Published in final edited form as:

Drug Alcohol Depend. 2002 April 1; 66(2): 161–171.

Neuropsychological performance of individuals dependent on crack–cocaine, or crack–cocaine and alcohol, at 6 weeks and 6 months of abstinence

Victoria Di Sclafani^a, Marina Tolou-Shams^b, Leonard J. Price^c, and George Fein^{a,*}

^a Neurobehavioral Research Inc., 201 Tamal Vista Boulevard, Corte Madera, CA 94925, USA

^b Department of Psychology, University of Illinois at Chicago, Chicago, IL 60612, USA

^c Herrick/Alta Bates Hospital, Berkeley, CA 94704, USA

Abstract

Background: Little data exist on the neuropsychological effects of crack–cocaine dependence or crack–cocaine and alcohol dependence. This study examined cognitive function in abstinent crack dependent and crack and alcohol dependent individuals at 6 weeks and 6 months abstinence.

Methods: a comprehensive neuropsychological battery, including the MicroCog computerized assessment, was administered to 20 abstinent crack dependent subjects, 37 abstinent crack and alcohol dependent subjects, and 29 normal controls. Depression was examined as a covariate, and the association between substance use variables and neuropsychological performance was examined.

Results: the two substance dependent groups had similar neuropsychological profiles at 6 weeks abstinent, with both groups exhibiting significant cognitive impairment in a wide range of functions compared to controls. The substance dependent groups were still impaired significantly at 6 months of abstinence. Only mild effects of depression on neuropsychological performance were observed.

Conclusions: crack dependence and crack and alcohol dependence may lead to severe and persistent neuropsychological deficits over a wide range of domains. The strongest predictor of brain damage associated with substance dependence in this sample was dose (particularly quantity and duration of peak dose).

Keywords

Brain damage; Cocaine; Alcoholism; Neuropsychological; Assessment

1. Introduction

There are approximately two million cocaine abusers in the USA (Kleber, 1994), making cocaine one of the most commonly abused psychoactive substances in this country. Cocaine was most often used as intranasally administered cocaine hydrochloride ('blow') until 1985, when 'crack' (cocaine sold and smoked in the free base form) was introduced; since then, the number of users has increased dramatically (Barnes, 1988). Smoking crack is similar to intravenous injection for obtaining rapid systemic absorption and high brain concentrations

(Johanson and Fischman, 1989), with repeated dosing being easier with crack than with intravenous administration. Crack addicts often go on 'missions', a 3–4-day binge during which they smoke almost constantly, and rarely eat, drink, or sleep (Inciardi, 1992). The wholesale movement to crack use, and the resulting increased magnitude of potential neurological effects (Cregler and Mark, 1986; Jacobs et al., 1989), has not been adequately studied. Moreover, many of the studies that do exist are undermined by methodological problems that are inherent in studying substance abuse. At the same time, there is no fully adequate therapy for cocaine addiction, probably because we have not evolved a neurobiologic model of cocaine abuse that addresses the neurological sequelae of repeated use (Bolla et al., 1998).

The majority of cocaine abusers also abuse alcohol (Grant and Harford, 1990), with a growing number of individuals who present for substance abuse services exhibiting both alcohol and cocaine dependence (Brown et al., 1994). Despite this, there is little literature to date that reports on the comorbid effects of chronic cocaine and alcohol abuse, and the findings are inconsistent. A study by Brown et al. (1994) looked at the differences between 82 cocaine dependent alcoholics and 64 'pure' alcoholics on admission and at discharge from a 28-day treatment program; there was no difference in the groups' neuropsychological performance at 28 days abstinent. Easton's (Easton and Bauer, 1997) investigation compared three groups abstinent for 1–5 months: alcohol only dependent individuals, and a cocaine and alcohol codependent group divided into two samples split at the median score of the Michigan Alcoholism Screening Test (MAST). The cocaine dependent subjects with lower MAST scores ($N=29$) were impaired on the Shipley abstraction subtest in comparison to both the cocaine dependent subjects with higher MAST scores ($N=18$) and the alcohol dependent subjects. This finding was associated with a higher level of cocaine use in the cocaine dependent subjects with lower MAST scores. Robinson et al. (1999) compared cocaine and alcohol coabusers with demographically matched cocaine abusers and normals (all N values=30) using the Halstead–Reitan neuropsychological test battery. The abusers of cocaine only performed more poorly than cocaine and alcohol coabusers in complex psychomotor functioning and simple motor functioning, and on a measure of global functioning. Cocaine and alcohol coabusers did not differ from controls on the majority of measures. Beatty et al. (1995) did not study subjects dependent on both cocaine and alcohol; however, they did study differences between 24 alcoholics, 23 cocaine (primarily free-base) abusers and 22 healthy controls. They found that, at 3–5 weeks of abstinence, both alcoholics and cocaine abusers performed more poorly than controls on most measures of learning, memory, problem solving, executive function and perceptual-motor speed, but not on measures of sustained attention. The deficits observed in the cocaine-abusing group closely resembled those shown by the alcoholic group.

Relatively few studies of cocaine abusers have examined the persistence of cognitive impairment with extended abstinence. Strickland et al. (1993) studied a small sample of eight crack–cocaine abusers (without a comparison group of normal controls), who were drug-free for at least six months before evaluation, and found that these chronic heavy crack users exhibited deficits in attention, concentration, new learning, visual and verbal memory, word production, and visuomotor integration. They concluded that long-term cocaine use produces persistent neuropsychological (NP) compromise in at least some subgroups of cocaine-abusing patients. O'Malley and Gawin (1990) examined the residual effects of chronic cocaine abuse in a different cohort of 25 outpatient chronic cocaine (74% crack) users abstinent for an average of 135 days. The cocaine abusers, although performing in the clinically normal range, performed more poorly than controls in all domains of functioning (including motor skills). O'Malley et al. (1992) also studied NP impairment in 20 inpatient chronic cocaine abusers (70% crack users) at 24 days abstinence. They found the cocaine abusers to be more impaired than controls in all areas except motor skills (in which there

was no difference between groups) and verbal fluency (in which cocaine abusers performed better than controls). Fifty percent of the cocaine abusers studied at 24 days abstinence had mild clinical impairment in contrast to 15% of controls. Bolla et al. (1999) found few effects when comparing the NP performance of 21 controls to 30 chronic crack abusers who were abstinent 28 days; however, there was a strong relationship between increased dose (grams per week) and NP deficits within the crack-abusing group in the areas of attention, planning, mental flexibility, executive function, and psychomotor function. In more recent analyses of a larger sample of cocaine abusers, Bolla et al. (2000) compared effects of cocaine and cocaine and alcohol co-abuse on neurocognitive performance after 1–3 days and after 4 weeks of abstinence (note: no data for controls were reported). Within the cocaine abusing samples, they found dose-related associations of neurobehavioral performance with both cocaine and alcohol dose. Cocaine and alcohol dose were negatively associated with performance on different neurobehavioral tests at 1–3 days abstinence, with effects persisting at 4 weeks of abstinence.

There are very few longitudinal studies of abstinent cocaine abusers in the literature, although a longitudinal design is essential to address the question of recovery of NP function over time. The aforementioned study by Brown et al. (1994) found that the cognitive test scores in both the abstinent cocaine dependent alcoholics and the alcohol dependent only group improved significantly in the 28 days of the treatment program. Berry et al. (1993) tested 16 cocaine-abusing inpatients (abusing for at least 6 months prior to treatment) at 3 and 14 days abstinence; 21 controls were also retested at the same interval. They found memory, concentration, and visuospatial impairments in acute withdrawal, and less improvement on repeat testing in the cocaine abusers compared to the controls on tests of memory, concentration, and psychomotor ability. van Gorp et al. (1999) studied 37 cocaine abusers at 3, 10, 21 and 45 days abstinent, along with 27 control subjects. They found a persistent deficiency in visual memory, but a sustained improvement on a motor learning test in the cocaine abusers relative to controls. However, these results must be interpreted with caution due to a lack of information on route of administration of cocaine, specific dose of cocaine, and lack of differentiation between subjects who had been alcohol dependent in the past, and those who had not.

In the present study, we compared the NP performance of normal controls (NC) to the NP performance of sober subjects who had been dependent on crack–cocaine only (CrO) or dependent on both crack–cocaine and alcohol (CrA). The substance dependent subjects were tested in both ‘early’ and ‘later’ abstinence. In addition, the early abstinence data from those subjects who later relapsed was compared to the early abstinence data from those that remained abstinent for the entire six months to test the hypothesis that less impaired subjects have a better chance of maintaining long-term sobriety.

2. Methods

2.1. Subjects

Substance dependent subjects were either inpatients in the Substance Abuse Inpatient Unit at the San Francisco Department of Veterans Affairs Medical Center or patients in substance abuse residential treatment centers in the San Francisco Bay area. All substance dependent subjects met DSM-IV criteria for crack–cocaine (only) or both crack–cocaine and alcohol dependence. Although subjects were included who met DSM-IV criteria for abuse of other substances, no subject met DSM-IV criteria for dependence on any substance other than crack or alcohol. In addition, no subject in the CrO group met criteria for abuse or dependence on alcohol. Subjects were monitored via urine screens that tested for the presence of alcohol, cocaine, amphetamines, benzodiazapines, and opiates. Random urine screens were performed on a weekly basis by the residential treatment centers, and every

other day on the inpatient unit. We conducted random urine screens biweekly on subjects who graduated from the inpatient unit with 6 weeks of abstinence (for those who did not enter a residential treatment center). On the day of the NP testing all individuals (including NC) had a urine screen, as well as a 'breathalyzer' for alcohol.

Self-report measures of crack and alcohol use were used to estimate dose and duration of peak use and of average lifetime use (Table 1). Alcohol use was quantified in terms of standard drinks (4 oz. of wine, 12 oz. of beer, or 1 oz. of eighty-proof liquor). We quantified crack use by average monthly cost of crack consumed (because of the difficulty in assessing the quality and quantity of an illicit drug).

Normal controls were recruited by flyers posted in community centers, through newspaper advertisement, and by 'word of mouth'. They were non-drinkers or light social drinkers, had never used cocaine, and had no history of other drug abuse. Normal controls did not return for repeat testing. The UCSF Committee on Human Research approved all procedures, and written consent was obtained from all individuals prior to study.

A trained clinician used the SCID (Structured Clinical Interview for DSM-IV, non-patient version) to assess both subjects and NC. All individuals in the study were screened to exclude those with any neurologic or Axis I disorder unrelated to substance abuse, and those who were HIV-seropositive by PCR (polymerase chain reaction) testing. Individuals were also excluded from the study for any loss of consciousness that required medical attention.

Substance dependent subjects were studied at 5–6 weeks of abstinence and retested at 6 months if they did not relapse (23/57). The 6-month abstinence data for the non-relapsers was supplemented by recruiting and studying an additional 6 CrO and 12 CrA dependent subjects at 6 months of abstinence. These subjects were comparable both demographically and in substance use history to the subjects recruited at 5–6 weeks of abstinence.

2.2. Neuropsychological measures

All individuals were given the computerized, self-administered standard version of the MicroCog (MC) Assessment of Cognitive Functioning (Powell et al., 1993), which yields age and education adjusted scores. The MC includes 18 subtests (described in Table 2) that assess performance in the attention, executive function, spatial processing, immediate and delayed memory, calculation, and reaction time domains. We did not include the MC math subtest (which comprises the calculation domain) in our battery because we have demonstrated that it is not a valid assessment of arithmetic skills (DeVivo et al., 1997). Approximately one-quarter of the way through the study, we expanded the NP battery by adding tests assessing the verbal fluency, psychomotor, and motor domains, as well as supplementing some of the original MC domains with additional tests. The tests added to the NP battery included: the Rey–Osterrieth complex figure (immediate and delayed recall) (Osterrieth, 1944; Denman, 1987), trail-making test A and B (Reitan and Wolfson, 1985; Heaton et al., 1991), the written symbol digit modalities test (Wechsler, 1981; Smith, 1982), the controlled oral word association test (COWAT) (Benton and Hamsher, 1978; Ruff et al., 1996), the grooved pegboard test (Trites, 1977; Heaton et al., 1986), the short category test (booklet format) (Wetzel and Boll, 1987), and the stroop color and word test (Stroop, 1935; Golden, 1978). We also added the Beck depression inventory (short form) at this time (Beck et al., 1961). (The second reference is for the test norms, if different from the original test reference.)

The final NP battery consisted of the following nine domains (and their component tests): (1) attention (MC numbers forward, MC numbers reversed, MC alphabet, MC word list 1) (2) executive function (short categories, stroop interference score, trail making test B, MC

analogies, MC object match A and B), (3) spatial processing (MC Tic Tac 1 and 2, MC clocks), (4) immediate memory (MC story immediate 1 and 2, Rey immediate, MC word list 2), (5) delayed memory (MC story delay 1 and 2, MC address delay, Rey delayed recall), (6) reaction time (MC timers 1 and 2) (7) verbal fluency (COWAT), (8) psychomotor (trails A, symbol digit), and (9) motor (grooved pegboard). The MC assessment took approximately 45–60 min to complete, and the expanded battery added an additional hour of testing. The same test battery (without alternate forms) was used at all assessments.

Z-scores (adjusted for each test's norms) were calculated for all of the tests taken by each participant. These Z-scores were averaged within each of the original six MC domains (these tests were taken by all of individuals in the study) and within each of the nine domains in the expanded and supplemented NP battery (taken by the subjects in the latter three-quarters of the study).

We created a global clinical impairment score (GCIS), using only the original MC assessment (in order to have comparable data on the full sample), and using the expanded and supplemented NP battery (taken by the attenuated sample). Each domain's average Z-score was first converted to a clinical impairment score. The cutoff points for the clinical impairment scores were designed to make the GCIS highly sensitive to impairment. A clinical impairment score of 0, or no impairment, was assigned to domain Z-scores falling above the 15th percentile (one standard deviation below the norm is approximately the 15th percentile), a score of 1, or moderately impaired, was assigned to domain Z-scores falling at or below the 15th and above the 5th percentile (approximately 1–1.5 standard deviations below the norm), and a score of 2, or severely impaired, was assigned to domain Z-scores falling at or below the 5th percentile (more than 1.5 standard deviations below the norm). The domain clinical impairment scores (0, 1 or 2) were then summed across domains to yield the GCIS, with greater GCIS scores indicating more severe impairment.

2.3. Analysis

There were no significant differences in demographics, substance use measures, or depressive symptom levels at 6 months of abstinence between the substance dependent subjects recruited at 5–6 weeks ('early') abstinence and followed to 6 months ('later') abstinence, and the group recruited and studied only at 6 months abstinence. Six-month abstinence data were compared to NC for longitudinal subjects only and for the combined (longitudinal plus supplemental) 6-month abstinent substance dependent subjects. Our general analytic approach for all measures was to compare substance dependent subjects (the combined CrO and CrA groups) to NC, and to compare the CrO and CrA groups to each other. We dealt with the issue of multiple dependent variables by first computing a one-way multivariate analysis of variance (MANOVA with planned comparisons) on the six MC domain Z-scores. We proceeded with analysis of the individual NP domains only if the MANOVA test was significant. This approach was used to assess NP impairment at early and later abstinence, to compare NP performance at early abstinence between relapsers and non-relapsers, and to determine whether NP performance recovered from early to later abstinence. Wilcoxon tests were used to evaluate the GCIS, since it is not an interval scaled variable.

We used the Beck depression score in analysis of covariance (ANCOVA), to determine whether differences between the groups (substance dependent vs. NC) in the NP data were present after controlling for group differences in depression. Finally, Spearman correlations were used to determine if there were any associations of substance use variables with NP domain Z-scores.

3. Results

3.1. Demographic and substance use variables

The demographic and substance use variables for subjects from all study groups are presented in Table 1. The abstinent CrO and CrA samples did not differ in age from each other or from NC ($t=-1.43$, $df=60$, $P=0.16$ and $t=-1.48$, $df=83$, $P=0.24$). The substance dependent group (combined CrO and CrA samples) did have less education than NC ($t=5.28$, $df=83$, $P=0.0001$), but the CrO and CrA samples did not differ from each other ($t=-0.41$, $df=60$, $P=0.68$). The CrO and CrA samples did not differ on any cocaine use measure (average lifetime dose and duration, $P=0.60$ and $P=0.14$; peak dose and duration, $P=0.80$ and $P=0.32$).

3.2. NP impairment at early abstinence

The MANOVA across the MC domain Z-scores after 6 weeks abstinence revealed significant impairment in the substance dependent group versus NC (Wilks' λ , $F_{6,79}=3.88$, $P=0.002$). The ANOVA used to compare the unsupplemented MC domain Z-scores (available for the entire sample) showed poorer performance in all domains except reaction time in the substance dependent group versus NC (Table 3). The largest effects were in the executive function and spatial processing domains (accounting for 15.4 and 12.4% of the variance of the domain Z-score). The substance dependent group also had a higher (more impaired) GCIS score than NC (Wilcoxon $z=-4.48$, $P=0.0001$; Fig. 1), with group membership explaining 16.6% of the variance in the GCIS. The CrO and CrA groups did not differ from each other across MC domains (Wilks' λ , $F_{6,50}=0.50$, $P=0.80$), or on the GCIS (Wilcoxon $z=-0.10$, $P=0.92$). The lack of a significant multivariate test did not allow for comparison of the CrO and CrA groups on individual NP domains; however, group membership in CrO or CrA explained less than 2.3% of the variance in any NP domain.

Analysis of the expanded NP battery (although on attenuated samples) revealed the same pattern of impairment across MC domains (now supplemented by additional tests). The classification as substance dependent accounted for 0.5% (ns), 5.2% (ns) and 3.5% (ns) of the variance in the verbal fluency, psychomotor, and motor domains (added in the expanded battery). There were no differences in these domains between the CrO and CrA groups.

3.3. Association of NP impairment at early abstinence with maintenance of sobriety

Twenty-three out of 57 (40%) substance dependent subjects (who were initially studied at 5–6 weeks of abstinence) maintained sobriety for 6 months. We used MONOVA to compare the early abstinence MC domain Z-scores of relapsers ($N=34$) versus non-relapsers ($N=23$). There was no difference between relapsers and non-relapsers across MC domains (Wilks' λ , $F_{6,49}=1.21$, $P=0.31$), nor was there a difference on the GCIS (Wilcoxon $z=-0.99$, $P=0.32$).

3.4. NP Impairment at later abstinence

As noted above, the portion of the initial sample that remained abstinent for six months was supplemented by recruiting 6 CrO and 12 CrA dependent subjects at 6 months of abstinence. We examined this later abstinence data for possible biases between the subjects who had been studied longitudinally versus subjects who were studied only at 6 months. The sample size for this comparison was small, with seven versus six subjects for the CrO group, and 16 versus 12 subjects for the CrA group. There was no difference at later abstinence between longitudinal and non-longitudinal samples across MC domains (Wilks' λ , $F_{6,29}=1.16$, $P=0.35$), or on the GCIS (Wilcoxon $z=-1.16$, $P=0.25$).

Table 3 shows the comparison of NP performance at 6 months abstinence for substance dependent subjects versus NC, both for the subjects who had been studied longitudinally and

for all 6-month abstinent subjects (longitudinal subjects plus the subjects studied only at 6 months). The results of these two comparisons were essentially the same. There was poorer performance at 6 months abstinence across MC domains for longitudinal subjects versus NC (Wilks' λ , $F_{6,45}=2.69$, $P=0.03$) and for all 6-month abstinent subjects versus NC (Wilks' λ , $F_{6,63}=3.03$, $P=0.01$), as well as more impaired GCIS scores for longitudinal subjects versus NC (Wilcoxon $z=-1.70$, $P=0.09$) and for all 6-month abstinent subjects versus NC (Wilcoxon $z=-2.57$, $P=0.01$). The largest effects were in the executive function and spatial processing domains (for longitudinal subjects, explaining 12.1 and 5.4% of the variance; for all 6-month abstinent subjects explaining 11.1 and 10.4% of the variance). Comparison of 6-month abstinence data between the CrO and CrA for all subjects (longitudinal subjects plus the subjects studied only at 6 months) revealed no difference across the MC domains (Wilks' λ , $F_{6,29}=1.24$, $P=0.32$), or on the GCIS (Wilcoxon $z=-0.63$, $P=0.53$).

3.5. NP Impairment at early versus later abstinence

Finally, we compared the longitudinal NP data of the substance dependent group at early versus later abstinence. There was improvement from early to later abstinence across the MC domains (Wilks' λ , $F_{1,20}=4.29$, $P=0.05$), and on the GCIS ($P=0.02$). The only individual domain which showed improvement was immediate memory ($P=0.02$). There were no differences between CrO and CrA groups in the early versus later abstinence change scores, either across MC domains (Wilks' λ , $F_{1,20}=1.02$, $P=0.33$) or on the GCIS ($P=0.66$).

3.6. Correlation of substance use variables with NP performance at early and later abstinence

3.6.1. Early abstinence—The attention domain score was negatively correlated with both the average crack dose and the peak crack dose ($r=-0.35$, $P=0.01$ and $r=-0.29$, $P=0.03$). Memory function (both immediate and delayed) was negatively correlated with duration of peak crack use ($r=-0.35$, $P=0.01$ and $r=-0.30$, $P=0.03$). The GCIS showed a trend toward a positive correlation with average crack dose in the combined substance dependent group ($r=0.25$, $P=0.06$), and with duration of peak alcohol use in the CrA group ($r=0.30$, $P=0.07$). The spatial domain score was positively correlated with duration of abstinence ($r=-0.30$, $P=0.03$) and the immediate and delayed memory domain scores also showed trends to be positively correlated with duration of abstinence ($0.05 < P$ values < 0.10).

3.6.2. Later abstinence—Duration of peak alcohol use was correlated with the GCIS ($r=0.38$, $P=0.05$), and showed a trend to be negatively correlated with the executive function domain score. The peak cocaine dose was correlated with a more impaired GCIS ($r=0.52$, $P<0.001$), poorer spatial processing and immediate memory ($r=-0.36$, $P=0.02$; $r=-0.39$, $P=0.01$), and poorer delayed memory, reaction time and attention (trends only). Given that we did not correct the correlations between substance use and NP variables for multiple comparisons, the associations reported above must be interpreted with caution.

3.7. Association of education and depression with NP performance at early and later abstinence

Although all but three of the NP tests were education-normed (all were age-normed), we tested for a residual effect of education on NP tests scores (to determine whether the education differences between the groups contributed to the significant group differences in NP performance). There were no significant correlations between education and GCIS or domain scores in the NC (all P values > 0.26) or substance dependent samples (all P values > 0.11). In addition, using education as a covariate did not modify any of the effects presented above.

Table 1 shows that there was a considerable variability of severity of depression within each group, with Beck scores ranging from 0 (normal mood) to 32 (severe depression) within the abstinent substance dependent group, and from 0 to 12 (minimal depression) within NC. We performed an ANCOVA of the NP data with the Beck depression inventory (BDI) score as a covariate to determine the possible effect of depression on NP performance. The BDI was part of the assessment added after the study began, so this analysis was performed on most (but not all) of the sample.

As expected, the substance dependent group was more depressed in both early and later abstinence than NC. In early abstinence, there was a trend toward a negative correlation of BDI score with NP performance for the substance dependent group ($N=43$) in the domains of spatial processing ($P=0.08$) and immediate memory ($P=0.06$), and for the GCIS ($P=0.07$). After removing the effect of depression, group differences in NP performance were still observed in all domains and the GCIS ($P\leq 0.06$), except for attention ($P=0.33$), immediate memory ($P=0.18$) and reaction time ($P=0.46$). At later abstinence, although the mean BDI score had increased slightly from early abstinence, there were no significant correlations of severity of depression with NP performance ($N=36$, all p values >0.29).

4. Discussion

The primary finding in this study was that the substance dependent sample was cognitively impaired in most NP domains compared to NC. These impairments were present at approximately 5–6 weeks abstinence, with the CrO and CrA subgroups showing the same magnitude and pattern of impairment. The cognitive impairments were still present for both CrO and CrA groups after approximately 6 months of abstinence.

We believe that the majority of the cognitive deficits shown by the substance dependent sample are evidence of damage associated with their substance abuse; that is, that these deficits are not premorbid. Premorbid deficits are not consonant with the improvement in NP performance from early to later abstinence, or with the associations between NP performance measures and drug and alcohol use indices. However, it is reasonable to acknowledge that some of the NP differences between the substance dependent sample and NC could reflect premorbid differences. The literature describes possible premorbid prefrontal lobe abnormalities in individuals at risk for alcoholism (and other substance abuse); a subset of these individuals show insensitivity to reinforcement, and exhibit externalizing disorders such as attention problems, impulsivity, and antisocial personality disorder ((Hesselbrock et al., 1991; Pihl and Peterson, 1991).

We found some improvement in NP performance from 6 weeks to 6 months abstinence in the substance dependent subjects that maintained abstinence. However, we believe that much of that improvement was due to practice effects since immediate memory, which is highly sensitive to previous experience with the test materials, was the only domain to show significant improvement from 6 weeks to 6 months abstinence. In addition, given that we did not use alternate form tests at the two testing sessions, and that we did not have repeat testing of the control subjects (to control for the effects of prior exposure to the tests and test materials), we cannot rule out the possibility that all of the improvement shown by the substance dependent group was the result of prior exposure to the tests and test materials.

The abstinent substance dependent subjects were more depressed than NC at both early and later abstinence, replicating earlier findings (O'Malley et al., 1992; Volkow et al., 1992; Berry et al., 1993; Beatty et al., 1995; Hoff et al., 1996). The NP deficits in these subjects were present after statistically controlling for the severity of depressive symptoms. Other investigators have also found that depression is, at most, only mildly associated with NP

performance in substance abusers (O'Malley et al., 1992; Berry et al., 1993; Beatty et al., 1995).

Comparing these results to studies of cocaine dependence in the literature is difficult because of differences across studies in sample size, intensity and duration of drug use, length of abstinence, the NP battery employed, and the presence or absence of a control group. Obtaining accurate information on the specific dose of cocaine is a particular conundrum, since the purity of the cocaine sold on the street varies dramatically. Given these caveats, our finding of cognitive deficits among abstinent cocaine abusers is a replication of most previous studies of this nature (O'Malley and Gawin, 1990; O'Malley et al., 1992; Berry et al., 1993; Strickland et al., 1993; Beatty et al., 1995; Hoff et al., 1996; Bolla et al., 1999; van Gorp et al., 1999; Bolla et al., 2000, 3143). The difference among studies lies not in whether cocaine abusers evidence cognitive impairments, but in the specific type of deficits observed. Although we found some impairment of attention in our substance dependent group (Robinson et al., 1999), Horner's (1999) review of 17 studies of cocaine abusers (some samples also abused alcohol) found attention largely unimpaired in individuals abstinent several days or weeks to several months. Some investigators report cocaine abuse affects visual memory (O'Malley and Gawin, 1990; Hoff et al., 1996); others report verbal (but not visual) memory deficits among abusers (Beatty et al., 1995). Similar to our findings (deficits in both verbal and visual memory at early abstinence), Berry et al. (1993) reported impairment at early abstinence in verbal memory, and a trend towards impairment in visual memory.

Other studies find that performance in the areas of verbal fluency (O'Malley et al., 1992; Hoff et al., 1996) and concept formation (Hoff et al., 1996) are actually improved with cocaine use. We examined this issue by performing post-hoc analyses of performance on the COWAT and categories tests. Performance for the substance abusing group on the COWAT was comparable to performance in NC. On the categories test, however, the substance abusing group evidenced large deficits, close in magnitude to the impairment present in the executive function and spatial processing domains.

Although we found no difference between relapsers and non-relapsers on any NP measures, it may be beneficial for other studies to look at this association; the determination of the predictors of relapse is crucial in the optimization of substance abuse treatment. Unfortunately, most treatment centers' evaluation of new patients does not include a NP screening to discern the nature and extent of cognitive function (Strickland et al., 1993). This is particularly problematic because residential treatment centers often favor rigorous rehabilitation programs in which intact cognitive abilities (such as abstract problem solving skills, verbal skills, and memory) are required for the patient to benefit from the treatment regimen.

Given the results of this study, the most potent predictors of brain damage associated with substance dependence are measures of dose (particularly quantity and duration of peak dose). The relationship of NP impairment and dose was also proposed by Bolla et al. (1998), in their review of the neuropsychiatry of chronic cocaine abuse. They hypothesized a dose-related model of brain damage that was extrapolated from level of exposure studies in clinical neurotoxicology. This hypothesis was supported in her studies of the cognitive deficits of 3-day and 4-week abstinent chronic heavy cocaine users (Bolla et al., 1999, 2000), where deficits were associated with the heaviest use.

Clinical studies of the NP consequences of addiction (particularly to 'street' drugs) are inherently 'dirty'. Sample sizes are usually small (particularly for longitudinal studies, where the majority of subjects relapse), and therefore differences between groups may not

be detectable due to a lack of power in statistical analyses. Additionally, the separation of the effects of disease from premorbid cohort differences is fraught with major methodological difficulties. For example, what are the characteristics of an appropriate control sample? Once determined, is it possible or practical to find that sample? Our experience has been that crack–cocaine abusers in residential treatment in the San Francisco Bay Area are predominantly African–American men, and that finding age-comparable African–American men without any substance abuse history is very difficult. Moreover, it is not clear whether recruiting age and ethnicity comparable control samples completely addresses the issue of premorbid cohort differences. There is evidence suggesting that genetic differences in NP function that are associated with an increased vulnerability to addiction. In addition, it is likely that substance abuse not only damages functions already acquired, but also affects the initial acquisition and solidification of skills in adolescence and early adulthood.

In summary, the current study suggests that substance dependency is associated with various forms of long-term cognitive impairment. While this study had certain methodological limitations that are common to many neuropsychological studies in the area of substance abuse, the impossibility of pristine experimental designs in studying these populations in the real world should not deter further investigation.

Acknowledgments

This work was supported by NIDA grant DA09453 (George Fein).

References

- Barnes DM. Drugs: running the numbers. *Science* 1988;240:1729–1731. [PubMed: 3381095]
- Beatty WW, Katzung VM, Moreland VJ, Nixon SJ. Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend* 1995;37:247–253. [PubMed: 7796719]
- Beck AT, Ward CH, Mendelson M, Erbaugh JK. An inventory for measuring depression. *Arch. Gen. Psychiatry* 1961;4:561–571. [PubMed: 13688369]
- Benton, AL.; Hamsher, KD. *Multilingual Aphasia Examination: Manual of Instructions*. University of Iowa; Iowa City: 1978.
- Berry J, van Gorp WG, Herzberg DS, Hinkin C, Boone K, Steinman L, Wilkins JN. Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after 2 weeks of abstinence. *Drug Alcohol Depend* 1993;32:231–237. [PubMed: 8394237]
- Bolla KI, Cadet JL, London ED. The neuropsychiatry of chronic cocaine abuse. *J. Neuropsychiatry Clin. Neurosci* 1998;10(3):280–289. [PubMed: 9706535]
- Bolla KI, Rothman R, Cadet JL. Dose-related neurobehavioral effects of chronic cocaine abuse. *J. Neuropsychiatry Clin. Neurosci* 1999;11(3):361–369. [PubMed: 10440013]
- Bolla KI, Funderburk FR, Cadet JL. Differential effects of cocaine and cocaine+alcohol on neurocognitive performance. *Neurology* 2000;54:2285–2292. [PubMed: 10881254]
- Brown TG, Seraganian P, Tremblay J. Alcoholics also dependent on cocaine in treatment: do they differ from ‘pure’ alcoholics? *Addict. Behav* 1994;19(1):105–112. [PubMed: 8197888]
- Cregler LL, Mark H. Special report—medical complications of cocaine abuse. *N. Engl. J. Med* 1986;315(23):1495–1500. [PubMed: 3537786]
- Denman, SB. Denman, SB., editor. *Charleston; Denman Neuropsychology Memory Scale*: 1987.
- DeVivo K, Rothlind J, Price L, Fein G. Computerized assessment of arithmetic computation skills with MicroCog. *J. Int. Neuropsychol. Soc* 1997;3:199–200. [PubMed: 9126861]
- Easton C, Bauer LO. Neuropsychological differences between alcohol-dependent and cocaine-dependent patients with or without problematic drinking. *Psychiatry Res* 1997;71:97–103. [PubMed: 9255854]

- Golden, CJ. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Western Psychological Services; Los Angeles: 1978.
- Grant BF, Harford TC. Concurrent and simultaneous use of alcohol with cocaine: results of national survey. *Drug Alcohol Depend* 1990;25:97–104. [PubMed: 2323315]
- Heaton, R.; Grant, I.; Matthews, C. Neuropsychological Assessment of Neuropsychiatric Disorders. Oxford, NY: 1986. Differences in neuropsychological test performance associated with age, education and sex.
- Heaton, RK.; Grant, I.; Matthews, CG. Comprehensive Norms for an Expanded Halstead–Reitan Battery Demographic Corrections, Research Findings, and Clinical Applications. Psychological Assessment Resources Inc.; Odessa, FL: 1991.
- Hesselbrock V, Bauer LO, Hesselbrock MN, Gillen R. Neuropsychological factors in individuals at high risk for alcoholism. *Recent Dev. Alcohol* 1991;9:21–40. [PubMed: 1758985]
- Hoff AL, Riordan H, Morris L, Cestaro V, Wieneke M, Alpert R, Wang GJ, Volkow N. Effects of crack cocaine on neurocognitive function. *Psychiatry Res* 1996;60:167–176. [PubMed: 8723307]
- Horner MD. Attentional functioning in abstinent cocaine abusers. *Drug Alcohol Depend* 1999;54:19–33. [PubMed: 10101614]
- Inciardi JA. The crack epidemic revisited. *J. Psychoactive Drugs* 1992;24(4):305–306. [PubMed: 1491280]
- Jacobs IG, Roszler MH, Kelly JK, Klein MA, Kling GA. Cocaine abuse: neurovascular complications. *Radiology* 1989;170:223–227. [PubMed: 2909100]
- Johanson CE, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol. Rev* 1989;41(1):3–52. [PubMed: 2682679]
- Kleber HD. Our current approach to drug abuse—progress, problems, proposals. *N. Engl. J. Med* 1994;330(5):361–365. [PubMed: 8277959]
- O'Malley SS, Gawin FH. Abstinence symptomatology and neuropsychological impairment in chronic cocaine abusers. *NIDA Res. Monogr* 1990;101:179–190. [PubMed: 2092215]
- O'Malley S, Adamse M, Heaton RK, Gawin FH. Neuropsychological impairment in chronic cocaine abusers. *Am. J. Drug Alcohol Abuse* 1992;18(2):131–144. [PubMed: 1562011]
- Osterrieth PA. Le test de copie d'une figure complex. *Arch. Psychol* 1944;30:206–356.
- Pihl RO, Peterson JB. A biobehavioural model for inherited predisposition to alcoholism. *Alcohol Suppl* 1991;1:151–156.
- Powell, DH.; Kaplan, EF.; Whitla, D.; Weintraub, S.; Catlin, R.; Funkenstein, HH. The Psychological Corporation; San Antonio, TX: 1993. MicroCog Assessment of Cognitive Functioning.
- Reitan, RM.; Wolfson, D. The Halstead–Reitan Neuropsychological Test Battery. Neuropsychology Press; Tucson: 1985.
- Robinson J, Heaton R, O'Malley S. Neuropsychological functioning in cocaine abusers with and without alcohol dependence. *J. Int. Neuropsychol. Soc* 1999;5(1):9–10.
- Ruff RM, Light RH, Parker SB, Levin HS. Benton controlled oral word association test: reliability and updated norms. *Arch. Clin. Neuropsychol* 1996;11(4):329–338. [PubMed: 14588937]
- Smith, A. Symbol Digit Modalities Test: Manual. Western Psychological Services; Los Angeles: 1982.
- Strickland TL, Mena I, Villanueva-Meyer J, Miller BL, Cummings J, Mehninger CM, Satz P, Myers H. Cerebral perfusion and neuropsychological consequences of chronic cocaine use. *J. Neuropsychiatry Clin. Neurosci* 1993;5:419–427. [PubMed: 8286941]
- Stroop JR. Studies of interference in serial verbal reaction. *J. Exp. Psychol* 1935;18:643–662.
- Trites, RL. Neuropsychological Test Manual. Royal Ottawa Hospital; Ottawa, Ont: 1977.
- van Gorp WG, Wilkins JN, Hinkin CH, Moore LH, Hull J, Horner MD, Plotkin D. Declarative and procedural memory functioning in abstinent cocaine abusers. *Arch. Gen. Psychiatry* 1999;56(1):85–89. [PubMed: 9892260]
- Volkow ND, Hitzeman R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, Handlesman L. Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 1992;11:184–190. [PubMed: 1636149]
- Wechsler, D. Psychological Corporation; San Antonio, TX: 1981. WAIS-R Psychological Corporation.

Wetzel, L.; Boll, T. Short Category Test, Booklet Format. Western Psychological Services; Los Angeles: 1987.

NIH-PA Author Manuscript

Table 1

Demographic, substance use, and Beck depression inventory variables

	Normal controls (n=29)	Subjects (n=57) at 6 weeks abstinence	Subjects (n=41) at 6 months abstinence (retest data on 23 non-relapsers combined with single timepoint data on 18 subjects tested at 6 months abstinence only) ^d
		Crack dependent only (n=20)	Crack and alcohol dependent (n=37)
Men/women	18 men, 11 women	19 men, 1 woman	9 men, 4 women
Age	37±8	40±7	39±8
Years of education	15±2	13±2	13±2
Ethnicity ^b	16 AA, 11 C, 1 H, 1 NA	18 AA, 1 C, 1 A	12 AA, 1 C
Weeks abstinent at early abstinence	N/A	5±2	N/A
Weeks abstinent at later abstinence	N/A	(relapsers; n=13) 28±5	28±5
Beck depression inventory score	4±3 ^c	11±8 ^c	13±8 ^c
Average lifetime alcohol use (drinks per month)	9±9	22±29	270±192
Duration of average lifetime alcohol use (months)	N/A	N/A	257±87
Peak alcohol use (drinks per month)	N/A	N/A	593±414 ^d
Duration of peak alcohol use (months)	N/A	N/A	85±64 ^d
Average lifetime crack use (dollars per month)	N/A	957±1056	740±707
Duration of average lifetime crack use (months)	N/A	169±72	167±67
Peak crack use (dollars per month)	N/A	3175±3536	3582±5521
Duration of peak crack use (months)	N/A	26±27	36±35
			20 men, 8 women
			40±8
			13±2
			17 AA, 6 C, 5 H
			N/A
			29±3
			278±208
			242±112
			613±372
			59±61
			882±812
			151±75
			2918±5004
			41±39

^aThere were no significant differences on any variable between subjects recruited in early abstinence and those recruited at later (6 months) abstinence.

^bAA=African American, C=Caucasian, H=Hispanic, NA=Native American, A=Asian.

^cBeck depression inventory was part of the expanded assessment; therefore scores are on attenuated samples (controls n=21; subjects studied in early abstinence n=43; subjects studied in later abstinence n=36).

^dn=27; 27% of subjects dependent on both crack and alcohol could not accurately recall this information.

Table 2**MicroCog Assessment of Cognitive Functioning**

Domain	Subtest	Description
Attention	Numbers forward	Forward visual digit span up to nine digits. The examinee reproduces the span using the numeric keypad.
	Numbers reversed	Backward visual digit span up to nine digits. The examinee reproduces the span using the numeric keypad.
	Alphabet	A continuous performance test in which letters of the alphabet (A–O) are presented, embedded in a random series of letters. The examinee responds to the letters in sequence.
	Word list 1	A list of 16 words, containing five groups of category-related items, is presented four times. Each time, the examinee is instructed to respond to words that are members of one of the four given categories. A response is not requested for the fifth category.
Executive function	Analogies	Eleven pairs of verbal analogies are presented and answered by multiple choice.
	Object match	Twelve sets of four stimuli are presented to test for abstraction and conceptual flexibility.
Spatial Processing	Tic tac 1	A 3×3 block matrix is presented in which three to five blocks contain a colored square. Immediately after presentation, the examinee reproduces the pattern using the number keypad.
	Tic tac 2	Same as Tic Tac 1, with different items.
	Clocks	Seven analog clock faces indicating the time with and without associated hour markings are presented with five digital choices from which the correct time is chosen.
Memory—immediate	Story 1: immediate recall	Immediately following the screen presentation of a brief story, six multiple-choice questions assess recognition of story details.
	Story 2: immediate recall	Similar to story 1, with different content.
	Word list 2	A list of 36 words, including the 16 from word list 1, is presented and the examinee must indicate which words were previously presented, including the four that were learned incidentally.
Memory—delayed	Story 1: delayed recall	After a filled delay (other MicroCog Tasks) of ~20–30 min, answers 11 multiple-choice questions about story 1 assess delayed recognition of content.
	Story 2: delayed recall	Same as above, but 12 multiple-choice questions concerning the second story.
	Address	Near the beginning of the test session, a name and address are presented on the screen to be memorized for later recognition. About three-quarters of the way through the test session, four multiple-choice questions are presented to test recognition of the previously presented name and address.
Reaction time	Timers 1	As the first task in the testing session, reaction time to five auditory signals, five visual signals, and five visual signals preceded by an auditory signal is recorded by pressing the enter key.
	Timers 2	Administered at the end of MicroCog test session, identical to timers 1

Our battery did not include the Math subtest (see text).

Neuropsychological performance at early and later abstinence

MicroCog domains	6 Weeks abstinence				6 Months abstinence					
	Normal controls (n=29)	Crack-only dependent sample (n=20)	Crack and alcohol dependent sample (n=37)	Combined substance dependent group vs. controls (n=57)	Crack-only dependent		Crack and alcohol dependent		Combined substance dependent group	
					M±S.D. (%ile)	M±S.D. (%ile)	M±S.D. (%ile)	M±S.D. (%ile)		
M±S.D. (%ile)	M±S.D. (%ile)	M±S.D. (%ile)	Effect size (% variance explained)	M±S.D. (%ile)	M±S.D. (%ile)	M±S.D. (%ile)	M±S.D. (%ile)	Effect size (% variance explained)	Effect size (% variance explained)	
Attention	-0.07±0.62 (47)	-0.41±0.82 (34)	-0.53±0.80 (30)	6.4*	0.05±0.67 (52)	-0.76±0.53 (22)	-0.46±0.86 (32)	-0.62±0.88 (27)	2.6	6.3*
Executive function	0.06±0.49 (52)	-0.53±0.71 (30)	-0.50±0.70 (31)	15.4***	-0.11 +0.53 (46)	-0.40±0.77 (34)	-0.60±0.98 (27)	-0.46±0.83 (32)	12.1**	11.1**
Spatial processing	-0.08±0.43 (47)	-0.61±0.69 (27)	-0.52±0.66 (30)	12.4***	-0.10±0.32 (46)	-0.61±0.63 (27)	-0.45±0.76 (33)	-0.58±0.46 (28)	5.4(0.10)	10.4**
Immediate memory	-0.13±0.72 (45)	-0.58±0.79 (28)	-0.47±0.78 (32)	5.5*	0.05±0.49 (48)	.06±0.33 (52)	-0.21±0.85 (42)	-0.58±0.79 (28)	0.0	0.6
Delayed memory	-0.15±0.80 (44)	-0.91±0.93 (18)	-0.78±1.16 (22)	9.7***	-0.41±1.00 (34)	-0.61±0.77 (27)	-0.54±1.13 (29)	-0.61±0.84 (27)	3.6	4.9(0.07)
Reaction time	0.04±0.78 (52)	-0.15±0.67 (44)	-0.39±0.86 (35)	2.6	0.27±0.72 (61)	.06±0.34 (52)	-0.23±0.80 (41)	-0.50±0.97 (31)	0.1	0.8
WCST	0.38±0.78	2.10±1.83	2.59±2.98	16.6***	0.43±1.13	1.50±1.22	1.75±2.54	2.00±2.41	8.5*	10.4**
Additional domains ^b	(n=21)	(n=14)	(n=29)		(n=7)	(n=3)	(n=15)	(n=11)		
Verbal fluency	0.44± 1.02 (67)	0.03±1.64 (51)	0.36±1.29 (64)	0.5	0.66±1.02 (75)	-0.58±0.64 (28)	0.50±1.68 (69)	0.48±1.00 (68)	0.2	0.0
Psychomotor	-0.34±0.76 (37)	-0.88±0.60 (19)	-0.60±0.71 (27)	5.2	-0.39±0.57 (35)	-0.99±0.65 (16)	-0.81±1.00 (21)	-0.98±0.69 (16)	4.1	8.4*
Motor	0.53±0.74 (70)	-0.35±0.93 (36)	0.01±2.18 (50)	3.5	-0.14±0.64 (44)	-0.62±1.62 (27)	0.81±2.42 (79)	-0.53±1.21 (30)	0.0	1.5

b Attenuated sample.

*
F-test for all domain scores and Wilcoxon test for GCIS: $P \leq 0.05$.

** F -test for all domain scores and Wilcoxon test for GCIS: $P \leq 0.01$.

*** F -test for all domain scores and Wilcoxon test for GCIS: $P \leq 0.001$.