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Cocaine dependence modulates the effect of HIV infection on brain activation during intertemporal decision making

Christina S. Meade^{a,b}, Andrea L. Hobkirk^c, Sheri L. Towe^d, Nan-kuei Chen^{e,f}, Ryan P. Bell^g, and Scott A. Huettel^{h,i,j}

^aDuke University School of Medicine, Department of Psychiatry & Behavioral Sciences, Durham, NC, 27705, USA

^bDuke University, Department of Psychology & Neuroscience, Durham, NC, 27708, USA

^cDuke University School of Medicine, Department of Psychiatry & Behavioral Sciences, Durham, NC, 27705, USA

^dDuke University School of Medicine, Department of Psychiatry & Behavioral Sciences, Durham, NC, 27705, USA

^eBrain Imaging and Analysis Center, Duke University Medical Center, Durham, NC 27710, USA

^fDuke University School of Medicine, Department of Radiology, Durham, NC, 27705, USA

^gDuke University School of Medicine, Department of Psychiatry & Behavioral Sciences, Durham, NC, 27705, USA

^hDuke University, Department of Psychology & Neuroscience, Durham, NC, 27708, USA

ⁱBrain Imaging and Analysis Center, Duke University Medical Center, Durham, NC 27710, USA

^jDuke University, Center for Cognitive Neuroscience, Durham, NC, 27708, USA

Abstract

Background—Both HIV infection and chronic cocaine use alter the neural circuitry of decision making, but the interactive effects of these commonly comorbid conditions have not been adequately examined. This study tested how cocaine moderates HIV-related neural activation during an intertemporal decision-making task.

Methods—The sample included 73 participants who differed on cocaine and HIV status (18 COC+/HIV+, 19 COC+/HIV-, 19 COC-/HIV+, 17 COC-/HIV-). Participants made choices

Corresponding author: Christina S. Meade, PhD, Duke University, Box 102848, Durham, NC 27708, USA, christina.meade@duke.edu, tel. 919-613-6549, fax. 919-660-9234.

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between smaller, sooner and larger, delayed rewards while undergoing functional MRI. Choices varied in difficulty based on subjective value: hard (equivalently valued), easy (disparately valued), and control choices. A mixed-effects model controlling for education and smoking identified main and interactive effects of HIV and COC during hard relative to easy choices (difficulty contrast).

Results—COC+ status was associated with lower activation in bilateral frontal gyri and right insular and posterior parietal cortices. HIV+ status was associated with higher activation in the visual cortex, but lower activation in bilateral prefrontal cortices and cerebellum and left posterior parietal cortex. COC moderated the effects of HIV in several clusters centered in the bilateral prefrontal cortices and cerebellum. In post-hoc analyses, there were significant effects of HIV status on activation for COC+, but not COC-, participants; interaction effects remained after controlling for polysubstance use.

Conclusion—Cocaine use may diminish the compensatory neural activation often seen among HIV+ samples during decision making. Our results highlight the importance of examining the neuropsychiatric effects of comorbid medical conditions to identify potential neural targets for cognitive remediation interventions.

Keywords

functional magnetic resonance imaging (fMRI); cocaine dependence; drug addiction; HIV/AIDS; decision making; temporal discounting

1. Introduction

Drug abuse disrupts neural circuitry through altered dopaminergic transmission in limbic regions and reduced frontal activation in response to non-drug stimuli (Feltenstein & See, 2008; Volkow et al., 2004). These changes contribute to decision-making deficits that are associated with impulsive and risky behaviors (Gonzalez et al., 2005; Wardle et al., 2010). An important aspect of impulsivity is intertemporal discounting, which is the tendency to devalue delayed rewards (Ainslie, 1975). Excessive discounting is associated with a range of health risk behaviors, including drug abuse, problematic gambling, and risky sex (Bickel et al., 2012). Individuals who abuse drugs have an exaggerated preference for immediate rewards, with the largest effect for stimulants ($d = .87$) and moderate effects for alcohol and nicotine ($d = .50$ and $.56$, respectively) (MacKillop et al., 2011).

The use of illicit stimulants is disproportionately high among HIV-positive persons. In a large multi-city study of HIV patients in the United States, 9% had used crack-cocaine and 9% had used methamphetamine in the past 3 months (Mimiaga et al., 2013), compared to 0.1% and 0.3% in the general population, respectively (Substance Abuse and Mental Health Services Administration, 2016). While the prevalence of other drugs is also higher in HIV-positive persons (e.g., 24% vs. 8% for marijuana) (Mimiaga et al., 2013; Substance Abuse and Mental Health Services Administration, 2016), the discrepancy is not as stark as it is for stimulants. Like in the general population (Ford et al., 2009; Hartzler et al., 2011), polydrug use is common among HIV-positive persons (Mimiaga et al., 2013), with marijuana and alcohol most commonly co-occurring with cocaine (Green et al., 2010; Parsons et al., 2014).

Stimulant abuse has been found to accelerate HIV disease progression (Carrico, 2010), and it may also exacerbate HIV effects on neural substrates that support decision making. HIV can alter brain structure and function, with HIV-positive persons showing hyperactivation compared to HIV-negative counterparts in frontostriatal regions (Plessis et al., 2014; Valcour et al., 2011). One study on decision making found that HIV-positive participants had greater activation in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), insula, and dorsal/corpus striatum during risky choices (Connolly et al., 2014). This hyperactivity may be a compensatory mechanism for maintaining cognitive performance in the context of decreased efficiency due to neural injury (Barulli & Stern, 2013; Stern, 2009), including neuroHIV (Chang et al., 2004; Connolly et al., 2014; Ernst et al., 2009; Melrose et al., 2008).

Intertemporal discounting relies on regions that support valuation [e.g., ventral striatum, ventromedial prefrontal cortex (vmPFC)] and cognitive control [e.g., dlPFC, ACC, posterior parietal cortex (PPC)] (Kable & Glimcher, 2007; McClure et al., 2004; Peters & Buchel, 2011; Tanaka et al., 2004). The cognitive control network is increasingly recruited during “hard” choices in which the subjective value of the immediate and delayed rewards are equivalent compared to “easy” choices in which the values are highly discrepant (McClure et al., 2004; Tanaka et al., 2004). The few fMRI studies examining intertemporal discounting in substance users have generally reported hypoactivity in task-relevant regions. In two studies on methamphetamine, active users had smaller increases in signal change between hard and easy choices in dlPFC, ACC, and PPC compared to healthy controls (Hoffman et al., 2008; Monterosso et al., 2007). One study on nicotine reported that smokers had less activation in the precuneus, posterior cingulate, caudate, and hippocampus during decisions than non-smokers (Kobiella et al., 2014), while another found that smokers had smaller increases in activation during hard compared to easy choices in the right frontoparietal network (Clewett et al., 2014). In contrast, a study on alcohol found no differences in activation during an intertemporal choice task between alcohol-dependent men and healthy controls (Schmaal et al., 2014). Finally, in an HIV-positive sample, cocaine users had smaller increases in activation than non-users during hard compared to easy choices in the bilateral ACC and precentral gyrus and right dl/vIPFC (Meade et al., 2011). However, without HIV-negative comparison groups, this study could not identify the unique effects of HIV versus cocaine.

Although cocaine and HIV disrupt neural processing in similar frontostriatal regions, their mechanisms differ. Chronic cocaine use causes functional neuroadaptations within reward circuitry, including ACC, dlPFC, orbitofrontal cortex (OFC), and basal ganglia, that produce a reorganization of reward salience towards drug-related stimuli (Everitt & Robbins, 2016; Volkow et al., 2011). In contrast, HIV indirectly causes widespread cortical and subcortical damage via neurotoxic viral proteins and neuroinflammation (Burdo et al., 2013; Guha et al., 2016; Hong & Banks, 2015; Lindl et al., 2010). Thus, while cocaine users have hypoactivity due to circuitry that has become under-responsive to non-drug stimuli, HIV-positive persons may show compensatory hyperactivation in response to neural and glial cell damage.

In a prior fMRI study of intertemporal discounting, we found that HIV was associated with greater activation in the bilateral dlPFC, dorsomedial PFC (dmPFC), and frontal pole and the

left PPC during easy trials and in the bilateral ACC and right frontal pole during hard trials (Meade et al., 2016). This study included “non-drug users” who had no history of hard drug use (e.g., opioids, stimulants), though moderate alcohol and marijuana use was permitted. As an extension, the current study examined the independent and interactive effects of cocaine and HIV on neural activation during intertemporal decision making. In addition to the sample of non-drug users from the prior analysis, we added a sample of active cocaine users, many of whom also used alcohol and marijuana. We expected to replicate our prior finding of HIV-associated hyperactivation in frontoparietal regions. The primary hypothesis was that cocaine would be independently associated with lesser activation in the dlPFC, ACC, and PPC during difficult choices, and that cocaine would moderate the effect of HIV on neural function, such that it would diminish HIV-associated hyperactivation in frontoparietal regions.

2. Material and methods

2.1 Participants

The sample included adults aged 18-55 years who were active cocaine users with HIV (COC+/HIV+, n= 18) and without HIV (COC+/HIV-, n=19) and non-cocaine users with HIV (COC-/HIV+, n=19) and without HIV (COC-/HIV-, n= 17). The COC+ groups met the following criteria: lifetime cocaine dependence, regular cocaine use for 1 year, and repeated use in the past month (defined as 2 days or positive drug screen). Current alcohol and marijuana dependence were permitted, although cocaine dependence had to be the principal diagnosis. The COC- groups met the following criteria: no lifetime cocaine use disorder, no history of regular cocaine use, 0 days of cocaine use in the past year, cocaine-negative drug screen, and no current alcohol or marijuana dependence. Alcohol, marijuana, and nicotine use were permitted in all groups. For other drugs, individuals were excluded for lifetime regular use or dependence, use in the past year, or a positive drug screen. HIV-negative status was verified by an OraQuick© rapid test, and HIV-positive status was verified by medical record review.

Additional exclusion criteria were: English non-fluency or illiteracy; <8th grade education; severe learning disability; serious neurological disorders not due to HIV (e.g., seizure disorder, multiple sclerosis); acute opportunistic brain infections or history of such infections without return to normal cognition; severe head trauma with loss of consciousness >30 minutes and persistent functional decline; severe mental illness; current use of antipsychotic or mood stabilizing medications; MRI contraindications; and/or impaired mental status. These exclusions are consistent with current guidelines for classifying contributing or confounding conditions to HIV-associated neurocognitive disorders (Antinori et al., 2007).

2.2 Procedures

Participants were recruited via advertisements in local newspapers, websites, community-based organizations, and infectious diseases clinics. After a brief pre-screener, individuals completed an in-person screening. Eligible participants returned for the MRI scan.

Procedures were approved by the institutional review boards at Duke University Health System and University of North Carolina at Chapel Hill.

2.3 Measures

Participants completed clinical interviews, computerized surveys, urine drug screening, and pregnancy tests. Module E of the Structured Clinical Interview for DSM-IV-TR identified substance use disorders (First et al., 1996), and the Addiction Severity Index-Lite assessed substance use and associated impairments (McLellan et al., 1992). Healthcare records were reviewed to obtain medical history and, if applicable, HIV disease indicators (e.g., CD4 cell counts). Timeline follow-back methodology was used to assess substance use in the past 90 days at screening and past 30 days at the MRI scan (Robinson et al., 2014).

2.4 fMRI task

The Intertemporal Choice Task (ICT) was designed to probe cognitive control during hard relative to easy monetary choices (Meade et al., 2011; Monterosso et al., 2007). Given that the difficulty of choices is subjective, the ICT is individualized for each participant. On the day of the scan, participants completed a modified version of the Monetary Choice Questionnaire (MCQ) to determine their delay discounting score (Kirby et al., 1999; Towe et al., 2015). Participants were presented with 38 choices between smaller, immediate and larger, delayed rewards. The monetary values and duration of the delay were matched to those in ICT. k-values associated with each trial were computed using the hyperbolic discounting equation: $V_{\text{immediate}} = V_{\text{delayed}} / (1 + kD)$, where V is value in dollars and D is delay in days. Higher k-values indicate greater discounting (range: 0.001 to 3.108).

Details of the current version of the ICT have been previously described (Meade et al., 2016). In brief, the ICT consists of monetary choices between smaller, sooner rewards (\$3-\$53) available in 0-6 days, and larger, delayed rewards (\$10-\$55) available in 1-30 days. Trials are characterized by degree of difficulty: “hard,” “easy,” and “control,” with choices individualized based on participants' pre-determined k-value from the MCQ. The delayed options were constant across participants, while the reward amount for the sooner options were computed. For hard choices, the exact k-value was used to generate sooner values that were subjectively equivalent to the delayed options. For easy choices, the k-value was multiplied by 10 or 0.1, generating sooner values that were subjectively much less or much more valued than the delayed values. For control choices, the sooner reward was \$0 or equivalent to the delayed reward. Participants completed two runs of 60 trials for a total of 120 trials (48 hard, 48 easy, 24 control), with the order randomized across participants (Figure 1). Participants' choice on a randomly selected trial was honored by adding the reward (scaled to \$10 max) to a gift card on the day corresponding with their choice (i.e., 0-30 days from the scan).

2.5 MRI data acquisition

Functional and structural MRI data were acquired using a 3.0T GE scanner with an 8-channel head coil. Whole-brain blood-oxygen-level dependent (BOLD) images were collected using high-throughput T2*-weighted echo-planar imaging with the following parameters: TR= 2000ms; TE= 27ms; FOV= 24.0cm; flip angle= 77°; in-plane matrix size=

64 × 64; and slice thickness= 3.80mm. This resulted in functional data from 39 axial slices with voxels of 3.75mm × 3.75mm × 3.80mm. High-resolution T1-weighted structural images were acquired with the following parameters: TR= 8.096ms; TE= 3.18ms; FOV= 25.6cm; flip angle= 12°; in-plane matrix size= 256 × 256; slice thickness= 1mm; and number of slices= 166.

Quality control—Of 88 study completers, 11 were excluded for >25% incorrect choices on control trials and three for skipping >20% of trials. One participant and three runs were excluded for mean relative motion >0.3mm. Mean change in framewise displacement was calculated for each run with FSL's motion outliers tool and averaged for each participant. There was no significant group effect on framewise displacement in the final sample [$F(3,69)= 1.88, p= .14$]. Six motion parameters calculated via FSL's MCFLIRT and volume motion outliers were included as regressors of no interest in the first level analyses to control for linear movement and large, nonlinear spikes in motion, respectively.

2.6 Data analysis

Non-MRI data—Descriptive statistics and group comparisons were run on demographic, substance use, and HIV disease characteristics and metrics of task performance using SPSS 24.0.0.0 (IBM Corp, 2016). A series of 2 (COC group) × 2 (HIV status) between-subjects ANOVAs tested for main and interaction effects on task performance.

MRI data—Imaging data were processed using FSL 5.0.1 (FMRIB Software Library, Oxford, UK) (Jenkinson et al., 2012). Functional images were first aligned to the high-resolution T1-weighted main structural image [full search linear registration, 12 degrees of freedom (DOF)] and then to MNI152 standard space (normal search nonlinear registration, 12 DOF, 10mm warp resolution) (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Functional images were corrected for motion (MCFLIRT) and slice timing, spatially smoothed using a 5-mm FWHM Gaussian kernel, and highpass temporal filtered. Individual time-series statistical analysis was carried out using FILM with local autocorrelation correction. An event-related design was utilized for our regressors of interest (hard, easy, and control trials), which were convolved with a double-gamma hemodynamic response function. A first-level analysis was conducted for each run and each individual using a general linear model (GLM) consisting of the contrasts of easy choices (easy>control), hard choices (hard>control) and difficulty contrast (hard>easy). The motion-correction time courses and outliers were included as covariates of no interest.

For each participant, data from individual runs were combined using a fixed-effects analysis (Beckmann et al., 2003). Mean task activation for each group and contrast were modeled using fixed-effects. Main and interaction effects were examined using a 2 (COC group) × 2 (HIV status) between-subjects mixed-effects (FLAME 1+2) ANOVA, with years of education and smoking status included as covariates of no interest. All group-level results were cluster thresholded at $Z>2.3$ and $p<.05$, corrected over the entire brain using Gaussian random field theory (Worsley et al., 1992). Mean percent signal change was extracted from each significant cluster using Featquery. For the main effects, group averages were examined to determine directionality. To interpret the interaction effects, the least squares difference

between the marginal means of percent signal change were contrasted across HIV status within COC+ and COC- groups separately. The Harvard-Oxford cortical and subcortical structural atlases were used to identify the center of gravity and additional neural regions within significant clusters (Desikan et al., 2006). Post-hoc ANOVAs examined interaction effects on percent signal change while controlling for heavy alcohol and marijuana use, and to test for 3-way interactions with sex.

3. Results

3.1 Participant characteristics

Table 1 summarizes the sample by group. Overall, participants were 63% male and ranged in age from 22 to 55 years ($M = 42.73$, $SD = 8.32$). The majority were non-Hispanic (97%) and Black (82%). Most had at least a high school diploma or GED certificate (86%), with a mean of 13.41 ($SD = 2.54$) years of education. There were no significant group differences on demographics, but COC+ had meaningfully lower socio-economic status than COC-.

Among COC+, participants on average reported on average using cocaine regularly for 17.53 years ($SD = 8.35$) and on 32.16 days of the past 90 ($SD = 24.58$). The majority (92%) met criteria for current cocaine dependence. Most (87%) smoked crack-cocaine; the rest reported nasal administration. There were no significant differences between HIV+ and HIV- participants on cocaine characteristics. Compared to COC-, COC+ were more likely to smoke cigarettes [$\chi^2(1) = 16.85$, $p < .001$], drink alcohol heavily [$\chi^2(1) = 20.38$, $p < .001$], and use marijuana [$\chi^2(1) = 5.44$, $p < .020$] in the past 30 days.

HIV+ participants had been diagnosed for an average of 10.22 years ($SD = 7.48$, range: 4 months to 26 years), and 43% had an AIDS diagnosis. All were currently in HIV care, and all but one was receiving antiretroviral therapy. Nadir CD4 cell counts ranged 0-718 (Median = 198, IQR = 343). Current CD4 cell counts ranged from 36-2,377 (Median = 598, IQR = 540), and 24% had a detectable viral load at 50 copies/mL. There were no significant differences between COC+ and COC-.

3.2 Behavioral performance

Table 2 summarizes task performance by group. On the MCQ, there was a main effect of cocaine [$F(1,69) = 5.87$, $p = .018$], with COC+ having greater discounting than COC-. This effect remained after controlling for education [$F(1,68) = 6.86$, $p = .011$]. There were no HIV or interaction effects.

During the ICT, latency to respond following the 2s presentation period was longest for hard trials ($M = 1.46$ s, $SD = 0.40$), intermediate for easy trials ($M = 1.30$ s, $SD = 0.36$), and shortest for control trials ($M = 1.08$ s, $SD = 0.33$). There was a main effect of trial type [$F(2,144) = 68.19$, $p < .001$] and an interaction effect for trial type by group [$F(6,138) = 2.59$, $p = .021$]. While other groups gradually increased response time as trial difficulty increased, the COC+/HIV+ had a larger increase between control and easy trials and no additional increase between easy and hard trials. On average, participants responded as predicted on 94.84% ($SD = 6.10$) of control trials and 82.27% ($SD = 17.86$) of easy trials. For hard trials, the sooner and delayed choices were equivalently valued; as expected, participants chose the

two options similarly often (sooner: $M = 54.44\%$; $SD = 26.34$). There were no main or interaction effects of HIV and cocaine on choice for all three trial types, even when controlling for education.

3.3 Task-related brain activation

Figure 2 shows the patterns of activation for the three contrasts. Both HIV- groups demonstrated the expected pattern, in which activation of cognitive control regions was evident during hard but not easy choices. The difficulty contrast shows that both HIV- groups had greater activations in bilateral dorsal ACC (dACC), dmPFC, vlPFC, dlPFC, lateral OFC (lOFC), PPC [superior lateral occipital cortex (LOC), inferior parietal lobule (IPL), superior parietal lobule (SPL)], inferior LOC, and occipital pole. For HIV+ groups, activation in cognitive control regions was evident during easy choices, with minimal additional increases during hard choices. The COC+/HIV+ was the only group that showed lower activation during hard relative to easy choices, resulting in deactivation in the difficulty contrast.

3.4 Main effects of cocaine and HIV

The F-tests revealed main effects of both COC and HIV for the difficulty contrast (Figure 3, Table 3). COC+ was associated with lower activation than COC- in three clusters that included the bilateral pre- and postcentral gyri, vlPFC, and visual cortex, the right insula and IPL, and the left dlPFC and central operculum. Relative to HIV-, HIV+ was associated with higher activation in one cluster encompassing the bilateral visual cortex and posterior precuneus and lower activation in six clusters that included bilateral frontal pole, dmPFC, dlPFC, vlPFC, dACC, inferior temporal gyrus, inferior LOC, and cerebellum, the left lOFC, insula, PPC (superior LOC, IPL/SPL), and middle temporal gyrus.

3.6 Cocaine-by-HIV interaction effects

Interaction effects emerged for the difficulty contrast in five clusters that encompassed bilateral frontal pole, vlPFC, dlPFC, dmPFC, precentral gyrus, juxtapositional lobule, and cerebellum. To illustrate these effects, Figure 4 shows the percent signal change for the easy and hard contrasts by group in representative clusters. All groups except HIV+/COC+ had higher mean activation for hard compared to easy choices. In contrast, HIV+/COC+ had higher mean activation for easy choices, but their mean activation was less for hard choices than for easy choices. This resulted in a negative percent signal change in the difficulty contrast. Post-hoc analyses compared the least square mean difference (M_{diff}) in percent signal change for each interaction cluster by HIV status in COC+ and COC- groups separately. In COC+, there were significant differences between HIV+ and HIV- (M_{diff} ranged 0.14 to 0.28, all $p < .05$). In COC-, there were no significant differences between HIV+ and HIV- (M_{diff} ranged -0.07 to 0.02, all $p > .05$). In post-hoc analyses controlling for heavy alcohol and marijuana use, the HIV*COC interaction effect remained significant in all clusters (p -values ranged from .001 to .045), and there were no independent effects for alcohol nor marijuana (all $p > .05$). Finally, there were no main or interactive effects of sex in these clusters.

4. Discussion

This study demonstrates that cocaine use can exacerbate HIV-associated alterations in neural functioning within cognitive control regions that are relevant to decision making. In hard (equivalently valued) compared to easy (disparately valued) choices, we found independent effects of both cocaine and HIV, as well as interaction effects. Specifically, cocaine moderated the effects of HIV, such that HIV+ cocaine users had lower activation bilaterally in the dl/vlPFC, dmPFC, and frontal pole compared to all other groups. These findings have implications for understanding impairments in decision making and real-world risk behaviors that are prevalent among HIV+ cocaine users, such as non-adherence to antiretroviral medications (Baum et al., 2009; Hinkin et al., 2007) and unprotected intercourse with multiple partners and sex trading (Harzke et al., 2009; Timpson et al., 2010).

The identified HIV effects in this study contribute to a growing neuroHIV literature on alterations in the fronto-striatal-parietal network during higher-order cognitive tasks (Plessis et al., 2014), including our previous report of HIV-associated hyperactivity in response to intertemporal choice in a sample of non-drug users (Meade et al., 2016). In this analysis, however, the HIV-associated hyperactivity was isolated to the bilateral visual cortex and posterior precuneus. Unexpectedly, we found hypoactivity in the bilateral dACC, mPFC, vl/dlPFC and left PPC regions typically engaged in intertemporal decision making. We speculate that this difference was driven by the inclusion of active cocaine users, who demonstrated a different pattern of activation.

The most novel result of the present study is that cocaine use appears to make HIV+ persons vulnerable to greater alterations in brain functioning during decision making. When making hard compared to easy choices, interaction effects emerged in multiple prefrontal regions implicated in cognitive control, with hypoactivation evident only for HIV+ persons. This result is consistent with a prior study of intertemporal discounting conducted in an HIV+ sample, which found hypoactivity in similar regions among active cocaine users relative to non-drug users (Meade et al., 2011). Additionally, in a sample of HIV+ women, lifetime cocaine use was associated with hypoactivity in the ACC and vl/dlPFC during components of a verbal memory task when compared to non-users (Meyer et al., 2014). Altogether, these findings suggest that co-occurring cocaine use may further alter the effects of HIV on neural functioning.

Of note, many cocaine users in our sample also used marijuana and/or alcohol. We excluded individuals with a history of other drug use, but permitted alcohol and marijuana use in all groups due to their pervasiveness among cocaine users. Since the prevalence of these substances was indeed higher in cocaine users compared to non-users, the identified effects may not be specific to cocaine, but rather the combined effects of polydrug use. Prior studies have found additive effects of alcohol and HIV on the brain (i.e., ventricular enlargement, callosal thinning, white matter integrity) (Rosenbloom et al., 2010), but a recent study reported no interactive effects of marijuana and HIV on brain structure (Thames et al., 2017). Controlling for alcohol and marijuana use in post-hoc analyses did not change the HIV by cocaine interaction effect on neural activation. However, our study was not designed

to test for the effects of polysubstance use. Further research is necessary to characterize whether the neurobehavioral alterations arising from polydrug use differ from those observed in single-drug use.

Though this study has multiple strengths, there are also limitations. Despite our sample size of 73, we may have been underpowered to detect small effects given the 2×2 design. In addition, prior studies have found that women may be more vulnerable than men to HIV-associated neurocognitive impairments (Martin et al., 2011; Martin et al., 2016), especially in the context of co-occurring drug abuse (Keutmann et al., 2016). While we did not detect an effect of sex, larger sample sizes are needed to sufficiently explore the potential moderating effects of sex and other biological factors. Furthermore, the cross-sectional design precludes inferences regarding causality. With one exception (Ernst et al., 2009), fMRI studies in the neuroHIV field have been cross-sectional. Longitudinal designs that can track the course of both HIV disease progression and substance abuse on neurobehavioral functioning are needed to draw clear conclusions about the complex effects of these two conditions.

5. Conclusion

This study provides evidence that HIV+ cocaine users, many of whom also abuse other substances, may be especially vulnerable to deficits in neural functioning during decision making due to the independent and interactive effects of both HIV infection and cocaine dependence on the brain. In HIV+ persons, cocaine use may impair the brain's ability to mount a compensatory neural response during difficult intertemporal choices. Future research should examine how these neural changes affect cognitive function and real-world decision making. Effective decision making is integral for maintaining independence and quality of life, particularly for individuals living with HIV who make decisions regarding the immediate and delayed benefits of health behaviors such as medication adherence, healthcare visits, and sexual risk. The development of clinical interventions to treat these cognitive deficits are urgently needed.

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Highlights

- HIV infection and chronic polydrug abuse are commonly comorbid conditions.
- Although mechanisms differ, decision making is deficient in both conditions.
- We used an fMRI decision task to examine neural main and interactive effects.
- Cocaine dependence moderated neural function of decision making in HIV infection.
- HIV+ polydrug cocaine users may be prone to decisions with harmful consequences.

Figure 1.

Illustration of the Intertemporal Choice Task (ICT). For each trial, there was a 2s presentation period, followed by a 4s response period. To signal the beginning of the response period, left and right arrows appeared on the screen to indicate which button on the response pad corresponded to each of the two options. The left/right location of the sooner and delayed options were randomized across trials within individuals to minimize lateralized motion preparation to the choice period. Once a choice was made, that choice was underlined. During the inter-trial interval (ITI), which ranged 2-8 s ($M = 3.31$), a cross hair appeared. The choices presented in the example easy trial are for an individual with a k -value of 0.15.

Figure 2. Clusters with significantly greater activation (red-yellow scale) and deactivation (blue-green scale) by study group for easy choices (easy>control), hard choices (hard>control), and the difficulty contrast (hard>easy). Images are in radiological orientation (Left = Right; Right = Left).

Figure 3.

Main effects of cocaine and HIV and their interaction in the difficulty contrast. The clusters represent the results of the 2 (COC status) by 2 (HIV status) between subjects ANOVA controlling for education and smoking status. For the main effects, thresholded color bars were applied based on the direction of the contrast, with red/yellow representing z-values of the COC+ > COC- or HIV+ > HIV- contrasts and blue representing COC+ < COC- or HIV+ < HIV-. Images are in radiological orientation (Left = Right; Right = Left). These clusters are characterized further in Table 3.

Figure 4.

Regions in which there was a significant HIV*COG interaction effect in the three cognitive control clusters during the difficulty contrast. The plots show percent BOLD signal change for the easy choices (easy>control) and hard choices (hard>control) for each group within the cluster displayed to the right. Images are in radiological orientation (Left = Right; Right = Left).

Table 1

Participant characteristics of the four study groups (N=73)

	COC+			COC-			Statistic	Effect Size ^c
	HIV+ (N = 18)	HIV- (N = 19)	HIV+ (N = 19)	HIV+ (N = 19)	HIV- (N = 17)	HIV- (N = 17)		
Demographic characteristics								
Male, n (%)	12 (66.7%)	13 (68.4%)	12 (63.2%)	9 (52.9%)			$\chi^2(3) = 1.08$	$V = 0.12^d$
Age in years, M (SD)	44.00 (7.37)	43.84 (6.56)	41.47 (9.24)	41.53 (10.13)			$F(3,69) = 0.51$	$\eta^2 = 0.02^d$
Race, n (%)							$\chi^2(12) = 10.35$	$V = 0.22^d$
African American	17 (94.4%)	16 (84.2%)	13 (68.4%)	14 (82.4%)				
Caucasian	1 (5.6%)	1 (5.3%)	4 (21.1%)	2 (11.8%)				
Other/mixed	0 (0.0%)	2 (10.6%)	2 (10.6%)	1 (5.9%)				
Education in years, M (SD)	13.06 (3.24)	12.68 (2.56)	13.79 (1.99)	14.18 (2.13)			$F(3,69) = 1.30$	$\eta^2 = 0.05^e$
Below poverty line, n (%)	8 (44.4%)	13 (68.4%)	10 (52.6%)	4 (23.5%)			$\chi^2(3) = 7.51$	$V = 0.32^e$
Unemployed, n (%)	6 (33.3%)	9 (47.4%)	5 (26.3%)	2 (11.8%)			$\chi^2(3) = 5.62$	$V = 0.28^d$
Cocaine use characteristics								
Days of use in past 90 days, M (SD)	32.17 (27.41)	32.16 (22.34)	--	--			$\chi(35) = 0.01$	$d = 0.01$
Years of regular use, M (SD) ^a	19.24 (9.10)	16.00 (7.54)	--	--			$\chi(34) = 1.17$	$d = 0.39^d$
Primary route of administration, N (%)			--	--			$\chi^2(1) = 0.23$	$\phi = 0.09$
Smoking	15 (83.3%)	17 (89.5%)						
Intra-nasal	3 (16.7%)	2 (10.5%)						
Current cocaine dependence, N (%) ^a	15 (88.2%)	18 (94.7%)	--	--			$\chi^2(1) = 0.50$	$\phi = 0.12^d$
Days since last use at MRI, M (SD)	3.39 (5.01)	2.63 (2.63)	--	--			$\chi(35) = 0.57$	$d = 0.19$
Other substance use (30 days prior to MRI)								
Any heavy alcohol use, N (%) ^b	9 (50.00%)	11 (57.9%)	0 (0.00%)	2 (11.8%)			$\chi^2(3) = 21.25^{***}$	$V = 0.54^f$
Average days of use, M (SD)	7.67 (9.54)	10.73 (10.19)	--	--			$F(3,15) = 0.777$	$\eta^2 = .07^e$
Range of days of use, low-high	2-30	1-30	--	--			1-3	
Any marijuana use	5 (27.8%)	9 (47.4%)	4 (21.1%)	1 (5.9%)			$\chi^2(3) = 8.35^*$	$V = 0.34^e$
Days of use among users, M (SD)	8.40 (7.47)	9.56 (10.05)	8.25 (14.5)	2.00			$F(3,15) = 4.599^*$	$\eta^2 = 0.03^d$
Range of days of use, low-high	2-18	3-30	3-30	1				

	COC-				Statistic	Effect Size ^e
	HIV+ (N = 18)	HIV- (N = 19)	HIV+ (N = 19)	HIV- (N = 17)		
Current tobacco smoker, N (%)	14 (77.8%)	15 (78.9%)	6 (31.6%)	5 (29.4%)	$\chi^2(3) = 16.87^{***}$	$V = 0.48^e$
<u>HIV characteristics</u>						
Years since HIV diagnosis, M (SD)	12.39 (6.83)	--	8.16 (7.67)	--	$t(35) = 1.77$	$d = 0.58^e$
Nadir CD4 cell count, Mdn (IQR)	180.5 (236)	--	198 (382)	--	$U = 145.00$	$\eta^2 = 0.02^d$
Current CD4 cell count, Mdn (IQR)	552 (476)	--	598 (661)	--	$U = 165.00$	$\eta^2 < 0.01$
Detectable HIV viral load, n (%)	3 (16.7%)	--	6 (31.6%)	--	$\chi^2(1) = 1.12$	$\phi = 0.17^d$
AIDS diagnosis, n (%)	9 (50.0%)	--	7 (36.8%)	--	$\chi^2(1) = 0.65$	$\phi = 0.13^d$
Current antiretroviral therapy, n (%)	17 (94.4%)	--	19 (100%)	--	$\chi^2(1) = 1.09$	$\phi = 0.17^d$

* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$;

^a Coc+/HIV+ n=17 and % out of 17

^b Defined as 4 drinks for women and 5 drinks for men

^c η^2 = eta squared; d = Cohen's d; V = Cramer's V; and ϕ = phi

Effect size categories:

^d small,
^e medium,

^f large (Richardson, 2011; Lakens, 2013; Cohen, 1988)

Table 2
Behavioral performance on the temporal discounting tasks by study group (N=73)

	COC+		COC-	
	HIV+ n= 18	HIV- n= 19	HIV+ n= 19	HIV- n= 17
<u>Monetary Choice Questionnaire</u>				
k-value estimates, M (SD)				
Raw	0.15 (0.20)	0.14 (0.17)	0.08 (0.15)	0.09 (0.09)
Natural log transformed	-2.40 (1.02)	-2.50 (.98)	-3.23 (1.27)	-2.90 (1.00)
<u>Intertemporal Choice Task</u>				
Reaction times (s), M (SD)				
Control trials	1.12 (0.34)	1.01 (0.32)	1.15 (0.37)	1.04 (0.27)
Easy trials	1.52 (0.41)	1.15 (0.29)	1.30 (0.35)	1.22 (0.33)
Hard trials	1.50 (0.40)	1.34 (0.35)	1.54 (0.44)	1.47 (0.39)
Responses (%), M (SD)				
Control trials: predicted choice	96.04 (4.84)	96.23 (5.12)	94.38 (5.30)	92.51 (8.44)
Easy trials: predicted choice	77.24 (21.27)	85.76 (14.12)	83.17 (22.20)	82.69 (11.52)
Hard trials: sooner option	62.33 (28.55)	52.99 (23.74)	55.28 (26.41)	46.78 (26.48)

Significant clusters in the ANOVA showing the effects of cocaine and HIV on neural activation during the difficulty contrast of the Intertemporal Choice Task

Table 3

Anatomical region at peak	Other anatomical regions in cluster	MNI coordinates (x, y, z)	Number of voxels	Max Z-score
Main effect of cocaine				
COC+ < COC- L precentral gyrus	L inferior frontal gyrus (vIPFC), middle frontal gyrus (dlPFC), pre and postcentral gyrus, central opercular cortex	-49, -8, 30	1102	3.88
R postcentral gyrus	R insula, inferior frontal gyrus (vIPFC), inferior parietal lobule, pre and postcentral gyrus	51, -14, 29	912	3.40
R Lingual gyrus	L occipital pole, intracalcarine cortex	1, -78, -11	886	3.58
Main effect of HIV				
HIV+ > HIV- B cuneal cortex	B precuneus (posterior), occipital pole, intracalcarine cortex	1, -85, 19	950	3.40
HIV+ < HIV- L middle frontal gyrus (dlPFC)	L frontal pole, frontal orbital cortex (lateral OFC), inferior frontal gyrus (vIPFC), frontal operculum cortex, insula	-43, 22, 24	2773	4.85
R cerebellum	R lateral occipital cortex, inferior temporal gyrus	33, -72, -40	2097	4.66
L cerebellum	L middle and inferior temporal gyri	-39, -66, -35	2042	4.38
B superior frontal gyrus (dmPFC)	B frontal pole, superior frontal gyrus (dmPFC), paracingulate gyrus (ACC)	-1, 40, 45	1795	3.88
R middle frontal gyrus (dlPFC)	R inferior frontal gyrus (vIPFC)	44, 24, 43	1276	2.74
L lateral occipital cortex (superior)	L inferior parietal lobule, superior parietal lobule	-36, -60, 45	1102	4.96
HIV*Cocaine interaction effect				
R frontal pole	R middle and inferior frontal gyrus (dlPFC and vIPFC)	34, 44, 17	1472	3.98
L inferior frontal gyrus (vIPFC)	L middle frontal gyrus (dlPFC), frontal operculum cortex, insula, frontal orbital cortex (lateral OFC), frontal pole	-46, 35, -2	1087	3.65
L superior frontal gyrus (dmPFC)	R superior frontal gyrus (dmPFC); L middle frontal gyrus (dlPFC); B precentral gyrus, juxtapositional lobule cortex	-5, 9, 64	1075	4.02
L cerebellum	N/A	-40, -70, -45	998	4.14
R cerebellum	R lateral occipital cortex (inferior)	27, -81, -33	766	3.43

Note: R= right hemisphere, L= left hemisphere, B= bilateral

vIPFC= ventrolateral prefrontal cortex; dlPFC= dorsolateral prefrontal cortex; dmPFC= dorsomedial prefrontal cortex; ACC= anterior cingulate cortex; OFC= orbitofrontal cortex