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The Neuropsychology of Cocaine Addiction: Recent Cocaine Use Masks Impairment

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Individuals with current cocaine use disorders (CUD) form a heterogeneous group, making sensitive neuropsychological (NP) comparisons with healthy individuals difficult. The current study examined the effects on NP functioning of four factors that commonly vary among CUD: urine status for cocaine (positive *vs* negative on study day), cigarette smoking, alcohol consumption, and dysphoria. Sixty-four cocaine abusers were matched to healthy comparison subjects on gender and race; the groups also did not differ in measures of general intellectual functioning. All subjects were administered an extensive NP battery measuring attention, executive function, memory, facial and emotion recognition, and motor function. Compared with healthy control subjects, CUD exhibited performance deficits on tasks of attention, executive function, and verbal memory (within one standard deviation of controls). Although CUD with positive urine status, who had higher frequency and more recent cocaine use, reported greater symptoms of dysphoria, these cognitive deficits were most pronounced in the CUD with negative urine status. Cigarette smoking, frequency of alcohol consumption, and dysphoria did not alter these results. The current findings replicate a previously reported statistically significant, but relatively mild NP impairment in CUD as compared with matched healthy control individuals and further suggest that frequent/recent cocaine may mask underlying cognitive (but not mood) disturbances. These results call for development of pharmacological agents targeted to enhance cognition, without negatively impacting mood in individuals addicted to cocaine.
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INTRODUCTION

Inconsistent results characterize studies of neuropsychological (NP) functioning in drug addicted individuals (Rogers and Robbins, 2001; Goldstein *et al*, 2004; Jovanovski *et al*, 2005). For example, comparing cocaine-addicted individuals with healthy control subjects on tasks of attention, executive function, and memory, several studies have reported severe deficits (Ardila *et al*, 1991; Gillen *et al*, 1998), while other studies reported no deficits on similar NP tasks (O'Malley *et al*, 1992; Hoff *et al*, 1996). In a recent factor-analytic study, our group reported statistically significant, but mild, deficits (ie, <1 SD below a control group mean) in verbal knowledge, visual, and verbal memory, and attention/executive functioning in 42 cocaine abusers and 40 alcohol-dependent individuals as compared with 72 control subjects (Goldstein *et al*, 2004). The main goal aim of the current study was to test the reliability of our previous results in a larger sample of individuals with cocaine use disorders (CUD). In addition, we aimed to test the effects of four factors that commonly vary within cocaine-addicted groups, namely urine status for cocaine, history of cigarette smoking and alcohol consumption, and dysphoric symptoms (Budney *et al*, 1993; Rusted *et al*, 1994, 1995; Di Sclafani *et al*, 2002; Richter *et al*, 2002; Poling *et al*, 2007). These factors may influence NP performance in drug abusers and possibly account for the inconsistencies in this literature.

Drug Urine Status as a Measure of Abstinence/ Withdrawal Symptoms, Including Dysphoria

Previous research suggests that NP function varies with the length of abstinence or withdrawal severity in CUD. For example, set shifting, a core executive function, is impaired when tested 2–4 weeks after last drug use in CUD (Ardila *et al*, 1991; Berry *et al*, 1993); this impairment is not evident at shorter abstinence periods (within 72 h of last drug use) (Berry *et al*, 1993). Since screening urine for drugs of abuse

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is common in clinical practice (eg, to assess adherence to treatment goals), we examined whether NP performance in CUD differs as a function of this objectively measured index of abstinence. In addition, we examined the extent to which dysphoric symptoms affect NP function, since depression/dysphoria is a common psychostimulant withdrawal symptom (Association, 2000). Depression/dysphoria is also associated with more severe dependence (Schuckit *et al*, 1999; Sofuoglu *et al*, 2003), exacerbating NP deficits in drug-abusing (Di Sclafani *et al*, 2002) and non-drug abusing (Fossati *et al*, 2002) populations.

Nicotine and Alcohol Use

Cocaine abusers are more likely to smoke cigarettes compared with healthy control subjects; moreover, the frequency of cigarette smoking is positively related to their chronic use of cocaine (Budney *et al*, 1993; Roll *et al*, 1996). However, although nicotine has been shown to improve attention and memory in cigarette smokers (Rusted *et al*, 1994, 1995; Warburton *et al*, 2001), its effects on cognition in CUD have not been extensively explored. Concurrent use of alcohol is also common among CUD. It is associated with more severe cocaine dependence (Higgins *et al*, 1994) and higher reports of adverse cocaine use consequences (Heil *et al*, 2001). NP deficits, such as attention, memory, and executive and motor functions, are commonly impaired with chronic alcohol use (Parsons and Nixon, 1993; Beatty *et al*, 2000; Ikeda *et al*, 2003); however, it is unclear how alcohol is related to NP deficits in cocaine addiction. Therefore, the current study examined whether cigarette smoking and alcohol use are differentially associated with NP performance in CUD.

MATERIALS AND METHODS

Participants and Procedure

All protocols within the current study were approved by the ethical committee of the institutional review board and therefore were conducted in accordance with the ethical standards presented in the 1964 Declaration of Helsinki Principles.

Eighty-four cocaine-addicted subjects who consented for participation in 16 of our neuroimaging protocols at Brookhaven National Laboratory (these protocols use positron emission tomography and/or magnetic resonance imaging; for additional information on imaging procedures we refer the reader to other published works, Wang *et al*, 2001, 2004; Goldstein *et al*, 2007a, b, c) completed the NP battery. Of these, we selected 64 subjects based on their history of cocaine use, age (18–55 years), and the ability to match them to control subjects on gender and race (one cocaine-addicted subject was matched on gender but not race). This process yielded 128 subjects for the current analysis (64 CUD and 64 control). Cocaine abusers met DSM-IV diagnostic criteria for history of cocaine dependence or abuse (reporting cocaine as their preferred drug and with primary use of cocaine by smoked route). Comparison subjects were 64 healthy individuals with no history of drug addiction. Subjects were initially screened by phone and then evaluated by a neurologist to ensure that they met inclusion and exclusion criteria. Exclusion criteria for all subjects were history of head trauma with loss of consciousness greater than 30 min and/or a history of neurological, cardiovascular, endocrinological, and/or current psychiatric disorders (apart from cocaine and alcohol abuse or dependence for the cocaine group or nicotine dependence for the control and cocaine groups). Five cocaine subjects who reported cocaine as their preferred drug and who met DSM-IV criteria for cocaine abuse/dependence also met criteria for current alcohol dependence. No subject was taking medications at the time of the study.

Participants were administered the NP assessment either on a separate random day or as a separate module that was independent of the imaging procedures (completion of the study ranged from 2–5 days depending on the protocol). On the morning of each study day, a triage urine panel for drugs of abuse (Biopsych) was used to test for presence of cocaine and its metabolites in all study subjects. A positive result indicated cocaine use within 72 h (the maximal resolution of the urine test) of NP testing (CUD+, $N=43$), and a negative result indicated longer term abstinence (CUD−, $N=21$). With the exception of cocaine in CUD, a positive result for any other drugs (ie, marijuana, opiates, benzodiazepines, phencyclidine, amphetamine/methamphetamine, barbiturates) was exclusionary. All other information, including history of cocaine use, alcohol consumption (for cocaine abusers only), cigarette smoking, and dysphoria (depressive symptoms in the past two weeks as assessed with Beck's Depression Inventory II (BDI)) (Beck *et al*, 1996) was collected via self-report.

NP Battery

The NP battery (see Table 2) was composed of well-validated NP measures of attention and executive function, memory, facial and emotion recognition, and motor function (Lezak, 1995). Also included in the battery were measures of verbal and non-verbal intelligence estimated with age-corrected scores from the reading subscale of the Wide Range Achievement Test 3 (WRAT 3) (Wilkinson, 1993) and matrix reasoning subscale of the Wechsler Abbreviated Scale of Intelligence III, respectively. Although the WRAT 3 reading subtest is considered an achievement test, it is also used as an estimate of verbal IQ and premorbid intelligence and is highly related to other word-based IQ indices such as the National Adult Reading Test (r=0.8) and verbal IQ indices from the Wechsler intelligence scales for children and adults (r=0.7). It is also a better verbal IQ estimate in lower SES and minority populations (Strauss *et al*. 2006). Tasks measuring attention/executive function were the (1) Controlled Oral Word Association Task (Benton, 1968) assessing flexibility of verbal thought processes and the ability to update working memory (number of correct words produced for phonemic (2 categories—letters 'F' and 'S') and semantic categories (2 categories—'animals' and 'fruits and vegetables'), 1 min per category); sensitivity and specificity for both indices are reliable in discriminating controls from those with impaired frontal function (sensitivity of 88 and 100% has been reported for phonemic and semantic categories, respectively) (Lezak, 1995); (2) digit span (standardized scores

based on the sum of raw scores for both forward and backward tests) and letter-number sequencing subtests from the Wechsler Adult Intelligence Scale III; Wechsler, 1997) assessing attentional capacity and verbal working memory; both subtests have adequate sensitivity and specificity (Lezak, 1995); (3) Symbol Digit Modalities Test (Smith, 1982) assessing attentional capacity (written; number of correct responses in 90 s; possessing ample sensitivity (approximately 80%) in detecting brain injury and learning disorders) (Lezak, 1995); (4) Trail Making Test (Reitan, 1955) assessing visual motor tracking, cognitive flexibility, and planning (trails A and B are very sensitive to cognitive decline and differentiate controls from both mild and severe head trauma patients; sensitivity of 77 and 79% has been reported for trails A and B, respectively) (O'Donnell *et al*, 1984; Lezak, 1995); (5) Mazes subtest from the Wechsler Intelligence Scale for Children III (Wechsler, 1987) assessing planning and sustained attention (this subtest is a 'satisfactory substitute for longer adult tests such as the Porteus mazes' in assessing executive functioning for most clinical purposes; (we used scaled scores based on norms for the highest (16 years) age) (Lezak, 1995); (6) Wisconsin Card Sort Test 3 (Berg, 1948) computerized version (Heaton, 1999) assessing set shifting and planning (specificity for the Wisconsin Card Sort Test is reported to be low, however it is very sensitive to the effects of frontal damage); and the (7) Color-Word Stroop Task (Golden, 1978), an index of directed attention and cognitive flexibility (the Color-Word Stroop is sensitive to both mild and severe frontal lobe impairment, differentiating those with learning disabilities or Attention Deficit Hyperactivity disorder from controls (eg, sensitivity, 89%)) (Homack and Riccio, 2004; Lezak, 1995). Two newly developed tasks of executive function were also included in this NP battery, and although more studies are needed to test their validity, recent reports have provided evidence for their utility in distinguishing specific executive domains: (8) the Attention Network Test (Fan *et al*, 2002) using reaction time to measure alerting (response readiness), orientating (scanning/selection), and executive control (conflict resolution); and the (2) Iowa Gambling Task (Bechara *et al*, 1994) measuring advantageous decision making. Verbal learning and memory was assessed by the (10) California Verbal Learning Task II (CVLT) (Delis *et al*, 2000) involving list learning, recall, recognition, semantic and serial learning strategies, and the degree of vulnerability to cognitive interference (performance on the CVLT effectively discriminates patients with left *vs* right temporal lobe dysfunction from control subjects) (Lezak, 1995). Emotion and facial recognition was measured with the (11) Ekman Faces test (Ekman, 1993) measuring recognition of six different emotions (sensitivity and specificity for the Ekman tests are good (eg, 94% sensitivity and 100% specificity in discriminating patients with frontotemporal dysfunction from healthy controls)) (Diehl-Schmid *et al*, 2007) and (12) Benton Facial Recognition Test (corrected long form scores) (Benton, 1990) that measured the ability to match faces. Motor function was measured by the (13) Timed Gait test (Robertson *et al*, 2006) (average time to walk a 12-foot floor-length back and forth for a total of three trials), with fine motor coordination assessed by the (14) Finger Tapping Test (the mean of the closest three out of five trials for each hand) (Reitan, 1985), a simple test of motor speed and motor control (tests of its sensitivity/specificity indicates that this test is a poor screening instrument but is useful as a diagnostic supplement) (Lezak, 1995), and (15) Grooved Pegboard Test (Ruff and Parker, 1993), a motor task including complex coordination (there is adequate sensitivity for this test in classifying brain damaged patients) (Lezak, 1995). All tests were presented in the same fixed order for all subjects. The complete battery was administered in a quiet room with all but three subjects completing the NP battery in one sitting. To minimize fatigue, subjects were encouraged to take a short break toward the middle of the battery. Cigarette smokers were asked to refrain from smoking throughout the NP session and the short break; nevertheless, two subjects smoked a partial cigarette during the short break. In addition, nine smokers reported smoking a cigarette just prior to the NP assessment.

Statistical Analyses

χ^2-Tests (for categorical variables) or analyses of variance (for continuous variables, omnibus results followed with Tukey's *post-hoc* comparisons) were conducted on all demographic variables and NP tests. The potential impact of all demographic variables that differed between the study groups (Table 1) was examined as follows: if significantly correlated with the dependent variables (NP measures), the demographic variable was entered as a covariate in an analysis of covariance (Tabachnick and Fidel, 1983). The effect of dysphoria on cognitive function was examined with correlations between BDI scores and all NP tests for each study group separately, across all CUD, and across all study subjects. Since BDI scores (and two of the alcohol consumption measures) did not follow a normal distribution, Spearman's ρ correlations were computed. For cigarette smoking, we conducted parametric correlations between frequency of current cigarette smoking and all NP measures for the current smokers only (again, for each study group separately, across all CUD, and across all study subjects). Finally, for both CUD subgroups (separately and combined), we also inspected Pearson product–moment correlations between all NP measures with selected cocaine and alcohol use variables. Analyses of covariance were also conducted for the NP measures that both significantly differed between the groups and were associated with any of these other variables (dysphoria, cigarette smoking, alcohol use, or cocaine use). Across all between-group analyses, $p<0.05$ was considered significant; to protect against type-I error, a Bonferroni correction was applied to all correlation analyses involving NP measures ($0.05/15=0.01$).

RESULTS

Sample Demographics and Characteristics

There were no differences between the study groups in distributions of gender, race, English as first language, handedness, and in estimates of verbal and non-verbal intelligence (scores on these measures followed a normal distribution with no outliers (no cut-off criteria were

Table 1 Demographics, General Intellectual Functioning, Dysphoria, and Self-Reported Alcohol and Drug Use

	Significance test (χ^2 or F or (*Z*))	C (*N* = 64)	CUD+ (*N* = 43)	CUD− (*N* = 21)
Gender (male/female)	0.8	50/14	35/8	15/6
Race (Caucasian/African American/other)	5.5	12/47/5	8/34/1	3/14/4
First language (English/other)	2.7	60/4	43/0	20/1
Laterality quotient (Modified Edinburgh Handedness Inventory	0.7	0.8 ± 0.4	0.7 ± 0.6	0.7 ± 0.6
Socioeconomic status (Hollingshead index)	8.8**	35.3 ± 11.7[b,c]	28.7 ± 12.1[a]	24.2 ± 9.9[a]
Age (years)	3.1[†]	38.7 ± 6.5[b]	41.7 ± 6.2[a]	40.9 ± 6.1
Education (years)	3.6[†]	13.6 ± 2.1	12.6 ± 2.1	12.5 ± 2.1
Reading (Wide Range Achievement Test Revised III)	2.6	96.6 ± 12.9	91.3 ± 13.3	90.7 ± 16.2
Matrix reasoning (WASI III)	0.2	10.4 ± 3.3	10.3 ± 2.9	9.8 ± 3.6
State symptoms of dysphoria	28.6**	3.4 ± 5.3[b,c]	13.1 ± 10.7[a,c]	6.8 ± 6.1[a,b]
Cigarette smokers (current smokers/past and nonsmokers) (*N* = 116)	42.6**	10/49[b,c]	31/8[a]	13/5[a]
Cigarettes per day (current smokers only) (*N* = 9/29/13 for C/CUD+/CUD−)	1.6	8.5 ± 6.3	10.9 ± 6.8	7.2 ± 5.3
Lifetime use (years) of alcohol (*N* = 38/17 for CUD+/CUD−)	2.1	—	13.4 ± 8.4	17.4 ± 11.3
Frequency of alcohol consumption (days) during the past 30 days (*N* = 40/17 for CUD+/CUD−)	(−1.2)	—	6.9 ± 7.3	5.6 ± 9.1
Frequency of alcohol consumption to intoxication (days) during the past 30 days (*N* = 40/17 for CUD+/CUD−)	(−1.4)	—	3.2 ± 5.3	1.0 ± 3.0
Lifetime use (years) of cocaine (*N* = 35/13 for CUD+/CUD−)	0.0	—	18.1 ± 7.6	18.5 ± 5.7
Frequency of cocaine use (days) during the past 30 days (*N* = 37/14 for CUD+/CUD−)	12.0**	—	15.5 ± 8.0[c]	7.1 ± 6.9[b]
Current abstinence (days since last cocaine use) (*N* = 39/16 for CUD+/CUD−)	7.9*	—	3.1 ± 6.5[c]	15.0 ± 24.9[b]

Note: C, control subjects; CUD+, participants testing positive for cocaine on the day of NP testing; CUD−, participants testing negative for cocaine on the day of NP testing; all values under group categories are either distributions or the mean ± the standard deviation;
**$p < 0.001$, *$p < 0.01$, [†]$p < 0.05$. *Post hoc* tests were not significant for education.
[a]Mean value significantly differs from that of the control group.
[b]Mean value significantly differs from that of the cocaine positive group.
[c]Mean value significantly differs from that of the cocaine negative group.

imposed). Mean socioeconomic status, age, and education differed between the groups. These group differences were accounted for as described in Statistical Analyses. There were no group differences in time to complete the entire NP Battery. Means and SDs for these variables are presented in Tables 1 and 2.

As expected, the CUD + subgroup reported a shorter abstinence period and higher frequency of recent cocaine use than the CUD− subgroup (Table 1). Consistent with the effects of acute withdrawal on mood (Johanson *et al*, 1999; Dudish-Poulsen and Hatsukami, 2000), the CUD + also reported more dysphoria than both CUD− and controls (CUD + > CUD− > controls). The F-value for BDI (reported in Table 1) was computed using transformed BDI scores (ie, square root transformation) as raw BDI scores were non-normally distributed; however, to facilitate interpretation, means and SDs presented in the table are raw scores. Further, history of cigarette smoking was more frequent in both CUD subgroups as compared with that in control subjects. Consistent with prior reports (Budney *et al*, 1993; Roll *et al*, 1996), the complete CUD group showed a positive association between cocaine use and frequency of current cigarette smoking: the more frequent the recent cocaine use and the longer the lifetime use of cocaine, the higher the number of cigarettes smoked per day ($r = 0.5$ and 0.4, $p < 0.05$, respectively). This effect was driven by the CUD + subgroup. Alcohol consumption did not differ among the cocaine subgroups (Mann–Whitney tests were conducted on two measures of alcohol use with skewed distributions (the number of days of alcohol consumption in the last 30 days and the number of days it was consumed to intoxication in the last 30 days). The *Z*-values yielded from these tests are presented in Table 1.), and was not associated with cocaine or nicotine use.

Attention and Executive Function

There were significant group main effects on four of the attention/executive function measures including: digit span, letter-number sequencing, Wisconsin Card Sort Test (percent correct), and the executive control index of the Attention Network Test (Table 2). Follow-up tests for these NP measures showed statistically significant differences between the controls and CUD− only. Although the CUD + outperformed the CUD−, while performing worse than controls on all of these measures, these differences for the CUD + subgroup did not reach the nominal statistical significance level.

Controlling for the potential demographic covariates (one at a time), the effect for digit span was no longer significant,

Table 2 Means and SDs for all Neuropsychological Tests

Neuropsychological domain and task	F	Sample *N* for task C/CUD+/CUD−	C M ± SD	CUD+ M ± SD	CUD− M ± SD
Attention/executive function					
1. Controlled Oral Word Association Task: phonemic (correct words)	0.3	63/43/21	28.5 ± 9.1	27.2 ± 8.4	27.2 ± 8.0
Controlled Oral Word Association Task: semantic (correct words)	0.2	63/43/21	39.4 ± 10.3	40.2 ± 8.6	38.7 ± 10.2
2. Wechsler Adult Intelligence Scales III: digit span (standardized scores)	4.1††	64/43/21	10.4 ± 3.4[c]	9.0 ± 2.9	8.4 ± 2.6[a]
Wechsler Adult Intelligence Scale III: letter–number sequencing	5.4**	51/39/17	9.8 ± 3.3[c]	9.0 ± 3.1	6.9 ± 3.0[a]
3. Symbol Digit Modalities Test	1.6	57/42/17	49.3 ± 12.9	45.9 ± 11.6	44.2 ± 11.4
4. Trail making test A (seconds to complete)	1.1	63/43/21	34.5 ± 12.9	31.3 ± 9.4	31.9 ± 11.3
Trail making test B (seconds to complete)	0.0	62/43/21	78.6 ± 29.9	78.3 ± 25.8	78.0 ± 39.4
Trail making test B−test A	0.1	62/43/21	44.6 ± 27.8	47.0 ± 23.8	46.1 ± 35.5
5. Wecshler Intelligence Scales for Children III: mazes (scaled score)	2.4	62/43/21	8.4 ± 4.0	7.6 ± 3.2	6.5 ± 7.8
6. Wisconsin Card Sort Test 3: categories completed	2.0	63/43/21	5.1 ± 1.6	4.4 ± 1.9	4.5 ± 1.9
Wisconsin Card Sort Test 3: percent correct	3.8†	63/43/21	75.3 ± 12.6[c]	69.9 ± 16.8	66.1 ± 15.7[a]
Wisconsin Card Sort Test 3: perseverative errors	0.7	62/40/20	12.1 ± 6.9	13.7 ± 7.4	13.8 ± 7.8
7. Stroop task: age corrected interference	0.3	63/43/20	−0.3 ± 8.0	−0.6 ± 7.5	−2.0 ± 6.5
8. Attention network test: alerting	0.7	63/43/21	33.1 ± 33.2	39.2 ± 37.3	44.2 ± 62.3
Attention network test: orienting	1.9	64/43/21	42.7 ± 37.9	59.4 ± 42.7	63.1 ± 13.8
Attention network test: conflict	4.1†	63/43/21	129.1 ± 56.4[c]	150.9 ± 68.0	173.4 ± 79.7[a]
9. Iowa gambling task (total disadvantageous cards)	0.1	55/35/16	52.5 ± 15.1	53.7 ± 13.6	54.1 ± 10.2
Memory					
10. California Verbal Learning Test II: total recall (trials 1–5)	4.2*	56/42/17	48.1 ± 10.9[c]	47.3 ± 9.1[c]	40.2 ± 8.8[a,b]
California Verbal Learning Test II: long delay-free recall	3.7*	56/42/17	10.3 ± 3.4[a]	9.7 ± 2.9	7.9 ± 3.2[b]
California Verbal Learning Test II: long delay cued recall	2.1	56/42/17	10.6 ± 3.4	10.8 ± 2.7	9.1 ± 2.8
California Verbal Learning Test II: recognition hits	1.1	55/42/17	14.5 ± 1.9	14.1 ± 1.7	13.8 ± 2.0
Facial and emotion recognition					
11. Ekman Faces (total percent correct)	1.9	64/43/21	65.2 ± 34.5	74.8 ± 26.9	59.2 ± 37.2
12. Benton Facial Recognition Test	1.4	51/39/16	47.3 ± 5.0	45.8 ± 4.1	47.4 ± 4.1
Motor function					
13. Timed gait (s)	2.8	58/42/16	10.3 ± 2.1	9.8 ± 1.4	11.1 ± 2.5
14. Finger tapping: RH (number of taps)	0.3	64/42/21	49.1 ± 7.9	49.5 ± 8.6	50.1 ± 8.2
Finger tapping: LH (number of taps)	0.9	64/43/21	44.6 ± 6.9	43.6 ± 9.1	46.4 ± 7.3
15. Grooved pegboard: RH (s)	1.5	57/43/17	75.6 ± 12.3	77.2 ± 14.9	77.3 ± 18.3
Grooved pegboard: LH (s)	0.1	56/43/17	83.2 ± 18.0	82.2 ± 14.2	83.9 ± 20.5
Completion time for NP battery (min)	1.4	64/42/21	154.0 ± 24.8	157.7 ± 27.0	145.7 ± 30.3

Note: *N*, number of subjects with complete data; C, control subjects; CUD+, participants testing positive for cocaine the day of NP testing; CUD−, participants testing negative for cocaine the day of NP testing;
**$p<0.01$, *$p<0.05$. †Indicates significant effect in the ANOVA ($p<0.05$), but reduced to a trend ($p<0.10$) in ANCOVA; ††indicates significant effect in the ANOVA ($p<0.05$), but insignificant result in ANCOVA ($p<0.10$).
[a]Mean value significantly differs from that of the control group.
[b]Mean value significantly differs from that of the cocaine positive group.
[c]Mean value significantly differs from that of the cocaine negative group.

and the effects for Attention Network Test and Wisconsin Card Sort Test were reduced to trends ($F(2, 127) = 2.5$, $p<0.09$ and $F(2, 127) = 2.4$, $p<0.10$, respectively) (Figure 1; Supplementary Table 1). The effect for letter-number sequencing remained significant [$F(2, 107) = 5.08$, $p<0.01$].

There were no significant correlations between the attention/executive function NP measures and frequency of cigarette smoking in the current smokers (correlations ranged from 0.02 to 0.2, all $p>0.07$). However, the number of days that alcohol was consumed (and consumed to

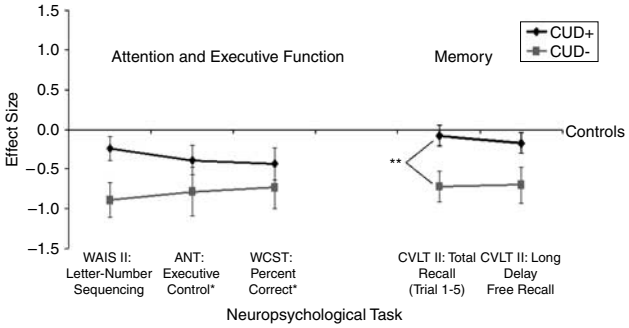

Figure 1 Neuropsychological performance of cocaine-addicted subjects as compared with control subjects. CUD+ and CUD− = cocaine subjects who tested positive or negative for cocaine, respectively. WAIS III = Wechsler Adult Intelligence Scale III; ANT= Attention Network Test; WCST Wisconsin Card Sort Test CVLTII=California Verbal Learning Test II; Z-scores were computed for all NP variables to present effect sizes for each cocaine subgroup as compared to control subjects whose mean score was converted to zero and standard deviation to 1. All effect sizes for CUD− are significantly different from controls, $p<0.05$; error bars are the standard error mean; **CUD+ scores are significantly different from CUD−, $p<0.05$; *p<0.10 in ANCOVA analysis.

intoxication) in the past 30 days was significantly related to poorer performance on the Symbol Digit Modalities Test for all CUD ($r=-0.4$ for both indices, $p<0.01$). Current abstinence from cocaine, lifetime use of cocaine, and frequency of cocaine use did not correlate with any of the NP attention/executive function measures in the CUD subjects (complete group or subgroups).

There was a trend for symptoms of dysphoria to be associated with poorer performance on digit span ($r=-0.2$) and letter-number sequencing ($r=-0.3$) in the entire sample (all $p<0.01$) as driven by the control group ($p<0.05$). A *post hoc* analysis of covariance controlling for dysphoric symptoms showed no impact on the significant group differences reported for letter-number sequencing (the NP measure that remained significantly different between the groups after accounting for other relevant covariates in Table 1) ($F(2, 107)=5.08$, $p<0.01$).

Memory Function

There were significant group main effects on the CVLT measures of total recall and long-delay-free recall (Table 2; Figure 1). Follow-up tests showed that the healthy control subjects outperformed the CUD− in both measures. For total recall, the CUD+ subgroup performed similarly to controls, outperforming the CUD− subgroup at a statistically significant level (Figure 1; Supplementary Information). There were no significant correlations between the demographic variables that differed between the study groups and the CVLT measures; analyses of covariance were therefore not performed. No significant associations were found between any of the CVLT measures with cigarette smoking, alcohol consumption, or the selected cocaine use variables for the complete sample or the selected subgroups as explained above.

Greater dysphoria was associated with less recognition hits on the CVLT in the CUD− subgroup ($r=-0.4$, $p<0.01$).

Emotion and Facial Recognition and Simple and Complex Motor Function

There were no significant differences between the groups on these selected tests. In addition, we found no significant associations between these tests with symptoms of dysphoria, cigarette smoking, alcohol, or cocaine use for the complete sample or selected subgroups.

DISCUSSION

A Neuropsychological Profile of Cocaine Abuse

We previously reported that compared with healthy control subjects, subjects with CUD exhibit statistically significant and generalized, but mild, cognitive impairment as measured with classical NP tasks (Goldstein *et al*, 2004). Our current findings (group main effects) in a larger sample of CUD and healthy control subjects replicate these previous results, pointing again to statistically mild impairments in attention/executive function and verbal memory. Together, results of both studies are consistent with a recent meta-analytic review indicating performance deficits in similar cognitive domains (ie, memory and executive function) in CUD (Jovanovski *et al*, 2005). The statistical modest extent of this NP impairment may be a contributing factor to the reluctance to define drug addiction as a disorder of the brain in the general public. Nevertheless, these deficits, although statistically mild, negatively affect treatment outcome/retention (see negative correlations between performances on the MicroCog Assessment of Cognitive Functioning and Wisconsin qCard Sort Test with the number of weeks in cognitive-behavioral treatment and program dropout rate) (Aharonovich *et al*, 2003, 2006) and may have pronounced consequences to daily functioning. Note that, as with all cross-sectional designs, our study cannot affirm whether these deficits have predated the development of drug addiction, predisposing vulnerable individuals to developing addiction, or whether these cognitive deficits are a consequence of drug use.

Our secondary goal was to inspect the potential impact on this NP profile of variables that frequently vary within addicted subgroups: urine status for cocaine as an abstinence/withdrawal index, cigarette smoking, alcohol use, and symptoms of dysphoria. Our results indicate a consistent trend for a more severe level of attention/executive and verbal memory impairment in the CUD− than the CUD+ subgroup. However, these findings should be cautiously interpreted, as there was only one statistically significant difference between the CUD subgroups (on CVLT total recall; for all other NP measures, the significant difference was between CUD− and controls).

In general, the relatively better performance in the CUD+ group could not be attributed to current cigarette smoking or alcohol use (that did not differ between the CUD subgroups) or dysphoria (that was higher in the CUD+). Consistent with the more frequent and recent cocaine use in the CUD+ group, this pattern of results may be attributed to the neurocognitive enhancing effects of acute cocaine in CUD (Higgins *et al*, 1990; Johnson *et al*, 1998, 2005), discussed below.

Impairment of Attention and Executive Function in Cocaine Abusers

The CUD− group exhibited impairments on the letter-number sequencing test with similar trends for the WCST and ANT. These tasks encompass attention/working memory, concept formation, and behavioral control, all functions that rely heavily on the prefrontal cortex (Miller and Cohen, 2001). Our current NP results are therefore consistent with numerous neuroimaging studies that report hypofrontality in abstinent CUD, while performing attention/executive function tasks (eg, Bolla *et al*, 2004; Goldstein *et al*, 2007a,b; Tomasi *et al*, 2007a), underscoring the importance of the prefrontal cortex in underlying the core addiction symptoms (Goldstein and Volkow, 2002).

A trend for deficits on the executive control subtest of the Attention Network Test (but not on alerting or orienting subtests) was observed in the CUD− subgroup (as compared with controls), a novel finding in the drug addiction literature; such specificity was previously reported only in patients with schizophrenia (Wang *et al*, 2005; Neuhaus *et al*, 2007). Performance on this particular subtest of the Attention Network Test is associated with the anterior cingulate cortex, and with left lateral prefrontal, primary, and supplementary motor areas as measured with functional magnetic resonance imaging and source analysis of an event related potential component (P300) latency (Fan *et al*, 2003, 2005, 2007). Interestingly, these brain regions have also been associated with abstinence, drug craving, and relapse (Sinha and Li, 2007). It is therefore possible that this specific executive impairment in the CUD− subgroup is a manifestation of an underlying prefrontal brain dysfunction that may predispose individuals to impulsivity, drug use, and relapse even after extended periods of abstinence.

Note that despite the documented role for the prefrontal cortex in performance on the Iowa Gambling Task (IGT) (Bechara *et al*, 1994, 2001), and in contrast to previous functional neuroimaging studies in substance abusers (Bartzokis *et al*, 2000; Grant *et al*, 2000; Bolla *et al*, 2003), we found no significant differences between controls and the CUD subgroups in decision-making as measured with this task (including net scores (the percentage of disadvantageous cards selected from the total deck) for each of the five trials in the task). This negative result might be attributed to sample differences between the studies (eg, earlier studies have relied on smaller samples of CUD who were treatment-seeking or closely monitored), but also highlights the importance using novel/more targeted functional neuroimaging paradigms. Promising paradigms encompass cognitive-emotional processes that uniquely engage prefrontal corticolimbic brain areas as a function of drug addiction. For example, Goldstein *et al* (2007a,b), observed a relationship between reward sensitivity and frontolimbic brain function using a monetary reward task; Kaufman *et al* (2003 observed a relationship between behavioral inhibition and cingulate hypoactivity; and Tomasi *et al* observed relationships between both sustained attention (Tomasi *et al*, 2007a), working memory (Tomasi *et al*, 2007b), with prefrontal functional abnormalities using visuospatial attention and verbal memory (N-back) tasks.

Memory Impairments in Cocaine Abusers with a Negative Urine Status: Withdrawal/Abstinence Effects

Consistent with other reports (Pace-Schott *et al*, 2005), and with a previously suggested 'learning lag' in drug abusers (Verdejo-Garcia *et al*, 2007), our results revealed immediate verbal learning (CVLT total recall) and delayed verbal memory (CVLT delay-free recall) deficits that were most pronounced in the CUD− subgroup. These findings are noteworthy in light of recent evidence from animal research that points to modulation of memory function based on the cocaine withdrawal period; synaptic activity (long-term potentiation) was significantly compromised in the CA 1 region of the hippocampus in rats which had undergone a longer withdrawal period from cocaine (100 days) *vs* those with shorter periods of withdrawal (3 days) (Thompson *et al*, 2004). The notion that memory deficits are more pronounced with longer abstinence, an effect that until now was not reliably observed in humans, is clinically relevant. Indeed, it may explain why drug abusers in treatment often fail to use newly 'learned' strategies aimed to prevent relapse. However, we cannot rule out the possibility that CVLT total recall reflects attention/executive dysfunction rather than a primary learning/memory deficit. Therefore, this finding remains to be replicated using additional memory tasks (including non-verbal tasks).

No Effects of Cocaine Abuse on Facial and Emotional Recognition

Using Ekman task, no differences were found between the CUD and controls in recognition of facial emotional expression in the current study. This negative result contrasts with evidence of impaired fear recognition in recreational cocaine users (average use = once per month) (Kemmis *et al*, 2007) and of similar difficulties as documented using additional emotional recognition tasks in current and abstinent abusers of other drugs (eg, 3,4-methylenedioxy-N-methylamphetamine, opiates, alcohol) (Hoshi *et al*, 2004); (Kornreich *et al*, 2003; Townshend and Duka, 2003). A possible explanation for this difference may pertain to the inclusion criteria. For example, in the study by Kemmis, history of other drug dependence (eg, ecstasy, heroin, cannabis) was not exclusionary, whereas in our study it was; drugs other than cocaine may, therefore, drive impairments in emotion recognition. Therefore, it remains to be determined whether deficits in emotion recognition, particularly fear recognition, are associated with cocaine use.

No Effects of Cocaine Abuse on Motor Function

The current results suggest intact simple and complex motor function in cocaine abusers. These results contrast with findings in methamphetamine-addicted individuals in whom motor function was compromised (as measured with the grooved pegboard) compared with healthy control subjects and attributed to reductions in striatal dopamine transporter levels (Volkow *et al*, 2001). These differential results for cocaine *vs* methamphetamine abusers may reflect the unique impact of these psychostimulants on dopaminergic, serotonergic or noradrenergic

motor-output systems (Muller *et al*, 2003, 2007; Jones *et al*, 2007), possibly revealing more methamphetamine-induced neurotoxicity.

Cigarette Smoking, Alcohol Consumption, and Dysphoria

Consistent with previous research (Budney *et al*, 1993; Roll *et al*, 1996), we found that lifetime and recent cocaine abuse were associated with increased cigarette smoking. Both nicotine and cocaine influence reward-processing mechanisms (Pich *et al*, 1997) such that when used simultaneously, dopamine is increased in limbic brain areas (Gerasimov *et al*, 2000). In contrast to recent cocaine use, however, cigarette smoking was unrelated to NP function in the current study. These results are consistent with those of other studies that showed minimal or no effect of nicotine on certain cognitive tests (eg, logical reasoning) in drug abusers (Bell *et al*, 1999). Nevertheless, nicotine has been known to enhance cognition (verbal memory and attention) in healthy smokers (Jacobsen *et al*, 2005) and non-smokers (Kumari *et al*, 2003). Because in our study there was some variability in recency of cigarette smoking (11 subjects smoked a cigarette close to the NP assessment, see section NP Battery), our current results that pertain to cigarette smoking should be cautiously interpreted. Future studies incorporating objective measures of cigarette smoking history and severity (eg, breath CO, or nicotine and cotinine in urine) and targeted test-retest designs (eg, assessment of NP function before and after cigarette smoking) are needed to test the reliability of these results. It should be noted, however, that our findings largely pertain to CUD−, which did not differ from CUD+ in smoking history. Therefore, the main findings for CUD− cannot be fully explained by withdrawal from cigarette smoking.

The current results suggest a relationship between alcohol use frequency in CUD and specific attention/executive processes (ie information processing speed and sustained attention as indexed by the Symbol Digit Modalities Test; Lezak, 1995). Cocaine-addicted individuals often report use of alcohol to reduce the negative effects brought on by a cocaine binge (Magura and Rosenblum, 2000). However, this practice may be cognitively detrimental. This remains to be investigated in future studies.

Greater dysphoria was associated with worse performance on two attention/executive function measures, a finding that reached significance in the entire sample as driven by the healthy control subjects. This is consistent with studies in individuals with clinical depression where executive deficits, as associated with frontal lobe dysfunction, have been widely reported (Fossati *et al*, 2002). However, similar correlations with attention/executive function measures were not observed in the CUD subjects in the current study. Because the CUD+ reported the highest levels of dysphoria, but evidenced less NP dysfunction than the CUD− group, our findings suggest that other factors, independent of dysphoric symptoms, may account for the cognitive dysfunction-characterizing CUD.

Study Limitations and Future Research

Limitations to the current study include (1) the reduced number of subjects in the CUD− as compared with the CUD+ subgroup, which may have underestimated differences between groups. However, our total CUD sample was larger than in previous NP studies and we controlled for key demographic factors, reducing the influence of unique sample error on our results; (2) cross-sectional (*vs* longitudinal) designs restrict interpretations about the effects on NP function of acute *vs* longer term withdrawal; and (3) a wider extent of group differences may have been identified with newer/more tailored NP measures. For example, we reported that chronic cocaine abusers, especially CUD+, produce more words than control subjects on a newly developed Drug Fluency task; this result was absent when using the traditional phonemic or semantic fluency categories of the Controlled Oral Word Association Task, suggesting greater salience of or attention bias to drug related information in currently using addicted individuals (Goldstein *et al*, 2007a, b, c). Other novel behavioral measures have been used to successfully assess deficits in reflection impulsivity (the collection and assessment of information prior to decision making) in current and former amphetamine or opiate abusers (Clark *et al*, 2006). Together these studies reflect new directions in addiction NP research.

CONCLUSIONS

Consistent with previous studies, we report NP impairment in cocaine addiction that is modest but statistically discernible. These NP deficits encompassed attention/executive function and verbal learning and memory, and could not be attributed to measures that frequently vary between healthy control and cocaine-addicted individuals (eg, dysphoria and cigarette smoking, and also socioeconomic status and general intellectual functioning). As these impairments were most accentuated in the CUD− subgroup, it may be speculated that the relatively better cognitive functioning in the CUD+ subgroup reflects the mild cognitive improvement with active cocaine use (Johnson *et al*, 2005) that may potentially predispose to relapse. This speculation emphasizes the importance of developing or using a pharmacological agent that could improve neurocognitive function without negatively impacting mood thereby increasing positive outcome in treatment trials. Our results further indicate that determining urine status for drugs, a common practice in treatment settings, may provide an estimate of the cognitive and emotional impairments in cocaine abusers at time of treatment entry. This objective information may allow treatment providers to individually customize appropriate interventions.

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DISCLOSURE/CONFLICT OF INTEREST

The authors of this paper declare that no financial support or compensation has been received from any individual or corporate entity for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)