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Progressive Brain Atrophy Despite Persistent Viral Suppression in HIV Over Age 60

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Abstract

Background—Current HIV treatments are successful at suppressing plasma HIV RNA to undetectable levels for most adherent patients. Yet, emerging evidence suggests viral suppression will inadequately control inflammation and mitigate risk for progressive brain injury. We sought to quantify differences in longitudinal brain atrophy rates among older virally suppressed HIV-infected participants compared to that of healthy aging.

Methods—We examined longitudinal structural brain MRI atrophy rates employing region of interest assessments and voxel-wise tensor-based morphometry in HIV-infected participants over age 60 years (n=38) compared to age-matched HIV-uninfected healthy and cognitively normal controls (n=24).

Results—The mean age of participants was 63 years, the mean estimated duration of infection was 21 years and the median of duration of documented viral suppression was 3.2 years. Average proximal and nadir CD4 counts were 550 and 166, respectively; 15/38 (39%) met criteria for HIV-associated neurocognitive disorder. In models adjusting for age and sex, HIV serostatus was associated with more rapid average annualized rates of atrophy in the cerebellum (0.42% vs. 0.02%, $p=0.016$), caudate (0.74% vs. 0.03%, $p=0.012$), frontal lobe (0.48% vs. 0.01%, $p=0.034$), total cortical gray matter (0.65% vs. 0.16%, $p=0.027$), brain stem (0.31% vs. 0.01%, $p=0.026$), and pallidum (0.73% vs. 0.39%, $p=0.046$). Among those with HIV, atrophy rates did not differ statistically by cognitive status.

Conclusion—Despite persistent control of plasma viremia, these older HIV-infected participants demonstrate more rapid progressive brain atrophy when compared to healthy aging. Either HIV or

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other factors that differ between older HIV-infected participants and healthy controls could be responsible for these differences.

Keywords

HIV; Magnetic Resonance Imaging; atrophy; antiretroviral agents

INTRODUCTION

In 2014, over a quarter of people living with the human immunodeficiency virus (HIV) in the United States were above the age of 55.¹ This older HIV-infected demographic is rapidly expanding and many of these patients have been on combination antiretroviral therapy (cART) for nearly two decades.² By virtue of older age and longer exposure to HIV and its treatments, they are at risk for detrimental central nervous system (CNS) outcomes and may be particularly vulnerable to faster rates of brain atrophy.³

HIV-related brain injury prior to the cART era is well documented and includes global brain atrophy, subcortical volumetric reductions, and cognitive impairment.^{4–7} Despite increased access to cART, cognitive manifestations of HIV, classified in research settings as HIV-associated Neurocognitive Disorder (HAND), remain a substantial concern with frequency increasing with age.^{8,9} Some studies demonstrate CNS inflammation persisting despite suppressive cART, suggesting that cART alone is insufficient in preventing progressive brain injury.^{10,11} Autopsy studies further note persistent HIV DNA in brain tissue of virally suppressed individuals on stable cART.¹² Detectable HIV DNA in the peripheral blood despite viral suppression is linked to smaller subcortical and cerebellar gray matter volumes.¹³

The literature is replete with cross-sectional analyses describing brain volumetric reductions associated with HIV serostatus, but do not typically examine rates of change and tend to include individuals not on cART or without plasma viral suppression. These reports often note smaller subcortical and corpus callosum volumes and sometimes note associations to duration of HIV infection, plasma HIV RNA levels, or proximal and nadir CD4 T-lymphocyte counts.^{14–18} Collectively, these cross-sectional studies conclude HIV-associated effects that others note are independent of gray and white matter volumes from aging itself.^{14,19,20} These independent effects collectively decrease brain reserve, likely placing older HIV-infected patients at increased vulnerability to HAND and age-associated neurodegenerative disorders.

Several recent longitudinal studies examined volumetric changes among participants on cART with variable viral suppression, noting smaller white matter and gray matter volumes and expanded ventricular regions compared to HIV-uninfected controls. One study's sample varied in age from 21–55 years and only 54% were virally suppressed in plasma.¹⁶ In analyses focused on those with plasma suppression, widespread white matter atrophy was noted. Another study examined adults aged 20–67 years old where 20% were not on cART and mean plasma HIV RNA at baseline was 9,609 copies/ml, documenting increased rate of change in the lateral ventricles, insula, and hippocampus volume of HIV infected participants versus controls. Evidence of faster atrophy in the frontal, sensorimotor, and

temporal-parietal cortex was also found in the HIV infected group.²¹ Another analysis conducted with Freesurfer over 26.6 months showed no longitudinal volume change in 21 virally suppressed (mean 53.9 years, range: 44–61).²²

The present work aimed to examine longitudinal rates of volumetric brain changes among HIV-infected older adults on cART maintaining persistent suppression of plasma HIV RNA compared to cognitively normal age- and sex-matched HIV-uninfected controls. There is controversy as to whether plasma viral suppression is sufficient to halt detrimental brain changes with some arguing that volumetric reductions described in HIV are due to past injury. This study was designed to test whether plasma viral suppression is sufficient to halt progressive atrophy in older HIV-infected participants. We employ region of interest (ROI) comparisons from neuroanatomy informed by prior studies. Secondly, we employ Tensor Based Morphometry (TBM) at a voxel-wise level to explore volumetric reductions across all brain regions.

METHODS

Participant selection

HIV-infected participants were recruited into the University of California San Francisco (UCSF) HIV Over 60 Cohort. All were over age 60 years and excluded from enrollment if they had factors confounding a HIV-related cognitive diagnosis, including major neurological or psychiatric conditions (e.g. multiple sclerosis, major depression), current or past brain infection, active neoplastic disease (except skin cancer), current substance abuse or dependence, thyroid abnormality or vitamin B₁₂ deficiency, major stroke, or traumatic brain injury. All reported English as their primary language and had been on cART for at least 12 months. The HIV-uninfected healthy control participants were selected from a longitudinal cohort of healthy brain aging at our center, as previously described.^{23–25} In addition to exclusions described above for the HIV sample, all HIV-uninfected controls denied memory issues or functional complaints due to cognitive impairment, had Mini-mental State Exam scores above 26, Clinical Dementia Rates of 0 and were reviewed at a consensus conference to have normal cognitive function.²⁶

For these analyses, we selected only HIV-infected participants with documented persistently suppressed plasma HIV RNA defined as <400 copies/ml to accommodate for historical changes in lower level of detection during the enrollment period (05/2008 to 01/2016) and occasional viral blips of unclear significance.²⁷ Healthy controls were matched to the HIV-infected group by age and sex by including all healthy control males enrolled between the ages of 60 and 75 years and two randomly selected women to match the two HIV-infected women. Participants in both groups were required to have at least two longitudinal MRI acquisitions. The average number of follow up scans was 2.74 with most (n=35) having only 2 scans.

At baseline and follow-up annual visits, we completed standardized Alzheimer's Disease Research Center (ADRC) evaluations that included a neurological examination, neuropsychological testing, and 3-Tesla structural brain MRI. For HIV-infected participants, clinical parameters including CD4 T-lymphocyte count and plasma HIV RNA were acquired

through a local reference laboratory if not available from clinical reports captured within the three months prior to study entry. Cognitive evaluations were conducted \pm 6 months to imaging with 31/38 (82%) concurrent by three months and the mean (SD) time between neuropsychological testing and imaging being 45 (36) days for baseline and 28 (45) days at follow-up. All participants provided IRB-approved informed consent.

Imaging Acquisition

Participants underwent whole-brain imaging on a Siemens TIM Trio 3-Tesla MRI scanner with a 12-channel head coil. We acquired 3D-T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequences (240 \times 256 matrix; FOV=256 mm; 160 slices; voxel size=1.0 \times 1.0 \times 1.0mm³; TR=2300 ms; TE=2.98 ms; flip angle=9°). Images were visually inspected for quality; images with excessive motion or image artifact were excluded (n=6).

Brain volumetric analyses

Images were segmented into gray matter, white matter, and cerebrospinal fluid and longitudinal TBM was implemented using the Statistical Parametric Mapping (SPM12) package. We performed registration and segmentation according to previously described methods employing SPM's longitudinal registration package.^{28,29} Intra-subject template images were created and warps were estimated between a subject's given time point and their intra-subject template. To calculate the amount of volume change locally, change maps (the rate of change in Jacobians per voxel for each participant), were created using the difference in Jacobian determinants for two time points divided by time between the scans. Each Jacobian encoded the amount of local expansion or contraction of the deformation fields needed to transform the image to the subject average, the difference was subsequently divided by years between the two acquisitions, describing volume change over time.²⁸⁻³⁰ Images were aligned by comparing gray and white matter intensities for images across cases on a voxel-wise basis. Each participant's average template was warped to construct a study-specific template (DARTEL) then images were smoothed using an isotropic 6mm full width at half-maximum Gaussian kernel. All segmentations were carefully inspected by two contributors to ensure labeling errors associated with white matter hyperintensities or other aberrations were not included in the analysis.

For ROI analyses, volumes were extracted based on the Desikan-Killiany atlas with tissues that were smoothed, warped, and modulated from native space to International Consortium for Brain Mapping (ICBM) space using the longitudinal framework described in the previous section.^{31,32} Volume for the last time point was subtracted from the first time point and divided by inter-scan periods in years provided a calculation for annualized atrophy rates for each participant. These atrophy rates were used to examine group-wise differences. Baseline volumes from these time points were used for cross-sectional analyses.

Statistical Approach

We examined group differences between HIV-infected and uninfected controls, between HIV-infected participants with HAND compared to without HAND, and between HIV-infected participants with HAND compared to controls. We examined cross-sectional difference by groups using voxel-based morphometry (VBM). Two-sample t-tests were

conducted at each voxel at baseline in models that included age, sex, and total intracranial volume (TIV).

For longitudinal analyses, we employed both ROI and TBM approaches. Differences in ROI volumes were compared using Stata v13.1 to determine rates of change in targeted ROIs. While consecutive time point scans were used for intra-participant registration, segmentation, and the construction of a study-specific template, statistical comparisons considered the first and last time point scans. Based on extant literature, we examined cerebellum, deep gray matter structures (e.g. putamen, caudate, thalamus, nucleus accumbens, and pallidum) temporal lobes, frontal lobes, brain stem, lateral ventricles, total white matter, total cerebral white matter and total cortical gray matter.

To explore voxels across the full brain (TBM analyses), we performed voxel-wise statistics using general linear modeling in SPM12. Two-sample t-tests were employed to compare change maps between groups applying a gray or white matter mask to restrict the area of statistical comparison. A significance threshold of $p < 0.05$ was applied for multiple comparisons across the whole brain using family-wise error (FWE) correction and, secondarily, a lower height threshold using cluster-based thresholding at a significance of $p < 0.001$, uncorrected. Significant clusters were described using automated anatomical labeling (AAL) in Montreal Neuroimaging Institute (MNI) space with age and sex as covariates³³. FMRIB Software Library's (FSL) permutation algorithm (randomize) with 5000 iterations was employed with threshold-free cluster enhancement (TFCE), for analyzing non-parametric distributions in cluster mass.

Regression models were used to examine relationships between cross-sectional ROI measurements and major cognitive domains spanning from information processing, manual dexterity, executive, and global cognition, as previously described.^{25,34} Similarly, we employed regression models to examine clinical variables including duration of HIV, nadir and proximal CD4 counts. These analyses comprised of two different levels, first assessing relationships between baseline volume and all clinical variables simultaneously, correcting for age, sex and TIV. Second, a model relating neuropsychological performance with clinical variables in conjunction with baseline volume was used, without need to control for age and sex for neuropsychological performance (z score) as the outcome variable.

RESULTS

Clinical characteristics of participants

The mean duration of follow-up was 3.4 years (range: 0.9–6.5 years) for the 38 HIV-infected participants and 3.4 (0.8–6.4) years for the 24 HIV-uninfected healthy controls (Table 1). Among HIV-infected participants, 15/38 (39%) met research criteria for HAND, with four (11%) having Asymptomatic Neurocognitive Impairment and eleven (29%) having Mild Neurocognitive Disorder.³⁵ All other HIV-infected and all healthy participants were cognitively normal by consensus conference.

On average, HIV-infected participants reported 21 years (range: 7–31 years) since HIV diagnosis with 74% reporting being on cART for >10 years at baseline. All had documented

plasma viral suppression for each visit during longitudinal follow-up. Additionally, among the HIV-infected participants, 57% self-reported persistent viral suppression for between 5–10 years, while 39% self-reported suppression for >10 years, although 17% reported either small “blips,” or a planned drug holiday prior to enrollment, where their plasma HIV RNA was elevated for a short time but then returned to undetectable. Over the duration of follow-up, cognitive status remained stable for 66% of participants ($n=25$), whereas 5/15 participants with HAND no longer met HAND criteria at follow-up and 8/23 without HAND at baseline met criteria at follow-up, consistent with the fluctuating pattern described by others.³⁵ As a group, neuropsychological performance, measured as a summary z-score of all tests administered, did not change over time ($p=0.585$).

Baseline cross-sectional volumetric analyses

In ROI analyses and within the HIV-infected group, HAND participants had reduced volume in the cerebellum ($p=0.023$), nucleus accumbens ($p=0.003$), and brain stem ($p=0.016$) compared to those without HAND, and reduced volumes in the cerebellum ($p=0.019$), nucleus accumbens ($p=0.014$), and brain stem ($p=0.012$) compared to controls with expansion noted in ventricular volumes in HIV, suggestive of central brain atrophy ($p=0.032$, Table 2, top panel and Figure 1). Examining all HIV-infected participants regardless of cognitive impairment and compared to controls, HIV serostatus alone was not associated with a reduced volume in any *a priori* regions compared to controls.

Among HIV-infected participants, no associations were found between clinical HIV variables and baseline volumes. Better executive functioning performance was associated with larger total baseline volume of deep gray structures, particularly, the caudate ($p=0.005$) and nucleus accumbens ($p=0.001$). Similarly, we found associations between executive function performance and frontal ($p=0.017$), temporal ($p=0.006$) and total cortical gray matter volumes ($p=0.010$) and a positive association between motor performance and both cerebellum volume ($p=0.001$) and thalamus ($p=0.003$).

The VBM analyses across all brain regions similarly did not identify differences by serostatus. However, a new finding emerged in the right cerebellum where the HAND group had focal volumetric reductions compared to those without HAND ($p<0.001$ uncorrected) and compared to controls ($p<0.001$ uncorrected). While these regions met voxel-wise peak level significance, they did not meet cluster-level significance ($p=0.002$, uncorrected for both comparisons), despite cluster size nearing 330 voxels. In a complementary approach that employed the non-parametric modeling with FSL, the HAND group had volumetric reductions in right cerebellum crus II compared to controls [$p<0.05$ TFCE and FWE-corrected] and compared to non-HAND ($p<0.05$ TFCE FWE-corrected) when adjusted for age, sex, and TIV. There were no associations noted between HIV duration or nadir CD4 count with voxel-based volumes at baseline.

Longitudinal atrophy rates—In longitudinal ROI models adjusted for age and sex, we uncovered progressive atrophy in the HIV-infected group exceeding rates seen among healthy controls (Table 2, bottom panel) with faster annualized rates of progressive atrophy in the cerebellum (0.42% vs 0.02%, $p=0.016$), caudate (0.74% vs 0.03%, $p=0.012$), frontal

lobe (0.48% vs 0.01%, $p=0.034$), total cortical gray matter (0.65% vs 0.16%, $p=0.027$), brainstem (0.31% vs 0.01%, $p=0.026$), and pallidum (0.73% vs 0.39%, $p=0.046$) (Figure 1). We did not identify differences in longitudinal volume rates of change between those with compared to without HAND; however, the HAND group differed from controls with faster rates of progressive atrophy in the cerebellum (0.50% vs 0.02%, $p=0.006$), caudate (1.07% vs 0.03%, $p=0.015$), temporal lobes (0.83% vs 0.18%, $p=0.049$), total cortical gray matter (0.87% vs 0.16%, $p=0.039$), brainstem (0.52% vs 0.01%, $p=0.005$), pallidum (0.81% vs 0.39%, $p=0.047$), and thalamus (0.82% vs 0.44%, $p=0.018$) but not in total cerebral white matter (0.50% vs 0.55%, $p=0.821$). Analyses comparing controls to those without HAND did not identify any significant differences in atrophy rates.

Sensitivity analyses were completed to examine the impact of one outlier control demonstrating a >3 standard deviation above the mean positive change in brain volumes in multiple regions. Excluding this subject, significant differences in atrophy rates by serostatus remained in cerebellum, caudate, and pallidum but no longer were seen for frontal lobes, brainstem, and total cortical gray matter. Similarly, in analyses of HAND vs. controls, significant differences in atrophy rates remained in all regions except total cortical gray matter. We re-examined atrophy rates in models adjusted for baseline volumes noting little impact on our models; however, significance emerged at the $p<0.05$ level in temporal lobes ($p=0.045$) and lost in the pallidum ($p=0.085$). Finally, sensitivity analyses that examined only cases where plasma HIV RNA <50 copies/mL at any time point identified no discrepancies from primary results.

Employing a complementary longitudinal TBM technique, we uncovered faster rates of atrophy in HAND compared to controls at the right lateral cerebellum (cerebellum VI, $p<0.001$, uncorrected for FWE, a pattern mimicking cross-sectional findings). Within the HIV-infected group, HAND participants had a greater rate of atrophy in the right lateral cerebellum (cerebellum VI, $p<0.001$, uncorrected) and the right middle temporal lobe ($p<0.001$, uncorrected) compared to those without HAND. We did not identify differences in total white matter atrophy rates among HIV-infected compared to uninfected groups adjusted for age and sex. However, HAND was associated with a faster rate of atrophy in the white matter medial to the right cerebellum crus II ($p=0.000$, $p<0.001$ uncorrected) among HIV-infected participants.

DISCUSSION

Our study investigated longitudinal rates of brain atrophy among older, HIV-infected individuals on suppressive antiretroviral therapy to determine if persistent viral control is sufficient to halt structural brain changes defined by prior studies where some participants had suboptimal viral suppression. Our cross-sectional analyses confirm limited volumetric reductions in HIV-infected participants with cognitive impairment compared to healthy controls, including regions previously noted to be affected in the setting of HIV, such as the cerebellum, nucleus accumbens and brainstem.^{36–38} These findings were driven by HIV-infected participants with HAND and we did not identify differences by HIV serostatus alone. Among the HIV infected group, the baseline volume of the nucleus accumbens and its association to executive functioning is notable. A recent publication among HIV-uninfected

adults found that the volume of the nucleus accumbens modulated the transition from Mild Cognitive Impairment to dementia of the Alzheimer's type disease.³⁹ One could speculate parallels in HAND and Alzheimer's disease among older study participants as it demonstrates similarly affected subcortical structures.

Our primary hypotheses related to brain atrophy noted broad and sizably different longitudinal atrophy rates in HIV despite plasma viral suppression compared to age- and sex-matched cognitively normal and healthy controls. Faster atrophy rates were noted in the cerebellum, caudate, frontal lobe, total cortical gray matter, brainstem, and pallidum. HAND subjects additionally had greater atrophy rates in the temporal lobe and thalamus compared to controls. As some systematic variability in measures is expected with these technical approaches, we examined individual cases and ran sensitivity analyses excluding one individual with greater than 3 standard deviation change from the mean, retaining most of the primary findings.

Larger longitudinal volumetric reductions were noted in regions previously associated with HIV in cross-sectional studies which typically included some participants without viral suppression. Thus, there is some support that our findings may be due to HIV and HIV-related factors.^{13–15,19,21,23} The longitudinal nature of this work adds to extant literature, clarifying that reduction in brain volumes over time in HIV are not simply archival damage from the pre-cART era. This does not exclude the possibility that pre-cART brain changes set the stage for later amplified brain changes.

Yet, other factors could have influenced these faster rates of compared to healthy controls, including HIV-independent factors such as smoking, cognitive reserve, noted by lower total educational attainment in table 1, and alcohol use as well as HIV-associated factors, including chronic inflammation, medication effects, and small vessel ischemic disease (SVID). A history of alcohol abuse was reported in 7/38 (18%) HIV-infected participants with 6/38 (16%) reporting past abuse in substances besides alcohol (e.g. marijuana, cocaine, methamphetamine). Within the HIV-infected group, two participants (5.3%) reported having a history of both alcohol and other substance abuse. In comparison, only 2/24 (8.3%) controls reported past substance abuse with none attributed to alcohol. Given that participants in each group were excluded for current substance use disorders, these differences are more likely to inform baseline volumes than longitudinal change.

We add to a growing number of studies identifying detrimental neuropathogenic pathways, typically associated with persistent inflammation. This includes one study using positron emission tomography (PET) that identified persistent microglial activation in the brain parenchyma of cognitively asymptomatic participants with viral suppression, noting the degree of PET activity inversely linked to performance on tests of executive functions.¹⁰ Other groups document persistent monocyte activation as measured by soluble CD163 in plasma linked to poor cognitive performance despite plasma viral suppression.^{40,41}

By virtue of the older age of our study participants compared to other studies, they may be particularly vulnerable to faster changes in brain atrophy as age-associated brain atrophy rates do not appear to have linear slopes in healthy aging.⁴² Furthermore, our data examined

participants in age over 60 years, surpassing age set points thought to represent the ‘tipping point’ from linear to faster atrophy in presumed healthy aging. For example, a study of 1100 healthy elders noted nonlinear atrophy trajectories dominate in most subcortical regions after age 60 years.³

The presence of cerebrovascular disease (CVD) is known to be more frequent in the setting of HIV and its treatments.⁴³ Volumetric reductions are correlated to the frequency of white matter lesions thought to be due to SVID in HIV-uninfected study groups, providing another underlying factor that may be disproportionately present in the setting of HIV.^{34,42} Our findings in both grey and white matter suggest SVID alone is insufficient to explain our findings.

Our analytic approach employed dual and complementary methods. One method examined volumetric differences based on voxel-based cluster thresholds both longitudinally and cross-sectionally after selecting *a priori* regions informed by existing literature. This approach improves power by reducing the scrutiny of false discoveries across the full brain region because it does not require accounting for spatial extents of voxels or a contiguous set of voxels to show significance.⁴⁴ However, this approach is limiting by its reliance on parametric comparisons informed by past published work. The TBM analyses overcomes this limitation, consequently, a unique focal finding in the cerebellum emerged, consistent, in general, with the total cerebellar differences noted in our ROI examination and with extant literature.³⁶

Cerebellar atrophy, white matter degeneration, and diffuse granule cell loss has been observed in post-mortem studies of HIV-infected patients with cerebellar degeneration, cerebellar dysfunction, and gait ataxia.⁴⁵ Although the cerebellum has long been considered an important component of the motor control network, several studies provided evidence of its involvement in different cognitive processes.⁴⁶ Our findings in the HAND group are lateralized to right lobules 6 and 7 of the cerebellar hemisphere (including the gray and white matter around cerebellar crus II), regions that play a role in cognition and emotion.⁴⁶ We did not find associations between the amount of atrophy in this region and cognitive measures, possibly owing to limited power. Findings from another study report of a speech motor control disorder following HIV infection, noting ataxic dysarthria along with periods of vocal and respiratory halting, slowed processing on motor and attention tasks, indicating possible deficits in the basal ganglia and cerebellum, similarly affected regions we have identified in our work (table 2).⁴⁷

Most of our participants were infected with HIV in the 1980s, before cART was accessible, thus may differ from younger cohorts in brain vulnerability or survivor tendencies. A previous study conducting similar cross-sectional analysis confers HIV-infection in conjunction with aging is related to cortical volume loss.⁴⁸ Our findings of no cross-sectional differences by serostatus alone was unexpected, suggesting the uniqueness of this sample of long-term survivors, although, differences emerged when examining those with HAND compared to controls. Nevertheless, we note progressive atrophy despite minimal baseline cross-sectional findings and can conclude that these changes are not limited to those with past injury. A lack of difference between HAND and non-HAND individuals further

supports this contention. Our findings complement past work in this cohort noting Diffusion Tensor Imaging (DTI) deficits in white matter fiber integrity in older HIV participants compared to age-matched controls.²⁴ Thus, we have identified multi-modal evidence of detrimental outcomes despite cART.

In summary, we find that long-term virally suppressed HIV-infected individuals have brain atrophy rates that exceed that expected from healthy controls. These results inform a potential gap in neuroprotection despite adherence to cART with long-term maximal viral suppression in plasma.

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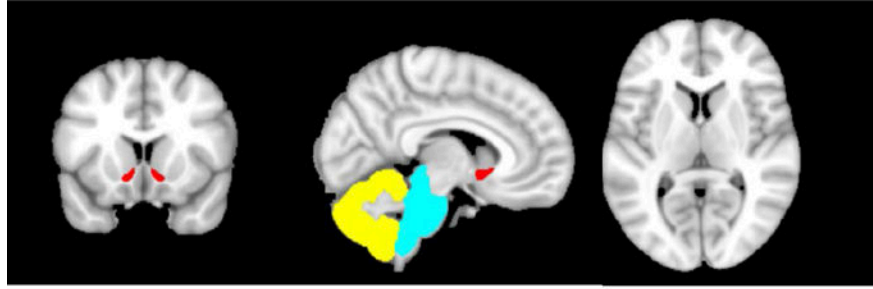
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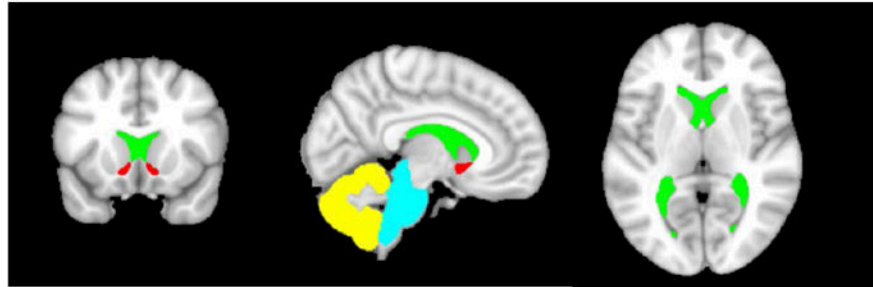
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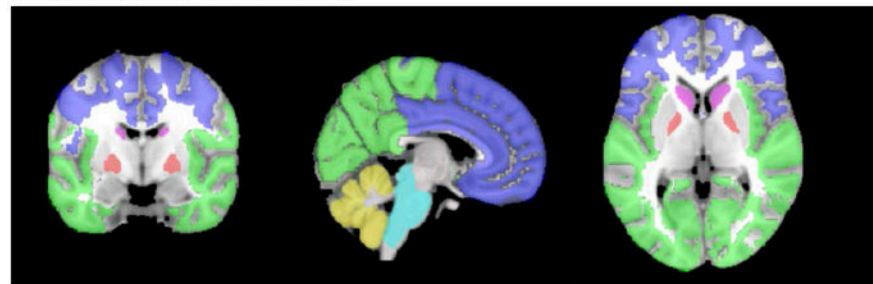
Baseline: HAND versus NonHAND



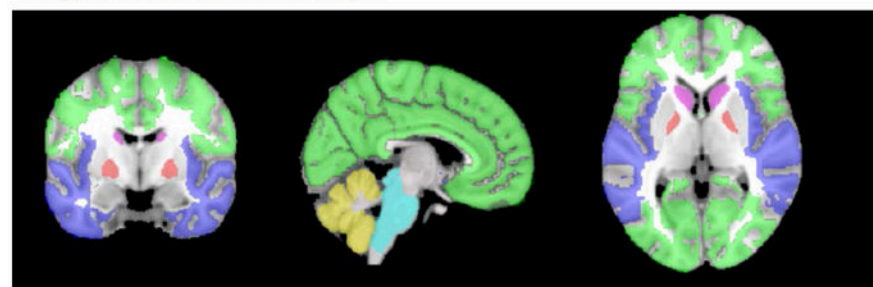
Baseline: HAND versus control



Longitudinal: HIV versus control



Longitudinal: HAND versus control

**Figure 1. Regional Differences across groups at baseline and longitudinally**

Baseline regional differences are observed in nucleus accumbens (red), brainstem (cyan), and cerebellum (yellow) in the NonHAND versus HAND group (top panel), and additionally in the lateral ventricles (green) in the control versus HAND group (second panel). Longitudinal regional differences in the HIV versus control group (third panel) were found in the caudate (violet), pallidum (red), cerebellum (yellow), brainstem (cyan) and the frontal lobes (blue), as well as total cortical gray matter (blue and green). The same regions

were found to be affected in the HAND versus control group (fourth panel), but with the temporal lobes showing regional differences (blue).

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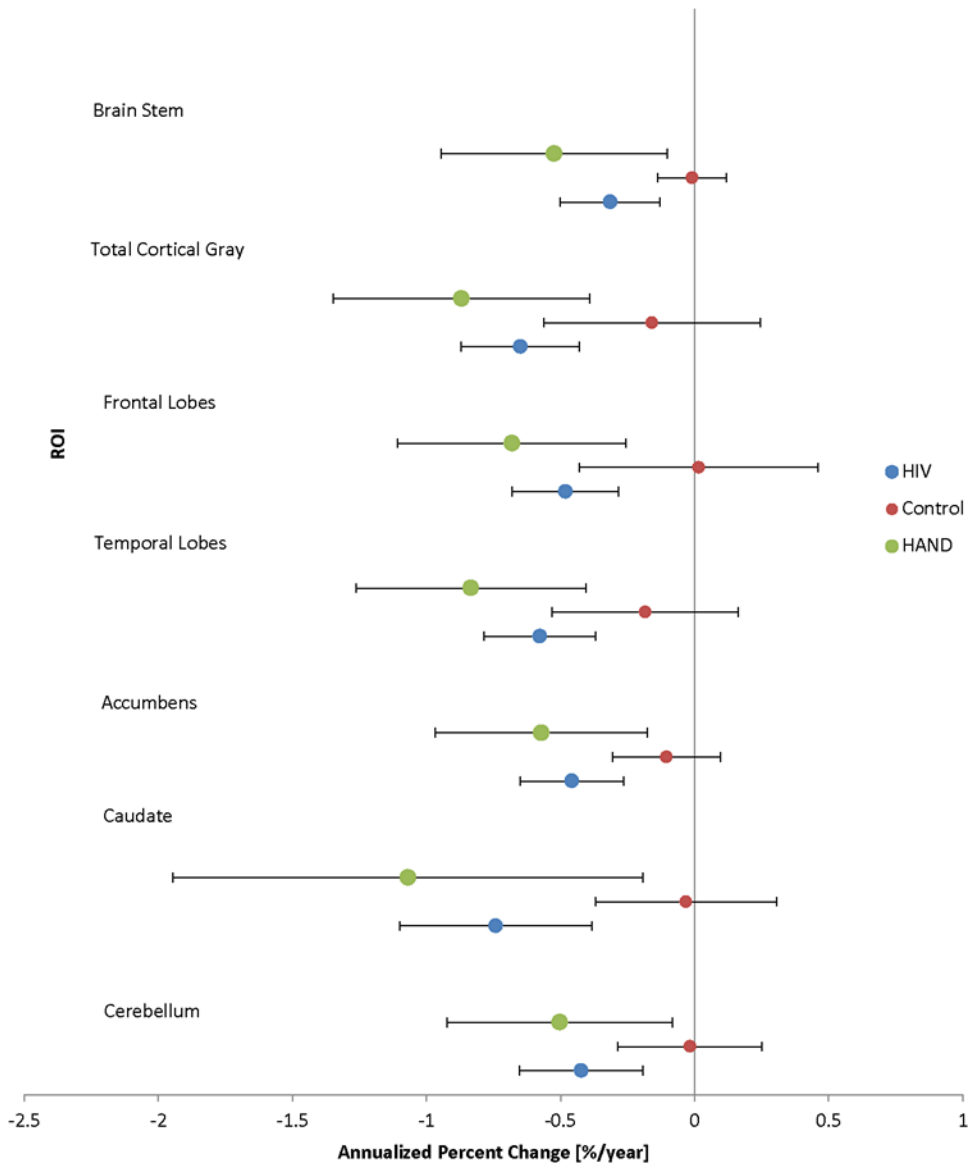


Figure 2. Annualized atrophy rates across groups
Dots represent group means with whiskers demonstrating the 95% confidence interval.

TABLE 1

Baseline Demographic Characteristics of Participants

	Controls (n = 24)	NonHAND (n = 23)	p-value non-HAND vs. Control	HAND (n = 15)	p-value HAND vs. Control	HIV+ (n = 38)	p-value HIV vs Control
Age (years), mean (range)	65.4 (59–70)	64.6(3.89)	0.390	63.6(3.16)	0.066	64.2 (60–76)	0.158
Sex (Male/Female)	22/2	22/1	0.576	14/1	0.849	36/2	0.632
Ethnicity (% Caucasian)	96%	91%	0.526	87%	0.296	89 %	0.370
Education (years), mean (SD)	17.7 (1.7)	17(2.0)	0.195	16.3(2.6)	0.052	16.7 (2.2)	0.073
Estimated IQ, mean (SD) ¹	65.6 (2.0)	65.1(2.5)	0.543	63.3(3.45)	0.025	64.4 (3.04)	0.145
Duration of follow-up (years), mean (SD)	3.39 (1.60)	3.64(1.52)	0.583	3.04(1.6)	0.510	3.41 (1.57)	0.974
Past Smoker	46 %	83%	0.008	53%	0.649	71 %	0.047
Current Smoker	0 %	9%	0.140	7%	0.200	8 %	0.158
Hypertension	33%	39%	0.909	47%	0.571	42 %	0.489
CD4 count, mean (SD) ²	–	586.9(238.8)	–	554.7	–	574.2 (223.7)	–
Nadir CD4, mean (SD)	–	178(132.8)	–	148(141.4)	–	166 (135.2)	–
Plasma HIV RNA, log ₁₀ , mean (SD)	–	1.78(1.64)	–	1.86(1.96)	–	1.83 (1.82)	–
Duration of HIV infection (years), median (range)	–	21.5(11–28)	–	20.1(7–31)	–	22.5 (7–31)	–
Geriatric Depression Scale, mean (SD) ³	2.7 (3.2)	6.7(5.6)	0.006	11.2(6.0)	<0.001	8.5 (2.6)	<0.001
Global Neuropsychological Performance, mean(SD)	0.19 (0.35)	–0.09(0.39)	0.012	–0.65(0.50)	<0.001	–0.31 (0.51)	<0.001

* All p-values were obtained with two sample t-tests or chi-squared tests for continuous and categorical variables, respectively.

¹ By Wide Range Achievement Test (WRAT-4), data missing for 7 HIV-uninfected participants.

² Self-reported CD4 counts were used for 2 participants who did not have a proximal count available.

³ Data missing for one HIV-uninfected participant.

TABLE 2

Volumetric differences in baseline volume (top panel) and atrophy rates (bottom panel)

ROIs	Baseline Volume		NonHAND		Control	
	Mean(SD) [mm ³]	p vs HAND	Mean(SD) [mm ³]	p vs HAND	Mean(SD) [mm ³]	p vs HAND
Frontal lobes	129682.6 (12837)	0.491	131400.5 (13156)	0.491	134865.1 (12697)	0.606
Temporal lobes	104330.0 (9450)	0.243	106279.9 (9225)	0.243	108580.8 (10624)	0.297
Caudate	4114.9 (597)	0.066	4391.2 (504)	0.066	4489.7 (5294)	0.092
Nucleus Accumbens	648.3 (65)	0.003*	709.3 (72)	0.003*	731.8 (91)	0.014*
Pallidum	3067.2 (366)	0.381	3092.9 (346)	0.381	3272.7 (347)	0.313
Putamen	7983.4 (919)	0.067	8009.6 (737)	0.067	8514.6 (862)	0.115
Thalamus	11056.3 (1033)	0.128	11309.9 (1043)	0.128	11606.8 (856)	0.141
Brain Stem	14890.2 (1119)	0.016*	15738.2(1904)	0.016*	1672.0 (1365)	0.012*
Cerebellum	79083.3 (5024)	0.023*	83147.4(7677)	0.023*	83776.1 (6954)	0.019*
Lateral Ventricles	22378.0 (8975)	0.413	20528.5(8516)	0.413	21752.3 (8100)	0.032*
Cortical Gray Matter	255689.9 (23242)	0.674	260206.2 (24195)	0.674	266099.6 (23782)	0.375
Cerebral White Matter	234490.7 (35994)	0.142	222481.5(28605)	0.142	240538.4 (26897)	0.355
Total White Matter	495513.9 (71263)	0.185	473921.7(58236)	0.185	511339.8 (54703)	0.500

ROIs	Annualized Atrophy Rate		HIV		HAND	
	Mean(SD) [mm ³ /year]	p vs Control	Mean(SD) [mm ³ /year]	p vs Control	Mean(SD) [mm ³ /year]	p vs control
Frontal lobes	-34.4 (1370)	0.034*	-617.3 (770)	0.034*	-882.8 (1037)	0.053
Temporal lobes	-219.4 (878)	0.069	-594.6 (655)	0.069	-853.3 (849)	0.049*
Caudate	-2.7 (38)	0.012*	-31.2 (47)	0.012*	-43.8 (71)	0.015*
Nucleus Accumbens	-0.9 (4)	0.087	-2.9 (4)	0.087	-3.5 (5)	0.111
Pallidum	-12.8 (12)	0.046*	-21.4 (19)	0.046*	-23.7 (24)	0.047*
Putamen	-24.8 (27)	0.073	-40.8 (37)	0.073	-49.5 (50)	0.057
Thalamus	-51.0 (39)	0.100	-71.2 (51)	0.100	-89.5 (66)	0.018*
Brain Stem	-1.9 (53)	0.026*	-47.9 (92)	0.026*	-80.4 (133)	0.005*
Cerebellum	-13.7 (589)	0.016*	-344.6 (578)	0.016*	-390.9 (637)	0.006*

ROIs	Annualized Atrophy Rate		HIV		HAND	
	Control	Mean(SD) [mm ³ /year]	Mean(SD) [mm ³ /year]	p vs Control	Mean(SD) [mm ³ /year]	p vs control
Lateral Ventricles	653.1 (377)	779.0 (596)	779.0 (596)	0.334	930.5 (720)	0.070
Cortical Gray Matter	-491.1 (2537)	-1648.0 (1690)	-1648.0 (1690)	0.027 *	-2201.3 (2306)	0.039 *
Cerebral White Matter	-1302.9 (1878)	-1174.5 (1141)	-1174.5 (1141)	0.873	-1093.7 (1435)	0.821
Total White Matter	-3178.1 (4262)	-2458.5 (3236)	-2458.5 (3236)	0.574	-2682.0 (4358)	0.835

Baseline volumes mean (SD); annualized rates mean(SD). P values are reported for disease status as a predictor of atrophy in a multiple regression model after adjusting for age, sex and TIV for baseline volumes and only age and sex for annualized atrophy rates.

* p < 0.05.