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SHORT COMMUNICATION

Chronically elevated depressive symptoms interact with acute increases in inflammation to predict worse neurocognition among people with HIV

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Abstract
We examined the joint effects of depressive symptoms (Beck Depression Inventory-II (BDI-II)) and systemic inflammation (plasma C-reactive protein (CRP)) on longitudinal profiles of neurocognition in a cohort of 143 people with HIV (PWH) on antiretroviral therapy. Global neurocognition, processing speed, motor skills, and attention/working memory all worsened as CRP increased but only among PWH who, on average, exhibited moderate to severe depressive symptoms (BDI-II > 22). Findings suggest that some PWH with chronically elevated depressive symptoms may have an inflammatory subtype of depression and a particular vulnerability to neurocognitive changes that may respond to drugs targeting inflammation or its neural sequelae.

Keywords Depression · Inflammation · Cognition · HIV-associated neurocognitive disorder · C-reactive protein · Processing speed

Introduction

HIV disease can be effectively managed with antiretroviral therapy (ART), yet people with HIV (PWH) are disproportionately impacted by neuropsychiatric comorbidities that compromise HIV care (Bing et al. 2001; Gaynes et al. 2008; Pence et al. 2018). Among these comorbidities, depressed mood and depressive disorders are highly prevalent and predictive of adverse medical outcomes, including functional disability, poorer ART adherence, accelerated HIV disease progression, and mortality (Leserman 2008; Pence et al. 2018; Rabkin 2008; Rubin and Maki 2019). The debilitating effects of depression may be partly related to its influence on neurocognitive functioning. Neurocognitive deficits of psychomotor slowing and poor attention are included in the DSM-5 criteria for major depressive disorder (MDD). Other diagnostic criteria such as sleep disturbance and fatigue are established risk factors for neurocognitive dysfunction (American Psychiatric Association 2013; Perini et al. 2019).

Consistent with the link between depression and functional decline in PWH, a recent longitudinal investigation from our group identified both acute and chronic effects of depressive symptoms on neurocognitive function among PWH (Paolillo et al.2020a). Specifically, PWH who experienced greater chronicity of depressive symptoms exhibited steeper declines in neurocognition than those with a less severe burden of depressive symptoms over time. In addition to cumulative effects of depressive symptoms, within-person analyses demonstrated that neurocognition also varied concurrently with depressive symptoms, such that speed of information processing and motor skills were slower on visits when participants were experiencing more

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severe depressive symptoms. The deleterious effects of high cumulative burden of depressive symptoms and transient depressive symptoms on neurocognition among PWH underscore the need to identify potential mechanism(s) that bridge these facets of neurobehavior.

One potential link between depression and neurocognition in PWH is inflammation (Ellis et al. 2020), a cardinal feature of HIV disease (Bandera et al. 2019; Beurel et al. 2020; Deeks et al. 2013). Similar to the chronicity of depressive symptoms, PWH often exhibit chronically elevated levels of systemic inflammation. In persons without HIV, strong evidence is emerging for a subgroup of depressed patients who present with high levels of generalized peripheral inflammation, commonly indexed by blood levels of c-reactive protein (CRP;Haroon et al. 2018; Miller et al. 2017). In these depressed patients elevated CRP is associated with aberrant functional connectivity in corticostriatal pathways, which is in turn linked to core depressive phenotypes characterized by anhedonia, apathy, and psychomotor slowing (Felger 2017; Felger et al. 2016). These corticostriatal structures, including the striatum and prefrontal cortex, are also prominent neuroanatomical substrates for HIV-associated neurocognitive disorders (HAND). Furthermore, patients with HAND consistently exhibit elevated levels of inflammation compared with those without HAND (Bandera et al. 2019; Ipser et al. 2015; Woods et al. 2009). Given that systemic inflammation may act as a fulcrum upon which depression exerts both acute and chronic effects on neurocognition, the present communication expands on our prior longitudinal analysis by examining the joint influence of chronic systemic inflammation and depressive symptoms on neurocognition in a cohort of PWH on ART. Our primary aim was to examine the influence of generalized peripheral inflammation (i.e., plasma CRP) on neurocognition within individuals, and whether the strength of this relationship depended on the person's average intensity of depressive symptoms on the Beck Depression Inventory-II (BDI-II). We hypothesized that within individuals, neurocognition would be worse on visits with high CRP levels and that this relationship would be strongest among those with higher average BDI-II scores across the study period.

Methods

Participants

Participants were 143 PWH who underwent 3–6 study visits (12–59 months of follow-up; mean, 33 months) in NIH-funded longitudinal studies at the UCSD HIV Neurobehavioral Research Program. Participants provided written, informed consent to undergo study procedures, which were approved by the UCSD Institutional Review Board. Participants were included in the present analysis if they completed at least three study visits (at least 6 months apart) with neuromedical, neurobehavioral, and CRP data, all collected on the same day. Consistent with Frascati research criteria for HAND (Antinori et al. 2007), participants were excluded if they had a baseline diagnosis of a psychotic or mood disorder with psychotic features, neurological or medical condition that may confound the interpretation of neuropsychological test results. Participants not taking ART at baseline also were excluded from analysis as this could confound interpretations of inflammation.

Procedures

HIV disease and treatment characteristics (i.e., nadir and current CD4 count, plasma HIV RNA, AIDS status, estimated duration of HIV disease, and ART use) and medical comorbidities (i.e., hypertension, hyperlipidemia, diabetes, and hepatitis C co-infection) were ascertained via comprehensive neuromedical evaluations consisting of a structured clinician-administered interview and standard laboratory assays. Levels of HIV RNA in plasma were measured via reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostics, Indianapolis, IN) and were considered undetectable below the lower limit of quantitation of 50 copies/ml. CRP was measured in blood plasma using a commercially available electrochemical luminescence immunoassay (MesoScale Discovery, USA) and run according to the manufacturers protocol. Biomarker precision was ensured by (a) assaying all specimens in duplicate, (b) repeating assays of specimens with coefficients of variation greater than 20%, (c) repeating 10% of all assays to assess operator and batch consistency, and (d) regularly assessing batch effects. CRP values were $\log_{10}$-transformed to improve normality for use in statistical analyses.

Participants also underwent a comprehensive neurobehavioral evaluation including a standardized 7-domain battery of neuropsychological tests and self-report inventories of psychological functioning at each visit (Carey et al. 2004). Raw neuropsychological test scores were converted to practice-effect corrected scaled scores (M = 10; SD = 3) and averaged across the entire battery and within cognitive domains to generate global and domain-specific scaled scores, which were used as outcome variables (Cysique et al. 2011). The BDI-II was administered to assess depressive symptoms (Beck et al. 1996). Participants also were evaluated for DSM-IV lifetime and current (last 30 days) diagnoses of substance use disorders and Major Depressive Disorder (MDD) using the Composite International Diagnostic Interview (World Health Organization 1998).

Statistical analyses

Multilevel modeling was used to examine the within- and between-person effects of inflammation and depressive symptoms on global neurocognitive functioning over time. To determine the neurocognitive domains driving significant associations with global neurocognitive function, additional exploratory multilevel models for each domain-specific neurocognitive outcome were conducted. The within-person level of each multilevel model examined the acute effect of fluctuations in $\log_{10}$ plasma CRP (person-centered) and BDI-II score (person-centered) on neurocognition, covarying for time (i.e., years since baseline). CRP and BDI-II were both person-mean centered for use at the within-person level of this analysis, meaning that values of 0 represent the participant's own average, and negative and positive values represent measurements that are below and above their own average, respectively. Other potential time-varying covariates (i.e., plasma HIV RNA detectability, current CD4 count) were only included if they showed a significant ($p < 0.05$) within-person relationship with global scaled score, CRP, or BDI-II score. The between-person level of each multilevel model examined the chronic effect of participants' average levels of CRP and average BDI-II scores on their average levels of neurocognition across visits. Potential time-invariant covariates (i.e., all demographic and clinical factors except current and lifetime MDD) were only included if they showed a significant univariable relationship with global scaled score, CRP, or BDI-II score at baseline. To test the primary aim of this study, each multilevel model also included a cross-level interaction between person-centered CRP and average BDI-II score. Random intercepts and a random effect of person-centered CRP were specified. Unstandardized model estimates are reported. To follow-up on a significant cross-level interaction, the Johnson-Neyman method (Johnson and Neyman 1936; Preacher et al. 2006) was used to identify "regions of significance" (i.e., the levels of the moderator (average BDI-II score) at which the within-person relationship between CRP and neurocognition is significant). Finally, additional sensitivity analyses were conducted to examine whether results held among (1) a subset of participants who had undetectable plasma HIV RNA at all visits and (2) a subset of participants who did not meet criteria for a current substance use disorder at any visit. All analyses were conducted using R version 3.5.0. Multilevel models were examined with the "lme4" package (Bates et al. 2015).

Results

The study sample of 143 PWH was 80% male and 47% non-Hispanic White with a mean baseline age of 50.7 years (range 25–79) and mean baseline education of 13.4 years. Participants had an average of 33 months of follow-up (range 12–59 months). Participants' demographic, psychiatric, medical, and HIV disease characteristics from their baseline visit are displayed in Table 1. Neither plasma HIV RNA detectability nor current CD4 count were related to global neurocognition, CRP, or BDI-II score within persons, and thus, they were not included as covariates in the final multilevel models. Out of all remaining demographic and clinical characteristics that were considered for inclusion in the multilevel models as time-invariant covariates (i.e., all except current and lifetime MDD), seven were selected. Five were significantly related to lower global neurocognitive performance at baseline (i.e., older age, fewer years of education, non-White race/ethnicity (vs. White), hepatitis C, and hypertension), one was significantly related to higher plasma CRP (i.e., history of AIDS), and one was significantly related to higher BDI-II score (i.e., lifetime substance use disorder).

Table 1 Baseline demographic and clinical characteristics ($N = 143$)

	Mean (SD), Median (IQR), or *n* (%)
Demographics	
Age (years)	50.7 (9.6)
Sex (male)	115 (80%)
Years of education	13.4 (2.7)
Race/Ethnicity	
Non-Hispanic White	67 (47%)
Black	51 (36%)
Hispanic	18 (13%)
Other	7 (4%)
Employed	57 (40%)
Psychiatric and medical characteristics	
Beck Depression Inventory-II	9.9 (10.2)
Current major depressive disorder	18 (13%)
Lifetime major depressive disorder	81 (57%)
Current substance use disorder	10 (7%)
Lifetime substance use disorder	97 (68%)
Hepatitis C coinfection	34 (24%)
Hypertension	69 (48%)
Hyperlipidemia	51 (36%)
Diabetes	29 (20%)
Log_{10} plasma C-reactive protein	6.3 (0.6)
HIV disease characteristics	
History of AIDS (yes)	105 (73%)
Estimated years living with HIV	16.1 (7.2)
Current CD4 count	569 (380–755)
Nadir CD4 count	120 (26–238)
Plasma HIV RNA detectability (undetectable)	110 (79%)
Antiretroviral therapy status (on)	143 (100%)

Substance use disorder includes meeting criteria for DSM-IV substance abuse or dependence for alcohol, cannabis, cocaine, methamphetamine, opioids, sedatives, hallucinogens, inhalants, or PCP

Current substance use disorder was also related to higher BDI-II score but was not included as a covariate due to multicollinearity with lifetime substance use disorder.

The cross-level interaction between person-centered CRP and average BDI-II score on global neurocognition was significant ($p = 0.012$; Table 2). The follow-up Johnson-Neyman analysis revealed that the within-person effect of CRP on global neurocognition is significantly negative only among participants whose average BDI-II scores are > 22.34 (Fig. 1a). Specifically, neurocognitive performance was worse on visits when CRP was higher (and vice versa), only among those with average BDI-II scores > 22.34 (Fig. 1b). Examination of other neurocognitive domain-specific outcomes (Table 2) showed that this was driven by significant effects in processing speed ($p = 0.047$), attention/working memory ($p = 0.040$), and fine motor skills ($p = 0.029$). Sensitivity analyses showed that results held among the subset of individuals who were virally suppressed at every visit ($n = 102$), and the subset of individuals who never met criteria for a current substance use disorder ($n = 124$).

Discussion

Within ART-treated PWH with moderate to severe depressive symptoms, we observed that global neurocognitive performance decreased as systemic inflammation increased relative to each person's average level of systemic inflammation. Conversely, among individuals who on average experienced none to mild levels of depressive symptoms across the study, neurocognition did not significantly vary as a function of average CRP or visit-specific CRP. These observations expand on our prior report (Paolillo et al. 2020a) by directly implicating inflammation as a moderator of the deleterious effects of cumulative burden of depressive symptoms on neurocognition among PWH. Moreover, these effects were robust to co-occurring medical conditions and remained significant in patients with fully-suppressed HIV across the entire study period, underscoring the relevance of inflammation and depressive symptoms for even successfully treated HIV.

Table 2 Multilevel model results for each neurocognitive outcome; values are unstandardized regression estimate (SE)

	Global	Verbal fluency	Executive functioning	Processing speed	Learning	Delayed recall	Attention/working memory	Motor skills
Within-person level								
CRP (person-centered)[a]	0.023 (0.094)	0.111 (0.145)	− 0.153 (0.185)	− 0.023 (0.136)	0.158 (0.187)	0.089 (0.204)	0.117 (0.176)	0.058 (0.171)
BDI-II (person-centered)	− 0.010 (0.007)	− 0.019 (0.011)[b]	− 0.010 (0.014)	− 0.015 (0.011)	− 0.013 (0.015)	0.002 (0.016)	− 0.003 (0.014)	0.002 (0.014)
Years since baseline	− 0.006 (0.027)	− 0.001 (0.004)	− 0.060 (0.050)	0.029 (0.039)	− 0.012 (0.054)	0.011 (0.058)	0.015 (0.049)	− 0.155 (0.049)**
Between-person level								
Average CRP	− 0.525 (0.294)[b]	− 0.375 (0.393)	− 0.238 (0.384)	− 0.607 (0.404)	− 0.546 (0.431)	− 0.438 (0.417)	− 0.584 (0.435)	− 0.609 (0.399)
Average BDI-II[a]	− 0.033 (0.016)*	− 0.035 (0.021)	− 0.022 (0.021)	− 0.022 (0.022)	− 0.027 (0.023)	− 0.021 (0.023)	− 0.032 (0.024)	− 0.074 (0.022)**
Cross-level interaction								
Person-centered CRP x Average BDI-II	− 0.025 (0.010)*	− 0.024 (0.015)	0.011 (0.019)	− 0.028 (0.014)*	− 0.022 (0.019)	-0.032 (0.021)	− 0.038 (0.018)*	− 0.039 (0.018)*

All multilevel models included the following time-invariant covariates at the between-person level: baseline age, sex (female vs. male), education, race/ethnicity (White vs. non-White), hepatitis C (yes vs. no), hypertension (yes vs. no), history of AIDS (yes vs. no), and past substance use disorder (yes vs. no)

*$p < 0.05$; **$p < 0.01$

[a]Values represent a conditional main effect

[b]$p < 0.10$

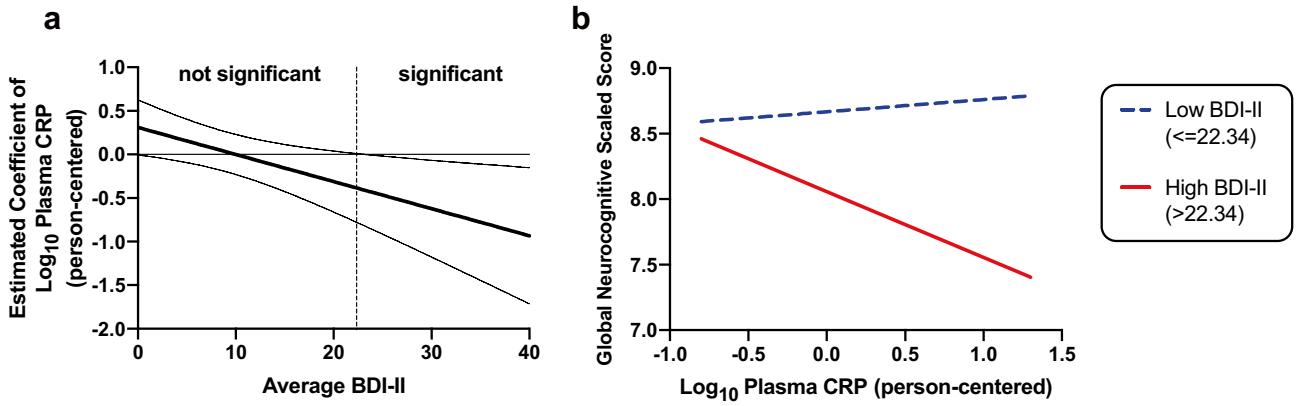

Fig. 1 **a** Effect sizes (beta coefficients) of $\log_{10}$ plasma CRP (person-centered) on global neurocognitive scaled scores are plotted across average BDI-II scores. When the *X*-axis zero-line is included in the confidence band, the effect of $\log_{10}$ plasma CRP (person-centered) is not statistically significant at that average BDI-II value. The region of significance occurs to the right of the dashed line, showing that the within-person effect of $\log_{10}$ plasma CRP (person-centered) is significantly negative at average BDI-II levels greater than 22.34. This indicates that among individuals whose average BDI-II levels are > 22.34, their global neurocognition is lower (worse) on visits when their $\log_{10}$ CRP levels are higher than their own average and vice versa. **b** Log_{10} plasma CRP (person-centered) by global scaled scores, stratified by average BDI-II scores using the empirically derived average BDI-II cut-point of 22.34. The within-person relationship between $\log_{10}$ plasma CRP (person-centered) and global neurocognition is negative in the high BDI-II group only

Using a multilevel model approach, we observed a significant cross-level interaction between average BDI-II scores and visit-specific CRP levels such that CRP exhibited a negative relationship with global neurocognition once average BDI-II scores reached 10 (based on visual inspection of Fig. 1a), and this effect reached formal statistical significance at an empirically-derived threshold of average BDI-II > 22.34, indicating moderate to severe levels of depressive symptoms across the study period. This cross-level interaction between study-average depressive symptoms and visit-specific inflammation on global neurocognition was driven by statistically significant interactions in the domains of processing speed, fine motor skills, and attention/working memory. We previously detected acute deleterious effects of depressive symptoms on processing speed and motor skills in a separate sample of PWH (Paolillo et al. 2020a), and Montoya et al. (2019) found that higher peripheral inflammation mediated the adverse effect of HIV on motor skills (Montoya et al. 2019). In HIV-seronegative patients with MDD, higher plasma CRP has been related to elevated extrasynaptic glutamate in the basal ganglia as measured by magnetic resonance spectroscopy, which in turn related to anhedonia and slower performance on psychomotor tests (Haroon et al. 2016). A decline in speed of information processing may also contribute to our observations of poor attention/working memory among PWH with high depressive symptoms and CRP, as some attention components overlap with processing speed (e.g., focus/execute) and may be particularly compromised as working memory demands increase among PWH (Woods et al. 2009). Overall, our findings point toward a generalized pattern of cognitive and psychomotor slowing coupled with poor attention/working memory, suggesting corticostriatal circuit involvement and consistent with the clinical phenotype of patients with depression and elevated CRP (Felger and Treadway 2017).

Our findings add to the growing body of longitudinal studies highlighting CRP as a salient predictor of adverse neurocognitive outcomes (Bettcher and Kramer 2014; Metti et al. 2014; Walker et al. 2019; Zheng and Xie 2018). In the general population, higher levels of CRP elevate risk for all-cause dementia by 45% and Alzheimer's disease by 21% (Koyama et al. 2013). In a recent analysis among women with HIV (Rubin et al. 2018), higher average intra-individual variability in CRP (average standard deviation of CRP levels) was the strongest predictor of neurocognitive impairment among a broader panel of peripheral immune biomarkers. As an acute phase reactant, blood concentrations of CRP rise during the inflammatory response to biological and psychological stress induced across multiple physiologic systems, including cardiometabolic, immune, and neurologic systems (Metti et al. 2014). Our current findings suggest that chronically depressed PWH, who already exhibit low levels of physiologic reserve due to HIV (Guaraldi et al. 2015; Oppenheim et al. 2018; Paolillo et al. 2020b), may exhibit an even lower capacity to withstand the neurocognitive stressors associated with an increase in systemic inflammation.

This study is among the first to employ robust statistical methods (i.e., multilevel models, Johnson-Neyman technique) to examine the combined effects of depressive symptoms and systemic inflammation on neurocognition in a well-characterized sample of PWH with at least three timepoints of longitudinal data. The study is not

without limitations. As a routinely assessed laboratory measure, CRP was the most widely available marker of inflammation in our research cohort dataset, which makes our findings clinically relevant. Nevertheless, although CRP has been associated with inflammatory markers in the blood and CSF in other studies (Felger et al. 2020), future studies may want to include additional peripheral and CNS markers of inflammation and immune activation to uncover granular mechanistic insights. Similarly, inclusion of monoamine neurotransmitters and their metabolites would help further disentangle the associations between depression, inflammation, and neurocognition among PWH (Saloner et al. 2020). The BDI-II importantly captures greater variation in global depressive symptomatology compared with a dichotomous disorder-based classification (e.g., MDD); however, future investigations should incorporate other instruments that comprehensively target dimensions of depression with putative relevance to inflammation, including anhedonia and apathy (Lee et al. 2018; Nakonezny et al. 2010; Yao et al. 2019). Our inclusion of inflammation, depression, and neurocognitive data importantly integrates physiological and behavioral units of analysis; yet, neuroimaging data would better allow for examining the underlying neurocircuitry, which would allow for examination of corticostriatal pathways in inflammation-related neurobehavioral disturbance among PWH. Last, given that non-Hispanic White men made up 42% of the overall study sample, these analyses should be replicated in larger samples with greater representation of women and racial/ethnic minorities.

Taken together, these findings demonstrate that among PWH with chronically elevated depressive symptoms, increases in systemic inflammation jointly track with neurocognitive impairments, particularly psychomotor slowing and diminished attention/working memory capacity. These novel observations among PWH are consistent with the growing body of literature among people without HIV pointing toward an inflammatory subtype of depressed individuals with neurobehavioral disturbances (e.g., altered motivation and motor activity) that may be non-responsive to standard antidepressants. Given that neurocognitive performance improved as CRP levels decreased among the subset of PWH with high cumulative depressive symptoms, reducing inflammation or its downstream impact on neurotransmitter systems such as dopamine and glutamate may confer greater neurocognitive benefits for these individuals than traditional antidepressants that preferentially target serotonergic and noradrenergic pathways (Miller and Raison 2016). Importantly, addressing these mood and neurocognitive symptoms in PWH may subsequently improve HIV-related medical outcomes and quality of life (Rooney et al. 2019; Rubin and Maki 2019).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Disclaimer The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the US Government.

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