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Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons

JULIE D. RIPPETH,[1] ROBERT K. HEATON,[1,2] CATHERINE L. CAREY,[2] THOMAS D. MARCOTTE,[1,2] DAVID J. MOORE,[2] RAUL GONZALEZ,[2] TANYA WOLFSON,[1] IGOR GRANT,[1,2,3] AND THE HNRC GROUP

[1]Department of Psychiatry, University of California, San Diego School of Medicine, San Diego, California
[2]San Diego State University and University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California
[3]Veterans Affairs San Diego Healthcare System

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Abstract

Both HIV infection and methamphetamine dependence can be associated with brain dysfunction. Little is known, however, about the cognitive effects of concurrent HIV infection and methamphetamine dependence. The present study included 200 participants in 4 groups: HIV infected/methamphetamine dependent (HIV+/METH+), HIV negative/methamphetamine dependent (HIV−/METH+), HIV infected/methamphetamine nondependent (HIV+/METH−), and HIV negative/methamphetamine nondependent (HIV−/METH−). Study groups were comparable for age, education, and ethnicity, although the HIV−/METH− group had significantly more females. A comprehensive, demographically corrected neuropsychological battery was administered yielding a global performance score and scores for seven neurobehavioral domains. Rates of neuropsychological impairment were determined by cutoff scores derived from performances of a separate control group and validated with larger samples of HIV+ and HIV− participants from an independent cohort. Rates of global neuropsychological impairment were higher in the HIV+/METH+ (58%), HIV−/METH+ (40%) and HIV+/METH− (38%) groups compared to the HIV−/METH− (18%) group. Nonparametric analyses revealed a significant monotonic trend for global cognitive status across groups, with least impairment in the control group and highest prevalence of impairment in the group with concurrent HIV infection and methamphetamine dependence. The results indicate that HIV infection and methamphetamine dependence are each associated with neuropsychological deficits, and suggest that these factors in combination are associated with additive deleterious cognitive effects. This additivity may reflect common pathways to neural injury involving both cytotoxic and apoptotic mechanisms. (*JINS*, 2004, *10*, 1–14.)

Keywords: HIV infection, Methamphetamine, Stimulants, Drug effects, Neuropsychology

INTRODUCTION

The co-occurrence of human immunodeficiency virus (HIV) infection and drug abuse is relatively common, due both to mode of infection and lifestyle choices/risk behaviors associated with the HIV+ population. Even with excluding injection drug users, HIV+ individuals and those at high risk for contracting HIV still have high rates of illicit drug use (40% in a recent study; Bing et al., 2001) and demonstrate elevated prevalence rates of lifetime substance abuse disorders (approximately 20–40%; Atkinson et al., 1988; Ferrando et al., 1998; Rabkin, 1996). Methamphetamine is one of the most common drugs of abuse for HIV+ individuals and those at high-risk for HIV infection, and is associated with high-risk sexual activity among men who have sex with men (Woody et al., 1999).

While the separate neuropsychological effects of HIV infection and drug abuse are well documented, less is known

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Reprint requests to: Igor Grant, MD, HIV Neurobehavioral Research Center, 150 West Washington Street, 2nd Floor, San Diego, CA 92103.

about these risk factors in combination. Several researchers have utilized drug abusing cohorts (usually injection drug users) to study the cognitive effects of HIV infection, although only a few of these studies have specifically examined the cognitive effects of the combination of HIV infection and drug abuse (Durvasula et al., 2000; Grassi et al., 1993, 1995). Additionally, previous studies investigating the cognitive effects of the concurrent combination of these factors typically have included polydrug users. To date, there have been few neuropsychological studies focusing primarily on methamphetamine abusers and, to our knowledge, none that considered comorbid HIV infection and methamphetamine use disorders.

Central Nervous System Effects of Methamphetamine

Early studies of the cognitive effects of amphetamine, a CNS stimulant chemically similar to methamphetamine, found that abusers demonstrated deficits on tests of visual memory (Rylander, 1969), visuoperceptual skills, and cognitive flexibility (Trites et al., 1974). An early study of polydrug users (Grant et al., 1978) failed to detect an independent effect for stimulants; however, this study focused primarily on heavy polysubstance users, the majority of whom abused central nervous system depressants. McKetin and Mattick (1997, 1998) reported that more severe amphetamine dependence was associated with decreased neuropsychological performance in areas of attention and memory. More recently, Simon and colleagues (2000, 2002) documented impairments in learning, delayed recall and processing speed in samples of methamphetamine abusers who were current users or who had minimal abstinence.

In contrast to the relative paucity of studies examining neuropsychological performance in methamphetamine abusers, several recent neuroimaging studies have demonstrated alterations in brain chemistry and function in this group. Perfusion deficits and hypometabolism have been demonstrated in frontal and temporal cortical areas, as well as subcortical regions (Alhassoon et al., 2001; Gouzoulis-Mayfrank, 1999; Iyo et al., 1997; Volkow et al., 2001a). Magnetic resonance spectroscopy has shown evidence of neuronal damage in the basal ganglia and frontal white and gray matter (Ernst et al., 2000; Taylor et al., 2000), while positron emission tomography (PET) has demonstrated decreased density of dopaminergic neurons in the caudate and putamen (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001b). In one of the PET studies (Volkow et al., 2001b), decreased dopamine density was correlated with motor slowing and memory impairment.

Central Nervous System Effects of HIV Infection

HIV-related brain dysfunction is associated with a frontal–subcortical pattern of cognitive deficits, characterized by impairments in attention/working memory, psychomotor/processing speed, abstraction/executive functioning, learning, and motor skills (Durvasula et al., 2001; Heaton et al., 1995; Martin et al., 2001; Peavy et al., 1994). While frank dementia (HIV-Associated Dementia, HAD) occurs in only about 5% of people with AIDS, milder neuropsychological impairment is relatively common, occurring in approximately 50% of people with AIDS and about 35% of medically asymptomatic HIV+ individuals (Grant et al., 1987; Heaton et al., 1995; White et al., 1995). Although there is evidence of a decline in the incidence of HIV neurocognitive disorders following the introduction of more potent antiretroviral therapies (Bloom & Rausch, 1997; Deutsch et al., 2001; Dore et al., 1999; Maschke et al., 2000; Rausch & Stover, 2001; Sacktor et al., 2001), there is speculation that the prevalence of HIV-associated neuropsychological impairment might rise in the future if some of the newer, potent antiretroviral agents (e.g., protease inhibitors) have poor penetration into the CNS.

Neuroimaging techniques have demonstrated that, similar to methamphetamine, HIV is associated with structural and functional alterations in white matter and associated subcortical brain regions (Jernigan et al., 1993; Stout et al., 1998). Increased signal in the deep gray matter, as measured by functional MRI, has been associated with degree of neuropsychological impairment (Tracey et al., 1998). Changes in basal ganglia metabolism also have been demonstrated with PET, with hypometabolism associated with impaired performance on a motor task (von Giesen et al., 2000).

Rationale for Additive Deleterious Effects of Methamphetamine and HIV

Current theories of the neurotoxicity of HIV and methamphetamine suggest that some of the mechanisms of injury might converge on common pathways. In addition to vascular injury, ischemia, and hyperthermia, acute methamphetamine use causes increased dopamine and glutamatergic transmission that can lead to excitotoxic injury and death of selected neuronal populations (Davidson et al., 2001; Langford et al., 2002; Marshall et al., 1993; Ohmori et al., 1996; Rumbaugh et al., 1971; Stephans & Yamamoto, 1994; Wilson et al., 1996). Similarly, HIV products (e.g., the envelope protein gp120, the gene product Tat) and/or cytokines or other neurotoxins released by activated macrophages may stimulate glutamatergic receptors leading to excitotoxic death or injury of certain vulnerable neuronal populations, which ultimately may lead to white matter injury (Haughey et al., 2001; Langford et al., 2002; Lipton & Gendelman, 1995). The striatal and striatal–cortical circuitries appear to be vulnerable both to methamphetamine (Eisch et al., 1996; Wilson et al., 1996) and HIV (Itoh et al., 2000; Reyes et al., 1991) toxicity.

Recent work by Taylor et al. (2000) indicated that metabolite disturbances (reduced N-acetyl aspartate in anterior cingulate) measured by proton magnetic resonance spectroscopy (MRS) were worse in those with combined stimulant abuse and HIV. In addition, a neuropathologic

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study of HIV infected persons with and without histories of methamphetamine dependence found greater damage to interneurons in frontal cortex in the brains of those with both risks rather than those singly affected (Langford et al., 2002). Moreover, an animal study by Czub et al. (2001) observed enhancement of neuropathologic changes within monkeys with Simian Immunodeficiency Virus infection that received dopaminergic drugs.

Therefore, the overall aim of this study was to investigate the potentially additive effects of methamphetamine dependence on cognitive functioning in persons with HIV infection. It was hypothesized that methamphetamine dependence and HIV infection would be independently associated with increased rates of neuropsychological impairment. Additionally, it was expected that the concurrent presence of these two factors would be associated with an additive risk of neuropsychological impairment, such that a group of HIV-infected individuals with methamphetamine dependence would demonstrate a higher rate of impairment than groups with HIV infection or methamphetamine dependence alone.

METHODS

Research Participants

The sample was comprised of 200 participants within the following four groups: HIV infected/methamphetamine dependent (HIV+/METH+; $n = 43$); HIV negative/methamphetamine dependent (HIV−/METH+; $n = 47$); HIV infected/methamphetamine nondependent (HIV+/METH−; $n = 50$); and HIV negative/methamphetamine nondependent (HIV−/METH−; $n = 60$). HIV serological status was determined by enzyme linked immunosorbent assays (ELISA) plus a confirmatory test. Participants with a history of methamphetamine dependence were primarily recruited from residential drug treatment programs in the San Diego area, while those participants without a history of methamphetamine abuse were recruited from the larger San Diego community through the use of flyers and appearances at community events. All participants gave written consent prior to enrollment in the study.

Selected modules of the Structured Clinical Interview for DSM–IV (SCID; First et al., 1996) were administered by research psychologists, trained postdoctoral fellows or clinical psychology graduate students to assess current and lifetime history of alcohol and other substance abuse and dependence. Participants included in the methamphetamine dependent groups met DSM–IV criteria for methamphetamine dependence during their lifetime. They also met criteria for at least methamphetamine abuse within 24 months of the examination, but a minimum of 10 days of abstinence was required at the time of the evaluation. Potential participants were excluded if they had a history of head injury with loss of consciousness greater than thirty minutes, or a history of neurological or psychiatric illness that affected cognitive functioning (e.g., seizure disorder, schizophrenia, bipolar affective disorder with psychotic features).

Participants from all groups were excluded if they met DSM–IV criteria for alcohol dependence within a year of the evaluation or if they had a "significant" length of alcohol dependence during their lifetime. A "significant" length of alcohol dependence was determined largely on a case-by-case basis. Generally participants were excluded for periods of alcohol dependence that were greater than or equal to 5 years, particularly when the period of dependence was within 10 years of their assessment. The recency of the dependence also was considered; if the span of dependence occurred within 10 years of the exam date, these participants were also excluded. Participants were also excluded if they met criteria for (1) dependence on another substance (other than marijuana) within 5 years of the evaluation; (2) other substance dependence (excluding marijuana) for a period of greater than 5 years during their lifetime; or (3) abuse of a substance other than methamphetamine within 1 year of the evaluation. Participants were not excluded for history of alcohol or marijuana abuse or past marijuana dependence, given the frequency of these comorbid diagnoses in methamphetamine dependent individuals.

All participants completed a urine toxicology screen and a Breathalyzer test for alcohol prior to beginning the neuropsychological assessment procedures. A positive urine toxicology screen suspended the assessment and the participant was rescheduled. The urine toxicology screen assessed for the following substances: amphetamine, methamphetamine, cocaine, opiates, phenylcyclidine, and cannabis. No subject had a positive Breathalyzer test on the morning of the evaluation.

Table 1 details the demographic characteristics of the four study groups. The groups were comparable for age and education, as well as proportion of ethnic minorities. The three groups with neurocognitive risk factors had a significantly greater proportion of males than did the HIV−/METH− group [$\chi^2(1,200) = 26.1$, $p < .0001$]. Additionally, the HIV+/METH+ group had a significantly greater proportion of males than the HIV−/METH+ group [$\chi^2(1, 90) = 4.2$, $p < .05$]. Results of a one-way ANOVA indicated a significant group difference in an estimate of premorbid functioning, reading ability as measured by the Wide Range Achievement Test–Third Edition (WRAT–3; Wilkinson, 1993) [$F(3,196) = 2.67$, $p < .05$; $d = -0.48$]. *Post-hoc* analyses revealed that the HIV−/METH+ group had a significantly lower mean WRAT–3 Reading score than did the HIV−/METH− group. Although statistically significant, the difference in WRAT–3 scores between these two groups is likely to have minimal clinical significance.

Characteristics of the HIV+ groups

The HIV+ groups (HIV+/METH+ and HIV+/METH−) were comparable for CD4 count ($M = 388$, $SD = 240$ *vs.* $M = 410$, $SD = 244$) and plasma viral load ($M = 2.7$ log; $SD = 2.0$ *vs.* $M = 2.9$ log; $SD = 2.2$), as well as for proportion of participants with an AIDS diagnosis (55% *vs.* 47%).

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Table 1. Demographic characteristics of the four study groups

	METH+		METH−		
M (*SD*) *N* = 200	HIV+ (*n* = 43) a	HIV− (*n* = 47) b	HIV+ (*n* = 50) c	HIV− (*n* = 60) d	
Age	37.0 (6.1)	37.7 (9.7)	39.4 (9.3)	34.4 (11.9)	
Education	12.6 (1.8)	12.9 (1.7)	13.5 (1.5)	13.2 (1.6)	
WRAT–3 Reading*	99.3 (11.1)	97.2 (11.4)	101.7 (8.8)	102.6 (11.1)	b < d
Male**	91%	74%	84%	50%	a, b, c > d; a > b
Ethnicity					
Caucasian	67%	75%	62%	69%	
African American	19%	4%	18%	8%	
Hispanic	14%	17%	16%	20%	
Asian/Other	0%	4%	4%	3%	

* = $p < .05$; ** = $p < .0001$.

Drug use characteristics

The lifetime rates for alcohol dependence differed significantly among the groups [$\chi^2(1,200) = 11.5$, $p < .01$). The rates were as follows: HIV+/METH+ group (26%), HIV−/METH+ group (34%), HIV+/METH− group (14%), HIV−/METH− group (10%). The lifetime rates of "other" drug dependence (not including methamphetamine) also differed between the four groups [$\chi^2(1,200) = 16.1$, $p < .005$]. These rates were as follows: HIV+/METH+ group (19%), HIV−/METH+ group (28%), HIV+/METH− group (8%), HIV−/METH− group (3%).

Substances for which participants in the HIV+/METH+ group met DSM–IV criteria for past dependence, in addition to methamphetamine, included marijuana ($n = 4$), cocaine ($n = 4$), and hallucinogens ($n = 1$). Other substances for which participants in the HIV−/METH+ group met criteria for past dependence included marijuana ($n = 6$), cocaine ($n = 7$), opiates ($n = 1$), and hallucinogens ($n = 1$). These classifications were not mutually exclusive. Three people in the HIV+/METH− group met lifetime dependence for marijuana and 1 person met criteria for lifetime cocaine dependence. Two people met criteria for lifetime marijuana dependence in the HIV−/METH− group. Use of MDMA and other club drugs was minimal in the sample. Only 2 subjects, 1 each from the HIV+/METH+ and HIV−/METH+ groups, met criteria for lifetime abuse of MDMA.

The methamphetamine use characteristics of the two METH+ groups are in Table 2. These groups were comparable for reported age at first use, total years of methamphetamine use, length of abstinence at the time of the evaluation, and primary methods of use. Lifetime peak frequency [$\chi^2(1,90) = 8.7$, $p < .05$] and peak amount of methamphetamine use ($\chi^2(1,90) = 12.1$, $p < .05$] were greater in the HIV−/METH+ group than in the HIV+/METH+ group. The HIV−/METH+ group also demonstrated higher levels of methamphetamine use prior to achieving abstinence, as measured by quantity and frequency of recent use [$\chi^2(1,90) = 14.8$, $p < .005$]. Seventy percent of the HIV−/METH+ group reported recent "high" frequency (daily) and "high" use (>1.0 g), as opposed to 36% of the HIV+/METH+ group. Note that, to the degree that these differences may have affected neuropsychological functioning in this study, the significantly greater use of methamphetamine in the HIV−/METH+ group would make it more difficult to find an additive effect of methamphetamine and HIV.

Procedures

A neuropsychological assessment was part of a larger full-day evaluation, which included physical and neurological examinations, collection of a standardized medical history, a psychiatric and substance use interview, and blood tests.

Neuropsychological evaluation

Trained psychometrists administered and scored the neuropsychological tests. The neuropsychological battery was chosen to be comprehensive yet efficient, with an emphasis on tests that are known or expected to be sensitive to the frontal–subcortical deficits associated with HIV infection and methamphetamine dependence. The neuropsychological battery consisted of the following tests within seven cognitive domains:

1. *Speed of information processing*: Wechsler Adult Intelligence Scale–III (WAIS–III) Digit Symbol and Symbol Search subtests (Psychological Corporation, 1997); Trail Making Test Part A (Reitan & Davison, 1974)
2. *Learning*: Hopkins Verbal Learning Test–Revised (HVLT–R; Benedict et al., 1998) Total Trials 1–3 Recall; Brief Visuospatial Memory Test–Revised (BVMT–R; Benedict, 1997) Total Trials 1–3 Recall
3. *Recall*: HVLT–R Delay Recall; BVMT–R Delay Recall

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Table 2. Methamphetamine use characteristics of the METH+ groups

M (*SD*) *N* = 90	METH+ HIV+ (*n* = 43)	METH+ HIV− (*n* = 47)	*p*[a]
Age at first METH use	23.6 (6.7)	23.7 (7.5)	
Total years of METH use	11.2 (5.8)	12.1 (5.4)	
Length of abstinence (months)	5.9 (6.2)	4.5 (3.4)	
Primary method of use			
Smoking	7%	17%	
Ingestion	0%	2%	
Intranasal	42%	51%	
Injection	51%	30%	
Recent use/frequency			<.005
Low use/low freq.	17%	2%	
Mid/high use & low freq. or low use & mid/high freq.	48%	28%	
High use/high freq.	36%	70%	
Recent frequency			
< 1 day per week	32%	19%	
1–3 days/week	26%	15%	
4–6 days/week	16%	17%	
Daily	26%	49%	
Recent use			<.05
0–0.25g	51%	19%	
0.26g–0.50g	12%	28%	
0.51g–1.00g	18%	19%	
> 1.00g	19%	34%	
Peak frequency			<.05
1–3 days per week	30%	10%	
4–6 days per week	21%	13%	
Daily	49%	77%	
Peak use			<.05
0–0.25g	33%	8%	
0.26g–0.50g	14%	22%	
0.51g–1.00g	21%	32%	
> 1.00g	32%	38%	

Note. [a]The listed *p* level refers to the test for the overall chi-square for each listed variable. Low use = ≤0.25g; Mid use = >0.25 g and ≤1.0 g; High use = >1.0 g. Low frequency = 0–3 days/week; Mid frequency = 4–6 days/week; High frequency = 7 days/week.

4. *Abstraction/executive functioning*: Category Test (Halstead, 1947), Wisconsin Card Sorting Test (64-item version; Kongs et al., 2000) perseverative responses; Trail Making Test Part B (Reitan & Davison, 1974); Stroop Color and Word Test (Golden, 1974) Interference Score
5. *Verbal fluency*: FAS Letter Fluency and Category Fluency for animals (Borkowski et al., 1967)
6. *Attention/working memory*: WAIS–III Letter–Number Sequencing; Paced Auditory Serial Addition Task (Gronwall, 1977)
7. *Motor skills*: Grooved Pegboard Test (Kløve, 1963) dominant and nondominant hand performances.

As mentioned previously, the WRAT–3 Reading subtest was administered as an estimate of premorbid verbal intellectual functioning. Raw scores for all tests were transformed into T-scores using methods that corrected for age, and whenever possible, education, sex, ethnicity (Benedict, 1997; Benedict et al., 1998; Diehr et al., 1998; Gladsjo et al., 1999; Golden, 1974; Heaton et al., 1991, 2002; Kongs et al., 2000).

Also collected at the time of the evaluation were several self-report measures used to assess the prevalence and degree of several possible confounding factors, including depression and learning difficulties. The Beck Depression Inventory (Beck and Steer, 1987) was used to assess self-reported degree of depressed mood. Also ascertained were rates of learning difficulties, as defined by self-report of grade retention, diagnosis of learning disability, or history of special education courses, and the prevalence of Attention Deficit Hyperactivity Disorder, as assessed by self-report of symptoms on the Diagnostic Interview Schedule for DSM–IV (Robins et al., 1995).

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Global Deficit Scores

An objective summary score of neuropsychological impairment, a Global Deficit Score (GDS), was derived for the entire test battery (Heaton et al., 1994, 1995). The GDS reflects the number and severity of impaired performances throughout the test battery, giving relatively less weight to test performances that are within normal limits. The demographically corrected T-score for each test measure was converted to a zero to five-point deficit rating, as follows: T > 39 = 0 (*no impairment*); T = 35–39 = 1 rating point; T = 30–34 = 2 points; T = 25–29 = 3 points; T = 20–24 = 4 points; T < 20 = 5 points. The GDS was computed by adding the deficit ratings of the individual test measures and dividing by the total number of measures administered. This same method was used to create Domain Deficit Scores (DDS) for each of the seven cognitive domains, by adding the deficit ratings of the tests within each domain and dividing by the total number of measures within the domain. Previous studies have indicated that the GDS achieves good diagnostic agreement with the classifications made by blind clinical ratings (Heaton et al., 1995).

Tentative cutpoints for neuropsychological impairment, both for the GDS and the DDS, were determined based on the test scores of an independent group of control participants from the HIV Neurobehavioral Research Center (n = 54). This sample, subject to the same exclusion criteria as the study groups, was comprised of HIV seronegative individuals who had no history of substance dependence. The mean age and education of this sample were 43.2 (SD = 8.5) and 14.4 (SD = 3.5) years, respectively, and 67% of the sample was male (again, the deficit scores were based on T-scores that already are demographically corrected). The cutpoints for the GDS and the DDS, as derived from this cohort, were validated through the use of clinical ratings of a larger group of HIV+ (n = 192) and HIV− (n = 26) participants who were enrolled in studies at the HIV Neurobehavioral Research Center. This group had a mean age of 41.1 (SD = 7.54) years and a mean education of 13.4 (SD = 2.62) years. Seventy-nine percent of this group was male and 41% were ethnic minorities. Additionally, 63% of the HIV+ participants in this group had an AIDS diagnosis. The GDS cutpoint was > 0.40, while the cutpoints for each of the cognitive domains were as follows: Processing Speed (≥ 0.33), Learning (> 0.50), Recall (≥ 0.50), Abstraction/Executive Functioning (> 0.50), Verbal Fluency (≥ 0.50), Attention/Working Memory (≥ 0.50), and Motor Skills (> 0.50). The sensitivity and specificity for the GDS cutpoint relative to the clinical rating "gold standard" in this larger sample were excellent (sensitivity = 92%; specificity = 90%). The cutpoints for the DDS also demonstrated good diagnostic concordance, with median sensitivity and specificity estimates of 93% and 84%, respectively.

Statistical considerations

In order to reduce the likelihood of Type I error, an alpha level of 0.01 was used for *post-hoc* Chi-Square analyses. The 0.01 level also was utilized for the series of ANOVAs involving the individual NP tests, including the *post-hoc* tests for significant mean differences, which were performed using Tukey-Kramer Honestly Significant Difference tests.

A nonparametric test, the Jonckheere-Terpstra test for ordered alternatives (Jonckheere, 1954; Terpstra, 1952), was utilized to test the hypothesis that HIV infection and methamphetamine confer an additive risk of neuropsychological impairment. The Jonckheere-Terpstra test for ordered alternatives is a between group trend test assessing the null hypothesis that the distribution of the dependent variable, in this case GDS, does not differ among the groups. Essentially, to reject the null hypothesis, the median level of NP impairment would increase in an orderly fashion as the number of neurocognitive risk factors increases (e.g. HIV−/METH− group would have the lowest median GDS, while the HIV+/METH+ would have the highest). Further details of the Jonckheere-Terpstra test can be found in Pirie (1983) and Hollander and Wolfe (1973).

RESULTS

Global Deficit Score and Domain Deficit Scores

The GDS and DDS for the four subject groups are listed in Table 3. Main effects on the GDS were observed for both HIV status [$F(3,196) = 4.81$, $p < .05$] and methamphetamine dependence [$F(3,196) = 11.81$, $p < .001$]. The interaction term was nonsignificant ($F = 1.67$, $p = .19$). Nevertheless, the groups with risk factors for cognitive impairment (HIV+/METH+, HIV−/METH+, HIV+/METH−) demonstrated significantly higher GDSs than the HIV−/METH− group [$F(3,196) = 6.65$, $p < .001$]. The Hedges bias-corrected effect sizes for the groups (with the HIV−/METH− group as the reference group) were as follows: HIV+/METH+ (1.04), HIV−/METH+ (0.69), and HIV+/METH− (0.59).

Analyses for the Attention/Working Memory [$F(3,196) = 2.91$, $p < .05$], Learning [$F(3,196) = 5.26$, $p < .005$], Recall [$F(3,196) = 6.63$, $p < .001$], and Motor Skills [$F(3,196) = 3.86$, $p < .05$] domains also showed significant between group differences. *Post-hoc* Tukey-Kramer HSD tests indicated that the HIV−/METH+ group had a significantly higher Attention DDS than the HIV−/METH− group (d = 0.53), while the HIV+/METH+ group demonstrated significantly higher DDS than the HIV−/METH− group in the Learning (d = 0.86), Recall (d = 0.90), and Motor Skills domains (d = 0.58). The HIV−/METH+ (d = 0.76) group also exhibited higher DDS in the Recall domain compared to the HIV−/METH− group.

The Jonckheere-Terpstra test for ordered alternatives (Jonckheere, 1954; Terpstra, 1952) was performed to test for a trend in the median GDSs for the groups. Data for the groups with one risk factor each (HIV−/METH+ and

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Table 3. Global Deficit Scores and Domain Deficit Scores for the four study groups

	METH+		METH−			
M (*SD*) *N* = 200	HIV+ (*n* = 43) a	HIV− (*n* = 47) b	HIV+ (*n* = 50) c	HIV− (*n* = 60) d		η^2
Global Deficit Score***	0.57 (0.45)	0.51 (0.58)	0.43 (0.47)	0.22 (0.21)	a, b, c > d	.092
Verbal Fluency	0.21 (0.44)	0.39 (0.70)	0.30 (0.47)	0.22 (0.43)		.020
Processing Speed	0.18 (0.36)	0.33 (0.56)	0.29 (0.49)	0.12 (0.28)		.040
Attention/Working Memory*	0.34 (0.52)	0.47 (0.69)	0.37 (0.50)	0.18 (0.39)	b > d	.043
Learning**	1.05 (1.16)	0.72 (1.07)	0.61 (1.01)	0.30 (0.58)	a > d	.074
Recall*	0.94 (1.18)	0.81 (1.12)	0.63 (0.98)	0.18 (0.49)	a, b > d	.092
Abstraction/Executive Function	0.44 (0.46)	0.40 (0.51)	0.43 (0.71)	0.23 (0.39)		.030
Motor Skills*	0.81 (1.09)	0.43 (0.68)	0.40 (0.69)	0.30 (0.68)	a > d	.056

*** = $p < .001$; ** = $p < .005$; * = $p < .05$.

HIV+/METH−) were combined in order to assess trends between groups with two risk factors, one risk factor, and no risk factors. The Jonckheere-Terpstra test was significant for the GDS (J* statistic = 4.27, $p < .001$), as well as for the Learning (J* statistic = 3.23, $p < .001$), Recall (J* statistic = 3.85, $p < .001$) and Motor Skills (J* statistic = 2.60, $p < .005$) domains, indicating the presence of a monotonic trend among the three groups and, hence, an additive risk of the presence of the two risk factors.

Rates of Neuropsychological Impairment

Figure 1 displays the rates of neuropsychological impairment for the four study groups based on the cut-off scores for the GDS. Similar to the GDS analysis, the HIV+/METH+, HIV−/METH+, and HIV+/METH− groups showed significantly higher rates of global neuropsychological impairment than the HIV−/METH− group [$\chi^2(1,200) = 13.6$, $p < .005$]. Table 4 shows the rates of impairments for the individual cognitive domains. The three groups with risk factors demonstrated higher rates of impairment (based on cut-offs for DDS) in the Recall domain [$\chi^2(1,200) = 23.1$, $p < .0001$]. In the Attention/Working Memory domain [$\chi^2(1,200) = 8.5$, $p < .05$], the HIV+/METH− group had a significantly higher rate of impairment than the HIV−/METH− group, while in the Motor Skills domain [$\chi^2(1,200) = 10.4$, $p < .05$] the HIV+/METH+ and HIV−/METH+ groups showed higher rates of impairment than the HIV−/METH− group. In the Learning domain [$\chi^2(1,200) = 11.2$, $p < .05$], the two METH+ groups had significantly higher rates of impairment than the HIV−/METH− group.

Individual NP Test Results

Raw scores and T-scores for the individual tests used in the neuropsychological battery are shown in Table 5. Tests in

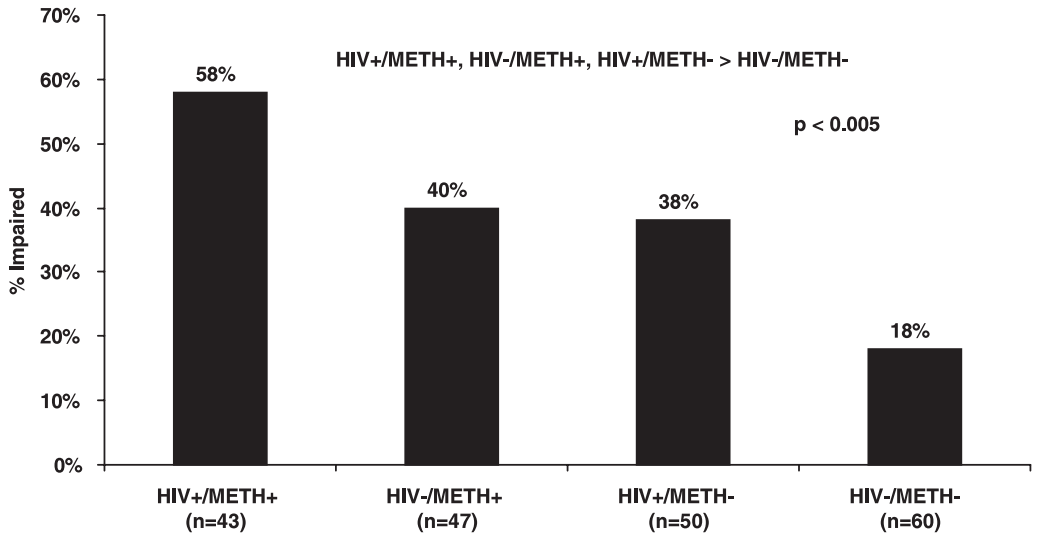

Fig. 1. Percent of global neuropsychological impairment as determined by GDS cut-off scores.

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Table 4. Rates of neuropsychological impairment for the individual cognitive domains

	METH+		METH−		
	HIV+ (n = 43)	HIV− (n = 47)	HIV+ (n = 50)	HIV− (n = 60)	
N = 200	a	b	c	d	
Verbal Fluency	26%	36%	36%	28%	
Processing Speed	33%	40%	38%	20%	
Attention/Working Memory*	37%	38%	44%	20%	c > d
Learning*	44%	32%	34%	17%	a, c > d
Recall**	54%	51%	40%	15%	a, b, c > d
Abstraction/Executive	26%	26%	16%	13%	
Motor Skills*	40%	23%	20%	12%	a > d

** = $p < .005$, * = $p < .05$.

the Learning, Abstraction/Executive Functioning, and Motor Skills domains exhibited significant between group differences. More specifically, the HIV+/METH+ group demonstrated significantly worse performances than the HIV−/METH− group on the Wisconsin Card Sorting Test-64 item version perseverative responses [$F(3,195) = 4.4$, $p < .01$], the Grooved Pegboard nondominant hand [$F(3,194) = 4.1$, $p < .01$], and the learning trial for the Brief Visuospatial Memory Test–Revised [$F(3,196) = 5.3$, $p < .005$]. Lastly, the HIV+/METH+ group performed significantly worse than the HIV−/METH− group on the Interference score of the Stroop Color and Word Test [$F(3,172) = 5.3$, $p < .005$].

Beck Depression Inventory

The Beck Depression Inventory (BDI) scores also are listed in Table 5. The HIV+/METH+, HIV−/METH+, and HIV+/METH− groups had significantly higher BDI scores compared to the HIV−/METH− group [$F(3,195) = 10.9$, $p < .0001$]. To ensure that the group differences were not solely due to medical symptoms associated with HIV infection, the analysis also was performed after excluding BDI items that assess somatic symptoms (e.g., insomnia, appetite changes). The results of this analysis were similar [$F(3,195) = 7.9$, $p < .0001$], with the three groups having neuropsychological risk factors continuing to demonstrate significantly higher scores than the HIV−/METH− group. The modified BDI score, controlling for physical symptoms, was used to measure the relationship between degree of reported depressive symptoms and GDS. The correlation between the modified BDI score and GDS was modest [$r(199) = .14$, $p < .05$], but reached statistical significance.

An analysis of covariance was performed to examine whether the observed between group differences in neuropsychological impairment, as measured by the GDS, were due to degree of depressive symptoms. The group differences persisted after controlling for the modified BDI score [$F(3,195) = 5.02$, $p < .005$].

Additional Analyses Involving Potential NP Confounds

Several potential confounding factors were assessed to determine if their effects accounted for the observed between group differences. First, there were differential rates of males within the four study groups. Normative data for only one of the NP tests does not correct for sex where it has been shown to be warranted (HVLT–R). Nonetheless, analyses were performed with a subset comprised of only males. Similar to the full sample, the groups in the subset were comparable for age, education and ethnicity. There was a significant group difference for GDS [$F(3,146) = 4.71$, $p < .005$], with *post-hoc* tests revealing that the HIV+/METH+ and HIV−/METH+ groups performed significantly worse than the HIV−/METH− group.

Secondly, given the statistically significant difference in WRAT-3 Reading scores among the HIV−/METH+ and HIV−/METH− groups, an analysis of covariance was performed with GDS as the dependent variable, group membership as the independent variable, and WRAT–3 Reading standard score as the covariate. The ANCOVA revealed a significant effect of group [$F(4,195) = 5.32$, $p < .05$], with the *post-hoc* tests (Tukey HSD) indicating that the HIV+/METH+ and HIV−/METH+ groups demonstrated significantly higher GDSs than the HIV−/METH− group.

Rates of self-reported Attention Deficit Hyperactivity Disorder and learning difficulties (as defined by self-report of grade retention, diagnosis of learning disability, or history of special education courses) were assessed. The rates of Attention Deficit Hyperactivity Disorder were comparable among the four groups ($p = .27$), while the rates of learning difficulties were significantly different [$\chi^2(1,200) = 8.0$, $p = .047$]. The HIV−/METH+ group had the highest rate of self-reported learning difficulties (27%), followed by the HIV+/METH− (12%), the HIV−/METH− (10%) and the HIV+/METH+ (9%) groups. *Post-hoc* tests ($p < .01$) did not reveal any specific between-groups differences. While learning difficulties may be a possible confound to NP performance, the pattern of group rates indicates a conserva-

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Table 5. Raw scores (total correct except where indicated) and T-scores for the individual tests within the seven cognitive domains as well as Beck Depression Inventory scores

	METH+				METH−				
	HIV+ (n = 43) a		HIV− (n = 47) b		HIV+ (n = 50) c		HIV− (n = 60) d		
M (*SD*) N = 200	Raw	T-score	Raw	T-score	Raw	T-score	Raw	T-score	
Verbal Fluency									
Letter	41.6 (9.8)	49.2 (8.6)	39.7 (11.0)	46.6 (9.9)	39.8 (10.0)	47.4 (8.6)	40.1 (9.6)	47.0 (8.1)	
Category	20.9 (4.9)	48.2 (9.3)	21.3 (5.5)	48.4 (11.5)	20.0 (4.8)	46.7 (9.5)	21.4 (4.2)	48.0 (8.7)	
Processing Speed									
WAIS–III Digit Symbol	68.6 (16.9)	48.9 (10.3)	66.4 (14.4)	45.2 (10.0)	71.0 (14.6)	49.8 (11.3)	76.4 (12.5)	50.5 (8.9)	
WAIS–III Symbol Search	31.2 (7.6)	49.5 (8.2)	31.3 (8.0)	48.9 (11.0)	31.4 (7.7)	49.9 (10.5)	33.1 (7.2)	50.3 (9.3)	
Trail Making Test, Part A (seconds)	26.3 (7.7)	50.4 (10.1)	26.6 (8.1)	50.3 (9.1)	27.8 (11.5)	50.5 (11.4)	24.2 (6.0)	51.8 (8.4)	
Attention/Working Memory									
PASAT	107.6 (10.0)	45.2 (10.0)	104.3 (35.8)	43.4 (11.3)	101.3 (31.7)	43.6 (9.0)	113.6 (27.8)	45.6 (8.0)	
WAIS–III Letter–Number Sequencing	10.1 (2.2)	48.5 (7.8)	10.5 (3.0)	49.4 (11.0)	10.4 (2.9)	49.7 (9.5)	11.0 (2.4)	50.8 (8.6)	
Learning									
HVLT–R Trials 1–3	25.9 (4.6)	43.0 (10.5)	26.3 (4.1)	43.5 (9.5)	26.8 (4.0)	45.2 (9.4)	27.9 (3.6)	47.2 (8.6)	
BVMT–R Trials 1–3**	21.4 (7.4)	40.9 (14.0)	22.7 (6.3)	43.1 (12.9)	24.4 (7.4)	47.8 (14.2)	26.6 (5.5)	50.1 (11.5)	a < d
Recall									
HVLT–R Delay Recall	8.9 (2.8)	41.7 (10.2)	9.0 (2.1)	41.2 (9.1)	9.3 (2.1)	42.9 (9.0)	10.1 (1.4)	45.7 (7.3)	
BVMT–R Delay Recall	8.7 (2.9)	44.6 (14.7)	9.0 (2.4)	45.7 (13.3)	9.5 (2.6)	49.3 (13.8)	10.2 (1.6)	51.1 (9.3)	
Abstraction/Executive Functioning									
Category Test (errors)	49.9 (23.5)	43.0 (8.9)	48.0 (22.5)	44.6 (9.7)	46.5 (24.4)	44.5 (10.2)	38.3 (24.7)	48.1 (9.7)	
WCST-64 item (perseverations)**	14.2 (10.3)	41.2 (7.4)	12.9 (6.9)	42.2 (7.3)	11.4 (9.0)	43.9 (9.1)	9.6 (5.8)	46.2 (6.7)	a < d
Trail Making Test Part B (seconds)	69.7 (29.6)	50.4 (11.1)	72.2 (28.2)	49.1 (11.3)	69.4 (38.1)	51.1 (11.4)	65.4 (33.3)	51.7 (11.9)	
Stroop Color and Word Interference**	38.7 (8.6)	47.6 (6.7)	38.4 (9.1)	48.8 (6.5)	36.2 (8.9)	47.7 (8.7)	43.3 (7.7)	52.6 (6.8)	c < d
Motor Skills									
Grooved Pegboard Dominant (seconds)	72.1 (19.5)	44.7 (14.0)	67.0 (8.6)	47.2 (9.5)	67.6 (9.9)	47.8 (10.0)	63.8 (10.4)	48.7 (9.9)	
Grooved Pegboard Nondominant (seconds)*	78.9 (16.8)	41.0 (9.2)	74.7 (11.8)	44.3 (8.7)	74.5 (13.0)	45.2 (10.4)	69.6 (13.7)	47.7 (10.0)	a < d
Beck Depression Inventory**	14.0 (8.9)		11.6 (10.6)		13.2 (9.2)		5.5 (5.8)		a, b, c > d

** = $p < .005$; * = $p < .01$.

tive bias toward finding an additive effect since the most impaired group, the HIV+/METH+ group, reported the lowest prevalence of learning disability.

Follow-up analyses were also performed within the HIV+/METH+ group and within the HIV−/METH+ group to determine whether neuropsychological performance, as measured by the GDS, was associated with measures of quantity and frequency of methamphetamine use, as listed in Table 2. *T* tests were performed comparing dichotomous subgroups of each of the following methamphetamine use/frequency variables of interest: peak frequency (daily *vs.* less than daily), peak use (≥ 0.50 g *vs.* < 0.50 g), and amount of recent use (≥ 0.50 g *vs.* < 0.50 g). Results of the *t* tests were nonsignificant for all of the variables. Also of note, there were no differences for GDS within the groups for those with history of injection drug use *versus* those without.

DISCUSSION

The results of the present study indicate that HIV infection, methamphetamine dependence, and the combination of HIV infection and methamphetamine dependence are all associated with neuropsychological impairment. In addition to global cognitive status, impairments were noted among the groups with risk factors in several cognitive domains, including attention/working memory, learning, delayed recall, and motor skills. Consistent with our hypothesis, the results suggest that the combination of HIV and methamphetamine dependence is associated with additive deleterious effects on neuropsychological functioning relative to either risk factor alone.

With the exception of a single case report that suggested acceleration of HIV dementia in a person with methamphetamine and cocaine abuse (Nath et al., 2001) there have been no neuropsychological studies specifically addressing combined methamphetamine and HIV effects. A preliminary study by Taylor et al. (2000) provided the first evidence that there might be additive effects on brain metabolite alterations, suggesting greater brain injury when stimulants and HIV coexisted. Neuropathological evidence of additivity was also noted in a recently completed study by Langford and associates (2002). This study found greater reduction in calbindin immunostaining interneurons in frontal cortex in those dying with HIV who also had histories of methamphetamine dependence.

The mechanisms of possible enhancement of neurotoxicity by HIV and methamphetamine remain speculative at this time. Methamphetamine is thought to produce neural injury in at least three ways: by vascular injury; hyperthermia; and by metabolic changes that can lead to neurotoxicity and apoptosis. The injury to small vessels may include excess vasospasm, regional ischemia, and microinfarction. In addition, ischemic strokes and intracranial hemorrhage have been reported (Rothrock et al., 1988). Reduction in global cerebral perfusion has been observed in methamphetamine dependent persons who have been abstinent many months (Alhassoon et al., 2001). However, the relationship of lowered tracer uptake to neuropsychological deficit is unclear. Methamphetamine induced hyperthermia is another factor in neural injury. Though the precise mechanism remains unclear, in animal models efforts to reduce core temperature afford some neuroprotection.

Of more theoretical interest in terms of potentiation of HIV effects is the third pathway, wherein methamphetamine is thought to produce acute necrotic cell destruction and also programmed cell death (apoptosis; see review by Davidson et al., 2001). In brief, methamphetamine is believed to enter cells (particularly dopaminergic neurons) and displace dopamine (DA) from intracellular vesicular stores. Some DA released within the cell undergoes oxidation with resultant production of highly reactive species of oxygen and nitrogen containing molecules. One of these, peroxynitrite, is highly active and can damage proteins and lipids that support processes essential to cell survival. In this way, reactive oxygen and nitrogen species (RONS) can lead to necrotic cell death. RONS also can damage the cell's DNA and induce molecular changes that activate various enzymes (e.g., caspase 3) that lead to apoptosis. Because methamphetamine also enters mitochondria where its ability to raise pH interferes with the electron transport chain, the result can be disruption of the neuron's energy metabolism and calcium regulation, forming yet another path to cell injury and death.

Neurons damaged in this way release various molecules into the surrounding extracellular space, including RONS and glutamate, a molecule that binds to N-methyl-D-aspartate (NMDA) receptors resulting in influx of calcium into neurons. Such calcium influx can have wide ranging effects, including induction of an apoptotic cascade. Other molecules released into this "toxic soup" can activate astrocytes, and this may account for the observation that brains of animals receiving chronic methamphetamine, and some human brains, are characterized by regions of gliosis as well as neuronal loss (Langford et al., 2002).

The DA freed by methamphetamine's entry into cells can also be released by that cell, and this neurotransmitter then can affect cells downstream. Many of methamphetamine's behavioral effects are so mediated, but in addition, DA can cause other neurons to release glutamate, providing yet another possible pathway to the excitotoxic cascade.

The manner in which HIV produces brain injury remains imperfectly understood. Most current models hypothesize that neurons can be damaged both by direct actions of HIV products, as well as through more indirect mechanisms. For example, HIV molecules such as the viral envelope protein gp120 and the gene product tat each appears capable of enhancing glutamate release, activating NMDA receptors (Haughey et al., 2001; Lipton & Gendelman, 1995). Thus, one of the paths of cellular injury both in methamphetamine and HIV may involve disturbance in calcium homeostasis and excitotoxicity. GP120 also may attach to cell surface receptors (e.g., CXCR4) that may lead to molecular changes activating the apoptotic cascade (Hesselgesser et al.,

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1998). Therefore, there are at least two mechanisms that have some commonalities between HIV and methamphetamine induced injury.

Another mechanism might involve damage to cells and white matter from release of excess immune signaling molecules, such as interleukin 6 (IL6) and tumor necrosis factor alpha (TNF). Preliminary studies by Langford et al. (2002) indicate that methamphetamine dependent persons dying with HIV had more damage to interneurons than those with either factor alone. The authors suggested that augmented inflammatory responses with the combined insults might be responsible. Strengthening the possibility that one of the pathways of methamphetamine neurotoxicity involves IL-6 is the observation by Ladenheim et al. (2000) that transgenic mice with a null mutation for IL-6 had less neural injury from methamphetamine administration.

Although our findings are in agreement with early data emerging from other levels of observation, e.g., MRS and neuropathology, the results must be interpreted in the context of possible confounds, on the one hand, and conservative biases, on the other. In terms of confounds, the methamphetamine groups had relatively frequent histories of abuse and/or dependence on other substances. This problem is inherent in research on drug abusing populations, as it is rare to find people who exclusively abuse methamphetamine but no other drug.

Reducing the likelihood that other substances account for our findings is the fact that we excluded subjects who had recent histories of dependence on other drugs, and that the lifetime prevalence of combined and other substance dependence in the METH+ groups was 12 to 15%, meaning that a minority had such confounds. In regard to alcohol, which arguably would be the most likely to contribute impairment, the lifetime prevalence of alcohol dependence in our most impaired group (HIV+/METH+) was 26%, not statistically different from the HIV−/METH− group (10%). Moreover, the group with highest numbers of subjects with alcohol dependence history (HIV−/METH+ 34%) was actually less impaired than the HIV+/METH+ group. While the METH+ groups appear somewhat confounded, and it is not possible to perfectly discern the effects of methamphetamine, we would argue that the results with these groups are more generalizable to the methamphetamine-abusing population as a whole.

It is also possible that some characteristics of the subject groups may have limited our ability to estimate the additive effects of methamphetamine and HIV infection. For example, the HIV−/METH+ group reported significantly greater recent and peak quantity/frequency of methamphetamine use compared to the HIV+/METH+ group, and this might have increased impairment in the former. Differences such as these in subject characteristics may not be adequately controlled through statistical methods (Adams et al., 1985).

A second potential cause of conservative bias is reflected in the HIV−/METH− control group, which demonstrated a slightly higher rate of neuropsychological impairment than is typically observed in the general population. This result likely reflects our strategy of recruiting individuals for the control group who were as similar as possible to those individuals in the risk factor groups, particularly for characteristics that could affect neuropsychological functioning, such as demographics and history of other drug use. For example, the substance abusing population generally is less educated (21% of people admitted to treatment programs completed education beyond high school compared to 49% of the general population) and more likely to be unemployed or not in the labor force than the general population (33% *vs.* 71%; Substance Abuse and Mental Health Administration, 2000). The somewhat higher rate of neuropsychological impairment in the HIV−/METH− group may thus reflect its demographic characteristics, such as relatively high rates of unemployment (33%) as well as relatively higher prevalence rates of alcohol and other substance use compared to the general population. Although our recruitment strategy increases the likelihood that the HIV−/METH− group is not representative of the non-drug using population, it enhances the confidence that the observed group differences are due to methamphetamine use and/or HIV infection by taking into account some psychosocial variables that might independently influence neuropsychological performance in persons at risk for HIV infection or substance dependence.

Participants were not excluded for history of self-reported Attention Deficit Hyperactivity Disorder or learning difficulties, which promotes the generalizability of the current results. These variables, as well as other potential confounds, including differential proportion of males in the HIV+ groups and lower WRAT–3 scores in the HIV−/METH+ group, did not significantly influence the observed between group differences in rates and severity of NP impairment. Also promoting the generalizability of the test results is that the demographics of the current sample are comparable to those of the methamphetamine abusing population within the United States (predominantly White males in their early 30's).

Future research attempting to replicate the current findings should aim to determine what factors are predictive of neuropsychological impairment in these complex subject groups. In this regard, identifying, operationally defining and controlling for these factors will present ongoing challenges. For example, future research should assess the extent to which quantity and frequency of methamphetamine use may predict presence and degree of neuropsychological impairment. Although one study of amphetamine users demonstrated a relationship between severity of use and cognitive impairment (McKetin & Mattick, 1997), dose response relationships typically have been difficult to demonstrate in research with alcohol and other substance abuse. Longitudinal study of participants with comorbid HIV infection and methamphetamine abuse also will be important to determine if changes in use (abstinence or relapse) are associated with alterations in neurobehavioral or immune status. For example, beyond the effects of neuropsychological functioning, methamphetamine use may affect medication ad-

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herence and survival rates or disease progression in the HIV seropositive population.

The current results represent an initial attempt to characterize the neuropsychological effects of concurrent HIV infection and methamphetamine dependence. Despite limitations due to subject characteristics that are inherent in research with the substance abusing population, our results indicate that seropositive individuals with methamphetamine dependence are at a greater risk for neuropsychological impairment than individuals with either of these risk factors alone. If confirmed, these data point to the possibility of some commonalities in underlying mechanisms of neuropathogenesis.

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