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Psychological stress is associated with arterial inflammation in people living with treated HIV infection

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ABSTRACT

Stress and depression are increasingly recognized as cerebrovascular risk factors, including among high stress populations such as people living with HIV infection (PLWH). Stress may contribute to stroke risk through activation of neural inflammatory pathways. In this cross-sectional study, we examined the relationships between stress, systemic and arterial inflammation, and metabolic activity in stress-related brain regions on ^{18}F-fluorodeoxyglucose (FDG)-PET in PLWH. Participants were recruited from a parent trial evaluating the impact of alirocumab on radiologic markers of cardiovascular risk in people with treated HIV infection. We administered a stress battery to assess different forms of psychological stress, specifying the Perceived Stress Scale as the primary stress measure, and quantified plasma markers of inflammation and immune activation. Participants underwent FDG-PET of the brain, neck, and chest. Age- and sex-matched control participants without HIV infection were selected for brain FDG-PET comparisons. Among PLWH, we used nonparametric pairwise correlations, partial correlations, and linear regression to investigate the association between stress and 1) systemic inflammation; 2) atherosclerotic inflammation on FDG-PET; and metabolic activity in 3) brain regions in which glucose metabolism differed significantly by HIV serostatus; and 4) in *a priori* defined stress-responsive regions of interest (ROI) and stress-related neural network activity (i.e., ratio of amygdala to ventromedial prefrontal cortex or temporal lobe activity). We studied 37 PLWH (mean age 60 years, 97% men) and 29 control participants without HIV (mean age 62 years, 97% men). Among PLWH, stress was significantly correlated with systemic inflammation ($r = 0.33$, $p = 0.041$) and arterial inflammation in the carotid ($r = 0.41$, $p = 0.023$) independent of age, race/ethnicity, traditional vascular risk factors and health-related behaviors. In voxel-wise analyses, metabolic activity in a cluster corresponding to the anterior medial temporal lobes, including the bilateral amygdalae, was significantly lower in PLWH compared with controls. However, we did not find a significant positive relationship between stress and this cluster of decreased metabolic activity in PLWH, *a priori* defined stress-responsive ROI, or stress-related neural network activity. In conclusion, psychological stress was associated with systemic and carotid arterial inflammation in this group of PLWH with treated infection. These data provide preliminary evidence for a link between psychological stress, inflammation, and atherosclerosis as potential drivers of excess cerebrovascular risk among PLWH.

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1. Introduction

Excess stroke risk in people living with HIV (PLWH) may be attributed, in part, to traditional cardiovascular disease (CVD) risk factors and HIV-related variables, including chronic immune activation and adverse effects of antiretroviral therapy (ART) (Chow et al., 2021; Ryom et al., 2018). Even after accounting for these factors, however, PLWH may still face a higher risk of stroke compared with the general population. In one study from an integrated U.S. healthcare system in Northern California, the risk of coronary heart disease and ischemic stroke remained significantly elevated for PLWH with well-controlled hypertension compared with individuals without HIV with controlled hypertension (Silverberg et al., 2021). Thus, the mechanisms underlying elevated stroke risk in PLWH with virologically suppressed infection and treated CVD risk factors are not well understood.

Psychological stress has been identified as one of ten potentially modifiable risk factors that collectively account for more than 90% of the population attributable risk of stroke worldwide (O'Donnell et al., 2016). One study estimated that if psychosocial factors, including stress and depression, were removed from the population, over 17% of strokes could be prevented (O'Donnell et al., 2016). Similar to its established role as a cerebrovascular risk factor in the general population (Everson-Rose et al., 2014; Booth et al., 2015), stress may be an integral component in a novel pathway that contributes to elevated stroke risk in PLWH (Levy et al., 2020). Stress is prevalent among PLWH and strongly correlates with inflammation (Fumaz et al., 2012; Siyahhan Julnes et al., 2016). In turn, inflammation, which has been linked to stroke and CVD in PLWH (Duprez et al., 2012; Tenorio et al., 2014), may serve as a critical mediator of the relationship between psychological stress and elevated stroke risk.

In the general population, psychological stress and stress-related neural network activity – a key driver of the neural inflammatory response to stress – have been shown to be independently associated with atherosclerotic inflammation and CVD outcomes, including stroke (Tawakol et al., 2017). We hypothesized that psychological stress may play a role in the pathogenesis of cerebrovascular disease in a high-stress population like PLWH by 1) increasing systemic and arterial inflammation and 2) activating stress-related neural networks. To test these hypotheses, we examined the relationships between stress, systemic and arterial inflammation on ^{18}F-fluorodeoxyglucose (FDG)-PET, and metabolic activity in stress-related brain regions including in the amygdalae in virologically suppressed PLWH.

2. Materials and methods

2.1. Study population

We recruited participants between 2018 and 2021 from a parent trial evaluating the impact of alirocumab on radiologic markers of cardiovascular risk in PLWH (NCT03207945). Inclusion criteria for the parent trial included age 40 years or older, on stable ART with undetectable plasma viral load, and at moderate to high cardiovascular risk, defined as: history of CVD (i.e., coronary heart disease, cerebrovascular disease, or peripheral arterial disease) or of at least one cardiometabolic risk factor (e.g., hypertension, hyperlipidemia, diabetes mellitus, current smoker). Participants with a stroke or central nervous system (CNS) infection within the past 90 days, or who had signs or symptoms of an acute neurologic deficit at the time of imaging, were excluded. Procedures for this neurologic sub-study were performed prior to randomization and assignment to intervention in the parent trial. All demographic variables, cardiometabolic risk factors, health-related behaviors, and HIV-specific variables were obtained at screening and entry visits in the parent trial.

2.2. Assessments

2.2.1. FDG-PET imaging in PLWH

As part of the parent trial, participants underwent neck and chest FDG-PET at the UCSF Imaging Center at China Basin (San Francisco, CA) on a GE Discovery STE PET/CT scanner. For this neurologic sub-study, brain images were acquired over 15 min starting 45 min after injection of ~ 10 mCi of radiotracer. A low-dose computed tomography (CT) scan was performed for attenuation correction prior to PET acquisition. PET data were reconstructed using an iterative method with the ordered subset expectation maximization algorithm; scanner resolution was estimated to be $6 \times 6 \times 5.6$ mm using a Hoffman phantom. We received FDG-PET images in DICOM format and converted to NiFTI with in-house scripts. Each scan was warped to the Montreal Neurological Institute (MNI) standard space with SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) with a PET-only pipeline, using the PET template provided built-in with SPM12. After warping, the average FDG-PET uptake in the pons was extracted to rescale the images into parametric FDG-PET Standardized Uptake Value Ratio (SUVR) images. The pons region of interest was defined according to the Automatic Anatomical Labeling atlas in MNI space as provided by the Wake Forest University PickAtlas SPM12 toolbox. Warped FDG-PET SUVR images were smoothed using a Gaussian filter to reach a final resolution of 8 mm^3.

ROI analyses were performed using regional definitions from the Neuromorphometrics Atlas provided in SPM12 (Neuromorphometrics Inc., provided under academic subscription). Selection of ROIs was performed *a priori* based on brain areas involved in the stress circuitry, including the amygdala, hippocampus, anterior and posterior cingulate, and medial and dorsolateral prefrontal cortex. Because the left and right amygdala may differ in their structural and functional connectivity with other brain regions (Robinson et al., 2010), we evaluated each left and right ROI separately and as a weighted mean of the bilateral structures. We calculated stress-related neural network activity as a ratio of FDG uptake in the amygdala to the ventromedial prefrontal cortex and temporal lobe, as previously described (Radfar et al., 2021).

FDG uptake in the ascending aorta and carotid arteries (Fig. 1) was estimated using previously validated methods (Tawakol et al., 2017; Emami et al., 2015).

Measurements were made in the axial plane and maximum standardized uptake values (SUVmax) were recorded from pre-defined sections of the three target vessels (aortic and right and left carotid walls). The arterial target-to-background ratio was defined as the ratio of the mean of the SUVmax measurements along the length of the target vessel to the background venous activity derived from either the superior vena cava (for correction of aortic values) or the internal jugular veins (for correction of carotid values).

2.2.2. Brain FDG-PET in control participants

Previously collected FDG-PET data from age- and sex-matched control participants without HIV were used for brain FDG-PET comparisons. Control participants were cognitively normal individuals who underwent FDG-PET at the Lawrence Berkeley National Lab (Berkeley, CA) for the Berkeley Aging Cohort Study (Ossenkoppele et al., 2016), a longitudinal study designed to investigate how brains change with age. Eligibility criteria for the Berkeley Aging Cohort Study include normal performance on cognitive testing and absence of major medical illnesses that may affect brain structure and function. Acquisition and reconstruction details have been described previously (Iaccarino et al., 2021). Briefly, PET data were acquired on a Siemens Biograph 6 Truepoint PET/CT scanner at the Lawrence Berkeley National Laboratory. A low-dose CT scan was performed for attenuation correction prior to PET acquisition, and PET data were reconstructed using an iterative method (ordered subset expectation maximization algorithm) with weighted attenuation and smoothed with a 4 mm Gaussian kernel with scatter correction. Scanner resolution was estimated to be $6.5 \times 6.5 \times 7.25$ mm

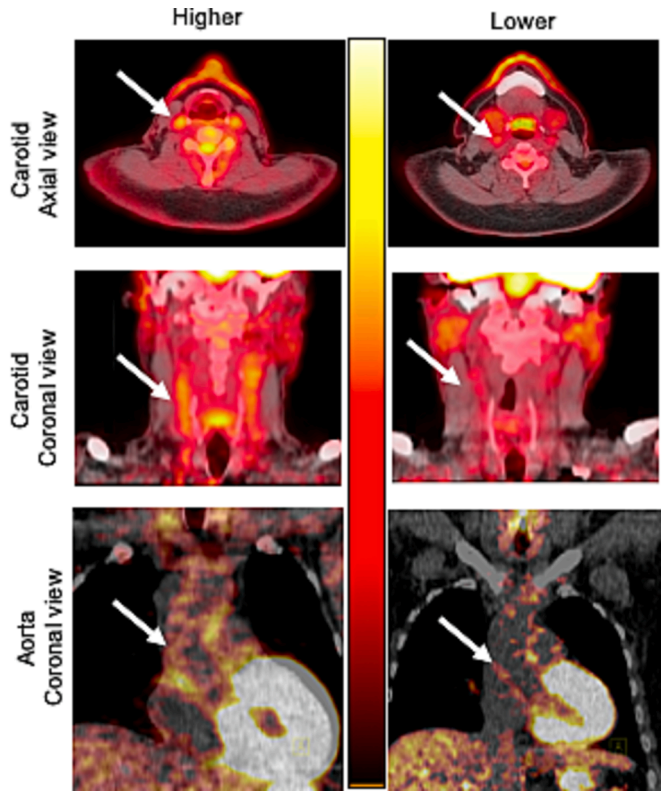

Fig. 1. Measurement of arterial inflammation. Arterial ^{18}F-fluorodeoxyglucose (FDG) uptake (corrected for background venous blood activity) in the carotid arteries and aorta was measured as a validated assessment of arterial inflammation. Axial and coronal views of the carotid arteries and coronal views of the aorta are shown. The left panels show a participant with higher arterial ^{18}F -FDG uptake compared with a participant with lower arterial uptake on the right.

based on a Hoffman phantom. Brain FDG-PET scans in the Berkeley Aging Cohort Study consisted of 30 min of acquisition starting 30 min after injection of ~ 10 mCi of radiotracer (30 to 60 min post-injection), and data were reconstructed as six 5-minute frames. To maximize comparability between PLWH and controls, we only used the last 3 frames acquired in control participants, corresponding to the 45 to 60 min post-injection acquisition time for PLWH. PET frames were realigned and averaged, and resulting maps were warped to MNI space following the pipeline described above and scaled to the same pons reference region to obtain FDG-PET SUVR images. Differential smoothing (gaussian filter = 4.5 mm FWHM isotropic) was applied to match the 8 mm^3 resolution of the final PLWH scans.

Data from control participants were only used to compare brain FDG-PET by HIV serostatus in voxel-wise analyses; measures of stress and systemic and arterial inflammation were not available for controls.

2.2.3. Psychological stress measurements in PLWH

The primary stress measure was the 10-item Perceived Stress Scale (Lee, 2012; Cohen), a widely used instrument that assesses self-appraisal of stress during the previous month and has been used in PLWH (Weinstein and Li, 2016). Responses to each of the 10 items are assigned a score of 0 to 4, with a higher score indicating higher stress. The scores are then summed across the 10 items with total scores ranging from 0 to 40. Perceived stress has been associated with inflammation in HIV and non-HIV populations (Fumaz et al., 2012), arterial inflammation on FDG-PET in non-HIV populations (Tawakol et al., 2017), and with several health outcomes, including stroke and CVD (Henderson et al., 2013; Xu et al., 2015). In addition to the Perceived Stress Scale, we captured exploratory measures reflecting the multi-dimensional nature of stress, including the Chronic Burden Scale, which assesses chronic stress greater than 6 months duration; Adverse Childhood Experiences to evaluate early life stress; the HIV Stigma Scale; and the Post-Traumatic Stress Disorder Civilian-Checklist. The Patient Health Questionnaire-9 (PHQ-9) was used to measure depression.

2.2.4. Markers of inflammation and immune activation in PLWH

For participants with HIV with stored biospecimens from the entry visit of the parent trial, we measured a panel of inflammatory and immune activation markers that have been 1) implicated in the biological stress pathway or 2) are predictive of stroke and CVD in HIV and non-HIV populations (Chow et al., 2021; Fumaz et al., 2012; Duprez et al., 2012; Tenorio et al., 2014; O'Donovan et al., 2012; Fitch et al., 20132013). Interleukin 6 (IL6; Catalog # D6050), soluble CD163 (sCD163; Catalog # DC1630) and CD14 (sCD14; Catalog # DC140), monocyte chemoattractant protein-1 (MCP1; Catalog # DCP00), and interferon γ (IFN-γ)–inducible protein 10 (IP10; Catalog # DIP100) were measured by enzyme-linked immunoassay (R&D Systems, MN, USA) in plasma samples per the manufacturer's protocols. No dilution factor was used for samples for IL6 and IP10. For sCD163, a 10-fold dilution was used, for sCD14 a 200-fold dilution, and for MCP1 a 2-fold dilution. High sensitivity C-reactive protein (CRP) was measured by chemiluminescence immunoassay (Siemens Medical Solutions, PA, USA).

2.3. Statistical analyses

We performed group-level comparisons unblinded to HIV serostatus of brain FDG-PET metabolism between PLWH and control participants. Analyses were run voxel-wise with SPM12, adjusting for age. Because FDG-PET SUVR results may be biased by the reference region selected, we repeated our main analyses using FDG-PET images normalized to the global gray matter uptake mean value ("proportional scaling" method (Verger et al., 2021; López-González et al., 2020; Yakushev et al., 2008). For these sensitivity analyses, the average gray matter signal was extracted from a customized mask encompassing the cerebral cortex, subcortical regions, cerebellar cortex, and the midbrain. Results were assessed using two statistical thresholds, as previously described (La Joie et al., 2021): a liberal threshold of $p < 0.001$ uncorrected for multiple comparisons at the voxel-level combined with a cluster-level Family Wise Error (FWE)-corrected $p < 0.05$ threshold, and a stringent approach based on a voxel-level FWE-corrected $p < 0.05$ threshold. Unthresholded and thresholded Tmaps are available on the neurovault platform (https://neurovault.org/collections/WMODAVHL).

The remainder of the analyses were among PLWH only. We first tested nonparametric pairwise correlations to evaluate relationships between the primary and exploratory measures of stress, depression, and markers of immune activation and inflammation, which were $\log_{10}$-transformed if they were not normally distributed. We then used partial correlations and linear regression analyses adjusted for age and race/ethnicity to examine the relationship between stress and arterial inflammation in the aorta and carotid. For significant correlations between measures of stress and arterial inflammation, we further adjusted for individual CVD risk factors (e.g., hypertension) and health-related behaviors (e.g., smoking, alcohol use) that may be more prevalent in high-stress individuals and are associated with atherosclerosis and stroke and CVD. For the ROI analyses, we extracted FDG-PET SUVR values from *a priori* defined ROIs and used partial correlations and linear regression analyses adjusted for age and race/ethnicity to investigate the associations of stress with metabolic activity in the ROI and in regions in which glucose metabolism differed significantly by HIV serostatus. For the analyses among PLWH evaluating the relationships between stress, systemic and arterial inflammation, and ROI metabolic activity, $p < 0.05$ was considered statistically significant. We used bootstrapping to estimate 95% confidence intervals for all partial correlation coefficients.

3. Results

Thirty-seven PLWH underwent FDG-PET in this neurologic substudy. The mean age of PLWH was 60 years [standard deviation (SD) 7 years], and 97% were men. Of the 29 control participants without HIV, the mean age was 62 years (SD 9 years), and 97% were men. Nearly half of PLWH had hypertension, three-quarters had dyslipidemia, and one-quarter had diabetes mellitus. As per the inclusion criteria of the parent trial, all participants with HIV were virologically suppressed. Other demographic and clinical characteristics are shown in Table 1.

Among PLWH, the mean Perceived Stress Scale score was 12 (SD 8), with scores ranging between 1 and 34. The results of other stress measures are included in Table 1. Perceived stress correlated with most other forms of stress, including chronic stress ($\rho = 0.54$, $p = 0.007$), post-traumatic stress ($\rho = 0.73$, $p < 0.0001$), and HIV stigma ($\rho = 0.37$, $p = 0.024$), along with depression ($\rho = 0.79$, $p < 0.0001$). Of these exploratory measures, chronic stress correlated with early life ($\rho = 0.44$, $p = 0.007$) and post-traumatic stress ($\rho = 0.56$, $p < 0.001$), and HIV stigma with early life ($\rho = 0.33$, $p = 0.049$) and post-traumatic stress ($\rho = 0.59$, $p < 0.001$). In addition to perceived stress, depression was moderately to strongly correlated with chronic ($\rho = 0.61$, $p < 0.001$) and post-traumatic stress ($\rho = 0.83$, $p < 0.0001$), as well as with HIV stigma ($\rho = 0.50$, $p = 0.002$).

Table 1
Demographic and clinical characteristics of participants with HIV infection.

No. (%) unless otherwise noted	n = 37
Demographics	
Age (years), mean (SD)	60 (7)
Assigned male sex at birth	36 (97)
Race/ethnicity	
Non-Hispanic White	32 (86)
Black / Other / Unknown	5 (14)
Education (years), mean (SD)	16 (2)
Cardiometabolic variables	
Hypertension	18 (49)
Dyslipidemia	27 (73)
Diabetes mellitus	9 (24)
History of prior myocardial infarction or stroke	4 (11)
Family history of cardiovascular disease	8 (22)
Total cholesterol (mg/dL), mean (SD)	180 (32)
LDL cholesterol (mg/dL), mean (SD)	100 (24)
HDL cholesterol (mg/dL), mean (SD)	51 (16)
Aspirin use	14 (38)
Statin use	22 (61)*
Health-related behaviors	
Any current alcohol use	20 (54)
Smoking	
Current	7 (19)
Prior	19 (51)
Never	11 (30)
Marijuana	
Current	15 (41)
Prior	16 (43)
Never	6 (16)
Cocaine use	
Current	2 (5)
Prior	21 (57)
Never	14 (38)
Methamphetamine use	
Current	1 (3)
Prior	18 (49)
Never	18 (49)
Injection drug use	
Current	0 (0)
Prior	5 (14)
Never	32 (86)
HIV-related variables	
CD4 count (cells/mm^3), mean (SD)	559 (168)
Undetectable plasma viral load	37 (100)
HIV duration (years), mean (SD)	27 (8)
Stress measures	
Perceived stress scale, mean (SD), range	12 (8), 1 to 34
Chronic burden scale, mean (SD), range	1 (1), 0 to 4
Adverse Childhood Experiences, mean (SD), range	2 (2), 0 to 7
HIV stigma scale, mean (SD), range	64 (17), 33 to 114
Post-traumatic Stress Disorder Civilian-Checklist, mean (SD), range	32 (14), 18 to 77
Patient Health Questionnaire-9, mean (SD), range	4 (4), 0 to 17

*Statin use was missing for 1 participant; Abbreviations: SD, standard deviation.

Among PLWH with stored biospecimens (n = 34), perceived stress correlated with CRP (Fig. 2). Several exploratory measures of stress also correlated with systemic inflammation, including chronic stress with IL6 and sCD163 (Fig. 2). Furthermore, perceived stress was significantly correlated with arterial inflammation in the carotid, independent of traditional vascular risk factors and health-related behaviors (Fig. 3).

In group-level voxel-wise analyses adjusted for age, metabolic activity in a cluster that corresponded to the bilateral anterior medial temporal lobes, which included the bilateral amygdalae (Fig. 4), was significantly lower in PLWH compared with control participants. This was observed in the primary and sensitivity analyses, using the pons and global gray matter as the reference regions, respectively. A few other scattered cortical areas also demonstrated lower metabolic activity in PLWH compared with controls, especially at the more liberal threshold (Fig. 4).

We did not find a statistically significant correlation between perceived stress and metabolic activity in the anterior medial temporal lobes in PLWH. We observed a moderate age- and race/ethnicity-adjusted correlation between perceived stress and hypometabolism in the left amygdala, scaled using both the pons ($r = -0.44$, 95% CI −0.70 to −0.17, $p = 0.009$) and global gray matter ($r = -0.37$, 95% CI −0.66 to −0.08, $p = 0.030$), but not among any of the other *a priori* defined ROIs in PLWH. In contrast to our prior analysis in a non-HIV population (Tawakol et al., 2017), we did not find a significant relationship between perceived stress and stress-related neural network activity (i.e., ratio of amygdala to ventromedial prefrontal cortex and temporal lobe activity) in PLWH.

4. Discussion

Among PLWH with well-controlled infection, perceived stress in the past month correlated with systemic inflammation and with FDG uptake in the carotid arteries—a well-validated measure of atherosclerotic inflammation that is predictive of subsequent ischemic stroke and CVD events (Figueroa et al., 2013; Tawakol et al., 2006). These data provide

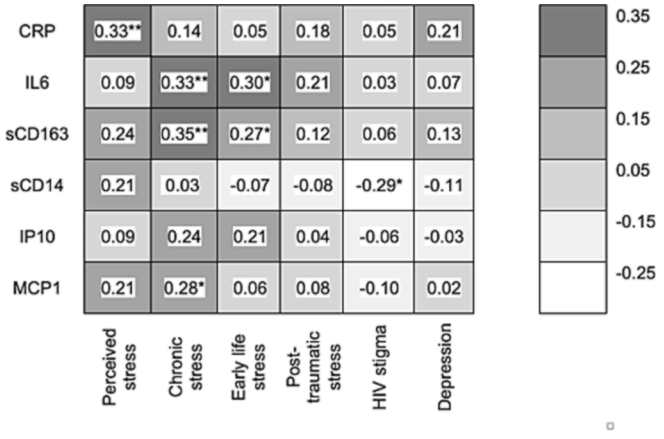

Fig. 2. Relationships between stress and systemic inflammation and immune activation among people living with HIV infection. Moderate significant correlations were present between several measures of stress and systemic inflammation, including perceived stress and CRP and chronic stress with IL6 and sCD163. Abbreviations: CRP, C-reactive protein; IL6, interleukin-6; sCD163, soluble CD163; sCD14, soluble CD14; IP10, interferon γ–inducible protein 10; MCP1, monocyte chemoattractant protein-1. *p < 0.10, **p < 0.05.

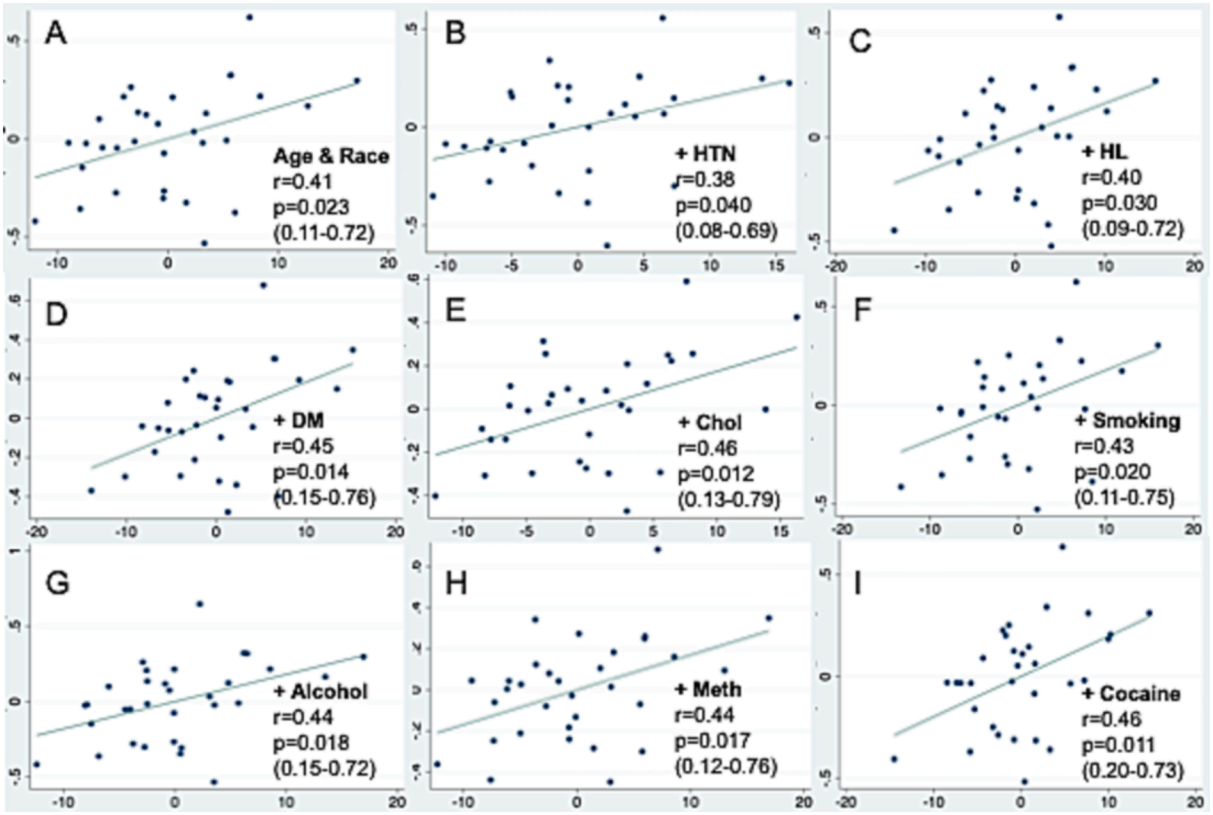

Fig. 3. Correlations between stress and arterial inflammation among people living with HIV infection. Perceived stress was positively correlated with carotid arterial inflammation adjusting for age and race/ethnicity (A). The significant correlation remained after additionally accounting for individual vascular risk factors (B-F) and other health-related behaviors (G-I). Abbreviations: HTN, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; Chol, total cholesterol; Meth, methamphetamine. Correlation coefficients and p values shown with bootstrap 95% confidence intervals in parentheses.

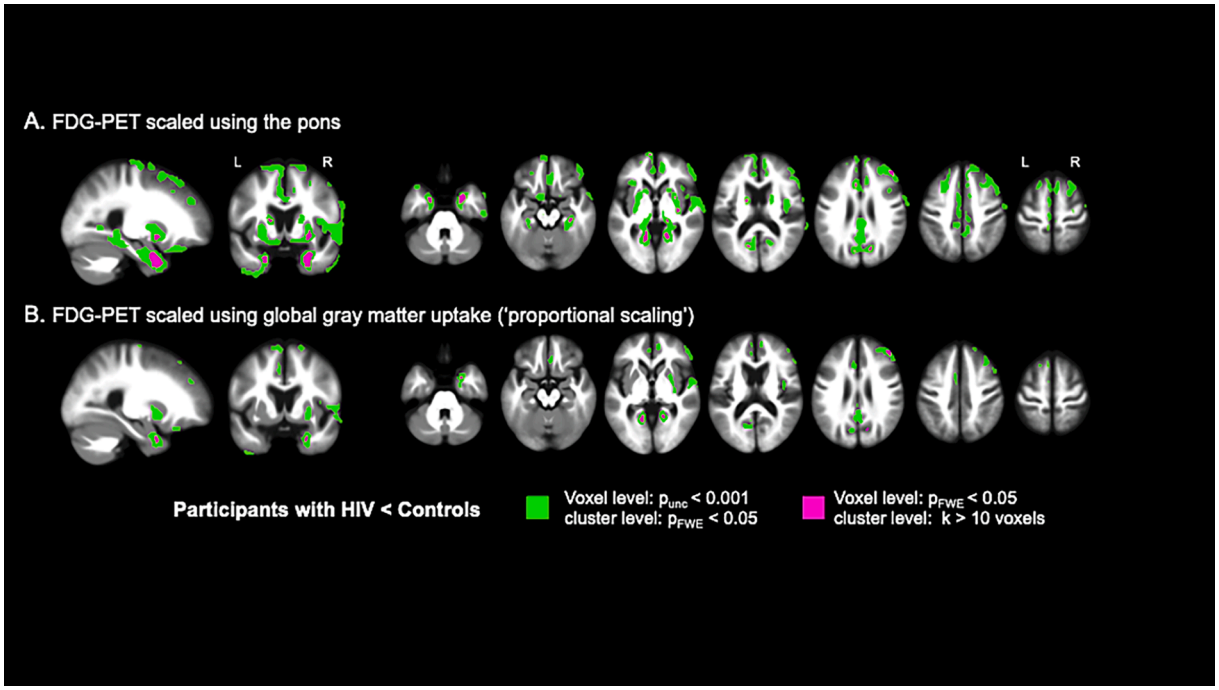

Fig. 4. Lower metabolic activity in the bilateral anterior medial temporal lobes of participants with HIV compared with controls. In age-adjusted group-level voxelwise analyses, metabolic activity was lower in the bilateral anterior medial temporal lobes, including the amygdalae, of participants with HIV compared with controls, using both the pons (A) and global gray matter (B) as the reference regions. The figure shows clusters in green where a difference in metabolic activity was present at a $p < 0.001$ threshold uncorrected for multiple comparisons combined with a cluster-size Family Wise Error (FWE)-corrected $p < 0.05$ threshold and in pink where a difference was present at a FWE-corrected $p < 0.05$ threshold.

preliminary evidence for a potential link between stress, inflammation, and atherosclerosis as potential drivers of excess stroke and CVD risk among PLWH.

In the general population, stress has been shown to be an independent contributor to stroke and CVD risk (O'Donnell et al., 2016; Everson-Rose et al., 2014; Henderson et al., 2013; Xu et al., 2015). In the INTERSTROKE (O'Donnell et al., 2016) and Multiethnic Study of Atherosclerosis (MESA) (Everson-Rose et al., 2014) cohorts, psychological stress was associated with a 30% to 50% higher stroke risk, independent of health-related behaviors (e.g., smoking, alcohol use, physical inactivity) that are more common in individuals reporting high stress (Everson-Rose et al., 2014; Kornerup et al., 2010; Gallo et al., 2014). Furthermore, cardiovascular risk has been shown to be elevated in other high stress populations, including in persons with post-traumatic stress disorder and depression (Cohen et al., 2015).

Depression, which is highly correlated with stress as observed in this study and in other cohorts (Hand et al., 2006), is a risk factor for ischemic stroke and myocardial infarction in PLWH (Sico et al., 2021; Khambaty et al., 2016). In the prospective Veterans Aging Cohort Study virtual cohort, depression was associated with an 18% higher risk of ischemic stroke in PLWH (Sico et al., 2021). The association, which was more pronounced among younger PLWH in the cohort, was attenuated after adjusting for alcohol and cocaine use, suggesting that some of the excess risk may have been mediated by comorbid health-related behaviors that increase cerebrovascular risk. In our cohort, the correlation between perceived stress and carotid arterial inflammation was independent of traditional vascular risk factors and health-related behaviors, such as smoking and alcohol use, that may be more prevalent in individuals who are experiencing high levels of stress or depression.

Few studies have investigated the specific impact of psychological stress, which cannot be readily captured by billing or administrative diagnosis data, on stroke risk in PLWH. Our finding that perceived stress was associated with carotid arterial inflammation is in line with results from the Women's Interagency HIV Study (WIHS) in which women with HIV in a high psychosocial risk category, which took into account perceived stress, post-traumatic stress, and depression, had higher prevalence of carotid artery plaque compared with women with HIV at low psychosocial risk (Levy et al., 2020). A similar relationship between psychosocial risk and carotid plaque was not observed, however, among women without HIV. Although this disparate finding may have been due to the smaller sample of women without HIV included in the analysis, it raises the possibility that the effect of psychological stress on stroke and CVD risk may be modified by HIV infection. One hypothesis is that the individual effects of HIV and stress on promoting inflammation and immune activation may interact, leading to an exaggerated inflammatory response that precipitates stroke and CVD events (Duprez et al., 2012; Tenorio et al., 2014). In our study, perceived stress correlated with systemic inflammation, measured by CRP. Other measures of stress and depression were also associated with markers of inflammation and monocyte activation. However, these data were not available for control participants to examine whether HIV modifies the association between stress and inflammation, which should be the focus of future investigation.

In HIV populations, perceived and post-traumatic stress have been linked with systemic inflammation (Fumaz et al., 2012; Siyahhan Julnes et al., 2016). Our study expands on these findings by establishing a potential association between perceived stress and arterial inflammation in PLWH. We originally hypothesized that psychological stress may exacerbate cerebrovascular risk through activation of neural inflammatory pathways. Preclinical and clinical studies have shown that prolonged exposure to stress can stimulate myelopoiesis and a shift to an immature, pro-inflammatory monocyte population, which promotes atherosclerotic inflammation (Heidt et al., 2014; Zhang et al., 2010). As part of this pathway, monocytes are recruited to critical neural regions involved in stress, including the amygdala (Wohleb et al., 2015; Wohleb et al., 2013). The amygdala has efferent projections to the hypothalamic–pituitary–adrenal axis and sympathetic nervous system (LeDoux et al., 1988), which regulate the inflammatory cascade and immune response to stress. In healthy individuals, heightened amygdala activity in response to a stressor is associated with increased peripheral inflammation (Muscatell et al., 2015). Inflammation may feed back to the amygdala, enhancing the amygdala response to threat(Engler et al., 2011; Inagaki et al., 2012) and modifying the functional connectivity between the amygdala and other critical neural areas involved in the stress response, including the cingulate and prefrontal cortex (Harrison et al., 2009; Gianaros et al., 2014; van Wingen et al., 2011).

Our original hypothesis that psychological stress may be a contributing factor to cerebrovascular risk in PLWH through activation of the stress-related neural network was based on findings from two coupled studies in the general population that demonstrated resting metabolic activity in the amygdala significantly correlated with systemic and arterial inflammation (Tawakol et al., 2017). In the longitudinal component of the study, participants with greater stress-related neural network activity were more likely to experience a CVD event, with approximately 60% higher risk of a CVD event for every 1 SD increase in amygdala signal. In an adjunct cross-sectional study of 13 individuals with post-traumatic stress disorder, higher perceived stress correlated with greater stress-related neural network activity, arterial inflammation, and systemic inflammation measured by CRP.

In contrast, we did not observe the same relationship between stress and heightened stress-related neural network activity in this cohort of PLWH. Rather, we found that perceived stress was negatively correlated with resting metabolic activity in the left amygdala. Notably, the majority of imaging studies of high stress conditions or depression have measured amygdala activation in response to an emotional stimulus or cognitive task. Fewer have evaluated basal glucose metabolism, which serves as a proxy for neuronal activity, in stress-responsive regions of the brain on FDG-PET, and findings from studies that are not stimulus or task-dependent have been mixed (Tawakol et al., 2017; Shin et al., 2009; Drevets et al., 2002; Abercrombie et al., 1998; Kang et al., 2021; Brendel et al., 2016; Bremner et al., 1997).

Differences in amygdala activity at rest in response to stress may also reflect the interaction between genetic vulnerability to developing post-traumatic stress disorder or depression and environmental stressors. One study compared resting cerebral blood flow between individuals with and without a common functional polymorphism in the promoter region of the serotonin transporter gene (Canli et al., 2006). Carriers of the polymorphism, who are more susceptible to depression and depressive symptoms when faced with stressful life events (Caspi et al., 2003), had heightened activation at rest in the amygdala and hippocampus in association with greater life stress. In contrast, among those without the polymorphism, greater life stress was negatively correlated with resting activation in the amygdala and hippocampus, similar to the relationship observed in our cohort of PLWH. One hypothesis that merits investigation is whether survivor bias and resilience among PLWH may shape the neural inflammatory response to stress, accounting for the observed negative correlation between stress and resting metabolic activity in the amygdala. Another consideration in the interpretation of FDG-PET is that FDG signal may not solely reflect neuronal metabolic activity. FDG-PET lacks cellular resolution, making it difficult to ascertain which cells are responsible for glucose uptake in the brain. In neurodegenerative disease models, FDG signal has been shown to be driven largely by activated microglial cells (Xiang et al., 2021). This may be particularly relevant in HIV, given the role that microglia – as a cellular reservoir for latent HIV infection – are postulated to play in ongoing inflammation and immune activation of the CNS in PLWH and in the pathogenesis of HIV-related neurologic disease (Wallet et al., 2019; Spudich, 2016). Thus, against this backdrop of persistent CNS inflammation observed in PLWH with virologically suppressed infection, the source of FDG signal could result from either inflammation or neural activity.

Our results should be interpreted in the context of several limitations. This cross-sectional study precludes inferences about direction or

causality of the observed association between stress and arterial inflammation. Furthermore, using cognitive and emotional tasks with functional imaging in addition to resting FDG-PET may provide adjunctive information on the response to stress in *a priori* selected ROIs that play a role in these neural inflammatory pathways. Although control participants were matched for age and sex, clinical data, including comorbid CVD risk factors, were not available for controls. While brain FDG-PET comparisons were not the main focus of the study, this could have affected the portion of the analysis in which we compared glucose metabolism by HIV serostatus, as prior studies in PLWH and people without HIV have observed differences in metabolic activity by cardiovascular risk (Hammoud et al., 2018). Furthermore, despite efforts to harmonize the data, we cannot exclude the possibility that technical differences resulting from acquisition of FDG-PET images on different scanners for PLWH and control participants may partly explain the observed group differences in metabolic activity in the bilateral amygdalae. This comparison by HIV serostatus, however, had no bearing on the primary finding of the study from analyses that were restricted to PLWH. Inflammatory and immune activation marker testing were also not performed in duplicate, which would have been a safeguard against potential variability in this sample size. Finally, we did not adjust for multiple comparisons in the ROI analyses to maximize our ability to detect potential associations of stress with metabolic activity in stress-responsive brain regions and with systemic and arterial inflammation in this modestly sized sample. As such, these findings are exploratory and should be confirmed in future studies that focus on select measures of stress and markers of inflammation.

In conclusion, this study builds on previous work demonstrating an association between stress and systemic inflammation in PLWH by providing preliminary evidence that psychological stress is also related to arterial inflammation, which may be one mechanism by which stress exacerbates cerebrovascular risk in PLWH. If these data supporting a plausible mechanistic link between stress and CVD through inflammation can be replicated, subsequent studies should include evaluation of a stress reduction intervention as a strategy to lower inflammation and CVD risk in PLWH.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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