

Cognitive Impairment in Acute Cocaine Withdrawal

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Objective: To perform a pilot study to examine a range of cognitive flexibility tasks early in cocaine withdrawal.

Background: Previous neuropsychological investigations of cocaine withdrawal have conflicted regarding whether impaired cognitive flexibility occurs. However, most studies have examined patients later in withdrawal. Anxiety and yohimbine-induced panic are greatest early in withdrawal, and both anxiety and increased noradrenergic tone can impair cognitive flexibility.

Method: Twelve patients acutely withdrawing from cocaine were compared with gender-, age-, and estimated premorbid intelligence-matched control subjects on tests of cognitive flexibility as well as verbal fluency, verbal memory, spatial memory, and attention.

Results: As predicted, impairments were found on the cognitive flexibility tasks. Impairments also were present in verbal fluency and verbal memory but not spatial memory or attention.

Conclusions: We propose that the cognitive flexibility impairment may relate to the increased noradrenergic activation recently described in cocaine withdrawal. Impairments on verbal tasks may also relate to an impaired flexibility in the search of semantic networks. Further research will explore the effects of pharmacologic manipulation of the noradrenergic system on cognition in acute withdrawal. Recently, propranolol has been shown to benefit patients in cocaine withdrawal. Further research will explore whether impaired cognitive flexibility related to altered noradrenergic tone could serve as a mechanism for this treatment response.

Key Words: cocaine, withdrawal, cognitive flexibility, memory, language, norepinephrine, neuropsychology

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Early theories of intelligence proposed that two types of intelligence are used in solving problems: fluid intelligence and crystallized intelligence.¹ Crystallized intelligence includes declarative knowledge such as “Columbus is the capital of Ohio,” whereas fluid intelligence is used for problems that cannot be solved exclusively with knowledge. Cognitive flexibility is a form of fluid intelligence, involving the ability to inhibit strong preferences to explore alternative solution paths.² If impairments were to exist in ability to explore such alternate solution paths among cocaine-withdrawal patients, we propose that this would seem detrimental since the strong preference, which the withdrawal patients must inhibit, would involve relapse to cocaine use.

However, in the investigation of cognitive impairments during cocaine withdrawal, reports have conflicted regarding whether cognitive flexibility impairments occur. Gillen et al³ studied male cocaine addicts at an average of 17 days' abstinence and found no impairment in cognitive flexibility using the Wisconsin Card Sort Test (WCST).⁴ Impairments were found in visual-motor integration and word fluency. Ardila et al⁵ studied cocaine addicts after 27.5 days of abstinence and found performance on the WCST at about 1 SD below normal; an overall pattern of difficulties with verbal memory and learning was found and noted to be consistent with that typically found in stimulant abusers. Beatty et al⁶ also found significant impairment on some aspects of the WCST as well as visuospatial tasks, perceptual motor speed, and verbal memory tasks at 3–5 weeks of cocaine and alcohol abstinence. O'Malley et al⁷ studied cocaine abusers at 23.6 days of abstinence and found impairment on categorization tasks probing abstraction and problem solving as well as concentration and memory. Hoff et al⁸ also found impairment on some measures of executive function (categorization tasks and Trail-Making Test, Part B)⁹ but no impairment on others (number of categories on the WCST) at an average of 24.5 days of crack cocaine abstinence.

Impairments in cognitive flexibility are associated with anxiety-provoking stressors.¹⁰ Furthermore, anxiety is associated with the acute phase of withdrawal from cocaine.¹¹ McDougale et al¹² administered yohimbine (an α_2 -adrenergic antagonist) or placebo to subjects in withdrawal from cocaine. Recovering addicts were divided into an early group, which was tested 1–2 days after last use, and a late group, which was tested 15–16 days after last use. They found that 71% of the early group had yohimbine-induced panic attacks. None of the early subjects exhibited panic attacks when given placebo. None of the subjects in the late group exhibited panic attacks on either yohimbine or placebo. The authors also noted that the early group exhibited increased fearfulness, increased

nervousness, and a larger increase in plasma 3-methyl-4-hydroxyphenylethylene glycol (MHPG) after administration of yohimbine when compared with the late group. The two groups did not differ in baseline blood pressure or plasma cortisol levels.

Therefore, it would be of particular interest to assess cognitive flexibility early in cocaine withdrawal. Berry et al¹³ assessed crack cocaine addicts at 72 hours and reassessed them at 14–18 days. Verbal memory, visuospatial tasks, and concentration were all found to be impaired at 72 hours relative to a matched control group, and set shifting (Trail-Making Test, Part B),⁹ visuospatial tasks, and verbal memory were impaired at 14–18 days. Word fluency and Stroop¹⁴ performance showed no difference between the groups during either assessment. However, cognitive flexibility was not tested in this study beyond the Stroop task and the Trail-Making Test, Part B.

The purpose of this work, therefore, is to perform a pilot study to examine whether individuals acutely withdrawing from cocaine exhibit a predicted impairment in performance on various tests of cognitive flexibility. Furthermore, the findings on yohimbine-induced panic¹² suggest adrenergic dysregulation in the acute phase of cocaine withdrawal, which exhibits some correction at later stages in withdrawal. Noradrenergic dysregulation is believed to be a major contributor to panic disorder,^{15–17} and the noradrenergic system is known to have a modulatory effect on certain types of cognitive flexibility tasks in normal individuals through a central mechanism.^{2,18,19} This raises the possibility that either increased overall adrenergic tone or increased sensitivity to the “normal” levels of adrenergic tone may be present early in cocaine withdrawal, providing a potential mechanism for impaired cognitive flexibility. Our hypothesis is therefore that individuals acutely withdrawing from cocaine would be impaired on performance on the anagram task, which is known to be modulated by the noradrenergic system.^{2,18,19} However, the anagram task may differ from other cognitive flexibility tasks used in previous withdrawal studies.^{4–6,13} Tasks such as the Trail-Making Test, Part B (used in the early withdrawal study by Berry et al)¹³ and the WCST (used in the studies of later withdrawal)^{4–6} involve response selection from a rather limited range of options, whereas the anagram task involves a search through a large solution set to determine a response.^{2,18,19} Therefore, we also wished to determine whether withdrawal subjects demonstrate impairment on these other types of cognitive flexibility–dependent tasks as well. We will also examine word fluency, to test whether other cognitive domains referable to the frontal lobe are affected, and attention and memory, to determine the extent of impairment in other domains.

MATERIALS AND METHODS

Subjects

Twelve subjects meeting the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM-IV) criteria for cocaine dependence²⁰ were recruited from a regional referral inpatient drug recovery program in the community (Talbot Hall at Ohio State University Medical Center East). All subjects had a drug screen upon entering the program and were

interviewed, examined, and diagnosed by a board-certified psychiatrist and addictionologist. Testing was incorporated into their therapy schedules, and there were no refusals from this group. All 12 reported cocaine as their primary addiction, and 1 also reported opiate use within the preceding 6 months. Three each also had a history of heavy alcohol consumption, regular tobacco use, and daily marijuana use. Two had a history of treatment of bipolar disorder. Only one subject reported a history of head injury with only brief loss of consciousness. All subjects were in the early stages of withdrawal. The mean duration of abstinence at evaluation was 4.7 ± 2.4 days (range 2–10 days). This range was selected for study to encompass the early range of withdrawal not assessed by most previous neuropsychological research on cocaine withdrawal and to include the timeframe of yohimbine-induced panic. All subjects reported regular use of cocaine for at least 1 year, escalating to either chronic daily use for at least 6 weeks or heavy weekend use for at least 3 months. Subjects had random urine screenings and blood draws while in the program to confirm abstinence from all substances of abuse. Furthermore, the inpatient setting may also have limited their access to substances. During withdrawal, all but two subjects reported significant anxiety (mean score on a scale of 0–7 = 4.1). Withdrawal symptoms reported by at least 50% of subjects included insomnia. Other withdrawal symptoms reported by at least 25% of the subjects included paranoia, mood swings, tremor, and diaphoresis. Twelve healthy control subjects were matched for age ($t[22] = 0.66, P = 0.49$, withdrawal subjects average 36.5 ± 9.1 years, controls 33.1 ± 12.0 years), gender (six males and six females for both groups), history of at least occasional alcohol use (seven withdrawal subjects, eight controls), and Verbal IQ ($t[22] = 1.724, P = 0.099$, withdrawal subjects average 105.9, controls 110.4), as estimated by the North American Adult Reading Test (NAART) to provide an estimate of the subject’s premorbid verbal functioning (Verbal IQ).^{21,22} Control subjects were recruited from the community, primarily from the campus and medical center, and had no history of illegal drug use or chemical dependence. All subjects reported English as their first language. No subjects reported any history of learning disabilities or concurrent medical illness. With the effort to match on the aforementioned variables, the groups did differ in educational level ($t[22] = 0.998, P = 0.002$, withdrawal subjects average 13.1 years, controls 16.4 years). Of the withdrawal subjects, nine were white, two African American, and one multiracial. Of the control subjects, 10 were white, 1 Asian, and 1 multiracial. Informed consent was obtained from each subject prior to participation in accordance with the Institutional Review Board for Research Involving Human Subjects at the Ohio State University.

Procedures

Both groups were studied using a series of neuropsychological tests assessing several cognitive domains, given in the same order to each subject. To determine whether patients acutely withdrawing from cocaine are impaired in cognitive flexibility, subjects were given the Wisconsin Card Sorting Test (WCST)⁴ and the anagram task.^{18,19} As with our previous research,^{2,18,19} subjects were allowed a maximum of

2 minutes to solve each anagram. Unsolved anagrams were given a time of 2 minutes. The two groups were compared for the sum of the natural log of the times to solve each of the anagrams. Separate analysis was also performed for 5-letter anagrams (the shortest anagrams given) to eliminate any potential "floor effect" from inability to solve the more difficult anagrams. The WCST provided an alternative test of cognitive flexibility dependent on set shifting rather than the analog network search that would be more likely used in solving anagrams. In the WCST, subjects sorted a set of cards and were given feedback as to whether their sorting strategy was correct. After repetitions of this sorting task, once the subjects reliably learned the correct strategy, the examiner would then change the sorting rule. Total number of tries required, percentage of tries correct, perseverations on known incorrect rules, and failures to maintain a newly learned correct rule were compared between groups.

To assess other cognitive domains referable to the frontal lobe, subjects were also given the Controlled Oral Word Association (COWA) test¹⁴ to assess verbal fluency (the letters F, A, and S as well as animal naming were used, with the subjects producing as many words as possible in 1 minute within each category).

Due to the finding of memory impairment in previous research in cocaine withdrawal, the California Verbal Learning Test (CVLT)²³ was given to assess verbal learning and memory (immediate, short-term, and long-term free recall memory for sets of 16 words from four categories was assessed, with cued recall for short- and long-term memory) and the Rey Complex Figure Test (Rey CFT)²⁴⁻²⁶ to assess visuospatial construction and memory. Accuracy of copying and 3-minute and 30-minute recall were scored on the Rey CFT using a 36-point scale.^{25,27} The Stroop test¹⁴ was also used to determine the role of sustained attention in cognitive impairment in early withdrawal as well as a supplementary measure of executive function. The time taken on word and color naming was scored; as an additional measure of executive function, color-word naming (where the word describes one color and the ink is a different color, and the subjects are asked to name the ink color) times were scored, and the interference score was calculated.

The test battery took 2 hours to administer.

RESULTS

The results of the neuropsychological tests are summarized in Table 1. As predicted, acute cocaine-withdrawal patients had a significantly worse performance on anagrams. Similarly, impairment was found on the WCST, suggesting impairment in cognitive flexibility.

With the performance on other cognitive domains not specifically predicted by our hypothesis, a general pattern can be observed in the results. Individuals withdrawing from cocaine tended to be impaired on tasks most dependent on verbal ability, including verbal memory (all measures of the CVLT) and verbal fluency (COWA for letters and a trend for animal names). No significant impairment was found on any tasks involving spatial construction or memory (Rey CFT) or some measures of attention (Stroop, aside from color naming and a trend for color-word naming, which became significant

with analysis of covariance [ANCOVA]). The color-word interference on the Stroop test, which isolates the response inhibition components of executive function, was not impaired in cocaine-withdrawal patients. An isolated impairment in Stroop color naming was observed.

All results except for the percentage correct score on the WCST remained significant when covaried for premorbid IQ and educational level using ANCOVA.

To determine whether our results were affected by duration of abstinence within the 2- to 10-day abstinence range examined, Pearson correlation coefficients were calculated between the duration of abstinence and performance on each neuropsychological measure found to be impaired in addicts. No significant correlation was found for any of the measures.

DISCUSSION

As predicted, performance on cognitive flexibility tasks (anagrams, WCST) appears to be impaired in acute withdrawal. Impairments were also found on verbal memory tasks (CVLT) and verbal fluency tasks (COWA). The addicts demonstrated no significant impairment on spatial memory or other spatial tasks and on some attentional measures. Other studies have inconsistently shown cognitive flexibility and verbal impairment as well as memory impairment.^{3,5-8} However, our patients were in more acute withdrawal than in those studies.

The anagram task involves searching through a large data set (the semantic/phonologic network) to identify the solution to the problem. Performance on this test is modulated by the noradrenergic system, possibly by altering the signal-to-noise ratio of neuronal activity in the cortex.^{2,18,19} Furthermore, recent evidence has suggested significant up-regulation of noradrenergic activation in cocaine withdrawal. Dysregulation of the noradrenergic system has been found in rhesus monkey brains during self-administered cocaine use, which is equivalent to or greater than the changes observed in the dopaminergic system.²⁸ β -Adrenergic antagonists have also been shown to attenuate withdrawal-related anxiety behaviors in cocaine- and morphine-dependent rats.²⁹ This is of particular interest owing to the recent finding of benefit for withdrawal from cocaine among patients taking propranolol.^{30,31} Future research will be needed to explore the role noradrenergic modulation of cognitive flexibility plays in cocaine withdrawal as well as the role of anxiety and potential treatment with anxiolytics such as the noradrenergic antagonists in this setting.

The impairment in acute withdrawal subjects on verbal fluency and verbal memory is not an obvious result of our hypothesis of noradrenergic modulation of cognitive flexibility in cocaine withdrawal. However, these tasks do involve a search of the semantic/phonologic network to produce a correct answer. This suggests the possibility of impaired network search strategies in general in acute cocaine withdrawal. Lack of impairment in spatial memory suggests that a general impairment in memory does not occur in cocaine withdrawal and therefore does not account for the impairment in verbal memory. Preservation of some measures of attentional function suggests against a general cognitive impairment in acute cocaine withdrawal. However, a more nonspecific cognitive impairment may be present, given the limitations of our small

TABLE 1. Summary of Results

Instrument	Index	Addict	Control	Significance, P =	t(22) =	ANCOVA, P =
Anagrams	In (total)	47.6	41.2	0.043	2.150	0.010
	In (5 letter)	15.4	11.5	0.010	2.824	0.001
WCST	Tries	108.3	84.7	0.010	2.812	0.009
	% correct	81.3	67.7	0.025	-2.397	0.638
	Preservative errors	26.7	9.58	0.016	2.606	0.043
	Failure to maintain set	1.4	0.5	0.051	2.069	0.018
COWA	Total words, F-A-S	37.0	46.4	0.024	-2.432	0.030
	Animals named	20.8	23.9	0.099	-1.723	0.063
Stroop	Word naming	104.6	116.6	0.121	-1.615	NA
	Color naming	69.9	83.5	0.008	-2.981	0.007
	Color-word	41.8	47.8	0.076	-1.865	0.006
	Interference	-0.068	-0.763	0.819	0.232	NA
Rey CFT	Copy score	35.1	36.0	0.305	-1.051	NA
	3-min recall	22.5	22.7	0.957	-0.054	NA
	30-min recall	21.8	23.0	0.689	-0.406	NA
CVLT	List A recall, trial 1	6.7	9.4	0.013	-2.713	0.040
	List A recall, trial 5	12.5	14.8	0.004	-3.189	0.020
	List A total, trials 1-5	51.8	63.3	0.010	-2.837	0.026
	List B recall	5.7	8.9	<0.0005	-5.101	0.001
	Short free recall	10.1	13.6	0.002	-3.614	0.015
	Short cued recall	11.7	14.3	0.006	-3.046	0.013
	Long free recall	11.5	14.1	0.006	-3.063	0.009
	Long Cued recall	12.1	14.6	0.005	-3.137	0.014

sample size in this pilot investigation. Several of the trends in our study, such as the Stroop results, may have reached significance in a larger study and might begin to support a more nonspecific effect of early cocaine withdrawal on cognition. Further research will be needed to better define the spectrum of impairments in acute cocaine withdrawal and their relation to noradrenergic modulation of cognitive functions; research is also necessary to determine how these impairments, and potential pharmacologic modulation thereof, change throughout the course of withdrawal.

While it was not an anticipated finding, impairment on the color-naming task in the Stroop test may relate to previous findings of color vision impairment in the acute phase of cocaine withdrawal,³² believed to be related to dopaminergic dysregulation in cocaine addicts, since dopamine is found in high concentrations in the retina and is important in color vision.

In our small pilot investigation, we attempted to minimize some of the premorbid differences between groups by matching the NAART, used as a predictor of premorbid function. Such a strategy, though, resulted in significant differences in educational level, which may also have contributed to the results of our study. However, ANCOVA correcting for differences in educational level and premorbid intelligence also yielded significant results for most of our measures. Efforts to more closely match other demographics such as educational level and ethnic origin and factors such as other drug use and premorbid psychiatric illness will be needed in larger follow-up studies. Unreported use of other substances could also contribute to the findings.

Treatment of early cocaine withdrawal is characterized by high dropout rates and a failure to sustain abstinence for a significant period of time.³³⁻³⁹ A better understanding of the impairments facing withdrawal patients and ultimately a refined treatment strategy would be helpful. While cocaine addicts in the acute phase of withdrawal demonstrate significant impairments in measures of verbal fluency, verbal memory, and cognitive flexibility, they face demands to make marked changes in their previously established pattern of behavior and to assimilate new information at what may be the nadir of cognitive flexibility during their abstinence. It is hoped that minimizing these deficits, if possible, may have a positive impact upon the outcome of treatment of cocaine withdrawal.

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