



# Verbal and spatial working memory among drug-using HIV-infected men and women

Eileen Martin<sup>1</sup> · M. K. Keutmann<sup>2</sup> · J. S. Fogel<sup>2</sup> · P. M. Maki<sup>2,3</sup> · R. Gonzalez<sup>4</sup> · J. Vassileva<sup>5</sup> · L. H. Rubin<sup>3,6</sup> · D. Hardy<sup>7</sup>

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## Abstract

Working memory (WM) is a critical component of many neurocognitive functions. The literature has demonstrated consistently that WM impairment is more frequent and severe among substance-dependent individuals (SDIs) infected with HIV compared with uninfected SDIs; however, the SDIs who participated in these previous studies were primarily male. There are few published data on WM performance among HIV+ women with or without substance use disorders, and essentially no direct comparisons of WM performance between HIV+ men and women, regardless of substance use. We investigated potential sex and serostatus effects on WM among a sample of 360 SDIs (114 with HIV; 66% female) verified abstinent from alcohol and drugs of abuse at testing and generally comparable on substance use and comorbid characteristics. Participants were tested with the n-back task, a well-established WM measure that is sensitive to HIV-associated cognitive impairment. HIV+ men and women performed spatial and verbal versions of the n-back significantly less accurately compared with HIV– participants. Women showed slower response times compared with men on both versions, regardless of HIV serostatus. Individuals dependent on cocaine showed faster RTs compared with non-dependent users, but this effect was not apparent among opioid- or alcohol-dependent groups. Findings on n-back accuracy are consistent with our previous proposal that WM impairment represents a signature deficit among HIV+ SDIs; however, WM impairment appears less common among HIV+ women without a substance use history. The pattern of sex differences in response speed but serostatus effects on response accuracy is comparable to a recent report by our group of sex differences in learning speed but serostatus effects on delayed recall.

**Keywords** HIV · Drug use · Sex differences · N-back · Working memory · Prefrontal cortex

## Introduction

Executive functions, such as decision making and assessing risk, are often impaired among HIV-seropositive (HIV+) individuals, reflecting disrupted activity in prefrontal-striatal circuitry (Walker and Brown 2017). Deficits in working memory, broadly defined as the executive capacity to maintain and process information on a temporary basis (Bartok et al. 1997; Goldman-Rakic 1991; Goldman-Rakic 1995), are particularly common among individuals living with HIV/AIDS (Chang et al. 2001; Bartok et al. 1997; Hinkin et al. 2002; Stout et al. 1995) and impede the capacity to engage in everyday functioning, manage finances, and maintain employment.

Working memory is frequently impaired among substance-dependent individuals (SDIs) (Hester and Garavan 2004; Rapeli et al. 2006; Yi et al. 2017), but these deficits are more common and severe among SDIs infected with HIV. In a series of cognitive neuropsychological studies, our group has

✉ Eileen Martin  
eileen\_martin@rush.edu

<sup>1</sup> Department of Psychiatry, Rush University Medical Center, 1645 W. Jackson Blvd, Chicago, IL 60612, USA

<sup>2</sup> Department of Psychology, University of Illinois-Chicago, Chicago, IL, USA

<sup>3</sup> Department of Psychiatry, University of Illinois-Chicago, Chicago, IL, USA

<sup>4</sup> Department of Psychology, Florida International University, Miami, FL, USA

<sup>5</sup> Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

<sup>6</sup> Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

<sup>7</sup> Department of Psychology, Loyola-Marymount University, Los Angeles, CA, USA

shown that HIV+ SDIs are consistently impaired compared with HIV-seronegative (HIV−) SDIs on a range of verbal and spatial tasks that engage working memory by varying processing demands and information load (e.g., Bartok et al. 1997; Farinpour et al. 2000; Martin et al. 2001). Based on these findings, we have posited that impaired working memory might be a signature deficit among HIV+ SDIs (Martin et al. 2001), a finding with considerable clinical significance, as recent studies have employed working memory successfully as a target for cognitive training for substance use disorders (Wesley and Bickel 2014; Bickel et al. 2014) and for HIV-associated neurocognitive disorder (Chang et al. 2017).

Previous studies of HIV serostatus effects on working memory among SDIs were conducted with largely male study samples. However, increasing evidence indicates that neurocognitive profiles are not identical for HIV-infected men and women (Maki and Martin-Thormeyer 2009; Martin et al. 2011, 2016; Hestad et al. 2012; Royal et al. 2016; Keutmann et al. 2017; but cf. Behrman-Lay et al. 2016; Robertson et al. 2004); further, sex differences have been found in multiple components of the addictive processes (Wetherington 2010), suggesting that sex differences in neurocognitive profiles among HIV+ SDIs might be more pronounced. We recently reported that HIV+ female but not male SDIs performed more poorly compared with HIV− SDIs on a measure of decision making under risk (Martin et al. 2016). This finding suggests that obtaining a more comprehensive profile of sex and serostatus effects on executive function is critically important as a first step toward identifying possible sex differences in HIV's disruptive effects on striatal-prefrontal cortical systems.

In the current study, we administered computerized verbal and spatial versions of the n-back task, a well-established working memory measure with known sensitivity to HIV-associated neurocognitive deficits (e.g., Hinkin et al. 2002; Chang et al. 2001), to a sample of 360 SDIs with and without a positive HIV serostatus. The primary goal of this study was to investigate potential sex and HIV serostatus effects on n-back performance by SDIs. We hypothesized that HIV+ participants would perform both verbal and spatial n-back tasks significantly more poorly compared with HIV− participants.

Working memory has not been well studied among HIV+ women (but cf. Maki et al. 2015; Sundermann et al. 2015). However, to our knowledge, n-back performance between HIV+ and HIV− men and women has not been compared directly. Consequently, we formulated a more conservative hypothesis regarding potential sex differences. Based on the non-clinical literature (e.g., Reed et al. 2017; Duff and Hampson 2001), we predicted that HIV+ and HIV− female participants would perform significantly more poorly compared with HIV− and HIV+ men on the spatial n-back, and that the magnitude of this male advantage (i.e., the extent of the sex difference) would differ significantly between HIV+

men and women compared with HIV− men and HIV− women, resulting in a significant sex  $\times$  HIV serostatus interaction.

## Method

### Participants

We tested 114 HIV+ ( $n = 51$  females) and 246 ( $n = 187$  females) enzyme immunoassay (EIA)—verified HIV—SDIs enrolled in a larger study of sex and HIV serostatus effects on neurocognition. Participants were recruited from Infectious Disease Clinics at Rush, the University of Illinois-Chicago (UIC), and the Ruth M. Rothstein CORE Center at Stroger (formerly Cook County) Hospital, community agencies and by word of mouth. All participants were age 18–60 years, fluent in English, had eight or more years of education, and met DSM-IV criteria for dependence on at least one substance other than caffeine or nicotine. Exclusion criteria included AIDS-defining or other CNS disorders, closed head injury with loss of consciousness greater than 30 min, open head injury of any kind, schizophrenia, or current antipsychotic medications. Participants were informed at recruitment that a breathalyzer and rapid urine toxicology screen would be administered at each study visit and that the visit would be terminated without payment if either test was positive. The study was approved by the Institutional Review Boards at Rush, the Core Center, and the UIC.

### Procedure

Tests administered were part of a larger study protocol administered over two 120–180-min visits to the Department of Psychiatry at Rush University Medical Center. Testing was conducted by bachelor's level research assistants under the supervision of a board-certified clinical neuropsychologist (EMM). Written informed consent was obtained on arrival for the first study visit. To ensure abstinence from drug and alcohol at the time of testing, on both study visits, the participant provided a urine sample for a ten-panel rapid toxicology screen (DrugCheck® NxStep) that tested for ten street and prescription drugs, including heroin, cocaine, cannabis, benzodiazepines, and amphetamines, as well as a breathalyzer test for alcohol. If a potential participant tested positive, the visit was terminated, the participant received no payment, and the visit was rescheduled.<sup>1</sup> 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

<sup>1</sup> These procedures were followed in all instances with the single exception that participants 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.

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 subject was administered the Wechsler Test of Adult Reading (WTAR: Wechsler 2001) to estimate premorbid verbal intellectual function. Subjects also completed a series of paper-and-pencil measures of conditions comorbid with substance use disorders with potentially confounding effects on neurocognition including post-traumatic stress symptoms (PTSD Checklist—Civilian Version; Keane et al. 1987), attention deficit disorder (Wender Utah Rating Scale; Stein et al. 1995), and antisocial personality traits (Levenson Self-Report Psychopathy Scale; Levenson et al. 1995).

### Substance use

Trained interviewers administered a Web-based computer-assisted version (NetSCID; TeleSage, <http://www.telesage.com/products/netscid.html>) of the Affective Disorders and Substance Abuse Modules of the Structured Clinical Interview for DSM-IV (SCID-SAM; First and Gibbon 2004), and the Addictions Severity Index (McLellan et al. 1980). Participants also completed the Kreek–McHugh–Schluger–Kellogg scale (Kellogg et al. 2003), a paper-and-pencil measure that indexes the severity of peak lifetime use of alcohol, cocaine, and opioids, derived from the participant's estimate of the amount of money spent, time duration, and frequency of use at the time of their maximum use of each substance. Finally, CNS Penetration Effectiveness (CPE) scores (Letendre et al. 2008), which index the capacity of specific antiretroviral compounds to cross the blood brain barrier were computed for all participants prescribed cART. Table 1 contains demographic, substance use, and comorbidity data for the individual groups (HIV– men, HIV+ men, HIV– women, HIV+ women).

### N-back task

Verbal and spatial working memory performance was assessed using a modified version of the computerized n-back task employed previously by Hinkin et al. (2002). This version is advantageous in that verbal and spatial conditions presented identical stimulus displays in the same order of appearance with the goal of minimizing extraneous variance associated with visual or perceptual processing.

The task was programmed by one of the authors (DLH) using SuperLab® version 4.5 software and administered on a Hewlett-Packard PC (Elite 8300). In this n-back task,

participants were presented with a pseudo-random series of letters (A, a, G, g, H, h, T, and t) one at a time on a computer monitor. Letters were black on a white background and subtended  $1.9 \times 1.6$  degrees (with an average viewer distance of 60 cm from the computer screen). Location of each target letter was pseudo-randomly assigned to 2.5 degrees above, below, left, or right of a central fixation (+). Thus, at the start of each trial, a small cross appeared at central fixation; 2500 ms later, a target letter appeared. The fixation and target letter remained on the screen until a participant response (a button press) was made. After the response (and disappearance of the fixation and target letter), there was a blank 1000-ms interstimulus interval, whereupon the fixation cross appeared for the next trial, followed by a target letter, and so on (see Fig. 1).

Working memory difficulty was manipulated via one-back and two-back versions of the task. In the one-back task, each letter had to be compared with the prior presented letter. In the verbal condition, the verbal identity of the presented letter was compared to the verbal identity of the previous letter. If the verbal identity matched (e.g., a currently presented *H* was preceded by an *H* or *h*, note that case of letter does not matter), then a “yes” response was required (by pressing a green left button on the response box with the left forefinger). A non-match required a “no” response (a right red button press with the right forefinger). In the spatial condition, the location of the presented letter had to be compared with the location of the previous letter. If the location matched (e.g., the currently presented letter was to the right of the fixation, as was the preceding letter, note that verbal identity of the letter does not matter), then a “yes” response was required. If not, then a “no” response was required. Both the verbal and spatial task conditions each consisted of 10 practice trials followed by one block of 32 trials. Identical stimulus displays were employed for the verbal and spatial task conditions, where each letter and location were presented an equal number of times. Practice trials included feedback. In the more difficult two-back task, each letter had to be compared with the letter presented two trials back. Otherwise, verbal and spatial task conditions were identical to the one-back task.

Participants completed the one-back first, then the two-back. The order of verbal and spatial conditions was counterbalanced across participants. Instructions for each task and condition were presented on the computer monitor and explained by the researcher administering the task. Response accuracy and reaction time data were recorded for each trial. The computer recorded RTs for error and no-response trials, but these were excluded from analysis. Mean accuracy (total correct) for each of the four trial blocks (one-back spatial, two-back spatial, one-back verbal, two-back verbal) was the dependent variable of primary interest for n-back performance, with response speed (reaction times, RTs) of secondary interest.

**Table 1** Demographic, substance use, comorbidity, and HIV disease data

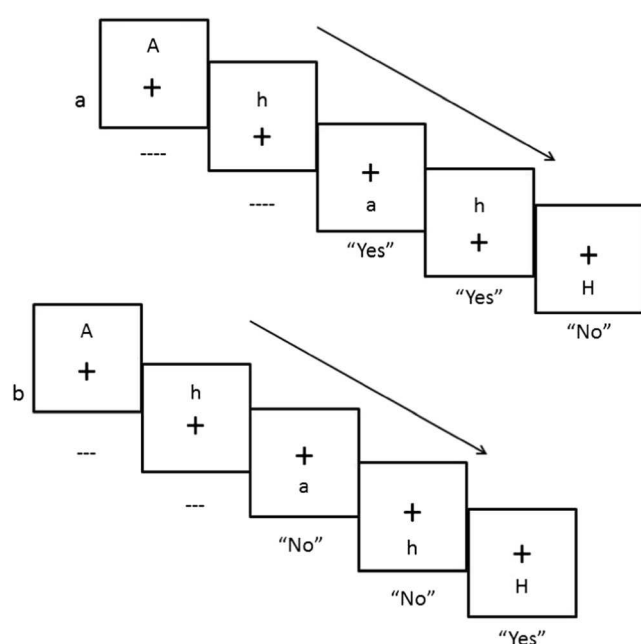
|                                | HIV– men     | HIV+ men    | HIV– women   | HIV+ women  | Statistic | <i>p</i> |
|--------------------------------|--------------|-------------|--------------|-------------|-----------|----------|
| <i>n</i>                       | 59           | 63          | 187          | 51          |           |          |
| Age <sup>a</sup>               | 51.2 (5.7)*  | 48.6 (7.1)  | 47.9 (8.7)*  | 47.9 (8.9)  | 2.69      | .046     |
| Education                      | 12.5 (1.6)   | 13.0 (1.8)* | 12.3 (2.0)*  | 11.3 (2.4)* | 7.27      | < .001   |
| WTAR FSIQ                      | 88.2 (8.6)*  | 88.7 (9.5)* | 86.6 (9.7)   | 83.1 (8.0*) | 4.05      | .008     |
| %African-American <sup>b</sup> | 97           | 87          | 79           | 94          | 15.2      | .002     |
| %HCV                           | 10           | 25          | 14           | 16          | 6.34      | .096     |
| ASI-Alcohol                    | 0.09 (0.18)* | 0.06 (0.11) | 0.03 (0.09)* | 0.03 (0.10) | 4.97      | .002     |
| ASI-Drug                       | 0.03 (0.08)  | 0.03 (0.06) | 0.03 (0.06)  | 0.03 (0.06) | 0.10      | .962     |
| KMSK-Alcohol                   | 10.6 (3.2)   | 11.1 (2.4)  | 10.0 (3.7)   | 10.5 (3.3)  | 2.09      | .102     |
| KMSK-Cocaine                   | 12.2 (5.1)   | 13.2 (4.3)  | 12.7 (4.8)   | 13.9 (4.2)  | 1.49      | .218     |
| KMSK-Heroin                    | 5.8 (5.5)    | 3.8 (4.9)*  | 6.7 (5.3)*   | 5.4 (5.4)   | 5.15      | .002     |
| % MDD                          | 22           | 30          | 37           | 33          | 5.10      | .165     |
| PCL-C                          | 37.4 (13.2)  | 35.0 (13.3) | 38.0 (13.8)  | 38.2 (14.2) | 0.80      | .494     |
| WURS                           | 28.2 (17.4)  | 30.1 (21.3) | 29.2 (20.4)  | 33.2 (23.7) | 0.63      | .594     |
| SRPS                           | 48.1 (9.9)   | 50.2 (9.3)  | 48.2 (9.7)   | 48.8 (7.7)  | 0.77      | .512     |
| CNS Penetrance                 |              | 8.1 (2.0)   |              | 7.3 (1.2)*  | 5.09      | .026     |
| Md current CD4                 |              | 491         |              | 537         | – 0.70    | .482     |
| Md nadir CD4                   |              | 182         |              | 227*        | – 1.93    | .054     |
| % CD4 < 200                    |              | 14          |              | 6           | 2.12      | .150     |
| % Undetectable VL              |              | 75          |              | 84          | 1.47      | .225     |

WTAR Wechsler Test of Adult Reading, FSIQ Full Scale Intelligence Quotient, ASI Addiction Severity Index, KMSK Kreek–McHugh–Schluger–Kellogg Scale, HCV hepatitis C virus, MDD major depressive disorder, PCL–C PTSD Checklist–Civilian Version, WURS Wender Utah Rating Scale, SRPS Levenson Self-Report Psychopathy Scale, CPE CNS Penetration Effectiveness, CD4 T4 lymphocyte count (200 cells/μL), VL viral load (copies/mL)

\*Significant post hoc group comparisons

<sup>a</sup> Means with (standard deviations)

<sup>b</sup> 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)



**Fig. 1** **a** Two-back stimulus display in verbal condition. **b** Two-back stimulus display in spatial condition

## Statistical analyses

We compared demographic, substance abuse, and comorbidity data from the four participant groups (HIV– men; HIV+ men; HIV– women; HIV+ women) to identify potential confounds, using one-way analysis of variance (ANOVA) and post hoc Tukey HSD tests for parametric data, Kruskal–Wallis tests for non-parametric data,<sup>2</sup> and  $\chi^2$  tests for categorical data. An  $\alpha$  level was set at 0.01 for all four-group comparisons to decrease likelihood of capitalizing on chance findings. Pearson and Spearman correlations were employed to index the strength of associations between n-back data and participant characteristics for parametric and non-parametric data, respectively.

N-back accuracy and RT data were analyzed separately for spatial and verbal conditions using mixed model analysis of covariance (ANCOVA), with Sex and HIV Serostatus as between-subjects factors and Task Demand (1 vs. 2 back) as the within-subjects factor, controlling for age and education.

<sup>2</sup> Mann–Whitney tests with *z* approximations were used to compare HIV disease variables among HIV+ men and women.



## Results

Table 1 shows demographic, comorbidity, and HIV disease characteristics for the four participant groups. The overall sample was 86.3% African-American and 66% female. The mean age was 49 ( $SD = 8.1$ ), and mean years of education was 12.3 ( $SD = 2.0$ ). Mean estimated verbal IQ using the Wechsler Test of Adult Reading (WTAR) was 87.4 ( $SD = 9.4$ ). All HIV+ participants were ambulatory and able to tolerate 2–3 h of testing. Their median CD4 lymphocyte count was 497 at time of testing,  $IQR = [285, 771]$  and median nadir CD4 count was 195,  $IQR = [100, 360]$ . Approximately 11% of the group had AIDS-defining CD4 counts ( $< 200$  cells/ $\mu$ L) at testing. Plasma viral load was undetectable at  $< 40$  copies/mL for 79% of HIV+ participants. A total of 97.4% were prescribed antiretroviral therapy at testing: 96.2% with combination antiretroviral therapy (cART).

A significantly higher percentage of HIV– men were African-American compared with HIV– women ( $\chi^2 = 15.24$ ,  $p = .002$ ). Mean years of education was significantly lower for HIV+ women compared with the other three study groups ( $F(3,356) = 7.27$ ,  $p < .001$ ; HSD  $p \leq .01$  for all tests). Mean WTAR-estimated IQ was significantly lower for HIV+ women compared with HIV– and with HIV+ men,  $F(3,353) = 4.05$ ,  $p = .008$ ; HSD  $p = .02$  and  $.01$ , respectively). There were small but significant correlations between years of age and education with mean n-back accuracy (age:  $r = -.15$ ,  $p = .004$ ; education:  $r = .19$ ,  $p < .001$ ) and overall RTs (age:  $r = .23$ ,  $p < .001$ ; education:  $r = -.11$ ,  $p = .04$ ), so both variables were employed as covariates for the analyses of n-back performance.<sup>3</sup>

Tables 1 and 2 show substance use data for all participants. Most participants met DSM-IV criteria for substance dependence in early or sustained remission (alcohol 91%, cocaine 92%, opioids 70%). The groups were generally comparable on substance abuse characteristics, with no significant group differences noted on mean ASI-Drug, KMSK-Alcohol, and KMSK-Cocaine subscores, or in prevalence of DSM-IV-diagnosed alcohol, opioids, cocaine, or cannabis dependence (all  $ps > .05$ ). Mean KMSK-Heroin scores were significantly higher ( $p = .002$ ) among HIV– women compared with HIV+ men. Finally, HIV– women reported significantly more days since their last use of cocaine compared with HIV– and HIV+ men, both  $ps < .01$ . Mean years of alcohol use were significantly higher and use of alcohol in the past 30 days was significantly more common among the male compared with the female participants,  $ps = .01$ ; and ASI-Alcohol scores were significantly higher among HIV– men compared with HIV– women ( $p = .002$ ).

No significant group differences were observed in prevalence of DSM-IV Major Depression or mean scores on measures of PTSD, ADHD, or antisocial personality traits ( $p > .17$  for all tests). Compared with HIV+ women, median nadir CD4 counts were significantly lower for HIV+ men ( $z = -1.93$ ,  $p = .05$ ) and mean CNS Penetration scores were significantly higher ( $F(1,103) = 5.09$ ,  $p = .03$ ). HIV+ men and women showed no significant differences in median current CD4 counts, or prevalence of AIDS-defining CD4 counts, undetectable HIV RNA levels, or currently prescribed cART ( $p \geq .23$  for all tests).

### N-back task

Approximately 3% of participants obtained at least one RT greater than 3 SDs above the mean. They were considered outliers, and their RT data were not analyzed further. Both accuracy and response speed were skewed and were therefore natural log-transformed. Mean error rates for the spatial and verbal task RTs did not differ significantly among the four subject groups (spatial:  $p = .12$ ,  $\eta^2 = 0.02$ ; verbal:  $p = .08$ ,  $\eta^2 = 0.02$ ). There were no significant inverse correlations between errors and overall RTs for either spatial or verbal data, indicating no significant speed/accuracy tradeoffs.

Preliminary analyses of each of the four dependent variables (spatial and verbal accuracy, spatial and verbal reaction times) showed expected significant main effects for Task Demand (all  $ps < .001$ ), verifying that response accuracy was lower, and RTs were slower for the two-back compared with one-back conditions. All interactions involving the Task Demand factor were non-significant ( $ps \geq .09$ ).

### Accuracy

Analyses of spatial and verbal accuracy data revealed significant main effects for serostatus (spatial:  $F(1, 354) = 5.82$ ,  $p = .02$ , Cohen's  $d = .23$ ; verbal:  $F(1, 354) = 4.86$ ,  $p = .03$ ,  $d = .21$ ); and inspection of the means indicated that the HIV– participants made significantly more correct responses compared with the HIV+ groups in both stimulus conditions. There were no significant main effects for Sex or for the Sex  $\times$  HIV Serostatus interactions ( $ps > .26$ ) for either stimulus condition. Mean spatial and verbal accuracy scores for HIV– and HIV+ groups are represented in Fig. 2a.

### Response speed

In contrast to accuracy scores, analyses of both spatial and verbal RTs showed significant main effects for Sex (spatial:  $F(1,349) = 7.64$ ,  $p = .006$ ,  $d = -0.43$ ; verbal:  $F(1,354) = 7.16$ ,  $p = .008$ ,  $d = -0.30$ ), with slower response times for women compared with men. The main effects for HIV Serostatus and the Sex  $\times$  HIV interactions did not reach statistical

<sup>3</sup> There was a highly significant correlation between education and mean WTAR IQ estimate,  $r = .52$ ,  $p < .001$ , so mean WTAR scores were not included as a covariate.

**Table 2** Substance abuse characteristics

|                                | HIV– men     | HIV+ men     | HIV– women  | HIV+ women  | Statistic | <i>p</i> |
|--------------------------------|--------------|--------------|-------------|-------------|-----------|----------|
| Years used <sup>a</sup>        |              |              |             |             |           |          |
| Alcohol                        | 17.3 (13.2)* | 15.0 (13.5)* | 10.8 (10.9) | 10.6 (9.4)  | 6.05      | .001     |
| Opioids                        | 10.1 (13.0)  | 4.9 (10.1)   | 9.0 (11.3)  | 7.4 (11.3)  | 2.93      | .034     |
| Cocaine                        | 14.2 (10.7)  | 14.5 (10.7)  | 12.6 (9.9)  | 15.3 (9.9)  | 1.26      | .289     |
| Cannabis                       | 13.8 (12.8)  | 15.3 (12.6)* | 9.0 (11.8)* | 10.1 (11.8) | 5.95      | .001     |
| Md days since use <sup>b</sup> |              |              |             |             |           |          |
| Alcohol                        | 491*         | 361*         | 693         | 732         | 13.5      | .004     |
| Opioids                        | 496          | 1448         | 676         | 768         | 2.64      | .450     |
| Cocaine                        | 966          | 730          | 1164*       | 768         | 11.9      | .008     |
| Cannabis                       | 4798         | 5153         | 4182        | 1460*       | 10.5      | .020     |
| % use last 30 days             |              |              |             |             |           |          |
| Alcohol                        | 42*          | 40*          | 24          | 20          | 13.39     | .004     |
| Opioids                        | 3            | 2            | 3           | 8           | 3.44      | .328     |
| Cocaine                        | 10           | 18           | 5           | 6           | 9.84      | .015     |
| Cannabis                       | 5            | 14           | 4           | 8           | 7.80      | .050     |
| % DSM-IV SUDs                  |              |              |             |             |           |          |
| Alcohol                        | 52           | 71           | 52          | 59          | 7.48      | .060     |
| Opioid                         | 37           | 29           | 49*         | 41          | 8.60      | .035     |
| Cocaine                        | 81           | 84           | 86          | 90          | 1.78      | .618     |
| Cannabis                       | 70           | 59           | 52          | 43          | 8.98      | .030     |
| %IDU                           | 17           | 25           | 17          | 20          | 2.29      | .515     |
| %Overdose                      | 17           | 14           | 25          | 20          | 3.83      | .280     |

DSM–IV Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition, SUDs substance use disorders, IDU injection drug use

\*Significant post hoc group comparisons

<sup>a</sup> Means with (standard deviations)

<sup>b</sup> Chi-square tests were used for categorical data (%) and Kruskal–Wallis tests for non-normally distributed data (Md). All other analyses used one-way analysis of variance (ANOVA)

significance for either analysis ( $ps \geq .61$ ). Mean spatial and verbal RTs for male and female groups appear in Fig. 2b.

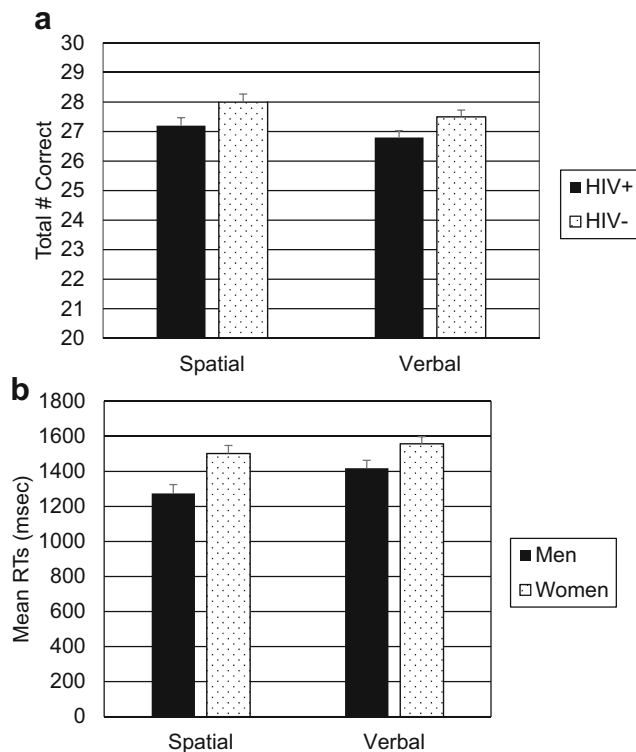
### HIV disease

To limit the number of group comparisons, only accuracy scores were used to investigate potential associations of n-back performance with HIV disease indicators. We found no significant group differences between verbal or spatial accuracy scores for HIV+ participants with or without AIDS-defining CD4 counts or undetectable HIV RNA levels ( $p \geq .15$ ) and no significant correlations between accuracy scores with current and nadir CD4 counts or mean CNS Penetration Effectiveness scores ( $ps \geq .36$ ).

### Additional analyses

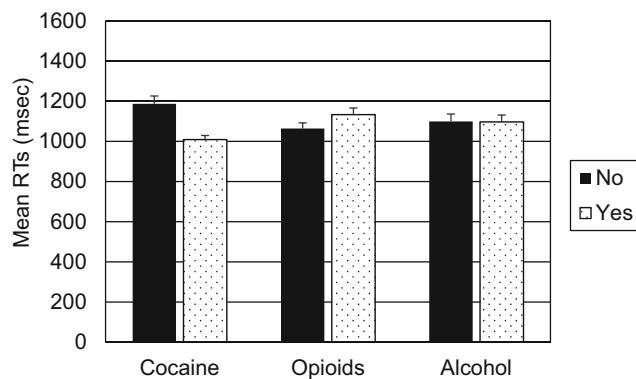
Finally, we conducted a series of exploratory analyses to compare our results with published findings on HIV and n-back. Previous studies (Meyer et al. 2013; Keutmann et al. 2017) have reported that risk of cognitive impairment is increased

among HIV+ women with a history of cocaine dependence. We repeated the primary Sex  $\times$  HIV Serostatus analyses adding Cocaine Dependence as an additional between-subjects factor. There were no significant main effects or interactions involving Cocaine Dependence for spatial or verbal accuracy scores,  $p > .40$  for each comparison. Spatial and verbal RTs were both significantly faster among the cocaine-dependent compared with non-dependent participants (spatial:  $F(1,350) = 22.3$ ,  $p < .001$ ,  $d = 0.62$ ; verbal:  $F(1,350) = 5.0$ ,  $p = .03$ ,  $d = 0.30$ ). There were no significant inverse correlations between RTs and total number of errors, indicating no speed-accuracy tradeoffs; thus, faster RTs for the cocaine-dependent participants could not be attributed to group differences in errors of commission. There were no significant differences in speed of responding between participants with and without opioid dependence, or alcohol dependence. Figure 3 shows mean spatial RTs for groups of cocaine-dependent, opioid-dependent, and alcohol-dependent participants. Hinkin et al. (2002) reported that HIV+ and HIV– groups performed significantly more accurately on the spatial compared with the verbal two-back. We compared participants' spatial and verbal



**Fig. 2** **a**. Mean n-back spatial and verbal accuracy scores for HIV+ compared with HIV- participants. Mean accuracy was significantly poorer among HIV+ compared with HIV- participants in both verbal and spatial conditions. **b** Mean spatial and verbal reaction times for male compared with female participants (high score = slower performance). Reaction times were significantly slower among women compared with men in both verbal and spatial conditions

accuracy using mixed model ANCOVA, adding Test Stimulus (spatial vs verbal) to the primary Sex and HIV Serostatus analyses. There were no significant main effects or interactions involving the Test Stimulus factor ( $ps \geq .17$ ). Caldwell



**Fig. 3** Mean spatial reaction times for participants with and without cocaine dependence, opioid dependence, and alcohol dependence (high score = slower performance). Reaction times were significantly faster among participants with cocaine dependence compared with participants without cocaine dependence. Note. All n-back measures were natural log-transformed prior to data analyses; data for each figure were back-transformed for clarity of presentation

and colleagues (Caldwell et al. 2014) reported that participants dually infected with HIV and hepatitis C virus (HCV) showed slower RTs and increased errors of commission on the verbal 2-back compared with HIV monoinfected and uninfected groups. We compared verbal two-back performance of uninfected, monoinfected (HIV+ or HCV+ but not both), and dually infected groups using univariate ANCOVA with Infection Status as the between-subjects factor. We found a significant linear trend toward poorer verbal accuracy and higher total errors (accuracy:  $F(1,355) = 4.5$ ,  $p = .01$ ; errors:  $F(1,355) = 4.7$ ,  $p = .01$ ) among groups ordered by infection status. No significant group differences in mean verbal RTs were observed.

## Discussion

Working or “representational” memory (WM) is an essential component of many complex cognitive functions, and critically dependent on the integrity of neural circuitry including prefrontal cortex and neostriatum. WM is frequently impaired among individuals infected with HIV, particularly HIV+ SDIs, but previous investigations of working memory among HIV+ SDIs generally involved all- or primarily male participant samples. In the current study, we administered a modified version of the n-back task with known sensitivity to HIV serostatus (Hinkin et al. 2002) to a group of 360 HIV+ and HIV- drug using men and women verified abstinent from alcohol and drugs of abuse at testing. Both HIV-infected men and women performed significantly less accurately compared with HIV- controls on verbal and spatial versions of the n-back, findings which replicate and extend Hinkin et al.’s earlier results from a primarily male study sample (2002). Participant groups were generally comparable on substance use and comorbid characteristics, and most participants met DSM-IV criteria for substance use disorders in remission, indicating that group differences in n-back performance could not be readily attributed to non-specific effects of recent drug use.

In a recent meta-analysis of studies of executive function and HIV serostatus, Walker and Brown (2017) concluded that working memory was the most commonly affected “cognitive” executive function among HIV+ individuals. Furthermore, among the working memory measures reviewed, the two-back was most sensitive to HIV effects. Their report and our current findings support our earlier proposal (Martin et al. 2001) that working memory impairment represents a “signature” deficit among HIV+ SDIs, who perform more poorly compared to HIV- SDIs on essentially all measures that engage working memory mechanisms through various task characteristics, such as response requirements, time delay, and memory load. These findings suggest that working memory represents a critically vital

component of neurocognitive screening for HAND, especially for the assessment of HIV+ individuals with a history of substance dependence.

We found that both HIV+ men and women performed the n-back significantly less accurately compared with HIV− participants, but the magnitude of this serostatus effect did not differ by sex. Although neurocognitive risk factors are more common among HIV+ women (Maki and Martin-Thormeyer 2009), the current findings indicate that HIV+ women's neurocognitive performance is not invariably poorer compared with HIV+ men. Additionally, although reports of female-specific impairment in visual memory and in decision making under risk support the hypothesis that neurocognitive profiles are not identical among HIV+ women and men (Keutmann et al. 2017; Martin et al. 2016), deficits in other neurocognitive functions are not necessarily sex-specific. In this regard, we recently reported a similar pattern of poorer performance on a spatial and navigational memory among both HIV+ men and women compared with HIV− controls, but no evidence of sex differences among HIV+ groups (Fogel et al. 2017). Taken together, these findings and Maki et al.'s report that verbal memory is more prominently affected among HIV+ women (2015), might contribute to characterizing sex-specific phenotypes of HIV-associated neurocognitive impairment and affected neural circuitry.

We found no evidence of slower reaction times (RTs) among HIV+ compared with HIV− groups. The clinical significance of psychomotor slowing as the predominant feature of HIV-associated neurocognitive impairment has declined since the introduction of cART; however, results of RT-based studies among individuals living with HIV/AIDS have historically been variable. Some early results suggested that RT tasks might be sensitive to mild cognitive slowing among asymptomatic HIV+ individuals (Martin et al. 1992), but a comprehensive review of RT studies at the time revealed that while fairly common, there was large variability in RT findings, with some but not all studies showing mental slowing in HIV+ groups (Hardy and Hinkin 2002). Some of the variability in these early findings may be attributable to differences in HCV serostatus or other variables not yet identified as potential contributors to HIV effects on neurocognition. However, at a more conceptual level, the assessment of specific cognitive functions using RTs remains complicated: the task response requirements can engage multiple cognitive processes in addition to response speed when participants are instructed to respond as quickly *and* as accurately as possible, which complicate interpretation of RT performance.

We had hypothesized tentatively that female SDIs would perform the spatial n-back more poorly compared with male SDIs. We found no evidence of sex differences in spatial accuracy. Women performed the spatial n-back more slowly compared to men; however, verbal RTs were also slower for women compared with men, suggesting that the RT results

might be attributed to more generalized slowing. Our findings are not incompatible with available literature; although a male advantage on spatial tasks is the most commonly reported sex-specific effect (Miller and Halpern 2014), evidence for sex differences in n-back performance has been less consistent (Anderson-Schmidt et al. 2009; Haut and Barch 2006; Lejbak et al. 2011; Evans and Hampson 2015).

In contrast with our findings, studies from the WIHS have not shown consistent WM impairment among HIV+ compared with HIV− women. Maki et al. (2015) reported that cross-sectional performance on the Letter Number Span Task (LNST) did not differ significantly between HIV+ and HIV− women; similarly, Sundermann et al. (2015) found no overall differences in n-back performance among HIV+ compared with HIV− women. However, Rubin et al. (2017) reported that HIV+ women with viral suppression performed the LNST significantly more poorly compared with HIV− women at baseline and at follow-up. These differing results might reflect the relatively low prevalence of substance dependence among the WIHS participants, suggesting a positive substance use disorder elevated the risk of WM impairment among HIV+ women.

In contrast with previous findings (Keutmann et al. 2017; Meyer et al. 2013), we found no evidence of poorer n-back performance specifically among cocaine-dependent HIV+ women; rather, RTs were *faster* among cocaine-dependent men and women, regardless of HIV serostatus. Additional neurocognitive and neuroimaging studies are necessary to determine if cocaine affects systematically a particularly subset of neurocognitive functions among HIV+ women and how these might be characterized further.

The pattern of sex differences in n-back response speed but serostatus differences in response accuracy is roughly comparable with a recent report by our group (Fogel et al. 2017) that both HIV+ and HIV− women performed Memory Island, a spatial-navigational learning task, more slowly on the immediate learning trials compared with men, but delayed recall was significantly poorer for both HIV+ men and women compared with HIV− participants. In both studies, women performed more poorly on the speeded component of the tasks compared with men, but HIV+ men and women showed impairment on the variables of primary importance (n-back accuracy and spatial delayed recall). These results illustrate the importance of considering time-based and accuracy-based components separately, since these two cognitive operations can be affected differentially by sex or HIV serostatus.

In an exploratory analysis, we found a linear trend toward poorer verbal accuracy among participants rank ordered as uninfected, monoinfected, or dually infected with HIV and hepatitis C virus (HCV). In a previous report, we found a monotonic trend toward slower RT Stroop performance among SDIs characterized by HIV and HCV serostatus, suggesting that deficits in multiple executive functions are



amplified among HIV+ individuals in the presence of a positive HCV serostatus.

Findings from this study are necessarily limited. All study participants met criteria for a current or lifetime DSM-IV diagnosis of dependence on at least one substance. We assumed a priori that study results would not necessarily generalize to non-substance-dependent men and women, regardless of serostatus: although not definitive, study results were consistent with this assumption. Additionally, the majority of participants were dependent on more than one substance, which is by far the most common pattern of substance use observed in North America studies of neuroAIDS and drug abuse, so specific neurocognitive effects of different substances cannot be isolated (Martin-Thormeyer and Paul 2009). On the other hand, the n-back procedure was advantageous by its administration at the second study visit; one might speculate that living situations were more stable and neurocognitive performance less vulnerable to potential confounds among those participants who kept both appointments.

In summary, results from the current study identify new details of the neurocognitive picture among HIV+ women compared with HIV+ men as well as HIV− women; suggest that working memory deficits among HIV+ women are critically affected by current or previous substance dependence; provide further support that working memory impairment may be a signature neurocognitive deficit among HIV+ substance-dependent individuals; and suggest that HIV+ female SDIs in substance abuse treatment are likely to derive benefit from working memory training.

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**Authors' contributions** All authors contributed scientifically to the manuscript and have read and approved the final version.

## Compliance with ethical standards

**Informed consent** Written informed consent was obtained upon arrival at the first study visit.

**Conflict of interest** The authors declare that they have no conflicts of interest.

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