

Sex-Related Differences in Self-Reported Neurocognitive Impairment among High-Risk Cocaine Users in Methadone Maintenance Treatment Program

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ABSTRACT

BACKGROUND: Previous research has suggested possible sex-related differences in executive functioning among cocaine users; however, no studies specifically explain sex-related differences in neurocognitive impairment (NCI) among cocaine users receiving clinical care. Knowledge about this association can aid in the development of targeted prevention strategies to reduce adverse health outcomes. This study was designed to examine the sex-related differences in NCI among high-risk cocaine users receiving substance-abuse treatment.

METHODS: The Neuropsychological Impairment Scale (NIS) was administered to 199 cocaine users (98 men; 101 women), receiving methadone maintenance treatment, to assess self-reported NCI by identifying the patients' awareness of neuropsychological symptoms. We used T-test comparison to find differences in NCI between men and women and multiple regression analysis to explore the relative contribution of sex to NCI.

RESULTS: Consistent with prior work, high NCI was evident within this sample, as indicated by high scores on most of the NIS subscales. Women reported greater impairment than men, as evidenced by significantly higher scores on several NIS subscales, after controlling for demographic and other confounding variables. Interestingly, cocaine craving significantly predicted NCI among men but not among women, as suggested by the significant association between cocaine craving and all except one of the NIS subscales.

CONCLUSIONS: These findings suggest that cocaine users enter into treatment with a range of NCI – with women having significantly more neurocognitive deficits than men – that may contribute to differential treatment outcomes. This highlights the need to include additional services such as neuropsychological screening and sex-specific treatment programs to optimally reduce adverse health outcomes in these high-risk, cognitively impaired patients.

KEYWORDS: cocaine, neurocognitive impairment, sex-related differences, substance abuse, methadone maintenance patients, behavioral intervention

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Introduction

Cocaine is one of the most commonly abused psychoactive substances in the United States. The National Survey on Drug Use and Health (NSDUH) estimated that in 2012 there were over 1.8 million current cocaine users, of which 639,000 persons had used cocaine for the first time within the past 12 months; this averages to approximately 1,800 initiates per day.¹ Studies on the neurocognitive effects of cocaine abuse have shown a significant association between neuropsychological impairment and affective dysfunction.^{2–5} Paralleling the effects on cognitive performance, evidence from magnetic resonance imaging (MRI) studies has shown that repeated exposure to cocaine produces significant structural and metabolic abnormalities in the brain, predominantly in the areas considered crucial for executive control.^{2,3,6–12} Given its addictive potential and negative health consequences, cocaine abuse has been regarded as a major public health issue.¹³

Accumulating research suggests that there are important differences in the patterns of cocaine abuse and addiction between the sexes. For example, women are more likely to have an earlier cocaine use debut than men,^{14,15} and women are just as likely as men to advance from first cocaine use to dependence¹⁶ but tend to experience a more rapid progression to the negative consequences associated with cocaine dependence (ie, “telescoping effect”).^{17,18} Additionally, some studies report that women seeking treatment tend to have more severe cocaine use problems than men, and have a higher occurrence of comorbid psychiatric conditions such as anxiety disorder, depression, and posttraumatic stress disorder.^{19–21} This vulnerability of women might be influenced by sex-related differences in cognitive impairment among cocaine users. Consistent with this assumption, a study by van der Plas et al found that decision making was significantly more impaired in women addicted to cocaine as compared to men.²²



These findings point to possible sex-related interactions between cocaine use and cognitive deficits; however, they do not specifically explain sex-related differences in neurocognitive impairment (NCI) among chronic cocaine users. Moreover, cocaine use is highly prevalent among patients receiving substance-abuse treatment and therefore is a clinical concern.²³ Nevertheless, the interplay of this relationship remains untested among cocaine-using patients receiving clinical care. Therefore, studying sex-related differences in NCI among high-risk cocaine users receiving substance-abuse treatment can aid in the development of targeted prevention strategies.

Accordingly, the objectives of the current study were to examine the sex-related differences in neurocognitive impairment among a sample of cocaine users receiving substance-abuse treatment (ie, methadone maintenance treatment; MMT) and to explore the relative contributions of cocaine-use variables and sex on self-reported NCI. We formulated two main hypotheses: 1) cocaine users participating in methadone maintenance treatment program will have high levels of neurocognitive impairment, and 2) compared to males, female cocaine users participating in methadone maintenance treatment program will have a higher degree of neurocognitive impairment.

Methods

Design. This was a retrospective secondary analysis of a subset of data collected from the parent study, which was a randomized clinical trial of a behavioral HIV-risk reduction intervention designed to reduce HIV risk among high-risk, drug-dependent individuals participating in drug treatment.²⁴ The study protocol was approved by the Investigational Review Board (IRB) at the University of Connecticut, the Human Investigation Committee at Yale University, and received board approval from the APT Foundation MMP, Inc. and the study complied with the principles of the Declaration of Helsinki. Variables for cocaine use had been created for the primary study, and self-reported NCI was assessed using the Neuropsychological Impairment Scale (NIS) described below.²⁵

Sample. The parent study included 304 HIV-negative individuals, without any psychiatric comorbidities, enrolled in a community-based methadone maintenance treatment (MMT) program who reported sex- or drug-related HIV transmission risk behavior.²⁴ For the purpose of this study, we included subjects who reported using cocaine in the past week. Among the 199 individuals who met the inclusion criteria for this study, 98 (49.2%) were male. One-hundred and forty-six subjects (73.4%) were white, 18 (9%) were African-American, 30 (15.1%) were Hispanic, and 5 (2.5%) described themselves as “other” minority. The subjects’ average age was 33.9 (± 9.5), years and the majority of the participants (67.8%) were never married. One-hundred and forty-nine subjects (74.9%) were high school graduates, and 156 (78.4%) were unemployed.

All subjects were enrolled in an inner-city MMT program and were maintained on a stable dose of methadone. The mean (\pm SD) daily methadone dose was 57.2 (± 24.9) mg. The subjects had been using cocaine regularly for about 11.9 (± 8.8) years. Forty-three (21.6%) subjects used cocaine by intravenous route of administration, 112 (56.3%) by smoking, and 44 (22.1%) intranasally. During the week prior to entering the study, subjects used 4.2 (± 12.4) g of cocaine over a period of 0.9 (± 1.7) days per week. Cocaine craving, which was assessed by asking the subjects to rate their desire for cocaine in the scale of 1 to 5 (1 = “not at all” and 5 = “extreme”) during the previous week, was found to be “extreme” in 7 (3.5%) subjects and “not at all” among 117 (58.8%) subjects.

Assessment instrument. *Neurocognitive measures.* The NIS was administered to patients individually upon meeting the criteria for the study. It is a brief, self-report screening measure used to assess NCI by identifying patients’ awareness of neuropsychological symptoms²⁵ and is generally used as a screening instrument in clinical settings. Although clinical diagnosis of NCI requires the use of a more comprehensive assessment battery of instruments, recent studies have stressed the need for rapid screening tools.²⁶ Validity studies that have compared the NIS with tests known to assess various cognitive impairments have found the NIS to be both a valid and reliable predictor of NCIs in diverse group of patient population.^{25,27-30}

The NIS is composed of 95 items rated on 5-point scales, ranging from 0 (not at all) to 4 (extremely). These responses are used to compute three summary scores and seven clinical subscale scores. There are also validity checks, which provide a background for the interpretation of the other scores (Table 1).²⁸ For each subscale, sums of the point scale scores were totaled and then transformed to T-scores, which were used in the current analysis as a continuous variable. Generally, high levels on any of these scores are an indication of NCI. NIS scores less than 30T were considered low, scores between 30T and 50T were considered average, scores between 50T and 60T were considered high, and any score above 60T was considered very high.³¹

Cocaine-use measures. For the purpose of this study, we used the constructs related to cocaine-use variables. For example, “What has been your primary method of cocaine use in the past 6 months?”, “For how many years have you been using cocaine?”, “To what extent were you experiencing cocaine craving in the past week?” “Do you plan to stop using cocaine completely in the next three months?”, and “When was the last time you used cocaine?” Cocaine-use items required the participants to categorize and quantify their use. Quantity and frequency data of cocaine use was collected for the past week. For example, “How many days did you use cocaine in the past week?” and “How much cocaine did you use in total in the past week?”

Procedure. Both the NIS and drug use measurements were assessed using the Audio Computer-Assisted Self-

**Table 1.** Subscale scores provided by the Neuropsychological Impairment Scale (NIS).

Three summary scores	
GMI	Global measure of impairment: Provides best general index of neuropsychological functioning.
TIC	Total number of symptoms endorsed.
SIM	Symptom intensity measure: ratio of GMI and TIC.
Seven clinical subscales	
COG	Cognitive efficiency: Assesses general symptoms of NCI (eg, “ <i>I get confused easily</i> ”).
CRIT	Critical items: Assesses patient’s history of neurological illness or injury (eg, “ <i>part of my body feels numb</i> ”).
ATT	Attention: Assesses patient’s ability to attend and concentrate (eg, “ <i>I have trouble concentrating</i> ”).
MEM	Memory: Assesses patient’s memory (eg, “ <i>I have trouble remembering important things</i> ”).
L-V	Learning-verbal: Assesses learning and expressive speech (eg, “ <i>I have trouble learning new things</i> ”).
FRU	Frustration tolerance: Assesses irritability, anger and temper (eg, “ <i>I feel easily annoyed and irritable</i> ”).
ACD	Academic skills: Assesses ability to carry out daily activities involving computing and reading (eg, “ <i>I have trouble understanding what I read</i> ”).
Three scales measuring test attitude	
DEF	Defensiveness: Provides indication of test-taking attitude (eg, “ <i>I like everyone I know</i> ”).
AFF	Affective disturbance: Provides an estimation of emotional state of the subject at the time of the test (eg, “ <i>I often feel sad and blue</i> ”).
INC	Internal inconsistency: Identifies inconsistent response pairs.

Interview (ACASI).^{24,31} For the purpose of this study, the NIS measurements – including seven impairment subscales, three validity scores, three summary scores (Table 1), and cocaine-use measurements – were taken only from the baseline assessment. All subjects were reimbursed for the time and effort needed to participate in the study, and this study was approved by the institution’s IRB.

Data analysis. Data analysis proceeded as follows: 1) T-tests (on continuous variables) and chi-square analyses (on categorical variables) were performed to determine whether the sex of participants were well-matched on relevant sociodemographic and drug use variables.) A *t*-test revealed that there was a difference between men and women in terms of age and years of cocaine use. Therefore, the effects of these characteristics as well as other variables including methadone dose, years in the MMT program, use of opiate in the past six months, and duration of opiate use were adjusted in all of our analyses. NIS summary scores, clinical subscale scores, and NIS test-taking attitude scores were then compared by sex using ANCOVA. 3) Multiple regression analysis was conducted to explore the relative contributions of cocaine-use variables and sex on self-reported NCI. 4) Regression analysis was conducted between NIS subscale scores and cocaine-use variables by sex in order to further explore sex-related differences between male and female cocaine users. Both subjective tests (visual examination of the standardized residual scatterplots) and objective tests (Shapiro—Wilk test) satisfied all assumptions of normality, linearity, and homoscedastic-

ity between the predicted dependent variable scores and errors of prediction. Furthermore, the Durbin–Watson test statistic revealed no correlation in adjacent residuals, and the variance inflation factor (VIF) and tolerance statistic suggested no problem with multicollinearity. *P*-Values were set at <0.05 for all our planned multiple measures.^{32–34} Effect sizes are reported as bivariate standardized beta coefficients in order to distinguish between different results with a clinical meaning.³⁵ The effect sizes can be classified following Cohen’s classification as small, medium, and large effect size – 0.1, 0.3, and 0.5, respectively – for bivariate standardized regression coefficients.^{36,37} There were no missing values in the dataset. SPSS software, version 20.0, was used for all statistical analyses.

Results

Comparison between male and female participants on sociodemographics and drug-use variables. Aside from age and years of cocaine use, there was no significant difference between male and female participants. Men tended to be older and to have used cocaine for a longer time as compared to women (Tables 2 and 3).

Comparison between male and female participants on the NIS summary scores, clinical scales, and test-taking attitude scales. NIS T-scores on each subscale were coded as “high” if they were within the range of the normative data provided in the NIS manual and used in prior study (ie, 50T–60T).^{25,31} The degree of impairment on all of the NIS subscales, except for symptom intensity measure (SIM)



Table 2. Comparison between male and female participants on sociodemographic variables.

VARIABLES	MALE	FEMALE	P
N	98 (49.2%)	101 (50.8%)	
Age	35.8 (±10.1)	32.1 (±8.7)	0.005*
Ethnicity	71 (%)		0.222
White	6 (%)	75 (%)	
African-American	19 (%)	12 (%)	
Hispanic	2 (%)	11 (%)	
Other		3 (%)	
Employment			0.217
Working	11 (%)	4 (%)	
Disability	8 (%)	13 (%)	
Unemployed	77 (%)	79 (%)	
Student	1 (%)	2 (%)	
Other	1 (%)	3 (%)	
Income			0.11
0–\$10,999	80 (%)	94 (%)	
\$11,000–\$20,999	5 (%)	2 (%)	
\$21,000–\$30,000	9 (%)	3 (%)	
> \$30,000	4 (%)	2 (%)	
Educational Level	12.1 (±1.7)	11.9 (±2.0)	0.218
Marital status			0.617
Married	9 (%)	9 (%)	
Never married	69 (%)	66 (%)	
Separated	6 (%)	9 (%)	
Divorced	14 (%)	15 (%)	
Widowed	0 (%)	2 (%)	
Number of children	1.1 (±1.4)	1.4 (±1.5)	0.168

Notes: Values in columns represent *n* (percent in sample) for categorical variables and mean (±SD) for continuous measures. *Significance $P < 0.05$.

and defensiveness (DEF), was found to be “high” (ie, ranged from 50T to 60T) among all participants in our sample relative to the general population norm. Furthermore, women had significantly higher scores on one of the three NIS summary scores: global measure of impairment (GMI) [$F(165) = 6.1, P < 0.015$]. Similarly, women had significantly higher scores on four of the seven clinical subscales scores: cognitive efficiency (COG) [$F(165) = 5.6, P < 0.019$], attention (ATT) [$F(165) = 5.6, P < 0.019$], frustration tolerance (FRU) [$F(165) = 9.8, P < 0.002$], and academic skills (ACD) [$F(165) = 5.1, P < 0.025$]. On the validity subscales assessing test-taking attitudes, female patients had higher affective disturbance scores (AFF) [$F(165) = 6.5, P < 0.012$] as compared to males (Fig. 1; Table 4).

The mean value of the response inconsistency (INC) score (male: 53.4T and female: 54.9T), which evaluates the individual’s ability to respond in a coherent and consistent manner, does not reflect any unusual inconsistency in the participants’ NIS responses. The mean DEF score (male: 39.5T

Table 3. Comparison between male and female participants on drug use variables.

VARIABLES	MALE	FEMALE	P
Methadone dose	57.5 (±25.7)	57.1 (±24.4)	0.913
Years using cocaine	13.3 (±9.7)	10.5 (±7.6)	0.029*
Route of cocaine administration	22 (%)	21 (%)	0.633
Intravenous	52 (%)	60 (%)	0.085
Smoke	24 (%)	20 (%)	0.149
Snort	55 (%)	62 (%)	0.716
Cocaine craving (Past week)	24 (%)	12 (%)	0.344
Not at all	13 (%)	15 (%)	0.187
Slightly	5 (%)	6 (%)	
Moderately	1 (%)	6 (%)	
A lot	2 (%)	0 (%)	
Extremely	96 (%)	101 (%)	
Plan to stop using cocaine	31.3 (±41.6)	33.5 (±42.4)	
No	0.9 (±1.4)	1.1 (±1.9)	
Yes	3.0 (±9.3)	5.3 (14.7)	
Last used cocaine			
Cocaine use in past week			
Days			
Grams/week			

Notes: Values in columns represent *n* (percent in sample) for categorical variables and mean (±SD) for continuous measures. *Significance $P < 0.05$.

and female: 38.3T) suggests that participants had a positive and open attitude in completing the assessment and did not appear to have any unusual difficulty making social judgments. A marginally elevated affective disturbance score (male: 56.6T and female: 60.7T) suggested some degree of anxiety, depression, or poor stress tolerance among participants at the time of testing, which is not unusual for this patient population. Further clinical examination is recommended to determine the nature and extent of affective disturbance.²⁵

Multiple regression analysis: prediction of NCI among participants. The following variables, together with the NIS summary and clinical subscales, were entered simultaneously into a standard multiple regression analysis that allowed each variable to be evaluated for its ability to add to the prediction of NCI among participants: sex (0/1: female/male), cocaine craving (0/1; not at all/yes), years of cocaine use, frequency (day) of cocaine use in the previous week, amount (in grams) of cocaine use in the previous week, plan to stop using cocaine (0/1; no/yes), and cocaine last used (day).

The full model accounted for between 32.4% and 38.6% of the variance in each of the NIS summary scales and between 17% and 37.8% of the variance in each of the clinical subscales. Out of the nine NIS subscales, four showed a statistically significant and unique relationship with sex, namely GMI, COG, ATT, and ACD, thus indicating a greater level of impairment for men vs women (Table 5).

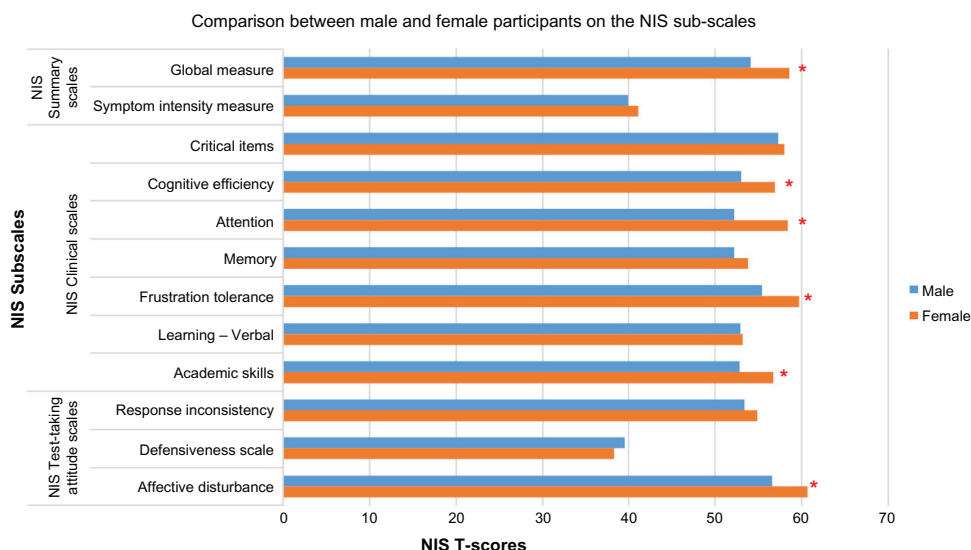


Figure 1. Comparison between male and participants on the NIS summary scores, clinical scales, and test-taking attitude scales.
Note: *Significance $P < 0.05$.

Exploration of associations between NCI and cocaine-use variables by sex. Regression analyses were conducted between NIS subscale scores and cocaine-use variables (ie, those found to be significant in regression model) by sex in order to further explore differences between men and women. Interestingly, cocaine craving contributed significantly to all NIS summary scores, and all clinical subscales except FRU for men. Similarly, the plan to use cocaine in the next three months was significantly associated with the cognitive impairment of

men as measured by FRU. In contrast, for women, only one of the nine NIS subscales, namely SIM, was found to have a significant association with cocaine craving. No significant association was found between any of the other NIS subscales and cocaine-use variables among women (Table 6).

Discussion

Over the past decade, studies have reported significant levels of neuropsychological impairment among individuals who

Table 4. Comparison between male and female participants on the NIS summary scores, clinical scales, and test-taking attitude scales.

VARIABLES	MALE (n = 98)	FEMALE (n = 101)	SIGNIFICANCE (165) df
NIS summary scales			
Global measure	54.1 (±12.9)	58.6 (±10.4)	$F = 6.1, P < 0.015^*$
Total items circled	39.9 (±11.2)	41.1 (±11.5)	$F = .4, P < 0.522$
Symptom intensity measure			
NIS clinical scales			
Critical items	57.3 (±11.8)	58.0 (±10.4)	$F = .8, P < 0.359$
Cognitive efficiency	53.0 (±12.2)	56.9 (±10.1)	$F = 5.6, P < 0.019^*$
Attention	52.2 (±12.9)	58.4 (±10.3)	$F = 9.8, P < 0.002^*$
Memory	52.2 (±12.3)	53.8 (±10.7)	$F = 1.0, P < 0.314$
Frustration tolerance	55.4 (±11.8)	59.7 (±9.9)	$F = 4.6, P < 0.034^*$
Learning-verbal	52.9 (±11.8)	53.2 (±10.1)	$F = .023, P < 0.880$
Academic skills	52.8 (±12.1)	56.7 (±9.2)	$F = 5.1, P < 0.025^*$
NIS Test-taking attitude scales			
Response inconsistency	53.4 (±10.1)	54.9 (±7.6)	$F = 1.7, P < 0.197$
Defensiveness scale	39.5 (±6.3)	38.3 (±5.6)	$F = 1.7, P < 0.189$
Affective disturbance	56.6 (±11.3)	60.7 (±8.2)	$F = 6.5, P < 0.012^*$

Notes: Values in columns represent mean (±SD). *Significance $P < 0.05$.

**Table 5.** Prediction of neurocognitive impairment among participants.

	NIS SUBSCALE SCORES								
	GMI	SIM	CRIT	COG	ATT	MEM	FRU	L-V	ACD
Explanatory variables									
Sex	-0.186*	-0.038	-0.061	-0.179*	-0.226*	-0.071	-0.152	-0.009	-0.181*
Cocaine craving	0.220*	0.238*	0.193*	0.259*	0.187*	0.198*	0.156	0.181*	0.239*
Years of cocaine use	0.216*	0.211*	0.261	0.220*	0.189	0.073	0.187	0.223*	0.117
Cocaine use (day) in past week	-0.058	-0.044	-0.047	-0.028	-0.109	-0.046	-0.041	-0.026	-0.101
Cocaine use (g) in past week	0.168	0.239	0.151	0.184	0.194	0.159	0.090	0.210	0.174
Plan to stop using cocaine	0.129	0.094	0.154*	0.108	0.191*	0.121	0.198*	-0.002	0.079
Cocaine last used (day)	-0.064	0.060	-0.075	-0.031	-0.056	-0.007	-0.022	-0.040	-0.080

Notes: Sex coded 0/1 (female/male); cocaine craving 0/1 (not at all/yes); plan to stop using cocaine 0/1 (no/yes). Values in columns represent standardized beta coefficients. *Significance $P < 0.05$.

repeatedly use cocaine.²⁻⁵ Consistent with other studies with this target population, relatively high levels of neurocognitive impairment was evident in this group of participants, as indicated by average scores between 50T and 60T for most of the NIS subscales [ie, GMI, critical items (CRIT), COG, ATT, MEM, FRU, learning-verbal (L-V), ACD, INC, and AFF]. In addition, the current study assessed the potential sex-related differences in self-reported NCI among cocaine users receiving clinical care. This is the first study, to our knowledge, to employ the NIS assessment to study sex-related differences in self-reported neurocognitive impairment among cocaine users enrolled in methadone-maintained treatment program.

Our sample of women reported more impairment than men, as indicated by significantly higher scores on GMI, COG, ATT, FRU, ACD, and AFF (after controlling for age, years of cocaine use, methadone dose, years in MMT program, use of opiate in the past six months, and duration of opiate use). The female participants' significantly higher score

on GMI scale ($P < 0.015$) indicates a stronger likelihood of neuropsychological impairment as compared to their male counterparts. This difference in elevated GMI score may have been partly explained by a history of neurological illness or injury, as suggested by a higher CRIT score among women as compared to men, although it was not significantly different (Table 4)²⁵. Also, a significantly higher AFF score among women ($P < .012$) suggests that general psychological distress may have contributed more to this differential cognitive difficulty compared to men.

In addition, women scored significantly higher than men on COG score ($P < 0.019$), which suggests a higher degree of cognitive impairment, such as slowness of mentation of praxis, fatigue, confusion, and mental efficiency, among women as compared to men. A significantly higher score on ATT scale among women ($P < 0.002$) signifies greater memory complaints and symptoms of general cognitive impairment. The FRU, which was also found to be significantly higher among women ($P < 0.034$), suggests the presence of a higher degree

Table 6. Associations between neurocognitive impairment and cocaine-use variables by sex.

	MALE ($n = 98$) COCAINE-USE VARIABLES ^a			FEMALE ($n = 101$) COCAINE-USE VARIABLES ^a		
	CRAVING	YEARS	PLAN	CRAVING	YEARS	PLAN
GMI	0.312*	0.073	0.068	0.173	0.035	-0.055
SIM	0.267*	0.037	0.109	0.232*	0.001	-0.042
CRIT	0.321*	0.198	-0.029	0.118	0.125	-0.091
COG	0.384*	0.050	0.066	0.198	0.103	-0.051
MEM	0.285*	0.031	0.207	0.121	0.037	-0.067
ATT	0.232*	-0.027	0.179	0.162	-0.017	-0.047
FRU	0.116	0.057	0.317*	0.205	-0.122	-0.014
L-V	0.317*	0.022	0.021	0.141	-0.034	0.120
ACD	0.304*	0.033	0.046	0.184	0.021	-0.026

Note: Craving, craving for cocaine in last 7 days week (0/1: not at all/yes). Years, number of years using cocaine. Plan, plan to stop using cocaine (0/1: no/yes). Values in columns represent standardized beta coefficients. ^aInclude only significant cocaine-use variables. *Significance $P < 0.05$.



of symptoms, consistent with “organic personality disorder”, such as irritability, anger, or temper. Furthermore, higher score on the ACD scale among women ($P < 0.025$), as compared to men, indicates higher degree of cognitive deficits associated with neurological impairment.

These findings provide support to the notion that sex-related differences in neurocognitive deficit exist among cocaine users, which may be both theoretically and clinically meaningful. This was consistent with our central prediction that NCI among cocaine users is sex-specific – with women having significantly higher degree of neurocognitive impairments than men. The results are also consistent with a previous finding, which reported significantly more executive impairment in women addicted to cocaine as compared to their male counterparts.²² The higher degree of cognitive impairment among female cocaine users is accompanied by higher patterns of psychiatric, medical, social, family, and employment problems compared to that of male cocaine users.²²

The sex-related differences in neurocognitive deficits among cocaine users may have been moderated to a degree by neurobiological development through hormonal influences, though this is well beyond the scope of this study. Estradiol, which is known to influence many drug-related behaviors, has been linked to greater sensitization to cocaine use.^{38,39} Studies have shown that women have higher extra-striatal dopamine receptor binding in the frontal cortex, temporal cortex, and thalamus^{40,41} and higher striatal dopamine transporter levels in the caudate nucleus and putamen.⁴² Likewise, neuroimaging studies have confirmed an increase in D_2 receptor levels in the frontal cortex of female cocaine users.^{40,43,44} Thus, the effects of higher doses of circulating estradiol in the neural circuits may lead to an increased vulnerability to cocaine use among women.⁴⁵ Overall, this evidence – along with findings from the current study – point to a differential sex-related interaction on NCI among cocaine users. Furthermore, it provides a platform for further and more exhaustive research to investigate sex-related association of neurocognitive deficits among male and female cocaine users.

One unexpected and intriguing finding was that cocaine craving significantly predicted NCI among men but not among women, as indicated by the significant association between cocaine craving and all NIS subscales, except for the FUS scale, among male cocaine users. This may suggest that impairment in this sample of men may be relatively temporary and moderated by cocaine craving. Similar relationships have been reported between self-reported impairment and cocaine craving among HIV-seronegative, cocaine-dependent, methadone-maintained patients.⁴⁶ Previous studies have shown that craving for food and nicotine has a significant impact on cognitive functioning, but the specific impact of cocaine craving, especially the differential impact between men and women, has not been investigated to date.^{47,48} Future studies will need to be conducted to examine the effects of repeated cocaine use

and cocaine craving on neuropsychological impairment – as well as the directionality of these effects – among cocaine-dependent patients at different stages of clinical care.

Limitations and future research. Several limitations of our study must be acknowledged. First, the symptoms of NCI were assessed using the NIS, which is a self-reported screening instrument. This instrument does not provide a comprehensive assessment of NCI and does not measure all possible cognitive domains. It is, however, an easy-to-administer assessment tool that provides a quick and accurate picture of neuropsychological symptoms, eliciting relevant diagnostic information, and has been used widely among this patient population.^{28–31,46} Second, we relied on the self-report assessment approach, which may have constrained our ability to precisely detect some variables due to the participants’ reluctance to report socially undesirable behaviors, such as cocaine use and NCI components. This may have been moderated, however, by the use of the ACASI assessment approach, which provided participants with a high level of privacy. Third, this study does not address directionality of the association between cognitive impairments and cocaine use – whether cognitive impairments represent predisposing traits or consequences of cocaine use. Such knowledge could further inform the development of tailored treatment approaches. Fourth, a number of studies have demonstrated that pharmacological treatments (ie. methadone maintenance treatment) for substance-abuse disorders can lead to neurocognitive deficits.^{49–52} Thus, the level of cognitive deficit seen among our sample may have been interfered due to use of methadone. We did, however, account for the effect of methadone on differences in NCI within our sample by controlling for “methadone use” and “years in MMT program”.

Conclusion and Recommendations

The present study contributes to the notion that cocaine-dependent, methadone-maintained women and men may enter into substance-abuse treatment with a range of cognitive impairments. Furthermore, a sex-related difference of neurocognitive deficits – with cocaine-addicted women having significantly more impaired decision-making ability than cocaine-addicted men – may contribute to differential treatment outcomes among male and female cocaine users. Indeed, there is evidence that tailoring behavioral interventions – based on demographics such as sex – can be more efficacious as opposed to using a one-size-fits-all approach. Surprisingly, there have been very few randomized trials of addiction treatment programs that include additional services such as neuropsychological testing services and sex-specific treatment programs.⁵³ Future work in this area is essential, as it may have direct implications for the development of specifically tailored interventions designed to optimally reduce adverse health outcomes in these high-risk, cognitively impaired patients.



Author Contributions

Conceived and designed the study: RS, TBH, MC. Analyzed the data: RS, TBH. Wrote the first draft of the manuscript: RS. Contributed to the writing of the manuscript: RS, TBH, MC. Agree with manuscript results and conclusions: RS, TBH, MC. Jointly developed the structure and arguments for the paper: RS, TBH, MC. Made critical revisions and approved final version: RS, TBH, MC. All authors reviewed and approved the final manuscript.

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