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Michael K. Keutmann
The University of Illinois at Chicago

Raul Gonzalez
Florida International University

Pauline M. Maki
University of Illinois at Chicago

See next page for additional authors

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Authors

Michael K. Keutmann, Raul Gonzalez, Pauline M. Maki, Leah H. Rubin, Jasmin Vassileva, and Eileen M. Martin



Sex differences in HIV effects on visual memory among substance-dependent individuals

Michael K. Keutmann^a, Raul Gonzalez^b, Pauline M. Maki^a, Leah H. Rubin^a, Jasmin Vassileva^c and Eileen M. Martin^d

^aDepartment of Psychiatry, University of Illinois, Chicago, IL, USA; ^bDepartment of Psychology, Florida International University, Miami, FL, USA; ^cDepartment of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; ^dDepartment of Psychiatry, Rush University Medical Center, Chicago, IL, USA

ABSTRACT

HIV's effects on episodic memory have not been compared systematically between male and female substance-dependent individuals. We administered the Brief Visuospatial Memory Test–Revised (BVMT–R) to 280 substance-dependent HIV+ and HIV– men and women. Groups were comparable on demographic, substance use, and comorbid characteristics. There were no significant main effects of sex or HIV serostatus on BVMT–R performance, but HIV+ women performed significantly more poorly on delayed recall. This effect was most prominent among cocaine-dependent HIV+ women. Our findings are consistent with recent speculation that memory impairment may be more common among HIV+ women, particularly those with a history of cocaine dependence.

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“Episodic memory” refers to a neurocognitive system that enables human beings to remember experiences such as details of a conversation or a list of words read aloud (Tulving, 1972). Episodic memory is frequently impaired among individuals living with HIV/AIDS (Murji et al., 2003), with estimates ranging from 40–60% of HIV+ individuals (Carey et al., 2004; Heaton et al., 2011), and such impairment significantly predicts rates of employment and critically important daily functions such as adherence with antiretroviral therapy regimens (Heaton et al., 1994, 2004; Obermeit, Morgan, Casaletto, Grant, & Woods, 2015; Woods et al., 2008).

Episodic memory is critically dependent on the integrity of hippocampal and prefrontal cortical circuitry (Dickerson & Eichenbaum, 2010), and neuroimaging studies of HIV and episodic memory have successfully detected alterations in prefrontal and hippocampal activity compared with HIV– control groups (Castelo, Sherman,

Courtney, Melrose, & Stern, 2006; Maki et al., 2009; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008). Early studies of episodic memory¹ impairment among HIV+ individuals often emphasized its clinical similarities with the pattern of deficits commonly observed among patients with Parkinson disease and other basal ganglia disorders (Martin, 1994; Sadek et al., 2004; Woods, Moore, Weber, & Grant, 2009), such as impaired free recall with relatively intact recognition, suggesting deficient retrieval in the context of relatively preserved encoding. More recently, HIV-associated memory impairment has been attributed primarily to breakdown of executive, or “strategic,” processes that facilitate recall, such as clustering words by semantic categories (Gongvatana, Woods, Taylor, Vigil, & Grant, 2007; Woods et al., 2005); or employing contextual (source) information (Morgan et al., 2012; Morgan et al., 2009), reflecting dysfunction of frontostriatal systems (Castelo et al., 2006; Meyer et al., 2014). Although the

CONTACT Eileen M. Martin  eileen_martin@rush.edu  Department of Psychiatry, Rush University Medical Center, 1645 W. Jackson Blvd., Suite 600, Chicago, IL 60612, USA

¹Although prospective memory is considered a type of episodic memory, it was not investigated in the current study, and throughout this article, the term “episodic memory” refers specifically to recall of previous information (“retrospective”).

majority of studies of HIV's effects on episodic memory have focused on the acquisition and retention of verbal material, similar deficits in strategic organizational processing of visual information have also been reported (Morgan et al., 2009).

Studies of HIV effects on episodic memory have typically been conducted with all- or primarily male participant groups. However, recent findings in the literature suggest that the profile of HIV-associated neurocognitive impairment may differ for men and women (e.g., Maki & Martin-Thormeyer, 2009; Maki et al., 2014). A recent report from the Women's Interagency HIV Study (WIHS), the largest study ($N = 1521$) of HIV disease progression in women to date (Maki et al., 2014) demonstrated that HIV+ women performed significantly more poorly than HIV- women on measures of verbal episodic memory, but not on measures of processing speed (Symbol Digit Modalities Test) or executive functioning (Stroop, Trail Making Test B), which are typically impaired among HIV+ men (Woods et al., 2009). Maki et al. (2014) speculated that verbal memory deficits might be more prominent among HIV+ women than among men, but limited evidence is available to address this question, since few studies have compared neurocognitive performance of HIV+ men and women directly (Behrman-Lay et al., 2016; Hestad et al., 2012; Robertson et al., 2005; Royal et al., 2004) with inconsistent results.

Studies that have targeted neurocognitive performance specifically among substance-dependent HIV+ men and women (Failde-Barrido, Alvarez, & Simón-López, 2008; Martin, Gonzalez, Vassileva, & Maki, 2011, 2016; Wisniewski et al., 2005) have reported more consistent evidence of sex differences in neurocognitive performance, although the cognitive domains affected have varied, suggesting that sex differences in HIV-associated neurocognitive impairment could be more prominent among individuals with substance use disorders (SUDs).

Drugs of abuse increase HIV's neurotoxic effects through multiple mechanisms, including accelerated viral replication (Liang et al., 2008), increased immunosuppression (Dhillon et al., 2007), and interaction with viral proteins such as tat and gp120 to facilitate breakdown of the blood brain barrier and release of TNF- α and other neurotoxic cytokines. (Flora et al., 2003; Hauser et al., 2006; Hu, Sheng, Lokensgard, &

Peterson, 2005; Theodore, Cass, & Maragos, 2006). Recent literature has reported a range of independent and combined effects of a positive HIV serostatus and substances of abuse on neurocognition and neurobehavioral function (e.g., Rippeth et al., 2004; Schulte et al., 2005), and these findings may inform development of new cognitive and behavioral interventions for substance use or HIV prevention.

In the current study, we administered the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997), a standardized measure of visual episodic memory routinely employed in studies of HIV and neurocognition (e.g., Heaton et al., 2011; Woods et al., 2009), to a sample of 280 HIV+ and HIV- male and female substance-dependent individuals (SDIs) verified abstinent at testing. We compared participant groups' performance on indices of immediate and delayed recall, and on recognition memory. Goals of the study were twofold: to determine whether HIV+ SDIs show poorer episodic visual memory performance than HIV- SDIs with comparable demographic, substance use and comorbid characteristics; and to investigate potential unique and interactive effects of sex and HIV serostatus on visual memory. Thus our primary study hypotheses predicted that: (a) mean BVMT-R Total (immediate) Recall, Delayed Recall, and Recognition Memory scores would be significantly lower among the HIV+ than among HIV- SDIs; and (b) mean Total and Delayed Recall scores and Recognition Discrimination indices would be significantly lower among the HIV+ women than among HIV+ men.

Based on recent reports from the WIHS that crack cocaine use among HIV+ women increases short-term morbidity and risk of neurocognitive impairment (Cook et al., 2008; Meyer et al., 2013), we also tested exploratory hypotheses that: (a) BVMT-R immediate and delayed recall and recognition scores would be lowest among HIV+ women than in the other participant groups, and (b) this deficit would be most prominent among HIV+ women with a history of crack cocaine use. Finally, we explored potential sex and HIV serostatus effects on item-associative and source memory components of BVMT-R Delayed Recall (Morgan et al., 2012) that index the functional integrity of hippocampal and prefrontal-striatal systems, respectively.

Method

Participants

Participants included 128 HIV+ and 152 enzyme immunoassay (EIA)-verified HIV- substance-dependent individuals (SDIs) enrolled in a larger study of sex and HIV serostatus effects on neurocognition among substance users. Participants were recruited from infectious disease clinics at Rush University Medical Center (RUMC), University of Illinois at Chicago (UIC), and Ruth M. Rothstein CORE Center at Stroger (formerly Cook County) Hospital, from community agencies, and by word of mouth. All participants were 18–60 years old, were fluent in English, had eight or more years of education, and met *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*; American Psychiatric Association, 1994) criteria for abuse or dependence on at least one substance (primarily crack cocaine

or heroin—see Table 1) other than caffeine or nicotine. The majority of participants met *DSM-IV* criteria for SUDs in “early” (had not met full criteria for at least 30 days but less than 1 year) or “sustained” (had not met full criteria for more than 1 year) remission (see Figure 1).

The HIV+ participants were required to be ambulatory and capable of completing two 90–120-min testing visits without excess fatigue. Study participants were primarily urban-dwelling African-Americans, reflecting the demographic characteristics of HIV+ and HIV- SDIs receiving medical and substance use care through UIC, CORE, Rush, and local substance use treatment programs. Exclusion criteria included AIDS-defining or other central nervous system disorders such as stroke or brain tumor, closed head injury with loss of consciousness greater than 30 min, open head injury of any kind, schizophrenia, or current neuroleptic medications. Participants were informed at recruitment that breathalyzer and rapid

Table 1. Demographic, substance abuse, and comorbidity characteristics for all participants.

| | HIV- men | HIV+ men | HIV- women | HIV+ women | Statistic+ | <i>p</i> | Group comparisons |
|--|-------------|-------------|-------------|-------------|------------|----------|-------------------|
| <i>Demographics</i> | | | | | | | |
| <i>n</i> | 75 | 76 | 77 | 52 | | | |
| Age (years) | 51.0 (5.3) | 48.4 (7.4) | 48.7 (8.6) | 46.0 (8.3) | 4.51 | .004 | M- > W+ |
| Years of education | 12.5 (1.4) | 12.8 (1.8) | 12.4 (1.9) | 11.3 (2.0) | 8.00 | .001 | M-, M+, W- > W+ |
| WTAR-estimated FSIQ | 90.5 (11.3) | 90.5 (11.5) | 89.1 (10.6) | 84.8 (8.2) | 3.46 | .017 | M-, M+ > W+ |
| % African American | 95 | 87 | 82 | 90 | 16.89 | .05 | M- > W- |
| <i>Substance use</i> | | | | | | | |
| Mean ASI scores | | | | | | | |
| Alcohol | .07 (.16) | .06 (.11) | .03 (.11) | .01 (.03) | 2.96 | .04 | M- > W+ |
| Drug | .03 (.08) | .03 (.06) | .04 (.07) | .02 (.06) | 0.38 | .78 | |
| Mean KMSK scores | | | | | | | |
| Alcohol | 10.9 (2.9) | 10.9 (2.7) | 10.2 (3.3) | 10.6 (3.2) | 0.85 | .47 | |
| Cocaine | 12.2 (5.2) | 12.9 (4.8) | 12.4 (5.5) | 13.5 (4.6) | 0.87 | .46 | |
| Heroin/opiates | 5.5 (5.4) | 3.5 (4.7) | 7.0 (5.2) | 5.8 (5.4) | 6.32 | <.001 | W- > M+ |
| % DSM-IV dependence | | | | | | | |
| Alcohol | 55 | 64 | 57 | 67 | 2.94 | .40 | |
| Cannabis | 36 | 43 | 32 | 27 | 4.08 | .25 | |
| Cocaine | 72 | 70 | 70 | 83 | 3.24 | .36 | |
| Opioid | 35 | 22 | 49 | 36 | 12.18 | .007 | W- > M+ |
| % Injection drug user | 16 | 22 | 17 | 23 | 1.75 | .63 | |
| % Overdose | 17 | 15 | 22 | 21 | 1.78 | .62 | |
| % HCV+ | 12 | 26 | 12 | 15 | 6.67 | .08 | |
| <i>Comorbidities</i> | | | | | | | |
| % MDD | 20 | 29 | 38 | 39 | 7.37 | .06 | |
| PCL-C | 36.3 (13.3) | 34.9 (13.4) | 40.9 (15.3) | 39.7 (14.4) | 2.89 | .04* | |
| WURS | 28.1 (17.9) | 30.2 (21.7) | 30.4 (20.4) | 36.1 (23.8) | 1.56 | .20 | |
| SRPS | 48.6 (9.8) | 50.0 (9.8) | 50.0 (10.4) | 49.3 (9.5) | 0.32 | .81 | |
| <i>HIV disease</i> | | | | | | | |
| Mean CPE scores | | | | | | | |
| | | 7.7 (2.4) | | 7.1 (2.5) | 1.41 | .16 | |
| Md current CD4 (cells μL^{-1}) | | 467 | | 540 | 1494 | .12 | |
| Md nadir CD4 (cells μL^{-1}) | | 186 | | 300 | 1035 | .01 | W+ > M+ |
| % Undetectable VL | | 71 | | 77 | 1.75 | .19 | |
| % cART | | 96 | | 94 | .26 | .61 | |

Note. WTAR = Wechsler Test of Adult Reading; FSIQ = Full Scale Intelligence Quotient; ASI = Addiction Severity Index; KMSK = Kreek–McHugh–Schluger–Kellogg Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition; HCV = hepatitis C virus; MDD = major depressive disorder; PCL-C = PTSD (posttraumatic stress disorder) Checklist—Civilian Version; WURS = Wender Utah Rating Scale; SRPS = Levenson Self-Report Psychopathy Scale; CPE = CNS (central nervous system) Penetration Effectiveness; VL = viral load; cART = combination antiretroviral therapy; M- = HIV- men; M+ = HIV+ men; W- = HIV- women; W+ = HIV+ women. Mean values, with standard deviations in parentheses. +Chi-square tests were used for categorical data (%) and Mann Whitney statistic with Z correction for non-normally distributed data (Md). All other analyses used one-way analysis of variance (ANOVA).

*PCL-C (omnibus *F*) *p* = .04; W- vs. HIV+, *p* = .065 by Tukey honestly significant difference (HSD).

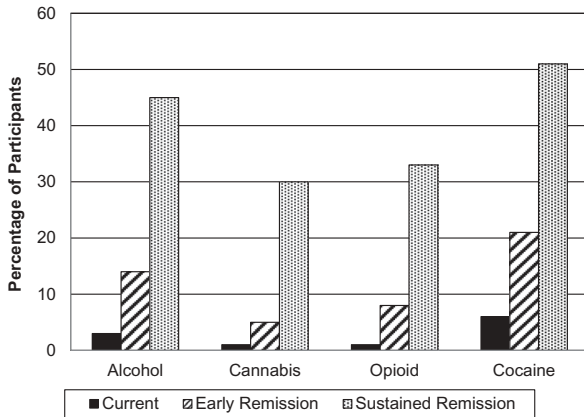


Figure 1. Percentage of all participants with *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM–IV)* diagnoses of “current,” “early remission,” and “sustained remission” for dependence on alcohol, cannabis, opioid, and cocaine.

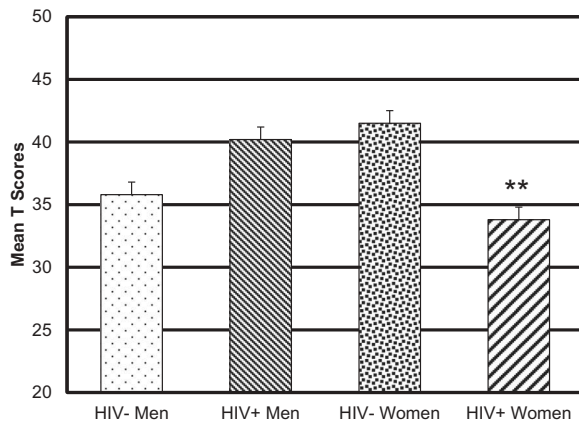


Figure 2. Mean Brief Visuospatial Memory Test–Revised (BVMt–R) delayed recall T-scores for cocaine-dependent male and female participants with and without a positive HIV serostatus. ** $p < .01$, HIV+ women < HIV– women, HIV+ men, HIV– men by one-way analysis of variance (ANOVA) with planned contrast.

urine toxicology screens would be administered at each study visit; the study visit would be terminated without payment if either test was positive. The study was approved by institutional review boards at Rush, the CORE Center, and UIC.

Procedure

Tests administered were part of a larger study protocol encompassing two 120–150-min visits at the

Department of Psychiatry at RUMC. Testing was conducted by bachelor’s level research assistants under the supervision of a board-certified clinical neuropsychologist (E.M.M.). Written informed consent was obtained on arrival for the first study visit. On both study visits, participants underwent a rapid urine toxicology screen that tested for 10 illicit and prescription drugs, including opioids, cocaine, cannabis, benzodiazepines, and amphetamine. Participants also completed a breathalyzer test to ensure abstinence from alcohol at the time of testing. If a potential participant tested positive for alcohol or other drugs, the visit was terminated, the participant received no payment, and the visit was rescheduled.² All participants were informed of these contingencies prior to the testing visit. They received \$75 cash compensation for their time and transportation costs at the completion of each study visit. Participants also received a \$10 bonus for passing both breathalyzer and urine drug screen tests and arriving at all appointments on time.

Measures

Clinical and personality measures

Each participant was administered the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) to estimate premorbid verbal IQ. Participants also completed a series of computerized and paper-and-pencil measures of potentially confounding conditions comorbid with substance use disorders. These included symptoms of mood disorder (Affective Disorder Module of the Structured Clinical Interview for DSM–IV, SCID; First, Spitzer, Gibbon, & Williams, 1995); posttraumatic stress disorder (PTSD Checklist–Civilian Version, PCL–C; Blake et al., 1995); attention deficit disorder (Wender Utah Rating Scale, WURS; Stein et al., 1995); and antisociality (Levenson Self-Report Psychopathy Scale, SRPS; Levenson, Kiehl, & Fitzpatrick, 1995). Finally, all HIV+ participants completed the central nervous system (CNS) Penetrance Effectiveness (CPE) scale (e.g., Letendre et al., 2008; Smurzynski et al., 2011), which ranks each antiretroviral compound in the participant’s current regimen according to its capacity to cross the blood–brain barrier; the total CPE

²Participants who tested positive for cannabis were not excluded if testing was negative for all other substances. The presence of THC metabolites in the urine did not necessarily indicate cannabis use within 1–2 days prior to testing due to its much longer half-life.

score is obtained by summing the individual ranks.

Substance use

Participants were administered Substance Abuse and Affective Disorder modules of the NetSCID (TeleSage, <http://www.telesage.com/products/netscid.html>), a computer-assisted version of the Structured Clinical Interview for DSM-IV (SCID; First et al., 1997) to derive DSM-IV substance use diagnoses for each participant. Additionally, participants completed the Addictions Severity Index (ASI; McLellan, Luborsky, Woody, & O'Brien, 1980) and the Kreek-McHugh-Schluger-Kellogg scale (KMSK; Kellogg et al., 2003). The KMSK is used to derive indices of peak lifetime severity of alcohol, cocaine, and opioid use; participants are queried about the amount of money spent, frequency of use, and duration of the period of their heaviest use.

Visual memory

All participants were administered the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997), a standardized clinical neuropsychological test of visual episodic memory routinely employed in neurocognitive studies of HIV (e.g., Heaton et al., 2011). The BVMT-R consists of three 10-s presentations of six geometric figures in a 2×3 array. After each presentation, the display is removed from view, and participants are asked to draw as many figures as they can recall in their correct positions on the page. Participants receive one point for each design recalled correctly and one point for each design's correct spatial location. The maximum raw score for the three initial learning trials is 36. Free recall is tested again following a 25-min delay. A recognition trial is then administered, in which the respondent is asked to identify which of 12 figures—six targets and six foils—were included among the original set of six designs.

The primary dependent variables used for this study were total (immediate) recall (the sum of points earned across the three initial learning trials) and delayed recall (the total number of points earned when recall is tested 25 min later, using norm-referenced T-scores (Benedict, 1997); and Recognition Discrimination Index raw scores (number of recognition hits minus false alarms; T-scores are not provided for this index).

Additionally, BVMT-R Delayed Recall raw scores were partitioned into separate "Item" and "Location" subscores, following methods introduced by Troyer and colleagues (Troyer et al., 2008) and previously employed by Morgan and colleagues to study BVMT-R performance among methamphetamine users (Morgan et al., 2012). Item (associative) and Location (source memory) scores provide indices of dissociable memory components critically dependent on integrity of hippocampal and frontostriatal systems, respectively (Kirwan & Stark, 2004). Each correctly recalled figure, regardless of its spatial position on the response sheet, received 1 point on the Item subscale. Any figure properly positioned in one of the six spatial locations on the response sheet received 1 point on the Location subscale. Both subscales yielded maximum scores of 6. We then transformed the raw Item and Location scores to T-scores using means and standard deviations for the HIV- group.

Overview of statistical analyses

Demographic, substance use, and comorbidity data for the four groups were compared using one-way analyses of variance (ANOVA) for parametric data. Tukey honestly significant difference (Tukey HSD) tests were used for post hoc testing. Mann-Whitney *U* tests with the *z* approximation were used for non-normally distributed data, and chi-square tests were used for categorical data. An alpha threshold of .05 was employed for all group comparisons. BVMT-R raw scores for both total and delayed recall were converted to age-adjusted T-scores using standardized norms (Benedict, 1997). Tests of the primary hypotheses employed Sex \times HIV Serostatus factorial analyses of covariance (ANCOVAs; selection of covariates is described below).

Results

Tests of potentially confounding variables

Prior to tests of the primary hypotheses, we compared demographic, substance use, and comorbid variables among the four groups to determine whether the groups differed significantly on any potentially confounding characteristics, or if HIV disease severity was different for men and women.

Table 1 provides detailed results of these group comparisons. Groups were generally comparable

overall on demographic variables (see Table 1 for omnibus F statistics); however, mean years of education were significantly lower for the HIV+ women than for the other three groups, $p < .001$ for all tests. HIV- men were older ($p = .002$) and had higher mean estimated Full-Scale Intelligence Quotient (FSIQ) scores than HIV+ women ($p = .02$). Mean estimated FSIQ scores were also lower for HIV+ women than for HIV+ men ($p = .03$). A higher percentage of the HIV- men than HIV- women were African American, $\chi^2(3) = 16.9, p = .05$.

The four participant groups were also generally comparable on comorbid characteristics, with the exception of a marginally significant trend ($p = .06$) toward higher PCL-C scores for the HIV- women than for the HIV+ men. Mean ASI³-Alcohol scores were significantly higher among HIV- men than among HIV+ women, $p = .04$. There were significant group differences in the prevalence of DSM-IV diagnoses of opioid dependence, $\chi^2(3) = 12.18, p = .007$: HIV- women had the highest rate of opioid dependence (49%), whereas HIV+ men had the lowest rate of the four groups (22%). Additionally, HIV- women obtained higher mean KMSK-Heroin scores than HIV+ men, $p < .001$.

HIV disease characteristics at testing were generally similar between men and women (see Table 1). However, median nadir CD4 count was significantly lower, Mann-Whitney $U = 1034.5, z = -2.55, p = .01$, and lifetime prevalence of immunologic AIDS was significantly more common among men than among women, $\chi^2(1) = 7.88, p = .005$. Essentially all HIV+ participants (96% of the HIV+ men and 94% of the HIV+ women) were prescribed combination antiretroviral therapy (cART).

Brief Visuospatial Memory Test-Revised

Mean Total and Delayed Recall T-scores and mean Recognition Discrimination Index (RDI) raw⁴ scores were positively correlated with WTAR-

estimated Verbal IQ scores ($r = .33, p < .005$; $r = .34, p < .001$; $r = .13, p < .05$, respectively), but not with age ($|r| \leq .09, p \geq .14$ for all tests), ASI-Alcohol scores ($|r| \leq .10, p \geq .18$ for all tests), or KMSK-Heroin scores ($|r| \leq .14, p \geq .18$ for all tests). Primary analyses of BVMT-R data were therefore conducted using Sex \times HIV Serostatus ANCOVA, controlling for WTAR-estimated IQ scores.⁵

Hypothesis 1 predicted that HIV+ SDIs would perform significantly more poorly on mean BVMT-R Total (immediate) and Delayed Recall T-scores and RDI raw scores than HIV- SDIs. There were no significant main effects of HIV serostatus for mean Total Recall T-scores, $F(1, 265) = 1.72, p = .19$; Delayed Recall T-scores, $F(1, 265) = 1.50, p = .22$; or mean RDI scores, $F(1, 265) = 0.51, p = .48$.

Hypothesis 2 predicted that HIV+ women would show poorer visual episodic memory than HIV+ men. Analyses of Delayed Recall T-scores revealed a significant Sex \times HIV Serostatus interaction, $F(1, 265) = 4.56, p = .03, \eta_p^2 = .02$. Analysis of simple main effects revealed that mean Delayed Recall T-scores were significantly lower for the HIV+ women than for HIV- women, $p = .03$, but not for HIV+ women than for HIV+ men, $p = .14$. The Sex \times HIV Serostatus interaction did not reach statistical significance for mean Total Recall T-scores, $F(1, 265) = 2.21, p = .14$; or for mean Recognition Discrimination Index scores, $F(1, 265) = 0.32, p = .57$.

Exploratory Hypothesis 1 predicted that mean Total and Delayed Recall T-scores and mean RDI raw scores would be lowest for the HIV+ women compared with the other three participant groups. One-way ANOVAs with planned contrasts (1 1 1-3) revealed that the HIV+ women showed a nonsignificant trend toward lower mean Total Recall T-scores than the other three groups, $t(276) = 1.81, p = .07$; while mean Delayed Recall T-scores were significantly lower for the HIV+

³ASI data were not available for approximately 91 participants; this measure was added to the protocol after data collection was initiated, and (unlike the BVMT-R) was administered during the second testing visit. Thus, interpretation of this finding is necessarily tentative.

⁴Published norm-referenced T-scores were available for Total and Delayed Recall, but not for the Recognition Discrimination Index. By convention we computed RDI by subtracting the total false positives from the total recognition hits.

⁵Years of education were significantly correlated with BVMT-R Total and Delayed Recall and RDI scores ($r = .26, .27, \text{ and } .19$, respectively, $p < .01$). However, forward linear regression analyses of BVMT-R scores with WTAR and Education as predictors showed evidence of collinearity (eigenvalue = .007). Thus analyses of BVMT-R scores employed WTAR scores but not education as covariates.

women than for the other groups, $t(276) = 2.58$, $p = .01$; there were no significant group differences in mean RDI scores between HIV+ women and the other three groups, $t(276) = 0.84$, $p = .40$.

Exploratory Hypothesis 2 predicted that mean Total and Delayed Recall T-scores and mean RDI scores would be lowest among cocaine-dependent HIV+ women compared with cocaine-dependent HIV+ men, HIV- women, and HIV- men. To test this hypothesis, we repeated the one-way ANOVAs of mean Total Recall and Delayed Recall T-scores and mean raw RDI scores with cocaine-dependent participants only ($n = 204$). Planned contrasts (1 1 1-3) revealed that cocaine-dependent HIV+ women obtained significantly lower mean Total Recall, $t(200) = 2.15$, $p = .03$, and Delayed Recall T-scores, $t(200) = 2.99$, $p = .003$, than the other groups, but mean RDI scores for cocaine-dependent HIV+ women did not differ significantly compared with those of the other three cocaine-dependent groups, $t < 1$. Figure 2 shows mean Delayed Recall T-scores for the four groups of cocaine-dependent participants.

Breakout analyses of cognitive components of BVMT-R Delayed Recall

Analyses of mean Item and Location T-scores were conducted in the same order as the analyses of BVMT-R Total, Delayed, and Recognition scores (see above). Hypothesis 1: There were no significant main effects of HIV serostatus for either the mean Item or Location Delayed Recall T-scores, $F < 1$ for both tests. Hypothesis 2: Analyses of mean Item Delayed Recall T-scores revealed a significant Sex \times HIV Serostatus interaction, $F(1, 262) = 4.56$, $p = .03$, $\eta_p^2 = .02$. Tests of simple main effects revealed that the HIV+ women performed significantly more poorly than HIV- women ($p = .04$), but not than HIV+ men ($p = .24$). The Sex \times HIV Serostatus interaction for mean Location Delay T-scores was nonsignificant, $F(1, 262) = 1.76$, $p = .18$. Exploratory Hypothesis 1: One-way ANOVA of mean Item Delay T-scores with planned contrast (1 1 1-3) revealed that mean scores for HIV+ women were significantly lower than those of the other groups, $t(269) = 2.01$, $p = .05$.

Exploratory Hypothesis 2: Among the cocaine-dependent participants, one-way ANOVA of mean Item Delayed Recall T-scores using planned contrast (1 1 1-3) revealed that mean scores for HIV+

women were significantly lower than those of the other groups, $t(193) = 2.10$, $p = .04$.

Additional analyses

We performed a series of correlations between BVMT-R Total and Delayed Recall T-scores with HIV disease, substance use, and other demographic characteristics. There were no significant correlations between the HIV+ participants' current or nadir CD4 counts or HIV RNA levels with mean BVMT-R Total or Delayed Recall T-scores or with RDI scores, $|r| \leq .14$, $p > .11$ for all tests. Mean BVMT-R Total and Delayed Recall T-scores and raw Recognition Discrimination Index scores were significantly correlated with CNS Penetration Effectiveness Scale Scores (Total Recall: $r = .24$, $p = .01$; Delayed Recall: $r = .24$, $p = .03$; RDI: $r = .19$, $p = .04$). We repeated the analyses of mean BVMT-R Total and Delayed Recall T-scores and RDI scores between the HIV+ men and women, controlling for WTAR IQ estimates and CPE scores, but results were unchanged.

Among the comorbid variables, mean Self-Report Psychopathy Scale (SRPS) scores correlated significantly and inversely with mean Total and Delay Recall T-scores, $r = -.24$ and $-.26$, $p < .001$, respectively, but not with RDI scores, $r = -.05$, $p = .43$. We repeated the Sex \times HIV Serostatus ANCOVAs comparing Immediate and Delayed Recall T-scores and Recognition while controlling for SRPS and WTAR IQ scores, and results were unchanged. We also repeated the analyses of the mean BVMT-R Total and Delayed T-scores of HIV+ men and women controlling for mean SRPS, WTAR IQ, and CPE scores, and results were unchanged. No significant correlations were observed between BVMT-R Total and Delayed Recall T-scores or RDI raw scores with any substance use variable, $p > .10$ for all tests.

Discussion

This study compared visual episodic memory performance among 280 HIV+ and HIV- men and women with a history of substance dependence but verified abstinent at testing. All participants completed the Brief Visuospatial Memory Test-Revised and a series of measures of substance abuse and comorbid psychiatric disorders and personality traits with potentially confounding effects on memory performance.

Contrary to prediction, we found no evidence of generalized visual memory impairment among HIV+ compared with HIV- SDIs. Rather, we found consistent evidence of selective impairment on the BVMT-R delayed recall component among the HIV+ women. This deficit was most prominent among HIV+ women with a history of cocaine dependence, and was only detectable on the cue/associative (item) component of BVMT-R recall.

The groups were generally comparable on demographic characteristics, with the exception of age, education, and estimated premorbid IQ; mean age was lowest for the HIV+ women and was uncorrelated with BVMT-R performance, which argues against attributing the HIV+ women's poorer performance to age effects, and we controlled for estimated IQ (but not education, due to collinearity between education and WTAR IQ scores) in all subsequent analyses of BVMT-R data. Participant groups were also generally comparable on substance use and comorbid characteristics. Notably, the HIV- women showed a significantly higher prevalence of opioid dependence, and severity of peak opioid use, and the HIV- men reported significantly more alcohol use in the last 30 days suggesting that the HIV+ women's poorer delayed recall performance was not readily explained by nonspecific group differences in addiction severity. Similarly, HIV+ women's impaired delayed recall could not be attributed to sex differences in HIV disease severity, as nadir CD4 counts were significantly lower for HIV+ men than for HIV+ women, and there were no significant associations between BVMT-R performance and viral load or AIDS-defining CD4 counts.

The HIV+ women's memory performance was characterized by impaired free recall with no evidence of rapid forgetting and essentially intact recognition, consistent with reports from previous studies of verbal episodic memory performance among HIV+ individuals (Maki et al., 2015; Woods et al., 2005). However, our findings could not address in detail the critically important question of whether the HIV+ women's poor performance was characterized primarily by impairment in "executive" strategies such as semantic clustering, since these constructs are not captured

adequately by the BVMT-R.⁶ Studies of verbal episodic memory performance, which will provide semantic clustering data, are currently in progress in our lab.

Our findings suggest that performance on episodic memory tasks is not identical for HIV+ men and women: Breakout analyses revealed that HIV+ women were selectively impaired on the "item" but not the "source" component of mean BVMT-R Delayed Recall scores. Notably, "item" and "source" components of episodic memory are considered indices of the integrity of hippocampal and frontostriatal circuitry (Morgan et al., 2012), respectively, raising the question of whether hippocampal involvement might be more common or severe among HIV+ women than among HIV+ men. HIV+ women show alterations in hippocampal function that correlate with performance on episodic memory tasks outside of the scanner (Maki et al., 2009). This hippocampal vulnerability may be compounded by low estrogen levels, as estradiol levels are lower in HIV+ women (Karim et al., 2013; Santoro et al., 2007), particularly cocaine-dependent HIV+ women (Santoro et al., 2007), than in HIV- women. Additionally, cortisol levels are high in recently abstinent cocaine-dependent women (Fox, Hong, Siedlarz, & Sinha, 2008), and high levels of cortisol are associated with decreased memory performance, particularly when estrogen levels are low (Maki et al., 2015). Inferences from study data are necessarily limited, since data regarding contraceptive use and menstrual cycling among our female participants were not available; however, studies of neurocognitive performance and fluctuations in sex steroid levels among HIV+ and HIV- women tested at two different phases of the menstrual cycle are currently in progress by our group, and findings may shed light on potential cognitive and neural mechanisms of episodic memory impairment among HIV+ women.

In contrast with our findings, Morgan and colleagues (Morgan et al., 2009) reported that HIV+ individuals performed significantly more poorly than controls on the source but not the item component (Morgan et al., 2009) of episodic visual memory testing. However, our findings do not necessarily contradict (Morgan et al.'s 2009) report, as our two studies differ in several critical

⁶However, Meyer et al. (2013) reported that HIV+ women showed significantly poorer semantic clustering than HIV- women on a verbal learning task.

methodological features. HIV+ participants in the Morgan study were 93% male with a much lower (53%) prevalence of substance dependence. Additionally, Morgan et al. employed a modified spatial Self-Ordered Pointing Task (Petrides & Milner, 1982) with an array of 12 visual designs presented over multiple trials. The designs appear in a new spatial arrangement at the start of each trial, and the participant must identify a design that had not been previously selected. In contrast, the BVMT-R presents an identical spatial array of six figures over three trials. Morgan et al.'s task appears considerably more difficult than ours, with greater demands on working memory processing and greater engagement of prefrontal-striatal systems.

Our data are also consistent with reports from the WIHS that disease-related morbidity is higher, and risk of neurocognitive impairment is increased, among HIV+ women who have used crack cocaine (Cook et al., 2008; Meyer et al., 2013). By contrast, we found no evidence of selective visual memory impairment among HIV+ cocaine-dependent men, consistent with previous reports of varying neurocognitive effects of cocaine use among primarily male HIV+ participant samples (Durvasula et al., 2000; Meade, Conn, Skalski, & Safren, 2011; but cf. Meade, Towe, Skalski, & Robertson, 2015). More basic and clinical studies are needed to characterize the increased risk of neurocognitive impairment among HIV+ cocaine-dependent women in more detail and to address the question of whether this vulnerability is HIV-specific; we note that regardless of HIV serostatus, women are more vulnerable to stimulant addiction than men: The addiction literature indicates that women escalate their use of stimulants more rapidly, and relapse more readily, than men (Becker & Hu, 2008; Greenfield, Back, Lawson, & Brady, 2010).

The current results suggest that HIV's effects on episodic memory processing are not modality-specific and can be detected on tests of visual as well as verbal memory; this raises the question of whether HIV disrupts core component mechanisms routinely engaged by episodic memory processing, similar to earlier findings by our group that working memory deficits are detectable among HIV+ SDIs regardless of information type or task demands (Bartok et al., 1997; Farinpour et al., 2000; Martin et al., 2001, 2003). However, preliminary findings from our group on verbal and

spatial episodic memory performance have not provided strong support for this hypothesis: For example, both HIV+ men and women showed impaired delayed recall on a measure of spatial/navigational learning compared with HIV- groups (Martin et al., 2015a); in contrast, HIV+ women, but not HIV+ men, showed impaired immediate but not delayed recall compared with HIV- groups on the Hopkins Verbal Learning Test (HVLT; Martin et al., 2015b). We note that the earlier working memory studies by our group were conducted with all- or predominantly male study samples, indicating that our proposal that HIV affects core working memory mechanisms may be applicable only to men; studies of working memory performance by HIV+ and HIV- male and female SDIs are currently in progress in our group (Martin et al., *in press*).

Notably, successful BVMT-R performance requires higher order visual processing of objects and spatial locations engaged by different neural circuits (Ungerleider, 1995; Ungerleider & Haxby, 1994). Neurons in the parietal association cortex and superior and middle temporal visual association cortex form the "dorsal stream," coding objects' spatial location (Rizzolatti & Matelli, 2003). Neurons in the inferior temporal visual association cortex form the "ventral stream," which processes information regarding the form, or "what" of objects, allowing for learning and remembering visual objects (Reddy & Kanwisher, 2006). Importantly, functional magnetic resonance imaging (fMRI) studies have documented disruption of fronto-striato-parietal (Schweinsburg et al., 2012) as well as fronto-striatal networks (Du Plessis et al., 2014) among HIV+ individuals. Follow-up studies will be needed to investigate sex- or HIV-related differences in object and spatial visual processing among substance-dependent individuals; a positive finding would suggest that disruption of upstream visual processing could contribute to poor performance on visual memory testing.

We found a significant positive correlation between BVMT-R delayed recall T-scores and CPE scores, indicating that memory scores were higher among HIV+ individuals receiving highly CNS-penetrant antiretroviral therapy (ARV) than among those on regimens with lower capacity to cross the blood-brain barrier. The significance of this incidental finding is unclear, however, since the literature on the relationship between neurocognitive

performance and ARV CNS penetrance is mixed (for a recent discussion, see Wilson, Martin-Engel, Vassileva, Gonzalez, & Martin (2013)).

The study has several limitations. These findings may not be generalizable to HIV+ women who are non-substance-dependent or dependent on substances other than cocaine; additionally, the polydrug use by virtually all our participants poses significant limits to interpretation of our finding of poorer performance by cocaine-dependent HIV+ women. This finding is consistent with previous reports from the WIHS and from our group, but detailed neuroimaging, neuroendocrine, and neuropharmacological studies will be critically important, to test the hypothesis that HIV+ cocaine-dependent women are at increased risk for neurocognitive impairment, and to investigate how known sex differences in the addictive process might complicate study findings. Finally, although our study was designed to limit threats to validity posed by psychiatric and medical disorders comorbid with substance dependence, these factors cannot be eliminated entirely, requiring careful monitoring and judicious application of inclusion/exclusion criteria.

This study is among the first to compare directly episodic memory processing among HIV+ male and female substance users. Sophisticated functional neuroimaging studies drawing from the addiction and cognitive neuroscience literature will enable us to investigate the integrity and underlying mechanisms of different episodic memory components among men and women living with HIV/AIDS.

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