-PWH, we found that sociodemographic and clinical/behavioral factors in general provided better discrimination than HIV disease variables. Among the sociodemographic factors, only WRAT4 reading score, a proxy for educational attainment and cognitive reserve, consistently related to profile membership (except for Profile 5), which indicates the

importance of cognitive reserve in cognitive impairment and/or weakness profiles in VS-PWH. WRAT4 reading scores have been consistently identified as a determinant of cognitive function among PWH (Fazeli et al., 2011; Manly et al., 2011; Sundermann et al., 2018). Dawes et al. (2008) found that only WRAT-3 scores (in addition to race) were associated with cluster membership. Reading level also may be a proxy for sociodemographic and clinical/behavioral factors underlying general health (e.g., socioeconomic status, self-efficacy) (Baker et al., 1998). Aside from the WRAT4 scores, sociodemographic factors such as age, biological sex, race, and education did not emerge among the top 10 important variables; this is likely because the T-scores used for clustering were demographically-adjusted for these factors (Sundermann et al., 2018).

Among the clinical/behavioral factors, subjective ratings of mood disturbances and everyday cognitive/function difficulties were the strongest and most consistent factors to distinguish cognitive profiles; however, there was heterogeneity in the specific type of mood disturbance or cognitive/function complaint that related to each profile. Conversely, clinically-diagnosed mood and substance use disorders and clinical comorbidities were not important factors. Current substance use disorders were not common in the overall sample (16%). Additionally, we only examined the major cardiovascular risk factors of hypertension, hyperlipidemia, and diabetes. One possibility is that other unmeasured medical comorbidities may be associated with the profiles such as kidney or liver disease or anemia. With respect to mood, numerous studies demonstrate relationships between mood symptoms, in particular depression and anxiety, and cognitive function in PWH (Paolillo et al., 2020; Rubin et al., 2014; Rubin & Maki, 2019). However, whether mood symptoms have a causative role in cognitive impairment or whether they have shared neuropathogenic pathways remains unknown. Possible mechanisms underlying the mood-cognition association in PWH include alterations in HPA axis function which can lead to blunted cortisol levels (Rubin et al., 2022; Rubin, Langenecker, et al., 2020) as well as neurotoxic effects of chronically elevated glucocorticoid levels (Sapolsky, 2000) and cytokine-driven inflammation (Bekhbat et al., 2017).

Subjective experience of cognitive and functional difficulties, as measured by the PAOFI were determinants of membership in each profile, demonstrating associations with objective cognitive weakness or impairment in some clusters more than others. In the dementia literature, these subjective experiences have been suggested as a valuable indicator of early, subtle cognitive change that is often not detected using one-time cognitive testing (Jessen, 2014). However, the dementia literature also suggests that the accuracy of subjective cognitive/functional difficulties have been inconsistent across clinical and demographic groups, with some showing very weak relationships (Howieson et al., 2015;

Mendonça et al., 2016) and others showing high correlation with depression, anxiety and other non-cognitive factors that may cloud rather than clarify diagnosis or progression (Edmonds et al., 2014). Among PWH, self-report of everyday functioning declines has shown validity (Morgan et al., 2012; Scott et al., 2011; Vigil et al., 2008); however, self-report of general cognitive ability has shown to be less accurate (Blackstone et al., 2012). One factor potentially contributing to this inconsistency is the relationship between subjective experiences of functional changes and mood symptoms, particularly depressive symptoms (Edmonds et al., 2014; Grambaite et al., 2013; Ryu et al., 2016; Slavin et al., 2010). Among PWH, self-reported cognitive deficits are often related to affective distress rather than objective cognitive performance (Blackstone et al., 2012; Hinkin et al., 1996; Juengst et al., 2012; van Gorp et al., 1991). In the current sample, PAOFI scores and scores on the POMS and BDI were conjointly associated with membership in most profiles and showed small-to-moderate, significant relationships with each other across most domains (R=0.3-0.5) suggesting that one symptom type may be driving the otherThe degree of cognitive impairment in a sample may also contribute to inconsistency in the relationship between subjective and objective cognition/function. Individuals with more objectively-detectable cognitive deficits may tend to underestimate their memory decline (Edmonds et al., 2014; Fragkiadaki et al., 2016; Grambaite et al., 2013; Ryu et al., 2016), and this pattern has been found among PWH as well (Casaletto et al., 2014; Chiao et al., 2013; Juengst et al., 2012). This loss of insight to one's own cognitive abilities may reflect our own results in that Profile 6 membership related to the least number of PAOFI domains.

Despite considerable overlap in the cognitive domains with deficits across the profiles, each profile related to a distinct panel of sociodemographic, clinical/behavioral and HIV disease factors. This suggests that there are a number of different factors leading to cognitive deficits in PWH and these factors reflect the influences of psychosocial stressors, mood, cognitive reserve, age-related and HIV-related mechanisms, and cardiovascular risk factors and the interactions among these factors. The overlap in the cognitive domains affected across profiles suggest that cognitive rehabilitation or training strategies that target a specific cognitive domain may benefit a large portion of PWH; however, optimal risk reduction strategies may differ from one individual to the next contingent upon a background of sociodemographic, clinical/behavioral and medical variables. Cognitive profiling methods will also inform aging-related effects on cognition in the context of HIV and perhaps early clinical indicators of age-related neurodegenerative disease that will help clinicians to distinguish early-stage neurodegenerative disease such as aMCI from HAND and to intervene and treat appropriately.

Our study has limitations that should be considered when interpreting results. Our analyses were cross-sectional, which precluded us from determining the longitudinal stability or evolution of cluster membership, and the temporal relationships between the sociodemographic, clinical/behavioral, and HIV disease characteristics and cognitive function. Although many of the related factors may be risk factors for cognitive impairment, reverse causality is possible with some of the factors resulting from cognitive impairment (e.g., depression, IADL impairments). Because our study focused on characterizing cognitive profiles among VS-PWH, we did not include a HIV-seronegative comparison group. Thus, we cannot determine the degree to which HIV contributes to the cognitive profiles although HIV disease variables were associated with membership of some profiles suggesting that HIV has a role. It would be beneficial and informative if certain biomarkers of HIV-associated cognitive impairment such as inflammatory markers could be integrated into these phenotype classifications; however, this data was not available to us. We did not include ART regimens as predictors in models because it is outside of the scope of this study focused on characterizing cognitive profiles in the context of viral suppression and due to the limitation of random forest modelling given the more than 100 unique regimens in our sample. However, given that certain types of ART regimens have been linked to adverse neuropsychiatric and neurocognitive outcomes) (Prats et al., 2021; Rubin et al., 2021; Spence et al., 2022), we acknowledge that ART regimen is informative to cognitive profiles and encourage future studies to examine this topic with the appropriate modelling approaches. The nature of the RF models also presents a barrier for interpretation. Of all ensemble machine learning models it is one of the most interpretable when we examine the variable importance metrics, but it is important to keep in mind that the non-linear nature of the model means that the importance of each variable in distinguishing profile membership is calculated in the context of every other variable. This is why some of the most important variables identified by the RF model do not show significant differences in univariate analysis. Therefore, the results of these models should be construed as hypothesis-generating models that identify variables for further investigation.

Constraints on generality

The generalizability of our results is limited since our sample is comprised strictly of PWH who volunteered for a research study in Southern California. Although the high male to female ratio and the average level of education (13.8 years) of our sample align with the demographics of the HIV positive population in San Diego County, they do not correspond to the broader HIV positive population in the U.S (Center for Disease Control, 2023), which limits the generalizability of our findings. Additionally, data on important social determinants of health were not available to us, such as lifetime trauma, stress, housing stability, etc. As these social determinants of health have been found to relate to

cognitive and brain health among PWH (Dastgheyb et al., 2021; Js et al., 2019; K. J. Petersen et al., 2023), this limited our ability to characterize the cognitive profiles and understand the factors driving them. While some work has been done examining social determinants of health in relation to cognitive health among PWH (Dastgheyb et al., 2021; Js et al., 2019; K. J. Petersen et al., 2023), more work is needed in large and diverse cohorts. Our prior findings suggest sex differences in the cognitive profiles of PWH (Rubin, Sundermann, et al., 2020); however, the small proportion of women in our sample (12%) precluded sex-stratified analyses that would be adequately powered. Lastly, it is worth noting that efavirenz and atazanavir were part of the most common ART regimens in our sample (although only in 15%) and, given evidence of their adverse cognitive effects, may have influenced results. Because these ARTs are no longer prescribed, generalizability of our results may be limited in future samples.

Conclusion

In conclusion, our results indicate heterogeneity both in the cognitive profiles and in the sociodemographic, clinical/behavioral and HIV disease factors associated with specific cognitive profiles among PWH. Even within cognitive domains, there was variability in impairment profiles as evidenced by the presence of cortical versus frontal/subcortical memory impairment profiles. These differing profiles suggest that aging and age-related neurodegenerative disease may be contributing to the heterogeneity, particularly since the lifespan of VS-PWH tends to approach that of the general population. Data-driven profiling methods such as those utilized in the present study may help to identify factors that could be leveraged to distinguish early-stage AD (e.g., aMCI) from HIV-associated cognitive impairment, especially when coupled with biomarker and longitudinal trajectory data in future studies. Mood-related and self-rated cognitive/functional difficulties were the factors that were most consistently associated across profiles; however, there was heterogeneity in the specific type of mood or cognitive/function complaints that related to each profile. This finding suggests that interventions to improve mood symptoms might mitigate their adverse health impact on both physical and cognitive health. By identifying cognitive profiles and underlying mechanisms, we seek to inform developments in personalized risk reduction and therapeutic strategies for cognitive impairment and functional losses among VS PWH. Again, future longitudinal research is needed to examine the stability of these profiles over time and whether a certain profile is a risk factor for future decline and other clinically important outcomes.

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Table 1. Sociodemographic, clinical/behavioral, and HIV disease characteristics in the total sample (N=704) of virally suppressed people with HIV.

	M (SD)
Age	44 (10)
Male	623 (88)
Years of education	13.8 (2.7)
Wide Range Achievement Test-4 (WRAT4) reading score	100 (13)
Race, n (%)	
White	415 (59%)
Black	129 (18%)
Hispanic	127 (18%)
Other	33 (5%)
Instrumental Activities of Daily Living (IADL) total score	2.2 (2.6)
Beck Depression Inventory (BDI) total score	13 (10)
Patients Assessment of Own Functioning Inventory (PAOFI)	
Total score	6 (7)
Higher cognitive functions subscale (e.g., executive functions)	1.4 (2.2)
Language and communication subscale	1.8 (2.3)
Memory subscale	2.4 (2.8)
Profile of Mood States (POMS)	
Total score	63 (40)
Tension or anxiety dimension	10 (7)
Confusion or bewilderment dimension	8.0 (5.8)
Anger or hostility dimension	8 (9)
Depression or dejection dimension	12 (13)
Fatigue or inertia dimension	9 (7)
Vigor or activity dimension	16 (7)
World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH-CIDI)	

Current major depressive disorder, n (%)	90 (16%)
Lifetime major depressive disorder, n (%)	258 (47%)
Current alcohol use disorder, n (%)	24 (4.4%)
Lifetime alcohol use disorder, n (%)	182 (33%)
Current substance use disorder, n (%)	33 (16%)
Lifetime substance use disorder, n (%)	297 (64%)
Use of medications with anticholinergic properties, n (%)	189 (27%)
Hypertension, n (%)	182 (27%)
Hyperlipidemia, n (%)	138 (20%)
Diabetes, n (%)	47 (6.9%)
Body mass index	26.4 (4.9)
Hepatitis C virus (HCV) seropositive, n (%)	128 (19%)
CD4+ T-cell count	540 (301)
Nadir CD4+ T-cell count	239 (225)
Estimated duration of HIV infection	11 (8)

M=mean; SD=standard deviation

Table 2. Neuropsychological test performance in the total sample (N=704) of virally suppressed people with HIV.

	Mean T-score (SD)	Range
Brief Visuospatial Memory Test Revised (BVMT)		
Total Learning	45 (10)	20-77
Delayed Recall	45 (11)	10-79
Recognition	45 (13)	0-64
Hopkins Verbal Learning Test Revised (HVLT)		
Total Learning	42 (12)	0-71
Delayed Recall	42 (12)	12-71
Recognition	44 (14)	0-71
Paced Auditory Serial Addition Task (PASAT-50)	45 (11)	13-75
WAIS-III Digit Symbol Test	47 (11)	15-86
Trail Making Test (TMT)		
Part A	48 (12)	6-87
Part B	46 (12)	5-88
Controlled Oral Word Association Test (COWAT)	48 (11)	12-78
Grooved Pegboard (GPEG)		
Dominant hand	46 (12)	8-84
Non-dominant hand	45 (11)	9-79

SD=standard deviation. T-scores are adjusted for age, sex, education and race/ethnicity based on a normative sample of HIV-negative persons. T-scores are scaled so that they have a mean of 50 and a standard deviation of 10, with higher T-scores reflecting better performance.

Table 3. Neuropsychological test performance by cognitive profile in virally suppressed people with HIV.

	Profile					
Mean T-score (SD)	1 (n=140)	2 (n=109)	3 (n=182)	4 (n=57)	5 (n=92)	6 (n=124)
Brief Visuospatial Memory Test Revised (BVMT)						
Total Learning	50 (9)	46 (7)***	46 (9)***	53 (9)*	39 (6)***	36 (7)***
Delayed Recall	51 (11)	46 (9) ***	47 (11)***	51 (9)	38 (7)***	35 (9)***
Recognition	47 (11)	50 (7)*	50 (7)*	54 (4)***	49 (9)	27 (16)***
Hopkins Verbal Learning Test Revised (HVLT)						
Total Learning	50 (10)	39 (10)***	41 (9)***	53 (8)*	39 (8)***	31 (9)***
Delayed Recall	49 (10)	42 (11)***	43 (9)***	56 (8)***	39 (8)***	31 (9)***
Recognition	50 (10)	43 (11)***	48 (9)*	52 (6)	48 (9)	25 (16)***
Paced Auditory Serial Addition Task (PASAT-50)	55 (8)	53 (8)*	39 (9)***	41 (8)***	39 (9)***	40 (10)***
WAIS-III Digit Symbol Substitution Test	57 (10)	49 (9)***	48 (9)***	44 (8)	39 (8)	42 (11)
Trail Making Test (TMT)						
Part A	58 (11)	46 (9)***	51 (9)***	44 (8)	39 (8)	42 (11)
Part B	57 (10)	45 (9)***	45 (10)***	44 (8)	39 (8)	42 (11)
Controlled Oral Word Association Test (COWAT)	54 (9)	55 (9)	43 (9)***	43 (11)***	46 (11)***	44 (12)***
Grooved Pegboard (GPEG)						
Dominant hand	52 (9)	46 (9)***	53 (10)	41 (7)***	34 (8)***	41 (12)***
Non-dominant hand	51 (9)	47 (11)**	50 (9)	41 (8)***	34 (7)***	41 (13)***

SD=standard deviation; [1] Each profile is compared to Profile 1. One-way ANOVA was used for continuous variables and Chi-squared for categorical variables (* $p < .05$; ** $p < .01$; *** $p < .001$). T-scores are adjusted for age, sex, education and race/ethnicity based on a normative sample of HIV-negative persons. T-scores are scaled so that they have a mean of 50 and a standard deviation of 10, with higher T-scores reflecting better performance.

Table 4. Sociodemographic, clinical/behavioral, and HIV disease characteristics by cognitive profile in virally suppressed people with HIV.

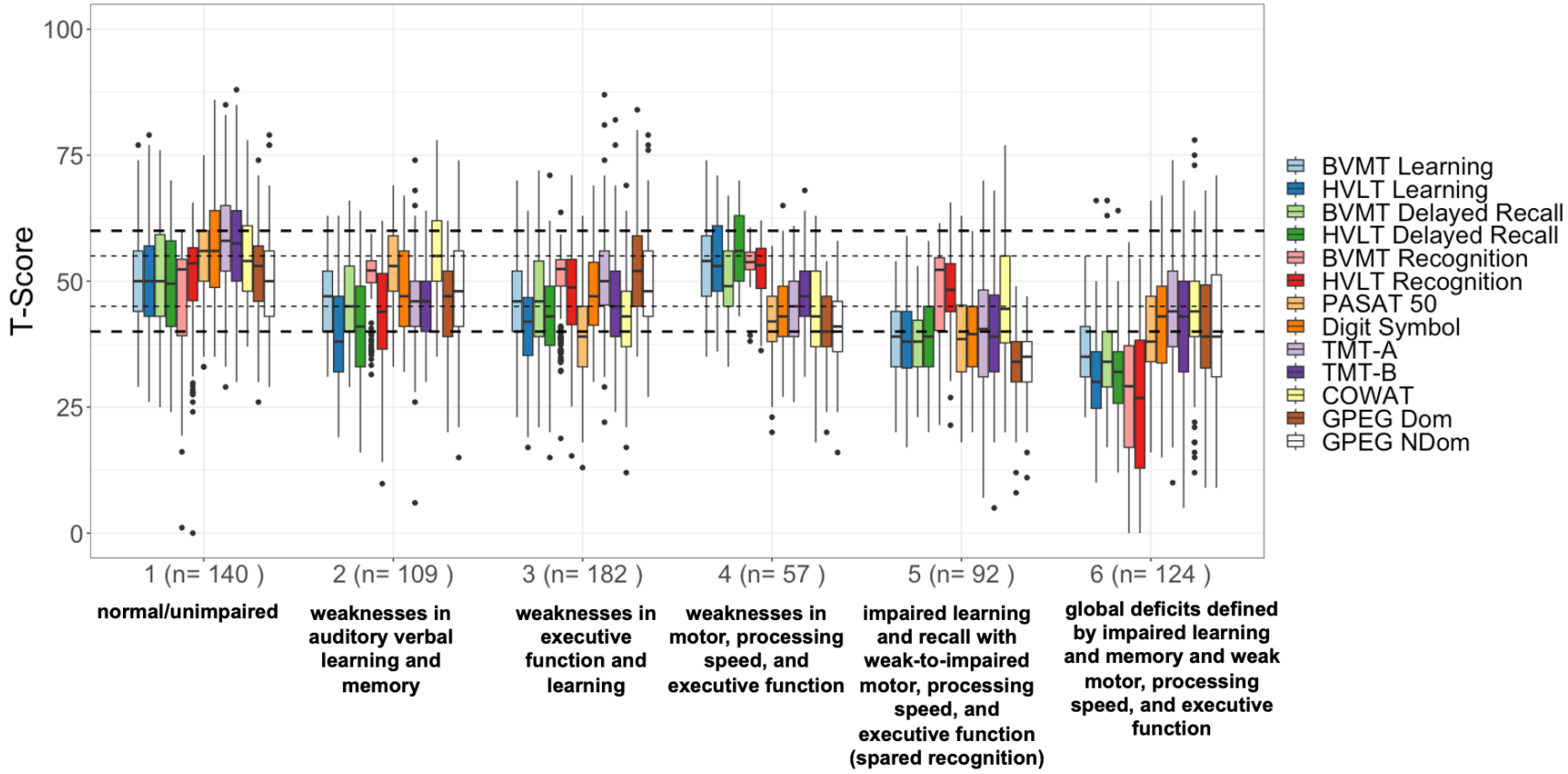
M (SD) except where noted	Profile					
	1 (n=140)	2 (n=109)	3 (n=182)	4 (n=57)	5 (n=92)	6 (n=124)
Age	45 (9)	45 (10)	42 (11)*	40 (10)**	44 (11)	46 (10)
Male, n (%)	126 (90%)	99 (91%)	158 (87%)	51 (89%)	73 (79%)*	116 (94%)
Years of education	13.6 (2.5)	14.5 (2.5)**	13.6 (2.6)	12.5 (2.6)**	13.8 (2.7)	14.2 (3.0)
Wide Range Achievement Test-4 (WRAT4) reading score	104 (10)	105 (12)	98 (12)***	101 (9)	99 (14)**	98 (14)***
Race, n (%)			**	*	*	
White	78 (56%)	73 (67%)	94 (52%)	34 (60%)	58 (63%)	78 (63%)
Black	38 (27%)	14 (13%)	33 (18%)	8 (14%)	17 (18%)	19 (15%)
Hispanic	16 (11%)	16 (15%)	47 (26%)	14 (25%)	17 (18%)	17 (14%)
Other	8 (5.7%)	6 (5.5%)	8 (4.4%)	1 (1.8%)	0 (0%)	10 (8.1%)
Instrumental Activities of Daily Living (IADL) total score	1.3 (1.6)	2.1 (2.6)**	2.0 (2.5)**	2.5 (2.8)***	3.0 (3.1)***	2.7 (3.0)***
Beck Depression Inventory (BDI) total score	10 (8)	12 (10)	14 (11)**	12 (10)	13 (10)*	15 (11)***
Patients Assessment of Own Functioning Inventory (PAOFI)						
Total score	4 (5)	5 (6)*	6 (7)***	7 (7)**	8 (8)**	8 (8)***
Higher cognitive functions subscale (e.g., executive functions)	0.6 (1.3)	0.9 (1.7)	1.5 (2.2)***	1.4 (2.1)**	1.9 (2.7)**	1.9 (2.6)***
Language and communication subscale	1.2 (1.8)	1.5 (1.9)	2.0 (2.5)***	1.6 (2.1)	2.3 (2.4)	2.3 (2.7)***

Memory subscale	1.5 (2.0)	2.5 (2.8)**	2.4 (2.8)**	2.9 (3.2)***	2.9 (3.0)	2.8 (3.3)***
Profile of Mood States (POMS)						
Total score	51 (35)	65 (39)**	66 (43)**	66 (41)*	68 (42)**	69 (39)***
Tension or anxiety dimension	9 (7)	10 (7)	11 (8)*	10 (7)	11 (7)*	12 (7)***
Confusion or bewilderment dimension	6.2 (5.0)	8.3 (5.1)**	8.3 (6.1)**	8.2 (5.8)*	8.1 (5.8)*	9.5 (6.3)***
Anger or hostility dimension	6 (7)	8 (9)*	9 (9)**	9 (9)*	9 (10)**	9 (8)**
Depression or dejection dimension	9 (10)	12 (12)*	14 (14)***	11 (11)	13 (13)**	15 (13)***
Fatigue or inertia dimension	8 (7)	9 (7)	9 (7)	9 (6)	10 (8)*	10 (7)**
Vigor or activity dimension	17 (7)	15 (7)*	16 (7)	15 (7)*	15 (7)*	15 (6)**
World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH-CIDI), n (%)						
Current major depressive disorder	10 (11%)	10 (12%)	29 (19%)	5 (12%)	15 (21%)	21 (20%)
Lifetime major depressive disorder	43 (46%)	40 (48%)	74 (48%)	21 (50%)	34 (47%)	46 (44%)
Current alcohol use disorder	4 (4%)	3 (4%)	8 (5%)	3 (7%)	2 (3%)	4 (4%)
Lifetime alcohol use disorder	53(57%)	49 (59%)	84 (55%)	23 (55%)	38 (53%)	49 (47%)
Current substance use disorder	5 (17%)	4 (13%)	7 (14%)	5 (22%)	9 (23%)	3 (9%)
Lifetime substance use disorder	72 (77%)	66 (80%)	118 (77%)	32 (76%)	56 (78%)	65(72%)*
Use of medications with anticholinergic properties, n (%)	29 (21%)	26 (24%)	51 (28%)	14 (25%)	26 (28%)	43 (35%)*
CPE Score	7.6 (2.4)	8.0 (2.2)	8.0 (2.1)	7.4 (2.6)	8.2 (2.0)	7.7 (2.3)

Cognitive impairment based on Global Deficit Score[¥], n (%)	2 (1%)	27 (25%)***	73 (40%)***	19 (33%)***	70 (76%)***	99 (80%)***
Hypertension, n (%)	31 (23%)	27 (25%)	42 (24%)	16 (29%)	25 (27%)	41 (34%)
Hyperlipidemia, n (%)	26 (19%)	21 (20%)	26 (15%)	12 (22%)	19 (21%)	34 (29%)
Diabetes, n (%)	5 (4%)	8 (7%)	10 (6%)	3 (5%)	12 (13%)*	9 (8%)*
Body mass index	26.4 (4.4)	26.3 (4.0)	26.4 (5.1)	26.3 (4.4)	26.1 (6.1)	26.7 (5.0)
Hepatitis C virus (HCV), n (%)	21 (15%)	21 (20%)	30 (17%)	13 (23%)	25 (27%)*	18 (15%)
Current CD4	572 (280)	539 (289)	560 (316)	499 (268)	486 (316)*	540 (312)
Nadir CD4	264 (224)	227 (222)	261 (240)	237 (215)	194 (199)	224 (226)
Estimated duration of HIV disease	11 (9)	10 (8)	11 (9)	11 (8)	9 (7)	12 (8)

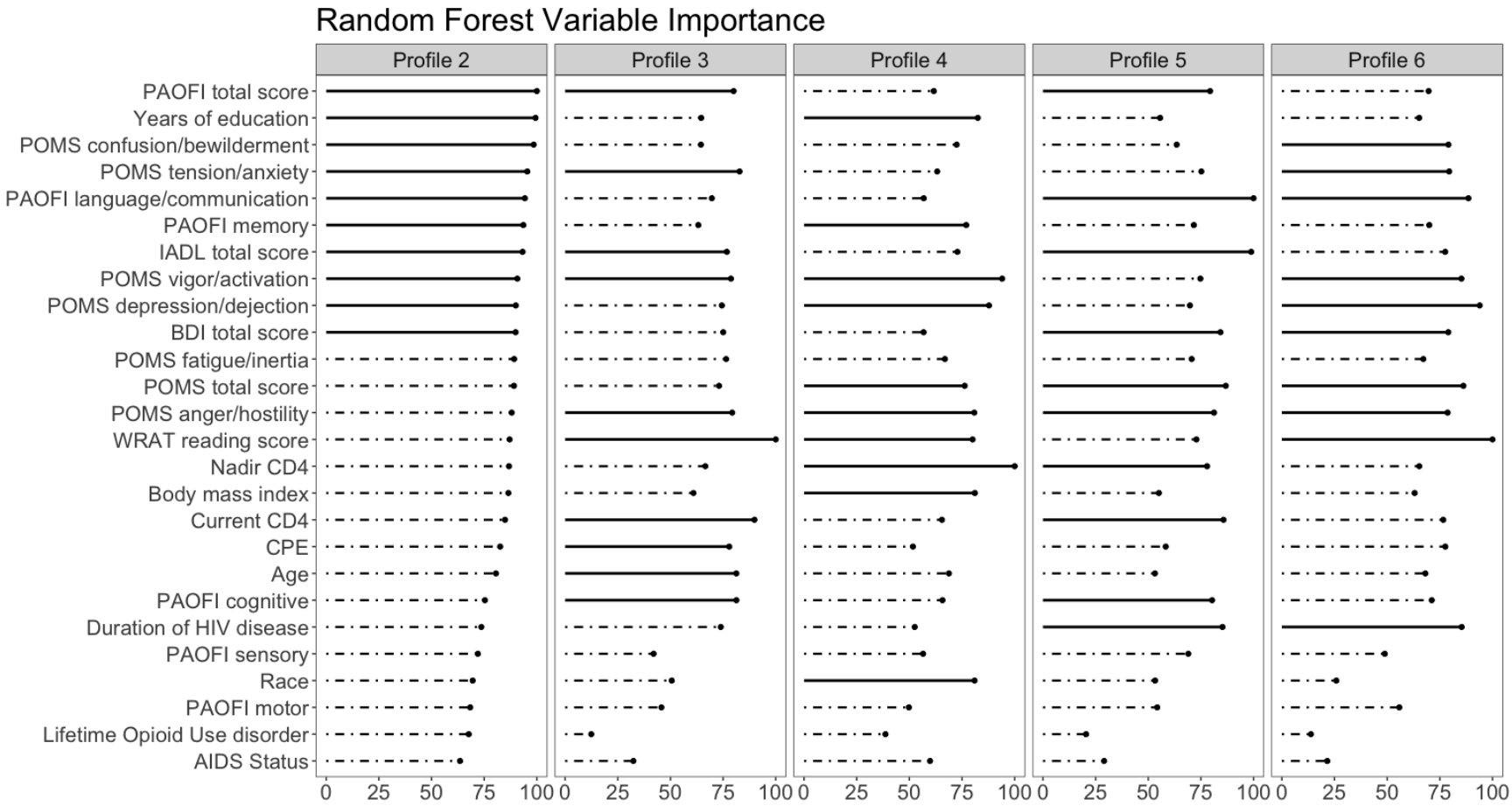
M=mean; SD=standard deviation; [1] Each profile is compared to Profile 1. One-way ANOVA was used for continuous variables and Chi-squared for categorical variables (* $p < .05$; ** $p < .01$; *** $p < .001$). [¥]Cognitive impairment was defined as a global deficit score (GDS) ≥ 0.5.

Figure 1. Neuropsychological profiles in virally suppressed people with HIV.



Note: BVMT=Brief Visual Memory Test. HVLT=Hopkins Verbal Learning Test. PASAT=Paced Auditory Serial Addition Test. TMT=Trail Makin Test. COWAT=Controlled Oral Word Association Test. GPEG Dom=Grooved Pegboard Test, Dominant Hand. GPEG NDOM=Grooved Pegboard Test, Non-dominant Hand.

Figure 2. Variable Importance results from the Random Forest Models in virally suppressed people with HIV.



Note: The length of the bars indicates the relative importance of the variable in that model. Solid lines represent the top 10 most important variables in each model. PAOFI=Patients Assessment of Own Functioning Inventory; POMS=Profile of Mood States; IADL=Instrumental Activities of Daily Living; WRAT4=Wide Range Achievement Test-4 Reading Score; CPE=central nervous system (CNS) penetration effectiveness score.