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Effects of clinical, co-morbid, and social determinants of health on brain aging in persons with and without HIV: a retrospective case-control study

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Abstract

Background.—Neuroimaging reveals structural brain changes linked with HIV infection and related neurocognitive disorders; however, group-level comparisons between persons with HIV (PWH) and persons without HIV (PWoH) fail to account for within-group heterogeneity. The aims of this study were to quantify the impacts of co-morbidities such as cardiovascular disease and adverse social determinants of health on brain aging in PWH and PWoH.

Methods.—PWH (n=379; age=44·8±15·5 yr.; 78·1% male; 68·6% African American; 77·8% undetectable viral load) and PWoH (n=259; age=38·3±17·1 yr.; 49·8% male; 56·4% African American) were clinically characterized and underwent 3-Tesla T_1-weighted magnetic resonance imaging (MRI) at Washington University in St. Louis between 2009 and 2022. In this retrospective case-control analysis, DeepBrainNet, a publicly available machine learning algorithm, was applied to estimate brain-predicted age from MRI for PWH and PWoH. The brain-age gap, defined as the difference between brain-predicted age and true chronological age, was modeled as a function of clinical, co-morbid, and social factors using linear regression. Variables were first examined singly

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Authors' contributions

KJP and BM were responsible for conceptualization of the study. KJP and TL performed formal analysis and data visualization. KJP, JR, and SC verified the data. JR, NM, and SC were responsible for data curation and software development. KJP wrote the original draft of the manuscript. KJP, SC, GB, RP, AS, FV, and BM edited the manuscript.

Conflict of Interest

All authors declare no competing interests in this manuscript.

Ethics Committee Approval

All studies from which data were drawn were approved by the Washington University in St. Louis Institutional Review Board.

for associations with brain-age gap, then combined into multivariate models using best-subsets variable selection.

Findings.—In PWH, brain-age gap was associated with Framingham cardiovascular risk score (p=0·0034), detectable viral load [>50 copies/mL] (p=0·0023) and hepatitis C co-infection (p=0·0065). After variable selection, the final model for PWH retained Framingham score and hepatitis C and added unemployment (p=0·0015). Educational quality assayed by reading proficiency was linked with reduced brain-age gap (p=0·016) for PWoH but not PWH, indicating a potential resilience factor. When PWH and PWoH were modeled jointly, selection resulted in a model containing cardiovascular risk (p=0·0039), hepatitis C (p=0·037), area deprivation index (p=0·033), and unemployment (p=0·00010). Male sex (p=0·078) and alcohol use history (p=0·090) were also included in the model but were not individually significant.

Interpretation.—These findings indicate that co-morbid and social determinants of health are associated with brain aging in PWH, alongside traditional HIV metrics such as viral load and CD4 lymphocytes, suggesting the need for a broadened clinical perspective on healthy aging with HIV, with additional focus on co-morbidities, lifestyle changes, and social factors.

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Keywords

HIV; social determinants of health; machine learning; MRI; aging; brain-predicted age; co-morbidities; cardiovascular disease; hepatitis C

Introduction

Aging persons with HIV (PWH) exhibit altered brain structure and function compared to persons without HIV (PWoH), including morphological changes detectable on magnetic resonance imaging (MRI)[1-3]. However, group-level differences conceal substantial within-group heterogeneity Although dementia is increasingly rare due to combination antiretroviral therapy (cART), subtler forms of cognitive impairment persist in a subset of PWH, in some instances diminishing quality of life[4].

To account for variability in aging, new models must consider a broader range of health drivers than previous paradigms, which focused mainly on clinical HIV metrics such as viral load. A growing literature quantifies the impact of co-morbid disease burden and social determinants of health (SDOH) such as poverty, stress, and social stigma[5,6]. However, relationships between such risk or resilience factors and MRI biomarkers are poorly understood. To address this gap, innovative methods are needed.

Machine learning algorithms can provide unexpected insights into latent patterns in large clinical and neuroimaging datasets, including in PWH[7,8]. One of the most fruitful lines of research has involved brain-predicted age, in which models are trained to estimate the age of individuals from their neuroimaging features. The difference between brain-predicted age and true chronological age defines the brain-age gap.

Positive brain-age gap (i.e. age overestimation) reflects the accumulation of pathology; for example, persons with Alzheimer's disease or mild cognitive impairment[9], schizophrenia[10], and HIV[11-13] have higher brain-age gap on average than controls. However, these studies have largely focused on between-group differences rather than explaining within-group variability. Moreover, they have typically examined the impact of the primary disease rather than the effects of co-morbidities and social factors. To meet these challenges, we utilized a large sample of PWH and PWoH who underwent neuroimaging at a single site and whose clinical profiles and socioeconomic statuses are well-characterized.

The goal of this study was to identify current and lifetime factors that explain brain aging in PWH and PWoH. These groups were first modeled separately, then a joint model was used to identify common factors affecting brain aging across both populations. The two groups were not compared directly, due to large differences in sample size and demographics. The outcome variable in all analyses was the brain-age gap, derived by applying a deep neural network to individual MRI. The analysis consisted of two methods. First, potential correlates of brain aging were examined singly, controlling for demographics, with correction for multiple comparisons. Then, multivariate models were built using variable selection.

While our approach was data-driven, previous findings enabled us to hypothesize specific associations. We predicted that cardiovascular risk[14] and detectable viral load[11] would show positive associations with brain-age gap in PWH. Based on known relationships between SDOH and mortality and morbidity in PWH, we predicted that greater neighborhood socioeconomic deprivation[15] and early life stress[16] would correspond to an elevated brain-age gap. By contrast, since education is linked with better neuropsychological functioning in PWH[17], we predicted an inverse association between educational quality and brain-age gap.

Methods

Participants.

Participants were drawn from several HIV studies conducted in a single laboratory for the primary purpose of examining the effects of HIV disease and prevalent health co-morbidities on brain structure and function. Adult PWH were recruited between December 2009 and January 2022 from the Washington University in St. Louis Infectious Disease Clinic, and PWoH were identified through community organizations or the Research Participant Registry in the same years. All participants provided written informed consent for study procedures, approved by the Institutional Review Board.

Exclusion criteria were established by a combination of self-report and medical records. Individuals who met DSM-5 criteria for current, severe substance use disorder or unmedicated major depressive disorder were excluded from parent protocols due to challenges with study compliance and the potential for confounding effects on neuroimaging. Individuals with depressive symptoms, anxiety, or mild-to-moderate substance use disorders were included to maximize external validity. Other exclusion criteria were incidental psychiatric disorders including schizophrenia and bipolar disorder, or neurological disorders such as epilepsy, traumatic brain injury with prolonged unconsciousness, or active opportunistic brain infections.

For PWH, viral load was measured with reverse-transcriptase PCR using blood obtained on the day of imaging. PWH with >50 HIV copies/mL in plasma were considered detectable. CD4 T-lymphocytes were measured using flow cytometry, and nadir levels were taken from self-report or medical records if available. Cardiovascular health was quantified with the 10-year Framingham score, which forecasts individual probability of developing cardiovascular disease[18], calculated from the following risk factors: age, sex, smoking, systolic blood pressure, high-density lipoprotein, total cholesterol, and blood pressure medications. Lifetime heaviest substance use was quantified with the Kreek-McHugh-Schluger-Kellogg (KMSK) scale for alcohol, tobacco, and cocaine, which corresponds to clinical rating scales such as the Structured Clinical Interview for the DSM (SCID). Heaviest use was assessed on a semi-quantitative 13-point scale based on duration, frequency, and amount of consumption. Cannabis was not examined due to limited data availability. Hepatitis C co-infection was self-reported.

Socioeconomic status was assayed using the Area Deprivation Index (ADI), which combines U.S. census tract-level housing, employment, education, and poverty data into a summary metric, with increasing scores indicating greater deprivation[19]. ADIs were obtained from geospatial coding of residential addresses. The 2015 ADI national ranking was utilized, as this was the nearest time-point to the mean visit (June 2014±2·6 years). Educational quality was quantified using the Wide Range Achievement Test (WRAT-III) reading component. WRAT-III reading is a better proxy for educational quality than years of schooling, and attenuates apparent racial discrepancies in neurocognitive test performance, suggesting better sensitivity to socioeconomic effects[20]. Self-reported unemployed status including disability was recorded. Childhood-and-adolescent stress was measured with the Early Life Stress Questionnaire (ELSQ), summing total adverse events experienced by age 17.

Neuroimaging.

MRI was conducted on two 3-Tesla Siemens scanners (Prisma, Trio) and included T_1-weighted magnetization prepared rapid gradient echo (T_1-MPRAGE) structural MRI (repetition time/echo time=2400/3·2 ms, spatial resolution=1x1x1mm). Minimal pre-processing was applied, including skull-stripping with the FMRIB Software Library Brain Extraction Tool, and linear registration to the 1-mm Montreal Neurological Institute template. To obtain brain structure volumes, FreeSurfer v5·3 was run, with manual inspection and correction.

Machine learning and brain-age prediction.

DeepBrainNet, a publicly available brain-predicted age model, was trained on 11,729 MRI scans from a diverse cohort of normative controls (ages 3-95 years), from 16 imaging databases including multiple scanners and sites. Model accuracy was tested on a previously unseen cohort of 2,739 healthy controls. DBN was built with the inception-resnet-v2 framework, which has high performance on complex computer vision challenges. DBN uses a 2D convolutional architecture, including a global maximum pooling layer, a dropout layer to prevent overfitting, and a fully connected 1024-node layer. The network was implemented in TensorFlow and Keras with five-fold cross-validation. Networks were initialized on ImageNet, a dataset of over 14 million hand-annotated images.

DBN takes minimally processed T_1-weighted scans as input, with brain extraction and linear registration but no segmentation or warping. Scans are represented as 80 axial slices; to obtain the brain-predicted age, each slice was used as a separate input, and the median age estimate was taken. Brain-age gap was obtained by subtraction of chronological age from DeepBrainNet-predicted age; thus, a positive brain-age gap indicates model overestimation. To ensure that brain-age gap was not hardware-dependent, we tested for statistical differences between scanners.

Machine learning interpretation.

Interpretation of spatial patterns detected by deep learning algorithms is non-trivial due to network complexity. To obtain a first-order approximation of volumetric features relevant to DeepBrainNet, we correlated normalized FreeSurfer gray and white matter volumes with brain-age gap. Correlation heatmaps for PWH and PWoH were applied to a standard atlas for cortex (Desikan-Killiany), subcortical structures, white matter (including T_1 hypointensities), and cerebrospinal fluid compartments.

Data preparation and transformation.

Potential predictors of brain-age gap were transformed to mitigate skewness. CD4 count and Framingham score were square-root transformed, ELSQ was $\log_{10}$-scaled, and ADI was logit transformed. Cocaine and tobacco use were binarized (user/never user); alcohol use (KMSK lifetime heaviest use) was continuous. As study participants were over 97% White or Black/African American, approximately consistent with demographics of PWH in the Saint Louis area, race was collapsed into a binary (Black and non-Black). Due to protocol differences between studies conducted over the 13-year timeframe, some missingness was present in the dataset. For a sensitivity analysis with complete observations and the use of Least Absolute Shrinkage and Selection Operator (LASSO) as additional validation, please see Supplemental Methods.

Univariate hypothesis testing.

All statistical analyses were performed in R 4·1·3 (Vienna). To test whether brain-age gap is associated with clinical, co-morbid, and social factors, we performed univariate testing for all predictors separately for PWH and PWoH, controlling for age, sex, and race. Thirteen predictors were tested: viral load, current CD4, nadir CD4, Framingham score, alcohol, tobacco, cocaine, hepatitis C, ADI, early life stress, WRAT-III reading, years of education, and employment status. To mitigate false positives, multiple comparisons correction was performed using Benjamini-Hochberg false discovery rate (FDR) correction (α=5%).

Multivariate analysis and variable selection.

To build multivariate models of brain aging in PWH and PWoH, we performed multiple linear regression modeling with best-subsets variable selection using the *Regsubsets* R package. This method involves fitting one regression model per combinatorial subset of predictors. Variable selection was performed by choosing the model with minimum Mallows' C_p, a measure commonly used for selective modeling[22]. Multivariate modeling

was performed separately for PWH and PWoH, and in the combined PWH+PWoH cohort, adding HIV serostatus as a predictor.

Results

Participants.

Participants included PWH (n=379; age=44·8±15·5 yr.; 78·1% male; 68·6% Black; 77·8% undetectable viral load) and PWoH (n=259; age=38·3±17·1 yr.; 49·8% male; 56·4% Black). PWH were older (p<0·0001) and more likely to be male (p<0·0001) and Black (p=0·0021). These core demographics were included as co-variates in all analyses.

In PWH, 10-year Framingham scores (p=0·0065), and lifetime alcohol (p=0·015), cocaine (p<0·0001), and tobacco use (p<0·0001) were greater than in PWoH (Table 1). PWH lived in neighborhoods with greater socioeconomic disadvantage as measured by ADI (p=0·0011), experienced more early life stressors (p=0·0023), and had lower educational quality on the WRAT-III reading subtest (p<0·0001). For PWH, mean viral load was 1·8 log units (63·1 copies/mL), and mean CD4 T-cell counts were 588·0±311·8 cells/μL, with a nadir of 224·3±199·7. Of 379 PWH, 25 (7·0%) reported a history of hepatitis C.

Machine learning and brain-age prediction.

DeepBrainNet predicted participant age from T_1-weighted images with a mean absolute error of 5·7 years (5·5 years for PWoH; 5·8 years for PWH). After linear bias correction, i.e., regression of chronological age from the brain-age gap, mean absolute error was reduced to 5·3 years. Brain-age gap was not different between T_1-weighted images from Prisma and Trio scanners (p=0·20). Spatial heatmaps of correlations between brain-age gap and regional volumes are shown in Fig. 1. Regardless of serostatus, all significant associations for gray and white matter regions were negative (i.e., greater brain-age gap correlated with smaller volume), while significant positive associations (greater brain-age gap with larger volumes) were limited to CSF compartments (lateral ventricles, e.g.; r=0·15-0·52) and T_1 white matter hypointensities (r=0·36 for PWH, r=0·12 for PWoH).

Univariate analysis.

Among HIV-specific variables (Fig. 2, Table S2), detectable viral load (p=0·0023) and hepatitis C co-infection (p=0·0065) were significantly, positively associated with brain-age gap. CD4 count was negatively associated (p=0·025) but fell short of significance after FDR adjustment. Other predictors were examined in both serostatus groups (Fig. 3). Framingham score, quantifying cardiovascular risk, was significantly, positively associated with brain-age gap in PWH (p=0·0034) but not PWoH (p=0·097), though the direction of effect was the same. Educational quality (WRAT-III reading) (p=0·016) and educational duration (p=0·033) were negatively associated with brain-age gap, indicating potential predictors of resilience, but these did not survive FDR correction. Unemployed status was associated with greater brain-age gap only in PWH (p=0·0019).

Multivariate analysis and variable selection.

To create multivariate brain-age gap models for PWH and PWoH, regression with best-subsets selection was used. The best model for PWH (Fig. 4A,B) included Framingham score (p=0·0019; β=1·43), hepatitis C (p=0·073; β=3·90), and unemployment (p=0·020; β=3·21). The best model for PWoH (Fig. 4C,D) included alcohol use (p=0·0041; β=0·40), early life stress (p=0·047; β=−3·27), WRAT-III reading (p<0·0001; β=−0·304), with a non-significant term for unemployment (β=0.327, p=0.79). Finally, the best model for the combined cohort (PWH+PWoH) (Fig. 5) included Framingham score (p=0·0039; β=1·06), hepatitis C (p=0·037; β=3·84), area deprivation index (p=0·033; β=0·684), and unemployment (p=0·00010), with retained non-significant terms for male sex (p=0·078; β=2·11) and alcohol use (p=0·090; β=0·224).

Sensitivity analysis using the complete-observation subset, using best-subsets selection and LASSO regression, yielded consistent findings and is discussed in Supplemental Results. In five-fold cross-validation, the best-subsets model predicted brain-age gap for persons in the complete-observations subset with a root-mean-square error (RMSE) of 6·72 years and a Pearson's r=0·44.

Interpretation

Using neuroimaging, machine learning, and model selection, we have demonstrated that a combination of clinical measures, co-morbidities and SDOH are associated with brain-predicted age in PWH and PWoH. Cardiovascular disease burden, detectable HIV viral load, and hepatitis C co-infection were identified as the strongest univariate correlates of brain-age gap in PWH. Additionally, the effects of social factors such as unemployment and area socioeconomic deprivation were identified in multivariate regression. Differences in significant variables between univariate and multivariate analyses may have several causes. For example, two predictors with high co-linearity, accounting for shared variance in the response variable, may both show significant effects on brain-age gap in independent univariate tests, but not in a multivariate model.

Brain-age gap was also modeled in PWoH. Because our primary goal was to explain *within-group* variability in brain aging rather than test for between-group differences, and due to sample size and demographic differences, we elected not to perform head-to-head comparisons between HIV serostatus groups. Best-subsets selection produced a multivariate model for PWoH that included significant terms for alcohol use, early life stress, and WRAT-III reading subscale. The latter showed a significant inverse relationship with brain-age gap, indicating that educational quality may be a resilience factor for brain aging. Finally, modeling PWH and PWoH together implicated Framingham score, alcohol use, area deprivation index, unemployment, male sex, and hepatitis C with older-appearing brain phenotypes. Notably, HIV itself was not significantly associated with brain-age gap when modeling these other factors, suggesting the relative importance of non-HIV drivers of brain aging in the cART era.

Substantial evidence now implicates non-HIV risk and resilience factors in aging effects for PWH[23,24]. Health disparities between PWH and PWoH partially reflect the legacy of

early uncontrolled infection, but these residual effects alone are insufficient to explain the persistence of neurocognitive impairment among persons with well-controlled HIV[25]. As a result, co-morbidities and SDOH are increasingly salient features in PWH with suppressed viral loads, immune reconstitution, and the expectation of longevity.

PWH have previously been shown to have increased average brain-age gap relative to seronegative peers; however, available data indicate that within-group variability in brain aging exceeds between-group differences, making it crucial to better account for heterogeneity[12,14]. Here we approach the question of brain aging using an array of multimodal predictors, including clinical measures, co-morbid disease burden, and SDOH. A novel aspect of this study is the incorporation of geospatial data on neighborhood characteristics into MRI data analysis.

The first group of factors that may impact brain aging are direct effects of HIV. We examined four key variables: viral load, current CD4 lymphocytes, nadir CD4 count, and hepatitis C co-infection. Detectable viral load was significantly associated with elevated brain-age gap, consistent with a large literature implicating viral suppression and immune reconstitution in preserved neurocognitive function[26]. Hepatitis C was associated with approximately four years of added brain-age gap in PWH, suggesting that the pathological effects of HIV and hepatitis C have additive impacts on brain health[27]. Thus, achieving control of both viruses is likely important for healthy brain aging.

The strongest and most consistent brain-age gap association was with Framingham cardiovascular risk score. The modeled difference in brain-age gap between those at minimum (<2%) and maximum (>60%) cardiovascular risk in this study was over 10 years. In univariate modeling, this association was significant in PWH; however, the effect size was similar in PWoH, marking cardiovascular disease as a good candidate for a general brain aging risk factor. However, it remains especially relevant for PWH, who have increased vascular disease compared to the general population[28]. These findings suggest that maintenance of normal blood pressure and cholesterol may be crucial for PWH who have established viral control but remain vulnerable to cardiovascular disease.

Substance use disorders are also more prevalent among PWH, and the effects of drug abuse history must be considered when studying neurocognitive deficits[29]. Prior work has linked drug use with brain structural and functional changes in PWH, but associations with brain-age gap have not been characterized. In multivariate analysis of PWoH, we found a positive association between brain-age gap and alcohol use in PWoH, potentially indicating that neurotoxic effects of heavy consumption influence MRI-based brain age. The absence of a similar effect in PWH may be a function of the co-linearity between alcohol use and other factors (e.g., cardiovascular disease) for which stronger links were found.

One unexpected finding was the detection of a protective effect of educational quality in PWoH alone, in contrast with years of formal education, which showed no significant association. WRAT-III reading score was found to have a significant negative correlation with brain-age gap in multivariate analysis, such that for each point of improvement WRAT-III, the mean brain-predicted age was reduced by 0·45 years. The apparent absence of this

effect in PWH is challenging to interpret but might indicate that the enhanced cognitive reserve conferred by quality of education may not be fully realized in PWH who experience clinical and social stressors related to lower rungs on the hierarchy of needs, i.e., those related to safety, food security, or other basic needs.

SDOH were given consideration in this study, as economic instability and social marginalization disproportionately affect PWH. In addition to education, we examined three major social factors: childhood stress, residential neighborhood quality from geospatially derived ADI, and unemployment status. While neither ELSQ nor ADI were associated with brain-age gap, ADI had positive associations with brain-age gap in the combined cohort model. Finally, unemployment status showed a strong linkage with increased brain-age gap in PWH, though causality remains unclear, since neurocognitive impairment associated with accelerated brain aging might precede loss of employment.

Anatomically, the brain-age gap was interpreted by correlation with FreeSurfer volumes. While this approach does not capture all the complex patterns identified by the neural network, it provides an approximation of relevant features. Results were congruent with literature on brain structure and aging: positive associations with brain-age gap were confined to CSF compartments and T_1 white-matter hypointensities, while the strongest negative correlations were in subcortical structures that atrophy with age, particularly amygdala, hippocampus, and corpus callosum[30]. These results suggest that DeepBrainNet identifies aging-relevant imaging features.

Some limitations should also be noted. The use of over ten years of participant data resulted in some differences in the measures collected, producing a degree of data incompleteness. To mitigate confounding effects of missing values, we performed a sensitivity analysis in the subset of PWH with complete data. Results thus obtained closely matched those derived from the full dataset, indicating that missing data were unlikely to drive results.

Self-reported data represent another limitation. For example, self-reported hepatitis C prevalence in PWH (n=25, 7·0%) was lower than expected, suggesting unawareness of infection in some participants. However, despite likely underestimation of co-infection, we nonetheless detected a substantial effect on brain-age gap (+4·0 years) in PWH with hepatitis C. Hepatitis C serostatus was not assessed in PWoH. Additionally, our sample represented almost exclusively persons who self-identified as Black or White, but not other racial or ethnic groups. Furthermore, PWH and PWoH were significantly different on self-identified race, sex, and age, limiting the comparability of serostatus groups.

The use of ‘best-subsets’ variable selection runs some risk of overfitting since all possible predictor combinations are modeled. This is partially remediated using Mallows’ C_p, a selection criterion which penalizes models with numerous predictors[22]. For further validation, we also performed variable selection using LASSO regression, an alternative method which utilizes coefficient shrinkage to eliminate weaker predictors. Again, results corresponded well to the main analysis, suggesting that findings are robust to overfitting and insensitive to methodology.

Taken together, these results paint a nuanced picture of aging with HIV. Traditional clinical variables such as viral load and T-cell counts impact neuropathology; however, non-HIV drivers of health such as co-morbid diseases and socioeconomic status are growing in importance. Together, such factors may account for heterogeneity in neurocognitive outcomes in older PWH and PWoH. Identification of brain-aging correlates may lead to a broadened perspective on health for people aging with chronic infectious disease while navigating challenging and often adverse socioeconomic landscapes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement

De-identified individual participant data, including imaging summary metrics but not original MRI scans, will be made available upon reasonable request to the corresponding author. Data will be shared over the HIPAA-compliant Box service (www.box.com).

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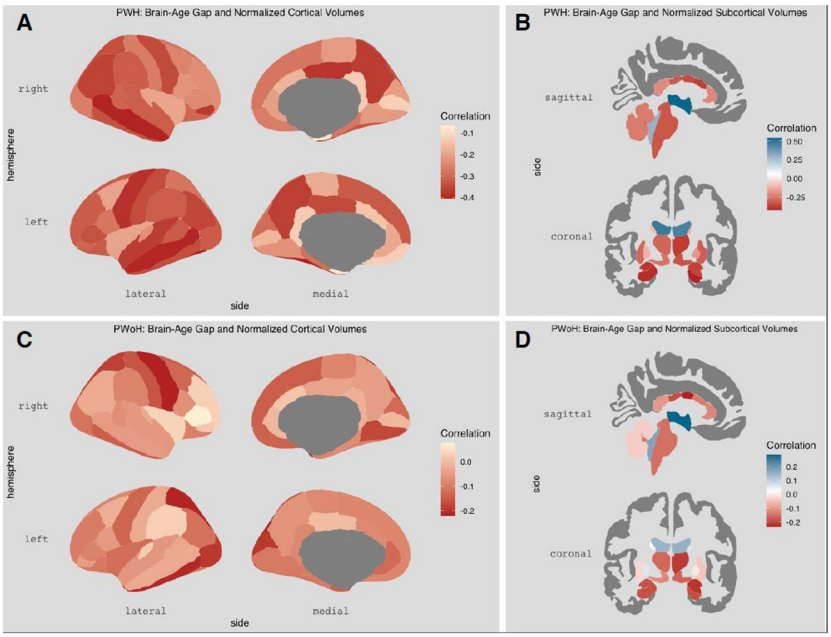

Figure 1. Spatial correlation map of brain-age gap and volumetric features.

To estimate the importance of volumetric features in the derivation of the brain-age gap by the convolutional neural network DeepBrainNet, correlations between brain-age gap and FreeSurfer volumes were calculated for PWH (A, B) and PWoH (C, D). All significant positive correlations (blue) were for ventricular cerebrospinal fluid compartments and for T_1 white matter hypointensities (not shown), while the strongest negative correlations were subcortical, in the hippocampus (bilateral), amygdala (bilateral), brainstem, and corpus callosum.

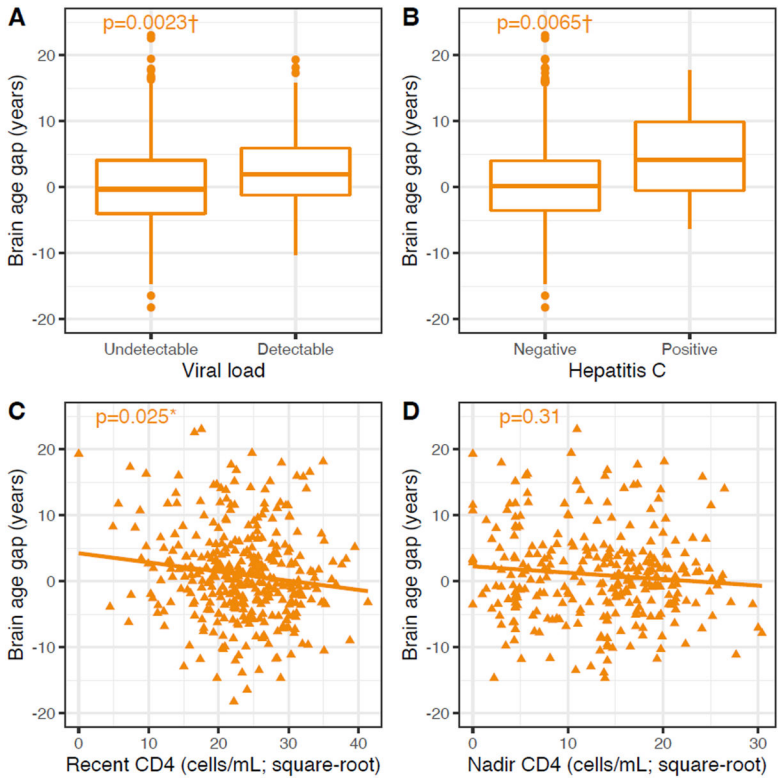

Figure 2. HIV-specific predictors of brain aging.

Univariate associations between potential predictors of brain aging and DeepBrainNet-derived brain-age gap, i.e., the difference between model-estimated age and chronological age. Four factors were considered only in persons with HIV (PWH): plasma HIV viral load (A), hepatitis C co-infection (B), current CD4 T-cells in plasma (C), and lifetime minimum (nadir) CD4 T-cells (D). *=significant at pre-corrected $p<0{\cdot}05$. †=significant at $p<0{\cdot}05$ after false discovery rate correction.

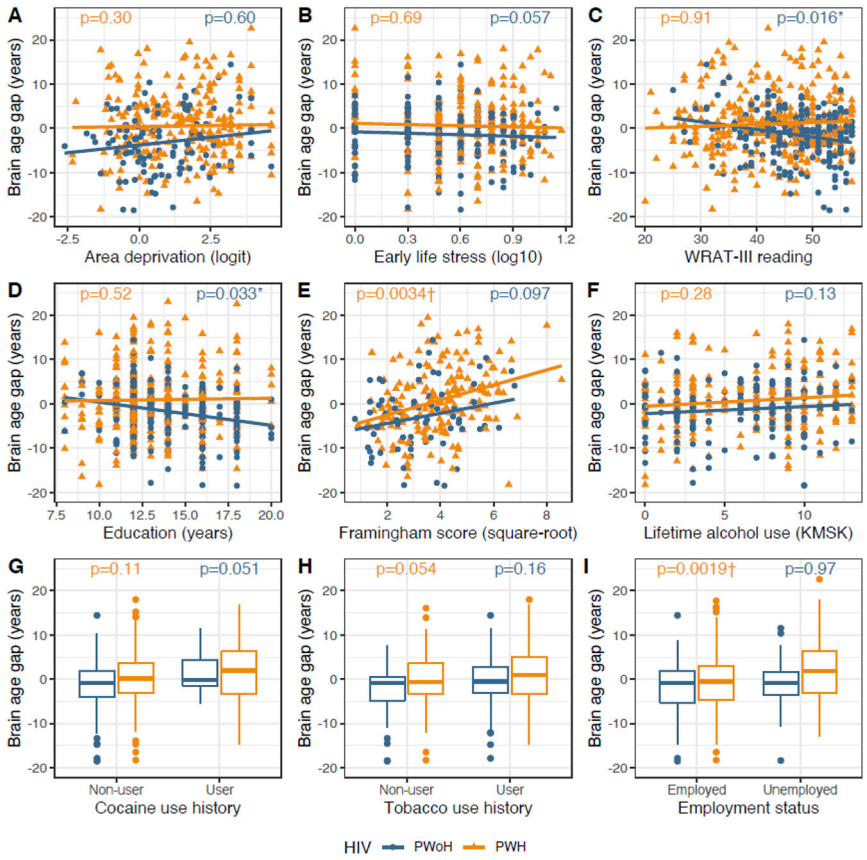

Figure 3. Predictors of brain aging for persons with and without HIV.

Univariate associations between potential predictors of brain aging and DeepBrainNet-derived brain-age gap. Seven factors were examined for both persons with and without HIV: area deprivation index (A), early life stressors (B), educational quality (C), educational duration (D), Framingham cardiovascular risk (E), alcohol (F), cocaine (G), tobacco (H), and employment status (I). *=p<0·05. †=significant at p<0·05 after false discovery rate correction.

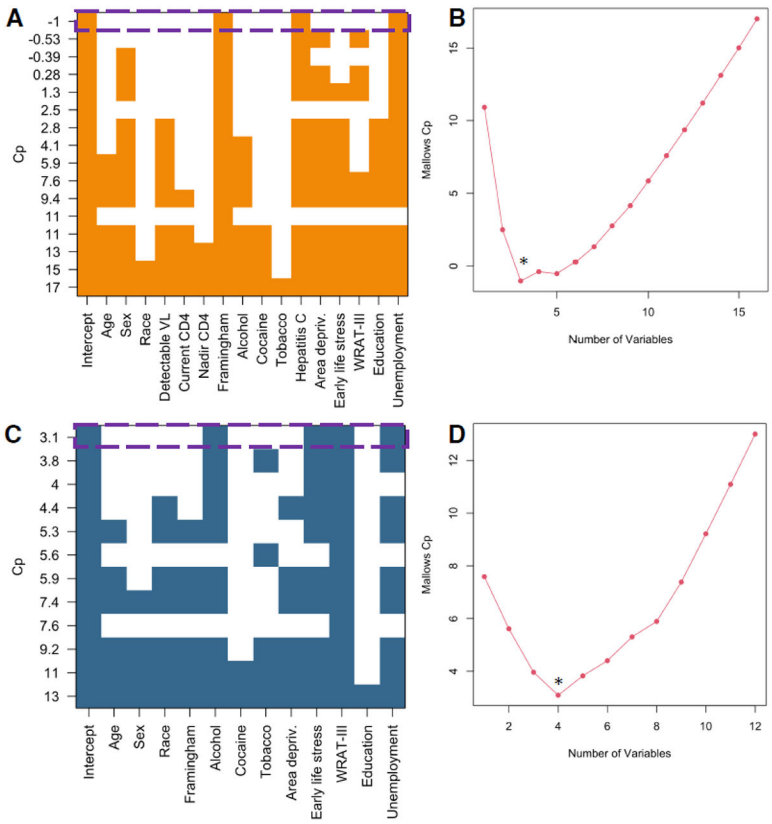

Figure 4. Multivariate prediction of brain-age gap in persons with and without HIV.

To identify predictor subsets that best explain the variability in the brain-age gap for persons with HIV (PWH, A and B) and persons without HIV (PWoH, C and D), best-subsets variable selection was performed using Mallow's C_p as selection criterion. Left panels (A, C) display the best result (lowest C_p) for each number of predictors; shaded panels indicate that the predictor in that column was included. The selected model (highlighted row) for PWH included Framingham cardiovascular risk, hepatitis C, and unemployed status. The model for PWoH included alcohol use, early life stress, WRAT-III reading score, and unemployed status. Right panels (B and D) show model fit across the number of predictors, where the minimum C_p is obtained with three predictors for PWH and four predictors for PWoH.

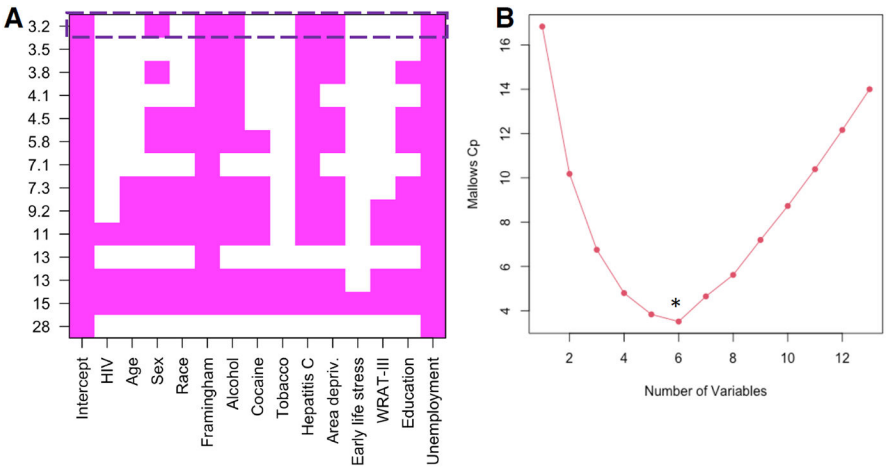

Figure 5. Multivariate predictors of brain aging in combined cohort of persons with and without HIV.

Best-subsets selection was also performed to model the brain-age gap for persons with HIV (PWH) and without HIV (PWoH). Panel A displays the best result (lowest C_p) for each number of predictors; shaded magenta panels indicate that the predictor in that column was included. The final model (top row) included male sex, Framingham risk score, lifetime alcohol use, hepatitis C, area deprivation index, and unemployment. Panel B shows the model fit across the number of predictors, where the minimum C_p is obtained with six predictors (asterisk).

Table 1.

Participant characteristics.

	PWoH	PWH	*p*-value
N	259	379	
Age (yr, mean±SD)	38·3±17·1	44·8±15·5	<0·0001 ***
Sex (%)			<0·0001 ***
Male	129 (49·8%)	296 (78·1%)	
Female	130 (50·2%)	83 (21·9%)	
Race			0·0021 **
Black / African-American (%)	146 (56·4%)	260 (68·6%)	
White	104 (40·2%)	111 (29·2%)	
Asian	7 (2·7%)	2 (0·5%)	
American Indian / Native American	0 (0·0%)	1 (0·2%)	
Multiracial	2 (0·8%)	4 (1·0%)	
Other	0 (0·0%)	1 (0·3%)	
Education (years)	14·0±2·4	13·2±2·4	<0·0001 ***
Unemployed (incl. disability)	28 (10·8%)	102 (27·6%)	<0·0001 ***
10-year Framingham risk score	12·7±10·8	17·1±12·1	0·0065 *
Alcohol use (KMSK total)	6·0±3·7	6·9±4·0	0·015 *
Cocaine use (KMSK total)	0·6±2·2	3·3±5·3	<0·0001 ***
Tobacco use (KMSK total)	4·4±4·8	6·6±4·9	<0·0001 ***
Area Deprivation Index (percentile)	63·8±25·0	73·4±24·8	0·0011 **
Early Life Stress total events	3·1±2·8	3·9±2·9	0·0023 **
WRAT-III reading subtest	47·1±7·1	43·0±8·7	<0·0001 ***
Viral load (copies/mL, $\log_{10}$)		1·8±1·1	
Undetectable VL (≤ 50 copies/mL)		295 (77·8%)	
Most recent CD4 count (cells/μL)		588·0±311·8	
Nadir CD4 count (cells/μL)		224·3±199·7	
Hepatitis C infection (%)		25 (7·0%)	

Quantitative values reported as mean ± standard deviation, and compared between groups with Analysis of Variance (ANOVA). Categorical values reported as *n* and percentage, and compared with χ^2 tests. Abbreviations: PWoH=persons without HIV, PWH=persons with HIV, yr=years, KMSK=Kreek-McHugh-Schluger-Kellogg, WRAT=Wide Range Achievement Test, Third Edition, VL=viral load. Significance key:

* =p<0.05

** =p<0.01

*** =p<0.001.