Effects of cocaine use on verbal memory and prefrontal cortex function in women infected with HIV

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THESIS

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This thesis is dedicated to my late father, Ernest Alan Meyer. Growing up, he instilled in me the value of hard work and a good education. “Education will set you free”, he would tell me. In the last conversation we ever had, I told him about my plans to pursue a PhD. I remember how he beamed with pride and told me how happy it would make him to one day call me Dr. Meyer. A desire to make him proud has helped me to persevere through discouragement and strengthened my determination to succeed. Cheers, Dad, this one’s for you!

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ANI	Asymptomatic Neurocognitive Impairment
ANOVA	Analysis of Variance
ART	Antiretroviral Therapy
BA	Brodmann Area
BOLD	Blood Oxygen Level Dependent
cART	Combination Antiretroviral Therapy
CESD	Center for Epidemiological Studies-Depression Scale
CHARTER	CNS HIV Antiretroviral Therapy Effects Research
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
DMPFC	Dorsal Medial Prefrontal Cortex
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
gp120	Glycoprotein 120
HAART	Highly Active Anti-Retroviral Therapy
HAD	HIV-Associated Dementia
HAND	HIV-Associated Neurocognitive Disorders
HNRC	HIV Neurobehavioral Research Center
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

LIST OF ABBREVIATIONS (continued)

HVLT	Hopkins Verbal Learning Task
HVLT-R	Hopkins Verbal Learning Task – Revised
MACS	Multicenter AIDS Cohort Study
MND	Mild Neurocognitive Disorder
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
SSRT	Stop Signal Reaction Time
Tat	Transactivator of Transcription
TNF- α	Tumor Necrosis Factor Alpha
Vpr	Viral Protein R
WIHS	Women's Interagency HIV Study
WHO	World Health Organization
WRAT-R	Wide Range Achievement Test - Revised

SUMMARY

Both HIV and illicit drug use are known to negatively impact cognitive function. This study was designed to investigate the effects of drug use on cognition in women with HIV. The approach was two-pronged and included a large-scale epidemiological study and a functional neuroimaging study.

The large scale study analyzed data from nearly 1400 women to investigate the independent and interactive effects of HIV infection and illicit drug use on verbal memory and executive function. HIV infection and recent illicit drug use interacted to negatively impact verbal memory. Among HIV-infected women, recent illicit drug users performed worse on verbal learning and memory than women who had never used illicit substances. This effect was driven by use of crack cocaine specifically. However, among uninfected women drug use had no effect on verbal learning and memory.

The neuroimaging study investigated the impact of crack cocaine use on brain activation patterns during a verbal memory task in women with HIV. Thirty HIV-infected women underwent a functional magnetic resonance imaging scan. Both recent and former crack cocaine users showed less activation of their left dorsal medial prefrontal cortex during encoding of words than women who had never used crack cocaine. Similarly, both recent and former crack cocaine users showed less activation of their bilateral prefrontal cortex during recognition of words than women who had never used crack cocaine. Importantly, activation in these areas was related to performance on the verbal memory task.

I. INTRODUCTION

A. HIV Epidemic

The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS), a disease which causes progressive failure of the immune system and ultimately leads to life-threatening opportunistic infections. Left untreated, the progression time from initial HIV infection to death is about 10 years. Once a person has developed AIDS, if untreated, the median survival is around 9 months (Morgan et al., 2002). Over the last 30 years, HIV has claimed more than 25 million lives worldwide. HIV infection continues to be a major global health concern; in 2011 there were an estimated 34 million people living with HIV. Each year, an estimated 2.7 million people are newly infected (WHO, 2011).

In the United States alone, over 1 million people are living with HIV, and there are approximately 50,000 new HIV infections each year (CDC, 2010). The cost of new infections is estimated at $36.4 billion, including $6.7 billion in direct medical costs and $29.7 billion in productivity losses (Hutchinson et al., 2006). Although there is currently no cure for HIV infection, advances in antiretroviral medication have allowed effective treatment to suppress the virus. With proper antiretroviral treatment, individuals living with HIV are able to live longer with greater quality of life. Life expectancies for individuals infected with HIV have increased since 1996 when combination antiretroviral therapy (cART) became available. In the US over 25% of people with HIV are now over 50 years of age (CDC, 2007). While antiretroviral treatment has extended life expectancies, there is a continuing need to improve overall health and quality of life among individuals living with HIV.

B. HIV-associated cognitive impairment

Neurocognitive impairment associated with HIV disease has been well studied since the beginning of the HIV epidemic (Janssen et al., 1991). Presently, HIV-associated neurocognitive

disorders (HAND) are categorized according to the "Frascati Criteria," updated guidelines that identify three levels of cognitive impairment (Antinori et al., 2007). HIV-associated asymptomatic neurocognitive impairment (ANI) is cognitive impairment in at least 2 cognitive domains that does not interfere with daily functioning. Mild neurocognitive disorder (MND) is cognitive impairment in at least 2 cognitive domains that mildly interferes with daily functioning. HIV-associated dementia (HAD) is marked cognitive impairment in at least two domains with significant interference with daily functioning.

The advent of cART led to a significant drop in the rate of overt HIV-associated dementia (HAD). Pre-cART incidence of HAD was around 15% in AIDS cases (McArthur et al., 1993) and post-cART estimates are around 2% (Heaton et al., 2010). However, higher rates of mild-to-moderate neurocognitive impairment are observed in the post-cART era compared to the pre-cART era (Heaton et al., 2011). A recent study of 1,555 HIV-infected adults in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study found 52% of the total sample demonstrated neurocognitive impairment. When severely confounded cases (e.g. brain trauma, history of seizures) were excluded, 33% were diagnosed with ANI, 12% were diagnosed with MND, and 2% were diagnosed with HAD (Heaton et al., 2010). Additionally, the pattern of neurocognitive impairment has changed. Impairments in motor skills, cognitive speed, and verbal fluency characterized deficits in the pre-cART era, while learning, memory, and executive function deficits characterize deficits in the post-cART era (Heaton et al., 2011). Although the incidence of dementia has decreased, it has become clear that HIV-infection is still associated with clinically and functionally significant cognitive dysfunction.

Several predictors of cognitive impairment in HIV-infected populations have been identified. A strong predictor of cognitive impairment is the lowest recorded CD4 count, often

referred to as nadir CD4, which is an indicator of immune function (Heaton et al., 2010, Heaton et al., 2011). CD4+ T helper cells are lymphocytes that fight infection; therefore, decreased CD4 counts indicate immune system compromise. Early after initial infection, low CD4 count and high plasma levels of HIV are both predictive of early onset of neurocognitive impairment (Marcotte et al., 2003). Co-infection with hepatitis C is also a significant predictor of cognitive impairment in persons with HIV (Cherner et al., 2005, Richardson et al., 2005, Hinkin et al., 2008), an important finding considering co-infection is present in 16% of HIV-infected patients (Sherman et al., 2002).

Certain factors may also be associated with resiliency to (or rebound from) HAND. There is evidence for preserved cognitive function in certain HIV-infected cohorts that are characterized by preserved immune function and high level of education (Cole et al., 2007). Therefore, factors such as well-controlled viral load and strong premorbid cognitive function are potentially protective against HAND (Cohen and Navia, 2007). Importantly, for individuals living with HIV, antiretroviral treatment can improve neuropsychological test performance. Initiating cART is associated with significant improvement on tasks of verbal memory, executive function, and psychomotor speed, and the most impaired patients demonstrate the most neuropsychological improvement (Sacktor et al., 1999, Cohen et al., 2001, Suarez et al., 2001, Sacktor et al., 2006, Cysique et al., 2009, Sacktor et al., 2009). However, it is important to note that antiretroviral regimens with high central nervous system penetration may have negative effects on cognitive performance (Marra et al., 2009).

Certain neuropsychological domains appear to be more negatively impacted by HIV infection. Early in the HIV epidemic the Multicenter AIDS Cohort Study (MACS), a longitudinal, multisite, epidemiological study of HIV in men, found HIV-associated deficits in

tasks of psychomotor functioning as well as verbal learning and memory (Miller et al., 1990). Other studies found similar results, with timed psychomotor tests and memory tasks being the most sensitive to early HIV-related cognitive impairment (Villa et al., 1996). A second large-scale longitudinal study of HIV, the HIV Neurobehavioral Research Center (HNRC) study, found that HIV negatively affected attention, speed of information processing, and learning efficiency (Heaton et al., 1995). A meta-analysis from 1984 through 2000 found that motor functioning, executive skills, and information processing speed were the cognitive domains that showed the greatest decline from early to later stages of HIV (Reger et al., 2002).

The pattern of HAND shifted after the advent of cART. Three studies directly compared HAND in the pre-cART and post-cART eras. First, Sacktor and colleagues compared an HIV-infected cohort that was tested prior to the advent of cART with an HIV-infected cohort that was given a nearly identical neuropsychological battery in the post-cART era (Sacktor et al., 2002). Although the two cohorts were demographically very different, they statistically controlled for group differences and found no differences in the pattern of cognitive deficits. In contrast, Cysique and colleagues (2004) compared two demographically similar HIV-infected cohorts that represented pre- and post-cART eras across nine neuropsychological domains and found a difference in the pattern of neuropsychological impairment. In the post-cART era, patients performed better on attention, verbal fluency, and visuoconstruction tasks, but worse on learning efficiency and complex attention tasks compared to the pre-cART era (Cysique et al., 2004). The largest direct comparison (pre-cART n = 857, post-cART n = 937) by Heaton and colleagues found that cognitive impairment in the pre-cART era was more often characterized by deficits in psychomotor processing, speed of information processing, and verbal fluency. In contrast, learning and executive functions such as working memory (Martin et al., 2001) were more

negatively affected in the post-cART era (Heaton et al., 2011). In summary, the incidence of the most severe forms of HIV-associated dementia have decreased since cART became widely available; however, milder forms of HAND are still common and learning and executive function domains are the most affected.

C. Neuropathological studies of HIV

In addition to deficits on neuropsychological tests, structural brain abnormalities have been observed since the onset of the HIV epidemic, and early studies showed reduced cortical grey matter volume in patients with HIV (Heindel et al., 1994). Cortical atrophy has been reported in both the pre-cART and post-cART eras (Jernigan et al., 1993, Heindel et al., 1994, Thompson et al., 2005). HIV-associated thinning of the cerebral cortex correlates with immune system deterioration as well as cognitive deficits (Thompson et al., 2005). Even in medically asymptomatic patients, HIV infection causes progressive cortical atrophy (Stout et al., 1998). Disease factors such as nadir CD4 count and duration of infection are related to overall cerebral volume as well as gray and white matter volumes (Cohen et al., 2010). Importantly, postmortem evidence of cortical neurodegeneration is positively associated with antemortem neuropsychological impairment (Moore et al., 2006).

Postmortem studies provide evidence that HIV causes white matter degradation and diffusion tensor imaging (DTI) studies show that HIV is associated with white matter hyperintensities (Budka, 1997, Archibald et al., 2004, Chiang et al., 2007, Stebbins et al., 2007). These white matter abnormalities are correlated with global cognitive impairment (Chiang et al., 2007). Structural magnetic resonance imaging (MRI) studies show reduction in white matter volume (Stout et al., 1998) and magnetic resonance spectroscopy studies (MRS) show neuronal injury and glial activation in frontal white matter that negatively correlate with performance on

executive function tasks (Chang et al., 2002). DTI studies have reported HIV-associated white matter abnormalities in several white matter tracts including the internal capsule, external capsule, superior and inferior cingulate bundles, corpus callosum, inferior longitudinal fasciculus, and the optic radiations (Gongvatana et al., 2009, Pfefferbaum et al., 2009). Importantly, these white matter abnormalities are related to global cognitive impairment (Gongvatana et al., 2009).

Functionally, HIV-infected patients demonstrate abnormal cerebral glucose metabolism (Rottenberg et al., 1996), cerebral metabolite abnormalities (Chang et al., 1999), altered cortical blood flow (Harris et al., 1994), and reduced resting cerebral blood flow (Ances et al., 2009). When comparing the effects of normal aging to the effects of HIV on the blood oxygen level dependent (BOLD) signal during a visual task, functional changes in the HIV-infected patients are equivalent to those of uninfected control subjects who were 15 years older (Ances et al., 2010), suggesting a potential acceleration of cognitive aging in individuals infected with HIV.

Functional magnetic resonance imaging (fMRI) studies provide evidence of alterations in brain activation patterns in patients with HIV during performance of cognitive tasks. Increased activation in the lateral prefrontal cortex in HIV-infected patients during cognitive tasks precedes deficits on a neuropsychological test battery (Ernst et al., 2002). During a semantic event sequencing task, HIV-infected patients demonstrated hypoactivation of left caudate, left dorsal lateral prefrontal cortex, and bilateral ventral prefrontal cortex but showed increased activation of right postcentral gyrus (Melrose et al., 2008). This increased activation in the frontal lobes during difficult tasks of working memory may be indicative of a compensatory mechanism, whereby more difficult tasks necessitate a greater use of brain reserve (Chang et al., 2001). Similarly, during performance of a visual attention task HIV-infected patients show less

activation in the normal visual attention network but more activation in adjacent or contralateral brain regions, suggesting that HIV infection leads to reduced cognitive efficiency that necessitates compensatory use of neural reserves (Chang et al., 2004).

HIV infection is also associated with altered activation patterns during encoding and retrieval conditions of episodic memory tasks. During encoding of a visual episodic memory task, HIV-infected patients demonstrate altered activation of hippocampal-prefrontal regions, with reduced activation in the right hippocampus, right frontal gyrus, and left lingual gyrus, and increased activation in lateral frontal and posterior parietal regions compared to uninfected controls (Castelo et al., 2006). While performing a verbal episodic memory task, HIV-infected women demonstrate decreased hippocampal activation during encoding and increased activation during recognition compared to uninfected women (Maki et al., 2009). These alterations correlated with worse episodic verbal memory performance (Maki et al., 2009). This evidence suggests that HIV-infected individuals have functional alterations in the neural networks underlying episodic memory.

HIV infection has consistently been associated with neurocognitive impairment throughout the epidemic. In the era following the advent of cART, deficits in learning, memory and executive function have become more prominent compare with the profound mental and motor slowing observed earlier in the epidemic. Importantly, functional neuroimaging studies also point to alterations in the cortex related to HIV-associated cognitive deficits. HIV-infected patients demonstrate decreased activation in the prefrontal cortex during tasks of both memory and executive function. This line of work demonstrates that understanding cortical deficits in HIV is critical to elucidating the functional impairments still seen in the cART era.

D. Neuropathogenesis of HIV

HIV is a lentivirus, a class of viruses characterized by a long incubation period and the unique ability to infect non-dividing cells. HIV enters the central nervous system (CNS) early after initial infection (An et al., 1999). The virus enters the CNS through a "Trojan Horse" mechanism whereby the virus infects peripheral monocytes which pass through the blood brain barrier (Gonzalez-Scarano and Martin-Garcia, 2005). Once inside, these infected monocytes differentiate into productively infected macrophages, capable of viral replication. The virus produced by infected macrophages then spreads to other cells in the brain, such as microglia. HIV infection is also associated with the upregulation of proteins that mediate the transmigration of leukocytes across the blood brain barrier (matrix metalloproteinases) as well as the upregulation of proteins which attract more leukocytes (monocyte chemotactic protein (MCP)-1) (Boven et al., 2000, Conant et al., 2004). Therefore, more leukocytes that are infected with HIV are able to migrate across an increasingly vulnerable blood brain barrier.

Although HIV does not directly infect neurons, infection of macrophages and microglia can disrupt neuronal function. In addition to producing more of the HIV virus (virions), infected cells shed neurotoxic viral proteins, such as gp120, transcriptional transactivator (Tat), and viral protein R (Vpr). Viral protein gp120 is an HIV envelope glycoprotein that is secreted by HIV-infected cells. In vitro experiments provide evidence that viral protein gp120 interacts with chemokine receptors to induce neuronal apoptosis (Meucci et al., 1998, Zheng et al., 1999). Gp120 can also induce neuronal cell death through NDMA ($_N$-methyl $_D$-aspartate) receptor mediated excitotoxicity (Barks et al., 1997). Tat is a regulatory protein that enhances viral transcription efficiency. Tat induces neuronal apoptosis via calcium dysregulation, oxidative stress, and mitochondrial dysfunction (Haughey and Mattson, 2002). Extracellular Tat increases

calcium influx which disrupts neuronal calcium homeostatis and leads to excitotoxic neuronal death (Hu et al., 2011, Wayman et al., 2012). Evidence also suggests that Tat may play a critical role in viral trafficking into the brain by altering tight junction proteins on brain endothelial cells and disrupting the integrity of the blood brain barrier (Andras et al., 2003). Vpr demonstrates a diversity of viral functions, including a role in virion production and replication, but is also capable of inducing apoptosis in human neuronal cells (Patel et al., 2000, Patel et al., 2002). Therefore, while the virus itself may not infect neurons there are multiple neurotoxic mechanisms of neuropathology, including release of viral proteins such as Tat and gp120.

Indirect mechanisms such as generalized inflammatory processes also cause neuronal damage in HIV infection. Infected cells promote activation of macrophages and microglia. These immune cells attempt to remove the infection from the brain but instead initiate the inflammatory neurotoxic cascades that lead to viral encephalitis (Wang et al., 2006). Activated macrophages produce factors with known neurotoxic effects such as cytokines and nitric oxide. Pro-inflammatory cytokines (chemokines) such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β activate uninfected cells and increase migration of activated leukocytes into the CNS, which may result in amplification of the detrimental inflammatory response (Gonzalez-Scarano and Martin-Garcia, 2005). In this way, HIV can cause neuronal cell death simply by initiating an exaggerated immune response in the brain.

Astrocytes may also be involved in HIV-associated neurotoxicity through an indirect mechanism. Astrocytes display restricted infection, in which viral proteins are expressed without viral replication (Saito et al., 1994). Infected macrophages release cytokines that interact with astrocytes and inhibit their protective function (Gonzalez-Scarano and Martin-Garcia, 2005). Activated astrocytes produce inflammatory cytokines, including TNF-α (Lafortune et al., 1996)

which amplifies excitotoxic glutamate release and decreases astrocytic uptake of glutamate (Bezzi et al., 2001). High glutamate levels then cause calcium influx in neurons, which destroys intracellular calcium homeostasis and leads to apoptosis (Foos and Wu, 2002). These studies collectively suggest that although HIV does not directly infect neuronal cells, it exerts both direct and indirect deleterious effects on the brain via neurotoxic viral proteins and induction of neuroinflammation and excitotoxicity.

Although cART is effective at reducing viral load and can exert neurocognitive benefits, we continue to see neuropsychological deficits, structural abnormalities, and functional alterations in the post-cART era. In vitro studies demonstrate that HIV is exerting its effects in the brain via neurotoxic viral proteins but also through increased inflammation and weakening of the blood brain barrier. These insults may contribute to the cognitive deficits we see in individuals living with HIV.

E. Importance of studying cognition in HIV-infected women

According to global estimates from the World Health Organization (WHO) and UNAIDS, 50% of people living with HIV are women and the proportion of women living with HIV has been increasing (WHO, 2008). Although in the United States the incidence of HIV is still higher in men than women, over 11,000 women each year are newly infected with HIV. The Centers for Disease Control and Prevention (CDC) report that women represent 24% of the total HIV diagnoses among adults and adolescents and more than 25% of new AIDS diagnoses (CDC, 2011). Black and Latina women are disproportionately affected by HIV compared with women of other races/ethnicities. The rate of new HIV infections among black women is 15 times that of white women and over 3 times the rate among Hispanic/Latina women. Of the total number of

newly infected women, 57% were blacks, 21% were whites, and 16% were Hispanic/Latina (CDC, 2011).

Most studies of the cognitive effects of HIV have been done in largely or exclusively male samples, due to the historically higher incidence of HIV in men in the United States, particularly early in the epidemic. Women have been underrepresented in neuropsychological studies of HIV even when accounting for differences in prevalence. A review of studies from 1988 to 1997 found that women were only included in half of the neurological and neuropsychological studies of HIV. More importantly, women were only included with approximate proportional representation in one-third of the studies. Additionally, only 3% of the studies examined sex differences (Fox-Tierney et al., 1999). There is evidence for sex differences in the effects of HIV on cognition, a study investigating nondeclarative learning found a negative effect of HIV on performance in women, but not men (Martin et al., 2011).

Women might be at an increased vulnerability to HIV-associated dementia. A large-scale European study found that women had twice the risk of developing HIV-associated dementia compared to men (Chiesi et al., 1996), although other studies failed to find this effect (Robertson et al., 2004, Jarrin et al., 2008). HIV-infected women may be at a higher risk for HIV-associated cognitive decline compared to HIV-infected men due lower cognitive reserve associated with lower education (Basso and Bornstein, 2000, Farinpour et al., 2003). Factors that are prevalent in minority urban women such as poverty, drug abuse, mental illness, and limited access to healthcare, can increase susceptibility for other diseases with negative cognitive effects such as hepatitis C and cardiovascular disease (Maki and Martin-Thormeyer, 2009). Substance dependence is often a comorbid condition with HIV and can increase risk for neurocognitive deficits (Martin-Thormeyer and Paul, 2009). This may be particularly important for women

living with HIV, as women escalate drug use more quickly and progress to addiction faster than men (Becker and Hu, 2008).

F. Intersection of HIV and drug use

Drug abuse and addiction are prevalent among individuals infected with HIV. An estimated one third of HIV-infected individuals have used illicit drugs in the past month and an estimated one quarter of HIV-infected individuals were in need of drug use treatment in the past year (SAMHSA, 2010). At the Chicago center of the Multicenter AIDS Cohort Study (MACS), 70% of participants reported use of marijuana and volatile nitrates (the most frequently used illicit drugs in this sample) and 30% of participants reported using intranasal cocaine at baseline (Ostrow et al., 1993). In the Women's Interagency HIV Study (WIHS), the largest longitudinal, multisite study of HIV in women, 28.9% reported use of illicit drugs in the past 6 months at their baseline visit. Crack cocaine was the most commonly used illicit drug, with 19.7% of HIV-infected women reporting use in the prior 6 months. Intranasal cocaine was reported by 15.4% and injection drug use by 8.8% of HIV-infected women. A more recent WIHS study indicated that 29% of HIV-infected women reported being intermittent or persistent users of crack cocaine during the study period (Cook et al., 2008).

Drug abuse and addiction have been inextricably linked with HIV since the beginning of the epidemic. Injection drug use has directly or indirectly accounted for transmission in more than one-third (36%) of AIDS cases in the United States. Among women, 57% of all AIDS cases have been attributed to injection drug use or sex with partners who have injected drugs (CDC, 2002). Although injection drug use is well known for its role in contraction and transmission of HIV, noninjection drug use (such as crack cocaine) also contributes to the spread of the virus. Crack cocaine users engage in high-risk sexual behaviors, such as the exchange of sex for money

or drugs, increasing their chances of contracting HIV (Chiasson et al., 1991, Edlin et al., 1992). A study of more than 2,000 young adults in three inner-city neighborhoods found that crack smokers were three times more likely to be infected with HIV than non-smokers (Edlin et al., 1994). Since crack cocaine use also increases the risk of viral transmission, it is critical to understand how crack use impacts disease progression and cognitive function in individuals infected with HIV.

Illicit drug use can affect the progression of HIV-infection. A longitudinal study of illicit drug use and disease progression found that persistent use of cocaine and/or heroin was associated with a two-fold risk of developing new opportunistic infections. Active drug use was temporally linked to negative disease outcomes. During periods of active use, intermittent drug users had a risk of disease progression similar to persistent users; however, during periods of abstinence, intermittent users had a risk of disease progression similar to nonusers (Lucas et al., 2006). A prospective study of HIV-infected opiate addicts found that the use of crack cocaine specifically was independently associated with progression to clinical AIDS (Webber et al., 1999). A study examining disease progression in HIV-infected individuals found that crack cocaine users were more than twice as likely to progress to AIDS (CD4 count below 200 cells/mL), independent of antiretroviral use. Viral load was also significantly higher in crack users, independent of antiretroviral use (Baum et al., 2009). In the WIHS, women who used crack cocaine were more than three times as likely to die from AIDS-related causes compared to nonusers, even when controlling for adherence to antiretroviral medication regimens. Crack users showed greater CD4 cell loss and higher viral load than non-users and were more likely to develop new AIDS-defining illnesses (Cook et al., 2008).

G. Impact of drug use on cognitive function in HIV

Illicit drug use may also impact cognitive function in HIV-infected individuals. Among studies of injection drug users, some have found increased risk of cognitive deficits among HIV-infected users compared to uninfected users, although results have been mixed (Egan et al., 1992, Marder et al., 1992, Bono et al., 1996, Selnes et al., 1997, Starace et al., 1998). There is consistent evidence that compared to uninfected substance-dependent individuals, HIV-infected substance-dependent individuals show increased vulnerability to specific cognitive deficits (Martin-Thormeyer and Paul, 2009). In a series of studies, HIV-infected substance-dependent individuals (cocaine and/or heroin) performed worse on measures of procedural learning (Gonzalez et al., 2008), prospective memory (Martin et al., 2007), decision-making (Martin et al., 2004a), and working memory (Martin et al., 2001, Martin et al., 2003). A study of noninjection drug abuse found no interaction of HIV serostatus and previous drug abuse disorders on working memory or executive function; however, the drug abuse group was heterogeneous and included abuse of marijuana, sedatives, stimulants, and hallucinogens (Basso and Bornstein, 2003). An interactive effect of marijuana and HIV on global cognitive impairment has been previously demonstrated (Cristiani et al., 2004). Similarly, an additive effect of methamphetamine dependence and HIV-infection on neuropsychological impairment has been documented (Rippeth et al., 2004).

To date, very few studies have evaluated cognitive performance among HIV-infected and uninfected crack or powder cocaine users. In a study that examined stimulant use (methamphetamine and/or cocaine), HIV-infected stimulant users showed poorer performance on a task of sustained attention than HIV-infected nonusers (Levine et al., 2006). The only previous study designed to investigate the interactive effects of HIV and cocaine use on

neuropsychological performance (n= 237 gay and bisexual African-American men) reported that both HIV and cocaine use were independently associated with cognitive deficits but found no evidence of an interactive effect (Durvasula et al., 2000). The interactive effects of HIV-infection and cocaine use on cognitive function have not been previously studied in women (Martin-Thormeyer and Paul, 2009).

Illicit drug use impacts the neuropathology of HIV infection. Injection drug use has been associated with progression of HIV-associated dementia (Bouwman et al., 1998), HIV encephalitis (Bell et al., 1998), and enhanced microglial activation in HIV-infected patients (Arango et al., 2004). Non-injecting psychostimulant use has also been associated with more severe HIV-associated neuropathology. HIV-infected methamphetamine users demonstrate increased microglial activation (Langford et al., 2003), increased loss of interneurons (Chana et al., 2006), metabolic abnormalities (Chang et al., 2005), and structural abnormalities (Jernigan et al., 2005). To date, relatively few studies have evaluated the effects of crack or powder cocaine on HIV neuropathology. One positron emission tomography (PET) study found reductions in dopamine transporters (DAT) and receptors (D2R) in HIV-infected patients compared to uninfected participants, with a small trend for further reduction in DAT and D2R in HIV-infected cocaine users compared to HIV-infected nonusers. This reduction was associated with greater cognitive dysfunction in the HIV-infected cocaine users compared to nonusers, even though their viral load and CD4 counts were comparable (Chang et al., 2008).

H. Synergistic neurotoxicity of HIV and drugs of abuse

Interestingly, a number of *in vitro* studies have demonstrated the potential for synergistic neurotoxicity of HIV and drugs of abuse such as opiates, cocaine, and methamphetamine (Nath et al., 2002, Ferris et al., 2008, Buch et al., 2011). Cocaine can amplify the neurotoxicity of Tat

and gp120 by enhancing oxidative cell damage and increasing reactive astrocytosis (Koutsilieri et al., 1997, Turchan et al., 2001, Aksenov et al., 2003, Kendall et al., 2005, Aksenov et al., 2006, Harrod et al., 2008). Both cocaine and Tat target the mitochondria and produce oxidative stress, so there is a possibility of synergistic interactions in producing mitochondrial dysfunction and cell death. Cocaine has also been shown to amplify the replication of HIV in monocytes, macrophages, and human astrocytes (Peterson et al., 1991, Bagasra and Pomerantz, 1993, Roth et al., 2002, Gekker et al., 2004, Reynolds et al., 2006, Dhillon et al., 2007), which would increase the amount of virions and viral proteins in the brain parenchyma.

Synergistic effects on the dopaminergic system may be another mechanism by which HIV and illicit drugs interact in the brain. Dopaminergic dysfunction has been associated with HIV-associated neuropathogenesis. Autopsy studies have found evidence of dopamine deficiency in HIV-infected patients (Sardar, Czudek et al. 1996; Kumar, Fernandez et al. 2009). A wealth of evidence from human, simian, and rodent studies indicate a connection between HIV infection and dysfunction of dopaminergic systems (for a review, see Purohit, Rapaka et al. 2011). The dopaminergic activation properties of drugs of abuse may accelerate this HIV-associated dopaminergic dysfunction. Drugs of abuse such as cocaine, amphetamines, and opiates all increase brain levels of dopamine well above basal levels (Di Chiara and Imperato 1988; Pontieri, Tanda et al. 1995). Increased dopamine can activate microglia which results in increased HIV replication and production of inflammatory cytokines, which can ultimately lead to increased neuronal death (Gaskill, Calderon et al. 2009).

Additionally, cocaine may alter blood brain barrier permeability. Cocaine alters expression and conformation of tight junction proteins and cell adhesion molecules in monocytes (Fiala et al., 1998, Fiala et al., 2005). Cocaine can increase glial activation and disrupt

cytoskeletal proteins (Kousik et al., 2012). All of these processes can lead to increased HIV-infected monocyte migration which increases both the penetration of the virus into the brain and the vulnerability of the brain to other toxins (Kousik et al., 2012).

I. Significance

Although synergistic neurotoxicity has been demonstrated in vitro and drug use has been associated with increased risk for HIV-associated cognitive deficits, the interactive effects of cocaine and HIV on cognitive function have not been fully elucidated. A series of neuropsychological and neuroimaging studies from the HIV Neurobehavioral Research Center (HNRC) illustrate the interaction of HIV and methamphetamine use on cognitive health (Rippeth et al., 2004, Chang et al., 2005, Ances et al., 2011). However, the potential for an additive or interactive effects of HIV and cocaine use on brain function has not been well studied (Martin-Thormeyer and Paul, 2009). Importantly, no studies to date have investigated the potential for an interactive effect of illicit drug use and HIV-infection in women. This question is critically important for three reasons. First, women may be predisposed to HIV-associated neurocognitive disorders. There is a high incidence of risk factors such as poverty, low literacy, and limited access to healthcare that that negatively affect the population of HIV-infected women (Maki and Martin-Thormeyer, 2009). Second, HIV-infected women may be at a higher risk for the negative impact of substance dependence than men. Compared to men, women escalate drug use more quickly, progress to addiction faster, and are at higher risk of relapse (Becker and Hu, 2008). Third, neurocognitive impairment is associated with 2.5 times greater risk of poor adherence to antiretroviral medication regimens (Hinkin et al., 2004). Thus, understanding risk factors for HIV-associated cognitive disorders has important implications for improving treatment adherence and improving health outcomes and transmission risk in women living with HIV.

The importance of studying verbal episodic memory and executive function stems from research demonstrating HIV-associated deficits in these two domains (Heaton et al., 2011). Illicit drug use is also associated with deficits in verbal memory and executive functions. Additionally, effective executive organizational strategies are under-utilized during memory tasks in both HIV-infected and drug-abusing populations (Woods et al., 2005a, Gongvatana et al., 2007). The prefrontal cortex is critical for performing episodic memory as well as executive function tasks (Masterman and Cummings, 1997, Wood and Grafman, 2003, Blumenfeld and Ranganath, 2007). HIV-infected individuals have demonstrated altered prefrontal activation on tasks of episodic memory and executive function (Chang et al., 2001, Ernst et al., 2002, Castelo et al., 2006). Similarly, cocaine users show altered prefrontal activation patterns during tasks of memory and other executive functions (Bolla et al., 2003, Bolla et al., 2004, Hester and Garavan, 2004). Taken together, previous research indicates that both HIV and illicit drug use may negatively impact performance on episodic memory tasks with executive, organizational components and that prefrontal cortical dysfunction may underlie these deficits.

This cross-sectional study involves both behavioral and neuroimaging substudies in order to examine the effects of HIV and illicit drug use, particularly crack cocaine, on verbal episodic memory and the prefrontal cortical systems underlying performance. The Hopkins Verbal Learning Task (HVLT) (Benedict et al., 1998) was used to assess episodic verbal memory, because it is standardized, normed neuropsychological test that has shown sensitivity to HIV-associated neurocognitive deficits (Woods et al., 2005b, Scott et al., 2006) and can also be used to measure the executive aspects of memory. Examining the HVLT component processes can reveal the underlying mechanisms of observed memory deficits. The semantic clustering index can be used to measure of the executive aspect of memory (Bruce and Echemendia, 2003).

Semantic clustering is an organizational strategy that involves categorizing words in a list according to semantic features. This strategy emphasizes relationships among to-be-learned items in order to improve encoding of the material (Blumenfeld and Ranganath, 2006). This strategic component of memory is tied to integrity of the frontal systems (Gershberg and Shimamura, 1995) and is related to other tasks of executive function (Woods et al., 2005a). Episodic memory tasks have shown reliable activation in the prefrontal cortex during information encoding (Kapur et al., 1994, Murray and Ranganath, 2007). A novel in-scanner verbal memory task was developed for the purpose of this study, to mirror the organizational strategic component of the HVLT. The task was structured similarly to the HVLT to allow for semantic clustering of the items to be remembered.

Given that illicit drug use negatively impacts function of the prefrontal cortex and HIV-infected individuals demonstrate episodic memory deficits, we predicted that HIV and drug use would interact to negatively impact episodic verbal memory. The first step was to investigate the independent and interactive effects of HIV infection and illicit drug use on a standardized verbal memory test in a large sample of women. The next step was to probe the mechanisms underlying this behavioral effect using an fMRI task specifically developed to mimic the standardized neuropsychological test, but adapted for the scanner environment. We hypothesized that memory in HIV-infected women would be more negatively impacted by illicit drug use than uninfected women and that alterations in activation of the prefrontal cortex would underlie this deficit.

J. Statement of Aims and Hypotheses

Specific Aim 1: to use neuropsychological test data from a large-scale epidemiologic study to examine behavioral effects of HIV and recent illicit drug use on verbal memory, processing speed, and executive function

***Hypothesis 1*:** HIV infection and illicit drug use will have an interactive effect on verbal memory and executive function, where illicit drug use will have a greater negative effect on task performance in HIV-infected women compared to uninfected women.

Specific Aim 2: to use functional magnetic resonance imaging (fMRI) to examine effects of recent crack cocaine use on activation patterns during a verbal episodic memory task among HIV-infected women

***Hypothesis 2a*:** HIV-infected women who have recently used crack cocaine will show less activation in the prefrontal cortex during verbal memory encoding than HIV-infected women who have not recently used crack cocaine

Hypothesis 2b: Decreased prefrontal cortex activation will be associated with lower behavioral measures of strategic encoding, as evidenced by less semantic clustering during recall.

II. BEHAVIORAL STUDY

In press at the Journal of Acquired Immune Deficiency Syndromes: "HIV and Recent Illicit Drug Use Interact to Affect Verbal Memory in Women". Accepted January 22, 2013

A. Abstract

Objective: HIV infection and illicit drug use are each associated with diminished cognitive performance. This study examined the separate and interactive effects of HIV and recent illicit drug use on verbal memory, processing speed and executive function in the multicenter Women's Interagency HIV Study (WIHS).

Methods: Participants included 952 HIV-infected and 443 HIV-uninfected women (mean age=42.8, 64% African-American). Outcome measures included the Hopkins Verbal Learning Test - Revised (HVLT-R) and the Stroop test. Three drug use groups were compared: recent illicit drug users (cocaine or heroin use in past 6 months, n=140), former users (lifetime cocaine or heroin use but not in past 6 months, n=651), and non-users (no lifetime use of cocaine or heroin, n=604).

Results: The typical pattern of recent drug use was daily or weekly smoking of crack cocaine. HIV infection and recent illicit drug use were each associated with worse verbal learning and memory (p's$<.05$). Importantly, there was an interaction between HIV serostatus and recent illicit drug use such that recent illicit drug use (compared to non-use) negatively impacted verbal learning and memory only in HIV-infected women (p's <0.01). There was no interaction between HIV serostatus and illicit drug use on processing speed or executive function on the Stroop test.

Conclusion: The interaction between HIV serostatus and recent illicit drug use on verbal learning and memory suggests a potential synergistic neurotoxicity that may affect the neural circuitry underlying performance on these tasks.

B. Introduction

Despite improved cognitive outcomes following the introduction of combination anti-retroviral therapy (cART), HIV-infected individuals continue to show cognitive impairment, particularly in verbal episodic memory and executive function (Sacktor et al., 2002). Episodic memory is impaired in up to 50% of HIV-infected individuals (Heaton et al., 1995), and these cognitive deficits predict daily functioning (Heaton et al., 1994, Benedict et al., 2000, van Gorp et al., 2007). HIV-associated deficits in verbal memory are characterized by deficits in executive control of encoding and retrieval mechanisms (Woods et al., 2005b, Scott et al., 2006, Cattie et al., 2012), a pattern consistent with a frontal-subcortical involvement. Dependence on illicit drugs is also consistently associated with deficits in cognitive function, including verbal memory (O'Malley et al., 1992, Berry et al., 1993, Strickland et al., 1993, Beatty et al., 1995, Bolla et al., 2000, Darke et al., 2000) and executive function (Bolla et al., 1999, Grant et al., 2000, Mintzer and Stitzer, 2002, Hester and Garavan, 2004). Given that the use of illicit substances is common in HIV-infected populations, it is important to understand how HIV-infection and illicit drug use might interact to impact cognitive function.

A number of recent *in vitro* and *in vivo* studies suggest that cocaine directly affects the neuropathogenesis of HIV (Peterson et al., 1991, Bagasra and Pomerantz, 1993, Fiala et al., 1998, Turchan et al., 2001, Roth et al., 2002, Aksenov et al., 2003, Gekker et al., 2004, Fiala et al., 2005, Kendall et al., 2005, Aksenov et al., 2006, Reynolds et al., 2006, Dhillon et al., 2007, Harrod et al., 2008). Cocaine amplifies HIV replication (Peterson et al., 1991, Bagasra and Pomerantz, 1993, Roth et al., 2002, Gekker et al., 2004, Dhillon et al., 2007), including in human astrocytes (Reynolds et al., 2006), which can function as cellular reservoirs for HIV in the brain (Brack-Werner, 1999). Cocaine may also increase HIV-infected monocyte migration across the

blood-brain barrier (Fiala et al., 1998, Fiala et al., 2005). Cocaine enhances the neurotoxic effects of the HIV viral protein Tat (Turchan et al., 2001, Aksenov et al., 2003, Kendall et al., 2005, Aksenov et al., 2006, Harrod et al., 2008). Similarly, opiates increase neurotoxicity of HIV proteins Tat (Gurwell et al., 2001, Khurdayan et al., 2004, Hu et al., 2005) and gp120 (Hu et al., 2005). Importantly, cocaine and opiates, in combination with HIV proteins, negatively impact hippocampal neurogenesis (Venkatesan et al., 2007). Given that the hippocampus is critical for episodic memory, translation of these preclinical findings into clinical studies may lend important new insights into memory function in HIV-infected cocaine users.

Although many studies have investigated the impact of illicit drug use on HIV disease progression, the effects of cocaine and heroin use on cognition in HIV-infected women have not been elucidated (Maki and Martin-Thormeyer, 2009). Such studies are critical in light of the myriad sex differences in illicit substance use disorders. Women have higher current and lifetime use of cocaine and are more likely than men to become cocaine-dependent (Chen and Kandel, 2002, O'Brien and Anthony, 2005, Lejuez et al., 2007). Women who use cocaine are three times more likely to become infected with HIV than women who do not use cocaine (Edlin et al., 1994). Cocaine use is also associated with accelerated disease progression in women with HIV, even when statistically controlling for anti-retroviral therapy use (Webber et al., 1999, Baum et al., 2009) and medication adherence (Cook et al., 2008). For example, in the Women's Interagency HIV Study (WIHS), HIV-infected women who used crack cocaine were three times more likely to die of AIDS-related causes than women who did not use crack cocaine, even when controlling for adherence to highly active anti-retroviral therapy (HAART) (Cook et al., 2008). Studies of illicit drug use in women generally have not found an effect of opiates on HIV disease progression (Webber et al., 1999, Thorpe et al., 2004).

Our aim was to investigate the impact of HIV infection and illicit drug use on cognition in women. We compared three categories of drug use: recent use, former use, and non-use. Primary outcomes were measures of verbal learning and memory, processing speed, and executive function based on neuropsychological tests with demonstrated sensitivity to HIV-related neurocognitive dysfunction (Hinkin et al., 1999, Carey et al., 2004, Martin et al., 2004a, Woods et al., 2004, Moore et al., 2006). We hypothesized that HIV and illicit drug use, especially cocaine use, would have an interactive effect on verbal learning and memory and executive function.

C. Methods

1. Subjects

All participants were enrolled in the WIHS, the largest prospective, longitudinal, multi-center study of HIV progression in women (Barkan et al., 1998, Bacon et al., 2005). Study methodology, standardized data collection, and training of interviewers have been previously reported (Barkan et al., 1998, Bacon et al., 2005). We analyzed cross-sectional data from 947 HIV-infected and 443 HIV-uninfected control participants (mean age=42.8, 64% African-American). The data were collected as part of a study of menopause, cognition, and mood that was incorporated into the WIHS core visits in April 2007 to April 2008 (WIHS visit 25) (Maki et al., 2012). Extensive information on demographic and behavioral variables was obtained, including self-report of recent and past use of alcohol, marijuana, crack cocaine, powder cocaine, and heroin.

Altogether 1901 participants were assessed during that WIHS core visit, and 1552 of those women completed the Hopkins Verbal Learning Test-Revised (HVLT-R). We excluded 157 of those participants because they reported: a) primary language other than English (n=14);

b) history of stroke/cerebrovascular accidents (n=18); and/or c) use of antipsychotic medication in the past 6 months (n=130). A comparison of women who were included in this analysis (n=1395; 73% of the overall sample) versus those who were excluded (n=506) showed similar rates of cocaine and heroin use, but women who were included completed more years of education (12.4 vs. 10.6 years, $p<0.001$), performed better on the Wide Range Achievement Test – Revised (WRAT-R) (92.2 vs. 87.3, $p<0.001$), were more likely to be African-American (64% vs. 41%, $p<0.001$) and less likely to be Hispanic (19% vs. 48%, $p<0.001$), were less likely to have depressive symptoms on the Center for Epidemiological Studies-Depression scale (CES-D; 32% vs. 46%, $p<0.001$) or report using antidepressant medication (12% vs. 19%, $p<0.001$), and were more likely to smoke (72% vs. 66%--recent or former, $p=0.01$) and use marijuana (75% vs. 60%--recent or former, $p<0.001$).

2. Illicit drug use

The WIHS collects information on drug use at 6 months intervals consistent with the twice yearly WIHS visit schedule. Women are asked if they have used drugs since their last WIHS visit. If they have used drugs since their last WIHS visit, they are queried about the route of administration (smoking, sniffing, injecting) of each substance as well as their frequency of use. For the current study, recent illicit drug use was defined as self-reported use of crack cocaine, powder cocaine, or heroin since the last WIHS study visit (past 6 months). Former use was defined as any lifetime use of cocaine and/or heroin, but no use since the last WIHS study visit (past 6 months). Non-use was defined as no lifetime use of cocaine and/or heroin. In follow-up analyses focusing on particular drugs, crack cocaine and powder cocaine were combined into one cocaine use variable, as there was insufficient statistical power to separate the two forms of

the drug. Frequency data were categorized as: once a month or less; at least once a week but less than once per day; or once a day or more.

3. Clinical neuropsychological measures

Participants completed the HVLT-R and Comalli Stroop test. The HVLT-R is a 12-item 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 25-minute delay (delayed recall), number of words correctly identified on a yes/no recognition test (recognition), percent retention (delayed recall/maximum score on Trial 2 or 3), and learning slope. Recognition scores were calculated by subtracting the number of false positives (incorrectly responding 'yes' to a word not presented) from the number of hits (correctly responding 'yes' to a word that was presented). The Comalli Stroop Test includes three trials (Comalli et al., 1962) Trials 1 and 2 measure attention and processing speed. Trial 3 measures response inhibition/executive function. On Trial 1, participants name the colors of a series of squares. On Trial 2 they read a series of color names printed in black ink. On Trial 3, participants name the color of the ink but ignore the word (e.g., when shown the word "red" printed in blue ink, say "blue" rather than "red") (Comalli et al., 1962). Completion times for all three trials were recorded. The WRAT-R measured reading achievement (Jastak et al., 1984) and served as an index of educational quality (Manly et al., 2002).

4. Covariates

Socio-demographic covariates and risk factors for cognitive impairment were selected based on previous literature and included study site, age, years of education, race/ethnicity, WRAT-R, CES-D (cutoff score of 16) (Radloff, 1977), recent self-reported use of

antidepressant medication and Hepatitis C virus seropositivity (HCV) (Goggin et al., 1997, Durvasula et al., 2001, Martin et al., 2004a, Ryan et al., 2004, Cherner et al., 2005, Letendre et al., 2005, Richardson et al., 2005, Manly et al., 2011, Valcour et al., 2012). Other covariates focused on risk behaviors and included smoking status (recent, former, never), recent hazardous alcohol use (> 7 drinks/week or more than 4 drinks in one sitting) (Willenbring et al., 2009), and marijuana/hash use (recent, former, never). Additional clinical variables of interest were cART use (i.e., no cART therapy, cART therapy and <95% compliant, cART therapy and ≥95% compliant), recent CD4 count <200 cells/mm3, recent HIV viral load >10,000 copies/mL, CD4 nadir <200 cells/mm3, and duration of ART use.

5. Statistical analysis

Five percent of participants were missing WRAT-R scores. Missing values were imputed using a regression based technique with race/ethnicity, age, education, site, and employment as predictors. Time-related outcomes on the Stroop were log-transformed to correct for skewness. All outcome measures were transformed to z-scores to allow for comparison of beta weights across outcome measures in models controlling for the same covariates.

Differences in demographic, behavioral, and clinical characteristics as a function of serostatus, illicit drug use, and their interaction were examined using ANOVAs for continuous variables and Chi-square (X^2) tests for categorical variables. In the overall sample we conducted two series of multivariable regression analyses. The first series focused on the independent effects of serostatus and illicit drug use, adjusting for age, years of education, WRAT-R, race/ethnicity, site, depressive symptoms, self-reported use of antidepressant medication and dementia/encephalopathy (n=59), marijuana use, smoking, hazardous alcohol use, and HCV. We also adjusted for number of prior exposures to the Stroop (range 1-3). (The HVLT had not been

previously administered.) The primary set of analyses focused on the interactive effect of serostatus and illicit drug use. When the interaction was significant, we further examined the effect of drug use and frequency within each serostatus group, controlling for the same set of covariates included in the first analyses. Other follow-up analyses focused on HIV-infected women and included recent CD4 count and HIV viral load, CD4 nadir, and use of antiretroviral therapy (ART). All *p* values are two-sided. The statistical significance level was set at $p<0.05$. Analyses were performed using SAS PROC GENMOD (version 9.2, SAS Institute Inc, Cary, NC).

D. Results

1. Population characteristics

Participants included 952 HIV-infected and 443 HIV-uninfected women. They ranged in age from 22 to 78 years (M=42.8, SD=9.5), with high minority representation (64% African-American, 19% Hispanic). Ten percent (n=140) reported use of cocaine and/or heroin since the previous study visit 6 months earlier; 47% (n=651) reported former use of cocaine and/or heroin, and 43% (n=604) reported never using cocaine and/or heroin in their lifetime. Among recent drug users, 70% had recently used only cocaine, 24% had recently used both cocaine and heroin, and 6% had recently used only heroin. Recent cocaine users mainly smoked crack (74%) or snorted cocaine (26%). Primary modes of recent heroin intake were snorting (17%) and injecting (14%). Critically, as shown in Table 5, the typical pattern of recent use was at least daily (32%) or weekly (38%) smoking of crack cocaine (e.g., 73%).

Compared to HIV-uninfected women, HIV-infected women were older, had a higher minority representation, were more likely to be HCV-seropositive and to use antidepressant medication and cigarettes, and were less likely to engage in hazardous drinking, marijuana, and

powder cocaine use (p's<0.05, Table 1). Compared to non-users, recent and former illicit drug users were older, less educated, were more likely to be HCV-seropositive, reported more depressive symptoms and antidepressant medication use, and were more likely to smoke, use marijuana, crack cocaine, powder cocaine, heroin, and engage in hazardous drinking (p's<0.05). Among recent users, HIV-infected women were less likely to sniff/snort cocaine and less frequently injected heroin than HIV-uninfected women (p's<0.05, Table 5). Among HIV-infected women, recent users were less likely to be on cART and to adhere to their medication, were on ART for a shorter duration of time, and were diagnosed with HIV more recently than former and non-users (p's<0.05).

2. Hopkins Verbal Learning Test-Revised (HVLT-R)

Table 2 shows the raw neuropsychological test scores as a function of serostatus and illicit drug use. HIV-infected women performed worse than HIV-uninfected women on total learning, learning slope, delayed recall, and recognition (p's<0.05; see Table 3). In adjusted analyses, recent illicit drug users performed worse than non-users on learning slope (p=0.04), delayed recall (p=0.007), and recognition (p=0.02). Recent drug users also performed worse than former drug users on recognition (p=0.03). Former drug users did not perform differently than non- users on any HVLT measure. The primary finding was that illicit drug use (recent versus non- use) interacted with serostatus to affect Trial 1, total learning, learning slope, and delayed recall (p's<0.05; see Figure 1), but not recognition (p=0.73). Among HIV-infected women, recent illicit drug users performed worse than non-users on total learning (B=-0.36, SE=0.12, p=0.002), learning slope (B=-0.42, SE=0.12, p<0.001), and delayed recall (B=-0.45, SE=0.12, p<0.001). In contrast, among the HIV-uninfected women, recent users performed similarly to non-users on total learning (B=0.22, SE=0.15, p=0.14), learning slope (B=0.18, SE=0.15,

p=0.23), and delayed recall (B=-0.05, SE=0.15, p=0.73), Whereas the interaction between serostatus and drug use for each of the four measures was driven by differences between recent users and non-users at the level of serostatus, for Trial 1 only, the interaction was driven by differences between HIV-infected and uninfected women at the level of drug use. Specifically for Trial 1, the interaction was driven by serostatus effects at the level of drug use; among recent users, HIV-infected women performed worse than HIV-uninfected women (B=-0.47, SE=0.16, p=0.004) whereas among non-users, HIV+ women perform similar to HIV-uninfected women (B=-0.02, SE=0.08, p=0.84).

Follow-up analyses probed the interaction between serostatus and recent drug use further to assess which particular drug (i.e., cocaine with or without heroin; heroin with or without cocaine) contributed to the interaction. Serostatus interacted with cocaine use (recent versus non-use; p's<.05) and heroin use (recent versus non-use; p's<.01) to impact total learning and learning slope. Serostatus interacted with cocaine use (non-use versus recent) but not heroin use to impact delayed recall (p=0.04). Additional analyses focused on dose response by examining the frequency of smoking crack on total learning, learning slope and delayed recall (see Table 6). Serostatus interacted with frequency of crack use ($\geq$ 1 week versus non-use) to affect total learning (p= 0.03) and delayed recall (p=0.005). Again the patterns were that drug use impacted performance among HIV-infected women only.

In analyses of HIV-infected women only, the effects of illicit drug use (recent versus non-use) on total learning, learning slope, and delayed recall remained significant after controlling for disease characteristics (i.e., CD4 count, viral load, medication use, duration on ART) (see Table 4). Recent users also performed worse than former users on learning slope and delayed recall, and former users performed worse than non-users on delayed recall. Comparing

recent users to non-users on total learning and learning slope, recent heroin use predicted poorer performance (B=-0.42, SE=0.19, p=0.03 and B=-0.58, SE=0.24, p=0.01, respectively). Cocaine use predicted poorer performance on delayed recall (B=-0.32, SE=0.15, p=0.03). There was also a trend for heroin use to predict poorer performance on delayed recall (B=-0.34, SE=0.20, p=0.08). In HIV-infected women, the effects of smoking crack/cocaine at least once a week versus non-use remained significant on both total learning (B=-0.39, SE=0.19, p=0.04) and delayed recall (B=-0.40, SE=0.19, p=0.04) after controlling for disease characteristics (i.e., CD4 count, viral load, medication use, duration on ART).

3. Stroop Test

Neither HIV-infection nor drug use significantly impacted performance on the Stroop test (Trials 1&2 or Trial 3, p's>0.05). In addition, there were no significant interactions between illicit drug use and serostatus on the Stroop Test (p's>0.05).

E. Discussion

The aim of this study was to investigate the separate and interactive effects of illicit drug use and HIV infection on verbal learning and memory, processing speed, and executive function. To our knowledge this is the first study to examine this issue, and we provide new evidence that in women recent illicit drug use may interact with HIV serostatus to negatively impact verbal learning and memory but not processing speed or response inhibition. The typical pattern of recent drug use was at least daily or weekly smoking of crack cocaine. The pattern of effects across different measures suggests that recent drug use (compared to non-use) affects learning and memory more among HIV-infected than HIV-uninfected women. Cocaine use interacted with HIV serostatus to affect learning and delayed recall, but not recognition. Heroin interacted with HIV serostatus to affect only learning. Serostatus also interacted with frequency of crack

cocaine use to negatively affect learning and delayed recall (but not recognition) more in HIV-infected women. HIV infection, regardless of substance use history, was associated with deficits in learning (i.e., impaired total learning, learning slope) and delayed memory (impaired delayed recall, recognition), with no impairment in retention or attention (trial 1). Deficits in verbal learning and memory encoding might have important implications for clinical management of HIV, as neurocognitive deficits have been shown to relate to poor medication treatment adherence among HIV-infected individuals (Hinkin et al., 2002). Our results underscore the importance of effective substance abuse treatment in HIV-infected individuals.

Few studies have sufficient statistical power to test for an interactive effect of HIV and drugs of abuse on cognition (Martin-Thormeyer and Paul, 2009). The HIV Neurobehavioral Research Center (HNRC) has investigated additive and potential interactive effects of methamphetamine and HIV. They found additive effects of methamphetamine use and HIV infection on neuropsychological function (Rippeth et al., 2004), neural and glial injury (Chang et al., 2005), and cerebral blood flow (CBF) (Ances et al., 2011). The only previous study to investigate the interactive effects of HIV and cocaine use on verbal memory (n= 237 gay and bisexual seropositive and seronegative African-American men) found no significant main effects for serostatus or cocaine use and no interaction of HIV and cocaine use on verbal memory, differences that were attributed to confounding effects of alcohol (Durvasula et al., 2000).

Several studies have provided important insights into how HIV serostatus influences cognition among individuals using illicit substances (Martin et al., 2001, Martin et al., 2003, Martin et al., 2004a, Martin et al., 2007, Gonzalez et al., 2008). Compared to HIV-uninfected drug users, HIV-infected drug users perform worse on tests of procedural learning (Gonzalez et

al., 2008), prospective memory (Martin et al., 2007), decision-making (Martin et al., 2004b), and working memory (Martin et al., 2001, Martin et al., 2003), deficits consistent with the affinity of HIV for the striatum and prefrontal cortex. However, study samples were typically male, of small size ($n < 100$) and did not include a non-drug using comparison group (Martin et al., 2001, Martin et al., 2003, Martin et al., 2004a, Martin et al., 2007, Gonzalez et al., 2008). A study of 43 women with a history of illicit drug use did not identify a relationship with cocaine or heroin use within the past 12 months and noted no interaction between HIV status and recent drug use on verbal memory or any cognitive domain; however, cell sizes were small (e.g. n=9) (Mason et al., 1998). We similarly did not find a difference between recent and former users on total learning or delayed recall.

In our full sample of HIV-infected and HIV-uninfected women there were no differences between former drug users and non-users on any neurocognitive outcome, suggesting recovery of cognitive function. In contrast, in our HIV-infected sample, former users performed worse than non-users on delayed recall. This pattern provides further evidence that drug use has a stronger negative impact on cognitive function in HIV-infected women. Recent use may have a larger negative impact than past use due to the synergistic neurotoxicity of HIV viral proteins with cocaine and heroin, with potential for recovery of cognitive function with sustained abstinence (Di Sclafani et al., 2002, Hanlon et al., 2011, Gould et al., 2012).

Other studies have looked within HIV-infected cohorts for effects of drug use on cognition, but without an HIV-uninfected control group. Our findings are consistent with other findings showing an effect of active cocaine dependence on delayed recall and visuospatial construction in HIV-infected individuals (n=64, 72% male), with recall having the largest effect size (d=.93) (Meade et al., 2011). As in the present study, the CNS HIV Antiretroviral Therapy

Effects Research (CHARTER) study (75% male) found no impact of lifetime history of substance use on tests of processing speed and executive function (Byrd et al., 2011). CHARTER also found that lifetime heroin dosage related to delayed memory. In comparison, we found that delayed memory related to recent use of cocaine, particularly use of crack cocaine more than once per week. Recent heroin use was associated with worse total learning in HIV-infected women. Recent stimulant use was associated with impairments in sustained attention in a sample of 40 HIV-infected individuals; but verbal memory was not examined and cocaine and methamphetamine use were combined (Levine et al., 2006).

Contrary to our hypothesis, serostatus and illicit drug use did not interact to affect inhibitory control. The scientific literature is mixed with respect to whether drug use impacts Stroop performance. A study of 159 men with at least one substance use disorder found a negative effect of HIV infection on performance during the incongruent condition of a computerized Reaction Time Stroop (Martin et al., 2004a). Other studies have failed to find a negative effect of cocaine use on Stroop performance in HIV-uninfected individuals (Berry et al., 1993, Bolla et al., 1999, Woicik et al., 2009) but have found effects on other executive measures such as the go/no test (Bolla et al., 1999, Hester and Garavan, 2004, Verdejo-Garcia et al., 2005).

The use of the HVLT precludes a clear understanding of whether the interactive effects of HIV and recent drug use represent a deficit in acquisition/encoding, retention, and/or retrieval. However, the pattern of interactions provides tentative support of potential effects on acquisition and retrieval, with spared retention. Specifically, HIV serostatus interacted with recent drug use to affect acquisition (total learning and learning slope) and retrieval (impaired delayed recall but spared recognition), with no effect on retention. Interestingly, that same pattern of effects was evident in follow-up analyses examining the impact of cocaine use specifically as well as

frequency of crack cocaine use. Crack cocaine was the primary drug of choice among recent users. Moreover, analyses of recent drug use in HIV-infected women alone showed deficits in acquisition (total learning and learning slope) and retrieval (impaired delayed recall but spared recognition), with no effect on retention. This pattern of interactive effects differs from the pattern of main effects associated with HIV serostatus and recent drug use, which were characterized by deficits in acquisition only. The apparent pattern of interactive effects on acquisition and retrieval suggests that HIV and cocaine might interact to influence subcortical-prefrontal circuitry. Chronic cocaine use has been associated with anatomical changes, cerebrovascular defects, and functional alterations in the prefrontal cortex (Volkow et al., 1988, Volkow et al., 1992, Volkow et al., 1993, Franklin et al., 2002, Bolla et al., 2004). Given the known executive component, such as encoding strategies, on episodic memory performance, deficits in subcortical-prefrontal circuitry may contribute to deficits in verbal memory (Peavy et al., 1994, Delis et al., 1995, Gongvatana et al., 2007). A neuroimaging study of delayed verbal memory in HIV-infected women demonstrated alterations in hippocampal function with decreased activation during verbal encoding and increased during verbal retrieval (Maki et al., 2009). Importantly, the magnitude of those alterations correlated with worse delayed recall on the HVLT (Maki et al., 2009). Together these findings suggest that cocaine and heroin use in HIV-infected women may also lead to further alterations in hippocampal function during verbal encoding.

Our study had several limitations. First, self-report data was used to determine drug use categories. If women who had recently used illicit drugs reported never using cocaine, the impact of illicit drug use on cognition may be underestimated. Second, toxicology screens were not administered in conjunction with neurocognitive testing, so it is possible that the recent users

could have been under the influence of drugs or experiencing drug withdrawal. WIHS staff are trained in detecting illicit substance use and reschedule women for cognitive testing if they appear to be under the influence of illicit substances. Third, given the use of multiple illicit substances in our cohort, we could not fully disentangle the effects of different substances on cognition. We found that cocaine use (with or without heroin) predicted worse total learning, learning slope, and delayed recall, and heroin use (with or without cocaine) predicted worse total learning and learning slope among HIV-infected women. Fourth, only two neurocognitive tests were administered, so we could not evaluate effects across a broader spectrum of cognitive domains. Fifth, although effect sizes are 0.11 or lower, the effect sizes for the interaction between serostatus and drug use are equal to or exceed the effect sizes associated with HIV serostatus alone or drug use alone. Lastly, the cross-sectional design of this study precludes the possibility of examining causality. We presume that illicit drug use leads to poor memory performance but it is possible that learning and memory deficits preceded drug use for at least some women. The last two limitations are being now addressed with the collection of longitudinal cognitive data in the WIHS.

III. NEUROIMAGING STUDY

A. Introduction

HIV-infected individuals continue to experience cognitive dysfunction despite advances in antiretroviral therapy. Over 50 percent of HIV-infected patients experience HIV-associated neurocognitive disorders (HAND) (Heaton et al., 2010), ranging from asymptomatic neurocognitive impairment to HIV-associated dementia (Antinori et al., 2007). Women may be at increased risk for HIV-associated cognitive deficits due to high prevalence of comorbid psychosocial and mental health problems, as well as lower cognitive reserve associated with lower education (Basso and Bornstein, 2000, Farinpour et al., 2003, Maki and Martin-Thormeyer, 2009). Illicit drug use is prevalent among HIV-infected patients. In the Women's Interagency HIV Study (WIHS), the largest study of women living with HIV, 30% of study participants reported using illicit drugs during the study period, with cocaine being the most common drug (Wilson et al., 1999, Cook et al., 2008). Among HIV-infected individuals, cocaine use is associated with both accelerated disease progression (Cook et al., 2008, Baum et al., 2009) and cognitive impairment (Levine et al., 2006, Meade et al., 2011).

HIV is characterized by prefrontal cortex dysfunction. Deficits in executive function, learning, and memory are well documented in HIV-infected patients (Heaton et al., 2011). Thinning of the prefrontal cortex is correlated with cognitive deficits in HIV-infected patients (Thompson et al., 2005). Evidence from a wealth of neuropsychological and neuroimaging studies indicates that prefrontal dysfunction contributes in large part to executive function deficits (Wood and Grafman, 2003). The prefrontal cortex is also critical for performing episodic memory tasks (Rugg et al., 2002). Left prefrontal cortex in particular plays a key role in the episodic encoding of verbal material (Kapur et al., 1994, Demb et al., 1995). During the encoding phase of verbal episodic memory tasks, left prefrontal cortex activation reflects

organizational processing (Tulving et al., 1994, Demb et al., 1995, Blumenfeld and Ranganath, 2006, Murray and Ranganath, 2007). Several neuroimaging studies have demonstrated prefrontal dysfunction in HIV, with HIV-infected patients showing increased activation in the lateral prefrontal cortex during executive function tasks (Chang et al., 2001, Ernst et al., 2002). This increased activation precedes behavioral deficits on these cognitive tests, suggesting that this additional neural recruitment is a compensatory mechanism to maintain normal levels of behavioral function (Chang et al., 2001, Ernst et al., 2002). During tasks of episodic memory, HIV-infected patients demonstrate altered activation patterns in the prefrontal cortex (Castelo et al., 2006, Maki et al., 2009) and show deficits in the use of executive, organizational strategies during encoding (i.e., semantic clustering) (Gongvatana et al., 2007).

Chronic cocaine use has also been characterized by prefrontal dysfunction and impaired executive function. Cognitively, cocaine dependence is associated with deficits on executive function domain scores, which include tasks of attention, planning, mental flexibility, and inhibition (Bolla et al., 1999, Di Sclafani et al., 2002, Hester and Garavan, 2004). Structurally, chronic cocaine users have reduced prefrontal gray matter concentration (Franklin et al., 2002) as well as reduced prefrontal cortical volume which is associated with lower executive function domain scores (Fein et al., 2002). Cocaine users also demonstrate altered metabolism and cerebrovascular deficits in the frontal cortex (Volkow et al., 1988, Volkow et al., 1992, Volkow et al., 1993). Functionally, cocaine users demonstrate reduced prefrontal activation during executive function tasks such as working memory/response inhibition (Hester and Garavan, 2004), decision making (Bolla et al., 2003, Bolla et al., 2004, Hester and Garavan, 2004) and attention/inhibition (Bolla et al., 2004). Additionally, more severe use is negatively associated with lateral prefrontal activation (Bolla et al., 2004).

Study 1 of this project demonstrated an interactive effect of HIV and illicit drug use. Drug use negatively impacted performance on a task of episodic learning and memory among women infected with HIV, but not uninfected women (Grauzas et al., 2013). Further analysis of the data showed that it was particularly cocaine use (with or without heroin use) that was associated with worse verbal memory. Additionally, recent cocaine use affected verbal memory, but former use had no impact on verbal memory. These results suggest that HIV and cocaine use may be interacting to negatively impact prefrontal cortex function. We propose that this observed deficit in women with HIV is due to the negative effects of cocaine use on organizational processing which contributes to verbal memory performance. One such organizational process is semantic clustering, a strategy used during learning and retrieval that involves categorizing words in a list according to semantic features. This strategic component of memory is tied to integrity of the frontal systems (Gershberg and Shimamura, 1995). Semantic clustering is related to other tasks of executive function and is associated with better learning and retrieval performance (Woods et al., 2005a, Woods et al., 2005b).

Our aim in this investigation was to examine alterations in the neural systems underlying verbal episodic memory in three groups of HIV-infected women: women who have recently used crack cocaine, women who formerly used cocaine, and women who have never used cocaine. We hypothesized that HIV-infected women who have recently used crack cocaine will show decreased prefrontal cortex activation during verbal memory encoding compared with HIV-infected women who have never used cocaine, and this decreased activation will be associated with lower behavioral measures of strategic encoding.

B. Methods

1. Subjects

HIV-infected women were enrolled from the Chicago WIHS Consortium. Participants were recruited for this neuroimaging substudy during semiannual WIHS core visits in 2010-2011. For this study, recent illicit drug use was defined as self-reported use of crack cocaine since the last WIHS study visit (past 6 months). Former use was defined as any self-reported lifetime use of crack cocaine but no use since the last WIHS study visit (past 6 months). Non-use was defined as no lifetime use of crack cocaine. Exclusion criteria were: 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); history of any AIDS-defining disorders; endocrine/systemic disease; or current psychiatric medication that affects cognition. Participants were also excluded for any evidence of acute intoxication or withdrawal at testing. Abstinence was verified with rapid urine toxicology screens (Express Diagnostics DrugCheck, Blue Earth, MN). Specific MRI exclusionary criteria included metal in the body, claustrophobia, or weight greater than 250 lbs (due to the dimensions of the scanner).

2. Functional MRI procedure

Blood oxygen level dependent (BOLD) fMRI was performed on a General Electric 3.0-Tesla Signa HDx scanner (General Electric Healthcare, Waukesha, WI) at the University of Illinois at Chicago Magnetic Resonance Center. The key data acquisition parameters were repetition time (TR) = 1500 ms, echo time (TE) = 25 ms, flip angle = 90 degrees, field of view (FOV) = 20 cm^2, image space matrix = 64 x 64, number of excitations

(NEX) = 1, slice thickness = 4mm, slice skip = 0mm, slice number = 30. All images were acquired axially, in parallel with the anterior commissure-posterior commissure (AC-PC) plane. The scan session lasted one hour and involved other neurocognitive tasks and structural scans that were not part of the current study including a working memory task, a simple reaction time task, and diffusion tensor imaging.

3. In-scanner verbal memory task

The fMRI verbal memory test included both an encoding and a recognition phase. The memory test was developed for the fMRI environment to mimic the Hopkins Verbal Learning Task (HVLT) with control conditions modeled after other fMRI studies (Sperling et al., 2002, Maki et al., 2009). To allow for semantic clustering, the fMRI task was developed to be similar to the HVLT in the use of concrete nouns from distinct semantic categories (e.g., body parts, furniture) (Brandt, 1991). Five semantic categories were selected from the same lists of category norms as the HVLT (Battig and Montague, 1969). Six words which represent common responses to each category name were chose from a list of updated category norms, with the exception of the two most common responses (Van Overschelde et al., 2004). The two most common responses to each category name were used as semantically-related distractors for the recognition task, as they were in the HVLT. Items were pseudo-randomized to ensure that no two category items were presented sequentially. Thirty words were used for the encoding task (six items in each of five categories) and presentation order was the same for each participant. A total of 60 experimental items were included in the recognition task, 30 items from encoding, 15 semantically related distractors, and 15 semantically unrelated distractors. The semantically related distractors were the most common category responses for each category in the encoding task. Fifteen unrelated distractor items were selected from the top exemplars in other categories.

Participants viewed each word individually on a projection screen and held a two-button response remote with the dominant hand. A block design was used with a 3s stimulus presentation and 1.5s interstimulus interval. The encoding task included 10 six-item blocks (total 60 stimuli). Blocks alternated between experimental (5 six-item blocks for 30 novel words) and control conditions (5 six-item blocks for 30 repeating stimuli). For the encoding task, participants were asked to remember each item for a later memory task and to indicate that they had seen each item by pressing the index finger button when a word appeared. Experimental blocks included single presentations of concrete nouns (e.g. pear, lake). Control blocks included repeated presentations of two concrete nouns (sailboat, ballet). This control condition places limited demands on memory because of repeated stimulus exposure but mimics the experimental condition in that it places demands on perceptual, motor, and lexical processes.

After a 12-minute delay during which structural scans were acquired, participants were asked to recall out loud all the words they could remember from the encoding task. Participants' answers were recorded but no scans were acquired during the free recall task. The recognition task began immediately after free recall. The recognition task included 20 six-item blocks (total 120 stimuli) that alternated between experimental and control tasks. Each experimental block included target stimuli from the encoding phase and distractor stimuli that had not been presented during the encoding task. Each control block involved the repeated administration of "sailboat" and "ballet." During the recognition phase, participants were asked to identify which words they recognized from the previous list, pressing the index finger button for "yes" responses and the middle finger button for "no" responses.

Outcome measures for the in-scanner task included number of words correctly recalled during free recall and percent correct on the recognition task. In addition, semantic clustering

scores were calculated. A semantic cluster is defined as two consecutive, correctly recalled items belonging to the same semantic category (e.g., "banana" followed by "pear"). Two outcomes were calculated, the total number of clusters and an overall clustering score. The total number of clusters was the number of times a distinct semantic cluster occurred. The overall clustering score takes into account the size of each cluster and 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.

4. Hopkins Verbal Learning Task – Revised (HVLT-R)

The HVLT-R is a 12-item list-learning test used to measure verbal episodic learning and memory (Benedict et al., 1998). Participants completed the HVLT during their regularly scheduled WIHS visit. A target list of 12 words belonging to three semantic categories (i.e. birds, articles of clothing, carpenters' tools) is read aloud three times. The order of words is randomized so no words from the same category are presented consecutively. The participant is asked to recall as many words as possible after each presentation. After a 20-minute delay, the participant is asked to recall the list again. Outcomes include total words recalled on Trial 1 (single trial learning) and across each of three learning trials (total learning), and number of words recalled after a 20-minute delay (delayed recall). Recognition scores were calculated by subtracting the number of false positives (incorrectly responding 'yes' to a word not presented) from the number of hits (correctly responding 'yes' to a word that was presented).

Semantic clustering scores were calculated per trial by counting the number of times a semantic cluster occurred, with a maximum score of nine (i.e., three potential clusters per each of the three categories). Semantic clustering scores were derived for each learning trial and the delayed trial.

5. Behavioral analyses

Differences in demographic, behavioral, and clinical characteristics as a function of crack cocaine use were examined using univariate ANOVAs for continuous variables and Chi-square (χ^2) tests for categorical variables. All analyses were done with SPSS Statistics Version 20 (IBM Corp, Armonk, NY).

6. Neuroimaging analyses

The data were preprocessed and analyzed the data using Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK). Movement was investigated using Analysis of Functional NeuroImages (ANFI) (Cox, 1996), and participants with greater than 2 voxels of motion were excluded from analyses. Functional images were realigned to the first volume of the task to correct for inter-scan motion. The realigned images were then co-registered to the SPM EPI template and smoothed with an 8-mm Gaussian kernel. A first-level analysis step was conducted to determine activated brain areas in individual participants using a general linear model and convolved with the hemodynamic response function. Four maps of brain activation were estimated for each participant to be used in second-level analyses - activation during the novel condition and activation during the repeat condition for both the encoding and recognition conditions. The second-level analysis step determined significant activation associated with the interactive effects of drug use group and task condition. In separate analyses of encoding and recognition, a full factorial design was used with two factors: drug use group (3 levels: recent, former, non-users) and condition (2 levels: experimental, novel). A mask was created for the *a priori* region of interest (ROI) using the Wake Forest University Pickatlas toolbox in SPM (Maldjian et al., 2003). The mask included Brodmann areas (BA) 6, 8-10, 44-47, the cingulate (BA 24 and 32), the hippocampus, and the

parahippocampal gyrus. The ROI mask was applied to the novel minus repeat contrast for the non-users to demonstrate the typical pattern of activation in the encoding and recognition tasks separately. Those brain maps were saved as binary masks to be used in subsequent analyses to constrain analyses to brain areas typically activated during the encoding and recognition tasks. The binary mask was then applied in the second level analysis in the overall interaction (F-test) of the interaction between drug use group and condition. When the overall F-test was significant, follow-up analyses were conducted to see which pairs of groups (i.e. recent users versus non-users, former users versus non-users, former users versus recent users) were driving the overall interaction. To constrain those follow-up analyses to regions significant in the overall F-test, follow-up analyses were conducted using a binary mask created from the overall F-interaction. Anatomical localization of significant activations was determined using the Talairach brain atlas (Talairach and Tournoux, 1988) and the Talairach Client (Lancaster et al., 2000). To examine the functional significance of group differences, the first eigenvariate of all voxel values contained in a 3-mm radial sphere around the peak voxel for each participant were extracted and were entered into correlational analyses with HVLT and in-scanner task outcomes.

C. Results

1. Demographics

Table 7 shows the demographic and clinical information by drug use group. 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), low effort on the in-scanner task (evidenced by chance performance on control task, n = 1) and technical problems (n = 3), leaving a final valid sample of 30. Of those 30 HIV-infected women, 10 reported using crack cocaine in the past 6 months (recent users), 11 reported having used cocaine during their lifetime

but not in the past 6 months (former users), and 9 reported never having used cocaine (non-users).

Participants ranged in age from 27 to 59 years (M = 44.1, SD = 7.5). Almost all participants were African-American (97%). In the total sample, 57% of women had CD4 counts above 500 cells/mm^3, 37% had CD4 counts between 200 and 500, and 6% had CD4 counts less than 200. The majority of our sample (80%) was on cART with 20% taking no antiretroviral therapy. Viral load was below detectable levels in 63% of the sample, below 10,000 copies/ml in 20% of the sample, and over 10,000 copies/ml in 17% of the sample. Groups differed on current cigarette smoking, with 80% of recent users, 55% of former users, and 22% of non-users reporting cigarette smoking ($p = 0.042$). Groups also differed on hepatitis C co-infection, with 50% of recent users, 18% of recent users, and 0% of non-users being HCV-positive ($p = 0.03$).

Table 8 shows drug use characteristics by drug use group. These data were collected during the substudy screening process conducted by WIHS staff prior to the neuroimaging visit. Two women reported no recent use of crack cocaine during the screening process but reported recent use on the day of the neuroimaging visit. Of the recent users, two reported using once a day or more in the past 6 months, two reported using at least once a week but less than once a day, four reported using less than once a week, and two reported not having used in the past 6 months. When examining peak use of crack cocaine across both recent and former user groups, most women reported that during the period of their heaviest crack cocaine use they were using more than once per week (7 out of 10 recent users and 9 out of 11 former users). The recent user group reported that their period of heaviest crack cocaine use was an average of 8.5 years ago (SD = 6.9, range = 17 years ago to current year). The former group reported that their period of

heaviest crack cocaine use was an average of 9.9 years ago (SD = 5.3, range = 17 years ago to 1 year ago).

2. Verbal memory performance

Table 9 shows the behavioral performance on the in-scanner verbal memory task and the HVLT by drug use group. Due to small sample sizes, Cohen's *d* effect sizes are also reported. On the HVLT, groups differed on the semantic clustering score for Trial 1. A Scheffe test indicated that the significant difference was between the recent and non-user groups ($p = 0.01$, $d = 1.44$). Although no other statistically significant group differences emerged ($p's < 0.05$), effect sizes were high for several outcomes. Comparing recent users to non-users, large effect sizes were observed for in-scanner recognition percent correct ($d = 0.53$), free recall total ($d = 0.70$), free recall number clusters ($d = 0.58$), and free recall cluster score ($d = 0.64$) as well as HVLT trial 1 ($d = 0.80$), HVLT delayed free recall ($d = 0.96$), HVLT delayed recall total clusters ($d = 0.72$) and HVLT delay cluster score ($d = 0.76$). Comparing former users to non-users, large effect sizes were observed for in-scanner recognition percent correct ($d = 0.86$), free recall number clusters ($d = 0.76$), free recall cluster score ($d = 0.84$) as well as HVLT trial 1 ($d = 0.50$) and HVLT trial 1 cluster score ($d = 0.72$).

3. Default activation pattern

We first evaluated the typical pattern of brain activation during encoding and recognition conditions in non-users. In the novel condition minus the repeated condition of the encoding task, we found diffuse activation in left prefrontal cortex and left hippocampus with very little activation in the right hemisphere (see Figure 2). In the novel condition minus the repeated condition of the recognition task, we observed diffuse activation in bilateral prefrontal cortex (see Figure 2).

4. Encoding condition

The overall F-test indicated significant group differences in the left medial frontal gyrus (Brodmann area 8, or BA8) (see Figure 3 and Table 10). Follow-up analyses demonstrated that this difference was driven by non-users showing more activation during encoding of novel words than both the recent users and former user groups. When comparing recent and former user groups, there were no differences in activation in this area.

Behaviorally, activation in this cluster correlated with better performance on the in-scanner, free recall cluster score ($r = .398$, $p = .029$) as well as trial 1 cluster score on the HVLT ($r = .375$, $p = .041$) (see Figure 4).

5. Recognition condition

The overall F-test indicated significant group differences in the right inferior frontal gyrus (BA9), middle frontal gyrus (BA10 and BA46), and medial frontal gyrus (BA8) (see Figure 5 and Table 10). In the left hemisphere group differences were in middle frontal gyrus (BA8) and middle frontal gyrus (BA9). Follow-up analyses demonstrated that differences in right inferior frontal gyrus (BA9), right middle frontal gyrus (BA10), and left middle frontal gyrus (BA8) were driven by non-users showing more activation than both the recent and former users. Differences in right medial frontal gyrus (BA8) were driven by non-users showing more activation than recent users. Differences in right middle frontal gyrus (BA46) and left middle frontal gyrus (BA9) were driven by non-users showing more activation than former users. There were no differences in activation between recent and former users in any of these regions.

Behaviorally, activation in the left middle frontal gyrus (BA9) correlated with better performance on the in-scanner recognition task ($r = .419$, $p < 0.05$) (see Figure 6). A negative correlation with activation in BA9 and HVLT recognition also emerged; however, on further

inspection of the data this finding was driven by one outlier with performance on HVLT recognition that was > 3 standard deviations below the mean (data not shown).

D. Discussion

The aim of this study was to investigate the impact of crack cocaine use on integrity of the neural systems underlying strategic verbal encoding in a group of HIV-infected women. Study 1 indicated that among women with HIV, recent cocaine use negatively impacted delayed recall on the HVLT. In the current study, we found that both recent and former use of cocaine were associated with less activation in left dorsal medial PFC (DMPFC) in women with HIV during verbal encoding. Importantly, we found that activation in this region was related to semantic clustering on both the in-scanner verbal memory task as well as standardized neuropsychological test of verbal memory (i.e., HVLT). A widely cited review of 120 functional neuroimaging studies of semantic processing drew particular attention to the role of left DMPFC (BA8) and described the consistent activation of this region during semantic processing tasks (Binder et al., 2009). Patients with lesions of the left DMPFC demonstrate a deficit in retrieval of semantic information as their ability to name objects is intact; however, they are unable to generate lists of words within a category (Gold et al., 1997, Robinson et al., 1998). This region has also been previously associated with strategic encoding (Bor et al., 2004) and successful encoding of words (Heinze et al., 2006).

During the recognition phase of the verbal memory task, women who had recently or formerly used cocaine showed less activation in bilateral PFC compared to women who had never used crack cocaine. Behaviorally, activation in one of the regions to show group differences during recognition (left dorsolateral PFC) was related to performance on the in-scanner recognition task. Previous studies have found that cocaine-dependent individuals show

activation in this area when viewing cocaine-related cues (Prisciandaro et al., 2012) and less activation in this area relative to controls during a memory task (Moeller et al., 2010).

This study is one of the very few functional neuroimaging studies to investigate episodic memory in HIV and is the first to focus on measures of strategic encoding. Previous studies have examined serostatus effects on brain function during episodic memory tasks. A study of visual episodic memory found altered activation in hippocampal-prefrontal regions during encoding in HIV-infected compared to uninfected participants (Castelo et al., 2006). An fMRI study of verbal episodic memory found differences in hippocampal function during encoding and retrieval of a verbal memory task in HIV-infected women compared to uninfected women (Maki et al., 2009). In the current study, we did not find effects of crack cocaine use on hippocampal function during our verbal episodic memory task; although the absence of an uninfected control group precludes evaluation of HIV serostatus effects.

Previous studies have found evidence for an HIV-associated deficit in semantic clustering. One of the first studies to examine semantic clustering in an HIV-infected sample was from the HIV Neurobehavioral Research Center (HNRC). In a sample of 134 men, medically symptomatic HIV-infected patients were less likely to use semantic clustering than uninfected controls. HIV-infected medically asymptomatic patients fell between the other two groups but did not statistically differ from either group (Peavy et al., 1994). A second HNRC study of 126 men found that HIV-infected men diagnosed with minor cognitive/motor disorder engaged in significantly less semantic clustering than both HIV-infected patients not diagnosed with minor cognitive/motor disorder and uninfected controls (Delis et al., 1995). A study directly aimed at investigating the validity of HVLT component process measures in HIV found that HIV-infected patients performed significantly worse than the uninfected controls on semantic clustering

(Woods et al., 2005b). Importantly, they found that semantic clustering correlated with an executive function composite score, suggesting that this measure is an indication of executive control of encoding and retrieval. They observed a positive correlation between semantic clustering and total recall among HIV-infected patients, indicating that the greater use of this strategy is associated with better recall. A study comparing 4 groups found a stepwise decline in the use of semantic clustering, where uninfected controls exhibited the highest clustering, followed by the HIV-infected neuropsychologically impaired group, HIV-infected minor-cognitive motor disorder group, and HIV-associated dementia group, respectively (Gongvatana et al., 2007). This study also demonstrated that semantic clustering was related to the executive function domain, but not to performance on measures of processing speed or general cognitive abilities. Although HIV-associated semantic clustering deficits have been fairly well characterized in all male or predominantly male samples, no studies to date have examined semantic clustering in HIV-infected women.

Our study is the first to investigate the impact of cocaine use on semantic clustering in HIV-infected patients. Previous studies have demonstrated worse performance on verbal memory tasks in HIV-infected cocaine users compared to HIV-infected non-users (Meade et al., 2011, Grauzas et al., 2013). Deficits in verbal learning and memory have been well documented among uninfected cocaine users (Manschreck et al., 1990, Berry et al., 1993, Mittenberg and Motta, 1993, Beatty et al., 1995, Fox et al., 2009). Dependence on methamphetamine, another psychostimulant, is associated with deficient utilization of semantic clustering (Woods et al., 2005a). Importantly, among methamphetamine users, greater use of semantic clustering was associated with better delayed recall and retention. Taken together, our findings suggest that the

verbal memory deficits associated with cocaine abuse may be partially accounted for by ineffective encoding strategies, such as semantic clustering.

The typical pattern of activation we observed with our task was diffuse left prefrontal and hippocampal activation during encoding, with bilateral prefrontal activation during recognition. This pattern of activation is consistent with the well-established hemispheric encoding/retrieval asymmetry (HERA) model of episodic memory, which delineates the left hemispheric role in episodic memory encoding and right hemispheric role in episodic memory retrieval (Tulving et al., 1994, Habib et al., 2003).

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, behavioral findings from Study 1 indicate that the interaction between HIV serostatus and drug use is driven by the differences in performance between HIV-infected recent users versus non-users. Recent drug use did not negatively impact verbal learning and memory in uninfected women. Second, the cross sectional design does not allow for investigation of the effects of chronic cocaine use over time. Third, our sample sizes were too small to detect group differences on behavioral outcomes, although effect sizes indicated large differences in performance in recent and former users compared to non-users. Fourth, self-report data was used to determine drug use categories. If women who had recently used cocaine did not report their use, the impact of cocaine on prefrontal function may be underestimated.

Future directions for this line of research include longitudinal analyses of neuropsychological data now being collected in the WIHS to examine the effects of cocaine use on strategic clustering during verbal encoding and retrieval over time. Additionally, projects investigating the impact of HIV serostatus on the neural systems underlying verbal memory as

well as cocaine use effects on other prefrontally-mediated cognitive tasks are currently underway.

IV. DISCUSSION

The three group design of both Study 1 and Study 2 allowed us to investigate the effects of current drug use as well as persistent effects of former use. Study 1 indicated that recent illicit drug use had a negative impact on verbal memory performance; however, former use was not associated with deficits on verbal memory. Additionally, the interaction of HIV serostatus and illicit drug use was with recent, not former, illicit drug use. These findings indicate the potential for cognitive recovery in long-term abstinence from illicit drug use. On the other hand, Study 2 found less prefrontal cortex activation in both recent users and former users compared to non-users. This finding may indicate that there are long-lasting effects of cocaine use on neural circuits underlying strategic encoding. In our large behavioral study, former users did not show deficits relative to non-users. In contrast, our neuroimaging study found that former users showed indication of lasting neural damage, which could potentially be indicative of effective compensatory mechanisms.

A. Persistent deficits in cocaine abusers

Few studies have investigated the effects of long-term cocaine abstinence on cognitive recovery. Studies examining recovery during short-term abstinence (24 days to 3 months) demonstrate cognitive impairments relative to controls. At 24 days of abstinence, cocaine abusers were more impaired than controls in all areas except motor skills and verbal fluency (O'Malley et al., 1992). Fifty percent of the cocaine abusers demonstrated mild clinical impairment after 24 days of abstinence. In a sample of chronic crack abusers that were tested after 28 days of abstinence, there was a significant dose-response relationship between increased severity of cocaine use and neurocognitive deficits (Bolla et al., 1999). Neuropsychological deficits have been shown to persist in chronic cocaine users after 4 weeks (Bolla et al., 2000) and 45 days of abstinence (van Gorp et al., 1999). A study that compared crack dependent subjects at

both 6 weeks and 6 months of abstinence found that at 6 weeks the patients were cognitively impaired on most neuropsychological domains and were still significantly impaired at 6 months of abstinence (Di Sclafani et al., 2002). Persistence of cognitive deficits (or recovery) over longer periods of abstinence has not been examined in cocaine users.

Studies of alcohol dependent individuals have evaluated cognitive recovery in abstinence and found evidence for a partial reversal of the cognitive deficits that occur in alcohol dependence (Crews et al., 2005). A study of long-term abstinent alcohol-dependent individuals with an average abstinence length of 6.7 years, found that long-term abstinence resolved most neurocognitive deficits associated with alcohol dependence although spatial processing deficits remained. The majority of cognitive recovery occurred during the first few years of abstinence (Fein et al., 2006). These studies, taken with our results, indicate that periods of abstinence longer than 6 months may be required to see cognitive recovery in substance-dependent individuals.

B. Cocaine and verbal memory

Outside of the context of HIV, cocaine use has consistently been associated with deficits in verbal learning and memory. Even occasional users of powder cocaine demonstrate deficits in immediate and delayed verbal recall but not recognition (Reske et al., 2010). Chronic cocaine users demonstrate impaired immediate and delayed recall as well as recognition on several verbal memory tests, such as the California Verbal Learning Task (CVLT) and Rey Auditory Verbal Learning Test (RAVLT) (Manschreck et al., 1990, Mittenberg and Motta, 1993, Beatty et al., 1995, Fox et al., 2009). Deficits on immediate recall, short and long delay recall, and recognition are apparent during withdrawal and abstinence in crack-dependent individuals (Berry et al., 1993, Kelley et al., 2005, Fox et al., 2009). These studies have been done in predominantly

male samples. In contrast, our Study 1 found that among uninfected women, cocaine use was not associated with worse performance on verbal learning and memory. This apparent discrepancy in findings may be explained by sex differences in both verbal memory ability and the effects of cocaine use on the brain. There is a well-established female advantage in verbal learning and recall which is attributed to greater use of semantic clustering (Kramer et al., 1997, Kramer et al., 2006).

Evidence from a wide range of species indicates that the behavioral effects of cocaine differ between males and females, and differ in response to hormone levels in women (Evans and Foltin, 2010). In particular, subjective effects of smoked cocaine show sex differences and menstrual cycle differences. Women, compared with men, had lower subjective ratings of feeling "high" which also differed depending on menstrual cycle phase (Sofuoglu et al., 1999). These results were not replicated in a study of intranasal cocaine, suggesting that sex and menstrual cycle differences may vary depending on route of administration (Collins et al., 2007). This line of work suggests that when investigating the impact of cocaine use on cognitive function, both sex and route of administration should be considered.

C. Cocaine and response inhibition

Contrary to our initial hypothesis, serostatus and illicit drug use did not interact to affect response inhibition as measured by the Stroop task in Study 1. We also did not find a main effect of either HIV infection or recent illicit drug use on the interference trial of the Stroop (trial 3). Early HIV infection has been associated with worse performance on a computerized version of a reaction time Stroop task (Martin et al., 1992). A study of antiretroviral-naïve HIV patients found that they performed worse on all three trials of the Stroop task compared to controls, but this effect was not specific to behavioral inhibition (the interference trial) (Chang et al., 2002).

Given that the women in our sample were not in the stages of initial infection and were not antiretroviral naïve, it is not surprising that we didn't find a main effect of serostatus on Stroop outcomes. Previous studies of the effects of cocaine on response inhibition have found that cocaine use is associated with worse performance on tasks such as a Go/No-Go task (Bolla et al., 1999, Hester and Garavan, 2004); however, several studies have failed to find a negative effect of cocaine use on Stroop performance (Berry et al., 1993, Bolla et al., 1999, Woicik et al., 2009). These findings, along with ours, indicate that the task we used (the Comalli Stroop task) may not be a sensitive measure of response inhibition in our sample.

Animal studies coincide with human studies to show that cocaine use is associated with loss of inhibitory control. Impaired response inhibition is difficulty withholding a prepotent response and can be measured with stop signal reaction time (SSRT) tasks. Human cocaine users show elevated response times during these tasks (Fillmore and Rush, 2002, Li et al., 2006). Using a touch-screen SSRT task, rhesus monkeys with a history of self-administering cocaine displayed worse performance on the task, even after 18 months of abstinence (Liu et al., 2009). Delay discounting is another measure of impulsivity that is fundamentally different from response inhibition but is commonly used to study impulsivity in rodent models of cocaine addiction. Impulsivity, as measured by delay discounting tasks, predicts acquisition of cocaine self-administration (Perry et al., 2005), escalation of cocaine self-administration (Anker et al., 2009), and reinstatement of cocaine seeking in rats (Perry et al., 2008). These studies point to an impairment in inhibitory control that may be proceeded by, as well as exacerbated by, cocaine use. We would expect that if we had used a more sensitive measure, such a SSRT task, that we would have seen differences between our recent user and nonuser groups on response inhibition.

D. Route of administration

Neuropsychological studies of cocaine addicts are done in samples of primarily crack cocaine addicts (Manschreck et al., 1990, Beatty et al., 1995, Ma et al., 2009), but many studies fail to mention route of administration (Berry et al., 1993, Mittenberg and Motta, 1993, Kelley et al., 2005, Fox et al., 2009). The physiological and psychoactive effects of cocaine are similar regardless of the route of administration; however, crack (or smoked) cocaine shows greater potential for both abuse and addiction in comparison with intranasal powder cocaine (Hatsukami and Fischman, 1996). Although a PET study demonstrated that dopamine transporter blockade effectiveness is similar between intranasal and smoked cocaine, smoked cocaine elicits a faster subjective "high" (Volkow et al., 2000). The faster delivery into the brain increases the reinforcing effects of the drug. There is some evidence that dependence on crack cocaine compared to powder cocaine may have differential negative effects on the brain. Individuals dependent on crack cocaine demonstrate lower measures of white matter integrity in the corpus callosum compared to individuals dependent on intranasal powder cocaine (Ma et al., 2009). However, the impact of cocaine route administration on neural function has not been fully explored.

For this project, we were aware that the route of cocaine administration might influence the cognitive effects of cocaine so we reported crack cocaine and powder cocaine use separately. In Study 1, our drug use groups combined crack cocaine, powder cocaine, and heroin use, but the typical pattern of drug use was daily or weekly smoking of crack cocaine. Probing crack cocaine use specifically, we found that HIV serostatus interacted with frequent crack cocaine use to impact verbal learning and memory. Using crack cocaine at least once a week was associated with worse total learning and delayed recall in HIV-infected women, even when accounting for

disease characteristics such as antiretroviral use, viral load, and immune function. In Study 2, we restricted our recent user group to women who had used crack cocaine in the past 6 months. Therefore, our results may not extend to users of exclusively powder (intranasal) cocaine.

E. Overall significance

Overall, our results indicate that illicit drug use, particularly crack cocaine use, negatively impacts cognitive function in women with HIV. This impaired cognitive function can have detrimental effects on HIV disease outcomes. Effective treatment of HIV is dependent upon strict adherence to antiretroviral medication regimens. Combined antiretroviral therapy regimens are complex with several pills being taken per day with specific dose timing and administration instructions. Cognitive impairment among women with HIV is associated with 2.5 times greater risk of poor adherence to antiretroviral medication (Hinkin et al., 2004). Since drug abuse is a risk factor for HIV-associated cognitive impairment, treating drug abuse in women living with HIV has important implications for improving treatment adherence, health outcomes, and lowering the transmission risk. An estimated 25% of individuals living with HIV were in need of drug abuse treatment in the past year (SAMHSA, 2010), and among drug dependent individuals, only 10% receive treatment for their disease (CASA, 2013). This underscores the importance of screening HIV-infected patients for drug abuse disorders and treating the substance abuse disorder in addition to their HIV disease.

CITED LITERATURE

Aksenov MY, Aksenova MV, Nath A, Ray PD, Mactutus CF, Booze RM (2006) Cocaine-mediated enhancement of Tat toxicity in rat hippocampal cell cultures: the role of oxidative stress and D1 dopamine receptor. Neurotoxicology 27:217-228.

Aksenov MY, Hasselrot U, Wu G, Nath A, Anderson C, Mactutus CF, Booze RM (2003) Temporal relationships between HIV-1 Tat-induced neuronal degeneration, OX-42 immunoreactivity, reactive astrocytosis, and protein oxidation in the rat striatum. Brain Res 987:1-9.

An SF, Groves M, Gray F, Scaravilli F (1999) Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. J Neuropathol Exp Neurol 58:1156-1162.

Ances BM, Sisti D, Vaida F, Liang CL, Leontiev O, Perthen JE, Buxton RB, Benson D, Smith DM, Little SJ, Richman DD, Moore DJ, Ellis RJ (2009) Resting cerebral blood flow: a potential biomarker of the effects of HIV in the brain. Neurology 73:702-708.

Ances BM, Vaida F, Cherner M, Yeh MJ, Liang CL, Gardner C, Grant I, Ellis RJ, Buxton RB (2011) HIV and chronic methamphetamine dependence affect cerebral blood flow. J Neuroimmune Pharmacol 6:409-419.

Ances BM, Vaida F, Yeh MJ, Liang CL, Buxton RB, Letendre S, McCutchan JA, Ellis RJ (2010) HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. J Infect Dis 201:336-340.

Andras IE, Pu H, Deli MA, Nath A, Hennig B, Toborek M (2003) HIV-1 Tat protein alters tight junction protein expression and distribution in cultured brain endothelial cells. J Neurosci Res 74:255-265.

Anker JJ, Perry JL, Gliddon LA, Carroll ME (2009) Impulsivity predicts the escalation of cocaine self-administration in rats. Pharmacol Biochem Behav 93:343-348.

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789-1799.

Arango JC, Simmonds P, Brettle RP, Bell JE (2004) Does drug abuse influence the microglial response in AIDS and HIV encephalitis? AIDS 18 Suppl 1:S69-74.

Archibald SL, Masliah E, Fennema-Notestine C, Marcotte TD, Ellis RJ, McCutchan JA, Heaton RK, Grant I, Mallory M, Miller A, Jernigan TL (2004) Correlation of in vivo neuroimaging abnormalities with postmortem human immunodeficiency virus encephalitis and dendritic loss. Arch Neurol 61:369-376.

Bacon MC, von Wyl V, Alden C, Sharp G, Robison E, Hessol N, Gange S, Barranday Y, Holman S, Weber K, Young MA (2005) The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol 12:1013-1019.

Bagasra O, Pomerantz RJ (1993) Human immunodeficiency virus type 1 replication in peripheral blood mononuclear cells in the presence of cocaine. J Infect Dis 168:1157-1164.

Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, Young M, Greenblatt R, Sacks H, Feldman J (1998) The Women's Interagency HIV Study. WIHS Collaborative Study Group. Epidemiology 9:117-125.

Barks JD, Liu XH, Sun R, Silverstein FS (1997) gp120, a human immunodeficiency virus-1 coat protein, augments excitotoxic hippocampal injury in perinatal rats. Neuroscience 76:397-409.

Basso MR, Bornstein RA (2000) Estimated premorbid intelligence mediates neurobehavioral change in individuals infected with HIV across 12 months. J Clin Exp Neuropsychol 22:208-218.

Basso MR, Bornstein RA (2003) Effects of past noninjection drug abuse upon executive function and working memory in HIV infection. J Clin Exp Neuropsychol 25:893-903.

Battig WF, Montague WE (1969) Category norms of verbal items in 56 categories A replication and extension of the Connecticut category norms. Journal of Experimental Psychology 80:1.

Baum MK, Rafie C, Lai S, Sales S, Page B, Campa A (2009) Crack-cocaine use accelerates HIV disease progression in a cohort of HIV-positive drug users. J Acquir Immune Defic Syndr 50:93-99.

Beatty WW, Katzung VM, Moreland VJ, Nixon SJ (1995) Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. Drug Alcohol Depend 37:247-253.

Becker JB, Hu M (2008) Sex differences in drug abuse. Front Neuroendocrinol 29:36-47.

Bell JE, Brettle RP, Chiswick A, Simmonds P (1998) HIV encephalitis, proviral load and dementia in drug users and homosexuals with AIDS. Effect of neocortical involvement. Brain 121 (Pt 11):2043-2052.

Benedict RH, Mezhir JJ, Walsh K, Hewitt RG (2000) Impact of human immunodeficiency virus type-1-associated cognitive dysfunction on activities of daily living and quality of life. Arch Clin Neuropsychol 15:535-544.

Benedict RHB, Schretlen D, Groninger L, Brandt J (1998) Hopkins Verbal Learning Test - Revised: Normative Data and Analysis of Inter-Form and Test-Retest Relability. The Clinical Neuropsychologist 12:43-55.

Berry J, van Gorp WG, Herzberg DS, Hinkin C, Boone K, Steinman L, Wilkins JN (1993) Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after two weeks of abstinence. Drug Alcohol Depend 32:231-237.

Bezzi P, Domercq M, Brambilla L, Galli R, Schols D, De Clercq E, Vescovi A, Bagetta G, Kollias G, Meldolesi J, Volterra A (2001) CXCR4-activated astrocyte glutamate release via TNFalpha: amplification by microglia triggers neurotoxicity. Nat Neurosci 4:702-710.

Binder JR, Desai RH, Graves WW, Conant LL (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 19:2767-2796.

Blumenfeld RS, Ranganath C (2006) Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 26:916-925.

Blumenfeld RS, Ranganath C (2007) Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist 13:280-291.

Bolla K, Ernst M, Kiehl K, Mouratidis M, Eldreth D, Contoreggi C, Matochik J, Kurian V, Cadet J, Kimes A, Funderburk F, London E (2004) Prefrontal cortical dysfunction in abstinent cocaine abusers. J Neuropsychiatry Clin Neurosci 16:456-464.

Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, Funderburk FR, Ernst M (2003) Orbitofrontal cortex

dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19:1085-1094.
Bolla KI, Funderburk FR, Cadet JL (2000) Differential effects of cocaine and cocaine alcohol on neurocognitive performance. Neurology 54:2285-2292.
Bolla KI, Rothman R, Cadet JL (1999) Dose-related neurobehavioral effects of chronic cocaine use. J Neuropsychiatry Clin Neurosci 11:361-369.
Bono G, Mauri M, Sinforiani E, Barbarini G, Minoli L, Fea M (1996) Longitudinal neuropsychological evaluation of HIV-infected intravenous drug users. Addiction 91:263-268.
Bor D, Cumming N, Scott CE, Owen AM (2004) Prefrontal cortical involvement in verbal encoding strategies. European Journal of Neuroscience 19:3365-3370.
Bouwman FH, Skolasky RL, Hes D, Selnes OA, Glass JD, Nance-Sproson TE, Royal W, Dal Pan GJ, McArthur JC (1998) Variable progression of HIV-associated dementia. Neurology 50:1814-1820.
Boven LA, Middel J, Breij EC, Schotte D, Verhoef J, Soderland C, Nottet HS (2000) Interactions between HIV-infected monocyte-derived macrophages and human brain microvascular endothelial cells result in increased expression of CC chemokines. J Neurovirol 6:382-389.
Brack-Werner R (1999) Astrocytes: HIV cellular reservoirs and important participants in neuropathogenesis. AIDS 13:1-22.
Brandt J (1991) The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. The Clinical Neuropsychologist 5:125-142.
Bruce JM, Echemendia RJ (2003) Delayed-onset deficits in verbal encoding strategies among patients with mild traumatic brain injury. Neuropsychology 17:622-629.
Buch S, Yao H, Guo M, Mori T, Su TP, Wang J (2011) Cocaine and HIV-1 interplay: molecular mechanisms of action and addiction. J Neuroimmune Pharmacol 6:503-515.
Budka H (1997) Neuropathology of myelitis, myelopathy, and spinal infections in AIDS. Neuroimaging Clin N Am 7:639-650.
Byrd DA, Fellows RP, Morgello S, Franklin D, Heaton RK, Deutsch R, Atkinson JH, Clifford DB, Collier AC, Marra CM, Gelman B, McCutchan JA, Duarte NA, Simpson DM, McArthur J, Grant I (2011) Neurocognitive impact of substance use in HIV infection. J Acquir Immune Defic Syndr 58:154-162.
Carey CL, Woods SP, Rippeth JD, Gonzalez R, Moore DJ, Marcotte TD, Grant I, Heaton RK (2004) Initial validation of a screening battery for the detection of HIV-associated cognitive impairment. Clin Neuropsychol 18:234-248.
Castelo JM, Sherman SJ, Courtney MG, Melrose RJ, Stern CE (2006) Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. Neurology 66:1688-1695.
Cattie JE, Woods SP, Arce M, Weber E, Delis DC, Grant I (2012) Construct validity of the item-specific deficit approach to the California verbal learning test (2nd Ed) in HIV infection. Clin Neuropsychol 26:288-304.
CDC (2002) Drug-Associated HIV Transmission Continues in the United States. vol. Feb 6.
CDC (2007) HIV/AIDS Surveillance Report, Volume 19. vol. 2013.
CDC (2010) HIV Surveillance Report Volume 22. vol. 2013.
CDC (2011) HIV among Women.

Chana G, Everall IP, Crews L, Langford D, Adame A, Grant I, Cherner M, Lazzaretto D, Heaton R, Ellis R, Masliah E (2006) Cognitive deficits and degeneration of interneurons in HIV+ methamphetamine users. Neurology 67:1486-1489.

Chang L, Ernst T, Leonido-Yee M, Walot I, Singer E (1999) Cerebral metabolite abnormalities correlate with clinical severity of HIV-1 cognitive motor complex. Neurology 52:100-108.

Chang L, Ernst T, Speck O, Grob CS (2005) Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. Am J Psychiatry 162:361-369.

Chang L, Ernst T, Witt MD, Ames N, Gaiefsky M, Miller E (2002) Relationships among brain metabolites, cognitive function, and viral loads in antiretroviral-naive HIV patients. Neuroimage 17:1638-1648.

Chang L, Speck O, Miller EN, Braun J, Jovicich J, Koch C, Itti L, Ernst T (2001) Neural correlates of attention and working memory deficits in HIV patients. Neurology 57:1001-1007.

Chang L, Tomasi D, Yakupov R, Lozar C, Arnold S, Caparelli E, Ernst T (2004) Adaptation of the attention network in human immunodeficiency virus brain injury. Ann Neurol 56:259-272.

Chang L, Wang GJ, Volkow ND, Ernst T, Telang F, Logan J, Fowler JS (2008) Decreased brain dopamine transporters are related to cognitive deficits in HIV patients with or without cocaine abuse. Neuroimage 42:869-878.

Chen K, Kandel D (2002) Relationship between extent of cocaine use and dependence among adolescents and adults in the United States. Drug Alcohol Depend 68:65-85.

Cherner M, Letendre S, Heaton RK, Durelle J, Marquie-Beck J, Gragg B, Grant I (2005) Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. Neurology 64:1343-1347.

Chiang MC, Dutton RA, Hayashi KM, Lopez OL, Aizenstein HJ, Toga AW, Becker JT, Thompson PM (2007) 3D pattern of brain atrophy in HIV/AIDS visualized using tensor-based morphometry. Neuroimage 34:44-60.

Chiasson MA, Stoneburner RL, Hildebrandt DS, Ewing WE, Telzak EE, Jaffe HW (1991) Heterosexual transmission of HIV-1 associated with the use of smokable freebase cocaine (crack). AIDS 5:1121-1126.

Chiesi A, Vella S, Dally LG, Pedersen C, Danner S, Johnson AM, Schwander S, Goebel FD, Glauser M, Antunes F, et al. (1996) Epidemiology of AIDS dementia complex in Europe. AIDS in Europe Study Group. J Acquir Immune Defic Syndr Hum Retrovirol 11:39-44.

Cohen RA, Boland R, Paul R, Tashima KT, Schoenbaum EE, Celentano DD, Schuman P, Smith DK, Carpenter CC (2001) Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. AIDS 15:341-345.

Cohen RA, Harezlak J, Schifitto G, Hana G, Clark U, Gongvatana A, Paul R, Taylor M, Thompson P, Alger J, Brown M, Zhong J, Campbell T, Singer E, Daar E, McMahon D, Tso Y, Yiannoutsos CT, Navia B (2010) Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. J Neurovirol 16:25-32.

Cohen RA, Navia BA (2007) Preserved cognitive functioning over time in asymptomatic HIV-infected people in the MACS cohort. Neurology 69:2195-2196.

Cole MA, Margolick JB, Cox C, Li X, Selnes OA, Martin EM, Becker JT, Aronow HA, Cohen B, Sacktor N, Miller EN (2007) Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. Neurology 69:2213-2220.

Comalli PE, Jr., Wapner S, Werner H (1962) Interference effects of Stroop color-word test in childhood, adulthood, and aging. J Genet Psychol 100:47-53.

Conant K, St Hillaire C, Anderson C, Galey D, Wang J, Nath A (2004) Human immunodeficiency virus type 1 Tat and methamphetamine affect the release and activation of matrix-degrading proteinases. J Neurovirol 10:21-28.

Cook JA, Burke-Miller JK, Cohen MH, Cook RL, Vlahov D, Wilson TE, Golub ET, Schwartz RM, Howard AA, Ponath C, Plankey MW, Levine AM, Grey DD (2008) Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women. AIDS 22:1355-1363.

Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162-173.

Cristiani SA, Pukay-Martin ND, Bornstein RA (2004) Marijuana use and cognitive function in HIV-infected people. J Neuropsychiatry Clin Neurosci 16:330-335.

Cysique LA, Maruff P, Brew BJ (2004) Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. J Neurovirol 10:350-357.

Cysique LA, Vaida F, Letendre S, Gibson S, Cherner M, Woods SP, McCutchan JA, Heaton RK, Ellis RJ (2009) Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. Neurology 73:342-348.

Darke S, Sims J, McDonald S, Wickes W (2000) Cognitive impairment among methadone maintenance patients. Addiction 95:687-695.

Delis DC, Peavy G, Heaton R, Butters N, Salmon DP, Taylor M, Stout J, Mehta P, Ryan L, White D (1995) Do patients with HIV-associated minor cognitive/motor disorder exhibit a “subcortical” memory profile? evidence using the California Verbal Learning Test. Assessment 2:151-165.

Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD (1995) Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J Neurosci 15:5870-5878.

Dhillon NK, Williams R, Peng F, Tsai YJ, Dhillon S, Nicolay B, Gadgil M, Kumar A, Buch SJ (2007) Cocaine-mediated enhancement of virus replication in macrophages: implications for human immunodeficiency virus-associated dementia. J Neurovirol 13:483-495.

Di Sclafani V, Tolou-Shams M, Price LJ, Fein G (2002) Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. Drug Alcohol Depend 66:161-171.

Durvasula RS, Miller EN, Myers HF, Wyatt GE (2001) Predictors of neuropsychological performance in HIV positive women. J Clin Exp Neuropsychol 23:149-163.

Durvasula RS, Myers HF, Satz P, Miller EN, Morgenstern H, Richardson MA, Evans G, Forney D (2000) HIV-1, cocaine, and neuropsychological performance in African American men. J Int Neuropsychol Soc 6:322-335.

Edlin BR, Irwin KL, Faruque S, McCoy CB, Word C, Serrano Y, Inciardi JA, Bowser BP, Schilling RF, Holmberg SD (1994) Intersecting epidemics--crack cocaine use and HIV

infection among inner-city young adults. Multicenter Crack Cocaine and HIV Infection Study Team. N Engl J Med 331:1422-1427.

Edlin BR, Irwin KL, Ludwig DD, McCoy HV, Serrano Y, Word C, Bowser BP, Faruque S, McCoy CB, Schilling RF, et al. (1992) High-risk sex behavior among young street-recruited crack cocaine smokers in three American cities: an interim report. The Multicenter Crack Cocaine and HIV Infection Study Team. J Psychoactive Drugs 24:363-371.

Egan V, Brettle RP, Goodwin GM (1992) The Edinburgh cohort of HIV-positive drug users: pattern of cognitive impairment in relation to progression of disease. Br J Psychiatry 161:522-531.

Ernst T, Chang L, Jovicich J, Ames N, Arnold S (2002) Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. Neurology 59:1343-1349.

Farinpour R, Miller EN, Satz P, Selnes OA, Cohen BA, Becker JT, Skolasky RL, Jr., Visscher BR (2003) Psychosocial risk factors of HIV morbidity and mortality: findings from the Multicenter AIDS Cohort Study (MACS). J Clin Exp Neuropsychol 25:654-670.

Fein G, Di Sclafani V, Meyerhoff DJ (2002) Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug Alcohol Depend 68:87-93.

Ferris MJ, Mactutus CF, Booze RM (2008) Neurotoxic profiles of HIV, psychostimulant drugs of abuse, and their concerted effect on the brain: current status of dopamine system vulnerability in NeuroAIDS. Neurosci Biobehav Rev 32:883-909.

Fiala M, Eshleman AJ, Cashman J, Lin J, Lossinsky AS, Suarez V, Yang W, Zhang J, Popik W, Singer E, Chiappelli F, Carro E, Weinand M, Witte M, Arthos J (2005) Cocaine increases human immunodeficiency virus type 1 neuroinvasion through remodeling brain microvascular endothelial cells. J Neurovirol 11:281-291.

Fiala M, Gan XH, Zhang L, House SD, Newton T, Graves MC, Shapshak P, Stins M, Kim KS, Witte M, Chang SL (1998) Cocaine enhances monocyte migration across the blood-brain barrier. Cocaine's connection to AIDS dementia and vasculitis? Adv Exp Med Biol 437:199-205.

Fillmore MT, Rush CR (2002) Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend 66:265-273.

Foos TM, Wu JY (2002) The role of taurine in the central nervous system and the modulation of intracellular calcium homeostasis. Neurochem Res 27:21-26.

Fox-Tierney RA, Ickovics JR, Cerreta CL, Ethier KA (1999) Potential sex differences remain understudied: A case study of the inclusion of women in HIV/AIDS-related neuropsychological research. Review of General Psychology 3:44-54.

Fox HC, Jackson ED, Sinha R (2009) Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes. Psychoneuroendocrinology 34:1198-1207.

Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, O'Brien CP, Childress AR (2002) Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biol Psychiatry 51:134-142.

Gekker G, Hu S, Wentland MP, Bidlack JM, Lokensgard JR, Peterson PK (2004) Kappa-opioid receptor ligands inhibit cocaine-induced HIV-1 expression in microglial cells. J Pharmacol Exp Ther 309:600-606.

Gershberg FB, Shimamura AP (1995) Impaired use of organizational strategies in free recall following frontal lobe damage. Neuropsychologia 33:1305-1333.

Goggin KJ, Zisook S, Heaton RK, Atkinson JH, Marshall S, McCutchan JA, Chandler JL, Grant I (1997) Neuropsychological performance of HIV-1 infected men with major depression. HNRC Group. HIV Neurobehavioral Research Center. J Int Neuropsychol Soc 3:457-464.

Gold M, Nadeau SE, Jacobs DH, Adair JC, Rothi LJ, Heilman KM (1997) Adynamic aphasia: a transcortical motor aphasia with defective semantic strategy formation. Brain Lang 57:374-393.

Gongvatana A, Schweinsburg BC, Taylor MJ, Theilmann RJ, Letendre SL, Alhassoon OM, Jacobus J, Woods SP, Jernigan TL, Ellis RJ, Frank LR, Grant I (2009) White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals. J Neurovirol 15:187-195.

Gongvatana A, Woods SP, Taylor MJ, Vigil O, Grant I (2007) Semantic clustering inefficiency in HIV-associated dementia. J Neuropsychiatry Clin Neurosci 19:36-42.

Gonzalez-Scarano F, Martin-Garcia J (2005) The neuropathogenesis of AIDS. Nat Rev Immunol 5:69-81.

Gonzalez R, Jacobus J, Amatya AK, Quartana PJ, Vassileva J, Martin EM (2008) Deficits in complex motor functions, despite no evidence of procedural learning deficits, among HIV+ individuals with history of substance dependence. Neuropsychology 22:776-786.

Gould RW, Gage HD, Nader MA (2012) Effects of chronic cocaine self-administration on cognition and cerebral glucose utilization in Rhesus monkeys. Biol Psychiatry 72:856-863.

Grant S, Contoreggi C, London ED (2000) Drug abusers show impaired performance in a laboratory test of decision making. Neuropsychologia 38:1180-1187.

Grauzas V, Rubin LH, Martin E, Weber KM, Cohen MH, Golub ET, Valcour V, Young MA, Crystal H, Anastos K, Aouizerat BE, Milam J, Maki PM (2013) HIV and Recent Illicit Drug Use Interact to Affect Verbal Memory in Women. J Acquir Immune Defic Syndr.

Gurwell JA, Nath A, Sun Q, Zhang J, Martin KM, Chen Y, Hauser KF (2001) Synergistic neurotoxicity of opioids and human immunodeficiency virus-1 Tat protein in striatal neurons in vitro. Neuroscience 102:555-563.

Habib R, Nyberg L, Tulving E (2003) Hemispheric asymmetries of memory: the HERA model revisited. Trends Cogn Sci 7:241-245.

Hanlon CA, Dufault DL, Wesley MJ, Porrino LJ (2011) Elevated gray and white matter densities in cocaine abstainers compared to current users. Psychopharmacology (Berl) 218:681-692.

Harris GJ, Pearlson GD, McArthur JC, Zeger S, LaFrance ND (1994) Altered cortical blood flow in HIV-seropositive individuals with and without dementia: a single photon emission computed tomography study. AIDS 8:495-499.

Harrod SB, Mactutus CF, Fitting S, Hasselrot U, Booze RM (2008) Intra-accumbal Tat1-72 alters acute and sensitized responses to cocaine. Pharmacol Biochem Behav 90:723-729.

Haughey NJ, Mattson MP (2002) Calcium dysregulation and neuronal apoptosis by the HIV-1 proteins Tat and gp120. J Acquir Immune Defic Syndr 31 Suppl 2:S55-61.

Heaton RK, Clifford DB, Franklin DR, Jr., Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I,

Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 75:2087-2096.

Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I (2011) HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol 17:3-16.

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, McCutchan JA, Taylor MJ, Kelly MD, Ellis RJ, et al. (1995) The HNRC 500--neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. J Int Neuropsychol Soc 1:231-251.

Heaton RK, Velin RA, McCutchan JA, Gulevich SJ, Atkinson JH, Wallace MR, Godfrey HP, Kirson DA, Grant I (1994) Neuropsychological impairment in human immunodeficiency virus-infection: implications for employment. HNRC Group. HIV Neurobehavioral Research Center. Psychosom Med 56:8-17.

Heindel WC, Jernigan TL, Archibald SL, Achim CL, Masliah E, Wiley CA (1994) The relationship of quantitative brain magnetic resonance imaging measures to neuropathologic indexes of human immunodeficiency virus infection. Arch Neurol 51:1129-1135.

Heinze S, Sartory G, Müller BW, de Greiff A, Forsting M, Jüptner M (2006) Neural encoding correlates of high and low verbal memory performance. Journal of Psychophysiology 20:68.

Hester R, Garavan H (2004) Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. J Neurosci 24:11017-11022.

Hinkin CH, Castellon SA, Durvasula RS, Hardy DJ, Lam MN, Mason KI, Thrasher D, Goetz MB, Stefaniak M (2002) Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. Neurology 59:1944-1950.

Hinkin CH, Castellon SA, Hardy DJ, Granholm E, Siegle G (1999) Computerized and traditional stroop task dysfunction in HIV-1 infection. Neuropsychology 13:306-316.

Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ (2008) Neurocognition in individuals co-infected with HIV and hepatitis C. J Addict Dis 27:11-17.

Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, Stefaniak M (2004) Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. AIDS 18 Suppl 1:S19-25.

Hu S, Sheng WS, Lokensgard JR, Peterson PK (2005) Morphine potentiates HIV-1 gp120-induced neuronal apoptosis. J Infect Dis 191:886-889.

Hu XT, Al-Harthi L, Napier TC (2011) Increased Ca2+ Influx and Pathophysiological Mechanisms Underlying the Excitotoxicity of HIV-1 Tat. Journal of Neuroimmune Pharmacology 6.

Hutchinson AB, Farnham PG, Dean HD, Ekwueme DU, del Rio C, Kamimoto L, Kellerman SE (2006) The economic burden of HIV in the United States in the era of highly active antiretroviral therapy: evidence of continuing racial and ethnic differences. J Acquir Immune Defic Syndr 43:451-457.

Janssen RS, Cornblath DR, Epstein LG, Foa RP (1991) Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force. Neurology 41:778-785.

Jarrin I, Geskus R, Bhaskaran K, Prins M, Perez-Hoyos S, Muga R, Hernandez-Aguado I, Meyer L, Porter K, del Amo J (2008) Gender differences in HIV progression to AIDS and death in industrialized countries: slower disease progression following HIV seroconversion in women. Am J Epidemiol 168:532-540.

Jastak S, Wilkinson GS, Jastak J (1984) Wide Range Achievement Test-Revised. Indianapolis: Jastak Associates Inc.

Jernigan TL, Archibald S, Hesselink JR, Atkinson JH, Velin RA, McCutchan JA, Chandler J, Grant I (1993) Magnetic resonance imaging morphometric analysis of cerebral volume loss in human immunodeficiency virus infection. The HNRC Group. Arch Neurol 50:250-255.

Jernigan TL, Gamst AC, Archibald SL, Fennema-Notestine C, Mindt MR, Marcotte TD, Heaton RK, Ellis RJ, Grant I (2005) Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am J Psychiatry 162:1461-1472.

Kapur S, Craik FI, Tulving E, Wilson AA, Houle S, Brown GM (1994) Neuroanatomical correlates of encoding in episodic memory: levels of processing effect. Proc Natl Acad Sci U S A 91:2008-2011.

Kendall SL, Anderson CF, Nath A, Turchan-Cholewo J, Land CL, Mactutus CF, Booze RM (2005) Gonadal steroids differentially modulate neurotoxicity of HIV and cocaine: testosterone and ICI 182,780 sensitive mechanism. BMC Neurosci 6:40.

Khurdayan VK, Buch S, El-Hage N, Lutz SE, Goebel SM, Singh IN, Knapp PE, Turchan-Cholewo J, Nath A, Hauser KF (2004) Preferential vulnerability of astroglia and glial precursors to combined opioid and HIV-1 Tat exposure in vitro. Eur J Neurosci 19:3171-3182.

Kousik SM, Napier TC, Carvey PM (2012) The effects of psychostimulant drugs on blood brain barrier function and neuroinflammation. Front Pharmacol 3:121.

Koutsilieri E, Gotz ME, Sopper S, Sauer U, Demuth M, ter Meulen V, Riederer P (1997) Regulation of glutathione and cell toxicity following exposure to neurotropic substances and human immunodeficiency virus-1 in vitro. J Neurovirol 3:342-349.

Kramer JH, Delis DC, Daniel M (2006) Sex differences in verbal learning. J Clin Psychol 44:907-915.

Kramer JH, Delis DC, Kaplan E, O'Donnell L, Prifitera A (1997) Developmental sex differences in verbal learning. Neuropsychology 11:577.

Lafortune L, Nalbantoglu J, Antel JP (1996) Expression of tumor necrosis factor alpha (TNF alpha) and interleukin 6 (IL-6) mRNA in adult human astrocytes: comparison with adult microglia and fetal astrocytes. J Neuropathol Exp Neurol 55:515-521.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10:120-131.

Langford D, Adame A, Grigorian A, Grant I, McCutchan JA, Ellis RJ, Marcotte TD, Masliah E (2003) Patterns of selective neuronal damage in methamphetamine-user AIDS patients. J Acquir Immune Defic Syndr 34:467-474.

Lejuez CW, Bornovalova MA, Reynolds EK, Daughters SB, Curtin JJ (2007) Risk factors in the relationship between gender and crack/cocaine. Exp Clin Psychopharmacol 15:165-175.

Letendre SL, Cherner M, Ellis RJ, Marquie-Beck J, Gragg B, Marcotte T, Heaton RK, McCutchan JA, Grant I (2005) The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: biological correlates of disease. AIDS 19 Suppl 3:S72-78.

Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, Hinkin CH (2006) The effect of recent stimulant use on sustained attention in HIV-infected adults. J Clin Exp Neuropsychol 28:29-42.

Li CS, Milivojevic V, Kemp K, Hong K, Sinha R (2006) Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. Drug Alcohol Depend 85:205-212.

Liu S, Heitz RP, Bradberry CW (2009) A touch screen based Stop Signal Response Task in rhesus monkeys for studying impulsivity associated with chronic cocaine self-administration. J Neurosci Methods 177:67-72.

Lucas GM, Griswold M, Gebo KA, Keruly J, Chaisson RE, Moore RD (2006) Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy. Am J Epidemiol 163:412-420.

Maki PM, Cohen MH, Weber K, Little DM, Fornelli D, Rubin LH, Perschler P, Gould F, Martin E (2009) Impairments in memory and hippocampal function in HIV-positive vs HIV-negative women: a preliminary study. Neurology 72:1661-1668.

Maki PM, Martin-Thormeyer E (2009) HIV, cognition and women. Neuropsychol Rev 19:204-214.

Maki PM, Rubin LH, Cohen M, Golub ET, Greenblatt RM, Young M, Schwartz RM, Anastos K, Cook JA (2012) Depressive symptoms are increased in the early perimenopausal stage in ethnically diverse human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. Menopause 19:1215-1223.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19:1233-1239.

Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y (2002) Reading level attenuates differences in neuropsychological test performance between African American and White elders. J Int Neuropsychol Soc 8:341-348.

Manly JJ, Smith C, Crystal HA, Richardson J, Golub ET, Greenblatt R, Robison E, Martin EM, Young M (2011) Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV+ and HIV- women: The Women's Interagency HIV Study (WIHS) Neurocognitive Substudy. J Clin Exp Neuropsychol 33:853-863.

Manschreck TC, Schneyer ML, Weisstein CC, Laughery J, Rosenthal J, Celada T, Berner J (1990) Freebase cocaine and memory. Compr Psychiatry 31:369-375.

Marcotte TD, Deutsch R, McCutchan JA, Moore DJ, Letendre S, Ellis RJ, Wallace MR, Heaton RK, Grant I (2003) Prediction of incident neurocognitive impairment by plasma HIV RNA and CD4 levels early after HIV seroconversion. Arch Neurol 60:1406-1412.

Marder K, Stern Y, Malouf R, Tang MX, Bell K, Dooneief G, el-Sadr W, Goldstein S, Gorman J, Richards M, et al. (1992) Neurologic and neuropsychological manifestations of human immunodeficiency virus infection in intravenous drug users without acquired immunodeficiency syndrome. Relationship to head injury. Arch Neurol 49:1169-1175.

Marra CM, Zhao Y, Clifford DB, Letendre S, Evans S, Henry K, Ellis RJ, Rodriguez B, Coombs RW, Schifitto G, McArthur JC, Robertson K (2009) Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. AIDS 23:1359-1366.

Martin-Thormeyer EM, Paul RH (2009) Drug abuse and hepatitis C infection as comorbid features of HIV associated neurocognitive disorder: neurocognitive and neuroimaging features. Neuropsychol Rev 19:215-231.

Martin E, Gonzalez R, Vassileva J, Maki P (2011) HIV+ men and women show different performance patterns on procedural learning tasks. Journal of clinical and experimental neuropsychology 33:112-120.

Martin EM, Nixon H, Pitrak DL, Weddington W, Rains NA, Nunnally G, Grbesic S, Gonzalez R, Jacobus J, Bechara A (2007) Characteristics of prospective memory deficits in HIV-seropositive substance-dependent individuals: preliminary observations. J Clin Exp Neuropsychol 29:496-504.

Martin EM, Novak RM, Fendrich M, Vassileva J, Gonzalez R, Grbesic S, Nunnally G, Sworowski L (2004a) Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. J Int Neuropsychol Soc 10:298-300.

Martin EM, Pitrak DL, Rains N, Grbesic S, Pursell K, Nunnally G, Bechara A (2003) Delayed nonmatch-to-sample performance in HIV-seropositive and HIV-seronegative polydrug abusers. Neuropsychology 17:283-288.

Martin EM, Pitrak DL, Weddington W, Rains NA, Nunnally G, Nixon H, Grbesic S, Vassileva J, Bechara A (2004b) Cognitive impulsivity and HIV serostatus in substance dependent males. J Int Neuropsychol Soc 10:931-938.

Martin EM, Robertson LC, Edelstein HE, Jagust WJ, Sorensen DJ, San Giovanni D, Chirurgi VA (1992) Performance of patients with early HIV-1 infection on the Stroop Task. J Clin Exp Neuropsychol 14:857-868.

Martin EM, Sullivan TS, Reed RA, Fletcher TA, Pitrak DL, Weddington W, Harrow M (2001) Auditory working memory in HIV-1 infection. J Int Neuropsychol Soc 7:20-26.

Mason KI, Campbell A, Hawkins P, Madhere S, Johnson K, Takushi-Chinen R (1998) Neuropsychological functioning in HIV-positive African-American women with a history of drug use. J Natl Med Assoc 90:665-674.

Masterman DL, Cummings JL (1997) Frontal-subcortical circuits: the anatomic basis of executive, social and motivated behaviors. J Psychopharmacol 11:107-114.

McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, Graham NM, McArthur JH, Selnes OA, Jacobson LP, et al. (1993) Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology 43:2245-2252.

Meade CS, Conn NA, Skalski LM, Safren SA (2011) Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. J Behav Med 34:128-138.

Melrose RJ, Tinaz S, Castelo JM, Courtney MG, Stern CE (2008) Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. Behav Brain Res 188:337-347.

Meucci O, Fatatis A, Simen AA, Bushell TJ, Gray PW, Miller RJ (1998) Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity. Proc Natl Acad Sci U S A 95:14500-14505.

Miller EN, Selnes OA, McArthur JC, Satz P, Becker JT, Cohen BA, Sheridan K, Machado AM, Van Gorp WG, Visscher B (1990) Neuropsychological performance in HIV-1-infected homosexual men: The Multicenter AIDS Cohort Study (MACS). Neurology 40:197-203.

Mintzer MZ, Stitzer ML (2002) Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend 67:41-51.

Mittenberg W, Motta S (1993) Effects of chronic cocaine abuse on memory and learning. Arch Clin Neuropsychol 8:477-483.

Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjome KL, Rathnayaka N, Kramer LA, Narayana PA (2010) Working memory fMRI activation in cocaine-dependent subjects: association with treatment response. Psychiatry Res 181:174-182.

Moore DJ, Masliah E, Rippeth JD, Gonzalez R, Carey CL, Cherner M, Ellis RJ, Achim CL, Marcotte TD, Heaton RK, Grant I (2006) Cortical and subcortical neurodegeneration is associated with HIV neurocognitive impairment. AIDS 20:879-887.

Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA (2002) HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? AIDS 16:597-603.

Murray LJ, Ranganath C (2007) The dorsolateral prefrontal cortex contributes to successful relational memory encoding. J Neurosci 27:5515-5522.

Nath A, Hauser KF, Wojna V, Booze RM, Maragos W, Prendergast M, Cass W, Turchan JT (2002) Molecular basis for interactions of HIV and drugs of abuse. J Acquir Immune Defic Syndr 31 Suppl 2:S62-69.

O'Brien MS, Anthony JC (2005) Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000-2001. Neuropsychopharmacology 30:1006-1018.

O'Malley S, Adamse M, Heaton RK, Gawin FH (1992) Neuropsychological impairment in chronic cocaine abusers. Am J Drug Alcohol Abuse 18:131-144.

Ostrow DG, Beltran ED, Joseph JG, DiFranceisco W, Wesch J, Chmiel JS (1993) Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. Chicago Multicenter AIDS Cohort Study (MACS)/Coping and Change Study. J Subst Abuse 5:311-325.

Patel CA, Mukhtar M, Harley S, Kulkosky J, Pomerantz RJ (2002) Lentiviral expression of HIV-1 Vpr induces apoptosis in human neurons. J Neurovirol 8:86-99.

Patel CA, Mukhtar M, Pomerantz RJ (2000) Human immunodeficiency virus type 1 Vpr induces apoptosis in human neuronal cells. J Virol 74:9717-9726.

Peavy G, Jacobs D, Salmon DP, Butters N, Delis DC, Taylor M, Massman P, Stout JC, Heindel WC, Kirson D, et al. (1994) Verbal memory performance of patients with human immunodeficiency virus infection: evidence of subcortical dysfunction. The HNRC Group. J Clin Exp Neuropsychol 16:508-523.

Perry JL, Larson EB, German JP, Madden GJ, Carroll ME (2005) Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology (Berl) 178:193-201.

Perry JL, Nelson SE, Carroll ME (2008) Impulsive choice as a predictor of acquisition of IV cocaine self- administration and reinstatement of cocaine-seeking behavior in male and female rats. Exp Clin Psychopharmacol 16:165-177.

Peterson PK, Gekker G, Chao CC, Schut R, Molitor TW, Balfour HH, Jr. (1991) Cocaine potentiates HIV-1 replication in human peripheral blood mononuclear cell cocultures. Involvement of transforming growth factor-beta. J Immunol 146:81-84.

Pfefferbaum A, Rosenbloom MJ, Rohlfing T, Kemper CA, Deresinski S, Sullivan EV (2009) Frontostriatal fiber bundle compromise in HIV infection without dementia. AIDS 23:1977-1985.

Prisciandaro JJ, McRae-Clark AL, Myrick H, Henderson S, Brady KT (2012) Brain activation to cocaine cues and motivation/treatment status. Addict Biol.

Radloff LS (1977) The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1:385-401.

Reger M, Welsh R, Razani J, Martin DJ, Boone KB (2002) A meta-analysis of the neuropsychological sequelae of HIV infection. J Int Neuropsychol Soc 8:410-424.

Reynolds JL, Mahajan SD, Bindukumar B, Sykes D, Schwartz SA, Nair MP (2006) Proteomic analysis of the effects of cocaine on the enhancement of HIV-1 replication in normal human astrocytes (NHA). Brain Res 1123:226-236.

Richardson JL, Nowicki M, Danley K, Martin EM, Cohen MH, Gonzalez R, Vassileva J, Levine AM (2005) Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. AIDS 19:1659-1667.

Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ, Gonzalez R, Wolfson T, Grant I (2004) Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. J Int Neuropsychol Soc 10:1-14.

Robertson KR, Kapoor C, Robertson WT, Fiscus S, Ford S, Hall CD (2004) No gender differences in the progression of nervous system disease in HIV infection. J Acquir Immune Defic Syndr 36:817-822.

Robinson G, Blair J, Cipolotti L (1998) Dynamic aphasia: an inability to select between competing verbal responses? Brain 121 (Pt 1):77-89.

Roth MD, Tashkin DP, Choi R, Jamieson BD, Zack JA, Baldwin GC (2002) Cocaine enhances human immunodeficiency virus replication in a model of severe combined immunodeficient mice implanted with human peripheral blood leukocytes. J Infect Dis 185:701-705.

Rottenberg DA, Sidtis JJ, Strother SC, Schaper KA, Anderson JR, Nelson MJ, Price RW (1996) Abnormal cerebral glucose metabolism in HIV-1 seropositive subjects with and without dementia. J Nucl Med 37:1133-1141.

Rugg MD, Otten LJ, Henson RN (2002) The neural basis of episodic memory: evidence from functional neuroimaging. Philos Trans R Soc Lond B Biol Sci 357:1097-1110.

Ryan EL, Morgello S, Isaacs K, Naseer M, Gerits P (2004) Neuropsychiatric impact of hepatitis C on advanced HIV. Neurology 62:957-962.

Sacktor N, McDermott MP, Marder K, Schifitto G, Selnes OA, McArthur JC, Stern Y, Albert S, Palumbo D, Kieburtz K, De Marcaida JA, Cohen B, Epstein L (2002) HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol 8:136-142.

Sacktor N, Nakasujja N, Skolasky R, Robertson K, Wong M, Musisi S, Ronald A, Katabira E (2006) Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. Neurology 67:311-314.

Sacktor N, Nakasujja N, Skolasky RL, Robertson K, Musisi S, Ronald A, Katabira E, Clifford DB (2009) Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda. Neurology 72:165-170.

Sacktor NC, Lyles RH, Skolasky RL, Anderson DE, McArthur JC, McFarlane G, Selnes OA, Becker JT, Cohen B, Wesch J, Miller EN (1999) Combination antiretroviral therapy

improves psychomotor speed performance in HIV-seropositive homosexual men. Multicenter AIDS Cohort Study (MACS). Neurology 52:1640-1647.
Saito Y, Sharer LR, Epstein LG, Michaels J, Mintz M, Louder M, Golding K, Cvetkovich TA, Blumberg BM (1994) Overexpression of nef as a marker for restricted HIV-1 infection of astrocytes in postmortem pediatric central nervous tissues. Neurology 44:474-481.
SAMHSA (2010) The National Survey on Drug Use and Health: HIV/AIDS and Substance Use. vol. 2013.
Scott JC, Woods SP, Patterson KA, Morgan EE, Heaton RK, Grant I, Marcotte TD (2006) Recency effects in HIV-associated dementia are characterized by deficient encoding. Neuropsychologia 44:1336-1343.
Selnes OA, Galai N, McArthur JC, Cohn S, Royal W, 3rd, Esposito D, Vlahov D (1997) HIV infection and cognition in intravenous drug users: long-term follow-up. Neurology 48:223-230.
Sherman KE, Rouster SD, Chung RT, Rajicic N (2002) Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis 34:831-837.
Sperling R, Greve D, Dale A, Killiany R, Holmes J, Rosas HD, Cocchiarella A, Firth P, Rosen B, Lake S, Lange N, Routledge C, Albert M (2002) Functional MRI detection of pharmacologically induced memory impairment. Proc Natl Acad Sci U S A 99:455-460.
Starace F, Baldassarre C, Biancolilli V, Fea M, Serpelloni G, Bartoli L, Maj M (1998) Early neuropsychological impairment in HIV-seropositive intravenous drug users: evidence from the Italian Multicentre Neuropsychological HIV Study. Acta Psychiatr Scand 97:132-138.
Stebbins GT, Smith CA, Bartt RE, Kessler HA, Adeyemi OM, Martin E, Cox JL, Bammer R, Moseley ME (2007) HIV-associated alterations in normal-appearing white matter: a voxel-wise diffusion tensor imaging study. J Acquir Immune Defic Syndr 46:564-573.
Stout JC, Ellis RJ, Jernigan TL, Archibald SL, Abramson I, Wolfson T, McCutchan JA, Wallace MR, Atkinson JH, Grant I (1998) Progressive cerebral volume loss in human immunodeficiency virus infection: a longitudinal volumetric magnetic resonance imaging study. HIV Neurobehavioral Research Center Group. Arch Neurol 55:161-168.
Strickland TL, Mena I, Villanueva-Meyer J, Miller BL, Cummings J, Mehringer CM, Satz P, Myers H (1993) Cerebral perfusion and neuropsychological consequences of chronic cocaine use. J Neuropsychiatry Clin Neurosci 5:419-427.
Suarez S, Baril L, Stankoff B, Khellaf M, Dubois B, Lubetzki C, Bricaire F, Hauw JJ (2001) Outcome of patients with HIV-1-related cognitive impairment on highly active antiretroviral therapy. AIDS 15:195-200.
Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain: Thieme New York:.
Thompson PM, Dutton RA, Hayashi KM, Toga AW, Lopez OL, Aizenstein HJ, Becker JT (2005) Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. Proc Natl Acad Sci U S A 102:15647-15652.
Thorpe LE, Frederick M, Pitt J, Cheng I, Watts DH, Buschur S, Green K, Zorrilla C, Landesman SH, Hershow RC (2004) Effect of hard-drug use on CD4 cell percentage, HIV RNA level, and progression to AIDS-defining class C events among HIV-infected women. J Acquir Immune Defic Syndr 37:1423-1430.

Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S (1994) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Natl Acad Sci U S A 91:2016-2020.

Turchan J, Anderson C, Hauser KF, Sun Q, Zhang J, Liu Y, Wise PM, Kruman I, Maragos W, Mattson MP, Booze R, Nath A (2001) Estrogen protects against the synergistic toxicity by HIV proteins, methamphetamine and cocaine. BMC Neurosci 2:3.

Valcour V, Maki P, Bacchetti P, Anastos K, Crystal H, Young M, Mack WJ, Cohen M, Golub ET, Tien PC (2012) Insulin resistance and cognition among HIV-infected and HIV-uninfected adult women: the Women's Interagency HIV Study. AIDS Res Hum Retroviruses 28:447-453.

van Gorp WG, Rabkin JG, Ferrando SJ, Mintz J, Ryan E, Borkowski T, McElhiney M (2007) Neuropsychiatric predictors of return to work in HIV/AIDS. J Int Neuropsychol Soc 13:80-89.

Van Overschelde JP, Rawson KA, Dunlosky J (2004) Category norms: An updated and expanded version of the norms. Journal of Memory and Language 50:289-335.

Venkatesan A, Nath A, Ming GL, Song H (2007) Adult hippocampal neurogenesis: regulation by HIV and drugs of abuse. Cell Mol Life Sci 64:2120-2132.

Verdejo-Garcia AJ, Lopez-Torrecillas F, Aguilar de Arcos F, Perez-Garcia M (2005) Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav 30:89-101.

Villa G, Solida A, Moro E, Tavolozza M, Antinori A, De Luca A, Murri R, Tamburrini E (1996) Cognitive impairment in asymptomatic stages of HIV infection. A longitudinal study. Eur Neurol 36:125-133.

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP (1993) Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14:169-177.

Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, Handlesman L (1992) Long-term frontal brain metabolic changes in cocaine abusers. Synapse 11:184-190.

Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K (1988) Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. Br J Psychiatry 152:641-648.

Wang T, Rumbaugh JA, Nath A (2006) Viruses and the brain: from inflammation to dementia. Clin Sci (Lond) 110:393-407.

Wayman WN, Dodiya HB, Persons AL, Kashanchi F, Kordower JH, Hu XT, Napier TC (2012) Enduring cortical alterations after a single in-vivo treatment of HIV-1 Tat. Neuroreport 23:825-829.

Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Klein RS (1999) A prospective study of HIV disease progression in female and male drug users. AIDS 13:257-262.

WHO (2008) Gender, women and health. vol. 2013.

WHO (2011) Global HIV/AIDS Response: Progress Report 2011. vol. 2013.

Willenbring ML, Massey SH, Gardner MB (2009) Helping patients who drink too much: an evidence-based guide for primary care clinicians. Am Fam Physician 80:44-50.

Wilson TE, Massad LS, Riester KA, Barkan S, Richardson J, Young M, Gurtman A, Greenblatt R (1999) Sexual, contraceptive, and drug use behaviors of women with HIV and those at high risk for infection: results from the Women's Interagency HIV Study. AIDS 13:591-598.

Woicik PA, Moeller SJ, Alia-Klein N, Maloney T, Lukasik TM, Yeliosof O, Wang GJ, Volkow ND, Goldstein RZ (2009) The neuropsychology of cocaine addiction: recent cocaine use masks impairment. Neuropsychopharmacology 34:1112-1122.

Wood JN, Grafman J (2003) Human prefrontal cortex: processing and representational perspectives. Nat Rev Neurosci 4:139-147.

Woods SP, Rippeth JD, Conover E, Gongvatana A, Gonzalez R, Carey CL, Cherner M, Heaton RK, Grant I (2005a) Deficient strategic control of verbal encoding and retrieval in individuals with methamphetamine dependence. Neuropsychology 19:35-43.

Woods SP, Rippeth JD, Frol AB, Levy JK, Ryan E, Soukup VM, Hinkin CH, Lazzaretto D, Cherner M, Marcotte TD, Gelman BB, Morgello S, Singer EJ, Grant I, Heaton RK (2004) Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. J Clin Exp Neuropsychol 26:759-778.

Woods SP, Scott JC, Dawson MS, Morgan EE, Carey CL, Heaton RK, Grant I (2005b) Construct validity of Hopkins Verbal Learning Test-Revised component process measures in an HIV-1 sample. Arch Clin Neuropsychol 20:1061-1071.

Zheng J, Thylin MR, Ghorpade A, Xiong H, Persidsky Y, Cotter R, Niemann D, Che M, Zeng YC, Gelbard HA, Shepard RB, Swartz JM, Gendelman HE (1999) Intracellular CXCR4 signaling, neuronal apoptosis and neuropathogenic mechanisms of HIV-1-associated dementia. J Neuroimmunol 98:185-200.

Table 1. Study 1. Demographic Characteristics as a Function of Serostatus and Crack, Cocaine, and/or Heroin Use.

	Groups					
	Infected (n=952)			Uninfected (n=443)		
Background Characteristics (%)	Recent (n=91)	Former (n=463)	Non-users (n=398)	Recent (n=49)	Former (n=188)	Non-users (n=206)
Age (M, SD) [D, S, DxS]	46.8 (7.7)	46.9 (6.9)	40.6 (9.7)	42.8 (8.0)	44.4 (8.9)	34.4 (9.1)
WRAT-R[D]	88.7 (17.4)	90.6 (17.2)	94.8 (18.3)	89.7 (15.5)	89.8 (17.9)	95.4 (16.5)
Years of Education [D]	11.5 (2.8)	11.9 (3.1)	13.1 (2.9)	12.2 (3.0)	12.0 (2.7)	13.2 (2.8)
Race/Ethnicity [S]						
African American, non-Hispanic	70%	64%	64%	61%	58%	63%
White, non-Hispanic	10%	16%	16%	12%	11%	8%
Hispanic	14%	18%	15%	21%	28%	24%
Other	6%	2%	5%	6%	3%	5%
Hepatitis C virus antibody [S, D]	56%	45%	6%	29%	28%	4%
Recent						
Depressive Symptoms, CES-D $\geq$16 [D]	54%	35%	28%	50%	34%	19%
Antidepressant medication use [S, D]	20%	18%	9%	10%	11%	1%
Hazardous alcohol use[± S, D]	21%	5%	3%	35%	9%	6%
Crack cocaine use	78%	0%	0%	65%	0%	0%
Powder cocaine use [S]	24%	0%	0%	45%	0%	0%
Heroin use	29%	0%	0%	33%	0%	0%
Crack, cocaine, and/or heroin use prior to entry into WIHS	92%	98%	0%	92%	94%	0%
Proportion of WIHS visits where crack, cocaine, and/or heroin use was yes [S, D, DxS]	53%	7%	0%	52%	19%	0%
Smoking [S, D]						
Never	4%	10%	56%	0%	9%	50%
Former	85%	50%	19%	84%	60%	32%
Recent	11%	39%	25%	16%	31%	18%
Marijuana Use [S, D]						
Never	7%	9%	53%	2%	7%	40%
Former	51%	76%	38%	39%	70%	43%
Recent	43%	15%	9%	59%	23%	17%
Disease						
CD4 nadir [D]	208 (163)	230 (172)	254 (175)			
CD4 Count (cells/cubic millimeter) [D]			51%	-	-	-
> 500	29%	44%	39%			
$\geq$ 200 and < 500	44%	43%	10%			

< 200	27%	13%				
Viral Load (HIV RNA (copies			57%	-	-	-
per millilter)) [D]	27%	56%	29%			
Undetectable	44%	30%	14%			
< 10,000	29%	14%				
≥ 10,000						
Medication Use [D]						
No cART	50%	33%	32%	-	-	-
cART <95% compliance	25%	15%	16%	-	-	-
cART ≥95% compliance	25%	52%	52%	-	-	-
ART duration (years)(M, SD) [‡D]	8.1 (3.4)	9.6 (2.7)	8.6 (3.2)	-	-	-

Note. [D] Main effect of drug use significant at p<.05; [S] Main effect of serostatus significant at p<.05, [DxS] Drug use x Serostatus interaction significant at p<.05; "Recent" refers to within 6 months of the most recent WIHS visit. "Former" refers to any previous use, but not in the past 6 months. cART = combination antiretroviral therapy; ART = antiretroviral therapy. [^] Hazardous alcohol use reflects >7 drinks per week or more than 4 drinks in one sitting. [‡]Reflects the mean for 859 HIV-infected women (90%) who started ART prior to data collection (WIHS visit 25).

Table 2. Study 1. Raw Neuropsychological Test Score Means and Statistical Comparisons by Serostatus and Crack, Cocaine, and/or Heroin Use.

		Group					
		Infected (n=952)			Uninfected (n=443)		
Tests	n	Recent (n=91) M (SD)	Former (n=463) M (SD)	Non-users (n=398) M (SD)	Recent (n=49) M (SD)	Former (n=188) M (SD)	Non-users (n=206) M (SD)
HVLT							
Trial 1	1395	5.23 (1.84)	5.47 (1.66)	5.83 (1.67)	6.12 (1.45)	5.59 (1.69)	5.95 (1.69)
Total learning	1395	19.46 (5.26)	21.17 (5.22)	22.44 (4.82)	23.47 (4.34)	21.92 (4.85)	23.26 (4.75)
Learning slope	1395	1.31 (0.34)	1.45 (0.35)	1.52 (0.31)	1.59 (0.26)	1.50 (0.29)	1.58 (0.30)
Delayed recall	1395	6.26 (2.40)	7.27 (2.60)	8.03 (2.46)	8.02 (2.18)	7.76 (2.45)	8.34 (2.34)
Percent retention	1395	81.13 (29.71)	83.73 (25.76)	88.40 (21.13)	85.36 (19.84)	87.11 (23.40)	88.36 (19.77)
Recognition	1390	9.59 (2.29)	10.08 (2.01)	10.24 (1.99)	10.29 (2.28)	10.49 (1.75)	10.75 (1.50)
Stroop Test							
Trials 1&2[a]	1313	67.79 (26.02)	63.83 (15.57)	60.71 (13.53)	61.49 (14.32)	61.91 (13.88)	58.46 (10.65)
Trial 3[a]	1247	140.34 (42.60)	132.35 (36.21)	126.09 (33.82)	126.37(26.87)	125.50 (32.63)	120.37 (26.55)

Note. HVLT = Hopkins Verbal Learning Test. [a]Unadjusted means are displayed, but log-transformed scores were used in the statistical comparisons.

Table 3. Study 1. Results from Adjusted Analysis Examining the Effect of Serostatus, Crack, Cocaine, and/or Heroin use, and their Interaction on Cognitive Function.

	Multivariable Linear Regression Models							
	Model 1: No interactions in model					**Model 2: Interactions included in model**		
	Serostatus	Drug use						
	HIV+ vs. HIV-	Recent vs. Non-users	Former vs. Non-users	Recent vs. Former	Adjusted R^2	Recent vs. non-users x Status	Former vs. non-users x Status	Adjusted R^2
Tests	B (SE)	B (SE)	B (SE)	B (SE)		B (SE)	B (SE)	
HVLT								
Trial 1	-.07 (.06)	-.04 (.10)	-.09 (.07)	.05 (.09)	.16	-.43 (.18)*	-.01 (.11)	.17
Total learning	-.14 (.05)**	-.16 (.09)	-.11 (.06)	-.05 (.09)	.25	-.58 (.17)**	.01 (.11)	.26
Learning slope	-.16 (.05)**	-.20 (.10)*	-.10 (.07)	-.10 (.09)	.19	-.60 (.18)***	-.01 (.11)	.20
Delayed recall	-.11 (.05)*	-.27 (.10)**	-.12 (.07)	-.15 (.09)	.22	-.50 (.17)**	-.11 (.11)	.23
Percent retention	-.02 (.06)	-.15 (.11)	-.05 (.07)	-.09 (.10)	.03	-	-	-
Recognition	-.16 (.06)**	-.24 (.11)*	-.04 (.07)	-.20 (.09)*	.15	-	-	-
Stroop Test								
Trials 1&2[a]	-.05 (.05)	-.04 (.10)	.02 (.07)	-.07 (.09)	.25	-	-	-
Trial 3[a]	-.05 (.06)	.04 (.11)	.06 (.07)	-.02 (.10)	.21	-	-	-

Note. *p<0.05; **p<0.01; ***p<0.001. B = Parameter estimates for each factor modeled individually. SE = standard error. HVLT = Hopkins Verbal Learning Test. All models are adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody. [a]For Stroop we also controlled for the number of times a woman was exposed to the test (range 1-3 times).

Table 4. Study 1. Results from Adjusted Analysis Examining the Effect of Crack, Cocaine, and/or Heroin use in HIV-infected Women on Cognitive Function.

	Hopkins Verbal Learning Test (HVLT)			
	Trial 1	Total learning	Learning Slope	Delayed Recall
Models	B (SE)	B (SE)	B (SE)	B (SE)
Adjusted for only non-HIV specific factors [a]				
Recent vs. non-users	-.16 (.13)	-.32 (.12)*	-.45 (.15)**	-.43 (.12)***
Former vs. non-users	-.10 (.08)	-.13 (.08)	-.14 (.10)	-.19 (.08)*
Recent vs. Former	-.05 (.11)	-.19 (.11)	-.31 (.13)*	-.24 (.11)*
Adjusted R^2	**.17**	**.27**	**.20**	**.25**
Adjusted for non-HIV specific factors and CD4, viral load, medication use, and duration on ART [b]				
Recent vs. non-users	-.14 (.16)	-.29 (.12)*	-.42 (.15)**	-.44 (.13)***
Former vs. non-users	-.10 (.08)	-.12 (.08)	-.12 (.10)	-.17 (.08)*
Recent vs. Former	-.04 (.11)	-.17 (.11)	-.30 (.13)*	-.27 (.11)*
Adjusted R^2	**.17**	**.27**	**.21**	**.25**

Note. *p<0.05; **p<0.01. B = Parameter estimates for each factor modeled individually. SE = standard error.
[a] Adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody
[b] Adjusted for site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, Hepatitis C virus antibody, recent cd4 count and viral load, cd4 nadir, medication use, and duration on ART.

Table 5. Study 1. Among Recent Crack, Cocaine, and/or Heroin Users: Frequency of Use as a Function of Serostatus.

Drug (%)	Group	
	Infected (n=91)	Uninfected (n=49)
Crack cocaine use		
Smoked	78%	65%
Once a month or less	28%	35%
At least once a week, but < once per day	41%	31%
Once a day or more	31%	34%
Injected	1%	2%
Once a month or less	-	-
At least once a week, but < once per day	100%	100%
Once a day or more	-	-
Powder cocaine use		
Sniffed/snorted[S]	19%	39%
Once a month or less	76%	73%
At least once a week, but < once per day	24%	16%
Once a day or more	-	11%
Injected	3%	6%
Once a month or less	67%	33%
At least once a week, but < once per day	33%	67%
Once a day or more		-
Heroin use		
Sniffed/snorted	16%	18%
Once a month or less	40%	33%
At least once a week, but < once per day	33%	67%
Once a day or more	27%	-
Smoked	1%	4%
Once a month or less	100%	100%
At least once a week, but < once per day	-	-
Once a day or more	-	-
Injected	13%	14%
Once a month or less [S]	83%	14%
At least once a week, but < once per day	-	14%
Once a day or more [S]	17%	72%
Cocaine + Heroin (speedball)	8%	2%
Once a month or less	100%	100%
At least once a week, but < once per day	-	-
Once a day or more	-	-

Note. [S] Main effect of serostatus significant at $p<.05$; [1] "Recent Use" refers to self-reported use within 6 months of the WIHS visit at which the cognitive tests were completed.

Table 6. Study 1. Results from Adjusted Analysis Examining the Interactive Effects of Serostatus and Frequency of Crack Cocaine use (via Smoking) on the HVLT among Recent and Non-users.

	Hopkins Verbal Learning Test (HVLT)			
	Trial 1	Total Learning	Learning Slope	Delayed Recall
Models	B (SE)	B (SE)	B (SE)	B (SE)
Serostatus x				
Once a month or less	-0.13 (0.35)	-0.39 (0.32)	-0.52 (0.33)	-0.55 (0.33)
At least once a week, but < once per day	-0.56 (0.35)	-0.68 (0.32)*	-0.57 (0.33)	-0.90 (0.32)**
Once a day or more	-0.19 (0.35)	-0.24 (0.32)	-0.33 (0.33)	0.30 (0.30)

Note. *p<0.05; **p<0.01. Non-user is the referent. B = Parameter estimates for each factor modeled individually. SE = standard error. Among HIV-infected women who used at least once a week but less than once per day performed worse than non-users on delayed recall (p=0.004) and total learning (p=0.002). However, HIV-uninfected women who used at least once a week but less than once per day performed similarly to non-users on delayed recall (p=0.18) and total learning (p=0.68). All models are adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody.

Table 7. Study 2. Demographic and clinical characteristics for HIV-infected women as a function of crack cocaine use.

Background Characteristics (%)	Recent (n = 10)	Former (n = 11)	Never (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	12.4	12.5	14.4
Race/Ethnicity			
African-American	100%	91%	100%
White	0%	9%	0%
Hispanic/Other	0%	0%	0%
Hepatitis C antibody positive*	50%	18%	0%
CES-D greater than 16	40%	9%	22%
Hazardous alcohol use^	20%	9%	11%
Currently Smoking*	80%	55%	22%
Used marijuana in past 6 months	20%	18%	11%
CD4 nadir (M, SD)	213 (124)	372 (144)	319 (300)
CD4 count (cells/ cubic millimeter)			
> 500	30%	82%	56%
$\geq$ 200 and < 500	50%	18%	44%
< 200	20%	0%	0%
Viral Load			
Undetectable	50%	91%	44%
Less than 10,000 cp/ml	20%	9%	33%
Greater than or equal to 10,000 cp/ml	30%	0%	22%
Current cART use	70%	91%	78%
cART > 95% compliance	86%	100%	71%

Note: * $p < 0.05$. "Recent" refers to crack cocaine use within 6 months of the most recent WIHS visit. "Former" refers to any previous crack cocaine use, but not in the past 6 months. cART = combination antiretroviral therapy. ^Hazardous alcohol use reflects >7 drinks per week or more than 4 drinks in one sitting.

Table 8. Study 2. Drug use characteristics for HIV-infected women as a function of cocaine use.

Background Characteristics (Frequency)	Recent (n = 10)	Former (n = 11)	Never (n=9)
Crack recent use frequency			
Never	2[a]	11	-
Less than once a week	4	-	-
At least once a week but < once per day	2	-	-
Once a day or more	2	-	-
Crack peak use frequency			
Never	1[b]	2[c]	-
Less than once a week	2	-	-
At least once a week but < once per day	3	6	-
Once a day or more	4	3	-
Crack peak use duration			
Over a year	8	7	-
6 months to 1 year	-	1	-
Less than 6 months	1	1	-
Powder cocaine recent frequency			
Never	10	11	9
Powder cocaine peak use frequency			
Never	3	7	-
Less than once a week	3	1	-
At least once a week but < once per day	3	1	-
Once a day or more	1	2	-
Powder cocaine peak use duration			
Over a year	2	4	-
6 months to 1 year	5	-	-
Less than 6 months	-	-	-
Methamphetamine recent frequency			
Never	10	11	9

Methamphetamine peak frequency			
Never	10	11	9

Note: Peak is defined as the time of heaviest use, Recent is defined as in the past 6 months.
[a] One recent user reported to have never used any crack cocaine on the drug use questionnaire but classified as recent user based on toxicology screen and self-report at scanning visit
[b] Two recent users reported not using crack cocaine in the past 6 months on drug use questionnaire but classified as recent user based on toxicology screen and self-report at scanning visit
[c] Two former users reported former use of powder cocaine but not crack cocaine

Table 9. Study 2. Verbal memory performance for HIV-infected women as a function of crack cocaine use.

Background Characteristics (%)	RECENT (n = 10)	PAST (n = 11)	NEVER (n=9)	Recent vs Never Cohen's *d*	Past vs Never 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 number clusters	0.90 (1.1)	.82 (.75)	1.6 (1.3)	0.58	0.76
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

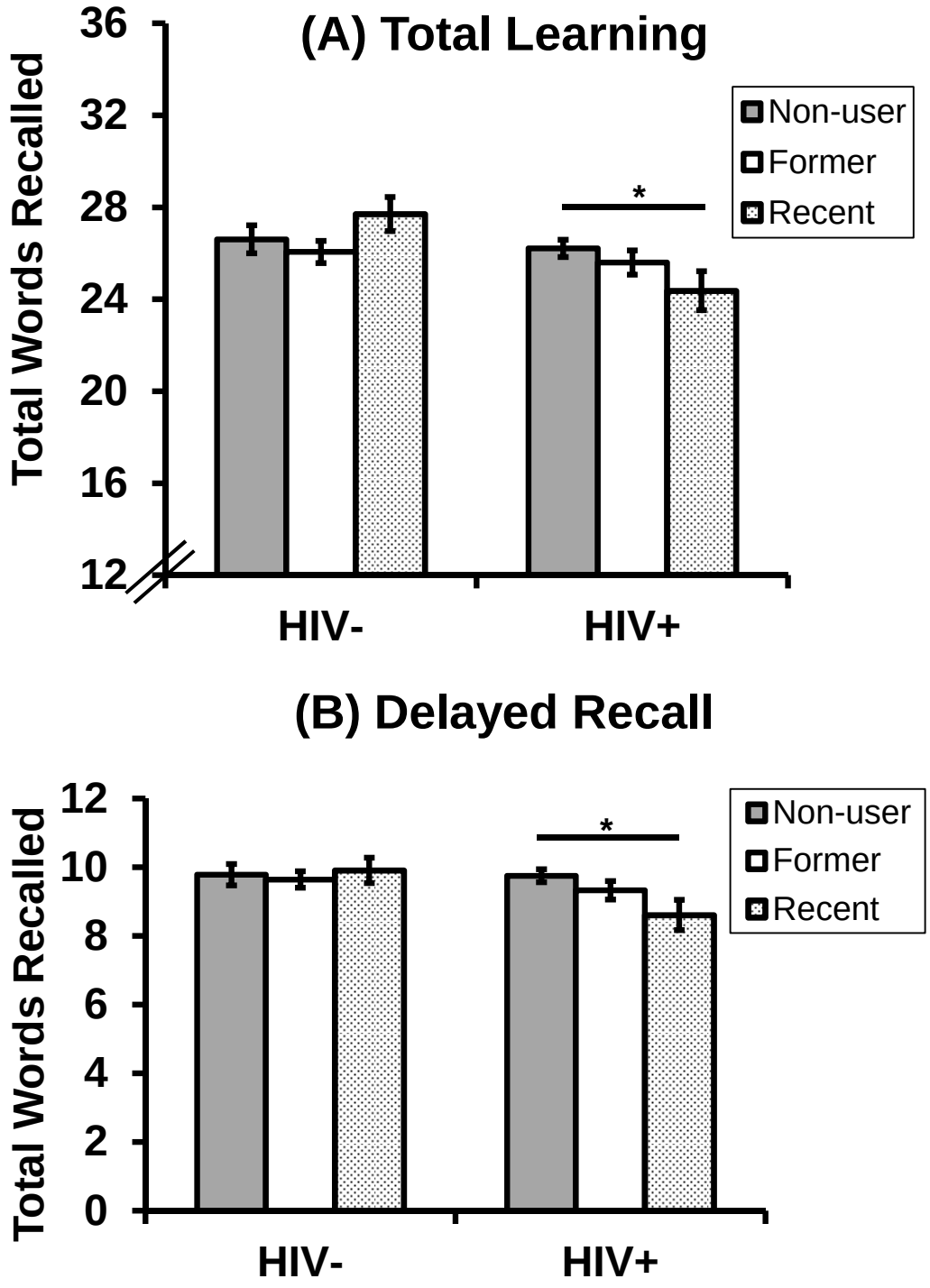
Note: * $p < 0.05$. Trial 1 cluster score differed by drug use group, $p = 0.011$; differences were between recent and never users, $p = .006$.

Table 10. Study 2. Group differences in activation during encoding and recognition: Brain region, Brodmann area (BA), Talairach coordinates, cluster size (k), and statistical information

Brain Region	BA	Talairach Coordinates (x, y, z)	Cluster size (k)	Z score	P-value (uncorrected)	Follow up test
ENCODING						
L medial frontal gyrus	8	-6, 20, 46	31	2.31	p =.010	Never users > Recent users Never users > Former users
RECOGNITION						
R inferior frontal gyrus	9	46, 12, 30	36	2.67	p = 0.004	Never users > Recent users Never users > Former users
L middle frontal gyrus	8	-44, 36, 40	73	2.62	p = 0.004	Never users > Recent users Never users > Former users
R middle frontal gyrus	46	44, 32, 20	44	2.22	p = 0.013	Never users > Former users
L middle frontal gyrus	9	-58, 22, 32	10	2.06	p = 0.020	Never users > Former users
R middle frontal gyrus	10	40, 52, 18	21	2.05	p = 0.020	Never users > Recent users Never users > Former users
R medial frontal gyrus	8	10, 20, 46	14	2.00	p = 0.023	Never users > Recent users

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

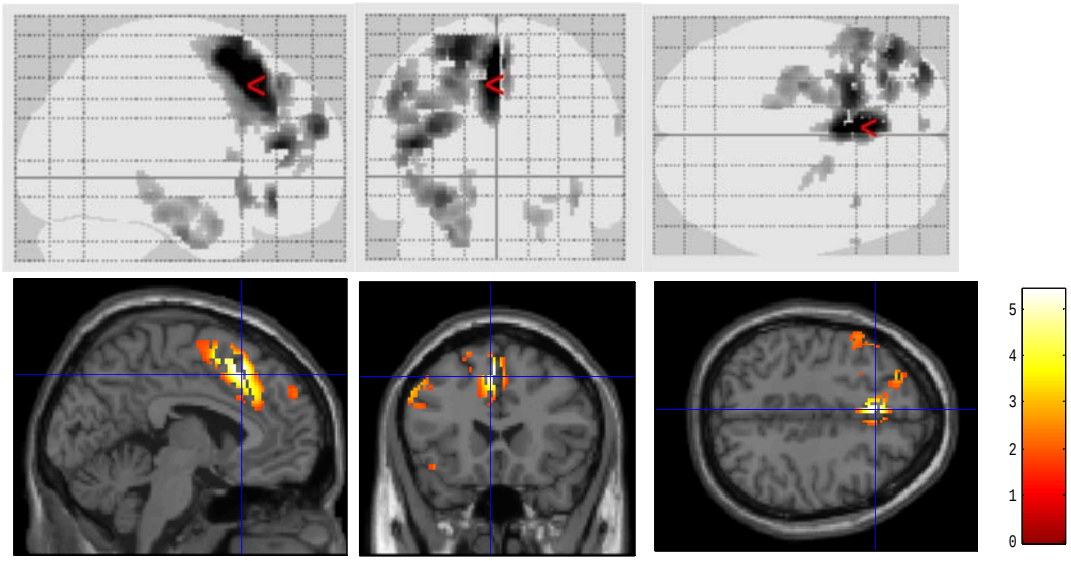
Figure 1. Study 1. Results from adjusted analysis examining the effect of serostatus, crack, cocaine, and/or heroin use, and their interaction on the HVLT total learning and delayed free recall.



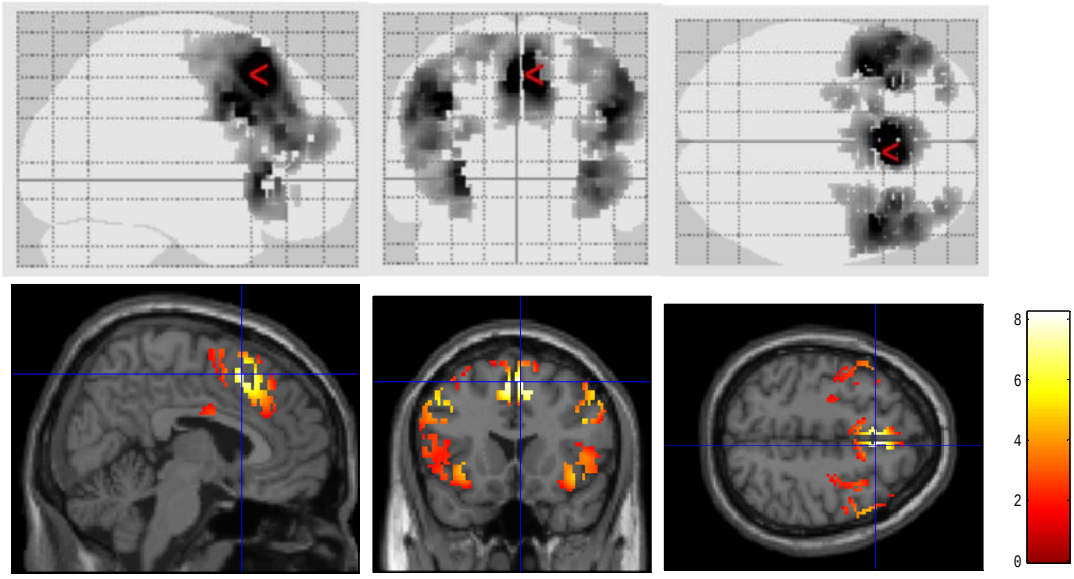
Note. *p<0.01.There was a significant interaction between crack, cocaine, and/or heroin use (specifically current versus non-users) and serostatus on total learning (p<0.01) and delayed

recall ($p<0.01$). Among HIV-infected women, recent illicit drug users performed worse than non-users on total learning ($p=0.002$) and delayed recall ($p<0.001$). All models are adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody.

Figure 2. Study 2. Typical pattern of activation during encoding and recognition: Findings from HIV-infected non-users

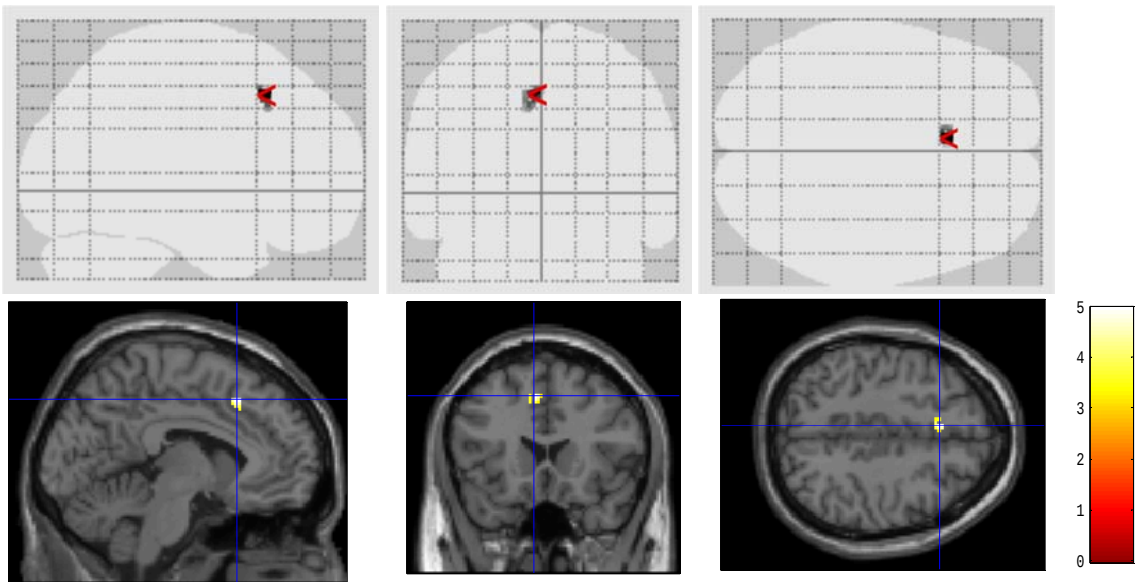


*Note: Encoding: activation in never users during encoding of novel words (experimental condition) minus repeated encoding of the same two words (control condition); Pickatlas mask applied: PFC, cingulate, and hippocampus; p = 0.05, k = 10



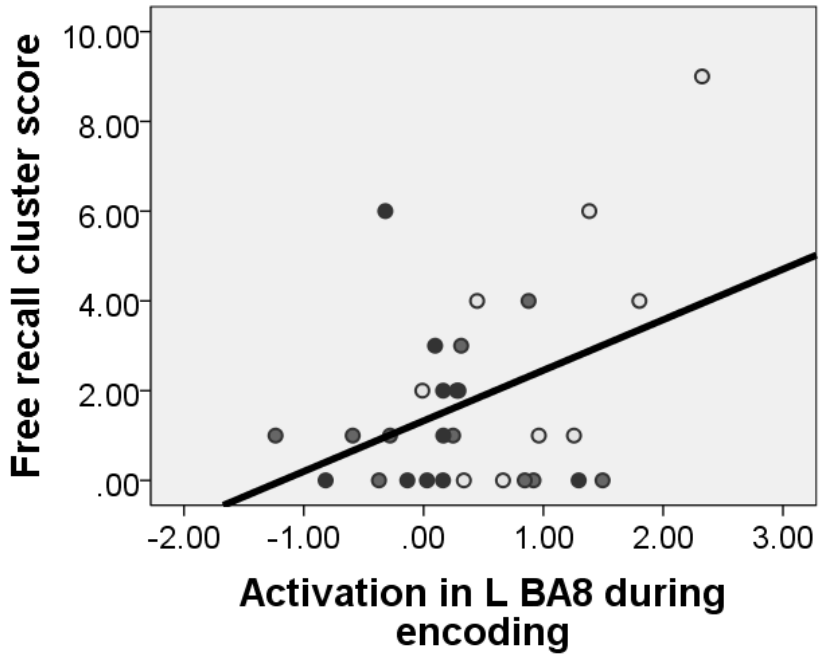
*Note: Recognition: activation in never users during recognition of novel words (experimental condition) minus repeated recognition of the same two words (control condition); Pickatlas mask applied: PFC, cingulate, and hippocampus; p = 0.05, k = 10

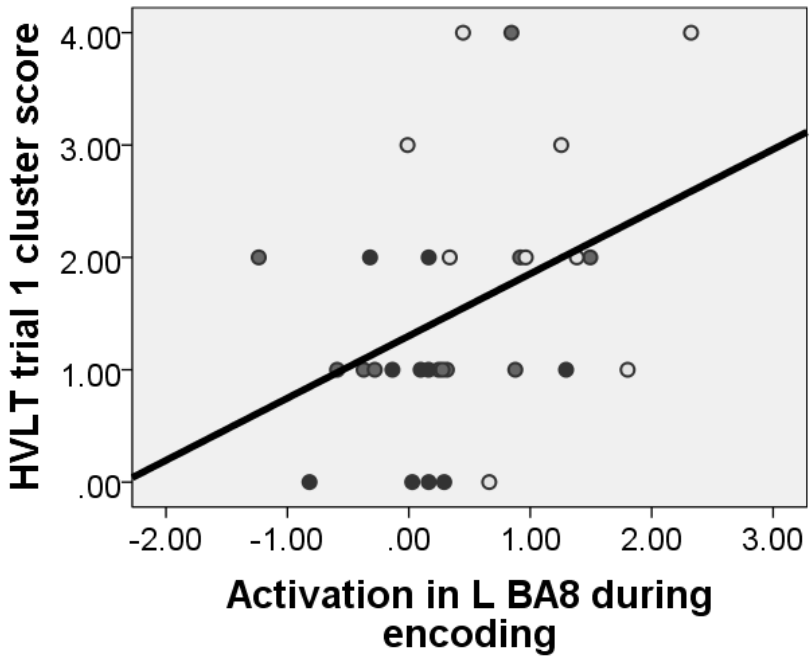
Figure 3. Study 2. Encoding: Interaction of group (recent, former, non-user) x condition (experimental, control)



*Note: $p = 0.01$, k = 30. Never users activated left BA8 more during encoding than both recent users and former users.

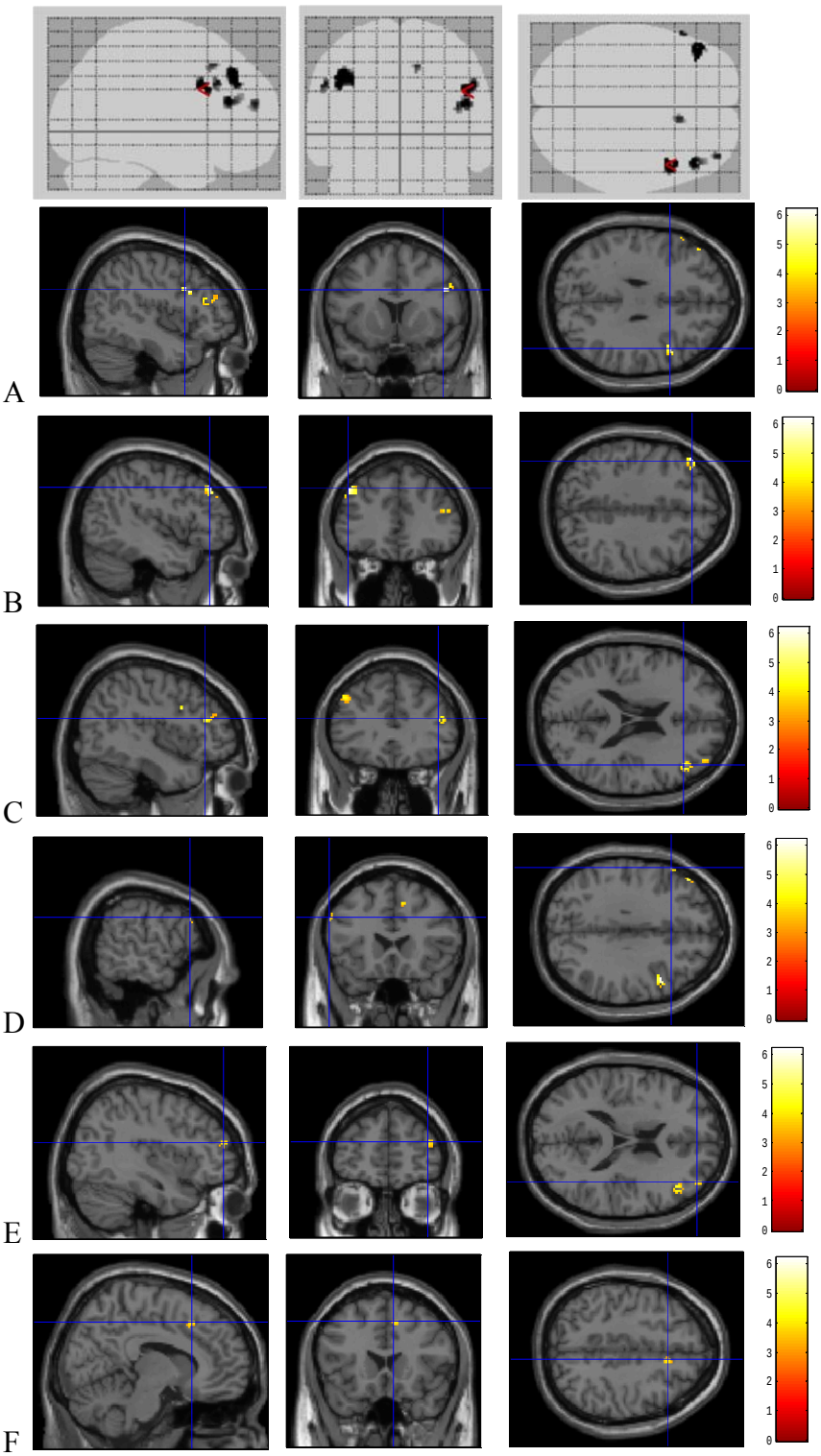
Figure 4. Study 2. Behavioral correlates of activation in BA8 during encoding





*Note: Activation in left medial frontal gyrus (BA8) during encoding positively correlated with in-scanner free recall score (r = .398, $p < 0.05$, R^2 linear = 0.158) and trial 1 cluster score on the Hopkins Verbal Learning Task (r = .375, $p < 0.05$, R^2 linear = 0.140). Black circles = recent users, grey circles = former users, white circles = never users.

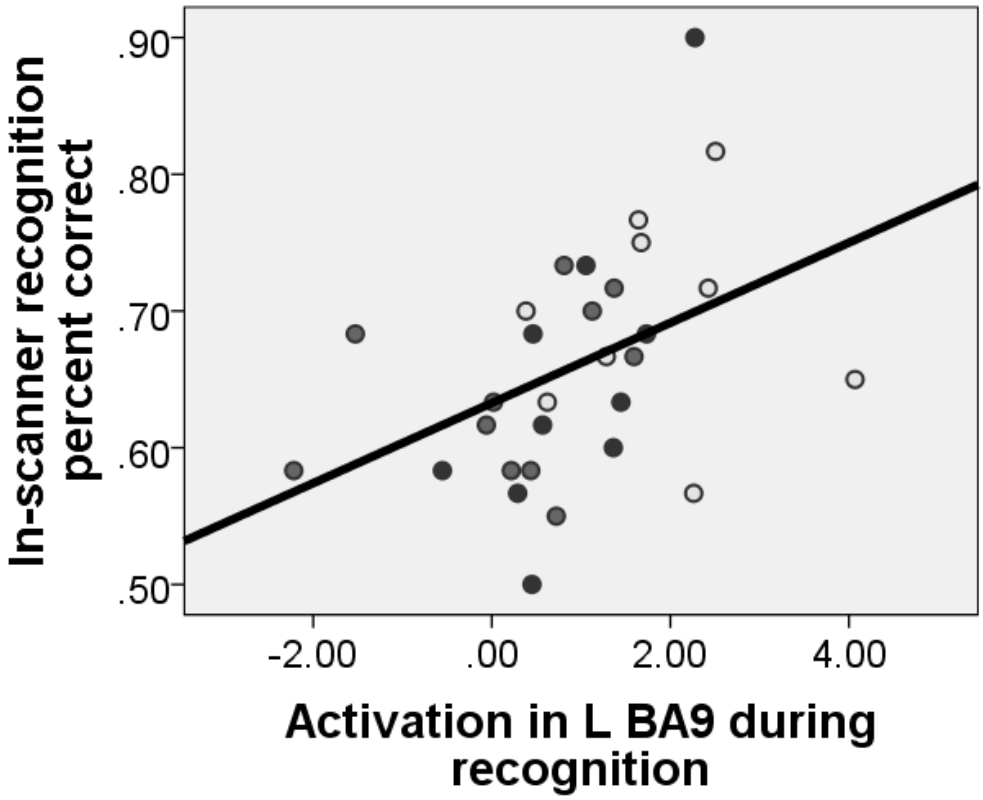
Figure 5. Study 2. Recognition: Interaction of group (recent, former, non-user) x condition (experimental, control)



*Note: All *p*'s > 0.05 and k > 10. A) Non-users activated right BA9 more during recognition than both recent users and former users; B) Non-users activated left BA8 more during

recognition than both recent users and former users; C) Non-users activated right BA46 more during recognition than former users; D) Non-users activated left BA9 more during recognition than former users; E) Never users activated right BA10 more during recognition than both recent users and former users; F) Never users activated right BA8 more during recognition than recent users

Figure 6. Study 2. 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 = .419, $p < 0.05$, R^2 linear = 0.175). Black circles = recent users, grey circles = former users, white circles = never users.

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Continuing Review

July 17, 2012

Pauline M. Maki, PhD
Psychiatry
912 S. Wood Street, Room 120G
M/C 913
Chicago, IL 60612-7325
Phone: (312) 996-6941 / Fax: (312) 413-7856

RE: Protocol # 2009-0652
"Predictors of Brain Functioning in Women with HIV"

Dear Dr. Maki:

Your Continuing Review was reviewed and approved by the Expedited review process on July 11, 2012. You may now continue your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: July 11, 2012 - July 10, 2013
Approved Subject Enrollment #: 78 (63 enrolled to date) - Research Limited to Data Analysis
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: 1) UIC, 2) Cook County CORE Center
Sponsor: 1) NIAID, NIDA, NCI, 2) National Institute on Drug Abuse (NIDA/NIH)
PAF#: 1) 2009-06134, 2) 2010-00282
Grant/Contract No: 1) F31DA028573, 2) 2 U01AI034993 (NIAID)
Grant/Contract Title: Effects of Drug Use on Prefrontal Cortex Function in HIV+ Women,Effects of Drug Use on Hippocampal Function in HIV+ Women
Research Protocol(s):

a) Predictors of Brain Functioning in Women with HIV, Version #7, 05/04/2011

Recruitment Material(s):

a) N/A; Research Limited to Data Analysis

Informed Consent(s):

a) N/A; Research Limited to Data Analysis

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories:

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.).,
(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).,
(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
07/03/2012	Continuing Review	Expedited	07/11/2012	Approved

Please remember to:

→ Use your **research protocol number** (2009-0652) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"**UIC Investigator Responsibilities, Protection of Human Research Subjects**"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 996-0865. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Tricia Hermanek, BS
IRB Coordinator, IRB # 1
Office for the Protection of Research Subjects

Enclosure(s):

1. **UIC Investigator Responsibilities, Protection of Human Research Subjects**

cc: Anand Kumar, Psychiatry, M/C 912
OVCR Administration, M/C 672

CURRICULUM VITAE

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EDUCATION AND TRAINING

B.S.	Psychology (2005) University of Iowa, Iowa City, IA
Predoctoral Fellowship	Ruth L. Kirschstein National Research Service Award, F31 (2010-2013) University of Illinois at Chicago, Chicago, IL

APPOINTMENTS AND POSITIONS

2002-2005	Research Assistant: Department of Psychology, University of Iowa, Iowa City, IA
2003-2006	Research Assistant: Iowa Gambling Research Center, University of Iowa Hospitals and Clinics, Iowa City, IA
2006-2007	Research Assistant: Biological Rhythms Research Lab, Rush University Medical Center, Chicago, IL
2007-2008	Clinical Trial Coordinator: Comprehensive Neuroscience, Inc., Park Ridge, IL
2008-present	Graduate Research Assistant: University of Illinois at Chicago, Chicago, IL

HONORS AND AWARDS

2002-2004	University of Iowa Dean List
2004-2005	USA-IA Undergraduate Scholar Assistantship
2005	B.S. with Honors and Distinction
2010-2013	NIDA NRSA Training Grant (F31)
2012	Alice J Dan Dissertation Research Award, Honorable Mention

PUBLICATIONS

Grauzas VM, Rubin LH, Martin E, Weber KM, Cohen MH, Golub ET, Valcour V, Young MA, Crystal H, Anastos K, Aouizerat BE, Milam J, Maki PM. HIV and recent illicit drug use interact to affect verbal memory in women. *JAIDS*, *accepted January 22, 2013.*

Lazarov O, Demars MP, Zhao KDT, Ali H, **Grauzas VM**, Kney A, Larson J. (2012) Impaired survival of neural progenitor cells in the dentate gyrus of adult mice lacking FMRP. *Hippocampus*, 6, 1220-1224.

Black, DW, Forbush, KT, Langer, A, Graeber, MA, Shaw, M, Hovick, L, **Meyer, VJ**, Moser, DJ, Bayless, J, Watson, D. (2009) The neuropsychology of borderline personality disorder: The predictive variance of neuropsychological tests versus selected personality trait dimensions. *Personality and Mental Health*, 3, 128-141.

Forbush KT, Shaw M, Graeber MA, Hovick L, **Meyer VJ**, Moser DJ, Bayless J, Watson D, Black DW. (2008) Neuropsychological characteristics and personality traits in pathological gambling. *CNS Spectrums*, 13(4), 306-315.

SCIENTIFIC CONFERENCE PRESENTATIONS

Grauzas VM, Sunderman E, Little DM, Weber K, Cohen M, Maki PM. (10/14/2012). *Alterations in hippocampal function in HIV-infected women*. Society for Neuroscience Annual Meeting, New Orleans LA.

Grauzas VM, Rubin, LH, Martin, EM, Weber K, Cohen M, Golub ET, Valcour V, Young M, Crystal H, Anastos K, Aouizerat B, Milam J, Maki PM. (4/7/2011). *HIV infection and recent illicit drug use synergistically affect verbal learning and memory in women*. Society for Neuroimmune Pharmacology Annual Meeting, Clearwater Beach FL.

Drogos L, **Meyer VJ**, Fogg LF, Smith MR, Geller S, Shulman LP, Banuvar S, Maki, P. (10/1/2009). *Circadian rhythm of hot flashes in highly symptomatic postmenopausal women*. North American Menopause Society, San Diego, CA.

Kotov R, Gamez W, MacDonald M, **Meyer VJ**, Huse J, Watson D. (11/24/2004). *Personality and symptoms of anxiety and depression: A new approach to the problem of comorbidity*. Annual Conference of the Association for Advancement of Behavior Therapy, New Orleans, LA.

Kotov R, Johnston A, Benoit R, Huse J, & **Meyer VJ**. (11/20/2004). *Integrating clinical measures of vulnerability to anxiety and depression with personality literature: Challenges to construct validity*. Annual Conference of the Association for Advancement of Behavior Therapy, New Orleans, LA.