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Contributors to neuropsychological impairment in HIV-infected and HIV-uninfected opiate-dependent patients

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Abstract

Neuropsychological (NP) impairment is multiply determined among HIV-infected and HIV-uninfected individuals who are also dually diagnosed with depression and who use illicit substances. The purpose of the present study was to assess the impact of HIV status, depression, and problematic substance use on NP performance. A total of 160 opiate-dependent outpatients undergoing methadone maintenance (80 HIV-infected, 80 HIV-uninfected) completed diagnostic and NP evaluations. Raw scores from individual NP tests were converted to *Z* scores relative to standard norms and were averaged to form a composite score. HIV-infected participants had significantly lower overall NP performance—as well as lower performance on tests of attention, motor speed, and verbal memory—than HIV-uninfected participants. In multiple regression analyses considering the role of depression and substance use, only HIV status emerged as a significant predictor of NP impairment. These findings confirm NP impairment in HIV-infected substance abusing patients independent of comorbid depression and severity of substance use.

Keywords

HIV; Neuropsychological impairment; Depression; Opiate dependence; Methadone maintenance therapy

INTRODUCTION

The presence of neuropsychological (NP) impairment is detrimental for adults in the general population. It is particularly hazardous for those with chronic illnesses such as HIV, given the potential for such impairments to negatively impact essential activities of daily living, such as self-care behaviors or the utilization of health services. Among HIV-infected adults, NP impairment can result from the cognitive sequelae of HIV, as well as common, often intertwined comorbidities, such as depression and substance abuse.

The introduction of highly active antiretroviral therapy (HAART) in 1996 was met by a decrease in the frequency and severity of neuropsychological complications of HIV (D'Arminio et al., 2004; Deutsch et al., 2001; Ferrando, Gorp, & McElhiney, 1998; Sacktor, 2002; Tozzi et al., 1999). However, less severe NP deficits in the cognitive realms of

attention, concentration, working memory, executive functioning, learning and memory, and psychomotor speed remain common (Cysique, Maruff, & Brew, 2004; Dawes et al., 2008; Dunbar & Brew, 1997; Rausch & Stover, 2001; Reger, Welsh, Razani, Martin, & Bone, 2002; Vazquez-Justo, Alvarez, & Ramos, 2003b; Wojna et al., 2006; Woods et al., 2008; York, Franks, Henry, & Hamilton, 2001). Accordingly, prevalence estimates of mild NP impairment as high as 60% have been reported (e.g., Tozzi et al., 2005). There is also evidence that the likelihood of NP deficits increases with disease progression (i.e., decreases in CD4 cell count and increased potential for opportunistic infections to occur; Antinori et al., 2007; Wilkie et al., 2000).

Depression is also common among HIV-infected adults, with lifetime rates of depressive disorders ranging from 22 to 43% (e.g. Bing et al., 2001; Ciesla & Roberts, 2001; Cysique et al., 2007; Gaynes, Pence, Eron, & Miller, 2008; Jin et al., 2006; Pence, Miller, Whetton, Eron, & Gaynes, 2006; Rabkin et al., 2000).

In the general population, many areas of NP functioning are compromised by depression, including memory, verbal and nonverbal learning, attention, psychomotor speed, and executive functioning (Elderkin-Thompson et al., 2003; Harvey et al., 2004; Moreaud et al., 1996; Otto et al., 1994; Paelecke-Habermann, Pohl, & Leplow, 2005; Seigniny, Everett, & Grondin, 2003; Weiland-Fiedler et al., 2004). Similar areas of functioning are often impacted by depression in HIV-infected adults (e.g., Castellon, Hinkin, Wood, & Yarema, 1998; Corless et al., 2000; Durvasala, Miller, Myers, & Wyatt, 2001; Honn & Bornstein, 2002; Waldrop-Valverde, Ownby, & Kumar, 2005), although these findings are inconsistent across studies (cf., Bornstein et al., 1993; Carter, Rourke, Murji, Shore, & Rourke, 2003; Goggin et al., 1997; Kalechstein, Hinkin, Van Gorp, & Castellon, 1998; Levin, Berger, Didona, & Duncan, 1992; Richardson et al., 1999).

A third, highly prevalent comorbidity in HIV is substance abuse (Applebaum et al., 2009; Bing et al., 2001; Burnam et al., 2001; Gaynes et al., 2008; Norman & Kumar, 2006; Pence et al., 2006; Tucker, Burnam, Sherbourne, Jung, & Gifford, 2003; Turner et al., 2001). Estimates of current substance abuse are as high as 50% (Turner et al., 2001), and those of current and lifetime substance dependence range from 12% to 60% (Becket, Burnam, Collins, Kanouse, & Beckman, 2003; Bing et al., 2001; Kelly et al., 1998; Rabkin, 1996).

HIV-uninfected drug-abusing patients have been found with deficits in executive functioning, attention, verbal ability, memory, psychomotor speed, and impulse control (Fals-Stewart & Bates, 2003; Grant, Contagaggi, & Londong, 2000; Lee & Pau, 2002; Levine et al., 2006). These same areas of functioning are often impaired among HIV-infected drug-abusing patients (e.g., Norman & Kumar, 2006; Vasquez-Justo et al., 2003b; Waldrop-Valverde et al., 2006). The risk of NP impairment appears particularly high among opiate users (Davis, Liddiard, & McMillan, 2002; Starace et al., 1998). Opiates have been found to induce impairments in the areas of attention, information processing, problem solving, coordination, working memory, and psychomotor speed (Davis et al., 2002; Mintzer, Copersino, & Stitzer, 2005). Research also indicates that NP deficits are common among patients engaged in methadone maintenance therapy (Darke, Sims, McDonald, & Wickes, 2000; Davis et al., 2002; Failde Garrido, Lopez Castro, Fernandez Rodriguez, & Fernandez Rodriguez, 2005; Mintzer et al., 2005; Mintzer & Stitzer, 2002; Prosser et al., 2006; Specka et al., 2000; Verdejo, Toribio, Orozco, Puente, & Perez-Garcia, 2005).

Independent of HIV status, the rate of depression in opiate-dependent patients engaged in methadone maintenance therapy is also high. Reported lifetime prevalence rates range from 19 to 74.3%, and current prevalence rates range from 10 to 30% (Brienza et al., 2000; Brooner, King, Kidforf, Schmidt, & Bigelow, 1997; Darke & Ross, 1997; Havard, Teesson,

Darke, & Ross, 2006; Peles, Schreiber, Naumovsky, & Adelson, 2007; Teeson, Baillie, Lynskey, Manor, & Degenhardt, 2005). However, even higher rates have been reported among HIV-infected methadone maintenance patients (e.g., Grella, Anglin, & Annon, 1996; Nemoto, Foster, & Brown, 1991; Turrina et al., 2001).

Studies have also examined the effects of HIV status, depression, and substance abuse on NP functioning (e.g., Avants, Margolin, McMaon, & Kosten, 1997; Durvasula et al., 2001; Grassi et al., 1997; Margolin, Avants, Warbutron, & Hawkins, 2002; Rodriguez Salgado, Rodriguez Alvarez, & Seoane Pesqueira, 2006; Vasquez-Justo, Alvarez, & Otero, 2003a; Vasquez-Justo et al., 2003b; Waldrop-Valverde et al., 2005; Wisniewski et al., 2005, and have highlighted the unique role played by depression (Waldrop-Valverde et al., 2005) and HIV status (Rodriguez Salgado et al., 2006) in the prediction of NP impairment. However, to our knowledge, none of these studies examined the unique contribution of each of these variables to NP functioning in a sample of opiate-dependent patients engaged in methadone therapy. The present study therefore allows us to better understand which of these factors have unique versus redundant prediction of NP functioning by examining them in a cohort with variable loadings on these risk factors.

METHOD

Design overview

To provide the relevant comparisons to best identify the independent contributions of HIV status, depression, and substance use to NP impairment, the following design was selected. The primary selection criterion was HIV status (infected or uninfected) within an opiate-dependent population of adults who were in treatment with methadone maintenance. In both groups, approximately one third of participants were nondepressed according to the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* (American Psychiatric Association, 1994) criteria (65% of HIV-infected and 70% of HIV-uninfected participants met criteria for a major depressive disorder, single episode, recurrent, or chronic). Additionally, the HIV-infected group was selected to be matched according to age and gender, such that neither of these variables was outside the 95% confidence interval for the HIV-uninfected group. Participants were expected to exhibit varying levels of substance abuse, outside of opiates. This design allowed for the assessment of the hypothesis that depression, substance use, and HIV status are each negatively associated with, and offer nonredundant prediction of, levels of NP performance in this cohort of patients. All participants were given an identical battery of tests that assessed current depression and substance abuse, as well as NP impairment, as defined by an average *Z* score of NP test performance (NPZ score; see below for description).

Participants were 80 HIV-uninfected and 80 HIV-infected opiate-dependent patients undergoing methadone maintenance. The HIV-infected participants were drawn from an ongoing National Institute on Drug Abuse (NIDA)-funded project investigating cognitive behavior therapy for enhancing medication adherence and treating depression in individuals with HIV (NIDA RO1 DA 214120). The 80 HIV-uninfected individuals were recruited from the same methadone treatment centers as those for the HIV study. Both groups (HIV-infected and HIV-uninfected) completed identical assessment protocols and together formed comparison groups for understanding the association between HIV status and the outcomes of interest. The assessment protocol completed by all participants represented the baseline assessment of the parent study's design.

Inclusion criteria for the HIV-infected group were: (a) being HIV seropositive and taking HIV antiretroviral medication; (b) current enrollment in a methadone maintenance program; and (c) between the ages of 18 and 65 years. Inclusion criteria for the HIV-uninfected group

were: (a) being HIV seronegative (by self-report); (b) current enrollment in a methadone maintenance program; and (c) between the ages of 18 and 65 years. Participants were excluded from both the study samples if they were currently in cognitive behavior therapy (CBT) for depression, had such severe mental illness that required immediate treatment (i.e., active psychotic episode), or were unwilling to consent. Patients with no depression—or no history of depression—were also excluded.

Recruitment

As in the existing parent study, participants for the cohort of HIV-uninfected individuals were recruited through clinicians and advertisements at methadone treatment clinics where patients receive daily methadone treatment. Each participant was invited to participate when they met with their counselor or other provider at the clinic. If a clinic staff member invited an individual to participate, and he or she agreed, the participant completed an information card with his or her name and contact information on it for the clinical assessor to contact him or her. A detailed informed consent process occurred, including signing a consent form by each participant following the explanation by the clinical assessor. The procedures were approved by the institutional review board at relevant institutions.

Materials

Clinician-administered psychological assessments

Diagnostic evaluation: The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) is a short structured diagnostic interview with acceptable test–retest and interrater reliability (Sheehan et al., 1998), and reliability and validity estimates that are comparable to the Structured Clinical Interview for DSM–IV (SCID–IV; Sheehan et al., 1998; Sheehan et al., 1997). The MINI was used to assess current and lifetime alcohol use, anxiety disorders, mood disorders, and psychosis for screening and diagnostic purposes.

Rating of depression: The Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) is a clinician-rated assessment of 10 commonly occurring symptoms of depression experienced over the past week and is a widely used and valid instrument. The MADRS appears to be a relatively unidimensional scale oriented more towards the psychic, as opposed to somatic, aspects of depression (Galinowski & Lehert, 1995). Scores on the MADRS range from 0 to 60, with scores between 0 and 6 indicating no depression, scores between 7 and 19 indicating mild depression, scores between 20 and 34 indicating moderate depression, and scores between 35 and 60 indicating severe depression (Mittmann et al., 1997; Muller, Himmerich, Kienzle, & Szegedi, 2003; Muller, Szegedi, Wetzel, & Benkert, 2000; Zimmerman, Posternak, & Chelminski, 2004).

Rating of drug and alcohol use: The Addictions Severity Index–Lite (ASI-Lite; McLellan et al., 1992) measures the severity of problems in seven areas of functioning that are frequently affected in patients with substance use disorders. The ASI-Lite was used to determine the number of days of drug use. For the present study, the number of days of use of substances (excluding alcohol) over the past month and the number of days of use of alcohol over the past month were used as indicators of substance abuse (hereafter labeled *drug use* and *alcohol use*). Since participants may have used more than one substance over the past month, the variable indicating the days of drug use over the past month reflected the sum of all days of use of any illicit substances and was therefore not limited to 30. We selected this measurement strategy to try to capture the total impact of the variety of substances used by patients during this time period.

Demographic questionnaire: This self-report measure included questions about age, gender, sexual orientation, race/ethnicity, educational attainment, and employment status.

Neuropsychological assessments—Participants completed several neuropsychological tasks designed to assess estimated verbal intelligence, processing speed, organization and planning, working memory, episodic (verbal) learning and memory, and visuospatial constructional ability.

Wechsler Test of Adult Reading (WTAR; Wechsler, 2001a, 2001b): The WTAR is a reading test consisting of 50 words that were presented visually, and participants were asked to correctly pronounce them out loud. The words included on this test have atypical grapheme to phoneme translations (i.e., again, cough, aisle). The WTAR was used to estimate verbal intelligence, and it has a large national normative sample (Wechsler, 2001b) against which participants' performance was evaluated and excellent clinical validity. The target variable was the number of words pronounced accurately.

Hopkins Verbal Learning Test–Revised (HVLT–R; Brandt & Benedict, 2001): This test measured episodic memory and gave information about how well participants were able to remember new information and whether they used organizational strategies in order to facilitate recall. The HVLT–R is a valid screening test for dementia and has demonstrated high degrees of diagnostic reliability and validity in HIV-infected adults (Carey et al., 2004; Woods et al., 2005). Norms from Brandt and Benedict (2001) were used to evaluate the sample's performance. Participants were read a list of 12 words, after which they were asked to recall as many of the words as they could, across three separate trials. Participants were also asked to give a delayed recall of these words after 20 minutes. The HVLT–R has high test–retest reliability, a large normative sample, and excellent construct, concurrent, and discriminant validity. Here, the target variables were total recall across learning trials (the total number correct over Trials 1–3: immediate recall) and delayed recall (Trial 4).

Trails A, B (Lezak, 1995): Trails A and B are sensitive to a variety of disorders, including HIV infection (Di Sclafani et al., 1997), substance use (McCaffrey, Krahula, Heimberg, Keller, & Purcell, 1988; Miller, 1985), and engagement in methadone maintenance therapy (Mintzer & Stitzer, 2002). Normative data from Tombaugh (2004) were used to evaluate participants' performance. Trails A is an assessment of motor speed, visual scanning, and visual–motor integration, and it required participants to connect a series of 25 numbered circles in numeric order as quickly and as accurately as possible. Trails B is an assessment of cognitive flexibility, attention, and planning, as well as visual scanning and motor speed. Trails B is similar to Trails A, but the circles contain both letters and numbers. Participants were asked connect the circles in sequence as quickly as possible, alternating between numbers and letters (i.e., 1–A–2–B–3–C, etc). The target variables were time to completion on Trails A and Trails B.

Symbol Digit Modalities Test (SDMT; Smith, 1991): This test was used to assess divided attention, visual scanning, tracking, and motor speed and is sensitive to a number of psychological and neurological conditions, including HIV (Sacktor et al., 1999, 2005). Normative data from Smith (1991) were used to evaluate participants' performance. Participants were asked to pair specific numbers with specific symbols, using a reference key. The target variable was the number of correct pairings over a 90-second interval.

Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1983): This test (FAS and category versions) is a measure of verbal fluency and involved having participants rapidly retrieve and verbally report exemplars of specific phonemic and

semantic categories (i.e., words starting with the letters F, A, and S, and animals) from memory over 60-second periods. The COWAT has been found to be a reliable and valid test of executive cognitive functions (Lezak, 1995; Spreen & Strauss, 1998). Normative data from Tombaugh, Kozak, and Rees (1999) were used to evaluate participants' performance. Two variables were obtained from this instrument including the total number of words reported across the F, A, and S categories and the total number of words reported in the animal category.

Key Complex Figure Test (RCFT, Copy trial; Meyers & Meyers, 1995): This assessment of visuospatial constructional ability required participants to copy a target figure that was presented in a standardized manner, without time constraints. Accuracy and organization of reproduction comprised the scoring of 18 distinct figural elements. The RCFT has published norms (Lezak, Howieson, & Loring, 2004), which were used to evaluate participants' performance, and excellent clinical validity (Knight, Kaplan, & Ireland, 2003). The total score was the target variable.

Calculation of the NPZ score—Neuropsychological (NP) functioning was assessed using the HVLt-R, Trails A and B, SDMT, COWAT (FAS and category subtests), and RCFT. Using the external norms cited above, the results of each of the neuropsychological tests were converted to *Z* scores, which were then averaged to form an overall neuropsychological *Z* score (NPZ), or estimate of NP functioning, for each participant. These external norms were adjusted for participants' age on all of the NP tests and for education on the SDMT, Trails A/B, and HVLt. This method of using NPZ scores as an indicator of overall NP functioning is commonly used in the HIV literature (e.g., Brew et al., 2007; Evans et al., 2007; Marra et al., 2003; Paul et al., 2007; Schiffito et al., 2007; Sidtis et al., 1993).

Statistical analyses—Descriptive statistics for the demographic characteristics and for the major study variables were first reviewed. Next, independent samples *t* tests were used to assess for differences in depression (total MADRS), substance use (total days of alcohol use over the past month, and the total days of all non-alcohol substance use over the past month), and NP performance (NPZ score and individual NP tests) between HIV-infected and HIV-uninfected participants. In order to examine the impact of HIV, depression, and substance use on NP performance, three separate regression analyses were conducted in which age, education, gender, and WTAR scores were entered in the first block, and the variables of interest—HIV, depression, and drug and alcohol use—were added in the second block in separate regression equations, with NPZ scores serving as the outcome variable. Separate regressions were completed to examine the independent prediction afforded by these variables; such independent prediction is appropriate for comparison to previous studies that did not evaluate all of these potential predictors in the context of each other. Nonetheless, to control for inflations in alpha, and to examine redundancies in prediction, we subsequently examined these variables in a single stepwise regression analysis.

Procedure

Once a patient was referred to the study, an initial screening was conducted over the telephone. If the participant appeared to be eligible and was interested, he or she was scheduled for a study visit. At the study visit, the participant first completed informed consent procedures. The clinical assessor then conducted a diagnostic assessment using the MINI, MADRS, and ASI-Lite and administered the NP battery. Participants also completed the self-report psychosocial assessment battery.

Assessment procedures took approximately three hours to complete, and participants were compensated \$75 in cash for the entire study visit.

RESULTS

Sample demographics

Participants included 80 HIV-uninfected and 80 HIV-infected adults. Of the 160 participants, 47% were male. A total of 79% of the entire sample self-identified as non-Hispanic/Latino. Additionally, 25% identified as African American, 56% as White, 2.5% as Native American, 1.3% as Asian, and fewer than 1% as Native Hawaiian/Pacific Islander, and 14.3% reported that they did not identify with any of these ethnic categories. A total of 79% of the sample identified as exclusively heterosexual, about 3% as exclusively homosexual, and about 4% as bisexual, and 14% reported identifying primarily as heterosexual or homosexual, but having had some experience with same- or opposite-sex partners. The mean age of the overall sample was 42.7 ($SD = 8.92$) years, and the mean numbers of years of education was 11.7 ($SD = 3.60$).

Demographic characteristics, according to HIV status, are presented in Table 1. There were no significant differences between groups on gender, age, ethnicity, and years of education.

Additionally, there were no significant differences between groups in potential premorbid verbal intellectual capacity, as indicated by scores on the WTAR.

All of the HIV-infected participants were taking antiretroviral medications at the time of their assessment. The mean CD4+ cell count and viral load for these participants was 384.60 and 4,311.95, respectively.

Description of major study variables

Depression: Mean MADRS scores for HIV-infected and uninfected participants were 23.6 and 17.9, respectively, which fall into the moderate and mild range of depressive symptom levels per the guidelines for this measure (Montgomery & Asberg, 1979). These scores were significantly higher for HIV-infected, $t(158) = 3.67$, $p < .001$, than for HIV-uninfected participants. However, there were no significant differences in the proportion of individuals who met diagnostic criteria for current major depression as assessed by the MINI (65% of HIV-infected, 70% of HIV-uninfected, Fisher's Exact Test, $p = .864$).

Substance use: HIV-infected participants used alcohol, on average, 1.7 days over the past month, compared to 0.6 days over the past month for HIV-uninfected participants. Although this difference did not reach statistical significance, there was a trend indicating that HIV-infected participants used alcohol more frequently over the past month, $t(193) = 4.41$, $p = .056$, than HIV-uninfected participants. There was also no significant difference in illicit drug use between groups; HIV-infected and HIV-uninfected participants used illicit substances an average of 16.9 and 20.5 days over the past month, respectively. Additionally, 77% of participants reported the use of at least one substance each day over the past month, and 68% reported the use of two or more substances of any kind (in addition to methadone). There was no significant difference in the proportion of HIV-infected and HIV-uninfected participants who used one or more substances (of any kind) over the past month.

NP performance: Overall NP performance, as indicated by the NPZ score, was poor among the entire sample of opiate-dependent outpatients. Compared to general population norms, participants performed well below expected levels; the average NPZ score for all participants was 1.61 standard deviation units below the mean relative to external norms,

$t(159) = -17.86, p < .001$, and indicated that approximately 95% of the sample scored below the mean level expected for the general population. The average NPZ score for HIV-infected and HIV-uninfected participants was -1.87 and -1.36 , respectively.

Table 2 presents descriptive statistics for the NP tests. HIV-infected participants generally performed below average relative to these norms for all NP tests; as a group, HIV-uninfected participants performed below average relative to these norms for all except the SDMT. Performance among HIV-infected participants was strongest on the COWAT Category and Trails A tests and poorest on the Trails B test. Among HIV-uninfected participants, performance was strongest on the SDMT and Trails A tests and (similar to the HIV-infected group) poorest on the RCFT and HVLt.

Independent samples t tests were conducted to assess for differences in performance across NP tests between HIV-infected and HIV-uninfected participants. HIV-infected participants performed significantly worse than their uninfected counterparts on Trails B, $t(158) = -4.12, p < .001$, the SDMT, $t(158) = -6.13, p < .001$, and the HVLt (total score), $t(158) = -2.10, p < .05$, and had lower NPZ scores than HIV-uninfected participants, $t(158) = -2.87, p < .01$.

Contributors to NP performance—In order to examine the potential impact of depression, drug and alcohol use, and HIV status on NP performance, three separate regression analyses were conducted in which age, education, gender, and WTAR scores were entered in the first block, and the variables of interest—HIV, depression (total MADRS), total days of drug use, and total days of alcohol use—were added in the second block in separate regression equations, with NPZ scores serving as the outcome variable. Of these regression analyses, only the analysis with HIV status as a predictor of NPZ scores (Table 3) emerged as significant on the second block, with the linear combination of the predictors accounting for 23.3% of the variance in NPZ scores, $R^2 = .233, F(5, 152) = 9.25, p < .001$, and HIV status contributing a significant change in prediction (2.7%). When this regression was re-examined without the WTAR (in order to evaluate the model without the potential confounding influence of the shared variance between NPZ and WTAR scores), HIV status remained a significant predictor of NPZ scores, $R^2 = .074, F(4, 153) = 3.06, p < .05$. None of the other results were altered when the remaining two models were re-run without the WTAR. Finally, a stepwise regression equation was examined, which included all of the variables of interest. The results of this analysis confirmed that only HIV status served as a significant predictor of NPZ scores, $R^2 = .224, F(2, 155) = 22.42, p < .001$.

DISCUSSION

This study was one of the first to examine the independent contributions of HIV, depression, and substance use to NP impairment in a sample of patients engaged in methadone maintenance therapy. Among these variables, we found that only HIV status was a significant predictor of NP functioning, and it uniquely accounted for approximately 3% of the variance in NPZ scores.

It was surprising that neither depression nor drug or alcohol use emerged as significant predictors of NPZ scores. Previous studies have found an association between depression and NP performance (e.g., Castellon et al., 1998; Weiland-Fiedler et al., 2004), and at least one study (i.e., Waldrop-Valverde et al., 2005) identified depression as a more significant predictor of NP functioning than HIV status. However, a number of studies have not shown a significant relationship between depression and NP functioning in the context of HIV (e.g., Carter et al., 2003; Kalechstein et al., 1998; Richardson et al., 1999). Hence, as assessed across studies, depression appears to be an inconsistent predictor of NP functioning within drug-abusing and HIV samples. Our own assessment of the significance of depression as a

predictor may have been further weakened by the rate of depressive symptoms in the sample; close to 90% of the entire sample demonstrated mild depressive symptoms on the MADRS, limiting the variance available for prediction.

Studies have also demonstrated an association between substance use and NP functioning (e.g., Abdelwahab, Shaheen, & Nasr, 2004; Davis et al., 2002; Mintzer, & Stitzer, 2002; Nixon, Paul, & Phillips, 1998; Norman & Kumar, 2006; Prosser et al., 2006). We did not replicate that finding. Additionally, 77% of the sample had used at least one substance (aside from methadone) each day over the past month. Accordingly, like depression scores, our attempts to partition the relative influence of substance use on the prediction of NPZ scores was challenged by the low rate of substance-free individuals. Nonetheless, our data did support a significant role for HIV status in predicting overall neuropsychological functioning, even against the backdrop of other impairing factors such as chronic and ongoing drug abuse and depression.

Overall NP performance was poor among the entire sample; across tests 95% of the entire sample performed well below expected levels compared to general population norms. We expected participants to demonstrate NP impairments, as such deficits have been shown to be prevalent among substance-abusing patients (e.g., Fals-Stewart & Bates, 2003; Grant et al., 2000; Lee & Pau, 2002; Levine et al., 2006; Norman & Kumar, 2006) and patients engaged in methadone maintenance therapy (e.g., Darke et al., 2000; Davis et al., 2002; Failde Garrido et al., 2005; Loeber, Kniest, Diehl, Mann, & Croissant, 2008; Mintzer et al., 2005; Mintzer & Stitzer, 2002; Prosser et al., 2006; Soyka et al., 2008; Specka et al., 2000; Verdejo et al., 2005), regardless of HIV status.

HIV-infected participants had lower overall NP performance (as indicated by the NPZ score) than HIV-uninfected participants. Additionally, HIV-infected participants performed significantly worse on tests of executive functioning (Trails B), visual attention (SDMT), and verbal learning (HVLt total score). These results are in accord with previous studies that have indicated that NP deficits are common among HIV-infected adults (e.g., Lawrence & Major, 2002; Norman & Kumar, 2006; Reger et al., 2002; Rodriguez Salgado et al., 2006; Wojna et al., 2006), and that deficits are often found in the areas of attention, learning and memory, and executive functioning (Chang et al., 2001; Delis et al., 1995; Dunbar & Brew, 1997; Martin et al., 1992; Reger et al., 2002; Sorenson, Martin, & Robertson, 1994).

Several limitations of this study should be noted. It is possible that this sample's poor overall performance may in part reflect the timing of the assessments. Many of NP evaluations occurred soon after patients had taken their daily dose of methadone and may therefore have been negatively impacted by the medication's immediate side effects (e.g., impairment in attention and concentration; Soyka et al., 2008). Data describing the timing of methadone dosing and study assessment would have allowed us to have a clearer sense of the role played by methadone in participants' NP presentation. Likewise, more detailed information on individual patterns and types of substances used may have led to greater prediction of NP presentations.

It is also possible that the NPZ score may have provided a biased indication of overall NP functioning in this sample. The NPZ was calculated by taking the average of the *Z* scores on all of the NP tests (excluding the WTAR), a method that has been commonly used to assess overall NP functioning (e.g., Brew et al., 2007; Marra et al., 2003; Paul et al., 2007). As an average, however, the NPZ is strongly affected by extreme scores on individual tests (i.e., particularly high or low *Z* scores). Subsequently, a participant could potentially perform in the average range on most tests and—due to very poor performance on a single measure—obtain a low NPZ score. In this case, this NPZ score would be an underestimation of the

participant's overall impairment, as opposed to an indicator of generally average performance with a relative weakness in one area of functioning. Indeed, upon reinspection of the data, it was evident that for many participants, extremely poor performance on several of the NP tests may have negatively impacted their NPZ scores. Assessment of both general performance and domain-specific importance thus appears important for future research.

Finally, the composition of the study sample may have limited our ability to examine HIV, depression, and substance use as independent predictors of NP functioning. As noted in the Method section, participants with no current or historical experience of significant depression were excluded from the study sample, and, as a result, 90% of the sample currently demonstrated at least mild depressive symptoms according to the MADRS. Additionally, all participants were active patients at methadone maintenance treatment centers, and 77% of participants were concurrently using at least one substance other than methadone at the time of testing. Therefore, our ability to examine the unique influence of each of these variables on NP functioning was challenged by the high rate of comorbid depression and substance use in this sample. However, high rates of depression and substance use are common among people engaged in methadone maintenance therapy; hence, our results are beneficial for understanding the functioning of this population.

To our knowledge, this is the largest investigation of the unique contribution of HIV, depression, and substance use to NP impairment among a sample of opiate-dependent patients enrolled in methadone therapy. The results of this study add to the already robust body of literature that documents NP impairment among HIV-infected adults. Here, HIV-infected participants demonstrated greater overall NP impairment and deficits in attention, executive functioning, and verbal memory than did HIV-uninfected participants. HIV status also accounted for a significant amount of variance in overall NP performance in this sample.

NP impairment—particularly among adults triply diagnosed with HIV, depression, and a substance use disorder—is multiply determined, and therefore additional studies are needed in order to gain a clearer sense of the contribution of each of these variables to NP functioning. Such studies will help with the development of more effective psychosocial interventions tailored towards the particular needs of this vulnerable population.

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TABLE 1

Sociodemographic characteristics of respondents, according to HIV status

Variable	<u>HIV-infected (N = 80)</u>		<u>HIV-uninfected (N = 80)</u>	
	N	%	N	%
Gender				
Female	42	52.5	43	53.8
Hispanic/Non-Hispanic				
Non-Hispanic/Latino	54	67.5	72	90.0
Ethnicity				
African American/Black	19	23.8	21	26.3
White	41	51.2	49	61.2
Asian	2	2.5	0	0.0
Native Hawaiian/Pacific Islander	1	1.3	0	0.0
Native American	2	2.5	2	2.5
Other	15	18.7	8	10.0
Sexual orientation				
Exclusively heterosexual	58	72.5	68	85.0
Bisexual	4	5.0	3	3.8
Exclusively homosexual	2	2.5	3	3.8
Other	16	20.0	6	7.4
Religion				
Catholic	45	56.2	41	51.2
Protestant	10	12.5	15	18.7
Jewish	1	1.3	1	1.3
Other	24	30.0	23	28.8
Relationship status				
Married/Living with	26	32.5	32	40.0
Noncohabitating relationship	6	7.5	7	8.7
Single	33	41.3	32	40.0
Divorced/separated	8	10.0	6	7.5
Loss of long-term partner	7	8.7	3	3.8
Employment				
Full-time work/school	2	2.5	3	3.8
Part-time work/school	6	7.5	11	13.7
Neither work nor school	21	26.3	25	31.2
On disability allowance	47	58.7	32	40.0
Other	4	5.0	9	11.3
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (years)	43.96	6.18	41.36	10.89
Years of education	11.15	2.35	12.16	4.48

Note. Living with = living with someone as if married.

TABLE 2

Descriptive statistics for NP tests

	HIV-infected Mean (SD)	Test	HIV-uninfected Mean (SD)	Test
WTAR	-0.90 (0.99)	$t(79) = -8.08^*$	-0.71 (0.99)	$t(79) = -6.36^*$
Trails A	-0.79 (2.12)	$t(79) = -3.34^*$	-0.49 (1.41)	$t(79) = -3.08^*$
Trails B	-3.07 (3.68)	$t(79) = -7.45^*$	-1.18 (1.81)	$t(79) = -5.83^*$
SDMT	-1.55 (1.17)	$t(79) = -11.82^*$	-0.22 (1.55)	$t(79) = -1.27$
HVLT Total	-2.27 (1.45)	$t(79) = -14.01^*$	-1.80 (1.37)	$t(79) = -11.77^*$
HVLT Delayed	-2.44 (1.64)	$t(79) = -13.28^*$	-2.24 (1.62)	$t(79) = -12.39^*$
COWAT FAS	-1.26 (.99)	$t(79) = -11.42^*$	-1.15 (0.90)	$t(79) = -11.40^*$
COWAT Category	-0.77 (2.12)	$t(79) = -3.24^*$	-1.07 (0.70)	$t(79) = -13.55^*$
Rey Copy Total	-2.80 (2.74)	$t(79) = -9.13^*$	-2.75 (2.50)	$t(79) = -9.84^*$
NPZ	-1.87 (1.23)	$t(79) = -13.56^*$	-1.36 (0.99)	$t(79) = -12.28^*$

Note. Z scores. NP = neuropsychological. WTAR (Wechsler Test of Adult Reading), SDMT (Symbol Digit Modalities Test), HVLT (Hopkins Verbal Learning Test), COWAT (Controlled Oral Word Association Test), NPZ (neuropsychological Z score).

* Significant at $p < .01$ according to single sample t tests.

TABLE 3

The contribution of HIV status to NPZ score

Regression variable	R ²	R ² Δ	F	p value	B	Beta
Block 1	.206	.206**	9.93	.000		
Age					-.01	-.09
Education					.01	.04
Gender					.19	.09
WTAR					.49	.44**
Block 2	.233	.027*	9.25	.000		
Age					.01	-.06
Education					.01	.02
Gender					.17	.06
WTAR					.48	.43**
HIV status					-.38	-.17*

Note. WTAR (Wechsler Test of Adult Reading), NPZ (neuropsychological Z score).

* Significant at $p < .05$.
** Significant at $p < .01$.