Impairments in memory and hippocampal function in HIV-positive vs HIV-negative women

A preliminary study

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ABSTRACT

Objective: Neurocognitive studies of HIV typically target executive functions dependent on frontostriatal circuitry. The integrity of medial temporal systems has received considerably less attention despite high hippocampal viral load. Studies also predominately involve HIV+ men, though HIV+ women may be at increased risk for cognitive dysfunction due to the high prevalence of psychosocial/mental health problems and lower educational attainment. Our aim was to conduct a preliminary investigation of episodic memory and its neural correlates in HIV-infected and at-risk uninfected women.

Methods: Participants included 54 HIV+ and 12 HIV− women (mean age = 43 years; 86% African American) recruited from the Chicago site of the Women's Interagency HIV Study. Participants completed standardized tests of verbal and visual episodic memory, working memory, and executive function. A subset of 11 women also underwent functional MRI during a delayed verbal episodic memory task.

Results: HIV serostatus predicted significantly lower immediate and delayed verbal episodic memory, working memory, and visual memory. Preliminary neuroimaging findings revealed group differences in bilateral hippocampal function, with HIV+ women showing decreased activation during encoding and increased activation during delayed recognition. These alterations correlated with worse episodic verbal memory.

Conclusions: Verbal episodic memory deficits are evident in HIV+ women and may be associated with hippocampal dysfunction at both encoding and retrieval. ***Neurology***® **2009;72:1661–1668**

GLOSSARY

ARV = antiretroviral therapy; **CES-D** = Center for Epidemiologic Studies–Depression Scale; **fMRI** = functional MRI; **HAART** = highly active antiretroviral therapy; **HCV** = hepatitis C virus antibody; **HVLT** = Hopkins Verbal Learning Task; **ROI** = region of interest; **TE** = echo time; **TR** = repetition time; **WIHS** = Women's Interagency HIV Study; **WRAT-R** = Wide Range Achievement Test–Revised.

Until recently, the functional integrity of medial temporal systems in neuroAIDS has received little attention despite considerable evidence of hippocampal injury associated with HIV. Brain viral loads of HIV are particularly high in the hippocampus.[1,2] Postmortem evidence of neuroinflammation by microglial/macrophage activation was found to be high in the hippocampus of HIV+ individuals treated with highly active antiretroviral therapy (HAART), higher even than levels found in pre-HAART neuropathologic studies.[3] Regional neurodegeneration of hippocampus and putamen each contributed unique variance in prediction of antemortem neurocognitive status in HIV.[4] A functional MRI (fMRI) study of well-educated HIV+ men demonstrated reduced signal intensity in right posterior hippocampus, right inferior frontal gyrus, and left lingual gyrus during encoding of scenes.[5] Further detailed multimodal investiga-

Supplemental data at www.neurology.org

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Support information is provided at the end of the article.

Disclosure: The authors report no disclosures.

Disclaimer: The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH, the University of Illinois at Chicago, Stroger Hospital, or the Cook County Bureau of Health Services.

tion of the functional integrity of medial temporal systems among persons with HIV/AIDS has considerable potential utility for development of targeted treatment.

In the current study, we investigated 1) integrity of episodic memory in HIV-infected and at-risk HIV-uninfected women using standardized neuropsychological tasks; 2) patterns of regional cerebral blood flow in the hippocampus and parahippocampal gyrus using fMRI during performance of an episodic verbal memory test; and 3) relationship between hippocampal activation patterns and verbal memory scores. Participants were a subset of women enrolled in the Chicago site of the Women's Interagency HIV Study (WIHS), a cohort that is quite representative of women living with HIV/AIDS in the United States.[6,7] Neurocognitive complications of HIV are rarely studied in women, though women may be at risk for episodic memory impairment due to poverty, low literacy levels, substance abuse, poor mental health, and other risk factors prevalent in our cohort of predominantly minority urban-dwelling women.

METHODS

Subjects. Sixty-three women (51 HIV+ and 12 HIV−) were enrolled from the CORE Center/Stroger Hospital and UIC sites of the Chicago WIHS, a longitudinal multicenter study of HIV disease progression in women.[6,7] Participants were recruited for the cognitive substudy during semiannual WIHS core visits in 2005–2006. Because of the known effects of ovarian hormone on memory performance, neuropsychological test sessions were conducted on days 2–4 of the menstrual cycle based on self-reported menses and any day for women who self-reported menopause, defined as no menstrual bleeding for the past 12 consecutive months. All cognitive testing was conducted at UIC, on average 42 days from the core WIHS visit. Participants had no evidence of overt cognitive deficits on interview and no history of HIV-associated dementia or other central neurologic impairment by medical record review or physician report. Women with a history of closed head injury with loss of consciousness greater than one-half hour, open head injury, schizophrenia, epilepsy, evidence of intoxication or withdrawal at testing, or current neuroleptic use were excluded. Additional exclusion criteria for MRI studies included prohibitive metal implants, claustrophobia, and weight over 250 pounds. The institutional review boards at UIC and Stroger Hospital approved the protocol and consent forms, and investigators obtained informed written consent from all subjects. Participants received monetary incentives as compensation for their time and transportation costs.

Clinical neuropsychological measures. All 63 participants completed neuropsychological measures of verbal and visual episodic memory, executive function, and working memory as part of an extensive test battery requiring approximately 90 minutes to complete. Test selection was guided by known sensitivity to HIV-associated cognitive impairment; appropriate difficulty level; brevity of administration; and comparability with protocols employed in other neuroAIDS studies (e.g., MACS and CHARTER). The Hopkins Verbal Learning Task (HVLT),[8] a 12-item list learning task, was used to measure verbal episodic memory, indexed by total words recalled after three trials, and delayed free recall and recognition trials. The Rey Osterrieth Complex Figure Task served as a measure of visuoconstruction abilities and visual episodic memory.[9] Outcome measures included total score on the copy and 20-minute delayed recall trials. The Stroop Color Word Test indexed mental speed, attention, and inhibition (executive function)[10] by computing times to 1) name colors, 2) read color words, and 3) name the ink color in which noncongruent color words are printed (i.e., interference trial). The Letter-Number Sequence Test served as a measure of working memory.[11] In addition, the Wide Range Achievement Test–Revised (WRAT-R) measured reading achievement[12] and served as a measure of education quality, since years of education has been shown to be inadequate in measuring the educational experience of African Americans.[13] The Center for Epidemiologic Studies–Depression Scale (CES-D) measured presence of significant depressive symptoms (i.e., score of 16 or higher).[14]

Functional MRI procedure. A subset of 22 women participated in an optional fMRI study, and seven HIV+ and four HIV− women had valid data. Invalid data were due to organic brain abnormality (n = 1), incomplete scan data (n = 2), technical problems (n = 2), and below-chance performance on the behavioral task (n = 6).

Blood oxygen level dependent fMRI was performed on a 3.0-Tesla whole-body scanner (Excite 2.0; GE Healthcare, Waukesha, WI). Twenty-four obliqued images prescribed parallel to the plane defined by points of intersection including both the anterior and posterior commissure were acquired through the cerebral hemispheres using gradient-echo echoplanar imaging (flip = 90°, echo time [TE] = 25 msec, voxel size = 3.125 × 3.125 × 5 mm^3, repetition time [TR] = 1.5 s, 24 slices). A single T1-weighted volume (three-dimensional IRfSPGR) was also acquired, plane = axial, TR = 9 msec, TE = 2.0 msec, flip angle = 25°, number of excitations = 1, bandwidth = 15.6 kHz, voxel size = 0.5 × 0.06 × 1.5 mm^3, slices = 120).

The fMRI memory test included two tasks—encoding and recognition—separated by a 20-minute delay during which structural scans were acquired. The memory test was adapted for the fMRI environment (e.g., block design, timing of stimulus presentation) from a PET task used in the Baltimore Longitudinal Study of Aging[15] with control conditions modeled after other fMRI studies.[16] A block design was used with a 3-s stimulus presentation and 1,500-ms interstimulus interval. The encoding task included 10 eight-item blocks (total = 80 stimuli). Blocks alternated between experimental (5 eight-item blocks for 40 novel words) and control conditions (5 eight-item blocks for 40 repeating stimuli). During both conditions, participants viewed targets individually on a back-projection screen and grasped a two-button response unit with the dominant hand. Participants were instructed to "try to remember each item for a later memory task" and to indicate that they had seen the item by pressing the index finger button whenever an item appeared. Participants were also told that the words "edition" and "region" would be repeatedly shown. Before entering the scanner, participants completed practice items to ensure that they understood the task.

Table 1 Participant characteristics as a function of serostatus

	Serostatus	
Variables	**HIV+ (n = 51)**	**HIV− (n = 12)**
Age, y, mean (SD)	43.37 (6.79)	42.92 (5.52)
Years of education, mean (SD)	11.86 (2.34)	12.92 (2.19)
WRAT Reading Test-Revised, mean (SD)	40.75 (8.30)	42.83 (7.72)
Race, %		
African American	84	92
Caucasian	10	0
Other	6	8
CES-D depressive symptoms, %		
No	57	58
Yes	43	42
Recent drug use, %*		
No	86	58
Yes	14	42
Past drug use, %		
No	24	25
Yes	76	75
Recent alcohol use, %		
Abstainer	59	25
<3 drinks/wk	27	50
3–13 drinks/wk	12	25
14 or more drinks/wk	2	0
History of >14 drinks/wk, %		
No	72	67
Yes	28	33
Current smoking, %		
No	47	42
Yes	53	58
Peak viral load (copies/mL)	169,169.6 (416,057.8)	
<10,000, %	23	—
≥10,000, %	77	—
Current viral load (copies/mL)		
<10,000, %	25	—
≥10,000, %	28	—
Undetectable	47	—
CD4 nadir†		
Absolute count/μL (median)	249.8 (187.8)	—
% <200	47	—
% >200	53	—
Current CD4		
Absolute count/μL	443.20 (316.22)	—

—Continued

Experimental blocks included unique, abstract nouns (e.g., system, position). Control blocks included repeated presentations of two abstract nouns (i.e., region, edition). This control condition places limited demands on memory because of repeated stimulus exposure, but, like the experimental condition, places demands on perceptual, motor, and lexical processes.

The recognition task included 20 eight-item blocks (total stimuli = 160) that alternated between experimental and control tasks. Each experimental block included target stimuli from the encoding task and distractor stimuli that had not been presented during the encoding task. Each control block involved the repeated presentation of "region" and "edition." The number of target and distractor items varied across control blocks. During both experimental and control recognition conditions, participants viewed targets individually on a back-projection screen and indicated whether they recognized the word from the encoding task by pressing the index finger button for "yes" responses and middle finger button for "no" responses. The primary outcome was the number correct during the experimental blocks (max = 80).

Neuroimaging analysis. We preprocessed and analyzed the data using Statistical Parametric Mapping (SPM2; Welcome Department of Cognitive Neurology, London, UK) (see table e-1 on the *Neurology*® Web site at www.neurology.org for a description of preprocessing steps). Data were modeled using a boxcar function convolved with a canonical hemodynamic response function and were analyzed using a two-level mixed effects model (random effect analysis). The WFU Pickatlas[17] and the AAL template[18] were used to define a priori regions of interest (ROIs), including the primary ROI, which included the hippocampus and parahippocampal gyrus. The PickAtlas small volume correction was applied during thresholding. Linear contrasts of the parameter estimates for effects of interest were obtained for each participant and then entered into a between-subjects analysis that produced a statistical parametric map of the *t* statistic at every voxel within the ROIs. The primary contrasts of interest were the group differences (HIV+ vs HIV−) in the experimental vs control conditions for the encoding and recognition tasks. Given the relatively small sizes of the ROIs and corresponding small number of voxel-wise comparisons, group differences are presented at a $p < 0.05$ (uncorrected) threshold and a minimum cluster size (k) of 30 contiguous voxels. This conservative cluster size was chosen to reduce the likelihood of Type II errors. To examine the functional significance of group differences, we extracted the first eigenvariate of all voxel values contained in a 3-mm radial sphere around the peak voxel for each participant and correlated these values with HVLT scores. Anatomic localization of significant clusters was determined by converting MNI coordinates to standard Talairach coordinates using a nonlinear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/downloads/MNI2tal/mni2tal.m) and by consulting brain atlases[19,20] and the Talairach Daemon.[21]

RESULTS

Cognitive results. HIV+ and HIV− participants were similar in mean age, years of education, educational quality as measured by the WRAT-R, race, and depressive symptoms (table 1). Participants were 86% African American, 5% non-Hispanic white, 8% Hispanic, and 1% other. Groups differed significantly on self-reported recent drug use, 14% of HIV+ vs 42% of HIV− women, χ^2 (1) = 4.91, $p < 0.05$, but not on previous drug use, current or past alcohol use, or current smoking. For HIV+ participants, the mean CD4

Table 1 Continued

	Serostatus	
Variables	HIV+ (n = 51)	HIV− (n = 12)
% <200	22	—
% >200	78	
HAART use, %		
HAART	61	—
Non-HAART	8	—
ARV naive	31	—
HCV, %		
Negative	41	67
Positive	59	33

Depressive symptoms measured by CES-D scale, with >16 cutoff. Recent and past drug use were ascertained by self-report. Recent refers to within 6 months of the most recent CORE visit.Undetectable viral load levels were fewer than 80 copies as measured by NucliSens test kit.
*χ^2 (1) = 4.91, $p < 0.05$ for group difference in recent drug use.
†CD4 nadir was the lowest CD4 level to date regardless of HAART therapy.
WRAT = Wide Range Achievement Test; CES-D = Center for Epidemiologic Studies Depression; HAART = highly active antiretroviral therapy; ARV = antiretroviral therapy; HCV = hepatitis C virus antibody.

Table 2 Performance on behavioral measures of verbal memory and other cognitive abilities in HIV+ and HIV− women: Results from unadjusted and adjusted group comparisons

	Unadjusted group means and group comparisons, mean (SD)		Regression results (standardized β)	
Outcome measures	HIV+	HIV−	Serostatus	Drug use
HVLT				
Total recall trials 1–3	22.45 (5.14)*	26.83 (4.97)	−0.32*	NS
Delayed recall	7.43 (2.62)†	9.08 (2.23)	−0.25†	NS
Recognition	10.45 (1.59)	10.75 (1.29)	NS	NS
Rey				
Copy	25.05 (5.34)†	28.71 (2.74)	−0.28†	NS
Immediate	9.99 (5.12)†	13.38 (5.03)	−0.26†	NS
Delay	10.25 (4.80)†	13.67 (5.80)	−0.26†	NS
Letter number sequence	10.67 (3.98)†	13.42 (3.96)	−0.38*	−0.40*
Stroop				
Color	66.45 (14.98)	62.17 (11.16)	NS	NS
Word	51.59 (11.47)‡	44.83 (8.47)	0.24‡	NS
Inhibition	132.75 (31.45)	121.17 (24.73)	NS	NS

Drug use included self-reported crack, heroin, or cocaine use since the previous Women's Interagency HIV Study visit (i.e., on average within the previous 6 months). Regressions were run because both serostatus and drug use differed between groups.
*$p < 0.01$.
†$p < 0.05$.
‡Trend, $p = 0.06$.
HVLT = Hopkins Verbal Learning Test, recognition computed as (hits − false-positive errors).

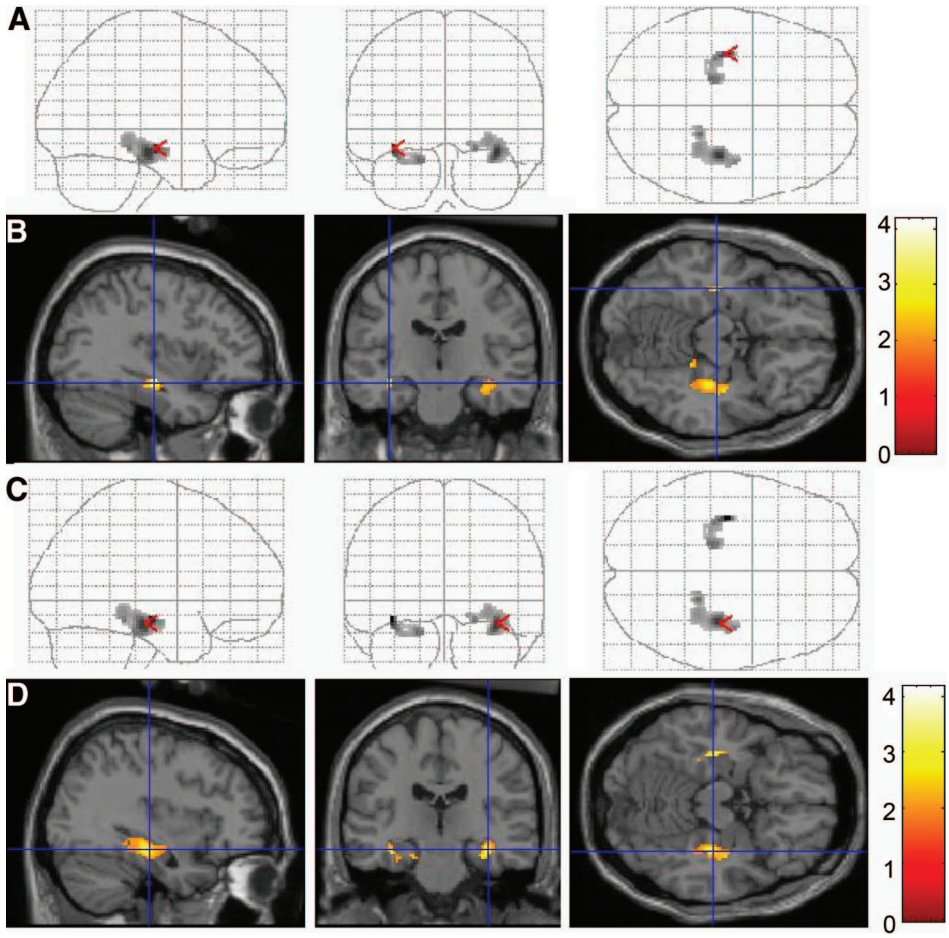
lymphocyte count at the time of testing was 443 (range, 0–1,345), and 22% had AIDS-defining (<200) CD4 counts.

Sixty-nine percent were prescribed antiretroviral therapy at testing, including HAART (61%) and non-HAART therapy (8%).[22] Current plasma viral load was undetectable for 47%, <10,000 for 25%, and >10,000 for 28% HIV+ participants. The hepatitis C antibody (HCV) test was positive for 33% of HIV− and 59% of HIV+ women, χ^2 (1) = 2.54, NS.

Three sets of analyses were performed on neuropsychological outcomes (SPSS 15.0 for Windows, Chicago, IL). First, *t* tests were performed to examine group differences in unadjusted scores. Next, data were analyzed using a stepwise multivariate regression with HIV serostatus and recent drug use as predictor variables. As shown in table 2, in both adjusted and unadjusted analyses, HIV+ women performed significantly worse than HIV− women on HVLT immediate and delayed recall, each Rey outcome, and Letter-Number Sequence subtest, $p < 0.05$. Finally, a stepwise multivariate regression with HIV+ women only was conducted using only demographic and clinical variables that correlated significantly with performance. Recent drug use predicted significantly lower scores on the Stroop Color trial. Analyses within HIV+ women showed no association between cognitive performance and HAART use. Higher viral load predicted lower scores on the Rey immediate recall, standardized $\beta = -0.271$, $p < 0.05$.

Neuroimaging results. HIV+ and HIV− women with valid neuroimaging data did not differ significantly in mean age (41.1 vs 42.8 years), education (11.7 vs 12.3 years), WRAT-R scores (43.9 vs 42.0), mean percent correct on the fMRI verbal memory task (63% vs 62%), or frequency of positive HCV antibody results (57% vs 50%), depressive symptoms (58% vs 75%), or drug use (29% vs 50%), all $p > 0.53$. African Americans comprised 91% of this subsample. Three HIV+ women reported being on HAART. In this subsample, scores on the immediate HVLT trials were lower in HIV+ (mean = 21.85) vs HIV− women (29.00), t (9) = 2.42, $p < 0.05$. Scores on the HVLT delayed trial were also lower (7.28 vs 8.75), though this was not significant, $p > 0.10$. The average lag time between cognitive testing and MRI was 102 days, and women were scanned during the follicular phase. In HIV+ women, educational attainment (i.e., WRAT-R score) predicted all cognitive outcomes. Additionally, depressive symptoms predicted verbal learning, verbal delayed recall, and Rey Copy, and age predicted delayed recall. Recent illicit drug use predicted delayed recall (trend only) and letter-number sequencing. Disease charac-

Figure 1 Greater activation in the hippocampus and parahippocampal gyrus in HIV− vs HIV+ women during encoding of novel words (experimental condition) minus repeated encoding of the same two words (control condition)

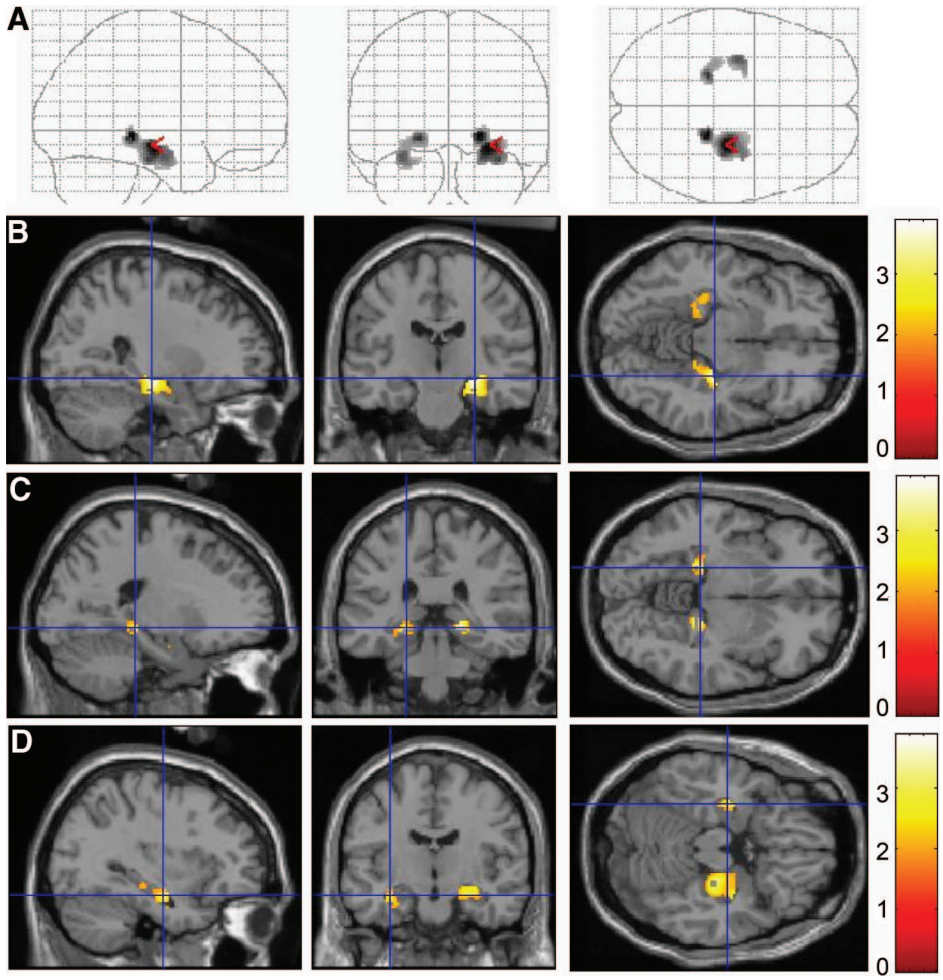


Results of primary region of interest analyses. Hippocampal and parahippocampal regions where HIV− women showed significant ($p < 0.05$) increases in activation compared to HIV+ women, including (A) glass brain sagittal, coronal, and axial projections centered on cluster with threshold at Talairach coordinates (−36, −18, −11); (B) right hemisphere blood oxygen level dependent (BOLD) signal superimposed on single subject fMRI template at Talairach coordinates (−36, −18, −11) at crosshairs; (C) glass brain sagittal, coronal, and axial projections centered on cluster with threshold at Talairach coordinates (36, −22, −12); and (D) left hemisphere BOLD signal superimposed on single subject fMRI template at Talairach coordinates (36, −22, −12) at crosshairs (see also figure e-1, where upper two scatterplots depict the functional significance of this activation). R = right hemisphere; L = left hemisphere.

teristics predicted performance only on the inhibition trial of the Stroop (i.e., highest viral load, trend).

Table e-1 and figure 1 show the results from the primary contrasts of interest in the hippocampus and parahippocampal gyrus. For the encoding contrast, there were no regions where HIV+ women showed greater activation compared to HIV− women. However, the HIV− group showed greater bilateral activation in the hippocampus and parahippocampal gyrus compared to HIV+ group. These differences were particularly pronounced in the left hemisphere (figure 1). This differential increase in activation by HIV− group reflects a combination of two influences: 1) greater activation in HIV− vs HIV+ women during the experimental encoding condition (i.e., encoding of unique words); and 2) greater activation in HIV+ vs HIV− group during the control encoding condition (i.e., repeated encoding of the same two words). In the recognition contrast, there were no regions where HIV− women showed greater activation compared to HIV+ women. However, the HIV+ group showed greater activation in the right hippocampus and bilateral parahippocampal gyrus (figure 2). This differential increase in activation by HIV+ vs HIV− group reflects 1) greater activation in the right parahippocampal gyrus and hippocampus in HIV+ vs HIV− women during the experimental recognition condition (i.e., recognition of unique words) and 2) greater activation in HIV− women in the left and right parahippocampal gyrus during the control recognition task (i.e., recognition of repeated words). In summary, compared to HIV−

Figure 2 **Greater activation in the hippocampus and parahippocampal gyrus in HIV+ vs HIV− women during recognition of unique words (experimental condition) minus repeated recognition of the same two words (control condition)**



Results of primary region of interest analyses. Hippocampal and parahippocampal regions where HIV+ women showed significant ($p < 0.05$) increases in activation compared to HIV− women, including (A) glass brain sagittal, coronal, and axial projections centered on cluster with threshold at Talairach coordinates (28, −20, −7); (B) left hemisphere blood oxygen level dependent (BOLD) signal superimposed on single subject fMRI template at Talairach coordinates (28, −20, −7) at crosshairs; (C) BOLD signal superimposed on single subject fMRI template at Talairach coordinates (−20, −31, −3) at crosshairs; and (D) right hemisphere BOLD signal superimposed on single subject fMRI template at Talairach coordinates (−32, −12, −15) at crosshairs (see also figure e-1 where lower two scatterplots depict the functional significance of this activation). R = right hemisphere; L = left hemisphere.

women, HIV+ women showed decreased hippocampal activation during encoding and increased hippocampal activation during recognition.

Table 3 shows the correlations between the magnitude of signal intensity in the hippocampus and HVLT memory indices. Higher signal intensity in the left hippocampus during encoding was associated with better performance on the HVLT (see figure e-1). Thus, in a hippocampal region where HIV+ women showed less activation compared to HIV− women, less activation was associated with worse memory on standardized tests. Higher signal intensity in the right hippocampus during recognition was associated with worse performance on the HVLT (see figure e-1). Thus, in a hippocampal region where HIV+ women showed more activation compared to HIV− women, more activation was associated with worse memory. There were no correlations between hippocampal activation and performance on the scanner task (r range −0.38 to 0.15, all $p > 0.24$).

We also conducted a post hoc, exploratory whole-brain analysis, using a more conservative threshold of $p < 0.01$, a minimum cluster size of 30 voxels, and an uncorrected cluster threshold of $p < 0.05$ (see table e-2). For the encoding contrast, significantly greater activation was evident for HIV− vs HIV+ women in clusters including (A) right middle temporal cortex, parahippocampal gyrus, and hippocampus; (B) left parahippocampal gyrus, middle temporal cortex, and hippocampus; and (C) right superior frontal gyrus. For that same contrast, HIV+

Table 3 Correlations between activation levels within significant clusters and scores on the Hopkins Verbal Learning Test

Condition, group contrast	k	Talairach coordinates x	Y	z	Z score	Correlations (r) with HVLT outcomes: Learning	Delayed recall
Encoding minus control							
HIV− > HIV+	112	−36	−18	−11	3.04	0.28	0.01
	365	36	−22	−12	2.63	0.74*	0.54‡
Recognition minus control							
HIV+ > HIV−	517	28	−20	−7	2.90	−0.53‡	−0.32
	107	−20	−31	−3	2.56	−0.56‡	−0.40
	116	−32	−12	−15	2.36	−0.83*	−0.62†

Positive x values indicate left hemisphere activation.
*$p < 0.01$.
†$p < 0.05$.
‡Trend, $p < 0.10$.
HVLT = Hopkins Verbal Learning Test.

vs HIV− women showed more activation in the right posterior cerebellum. For the recognition contrast, HIV− women vs HIV+ women showed greater activation in (A) right and left prefrontal cortex and (B) right precuneus, whereas HIV+ vs HIV− women showed greater activation in (A) left superior temporal gyrus and hippocampus and (B) right insular cortex. Thus, both the exploratory and ROI analyses indicate hippocampal dysfunction.

DISCUSSION The aim of this preliminary study was to investigate the integrity of episodic memory and patterns of neural activation during performance of a delayed verbal episodic memory test in a group of HIV-infected and at-risk, HIV− women. The cohort was 86% African American, frequently used illicit drugs, and had low socioeconomic status and low quality of education. In unadjusted analyses and analyses adjusting for drug use, HIV+ women vs HIV− women showed deficits in verbal learning, verbal delayed recall on the HVLT, visuoconstructional abilities, figural episodic memory, and working memory. Neuroimaging results indicated that compared to the HIV− group, the HIV+ group showed decreased hippocampal activation during encoding and increased hippocampal activation during recognition. The magnitude of hippocampal activation correlated with performance on the HVLT. The direction of these correlations indicated that underactivation of left hippocampus during encoding and overactivation of the right hippocampus during retrieval were associated with worse memory on the HVLT but not the scanner task. These findings suggest that HIV might affect the functional integrity of medial temporal systems underlying verbal memory performance.

Although HIV+ vs HIV− men perform worse on the HVLT,[23] most previous neuropsychological investigations have found little evidence of impairments in episodic verbal memory in HIV+ women.[24-28] Comparisons with the present study are limited by sample sizes of less than 45 women[24,25] and the use of factor scores[26] or dichotomous impaired vs unimpaired scores[27,28] as outcomes. The fMRI findings provide insights into the neurobiological underpinnings of the verbal memory impairment observed on the HVLT, because the fMRI task, like the HVLT, comprised a verbal encoding task, followed by a delayed retrieval task 20 minutes later. HIV+ women showed decreased activation of the hippocampus and parahippocampal gyrus during verbal encoding, particularly in the left hemisphere. These findings parallel findings where HIV+ vs HIV− men showed decreased activation in the right parahippocampal gyrus during encoding of scenes, a task that relies more heavily on the right hemisphere.[5] Our finding of overactivation of the hippocampus during recognition in HIV+ women argues against the view that hippocampal damage is producing a universal decrease in activation across tasks. Nevertheless, replication of the findings, particularly the neuroimaging findings, is important because the sample size was limited and six women were excluded for below-chance performance. Also, although fewer HIV+ vs HIV− women reported recent illicit drug use, among HIV+ women there was a trend for drug use to predict lower delayed verbal recall. The lower rate of recent drug use among HIV+ women is probably related to more treatment options and attention to drug use within HIV care settings. Future larger studies should investigate the individual and interactive effects of HIV infection and drugs of abuse on hippocampal function. Future studies should also focus on the possibility that the hippocampus contributes to the disruption of a larger neural network that drives HIV-associated memory impairments.

FINANCIAL SUPPORT

This work was supported by NIH/NIAID grant U01-AI-34993, the Chicago Consortium Women's Interagency HIV Study, to Mardge Cohen, MD (PI). Chicago WIHS is cofunded by the NCI and NIDA. Dr. Maki has received grant support from the National Institute on Allergy and Infectious Disease (NIAID), National Center on Complementary and Alternative Medicine, Soy Health Research Board, and Wyeth Ayerst. Dr. Maki has also received honorarium from the National Institutes of Health (NIH), Soy Research Foundation, Northwestern Memorial Hospital, the North American Menopause Association, Wyeth Pharmaceuticals, Fanizzi Associates, and Genaera Corporation. Dr. Cohen and Kathleen Weber received grant support from the NIAID and the National Institute on Mental Health (NIMH). Dr. Little has received research grants from the National Institute on Aging, NIMH, Congressionally Directed Medical Research Program, Department of Defense, and the Chicago Institute for Neuroscience and Neuroresearch. Dr. Little has also received honoraria from the Centre for Neuroskills and serves on the advisory board of the Sarah Jane Brain Foundation. Leah Rubin received NIH grant sup-

port from the NIMH. Dr. Gould received grant support from the University of Miami Developmental Center for AIDS Research (D-CFAR) and National Institute on Child Health and Human Development. Dr. Martin has received grant support from the NIAID, National Institute on Drug Abuse, Veterans Administration Merit Review Board, Glaxo-Wellcome, University of Illinois Campus Research Board, and University of Illinois Center for Research on Women and Gender. Dr Martin has received honorarium from the NIH, University of California-San Diego, San Francisco VAMC, and the Michael Smith Research Foundation.

Received September 25, 2008. Accepted in final form February 11, 2009.

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