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Recent Cocaine Use and Memory Impairment in HIV

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Abstract

Both Human Immunodeficiency Virus (HIV) and cocaine use have been associated with impairment in neuropsychological functioning. The high comorbidity between HIV and cocaine use highlights the importance of ascertaining whether there is a compounding effect of cocaine use in individuals with HIV. Among neuropsychological domains impacted by HIV, verbal memory deficits have received substantial attention partly because they have been associated with declines in functional status in HIV positive individuals. We collected California Verbal Learning Test-II data from HIV participants who met lifetime diagnostic criteria of cocaine abuse and/or dependence (HIV/CocDx+, $N = 80$ & HIV/CocDx−, $N = 30$, respectively) and those with and without recent cocaine use, which was confirmed by toxicology analysis (HIV/Coc+, $N = 56$ & HIV/Coc−, $N = 57$, respectively). The Item Specific Deficit Approach (ISDA) was employed to determine any additional cocaine-associated deficits in encoding, consolidation, and retrieval, which attempts to control for potential confounding factors of memory such as attention. Using conventional methods of evaluating memory profiles, we found that the HIV/Coc+ group demonstrated worse learning, immediate and delayed free recall, and recognition in contrast to the HIV/Coc− group; although using the ISDA, we found that encoding was the only significant difference between HIV/Coc+ and HIV/Coc−participant, with HIV/Coc− performing better. Our

data suggest that for individuals with HIV, cocaine use is associated with a temporary decline in verbal memory, is characterized by greater encoding deficits, and these effects may reduce with abstinence. Clinically, our findings suggest that reduced encoding is the likely contributor to verbal memory decline in HIV/Coc+ and these effects are partially reversible—at least to the level of their HIV/Coc− counterparts.

Keywords

HIV/AIDS; Substance Use; Cocaine; Memory; Neuropsychology

Introduction

Cocaine use is common among individuals infected with human immunodeficiency virus (HIV; Cofrancesco et al., 2008; Hatfield, Horvath, Jacoby, & Rosser, 2009; Kral, Bluthenthal, Booth, & Watters, 1998). The high comorbidity between HIV and cocaine use (i.e., up to 9% in HIV and 0.1% in the general population) highlights the importance of ascertaining the potential compounding effect of HIV infection and cocaine use on neuropsychological functioning (Mimiaga et al., 2013; Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2014). Neuroimaging studies have found significant overlap with respect to changes resulting from HIV infection and cocaine use. Both conditions are associated with grey and white matter pathology in frontal, temporal, and cerebellar regions (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Bartzokis et al., 2000; Becker et al., 2012; Cardenas et al., 2009; Navia, Jordan, & Price, 1986; Sim et al., 2007).

Despite widespread use of highly active anti-retroviral therapies (HAART) and subsequent reduced incidence of HIV-related dementia and cognitive dysfunction (Bhaskaran et al., 2008; Brodt et al., 1997; Sacktor et al., 1999), a subset of those with HIV still demonstrate neuropsychological deficits (Heaton et al., 2004, Heaton et al., 2011; Hinkin et al., 2008; Joska et al., 2010; Nightingale et al., 2014; Saylor et al., 2016). HIV-associated cognitive impairments include deficits in attention (Scott et al., 2006), processing speed and psychomotor abilities (Baldewicz et al., 2004), working memory (Castelo et al., 2006), and executive functioning (Durvasula et al., 2000; Heaton et al., 1995; Hinkin et al., 1990, 1995; Miller et al., 1990; Reger et al., 2002; Schiller et al., 2009).

Among the neuropsychological domains impacted by HIV, verbal memory deficits have received considerable attention. Verbal memory impairment in HIV is associated with functional declines, such as decreased employability, poor medical adherence, and other functional impairments (Barclay, Wright, & Hinkin, 2010_; Castellon, Hinkin, Wright, & Barclay, 2009; Ettenhofer, Foley, Castellon, & Hinkin, 2010; Heaton et al., 1995; Heaton et al., 2004; Hinkin et al., 2002; Torres et al., 2019; van Gorp et al., 1999a; Wright, Woo, Barclay, & Hinkin, 2009a; Wright et al., 2011).

Some studies suggest that verbal memory impairment in HIV is due to a retrieval deficit, evidenced by impairments in recall in contrast to intact recognition or cued recall (Becker et al., 2009; Murji et al., 2003; Peavy et al., 1994; Reger et al., 2002; Schiller et

al., 2009; White et al., 1997; Woods et al., 2005). Indeed, other work suggests that encoding deficits may also play a significant role in HIV-related verbal memory impairment. Specifically, studies have demonstrated HIV-related increased recency effects (Scott et al., 2006), decreased primacy effects (Waldrop, Ownby, & Kumar, 2004), decreased semantic clustering (Gongvatana et al., 2007; Murji et al., 2003; Peavy et al., 1994; Woods et al., 2005), and deficient patterns of item recall during list learning (Scott et al., 2006; White et al., 1997; Woods et al., 2005). Moreover, other studies suggest that encoding deficits may be the primary contributing factor to HIV-associated memory impairment (Scott et al. 2006; Wright et al., 2011).

There are two likely explanations for these discrepant findings. First, differences in the HIV-associated memory deficit profile between studies may be related to variable use of HAART. Many of the studies that found both encoding and retrieval deficits were either conducted in the pre-HAART era (Delis et al., 1995; Murji et al., 2003; White et al., 1997) or included participants that had low HAART adherence (Murji et al., 2003), whereas studies that found encoding deficits included participants on HAART (Gongvatana et al. 2007; Scott et al., 2006; Waldrop et al., 2004; Wright et al., 2011)—although there are exceptions (e.g., Schiller et al., 2009). Second, researchers who argue that HIV is generally associated with encoding and not retrieval deficits point out that recall and recognition likely reflect discrepant processes. Specifically, recall appears to be the product of recollection while recognition seems to be comprised of both recollection and familiarity (Aggleton & Brown, 2006) and it may be misleading to infer a retrieval deficit from recognition-recall discrepancies when recognition performances are greater than recall performances. That is, the recognition-recall discrepancies may be due to poor initial encoding rather and a true retrieval deficit.

Cocaine Use

Cocaine is a potent stimulant that elevates synaptic levels of dopamine (DA), norepinephrine (NE), and serotonin (5-HT), binds to DA, NE, and 5-HT transporters, and blocks neurotransmitter reuptake, although most of the literature has examined the effect of cocaine on the mesocorticolimbic DA pathway, since it has been posited to play an important role in addiction (Kalivas & Volkow, 2005; Volkow, Koob, & McLellan, 2016). Elevated DA levels lead to increased D1 and D2 receptor signaling and subsequent intracellular signaling pathways associated with G proteins (Beaulieu & Gainetdinov, 2011). G proteins impact cyclic AMP-dependent protein kinase, which influences ion channels, vesicles, receptor expression, and glutamine neurotransmitters (Dolphin, 2003; Gao & Wolf, 2008; Kislevsky et al., 2008). These changes lead to increased excitability of the prefrontal cortex and are thought to account for the effects of cocaine (Frazer, Richards, & Keith, 2018; Sun, Zhao, & Wolf, 2008). Neuroimaging studies have implicated structural, metabolic and white matter changes related to long-term use of cocaine (Bell et al., 2011), although recent critical review has questioned the methodology of these studies (Frazer, Richards, & Keith, 2018).

Regarding the neuropsychological profile of cocaine use, acute effects of cocaine (in a laboratory setting) include enhanced response inhibition and psychomotor speed (Spronk, van Wel, Ramaekers, & Verkes, 2013) while chronic use is associated with deficits in

processing speed (Fernandez-Serrano, Pérez-García, & Verdejo-Garcia, 2011), attention and working memory (Fernandez-Serrano, Pérez-García, & Verdejo-Garcia, 2011; Levine et al., 2006; Madoz-Gurpide, Blasco-Fontecilla, Baca-Garcia, & Ochoa-Mangado, 2011; Spronk, van Wel, Ramaekers, & Verkes, 2013), executive functioning (Fernandez-Serrano, Pérez-García, & Verdejo-Garcia, 2011; De Oliveira et al., 2009; Vergara-Moragues et al., 2017; Viola et al., 2019), and verbal memory (De Oliveira et al., 2009; Meyer et al., 2013; Spronk et al., 2013). Studies examining abstinence from cocaine suggest at least partial reversal of cognitive deficits with 1 year of abstinence (De Oliveira et al., 2009; Vonmoos et al., 2014) with residual deficits in reversal learning and emotional processing (Fernandez-Serrano, Pérez-García, & Verdejo-Garcia, 2011); however, a recent systematic critical review by Frazer, Richards, and Keith (2018) warns against overinterpreting group differences between cocaine users and non-users on cognitive measures and neuroimaging, as they may not indicate clinically significant discrepancies despite being statistically significant.

Cocaine and HIV

Cocaine use in HIV has a synergistic impact on neuroimmune functioning, particularly the dopaminergic neurotransmission. While cocaine blocks DA transporters and acts as a reuptake inhibitor, the Tat protein of HIV functions as an allosteric modulator of DA transporter (Dahal, Chitti, Nair, & Saxena, 2015). Consequently, in both cocaine use and HIV, elevated synaptic DA increases macrophages lead to neuroinflammation and accelerates the production of platelet monocyte complexes, which is related to HIV-associated neurocognitive disorder (HAND; Dahal, Chitti, Nair, & Saxena, 2015; Meade, Conn, Skalski, & Safren, 2011). Moreover, both cocaine use and HIV, directly and indirectly, impact the N-methyl-D-aspartate receptor (NMDAR), which represents a significant aspect of reward circuitry in the brain and it has been posited that changes NMDAR secondary to HIV infection may reinforce psychostimulant abuse and addiction (Buch et al., 2011). In fact, HIV infected individuals have a stronger preference for the immediate effects of stimulant drugs (d=.87) over alcohol (d=.50) and nicotine (.56) (MacKillop et al., 2011).

A recent neuroimaging study (i.e., functional magnetic resonance imaging) by Meade et al. (2017) of active cocaine use in HIV during intertemporal decision-making task revealed that cocaine use moderated the effects of HIV with clustered activations in the bilateral prefrontal cortices and cerebellum. Independently, cocaine use was associated with lower activation in bilateral frontal gyri and right insular and posterior parietal cortices while HIV was associated with higher activation in the visual cortex and reduced activation in bilateral prefrontal cortices and cerebellum and left posterior parietal cortex (Meade et al., 2017).

From a neurocognitive perspective, as mentioned previously, chronic use of cocaine has a striking resemblance to the cognitive dysfunction associated with HIV, with overlap in impairments in attention, processing speed, verbal memory, and executive functioning. Of the aforementioned domains, verbal memory is a complex cognitive process that requires multiple abilities working in tandem (e.g., attention and strategic organization) and warrants further inspection—namely, dissecting what aspects of verbal memory is impacted (i.e., encoding, consolidation, and/or retrieval). While some studies have found an impact on

verbal memory (e.g., De Oliveira et al., 2009; Meyer et al., 2013; Spronk et al., 2013), these finding may be impacted by reduced executive functioning and processing speed related to the synergistic impact of both cocaine and HIV. Specifically, Meade, Towe, Skalski, and Robertson (2015) found main effects for processing speed and executive functioning in HIV cocaine users with no significant effects for learning or memory.

Traditional metrics of verbal memory (e.g., encoding, consolidation, retrieval) of maybe confounded by attention and executive ability (e.g., organizational strategy) (Wright et al., 2009), which are domains that are dependent on the integrity of frontostriatal networks impacted by both HIV and cocaine use (Spronk et al., 2013). Encoding metrics on verbal memory list tasks include learning slope, total correct on Trial 1, and other contrasts (e.g., Trial 1 vs Trial 5) (Delis, Kramer, Kaplan, & Ober, 2000); unfortunately, attentional difficulties are inherent in many neurological and psychiatric conditions can impact these scores (Cohen, Malloy, Jenkins, & Paul, 2006). Similarly, consolidation metrics for verbal memory list tasks contrast total items recalled against recall following a delay with a decline signifying a loss of information or forgetting over time (Delis et al., 2000) and another metric relies on proactive interference (adverse effect of older learning on new learning); however, these metrics either provide non-specific findings of memory storage or do not account for initial learning (Wright et al., 2009). Retrieval metrics on verbal memory list tasks involve contrasting recall performances against recognition performances, although as mentioned previously, it may be misleading to infer a retrieval deficit from recognition-recall discrepancies when recognition performances are greater than recall performances (Aggleton & Brown, 2006) since these discrepancies may be due to poor initial encoding rather and a true retrieval deficit.

The Item-Specific Deficit Approach (ISDA) is a psychometrically valid method that aims to mitigate the impact of inattention on encoding, consolidation, and retrieval on list-learning tasks (Wright et al., 2009). The ISDA was initially validated in a healthy comparisons sample, seropositive HIV, and traumatic brain injury (Wright et al., 2009), replicated in these populations (Obermeit et al., 2015; Wright et al., 2010; Wright et al., 2011; Wright et al., 2013), and has since been applied in other settings including amyotrophic lateral sclerosis (Christidi, Zalonis, Smyrnis, & Evdokimidis, 2012), amnestic mild cognitive impairment (Andrés et al., 2019), and Alzheimer disease (Oltra-Cucarella, Pérez-Elvira, & Duque, 2014). Most recently, Lueke and Lueke (2019) used the ISDA to evaluate the impact of mindfulness on encoding, consolidation, and retrieval. Generally, the ISDA has demonstrated superiority over traditional metrics, with one exception—Cattie et al. (2012) raised concerns about the incremental value of the ISDA and noted that the ISDA encoding index was collinear with other memory tests (i.e., r_s=.92 on total Trials 1–5 on the California Verbal Learning Test and the ISDA encoding index in their HIV sample).

In the current study, we attempted to ascertain the additive impact of recent and past cocaine use on the different aspects of verbal memory (encoding, consolidation, and retrieval) in a seropositive HIV sample using both traditional memory metrics and ISDA memory indices. Specifically, we examined if recent cocaine use impacted memory performances and also if a lifetime diagnosis of cocaine dependence or abuse impacted memory performances. We hypothesized that recent cocaine (HIV/Coc+) and not past use (HIV/Coc−) will adversely

impact verbal memory given cocaine's state-like effect on cognitive functioning (i.e., Frazer, Richards, & Keith, 2018). Additionally, a lifetime diagnosis of cocaine dependence or abuse (HIV/CocDx+) and not subclinical use of cocaine (HIV/CocDx−) the was hypothesized to adversely impact verbal memory given that some reach has posited at least some residual impact on brain structure (Bell et al., 2011). We also predicted that recent cocaine use would amplify the effects of historical use in HIV as assessed by traditional and ISDA memory metrics. Relative to other memory metrics, we posited that encoding would adversely be impacted given that both cocaine and HIV have been documented to impact frontostriatal networks (Spronk et al., 2013).

Methods

Participants

Data from 113 community-dwelling HIV infected participants were used for the current analysis. This sample was extracted from a prior study (Levine et al., 2006; Hinkin et al., 2007), which was funded by the National Institute on Drug Abuse (Grant Number: 1R01DA013799–01A1). The initial study was adequately powered to detect the effects of . No control group was available in the sample (i.e., HIV negative participants). Participants were recruited from community health agencies in the Los Angeles area through fliers posted in infectious disease clinics at two University-affiliated medical centers. Exclusion criteria included meeting diagnostic criteria for lifetime or current history of psychotic spectrum or manic disorders and any neurological disorder other than HIV-infection (i.e., seizure disorder, stroke, closed-head injury with loss of consciousness in excess of 30 minutes, or any other neurological disease, CNS opportunistic infection, or neoplasm). For our analyses, the participants were stratified by 1) recent cocaine use (self-report and urinary analysis) and 2) if participants ever met diagnostic criteria for cocaine dependence or abuse in their lifetime. The stratification for the recent cocaine abuse, participants 1) reported using cocaine within 4 weeks of testing and/or had positive urinalysis results for cocaine use on the day of testing (HIV/Coc+, $N = 56$) or 2) denied cocaine use 4 weeks prior to testing and had negative cocaine urinalysis results (HIV/Coc−, $N = 57$). A period of four weeks was selected for self-report to ensure that there was sufficient time for such substances to adequately clear their system. Urine toxicology conducted on the day of testing, which screened for cocaine, amphetamine, cannabis, and opiate metabolites. The stratification for presence (HIV/CocDx+, $N = 80$) or absence (HIV/CocDx−, $N = 30$) of lifetime cocaine dependence or abuse was determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorder 4th Edition, Clinical Version (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1996).

HIV status was confirmed with ELISA and Western blot. Seventy percent of the HIV/Coc+ ($N = 35/55$), 63 percent of the HIV/Coc− ($N = 40/57$), 65 percent of HIV/CocDx+ ($N = 51/79$), and 72 percent of HIV/CocDx− ($N = 24/33$) participants met the Centers for Disease Control and Prevention diagnostic criteria (e.g., CD4 < 200) for Acquired Immunodeficiency Syndrome (AIDS). There were no group differences in the proportion of participants meeting criteria for AIDS (see Tables 1 and 2). All of the participants were on self-administered HAART at the time of testing.

Materials and Procedure

All participants were administered the North American Adult Reading Test (NAART; Blair & Spreen 1989) and the California Verbal Learning Test-2nd edition (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 1987, 2000). Trained psychometrists administered all instruments under the supervision of a board-certified neuropsychologist. Participants received $80 for their participation. This study underwent an ethics committee review and was approved by the institutional review boards of the University of California, Los Angeles, and the West Los Angeles VA Medical Center.

Verbal Memory

The CVLT-II (Delis, Kramer, Kaplan, & Ober, 1987, 2000) is a verbal list-learning test comprised of 16 items that can be grouped into four semantic categories. The list is presented orally to participants over five learning trials, followed by a short-delay free and cued recall, long-delay free and cued recall, and recognition trials. The CVLT-II yields numerous indices. For the current study, we were interested primarily in the sum of items recalled across all five learning trials (total learning), short-delay free recall, and long-delay free recall.

Item level data from the CVLT-II were evaluated via the Item Specific Deficit Approach (ISDA), a quantitative process method for deriving indices of encoding, consolidation, and retrieval deficits. These indices have demonstrated increased sensitivity to cognitive impairment compared to traditional indices calculated from list-learning data (Wright, Woo, Schmitter-Edgecombe, et al., 2009b). Furthermore, these indices seem to be less contaminated by other cognitive factors (e.g., attention; Wright et al., 2009b).

The ISDA encoding deficit index is derived by summing the items that were not recalled at least three times during the five initial CVLT-II learning trials (higher scores indicate greater encoding difficulties; maximum value = 16). The consolidation deficit index is calculated by summing the items that were recalled at least once during the list learning, but not recalled during either the short or long delay free or cued recall trials. The retrieval index is calculated via the sum of items that were recalled during list learning but recalled inconsistently across the short and long-delay free and cued recall trials (i.e., recalled between one and three times over the four delayed recall trials). The consolidation index and retrieval index totals are divided by the number of items recalled at least once during the list learning trials (maximum value = 16) to control for learning differences between groups.

Statistical Analysis

Descriptive statistics were computed on basic demographic variables, CD4 count, AIDS diagnosis, and substances use for all groups (HIV/Coc+ vs. HIV/Coc− and HIV/CocDx+ vs. HIV/CocDx−; see Table 1 and 2). We compared these data across the groups with independent sample T-tests for continuous variables and chi-square frequency for categorical variables. Additionally, collinearity between the traditional memory metrics and the ISDA was computed (see Table 3).

While the HIV/Coc+ and HIV/Coc− groups were well matched in terms of premorbid intelligence, age, education, sex, and history of depression (see Table 1), the HIV/Coc− group was comprised of a larger proportion of Caucasian participants (19%) than the HIV/Coc+ group. That said, ethnic/racial membership (Caucasian vs. minority) was not significantly associated with any of the dependent variables in the current study ($r_{pb}s = -0.11 - 0.07$, $ps > .05$). Additionally, the HIV/Coc− had greater duration of lifetime cocaine and stimulant use, than the HIV/Coc+ group, while the HIV/Coc+ had a greater number of participants with positive cannabis toxicology. Total duration of cocaine and stimulant use was not associated with any of the dependent variables in the study ($r_{pb}s = -.23 - .27$, $ps > .05$). Similarly, positive cannabis toxicology was exclusive to HIV/Coc+ in our sample and was not associated with any of the dependent variables in the study ($r_{pb}s = -.22 - .20$, $ps > .05$). While HIV/CocDx+ and HIV/CocDx− were well matched in terms of premorbid intelligence, age, education, sex, ethnicity, and history of depression (see Table 2), the HIV/CocDx− group had greater incidence of lifetime alcohol abuse and/or dependence and cannabis abuse and/or dependence than the HIV/CocDx+ group. That said, lifetime alcohol abuse and/or dependence and cannabis abuse and/or dependence were not significantly associated with any of the dependent variables in the current study ($r_{pb}s = -0.06 - 0.08$, $ps > .05$).

In order to determine the impact of cocaine use on CVLT-II performances, we performed 2 group (recent cocaine use [HIV/Coc+] vs. no recent cocaine use [HIV/Coc−]) X 2 cocaine use history (history of having met lifetime DSM-IV-TR criteria for cocaine abuse and/or dependence [HIV/CocDx+] vs. no history of having met lifetime DSM-IV-TR criteria for cocaine abuse/dependence [HIV/CocDx−]) ANOVAs for the CVLT-II total learning sum, CVLT-II short-delay free recall, CVLT-II long-delay free recall, and ISDA indices (i.e., encoding, consolidation, and retrieval). A significance level of $a < 0.05$ was used as the threshold for significance. To correct for family-wise error, we calculated q-values with a predetermined false discovery rate cut-off of .05 for each p value across all memory metrics (Storey, 2002).

Results

With regard to total learning, we found a significant main effect of recent cocaine use $F(1,109) = 4.477$, $p = 0.037$, $q = 2.067^{-13}$, $\eta_p^2 = 0.039$. Specifically, the HIV/Coc− group ($M = 47.11$, $SD = 9.15$) recalled more items than the HIV/Coc+ group ($M = 44.30$, $SD = 8.56$). The effect of cocaine use history, $F(1,109) = 0.014$, $p > .05$, $q = 1.660^{-12}$, $\eta_p^2 = 0.000$, and the recent use by lifetime history of cocaine abuse and/or dependence interaction were not significant, $F(1,109) = 2.064$, $p > .05$, $q = 5.644^{-13}$, $\eta_p^2 = 0.019$.

Regarding short-delay recall, a main effect of recent cocaine use was observed, $F(1,109) = 4.046$, $p = .047$, $q = 2.067^{-13}$, $\eta_p^2 = 0.036$, with the HIV/Coc− group ($M = 9.37$, $SD = 3.35$) recalling more items than the HIV/Coc+ group ($M = 8.38$, $SD = 3.02$). Univariate ANOVAs did not show any significant effects of lifetime history of cocaine abuse and/or dependence, $F(1,109) = 0.147$, $p > .05$, $q = 1.487^{-12}$, $\eta_p^2 = 0.001$. Similarly, there was not a significant interaction between recent cocaine use and lifetime history of cocaine abuse and/or dependence, $F(1,109) = 1.341$, $p > .05$, $q = 7.822^{-13}$, $\eta_p^2 = 0.012$.

For long-delay free recall, an univariate ANOVA revealed a significant main effect of recent cocaine use, $F(1,109) = 4.032$, $p = .047$, $q = 2.067^{-13}$, $\eta_p^2 = 0.036$, with the HIV/Coc− group ($M = 9.86$, $SD = 3.54$) recalling more items than the HIV/Coc+ group ($M = 9.30$, $SD = 3.23$). The effect of history of use, $F(1,109) = .969$, $p > .05$, $q = 7.989^{-13}$, $\eta_p^2 = 0.012$, and the interaction between recent and historical use, $F(1,123) = 0.772$, $p > .05$, $q = 7.989^{-13}$, $\eta_p^2 = 0.006$, were not significant.

For total recognition discriminability (d'), an univariate ANOVA revealed a significant main effect of recent cocaine use, $F(1,109) = 7.655$, $p = .007$, $q = 1.539^{-13}$, $\eta_p^2 = 0.066$, with the HIV/Coc− group ($M = 2.92$, $SD = 0.78$) displaying better total recognition discriminability than the HIV/Coc+ group ($M = 2.63$, $SD = 0.71$). The effect of history of use, $F(1,109) = .107$, $p > .05$, $q = 1.48^{-12}$, $\eta_p^2 = 0.001$ was not significant. An interaction emerged between recent and historical use, $F(1,109) = 4.258$, $p = .041$, $q = 2.067^{-13}$, $\eta_p^2 = 0.038$, such that those with a lifetime history of cocaine use and/or dependence and who recently used cocaine had better recognition discriminability ($M = 2.72$, $SD = 0.73$) than those with a lifetime history of cocaine use and/or dependence but had no recent cocaine use ($M = 2.35$, $SD = 0.54$); however, those with ($M = 2.83$, $SD = 0.76$) and without ($M = 3.09$, $SD = 0.84$) a lifetime history of cocaine use and/or dependence performed similarly when they abstained from cocaine for at least 4 weeks and had negative toxicology for cocaine.

For the ISDA encoding index, a main effect of recent cocaine use was observed, $F(1,109) = 4.685$, $p = 0.033$, $q = 1.151^{-12}$, $\eta_p^2 = 0.041$, such that participants who had recently used cocaine ($M = 6.61$, $SD = 2.49$) showed statistically inferior encoding relative to participants without recent cocaine use ($M = 5.73$, $SD = 3.09$) (see Figure 1). Analysis of variance did not show any significant effects of use history, $F(1,109) = 0.008$, $p > .05$, $q = 1.078^{-11}$, $\eta_p^2 = 0.000$, nor an interaction between recent cocaine use and use history on encoding, $F(1,109) = 2.641$, $p > .05$, $q = 1.867^{-12}$, $\eta_p^2 = 0.024$.

ANOVAs computed for the consolidation index did not reveal significant group, $F(1,109) = 0.529$, $p > .05$, $q = .699$, $\eta_p^2 = 0.005$, use history, $F(1,109) = 0.151$, $p > .05$, $q = .699$, $\eta_p^2 = 0.001$, or interaction effects, $F(1,109) = .328$, $p > .05$, $q = .699$, $\eta_p^2 = 0.003$. Similarly, an ANOVA for the retrieval index did not reveal significant effects for recent cocaine use, $F(1,109) = 1.070$, $p > .05$, $q = .966$, $\eta_p^2 = .010$, or use history, $F(1,109) = 0.036$, $p > .05$, $q = .966$, $\eta_p^2 = 0.000$, and did not reveal any interaction effects, $F(1,109) = 0.002$, $p > .05$, $q = .966$, $\eta_p^2 = 0.000$.

Discussion

We hypothesized that 1) recent cocaine use will exacerbate encoding deficits and verbal memory difficulties in HIV infected individuals and 2) meeting lifetime diagnostic criteria for cocaine dependence and/or abuse would adversely impact memory performances, 3) recent cocaine use would amplify the effects of historical use in HIV, and 4) encoding would be adversely impacted over consolidation and retrieval. Our data partially supported these hypotheses. Specifically, using traditional verbal memory metrics that do not control for (inattention or executive ability), recent cocaine use impacted total learning, short and long delay, and recognition discriminability, and interactive effects between recent use and

historical use emerged only for the recognition discriminability metric. Specifically, the interactive effects revealed recognition discriminability performance differences in recent cocaine users with and without a lifetime history of cocaine abuse or dependence; the interaction further suggested that with abstinence, recognition discriminability performances of those with and without cocaine abuse and dependence are similar. Overall, the traditional memory metrics revealed general and non-specific findings that recent cocaine abuse and not historical use impacts all memory domains.

However, given that traditional metrics do not account for inattention and dysexecutive symptoms (e.g., poor organizational strategies), an alternative approach was employed (i.e., ISDA) as both cocaine and HIV influence frontostriatal networks subservient to these functions (Spronk et al., 2013). Indeed, using the ISDA, our findings revealed that only encoding was compromised in the HIV/Coc+ group when compared to the HIV/Coc− group. Additionally, using the ISDA, we found that historical cocaine use and/or dependence did not have an impact on encoding, consolidation, or retrieval. In contrasting traditional memory metrics and the ISDA, the ISDA memory metrics isolated statistically inferior performances to encoding, while the traditional metrics provided non-specific findings, despite being statistically collinear to traditional memory metrics (i.e., ISDA encoding deficit index correlated at $r=.92$ to CVLT-II Total Trials 1–5). Similar collinearity among memory metrics has been reported by other researchers (Cattie et al., 2012).

These findings speak to the incremental utility of the ISDA in an HIV setting and suggests that reduced memory performances in the context of HIV and cocaine use are likely secondary to disrupted learning, which is concordant with prior research suggesting frontostriatal involvement (Meade et al., 2017) and reduced executive ability (Meade et al., 2015) that likely impacts strategic encoding strategies (Scott et al., 2006; White et al., 1997; Woods et al., 2005; Wright et al., 2011). Of note, our findings are also in line with prior research supporting the notion that the deleterious effects of cocaine use on cognition in HIV are, at least to some extent, state-like in nature and transitory (De Oliveira et al., 2009; Durvasula et al., 2000; Frazer, Richards, & Keith, 2018). Moreover, a recent longitudinal study found that in some cases, 1-year abstinence led to cognitive performances (i.e., attention, memory, and global cognition) similar to that of healthy control participants (Vonmoos et al., 2014). Our findings further add to the literature against the lasting impact of cocaine use (Frazer, Richards, & Keith, 2018); however, given the cross-sectional nature of the study and a lack of healthy comparison subjects, we cannot affirm that reduced encoding will be fully ameliorated, although this study converges with other research that suggests performance comparable to HIV/Coc− groups. At first blush, our findings appear to differ from another study reporting no differences in verbal memory between HIV participants with and without cocaine use (Durvasula et al., 2000). However, in the Durvasula et al. (2000) study, HIV/Coc+ participants were younger and there is evidence to suggest that older individuals with HIV, even a remote history of stimulant use seems to have an effect as persons age (Iudicello et al., 2014). Additionally, the authors note that their findings may have been confounded by alcohol use and largely recreational drug users (Durvasula et al., 2000).

The results of the current study underscore the importance of interventions that aid in the cessation of cocaine use among individuals with HIV. The immediate concern is that cocaine use could lead to worse cognitive status that could reduce HAART adherence. Indeed, declines in cognitive functioning (Ettenhofer et al., 2009, 2010), including memory (Wright et al., 2011; Wright et al., 2009a; Barclay et al., 2007; Hinkin et al., 2004), are associated with decreased medical compliance; this phenomenon also appears to be the case for cocaine use (Barclay et al., 2007; Ettenhofer et al., 2009; Hinkin et al., 2004, 2007). This is a particularly vexing problem since cocaine-related verbal memory deficits may not only lead to worse functional outcomes, but active cocaine use may accelerate HIV replication (Tashkin et al., 2004), further highlighting the importance of targeted substance use/abuse interventions for persons with HIV.

Our results have implications for clinical practice. Of notable importance, is the HIV/Coc+ memory profile of acquisition adjusted versus non-adjusted measurement of memory. Our findings highlight the importance of clinically correcting for inattention and a decline in executive ability (e.g., organizational strategy), especially in the context of HIV and cocaine given the neurocircuitry involved (Spronk et al., 2013). Relying solely on traditional metrics can be misleading, as seen in this study. Specifically, memory performances should adjust for acquisition, if memory is being evaluated (see Wright et al., 2009 for a review). Additionally, HIV-related memory deficits are associated with decreases in medical compliance and daily functioning (Hinkin et al., 2002), so additional memory deficits caused by cocaine use could potentially exacerbate functional impairment in areas such as medication management, driving, employment, money management, cooking, and shopping (Heaton et al., 2004; Hinkin et al., 2002; Marcotte et al., 1999, 2004; see Wright et al., 2009a for review). Additionally, our data suggest recommendations that specifically target the HIV-associated memory deficits, such as methods that improve the acquisition of new information rather than retrieval practice (Avci et al., 2017; Roediger & Butler, 2011). Finally, our findings also offer hope and incentive to patients, suggesting that abstinence from cocaine may confer cognitive benefit.

While our study suggests that recent, not past, cocaine use exacerbates verbal memory difficulties in HIV/AIDS via greater encoding deficits, our study also suffered from some limitations. The study did not include a healthy control group or a HIV-negative group with a history of cocaine use. Such comparisons would have allowed for a more detailed analysis and stronger conclusions about the independent, additive, and interactive effects of HIV serostatus and cocaine use. As such, this study can only speak to the effects of recent COC use in the setting of HIV and without a normative sample, differences observed between groups may not represent clinically relevant discrepancies (Frazer, Richards, & Keith, 2018). Nevertheless, discrepancies between healthy comparisons and participants with HIV are well documented (Heaton et al., 2004, Heaton et al., 2011; Hinkin et al., 2008; Joska et al., 2010; Nightingale et al., 2014; Saylor et al., 2016). Our study evaluated the impact of cocaine use in HIV only on verbal memory and is a notable limitation, as other research has demonstrated discrepancies in attention, working memory, psychomotor speed, and executive functions (Baldewicz et al., 2004; Castelo et al., 2006; Durvasula et al., 2000; Heaton et al., 1995; Hinkin et al., 1990, 1995; Miller et al., 1990; Reger et al., 2002; Schiller et al., 2009; Scott et al., 2006). The present study utilized a cross-sectional

design. A longitudinal and within-subjects design, in which participants' performances are assessed while accounting for natural variation in the level of cocaine use over time, would have allowed us to better ascertain the impact of cocaine use on verbal memory in persons with HIV. Additionally, Finally, our methodology for determining history of cocaine use entailed self-report and urinalysis screen; while urinalysis is very accurate in this regard, it is only effective for a limited temporal window and, thus, we had to rely on self-reports regarding cocaine use that occurred several weeks prior to urine collection. That said, future research should also consider whether there are thresholds in terms of duration and severity of cocaine use that are related to long term declines in verbal memory in individuals with HIV.

Acknowledgments

References

Aggleton JP, & Brown MW (2006). Interleaving brain systems for episodic and recognition memory. Trends in Cognitive Science, 10, 455–463.

Ances BM, Ortega M, Vaida F, Heaps J, Paul R (2012). Independent effects of HIV, aging, and HAART on brain volumetric measures. Journal of Acquired Immune Deficiency Syndrome, 59, 469–477.

Andrés P, Vico H, Yáñez A, Siquier A, & Ferrer GA (2019). Quantifying memory deficits in amnestic mild cognitive impairment. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 11, 108–114.

Avci G, Woods SP, Verduzco M, Sheppard DP, Sumowski JF, Chiaravalloti ND, ... & HIV Neurobehavioral Research Program (HNRP) Group (2017). Effect of Retrieval Practice on Short-Term and Long-Term Retention in HIV+ Individuals. Journal of the International Neuropsychological Society, 23, 214–222. [PubMed: 28067192]

Baldewicz TT, Leserman J, Silva SG, Petitto JM, Golden RN, Perkins DO, . . . Evans DL (2004). Changes in neuropsychological functioning with progression of HIV-1 infection: results of an 8-year longitudinal investigation. AIDS and Behavior, 8, 345–355. [PubMed: 15475681]

Barclay TR, Hinkin CH, Castellon SA, Mason KI, Reinhard MJ, Marion SD, . . . Durvasula RS (2007). Age-associated predictors of medication adherence in HIV-Positive Adults: Health beliefs, self-efficacy, and neurocognitive status. Health Psychology, 26, 40–49. [PubMed: 17209696]

Barclay TR, Wright MJ, & Hinkin CH (2010). Medication management. In Marcotte TD & Grant I (Eds.). The Neuropsychology of Everyday Functioning. (pp. 136–167). New York, NY, Guilford Press.

Bartzokis G, Beckson M, Lu PH, Edwards N, Rapoport R, Wiseman E, & Bridge P (2000). Age-related brain volume reductions in amphetamine and cocaine addicts and normal controls: implications for addiction research. Psychiatry Research, 98, 93–102. [PubMed: 10762735]

Beaulieu JM, & Gainetdinov RR (2011). The physiology, signaling, and pharmacology of dopamine receptors. Pharmacological reviews, 63, 182–217. [PubMed: 21303898]

Becker JT, Kingsley L, Mullen J, Cohen B, Martin E, Miller EN, . . . Visscher BR (2009). Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology, 73, 1292–1299. [PubMed: 19841381]

Becker JT, Maruca V, Kingsley LA, Sanders JM, Alger JR, Barker PB, . . . Selnes O (2012). Factors affecting brain structure in men with HIV disease in the post-HAART era. Neuroradiology, 54, 113–121. [PubMed: 21424708]

Bhaskaran K, Mussini C, Antinori A, Walker AS, Dorrucci M, Sabin C, ... & Cascade Collaboration. (2008). Changes in the incidence and predictors of human immunodeficiency virus–associated

dementia in the era of highly active antiretroviral therapy. Annals of Neurology, 63, 213–221. [PubMed: 17894380]

Blair JR, & Spreen O (1989). Predicting premorbid IQ: a revision of the National Adult Reading Test. The Clinical Neuropsychologist, 3, 129–136.

Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S, & Helm EB (1997). Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS, 11, 1731–1738. [PubMed: 9386808]

Buch S, Yao H, Guo M, Mori T, Su TP, & Wang J (2011). Cocaine and HIV-1 interplay: molecular mechanisms of action and addiction. Journal of Neuroimmune Pharmacology, 6, 503–515. [PubMed: 21766222]

Cai Y, Yang L, Callen S, & Buch S (2016). Multiple faceted roles of cocaine in potentiation of HAND. Current HIV research, 14, 412–416. [PubMed: 27009095]

Cardenas VA, Meyerhoff DJ, Studholme C, Komak J, Rothlind J, Lampiris H, . . . Weiner MW (2009). Evidence for ongoing brain injury in human immunodeficiency virus-positive patients treated with antiretroviral therapy. Journal of Neurovirology, 15, 324–333. [PubMed: 19499454]

Castellon SA, Hinkin CH, Wright MJ, & Barclay TR (2009). Neuropsychological performance and adherence to medical treatments. In Grant I & Adams K (Eds.). Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders (pp. 688–712). New York, NY: Oxford University Press.

Castelo JMB, Sherman SJ, Courtney MG, Melrose RJ, Stern CE, & Phil D (2006). Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. Neurology, 66, 1688–1695. [PubMed: 16769942]

Cattie JE, Woods SP, Arce M, Weber E, Delis DC, Grant I, & HIV Neurobehavioral Research Program Group. (2012). Construct validity of the item-specific deficit approach to the California verbal learning test in HIV infection. The Clinical Neuropsychologist, 26, 288–304. [PubMed: 22394206]

Chang SL, Connaghan KP, Wei Y, & Li MD (2014). NeuroHIV and use of addictive substances. In International review of neurobiology, 118, 403–440. [PubMed: 25175871]

Christidi F, Zalonis I, Smyrnis N, & Evdokimidis I (2012). Selective attention and the three-process memory model for the interpretation of verbal free recall in amyotrophic lateral sclerosis. Journal of the International Neuropsychological Society, 18, 809–818. [PubMed: 22676844]

Cofrancesco J Jr, Scherzer R, Tien PC, Gibert CL, Southwell H, Sidney S, ... & Grunfeld C (2008). Illicit drug use and HIV treatment outcomes in a US cohort. AIDS, 22, 357. [PubMed: 18195562]

Cohen RA, Malloy P, Jenkins M, & Paul R (2014). Disorders of attention. In Parsons MW and Hammeke TA (Eds.) Clinical neuropsychology: A pocket handbook for assessment (pp 463–497). American Psychological Association, Washington, DC.

Dahal S, Chitti SV, Nair MP, & Saxena SK (2015). Interactive effects of cocaine on HIV infection: implication in HIV-associated neurocognitive disorder and neuroAIDS. Frontiers in microbiology, 6, 931. [PubMed: 26441868]

De Oliveira LG, Barroso LP, Silveira CM, Sanchez ZVDM, De Carvalho Ponce J, Vaz LJ, & Nappo SA (2009). Neuropsychological assessment of current and past crack cocaine users. Substance Use & Misuse, 44, 1941–1957. [PubMed: 20001290]

Delis DC, Kramer JH, Kaplan E & Ober BA (2000): California Verbal Learning Test, (2nd *Ed.) (CVLT-II).* San Antonio, TX: The Psychological Corporation.

Delis DC, Kramer JH, Kaplan E, & Ober BA (1987): California Verbal Learning Test (CVLT). San Antonio, TX: The Psychological Corporation.

Delis DC, Peavy G, Heaton R, Butters N, Salmon DP, Taylor M, . . . HNRC Group (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.

Dolphin AC (2003). G protein modulation of voltage-gated calcium channels. Pharmacological reviews, 55, 607–627. [PubMed: 14657419]

Durvasula RS, Myers HF, Satz P, Miller EN, Morgenstern H, Richardson MA, . . . Forney D (2000). HIV-1, cocaine, and neuropsychological performance in African American men. Journal of the International Neuropsychological Society, 6, 322–335. [PubMed: 10824504]

Ettenhofer ML, Foley J, Castellon SA, & Hinkin CH (2010). Reciprocal prediction of medication adherence and neurocognition in HIV/AIDS. Neurology, 74, 1217–1222. [PubMed: 20220123]

Ettenhofer ML, Hinkin CH, Castellon SA, Durvasula R, Ullman J, Lam M, . . . Foley J (2009). Aging neurocognition, and medication adherence in HIV infection. American Journal of Geriatric Psychiatry, 17, 281–290.

Fernandez-Serrano MJ, Pérez-García M, & Verdejo-Garcia A (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance?. Neuroscience & Biobehavioral Reviews, 35, 377–406. [PubMed: 20451551]

First MB, Spitzer RL, Gibbon M, & Williams JBW (1996). Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-CV). Washington, D.C.: American Psychiatric Press, Inc.

Frazer KM, Richards Q, & Keith DR (2018). The long-term effects of cocaine use on cognitive functioning: A systematic critical review. Behavioural brain research, 348, 241–262. [PubMed: 29673580]

Gao C, & Wolf ME (2008). Dopamine receptors regulate NMDA receptor surface expression in prefrontal cortex neurons. Journal of neurochemistry, 106, 2489–2501. [PubMed: 18673451]

Gongvatana A, Woods SP, Taylor MJ, Vigil O, & Grant I (2007). Semantic clustering inefficiency in HIV-Associated Dementia. Journal of Neuropsychiatry and Clinical Neuroscience, 19, 36–42.

Hatfield LA, Horvath KJ, Jacoby SM, & Simon-Rosser BR (2009). Comparison of substance use and risky sexual behavior among a diverse sample of urban, HIV-positive men who have sex with men. Journal of Addictive Disorders, 28, 208–218.

Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, ... & Collier AC (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. Journal of Neurovirology, 17, 3–16. [PubMed: 21174240]

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, . . . Abramson I (1995). The HNRC 500- Neuropsychology of HIV infection at different disease stages. Journal of the International Neuropsychological Society, 1, 231–251. [PubMed: 9375218]

Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, . . . Grant I (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. Journal of the International Neuropsychological Society, 10, 317–331. [PubMed: 15147590]

Hinkin CH, Barclay TR, Castellon SA, Levine AJ, Durvasula RS, Marion SD, . . . Longshore D (2007). Drug use and medication adherence among HIV-1 infected individuals. AIDS and Behavior, 11, 185–194. [PubMed: 16897351]

Hinkin CH, Castellon SA, Durvasula RS, Hardy DJ, Lam MN, Mason KI, … & Stefaniak M (2002). Medication adherence among HIV+ adults: Effects of cognitive dysfunction and regimen complexity. Neurology, 59, 1944–1950. [PubMed: 12499488]

Hinkin CH, Castellon SA, Levine AJ, Barclay TR, & Singer EJ (2008). Neurocognition in individuals co-infected with HIV and hepatitis C. Journal of Addictive Disorders, 27, 11–17.

Hinkin CH, Cummings JL, van Gorp WG, Satz P, Mitrushina M, & Freeman D (1990). Frontal/subcortical features of normal aging: An empirical analysis. Canadian Journal on Aging, 9, 104–119.

Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, & Stefaniak M (2004). Medication adherence in HIV-infected adults: Effects of patient age, cognitive status, and substance abuse. AIDS, 18, S19–S25.

Hinkin CH, van Gorp WG, Mandelkern MA, Gee M, Satz P, Holston S, . . . Ropchan JR (1995). Cerebral metabolic change in patients with AIDS: Report of a six-month follow-up using positron-emission tomography. Journal of Neuropsychiatry and Clinical Neurosciences, 7, 180–187.

Iudicello JE, Morgan EE, Gongvatana A, Letendre SL, Grant I, Woods SP, & Translational Methamphetamine AIDS Research Center (TMARC) Group. (2014). Detrimental impact of remote methamphetamine dependence on neurocognitive and everyday functioning in older but not younger HIV+ adults: evidence for a legacy effect?. Journal of neurovirology, 20, 85–98. [PubMed: 24470237]

Joska JA, Gouse H, Paul RH, Stein DJ, & Flisher AJ (2010). Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. Journal of Neurovirology, 16, 101–114. [PubMed: 20345318]

Kalivas PW, & Volkow ND (2005). The neural basis of addiction: a pathology of motivation and choice. American Journal of Psychiatry, 162, 1403–1413.

Kisilevsky AE, Mulligan SJ, Altier C, Iftinca MC, Varela D, Tai C, ... & Zamponi GW (2008). D1 receptors physically interact with N-type calcium channels to regulate channel distribution and dendritic calcium entry. Neuron, 58, 557–570. [PubMed: 18498737]

Kral AH, Bluthenthal RN, Booth RE, & Watters JK (1998). HIV seroprevalence among street-recruited injection drug and crack cocaine users in 16 US municipalities. American Journal of Public Health, 88, 108–113. [PubMed: 9584014]

Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, & Hinkin CH (2006). The effect of recent stimulant use on sustained attention in HIV+ adults. Journal of Clinical and Experimental Neuropsychology, 28, 29–42. [PubMed: 16448974]

Lueke A, & Lueke N (2019). Mindfulness improves verbal learning and memory through enhanced encoding. Memory & Cognition, 1–15. [PubMed: 30097907]

MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, & Munafò MR (2011). Delayed reward discounting and addictive behavior: A meta-analysis. Psychopharmacology, 216, 305–321. [PubMed: 21373791]

Madoz-Gurpide A, Blasco-Fontecilla H, Baca-Garcia E, Ochoa-Mangado E (2011). Executive dysfunction in chronic cocaine users: an exploratory study. Drug and Alcohol Dependence, 117, 55–58. [PubMed: 21277707]

Marcotte TD, Heaton RK, Wolfson T, Taylor MJ, Alhassoon O, Arfaa K, Grant I, & the HNRC Group. (1999). The impact of HIV-related neuropsychological dysfunction on driving behavior. Journal of the International Neuropsychological Society, 5, 579–592. [PubMed: 10645701]

Marcotte TD, Wolfson MA, Rosenthal ME, Heaton RK, Gonzalez MA, & Ellis RJ (2004). A multimodal assessment of driving performance in HIV infection. Neurology, 63, 1417–1422. [PubMed: 15505158]

Meade CS, Conn NA, Skalski LM, & Safren SA (2011). Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. Journal of Behavioral Medicine, 34, 128–138. [PubMed: 20857187]

Meade CS, Hobkirk AL, Towe SL, Chen NK, Bell RP, & Huettel SA (2017). Cocaine dependence modulates the effect of HIV infection on brain activation during intertemporal decision making. Drug and alcohol dependence, 178, 443–451. [PubMed: 28711810]

Meade CS, Towe SL, Skalski LM, & Robertson KR (2015). Independent effects of HIV infection and cocaine dependence on neurocognitive impairment in a community sample living in the southern United States. Drug and Alcohol Dependence, 149, 128–135. [PubMed: 25697913]

Meyer VJ, Rubin LH, Martin E, Weber KM, Cohen MH, Golub ET, ... & Aouizerat BE (2013). HIV and recent illicit drug use interact to affect verbal memory in women. Journal of Acquired Immune Deficiency Syndromes, 63, 67–76. [PubMed: 23392462]

Miller EN, Seines OA, McArthur JC, Satz P, Becker JT, Cohen BA, . . . Visscher B (1990). Neuropsychological performance in HIV-1-infected homosexual men: the multicenter AIDS cohort study (MACS). Neurology, 40, 197–203. [PubMed: 2405289]

Mimiaga MJ, Reisner SL, Grasso C, Crane HM, Safren SA, Kitahata MM, ... & Mayer KH (2013). Substance use among HIV-infected patients engaged in primary care in the United States: findings from the Centers for AIDS Research Network of Integrated Clinical Systems cohort. American journal of public health, 103, 1457–1467. [PubMed: 23763417]

Murji S, Rourke SB, Donders J, Carter SL, Shore D, & Rourke BP (2003). Theoretically derived CVLT subtypes in HIV-1 infection: Internal and external validation. Journal of the International Neuropsychological Society, 9, 1–16. [PubMed: 12570353]

Navia BA, Jordan BD, & Price RW (1986). The AIDS dementia complex: I. Clinical features. Annals of Neurology, 19, 517–524. [PubMed: 3729308]

Nightingale S, Winston A, Letendre S, Michael BD, McArthur JC, Khoo S, & Solomon T (2014). Controversies in HIV-associated neurocognitive disorders. The Lancet Neurology, 13, 1139–1151. [PubMed: 25316020]

Obermeit LC, Morgan EE, Casaletto KB, Grant I, Woods SP, & HIV Neurobehavioral Research Program (HNRP) Group. (2015). Antiretroviral non-adherence is associated with a retrieval profile of deficits in verbal episodic memory. The Clinical Neuropsychologist, 29, 197–213. [PubMed: 25781903]

Oltra-Cucarella J, Pérez-Elvira R, & Duque P (2014). Benefits of deep encoding in Alzheimer's disease. Analysis of performance in a memory task using the Item Specific Deficit Approach. Neurología, 29, 286–293. [PubMed: 24035297]

Peavy G, Jacobs D, Salmon DP, Butters N, Delis DC, Taylor M, . . . Grant I (1994). Verbal memory performance of patients with human immunodeficiency virus infection: Evidence of subcortical dysfunction. Journal of Clinical and Experimental Neuropsychology, 16, 508–523. [PubMed: 7962355]

Reger M, Welsh R, Razani J, Martin DJ, & Boone K (2002). A meta-analysis of the neuropsychological sequelae of HIV infection. Journal of the International Neuropsychological Society, 8, 410–424. [PubMed: 11939699]

Roediger III HL, & Butler AC (2011). The critical role of retrieval practice in long-term retention. Trends in cognitive sciences, 15, 20–27. [PubMed: 20951630]

Sacktor N, Lyles RH, Mcfarlane G, Skolasky RL, Kleeberger C, Becker JT, ... & Mcarthur JC (1999). HIV-1-related neurological disease incidence changes in the era of highly active antiretroviral therapy. Neurology, 52, 252–253.

Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, ... & McArthur JC (2016). HIV-associated neurocognitive disorder—pathogenesis and prospects for treatment. Nature Reviews Neurology, 12, 234. [PubMed: 26965674]

Schiller A, Foley J, Burns W, Sellers AL, & Golden C (2009). Subcortical Profile of Memory Compromise Among HIV-1-Infected Individuals. International Journal of Neuroscience, 119, 1779–1803.

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, 1336–43. [PubMed: 16504221]

Sim ME, Lyoo IK, Streeter CC, Covell J, Sarid-Segal O, Ciraulo DA, … & Renshaw PF (2007). Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology, 32, 2229–2237. [PubMed: 17299505]

Spronk DB, van Wel JH, Ramaekers JG, & Verkes RJ (2013). Characterizing the cognitive effects of cocaine: a comprehensive review. Neuroscience & Biobehavioral Reviews, 37, 1838–1859. [PubMed: 23876288]

Storey JD (2002). A direct approach to false discovery rates. Journal of the Royal Statistical Society: Series B, 64, 479–498.

Sun X, Zhao Y, & Wolf ME (2005). Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons. Journal of Neuroscience, 25, 7342–7351. [PubMed: 16093384]

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality (2014). Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health. Rockville, MD, Substance Abuse and Mental Health Services Administration.

Tashkin DP (2004). Evidence implicating cocaine as a possible risk factor for HIV infection. Journal of Neuroimmunology, 147, 26–27. [PubMed: 14741422]

Torres AG, González-Andrade A, Fernández Muñoz JJ, García MP, & Vergara-Moragues E (2019). Objective memory as an indicator of functional impairment in native Spanish-speaking patients with HIV infection. AIDS care, 1–8.

van Gorp WG, Baerwald JP, Ferrando SJ, McElhiney MC, & Rabkin JG (1999a). The relationship between employment and neuropsychological impairment in HIV infection. Journal of the International Neuropsychological Society, 5, 534–539. [PubMed: 10561934]

van Gorp WG, Wilkins JN, Hinkin CH, Moore LH, Hull J, Horner MD, & Plotkin D (1999b). Declarative and procedural memory functioning in abstinent cocaine abusers. Archives of General Psychiatry, 56, 85–89. [PubMed: 9892260]

Venton BJ, Seipel AT, Phillips PE, Wetsel WC, Gitler D, Greengard P, ... & Wightman RM (2006). Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. Journal of Neuroscience, 26, 3206–3209. [PubMed: 16554471]

Vergara-Moragues E, Verdejo-García A, Lozano OM, Santiago-Ramajo S, González-Saiz F, Espinosa PB, & García MP (2017). Association between executive function and outcome measure of treatment in therapeutic community among cocaine dependent individuals. Journal of substance abuse treatment, 78, 48–55. [PubMed: 28554603]

Viola TW, Niederauer JPO, Kluwe-Schiavon B, Sanvicente-Vieira B, & Grassi-Oliveira R (2019). Cocaine use disorder in females is associated with altered social decision-making: a study with the prisoner's dilemma and the ultimatum game. BMC psychiatry, 19, 211. [PubMed: 31277620]

Volkow ND, Koob GF, & McLellan AT (2016). Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine, 374, 363–371.

Vonmoos M, Hulka LM, Preller KH, Minder F, Baumgartner MR, & Quednow BB (2014). Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. Neuropsychopharmacology, 39, 2200. [PubMed: 24651468]

Waldrop D, Ownby RL, & Kumar M (2004). Serial position effects in HIV+ injecting drug users. International Journal of Neuroscience, 114, 493–516.

White DA, Taylor MJ, Butters N, Mack C, Salmon DP Peavy G, . . . Grant I (1997). Memory for verbal information in individuals with HIV-associated dementia complex. Journal of Clinical and Experimental Neuropsychology, 19, 357–366. [PubMed: 9268810]

Woods SP, Scott JC, Dawson MS, Morgan EE, Carey CL, Heaton RK, . . . HIV Neurobehavioral Research Center (HNRC) Group. (2005). Construct validity of Hopkins Verbal Learning Test-Revised component process measures in an HIV-1 sample. Archives of Clinical Neuropsychology, 20, 1061–71. [PubMed: 16198529]

Wright MJ, Schmitter-Edgecombe M, & Woo E (2010). Verbal memory impairment in severe closed head injury: The role of encoding and consolidation. Journal of clinical and experimental neuropsychology, 32, 728–736. [PubMed: 20175012]

Wright MJ, McArthur DL, Alger JR, Van Horn J, Irimia A, Filippou M, ... & Vespa P (2013). Early metabolic crisis-related brain atrophy and cognition in traumatic brain injury. Brain imaging and behavior, 7, 307–315. [PubMed: 23636971]

Wright MJ, Woo E, Barclay TR, & Hinkin CH (2009a). The functional impact of HIV-associated neuropsychological decline. In Paul R, Sactor N, Tashima K, & Valcour V (Eds.). HIV and the Brain: New Challenges in the Modern Era. (pp. 233–248). New York, NY: Humana Press.

Wright MJ, Woo E, Schmitter-Edgecome M, Hinkin CH, Miller EN, & Gooding AL (2009b). The item-specific deficit approach to evaluating verbal memory dysfunction: Rationale, psychometrics, and application. Journal of Clinical and Experimental Neuropsychology, 31, 790–802. [PubMed: 19142773]

Wright MJ, Woo E, Foley J, Ettenhofer ML, Cottingham ME, Gooding AL, ... Hinkin CH (2011). Antiretroviral Adherence and the Nature of HIV-Associated Verbal Memory Impairment. The Journal of Neuropsychiatry and Clinical Neurosciences, 23, 324–331. [PubMed: 21948894]
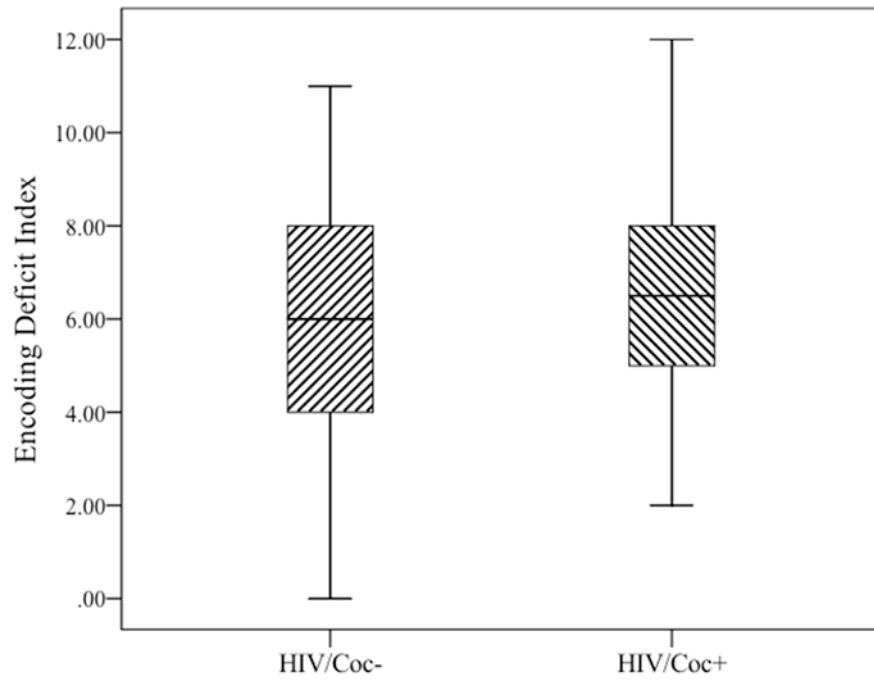
Figure 1.
Item Specific Deficit Approach (ISDA) Encoding Deficit Index for HIV/Coc− (*N*=57) and HIV/Coc+ (*N*=56) groups. Confidence intervals represent +/− one standard error of the mean (SEM).

Table 1

Demographic Characteristics of HIV/Coc– and HIV/Coc+ Groups

Demographic Variable	Group		Test Statistic	Effect size
	HIV/Coc– (N=57) M (SD)	HIV/Coc+ (N=56) M (SD)		
Age	41.98 (7.75)	43.54 (5.91)	$t(111)=-1.20$	$d=.23$
Education (years)	12.93 (1.87)	13.43 (2.09)	$t(111)=-1.34$	$d=.25$
Estimated Verbal IQ	105.02 (8.50)	104.64 (8.14)	$t(110)=.24$	$d=.04$
% Male	75%	79%	$X^2(1,N=113)=.157$	$\emptyset_c=-.04$
% Caucasian	19%	4%	$X^2(1,N=113)=6.862^*$	$\emptyset_c=.25$
CD4 Count	471.61 (294.08)	434.49 (227.30)	$t(107)=.73$	$d=.14$
% AIDS	70%	63%	$X^2(1,N=112)=.541$	$\emptyset_c=-.07$
Major Depression	42%	29%	$X^2(1,N=113)=2.263$	$\emptyset_c=-.14$
Cocaine				
Abuse or Dependence	35%	22%	$X^2(1,N=112)=2.415$	$\emptyset_c=.15$
Duration of Abuse and/or Dependence	248.23 (145.31)	161.85 (150.64)	$t(66)=2.41^*$	$d=.58$
Alcohol				
Abuse or Dependence	46%	41%	$X^2(1,N=113)=.237$	$\emptyset_c=.05$
Duration of Abuse and/or Dependence	225.73 (186.85)	133.10 (209.15)	$t(40)=2.01$	$d=.47$
Stimulants				
Abuse or Dependence	74%	87%	$X^2(1,N=112)=3.274$	$\emptyset_c=-.17$
Positive Toxicology[a]	0%	0.01%	$X^2(1,N=111)=1.065$	$\emptyset_c=.10$
Duration of Abuse and/or Dependence	199.54 (142.01)	59.20 (41.03)	$t(16)=2.14^*$	$d=1.34$
Opiates				
Abuse or Dependence	88%	78%	$X^2(1,N=112)=1.808$	$\emptyset_c=.13$
Positive Toxicology	0%	4%	$X^2(1,N=111)=2.150$	$\emptyset_c=.14$
Duration of Abuse and/or Dependence	379.20 (420.31)	197.50 (267.38)	$t(11)=.96$	$d=.52$
Cannabis				
Abuse or Dependence	58%	51%	$X^2(1,N=112)=.551$	$\emptyset_c=.07$
Positive Toxicology	0%	33%	$X^2(1,N=111)=22.677^{**}$	$\emptyset_c=.45$
Duration of Abuse and/or Dependence	206.57 (176.77)	254.00 (214.76)	$t(18)=-.50$	$d=.24$

Abbreviation key. M (SD)=Mean and standard deviation. HIV/Coc–=HIV infected participants who report no cocaine use for four weeks prior to testing and verified by urine analysis. HIV/Coc+=HIV infected participants reporting cocaine use within four weeks of testing and/or were urine positive for cocaine metabolites; IQ=Intelligence Quotient; CD4= Cluster of Differentiation 4; AIDS=Acquired Immunodeficiency Syndrome

*
$p < .05$

**
$p < .001$

[a]Amphetamines

Table 2

Demographic Characteristics of HIV/CocDx− and HIV/CocDx+ Groups

	Group			
Demographic Variable	**HIV/CocDx− (N=33) M (SD)**	**HIV/CocDx+ (N=80) M (SD)**	**Test Statistic**	**Effect size**
Age	42.76 (7.93)	42.75 (6.50)	$t(111)=.01$	$d=.00$
Education (years)	13.55 (2.21)	13.03 (1.88)	$t(111)=1.27$	$d=.25$
Estimated Verbal IQ	105.36 (8.37)	104.61 (8.29)	$t(110)=.43$	$d=.09$
% Male	85%	73%	$X^2(1,N=113)=1.624$	$\emptyset_c=.12$
% Caucasian	18%	9%	$X^2(1,N=113)=2.041$	$\emptyset_c=.13$
CD4 Count	450.36 (242.16)	454.95 (273.34)	$t(107)=-0.08$	$d=.02$
% AIDS	72%	65%	$X^2(1,N=112)=.702$	$\emptyset_c=-0.08$
Major Depression	33%	36%	$X^2(1,N=112)=.087$	$\emptyset_c=0.03$
Cocaine				
Positive Toxicology	34%	58%	$X^2(1,N=111)=.087$	$\emptyset_c=0.07$
Duration of Abuse and/or Dependence	-	206.31 (153.12)	-	-
Alcohol				
Abuse or Dependence	67%	34%	$X^2(1,N=113)=10.307*$	$\emptyset_c=0.30$
Duration of Abuse and/or Dependence	128.00 (82.68)	208.89 (217.39)	$t(40)=-.89$	$d=.49$
Stimulants				
Abuse or Dependence	88%	78%	$X^2(1,N=112)=1.448$	$\emptyset_c=0.11$
Positive Toxicology[a]	0%	0.01%	$X^2(1,N=111)=.409$	$\emptyset_c=.06$
Duration of Abuse and/or Dependence	172.00 (144.07)	157.29 (140.57)	$t(16)=.18$	$d=.10$
Opiates				
Abuse or Dependence	88%	81%	$X^2(1,N=112)=.634$	$\emptyset_c=0.08$
Positive Toxicology	0%	3%	$X^2(1,N=112)=.825$	$\emptyset_c=0.09$
Duration of Abuse and/or Dependence	156.29 (40.60)	300.80 (373.72)	$t(11)=-.65$	$d=.54$
Cannabis				
Abuse or Dependence	78%	45%	$X^2(1,N=112)=10.113*$	$\emptyset_c=0.08$
Positive Toxicology	9%	19%	$X^2(1,N=112)=1.55$	$\emptyset_c=0.12$
Duration of Abuse and/or Dependence	57.00 (72.12)	257.44 (199.07)	$t(18)=-1.39$	$d=1.34$

Abbreviation key. M (SD)=Mean and standard deviation. HIV/CocDx−=HIV infected participants who did not meet diagnostic criteria for lifetime or current cocaine abuse or dependence. HIV/CocDx+=HIV who did not meet diagnostic criteria for lifetime or current cocaine abuse or dependence; IQ= Intelligence Quotient; CD4=Cluster of Differentiation 4; AIDS=Acquired Immunodeficiency Syndrome

[*]
$p < .005$

[a]Amphetamines

Table 3

Collinearity Between Traditional and ISDA CVLT-II Memory Metrics

	1	2	3	4	5	6	7
1. CVLT-II Total Trials (1-5)	-	.773*	.780*	.697*	−.922*	−.633*	−.309*
2. CVLT-II Short Delay Free Recall		-	.840*	.683*	−.727*	−.740*	−.575*
3. CVLT-II Long Delay Cued Recall			-	.725*	−.727*	−.772*	−.324*
4. CVLT-II Recognition Discriminability (d')				-	−.662*	−.618*	−.208*
5. ISDA Encoding Deficit Index					-	.616*	.288*
6. ISDA Consolidation Deficit Index						-	.002
7. ISDA Retrieval Deficit Index							-

Abbreviation key. ISDA=Item Specific Deficit Approach; CVLT-II=California Verbal Learning Test

* *p* < .01 (two-tailed).