Declarative and Procedural Memory Functioning in Abstinent Cocaine Abusers

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Background: We determined the nature and recovery of procedural and declarative memory functioning in a cocaine-abusing cohort in the 45-day period following use.

Methods: Thirty-seven cocaine abusers and 27 control subjects were administered the following memory and mood measures: California Verbal Learning Test, recall of the Rey-Osterrieth Complex Figure Test, Pursuit Rotor Task, and Profile of Mood States at 4 visits (within 72 hours of admission and at 10, 21, and 45 days following abstinence).

Results: Analysis of performance on the Rey-Osterrieth Complex Figure Test revealed that both groups improved in their recall over repeated administrations, though the control group recalled significantly more of the information than cocaine subjects during the 45-day interval. Results for the California Verbal Learning Test indicated improved learning for both subject groups over time, but no group × time interaction. On the Pursuit Rotor Task, cocaine abusers improved their performance at a faster rate than controls at visit 1. At day 45 (visit 4), cocaine abusers again showed improvement on the Pursuit Rotor Task, whereas controls demonstrated a relative plateau in rate of learning.

Conclusions: This study documented a lasting detrimental effect on a sensitive nonverbal declarative memory task in cocaine-dependent subjects following abstinence of 45 days. In contrast, abstinence from cocaine during this 45-day period was associated with sustained improvement on a motor learning test in the cocaine abusers relative to controls.

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Despite the significant public health challenges posed by cocaine abuse, there have been surprisingly few adequately controlled, longitudinal studies investigating the acute, intermediate, and longer-term effects of long-term cocaine use on cognitive functioning. Cognitive sequelae associated with cocaine abuse have been reported on tasks of attention, declarative memory, spatial functions, and psychomotor speed. The evidence for most of these deficits has come from studies that examined subjects when they were in the acute phase of withdrawal and have found generally better performance with increased abstinence.1-8 In many of these studies, however, abstinence was not objectively verified.

Neuroimaging and neurochemical studies provide some insights into the neuroanatomic changes responsible for these cognitive deficits. Strickland et al6 found regions of significant cerebral hyperperfusion in the frontal, periventricular, and/or temporoparietal areas using single-photon emission computed tomography. This correlated with cognitive deficits in attention, concentration, new learning, visual and verbal memory, word production, and visuomotor integration that were evident in the same sample. Altered dopamine levels have been demonstrated in neurochemical studies using animals exposed to “binge” pattern cocaine use.10-14 Consistent with these data, at least one positron emission tomography study15 has reported evidence implicating disruption of γ-aminobutyric acid–aminergic pathways in subjects undergoing cocaine withdrawal.

Because alteration of dopamine has been shown to affect procedural memory16 but not declarative memory processes, 2 types of memory may be affected in cocaine users. Procedural learning (eg, the learning of a motor act such as learning to shift gears in a manual-transmission automobile) has been shown to be affected in disorders in which subcortical structures are differentially affected or in populations in whom dopamine abnormalities exist.16 De-
SUBJECTS AND METHODS

SUBJECTS

Sixty-four subjects participated in this study. Thirty-seven were long-term cocaine abusers who were consecutively admitted to a 21-day inpatient substance abuse treatment program at the West Los Angeles VA Medical Center, Los Angeles, Calif. Twenty-seven community-dwelling, non–substance abusing subjects served as controls. All control subjects were matched with the clinical subjects on sex, the majority of subjects in each group were African American (92% of the cocaine abusers and 96% of the normal controls), and all were male and native English speakers. This study was approved by the Human Studies Subcommittee of the Research and Development Committee of the West Los Angeles VA Medical Center, and all subjects signed an informed consent statement agreeing to participate.

Subjects in the cocaine-dependent group met the following inclusion criteria: (1) DSM-IV criteria for substance dependence as assessed by the Structured Clinical Interview for DSM-IV (SCID); (2) reported cocaine use within 72 hours prior to admission, verified by urine toxicology assay obtained at admission; and (3) reported cocaine use to be at least 4 g in the month prior to admission as well as duration of cocaine use for a period of at least 6 months preceding enrollment into the study. So as to maintain the generalizability of our findings in light of the relatively high comorbidity of alcohol abuse in cocaine abusers, we allowed subjects to enroll in the study if they met DSM-IV criteria for past alcohol abuse (as assessed by the SCID) more than 6 months prior to enrollment, but we did not enroll any subject with a history of alcohol dependence or who had reported alcohol abuse within 6 months of study enrollment.

Exclusion criteria for the cocaine-dependent and normal control subjects included (1) prescription or over-the-counter medication use that might affect central nervous system functioning other than the substances of abuse described above; (2) report of using phenylcyclidine (PCP) more than 10 times during the subject’s lifetime or any time within 1 year prior to the study or evidence of a positive urine toxicology screen for PCP at enrollment; (3) meeting DSM-IV criteria for current or lifetime alcohol dependence; (4) meeting DSM-IV criteria for substance abuse or dependence other than cocaine dependence or alcohol abuse within the past year for the subjects in the cocaine-dependent group; (5) history of head injury with loss of consciousness exceeding 1 hour; (6) meeting DSM-IV criteria for schizophrenia or bipolar disorder; (7) having a history of seizure disorder; (8) liver function abnormalities (liver function test values outside the range considered clinically normal by the reference laboratory) providing evidence of liver damage; (9) prior diagnosis of learning disability; (10) seropositivity for the human immunodeficiency virus (HIV), as determined by enzyme-linked immunosorbent assay with Western blot confirmation; or (11) evidence of prior syphilis exposure (positive rapid plasma reagin test result). Table 1 presents information on subject demographics including age, education, race, number of days of cocaine use in the last 30 (for cocaine abusers), and number of years of lifetime use of cocaine (for cocaine abusers).

DRUG SCREEN

All subjects were administered a urine screen to confirm the presence or absence of recent cocaine use and to examine for other substances of abuse. Validation of abstinence from alcohol for duration of the study for all subjects was accomplished by breath sample examination. Specifically, in the urine screens we tested for the presence of benzoylecgonine (the major metabolite of cocaine), Δ9-tetrahydrocannabinol (THC), morphine, barbiturates, amphetamines, and PCP. Blood samples and 24-hour urine specimens were also collected prior to each assessment for all subjects. Subjects in the cocaine-dependent group were also given twice-weekly random urine screens during the first 21 days of the study (during their inpatient stay), as well as on a twice-weekly basis during their outpatient follow-up period (up to day 45) to verify abstinence. Normal controls received urine screen assessments each week during the 45-day course of study to verify abstinence. At each cognitive assessment, all subjects were administered a breath sample examination as well as an alcohol use questionnaire to rule out recent alcohol use. Subjects testing positive for these substances were excluded from the study. Subjects also underwent an HIV antibody test at enrollment to confirm their HIV-seronegative status.

NEUROPSYCHOLOGICAL TESTING

Subjects were seen for 4 testing visits: (1) within 72 hours of admission (visit 1) following acute cocaine use for the subjects in the cocaine-dependent group (corresponding to enrollment for the controls); (2) 10 days after the first testing session (visit 2); (3) 21 days after the first testing session (visit 3); and (4) 45 days after the first testing ses-
sion (visit 4). Data for all subjects were available for the first 3 visits. At visit 4 (45 days of abstinence), 56% of the cocaine-dependent subjects and all of the controls were available for follow-up. The remainder of the cocaine abusers had either relapsed or dropped out of the study.

The following memory and mood measures were administered to all subjects: the California Verbal Learning Test (CVLT), a list of 16 shopping-list items presented over 5 trials; Pursuit Rotor Task, recall of the Rey-Osterrieth Complex Figure Test, consisting of the delayed recall of a complex figure; and the Profile of Mood States (POMS) to assess subjects’ mood. The Pursuit Rotor Task and Rey-Osterrieth Complex Figure Test were not administered at visit 2 in an attempt to limit testing burden on subjects during their inpatient treatment. All testing was performed by a trained research assistant or neuropsychology postdoctoral fellow under the supervision of a board-certified neuropsychologist (W.v.G. and C.H.). The examiner was blind to subject status.

The CVLT and recall of the Rey-Osterrieth Complex Figure Test are standard measures of declarative memory and were administered according to standard administration procedures described elsewhere. The Pursuit Rotor Task was used as a well-known measure of procedural memory. For the Pursuit Rotor Task, subjects were required to hold a stylus in their preferred hand directly over a disk 2 cm in diameter, positioned on a turntable (30.5 cm in diameter). The rate of rotation for the turntable was adjustable with an initial block of 4 trials administered at 15, 30, 45, and 60 revolutions per minute. The speed at which the subject remained on target to the closest 5 seconds served as the rate at which the remaining trials were performed to minimize any absolute differences in motor speed that might exist across subjects. After a baseline was established for each subject, 3 blocks of eight 20-second trials were administered, with a 60-second rest period after the first 4 trials. Thirty minutes of rest were given between blocks 1 and 2 and between blocks 2 and 3 to minimize fatigue effects. The dependent variable was time on target divided by the total time per trial. Data for the 24 total trials were averaged across learning trials 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, and 21 to 24, yielding a total of 6 blocks. The final variables provide measures of time on target relative to the time it took the subjects to complete each trial. By comparing subjects’ performance over the blocks of trials, a learning slope of the motor act can be examined.

Urine sample collection was monitored by a research assistant to ensure that a legitimate sample was provided. Urine samples were stored at 4°C until transported to the research toxicology laboratory and then stored at −20°C until later assayed. The assays were performed by fluorescence polarization immunoassay. Detection was performed with fluorescence detectors, which offer a high degree of sensitivity comparable to standard radioimmunoassay procedures. Urine toxicology measures consisted of assays for 6 separate drugs of abuse: cocaine (in the form of its major metabolite, benzoylegonine), marijuana (in the form of Δ9-tetrahydrocannabinol), opiates (in the form of morphine), barbiturates, amphetamines, and PCP.

Subjects were paid $10 for weekly visits for urine screens and $50 for their day-long participation in the neuropsychological testing. Cocaine abusers were offered payment in the form of coupons that could be redeemed at the Veterans’ Canteen Service Store during the visits at which they were inpatients.

**DATA ANALYSES**

Data analyses sought to model differences in test performance across the 4 visits for each of the 3 memory measures (CVLT Sum 1-5, recall of the Rey-Osterrieth Complex Figure, and the Pursuit Rotor Task). Each model attempted to predict performance based on time (ie, visits 1-4, except for the Pursuit Rotor Task and recall of the Rey-Osterrieth Complex Figure, which were not collected at visit 2), group (cocaine abusers vs controls) and the interaction of time × group. In the Pursuit Rotor analyses, trial (ie, blocks 1-6) also was included as a predictor. Prior to analysis, each dependent variable was tested for possible violations of the normality assumption; based on these tests, no transformations were necessary.

To assess the effects of an acute withdrawal-associated depression on memory test performance, the POMS depression score was used as a covariate in the models, although to keep the models relatively simple the interactions between the POMS and trial or group were not evaluated. Group was specified as a fixed effect, while time, trial, time × group interaction, and POMS depression score were specified as random effects. All model-fitting was performed using linear mixed effect regression, a procedure for evaluating linear mixed effect regression models following the approach of Davidian and Giltinan. Mixed effects models allow specified parameters of the model to vary randomly across subjects in the estimate of group effects for both fixed and time-varying covariates. This approach also takes advantage of all available data in fitting models and estimating parameters; data from subjects who dropped out therefore do not need to be excluded from the analysis. Data are presented as mean ± SD unless otherwise indicated. Statistical significance was defined as *P* < .05.

**DELAYED RECALL OF THE REY-OSTERRIETH COMPLEX FIGURE**

For delayed recall of the Rey-Osterrieth Complex Figure, the group × visit interaction was not significant (likelihood ratio = 0.65, *df* = 2, *P* < .72), nor was the effect of the POMS depression score (likelihood ratio = 2.35, *df* = 2, *P* = .31). There was a significant group (likelihood ratio = 6.28, *df* = 1, *P* < .02) and visit effect (likelihood ratio = 45.52, *df* = 2, *P* < .001), indicating that both groups improved in their recall during repeated administrations, but the control group recalled more of the information than subjects in the cocaine group.
CVLT ACROSS VISITS 1 THROUGH 4

A similar data analytic approach was used for the sum words recalled on the CVLT across the 5 learning trials. A log transformation was carried out on the time variable (ie, log10[time]) to make the profiles linear. This approach was chosen rather than including quadratic terms in the model (ie, time2), to fit simpler models for easier interpretation.

The visit × group interaction was not significant (likelihood ratio=2.32, df=2, P<.32). Effects also were not significant for group (likelihood ratio=2.06, df=1, P<.16) or POMS depression score (likelihood ratio=3.16, df=2, P<.08). The visit (ie, time) effect was significant (likelihood ratio=132.26, df=2, P<.001), indicating improved learning for both subject groups over time.

Pursuit Rotor Task

Exploratory plots of subjects’ performance across trials (Figure) for controls and cocaine abusers suggested that the 2 subject groups exhibited different response profiles, particularly by day 21. The plots also suggested that the effect of time was linear, while the effect of trial was linear for days 21 and 45 but quadratic at visit 1.

Based on these plots, the Pursuit Rotor Task data were log transformed across trial at visit 1, which linearized the profiles for that administration. We then fit separate linear mixed effect models for visits 1, 3, and 4. Each model attempted to predict Pursuit Rotor Task performance based on trial and group, as well as the interaction of trial × group. The Figure shows the subjects’ performance for the Pursuit Rotor Task for the 6 blocks of trials for both groups.

At visit 1, there was a significant trial × group interaction (likelihood ratio=368.84, df=2, P<.001), indicating that the cocaine abusers increased their performance at a significantly faster rate than the controls. There was no main effect for POMS depression score (likelihood ratio=2.55, df=2, P<.28).

By day 21, the trial × group interaction was not significant (likelihood ratio=1.03, df=2, P>.60), nor was there a significant effect for the POMS depression score (likelihood ratio=0.75, df=2, P>.69). There was an overall group effect (likelihood ratio=9.74, df=1, P<.002), indicating that performance level of the cocaine abusers was significantly better than that of the controls. There was also a significant trial effect (likelihood ratio=30.24, df=2, P<.001), indicating that both groups improved in a similar fashion during the course of the testing.

At day 45, there was again a significant trial × group interaction (likelihood ratio=26.39, df=2, P<.001), indicating that the rate of improvement for the 2 subject groups differed significantly. There was no overall POMS depression score effect interaction with Pursuit Rotor Task score (likelihood ratio=1.18, df=2, P>.56). As can be seen in the Figure, there is a continuing increase in motor learning in the cocaine abusers and a plateau or slight decrease in motor learning in the controls.

COMMENT

This study documents the effects of cocaine dependence on 2 aspects of memory, each mediated by distinct neuroanatomic structures. On a sensitive declarative memory task involving recall of complex nonverbal material, the cocaine-abusing subjects evidenced poorer recall relative to the normal controls, a finding consistent with prior studies. For our measure of procedural learning, cocaine-dependent subjects evidenced a more rapid and lasting rate of learning than the controls during the 45 days of cocaine abstinence, and this effect became even more apparent as length of abstinence in-
increased. This finding was evident across subjects and inspection of data for each individual indicated that this result was not simply the product of one or more “outliers” producing the findings but rather was a consistent and reproducible effect across subjects in the cocaine-dependent group.

The results involving enhanced procedural memory in the cocaine abusers were surprising. One possible explanation includes increasing levels of central nervous system dopamine acting at supersensitive dopamine D1 and/or dopamine D2 receptors following abstinence from long-term cocaine use. The increased sensitivity of the dopamine receptors would have occurred as an adaptation to cocaine-induced depletion of dopamine\textsuperscript{10-12} and the progressive increase in dopamine levels would have resulted from a normalization of dopamine levels occurring during abstinence from cocaine.\textsuperscript{14} It has been demonstrated that alterations in dopamine affect neuropsychological tasks of motor speed.\textsuperscript{15} Hyperfunction of the dopamine system might be expected to produce better performance on tasks of psychomotor function until the sensitivity of the dopamine receptor system has abated. This mechanism could account for the findings of faster motor performance (increased motor speed) in cocaine-abusing subjects relative to controls.\textsuperscript{6}

It may be that the results of some studies that have found more severe and widespread effects of cocaine on measures on declarative memory were affected by unreported substance use by their subjects. Additionally, many studies failed to obtain a demographically matched control group in which ethnicity and sex were carefully controlled. Also, all subjects in our study had at least a 6-month abstinence from alcohol. Because other studies have not generally required a prolonged period of abstinence from alcohol prior to the cognitive assessment, our abstinence requirement could have contributed to the lower frequency of declarative memory impairment found in the present study, especially given the high comorbidity of alcohol abuse among cocaine abusers.

Our study also raises intriguing issues regarding potential predictors of those who remain in a study (and possibly treatment) and those who drop out during a 6-week interval. Depression, anxiety, and poorer memory function at entry were all associated with drop-out within the cocaine-dependent group by day 45. The replicability and meaning of these findings warrant further study.

A limitation of the present sample includes the sample size, as well as the attrition in our cocaine-abusing sample by day 45. Nevertheless, our findings do not seem to be simply the result of an atypical subgroup of subjects who were responsible for these anomalous findings. They are also not the result of the effects of a withdrawal-induced depression, which could have affected some subjects’ performance. Finally, these findings are not the result of undetected intercurrent substance abuse as all subjects had confirmed use of cocaine at visit 1, and confirmed abstinence of other substance abuse at (and between) the 3 follow-up visits. Future studies would benefit from further investigation of dopamine receptor systems during cocaine abstinence since these systems seem to have various effects on cocaine-seeking behavior.\textsuperscript{21}

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