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Apathy is Not Associated with a Panel of Biomarkers in Older Adults with HIV Disease

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Abstract

Objective: Apathy is prevalent in HIV disease and can significantly impact personal well-being; however, little is known about its neurobiological substrates in persons with HIV (PWH) disease.

Methods: This cross-sectional, correlational study examined the association between apathy and several plasma biomarkers (tumor necrosis factor alpha, kynurenine, tryptophan, quinolinic acid, brain-derived neurotrophic factor, glial fibrillary acidic protein, neurofilament light chain, and phosphorylated tau at position threonine 181) in 109 PWH and 30 seronegative participants ages 50 and older. Apathy was measured with a composite score derived from subscales of the Frontal Systems Behavior Scale and the Profile of Mood States.

Results: Multiple regressions showed that PWH had significantly greater severity of apathy symptoms, independent of both data-driven and conceptually-based covariates. Pairwise correlations in the PWH sample indicated that apathy was not significantly associated with any of the measured biomarkers and all of the effect sizes were small.

Conclusion: Findings suggest that apathy is not strongly associated with peripheral biomarkers of inflammation, neurotrophic support, or neurodegeneration in older PWH. Limitations of this study include the cross-sectional design, the use of self-report measures of apathy, and low rates of viremia. Longitudinal studies in more representative samples of PWH that include a more

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Declarations of Interest

The authors have no competing interests to report.

comprehensive panel of fluid biomarkers, informant and behavioral indicators of apathy, and relevant psychosocial factors might help to further clarify the neurobiological substrates of this complex neuropsychiatric phenomenon.

Keywords

AIDS; biological factors; emotions; infectious disease; motivation; neuropsychiatry

1. Introduction

Apathy is a neuropsychiatric syndrome characterized by reduced motivation for self-initiated goal-directed behavior and cognitive activity, and blunted affect[1]. Neurological diseases can lead to apathy directly via shared neurobiological underpinnings (i.e., fronto-striatal pathways)[2] or indirectly via vulnerability to individual (e.g., psychosocial, genetic) and environmental (e.g., under-stimulation) factors[3]. HIV is associated with both direct neurobiological (i.e., fronto-striatal pathology[4]) and indirect (e.g., psychosocial and environmental) risk factors for apathy. Approximately 46% (range 12%−65%) of people with HIV (PWH) exhibit clinical apathy[5]. Apathy can emerge early in HIV infection, independent of other neuropsychiatric syndromes[6]. Among PWH, apathy is associated with lower quality of life[7], cognitive symptoms, functional dependence[8], and medication mis-management[9].

The relationship between apathy and HIV-associated white matter abnormalities in frontal systems is well-established[10], but we know little about the neuropathogenesis of apathy in PWH. There is spotty evidence that higher viral load is associated with apathy[11]. However, a majority of studies failed to demonstrate a consistent association between immune markers (e.g., current and nadir CD4 count) and apathy in HIV[12]. Therefore, the present study evaluated the association between apathy and plasma biomarkers reflecting the neuropathogenesis of HIV, including inflammation (tumor necrosis factor alpha, TNF-α), the kynurenine pathway (kynurenine [KYN], tryptophan [TRYP], quinolinic acid [QA]), neurotrophic support (brain-derived neurotrophic factor [BDNF]), astrocytosis (glial fibrillary acidic protein [GFAP]), and neurodegeneration (neurofilament light chain [NFL] and phosphorylated tau [pTau181]). We hypothesized that apathy would be associated with increased inflammation and, therefore, subsequent activation of the kynurenine pathway, decrease in neurotrophic support, and neuronal degeneration.

2. Methods and Materials

2.1 Participants

Participants were 30 seronegative and 109 PWH who had stored blood samples from an IRB-approved parent study on prospective memory in persons ages 50 and older[13]. All participants provided informed consent and HIV serostatus was confirmed with Medmira rapid tests. Study exclusions were history of severe psychiatric disorders (e.g., psychosis), neurological conditions (e.g., seizure disorders, dementia, major head injury), estimated verbal IQ <70, and active substance dependence. Seronegative participants with histories of major depression were excluded.

2.2 Procedure

2.2.1 Apathy—Apathy was measured with subscales of the Frontal Systems Behavior Scale (FrSBe[14]) and the Profile of Mood States (POMS[15]). The apathy subscale of the FrSBe asks participants to rate 14 statements (e.g., "*Have lost interest in things that used to be fun or important to me"*) from one ("almost never") to five ("almost always"). Items were summed (α=.85) and converted to z-scores using the published manual, which adjusts for age and sex. The POMS Vigor-Activation subscale asks participants to rate the personal applicability of eight words (e.g., *lively*) ranging from zero ("not at all") to four ("extremely"). Items were summed (α=.91) and converted to age- and sex-adjusted z-scores[16]. The moderate intraclass correlation between these scales (−.57 [−.68, −.45]) supported their use as a composite, which was calculated as the average normative z-score. Since apathy is a complex phenomenon with no gold standard measure, a composite score provides fuller coverage of the construct and helps to reduce the risk of Type I error. Primary study findings did not differ if raw scores were used, if the two apathy subscales were analyzed separately, or if a categorical clinical elevations in apathy (i.e., >1.5 SD elevations) was used in place of the continuous normed composite score.

2.2.2 Clinical Characterization—Lifetime major depressive disorder and substance use disorder diagnoses were determined with the Composite International Diagnostic Interview[17]. Neurocognitive impairment was measured with a normed computerized battery[13]. A medical evaluation was conducted by a research nurse and included a blood draw, from which current CD4 cell counts and viral loads were derived.

2.2.3 Biomarker Assessment—Plasma levels of BDNF (DuoSet, R&D Systems, Minneapolis, MN), KYN, TRYP, QA (ImmuSmol Bordeaux, France), NFL, and pTau181 (MyBioSource, San Diego, CA), and GFAP (Millipore, Temecula, CA) were measured by enzyme-linked immunosorbent assay according to manufacturer procedures. All samples were assayed in duplicate, and the technician was blind to group and apathy scores. The inter- and intra-assay coefficients of variation were below 5%. Plasma levels of TNF-α were measured using a Bio-Plex Pro™ assay per the manufacturer's instructions. Data were acquired with the Bio-Plex 200 System (Bio-Rad CA) and analyzed using Bio-Plex Manager 6.1 software. The results are shown as log10 pg/mL.

2.2.3 Data Analysis—The critical alpha was set to .05 and all analyses were conducted in JMP 16.0. Serostatus group differences on the variables in Table 1 were evaluated using t-tests with Cohen's *d* or with chi-square tests. All descriptive variables that differed by serostatus were included as covariates in a multiple regression model with HIV status as the predictor and the composite apathy z-score as the criterion. We also conducted a parallel multiple regression that included only conceptually-driven covariates (i.e., age, substance use, neurocognitive impairment, and anxiety). The primary hypotheses about the associations between apathy and biomarkers were tested with Spearman's rho in the HIV sample (n=109), which had adequate power (1-B=.89) to detect medium effect sizes using a two-tailed correlation.

3. Results

Table 1 shows that the PWH were significantly younger and had higher frequencies of medical comorbidities, White/Non-Hispanics, men, and substance disorders (*p*s<.05). A multiple regression that included HIV alongside those five data-driven covariates predicting apathy was significant (adj R^2=0.11, *p*=.003), with HIV (*B*=−0.96, *p*=.001) and substance disorders (*B*=−0.58, *p*=.023) being the only significant contributors (all other *p*s>.05). These medium effects were in the expected directions, with higher apathy scores in those with HIV (Cohen's *d*=0.75) or substance disorders (Cohen's *d*=0.58). A parallel multiple regression with HIV as the predictor, apathy as the criterion, and conceptually-driven covariates (i.e., age, substance disorders, global neurocognitive impairment, and generalized anxiety) was also significant (adj R^2=0.11, *p*=.001) and HIV was the only significant contributor (*B*=−0.85, *p*=.003).

Table 2 shows that there were no significant correlations (*p*s>.05) between apathy and biomarkers in the PWH sample and the associated effects were small (*M rho* =.02, range =−.09 to .10).

4. Discussion

In contrast to our hypothesis, apathy was not associated with any peripheral biomarker of inflammation, kynurenine pathway, astrocytosis, neurotrophic support, or neurodegeneration in people with HIV. These null findings were surprising, particularly since the study was powered to detect medium effect sizes and the observed severity and rates of apathy in this HIV sample were higher than in seronegative participants and were consistent with prior prevalence estimates[5,18]. The pathophysiological basis of apathy in HIV is still poorly understood, with the exception of evidence for the role of white matter abnormalities (especially in frontal systems[10]) and viremia[11]. However, <10% of our sample had detectable circulating viral RNA, which might partly explain the absence of differences in biomarker levels between PWH and seronegatives[19]. It is also worth noting that the seronegative group was more of a comparison sample than a healthy control group, as it included persons with risk factors for CNS injury (e.g., substance use disorders) and did not differ from PWH in overall neurocognitive functioning. This might also explain some of the null between-group findings for the panel of biomarkers, with the exception of pTau, which previous studies show is elevated in cerebrospinal fluid in PWH[20]. Future studies might focus on relevant psychosocial (e.g., social support, engagement) and environmental (e.g., under-stimulation, reward structures) factors in aviremic PWH[9].

The results of this study suggested that apathy was not associated with biomarkers of neurodegeneration (NFL and pTau181) or the neurotrophic factor BDNF in PWH. Plasma NFL has been negatively associated with neurocognition in PWH, declining with initiation of antiretroviral treatment[21]. However, the relationship between apathy and neurocognition in PWH is complex and inconsistent[22]. Conversely, in neurodegenerative diseases, apathy has been associated with biomarkers of neurodegeneration and BDNF[23]. Also contrary to our hypothesis, there was no association between our biomarkers of inflammation and apathy [24]. Moreover, apathy *per se* has been associated with peripheral

biomarkers of inflammation, such as C-reactive protein and soluble-TNF-α receptors, in older adults[25]. The kynurenine pathway is initiated by the degradation of TRYP by indoleamine 2,3-dioxygenase and can be upregulated by pro-inflammatory stimuli[26]. The kynurenine pathway then branches into one pathway leading to the production of kynurenic acid through the action of kynurenine aminotransferases and another that produces toxic metabolites, including QA, through kynurenine-3-monooxygenase. The activation of the kynurenine pathway has also been directly associated with inflammation-induced behavioral symptoms, including anhedonia[27].

There are several limitations to the current study, most notably the cross-sectional and correlational design. While biomarkers indicative of multiple biological processes or mechanisms were assessed, only a few molecules per process were measured. In addition, there is the long-standing debate on the value of peripheral biomarkers in relation to CNS pathophysiology. The measurement of apathy was limited by the exclusive use of self-report measures, which are vulnerable to insight bias. Future studies might incorporate clinician-based, informant-report, and behavioral measures of apathy in relation to biomarkers in HIV. Moreover, the inclusion of measures that tap into specific dimensions of apathy (e.g., cognitive, behavioral, and emotional) may provide some unique insights. Finally, the HIV sample was mostly White men from urban Southern California, which limits our ability to draw inferences about the associations between biomarkers and apathy in women and people from rural communities and under-represented ethnoracial groups in whom these relationships may differ meaningfully[28].

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Highlights

- A cross-sectional study was conducted to examine the neuropathological substrates of apathy in HIV disease.
- People with HIV had higher levels of apathy than seronegatives.
- Surprisingly, no peripheral biomarkers correlated with apathy in HIV and the effect sizes were small.

Table 1.

Sociodemographic and clinical characteristics of HIV+ and HIV- individuals.

Variable	HIV+ (*n* = 109)		HIV− (*n* = 30)		*p*	*Cohen's d*
	Mean/%	SD	Mean/%	SD		
Demographics						
Age	56.4	(5.5)	59.8	(7.9)	**.007**	−0.56
Education (years)	14.2	(2.7)	14.8	(2.6)	.276	−0.22
Sex (% women)	10.1	—	30.0	—	**.006**	—
Race/Ethnicity (%)					.097	—
Asian	0.0	—	3.4	—		
Black/African American	15.6	—	23.3	—		
Hispanic/Latino	18.3	—	16.7	—		
White/Caucasian	63.3	—	53.3	—		
Other	2.8	—	3.3	—		
Neuropsychiatric Factors						
Apathy Composite (*z*-score)	0.8	(1.4)	−0.2	(1.0)	**<.001**	0.75
POMS Vigor-Activity raw score	16.4	(7.5)	21.6	(6.3)	**<.001**	−0.72
FrSBe Apathy raw score	31.7	(9.1)	23.9	(7.0)	**<.001**	0.90
Clinical elevation (%)[a]	44.0	—	13.3	—	**.002**	—
Generalized Anxiety Disorder (%)						
Current	6.5	—	0.0	—	.150	—
Lifetime	17.4	—	3.3	—	.051	—
Substance Abuse Disorder (% lifetime)	73.4	—	53.3	—	**.035**	—
Global neurocognitive impairment (%)	28.9	—	28.6	—	**.977**	—
Biomarkers						
Neurofilament Light (log10)	3.2	(0.2)	3.2	(0.2)	.712	0.00
pTau181 (log10)	2.4	(0.1)	2.5	(0.1)	**.043**	**−1.00**
GFAP (log10)	3.1	(0.5)	3.0	(0.5)	.388	0.20
Kynurenine/Tryptophan Ratio (log10)	0.5	(0.1)	0.5	(0.1)	.142	0.00
Quinolinic Acid (log10)	1.8	(0.2)	1.8	(0.2)	.849	0.00
BDNF (log10)	3.7	(0.3)	3.7	(0.2)	.582	0.00
TNF-α (log10)	1.7	(0.2)	1.7	(0.2)	.888	0.00
Medical Characteristics						
Number of Medical Comorbidities	2.0	(1.5)	1.4	(1.3)	**.043**	**0.41**
AIDS (%)	65.1		—	—	—	—
Duration of infection (years)	21.3	(8.7)	—	—	—	—
Current CD4 (cells/μL)	666.0	(311.6)	—	—	—	—
Nadir CD4 (cells/μL)	203.7	(195.0)	—	—	—	—
Plasma RNA Detectable (% detectable)	6.5	—	—	—	—	—
Antiretroviral therapy (% prescribed)	86.2	—	—	—	—	—
Hepatitis C Virus (%)	23.0	—	—	—	—	—

Note. Values are sample mean (standard deviation) unless otherwise specified.

[a]Clinical elevations in apathy were operationalizes as >1.5 SD above the normative mean. POMS = Profile of Mood States; FrSBe = Frontal Systems Behavior Scale; BDNF = Brain-Derived Neurotrophic Factor; TNF-α = Tumor Necrosis Factor alpha; pTau181 = phosphorylated Tau 181; GFAP = Glial Fibrillary Acidic Protein; AIDS = Acquired Immunodeficiency Syndrome; CD4 = Cluster of Differentiation 4; RNA = Ribonucleic Acid. **Bold** indicates $p < .05$.

Table 2.

Pairwise correlations among apathy and biomarkers in HIV+ participants.

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Apathy Composite	—										
2. Nadir CD4 (cells/μL)	.05	—									
3. Current CD4 (cells/μL)	.06	.45**	—								
4. Plasma RNA (% detectable)	.07	.10	.41*	—							
5. NFL (log10)	−.09	−.02	.13	.08	—						
6. pTau181 (log10)	.09	−.10	−.13	.12	−.06	—					
7. Kyn/Tryp Ratio (log10)	.01	.02	−.03	.49*	.26**	.12	—				
8. Quinolinic Acid (log10)	−.07	−.01	−.07	.14	.12	.03	.21*	—			
9. BDNF (log10)	−.06	.27**	.21*	.02	.10	.04	.10	−.11	—		
10. TNF-α (log10)	.06	.02	−.01	.36	.19*	.11	.24*	.41**	−.15	—	
11. GFAP (log10)	.10	.15	.02	−.02	.04	.05	.10	.00	−.05	.02	—

Note. Apathy Composite is a sample-based z-score. CD4 = Cluster of Differentiation 4; RNA = Ribonucleic Acid; NFL = Neurofilament Light; pTau181 = phosphorylated Tau 181; Kyn/Tryp = Kynurenine/Tryptophan; BDNF = Brain-Derived Neurotrophic Factor; TNF-α = Tumor Necrosis Factor alpha. GFAP = Glial Fibrillary Acidic Protein.

* $p < .05$

** $p < .01$