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Increased brain-predicted ageing in treated HIV disease

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Abstract

Objective: To establish whether HIV disease is associated with abnormal levels of age-related brain atrophy, by estimating apparent "*brain age"* using neuroimaging and exploring whether these estimates related to HIV-status, age, cognitive performance and HIV-related clinical parameters.

Methods: A large sample of virologically-suppressed HIV-positive adults (N = 162, aged 45-82 years) and highly-comparable HIV-negative controls (N = 105) were recruited as part of the COBRA collaboration. Using T1-MRI scans, a machine-learning model of healthy brain ageing was defined in an independent cohort (N = 2001, aged 18-90 years). Neuroimaging data from HIV-positive and HIV-negative individuals were then used to estimate *brain-predicted age*; then brain-predicted age difference (brain-PAD = brain-predicted brain age - chronological age) scores were calculated. Neuropsychological and clinical assessments were also carried out.

Results: HIV-positive individuals had greater brain-PAD score (mean ± SD = 2.15 ± 7.79 years) compared to HIV-negative individuals (-0.87 ± 8.40 years; b = 3.48, p < 0.01). Increased brain-PAD score was associated with decreased performance in multiple cognitive domains (information processing speed, executive function, memory) and general cognitive performance across all participants. Brain-PAD score was not associated with age, duration of HIV-infection or other HIV-related measures.

Conclusions: Increased apparent brain ageing, predicted using neuroimaging, was observed in HIV-positive adults, despite effective viral suppression. Furthermore, the magnitude of increased apparent brain ageing related to cognitive deficits. However, predicted brain age difference did not correlate with chronological age or duration of HIV-infection, suggesting that HIV disease may accentuate, rather than accelerate brain ageing.

Introduction

Despite effective viral suppression due to combination anti-retroviral therapy (cART), chronic HIV disease has been linked with a higher risk of multiple diseases of old age. These include cardiovascular, renal, hepatic or pulmonary disease, cancer, osteoporosis and physical frailty.[1-4] This has led researchers to consider whether chronic HIV disease accelerates the normal ageing process,[5] a hypothesis potentially supported by the increased prevalence of cognitive impairment.[6-8] If HIV accelerates *cognitive* ageing, this has huge implications for HIV-positive individuals, their families and the healthcare systems tasked with providing future care.

Cognitive ageing is a consequence of physiological changes in the brain (i.e., *brain* ageing), including a loss of brain volume.[9] Deviations from a typical brain-ageing trajectory (e.g., acceleration) may result from a brain injury, neurodegenerative disease or potentially, chronic HIV. While reduced brain volumes are frequently reported in HIV disease,[10-19] the evidence supporting *accelerated* brain ageing is more equivocal.[10,20,21] These studies used macroscopic brain volume measures to correlate with chronological age. In contrast, we employed machine learning to make explicit estimations of age, based on three-dimensional brain volume maps.[22] Such neuroimaging-based 'brain age' estimations appear sensitive to pathological aspects of ageing and cognitive impairment,[22-24] thus represent a potential biomarker of brain ageing.

Here, we generated brain-predicted age difference (brain-PAD) scores in HIV-positive individuals and highly-comparable HIV-negative controls, testing the following hypotheses: (1) HIV-positive individuals would have greater brain-PAD than HIV-negative individuals; (2) brain-PAD would be associated with deficits in cognitive performance; (3) that HIV-related parameters would be associated with brain-PAD.

Materials and Methods

Participants

The study included 162 HIV-positive individuals and 105 HIV-negative controls who had highly similar demographic and lifestyle characteristics (Table 1). These participants comprised the test set in the machine-learning analysis. Participants were recruited from two sites: London and Amsterdam, as part of the COmorBidity in Relation to AIDS (COBRA) collaboration.Exclusion criteria for COBRA were: age under 45 years, current major depression (PHQ-9 questionnaire score of ≥15), confounding neurological diseases, previous severe head injury (loss of consciousness ≥30 minutes), previous cerebral infections (including AIDS-defining CNS diseases), self-reported intravenous drug use within the past six months, daily use of recreational drugs (with the exception of cannabis), excess alcohol intake (>48 units per week), severe psychiatric disease or MRI contraindications. All HIV-positive participants were required to be on cART and to have had undetectable plasma HIV RNA (<50 copies/mL) for ≥12 months prior to enrolment.

A further 2001 individuals (1016 males, age mean ± SD = 36.95 ± 18.12 years; range, 18-90) comprised the training dataset. These individuals were drawn from publicly-available data repositories (table e-1) and were screened according to each study's local inclusion protocols to ensure the absence of neurological or psychiatric diseases and major health conditions.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the institutional review board of the Academic Medical Center (AMC) and the London (Stanmore) Research Ethics Committee. All participants gave written informed consent. For participants comprising the training dataset, ethical approval was granted for each contributing study and permission for subsequent data sharing was verified for each data repository.

Neuropsychological assessment

Participants completed a comprehensive neuropsychological assessment, with tests of attention, executive function, language fluency, memory, speed of information processing and motor function (see table e-2). Raw test scores were standardised as T-scores, (age, sex and education level adjusted). Higher T-scores represented better cognitive function. Test scores were averaged within domains to calculate domain specific T-scores and across domains to calculate a global T-score. Three HIV-positive participants were missing data for one or more domains. Categorical classifications of cognitive impairment in HIV were made based on the global deficit score.[25] The global deficit score is obtained by converting cognitive domain T-scores to deficit scores and then averaging them. A score ≥0.5 was defined as cognitively impaired.

Neuroimaging data acquisition

Acquisition parameters were harmonised between sites and scanners (London: Siemens Verio 3T; Amsterdam Philips Intera, upgraded to Ingenia 3T). This resulted in the following protocols for three-dimensional T1-weighted structural images: London; magnetisation-prepared rapid gradient-echo (MPRAGE), TE = 2.98 ms, TR = 2300 ms, TI = 900ms, flip angle = 9°, field-of-view = 256 mm, 160 slices of 1.0 mm thickness, in-plane resolution = 1.0 x 1.0 mm. Amsterdam; sagittal Turbo Field Echo (T1-TFE), TE = 3.1ms, TR = 6.6ms, flip angle = 9°, field-of-view = 270 mm, 170 slices of 1.2 mm thickness, in-plane resolution = 1.1 x 1.1 mm. Three-dimensional structural images for the training set were acquired using various parameters and field strengths (1.5T and 3T), according to local study protocols (table e-1).

Brain age prediction procedure

An overview of the brain age prediction procedure is presented in figure 1. We followed the protocol as previously outlined,[22] with the minor adaptation that grey matter (GM) and white

matter (WM) images were analysed together, to generate a whole-brain predicted age, rather than tissue specific age predictions. In brief, all images were pre-processed using SPM12 (University College London, London, UK) to generate normalised 3D maps of GM and WM volume, in MNI152 space. Normalisation used SPM-DARTEL for non-linear registration and resampling included modulation and 4mm smoothing. Information from four individuals was excluded at this stage (one HIV-positive, three HIV-negative), due to excess motion artefact or poor head positioning, resulting in a final sample size of N = 161 HIV-positive and N = 102 HIV-negative participants for the test set, alongside N = 2001 individuals in the training set.

Brain age prediction was carried by defining a Gaussian Processes regression to model the relationship between 3D GM and WM volume maps and chronological age in the training set, using PRoNTo v2.0 (www.mlnl.cs.ucl.ac.uk/pronto). Age predictions on all participants were generated using ten-fold cross-validation. Model accuracy was expressed as the correlation between age and predicted age (Pearson's r), total variance explained (R^2), mean absolute error (MAE) and root mean squared error (RMSE). Statistical significance of this model was assessed using permutation testing (n = 1000).

Coefficients from the validated regression model were then applied to the test data (i.e. HIV-positive and HIV-negative individuals). This generated a brain-predicted age estimate per subject. Finally, brain-predicted age difference (brain-PAD) scores were calculated for each test subject by subtracting chronological age from brain-predicted age. Hence, a positive brain-PAD indicates that the subject's brain was predicted to be 'older' than their chronological age. Brain-PAD scores were used in subsequent analysis to index age-adjusted, or relative, brain ageing.

As neuroimaging data were acquired on multiple scanners, a separate sample of healthy volunteers were scanned in both London and Amsterdam (N = 11, age range = 23-42 years old) to assess between-scanner reliability. Brain-PAD scores were calculated for each participant from scans at both sites. The absolute agreement of brain-PAD score between

scanners was high; intra-class correlation coefficient = 0.95, 95% confidence intervals [0.84, 0.99], $p < 0.01$.

Statistical analysis

Further statistical analyses were conducted using *R*, v3.2.3. With brain-PAD scores as the dependent variable, HIV-positive and HIV-negative groups were compared using a linear regression. Covariates included scanner type, sex and intra-cranial volume (ICV) and smoking status, but not age. For analysis of neuropsychological performance, linear regression models were fit using domain T-scores as the dependent variable, and brain-PAD score, HIV-status, sex and ICV as predictor variables. Interactions between HIV-status and brain-PAD score were then modelled by repeating the above linear regressions with the addition of an interaction term. Multiple comparison correction across the six domains were not carried out due to the non-independent nature of the neuropsychological tests. Effect sizes for linear regression was quantified using partial η^2. Group differences in categorical variables (e.g., smoking status, sex, cognitive impairment) were assessed using Fisher's exact tests. Group comparisons in neuropsychological test performance were performed using the Wilcoxon rank-sum test.

Results

Age can be accurately predicted using neuroimaging data

Cross-validation in the training set indicated that data from 3D brain volume maps accurately predicted chronological age in the training set ($r = 0.94$, $R^2 = 0.88$, MAE = 5.01, RMSE = 6.31; figure 2). This remained significant after permutation correction (corrected $p < 0.01$).

Brain-predicted age difference is higher in HIV-positive individuals

HIV-positive individuals showed increased brain-PAD (brain-predicted age - chronological age) scores, compared to HIV-negative individuals ($b = 3.31$, SE = 1.0, t = 3.30, $p < 0.01$, $\eta^2 = 0.031$; figure 3A). Mean brain-PAD score in HIV-positive individuals was 2.15 (SD = 7.79)

years, while in HIV-negative individuals it was -0.87 (SD = 8.4) years. HIV-positive individuals' brain-PAD scores were greater than the training set mean (i.e. brain-PAD of 0) (t = 3.51, p < 0.01), while HIV-negative individuals' brain-PAD scores were not (t = -1.05, p = 0.3). Brain-predicted age correlated with chronological age in both groups (HIV-positive: r = 0.75, p < 0.01; HIV-negative: r = 0.69, p < 0.01; figure 3B). Importantly, there was no interaction between age and group in predicting brain-PAD (p = 0.28), indicating that the association with HIV disease did not vary as a function of chronological age.

HIV-positive individuals show evidence of impaired cognitive performance

HIV-positive individuals showed impaired neuropsychological performance relative to HIV-positive controls in multiple cognitive domains. These were: attention (W = 10683.5, p < 0.01), processing speed (W = 10674.5, p < 0.01), executive function (W = 10004.5, p = 0.01) and motor function (W = 9874, p = 0.02), alongside global cognitive performance (W = 10499.5, p < 0.01). For language fluency (p = 0.30) and memory (p = 0.38), T-scores did not differ between HIV-positive and HIV-negative groups. Global deficit score categorisation showed that cognitive impairment was more common in the HIV-positive group compared to HIV-negative controls (N cognitively impaired: HIV-positive = 31 [19.1%], HIV-negative = 6 [5.7%], odds ratio = 3.92 [95% CI: 1.53, 11.94], p < 0.01).

Brain-predicted age difference correlates with cognitive performance

Brain-PAD related to cognitive performance across HIV-positive and HIV-negative participants. Brain-PAD was inversely associated with performance in the domains of information processing speed, executive function and memory, and with global cognitive performance (table 2). Trend-level associations were evident for attention, language and motor function (0.05< p < 0.1). Interactions between HIV status and brain-PAD were not significant for any cognitive domain (p > 0.1), indicating that the influence of brain-PAD on cognitive performance did not vary according to HIV-status. Brain-PAD score did not differ

based on global deficit score categorisation of cognitive impairment ($p > 0.1$), either when grouping all participants together or when looking solely within HIV-positive individuals.

Associations with HIV-related factors

HIV-related clinical measures were generally unrelated to brain-PAD score in HIV-positive individuals (all $p > 0.1$). These included years since HIV diagnosis, duration of cART, nadir CD4 count, months spent with CD4 count <500 cells/uL, current CD4 count, current CD8 count and CD4:CD8 ratio or a prior diagnosis of AIDS. We also assessed whether factors such as a history of hepatitis B or C infection, syphilis, cigarette smoking (pack years) and recreational drug use within six months influenced brain-PAD in HIV-positive individuals, however no associations were evident (all $p > 0.1$).

Discussion

Increased levels of age-associated changes to brain structure were evident in HIV-positive individuals with suppressed plasma HIV-viraemia, compared to a highly comparable HIV-negative group. The magnitude of increased brain ageing (i.e. brain-PAD score), derived from structural neuroimaging, related to neuropsychological test scores. Individuals with 'older' brain-predicted ages, relative to chronological age, showed deficits in information processing speed, executive function, memory and global cognitive performance. Brain-PAD score did not correlate with chronological age or duration of infection, suggesting that HIV disease does not accelerate the rate of age-associated brain atrophy.

Increased brain-PAD was associated with poorer cognitive performance in multiple domains. The characteristic pattern of age-related cognitive decline is associated with impairments in processing speed, executive function and memory, while vocabulary and general knowledge are thought to be relatively stable.[26] The largest effect sizes for a relationship with brain-PAD score were found for memory, executive function and processing speed, similar to the expected pattern of typical cognitive ageing. However, at least borderline effects were seen

in all domains and the strength of these associations were relatively modest. This means we cannot definitively conclude whether changes in brain-PAD score relate specifically to cognitive ageing or more general cognitive impairment. Moreover, cognitive performance between domains is likely to be inter-related, potentially driven by information processing speed,[27] or general intelligence. Interestingly, the relationship between brain-PAD and cognitive performance was seen in both HIV-positive and HIV-negative groups, despite observing greater cognitive impairment in HIV-positive individuals. This implies that brain-PAD reflects a general relationship between brain structure and cognition. HIV is potentially accentuating these age-related changes in brain structure, which then drives deficits in cognitive performance. That the damage to the brain in HIV relates to that seen in normal ageing agrees with previous work which has reported a spatial overlap between HIV-associated brain regions and regions associated with ageing and cognitive performance in both HIV-positive and HIV-negative individuals.[11] Hence, it is plausible that chronic HIV disease could be driving atrophy in brain regions that commonly change with advancing age, resulting deficits in cognitive performance.

Our results suggest that chronic HIV disease may cause abnormal brain ageing, which could be either *accelerated* or *accentuated*.[28] Accelerated ageing implies an interaction with ageing that progressively increases the risk of age-related morbidity; while accentuated ageing implies that some initial process increased the burden of ageing-related damage but remains static over time. Our findings favour the latter interpretation, as we found no relationship between brain-PAD score and chronological age or duration of HIV diagnosis. This fits with evidence from neuroimaging studies that have demonstrated independent effects of ageing and HIV on the brain,[10,11,16,19,29] and does not support reports of accelerating effects.[12,21,30] However, these previous studies often included a preponderance of untreated individuals, those with detectable HIV-viraemia or younger adults (i.e. < 50 years old). These findings are harder to extrapolate to older, well-treated HIV-positive populations, where the effects of

aberrant ageing will be more pertinent. Furthermore, inferences regarding duration of HIV diagnosis as a proxy of duration of *actual* HIV-infection must be made cautiously, when date of seroconversion is unknown.

Clinical parameters relating to HIV were not associated with brain-PAD. Previous research has associated nadir CD4 count[14,15] and duration of known HIV-infection[13,17] with measures of brain structure, although not universally.[10,16,19] The nature of the participants in these studies differs substantively from ours. In general, HIV-positive individuals in our study were older, all were effectively treated with cART and had higher CD4 counts. Crucially, our HIV-negative control group was recruited to be highly comparable, reducing the influence of important confounding factors such as cigarettes, alcohol and recreational drugs use. The lack of association with current HIV-related parameters indicates that when viral replication is suppressed, such factors may have limited on-going relevance to brain health.

Neuroimaging-based age predictions may represent a biomarker of the ageing process. Such measures could potentially track neurodegeneration in the ageing HIV-positive population and identify those at greater risk for poor cognitive outcomes. Cellular and molecular markers of biological ageing have also indicated ‘age-like’ increases in HIV, using telomere length, markers of CD8 T-cell senescence and DNA methylation levels.[31-35] Our findings generally concur with these reports, which suggests that individuals with chronic HIV disease also experience increased accumulation of the cellular damage associated with ageing, resulting in ‘age-like’ brain atrophy. HIV-positive individuals were on average greater than 3 years older compared to the control group. This is a lower estimate compared to age predictions from the ‘epigenetic clock’, where brain tissue and blood resulted in 7.4 years and 5.2 years of increased ageing respectively.[32] Whether this is due to differences in the methods or the characteristics of the HIV-positive individuals is unclear. A major consideration of DNA-based ageing biomarkers is the type of cells used to derive the estimates. T-cells, for example, may well have been affected by the presence of HIV. While brain age and DNA-methylation age

prediction methods are conceptually similar and it would be of interest to compare age predictions made using DNA methylation profiles and structural neuroimaging. Furthermore, integrating multiple sources of molecular, cellular and physiological data could provide highly informative insights into distinct 'compartments' of biological ageing or improve estimates of a more global biological age measure. Accurate ageing biomarkers have great potential for detecting heightened risks of age-associated diseases in HIV-positive individuals and may aid in the design and recruitment of clinical trials of treatments aimed at reducing the burden of comorbid disease.

Here, we observed lower brain volumes in HIV-positive individuals, presumably due to atrophy. Our model allows us to quantify this change and relate it to brain structure in healthy individuals. HIV-positive individuals had brains that resembled individuals 2.15 years older. We interpret this as increased brain ageing, although one must be cautious in interpreting the results in this way. Brain atrophy does not necessarily mean 'ageing' *per se*. For example, neurological insults (e.g., stroke, focal lesions from a traumatic brain injury, encephalitis) can result in brain tissue loss that is not primarily due to ageing. However, our participants were free from a history of cerebral infections or focal neurological injury. Hence, gross insults are unlikely to be driving the results. The observed brain tissue loss is likely to be the result of historical damage or the gradual build-up of deleterious factors, such as persistent neuroinflammation. It is unclear whether the biological mechanisms underlying brain tissue loss in HIV are the same as the mechanisms involved in brain ageing. However, what is evident at the macroscopic level we have studied (i.e., volumetric MRI), is that the HIV brain appears prematurely aged.

Our study has further limitations. One is the cross-sectional design employed. Longitudinal studies are necessary for examining individual-specific trajectories of brain ageing,[36] to properly evaluate evidence for *accelerated* ageing. Also Brain-PAD showed high variability, indicating that it is potentially noise-prone. However, as ground truth 'brain age' is

unobtainable, this variation could be either measurement error or meaningful inter-individual variability. However, high between-scanner reliability (ICC = 0.95) and correlations with cognitive performance and other 'real-world' measures in this and previous studies,[22] support the use of such a measure to index age-related changes to brain structure. Other limitations are that our sample predominantly included white, northern European males. HIV is a global pandemic, thus corroboration of increased brain age in HIV in other populations is important.[37] Individuals in the training dataset used in the current study were generally not explicitly screened for HIV infection, though all were assessed to be cognitively normal and free of potentially confounding conditions. Undiagnosed rates of HIV are low (<1%) so this would have been unlikely to confound the results. Also, we did not investigate other HIV-related factors not directly associated with the virus that could also affect brain ageing, such as anti-retroviral toxicity, lifestyle and cardiovascular disease.[38] Finally, our machine learning method benefits from using a large independent 'normative' database, where the relationship between 3D brain volume maps and age is modelled across the adult lifespan. However, HIV disease may result in specific brain changes that are not captured by this model and may explain some of the observed cognitive deficits. For instance, treated-HIV has been associated with microstructural WM abnormalities[39] and WM hyperintensities[40] that would not be detected by our model. Future studies could incorporate further imaging modalities to better model differential patterns of brain ageing in HIV.

HIV-positive individuals with undetectable plasma HIV RNA showed increased 'brain age', estimated using structural neuroimaging. This increase in apparent brain age related to neuropsychological performance across multiple cognitive domains, indicating that brain-predicted age may tap into aspects of cognitive ageing, a major risk factor for negative long-term outcomes in older adults with HIV disease. However, chronological age was not associated with the magnitude of increased brain age. Thus our results are more consistent with the idea of accentuated, rather than accelerated, brain ageing in treated HIV disease.

Figure Legends

Figure 1. Study methods

Outline of machine learning brain age prediction methods used in the study. Data included three separate groups: healthy individuals (N = 2001) comprised the training data, HIV-positive individuals (N = 161) and HIV-negative controls (N = 102) comprised the test data, after quality control (N = 4 exclusions). A) All data were pre-processed with SPM to segment T1 images into grey and white matter images. These segmented images were then normalised to a custom template using DARTEL for non-linear registration, before being resampled to MNI152 ($1.5mm^3$) template space, using volumetric modulation and a 4mm smoothing kernel. Grey and white matter images were then concatenated for each subject. B) Machine learning age prediction used PRoNTo: i) representation of all data in a linear kernel form as a similarity matrix of the dot-products between pairs of vectorised and concatenated volume images. ii) Supervised learning stage. Data from the training set were run through a Gaussian Processes Regression model to define the correspondence between brain volume maps and chronological age. Model accuracy was assessed on predictions made during a ten-fold cross-validation procedure. iii) Test set prediction. The coefficients from the model trained on the healthy sample were used to generate predicted age values from the data in the HIV-positive individuals and HIV-negative controls. Prediction age difference (brain-PAD) scores were defined by subtracting chronological age from predicted age. C) Statistical analysis based on brain-PAD scores as an index of apparent brain ageing.

Figure 2. Brain-predicted age in the training dataset

Scatterplot of chronological age (x-axis) and predicted brain age (y-axis), based on results of ten-fold cross-validation of the Gaussian Processes regression model in the training dataset (N = 2001). Dashed line (black) represents the line of identity (y = x), where predicted age = chronological age.

Figure 3. Predicted age differences in HIV-infection

A) Grouped data plot of predicted age differences (brain-PAD) in HIV-positive individuals (red triangles) and HIV-negative controls (blue spots). Solid black lines indicate group mean brain-PAD values. B) Scatterplot of chronological age in years (x-axis) against predicted brain age (y-axis) generated using structural neuroimaging. Points indicate HIV-positive individuals (red triangles) and HIV-negative controls (blue spots) and lines are regression lines for each group (HIV-positive = red; HIV-negative = blue), with 95% confidence intervals displayed. Dashed grey line is the line of identity (y = x).

Tables

Table 1. Characteristics of HIV-positive and HIV-negative study participants

	HIV-positive	HIV-negative	p
N	162	105	
Age (years)	56 (50.9-62.0)	55.8 (50.1-62.0)	0.87
Sex			0.97
Female	9 (5.6)	6 (5.7)	
Male	153 (94.4)	99 (94.3)	
Study site			0.14
Amsterdam	103 (63.6)	76 (72.4)	
London	58 (36.4)	29 (27.6)	
Years of education	14 (13-16)	16 (14-16)	0.31
Smoking status			0.10
Current smoker	47 (29.0)	25 (23.8)	
Ex-smoker	72 (44.4)	39 (37.1)	
Never smoked	43 (26.5)	41 (39.0)	
Alcohol consumption (units per week)	5.5 (1.5-15.0)	5.5 (1.5-15.0)	0.66
Use of recreational drugs in past 6 months	53 (32.7)	26 (25.0)	0.17
CD4+ count (cells/µL)	622 (472-809.8)	-	
CD4+:CD8+ cell count ratio	0.8 (0.60-1.1)	-	
Nadir CD4+ count (cells/µL)	170 (90-250)	-	
Time since HIV diagnosis (years)	14.6 (9.2-19.3)	-	
Duration of antiretroviral therapy (years)	12.6 (7.5-16.8)	-	
Time with CD4+ < 500 cells/mm3 (months)	150.9 (65.0-246.1)	-	

Prior clinical AIDS	56 (34.6)	-
Hepatitis B infection	7 (4.3)	0 (0.0)
Hepatitis C infection	14 (8.6)	1 (1.0)
Syphilis infection	13 (8.0)	2 (1.9)

Values are shown as median (inter-quartile range) or N (%). *P* refers to group comparison Wilcoxon rank-sum or Fisher exact tests where appropriate.

Table 2. Brain-predicted age difference and neuropsychological assessments

Cognitive domain	Main effect of brain PAD					Brain PAD by HIV-status interaction	
	b	SE	t	p	η^2 [90% CI]	t	p
Processing speed	-0.13	0.06	-2.25	0.03	0.019 [0.0, 0.06]	0.73	0.46
Executive function	-0.15	0.06	-2.48	0.01	0.023 [0.0, 0.07]	0.17	0.87
Language	-0.13	0.07	-1.88	0.06	0.014 [0.0, 0.05]	0.48	0.64
Memory	-0.20	0.06	-3.32	<0.01	0.041 [0.01, 0.08]	1.04	0.30
Attention	-0.14	0.08	-1.71	0.09	0.011 [0.0, 0.04]	0.56	0.58
Motor function	-0.11	0.06	-1.73	0.09	0.012 [0.0, 0.05]	1.20	0.23
Global cognition	-0.14	0.04	-3.33	<0.01	0.040 [0.01, 0.09]	1.03	0.31

Results shown are from separate linear regression models with PAD score as the outcome variable and each cognitive domain T-score as the predictor variable. PAD = Predicted age difference [predicted brain age – chronological age]; b = unstandardized regression coefficient; SE = Standard Error; η^2 = partial eta-squared effect size estimate and 90% confidence intervals.

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