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Crack cocaine use impairs anterior cingulate and prefrontal cortex function in women with HIV infection

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Abstract

Objective—Crack cocaine use is associated with impaired verbal memory in HIV-infected women more than -uninfected women. To understand the neural basis for this impairment, this study examined the effects of crack cocaine use on activation of the prefrontal cortex (PFC) and strategic encoding during a verbal memory task in HIV-infected women.

Methods—Three groups of HIV-infected women from the Chicago Consortium of the Women's Interagency HIV Study were compared: current users of crack cocaine (n=10), former users of cocaine (n=11), and women who had never used cocaine (n=9). Participants underwent functional magnetic resonance imaging during a verbal memory task and completed a neuropsychological test of verbal memory.

Results—On the neuropsychological test, current crack users performed significantly worse than other groups on semantic clustering, a measure of strategic encoding, $p < .05$. During encoding, activation in left anterior cingulate cortex (ACC) was lower in current and former cocaine users compared to never users. During recognition, activation in bilateral PFC, specifically left dorsal medial PFC and bilateral dorsolateral PFC, was lower in current and former users compared to women who had never used cocaine. Lower activation in left dorsolateral PFC was correlated with worse performance on the recognition task, $p < .05$.

Conclusion—The verbal learning and memory deficits associated with cocaine use in women with HIV may be partially accounted for by alterations in ACC and PFC function.

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The authors declare that they have no conflict of interest.

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Conflict of Interest Statement

All authors declare that they have no conflict of interest: Vanessa Meyer, Deborah Little, Daniel Fitzgerald, Erin Sundermann, Leah Rubin, Eileen Martin, Kathleen Weber, Mardge Cohen, and Pauline Maki.

Keywords

HIV; crack cocaine; African American; verbal memory; fMRI; prefrontal cortex

INTRODUCTION

Cocaine use in HIV-infected individuals is associated with higher morbidity and mortality (Baum *et al*, 2009; Cook *et al*, 2008) and worse cognitive outcomes (Meade *et al*, 2011; Meyer *et al*, 2013) than in individuals infected with HIV who have never used cocaine. Although *in vitro* studies demonstrate interactive neurotoxic effects of HIV viral proteins and cocaine (Buch *et al*, 2011; Ferris *et al*, 2008), the combined effects of cocaine and HIV on cognition and brain function in humans has not been fully elucidated. Recently, we reported that the combined effects of HIV infection and illicit drug use negatively impact verbal episodic memory (Meyer *et al*, 2013). In 1,395 women from the Women's Interagency HIV Study (WIHS), drug use was associated with poorer verbal episodic memory in HIV-infected women but not in HIV-uninfected women (Meyer *et al*, 2013). Cocaine (with or without heroin) was the particular drug associated with worse verbal memory in HIV-infected women. Therefore, the present investigation used functional magnetic resonance imaging (fMRI) to examine the neural underpinnings of that behavioral finding.

We hypothesize that the negative effect of current cocaine use on episodic memory in HIV-infected women reflects the combined harmful effects of cocaine and HIV infection on prefrontally-mediated executive functions required for optimal verbal memory performance. Specifically, we hypothesized that cocaine use and HIV interact to negatively impact semantic clustering. Semantic clustering is an encoding strategy where words are organized into semantic categories (e.g., fruits, articles of clothing) to improve recall. The central role of the prefrontal cortex (PFC) in semantic categorization is exemplified through evidence of impairments in strategic encoding following dorsolateral PFC lesions (Gershberg and Shimamura, 1995).

Neuroimaging studies in healthy individuals demonstrate the role of the left dorsomedial PFC, ventromedial PFC, and inferior PFC (Brodmann areas 10, 45, 46, 47) in semantic organization (Binder *et al*, 2009; Domb *et al*, 1995; Kapur *et al*, 1994). HIV-infected individuals show deficits in semantic clustering (Delis *et al*, 1995; Gongvatana *et al*, 2007; Peavy *et al*, 1994; Woods *et al*, 2005) and altered activation of the lateral frontal and inferior PFC during memory encoding (Castelo *et al*, 2006).

Converging evidence supports our hypothesis that cocaine use will show a negative effect on verbal memory task performance and underlying prefrontal activation among individuals with HIV. Multiple studies have demonstrated verbal memory deficits among cocaine users without HIV infection; however, semantic clustering has not been evaluated (Beatty *et al*, 1995; Berry *et al*, 1993; Fox *et al*, 2009; Manschreck *et al*, 1990; Mittenberg and Motta, 1993). To our knowledge, no study has investigated the potential effects of cocaine use on the strategic component of verbal learning and underlying prefrontal activation patterns among HIV-infected individuals. Understanding the neural mechanisms underlying

cognitive deficits associated with HIV and cocaine use is critically important given the high prevalence of use among HIV-infected individuals (Cook *et al*, 2008; Ostrow *et al*, 1993). Elucidating risk factors for HIV-associated cognitive deficits could have important implications for treatment outcomes, as cognitive impairment is associated with poor treatment adherence (Hinkin *et al*, 2004).

The specific aim of the present research was to examine the effects of crack cocaine use on the neural circuitry underlying verbal episodic memory among HIV-infected women. We hypothesized that HIV-infected women who currently use crack cocaine would show decreased PFC activation during a verbal memory task compared with HIV-infected women who never used cocaine. We predicted this decreased activation would be associated with poorer performance on behavioral measures of strategic encoding, specifically semantic clustering.

METHODS

Subjects

Participants were HIV-infected women enrolled in the Chicago WIHS Consortium and were recruited for this substudy during their WIHS core semiannual visits in 2010–2011. The WIHS is a longitudinal, multisite study of women living with HIV (Bacon *et al*, 2005; Barkan *et al*, 1998). The sample consisted of 10 women who reported crack cocaine use at least once in the past 6 months (current users), 11 women who reported lifetime use of cocaine, but none in the past 6 months (former users), and 9 women who had never used cocaine (non-users). Exclusion criteria included first language other than English; history of dementia; uncontrolled diabetes; closed head injury with loss of consciousness; open head injury of any kind; seizure disorder; current pregnancy; less than eight years of formal education; diagnosis of schizophrenia; score of 27 or greater on the Center for Epidemiological Studies Depression (CESD scale) (Radloff, 1977; Schulberg *et al*, 1985); history of any clinical AIDS-defining disorders; endocrine/systemic disease; or current use of psychiatric medication known to affect cognition. Participants were also excluded for any evidence of withdrawal or acute intoxication at testing as verified with rapid urine toxicology screens administered before the neuroimaging session (Express Diagnostics DrugCheck, Blue Earth, MN). Additional MRI exclusionary criteria included metal in the body, claustrophobia, or weight greater than 250 pounds (due to bore size).

Functional MRI procedure

Blood oxygen level dependent (BOLD) fMRI was performed on a General Electric 3.0-Tesla SignaHDx scanner (General Electric Healthcare, Waukesha, WI). Images were acquired with 30 axial, 4-mm slices using a standard T2*-sensitive echo planar image sequence (1.5s repetition time; 25ms echo time; 64 × 64 matrix; 20cm field of view; flip angle 90°). The scan session lasted one hour and involved additional neurocognitive tasks (i.e. a working memory task and a simple reaction time task) and structural scans that were not analyzed as part of the current study but were acquired as part of this session.

In-scanner verbal memory task

The fMRI verbal memory test mimicked many aspects of the Hopkins Verbal Learning Task (HVLT) (Battig and Montague, 1969; Brandt, 1991) and included encoding, free-recall and recognition conditions. To facilitate the investigation of semantic clustering, the encoding phase included 30 concrete nouns (six of the most commonly generated exemplars from each of five distinct semantic categories, such as body parts and furniture)(Van Overschelde *et al*, 2004). The recognition task included the 30 targets, 15 semantically-related distractors and 15 unrelated distractors. Distractors were selected from the top exemplars in related or unrelated semantic categories.

The encoding task used a blocked design with 27s blocks (3s individual stimulus presentation and 1.5s interstimulus interval). Participants received instructions to remember each item for a later memory task and to indicate that they had seen each item by pressing a button on a response remote. Five experimental blocks alternated with five control blocks. Control blocks included repeated presentations of two concrete unrelated nouns (i.e., sailboat and ballet). Following a 12-minute delay, during which structural scans were acquired, participants were instructed say aloud all the words they could remember from the task. Their responses were recorded but no scans were acquired during this free recall phase. The recognition phase began immediately after free recall and included 27s blocks (3s stimulus presentation and 1.5s interstimulus interval) including 10 experimental blocks (target stimuli from the encoding phase and novel distractor stimuli) and 10 control blocks (repeated administrations of sailboat and ballet). Participants pressed one button to identify which words they remembered from the encoding phase and another button to identify words they did not remember from the encoding phase.

Outcome measures included the number of recalled words during free recall test and percent correct on the recognition task. A semantic cluster was defined as two consecutive, correctly recalled items belonging to the same semantic category (e.g., “banana” followed by “pear”). The clustering score was calculated by giving one point for each two-word cluster, two points for each three-word cluster, and three points for each four-word cluster.

Hopkins Verbal Learning Task – Revised (HVLT-R)

The HVLT-R is a 12-item word-list learning test used to measure verbal episodic memory(Benedict *et al*, 1998). Outcomes include total words recalled on Trial 1 (single trial learning) and across each of three learning trials (total learning), number of words recalled after a 20-minute delay (delayed recall), recognition score, and semantic clustering scores (Trial 1, all trials and delayed trial).

Behavioral Analyses

Group differences in demographic characteristics and task performance were examined using univariate analyses of variance (ANOVAs) for continuous variables and chi-square (χ^2) tests for categorical variables. Analyses were conducted using SPSS Version 20 (IBM Corp, Armonk, NY).

Neuroimaging Analyses

The data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London www.fil.ion.ucl.ac.uk/spm). Participants were excluded for excessive movement (> 2 voxels in any direction across the entire scan). Functional images were realigned to the first volume of the task to correct for inter-scan motion, normalized to a Montreal Neurological Institute (MNI) template and smoothed with an 8-mm Gaussian kernel. First-level regressors were created for the novel stimuli (experimental condition) and repeated stimuli (control) conditions. Similar contrasts were applied to the recognition data to examine group and condition.

In separate second-level analyses of encoding and recognition, full-factorial designs were run with two factors: Drug use (3 levels: current, former, non-users) and Condition (2 levels: experimental, control) to examine interactions between drug use and task conditions. An image mask was created including the *a priori* regions of interest (ROI) Brodmann areas (BA) 6, 8–10, 44–47, cingulate (BA 24 and 32), hippocampus, and parahippocampal gyrus using the Wake Forest University Pickatlas toolbox in SPM (Maldjian *et al*, 2003). First, the ROI mask was applied to the experimental versus control activation map for non-users, which was then saved as a binary mask to limit subsequent analyses to typical patterns of activation in the encoding and recognition phases. For hypothesis-driven analyses with homogeneous small patient subsets, use of ROI analyses is ideal for balancing type I and II error; therefore, no additional control for multiple comparisons was conducted. The binary mask was applied to the second-level interaction (F-test) between Drug use and Condition with follow-up analyses to determine which groups (current/former/non-user) differed significantly in activation for the task. Localization of significant activation clusters found in the interaction analysis were determined using the xjView toolbox in SPM (<http://www.alivelearn.net/xjview>). The functional significance of group differences was assessed using the following procedure. For each subject, we extracted the beta estimate of all voxel values within a 3-mm radial sphere centered in each significant cluster found in the group comparison (Table 3). The beta estimates were then entered into correlational analyses with HVLT and in-scanner task outcomes.

RESULTS

Demographics

A total of 39 HIV-infected women completed the neuroimaging assessments. Participants were excluded from the final analysis for excessive motion (> 2 voxels, $n = 5$, 1 current user), chance performance on control task ($n = 1$) and technical problems ($n = 3$). Participants were 27 to 59 years of age ($M = 44.1$, $SD = 7.5$) and were predominately African American (97%) (Table 1). Groups differed on cigarette smoking status, with 80% of current users, 55% of former users, and 22% of non-users currently smoking cigarettes ($p = 0.04$). Additionally, 50% of current users, 18% of former users, and 0% of non-users were seropositive for the hepatitis C virus (HCV) ($p = 0.03$).

Information on frequency of cocaine use was collected by WIHS staff prior to the neuroimaging visit. Among current users, two reported daily use of crack cocaine, two

reported using at least once a week but less than once a day, and four reported using less than once a week. Two women reported no current use of crack cocaine during the screening process but at the neuroimaging visit they reported recent use; therefore, they were considered current users. A majority of current and former users reported that during the period of their heaviest crack cocaine use they were using more than once per week (70% of current users and 82% former users).

Verbal memory performance

Table 2 shows the memory performance on the in-scanner task and the HVLTL. Due to small sample sizes, Cohen's d effect sizes are also reported (small effect = 0.2; medium effect = 0.5; large effect = 0.8)(Cohen, 1992). On the HVLTL, groups differed on the semantic clustering score for Trial 1. Post-hoc comparisons (Scheffe) indicated that the significant difference was between the current and non-user groups ($p = 0.01$, $d = 1.44$). Although no other statistically significant group differences emerged (all p 's > 0.05), effect sizes were large. Comparing current users to non-users, medium to large effect sizes in favor of non-users were observed for in-scanner recognition percent correct ($d = 0.53$), free recall total ($d = 0.70$), and free recall cluster score ($d = 0.64$), as well as HVLTL trial 1 ($d = 0.80$), HVLTL delayed free recall ($d = 0.96$), HVLTL delayed recall total clusters ($d = 0.72$) and HVLTL delay cluster score ($d = 0.76$). Comparing former users to non-users, medium to large effect sizes were observed for in-scanner recognition percent correct ($d = 0.86$), free recall cluster score ($d = 0.84$) as well as HVLTL trial 1 ($d = 0.50$) and HVLTL trial 1 cluster score ($d = 0.72$).

Typical activation pattern

We first evaluated the typical pattern of brain activation for our task in non-users. In the experimental > control contrast for the encoding task, we found diffuse activation in left PFC and left hippocampus with very little activation in the right hemisphere (p -value set at 0.05 and $k = 10$, see Figure 1). In the experimental > control contrast for the recognition task, we observed diffuse activation in bilateral PFC (p -value set at 0.05 and $k = 10$, see Figure 1).

Encoding

The overall F-test investigated the interaction of group (current, former, nonuser) by condition (experimental, control) for the encoding task (p -value set at 0.05 and $k = 10$, see Table 3). Group differences emerged in left anterior cingulate cortex (ACC) activity (BA32; $p = 0.01$, $k = 31$; see Figure 2). Follow-up analyses demonstrated that this difference was driven by greater activation among the non-users when encoding novel words than both the current users and former users. Activation in this region did not differ between current and former users ($p > 0.05$).

Recognition

The overall F-test examined the interaction of group (current, former, non-user) by condition (experimental, control) during recognition (p -value set at 0.05 and $k = 10$, see Table 3). In the right hemisphere, group differences were evident in the inferior frontal gyrus (BA9, $p =$

0.004, $k = 36$), middle frontal gyrus (BA10, $p = 0.02$, $k = 21$ and BA46, $p = 0.01$, $k = 44$), and ACC (BA32, $p = 0.02$, $k = 14$, see Figure 3). In the left hemisphere, group differences were found in middle frontal gyrus (BA9, 2 clusters: $p = 0.004$, $k = 73$ and $p = 0.02$, $k = 10$). Follow-up analyses demonstrated that differences in right inferior frontal gyrus (BA9), right middle frontal gyrus (BA10), and left middle frontal gyrus (BA9) were driven by greater activation among non-users compared with current and former users. Differences in ACC activity (BA32) were driven by greater activation among non-users compared with current users. Differences in right middle frontal gyrus (BA46) and left middle frontal gyrus (BA9) were driven by greater activation among non-users compared with former users. There were no differences in activation between current and former users in any of these regions. Activation in the left middle frontal gyrus (BA9) correlated with better performance on the in-scanner recognition task ($r_s = .54$, $p < 0.01$, see Figure 4).

DISCUSSION

Using fMRI to examine brain activity during a word list task, we found that both current and former cocaine users demonstrated reduced ACC activation while learning the words and reduced PFC activation during recognition testing. Lower PFC activation was significantly correlated with worse performance in recognition. These findings implicate alterations in ACC and PFC function as explanatory factors for our earlier demonstration of impaired verbal memory in HIV-infected cocaine users but not HIV-uninfected cocaine users (Meyer *et al*, 2013).

Neuroimaging studies in healthy controls implicate the ACC in verbal memory encoding (Bremner *et al*, 2004; Daselaar *et al*, 2003) and semantic coding (Kaneda and Osaka, 2008). Cocaine abusers show decreased ACC activation during working memory tasks (Kübler *et al*, 2005). Neuroimaging studies suggest that decreased dopamine-related activation of reward circuits may account for hypoactivation in the ACC (Volkow *et al*, 1993). Our finding of decreased ACC activation in former users is consistent with reports in the literature that cocaine abusers show reduced ACC activation three to four months after withdrawal (Volkow *et al*, 1992) and neuropsychological deficits up to 6 months of abstinence (Bolla *et al*, 2000; Di Sclafani *et al*, 2002; van Gorp *et al*, 1999). HIV-infected individuals with and without a history of cocaine abuse show decreased dopamine transporters in the dorsal striatum, and this reduction correlates with decreased cognitive performance on a variety of tests including verbal memory (Chang *et al*, 2008). Altered striatal dopaminergic function might therefore contribute to the hypoactivation in ACC observed in our current and former HIV-infected cocaine users as they encoded words.

In addition to reductions in ACC activation, current and former cocaine female cocaine users in our study showed reduced activation in left dorsomedial PFC (BA 9), right dorsolateral PFC (BA 9), and right anterior PFC (BA 10) during recognition. This is consistent with cocaine-dependent individuals demonstrating reduced PFC activation during working memory tasks (Moeller *et al*, 2010). However, our pattern of findings might be particular to females, given previous evidence for sex differences (Wetherington, 2007). Compared to male cocaine users, female cocaine users show relative decreases in glucose metabolism in the ACC, PFC (BA 9 and 10), and other brain areas comprising “control

networks” in response to cocaine cues (Volkow *et al*, 2011). Males show increased activation, suggesting a sex-related impairment in top down control in female cocaine abusers. Interpreted within the broader context of the literature, this pattern of ACC and PFC hypoactivation might represent a lack of top down control during a verbal memory test in female, predominately African-American, HIV-infected cocaine users.

To demonstrate the functional significance of ACC and PFC hypoactivation in our sample, we examined correlations between the magnitude of brain activation and performance on the in-scanner verbal memory task and on a clinical neuropsychological test of verbal memory (i.e., HVLT). We found that activation in BA9 was positively correlated with performance on the in-scanner recognition test, an effect driven by current drug users ($r_s = .66$, $p < 0.05$, $R^2 = .48$). Given that nonusers activated this region more than users, this pattern of effects suggests that more engagement of BA9 during recognition facilitated recognition performance. We did not find the hypothesized relationship between semantic clustering and prefrontal cortex activation during the verbal memory task. Given our sample size, we may have been underpowered to detect this association. In a separate analysis of the data, when we extracted the first eigenvariate of all voxel values contained in 3-mm radial sphere around the peak voxel for the ACC cluster, activation was correlated with better performance on the free recall cluster score on the in-scanner task $r = .398$, $p = .03$) as well as trial 1 cluster score on the HVLT ($r = .38$, $p = .04$).

This study had several limitations. First, the lack of an uninfected control group precludes the investigation of the interactive effects of HIV and cocaine use. However, findings from our previous study (Meyer *et al*, 2013) indicated that illicit drug use negatively impacted verbal memory only in HIV-infected women; therefore we focused this investigation on women infected with HIV. Second, the cross-sectional design does not allow for investigation of the effects of chronic cocaine use on cognitive function over time. We interpreted the results as indicative of the impact of cocaine on brain systems, but we cannot rule out the possibility that these findings reflect longstanding differences in brain function that may have preceded and possibly contributed to cocaine use. Third, our sample sizes were too small to detect group differences on behavioral outcomes; however, effect sizes indicated large differences in performance in current and former users compared to non-users. A review on HIV and drug abuse pointed out the dearth of neuroimaging studies investigating HIV and cocaine use (Martin-Thormeyer and Paul, 2009). The current study is the largest neuroimaging study to examine the impact of cocaine use on brain function in women. The only other neuroimaging on HIV-infected cocaine users ($n = 11$) and nonusers ($n = 24$) had similar sample sizes (Chang *et al*, 2008). Fourth, although toxicology screens were run before the neuroimaging assessment, self-report data was used to determine drug use categories. If women who used cocaine did not report their use, the impact of cocaine on brain function may be underestimated. Lastly, as expected, drug users were more likely to have Hepatitis C co-infection and to smoke, two factors which some studies, but not all, have shown to affect cognition among HIV-infected individuals (Bryant *et al*, 2013; Ellis *et al*, 2011; Letendre *et al*, 2005; Wojna *et al*, 2007). Since substance abuse, especially injecting practices, increases risk of HCV acquisition, HCV infection among a cohort of HIV-infected drug-abusing women is considered an organismic confound, and we are

unable to fully disentangle. We cannot rule out the possibility that these factors acted independently or interactively with cocaine to influence brain function. This is a limitation inherent in this population and it is not possible to statistically covary for these effects because HCV does not freely covary between groups. Importantly, a recent WIHS study found that active HCV infection was not associated with cognitive impairment in 1338 women (Crystal *et al*, 2012). Additionally, we previously demonstrated in a sample of 1395 WIHS participants that illicit drug use significantly predicted verbal memory deficits even when controlling for smoking and HCV infection (Meyer *et al*, 2013). We did not find a relationship between HCV infection and the beta estimates of activation in the ACC or PFC (all p 's > 0.05); although HCV infection was associated with worse performance on several of our verbal memory outcomes (in scanner free recall total and cluster score, HVLT delayed free recall, T1 cluster score, delay cluster score). In the current sample there was no relationship between cigarette smoking and any of our verbal memory outcomes or the beta estimates of activation in the ACC or PFC (all p 's > 0.05).

When considered in the broader context of literature, our findings suggest an overlap between the neural substrates of memory impairment and compulsive drug taking in HIV-infected cocaine using women. Hypoactivation in the ACC may be one of the mechanisms by which dopaminergic disruption leads to lack of control over drug intake (Volkow *et al*, 2002) and lack of control over cognitive processes. Broadly, these findings suggest that the same brain areas that are implicated in cocaine addiction in women (i.e. ACC and PFC) might contribute to cocaine-related memory deficits. Both drug use and cognitive impairment are associated with suboptimal adherence to HIV medications and consequent acceleration in disease progression (Hinkin *et al*, 2004). Females show higher rates of cocaine dependence during adolescence (Chen and Kandel, 2002; O'Brien and Anthony, 2005) and preclinical studies show that females have a greater propensity to self-administer cocaine (Morse *et al*, 1993). Continued investigation is needed to better understand the extent to which these relationships reflect common disruptions to neural circuitry and the extent to which these effects might be sex-dependent (Andersen *et al*, 2012).

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Figure 1.

Typical pattern of activation during encoding and recognition in HIV-infected women who never used cocaine.

Note: Encoding: activation in nonusers during encoding of novel words (experimental condition) minus repeated encoding of the same two words (control condition); $p = 0.05$, $k = 10$

Note: Recognition: activation in nonusers during recognition of novel words (experimental condition) minus repeated recognition of the same two words (control condition); $p = 0.05$, $k = 10$.

Figure 2.

Encoding: Interaction of group (current, former, non-user) x condition (experimental, control)

Note: $p = 0.01$, $k = 30$. Nonusers activated left BA32 more during encoding than both current users and former users.

Figure 3.

Recognition: Interaction of group (current, former, nonuser) x condition (experimental, control)

Note: All p 's > 0.05 and $k > 10$. A) Non-users activated right BA9 more during recognition than both current users and former users, $p = 0.004$, $k = 36$; B) Non-users activated left BA9 more during recognition than both current users and former users, $p = 0.004$, $k = 73$; C) Non-users activated right BA46 more during recognition than former users, $p = 0.013$, $k = 44$; D) Non-users activated left BA9 more during recognition than former users, $p = 0.02$, $k = 10$; E) Nonusers activated right BA10 more during recognition than both current users and former users, $p = 0.02$, $k = 21$; F) Nonusers activated right BA32 more during recognition than current users, $p = 0.02$, $k = 14$.

Figure 4.

Behavioral correlates of activation in left BA9 during recognition

Note: Activation in left middle frontal gyrus (BA9) during recognition positively correlated with percent correct on in-scanner recognition task ($r_s = .54$, $p < 0.01$, $R^2 \text{ linear} = 0.196$).

Table 1

Demographic and clinical characteristics for HIV-infected women as a function of crack cocaine use.

Background Characteristics (%)	Current (n = 10)	Former (n = 11)	Nonuser (n=9)
Age (M, SD)	46.1 (4.3)	43.8 (7.2)	42.3 (10.4)
WRAT-R scaled score (M, SD)	92.3 (8.3)	87.9 (20.2)	83.8 (19.9)
Years of education (M, SD)	12.4 (1.7)	12.5 (2.4)	14.4 (2.8)
Race/Ethnicity			
Black, non-Hispanic	100%	91%	100%
White, non-Hispanic	0%	9%	0%
Hepatitis C antibody positive *	50%	18%	0%
CES-D 16	40%	9%	22%
Current heavy alcohol use ^a	20%	9%	11%
Currently smoking *	80%	55%	22%
Current marijuana use	20%	18%	11%
CD4 nadir (M, SD)	213 (124)	372 (144)	319 (300)
CD4 count (cells/mm ³)			
> 500	30%	82%	56%
200 and < 500	50%	18%	44%
< 200	20%	0%	0%
Viral Load			
Undetectable	50%	91%	44%
Less than 10,000 copies/ml	20%	9%	33%
10,000 copies/ml	30%	0%	22%
Medication Use			
No cART	30%	9%	22%
cART + < 95% compliance	10%	0%	22%
cART + > 95% compliance	60%	91%	56%

Notes:

*
p < 0.05.

WRAT-R = Wide Range Achievement Test – Revised, CES-D = Center for Epidemiological Studies Depression Scale, cART = combination antiretroviral therapy, “Current” refers to use within 6 months.

^aThe National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommended limits for women are no more than three drinks per day and no more than seven drinks per week (Willenbring *et al*, 2009). “Heavy alcohol use” refers to amounts in excess of daily limits

Table 2

Verbal memory performance for HIV-infected women as a function of crack cocaine use.

	CURRENT (n = 10)	PAST (n = 11)	NONUSER (n=9)	Current vs Nonuser Cohen's d	Past vs Nonuser Cohen's d
In-scanner verbal memory task					
Recognition percent correct (M)	65% (11%)	64% (6%)	70% (8%)	0.53	0.86
Free recall total (M, SD)	3.5 (3.2)	4.4 (2.6)	6.0 (3.9)	0.70	0.49
Free recall cluster score (M,SD)	1.4 (2.0)	1.2 (1.3)	3.0 (3.0)	0.64	0.84
Hopkins Verbal Learning Task (HVLT)					
Trial 1	5.7 (1.3)	6.0 (1.9)	6.9 (1.7)	0.80	0.50
Immediate recall (trials 1–3 total)	22.9 (4.0)	24.2 (4.5)	24.3 (4.5)	0.33	0.02
Delayed free recall	6.9 (2.5)	8.7 (2.5)	9.2 (2.3)	0.96	0.21
Recognition	10.7 (1.1)	11.2 (1.0)	10.7 (1.9)	0.00	0.34
Trial 1 cluster score *	.80 (.78)	1.5 (.93)	2.3 (1.3)	1.44	0.72
Immediate total cluster score	6.3 (4.3)	7.3 (5.3)	7.0 (2.9)	0.19	0.07
Delayed recall total clusters	1.5 (1.2)	2.0 (1.0)	2.4 (1.3)	0.72	0.35
Delay cluster score	2.1 (1.7)	4.2 (3.3)	3.7 (2.5)	0.76	0.17

Note:

* p < 0.05. Trial 1 cluster score differed by drug use group, p = 0.011; differences were between current and nonusers where current users performed worse than nonusers, p = .006.

Group differences in activation during encoding and recognition: Brain region, Brodmann area (BA), SPM coordinates, cluster size (k), and statistical information

Table 3

Brain Region	BA	Coordinates (x, y, z)	Cluster size (k)	Z score	P-value (uncorrected)	Follow up test
ENCODING						
L anterior cingulate	32	-6, 20, 46	31	2.31	$p = .010$	Nonusers > Current users Nonusers > Former users
RECOGNITION						
R inferior frontal gyrus	9	46, 12, 30	36	2.67	$p = 0.004$	Nonusers > Current users Nonusers > Former users
L middle frontal gyrus	9	-44, 36, 40	73	2.62	$p = 0.004$	Nonusers > Current users Nonusers > Former users
R middle frontal gyrus	46	44, 32, 20	44	2.22	$p = 0.013$	Nonusers > Former users
L middle frontal gyrus	9	-58, 22, 32	10	2.06	$p = 0.020$	Nonusers > Former users
R middle frontal gyrus	10	40, 52, 18	21	2.05	$p = 0.020$	Nonusers > Current users Nonusers > Former users
R anterior cingulate	32	10, 20, 46	14	2.00	$p = 0.023$	Nonusers > Current users

Note: Brain regions that showed significant group differences in the overall F-test and the follow up tests that drove the interaction.