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Topographies of cortical and subcortical volume loss in HIV and aging in the cART era

Anika Guha¹, Matthew R. Brier¹, Mario Ortega¹, Elizabeth Westerhaus¹, Brittany Nelson¹, and Beau M. Ances^{1,2,3}

¹Department of Neurology, Washington University in Saint Louis

²Department of Bioengineering, Washington University in Saint Louis

³Department of Radiology, Washington University in Saint Louis

⁴Hope Center for Neurological Disorders, Washington University in Saint Louis

Abstract

Objectives—Studies of HIV-associated brain atrophy often focus on *a priori* brain regions of interest, which can introduce bias. A data-driven, minimally-biased approach was used to analyze changes in brain volumetrics associated with HIV and their relationship to aging, viral factors, and combination antiretroviral therapy (cART), as well as gender and smoking.

Design—A cross-sectional study of 51 HIV-uninfected (HIV–) and 146 HIV-infected (HIV+) participants.

Methods—Structural MRI of participants was analyzed using principal component analysis (PCA) to reduce dimensionality and determine topographies of volumetric changes. Neuropsychological (NP) assessment was examined using global and domain-specific scores. The effects of HIV disease factors (e.g. viral load, CD4, etc.) on brain volumes and NP were investigated using penalized regression (LASSO).

Results—Two components of interest were visualized using PCA. An aging effect predominated for both components. The first component, a cortically-weighted topography, accounted for a majority of variance across participants (43.5% of variance) and showed independent effects of HIV as well as smoking. A secondary, subcortically-weighted topography (4.6%) showed HIV-status accentuated age-related volume loss. In HIV+ patients, the cortical topography correlated with global NP scores and nadir CD4, while subcortical volume loss was associated with recent viral load.

Conclusions—Cortical regions showed the most prominent volumetric changes due to aging and HIV. Within HIV+ participants, cortical volumes were associated with immune history while subcortical changes correlated with current immune function. Cognitive function was primarily

Corresponding author: Beau Ances MD, PhD, MSc, Box 8111, 660 South Euclid Ave, Saint Louis, MO 63110, Phone: (314) 747-8423, Fax: (314) 747-8427, bances@wustl.edu.

¹For an important discussion on the limitations of step-wise regression, see Lockhart, Taylor, Tibshirani, & Tibshirani, 2014

CONFLICT OF INTEREST: The authors, Anika Guha, Matthew R. Brier, Mario Ortega, Elizabeth Westerhaus, Brittany Nelson, and Beau M. Ances, declare that they have no conflict of interest.

associated with cortical volume changes. Observed volumetric changes in chronic HIV+ patients may reflect both past infection history and current viral status.

Keywords

HIV; brain volume; aging; neuropsychology; topography

INTRODUCTION

HIV crosses the blood-brain barrier via infected T cells and monocytes and can cause cognitive dysfunction [1–3]. Combination antiretroviral therapy (cART) reduces morbidity and mortality due to HIV by controlling viral load and improving CD4 cell counts. However, cognitive dysfunction, as assessed by neuropsychological performance (NP) testing [4–7] and neuroimaging (e.g., brain volumetrics), persists despite the introduction of cART [4, 8–9].

cART has also improved the life expectancy of HIV+ individuals with many now having lifespans comparable to HIV– individuals [10–12]. Given longer lifespans, the potential effects of aging may contribute to observed neurological changes (e.g. brain atrophy) in older HIV+ individuals. The effects of HIV and aging may be independent [13–17] or interactive [18–20].

In studying HIV, particularly in an aging cohort, it remains important to consider additional risk factors for cerebrovascular disease. A greater proportion of HIV+ individuals smoke [21–23]. In general, smoking, has been implicated in lower health-related quality of life [24] and greater risk of cognitive impairment [25–26] or dementia [27]. Ingredients in cigarettes, such as nicotine, may induce oxidative stress and neuroinflammation that can lead to disruption of the blood-brain-barrier [28–29]. Relatively few studies have investigated the effects of smoking on neurological function in HIV+ individuals. A decrease in both cortical and subcortical volumes was observed in HIV+ smokers compared to HIV+ non-smokers, but this study was confounded by heavy alcohol abuse in all HIV+ participants [25].

Previous studies that have focused on HIV-associated atrophy have typically concentrated on subcortical regions of interest (ROIs) [15–16, 30–40]. More recently, cortical changes have also been detected and may contribute to cognitive dysfunction [32–38], though the relative contribution of cortical and subcortical atrophy to observed HIV-associated neurocognitive disorders (HAND) remains unclear [17]. Reduced brain volume has been found in frontal [46–47], temporal [41], and parietal [41, 46] regions. Much of the extant literature investigates small sets of *a priori* ROIs leaving large fractions of cortical and subcortical structures uninvestigated. Unbiased, data-driven techniques capable of considering changes across the entire brain are of increasing importance to the field as they may synthesize current results and/or reveal novel associations [46].

The profile of HAND has also changed due to cART. Historically, HIV-infection has been associated with subcortical neuropsychological dysfunction (e.g., motor dysfunction). Significant cognitive improvement has been attributed to cART [48–50] including improvements in psychomotor speed [51–53], verbal fluency [54–56], attention [57–58], and

memory [59]. Despite these improvements in cognitive functioning, deficits in learning, complex attention and executive function can continue to persist in HIV+ patients receiving cART [56, 60].

The continued prevalence of HAND may reflect both current disease status as well as disease natural history. Current immune function (e.g. CD4 cell count) and virologic control have been associated with atrophy in the basal ganglia and frontal lobes [42, 46]. Yet past immune function, in particular nadir CD4, has been linked to decreased cortical and hippocampal volumes [33]. Elucidation of the viral and immune factors as well as time scales of disease management that contribute the most to brain volumetric changes in HIV may inform treatments targeted at reducing neurocognitive impairment [37, 41, 61–64].

Neurocognitive decline can still occur despite viral control with cART. These results suggest that ongoing inflammation or inability of cART to penetrate the blood-brain-barrier may be important in neurocognitive outcome. Increasing interest in the ability of medications to enter the central nervous system (CNS) and their efficacy has led to the development and implementation of the CNS penetration-effectiveness (CPE) score. The effect of CPE score on disease severity remains controversial with some studies showing benefit for higher CPE [65–67], while others have seen no effect of CPE [38,42,68–70] or even potentially harmful effects of higher CPE [71–73]. The efficacy and safety of antiretroviral medications becomes particularly important as HIV+ individuals are prescribed these medications for the rest of their lifetime.

This study investigates the relationship between brain volumes analyzed across the entire brain, aging, smoking, and clinical variables (i.e. viral load, CD4 count, nadir CD4, duration of infection, CPE score of medication regimen). Here, a whole-brain, multivariate approach allowed us to study effects that would not otherwise be included using only *a priori* regions. Whole-brain volumetric studies yield large, high-dimensional data that can often be explained by a smaller set of orthogonal components or topographies. In using PCA, differences in brain volume by HIV– status were not predicted to respect regional boundaries but may differ over sets of regions, or topographies. Volumetric topographies, comprising both subcortical and cortical regions, were hypothesized to be decreased in HIV + compared to HIV– individuals. HIV-related clinical variables (nadir CD4 count, CPE score) were hypothesized to correlate with brain volume. Additionally, we examined the relationship between these brain volumetric topographies and cognitive performance in HIV + individuals.

METHODS

Participants

HIV+ participants were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic, the WUSM AIDS Clinical Trial Unit (ACTU), and Supportive Positive Opportunities with Teens (SPOT). HIV– participants, similar to HIV+ participants with regards to age and sex, were recruited from the Research Participant Registry at Washington University in St. Louis as well as from flyers distributed throughout the St. Louis area.

Exclusion criteria included history of claustrophobia or seizures, previous head injury with loss of consciousness greater than 30 minutes, developmental delays, psychiatric conditions associated with cognitive dysfunction, a Beck Depression Inventory (BDI) score greater than 29 [74], contradiction for MRI scanning (such as metal implants in head, pacemakers, etc.), fewer than eight years of education, or an inability to provide written informed consent. No participants with a reported significant history of cerebrovascular events (e.g. stroke) were included. This study was approved by the Washington University Institutional Review Board.

Clinical Characterization of Participants

Serologic status of all HIV– participants was confirmed using a rapid oral HIV test at the time of testing. For HIV+ individuals, laboratory and medical records were used for clinical variables including recent plasma viral load, CD4 T-cell count, nadir CD4 count, and antiretroviral history including current CPE score [65]. Duration of infection was based on self-reported time since the participant's diagnosis and verified by medical records when available. The majority of HIV+ participants (84.2%) were receiving cART and had been on a stable regimen for at least the past three months prior to their participation (Table 1). The CPE score was calculated by summing the individual penetration scores for each antiretroviral medication in the participant's regimen [75]. Individuals not currently on cART were given a CPE score of 0. Recent CD4 T-cell counts and HIV viral load measures were obtained within three months of an individual's participation in the study. Most of the HIV+ cohort (63.7%) had undetectable plasma viral load (< 20 copies/ml). Current smoking behavior was assessed using a self-reported measure ("do you currently smoke?") and treated as a dichotomous variable (yes/no). A neurological exam was performed on each participant.

Neuropsychological Examination

All participants completed a short neuropsychological performance battery using tests previously demonstrated to be sensitive to HIV neurocognitive impairment [76]. The battery assessed the following domains: executive function (Trail Making Test B, Animal Fluency), memory (Hopkins Verbal Learning Test-Revised: immediate recall on trials 1–3 and delayed recall), and psychomotor/processing speed (Digit Symbol Substitution Test, Trail Making Test A).

Standardized scores were computed using published normative data with adjustments made for age, ethnicity, education, and sex where available [77–79]. For NP analyses, only participants with complete datasets (47 HIV–, 93 HIV+) were included in this sub-analysis. Domain composite scores (executive function, memory, psychomotor/processing speed) were calculated as the mean of individual test Z-scores comprising a particular domain [80]. Additionally, a global Z-score was calculated as the average of the three domains.

Imaging

Neuroimaging was performed on a 3T Siemens Tim Trio MR scanner (Siemens AG, Erlangen Germany) with a 12-channel head coil. A high-resolution, 3-dimensional, sagittal, magnetization-prepared rapid gradient echo scan (MPRAGE) T1 scan was acquired

(repetition time [TR] = 2400ms, echo time (TE) = 3.16 ms, flip angle = 8°, inversion time = 1000 ms, voxel size = 1×1×1 mm³ voxels, 256×256×256 acquisition matrix, 162 slices).

Structural volumes were obtained using the FreeSurfer software suite (v5.1) (Martinos Center, Harvard University, Boston, MA, USA; <http://surfer.nmr.mgh.harvard.edu>). Briefly, this automated software program transforms MPRAGE images of an individual into a template space with the skull stripped and the brain segmented into white matter, gray matter, and ventricles. Cortical and subcortical image segmentation was completed using a surface deformation program [81–82]. Reviewers trained in FreeSurfer processing confirmed the quality of segmentation and volumes. Manual edits were performed only when outliers were identified. These manually-corrected scans were then reanalyzed. Regional brain volumes were normalized with respect to total intracranial volume (ICV) using a least square residual regression model across the entire cohort in order to account for possible variations in head size [36, 83–86].

Analyses

Demographic Information—Demographic variables were compared between HIV– and HIV+ participants. The age and education level of participants in the two groups were compared using *t*-tests. A chi-squared test was used to assess sex and smoking differences between the groups.

Neuropsychological Tests—Analyses for differences in NP performance were conducted between the two groups (HIV+ and HIV–). In order to examine the effect of HIV-status on cognitive domains (executive function, memory, psychomotor/processing speed, and global NP), MANOVAs included HIV-status and smoking as factors.

Principal Component Analysis of Volumetric Data—Regional brain volume analysis yields a volume estimate for each brain region in each participant. However, these measurements are not independent given the high spatial correlation present in brain volumetric data. Therefore, principal component analysis (PCA) was performed to reduce the dimensionality of volumetric neuroimaging data [87, 88]. The data were initially organized into a matrix with 197 rows (corresponding to participants) and 86 columns (corresponding to a set of FreeSurfer volumes [excluding white matter regions, cerebellum, and brainstem]). The original data was projected onto the PCA factor loadings to yield volumetric factor scores. These factor scores were subjected to an age (continuous) by HIV-status analysis of covariance.

HIV Disease Variables—A pathophysiologically important question is the extent that HIV-related clinical variables (i.e. viral load, CD4 count, nadir CD4 count, duration infection, CPE score of cART regimen) contribute to observed atrophy and cognitive dysfunction. For example, are atrophy and cognitive function more closely associated with disease severity (e.g., viral load) or duration? The straightforward approach to addressing this question involves fitting a linear model wherein, e.g., regional brain volume is expressed as a function of HIV disease factors. Ordinary least squares will fail due to a marked violation of the assumption that independent variables are (roughly) orthogonal (see Table,

Supplemental Digital Content 1, *which shows the correlations between HIV disease factors*). Penalized regression allows for straightforward circumvention of the limitations of ordinary least squares. Least absolute shrinkage and selection operator (LASSO), a form of penalized regression, has been introduced as a method of regression with variable selection that is robust to correlation among predictor variables [89]. For an outcome of interest y as a function of predictors X , LASSO is expressed:

$$\underset{\beta}{\operatorname{argmin}} \|y - \beta X\|^2 + \lambda \|\beta\|_1$$

The first term is the ordinary least squares regression. The second term enforces an L_1 penalty on the estimated β values. The severity of this penalty varies with λ ; high values of λ force most β to 0. As λ is reduced, more variables are allowed to enter the model. Similar to step-wise regression¹, the critical inferential step is to determine the point at which additional variables represent insignificant improvements to model fit (i.e., determine the value of λ). To determine the significance of each variable in the model, the ForwardStop criterion is applied at each point where a new variable is entered into the model. This criterion controls for the false discovery rate in a minimally biased manner.

RESULTS

Participant Demographics

The final sample included 51 HIV− (18–66 years old) and 146 HIV+ participants (18–84 years old) for volumetric analyses with a subset (N=140) having complete NP data. The HIV + group was significantly older, contained more males, and had a higher percentage of current smokers than the HIV− group (Table 1). No differences were present between the two groups with respect to race or education.

Volumetric Analysis

PCA—PCA was applied to the ICV-corrected regional volumes to reduce dimensionality and account for co-linearity between regions for the entire sample. A critical step of PCA analysis is determining the number of components (dimensionality) to retain. Multiple algorithms for determining the latent dimensionality of data exist and yield different results. The estimated dimensionality using empiric estimation based on the sample eigenspectra, an information criterion (AIC), was 3; the estimated dimensionality using repeated null simulations was 1. Because these two methods disagreed and we had no *a priori* reason to favor either method over the other, we investigated the first three components with an emphasis on the first. Accordingly, the first component explained a majority of variance across participants (43.5%) (*see Figure, Supplemental Digital Content 2, which shows the amount of variance explained for each component returned by PCA*). While the second and third components were significant, they explained 4.6% and 3.3% of the additional variance, respectively.

Author contributions: AG performed analyses and wrote the manuscript, MRB contributed analytic techniques and revised the manuscript, MO performed analyses, EW collected the data, BN collected the data, BMA conceptualized the study, revised the manuscript, and is responsible for the data and content.

Each principal component yields a factor loading that represents a particular topography (*see Table, Supplemental Digital Content 3, which shows the components in order of regions weighted greatest to least*). Topographies corresponding to the three retained principal components are shown in Figure 1. Color indicates loading or weight. For all topographies the factor loadings were highly symmetric, consistent with no anticipated laterality effect. The first component loaded highly on cortical regions whereas the second component loaded primarily on subcortical regions. The third component loaded highest on ventricles, entorhinal cortex, and some subcortical regions. As a matter of nomenclature, we identified the first two components as the cortical and subcortical topography respectively.

Effects of Aging and HIV—We examined the effects of age, HIV-status and currently smoking on the volumetric factor scores derived by projecting the original data onto the factor loadings for each principal component separately (Table 2a). Sex, which differed between groups, was included as a regressor of non-interest. A significant effect of age dominated both the cortical and subcortical topographies, where advancing age was associated with smaller volumes throughout the brain. A main effect of HIV-status was also present in the cortical topography with HIV+ status associated with smaller volumes (Fig. 2). An effect of current smoking was observed for the cortical topography with self-reported smoking associated with smaller cortical volumes (*see Figure, Supplemental Digital Content 4, which shows the effect of smoking on the cortical topography +/- standard error*). Current smoking did not affect the other two topographies. Finally, an interaction between age and HIV-status was present in the subcortical topography, though no main effect of HIV-status was present. The nature of the interaction was a relatively modest association between age and volume in the HIV- group; but a marked reduction with advancing age was observed in the HIV+ group. The third topography showed no main effects of age or HIV, no interaction effect, and was subsequently not investigated further. The low amount of variance explained by the third principal component and its non-intuitive topography suggest that a dimensionality estimate of 3 may be liberal.

Effects of HIV Disease Variables—LASSO with ForwardStop criterion was employed as a method to select variables for a linear regression that analyzed the relationship between HIV factors and brain volumes. Within the HIV+ group, a model incorporating age and nadir CD4 count best-estimated brain volumes in the cortical topography (Table 2b). This suggests that age and previous immune history most significantly affected cortical volume in the HIV+ group. A model that incorporated age and recent viral load best estimated brain volumes in the subcortical topography (Table 2c). Similarly, this suggests that age and current disease severity most significantly drive subcortical volume loss.

Neuropsychological Performance

A MANOVA was conducted to investigate the effects of HIV and current smoking on the global and domain-specific NP scores. HIV+ participants had significantly lower global Z-scores, as well as executive function and psychomotor/processing speed domain-specific Z-scores (*see Figure, Supplemental Digital Content 5, which shows NP domain Z-scores by HIV-status*). Memory performance was not significantly affected by HIV-status. There were no significant effects of current smoking on either global NP or domain-specific values.

Relationships Between Neuropsychological Performance, Volumetrics, and Clinical Variables—We further investigated if the degree of volume loss was related to cognitive function in HIV+ and HIV− individuals. HIV+ participants showed a modest correlation between volumetric factor scores for the cortical topography and global Z-scores ($r = 0.22$, $p = 0.04$) (Fig. 3). There was a weak association between the cortical volumetric factor scores and psychomotor/processing speed Z-scores ($r = 0.2$, $p = 0.05$). No relationship was observed between cortical volumetric measures and executive function ($r = 0.04$, $p = 0.69$) or memory Z-scores ($r = 0.12$, $p = 0.09$). No relationships were found between the cortical volumetric topography and NP measures in the HIV− cohort. The subcortical topography did not correlate with NP measures in either group.

Within the HIV+ group, we investigated potential relationships between clinical variables (plasma viral load, CD4 count, nadir CD4 count, CPE, duration infection) and NP using LASSO variable selection. No significant effects of any of these factors were found in HIV+ participants.

DISCUSSION

This work investigated the relationship between volumetric changes, cognitive function and HIV-related clinical variables in the context of HIV and aging. Volume loss in HIV was described by cortical and subcortical volumetric changes. Both cortical and subcortical regions saw reductions in volume with advancing age. Cortical volume loss was more marked in HIV+ individuals and severity correlated with previous immune status as measured by nadir CD4 count. Further, smaller cortical volumes predicted worse global cognitive function. Additionally, cortical volumes were smaller in self-reported current smokers, though an interaction with HIV-status was not observed. Subcortical volumes demonstrated an interaction between age and HIV-status wherein subcortical volume loss increased with age in the HIV+ group. In subcortical regions, brain volumes correlated with current immune function as measured by current viral load, but not NP performance. CPE score of cART regimen was not selected as a significant predictor for any volumetric topography.

The measurement of interest in this study was brain region volume, which was measured at many individual regions of interest ($M=86$). The application of a multivariate approach (compared to a mass-univariate approach) is beneficial in that it allowed examination of HIV and age-associated changes for several reasons. Application of PCA to regional brain volumes allowed for the consideration of the entire brain by reducing the number of comparisons from individual regions to combinations, or topographies, of regions. The whole brain coverage, reduction in the number of independent statistical tests, and appropriate modeling of correlations within the data are strengths of this approach. Finally, the application of penalized regression (i.e., LASSO) allowed for the identification of the most disease-relevant clinical variables.

The notable feature is the relatively negative slope of the regression line for both cortical and subcortical components in HIV+ individuals with respect to age compared to the HIV− group. Current findings are in agreement with previous studies and suggest that HIV is

associated with predominantly cortical changes in the cART era [41–43, 45–47]. Unlike prior findings that have shown overall gray matter volume in HIV+ patients correlates with cognitive function [85–86], the current analyses retained information regarding regional volumes and their weighting within brain topographies. Change in cortical volumes is associated with global cognitive performance in the HIV+ cohort. Current results agree with a previous finding demonstrating regional brain volume, specifically in prefrontal and parietal cortices, correlates with cognitive deficits [46] (*see Table, Supplemental Digital Content 3, which shows the components in order of regions weighted greatest to least*). Future longitudinal studies of well-controlled HIV+ patients receiving cART could focus on these brain regions.

Individual responses to HIV-infection vary widely despite common pathophysiology. Clinically, severity of HIV-infection can be assessed by two components: historical and current. Past HIV disease severity, often summarized as the nadir CD4 count, predicts morbidity [92–96] and succinctly summarizes exposure to potential neurological insult [97–99]. In the present result, HIV+ participants with a history of preserved immune function demonstrated less cortical volume loss and better cognitive function. In practice, the means of preventing disease related sequelae are early and effective therapies. Similarly, viral suppression due to cART may reduce subcortical volume loss.

In addition to viral and immunological factors, of interest was the impact of cART penetration into the CNS. The CPE score was used as a pseudocontinuous measure for each cART regimen. The LASSO regression model did not include CPE in estimations of volumetric factor scores for either topography. This work suggests that other factors, nadir CD4 and recent viral load, serve as more salient predictors of volumetric changes. The duration of infection prior to cART initiation and attainment of virologic control may influence volumetric changes more than current cART regimen. The lack of relationship between outcome variables of interest and CPE score may also be partially explained by adherence concerns. Although 84.2% of HIV+ participants in this study were on cART at the time of scanning, 27% had a detectable viral load. Patients may falsely report consistent use of cART with issues concerning adherence previously reported in the HIV+ community [100–109]. Of note, the majority (70%) of the HIV+ patients were prescribed stable, high CPE regimens (≥ 7) [65]. Application of the methods to a cohort with greater variation in CPE scores may elucidate subtle effects that are unable to be identified in the current study.

The prevalence of smoking is generally higher in HIV+ individuals than the general population [21–23] and was also seen in this cohort. The potential effects of smoking on volumetric topographies were examined and a modest yet significant negative effect was observed for the cortical topography that was independent of HIV-status. Prior work investigating smoking has also found decreased cortical volumes in smokers compared to non-smokers in general [110–111]. In a study of HIV+ individuals, decreased overall neocortical gray matter and subcortical structures were found in a group of heavy drinkers who smoked compared to non-smoking heavy drinkers [25]. In HIV+ cohorts, neurocognitive impairment has been associated with current use of tobacco [25, 26], yet no association was observed between smoking and NP in the current study. However, the current work is somewhat limited as only a single question regarding current smoking

behavior was asked. Additional comprehensive questionnaires like the Fagerstrom Test for Nicotine Dependence [112] or blood sampling of carbon monoxide [113] may help elucidate neurological implications of smoking as a comorbidity in HIV+ individuals.

A confound related to the natural history of HIV-infection in an aging cohort is that age may be a surrogate for other factors (e.g., duration of infection, time an individual has been on a stable cART regimen). Variable selection via LASSO regression is robust to correlation among predictor variables and selects the most predictive independent variables. The observation that nadir CD4 and age were selected by LASSO suggests that both of these factors are important considerations when examining volumetric changes in HIV-infection. Recent findings have supported nadir CD4 count as a significant factor in brain volume in the cART era [42,114–115]. Meanwhile duration of infection, which was more highly correlated with age, was not significant using the LASSO regression model and was not retained.

In summary, clinical disease factors of HIV-infection, such as viral load and nadir CD4 cell count, contribute to atrophy in different parts of the brain and result in distinct cognitive changes. Previous research looking at regional atrophy in HIV+ individuals has emphasized subcortical volume loss and continued to examine these regions. Utilizing a novel, whole-brain approach, additional regions of interest that were affected by HIV-infection were identified. Although evidence of decreased subcortical volumes was observed in older HIV+ participants, these results suggest that HIV-infection is largely associated with decreased cortical volumes. The present work suggests that both cortical and subcortical volume loss occur in HIV and that early versus continued viral control influences these structures differentially.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Component volumetric topographies

Principal component analysis (PCA) revealed three components. Each component corresponds to a topography presented on the surface maps. The first component accounted for 43.5%, the second 4.6% and the third 3.3% of variance across participants. Color bar represents the weighting of the regions of interest (ROIs) as a result of PCA (red = highest weighting, blue = lowest weighting). The first component was most heavily weighted in cortical regions, particularly frontal and parietal regions. The second component was most heavily weighted in subcortical regions, particularly the pallidum, putamen, and

hippocampus. The third component was most heavily weighted in the ventricles, caudate, amygdala, entorhinal cortex, and pallidum.

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Figure 2. Cortical, subcortical, and 3rd topography volumetric factor scores as a function of the age of the participant and HIV-status

The cortical and subcortical topographies showed predominant age effects. The cortical topography showed a main effect of HIV. The subcortical topography showed an interaction between HIV-status and age. A small positive relationship between subcortical factor scores and age was found in the HIV- group. This is likely the result of a large fraction of age-related volume loss being accounted by the first component (cortical). Of interest is the relative negative slope of subcortical factor scores for HIV+ individuals with age compared to the HIV-. The third component showed no age or HIV effects and no interaction.

Figure 3. Correlation between cortical volumetric factor scores and executive function Z-scores, psychomotor/processing speed Z-scores, and global Z-scores for all participants (blue = HIV-, red = HIV+) with complete NP testing (n = 140)

HIV+ participants showed a modest correlation between volumetric factor scores for the cortical topography and global Z-scores ($r = 0.22$, $p = 0.04$). There was a weak association trending towards significance between cortical volumetric factor and psychomotor/processing speed Z-scores ($r = 0.2$, $p = 0.05$), and no relationship was observed for executive

function Z-scores ($r = 0.04$, $p = 0.69$). Neither of these relationships was significant in HIV–participants.

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Table 1
Demographic, medical, laboratory, and NP comparisons between HIV– and HIV+ individuals

A) T-tests were used to determine if significant differences existed between HIV– and HIV+ participants with regards to age and education and chi-squared tests were used to determine if differences were present due to sex and smoking. **B)** The subset of participants (N = 140) with the complete neuropsychological battery (NP) for domain and global Z-scores is also shown. A MANOVA was conducted to investigate differences in neuropsychological performance Z (NPZ) scores between HIV– and HIV+ participants.

A)			
	HIV–	HIV+	p-value
N	51	146	NA
Age (years, SD)	34.5 (15)	41.0 (16.8)	<i>0.01</i>
Sex (% Male)	45.1	54.9	<i>< 0.01</i>
Education (years) (SD)	13.5 (2.6)	13.3 (2.4)	0.53
% Current Smokers	28	48	<i>< 0.01</i>
CD4 cell count (SD)	NA	540.8 (312.8)	NA
Nadir CD4 cell count (SD)	NA	242.3 (188.1)	NA
Recent log Viral Load (IQR)	NA	2.1 (1.5–2.8)	NA
% Detectable (> 20 copies/ml)	NA	36.3	NA
Currently on cART (%)	NA	84.2	NA
CPE Score (SD) for cART	NA	6.3 (3.1)	NA
Duration Infection in months (SD)	NA	107.7 (93.6)	NA

B)			
Participants Used in NP Analyses	HIV–	HIV+	p-value
N	47	93	NA
Executive Function Z-score (SD)	0.017 (1.1)	–0.35 (0.9)	<i>0.03</i>
Memory Function Z-score (SD)	–1.05 (0.8)	–1.3 (1.0)	0.16
Psychomotor/Processing Speed Z-score (SD)	0.28 (1.1)	–0.36 (1.0)	<i>< 0.01</i>
Global Z-score	–0.25 (0.8)	–0.50 (0.5)	<i>0.02</i>

IQR = Interquartile Range

SD = Standard Deviation

NA = Not Applicable

cART = combination antiretroviral therapy

CPE = central nervous system penetration-effectiveness score

NP = Neuropsychological

Table 2

Effects of HIV and age on component topographies (A) and results from LASSO least squares regression analysis of HIV-disease factors for cortical (B) and subcortical (C) topographies.

A	Sex	Age		HIV		Smoking		HIV* Age		HIV* Smoking		Age* Smoking		
		F	p	F	p	F	p	F	p	F	p	F	p	
Topography 1 (Cortical)														
	0.80	0.37	126.5	< 0.01*	6.6	0.01*	4.5	0.04*	0.3	0.6	0.2	0.3	1.0	0.3
Topography 2 (Subcortical)														
	0.05	0.8	15.5	< 0.01*	0.2	0.7	1.3	0.3	17.1	< 0.01*	0.2	0.7	0.1	0.7
Topography 3														
	3.0	0.09	0.04	0.8	1.3	0.3	3.1	0.08	0.6	0.4	0.05	0.8	2.8	0.1

B	Drop in Covariance		p-value from LASSO		ForwardStop criterion		Beta Coefficient	
Age	28.76		< 0.001		< 0.001*		-0.52	
Nadir CD4	2.85		0.06		0.03*		0.16	
CD4	0.05		0.96		2.45		-	
Duration Infection	0.03		0.97		2.66		-	
Viral Load (log)	0.01		0.99		2.94		-	
CPE	0.00		1.00		2.24		-	

C	Drop in Covariance		p-value from LASSO		ForwardStop criterion		Beta Coefficient	
Age	12.03		< 0.001		< 0.001*		-0.47	
Viral Load(log)	3.74		0.03		0.01*		-0.23	
Nadir CD4	0.12		0.89		0.75		-	
Duration Infection	0.06		0.94		2.30		-	
CD4	0.02		0.98		2.58		-	
CPE	0.00		1.00		2.17		-	

A) ANCOVA table with age (continuous factor), HIV-status, sex as factors. P-values were corrected for multiple comparisons.

* $p < 0.05$, Bonferroni corrected. HIV-disease factors were investigated in the B) cortical and C) subcortical topographies. Factors found to be significant in the model after ForwardStop criterion to control for the false discovery rate were retained and the analysis was re-run including only these factors to determine the beta coefficients.

* denotes significance after correction for false discovery rate (FDR).

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