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NEUROPSYCHOLOGICAL CORRELATES OF URINE TOXICOLOGY RESULTS

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Abstract

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1. The present study evaluated neuropsychological differences among 4 groups of men and women, aged 15 to 61 years. The groups were defined on the basis of urine toxicology screens indicating recent cocaine (n=12), cannabis (n=14), or multiple drug (n=7) use, or no such use (n=21).
2. The Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Trail Making Tests, and the Porteus Maze Test were administered to all subjects.
3. Analyses revealed no significant differences between the groups in age, gender composition, or in the proportion of group members with personal histories of alcohol/drug abuse or dependence, or Anti-Social Personality Disorder.
4. The cocaine positive group exhibited statistically significant impairments in Verbal IQ, as well as on Information, Vocabulary, Comprehension, Picture Completion, and Trails B subtests. The other experimental groups did not differ from the urine negative group.

Keywords: cocaine, intellectual functioning, neuropsychology, substance abuse, urine toxicology.

Abbreviations: antisocial personality disorder (ASPD), Collaborative Study on the Genetics of Alcoholism (COGA), Porteus maze test (PMT), Wechsler Adult Intelligence Scale-Revised (WAIS-R).

Introduction

During the past 10 to 15 years, there has been considerable discussion and debate regarding the diagnosis of problematic cocaine and problematic marijuana use (Cottler et al 1993; Gawin and Kleber 1986). The discussion has principally focused on the severity and persistence of these disorders and whether a diagnosable syndrome of abuse or dependence can be validly defined for either or both disorders. The definition of an abuse/dependence syndrome depends in part on the demonstration of neuropsychiatric signs and/or symptoms during periods of acute withdrawal and protracted abstinence. By measuring neuropsychological test differences associated with objectively indicated cocaine or marijuana use, the present study sought to demonstrate the existence of such neuropsychiatric sequelae.

A number of investigators have attempted to demonstrate neuropsychological effects of acute and chronic cocaine or marijuana use/abuse. Among cocaine-dependent patients, there is evidence of subtle but statistically significant motor system dysfunction. For example, O'Malley and Gawin (1989; 1990) studied 25 cocaine-dependent outpatients, abstinent for an average of 135 days, and found deficiencies on tests of simple and complex motor skills. In a longitudinal study of a similarly uncomplicated sample of cocaine-dependent patients, during the first 3 months of abstinence, Bauer (1996) detected persistent motor system abnormalities, evidenced by abnormal low frequency hand tremor (Bauer 1993a), slowed reaction times (Bauer 1994; Roberts and Bauer 1993), and abnormal eye movements (Bauer 1993b). The O'Malley and Bauer studies both focused on groups of DSM-IIIR (American Psychiatric Association 1987) defined cocaine-dependent patients without co-existing psychoactive substance dependence. Using a less rigorously defined patient sample and the Trail Making Test, Melamed and Bleiberg (1986) demonstrated motor impairments in cocaine abusers after a briefer period (48-72 hours) of abstinence.

Evaluations of more complex cognitive abilities in cocaine-dependent patients have yielded a more mixed pattern of results. O'Malley et al (1992) reported that cocaine-dependent patients, after an average 23.6 days of abstinence, were deficient in their performance on the Arithmetic and Symbol Digit Modalities tests, and on the Story Memory test. Berry and colleagues (1993) studied patients 72 hours after their last cocaine use and again 2 weeks later. Relative to controls, the cocaine-dependent patients exhibited impairments in memory, visuospatial abilities, and concentration. Gillen et al (submitted) reported that 1-5 day abstinent cocaine dependent males exhibited decrements on tests of information, expressive vocabulary, and verbal concept formation and fluency.

The literature associating marijuana use with higher level cognitive decrements is even more discrepant than for cocaine (Block et al 1992; Chait 1990). Acutely, marijuana use has been associated with disruptions in paired associate learning (Block et al 1992) and concentration (Heishman et al 1990). Solowij et al (1991) suggested that long-term cannabis use may be associated with attentional dysfunction, as indexed by event-related electroencephalographic potentials and signal detection task performance. However, Chait (1990) reported that marijuana smoking was not associated with a "hangover" syndrome. No decrements were found in performance tests or mood scales 24 hours after marijuana ingestion. Other investigators have also reported null findings (Chait et al 1985; Rafaelsen et al 1973; Zacny and Chait 1989; 1991).

The present study differs from the aforementioned studies by examining neuropsychological decrements associated with urine toxicology tests positive for cocaine, marijuana, or multiple drugs. The disadvantage of such an approach is its inability to distinguish between the effects of mere experimentation and regular pathological use (e.g., as defined by DSM-IIIR (American Psychiatric Association 1987) or ICD-10 (World Health Organization 1992), or between the effects of acute intoxication or withdrawal. The advantage of the present approach lies in its relevance to non-clinical applications of urine toxicology, where results are frequently used to infer the current and/or future neuropsychological competence of workplace employees.

Methods

Subjects and Procedures

Data were culled from a larger database that comprises the University of Connecticut's contribution to the Collaborative Study on the Genetics of Alcoholism (COGA). Subjects were recruited through newspaper advertisements and from treatment centers. Many had a history of alcohol/drug dependence or were genetically related to family members with such histories.

After providing written informed consent, subjects were interviewed at the Health Center by a trained bachelor's or master's level research assistant. Psychiatric and drug use data were collected using an interview specifically developed for the COGA project, the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al 1994). Family history data were obtained using the Family History Assessment Module (Rice et al 1995). Diagnoses were determined by computerized algorithms and confirmed by the site's principal investigator.

Subjects with histories of serious medical disorders, such as liver disease, or Multiple Sclerosis, epilepsy, stroke, Korsakoff's Syndrome, Alzheimer's Disease, Pick's Disease, Huntington's Disease, Dementia, HIV infection (by self report), head trauma, or neurosurgery were excluded. Subjects meeting DSM-IIIR (American Psychiatric Association 1987) criteria for schizophrenia were also excluded. Use of prescription medication during the previous 5 days was an additional exclusionary criterion.

Fifty-four subjects, aged 15-61 years, with complete neuropsychological test data were selected for analysis. The selection process was blind with respect to the results of these tests. A urine sample was obtained from each subject while he/she visited the Health Center for other study evaluations. The

average interval between the urine collection and neuropsychological testing was 14.4 days. This interval did not differ across study groups [$F(3,43)=1.19$, $p=0.32$].

Each urine sample was frozen and later tested (EZ Screen, Editek, Inc., Burlington, NC; Schwartz et al 1990), as part of a larger sample batch, for the presence of cocaine, cannabis, and opiate metabolites. A breathalyzer test for alcohol was also performed. Of the 54 urine samples, 12 tested positive for recent cocaine use, 14 for cannabis, 7 for some combination of opiates, cocaine, and/or cannabis, and 21 were negative for these drugs of abuse. Positive urine toxicology tests were confirmed by a repetition of the EZ Screen test. No subject included in the final analysis tested positive for recent alcohol use.

Neuropsychology

The Porteus Maze and Trail Making Tests, and the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981) were administered to all subjects. The Porteus Maze Test (PMT) requires manual navigation through 8 mazes of varying complexity. It primarily assesses planning and foresight. The two Trail Making Tests, Parts A and B, derived from the Halstead-Reitan Battery (Reitan and Wolfson 1985), also assess visual tracking, and sequencing and cognitive flexibility as well.

The WAIS-R yields three overall scores of intellectual functioning (Full Scale, Performance and Verbal IQ). In addition, the WAIS-R provides measures of several component skills (Lezak 1983). The components of the WAIS-R are the following:

(1) Information and Vocabulary. These are used to estimate general knowledge, remote memory, learning, verbal capacity, mental alertness, speed, and efficiency.
(2) Similarities. It is an index of verbal concept formation, and general intellectual ability.
(3) Comprehension. It measures remote memory, common-sense judgment, and both practical and abstract reasoning.
(4) Digit Span. It is comprised of two different tests, Digits forward and Digits Backward. Collectively, these tests serve as measures of attention and immediate memory.
(5) Digit Symbol. It is a measure of motor persistence, cognitive flexibility, sustained attention, response speed, and visuomotor coordination.
(6) Picture Completion. It measures general ability, visual recognition, visual organization, and reasoning ability.
(7) Block Design and Object Assembly. These provide measures of visuospatial organization and manipulation.

Statistical Analyses

Group differences in demographic, drug use, and family history variables were evaluated using one-way ANOVA for continuous variables and the Chi-Square Test for nominal/categorical variables.

Scaled sores from the Trails A and B tests (speed), Porteus Maze test (number of maze levels completed, number of motor errors, highest maze level completed), and the WAIS-R subtests, as well as Verbal and Performance IQ, were submitted to separate analyses of variance. Age and educational level were employed as covariates. Significant group differences revealed by the ANCOVAs were further evaluated using Tukey post hoc comparisons. Significance was assumed at $p < 0.05$.

Results

The demographic characteristics of the four groups of subjects are summarized in Table 1. It should be noted that the four groups were statistically equivalent in age, educational level, handedness, and gender and racial composition. Also, Table 2 reveals no significant differences among the groups with respect to the percentage of the membership meeting DSM-IIIR criteria for alcohol, opiate, cocaine, or marijuana abuse or dependence, or major depressive disorder (lifetime and current). Table 3 indicates no significant differences among the groups with respect to two potentially important premorbid variables, viz., the prevalence of Anti-Social Personality Disorder or a high density of familial alcoholism (>3 affected family members).

Table 1

Demographic characteristics

	Urine Toxicology Result					
Variable	Negative	Cannabis	Cocaine	Polydrug	Analysis	p=
No. Subj.	n=21	n=14	n=12	n=7		
Yrs. Educ*	12(1.9)	12(1.5)	11(1.8)	10(2.1)	ANOVA	p=0.72
% Male	52	57	41	28	Chi-Square	p= 0.60
% C/H/B**	42/0/58	50/0/50	16/0/84	28/0/72	Chi-Square	p=0.46
Age*	33(9.1)	30(9.2)	35(9.7)	34(5.2)	ANOVA	p=0.78
% R-handed	85	85	75	100	Chi-Square	p= 0.53

* M(SD), ** Percent Caucasian/Hispanic/Black

Table 2

Percentage of Subjects Meeting DSM-IIIR Axis I Diagnostic Criteria

	Urine Toxicology Results				
Variable	Negative	Cannabis	Cocaine	Polydrug	Chi-Square p=
Major Depressive Disorder	0	0	0	25	0.19
Dependence					
Alcohol	57	63	63	42	0.81
Opioid	4	1	0	0	0.68
Cocaine	47	1	36	42	0.12
Marijuana	28	27	20	42	0.78
Abuse					
Alcohol	0	0	0	0	–
Opioid	0	0	0	0	–
Cocaine	0	0	0	0	–
Marijuana	0	0	1	0	0.31

Table 3

Premorbid Diagnoses By Subject Group

	Urine Toxicology Result				
Variable	Negative	Cannabis	Cocaine	Polydrug	Chi-Square p=
% ASPD*	23	27	27	20	0.96
% FHA**	95	92	91	87	0.27

* Anti-Social Personality Disorder, ** Family History of Alcoholism (>3 biological relatives affected)

Table 4

Neuropsychological Test Performance [M(SE)] By Subject Group

Variable	Negative	Cannabis	Cocaine	Polydrug	F ratio	p=
			Urine Toxicology Result			
PMT (Highest Level)	16.52(0.43)	16.79(0.56)	16.14(0.58)	15.80(0.73)	0.49	0.69
Trails A sec	29.24(3.17)	33.70(4.06)	40.87(4.19)	30.75(5.30)	1.70	0.18
Trails B sec	68(11.0)	88(14.05)	130(14.51)*	69(18.35)	4.23	0.01
Information	8.59(0.49)	8.20(0.63)	6.01(0.65)*	7.97(0.82)	3.57	0.02
Similarities	8.60(0.67)	8.64(0.86)	6.48(0.89)	7.44(1.12)	1.50	0.23
Vocabulary	8.43(0.51)	8.60(0.65)	5.52(0.67)*	7.34(0.85)	4.88	0.01
Comprehend	8.72(0.55)	8.33(0.70)	5.99(0.72)*	8.65(0.92)	3.38	0.03
Digit Span	9.99(0.67)	9.51(0.86)	7.77(0.89)	7.93(1.13)	1.71	0.18
Digit Symbol	9.77(0.58)	8.30(0.74)	7.72(0.77)	7.73(0.97)	3.45	0.07
Pict Complete	8.33(0.52)	9.59(0.67)	5.21(0.69)*	9.71(0.87)	8.76	0.00
Block Desgn	8.28(0.52)	8.19(0.67)	7.14(0.69)	7.51(0.88)	0.70	0.56
Obj Assmbl	7.44(0.59)	6.86(0.76)	6.28(0.78)	6.11(0.99)	0.67	0.57
Verb IQ	93.28(2.65)	92.82(3.39)	80.02(3.50)*	88.19(4.42)	3.45	0.02
Perf IQ	91.94(2.62)	90.73(3.35)	81.04(3.46)	88.70(4.37)	2.25	0.10

* p < 0.05 re: negative control, Tukey HSD

Table 4 provides means and standard errors for all neuropsychological test scores. Univariate ANCOVAs revealed significant group differences on two nonverbal tests: Trails B time [$F(3,43)$= 4.23, $p < .010$] and Picture Completion [$F(3, 43)$=8.76, $p < .0001$]. Verbal deficits were suggested by significant group differences on the WAIS-R Information [$F(3,43)$=3.57, $p < .022$], Vocabulary [$F(3, 43)$= 4.88, $p < .005$], Comprehension [$F(3,43)$= 3.38, $p < .026$], and Verbal IQ [$F(3,43)$= 3.45, $p < .024$]. For all of these subtests, Tukey post-hoc analyses revealed that the performance of the cocaine-positive group was inferior to that of the urine negative group. The cocaine group differed significantly from both the negative and cannabis groups on the Vocabulary subtest. On the Picture Completion subtest, the cocaine-positive group differed significantly from all other groups.

Discussion

The present study revealed a number of neuropsychological differences between subjects testing positive for recent cocaine use and a similar group of subjects testing negative for cocaine and other drugs. In verbal intelligence and on the Information, Vocabulary, Comprehension, Picture Completion, and Trails B

tests, the performance of the cocaine-positive group was significantly lower than the control group. However, given the number of separate ANCOVAs performed presently, and the attendant increased likelihood of Type I error, subtest differences (viz., Picture Completion, Vocabulary, and Trails B time) associated with a more conservative significance criterion should probably be emphasized.

Premorbid and Comorbid Disorders.

ASPD and Family History of Alcoholism. It is important to recognize that the present findings cannot be attributed to the variety of pre-morbid and/or co-morbid disorders which have complicated other neuropsychological studies of cocaine abusers. For example, in the present study, there were no significant group differences in the prevalence of Anti-Social Personality Disorder (ASPD) or a family history of alcoholism. ASPD and a family history of alcoholism frequently predate drug use (Hesselbrock et al 1985a; Hesselbrock et al 1985b) and have been associated with an increased risk of early onset drug or alcohol dependence. Most importantly, ASPD (Gillen and Hesselbrock 1992) and, less reliably, a family history of alcoholism (Hesselbrock et al 1991) have been associated with neuropsychological test decrements. Balancing the prevalence of these two premorbid variables across groups therefore discounts two significant confounds in the analysis of drug effects.

Depression and Sleep Disorders. The present study also allows one to discount the contributions of depression and other drug abuse/dependence, since the groups were also balanced on these variables. The importance of considering and eliminating the effects of depression, particularly as caused by sleep deprivation, in neuropsychological studies of cocaine abusers has been asserted by others (Herning et al 1990), but has not been compellingly supported by data. Stone and colleagues (1994), for example, found minimal effects of frank insomnia on cognitive and psychomotor performance. Hayward et al (1992) concluded that night sleep problems in a non-clinical population were not associated with neuropsychological deficits.

The specific findings of the present study are remarkably consistent with the results of a similar study of DSM-IIIR diagnosed cocaine-dependent patients by Gillen and colleagues (submitted). In both studies, decrements were detected in areas associated with verbal learning and/or competence (information, vocabulary, comprehension). The present study's demonstration of impaired performance on measures of picture completion, and sequencing and alternation (Trails B), suggests that the dysfunction may be more widespread, at least in early abstinence.

Limitations.

Urine Toxicology. One cannot conclude this discussion without acknowledging a few limitations. The present study, for example, failed to detect neuropsychological impairments in subjects testing positive for recent marijuana or multiple drug use. This null result is consistent with the inability of other investigators to detect neuropsychological effects of marijuana (Chait 1990) and opiates (Guerra et al 1987). However, the null result may instead be a consequence of the longer time windows over which urine assays for marijuana and opiates remain positive (i.e., 29 days and 5 days, respectively). Thus, for the cannabis and polydrug groups, the duration of abstinence may have been longer and/or more variable than for the cocaine group. Unfortunately, self-reports of marijuana, opiate, and cocaine use rarely agreed with the urine toxicology results (Kramer et al, in preparation) and could not be used to resolve the issue.

Self-Reported Drug Use and Urine Toxicology Results. This lack of consistent agreement between self-reported drug use and the urine toxicology results raises another important methodological point. Because the interval between neuropsychological testing and urine collection was somewhat variable (average interval = 14.4 days), it is impossible to determine whether the neuropsychological decrements detected in the cocaine positive group reflect an acute residual effect, a withdrawal effect, and/or an accumulated effect of either previous cocaine experimentation or regular use. However, even if urine collection always occurred on the same day as neuropsychological testing (as it did for 54% of the present subject sample), one could still not make the determination with any degree of certainty. Unless subjects are willing to provide accurate and precise information regarding patterns of cocaine use, recency of use, and quantities used, the distinction between residual, withdrawal, and permanent effects of cocaine cannot be made on the basis of urine toxicology alone. Given the demand characteristics of the workplace, or of studies (such as the present) which do not involve treatment but verbally encourage abstinence, self-reports of use will most likely not contain the requisite level of accuracy or precision.

The present study is also limited with respect to identifying the specific source of the neuropsychological decrements associated with a urine test positive for cocaine. As noted above, the absence of significant group differences in the prevalence of ASPD and several other demographic and drug use variables argue against these as likely sources. Yet, accepting the null hypothesis of no differences is problematic. Indeed, some of the decrements (e.g., Verbal IQ, Vocabulary, Information) in verbal competence which distinguished the cocaine positive group may still be attributable to the operation of an unknown premorbid variable.

It is arguable whether this same premorbid variable can account for the most robust findings of the present study, i.e., the group differences in Trails B and Picture Completion test performance. To address this question, the authors performed a new analysis of the data using Verbal IQ as an estimate of each subject's premorbid level of functioning and as a covariate. Not surprisingly, the group differences in the Information, Vocabulary, and Comprehension components of Verbal IQ did not survive the statistical adjustment (all p's > 0.1). But the cocaine-related decrements on the Trails B (p = 0.08) and Picture Completion (p = 0.0077) tests remained. Thus, it appears that the decrements in cognitive flexibility and attention/concentration indexed by these latter tests are mediated by another factor. The authors hypothesize that this factor is the use of cocaine.

Practical Implications.

The practical implications of the Trails B and Picture Completion decrements in the cocaine positive group are worthy of consideration. Among patients with frank cerebral damage, impairments on the Trail Making Tests (Galski et al 1992; Quigley and DeLisa 1983) and the Picture Completion test (Sivak et al 1981) have been shown to predict impaired motor vehicle operation The results have been inconsistent, however (Ravestein et al 1982; van Zomeren et al 1987). In part, the inconsistencies in prediction may be related to the skill level and premorbid status of study subjects, as well as contextual or task factors (e.g., speed, driving conditions, difficulty). In interpreting the safety implications of the more modest Trails B and Picture Completion decrements in the cocaine positive group, one must be mindful of these factors and their mediating or moderating effects.   Yet, the existence of neuropsychological decrements   suggests a potential for increased accident involvement among a proportion of patients presenting with cocaine-positive urine samples.

Conclusion

This study examined neuropsychological differences among 4 groups of men and women defined by urine toxicology screens indicating cocaine use, cannabis, multiple drug, or no drug use. The cocaine positive group exhibited statistically significant impairments on Verbal IQ, Information, Vocabulary, Comprehension, Picture Completion, and Trails B.   The findings illustrate the importance of using objective screens such as urine toxicology to assess neuropsychological impairments among substance users.

Acknowledgment

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