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Markers of Macrophage Activation and Axonal Injury are Associated With Prospective Memory in HIV-1 Disease

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Abstract

Objective— To use clinical specimens to better understand the neuropathogenesis of prospective memory (ProM) functioning in persons with HIV-1 infection.

Background— Emergent evidence suggests that HIV-1 is associated with impaired ProM, but the underlying neuropathophysiology of this deficit is not known.

Methods— Thirty-five nondemented subjects with HIV-1 infection completed measures of both ProM (ie, memory for future intentions) and retrospective memory (RM; ie, memory for past episodes). A panel of biomarkers reflecting several possible neuropathogenic mechanisms of HIV was measured in plasma and cerebrospinal fluid, including HIV-1 RNA, total tau, monocyte chemoattractant protein-1 (MCP-1), soluble receptor for tumor necrosis factor type II, and fibroblast growth factor 1.

Results— After controlling for antiretroviral therapy and CD4 lymphocyte count, higher levels of MCP-1 in plasma, and soluble receptor for tumor necrosis factor type II and tau in cerebrospinal fluid were associated with ProM, but not RM. Markers of astrogliosis, growth factor depletion, and HIV-1 replication did not predict either ProM or RM.

Conclusions— ProM impairment in HIV-1 may be dissociable from RM, perhaps reflecting specific neuropathogenic mechanisms of macrophage activation and axonal injury.

Keywords

neuropsychology; HIV; memory; neuropathogenesis; biomarkers

HIV-1 is a lentivirus that crosses the blood brain barrier and infiltrates brain parenchyma early in the course of infection, where it replicates primarily in perivascular macrophages and microglia.¹ Infection triggers an inflammatory response in the central nervous system (CNS) that is characterized by chronic microglial activation and the release of neurotoxic viral protein

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byproducts (eg, tumor necrosis factor).² Although the resultant neuronal and glial pathology (eg, apoptosis and axonal degeneration) are evident throughout the CNS,³ the neural pathways connecting the frontal cortex and basal ganglia are particularly susceptible to HIV-1.⁴ Consistent with injury to frontostriatal circuits, the prototypic neuropsychologic profile of HIV-1 infection is marked by cognitive and motor slowing, executive dysfunction, and deficient encoding and retrieval within retrospective memory (RM).⁵

Prior research on HIV-1-associated memory deficits has almost exclusively focused on RM, which simply refers to the recollection of past experiences in response to explicit internal or external cues.⁶ Most standard clinical tests of memory are classified as measures of RM (eg, word list learning and recall). RM is dissociable from prospective memory (ProM), which describes the multi-faceted cognitive mechanisms involved in executing a future intention, or “remembering to remember.”^{6–7} Largely dependent on frontostriatal networks,⁸ ProM is heralded as a more ecologically relevant aspect of episodic memory than RM: common examples of ProM include remembering to take a medication after a meal or remembering to pay the household bills on the first of the month. Like many activities of everyday life, ProM tasks require the self-initiated detection of environmental cues (eg, time and events) to retrieve and execute a previously encoded intention, whereas RM tasks provide explicit cues (eg, examiner prompts) to recall information from the near past. Thus, ProM abilities may have a stronger contribution to the independent performance of instrumental activities of daily living (eg, medication adherence and financial management). Carey et al⁹ were the first to report evidence of ProM impairment in HIV-1, which was characterized by deficient time and event-cued ProM in the setting of intact recognition performance. These findings indicate that HIV-1 infection is associated with a breakdown in the strategic (ie, executive) aspects of retrieving future intentions, which is consistent with a disruption of prefrontostriatal circuit function. The primary aim of this study was to extend these preliminary findings by identifying biomarkers associated with ProM, and RM, in HIV-1-infected individuals.

MATERIALS AND METHODS

The study was approved by the University Human Research Protections Program and all participants provided written, informed consent. Study participants included 35 individuals with HIV-1 infection as determined by enzyme-linked immunosorbent assays and a Western Blot confirmatory test, who were recruited for participation in a study at the HIV Neurobehavioral Research Center. No participant met diagnostic criteria for HIV-associated dementia as determined by multi-disciplinary case conference diagnoses derived from comprehensive neuromedical and neuropsychologic evaluations.¹⁰ Exclusion criteria included histories of psychiatric (eg, mental retardation, psychotic disorders, bipolar disorders, or recent substance-related disorders) or neurologic (eg, seizure disorders, traumatic brain injury, or CNS neoplasms) conditions that might adversely impact cognition. Participants were also excluded if they evidenced a positive urine toxicology screen for illicit substances (eg, cocaine or methamphetamine) on the day of testing. Six participants produced positive urine toxicology screens for prescription benzodiazepines, but no other licit drugs with possible cognitive effects were recorded (eg, barbiturates, amphetamines, or opiates). Table 1 displays the demographic and disease characteristics of the study sample.

All participants were administered the Memory for Intentions Screening Test (MIST11), which is a standardized, 30-minutes measure comprised of 8 ProM trials. The MIST contains equally balanced ProM items that use: (1) a 2-minute or 15-minute delay; (2) a verbal (eg, “In 2 minutes, ask me what time this session ends.”) or physical (eg, “In 15 minutes, use that paper to write down the number of medications you are currently taking.”) response; and (3) a time-based (eg, “In 15 minutes, tell me that it is time to take a break.”) or event-based (eg, “When I hand you a postcard, self-address it.”) cue. A series of word search puzzles functions as an ongoing

distracter task separating the ProM trials. Age-corrected MIST summary z -scores were derived from available normative standards¹¹ and used as the primary ProM criterion in all statistical analyses.

RM was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R)¹² and the Brief Visuospatial Memory Test-Revised (BVM-T-R).¹³ The HVLT-R is a 12-item list learning task that contains 3 groups of semantically related words read aloud at a 2-second interstimulus interval. On the BVM-T-R, 6 geometric designs are presented in a 2×3 array. Administration protocols for both the HVLT-R and BVM-T-R require 3 consecutive learning trials, which are followed by a 25 minutes delayed free recall and forced-choice recognition trials prompted by the examiner. The delayed recall trials from the HVLT-R and BVM-T-R were selected for analysis because these measures possess adequate psychometric integrity (eg, reliability) and are sensitive to RM deficits in encoding, retrieval, and consolidation. Averaged age-corrected z -scores of the delayed recall trials were derived from published normative standards^{12,13} and used as the primary RM criterion variable of interest.

A panel of biomarkers reflecting several possible neuropathogenic mechanisms of HIV was measured in both plasma ($n = 35$) and cerebrospinal fluid (CSF) ($n = 19$) samples, which were obtained on the day of neuropsychologic evaluation. HIV-1 RNA was quantified by reverse transcription-polymerase chain reaction (Roche Amplicor). The standard assay (sensitivity 400 copies/mL) was used for plasma and the ultrasensitive assay (sensitivity 50 copies/mL) was used for CSF. HIV-1 viral loads were log transformed before analysis. Other biomarkers included monocyte chemoattractant protein-1 (MCP-1), soluble receptor for tumor necrosis factor type II (sTNFR II), and fibroblast growth factor 1 (FGF1). Total tau, MCP-1, sTNFR II, and FGF-1 were measured using commercial enzyme-linked immunosorbent assays kits (Quantikine; R&D Systems, Minneapolis, MN; limit of detection: 31.2 pg/mL for MCP-1, tau and FGF-1, and 7.8 pg/mL for sTNFR II).

Separate standard least squares regression procedures were conducted in which each biomarker was tested as a predictor of ProM or RM in plasma and CSF, while concurrently modeling antiretroviral therapy status and CD4 lymphocyte count. Although this exploratory analytical approach is associated with mild type I statistical error risk, type II error risk was also heightened due to limited statistical power associated with small sample sizes, particularly for the CSF analyses ($n = 19$). Accordingly, the critical α level was set at 0.05 in an effort to appropriately balance the risk of types I and II error. Moreover, effect sizes (R^2 values and partial correlations) are provided in an effort to minimize reliance on null hypothesis significance testing in interpreting the study results.

RESULTS

A paired-samples t test revealed no significant difference in ProM (M z -score = -0.30 , SD = 1.33) and RM (M z -score = -0.21 , SD = 0.93) functioning ($P > 0.10$, Cohen's $d = 0.08$). Relative to normative standards, 80% of the participants were within normal limits on ProM, whereas 6% were mildly impaired, 9% were moderately impaired, and 6% were severely impaired. Similarly, 80% of the sample was within normal limits on RM, with 14% and 6% in mildly and moderately impaired range, respectively. However, there was only a trend-level correlation between ProM and RM z -scores ($r = 0.31$, $P = 0.07$).

Descriptive statistics for the biomarkers and the data derived from the regression analyses are displayed in Table 2. Results revealed that plasma MCP-1 and CSF levels of tau and sTNFR II were all significant predictors of ProM (all P 's < 0.05). No other individual biomarker reached the threshold for statistical significance in predicting ProM (all P 's > 0.10). Similarly, there was no correspondence between any individual biomarker and RM (all P 's > 0.10).

DISCUSSION

Results from this small study indicate that poorer ProM performance in HIV-1 disease is associated with higher levels of MCP-1 in plasma and higher levels of tau and sTNFRII in CSF, even while accounting for antiretroviral therapy and the severity of immunocompromise. Thus, these preliminary data suggest that HIV-1-associated ProM impairment may be driven by macrophage activation (CSF sTNFRII and plasma MCP-1) and injury to axons (CSF tau), whereas the roles of astrogliosis (CSF MCP-1), depletion of neurotrophic factors (FGF-1), and HIV replication (HIV RNA) itself are less apparent. These findings are commensurate with prior studies that have demonstrated an association between HIV-1-associated dementia and tau, MCP-1, and sTNFRII.^{14–17}

To our knowledge, the current study is the first to demonstrate a dissociation between ProM and RM in a clinical sample using biomarkers of neuropathogenic mechanisms. The absence of a significant association between this panel of biomarkers and measures of RM suggests that axonal injury and macrophage activation have a specific relationship with ProM (ie, the execution of future intentions) in HIV-1 disease. Confirmatory post hoc analyses revealed no association between the biomarker panel and RM measures of retention (ie, savings scores), immediate recall, or recognition discrimination (all P 's > 0.10), indicating that these effects are not isolated to RM delayed free recall. Moreover, despite comparable performance on ProM and RM—indicating that the tasks were of comparable difficulty—these 2 variables were only modestly correlated in the current study sample. In other words, although the group demonstrated similar ability levels on ProM and RM relative to normative standards, the actual association between ProM and RM performance in individual participants was relatively weak. Accordingly, our findings are consonant with the hypothesized single dissociation between RM and ProM. It is theorized that RM is a necessary, but not sufficient condition for ProM, which relies more heavily on self-directed monitoring, search and retrieval capabilities. Although ProM and RM retrieval mechanisms use similar underlying processes in healthy controls, successful ProM demands auxiliary neural resources beyond that which is required for RM (eg, lateral frontal lobe activity),^{6–7} which in this study of HIV-1 infection was reflected by ProM's specific association with biomarkers of macrophage activation and axonal injury.

The potential limits to the interpretation of these data merit consideration. The external validity of this study is limited due to the fact that the sample was nondemented and in generally good immunologic health (eg, only 17% were immunosuppressed at the time of evaluation). Secondly, in an effort to reduce type I error, a restricted panel of biomarkers reflecting known neuropathogenic mechanisms of HIV-1-associated CNS injury was measured. Nevertheless, hypotheses generated from this study's findings will enable other investigators to further elucidate neuropathogenic mechanisms of HIV-1-associated ProM impairment; for example, might genetic factors related to macrophage activation and neuronal injury, such as the MCP-1-2578G allele¹⁸ be associated with increased risk of ProM impairment? Thirdly, only 54% of subjects had undergone lumbar puncture and had available CSF samples, which may have reduced statistical power. For example, higher plasma, but not CSF, MCP-1 levels were associated with ProM impairment, which differs from prior investigations.¹⁹ Despite this sample size limitation, the present study was adequately powered to detect an association between 2 CSF biomarkers (tau and sTNFRII) and ProM. Moreover, there were no significant demographic, disease, or ProM differences in subjects with and without CSF data (all P 's > 0.10). Finally, although 17% of the study sample was taking benzodiazepines at the time of evaluation, there were no differences in the ProM, RM, or biomarkers data for these participants (all P 's > 0.10). In addition, the primary study findings did not change when benzodiazepine toxicology was entered into the statistical models.

In summary, HIV-1-associated ProM impairment may be dissociable from the widely described deficits in RM, perhaps reflecting specific neuropathogenic mechanisms of macrophage activation and axonal injury. From a clinical perspective, persistent ProM failures will ostensibly result in profound problems in performing daily functional activities and thereby threaten independent living in persons with HIV-1 infection. Thus, increased understanding of the neuropathogenesis, neural substrates, and cognitive mechanisms of ProM in HIV-1 is an important area for future research, which may lead to the development of targeted pharmacologic therapies (eg, MCP-1 antagonists) to lessen the day-to-day impact of HIV-1-associated ProM impairment. Similarly, development of ProM-focused cognitive and behavioral interventions is needed, particularly in light of literature indicating that ProM deficits in brain-injured patients are remediable with appropriate training (eg, electronic memory aids).²⁰

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TABLE 1
Demographic and HIV-1 Disease Composition of the Study Sample

Variable	Value
Age	43.1 (7.8)
Education	13.9 (2.4)
Estimated verbal IQ *	99.2 (8.3)
Sex (% female)	23%
Ethnicity (%)	
White	60%
African American	20%
Hispanic	11%
Others	9%
Beck depression inventory [†]	5.0 (2.0, 8.0)
HIV Dementia Scale (range = 0–16) [†]	16.0 (15.0, 16.0)
CD4 lymphocyte count [†]	510.5 (288.0, 622.2)
Immunosuppressed (%)	17%
AIDS (%)	74%
Antiretroviral therapy	
Highly active antiretroviral therapy	74%
Other antiretroviral therapy	4%

Data represent means and standard deviations or percentages unless otherwise indicated.

* Measured with the oral word reading subtest of the Wide Range Achievement Test (Revision 3).

[†] Data are presented as the median value, with the interquartile range in parentheses.

TABLE 2
Biomarkers as Predictors of Prospective and Retrospective Memory in HIV-1 Disease

Biomarkers	Median (IQR)	Prospective Memory			Retrospective Memory		
		R ²	r	P	R ²	r	P
Plasma (n = 35)							
HIV RNA *	1.7 (0.0, 4.5)	0.16	0.01	0.17	0.19	-0.18	0.18
MCP-1	169.9 (129.7, 202.6)	0.29	-0.49	0.01	0.19	-0.21	0.20
sTNFRII	3360.6 (2208.6, 4696.2)	0.12	-0.09	0.46	0.14	-0.03	0.78
FGF-1	23.9 (17.7, 34.0)	0.11	0.01	0.63	0.15	0.11	0.54
CSF (n = 19)							
HIV RNA *	0.0 (0.0, 3.0)	0.18	-0.14	0.23	0.42	-0.26	0.20
MCP-1	702.2 (496.6, 837.5)	0.23	-0.39	0.15	0.35	0.08	0.77
sTNFRII	285.4 (195.0, 438.3)	0.44	-0.60	0.01	0.36	-0.16	0.54
FGF-1	36.3 (27.3, 342.4)	0.13	-0.20	0.52	0.34	0.06	0.84
Tau	1.0 (0.5, 2.0)	0.37	-0.54	0.03	0.35	0.07	0.80

* Log (10) transformed HIV RNA values. R² = overall fit of regression model, including CD4 lymphocyte count and antiretroviral therapy status; r = effect size (partial correlation values); P = effect test for each individual biomarker in the separate regression models.
IQR indicates interquartile range.