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"Frontal systems" behaviors in comorbid human immunodeficiency virus infection and methamphetamine dependency

María J. Marquine [a], Jennifer E. Iudicello [a], Erin E. Morgan [a], Gregory G. Brown [a,b], Scott L. Letendre [c], Ronald J. Ellis [d], Reena Deutsch [a], Steven Paul Woods [a], Igor Grant [a], Robert K. Heaton [a,*], The Translational Methamphetamine AIDS Research Center (TMARC) Group[1]

[a] Department of Psychiatry, University of California, San Diego, CA, United States
[b] Veterans Administration San Diego Healthcare System, San Diego, CA, United States
[c] Department of Medicine, University of California, San Diego, CA, United States
[d] Department of Neurosciences, University of California, San Diego, CA, United States

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ABSTRACT

Human immunodeficiency virus (HIV) infection and methamphetamine (MA) dependence are associated with neural injury preferentially involving frontostriatal circuits. Little is known, however, about how these commonly comorbid conditions impact behavioral presentations typically associated with frontal systems dysfunction. Our sample comprised 47 HIV-uninfected/MA-nondependent; 25 HIV-uninfected/MA-dependent; 36 HIV-infected/MA-nondependent; and 28 HIV-infected/MA-dependent subjects. Participants completed self-report measures of "frontal systems" behaviors, including impulsivity/disinhibition, sensation-seeking, and apathy. They also underwent comprehensive neurocognitive and neuropsychiatric assessments that allowed for detailed characterization of neurocognitive deficits and comorbid/premorbid conditions, including lifetime Mood and Substance Use Disorders, Attention-Deficit/Hyperactivity Disorder, and Antisocial Personality Disorder. Multivariable regression models adjusting for potential confounds (i.e., demographics and comorbid/premorbid conditions) showed that MA dependence was independently associated with increased impulsivity/disinhibition, sensation-seeking and apathy, and HIV infection with greater apathy. However, we did not see synergistic/additive effects of HIV and MA on frontal systems behaviors. Global neurocognitive impairment was relatively independent of the frontal systems behaviors, which is consistent with the view that these constructs may have relatively separable biopsychosocial underpinnings. Future research should explore whether both neurocognitive impairment and frontal systems behaviors may independently contribute to everyday functioning outcomes relevant to HIV and MA.

1. Introduction

Human immunodeficiency virus (HIV) infection and methamphetamine (MA) dependence are highly comorbid conditions, epidemiologically (Plankey et al., 2007; Purcell et al., 2005), and are thought to have synergistic neuropathologic effects (Cadet and Krasnova, 2007). Neuroimaging findings have shown both distinct and additive effects of HIV infection and MA dependence on brain

* Correspondence to: HIV Neurobehavioral Research Program, University of California San Diego, 220 Dickinson Street, Suite B (MC 8231), San Diego, CA 92103, United States. Tel.: +1 858 534 4044; fax: +1 619 543 1235.
E-mail address: rheaton@ucsd.edu (R.K. Heaton).

[1] The TMARC is comprised of: Director – Igor Grant, M.D.; Co-Directors – Ronald J. Ellis, M.D., Ph.D., Scott L. Letendre, M.D., and Cristian L. Achim, M.D., Ph.D.; Center Manager – Steven Paul Woods, Psy.D.; Assistant Center Manager – Aaron M. Carr, B.A.; Clinical Assessment and Laboratory (CAL) Core: Scott L. Letendre, M.D. (Core Director), Ronald J. Ellis, M.D., Ph.D., Rachel Schrier, Ph.D.; Neuropsychiatric (NP) Core: Robert K. Heaton, Ph.D. (Core Director), J. Hampton Atkinson, M.D., Mariana Cherner, Ph.D., Thomas D. Marcotte, Ph.D., Erin E. Morgan, Ph.D.; Neuroimaging (NI) Core: Gregory Brown, Ph.D. (Core Director), Terry Jernigan, Ph.D., Anders Dale, Ph.D., Thomas Liu, Ph.D., Miriam Scadeng, Ph.D., Christine Fennema-Notestine, Ph.D., Sarah L. Archibald, M.A.; Neurosciences and Animal Models (NAM) Core: Cristian L. Achim, M.D., Ph.D. (Core Director), Eliezer Masliah, M.D., Stuart Lipton, M.D., Ph.D., Virawudh Soontornniyomkij, M.D.; Administrative Coordinating Core (ACC) – Data Management and Information Systems (DMIS) Unit: Anthony C. Gamst, Ph.D. (Unit Chief), Clint Cushman, B.A. (Unit Manager); ACC – Statistics Unit: Ian Abramson, Ph.D. (Unit Chief), Florin Vaida, Ph.D., Reena Deutsch, Ph.D., Anya Umlauf, M.S.; ACC – Participant Unit: J. Hampton Atkinson, M.D. (Unit Chief), Jennifer Marquie-Beck, M.P.H. (Unit Manager); Project 1: Arpi Minassian, Ph.D. (Project Director), William Perry, Ph.D., Mark Geyer, Ph.D., Brook Henry, Ph.D.; Project 2: Amanda B. Grethe, Ph.D. (Project Director), Martin Paulus, M.D., Ronald J. Ellis, M.D., Ph.D.; Project 3: Sheldon Morris, M.D., M.P.H. (Project Director), David M. Smith, M.D., M.A.S., Igor Grant, M.D.; Project 4: Svetlana Semenova, Ph.D. (Project Director), Athina Markou, Ph.D., James Kesby, Ph.D.; Project 5: Marcus Kaul, Ph.D. (Project Director).

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structure and function, with preferential (although not exclusive) involvement of frontostriatal circuits (Chang et al., 2005; Jernigan et al., 2005). Independently, HIV and MA are associated with mild-to-moderate deficits in neurocognitive functions that also are typically mediated by frontostriatal brain systems, such as attention/working memory, psychomotor speed, executive functions, learning, and motor skills (Heaton et al., 2010; Scott et al., 2007). Although research on this topic is still sparse, there is some evidence to suggest that HIV infection and MA use might confer an additive vulnerability to neurocognitive impairment in these same areas (Carey et al., 2006; Cherner et al., 2005; Rippeth et al., 2004). For example Rippeth et al. (2004) demonstrated that neurocognitive impairment is increased in persons who have both conditions, with 58% of HIV-infected (HIV+) persons who also had a history of MA dependence showing neurocognitive impairment, as compared to 38-40% in those with only one risk factor. Neurocognitive deficits in HIV and MA are also each associated with notable functional outcomes, such as unemployment and problems in activities of daily living (Heaton et al., 1994, 2004a; Henry et al., 2010; Weber et al., 2012), and recent evidence suggests HIV infection might confer an increased concurrent risk of MA-associated disability (Blackstone et al., 2013). Identifying neurobehavioral factors contributing to functional decline in these risk groups is particularly important because such factors may be amenable to intervention.

Despite the high prevalence and adverse cognitive impact of the HIV/MA comorbidity, little is known about the combined effects of these risk factors on complex behavioral disturbances, other than cognition, that might also seriously affect functional outcomes. Research in other populations with frontostriatial injury, particularly involving medial prefrontal cortex, reveals behavioral disturbances in natural settings that may be relatively independent of abilities assessed by traditional neurocognitive tests, but can nevertheless impair everyday functioning (Anderson et al., 1999; Bechara et al., 1994). In fact, there is a large literature showing that frontally-mediated behavioral disturbances account for additional variance in real world outcomes, beyond that accounted for by cognition alone, in conditions such as Parkinson's disease (Leroi et al., 2011), Alzheimer's disease (Boyle, 2004; Boyle et al., 2003; Tekin et al., 2001), vascular dementia (Zawacki et al., 2002), schizophrenia (Velligan et al., 2002), stroke (Mikami et al., 2013), and traumatic brain injury (Reid-Arndt et al., 2007; Schwartz et al., 2003). The association between these complex behaviors and frontal-subcortical brain systems along with the potentially disabling effect of these behavioral disturbances, highlight the importance of further understanding their relationship to HIV infection and MA use (Bechara et al., 1994; Bonelli and Cummings, 2007). In the present study, we focus on impulsivity/disinhibition, sensation-seeking, and apathy because of existing evidence relating these behaviors to HIV infection and MA use separately (Castellon et al., 1998; Cattie et al., 2012; Gonzalez et al., 2005). Although the best way to conceptualize and measure these behaviors is a matter of debate, impulsivity/disinhibiton is generally understood to be a multidimensional concept that encompasses deficits in response inhibition, lack of premeditation or planning, and urgency (Grace and Malloy, 2001; Whiteside and Lynam, 2003). Sensation-seeking is defined as the tendency to prefer exciting, or novel stimulation or arousal, and readiness to take risks for the sake of such experiences (Zuckerman et al., 1964). Apathy has been referred to as a reduction in self-initiated, goal-directed behavior, and a lack of motivation (Marin, 1997). In the present study, we refer to these concepts as "frontal systems" behaviors, given the known importance of frontal brain areas and their underlying subcortical structures in their mediation (Bonelli and Cummings, 2007; Grace et al., 1999). However, we acknowledge that other brain regions, such as limbic systems (Horn et al., 2003; Martin et al., 2007) are also likely to be involved.

The aforementioned frontal systems behaviors have been related to HIV infection and MA use separately (Castellon et al., 1998; Cattie et al., 2012; Gonzalez et al., 2005). While research is still sparse, such neurobehavioral symptoms appear to be both prevalent and impactful in these risk groups. For example, studies have found clinically significant levels of self-reported disinhibiton in 36% of MA+ adults (Cattie et al., 2012) and apathy in 26-42% of HIV+ patients (Kamat et al., 2012; Tate et al., 2003). MA dependence has been associated with increased impulsivity/disinhibition as assessed by self-report instruments (Cattie et al., 2012; Lee et al., 2009; Semple et al., 2005; Winhusen et al., 2013). Further, the severity of these symptoms is related to declines in activities of daily living in MA use (Cattie et al., 2012). Higher impulsivity, as measured by the Iowa Gambling Task (Bechara, 2007), has been observed among HIV+ persons with a history of substance dependence (Martin et al., 2004). There is also evidence showing sensation-seeking to be associated with MA use (Brecht et al., 2004), and to risky sexual behavior in HIV+ mixed substance users (Gonzalez et al., 2005). Increased apathy has been related to MA use (Looby and Earleywine, 2007), and it is relatively common in HIV infection (Castellon et al., 1998; Rabkin et al., 2000), where it is independently associated with everyday functioning outcomes, including IADL declines (Kamat et al., 2012) and medication management (Barclay et al., 2007; Rabkin et al., 2000).

Although there is evidence linking these frontal systems behaviors to MA and HIV, behavioral disturbances in these conditions are not fully understood, especially regarding their comorbidity and possible influences of pre-existing/comorbid conditions (e.g., other substance use, mood, and relevant personality disorders). The main purpose of our study was to further our understanding of the patterns of behavioral dysfunctions related to MA dependence, HIV infection, and their combination. In order to do so, we evaluated frontal systems behaviors, as assessed by self-report measures of impulsivity, sensation-seeking and apathy, in a group of individuals with and without HIV-infection and histories of MA dependence.

As suggested above, an important challenge in studying these relationships is the need to account for comorbid/premorbid conditions, such as neurocognitive deficits, mood and personality disorders, and abuse of other substances, which may affect these frontal systems behaviors (Clarke, 2006). Thus, an important question is whether the potential relations between behavioral dysfunctions and HIV and/or MA might be better accounted for by these comorbidities. We measured these conditions, along with frontal systems behaviors, in order to look at the independent contribution of MA dependence and HIV infection. We hypothesized that MA dependence and HIV infection would be independently associated with increased behavioral disturbances, even after accounting for the effect of comorbid conditions. Moreover, we expected that the coexistence of HIV infection and MA dependence would be associated with an increased risk for behavioral dysfunction relative to groups with MA or HIV alone.

2. Methods

2.1. Participants

One-hundred and thirty-six individuals enrolled at the University of California San Diego Translational Methamphetamine AIDS Research Center (TMARC) were included in present analyses. Participants were recruited from the San Diego area through a variety of methods, such as flyers, and appearances at community events, HIV clinics, and residential drug treatment programs. Participants were recruited according to HIV serostatus and MA dependence into one of the following four groups: HIV-seronegative and MA-nondependent (HIV−/MA−; $n=47$); HIV-seronegative and MA-dependent (HIV−/MA+; $n=25$); HIV+ and MA-nondependent (HIV+/MA−; $n=36$); and HIV+ and MA-dependent (HIV+/MA+, $n=28$). The HIV+ groups included participants with self-reported HIV