

Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure

Raul Gonzalez^{a,b,1}, Julie D. Rippeth^{a,c}, Catherine L. Carey^{a,b}, Robert K. Heaton^{a,b,c}, David J. Moore^{a,b}, Brian C. Schweinsburg^{a,b,d}, Mariana Cherner^{a,c}, Igor Grant^{a,c,d,*}

^a HIV Neurobehavioral Research Center, University of California, San Diego, 150 W. Washington Street, 2nd Floor, San Diego, CA 92103, USA

^b San Diego State University/University of California, San Diego – Joint Doctoral Program in Clinical Psychology, 6363 Alvarado Court, Suite 103, San Diego, CA 92120, USA

^c Department of Psychiatry, University of California, San Diego 0680, 9500 Gilman Drive, La Jolla, CA 92093-0680, USA

^d VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA

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Abstract

Abuse of the stimulant drug methamphetamine is associated with neural injury and neuropsychological (NP) deficits, while the residual effects of marijuana use remain uncertain. We sought to determine if methamphetamine dependent persons who also met criteria for marijuana abuse or dependence evidenced different NP performance than those with dependence for methamphetamine alone. We examined three groups that did not differ significantly on important demographic factors: (1) subjects with a history of methamphetamine dependence and history of marijuana abuse/dependence (METH+/MJ+, $n = 27$); (2) methamphetamine dependent subjects without history of marijuana abuse/dependence (METH+/MJ–, $n = 26$); (3) a control group with minimal or no drug use ($n = 41$). A comprehensive NP battery was administered and performance was quantified for five cognitive ability areas. The METH+/MJ– group generally demonstrated the greatest NP impairment, with statistically significant differences observed between the METH+/MJ– and control group in learning, retention/retrieval, and a summary score of global NP performance. The METH+/MJ+ group did not differ significantly from the control or METH+/MJ– group on any NP ability. However, there was a significant linear trend in the global NP score suggesting that the METH+/MJ+ performed intermediate to the control and METH+/MJ– groups. Based on these findings, we cannot conclude that there is a protective effect of marijuana use in methamphetamine users; however, marijuana use clearly did not appear to exacerbate methamphetamine neurotoxicity. Further investigations are needed to determine if the emerging literature, suggesting that certain cannabinoids might have neuroprotective actions, is generalizable to community-dwelling substance abusers.

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1. Introduction

Marijuana and methamphetamine are two widely used illicit drugs in the United States. The results from the National Household Survey on Drug Abuse indicate that approximately 83 million Americans have used marijuana and 8.8 million have used methamphetamine (SAMHSA, 2001). Marijuana is the most common secondary drug of abuse among methamphetamine users (Simon et al., 2002).

Based on self-report and anecdotal data, we have noticed that participants at our research center are likely to take these substances in combination. While it is generally assumed that abuse of each additional substance augments damage to the brain, substances may interact differently with each other and modulate neurochemical processes in distinct ways. Thus, the neurocognitive outcome of combining substances is likely to be much more complex.

Preclinical studies indicate that the central nervous system stimulant methamphetamine may be neurotoxic, and initial clinical observations have associated abuse of methamphetamine with neurocognitive impairments. Complicating interpretation of such clinical data is the fact that methamphetamine is rarely used on its own; rather, contemporaneous or sequential abuse of other substances is commonplace.

* Corresponding author. Tel.: +1 858 534 3652; fax: +1 858 534 7723.

E-mail address: igrant@ucsd.edu (I. Grant).

¹ The lead author (RG) completed this investigation at the University of California, San Diego, and is currently on internship at the University of Illinois at Chicago.

As noted, one of the most frequently co-abused substances is marijuana, whose neurobehavioral effects have also been the subject of much interest. The question posed in the current study is how the comorbid dependence or abuse of methamphetamine and marijuana influence neurocognitive outcome. Below we discuss a few mechanisms by which methamphetamine may interact with cannabinoids.

Concerning methamphetamine, several theories have been proposed to account for its deleterious effects on the brain (reviewed in Davidson et al., 2001; Frost and Cadet, 2000; Kleven and Seiden, 1992; Seiden and Sabol, 1996), including its ability to damage cerebrovasculature through ischemia and vasculitis (Rumbaugh et al., 1971, 1980). In addition to cerebrovascular damage, methamphetamine also produces excitotoxic injury to neurons through dopaminergic and glutamatergic systems (Davidson et al., 2001; Marshall et al., 1993; Ohmori et al., 1996; Stephans and Yamamoto, 1994; Wilson et al., 1996). Methamphetamine induces increased transmission in these systems and may promote neuronal damage through the resulting formation of reactive oxygen and nitrogen species (Frost and Cadet, 2000; Yamamoto and Zhu, 1998). Neuroimaging studies have demonstrated that methamphetamine users exhibit various abnormalities in brain function relative to healthy controls. These include alterations in frontal, temporal, and subcortical brain metabolism (Gouzoulis-Mayfrank et al., 1999; Iyo et al., 1997; Volkow et al., 2001a), changes in brain metabolites suggestive of neuronal injury in the basal ganglia and frontal cortex (Ernst et al., 2000), and decreased density of dopaminergic neurons in the caudate and putamen (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001b). Although few studies have explicitly attempted to examine the cognitive functioning of methamphetamine users, recent investigations have documented deficits in learning, delayed recall, processing speed, and working memory (Rippeth et al., 2004; Simon et al., 2000).

While various lines of evidence converge on the conclusion that methamphetamine abuse may be associated with brain injury, the data concerning marijuana abuse are less clear. The literature on neurocognitive complications of heavy marijuana use has yielded mixed results. Recent reviews, including a meta-analytic study by our group, failed to reveal conclusive evidence of long-term, significantly deleterious effects on neurocognitive functioning (Gonzalez et al., 2002; Grant et al., 2003; Pope et al., 1995). Despite these findings, it might be plausible to speculate that even if the effects of chronic marijuana use in an otherwise normal person might be clinically insignificant, such use in the context of heavy exposure to drugs that are known to be neurotoxins might lead to additive damage.

Complicating matters further has been the emergence in recent years of evidence to suggest that some cannabinoids might actually protect the central nervous system from certain types of injury (Fride and Shohami, 2002; Guzman et al., 2001; Marsicano et al., 2002; Mechoulam, 2002; Mechoulam et al., 2002a,b). The mechanisms of neuropro-

tection may include the ability of cannabinoids to inhibit the release of the excitatory neurotransmitter glutamate, and to inhibit the production of reactive oxygen species (ROS). In various experiments, several cannabinoids have been shown to dampen experimentally induced excitotoxic injury in rodent brain tissue; these cannabinoids include tetrahydrocannabinol (THC) and cannabidiol (Abood et al., 2001; Hampson et al., 1998; van der Stelt et al., 2001a) as well as the synthetic cannabinoid agonists WIN-55,212 (Shen et al., 1996; Shen and Thayer, 1998a,b) and HU-211 (Nadler et al., 1993). Cannabidiol, THC, and HU-211 are also potent antioxidants (Hampson et al., 1998, 2000) and have been shown to successfully reduce ROS. Additionally, many of these compounds, as well as the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol, have been shown to attenuate brain injury in several animal models of ischemia (Lavie et al., 2001; Leker et al., 1999; Louw et al., 2000; Nagayama et al., 1999; Panikashvili et al., 2001; Sinor et al., 2000; van der Stelt et al., 2001b). In fact, a randomized, placebo controlled, phase II clinical trial reported that patients receiving HU-211 (dexanabinol) as a treatment for severe closed head injury improved on several outcome measures of recovery (Knoller et al., 2002).

Despite the suggestions that cannabinoids might be neuroprotective under certain circumstances, their impact on brain function in methamphetamine abusers is difficult to predict. To date, the complex neurochemical cascades associated with the administration of either substance, alone or in combination, are not fully understood. There is reason, however, to suspect that certain aspects of the mechanisms by which these substances produce their respective neurobiological effects may show some overlap. Despite the likelihood of comorbid abuse and possible neuropharmacological interactions, we have found no studies examining the combined effects of methamphetamine and cannabis on cognitive functions. In order to begin assessing the clinical impact of marijuana use on methamphetamine-associated neurotoxicity, we examined the neuropsychological (NP) performance of methamphetamine abusers with and without a significant history of heavy marijuana use, while controlling as much as possible for other influences, such as experience with other substances, psychiatric factors, and demographics. The existing knowledge base did not allow us to predict whether the combined users would perform worse, the same, or better than methamphetamine abusers who had less exposure to marijuana—any of these three outcomes would be theoretically plausible.

2. Methods

2.1. Participants

The study sample consisted of 94 HIV-seronegative participants from NeuroAIDS: Effects of Methamphetamine (a NIDA funded program project examining

the neuropsychological effects of methamphetamine dependence on HIV-positive individuals). These participants were selected from the same cohort that was examined in a previous study by Rippeth et al. (2004). Participants were categorized into one of three groups depending on their substance use history: (1) history of significant methamphetamine dependence [DSM IV criteria] but not marijuana abuse or dependence (METH+/MJ-, $n = 26$); (2) history of methamphetamine dependence and marijuana abuse or dependence (METH+/MJ+, $n = 27$); (3) no history of significant drug use (METH-/MJ-, $n = 41$). Participants were recruited from the San Diego area through the use of flyers, print advertisements, and appearances at community events. Additionally, participants for both methamphetamine-using groups (METH+/MJ- and METH+/MJ+) were also recruited from residential drug treatment programs in the San Diego area. All participants gave written consent prior to enrollment in the program project.

Participants in both methamphetamine-using groups met DSM-IV criteria for methamphetamine dependence during their lifetime as diagnosed by the structured clinical interview for DSM-IV Axis I disorders (SCID; First et al., 1996). They also met criteria for methamphetamine abuse or dependence within 18 months of the examination. Participants in the METH+/MJ+ group also met DSM-IV criteria for marijuana abuse or dependence during their lifetime. Potential participants were excluded if they had a history of head injury with loss of consciousness greater than 30 min, or had a history of other neurological or psychiatric thought disorders.

Participants in 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 and lengthy period” of alcohol dependence at any time during their lifetime, which was determined by a clinician on a case-by-case basis. Generally, participants were excluded for periods of alcohol dependence greater than or equal to 5 years, particularly when the period of dependence was within 10 years of their assessment. However, participants were not excluded for history of alcohol abuse given the high frequency of this diagnosis in methamphetamine dependent individuals. Participants in all groups were also excluded

if they (1) met dependence criteria for any other substance within 5 years of the evaluation; (2) met criteria for other substance dependence of “significant and lengthy” duration at any time in their lives; or (3) met abuse criteria for any other substance within 1 year of their evaluation. No participant met abuse or dependence criteria for any substance (including alcohol, methamphetamine, or marijuana) within 30 days of the examination.

Prior to their assessment, all participants completed a urine toxicology screen (QuickScreen™ Drug Abuse Panel; Phamatech Inc., San Diego, CA) and a breathalyzer test for alcohol (Alco Sensor™; Intoximeter Inc., St. Louis, MI). If a participant tested positive for specific substances of abuse (i.e., amphetamine, methamphetamine, cocaine, opiates, or phenylcyclidine) on urine toxicology screen or had a positive reading for alcohol on the breathalyzer test, their assessment was suspended and rescheduled for a later date.

Table 1 presents descriptive data for the three study groups. Individuals were selected to ensure that they did not differ significantly on demographics (i.e., age, sex, ethnicity), educational factors (i.e., years of education and history of academic difficulties), and performance on the Reading subtest of the Wide Range Achievement Test – Third Edition (WRAT-III; Wilkinson, 1993). Academic difficulties were defined as reported history of learning disabilities, failure to pass a grade, and/or placement in special classes to address academic deficits.

2.2. Assessment procedures

2.2.1. Neuropsychological testing

A comprehensive neuropsychological assessment was administered as part of a larger full-day evaluation, which also included physical and neurological examinations, collection of a standardized medical history, and a structured interview for psychiatric and substance use histories. All protocols were conducted by trained examiners, which included psychometrists, clinical psychology graduate students, post-doctoral researchers, and nurse practitioners.

The neuropsychological battery was comprehensive and assessed cognitive functioning in several ability areas. The ability areas with their respective measures are as follows:

Table 1

Demographic information (mean \pm S.D. or number and percentage) for three participant groups differing on history of marijuana and methamphetamine use

	METH-/MJ- ($n = 41$)	METH+/MJ- ($n = 26$)	METH+/MJ+ ($n = 27$)	Omnibus P -value
Age	34.63 (11.34)	39.38 (10.02)	36.11 (9.52)	0.20
Number of women	21 (51%)	12 (46%)	7 (26%)	0.10
Number of Caucasian participants	26 (63%)	20 (77%)	22 (82%)	0.22
Number of African-American	4 (10%)	1 (4%)	2 (7%)	–
Number of Hispanic	9 (22%)	3 (12%)	2 (7%)	–
Number of other ethnicity	2 (5%)	2 (8%)	1 (4%)	–
Years of education	12.93 (1.63)	12.12 (2.12)	12.15 (1.54)	0.10
WRAT-3 reading SS	101.54 (11.63)	96.08 (11.77)	99.74 (9.16)	0.15
Percent with Academic Difficulties	7.3	19.2	18.5	0.25

WRAT-3: Wide Range Achievement Test – Third Edition; SS: standard score; METH: methamphetamine; MJ: marijuana.

1. *Verbal fluency* (VF): Controlled Oral Word Association Test, letter fluency (FAS) (Borkowski et al., 1967) and category fluency, animals (Borkowski et al., 1967);
2. *Abstraction/executive functioning* (Exec): Halstead Category Test (Halstead, 1947); Trail Making Test, Part B (Army Individual Test Battery, 1944);
3. *Attention/working memory* (Attn/WM): WAIS-III Letter Number Sequencing (Wechsler, 1997); Paced Auditory Serial Addition Task (PASAT: Gronwall, 1977);
4. *Learning*: Hopkins Verbal Learning Test – Revised (HVLTR), Total Recall (Benedict et al., 1998); Brief Visuospatial Memory Test – Revised (BVMT-R), Total Recall (Benedict et al., 1996); Story Memory Test, Learning Score (Heaton et al., 1991); Figure Memory Test, Learning Score (Heaton et al., 1991);
5. *Delayed recall/retention* (Rec/Ret): HVLTR, delayed recall (Benedict et al., 1998); BVMT-R, delayed recall (Benedict et al., 1996); Story Memory Test, percent loss (Heaton et al., 1991); Figure Memory Test, percent loss (Heaton et al., 1991);
6. *Motor*: Grooved Pegboard Test, dominant and non-dominant hand (Kl ve, 1963).

Raw scores for all tests were converted to *T*-scores using the most comprehensive normative data available, correcting for age, education, sex, and ethnicity whenever possible (Benedict et al., 1996, 1998; Diehr et al., 1998; Gladsjo et al., 1999; Heaton et al., 1991, 2002). Deficit scores (*D*-scores) were calculated by converting demographically corrected *T*-scores for each test to a zero to five point 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 (Heaton et al., 1994, 1995). Much like clinicians' ratings, this method of transforming participants' scores emphasizes deficits in neuropsychological performance while minimizing the impact of superior performance on any particular NP test when averaging scores. Ability specific *D*-scores were computed by averaging the *D*-scores for tests within each cognitive ability area for each participant. In addition, a global deficit score (GDS) was calculated for each participant by averaging the *D*-scores for all NP battery tests. *D*-scores have been found to closely approximate clinical ratings of NP impairment in a sample with suspected frontal-subcortical dysfunction (Heaton et al., 1995). Furthermore, their utility at detecting NP impairment has been demonstrated in several additional investigations (Carey et al., in press; Gonzalez et al., 2003; Heaton et al., 1994; Rippeth et al., 2004).

2.2.2. Assessment of comorbid disorders

Structured clinical interviews were conducted to assess the prevalence of several comorbid factors that could potentially affect neuropsychological performance. The mood disorders module of the SCID was administered to determine if a participant met criteria for current or lifetime major depressive disorder or bipolar affective disorder. Antisocial

personality disorder (ASPD) was assessed with the ASPD module of the structured clinical interview for DSM-III-R personality disorders (SCID-II; Spitzer et al., 1987). The attention-deficit hyperactivity disorder (ADHD) section of the Diagnostic Interview Schedule for DSM-IV (DIS-L; Robins et al., 1999) was used to identify if a participant had a history of ADHD.

2.2.3. Substance use diagnosis and history

Current and lifetime history of alcohol and other substance abuse/dependence was assessed by administering selected modules of the SCID. Additionally, a detailed lifetime history of the participants' substance use was obtained through a semi-structured clinical interview. Frequency and quantity of substance consumption were gathered for each 5-year epoch over a participant's lifetime, the last 30 days, and for the last 12 months. For all substances, ordinal ratings for frequency were assigned using a six-point scale as follows: 0: no use; 1: more than once a month; 2: <1 day a week; 3: 1–3 days a week; 4: 4–6 days a week; 5: every day. Ordinal ratings for quantity were based on a five-point scale, the value of which depended on the substance queried. Midpoints for ranges represented by ordinal variables were calculated for both frequency and quantity of use for each substance. Their product was computed for each 5-year epoch and added across a participant's lifetime. In this manner, an estimate of lifetime substance use was obtained for each substance.

2.3. Data analysis

Statistical analyses were performed using JMP 3.2.6 (SAS Institute Inc., Cary, NC). In order to assess between-group differences on neuropsychological performance, *D*-scores for individual neuropsychological tests were averaged within each ability area and used as dependent variables in one-way ANOVAs. In order to conform to assumptions of normality, a square-root transformation was applied to *D*-score dependent variables. Statistically significant between-group differences in an ability area ($P < 0.05$) were followed-up by examining all pair-wise comparisons using the Tukey–Kramer honestly significant difference (H.S.D.) test at an alpha level of 0.05. Chi-square tests were used to compare between-group differences on rates of neuropsychological impairment, comorbid disorders, and past dependence for other substances (other than methamphetamine or marijuana). Due to the skewed distribution of estimates for lifetime substance use, between-group comparisons pertaining to amount of lifetime substance use were analyzed using nonparametric tests.

3. Results

3.1. Neuropsychological performance

Neuropsychological performance for each group across cognitive ability areas is presented in Table 2. Significant

Table 2

Deficit-scores (mean \pm S.D.) reflecting neuropsychological performance across cognitive ability areas for three participant groups differing on history of marijuana and methamphetamine use

	METH-/MJ- (<i>n</i> = 41)	METH+/MJ+ (<i>n</i> = 27)	METH+/MJ- (<i>n</i> = 26)	Omnibus <i>P</i> -value	Pair-wise comparisons ^a
Global	0.28 (0.25)	0.41 (0.40)	0.57 (0.50)	0.0093	Control < METH+/MJ-
Exec	0.33 (0.66)	0.30 (0.50)	0.54 (0.99)	0.75	ns
Attn/WM	0.21 (0.43)	0.37 (0.60)	0.48 (0.73)	0.22	ns
VF	0.23 (0.40)	0.17 (0.31)	0.27 (0.59)	0.84	ns
SIP	0.12 (0.26)	0.21 (0.35)	0.24 (0.48)	0.47	ns
Learning	0.50 (0.54)	0.62 (0.74)	0.97 (0.92)	0.032	Control < METH+/MJ-
Rec/Ret	0.27 (0.43)	0.51 (0.81)	0.78 (0.90)	0.020	Control < METH+/MJ-
Motor	0.23 (0.60)	0.63 (0.95)	0.58 (1.01)	0.076	ns

Deficit-score values are presented as means and standard deviations; higher deficit-scores indicate poorer performance; Exec: executive/abstraction; Attn/WM: attention/working memory; VF: verbal fluency; SIP: speed of information processing; Rec/Ret: recall/retention; ns: not statistically significant; METH: methamphetamine; MJ: marijuana.

^a All pair-wise comparisons were examined using Tukey's H.S.D. ($\alpha = 0.05$).

between-group differences ($P < 0.05$) were observed on average *D*-scores in learning ($F_{2,91} = 3.58$), recall/retention ($F_{2,91} = 4.09$), and global (GDS) performance ($F_{2,91} = 4.92$). Follow-up analyses examining all pair-wise comparisons revealed statistically significant differences between the METH+/MJ- group relative to the Control group, indicating poorer performance by the former. Although the METH+/MJ+ group showed better performance than the METH+/MJ- group across most ability areas, no statistically significant differences were observed between these two groups, or between the METH+/MJ+ and the

Control group. To provide readers with further information regarding participant performance, Table 3 provides raw scores for each of the neuropsychological measures administered for each cognitive ability area.

Classifications of overall NP impairment were determined based on participants' global performance across all NP tests (i.e., GDS). Those obtaining GDS >0.40 were classified as showing global NP impairment. This cut-point was previously determined and validated in another investigation (Rippeth et al., 2004). Fig. 1 presents rates of NP impairment across the three study groups. The METH+/MJ-

Table 3

Raw scores (mean \pm S.D.) reflecting neuropsychological performance across cognitive ability areas for three participant groups differing on history of marijuana and methamphetamine use

	METH-/MJ- (<i>n</i> = 41)	METH+/MJ- (<i>n</i> = 26)	METH+/MJ+ (<i>n</i> = 27)
Verbal fluency			
FAS: total words	40.1 (9.9)	40.1 (12.8)	42.1 (8.1)
Animals: total words	21.4 (4.4)	21.2 (4.1)	22.0 (5.2)
Abstraction/executive			
Halstead Category Test (number of errors) [†]	38.1 (22.6)	54.5 (26.9)	44.3 (24.0)
Trail Making Test B (s) [†]	68.0 (36.8)	85.8 (61.7)	63.8 (23.4)
Attention/working memory			
WAIS-III Letter Number Seq.: total score	10.8 (2.4)	10.4 (2.6)	11.1 (2.6)
Paced Auditory Serial Addition Test: total score	108.4 (27.1)	106.3 (40.2)	104.9 (29.6)
Learning			
Hopkins Verbal Learning Test-R: total recall	27.9 (3.6)	26.3 (4.3)	26.5 (3.4)
Brief Visuospatial Memory Test-R: total recall	26.0 (5.8)	21.7 (5.7)	24.4 (5.6)
Story Memory Test: learning score	13.7 (5.6)	9.7 (5.9)	10.3 (3.8)
Figure Memory Test: learning score	8.9 (4.3)	5.9 (2.8)	8.8 (4.7)
Delayed recall/retention			
Hopkins Learning Test-R: delayed recall	10.1 (1.4)	9.0 (2.2)	9.1 (1.6)
Brief Visuospatial Memory Test-R: delayed recall	10.1 (1.6)	8.8 (2.2)	9.8 (1.8)
Story Memory Test (%loss) [†]	10.7 (9.7)	16.0 (10.2)	9.5 (9.7)
Figure Memory Test (%loss) [†]	10.6 (14.8)	11.8 (20.1)	13.1 (28.5)
Motor			
Grooved Pegboard Test (dominant) (s) [†]	63.7 (6.1)	65.2 (8.4)	68.7 (13.4)
Grooved Pegboard Tests (non-dominant) (s) [†]	69.4 (8.6)	75.3 (11.4)	74.2 (11.1)

For most measures, higher scores indicate better performance.

[†] Denotes that higher scores indicate poorer performance.

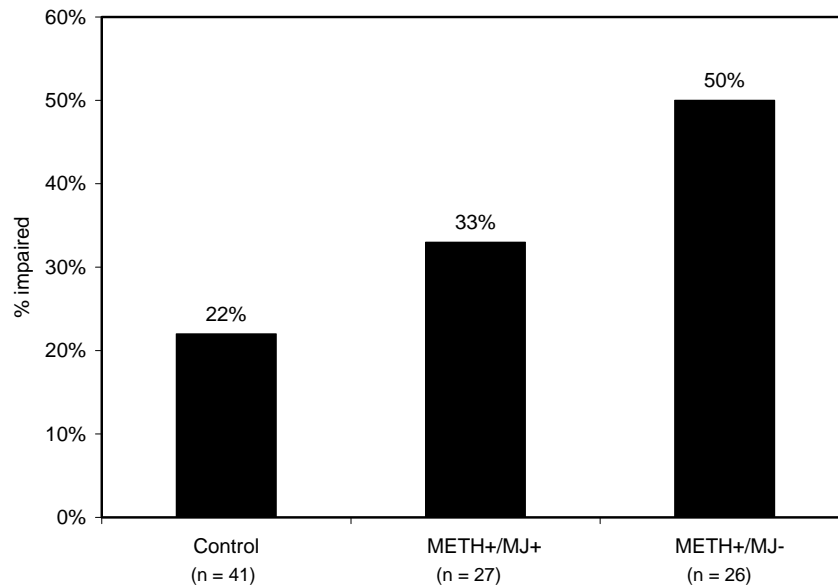


Fig. 1. Prevalence of global neuropsychological impairment (%) based on global deficit scores among three participant groups differing on history of marijuana and methamphetamine use.

group was found to have the highest prevalence of NP impairment, with lower rates of impairments observed in the METH+/MJ+ and Control groups, respectively. Again, statistically significant group differences were only observed between the Control and METH+/MJ- group (χ^2 (1, $N = 67$), $P = 0.012$). A visual inspection of impairment rates across the three groups (Fig. 1) suggested a linear increase in NP impairment. In order to test this hypothesis, a linear regression was conducted using GDS performance as a continuous dependent variable and group membership as an independent variable, such that the Control, METH+/MJ+, and METH+/MJ- groups were dummy-coded 0, 1, and 2, respectively. The results confirmed that overall NP performance worsened linearly across the three groups ($F_{1,92} = 9.75$, $R^2 = 0.096$, $P = 0.0024$).

3.2. Other substance use and comorbid psychiatric disorders

Analyses were conducted to determine if estimates for lifetime consumption of alcohol, methamphetamine, and/or marijuana differed between the methamphetamine-using groups. No statistically significant differences were observed ($z = -0.28$, $P = 0.78$) on estimates of lifetime methamphetamine consumption between the METH+/MJ- group (median = 2784 g, IQR [1345, 5158]) and the METH+/MJ+ group (METH+/MJ+: median = 3462 g, IQR [958, 5837]). As expected, the METH+/MJ+ group demonstrated significantly higher estimates for lifetime consumption of marijuana ($z = -2.89$, $P = 0.0038$; METH+/MJ-: median = 608 joints, IQR [40, 5103]; METH+/MJ+: median = 3614 joints, IQR [1542, 8133]).

The two groups did not differ ($z = 0.63$, $P = 0.53$) on estimates of lifetime alcohol consumption (METH+/MJ-: median = 17 460 drinks, IQR [2055, 45 353]; METH+/MJ+: median = 8250, IQR [1560, 34 500]). Our Control group reported relatively minimal use of these substances over their lifetime (alcoholic drinks: median = 570, IQR [90, 2880]; grams of methamphetamine: median = 0, IQR [0, 2.4]; marijuana joints: median = 8.3, IQR [0, 59.5]).

METH+/MJ- and METH+/MJ+ groups were also compared on prevalence of remote/episodic dependence for substances other than methamphetamine and marijuana. "Remote/episodic" dependence was examined on a case-by-case basis and was deemed to generally represent meeting dependence criteria for a substance (which was not the participant's substance of choice) greater than 5 years prior to the current examination. Significant differences did not emerge on rates of remote/episodic history of dependence for alcohol, hallucinogens, or opiates. No participants in either group met criteria for dependence of sedatives. However, the METH+/MJ+ group demonstrated a significantly greater prevalence of remote/episodic dependence for cocaine (χ^2 (1, $N = 53$) = 7.004, $P = 0.0081$). A summary of these results can be found in Table 4.

In addition, we compared the METH+/MJ- and METH+/MJ+ groups on rates of lifetime history for the following potential confounds: major depressive disorder, bipolar affective disorder, attention-deficit hyperactivity disorder, and antisocial personality disorder. The METH+/MJ- and METH+/MJ+ groups showed no significant differences in lifetime prevalence for any of these comorbid disorders (Table 4).

Table 4

History of DSM-IV substance dependence and psychiatric disorders among three participant groups differing on history of marijuana and methamphetamine use

	METH–/MJ– (n = 41)	METH+/MJ– (n = 26)	METH+/MJ+ (n = 27)	METH+/MJ– vs. METH+/MJ+ <i>P</i> -value
With remote/episodic dependence (%)				
Alcohol	7.0	44.0	40.7	0.81
Opiates	0	0	7.4	0.096
Cocaine	0	7.7	37.0	0.0081
Hallucinogens	0	3.9	0	0.23
With other psychiatric disorders (%)				
Major depressive disorder	22.5	40.0	28.0	0.37
Bipolar affective disorder	0	4.0	7.4	0.59
ADHD	12.2	15.4	18.5	0.72
ASPD	0	20.0	30.8	0.40

ADHD: attention deficit, hyperactivity disorder; ASPD: antisocial personality disorder; METH: methamphetamine; MJ: marijuana.

4. Discussion

In this study we explored how comorbid, heavy exposure to marijuana affected the neuropsychological status of methamphetamine dependent persons. The literature suggested that any of three scenarios was plausible. First, assuming that use of multiple drugs would result in additive damage to brain functions, persons with a history of heavy use of both marijuana and methamphetamine might manifest more neuropsychological disturbance than those using methamphetamine alone. Second, because some cannabinoids are shown to have actions that might counteract the neurotoxic cascade produced by methamphetamine, individuals with patterns suggestive of combined use might actually perform better on neuropsychological tests than those that used methamphetamine alone. Finally, marijuana use might make no difference in the cognitive performance of methamphetamine users.

Our results are most compatible with the second scenario. A regression analysis for ordinal trends in the global deficit score revealed a statistically significant linear trend, indicating that neurocognitive performance worsened across the three groups. That is, the neuropsychological performance of the METH+/MJ+ group tended to fall between that of minimally substance using controls and the METH+/MJ– group. Despite the intriguing conclusions from the linear trend analysis, the results must be viewed cautiously. Although ANOVAs for global and individual cognitive ability areas detected differences between controls and the METH+/MJ– group in several analyses, statistically significant differences between the METH+/MJ+ group and the METH+/MJ– group were not revealed. Therefore, we cannot conclude that marijuana use exhibited a protective effect in our sample of methamphetamine users. Our results do suggest, however, that history of marijuana use does not appear to exacerbate methamphetamine-associated cognitive impairments.

If we accept for the moment that the METH+/MJ+ group demonstrated less neurocognitive impairment than might

be expected based on the performance observed in the METH+/MJ– group, then several questions arise. First, is the “protective” effect of marijuana seen across all ability areas, or is it selective? Once again, our data provide clues, but no firm conclusions. From Table 2 we note that the METH+/MJ– group differs from controls in learning and recall/retrieval of new information. In terms of motor skills, there was a possible trend toward statistically significant differences between both METH groups and controls. This pattern of results suggests that the ability area that may be best preserved in METH+/MJ+ users is learning of new information, while motor skills do not show a similar “benefit.” If such pattern differences are replicated in future analyses, it may provide information regarding the underlying interactions between methamphetamine and marijuana. Langford and colleagues (in submission) have reported selective loss of calbindin containing GABA-ergic interneurons in the autopsies of some methamphetamine users. They suggested that resultant loss of inhibitory control might lead to nervous system excitability, with susceptibility to seizures and glutamate mediated excitotoxic cellular injury. Because the hippocampus may be particularly vulnerable to this mechanism of injury, it follows that whatever beneficial effects cannabinoids may exert through the dampening of neural excitability would be most apparent in this brain region. The antioxidant properties of cannabinoids might also protect against the downstream effects of hyperexcitability by scavenging toxic products such as reactive oxygen and nitrogen species (Hampson et al., 1998, 2000).

While human studies with larger sample sizes would be helpful in confirming whether marijuana using methamphetamine addicts are more susceptible to cognitive impairments, the unraveling of mechanisms may require animal models in which experimental conditions can be controlled. The chronic methamphetamine rat model developed by Segal and Kuczenski (1997a,b) might prove a fruitful approach. This experimental animal model may better address our question by examining if pre-treatment

with selected cannabinoids can attenuate the neural injury produced by chronic methamphetamine administration.

Beyond the small sample sizes and resultant attenuation of power, several other factors and limitations need to be considered in interpreting the present data. For example, it is possible that the two METH groups differed in ways other than marijuana exposure. Nevertheless, Table 3 reveals that the groups were actually fairly equivalent in terms of other drug use, with the exception that the prevalence for a history of cocaine dependence was greater in the METH+/MJ+ group. We do not expect that our conclusions were affected by this finding as it would have introduced a conservative bias; that is, we might expect greater cocaine use to predict more NP impairment, rather than less. In addition, as described in Section 2, history of dependence for cocaine was remote and episodic. It is also worth noting that the two METH groups were statistically similar in alcohol exposure, though the median use in the METH+/MJ– group was higher. Another point to consider is that many individuals in our METH+/MJ– group also had a history of cannabis use, albeit significantly less so than observed in the METH+/MJ+ group. Therefore, to the degree that marijuana may indeed provide neuroprotection, the degree of impairment in the METH+/MJ– group may be underestimated. Other factors which might independently influence NP results (i.e., age, education, or history of ADHD or ASPD) were not found to differ significantly between both methamphetamine-using groups. Finally, we did not ascertain whether individuals in our METH+/MJ+ group consumed marijuana and methamphetamine concurrently (i.e., within hours of each other). Although we know that participants in this group were heavy users of marijuana and met criteria for lifetime history of cannabis dependence or abuse, it is likely that many of them may have used methamphetamine on occasion, without consuming cannabis. It would be useful if further studies examined whether the amount of time between administration of methamphetamine and marijuana mediates cognitive performance.

In conclusion, we report that the neuropsychological performance of people with histories of both methamphetamine dependence and heavy marijuana use was at a level between non-substance using controls and methamphetamine dependent persons who did not have histories of heavy marijuana use. If confirmed, these data may be consistent with emerging evidence from laboratory and animal research that some cannabinoids might protect against mechanisms of neural injury such as those thought to occur in chronic users of methamphetamine. Additionally, our findings support the assertion that neuropsychological impairments do not invariably increase with the use of additional substances. Each substance of abuse has a distinct neurobiologic signature, and can interact with other substances, both in terms of modulating their effects or altering their metabolism in unique ways. Therefore, it is important to consider these interactions when examining the impact of specific substances on

the neuropsychological abilities of “real world” drug users. Investigations of this kind not only provide information on the impact of drug abuse on cognitive functions, but can also serve to inform studies using animal models designed to explore underlying mechanisms of neurotoxicity and neuroprotection.

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The San Diego HIV Neurobehavioral Research Center (HNRC) group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the San Diego Veterans Affairs Healthcare System, and includes: Director: Igor Grant, M.D.; Co-Directors: J. Hampton Atkinson, M.D. and J. Allen McCutchan, M.D.; Center Manager: Thomas D. Marcotte, Ph.D.; Naval Hospital San Diego: Mark R. Wallace, M.D. (P.I.); Neuromedical Component: J. Allen McCutchan, M.D. (P.I.), Ronald J. Ellis, M.D., Scott Letendre, M.D., Rachel Schrier, Ph.D.; Neurobehavioral Component: Robert K. Heaton, Ph.D. (P.I.), Mariana Cherner, Ph.D., Julie Rippeth, Ph.D., Joseph Sadek, Ph.D., Steven Paul Woods, Psy.D.; Imaging Component: Terry Jernigan, Ph.D. (P.I.), John Hesselink, M.D.; Neuropathology Component: Eliezer Masliah, M.D. (P.I.); Clinical Trials Component: J. Allen McCutchan, M.D., J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., Scott Letendre, M.D.; Data Management Unit: Daniel R. Masys, M.D. (P.I.), Michelle Frybarger, B.A. (Data Systems Manager); Statistics Unit: Ian Abramson, Ph.D. (P.I.), Reena Deutsch, Ph.D., Deborah Lazzaretto, M.A.

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