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Prefrontal Cortex Volume Mediates the Relationship Between Lifetime Chronic Stressor Exposure and Cognition in People Living With and Without HIV

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ABSTRACT

Objective: Despite considerable research documenting how stress affects brain and neurobehavioral outcomes, few studies have assessed stressor exposure occurring over the entire life span, and no studies have investigated these associations in people living with HIV (PLWH), despite the high stress and disease burden experienced by this population. To address this issue, we examined how cumulative lifetime chronic stressor exposure related to cognition and brain integrity (i.e., gray matter volume) in White and African American PLWH and HIV-uninfected (HIV−) adults.

Method: Participants were 91 community-dwelling adults (47.3% PLWH) who completed a comprehensive interview assessing lifetime stressor exposure using the Stress and Adversity Inventory and underwent neuropsychological testing and structural magnetic resonance imaging. Regional brain volumes were derived from T1-weighted images processed through Freesurfer.

Results: As hypothesized, greater lifetime chronic stressor exposure was related to worse global cognition ($b = -0.06$, standard error [SE] = 0.03, $p = .032$), processing speed ($b = -0.04$, SE = 0.14, $p = .041$), and executive functioning ($b = -0.06$, SE = 0.02, $p = .02$), and smaller prefrontal cortex (PFC) volume ($b = -16.20$, SE = 5.78, $p = .007$). HIV status did not moderate any of these associations. Moreover, results from mediation analyses demonstrated that the relationship between lifetime chronic stressor exposure and processing speed was fully mediated by PFC volume.

Conclusions: These results highlight the critical role of the PFC in the maintenance of processing speed abilities and its vulnerability to cumulative stressor exposure. Specifically, the negative impact of lifetime chronic stressor exposure on cognition—particularly functions reliant on frontal lobe integrity—may be partly driven by smaller volumes in the PFC.

Key words: HIV, stress, adversity, cognition, neuroimaging, brain volume.

INTRODUCTION

Exposure to major life stressors and high levels of perceived stress are widely recognized risk factors for cognitive dysfunction that are being increasingly investigated as potential contributors to cognitive dysfunction in people living with human immunodeficiency virus (PLWH) (1,2). PLWH are disproportionately members of minoritized groups of low socioeconomic status (SES) and have higher rates of major and traumatic life events as compared with the general population (3). Moreover, living with human immunodeficiency virus (HIV) is associated with several stressors that are directly and indirectly related to HIV, such as health maintenance, stigma, and histories of trauma and adversity (4). Although the exact manner by which stress leads to cognitive dysfunction is unclear, increased stress in PLWH has important implications for brain and immune functioning and may negatively affect disease progression and treatment adherence and promote risk taking behaviors, all of which affect cognition, behavior, and longevity (5).

Although operational definitions of stress vary widely across studies, there is substantive evidence showing that stress affects cognition and brain structure, particularly in regions that are involved in stress signaling and emotion regulation. Stress is posited to negatively influence the brain in part via glucocorticoid stress hormones released by activation of hypothalamic-pituitary-adrenal (HPA) axis (6). The glucocorticoid cascade hypothesis (7), now

BVMT-R = Brief Visuospatial Memory Test—Revised, **CVD** = cardiovascular disease, **dlPFC** = dorsolateral prefrontal cortex, **HIV** = human immunodeficiency virus, **HIV−** = HIV-uninfected, **HPA** = hypothalamic-pituitary-adrenal, **HVLT-R** = Hopkins Verbal Learning Test—Revised, **OFC** = orbitofrontal cortex, **PFC** = prefrontal cortex, **PLWH** = people living with HIV, **ROI** = region of interest, **SES** = socioeconomic status, **vlPFC** = ventrolateral prefrontal cortex

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known as the neurotoxicity hypothesis, proposes that chronic stress increases levels of glucocorticoids in the brain, leading to dysregulation of HPA axis resulting in structural brain changes (e.g., decreased prefrontal cortical [PFC] volume and hippocampal volumes and increased amygdala volumes) (8).

Moreover, the extant literature shows that early life stress exposure has detrimental effects on cognition and brain structure that can persist into adulthood. Indeed, early life stress has been associated with enlarged amygdalae, decreased corpus callosum integrity, and smaller subcortical volumes in children/adolescents and adult samples (9,10). Furthermore, research has shown that early life stress, particularly in PLWH, is associated with worse cognitive functioning in adulthood (9,11). Studies have also demonstrated associations between recent stress levels and cognitive dysfunction. In studies of PLWH, perceived current stress has been associated with worse cognitive performance (12,13) and lower frontal brain volumes, parahippocampal, and hippocampal volume in both PLWH and noninfected populations (14,15). In one study of women living with HIV, recent perceived stress was inversely related to worse cognitive function regardless of HIV status; however, an interaction between HIV status and verbal memory was also reported, which suggested that perceived stress may be particularly detrimental in women living with HIV (13).

Despite a wealth of research on stress and the brain, human stress studies have defined stress in a myriad of ways and typically assessed either time-limited stressors (e.g., those occurring in early life or over the past week or month) or time-limited stress appraisals (e.g., perceived stress over the past month). Furthermore, many instruments for assessing stressor exposure use checklists or Likert ratings that do not fully capture the specific characteristics of the stressors experienced. There is consensus that exposure to major stressors occurring over the course of one's lifetime can have a cumulative or additive effect on biological processes that increase the risk for clinical, behavioral, and cognitive outcomes (e.g., allostatic load) (6,16). As such, many contemporary models of stress and health posit that stressor exposure occurring across the lifetime affects health and longevity (6,17). However, few studies have examined how cumulative lifetime stressor exposure is related to neural and cognitive outcomes in the general population and even fewer studies that have done so specifically in PLWH, even though they experience a disproportionate amount of stress-related disease burden (18,19).

The present stress literature is also limited in that there is little differentiation between key types of stressor exposure (e.g., acute versus chronic) that may have different effects on cognition and health. There is evidence that exposure to chronic difficulties is particularly detrimental to health because, in part, of their ability to induce systemic low-grade inflammation (20). Moreover, chronic elevations in cortisol have been shown to predict cognitive dysfunction in attention and memory processing and reduced hippocampal volume in healthy older adults (21,22). However, most studies on this topic to date have investigated the effects of isolated stressors or posttraumatic stress disorder (23). Likewise, despite evidence that stressor appraisals are critical for regulating inflammatory pathways, most stressor assessment instruments do not measure individuals' subjective appraisal of the severity of the specific stressors experienced (24). This is a critical limitation because stressor-specific severity appraisals have been posited to drive the association between stressful events and adverse health outcomes (25).

To address these issues, we conducted the first study that we know to investigate how cumulative lifetime chronic stressor exposure is related to cognition and brain volume in community-dwelling PLWH and HIV-uninfected (HIV−) adults. To address the limitations of prior research on stress in HIV populations, we used the well-validated Stress and Adversity Inventory (STRAIN), which assesses the severity, frequency, timing, and duration of acute and chronic stressors occurring over the entire life span (26,27). Based on the literature reviewed previously, we hypothesized that greater lifetime chronic stressor exposure would be related to a) worse global cognition and individual cognitive domains; b) smaller PFC, hippocampal, and insula volume; and c) greater amygdala volume. In addition, we hypothesized that brain structure would mediate the association between lifetime chronic stressor exposure and cognition. Finally, we hypothesized that HIV status may moderate these relations such that PLWH would exhibit stronger associations between lifetime chronic stressor exposure and cognition and brain volumes compared with HIV− adults.

METHODS

All procedures were reviewed and approved by the University of California, Los Angeles, and the University of Southern California institutional review boards, and participants signed informed consent forms before participation. Data from the present study are part of a larger ongoing study; the present study data were collected between 2015 and 2020.

Participants

Middle-aged to older adult participants (ages, 30–74 years) were recruited from HIV clinics and the local community through local advertisements and participant word of mouth. HIV status was confirmed via serologic testing (i.e., Western blot confirmed by enzyme-linked immunosorbent assay). Questionnaires and screeners about medical, neurological, and psychiatric history were used to screen for potential confounds. Briefly, we screened for neurological, psychiatric, illicit drug use, and current substance abuse (e.g., opiates, cocaine, methamphetamine). However, we did not exclude participants if they reported alcohol, tobacco, or marijuana abuse. Medical and psychiatric confounds were screened using the Structured Clinical Interview for *DSM-IV*, Mini-Mental Status Examination, urine toxicology test, and questionnaires about neurological and medical history. Participants were excluded if they had a past head injury with loss of consciousness (>30 minutes), neurological disease (e.g., seizure disorder), psychosis or mania in the past 12 months, or likely cognitive impairment (e.g., Mini-Mental Status Examination score <26). Participants' data were also screened for additional exclusionary criteria, history of myocardial infarction or stroke, and history of HIV-related opportunistic infections. Ninety-one participants (43 PLWH, 38 HIV− controls) had cognitive and imaging data available.

Demographic Variables

Demographic data including age, education, racial/ethnic identity, and sex were obtained via self-report (Table 1). SES was measured using the Hollingshead Four-Factor Index of Social Status. The Hollingshead scale algorithm uses information about occupational prestige, income, sex, and marital status, with higher scores indicating higher SES.

Cumulative Lifetime Stressor Exposure

The STRAIN was used to assess the severity of all chronic stressors experienced over the life course (27). For each stressor endorsed, participants complete follow-up questions that assess the stressor's severity, frequency, timing, and duration. The stressors are all considered major stressors, and they span 12 primary life domains (e.g., housing, work, finances) and 5 social-psychological characteristics (e.g., interpersonal loss, physical danger). Across these stressor domains, the STRAIN computes the total count and severity of all many of major life stressors, including 26 acute life

TABLE 1. Demographic and Clinical Characteristics of Study Participants

	All Participants (N = 91)	Controls (n = 48)	PLWH (n = 43)	Statistic	p
Age, y	56.38 (7.92)	55.73 (8.08)	57.12 (7.77)	0.694	.407
Sex, % male	73.6	70.8	76.7	0.408	.523
Race, % Black	67.0	68.8	65.1	0.136	.713
Education, y	14.01 (2.33)	14.04 (2.34)	13.98 (2.34)	0.017	.895
WRAT (standardized)	99.76 (15.81)	99.58 (15.15)	99.95 (16.70)	0.012	.912
Hepatitis C, %	5.6	2.1	9.5	2.363	.124
Vascular risk burden	17.57 (8.93)	16.39 (8.69)	18.89 (9.11)	−1.338	.477
Socioeconomic status					
Hollingshead total	41.18 (12.45)	39.71 (12.90)	42.81 (11.86)	1.419	.237
Household income	32.63 (34.77)	43.14 (38.57)	21.87 (26.32)	436.00	**<.001**
Income per family member	27.01 (24.11)	33.12 (21.56)	20.28 (25.22)	455.00	**<.001**
Psychiatric/Stressors					
BDI-II	6.14 (6.24)	5.46 (6.05)	6.91 (6.43)	1.225	.271
Current major depressive disorder, %	2.2	4.2	0.0	1.832	.176
Past major depressive disorder, %	15.4	14.6	16.3	0.050	.823
Past mania or psychosis, %	4.4	0.0	9.3	4.670	**.031**
STRAIN lifetime chronic stressor exposure severity	36.76 (23.57)	35.81 (8.90)	37.81 (23.88)	979.00	.673
Substance use					
Past substance abuse, %	35.2	16.7	57.1	16.016	**<.001**
Current marijuana/alcohol abuse, %	11.0	12.5	9.5	0.201	.654
HIV characteristics					
Nadir CD4	—	—	286.34 (193.44)	—	—
Current CD4	—	—	638.62 (272.42)		
cART use, %	—	—	100	—	—
Years since HIV diagnosis			20.83 (8.11)	—	—

PLWH = people living with HIV; WRAT = Word Reading Association Test; BDI = Beck Depression Inventory; cART = combined antiretroviral therapy.

Boldface indicates statistical significance ($p < .05$).

Analysis of variance, Mann-Whitney, and χ^2 analyses were used as appropriate to compare PLWH and HIV− groups.

events and 29 chronic difficulties. Severity is calculated by adding Likert scale severity ratings, on a 1 to 5 scale, for each stressor endorsed.

For the purposes of the present study, we selected lifetime chronic stressor exposure severity, abbreviated as lifetime chronic stressor exposure, as the a priori STRAIN index of interest, given evidence of the relatively greater impact of chronic versus acute stress (28).

Psychiatric Measures

Depression symptom severity was assessed using the Beck Depression Inventory-II.

Vascular Risk Burden

Given the age of participants, particularly the number of older adults, we measured vascular risk burden because it has been well documented that vascular risk is associated with cognitive dysfunction in PLWH and HIV− adults (29). Vascular risk factors were determined with physical examinations, clinical interviews, and medication review. Seated brachial artery blood pressure, weight, and height were measured as part of the physical examination. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Diagnosis and treatment history for hypertension, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease (CVD) were documented using interviews and medication review. The Framingham Heart Study CVD 10-year risk algorithm was used to quantify vascular risk burden. The Framingham Heart Study CVD 10-year risk score has been associated with cognition and cognitive decline in both PLWH and HIV− populations (30). Body mass index was used in lieu of fasting total cholesterol and high-density lipoprotein cholesterol, given that these data were not collected in a majority of participants (n = 34 with data) and are suitable proxy for fasting cholesterol based on previous research (31).

Neuropsychological Assessment

Participants underwent a comprehensive neurocognitive assessment battery that assessed the following domains: attention and information processing speed (Wechsler Adult Intelligence Scale—Fourth Edition Coding and Symbol Search, Trail Making Test—Part A, and Stroop Interference Test—Color and Word Naming), verbal fluency (Controlled Oral Word Association Test—FAS and Animal Fluency), learning and memory (Hopkins Verbal Learning Test—Revised [HVLT-R], Total Learning, Delayed Recall; Brief Visuospatial Memory Test—Revised [BVMT-R], Total Learning, Delayed Recall), executive functioning (Trail Making Test—Part B, Stroop Interference Test—Interference, and Wechsler Adult Intelligence Scale—Fourth Edition Letter-Number Sequencing), and motor function (Grooved Pegboard). Raw test scores were converted into age-adjusted T scores for baseline cross-sectional analyses. Global and individual cognitive domain scores were computed by averaging T scores for individual tests (32).

For all analyses, we examined both global cognition the a priori–selected individual domains: processing speed (Trails A, Stroop Color, Stroop Word, Symbol Search, Coding), executive functioning (Trails B, Letter-Number Sequencing, Stroop Interference, FAS), learning (HVLT-R total recall, BVMT-R total recall), and memory (HVLT-R delayed recall, BVMT-R delayed recall). Premorbid estimated intelligence was assessed using a test of irregular word reading (Wide Range Achievement Test-4).

Structural Neuroimaging

Structural magnetic resonance imaging data were collected on 3T Siemens scanners. The parameters of the T1-weighted MPRAGE scan are repetition time/echo time/inversion time of 2500/1.81/1000 milliseconds, 8-degree flip angle, 1.0 × 1.0 × 1.0-mm^3 resolution, and acquisition time of 5:13 minutes. These structural scans were processed using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu). Standard FreeSurfer automated cortical parcellation processing procedures were used (33). Each participant's postprocessing outputs were manually inspected for reconstruction accuracy in the Talairach transform, skull strip, white and pial surfaces, and segmentations. Volumetric estimates were extracted from automatic surface parcellation labels using the Desikan/Killiany Atlas.

Volumetric region-of-interest (ROI) analyses were chosen based on the extant literature and included regions that have been found to be associated with emotion and stress regulation networks. The a priori–selected ROIs included the following: PFC composite, limbic system structures (amygdala, hippocampus), and associated limbic structures (insula). The composite PFC variable was computed using the average of all individual brain regions in the PFC specified previously, as well as subregion composites (e.g., ventrolateral PFC [vlPFC], dorsolateral PFC [dlPFC], anterior cingulate, and orbitofrontal cortex [OFC]). The OFC composite was calculated as the average of lateral OFC and medial OFC volumes. The anterior cingulate composite was calculated as the average of rostral anterior cingulate and caudal anterior cingulate volumes. The dlPFC composite was calculated as the average of superior frontal, caudal middle frontal, and rostral middle frontal gyri volumes. The vlPFC was calculated as the average of pars opercularis, pars triangularis, and pars orbitalis volumes.

Statistical Analysis

First, all variables were assessed for outliers and normality (e.g., skewness, kurtosis). For outlier analysis, dependent variables were screened by converting raw data to z scores and inspected for errors. For brain volumes, exclusion criteria of $z > 3.0$ and $z < -3.0$ were applied to each individual region analyzed (34); three outliers were removed for PFC region, and one outlier was removed for amygdala. Global cognition, processing speed, executive functioning, and all magnetic resonance imaging volumes were normally distributed according to Shapiro-Wilks test (p values > .10). Learning and memory were not normally distributed (p = .002 and p = .001, respectively). Log transformed did not resolve nonnormality; therefore, unadjusted values were used. For other nonnormally distributed variables (e.g., lifetime chronic stressor severity, depressive symptoms), nonparametric testing was used as appropriate (e.g., Spearman correlations, Mann-Whitney tests). SPSS version 27 was used for all analyses. The PROCESS macro was used to conduct all mediation analyses (35).

Demographic and Clinical Analyses

Analysis of variance, Mann-Whitney, and χ^2 analyses were used to compare PLWH and HIV− groups on demographic variables, SES, and psychosocial variables (Table 1).

Correlates of Cumulative Lifetime Chronic Stressor Severity

Spearman correlation and Mann-Whitney analyses were conducted to examine how lifetime chronic stressor exposure was related to the demographic, psychosocial, and psychiatric variables assessed. Correlation analyses demonstrated that greater lifetime chronic stressor exposure was associated with more recent depressive symptoms ($\rho = 0.281$, $p = .007$), current major depression (ρ = 0.214, p = .042), and past psychosis/mania (ρ = 0.257, p = .014). Lifetime chronic stressor severity was unrelated to literacy, age, SES, education, past substance dependence, current substance abuse, HIV status, race, or sex (p values > .10).

Correlates of Cognitive Performance

The following variables were related to global cognitive performance: education ($r = 0.217$, $p = .04$), literacy/WRAT-4 ($r = 0.541$, $p < .0001$), and race ($\rho = -0.29$, $p = .005$). However, race was no longer statistically significant after adjusting for WRAT-4.

Identification of Covariates

Variables that were associated with predictors of HIV status and lifetime chronic stressor severity or outcomes of cognition or magnetic resonance imaging ROIs were initially included as covariates in tests of study hypotheses. Once these covariates were identified, we used an iterative multivariate fitting (36). For global cognition, eight variables (age, education, vascular risk burden, SES, current major depression disorder, current depressive symptoms, past substance dependence, and race) were eliminated one at a time because they were not significant in the multivariate model at the α level of 0.15 and, when removed, did not change any remaining parameter estimates by more than 20%. To test hypotheses with PFC as the outcome, six variables were eliminated (education, SES, current major depression disorder, current depressive symptoms, past substance dependence, and race).

Tests of Study Hypotheses

The following variables were entered into the final models: age, sex, literacy proxy (measured by raw WRAT-4 score), intracranial volume, HIV status, lifetime chronic stressor exposure, and HIV status by lifetime chronic stressor exposure interaction.

Hypothesis 1a: Lifetime Chronic Stressor Exposure Will Be Related to Worse Global and Individual Cognitive Domain Performance

We examined associations between lifetime chronic stressor exposure and cognitive function using the PROCESS model 1, with HIV status as a moderating variable (aim 1a, Figure 1). False discovery rate (FDR) correction was corrected for all individual cognitive domain analyses (e.g., processing speed, executive functioning, learning, memory).

Hypothesis 1b: Lifetime Stressor Exposure Would Be Related to Reduced PFC, Hippocampal, and Insula Volume and Increased Amygdala Volume

We examined associations between lifetime chronic stressor exposure and brain structure using PROCESS model 1 (aim 1n, Figure 1). Relations between lifetime chronic stressor exposure and eight a priori–selected volumetric ROIs were tested using HIV status as a moderator. The ROIs included PFC total volume, PFC regional volumes (dlPFC, vlPFC, OFC, anterior cingulate), amygdala, hippocampal, and insula volumes. FDR correction was applied to individual PFC regions to control for multiple comparisons.

Hypothesis 2: Brain Structure Will Mediate Associations Between Lifetime Chronic Stressor Severity and Cognition

Mediation analyses investigating whether brain volume mediated the association between lifetime chronic stressor exposure and cognition were conducted using PROCESS model 4 (Figure 1). Given the lack of HIV status interactions for aim 1, moderated mediation models were not used and HIV status was included as a covariate. Lifetime chronic stressor severity served as the predictor (X), global cognition or individual cognitive domains served as the respective dependent variables (Y), and brain volume served as the mediator (M). The specific parameter of interest is whether the effect of lifetime chronic stressor exposure on cognitive domain via brain volume measures ($a \times b$) is statistically significant, such that it accounts for all or part of the direct effect of lifetime chronic stressor exposure on cognitive performance (c). To obtain unbiased standard errors (ESs) to ensure a type I error rate of 0.05, 5000 bootstrap samples were generated with corresponding 95% confidence intervals (CIs).

RESULTS

Descriptive Statistics

Table 1 shows demographic, socioeconomic, and psychosocial data for the complete sample and for PLWH and HIV− participants

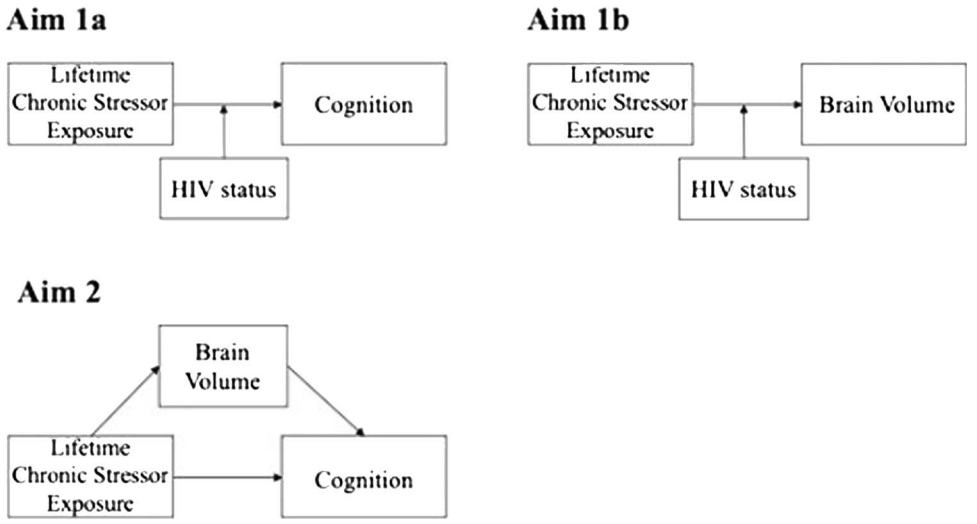

FIGURE 1. Conceptual diagram of the primary study aims. Aim 1 was to investigate relationships between lifetime chronic stressor exposure and cognition and brain volume. Aim 2 was to examine if brain volume mediates relationships between lifetime chronic stressor exposure and cognition.

separately. Relative to HIV− adults, PLWH had lower total household income and income per family member (p values < .001), and higher rate of past substance dependence (p < .001). These groups did not differ with respect to age, sex, race, years of education, WRAT-4 reading score (literacy proxy), current substance abuse (alcohol or marijuana), hepatitis C infection, STRAIN lifetime chronic stressor exposure severity, or SES (Hollingshead; p values > .10).

Hypothesis 1a: Lifetime Chronic Stressor Exposure Associations With Cognition

As hypothesized, greater lifetime chronic stressor exposure was associated with worse global cognition (b = −0.06, SE = 0.03, t = −2.059, p = .032), processing speed (b = −0.04, SE = 0.14, t = −3.032, p = .041), and executive functioning (b = −0.06, SE = 0.02, t = −2.301, p = .02). These findings remained significant after FDR correction.

There were no statistically significant HIV group differences in global cognition (p = .694), processing speed (p = .468), learning (p = .724), or memory (p = .907). There were marginal HIV status differences in executive functioning (p = .075), whereby PLWH had worse executive functioning relative to HIV− participants. Finally, there were no statistically significant lifetime chronic stressor exposure by HIV status interactions on global cognition (p = .518) or any individual domains (processing speed: p = .531; executive functioning: p = .707; learning: p = .480; memory: p = .117).

Hypothesis 1b: Lifetime Chronic Stressor Exposure Associations With Brain Volume

As hypothesized, greater lifetime chronic stressor exposure was associated with less PFC volume (b = −16.20, SE = 5.78, t = −2.751, p = .007, 95% CI = −27.87 to −4.53; Figure 2), including

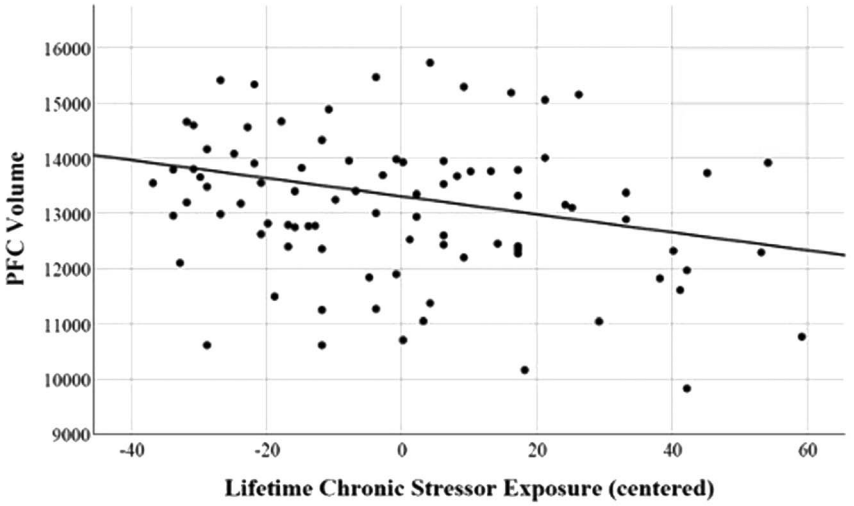

FIGURE 2. Association between lifetime chronic stressor exposure and PFC volume. As hypothesized, greater lifetime chronic stressor exposure was associated with less PFC volume (β = −0.277, p = .007; N = 88). PFC = prefrontal cortex.

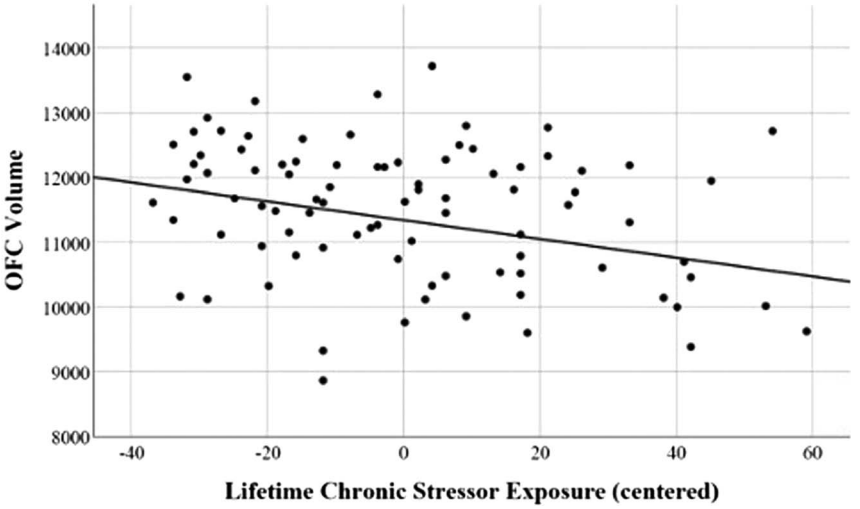

FIGURE 3. Association between cumulative lifetime chronic stressor exposure and OFC volume. As hypothesized, greater lifetime chronic stressor exposure was associated with less OFC volume ($\beta = -0.324$, $p = .002$; $N = 88$). OFC = orbitofrontal cortex.

the OFC ($b = -18.79$, SE = 5.82, $t = -3.224$, $p = .030$, 95% CI = −30.68 to −6.90; Figure 3) and dlPFC ($b = -29.95$, SE = 11.94, $t = -2.5073$, $p = .014$, 95% CI = −53.77 to −6.12; Figure 4). Greater lifetime chronic stressor severity was marginally associated with less vlPFC volume ($p = .058$). There were no relations with anterior cingulate volume ($p = .12$), amygdala volume ($p = .36$), hippocampal volume ($p = .12$), or insula volume ($p = .34$). Findings remained significant for the PFC composite and OFC after FDR correction.

PLWH did not differ from HIV− controls in volumes of the PFC, anterior cingulate, hippocampus, insula, or amygdala after FDR correction. Finally, there was no interaction between lifetime chronic stressor exposure and HIV status on PFC volume ($p = .18$), anterior cingulate volume ($p = .66$), dlPFC volume ($p = .25$), vlPFC volume ($p = .32$), OFC volume ($p = .24$), amygdala volume ($p = .93$), hippocampal volume ($p = .49$), or insula volume ($p = .81$).

Hypothesis 2: Mediation Analyses Examining Lifetime Chronic Stressor Severity, Brain Volume, and Cognition

Finally, mediation analyses were conducted to examine whether brain volumes mediated the effects of lifetime chronic stressor severity on global cognition, processing speed, and executive functioning.

Global Cognition

Greater lifetime chronic stressor severity was significantly associated with less PFC volume (*a*: $b = -16.20$, SE = 5.78, $t = -2.800$, $p = .007$). When controlling for lifetime chronic stressor severity, PFC volume was not significantly related to global cognition (*b*: $b = 0.00$, SE = 0.00, $t = 0.778$, $p = .44$). The estimated total effect of lifetime chronic stressor severity on global cognition was significant (*c*: $b = -0.07$, SE = 0.02, $t = -2.583$, $p = .013$, 95% CI = −0.129 to −0.015), and the estimated direct effect of lifetime chronic stressor severity was significant (*c′*: $b = -0.06$, SE = 0.03, $t = -2.059$, $p = .035$, 95% CI = −0.125 to −0.0013). The indirect effect of lifetime chronic stressor severity on global cognition through PFC volume was not significant (95% bootstrap CI = −0.04 to 0.02); therefore, there was no evidence of partial or full mediation. Follow-up analyses

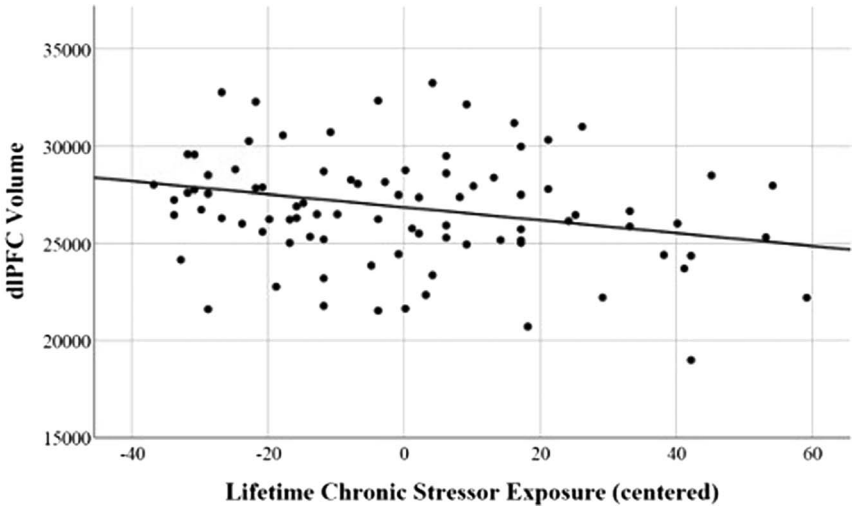

FIGURE 4. Association between cumulative lifetime chronic stressor exposure and dlPFC volume. As hypothesized, greater lifetime chronic stressor exposure was associated with less dlPFC volume ($\beta = -0.230$, $p = .032$; $N = 88$). dlPFC = dorsolateral prefrontal cortex.

showed no evidence of moderated mediation by HIV status (95% bootstrap CI = −0.01 to 0.03).

Processing Speed

Greater lifetime chronic stressor severity was significantly associated with less PFC volume (*a*: $b = -16.20$, SE = 5.78, $t = -2.800$, $p = .007$; Figure 5). When controlling for lifetime chronic stressor severity, PFC volume was significantly associated with processing speed (*b*: $b = 0.00$, SE = 0.00, $t = 2.513$, $p = .020$). The estimated total effect of lifetime chronic stressor severity on processing speed was significant (*c*: $b = -0.10$, SE = 0.04, $t = -2.241$, $p = .022$, 95% CI = −0.20 to −0.02), whereas the estimated direct effect of lifetime chronic stressor severity was not (*c*′: $b = -0.07$, SE = 0.05, $t = -1.495$, $p = .14$). The indirect effect of lifetime chronic stressor severity on processing speed through PFC volume was statistically significant (95% bootstrap CI = −0.08 to −0.00). Given that the direct path from lifetime chronic stressor severity to processing speed (*c*′) was not significant, we conclude that, as hypothesized, the relation between lifetime chronic stressor severity and processing speed was fully mediated by PFC volume. Follow-up analyses showed no evidence of moderated mediation by HIV status (95% bootstrap CI = −0.01 to 0.06).

Executive Functioning

Greater lifetime chronic stressor severity was significantly associated with less PFC volume (*a*: $b = -16.20$, SE = 5.78, $t = -2.800$, $p = .007$). While controlling for lifetime chronic stressor severity, PFC volume was not associated with executive functioning (*b*: $b = 0.00$, SE = 0.00, $t = 0.226$, $p = .821$). The estimated total effect of lifetime chronic stressor severity was significant (*c*: $b = -0.07$, SE = 0.02, $t = -2.301$, $p = .01$), and the direct effect was significant (*c*′: $b = -0.06$, SE = 0.03, $t = -2.301$, $p = .026$). The indirect effect of lifetime chronic stressor severity on executive functioning through PFC volume was not statistically significant (95% bootstrap CI = −0.03 to 0.02), suggesting the absence of partial or full mediation. Follow-up analyses showed no evidence of moderated mediation by HIV status (95% bootstrap CI = −0.01 to 0.03).

DISCUSSION

To our knowledge, this is the first study to document how major stressors experienced over the entire life span are related to cognition and brain structure in a diverse group of PLWH who are at high risk for stressor exposure and for experiencing subsequent stress-related disease burden and mortality. The resulting data suggest that greater cumulative chronic stressor exposure may negatively affect cognitive functioning and brain structures necessary for both cognition and emotion regulation.

Is Lifetime Chronic Stressor Exposure Related to Cognitive Function?

As hypothesized, we found that greater lifetime chronic stressor exposure was related to worse cognitive abilities, including processing speed and executive functioning. These results support the theory that stressors may have an additive effect on biological processes that promote the risk for disease and negative health outcomes (6,17). Recent STRAIN validation studies have reported inconsistent findings in the relationship between total lifetime stressor exposure and executive functioning (27,37). As compared with these prior studies, our study benefitted from a comprehensive neuropsychological battery.

Processing speed was associated with lifetime chronic stressor exposure in our study, which has been previously associated with early life stress and isolated chronic stressors (9,38,39). One study showed that processing speed mediated the relation between psychosocial stress and global cognition in older adults, suggesting that stress-related deficits in processing speed may be responsible for associations with overall cognitive dysfunction (40). Also, consistent with prior work examining recent perceived stress, we found that lifetime chronic stressor exposure was associated with executive functioning (13,41).

Contrary to expectations, we did not find any significant differences between HIV status groups on cognition, despite evidence that asymptomatic neurocognitive impairment and mild neurocognitive impairment persist in the combined antiretroviral therapy (cART) era (42). However, the Women's Interagency HIV Study reported that the effect size for HIV status on cognitive functioning was very small (e.g., 0.05–0.09 standard deviation units) and was smaller than that of other demographic correlates of cognitive function (43). It is likely that our lack of cognitive differences among HIV status groups is due to our well-matched HIV− comparison group and inclusion of important covariates (e.g., premorbid estimated intelligence, race, vascular risk burden) in cognitive analyses that are not universally included in studies. Furthermore, our inclusion of covariates such as race, premorbid estimated intelligence, and depressive symptoms may have attenuated group-based differences in cognition. Our investigative team recently published a systematic

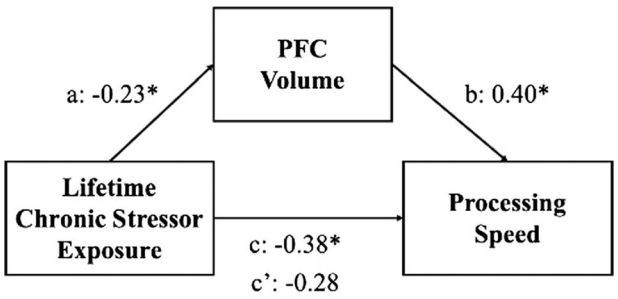

FIGURE 5. PFC volume mediates the relation between greater lifetime chronic stressor exposure and processing speed. Simplified path model to assess the indirect effect of lifetime chronic stressor exposure on processing speed through PFC volume. The path coefficients (*a*, *b*, *c*, *c*′) are shown as standardized β coefficients. *c*′ represents the direct effect of lifetime chronic stressor exposure on processing speed. *$p < .05$ ($N = 88$). PFC = prefrontal cortex.

review that revealed that many HIV studies do not include race or SES in models (29). Therefore, the ability to systematically control for these factors may be one reason for the differences observed between this and prior studies.

Another possible explanation for lack of HIV status differences in cognition may be that our HIV cohort is relatively healthy in comparison to some existing cohorts. Our HIV cohort reported high cART use (>98%), and all participants had current normal CD4 counts. Although a sizeable amount had nadir count <200 indicative of AIDS diagnosis (40.0%), most of our participants were not recently infected; thus, there may also be a survivor effect present.

As expected, PLWH did exhibit greater history of serious mental illness, past substance dependence, and health-related lifetime total stressor severity and lower current income relative to HIV− participants. This finding is consistent with the extant literature showing that PLWH have higher rates of substance use and psychiatric disorders relative to HIV− populations (3,44). Contrary to hypotheses, though, lifetime chronic stressor exposure-cognitive associations were not moderated by HIV status, which may be explained by decreased power compared with other studies that have reported interactions between HIV status and stress on cognition (12,13,45). Furthermore, this sample had both male and female participants, which may have added variance to our models. The extant literature shows that men and women may have different reactions to stressful life experiences as well as different stressors based on traditional gender roles (46). Prior studies have documented sex differences in cortisol responses to psychological stressors (47). Therefore, future research is warranted to investigate these associations in PLWH.

Furthermore, it is noteworthy that relations between lifetime chronic stressor exposure and cognition were independent of current depressive symptoms and remained significant after removing participants who met the criteria for current major depression. Depression is well known to negatively affect cognition, including attention, executive functioning, and memory (48). Accounting for depressive symptoms in examinations of chronic stress may be particularly important because chronic stress has been found to be a relatively stronger predictor of depressive symptoms than acute stress (49). In a recent study using the STRAIN, cumulative lifetime stressor exposure was associated with greater symptoms of depression and anxiety (50); therefore, it is important to account for depression when isolating the cognitive correlates of stress.

Is Lifetime Chronic Stressor Exposure Related to Brain Structures Implicated in Stress and Emotion Regulation?

In addition, we found that lifetime chronic stressor exposure was associated with PFC volume in the expected direction, with greater stressor exposure severity being associated with less PFC volume. This finding adds to the extant literature documenting associations between stress and PFC volume in human adults (15,51–53). Although the relation between stress and OFC volume has been reported previously (51,53), our data are the first to show this effect for lifetime chronic stressor exposure.

Interestingly, we did not find that lifetime stressor exposure was related to subcortical regions related to the HPA axis and limbic system. Despite strong theoretical underpinnings supporting an association between stress and hippocampal volume, there are mixed findings in the literature. Inverse relations between perceived stress and hippocampal volume have been reported in adolescents and older adults (14,53,54). In contrast, several studies have not reported such an association (15,51,52,55). One possibility for conflicting findings is that the brain may be more sensitive to stress-related damage to the hippocampus at certain ages. For example, the impact of stress exposure may be particularly detrimental in early age or late age because of developmental changes (55,56).

There was no relation between lifetime chronic stressor severity and amygdala volumes. Although the amygdala is hypothesized to be vulnerable to stress, the majority of studies that have documented positive relations between amygdala volume and stress has been limited to early life stress (9), which may be particularly detrimental to amygdala function and structure because of early development of this brain region in childhood (57). Indeed, in the literature focusing on recent stress, several studies have not found associations between recent stress and amygdala volume (51–53), or have found that recent stress was associated with lower amygdala volume (55,58). The one neuroimaging study that did measure cumulative adverse life events, which most closely resembles our measure, also did not find relations with amygdala volume (51). Given mixed findings, future studies are warranted.

Similarly, we did not find associations between stressor exposure and the insula. One study showed that cumulative adversity was inversely associated with volumes in the insular cortex, as well as the medial PFC and anterior cingulate (51). Similarly, another study showed that perceived stress in middle-aged adults was negatively associated with insula volume (55). Notably, these studies samples were younger than our sample and did not include PLWH. Differences in study demographics and stressor measures thus make it difficult to compare these findings. In terms of the subcortical regions and insula, one possible explanation for the lack of findings is small sample size and heterogeneity with respect to HIV status, sex, and age.

Does Brain Volume Mediate the Association Between Lifetime Chronic Stressor Exposure and Cognition?

Given the literature on stress, cognition, and brain volumes, we investigated whether the relationship between lifetime chronic stressor exposure and cognition was at least in part due to volume in brain regions that are known to be sensitive to stress. Few studies have used proper mediation techniques to investigate this question. One study in adolescents showed that lifetime stressor exposure was inversely associated with spatial working memory performance, which was mediated by PFC volumes (59). In another study of SES, which is closely related to stressor exposure, dlPFC volume partially mediated the relation between SES and executive function (60).

In the present study, mediation analysis showed that the relation between lifetime chronic stressor exposure and processing speed was mediated by PFC volume. Although we cannot infer causality, these results may suggest that lifetime stressor-related deficits in processing speed are driven by structural abnormalities in the PFC. Processing speed is associated with both white matter integrity and gray matter volume, including PFC volumes (61,62). Processing speed does not involve a single neural system but rather several neural networks. Consistent with the neurocognitive tests in our battery, processing speed tasks can encompass multiple skills including visuoperception skills, motor skills, and verbal skills; thus, processing speed can be associated with several different brain regions depending on the specific task, which may explain why our significant findings were observed using the PFC

composite. Future studies may benefit from using a voxel-based approach to better understand the relationship between processing speed and PFC structure in the context of stress.

Although we found that lifetime chronic stressor exposure was associated with executive functioning, this relation was not mediated by PFC volume, which may be attributed to the broad definition of executive functioning, which includes set shifting, working memory, phonemic fluency, problem solving, inhibitory control, and decision making. Although executive functions are thought to be largely governed by the PFC, individual aspects of executive functioning correspond to different areas of the PFC. For example, Trails B has been linked to dlPFC structure and function in numerous studies (59). Consistent with this broad definition, our executive functioning composite included tasks that assess its various abilities. Therefore, the heterogeneity in both executive function tasks may have diluted the association with PFC volume and any mediating relations. Future research would benefit from similar mediation analyses to understand if relations between stress and cognition are mediated by structural alterations in the brain.

Future Directions

One future direction may be to examine sex differences in relationship between stressor exposure and cognition. There is some evidence that women may be more susceptible to effects of stress on cognition. Several studies of stress and the brain in the HIV literature have performed studies in either all-male or all-female cohorts. Examination of both sexes within the same design will be helpful in discerning sex differences that are not confounded by differences between study demographics and methods.

Another potential future direction is to examine biological measures of chronic stress (e.g., cortisol from hair, inflammatory markers) to better understand the biological underpinnings of cumulative chronic stress and its relationship to the STRAIN.

Strengths and Limitations

This study had several strengths. First, we used a state-of-the-art instrument for assessing lifetime stressor exposure and severity and examined for the first time how lifetime chronic stressor exposure severity related to cognition and brain structure, thus filling a critical gap in the stress literature. Indeed, most studies on this topic have used the perceived stress scale, which measures psychological distress—not stressor exposure—and only over a very short period (e.g., 1 month) with no information about the characteristics of the stressors experienced. We also used a comprehensive neuropsychological battery to assess cognitive functioning. Finally, studying interrelations between stressors, cognition, and brain volumes in PLWH is notable because this population experiences a disproportionate amount of stressor burden along with many stress-related health problems but has not been studied using the combination of approaches used here to yield a more complete picture of how stress impacts cognitive and physical health in this population.

Several limitations should also be noted. First, although the STRAIN has been shown to be insensitive to mood and personality factors affecting self-report, it is still possible that such influences could have impacted participants' reports of the stressor experienced. Second, the results of the mediation analyses conducted here are provocative but should be considered with caution until they can be replicated in longitudinal studies. Finally, we did not examine the potential relevance of the constructs assessed here for health, which remains an important topic for future study.

Conclusions

In conclusion, these data are the first to demonstrate the negative impacts of lifetime chronic stressor exposure on global cognition and individual cognitive domains in PLWH and HIV− adults. Greater lifetime stressor exposure severity was related to worse global cognition, processing speed, and executive functioning, as well as smaller brain volumes in the PFC. Moreover, mediation analysis showed that stressor-related deficits in processing speed were attributed to reduced PFC volume. Finally, we did not find evidence of any significant interactions with HIV status, suggesting that cumulative lifetime stressor exposure is harmful to the brain regardless of HIV infection. Together, these findings may highlight the importance of developing of novel psychosocial interventions to address the harmful effects of stressor exposure on the brain with the aim of reducing cognitive dysfunction and potential premature brain aging.

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