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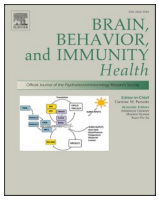

Medial prefrontal cortex connectivity with the nucleus accumbens is related to HIV serostatus, perceptions of psychological stress, and monocyte expression of TNF-a

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A B S T R A C T

Post-menopausal persons living with HIV (PWH) report elevated levels of psychological stress and monocyte activation compared to persons living without HIV (PWOH). Resting state functional connectivity (rsFC) of mesolimbic brain regions underpinning stress and emotion regulation are susceptible to inflammatory insult. Although psychological stress is elevated, rsFC reduced, and $CD16^{+}$ monocytes overexpressed in the brains of PWH, it is unclear whether the relationships amongst these variables differ compared to PWOH.

An ethnically diverse sample of postmenopausal women, 24 PWH and 30 PWOH provided self-report mood surveys and provided peripheral blood specimens to quantify LPS-stimulated $CD16^{+/-}$ expression of TNF-α via flow cytometric analysis. An anatomical and resting state functional MRI scan were used to derive time-series metrics of connectivity between the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAcc) as well as the amygdala.

A positive association was observed between levels of perceived stress and $CD16^{+/-}$ TNF-α in both LPS-stimulated and unstimulated cells. PLWH showed lower connectivity between mPFC and NAcc. In turn, lower rsFC between these regions predicted greater psychological stress and proportion of $CD16^{-}$, but not $CD16^{+}$, cells expression of TNF-α.

Neuroimmune effects of monocyte inflammation on the functional connectivity of mesolimbic regions critical for discrimination of uncertainty-safety and reward signals were observed in an ethnically diverse sample of postmenopausal women living with and without HIV. PWH showed lower mPFC-NAcc functional connectivity, which in turn was associated with greater perceived stress.

1. Introduction

It is estimated that over 50% of people living with HIV (PWH) are currently over the age of 50 (Ford et al., 2015). The incidence and prevalence of HIV among older Blacks and Hispanics/Latinos are over 10 and 5 times the rate amongst older Whites, respectively (Linley et al., 2012). These rates are further skewed when comparing older adult women living with the virus, who report disproportionately greater levels of stress during peri-to postmenopausal age, compared to controls (Brown et al., 2020; Heckman et al., 2002; Ferreira et al., 2007; McIntosh and Rosselli, 2012). Both psychosocial stress and peripheral inflammation are persistently elevated in individuals receiving treatment for chronic HIV disease. Several studies support a positive relationship between peripheral levels of IL-6 or TNF-α and reports of psychological stress, albeit in predominantly male cohorts (Tross and Hirsch, 1988; Fumaz et al., 2009, 2012). More recently, soluable markers of monocyte activation such as monocyte chemoattractant protein-1, IL-6, soluble CD163 and CD14, have been linked with greater levels of psychological stress in men living with HIV (Chow et al., 2023). While the afore-mentioned studies implicate peripheral blood monocyte proliferation in the dysregulation of emotion among PWH, the neuroimmune mechanisms linking these cell profiles to brain areas involved in stressperception are poorly understood, particularly in racially and ethnically-diverse women living with HIV (McIntosh et al., 2015).

Afferent vagus nerve receptor stimulation, passive diffusivity at circumventricular sites, and active transport across the blood brain barrier via myeloid chemotaxis are but a few mechanisms implicated in the neuroimmune signaling that underpins physiological stress and pain perception (Maier, 2003). This chemotaxis triggers a cascade of brain parenchymal responses including ramification of neuroglia as well as altered glutamatergic and dopaminergic signaling (Miller et al., 2013). Indeed, fMRI and positron emission tomography studies to date

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collectively support elevated levels of CRP, TNF-α, and IL-6, with aberrant activation in a host of brain regions including the medial prefrontal cortex (mPFC), anterior cingulate, amygdala, hippocampus, hypothalamus, striatum, and insula, extending into subcortical regions including midbrain and brainstem nuclei (Kraynak et al., 2018). Amongst these regions the mPFC has garnered particular interest as a major hub in the coordination of behavioral responses to sickness, i.e., inflammation (Kraynak et al., 2018). The medial frontal gyrus denotes a host of cortical regions including ventromedial (vmPFC) and orbitofrontal cortex (Andrewes and Jenkins, 2019). Cognitive, affective and behavioral neuroscience literature also supports mPFC as an important hub for the regulation of emotional responses and the generation of the affective meaning that precedes the appraisal of psychological stress (Roy et al., 2012). Human and animal research support the role of mPFC activation in the mitigation of psychophysiological stress response to threat (Alexander et al., 2023). Indeed, ventromedial regions of the mPFC show greater activation during regulation vs. non-regulation of stress through reciprocal communication with HPA-axis and autonomic nervous system relay structures including the amygdala, hippocampus, striatum, hypothalamus, insula, dorsal anterior cingulate, and midbrain in what has been described as a stress adaptation response network (Sinha et al., 2016; Kogler et al., 2015). Amongst the subcortical regions implicated in this network the communication of the mPFC with the nucleus accumbens (NAcc) and amygdala are most integral to emotional regulation. For the NAcc and mPFC this is in part achieved through dense reciprocal connections with the ventral tegmental area (Cauda et al., 2011; Tzschentke and Schmidt, 2000). By virtue of the dense innervation of inhibitory efferent signals from extending from mPFC and rostral ACC amygdala this signaling informs neuroendocrine and cardio-autonomic responses to stress (Andrewes and Jenkins, 2019). The consequence of aberrant communication between the mPFC and these subcortical hubs is poor socioemotional functioning by virtue of misinterpretation of the psychosocial cues that underpinning stress appraisal (Heberlein et al., 2008; Mah et al., 2004). Altogether, aberrant activation of this emotion regulation network is increasingly linked to acute inflammatory challenge as well as basal levels of peripheral inflammation (Muscatell et al., 2016; Voges et al., 2022; Conejero et al., 2019).

Given the limitations in elucidating neural time courses in response to inflammation inherent to task-based fMRI paradigms, many have turned to characterization of the functional connectivity between brain regions underpinning emotion regulation as a proxy of dysfunction (Felger and Miller, 2012; Han and Ham, 2021). The resting state functional connectivity (rsFC) paradigm quantifies temporal dependencies in low frequency oscillations from anatomically distinct brain regions in order to characterize the synchronicity between those regions (Aertsen et al., 1989; Fox and Greicius, 2010). An emergent body of literature has implicated a host of pro-inflammatory biomarkers in the aberrant structural and functional connectivity of mesolimbic brain regions amongst individuals demonstrating exaggerated behavioral response to psychosocial cues of threat (Goldsmith et al., 2022; Petruso et al., 2023). To date, the largest body of support for altered limbic processing in the pro-inflammatory state comes from studies of aberrant connectivity between the ventral striatum and mPFC among depressed and anhedonic cohorts (Haroon et al., 2018; Yin et al., 2019; Kitzbichler et al., 2021; Aruldass et al., 2021; Bekhbat et al., 2022; Goldsmith et al., 2023). Concomitantly, multiple studies also report lower rsFC between regions of interest adjacent to the medial frontal cortex and ventral striatum with elevated levels of CRP and depressive symptom severity (Yin et al., 2019; Bekhbat et al., 2022; Felger et al., 2016). Mechanistic support for neuroinflammatory insult may be inferred from greater proton density in the mPFC and the aberrant communication with the NAcc and other limbic structures (Kitzbichler et al., 2021). Connectivity between the mPFC and amygdala is also integral to the cognitive reappraisal of emotion and perception of psychological stress (Steward et al., 2021; Mehta et al., 2018). As a result of lower negative connectivity between the mPFC and amygdala, a greater magnitude of cortisol response to stress is observed (Veer et al., 2012). There is also evidence for altered activity and connectivity of mPFC in relation to inflammation in chronic inflammatory-immune conditions such as HIV. Our group has shown that higher levels of plasma IL-6 relates to lower mean amplitude of low frequency fluctuations in the vmPFC and elevated mood disturbance in a predominately adult male sample of PWH and PWOH (McIntosh et al., 2018).

Despite the dearth of neuroimaging studies characterizing brain connectivity as a function of inflammation, neurobehavioral deficits in PWH are inextricably linked to peripheral inflammation and, in particular, the signaling and trafficking of peripheral blood mononuclear cells, i.e., monocytes (McIntosh et al., 2015). Monocytes can be separated into heterogeneous subpopulations based on the proportional expression of the CD14 and CD16 cell surface on each cell (Passlick et al., 1989). Classical monocytes make up the largest proportion of the monocyte pool and express low levels of CD16, whereas intermediate and nonclassical monocytes are shown to expand in infectious disease states, and harbor more of HIV-1 virus in vivo (Ellery and Crowe, 2005; Veenhuis et al., 2023). Thus, given their ability to harbor virus, and cross the blood-brain barrier, the $CD16^{+}$ monocyte subset plays a critical role in promoting neuroinflammatory processes that precipitate behavioral impairment in PWH (Veenhuis et al., 2023; Ellery et al., 2007; Ancuta et al., 2008). It should be noted that TNF-α is among the peripheral pro-inflammatory cytokines most frequently implicated in this neuroimmune communication of sickness (D'Mello and Swain, 2017; Kiecolt-Glaser et al., 2003). Not only does TNF-α facilitate monocyte activation and microglial recruitment of peripheral monocytes in vitro, but it also plays an intricate role HIV neuropathogenesis (Tessier et al., 1997; Smith et al., 1998; Kumar et al., 2016; D'Mello et al., 2009). Furthermore, as an index of chronic inflammatory status, TNF-α has shows excellent intra-subject reliability (Koelman et al., 2019; Navarro et al., 2012). Several mechanisms may allow for the mitigation of TNF-α expression in human monocytes. One such mechanism is acetylcholinergic signaling (Huston and Tracey, 2011; Czura and Tracey, 2005). Bone marrow-derived mononuclear cells express multiple α7-nicotinic acetylcholine receptor (α7-nAChR) subunits that function to decrease the proliferation, and trigger the expression of TNF-α upon stimulation at the cell surface receptors (St-Pierre et al., 2016). In vitro studies also suggest that stimulation of α7-nAChR on stimulated $CD14^{+}$ monocytes attenuates expression of TNF-α, an action that was reversed by nonselective and selective α7-nAChR antagonists (Hamano et al., 2006). Furthermore, research examining the chronicity of inflammation in women living with HIV shows that the HIV-1 viral protein $gp120_{IIIB}$ upregulates α7-nAChR on $CD14^{+}$ macrophages in a paradoxical manner that ultimately contributes to the sustained proinflammatory phenotype in these individuals (Delgado Velez et al., 2015).

Given the myriad of pathways allowing monocyte-derived pro-inflammatory biomarkers to subjugate the brain, and the increased propensity for this biotype to emerge in persons living with chronic HIV, the current study sought to compare the effects of monocyte expression of TNF-α on perceived psychological stress and rsFC of the mPFC with NAcc and amygdala. It is hypothesized that expression of $CD16^{+}$, but not $CD16^{-}$, monocyte TNF-α will correlate with lower rsFC of the mPFC with the NAcc and amygdala, which in turn will predict reports of greater psychological stress in a racially and ethnically diverse sample of postmenopausal women living with or without HIV. Moreover, given lower levels of pro-inflammatory cytokines are observed in PWH with elevated vagal tone (Robinson-Papp et al., 2020; Cole et al., 2003), the current study will also explore whether heart rate variability (HRV) measured during the resting state relates to the proportion of monocyte TNF-α expression and whether that association varies as function of HIV + status.

2. Methods

The study sample was recruited between 2016 and 2019, through

flyers and direct referrals from physicians and service organizations. The PWOH were recruited by chain referral, and mostly consisted of friends and family members of the PWH, thus providing a sociodemographic-matched control group. All recruitment procedures and consent were approved by the University of Miami Institutional Review Boards. The exclusion criteria for current severe HIV disease were HIV viral load (>200 copies/ml) and current AIDS diagnosis (Castro et al., 1993; Eisinger et al., 2019). Additionally, persons who, at the time of intake were prescribed medications with immunomodulatory effects (e.g., cytotoxic chemotherapy, corticosteroids, or interferons), had a history of chemotherapy or whole-body radiation treatment for non-AIDS related cancer, or had a history of chronic immune illness such as Type 1 diabetes mellitus, chronic hepatitis, asthma, or chronic fatigue syndrome, or a history of smoking >50 packs of cigarettes per year were excluded. Other exclusion criteria were blood transfusions prior to 1985, antibiotic use for acute infection contracted within the past 2 weeks, hospitalization for surgery within the past 3-months, intravenous drug use within the previous 6-months and for PWH, changes in the HAART regimen over the past 2-months. In addition, participants were screened out at the initial appointment based upon the presence of severe cognitive impairment based on HIV-Dementia Scale score of less than 10 out of 16 points (Power et al., 1995), illiteracy at the 6th grade level based upon the WRAT-4, as well as the indication of current diagnosis or treatment for psychosis, substance dependence, suicidal ideation, and DSM-IV major psychiatric diagnoses including major depressive, bipolar affective, borderline personality, and anxiety disorders based upon the Mini-International Neuropsychiatric Interview (First et al., 1997). The average time reported since initial HIV diagnosis was 234.51 ± 114.64 months. The average time spent on antiretroviral therapy was 148.07 ± 130.84 months. The average time reported since AIDS diagnoses (n = 14) was 179.50 ± 92.84 months. Participant sociodemographic data and medical history are displayed as a function of HIV + status in Table 1.

Table 1
Comparison of study variables between HIV-positive and HIV-negative individuals.

	HIV+ (n = 24)	HIV- (n = 30)	T statistic
Age (years)	58.5 ± 7.4	56.2 ± 6.5	−1.10
Last menstrual cycle (years)	11.49 ± 12.52	10.91 ± 10.90	−0.16
Ethnicity (%)			−0.40[a]
- Black	20 (83.3)	24 (80.0)	
- White	0 (0.0)	1 (3.3)	
- Hispanic/Latina	4 (16.7)	5 (16.7)	
Body mass index	26.84 ± 4.19	29.14 ± 5.90	1.45
Hypertensive (%)	9 (37.5)	9 (30.0)	−0.58[a]
Perceived stress	17.08 ± 2.32	17.56 ± 2.91	0.66
Depression	10.52 ± 11.50	11.9 ± 12.11	0.42
SDNN (ms)	58.30 ± 20.38	64.44 ± 34.44	−0.73
RMSSD (ms)	64.61 ± 15.72	74.518 ± 33.55	−1.31
BFA total cells gated	$2.53 \times 10^5 \pm 1.83 \times 10^5$	$2.58 \times 10^5 \pm 1.97 \times 10^5$	0.09
BFA live cells gated	$2.03 \times 10^5 \pm 1.71 \times 10^5$	$2.17 \times 10^5 \pm 1.74 \times 10^5$	0.78
BFA live monocytes gated (%)	6.7	20.5	−2.49*[a]
LPS + BFA total cells gated	$2.53 \times 10^5 \pm 1.83 \times 10^5$	$2.25 \times 10^5 \pm 1.87 \times 10^5$	0.44
LPS + BFA live cells gated	$1.46 \times 10^5 \pm 1.53 \times 10^5$	$1.81 \times 10^5 \pm 1.64 \times 10^5$	0.83
LPS + BFA live monocytes gated (%)	6.7	26.8	−2.12*[a]
$CD3^+/CD4^+$ lymphocyte count/μL	587.28 ± 396.58	1228.90 ± 548.78	2.89**
Years w/HIV	18.0 ± 10.8		
Past AIDS Diagnosis (%)	12 (50)		
Antiretroviral therapy regimen (%)	100		
- NRTI	12 (50.0)		
- NtRTI	3 (12.5)		
- NNRTI	7 (29.2)		
- Protease inhibitor	3 (12.5)		
- Integrase inhibitor	8 (33.3)		
- Fusion inhibitor	3 (12.5)		

RMSSD – Root mean square of successive differences, SDNN – standard deviation of the NN interval, NRTI - Nucleoside Reverse Transcriptase Inhibitors, NtRTI - Nucleotide Analogue Reverse Transcriptase Inhibitor, NNRTI - Non-nucleoside Reverse Transcriptase Inhibitor.
[a] Mann-Whitney Test Statistic.

2.1. Psychological functioning

2.1.1. Psychological stress

Subjective ratings of psychological stress was assessed by the 14-item Perceived Stress Scale (PSS) (Cohen et al., 1983). The PSS measures frequency with which certain situations in their lives are perceived as being stressful on a scale of 0 (never) to 4 (very often). Positive items were reverse scored, and items were summed to create a total PSS score. This measure demonstrated good internal consistency (α = .85).

2.2. Analysis of monocyte inflammation from whole blood

Cellular inflammation regulation assays were performed on blood from heparin vacutainers within 1-h of collection. The proportion of unstimulated and stimulated PBMCs expressing TNF-α after incubation with and without lipopolysaccharide (LPS) (E.coli 0111:B4, catalog #L4391, Sigma-Aldrich, St. Louis, MO) was assessed on the isolated mononuclear cells. The endotoxin units (EU) for this specific lot were 10 EU per nanogram. Red blood cells were first removed via density centrifugation (Ficoll, BioLegend, San Diego). Approximately one million PBMCs were isolated, and the cell pellet were washed to remove cell debris in preparation for the intracellular assays. Isolated cells were divided into two samples. To halt cytokine secretion, thus allowing detection of intracellular cytokines), Brefeldin A (BFA) (10 μg/mL Sigma-Aldrich) was added to both cell pellets. In the second pellet 100 ng/mL of LPS (1 mg/mL Sigma-Aldrich) was added, which is standard for stimulation of macrophages in vitro. Numerous studies have used this dose, which is considered a moderate dose. Intracellular staining for TNF-α (catalog 502,928. BioLegend, San Diego, CA) was then performed. Both LPS-stimulated and LPS-unstimulated samples were incubated overnight (approximately 18 h) at 37 °C in a humidified 95% air-5% CO2 incubator in sterile 5 mL conical flow tube. After the cell pellets were washed and fixed (CytoFix/CytoPerm; Becton, Dickinson, and Company), intracellular TNF-α production by monocytes was evaluated using multicolor flow cytometry. Data were acquired on LSRII benchtop flow cytometer (Millipore Sigma, Burlington, MA). FACS data was imported into Kaluza Flow Cytometric analysis software (version 1.1) where monocyte analysis was performed. Following gating for monocyte subsets (see supplement), fluorescence intensity of intracellular TNF within $CD45^+CD14^+$ monocyte populations expressing low and high CD16 was reported as the percentage $CD16^-$ or $CD16^+$ expressing TNF-α. For additional details see supplemental file.

2.3. Resting state functional brain connectivity

2.3.1. Image acquisition

Both structural and functional MRI data scans were collected on a 3.0 T Discovery MR750 GE scanner. High-resolution T1-weighted images were also acquired for each subject using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE = 9.2/3.7 ms, FA = 12°, thickness = 1 mm, slices = 216, matrix = 256 × 256, FOV = 25.6 mm × 25.6 mm). Each participant also completed a 7-min resting-state fMRI scan with their eyes open. Resting-state scans were collected using an echo-planar imaging (EPI) sequence (Repetition time (TR)/TE = 2000/25 ms, flip angle = 90°, FOV = 24 mm × 24 mm, matrix = 96 × 96, slices = 42 thickness = 3 mm, 210 vol).

2.3.2. Data preprocessing

Pre-processing of rs-fMRI images was performed using the GRETNA package (http://www.nitrc.org/projects/gretna). The first 5 TRs of the rs-fMRI series were excluded to avoid instability of the MRI signal. The images were normalized into a $3 \times 3 \times 3$ mm^3 Montreal Neurological Institute (MNI-152) template, following correction for slice timing and head motion. The data was spatially smoothed using a 4-mm full-width half-maximum (FWHM) Gaussian kernel. Subsequently, the images were linearly detrended and temporally band-pass filtered 0.008–0.08 Hz. In the final step, the white matter, cerebrospinal fluid, and 6 motion signal parameters were regressed out of the rs-fMRI signal. Each ROI mask was applied to the preprocessed time series, for each location, and connectivity will be averaged across all voxels within the two ROI (see Fig. 1). The rsFC between each pair of seed regions with the combined mPFC seed was calculated across all voxels within the ROI using an in-house software tool for high-quality model-based fMRI data analysis. Subject-level functional connectivity measures between seed regions were transformed to Fisher's Z, $Z(R) = 0.5\ln[(1+R)/(1-R)]$ and then used for subsequent regression models. See supplemental file for additional details regarding seed selection.

2.4. Statistical analysis

The characteristics of the sample are summarized in Table 1 using the mean and standard deviation for continuous variables and the group percentage for categorical variables. The primary analyses were conducted to test three independent hypotheses: 1) inflammatory markers (LPS-stimulated and unstimulated $CD16^-$ and $CD16^+$ monocyte expression of TNF-α) would be positively associated with levels of perceived psychological stress, 2) inflammatory markers would be negatively associated with rsFC between the mPFC and various limbic ROIs (NAcc, and amygdala), and 3) greater rsFC between the mPFC and limbic ROIs would be negatively associated with psychological stress. Thus, individual-level psychological stress and mPFC to limbic ROI Z-scores were entered as dependent variables into linear regression models to assess relationships with stimulated and unstimulated $CD16^-$ and $CD16^+$ TNF-α expression and mPFC connectivity. Each model included HIV + serostatus as a factor and controlled for covariates that may potentially influence the psycho-neuro-immune associations described, including age, Hispanic ethnicity, and the proportion of live vs. dead PBMCs detected in the BFA or BFA + LPS pellets for the $CD16^-$ and $CD16^+$ analyses, respectively. Given the low levels of reported depressive symptom severity and the exclusion of any person diagnosed or treated for depression, we did not control for it in the models. All regression models were first tested for the main and interaction effects of HIV + serostatus. If a significant interaction was not detected, the model report included the main effect of serostatus as an independent variable. Exploratory analyses were also conducted to assess the influence of HRV on stimulated and unstimulated $CD16^-$ and $CD16^+$ monocyte expression of TNF-α. Significance was two-tailed, $\alpha < .05$, and all statistical analyses were conducted in IBM SPSS 29.0.1.0.

3. Results

3.1. Primary analyses comparing relationships between inflammatory markers and perceived psychological stress

3.1.1. Perceived stress is associated with greater TNF-alpha expression on $CD16^-$ monocytes

The model testing the interactive effect of HIV + status on the relationship between the proportion of unstimulated $CD16^-$ expression of TNF-α on PSS was significant despite the absence of an interactive effect (see Table 2). In the main effect model, an inverse effect was observed for $CD16^-$ TNF-α ($p < .05$) on PSS. Similar effects were observed for the stimulated $CD16^-$ TNF-α model. However, monocyte expression of TNF-α did not systematically vary as a function of HIV serostatus (see Fig. 2). After adjusting for multiple comparisons using an adjusted p-value of $p = .0125$, only the proportion of LPS-stimulated $CD16^-$ cells expressing TNF-α demonstrated an effect on perceived stress that was above threshold.

3.1.2. Perceived stress is associated with greater TNF-alpha expression on $CD16^+$ monocytes

The model testing the interactive effect of HIV + status on the relationship between the proportion of unstimulated $CD16^+$ expression of TNF-α on PSS was not significant (see Table 3). In the base model, positive effects were observed for $CD16^+$ TNF-α ($p < .05$) and ethnicity ($p < .05$) on PSS. The model testing the interactive effect for HIV + status on the relationship between the proportion of LPS-stimulated $CD16^+$ TNF-α on PSS was significant, as were the positive effects observed for $CD16^+$ TNF-α ($p < .05$) and Hispanic/Latina ethnicity ($p < .05$) on PSS (see Fig. 4). Despite this, none of the effects in these models survived after adjusting for multiple comparisons using an adjusted p-value of $p = .0125$.

3.2. Primary analyses comparing monocyte inflammation to VMPFC connectivity

3.2.1. TNF-alpha expression on $CD16^-$ monocytes and HIV + status is associated with lower mPFC connectivity with the NAcc

The models testing both the main and interactive effects for HIV + status on the association of unstimulated $CD16^-$ TNF-α on rsFC between the mPFC and NAcc were significant despite the absence of an interactive effect (see Table 3). In the main effect model negative effects were observed for $CD16^-$ TNF-α ($p < .05$) and HIV + serostatus ($p < .05$) on rsFC. Connectivity with both left and right hemispheres of the NAcc systematically varied as a function of HIV serostatus (see Fig. 3). Both the main effect and interaction models were significant for the LPS-stimulated $CD16^-$ cells. Again, significant effects were observed for LPS-stimulated $CD16^-$ TNF-α ($p < .01$) and HIV + serostatus ($p < .05$)

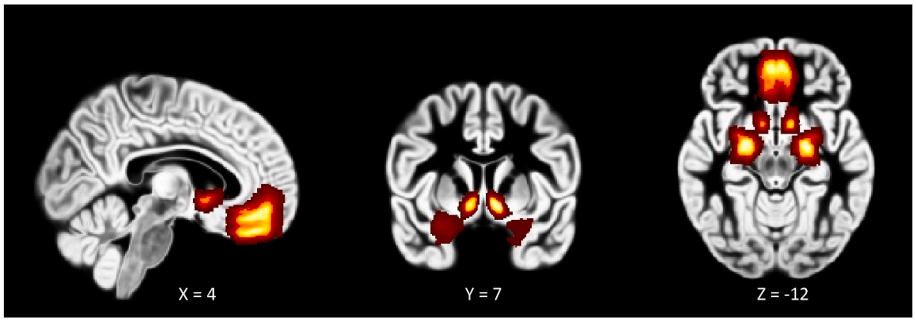

Fig. 1. Seed regions of interest (medial prefrontal cortex, bilateral nucleus accumbens and bilateral amygdala), selected from the Harvard-Oxford Atlas and displayed with probability distribution.

Table 2
Main effect model results for unstimulated and stimulated CD16$^-$ monocyte expression of TNF-alpha on perceived psychological stress.

Factor	β	SE	t	Sig	ULCI	LLCI	F	R-squared
Unstimulated CD16$^-$ model							2.968	0.236
CD16$^-$ % TNF-α	−0.317	0.001	−2.234	0.03	−0.003	−0.000		
HIV + status	−0.304	0.058	−2.39	0.021	−0.255	−0.022		
Age	−0.007	0.004	−0.053	0.958	−0.009	0.009		
Hispanic/Latina	−0.167	0.08	−1.276	0.208	−0.262	0.059		
% live monocytes	−0.019	0.002	−0.142	0.888	−0.004	0.003		
LPS-stimulated CD16$^-$ model							3.59	0.272
CD16$^-$ % TNF-α	−0.366	0.001	−2.759	0.008	−0.005	−0.001		
HIV + status	−0.273	0.057	−2.178	0.034	−0.239	−0.01		
Age	−0.074	0.004	−0.589	0.558	−0.01	0.006		
Hispanic/Latina	−0.167	0.077	−1.311	0.196	−0.257	0.054		
% live monocytes	0.007	0.002	0.051	0.959	−0.003	0.003		

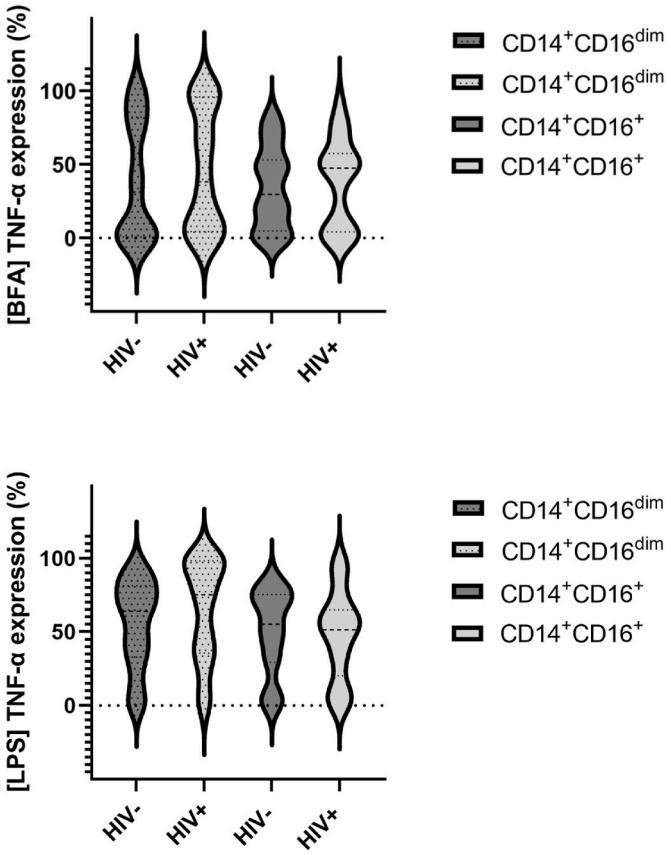

Fig. 2. a (top) Percentage of unstimulated CD16$^+$ and CD16$^-$ peripheral blood mononuclear cells expressing TNF-α plotted separately for HIV-positive and HIV-negative individuals. Fig. 2b. (bottom). Percentage of lipopolysaccharide-stimulated CD16$^+$ and CD16^{dim} peripheral blood mononuclear cells expressing TNF-α plotted separately for HIV-positive and HIV-negative individuals.

on lower mPFC-NAcc functional connectivity. The effects for the proportion of TNF- expression in both unstimulated and stimulated CD16$^-$ cells remained significant after adjusting for multiple testing ($p < .0125$). Moreover, the effect for HIV + status on NAcc connectivity in the LPS-stimulated model was also significant after the Bonferroni adjustment.

3.2.2. TNF-alpha expression on unstimulated CD16$^+$ monocytes is associated with lower mPFC connectivity with the NAcc

The model testing the main, but not the interactive, effect for HIV + status on the association of unstimulated CD16$^+$ TNF-α on rsFC between the mPFC and NAcc was significant (see Table 4). In the main effect model negative effects were present for CD16$^+$ TNF-α ($p < .05$) and HIV + serostatus ($p < .05$) on lower connectivity. For the LPS-stimulated model, the base model was significant with significant main effects only observed for HIV + serostatus ($p < .05$) on lower mPFC-NAcc functional connectivity. None of the effects in these models survived after adjusting for multiple comparisons using an adjusted p-value of $p = .0125$.

3.2.3. TNF-alpha expression on CD16$^-$monocytes is not associated with mPFC connectivity with the amygdala

The model testing the interaction of HIV + status and unstimulated CD16$^-$ TNF-α on mPFC- amygdala rsFC was not significant (see Table 5). There were no significant main or interactive effects present. The models testing the main and interactive effects of HIV + status and stimulated CD16$^-$ TNF-α on mPFC-amygdala rsFC were also not significant, nor were there any significant main or interactive effects present. No other effects were noted amongst the covariates.

3.2.4. TNF-alpha expression on unstimulated CD16$^+$ monocytes is not associated with mPFC connectivity with the amygdala

The model results for the CD16$^+$ cell experiments largely mirrored those findings reported for the CD16$^-$cells under LPS-stimulated and non-stimulated conditions. First, the baseline model and the model testing the interaction between HIV + status and unstimulated CD16$^+$ TNF-α on mPFC- amygdala rsFC were not significant (see Table 6). There were no significant main or interactive effects present. The models testing the main and interactive effects of HIV + status and LPS-stimulated CD16$^-$ expression of TNF-α on mPFC-amygdala rsFC were also not significant, nor were there any significant main or interactive effects present, suggesting these factors do not have a bearing on the connectivity between brain regions involved in affect regulation and those informing salience or threat detection.

3.3. Primary analyses comparing VMPFC rsFC and perceived psychological stress

3.3.1. Greater mPFC connectivity with NAcc is associated with lower psychological stress

The models testing both the main and interactive effect for HIV + status on the relationship between the mPFC-NAcc functional connectivity on PSS was significant (see Table 7). In the main effects model there was a significant effect for mPFC-NAcc connectivity wherein greater connectivity was associated with lower levels of PSS ($p = .003$). Moreover, there was an effect for Hispanic ethnicity on greater PSS ($p < .05$). However, there was no main effect for HIV + status nor was there an interaction with mPFC functional connectivity with the NAcc (see Table 7).

3.3.2. mPFC connectivity with amygdala is not associated with psychological stress

The models testing the main effect for mPFC-amygdala functional connectivity on PSS was not significant (see Table 7). Intriguingly, the

Table 3
Main effect and interaction models for stimulated and unstimulated CD16$^+$ monocyte expression of TNF-alpha on perceived psychological stress.

Factor	β	SE	t	Sig	ULCI	LLCI	F	R-squared
Unstimulated CD16$^+$ model							2.926	0.234
CD16$^+$ % TNF-α	−0.307	0.001	−2.194	0.033	−0.004	−0.000		
HIV + status	−0.292	0.058	−2.28	0.027	−0.25	−0.016		
Age	−0.015	0.004	−0.107	0.915	−0.009	0.008		
Hispanic/Latina	−0.141	0.079	−1.086	0.283	−0.245	0.073		
% live monocytes	−0.038	0.002	−0.28	0.78	−0.004	0.003		
LPS-stimulated CD16$^+$ model							2.562	0.211
CD16$^+$ % TNF-α	−0.242	0.001	−1.81	0.076	−0.004	−0.000		
HIV + status	−0.295	0.059	−2.269	0.028	−0.254	−0.015		
Age	−0.082	0.004	−0.631	0.531	−0.011	0.006		
Hispanic/Latina	−0.142	0.08	−1.076	0.287	−0.248	0.075		
% live monocytes	−0.063	0.002	−0.469	0.641	−0.004	0.003		

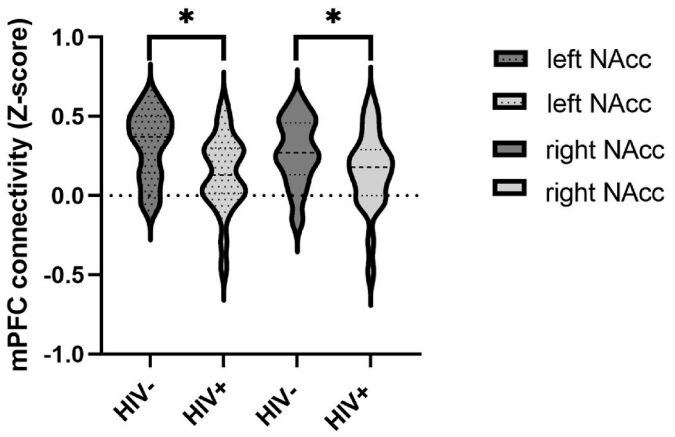

Fig. 3. Comparison of ventromedial prefrontal cortex resting state functional connectivity with left and right nucleus accumbens between HIV-positive and HIV-negative individuals. *$p < .05$.

interaction model was significant wherein there was a main effect noted for Hispanic ethnicity (p = .007). Moreover, there was a trending interaction for HIV + status and mPFC-amygdala connectivity on perceived psychological stress (p = .059) (see Fig. 5). There were no other interactions present (see Table 7) (see Fig. 6).

4. Discussion

Evidence has been amassed both in support (Ackerman et al., 1998; Bower et al., 2007) and contention (Rohleder et al., 2001; Gaab et al., 2005; Miller et al., 2005; Heesen et al., 2005) of a link between perceived psychological stress and peripheral inflammation. Monocyte expansion has since been implicated in stress-related processes for both healthy persons and those living with chronic cardiovascular disease (Gidron et al., 2003; van de Wouw et al., 2021; Baumer et al., 2023). However, there is limited work examining these processes in cohorts exposed to chronic stress and inflammatory immune activation such as in PWH. TNF-alpha expression on these cells is also relevant to chronic inflammation in postmenopausal women, given the distribution of estrogen receptor-dependent pathways involving TNF-α signaling (Gameiro et al., 2010; Bupp, 2015; Härkönen and Väänänen, 2006; Ralston et al., 1990). In the current study, perceived stress was associated with greater TNF-alpha expression on both CD16$^-$ and CD16$^+$ monocytes. TNF-alpha expression on all CD16$^-$ monocytes predicted mPFC connectivity with the NAcc, but only unstimulated CD16$^+$ TNF-α expression was a significant predictor in the multivariate models. We also observed that greater mPFC connectivity with NAcc was associated with reports of lower perceived psychological stress. Upon specification of three separate models for moderated mediation within the study variables it was evident that there was a greater effect for the percentage of CD16$^-$ TNF-α expression on perceived stress in PWOH compared to PWH. In contrast, the alternative model testing the mediating role of TNF-α expression on the inverse relationship between stress and mPFC connectivity revealed a greater in PWH compared to PWOH.

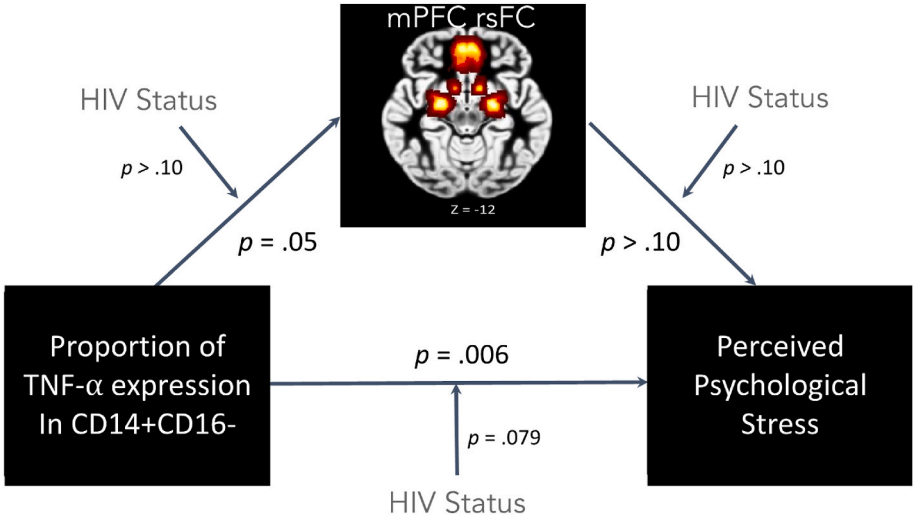

Fig. 4. Moderated mediation results for conceptual model controlling for the direct effects of HIV + status on each endogenous variable path as well as the effects for age, Hispanic/Latina ethnicity, and proportion of live monocytes (not depicted).

Table 4
Main effect models for stimulated and unstimulated CD16$^-$ monocyte expression of TNF-alpha on medial prefrontal cortex functional connectivity with the nucleus accumbens.

Factor	β	SE	t	Sig	ULCI	LLCI	F	R-squared
Unstimulated CD16$^-$ model							4.05	0.336
CD16$^-$ % TNF-α	−0.370	0.001	−2.602	0.012	−0.004	0.000		
HIV + status	−0.321	0.066	−2.249	0.030	−0.281	−0.015		
Age	−0.021	0.005	−0.152	0.880	−0.010	0.009		
Hispanic/Latina	−0.150	0.081	−1.124	0.268	−0.255	0.073		
% live PBMCs	0.090	0.002	0.631	0.532	−0.003	0.006		
LPS-stimulated CD16$^-$ model							4.667	0.368
CD16$^-$ % TNF-α	−0.348	0.001	−2.661	0.011	−0.004	−0.001		
HIV + status	−0.409	0.062	−3.031	0.004	−0.314	−0.063		
Age	−0.053	0.005	−0.411	0.683	−0.011	0.007		
Hispanic/Latina	−0.142	0.077	−1.120	0.269	−0.242	0.069		
% live monocytes	−0.230	0.002	−1.716	0.094	−0.006	0.000		

Table 5
Main effect models for stimulated and unstimulated CD16$^+$ monocyte expression of TNF-alpha on medial prefrontal cortex functional connectivity with the nucleus accumbens.

Factor	β	SE	t	Sig	ULCI	LLCI	F	R-squared
Unstimulated CD16$^+$ model							2.926	0.234
CD16$^+$ % TNF-α	−0.307	0.001	−2.194	0.033	−0.004	−0.000		
HIV + status	−0.292	0.058	−2.28	0.027	−0.25	−0.016		
Age	−0.015	0.004	−0.107	0.915	−0.009	0.008		
Hispanic/Latina	−0.141	0.079	−1.086	0.283	−0.245	0.073		
% live PBMCs	−0.038	0.002	−0.28	0.78	−0.004	0.003		
LPS-stimulated CD16$^+$ model							2.562	0.211
CD16$^+$ % TNF-α	−0.242	0.001	−1.81	0.076	−0.004	−0.000		
HIV + status	−0.295	0.059	−2.269	0.028	−0.254	−0.015		
Age	−0.082	0.004	−0.631	0.531	−0.011	0.006		
Hispanic/Latina	−0.142	0.08	−1.076	0.287	−0.248	0.075		
% live PBMCs	−0.063	0.002	−0.469	0.641	−0.004	0.003		

Table 6
Main effect models for stimulated and unstimulated CD16$^-$ monocyte expression of TNF-alpha on medial prefrontal cortex functional connectivity with the amygdala.

Factor	β	SE	t	Sig	ULCI	LLCI	F	R-square
Unstimulated cell model							1.89	0.165
CD16$^+$ % TNF-α	−0.015	0.001	−0.1	0.921	−0.002	0.002		
HIV + status	−0.028	0.066	−0.213	0.832	−0.146	0.118		
Age	−0.362	0.005	−2.534	0.015	−0.022	−0.003		
Hispanic/Latina	−0.145	0.09	−1.058	0.295	−0.277	0.086		
% live monocytes	−0.037	0.002	−0.258	0.798	−0.004	0.003		
LPS-stimulated model							1.894	0.165
CD16$^+$ % TNF-α	0.022	0.001	0.156	0.877	−0.002	0.002		
HIV + status	−0.033	0.066	−0.246	0.806	−0.149	0.117		
Age	−0.37	0.005	−2.769	0.008	−0.022	−0.004		
Hispanic/Latina	−0.14	0.09	−1.026	0.31	−0.273	0.088		
% live monocytes	−0.048	0.002	−0.337	0.737	−0.005	0.003		

Table 7
Main effect models for medial prefrontal cortex functional connectivity with the nucleus accumbens and amygdala on perceived psychological stress.

Factor	β	SE	t	Sig	ULCI	LLCI	F	R-square
Nucleus Accumbens model							4.614	0.274
mPFC – Nacc connectivity	−0.396	1.526	−3.005	0.004	−7.654	−1.519		
HIV + status	−0.217	0.682	−1.682	0.099	−2.519	0.224		
Age	−0.112	0.045	−0.911	0.367	−0.133	0.05		
Hispanic/Latina	0.302	0.869	2.444	0.018	0.377	3.871		
Amygdala model							2.061	0.144
mPFC – Amygdala connectivity	−0.071	1.546	−0.493	0.624	−3.868	2.345		
HIV + status	−0.091	0.699	−0.685	0.497	−1.884	0.926		
Age	−0.092	0.053	−0.647	0.52	−0.14	0.072		
Hispanic/Latina	0.349	0.945	2.599	0.012	0.557	4.354		

The most consistent finding was a positive association between stimulated and unstimulated CD16$^-$ and CD16$^+$ monocyte expression of TNF-α and perceived stress. TNF-α expression is reliably observed across LPS-stimulated and LPS-unstimulated conditions (Solomon et al., 1998). Based on the involvement of monocyte TNF-α expression in HIV-1 disease pathogenesis, the magnitude of these effects was expected to be

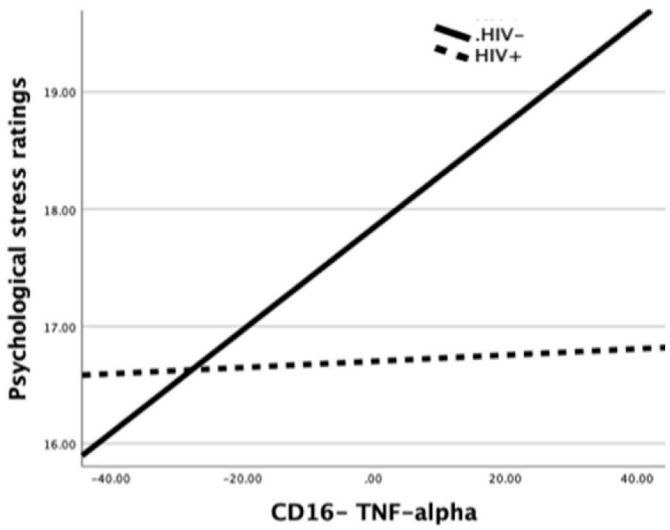

Fig. 5. HIV-negative status moderates the effect of CD16⁻ TNF-alpha on perceived stress.

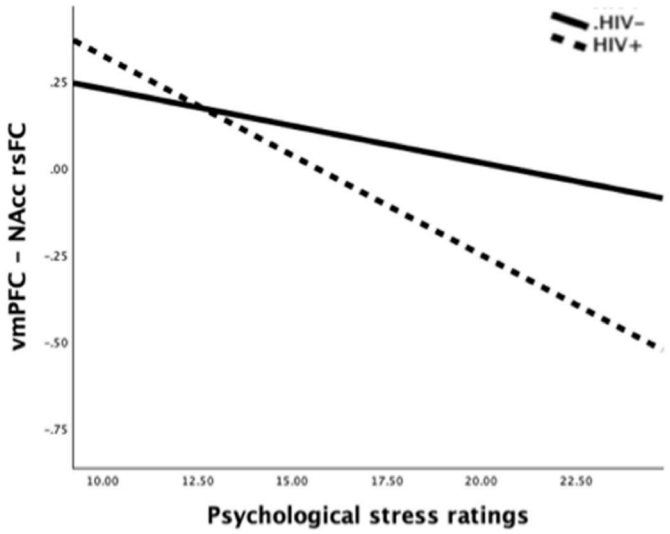

Fig. 6. HIV-positive status moderates the effect of ve on perceived stress.

greater in PWH, particularly in LPS-stimulated conditions (Kumar et al., 2016; Calin and Manduteanu, 2017; Lameijer et al., 2013; Kedzierska and Crowe, 2002; Wenzel, 2019; Rizzoni et al., 2022; Caillon et al., 2019; Pasquereau et al., 2017; Herbein and Khan, 2008). It is unclear why the effects were greater in PWOH, however, the findings are indirectly supported across several study designs. For example, randomized clinical trial data examining a single infusion of the TNF-α antagonist Infliximab resulted in a serendipitous reduction in perceived stress (Woelfer et al., 2020). Behavioral intervention data from a primarily African American sample of women further showed that increases in psychological resilience to racial and discriminatory stress predicted 4- and 8-month reductions in TNF-α and CRP (Saban et al., 2021). The translational significance of TNF-α antagonism for the alleviation of psychological symptom severity in chronic illness patients, e.g., Bavaresco et al. (2020); Ertenli et al. (2012), begs the question of why this stress-immune axis was not exacerbated for PWH. It is also unclear why effects were most consistently observed in LPS-unstimulated samples given that biomarkers of microbial translocation are not only a feature of chronic HIV disease, but coincide with neuropsychiatric complaints in PWH (Saylor et al., 2019; Marchetti et al., 2011; Nowroozalizadeh et al., 2010; Nasi et al., 2020). Future work will not only need to elucidate cellular phenotypes of monocyte activation that may be most germane to threat perception, but to also disentangle the time course for acute bouts of monocyte inflammation on psychosocial processes supported by interactions between the ventral striatum and mPFC.

Stimulated and unstimulated CD16 expression of TNF-α were both associated with lower mPFC connectivity to NAcc, but not the amygdala. TNF-α plays a prominent role inducing microglial recruitment of monocytes throughout the brain parenchyma (D'Mello et al., 2009; Ferro et al., 2021). Trafficking of peripheral leukocytes due to breakdown of tight junctions triggers a pro-inflammatory response within surrounding areas of the ventral striatum, a feature noted in multiple neuropsychiatric disorders (Menard et al., 2017; Greene et al., 2020). Although the current study touts monocyte expression of TNF-α as the primary source of inflammation, seminal work has shown acute changes in peripheral IL-6 correspond with decreased mPFC connectivity to sACC, NAcc, and amygdala in conjunction with mood disturbance (Harrison et al., 2009). Similarly, Felger and colleagues showed elevated CRP in major depression predicts lower rsFC between mPFC and ventral striatum, which in turn corresponds with greater reports of anhedonia (Felger et al., 2016). Overall, these findings of an inverse effect of monocyte TNF-α expression on mPFC connectivity with the NAcc may reflect susceptibility of this mesolimbic circuitry to cytokine-induced microglia activation and oxidation of cofactors vital to dopamine synthesis (Boyle et al., 2023; Block et al., 2007; Haruki et al., 2016). We found significant effects were absent for the amygdala, despite others showing elevation in anxiety symptoms as a function of lower mPFC connectivity with this region (Mehta et al., 2018). Inhibitory control and regulation of the amygdala by the mPFC is an important component of stress regulation, that entails multiple neurotransmitter systems dependent upon dopaminergic, glutamatergic and GABA-ergic transmission (Marowsky et al., 2005; Stevenson et al., 2003; Kienast et al., 2008; Akirav and Maroun, 2007). Therefore, the absence of amygdala effects of mPFC in lieu of nucleus accumbens connectivity, may suggest increased propensity for monocytic effects on dopaminergic neurotransmission (McIntosh et al., 2015).

An effect of HIV + serostatus on lower connectivity of mPFC to NAcc, but not the amygdala, was also observed across multivariate analyses. Meta-analysis of task-based fMRI studies clearly indicates frontal-striatal function is adversely impacted by chronic HIV-infection (Du Plessis et al., 2014). Extant research also implicates acute and chronic HIV-infection on aberrant functional connectivity across frontostriatal circuitry, but has been unable to attribute one single biomarker to this disease-related susceptibility (McIntosh et al., 2018; Thomas et al., 2013; Wang et al., 2011). Nonetheless, evidence of altered frontostriatal connectivity in PWH is pervasive. For example, intrinsic connectivity of the dorsolateral prefrontal cortex with the basal ganglia was reduced in PWH compared to PWOH (Al-Khalil et al., 2023). In line with the role of mPFC as a major control hub in the default mode network (DMN), HIV-related decrements in rsFC between the mPFC and striatum have been linked to greater depressive symptom severity (Ortega et al., 2015). Negative effects of HIV-1 on functional brain connectivity are consistent across different sequences of the virus. For example, HIV-related deficits in hubs supporting the mPFC and NAcc, i.e., DMN and basal ganglia network, were associated with global cognitive impairment in PWH from Australia (du Plessis et al., 2017). It is important to note that the current sample consisted of women living with HIV for several decades with nearly 50% having received a prior AIDS diagnosis. Thus, interpretation of the current study findings are limited to postmenopausal PWH on stable combination ART, despite extant research of individuals on long term combination ART reveal no differences in the density of within-striatum connectivity between virally-suppressed PWH and age-matched PWOH (Janssen et al., 2017). Furthermore, the temporal resolution of these findings will need to be examined in future work through the incorporation of culturally sensitive task-based fMRI paradigms designed to elucidate the interaction of peripheral inflammation

with BOLD responses to psychosocial stressors in real time.

The final leg of the model revealed a greater magnitude of mPFC connectivity with NAcc was predicted to lower chronic stress. The nucleus accumbens shares dense connections with several limbic and non-limbic regions throughout the brain, however, it shares the most functional connections with the mPFC. Meta-analytic evidence from task-based fMRI studies converges upon deactivation of the ventral striatum during experimental induction of psychosocial stress (Kogler et al., 2015). Deactivation of both mPFC and NAcc during gain or reward, but not loss processing, is also associated with trauma symptom severity (Sailer et al., 2008). Our findings are also supported by baseline data from a longitudinal cohort wherein persons reporting higher stressful life events showed lower rsFC between the left NAcc and ipsilateral orbitofrontal cortex (Ko et al., 2023). Those authors reported a reciprocal mediating effect of depressive symptom severity and stressful life events on the loss of connectivity between the NAcc and orbitofrontal cortex. Also evident was moderated effect wherein the inverse association between mPFC – NAcc connectivity and stress was greater for PWH, a finding that coincides with the HIV-related deficits in functional connectivity. This, again, was anticipated given the noted susceptibility to fronto-striatal dysfunction and HIV-related deficits in functional connectivity observed in the multivariate models (Rubin et al., 2015, 2017).

Photoplethysmography collected during the resting state scan was employed to characterize resting HRV in order to explore whether monocyte inflammation varies as a function of resting vagal tone (see supplemental methods). We observed lower TNF-α expression of stimulated $CD16^{+}$ monocytes in persons at the highest versus lowest quartile of SDNN. These general findings are also supported in the literature, with stronger and more consistent associations between SDNN, compared to RMSSD, and various serum and cellular markers of inflammation compared to RMSSD (Williams et al., 2019). The effect for SDNN on stimulated samples bodes well for the therapeutic utility of vagus nerve stimulation chronic inflammatory-immune conditions involving endotoxin-induced monocyte expansion (Bonaz et al., 2017; Bonaz, 2022; Williams et al., 2019).

4.1. Limitations and future directions

The principal limitation for exploration into alternative models of moderated mediation, which precludes any assumption of temporal precedence amongst the depicted pathways, is the study's cross-sectional design. For example, seminal work supporting LPS-stimulated monocyte TNF-α expression in response to acute stress exposure coincides with results from the alternative model that specified $CD16^{-}$ as the mediator of perceived stress (Landmann et al., 1984). Similarly, early life stress is shown to predict lower resting state connectivity between the mPFC and NAcc in adulthood (Cisler et al., 2013; Kaiser et al., 2018; Hanson et al., 2018). Furthermore, despite the utilization of a gating strategy that excluded those $CD16^{+}$ cells with forward and side scatter characteristics indicative of lymphocytes, natural killer cells, or granulocytes, the omission of key monocyte surface expression markers calls into question the purity of the mononuclear sample (Marimuthu et al., 2018). Although the participants were racially and ethnically diverse, the findings reflect biobehavioral processes within a U.S.-based cohort, limiting the generalizability of our findings to postmenopausal women outside the U.S. Additionally, data on important social determinants of health, such as lifetime trauma, early life stress, housing instability, and other syndemic factors associated with increased stress and susceptibility for neuropsychiatric disease, was not collected (Dale et al., 2023; Glynn et al., 2019; Petersen et al., 2023). Finally, although the groups were closely matched in terms of cardiovascular disease history future work will need to investigate the mechanistic role of certain risk factors on adrenergic-receptor mediated inflammatory control in stimulated and unstimulated mononuclear cells (Hong et al., 2015; Kohn et al., 2019).

4.2. Conclusion

In conclusion, HIV + serostatus differentially moderates the effect of monocyte TNF-α expression and mPFC-NAcc connectivity on perceived stress levels among a racially and ethnically diverse sample of post-menopausal women. While these findings are novel within the context of resting state fMRI, future biobehavioral models may be expanded to contextualize biobehavioral correlates of changes in white and gray matter microstructure (Burdo et al., 2023; Booiman et al., 2017; Chang et al., 2020; Kamkwalala et al., 2020; Jespersen et al., 2016). More work is needed to examine the time course of acute inflammation on neural networks underpinning active cognitive emotion regulation in persons living with chronic HIV disease.

CRediT authorship contribution statement

Roger McIntosh: Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Judith Lobo:** Methodology, Formal analysis, Data curation. **Angela Szeto:** Supervision, Methodology, Investigation, Formal analysis. **Melissa Hidalgo:** Methodology, Investigation. **Michael Kolber:** Supervision, Resources, Project administration.

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 article.

The authors declare there are no financial or non-financial interests which may be considered as potential conflicts of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100844.

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