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Independent effects of HIV infection and cocaine dependence on neurocognitive impairment in a community sample living in the southern United States

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ABSTRACT

Background: Prior studies have established that methamphetamine and HIV can have additive deleterious effects on neurocognitive functioning, but there has been relatively little research on other stimulants like cocaine. This study investigated the effects of cocaine and HIV on neurocognitive impairment in a large, well-characterized sample.
Methods: The sample included 193 adults across four groups: HIV-positive cocaine users ($n = 48$), HIV-negative cocaine users ($n = 53$), HIV-positive non-drug users ($n = 60$), and HIV-negative non-drug users ($n = 32$). Cocaine users met criteria for lifetime dependence and had past-month cocaine use. A comprehensive battery assessed substance abuse and neurocognitive functioning.
Results: Participants were mostly male (66%) and African-American (85%), with a mean age of 46.09 years. The rate of global impairment was 33%, with no significant main effects across groups on likelihood of impairment. There were main effects for cocaine on processing speed and executive functioning, with cocaine users having greater impairment ($F = 9.33$ and $F = 4.22$, respectively), and for HIV on attention, with HIV-infected persons having greater impairment ($F = 5.55$). There was an interaction effect for executive functioning, with the three patient groups having greater impairment than controls ($F = 5.05$). Nonparametric analyses revealed significant additive impairment in the presence of both HIV and cocaine for processing speed.
Conclusions: While cocaine does not appear to increase vulnerability to global HIV-associated neurocognitive impairment, it does have independent adverse effects on executive functioning and processing speed. Given prior evidence that domain-specific deficits predict real-world impairments, our results may help explain the poorer behavioral and functional outcomes observed in HIV-infected cocaine users.

1. Introduction

Drug abuse, particularly the use of stimulants such as cocaine and methamphetamine, is disproportionately prevalent in HIV-infected persons (Bing et al., 2001; Garin Escriva et al., 2014; Mimiaga et al., 2013; Pence et al., 2008; Siconolfi et al., 2013). In a recent study of >3000 patients receiving HIV care in four United States (US) cities, 9.0% used amphetamines and 8.5% used crack-cocaine in the past 3 months (Mimiaga et al., 2013). In the only nationally representative sample of adults receiving HIV care in the US, approximately half reported illicit drug use in the past year, and a quarter of these drug users met criteria for current dependence (Bing et al., 2001). In the South, where nearly half of new HIV infections are occurring (Reif et al., 2013), cocaine remains the greatest drug burden, with its societal impact exceeding that of any other region (US Department of Justice, 2011).

Within days of infection, HIV can infiltrate the central nervous system, causing direct and indirect damage to brain structure and functioning (Valcour et al., 2011). If untreated, HIV patients may experience severe cognitive impairments, including dementia (Sacktor, 2002). Since the introduction of antiretroviral therapy (ART), milder cognitive disorders are more common (Antinori

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et al., 2007; Brew and Gonzalez-Scarano, 2007). The CHARTER study, a large multi-site study in the US that enrolled >1500 persons between 2003 and 2007, reported a 52% prevalence of HIV-associated neurocognitive impairment, most prominently in learning, memory, attention, and executive functioning (Heaton et al., 2010, 2011). Neurocognitive impairment is most prevalent among patients with advanced HIV disease, including low nadir CD4 cell count, but high rates of mild impairment are present at all stages of HIV infection (Dawes et al., 2008; Heaton et al., 2010). HIV-associated neurocognitive impairment is of concern because it is associated with real-world impairments, including poorer medication adherence, declines in social and occupational functioning, and difficulty with instrumental activities of daily living (Doyle et al., 2013; Foley et al., 2013; Heaton et al., 2004a; Lovejoy and Suhr, 2009; Rabkin et al., 2004; Scott et al., 2011), which may be exacerbated by drug abuse (Meade et al., 2011; Morgan et al., 2014).

Addiction is a brain disease that disrupts neural circuitry, with reduced frontal activation in response to non-drug stimuli and altered dopaminergic transmission in limbic regions, especially the nucleus accumbens and ventral tegmental areas (Feltenstein and See, 2008; Nestler, 2005; Volkow et al., 2004). A recent meta-analysis concluded that cocaine users perform worse than controls on a range of neuropsychological tests, particularly sustained attention, memory, response inhibition, reward-based decision making, and psychomotor performance (Spronk et al., 2013). Similarly, a meta-analysis focused on methamphetamine reported poorer performance in memory, executive functioning, processing speed, motor skills, and attention (Scott et al., 2007). However, a subsequent critical review argues that modest differences have been over-interpreted, since most methamphetamine users perform within the normal range (Hart et al., 2012).

A small body of research has examined the potential additive effects of stimulant abuse and HIV infection on neurocognitive functioning. Much of this work, originating from the Western US, has focused on methamphetamine due to its relatively high prevalence in that region. Using a case-control design, one study found that HIV and methamphetamine had additive effects on rates of global neurocognitive impairment: 58% among HIV-positive methamphetamine users, 40% among HIV-negative methamphetamine users, 38% among HIV-positive non-drug users, and 18% among HIV-negative non-drug users (Rippeth et al., 2004). Subsequent studies also suggest that methamphetamine and HIV may have additive effects on neurocognitive impairment (Carey et al., 2006; Chang et al., 2005; Marquine et al., 2014).

While both cocaine and methamphetamine have neurotoxic effects, these stimulants appear to affect the brain differently (Simon et al., 2001; Winhusen et al., 2013), underscoring the importance of examining drug-specific effects. There has been relatively less research on the effects of cocaine on HIV-associated neurocognitive impairment. One study of HIV-infected adults found that current cocaine dependence was associated with poorer verbal memory and visuospatial construction (Meade et al., 2011). In a more recent analysis from the Women's Interagency HIV Study, frequency of crack-cocaine use was associated with poorer learning and memory in HIV-positive but not HIV-negative women (Meyer et al., 2013). Neurobiological studies support the hypothesis that cocaine use exacerbates HIV-associated neurocognitive impairment. At the cellular and molecular levels, cocaine exposure and HIV infection produce neuronal injury via overlapping mechanisms, including increased oxidative stress, induction of inflammatory cytokines, and greater permeability of the blood–brain-barrier (for a review, see Buch et al., 2012). Taken together, this research suggests that HIV-infected persons may be more vulnerable to cocaine-related neurocognitive impairment, but case-control designs with human subjects are needed to establish independent effects of cocaine and HIV.

While the CHARTER study concluded that substance abuse does not affect HIV-associated neurocognitive impairment, substance use risk was defined as meeting lifetime diagnostic criteria for a substance use disorder, self-report of marked lifetime substance use (≥5 lifetime uses), or a positive urine toxicology screen (Byrd et al., 2011). Since the sample included infrequent and past users, their findings may underestimate neurocognitive impairment in active drug users. Additionally, substance use risk was collapsed across categories of substances (Byrd et al., 2011). To fully understand the effects of drug use on neurocognitive impairment, studies must define clear criteria for recency, frequency, and quantity of use, including careful assessment at the time of the neuropsychological testing, and consider the potential differential effects of varying classes of substances.

This is the first case-control study to investigate whether HIV infection and cocaine dependence have additive effects on neurocognitive impairment. It was hypothesized that individuals with co-occurring HIV infection and cocaine dependence would have the highest rates of global impairment. Specifically, we expected additive effects in the domains of memory and executive functioning. A comprehensive substance use assessment ensured that our cocaine groups met diagnostic criteria for lifetime dependence and were currently using the drug, while our comparison group had no history of regular cocaine abuse. Moreover, we carefully controlled for confounding conditions (e.g., head trauma, other drug abuse, serious mental illness) that could bias results.

2. Methods

2.1. Participants

The sample included 193 adults across four groups: HIV-positive cocaine users (HIV+/COC+, $n=48$), HIV-negative cocaine users (HIV−/COC+, $n=53$), HIV-positive non-drug users (HIV+/COC−, $n=60$), and HIV-negative non-drug (HIV−/COC−, $n=32$). For individuals with documented HIV infection, HIV status was verified by medical record review. For others, an OraQuick© rapid HIV test was conducted; everyone who was screened tested negative. The COC+ groups had to meet the following three criteria: (1) ≥4 days of cocaine use in the past month or a positive urine drug screen for cocaine, (2) ≥1 year of regular cocaine use, and (3) lifetime cocaine dependence. The COC− groups had to meet the following five criteria: (1) no lifetime cocaine use disorder, (2) no history of regular cocaine use, (3) 0 days of cocaine use in the past year, (4) a cocaine negative drug screen, and (5) no current alcohol or marijuana dependence. In all groups, alcohol, marijuana, and nicotine use were permitted. For the COC+ groups, current alcohol and marijuana dependence were permitted if cocaine dependence was the principal diagnosis. For other drugs, individuals in all groups were excluded for lifetime abuse or dependence, history of regular use, any use in the past year, and/or a positive drug screen. Additional exclusion criteria were: English non-fluency or illiteracy; <9th grade education; documented severe learning disability with functional impairment; serious neurological disorders (e.g., seizure disorder, multiple sclerosis); acute opportunistic brain infections (e.g., cryptococcal meningitis, toxoplasmosis) or a history of such infections without documented return to normal cognition; severe head trauma with loss of consciousness >30 min and evidence of persistent functional decline; severe mental illness, use of mood stabilizing or antipsychotic medications, or acute psychiatric distress; pregnancy; physical disabilities impeding participation (e.g., blindness); and impaired mental status. These exclusions are consistent with current guidelines for classifying contributing or confounding conditions to HIV-associated neurocognitive disorders (Antinori et al., 2007).

2.2. Procedures

Participants were recruited from the Raleigh-Durham area between May, 2010 and May, 2014 via advertisements in local newspapers and websites, flyers posted and brochures distributed at community-based organizations and infectious diseases clinics, and participant referrals. Interested individuals completed a structured telephone screen to assess preliminary eligibility (e.g., HIV infection, drug use history). Eligible callers were invited for a comprehensive in-person screening.

At the screening, participants provided written informed consent. A breathalyzer was used to ensure sobriety. Participants then provided a urine sample for drug and pregnancy screening and completed clinical interviews and questionnaires. Eligible participants returned on another day to complete the neuropsychological testing, additional clinical interviews and questionnaires, and another urine drug test. Participants were paid $35 for the screening, regardless of eligibility, and $65