Inflammation Relates to Poorer Complex Motor Performance Among Adults Living With HIV on Suppressive Antiretroviral Therapy

Jessica L. Montoya, PhD, Laura M. Campbell, BS,† Emily W. Paolillo, MS,† Ronald J. Ellis, MD, PhD,‡ Scott L. Letendre, MD,§ Dilip V. Jeste, MD,*‡‖ and David J. Moore, PhD**

Background: Inflammatory processes have been suggested to underlie early neurologic abnormalities among persons living with HIV (HIV-positive), such as deficits in complex motor function, that are purported to remit with effective antiretroviral therapy (ART). We hypothesized that HIV will have negative direct and indirect effects through inflammation on complex motor performance.

Methods: The sample consisted of 90 ART-treated virally suppressed HIV-positive and 94 HIV-negative adults, aged 36–65 years, with balanced recruiting in each age decade (36–45, 46–55, and 56–65). Biomarkers of inflammation (d-dimer, IL-6, MCP-1/CCL2, sCD14, and TNF-α) were measured, and a composite inflammation burden score was calculated. Complex motor performance was evaluated using the Grooved Pegboard Test.

Results: The HIV-positive group had worse complex motor performance ($P = 0.001$; Hedges $g = -0.49$) and a higher average inflammation burden composite score ($P < 0.001$; Hedges $g = 0.78$) than the HIV-negative group. Path analyses indicated that the indirect effect of HIV disease on complex motor performance through inflammation burden was statistically significant, accounting for 15.1% of the effect of HIV on complex motor performance.

Conclusions: Although neurologic findings (eg, deficits in motor speed/dexterity) commonly associated with HIV infection typically remit with ART, our analysis indicates that inflammation plays an important role in worse complex motor skills among HIV-positive adults. Future studies of strategies for managing chronic inflammation in HIV should consider using an inflammation burden composite and examining its effect on complex motor performance.

Key Words: neuroAIDS, HIV/AIDS, HIV-associated neurocognitive disorders, inflammation composite, motor

(*J Acquir Immune Defic Syndr* 2019;80:15–23)

Received for publication June 16, 2018; accepted August 10, 2018.

From the *Department of Psychiatry, University of California San Diego, San Diego, CA; †SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA; ‡Department of Neurosciences, University of California San Diego, San Diego, CA; §Division of Infectious Diseases, School of Medicine, University of California San Diego, San Diego, CA; and ‖Sam and Rose Stein Institute for Research on Aging, University of California San Diego, San Diego, CA.

Supported by National Institute of Mental Health grant R01 MH099987 (multiple PI's: D.V.J. and D.J.M.). J.L.M., L.M.C., and E.W.P. were supported by NIDA T32 DA031098. The study was more broadly supported by the HIV Neurobehavioral Research Center (HNRC) Award P30MH062512 and NIH K24 MH097673 (PI: S.L.L.).

Presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI); March 5, 2018; Boston, MA.

The authors have no funding or conflicts of interest to disclose.

Correspondence to: David J. Moore, PhD, HIV Neurobehavioral Research Program, 220 Dickinson Street, Suite B (8231), San Diego, CA 92103 (e-mail: djmoore@ucsd.edu).

INTRODUCTION

Successful viral suppression from combination antiretroviral therapy (cART) has led to an increase in life expectancy among persons living with HIV (HIV-positive). Although severe HIV-associated neurocognitive disorder (HAND) is less prevalent in the cART era, mild to moderate HAND persists despite virologic suppression. HAND affects up to 50% of HIV-positive persons,[1,2] with older HIV-positive adults at 1.5–3 times greater risk of neurocognitive impairment than their younger counterparts.[3–5]

Among neurocognitive domains affected by HAND, complex motor skills are consistently compromised across time. Complex motor skills refer to a combination of cognitive and perceptual motor abilities, including perception, planning, continuous tracking, and sequential movements.[6] Although the prevalence of complex motor impairment has receded in comparison with the pre-cART era, deficits in complex motor functioning are still observed in approximately 30% of those with HAND.[2] Complex motor impairment is related to everyday functioning impairment, including driving ability, highlighting the clinical relevance in understanding mechanistic pathways underlying HIV-associated motor dysfunction.[6] A recent longitudinal study found that complex motor function is particularly vulnerable to the effects of age and stage of HIV infection, and implicated the basal ganglia as a neural correlate of interest.[7] The effects of acute HIV infection on the basal ganglia are well documented,[8] with greater atrophy associated with psychomotor slowing.[9]

Inflammation is one putative factor that may contribute to central nervous system (CNS) injury, including deficits in complex motor skills. Biomarkers of inflammation, such as cytokines and monocytes, are elevated in the context of HIV infection. HIV, viral products, and activated immune cells are able to cross the blood–brain barrier and contribute to inflammation in the CNS.[10] Neuroimaging studies have shown that peripheral inflammatory biomarkers are able to

alter neural activity in the basal ganglia, including dopaminergic activity, which is reflected by psychomotor slowing in HIV-negative adults.[11] Among HIV-positive persons, global neurocognitive impairment is associated with elevation of various peripheral biomarkers of inflammation and coagulation (eg, cytokines,[12] monocytes,[13,14] and d-dimer[15]).

Taken together, deficits in complex motor performance are commonly observed among HIV-positive persons, and elevation in peripheral biomarkers of inflammation may be a contributing factor. Thus, we hypothesize that HIV will have negative direct and indirect effects through inflammation on complex motor performance.

METHODS

Participants and Design

Participants were 90 HIV-positive and 94 HIV-negative persons, with balanced recruiting in each age decade (36–45, 46–55, and 56–65), from the 5-year Multi-Dimensional Successful Aging among HIV-Infected Adults study conducted at the University of California, San Diego (UCSD).[16] Only baseline data were included in this analysis. The study received approval from the UCSD Institutional Review Board. Participants provided written informed consent. Exclusion criteria for the parent study were diagnosis of a psychotic disorder and presence of a neurological condition known to impact cognitive functioning (eg, stroke). Additional exclusion criteria for current analyses included being off ART, having detectable HIV viral load (>50 copies/mL), and meeting criteria for a current substance use disorder. HIV infection was screened using a fingerstick test (Medmira, Nova Scotia, Canada) and confirmed with an Abbott RealTime HIV-1 test (Abbott Laboratories, IL) or by submitting specimens to a Clinical Laboratory Improvement Amendments–certified laboratory (ARUP Laboratories, UT) for HIV-1 viral load quantitation.

Complex Motor Skills

The Grooved Pegboard Test[17] was administered to participants to assess complex motor skills. The task involves placing 25 keyhole-shaped pegs into 25 keyhole-shaped holes that are oriented in varying directions on a 4 × 4 inch board. All participants completed 2 trials of the task: first using only their dominant hand, then using only their nondominant hand. Raw scores (ie, time required to complete the task) obtained from each trial were converted to demographically adjusted T-scores (M = 50, SD = 10), which correct for the effects of age, education, sex, and race/ethnicity, as appropriate.[18] The demographically adjusted T-scores were then averaged to derive a composite complex motor performance score, the main outcome of interest in statistical analysis.

Although often conceptualized as simply a measure of fine motor dexterity, the Grooved Pegboard Test involves the use of many complex operations for optimal performance (eg, holding instructions in memory, planning proper orientation of pegs, and visuospatial attention with sensorimotor integration). Performance on the Grooved Pegboard Test is correlated with a wide range of domain-specific cognitive functions[19] and is routinely used to assess cognitive and motor deficits in many clinical populations including HIV-positive persons.[20,21]

Neurocognitive Assessment

In addition to assessment of complex motor skills, participants completed a comprehensive neurocognitive test battery assessing 6 other neurocognitive domains (ie, speed of information processing, learning, memory, executive functioning, verbal fluency, and working memory; see the study by Heaton et al[1] 2010 for details on the specific test battery). Demographically adjusted T-scores were derived for each neurocognitive domain.[22–24] A global deficit score of ≥0.5 was used to determine global neurocognitive impairment.[20]

Plasma Biomarkers of Inflammation

Participants were instructed to fast before laboratory examination. Plasma for biomarker assays was collected using EDTA vacuum tubes using standard phlebotomy procedures. Biomarkers were measured using commercially available immunoassays and run according to the manufactures' protocol. Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-a) were measured by a multi-plex bead array, and monocyte chemoattractant protein-1 (MCP-1/CCL2) was assayed using individual single-plex kits (EMD Millipore, Billerica, MA). Soluble cluster of differentiation 14 (sCD14; Quantikine; R&D Systems, Minneapolis, MN) and d-dimer (Sekisui Diagnostics, Lexington, MA) were measured using a quantitative sandwich enzyme immunoassay. 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 4 SDs from the mean. In addition, 10% of all assays were repeated to assess operator and batch consistency.

For statistical analyses, we calculated a composite inflammation burden score using methodology from previous studies investigating inflammation among HIV-positive adults.[25–28] These previous studies assessed between 3 and 7 biomarkers of inflammation (eg, IL-6, d-dimer, and TNF-a) and used a 75th percentile threshold to categorize values as being "elevated." Thus, in this study, an elevation in an individual biomarker was defined as a value at or above the 75th percentile. The 75th percentile was defined by non-transformed biomarker values obtained from the HIV-negative control sample. Each individual biomarker was dichotomized into "elevated" (1) or not elevated (0). Next, we calculated a composite inflammation burden score by summing the number of elevated biomarkers. The composite had a range of 0–5, with 0 corresponding to having no elevations in inflammatory biomarker levels and 5 corresponding to having all 5 inflammatory biomarkers elevated.

Neuromedical Assessment

Presence of medical comorbidities (eg, dyslipidemia and diabetes mellitus) was determined by clinical interview

and/or specific drug treatment for the condition (eg, metformin for diabetes mellitus). The following HIV disease characteristics were collected: $CD4^+$ T-cell counts (nadir and current), estimated duration of HIV disease, AIDS status, and current ART regimen. Per inclusionary criteria for this study, all HIV-positive participants were on suppressive ART.

Psychiatric and Substance Use Disorders

The Composite International Diagnostic Interview was administered (CIDI, v2.1)[29] to assess for lifetime and current major depressive disorder (MDD) and substance use disorders (abuse or dependence) based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders.[30]

Statistical Analyses

Comparisons of demographic, neuromedical, psychiatric, and biomarker data between the HIV-positive and HIV-negative groups were performed using 2-tailed *t* test, Wilcoxon rank–sum test, likelihood ratio χ^2 test, or Fisher exact tests, as appropriate. Fisher exact tests and Kruskal–Wallis tests were conducted to examine whether complex motor performance, inflammatory biomarkers, and HIV disease characteristics differed by age decade. When appropriate, the biomarker values were $\log_{10}$-transformed for group comparisons. Hedges g statistic for continuous variables and odds ratios for binary variables were used to generate effect sizes for group comparisons. To adjust for multiple comparisons, the Benjamini–Hochberg (BH) method was used to limit false discovery rate (FDR) to 5%. Group comparisons were performed with JMP 11.0.0 (SAS, 2013).

Path analysis was used to test the indirect effect of HIV on complex motor performance through the pathway of inflammation. To conduct the path analysis, we calculated bias-corrected 95% confidence intervals (CIs) using bootstrapping with the Process Procedure.[31] The Process Procedure calculates the unstandardized path coefficients for all paths in the model. A significant indirect effect is indicated when the CI does not include the value zero. Covariates were selected based on which variables in Table 1 demonstrated univariable associations (ie, Pearson's correlations for continuous variables and *t* tests for categorical variables) with the primary dependent variable (complex motor performance T-score) at a critical $\alpha = 0.10$. The following covariates were identified as having met our criterion for inclusion in the analysis as control variables: hypertension, hyperlipidemia, diabetes mellitus, lifetime cannabis use disorder, and lifetime methamphetamine use disorder. Given that demographic variables (ie, age, education, sex, and race/ethnicity) were accounted for in the adjusted T-scores for complex motor performance, we did not include demographic variables as covariates for analyses involving complex motor performance as the outcome variable of interest. Path analyses were performed using IBM SPSS Statistics for Windows, Version 24.[32]

TABLE 1. Participant Characteristics by HIV Serostatus (N = 184)

	HIV− (n = 94)	HIV+ (n = 90)	
	Mean (SD) or n (%)		Group Comparison
Demographic variables			
Age decade			$\chi^2 = 0.08$, $P = 0.96$
36–45	28 (29.8%)	28 (31.1%)	
46–55	34 (36.2%)	33 (36.7%)	
56–65	32 (34.0%)	29 (32.2%)	
Education	15.0 (2.3)	14.1 (2.2)	$t = -2.8$, $P = 0.006$, $g = -0.40$
Male	66 (70.2%)	78 (86.7%)	$\chi^2 = 7.5$, $P = 0.006$, OR = 2.8
Non-Hispanic white	65 (69.2%)	50 (55.6%)	$\chi^2 = 3.6$, $P = 0.06$, OR = 0.6
Medical comorbidities			
Hyperlipidemia	17 (18.1%)	39 (43.3%)	$\chi^2 = 14.1$, $P < 0.001$, OR = 3.5
Hypertension	14 (14.9%)	38 (42.2%)	$\chi^2 = 17.4$, $P < 0.001$, OR = 4.2
Ever smoker	10 (10.6%)	41 (45.6%)	$\chi^2 = 29.5$, $P < 0.001$, OR = 7.0
Current smoker	10 (10.6%)	30 (33.3%)	$\chi^2 = 14.4$, $P < 0.001$, OR = 4.2
Diabetes mellitus	6 (6.4%)	11 (12.2%)	FET, $P = 0.17$, OR = 2.0
Hepatitis C	0 (0.0%)	15 (16.7%)	FET, $P < 0.001$
BMI*	28.2 (5.9)	27.9 (5.5)	$t = -0.3$, $P = 0.73$, $g = -0.05$
Psychiatric diagnoses			
LT MDD†	19 (20.7%)	49 (57.0%)	$\chi^2 = 25.5$, $P < 0.001$, OR = 5.1
Current MDD‡	0 (0.0%)	10 (11.8%)	FET, $P < 0.001$
LT alcohol use disorder§	28 (30.4%)	47 (53.4%)	$\chi^2 = 9.9$, $P = 0.002$, OR = 2.6
LT cannabis use disorder§	15 (16.3%)	21 (23.9%)	$\chi^2 = 1.6$, $P = 0.20$, OR = 1.6
LT methamphetamine use disorder§	0 (0.0%)	33 (37.5%)	FET, $P < 0.001$

*n = 179.
†n = 178.
‡n = 177.
§n = 180.
BMI, body mass index; FET, Fisher exact test; g, Hedges g statistic; LT, lifetime; OR, odds ratio.

RESULTS

Participants

On average, participants were non-Hispanic white (62.5%) men (78.3%) with some college education [mean 14.6 (SD 2.3) years of formal education]. Compared to the HIV-negative group, the HIV-positive group had fewer years of education, a greater proportion of males, and a greater proportion of individuals with medical comorbidities, MDD, and lifetime substance use disorders (*P*'s < 0.05; Table 1).

Among the HIV-positive participants, 60% had an AIDS diagnosis, median estimated duration of HIV infection was 18.5 years, median current $CD4^+$ T-cell count was 629

cells/mm^3, and median nadir CD4$^+$ T-cell count was 183 cells/mm^3. HIV disease characteristics did not differ by age decade (P's > 0.05; Table 2), with the exception of duration of HIV infection and duration of exposure to ART, which were longer for each increasing age decade (P's < 0.01).

HIV and Greater Inflammation Burden

Of the 5 individual inflammation biomarkers, the HIV serostatus groups differed on levels of MCP-1, sCD14, and TNF-a, which were higher in the HIV-positive group (P's < 0.05; Table 3). The HIV-positive group had a higher average composite inflammation burden score than the HIV-negative group ($P < 0.001$; Hedges g = 0.78). Among participant characteristics presented in Table 1, a higher composite inflammation burden score was significantly associated with having hepatitis C infection (Hedges g = 0.83), meeting criteria for lifetime methamphetamine use disorder (Hedges g = 0.79), having a hypertension diagnosis (Hedges g = 0.73), ever being a smoker (Hedges g = 0.59), having a diabetes mellitus diagnosis (Hedges g = 0.56), meeting criteria for lifetime MDD diagnosis (Hedges g = 0.49), female sex (Hedges g = 0.45), being a current smoker (Hedges g = 0.45), and having a hyperlipidemia diagnosis (Hedges g = 0.44) (P's < 0.05 after controlling for FDR using the BH method).

HIV and Inflammation Burden Are Associated With Worse Complex Motor Performance

HIV-positive participants had worse complex motor performance [T-score = 48.7 (SD 10.4)] than HIV-negative participants [T-score = 53.8 (SD 10.2); $P = 0.001$; Hedges g = −0.49]. Using a 1 SD cutoff in which a T-score <40 represents impaired complex motor performance, we found the rate of impairment to be significantly higher in the HIV-positive group (20.0%) than in the HIV-negative group (6.4%; $P = 0.008$, odds ratio = 3.67). Participants with impaired complex motor performance, on average, had a higher composite inflammation burden score [mean = 2.4 (SD 1.2)] than participants without impairment [mean = 1.6 (SD 1.2), $P = 0.003$; Hedges g = 0.66]. Inflammation burden had an inverse correlation with complex motor performance, such that higher composite inflammation burden scores were associated with lower T-scores ($\rho = -0.22$, $P = 0.002$). Next, we tested whether any single biomarker of inflammation was driving this association by examining associations between composite inflammation burden scores derived from 4 biomarkers (ie, we eliminated a single biomarker from the composite at a time) and complex motor T-scores. All possible 4-biomarker composites were significantly associated with complex motor performance (P's < 0.05 after controlling for FDR using the BH method). Furthermore, to test whether any of the individual biomarkers of inflammation were uniquely associated with complex motor T-scores (ie, the outcome variable), a multivariable regression model was evaluated, which included the 5 individual biomarkers of inflammation, HIV serostatus, and relevant covariates. In this model, none of the individual biomarkers were significantly associated with complex motor performance (P's > 0.05).

Direct and Indirect Effects of HIV on Complex Motor Performance

Path analysis results indicated that HIV serostatus was significantly associated with higher composite inflammation burden score (B = 0.50, SE = 0.21, 95% CI: 0.09 to 0.91, $P = 0.02$) when controlling for effects of relevant covariates (ie, see model of inflammation burden in Table 4). HIV serostatus was also associated with poorer complex motor performance (B = −3.98, SE = 1.83, 95% CI: −7.61 to −0.35 $P = 0.03$) when controlling for effects of relevant covariates (see total effect model of complex motor performance in Table 4). When HIV serostatus was entered simultaneously with the composite inflammation burden score, effects of HIV disease (B = −3.38, SE = 1.86, 95% CI: −7.05 to 0.29 $P = 0.07$) and inflammation burden (B = −1.20, SE = 0.67, 95% CI: −2.51 to 0.12 $P = 0.08$) were at a trend level for statistical significance (see model of complex motor performance in Table 4). The indirect effect of HIV disease through inflammation burden was

TABLE 2. HIV Disease Characteristics and Treatment by Age Decade (n = 90)

	36–45 (n = 28)	46–55 (n = 33)	56–65 (n = 29)	
Variable	**Median (IQR), Mean (SD), or n (%)**			**Group Comparison**
AIDS	13 (46.4%)	19 (57.6%)	22 (75.9%)	FET, $P = 0.07$
Current CD4$^+$ T-cell count*	668 (398–833)	637 (479–884)	576 (410–815)	$F_{(2, 82)} = 0.3$, $P = 0.76$
Nadir CD4$^+$ T-cell count†	180 (74–363)	113 (17–374)	187 (63–407)	$\chi^2(2) = 1.1$, $P = 0.58$
Duration of HIV infection (yr)	11.3 (4.8–18.8)	16.8 (11.3–25.0)	25.5 (19.4–27.3)	$\chi^2(2) = 27.1$, $P < 0.001$
Duration of exposure to ART (yr)	7.8 (3.5–14.8)	14.5 (9.9–17.9)	16.4 (7.0–22.9)	$F_{(2, 87)} = 7.0$, $P = 0.002$
On nucleoside reverse transcriptase inhibitor (NRTI)	27 (96.4%)	32 (97.0%)	28 (96.6%)	FET, $P = 1.00$
On protease inhibitor (PI)	11 (39.3%)	19 (57.6%)	16 (55.2%)	$\chi^2 = 2.3$, $P = 0.31$
On integrase inhibitor (II)	10 (35.7%)	12 (36.4%)	11 (37.9%)	$\chi^2 = 0.03$, $P = 0.98$
On nonnucleoside reverse transcriptase inhibitor (NNRTI)	10 (35.7%)	12 (36.4%)	9 (31.0%)	$\chi^2 = 0.2$, $P = 0.89$
CNS penetration effectiveness score	8.0 (1.5)	8.1 (2.0)	8.3 (2.2)	$F_{(2, 87)} = 0.2$, $P = 0.85$

*n = 85.
†n = 89.
ART, antiretroviral therapy; FET, Fisher exact test; IQR, interquartile range.

TABLE 3. Biomarker Values by HIV Serostatus Groups (N = 184)

	HIV− (n = 94)	HIV+ (n = 90)	
	Median (IQR) or n (%)		Group Comparison
MCP-1 (pg/mL)	139.4 (120.9–166.6)	177.6 (146.1–206.1)	Z = 5.03, $P < 0.001$, r = 0.37
Elevated MCP-1	23 (24.5%)	59 (65.6%)	OR = 5.88, $P < 0.001$
TNF-a (pg/mL)	2.01 (1.78–2.46)	2.34 (1.90–3.26)	Z = 2.97, $P = 0.003$, r = 0.22
Elevated TNF-a	23 (24.5%)	41 (45.6%)	OR = 2.58, $P = 0.003$
sCD14 (ng/mL)	1227.0 (1006.5–1364.5)	1452.8 (864.8–1725.4)	Z = 2.71, $P = 0.007$, r = 0.20
Elevated sCD14	23 (24.5%)	50 (55.6%)	OR = 3.86, $P < 0.001$
IL-6 (pg/mL)	0.71 (0.51–1.03)	0.67 (0.49–0.92)	Z = −0.85, $P = 0.40$, r = −0.06
Elevated IL-6	23 (24.5%)	17 (18.9%)	OR = 0.72, $P = 0.36$
d-dimer (ng/mL)	426.1 (343.5–569.9)	434.2 (339.6–573.1)	Z = −0.04, $P = 0.97$, r = 0.00
Elevated d-dimer	23 (24.5%)	23 (25.6%)	OR = 1.06, $P = 0.86$
Composite inflammation burden score	1.22 (1.15)	2.11 (1.21)	g = 0.78, $P < 0.001$
No biomarkers elevated	27 (28.7%)	7 (7.8%)	OR = 0.21, $P < 0.001$
1 biomarker elevated	39 (41.5%)	22 (24.4%)	OR = 0.46, $P = 0.01$
2 biomarkers elevated	13 (13.8%)	29 (32.2%)	OR = 2.96, $P = 0.005$
3 biomarkers elevated	11 (11.7%)	22 (24.4%)	OR = 2.44, $P = 0.02$
4 biomarkers elevated	3 (3.2%)	6 (6.7%)	OR = 2.17, $P = 0.27$
5 biomarkers elevated	1 (1.1%)	4 (4.4%)	OR = 4.33, $P = 0.15$

Biomarker values were log-transformed for statistical testing except sCD14.
Effect size for nonparametric group comparisons determined by $r = Z/\sqrt{n}$, with r = 0.1 indicating a small effect, r = 0.3 indicating a medium effect, and r = 0.5 indicating a large effect.
g, Hedges g statistic; OR, odds ratio.

statistically significant (B = −0.60, SE = 0.43, 95% CI: −1.95 to −0.05; Figure 1), accounting for 15.1% of the effect of HIV on complex motor performance.

In a second path analysis model, we tested whether the path between HIV on inflammation burden varied as a function of sex and age decade (ie, conditional indirect effect). For this model, the index of moderated mediation was nonsignificant for both sex and age decade (ie, the CI of the conditional indirect effects contained zero).

HIV Disease Characteristics and Treatment, Inflammation, and Complex Motor Performance

In the HIV-positive sample only, direct and indirect effects through inflammation burden of individual HIV disease and treatment variables (listed in Table 2) on complex motor performance were examined in a similar fashion as the previous section. The CI for the indirect effect of each individual HIV disease and treatment variable on complex motor performance contained zero and, therefore, each individual effect was considered statistically insignificant. At the univariable level, neither the composite inflammation burden score nor complex motor performance was associated with any of the HIV disease and treatment variables (P's > 0.05).

Post Hoc Analysis: Relation of Inflammation Burden With Global Neurocognitive Impairment and Other Neurocognitive Domains

A greater proportion of the HIV-positive group had global neurocognitive impairment (41.1%) compared with the HIV-negative group (25.5%; $P = 0.02$; odds ratio = 2.04). Composite inflammation burden scores were higher among participants with global neurocognitive impairment [mean = 2.0 (SD 1.4)] compared to those without impairment [mean = 1.5 (SD 1.2), $P = 0.02$; Hedges g = 0.38]. Finally, we examined whether other neurocognitive domains (ie, recall, executive functions, learning, verbal, working memory, and speed of information processing) would show similar associations with the composite inflammation burden score. After controlling for FDR using the BH method, only the complex motor domain showed a statistically significant association with the composite inflammation burden score.

DISCUSSION

Although neurologic findings commonly associated with HIV infection have been suggested to largely remit with initiation of cART, our cross-sectional study observed worse complex motor skills across the adult age continuum of HIV-positive, relative to HIV-negative, adults. Inflammation burden was higher among HIV-positive adults, compared with the HIV-negative comparison group. Consistent with our hypothesis, HIV infection was observed to have both direct and indirect effects through inflammation on complex motor performance, such that inflammation burden accounted for 15.1% of the effect of HIV infection on motor performance when controlling for relevant covariates. These results

TABLE 4. Models to Test the Direct and Indirect Effects of HIV on Complex Motor Performance

	Coefficient	SE	t	*P*	95% CI
Model of inflammation burden $R^2 = 0.20$, $F_{(6, 173)} = 7.20$, $P < 0.001$					
Constant	1.10	0.13	8.38	<0.01	0.84 to 1.35
HIV	0.50	0.21	2.42	0.02	0.09 to 0.91
Hyperlipidemia diagnosis	0.09	0.21	0.46	0.65	−0.31 to 0.50
LT cannabis use disorder	0.10	0.22	0.45	0.65	−0.34 to 0.54
Diabetes mellitus diagnosis	0.31	0.31	1.01	0.31	−0.30 to 0.92
LT methamphetamine use disorder	0.48	0.26	1.84	0.07	−0.04 to 0.99
Hypertension diagnosis	0.56	0.21	2.64	0.01	0.14 to 0.97
Total effect model of complex motor performance $R^2 = 0.12$, $F_{(6, 173)} = 3.78$, $P = 0.002$					
Constant	55.23	1.16	47.76	<0.01	52.95 to 57.52
HIV	−3.98	1.84	−2.17	0.03	−7.61 to −0.35
Hyperlipidemia diagnosis	−3.53	1.83	−1.93	0.06	−7.13 to 0.08
LT cannabis use disorder	−3.28	1.98	−1.66	0.10	−7.18 to 0.63
Diabetes mellitus diagnosis	−2.45	2.74	−0.89	0.37	−7.85 to 2.96
LT methamphetamine use disorder	0.67	2.30	0.29	0.77	−3.87 to 5.21
Hypertension diagnosis	−0.72	1.87	−0.38	0.70	−4.41 to 2.98
Model of complex motor performance $R^2 = 0.13$, $F_{(7, 172)} = 3.74$, $P < 0.001$					
Constant	56.54	1.36	41.50	<0.01	58.86 to 59.23
HIV	−3.38	1.86	−1.82	0.07	−7.05 to 0.29
Inflammation burden composite	−1.20	0.67	−1.79	0.08	−2.51 to 0.12
Hyperlipidemia diagnosis	−3.41	1.81	−1.88	0.06	−6.99 to 0.17
LT cannabis use disorder	−3.16	1.97	−1.61	0.11	−7.04 to 0.72
Diabetes mellitus diagnosis	−2.07	2.73	−0.76	0.45	−7.46 to 3.31
LT methamphetamine use disorder	1.24	2.31	0.54	0.59	−3.31 to 5.80
Hypertension diagnosis	−0.05	1.90	−0.03	0.98	−3.80 to 3.70

LT, lifetime.

indicate that inflammatory processes may contribute to worse complex motor skills in the context of cART-treated HIV.

Our sample consisted of virally suppressed, chronic HIV-positive patients; however, impairment in complex motor skills was still observed among 20% of the HIV-positive sample. This observed impairment rate is consistent with motor impairment rates (eg, 19%–25%) reported in previous literature.[33] Some evidence indicates a higher impairment rate in complex motor performance among persons with chronic HIV compared to persons with acute or early HIV infection,[34] which may reflect a history of immunosuppression and/or greater inflammation burden. For example, persons with AIDS performed significantly worse on a fine motor speed test than those without AIDS.[35] Deficits in motor skills may indicate injury to the basal ganglia, which are part of the motor control pathways.[36] The basal ganglia seem to be particularly vulnerable to alterations in blood–brain barrier permeability,[37,38] immune cellular infiltration,[39] and accumulation of HIV viral RNA.[40] Neuropathological studies have observed higher concentrations of macrophages, microglia, and viral proteins in the basal ganglia.[41]

Our path analyses indicate that inflammation burden may play a role in the association between HIV infection and worse complex motor performance. This finding is consistent with previous research demonstrating the detrimental impact of HIV and its proteins on the brain through peripheral and CNS pathways.[10] Monocytes and macrophages are observed to infiltrate the CNS in HIV infection.[10] Elevations in soluble markers of monocyte and cytokine activation, including sCD14, MCP-1/CCL2, and IL-6, have been observed among HIV-positive adults with neurocognitive impairment.[42–44] Expression of MCP-1/CCL2 may contribute to upregulation of HIV-1 replication, thereby contributing to an increased risk of neurocognitive impairment.[45] In addition to inflammation, coagulation imbalance, which includes upregulation of d-dimer, is associated with global neurocognitive functioning among HIV-positive adults.[15] In the current analysis, d-dimer was included in the inflammation burden composite, given the bidirectional relationship between inflammation and coagulation (ie, coagulation imbalance is considered to be both a consequence of inflammation and an amplifier of the inflammatory response[46]). Multiple factors likely contribute to activation of inflammatory and coagulation pathways observed among HIV-positive persons on cART, such as viral replication, excess levels of translocated microbial products and other chronic pathogens (eg, cytomegalovirus), and loss of immunoregulatory responses.[47]

HIV was observed to have both direct and indirect effects through inflammation burden on complex motor performance; however, inflammation burden only accounted for 15.1% of the effect of HIV on complex motor performance. These results suggest there are additional mechanisms by which HIV may have deleterious effects on complex motor performance. Other factors contributing to neurocognitive impairment may include vascular remodeling (eg, pathological angiogenesis),[48] metabolic disorders (eg, diabetes mellitus and visceral adiposity),[49] and coinfections.[50] This study evaluated a model that identified one plausible indirect pathway between HIV and worse complex motor performance; future research may build on this work by evaluating

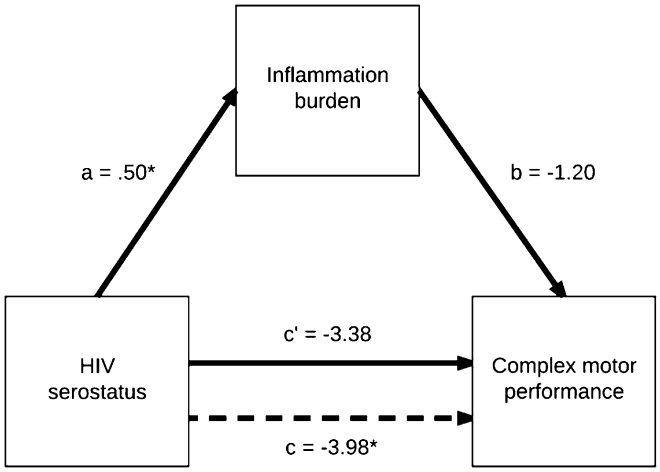

FIGURE 1. Path coefficients for mediation analysis of HIV serostatus to complex motor performance through inflammation burden for the overall sample (n = 184). The dotted line denotes the direct path from HIV serostatus to complex motor performance when inflammation burden is not included as a mediator. a, b, c, and c′ are standardized ordinary least squares regression coefficients. Covariates were included in the analysis but are not depicted in the figure. $*P < 0.05$.

models with multiple pathways to estimate the relative contribution of various plausible mediators. A better understanding of the interplay of factors contributing to neurologic dysfunction in HIV may lead to more accurate prognosis and and/or risk stratification of HIV-positive adults in regard to neurologic dysfunction.

Although some brain metabolite abnormalities may improve after initiating cART,[51] some abnormalities persist, including ongoing inflammatory processes.[52] A long-term prospective cohort study found interacting effects of aging and HIV disease stage, such that the magnitude of motor performance impairment was greater than the sum of the independent effects of age and HIV disease stage.[7] The interaction between aging and HIV disease stage suggest that complex motor skills may be particularly susceptible to aging-related progression of neurocognitive impairment among HIV-positive adults. The Grooved Pegboard Test seems to be particularly sensitive to detecting neurocognitive decline among HIV-positive persons.[53]

Our study findings should be considered in light of its limitations. First, although we used path analysis, this study was cross-sectional in nature, which precludes us from making inferences in regard to causation or mediation. Our results are also consistent with the alternative hypothesis that both inflammatory processes and complex motor skills may be mediated by an unobserved third variable. Given that the parent study involves repeated assessment of neurocognitive functioning and inflammation over 5 years, future analyses will examine whether changes in inflammation are associated with changes in complex motor functioning. Second, our study did not collect data on conditions (eg, hand arthritis, persistent traumatic hand injury, and peripheral neuropathy) that may confound interpretation of complex motor performance. Third, it is unclear how to best conceptualize inflammation burden because normative standards regarding biomarker measurement and conceptualization have not been established. However, our calculation of a composite inflammation burden score may be a viable method compared with reliance on a single biomarker, given our analysis indicated that complex motor performance was significantly associated with the composite but not any individual biomarker. Furthermore, conceptualization of an inflammation burden composite adds to the body of research aimed at developing clinically relevant risk indices (eg, Veterans Aging Cohort Index[54]). Fourth, our HIV-negative comparison group was relatively healthy and differed from the HIV-positive group on multiple characteristics. Fifth, our HIV-positive group consisted of mostly non-Hispanic white males with some college education, which is not fully representative of HIV-positive persons in the United States. Sixth, previous research indicates multitasks may better detect motor impairment compared with a single motor task (ie, finger tapping)[55]; the Grooved Pegboard Test, however, involves the use of many complex operations and is correlated with a range of cognitive functions.[19]

In summary, HIV has a deleterious impact on complex motor skills, which may be partially explained by inflammatory processes. Future studies of strategies for managing chronic inflammation in HIV may consider using an inflammation burden composite and examining how changes in inflammation burden affect complex motor performance, given the fact that this neurocognitive domain seems to be more strongly associated with inflammation relative to other domains.

ACKNOWLEDGMENTS

The San Diego HIV Neurobehavioral Research Center (HNRC) group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes: Director: Robert K. Heaton, PhD; Co-Director: Igor Grant, MD; Associate Directors: J. Hampton Atkinson, MD, Ronald J. Ellis, MD, PhD, and Scott Letendre, MD; Center Manager: Thomas D. Marcotte, PhD, Jennifer Marquie-Beck, MPH, and Melanie Sherman; Neuromedical Component: Ronald J. Ellis, MD, PhD (P.I.), Scott Letendre, MD, J. Allen McCutchan, MD, Brookie Best, PharmD, Rachel Schrier, PhD, and Debra Rosario, MPH; Neurobehavioral Component: Robert K. Heaton, PhD (P.I.), J. Hampton Atkinson, MD, Steven Paul Woods, PsyD, Thomas D. Marcotte, PhD, Mariana Cherner, PhD, David J. Moore, PhD, and Matthew Dawson; Neuroimaging Component: Christine Fennema-Notestine, PhD (P.I.), Monte S. Buchsbaum, MD, John Hesselink, MD, Sarah L. Archibald, MA, Gregory Brown, PhD, Richard Buxton, PhD, Anders Dale, PhD, and Thomas Liu, PhD; Neurobiology Component: Eliezer Masliah, MD (P.I.) and Cristian Achim, MD, PhD; Neurovirology Component: David M. Smith, MD (P.I.) and Douglas Richman, MD; International Component: J. Allen McCutchan, MD, (P.I.) and Mariana Cherner, PhD; Developmental Component: Cristian Achim, MD, PhD; (P.I.) and Stuart Lipton, MD, PhD;

Participant Accrual and Retention Unit: J. Hampton Atkinson, MD (P.I.) and Jennifer Marquie-Beck, MPH; Data Management and Information Systems Unit: Anthony C. Gamst, PhD (P.I.) and Clint Cushman; Statistics Unit: Ian Abramson, PhD (P.I.), Florin Vaida, PhD (Co-PI), Reena Deutsch, PhD, and Anya Umlauf, MS.

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, or the United States Government.

REFERENCES

1. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology.* 2010;75:2087–2096.
2. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol.* 2011;17:3–16.
3. Cherner M, Ellis RJ, Lazzaretto D, et al. Effects of HIV-1 infection and aging on neurobehavioral functioning: preliminary findings. *AIDS.* 2004; 18(suppl 1):S27–S34.
4. Sacktor N, Skolasky R, Selnes OA, et al. Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. *J Neurovirol.* 2007;13:203–209.
5. Valcour V, Shikuma C, Shiramizu B, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii aging with HIV-1 cohort. *Neurology.* 2004;63:822–827.
6. Marcotte TD, Heaton RK, Wolfson T, et al. The impact of HIV-related neuropsychological dysfunction on driving behavior. The HNRC Group. *J Int Neuropsychol Soc.* 1999;5:579–592.
7. Goodkin K, Miller EN, Cox C, et al. Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study. *Lancet HIV.* 2017;4:e411–e422.
8. O'Connor EE, Zeffiro TA, Zeffiro TA. Brain structural changes following HIV infection: meta-analysis. *AJNR Am J Neuroradiol.* 2018;39:54–62.
9. Wright PW, Pyakurel A, Vaida FF, et al. Putamen volume and its clinical and neurological correlates in primary HIV infection. *AIDS.* 2016;30: 1789–1794.
10. Hong S, Banks WA. Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. *Brain Behav Immun.* 2015;45:1–12.
11. Felger JC, Miller AH. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Front Neuroendocrinol.* 2012;33:315–327.
12. Cohen RA, de la Monte S, Gongvatana A, et al. Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *J Neuroimmunol.* 2011;233:204–210.
13. Burdo TH, Weiffenbach A, Woods SP, et al. Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. *AIDS.* 2013;27:1387–1395.
14. Imp BM, Rubin LH, Tien PC, et al. Monocyte activation is associated with worse cognitive performance in HIV-infected women with virologic suppression. *J Infect Dis.* 2017;215:114–121.
15. Montoya JL, Iudicello J, Oppenheim HA, et al. Coagulation imbalance and neurocognitive functioning in older HIV-positive adults on suppressive antiretroviral therapy. *AIDS.* 2017;31:787–795.
16. Moore RC, Paolillo EW, Heaton A, et al. Clinical utility of the UCSD performance-based skills assessment-brief (UPSA-B) in adults living with HIV: associations with neuropsychological impairment and patient-reported everyday functioning difficulties. *PLoS One.* 2017;12: e0183614.
17. Kløve H. Clinical neuropsychology. In: Forster FM, ed. *The Medical Clinics of North America*. New York, NY: Saunders; 1963.
18. Heaton RK, Miller SW, Taylor MJ, et al. *Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults*. Lutz, FL: Psychological Assessment Resources; 2004.
19. Fowler PC, Zillmer E, Newman AC. A multifactor model of the Halstead-Reitan neuropsychological test battery and its relationship to cognitive status and psychiatric diagnosis. *J Clin Psychol.* 1988;44:898–906.
20. Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *J Clin Exp Neuropsychol.* 2004;26:307–319.
21. Cysique LA, Franklin D Jr, Abramson I, et al. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. *J Clin Exp Neuropsychol.* 2011;33:505–522.
22. Cherner M, Suarez P, Lazzaretto D, et al. Demographically corrected norms for the brief visuospatial memory test-revised and Hopkins verbal learning test-revised in monolingual Spanish speakers from the U.S.-Mexico border region. *Arch Clin Neuropsychol.* 2007;22:343–353.
23. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc.* 2004;10:317–331.
24. Heaton RK, Taylor MJ, Manly JJ. Demographic effects and use of demographically corrected norms with the WAIS-III and WMS-III. In: Tulsky DS, Heaton RK, Chelune G, et al, eds. *Clinical Interpretation of the WAIS-III and WMS-III*. San Diego, CA: Academic Press; 2002.
25. Armah KA, McGinnis K, Baker J, et al. HIV status, burden of comorbid disease, and biomarkers of inflammation, altered coagulation, and monocyte activation. *Clin Infect Dis.* 2012;55:126–136.
26. Armah KA, Quinn EK, Cheng DM, et al. Human immunodeficiency virus, hepatitis C, and inflammatory biomarkers in individuals with alcohol problems: a cross-sectional study. *BMC Infect Dis.* 2013;13:399.
27. Mooney S, Tracy R, Osler T, et al. Elevated biomarkers of inflammation and coagulation in patients with HIV are associated with higher Framingham and VACS risk index scores. *PLoS One.* 2015;10: e0144312.
28. So-Armah KA, Tate JP, Chang CH, et al. Do biomarkers of inflammation, monocyte activation, and altered coagulation explain excess mortality between HIV infected and uninfected people? *J Acquir Immune Defic Syndr.* 2016;72:206–213.
29. World Health Organization. *Composite International Diagnostic Interview (CIDI, Version 2.1)*. Geneva, Switzerland: World Health Organization; 1997.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.
31. Hayes AF. *Introduction to Mediation, Moderation, and Conditional Processes: A Regression-based Approach*. New York, NY: The Guilford Press; 2013.
32. *IBM SPSS Statistics for Windows [computer Program]. Version 24*. Armonk, NY: IBM Corp; 2013.
33. Crum-Cianflone NF, Moore DJ, Letendre S, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. *Neurology.* 2013;80:371–379.
34. Moore DJ, Letendre SL, Morris S, et al. Neurocognitive functioning in acute or early HIV infection. *J Neurovirol.* 2011;17:50–57.
35. Baldewicz TT, Leserman J, Silva SG, et al. Changes in neuropsychological functioning with progression of HIV-1 infection: results of an 8-year longitudinal investigation. *AIDS Behav.* 2004;8:345–355.
36. Berger JR, Arendt G. HIV dementia: the role of the basal ganglia and dopaminergic systems. *J Psychopharmacol.* 2000;14:214–221.
37. Dallasta LM, Pisarov LA, Esplen JE, et al. Blood-brain barrier tight junction disruption in human immunodeficiency virus-1 encephalitis. *Am J Pathol.* 1999;155:1915–1927.
38. Nath A, Anderson C, Jones M, et al. Neurotoxicity and dysfunction of dopaminergic systems associated with AIDS dementia. *J Psychopharmacol.* 2000;14:222–227.
39. Sailasuta N, Ross W, Ananworanich J, et al. Change in brain magnetic resonance spectroscopy after treatment during acute HIV infection. *PLoS One.* 2012;7:e49272.
40. Kumar AM, Borodowsky I, Fernandez B, et al. Human immunodeficiency virus type 1 RNA Levels in different regions of human brain: quantification using real-time reverse transcriptase-polymerase chain reaction. *J Neurovirol.* 2007;13:210–224.
41. Berger JR, Nath A. HIV dementia and the basal ganglia. *Intervirology.* 1997;40:122–131.

42. Ancuta P, Kamat A, Kunstman KJ, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. *PLoS One.* 2008;3:e2516.
43. Ryan LA, Zheng J, Brester M, et al. Plasma levels of soluble CD14 and tumor necrosis factor-alpha type II receptor correlate with cognitive dysfunction during human immunodeficiency virus type 1 infection. *J Infect Dis.* 2001;184:699–706.
44. Lyons JL, Uno H, Ancuta P, et al. Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infection. *J Acquir Immune Defic Syndr.* 2011;57:371–379.
45. Gonzalez E, Rovin BH, Sen L, et al. HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. *Proc Natl Acad Sci U S A.* 2002; 99:13795–13800.
46. Funderburg NT, Lederman MM. Coagulation and morbidity in treated HIV infection. *Thromb Res.* 2014;133(suppl 1):S21–S24.
47. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity.* 2013;39:633–645.
48. Montoya JL, Iudicello J, Fazeli PL, et al. Elevated markers of vascular remodeling and arterial stiffness are associated with neurocognitive function in older HIV+ adults on suppressive antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2017;74:134–141.
49. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology.* 2012;78:485–492.
50. Letendre S, Paulino AD, Rockenstein E, et al. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. *J Infect Dis.* 2007;196:361–370.
51. Chang L, Ernst T, Leonido-Yee M, et al. Highly active antiretroviral therapy reverses brain metabolite abnormalities in mild HIV dementia. *Neurology.* 1999;53:782–789.
52. Chang L, Ernst T, Witt MD, et al. Persistent brain abnormalities in antiretroviral-naive HIV patients 3 months after HAART. *Antivir Ther.* 2003;8:17–26.
53. Yuen T, Brouillette MJ, Fellows LK, et al. Personalized risk index for neurocognitive decline among people with well-controlled HIV infection. *J Acquir Immune Defic Syndr.* 2017;76:48–54.
54. Justice AC, Freiberg MS, Tracy R, et al. Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? *Clin Infect Dis.* 2012;54:984–994.
55. Kronemer SI, Mandel JA, Sacktor NC, et al. Impairments of motor function while multitasking in HIV. *Front Hum Neurosci.* 2017;11: 212.