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Peripheral inflammation and depressed mood independently predict neurocognitive worsening over 12 years

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A B S T R A C T

Background: Neurocognitive (NC) impairment in people with HIV (PWH) is associated with important adverse outcomes, but no markers exist to predict long-term NC decline. We evaluated depressed mood and markers of persistent inflammation, oxidative stress and altered amyloid processing (all common in PWH) as predictors of NC worsening over 12 years.

Methods: PWH were enrolled and followed longitudinally in the CNS HIV Antiretroviral Effects Research (CHARTER) study at six US sites. At entry we quantified biomarkers in blood of inflammation: (interleukin-6 [IL-6], C-reactive protein [CRP], monocyte chemoattractant protein type 1 [MCP-1], D-dimer, soluble sCD14 (sCD14), soluble tumor necrosis factor receptor – type II [sTNFR-II], neopterin, and soluble CD40 ligand [sCD40L], oxidative stress (protein carbonyls, 8-oxo-2'-deoxyguanosine [8-oxo-dG]) and altered amyloid processing [amyloid beta (Aβ)-42, soluble amyloid precursor protein-α (sAPPα)] using commercial immunoassays. The Beck Depression Inventory-II (BDI-II) assessed depressed mood at entry. NC decline over 12 years was evaluated using the published and validated summary (global) regression-based change score (sRBCS). A factor analysis reduced dimensionality of the biomarkers. Univariable and multiple regression models tested the relationship between baseline predictors and the outcome of neurocognitive decline.

Results: Participants were 191 PWH, 37 (19.4%) women, 46.6% African American, 43.5% non-Hispanic white, 8.83% Hispanic, 15.7% white, 1.6% other; at study entry mean (SD) age 43.6 (8.06) years, estimated duration of HIV infection (median, IQR) 9.82 [4.44, 14.5] years, nadir CD4 104/μL (19,205), current CD4 568/μL (356, 817), and 80.1% had plasma HIV RNA <50 c/mL. Participants were enrolled between 2003 and 2007; median (IQR) duration of follow-up 12.4 [9.69, 16.2] years. Three biomarker factors were identified: Factor (F)1 (IL-6, CRP), F2 (sTNFR-II, neopterin) and F3 (sCD40L, sAPPα). Participants with higher F1, reflecting worse systemic inflammation at baseline, and higher F3, had greater decline in global neurocognition ($r = -0.168$, $p = 0.0205$ and $r = -0.156$, $p = 0.0309$, respectively). Of the F1 components, higher CRP levels were associated with worse decline ($r = -0.154$, $p = 0.0332$), while IL-6 did not ($r = -0.109$, $p = 0.135$). NC change was not significantly related to F2, nor to demographics, nadir and current CD4, viral suppression or baseline NC comorbidity ratings. Individuals with worse depressed mood at entry also experienced more NC decline ($r = -0.1734$, $p = 0.0006$). Together BDI-II ($p = 0.0290$), F1 ($p = 0.0484$) and F3 ($p = 0.0309$) contributed independently to NC decline ($p = 0.0028$); their interactions were not significant. Neither CRP nor IL-6 correlated significantly with depression.

Conclusions: PWH with greater systemic inflammation and more depression at entry had greater NC decline over 12 years. Understanding the basis of this inflammatory state might be particularly important. These findings raise the possibility that targeted anti-inflammatory or antidepressant therapies may help prevent NC worsening in PWH with depression and inflammation.

1. Background

Neurocognitive (NC) impairment in people with HIV (PWH) is associated with important adverse outcomes including poorer antiretroviral therapy (ART) adherence (Hinkin et al., 2002), and worse social and health-related quality of life (Tedaldi et al., 2015; Tozzi et al., 2003). Extensive reports have delineated the contributions of depression (Pinheiro et al., 2016; Rubin and Maki, 2019), inflammation (Alakkas et al., 2019; McGuire et al., 2015; Burdo et al., 2013) and neurodegeneration (Mackiewicz et al., 2019; Wenzel et al., 2019; Pulliam et al., 2019; Bryant

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et al., 2015) separately to neurocognition. For example, we examined the joint effects of depression (Beck Depression Inventory-II; BDI-II) and systemic inflammation (plasma CRP) on longitudinal profiles of neurocognition over and average of 33 months of follow-up in 143 PWH on ART (Saloner et al., 2020). Global cognition, processing speed, motor function, and attention/working memory all decreased as CRP increased, but only among PWH who exhibited moderate to severe depressive symptoms (BDI-II>22). Depression and inflammation are interrelated in HIV (Bryant et al., 2015; Matt and Gaskill, 2019) and in PWoH (Lee and Giuliani, 2019; Berk et al., 2013), and treatment-resistant depression is associated with a heightened inflammatory response (Yang et al., 2019). Further evaluating the conjoint impacts of depression, systemic and CNS inflammation and neurodegeneration on longitudinal NC outcomes would represent an important scientific advancement. We evaluated depressed mood and markers of persistent systemic inflammation, oxidative stress and altered amyloid processing (all common in PWH) as predictors of NC worsening over 12 years. We hypothesized that inflammation and depression together would contribute to poorer NC outcomes.

2. Methods

Participants. 191 PWH in the current study were enrolled and followed longitudinally in the CNS HIV Antiretroviral Effects Research (CHARTER) study at six US sites. Exclusion criteria were active neurological illnesses other than HIV, acute intoxication based on clinical judgment, and active psychiatric or substance use disorder (eg, psychosis) that might interfere with completing study evaluations. All participants signed a local IRB-approved informed consent document.

Clinical and laboratory evaluations. All participants underwent standardized evaluations as previously described. The Beck Depression Inventory – II (BDI-II) (Beck et al., 1996) assessed depressed mood at entry. The NC performance battery included tests of executive function, working memory, verbal fluency, processing speed, verbal and visual learning and delayed recall, and complex motor function (Heaton et al., 2004; Gonzalez et al., 2003). NC decline over 12 years was evaluated using the published summary (global) regression-based change score (sRBCS) (Cysique et al., 2011). Confounding neurocognitive conditions at baseline were judged by experienced HIV clinicians as Frascati NC comorbidity status incidental (not contributing to NC impairment), contributing (likely contributing to NC impairment, in addition to HIV itself) and confounding (the principal cause of NC impairment). These ratings showed good interrater agreement between clinicians (Heaton et al., 2010a). History of major depressive disorder (MDD) and substance use disorders were assessed using the computer-assisted Composite International Diagnostic Interview (CIDI) (Nelson, 1999), a structured instrument widely used in psychiatric research. The CIDI classifies current and lifetime diagnoses of mood disorders and substance use disorders, as well as other mental disorders. Additional assessments measured activities of daily living, disability, employment and quality of life. Quality of life was assessed using the Medical Outcomes Study HIV Health Survey Short Form 36 (MOS-HIV SF-36), a reliable and valid tool for assessing overall quality of life, daily functioning, and physical health (Wachtel et al., 1992; Wu et al., 1997). The MOS-HIV contains 36 questions that assess various physical and mental dimensions of health. Items are grouped into two overall categories (Physical and Mental Health), with 11 subcategories (Physical functioning, Role functioning, Pain, Social functioning, Emotional well-being, Energy/fatigue, Cognitive functioning, General health, Health distress, Overall QoL. These are scored as summary percentile scales ranging from 0 to 100, with higher scores indicating better health. Disability was assessed using the Karnofsy Scale (Mor et al., 1984). Dependence in instrumental activities of daily living (IADLs) was assessed with a modified version of the Lawton and Brody Scale (Lawton and Brody, 1969) that asks participants to rate their current and best lifetime levels of independence for 13 major IADLs such as shopping, financial management, transportation, and medication management (Heaton et al., 2004). An employment questionnaire asked about job loss, decreases in work productivity, accuracy, and quality, increased effort required to do one's usual job, and increased fatigue with the usual workload (Heaton et al., 2010b). The Patient's Assessment of Own Functioning (PAOFI) (Chelune et al., 1986) was used to assess participant-rated judgments of neurocognitive difficulties.

HIV disease was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. HIV RNA concentration in plasma was measured using commercial assays and deemed undetectable at a lower limit of quantitation (LLQ) of 50 copies/ml. CD4 T cells were measured by flow cytometry and nadir CD4 was assessed by self-report.

Biomarkers. We quantified biomarkers in blood at entry using commercial immunoassays. Markers of inflammation included C-reactive protein [CRP] (Laboratory Corporation of America, San Diego, CA), interleukin-6 [IL-6], soluble tumor necrosis factor receptor type II [sTNFR-II], and monocyte chemoattractant protein type 1 [MCP-1] (Meso Scale Discovery, Rockville, Maryland), D-dimer (BioMedica, Windsor, Nova Scotia, Canada), soluble CD14 [sCD14] (R&D, Minneapolis, Minnesota), neopterin (ALPCO, Salem, New Hampshire), and soluble CD40 ligand [sCD40L] (Millipore Sigma, Burlington, Massachusetts). Markers of oxidative stress included protein carbonyls (Sigma-Aldrich, St. Louis, Missouri) and 8-oxo-2'-deoxyguanosine [8-oxo-dG] (Tregiven, Gaithersburg, Maryland). Markers of altered amyloid processing included amyloid beta [(Aβ)-42], soluble amyloid precursor protein-α [sAPPα] (Meso Scale Discovery, Rockville, Maryland). All assay results were reviewed for quality assurance, and 10% of all assays were repeated to assess operator and batch consistency. Biomarker precision was ensured by assaying specimens in duplicate and repeating measurements with coefficients of variation greater than 20% or outliers that were more than 3 standard deviations (SDs) from the mean.

Statistics. A factor analysis with oblique Equamax rotation was conducted. Factor analysis is a statistical method used to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. Factor analysis reduces dimensionality and controls false discovery. It is important to check the identified factors against known physiological relationships. To validate the factors, we examined intercorrelations between the biomarkers assigned to each factor. BDI-II values were square root-transformed and biomarkers were log transformed to improve the normality of their distribution for analyses. Simple Pearson correlations and multiple linear regression models tested the relationships between baseline predictors and outcomes. Secondary analyses evaluated correlations with quality of life (MOS-HIV), ADLs and employment status. We used multivariable linear regression models to test interaction effects. In the absence of an interaction, additive effects were tested. Analyses were conducted using JMP Pro® version 15.0.0 (SAS Institute Inc., Cary, NC, 2018).

3. Results

Participant characteristics. Participants were 191 PWH, 37 (19.4%) women, 46.6% African American, 43.5% non-Hispanic White, 8.3% Hispanic, 1.6% Other. They were enrolled between 2003 and 2007, and at study entry had mean (SD) age 43.6 (8.06) years, estimated duration of HIV infection (median, IQR) 9.82 [4.44, 14.5] years, nadir CD4 104/μL (19, 205), current CD4 568/μL (356, 817), 80.1% plasma HIV RNA <50 c/mL. Median [IQR] duration of follow-up 12.4 [9.69, 16.2] years. BDI-II depression severity median was 10 [4, 20] (for reference, scores of 14–19 are considered mild depression, 20–28 moderate and 29–63 severe). These and additional participant characteristics are detailed in Table 1. Participants with on anti-depressant medications at baseline had higher BDI-II scores, reflecting worse depressed mood (16.2 ± 10.5 versus 12.3 ± 11.0, $p = 0.0307$) (see Table 2).

The factor analysis identified three baseline factors: F1 (IL-6, CRP), F2 (sTNFR-II, neopterin) and F3 (sCD40L, sAPPα). Higher IL-6 levels correlated with higher CRP levels ($r = 0.427$, $p = 1.10e\text{-}9$), higher levels of sTNFRII correlated with higher levels of neopterin ($r = 0.618$, $p <$

Table 1
Participant demographics and clinical characteristics at the baseline visit.

Baseline characteristics	N = 191
Age, years [mean (SD)]	43.6 (8.06)
Education [mean (SD)]	12.9 (2.58)
Female sex (N, %)	37 (19.4%)
non-Hispanic white (N, %)	83 (43.5%)
CD4 current (median, IQR)	568 (356, 817)
CD4 nadir (median, IQR)	104 (19, 205)
On ART (N, %)	185 (96.9%)
Plasma viral load undetectable (N, %)	149 (80.1%)
Lifetime history of major depressive disorder (N, %)	121 (63.3%)
On antidepressant (N, %)	74 (38.7%)
Lifetime substance use disorder (N, %)	147 (76.9%)
Diabetes mellitus (N, %)	37 (21.0%)
Hypertension (N, %)	89 (50.5%)
Hyperlipidemia (N, %)	69 (39.2%)
Globally neurocognitively impaired (N, %)	85 (44.5%)
BDI-II mild to severe (N, %)	78 (41.8%)

Table 2
Provides the individual neurocognitive domains and their association severity of depression (BDI-II score) and Factors 1 and 3. BDI-II (p = 0.0412 and p = 0.0206) and Factor 1 (p = 0.0346 and p = 0.00285) were significantly associated with worsening speed of information processing and executive function. Also worse BDI-II scores were correlated with worsening verbal functioning and higher Factor 3 levels with worsening speed of information processing. Significant p-values bolded.

Domain	Factor 1		Factor 3		BDI-II	
	r	p value	r	p value	r	p value
Verbal	−0.054	0.459	−0.112	0.123	**−0.185**	**0.011**
Working memory	−0.129	0.076	−0.118	0.103	−0.079	0.278
Speed of information processing	**−0.153**	**0.035**	**−0.153**	**0.034**	**−0.148**	**0.041**
Executive functioning	**−0.159**	**0.029**	−0.112	0.123	**−0.167**	**0.021**
Learning	−0.049	0.499	−0.092	0.207	−0.040	0.580
Recall	0.003	0.972	−0.092	0.207	−0.059	0.418
Motor	−0.131	0.0713	−0.066	0.371	−0.054	0.396

0.0001); and higher levels of sCD40L correlated with higher sAPPa levels (r = 0.389, p < 0.0001). Participants with higher F1, reflecting worse systemic inflammation at baseline, and higher F3, had greater decline in global neurocognition (r = −0.168, p = 0.0205 and r = −0.156, 0.0309, respectively, Fig. 1). Of the F1 components, higher CRP levels were associated with worse decline (r = −0.154, p = 0.0332), while IL-6 did not (r = −0.109, p = 0.135). NC change was not significantly related to F2, nor to demographics, nadir and current CD4, viral suppression or baseline Frascati NC comorbidity ratings (incidental, contributing, confounding). Individuals with worse depressed mood at entry also experienced more NC decline (r = −0.143, p = 0.0484, Fig. 1). Together BDI-II (p = 0.0290), F1 (p = 0.0484) and F3 (p = 0.0309) contributed independently to NC decline (p = 0.0028); their interactions were not significant. Older participants had greater NC decline (r = 0.147, p = 0.0420). NC decline was not significantly related to the other Factors, nor to other demographic factors, nadir and current CD4, viral suppression or Frascati NC comorbidity ratings (incidental, contributing, confounding). None of inflammation factors were related to viral suppression (ps > 0.20). Use of anti-depressant medications or anti-inflammatory medications was not related to the biomarker Factors.

Potential confounds (covariates). Those with and without lifetime MDD did not differ on global neurocognitive worsening −0.337 ± 0.71 versus −0.301 ± 0.598, p = 0.712). However, current MDD at the baseline visit did associate with neurocognitive decline (Current MDD, N = 21, mean ± SD sRBCS −0.641 ± 0.795 versus no current MDD N = 168, −0.278 ± 0.625, p = 0.0158). Global neurocognitive worsening did not correlate with education (r = −0.0359, p = 0.6224), female sex (−0.308 ± 0.652 versus −0.316 0.658, p = 0.939), ethnicity (non hispanic white vs. other (−0.374 ± 0.072 versus −0.269 ± 0.063 p = 0.276), nadir CD4 (r = −0.0754, p = 0.300), current CD4 (r = −0.0150, p = 0.837), being on ART versus off (n = 142, −0.29 ± 10.661 versus n = 49, −0.323 ± 0.655, p = 0.772), having an undetectable plasma viral load (−0.350 ± 0.641 versus 0.672 ± 0.466, p = 0.669), lifetime substance use disorder −0.364 ± 0.654 versus 0.149 ± 0.636, p = 0.0555), diabetes −0.257 ± 0.365 versus −0.318 ± 0.669, p = 0.389), hypertension (−0.320 ± 0.519 versus −0.313 ± 0.683, p = 0.954), or hyperlipidemia (−0.298 ± 0.545 versus - −0.317 ± 0.706, p = 0.905). Change in viral suppression did not associate with neurocognitive decline (p = 0.675), nor did viral suppression status at baseline and follow-up (ps > 0.50). Change in CD4, which on average increased by a median (IQR) 101 (−78, 299) cells/uL, did not relate significantly to neurocognitive decline (r = 0.0489, p = 0.503).

Impact of NC worsening on participant functional status. To evaluate how NC worsening affected participants' overall health, we assessed several variables reflecting functional status. Participants with greater global NC worsening at follow-up had worse scores on the HIV Medical Outcomes Survey General Health, Physical Health and Mental Health subscales (r = 0.244, p = 0.0008). Similarly, those with global NC worsening had more PAOFI cognitive symptoms (r = −0.320, p = 6.670e-6) and were less likely to be employed (unit odds ratio 0.456, p = 0.0037).

4. Conclusions

Participants with higher plasma CRP, IL-6, sCD40L, sAPP and worse depressed mood at entry had greater NC decline over 12 years, and both of these correlated with worse health-related quality of life, functional status and employment. The relationships were not abrogated by age or other demographic or clinical factors, including comorbidities. It is particularly intriguing that these factors predict outcomes many years later, suggesting a possible causal relationship or a potentially shared etiology. An abundant literature demonstrates the adverse impact of systemic and neuroinflammation on brain structure and function in HIV (Pinheiro et al., 2016; Dos Reis et al., 2020; Kallianpur et al., 2020). It is likely that common mechanisms underlie cognitive impairment and depressed mood (Formanek et al., 2020; Pan et al., 2019), raising the possibility that both might be ameliorated by anti-inflammatory medications.

Here plasma CRP, IL-6, sCD40L and sAPP were particularly strongly associated with decline in the domains of speed-of-information processing and executive function as compared to other domains. These domains are selectively affected by HIV brain disease (Kanmogne et al., 2018; Naveed et al., 2021; Haase et al., 2014) and in the modern treatment era are strongly associated with markers of vascular disease (Montoya et al., 2017; Becker et al., 2009) and inflammation (Rubin et al., 2020; Monnig et al., 2017).

This report is unique in evaluating the joint contributions of systemic inflammation and depression to long-term neurocognitive decline. Numerous reports link depression (Watkins and Treisman, 2015; Namagga et al., 2021; Kohn et al., 2021) and both systemic and neuroinflammation (Tedaldi et al., 2015; Hong and Banks, 2015; Gannon et al., 2011; Saloner et al., 2021) to neurocognitive impairment in HIV. Our work complements and extends these prior observations.

This study has several strengths, including the large cohort, extensive clinical characterization, and longitudinal design, yielding findings consistent with forward causation. Limitations include the observational nature of the data and the possibility of unobserved causal factors explaining the interrelationships between the predictors and the outcomes.

We propose that future studies evaluate the potential effectiveness of

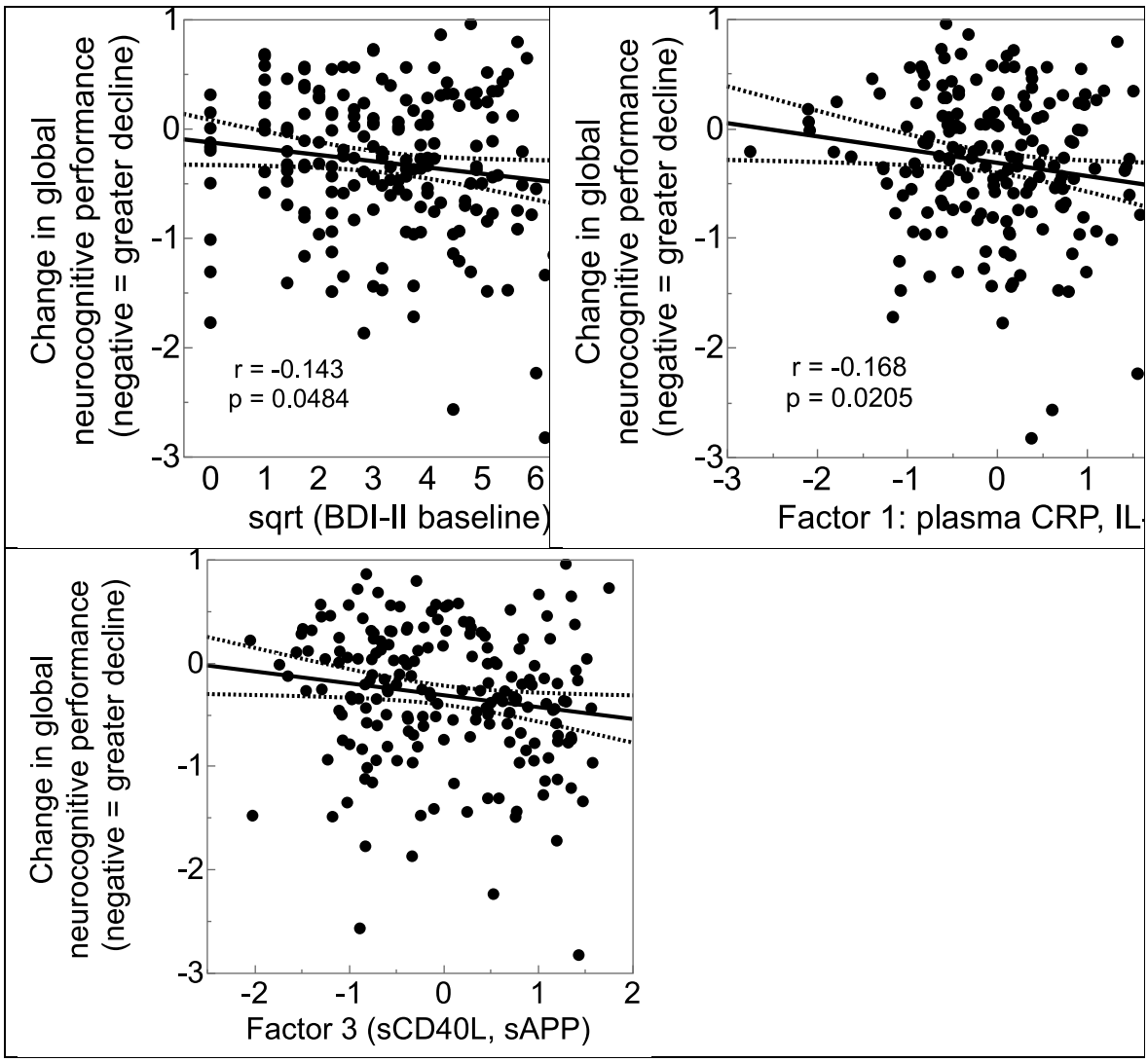

Fig. 1. Correlations of baseline depression severity and Factor 1 with change in global cognition. Shaded areas represent 95% confidence bands for the regression fit. sqrt (BDI-II), square root Beck Depression Inventory-II. CRP, C-reactive protein. IL-6, interleukin-6. sCD40L, soluble CD40 ligand. sAPP, serum amyloid precursor protein.

anti-inflammatories such as curcumin and cannabinoids, as well as antidepressants, to ameliorate cognitive impairment and HIV.

Declaration of competing interest

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

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