Method

Participants

The participants were recruited as part of a larger safety/tolerability study. The safety and tolerability data of the first 13 participants have been presented previously (1). Cue-reactivity data were not presented in that earlier report.

The participants were recruited through flyers and newspaper advertisements and by word of mouth. All participants satisfied DSM-IV criteria for current cocaine dependence, verified by a positive urine drug screen, and were not dependent on any other substances except nicotine, alcohol, or marijuana. The participants had no concurrent psychiatric disorder and no history of delusions/hallucinations, including during episodes of acute cocaine use. The participants were free of any psychotropic medications for at least 2 weeks before participating in the study and were in good physical health and required to be free of any history of asthma, seizures, or head injuries. The female participants were tested regularly for pregnancy and were required to use some form of birth control during the trial.

Eighteen participants were recruited initially, but three were excluded during the course of the study because of benzodiazepine use (N=1) or because they provided unreliable data (N=2) during the first cue-reactivity procedure. The remaining participants included seven men and eight women with a mean age of 37.4 years (SD=7.1, range=23–45); 11 were African American and four were Caucasian. Of those participants, 10 were primarily crack smokers, two primarily used nasal powder, and the remaining participants used a mixture of crack, powder, and freebase cocaine. Self-report accounts of cocaine use, assessed using the timeline follow-back procedure (2) for the 90 days before study participation indicated that the participants used

cocaine 38 of the 90 days on average (SD=22, range=10 to 90), spending a daily average of $31 (SD=$12, range=$10 to $47) and an average of $95 per use day (SD=$57, range=$10–$220). The participants received up to $900 for their participation ($100 per each day in the hospital plus $300 for completion of follow-up visits).

Procedures

After completing an anonymous phone screening for initial eligibility, the participants attended a 45-minute informed consent session during which procedures for screening and hospitalization, along with the psychophysiological cue reactivity procedure, were described in detail. All participants provided written informed consent approved by the Medical University of South Carolina institutional review board. The participants then completed a series of outpatient visits in which they received a psychiatric screening, a physical and medical history, and assessments of cocaine use, as described previously (1). The participants who satisfied inclusion/exclusion criteria were enrolled in the study and scheduled for two 3-day inpatient hospital stays over 2 consecutive weeks.

Immediately before admission to the hospital, all female participants were screened for pregnancy. All participants were cocaine free at the time of admission, as verified by urine drug screen. All were housed on a closely monitored inpatient unit and were not allowed to leave the unit without supervision; this monitoring made it possible to ensure that the participants were free of cocaine throughout their hospital stay, including during the cue-reactivity procedure. A number of safety screenings that were performed as part of the hospitalization (e.g., CBCs, EEGs, reports of side effects) have been reported elsewhere (1). Approximately 2 hours after admission, the participants received their first dose of either *N*-acetylcysteine 600 mg or an identically appearing placebo capsule containing lactose powder, and dosing was repeated three

times at 12-hour intervals. Approximately 2 hours after the fourth and final dose, the cue-reactivity procedure commenced and lasted approximately 2 hours. Upon completion, the participants were escorted back to the inpatient unit. They were discharged the following morning. Four days later, the participants were admitted to the hospital for a second stay. All procedures were identical except that the participants who received *N*-acetylcysteine during the first week were crossed over to receive placebo during the second week, and those who received placebo during the first week were crossed over to receive *N*-acetylcysteine during the second week.

Cue reactivity procedure

Experimental stimuli. Five cocaine-related slides, five neutral slides, five pleasantly valenced, and 10 negatively valenced slides were presented to the participants. The cocaine-related slides were selected from a larger set of photographs of in vivo cues (i.e., simulated powder and crack cocaine, simulated cocaine paraphernalia, simulated use of these items) previously used by our research group (3). The neutral slides depicted household objects (e.g., a stool, a book, an unmade bed). The pleasantly valenced slides consisted of emotionally evocative scenes intended to evoke pleasant emotions (e.g., amorous heterosexual couples, exhilarating sporting activities, etc.) whereas the negatively valenced slides consisted of scenes intended to evoke unpleasant emotions (e.g., assailants with knives, a bloody mafia hit, a mutilated face, a snake preparing to strike). The neutral and affective slides were selected from the International Affective Picture System (4), a collection of color photographs that have been standardized on the dimensions of pleasure, arousal, and dominance (specific identification numbers for the slides are available upon request from the first author). In all, 25 slides were presented in a fixed semirandom order, along with two additional slides that were presented at the beginning of the

session to orient the subject to the slide presentation. These first two slides were not included in the subsequent analyses.

In addition to slide presentations, acoustic startle probes consisting of 50-msec broadband white noise bursts were presented during 20 of the 25 slide presentations (evenly distributed across categories) between 2.8 and 5 seconds after slide onset. Because two participants had missing startle data and five participants were essentially nonresponders, there was not a sufficient amount of startle data to analyze for the present report.

Psychophysiological assessment. Physiological measures were collected for two seconds before presentation of slides then for 6 seconds during slide presentation. Heart rate data were collected using two Ag-AgCl sensors placed on the participants' forearms; a single ground electrode was placed on the forehead. Heart beats were detected and converted to beats per minute. Skin conductance data were collected with two Ag-AgCl sensors placed on the hypothenar eminence of the nondominant hand. Skin conductance data were sampled at 20 Hz and stored in arbitrary analog-to-digital units and then range-corrected (5). All physiological data were collapsed into 1-second averages; the two seconds before slide presentation were averaged as a single baseline level. For the six seconds of data collected during slide presentation, the maximum value was identified and the baseline level subtracted, which yielded the maximum change in response level for heart rate and skin conductance for each slide.

Behavioral and self report measures. After physiological data collection was completed, the slides were shown a second time to obtain self-report ratings. For each slide, the participants provided ratings using a joystick controller connected to the stimulus presentation machine. The participants were allowed to view the slide as long as they liked (0 to 20 seconds) and turned off the slides by a button press. The viewing time for each slide was recorded,

providing an objective measure of interest. Once the slide viewing was complete, the participants provided ratings for each slide in response the following questions: 1) How strong was your CRAVING for COCAINE? 2) How much did you feel you wanted to use cocaine? 3) How INTERESTING was this picture? These three questions were rated on a 21-point Likert scale (0 to 20) and were intended to tap into the following dimensions: craving, interest, and desire to use. Although these three dimensions are highly related, the literature has suggested that craving is a multidimensional concept that may not be accurately measured using single-item assessments (6). Thus, it was reasoned that using three similar, but not completely overlapping items, would provide a better opportunity to assess motivation to use cocaine than would a single rating for craving. Along with these motivational measures, general ratings of slide pleasantness (–10 to 10 on a Likert scale), arousal, and dominance (0 to 20 on a Likert scale) were collected as well. These ratings were assessed with the Self-Assessment Manikin, a nonverbal means for rapid assessment of pleasantness, arousal, and dominance (7). It presents a human-like manikin that can be made to smile or frown, to have a high or low level of arousal (the figure becomes "jumpy" with simulated "butterflies" in the stomach area), or dominance (the figure can be made large to depict high dominance or high control and small to depict low dominance or low control).

Approximately 2 hours after receiving the fourth and last dose of placebo/*N*-acetylcysteine, the participants were escorted to the psychophysiology suite at the Medical University of South Carolina General Clinical Research Center. They were seated in a comfortable chair and sensors were placed. The participants wore professional grade audiometric headphones through which startle probes were presented. The participants were informed that they would be viewing slides depicting cocaine, neutral, and emotional situations. As noted

above, the slides were presented twice. The first time involved passive viewing of each slide (6 seconds each) during which time physiological measures were collected and no ratings were made. During the second presentation, the participants viewed each slide as long as they liked and then provided ratings.

Statistical Analysis

Cue-Reactivity Data

The analyses were performed with the linear mixed-model routine of SPSS 12.0 (SPSS, Chicago). Physiological measures, heart rate, and skin conductance were analyzed separately with a 4 by 2 by 2 (category by medication condition by medication order) mixed-model analysis. Owing to equipment error, heart rate data were unavailable for three participants, and skin conductance data were unavailable for another. There were no significant findings for heart rate data, including no significant differences across categories and no medication effects. The 4 by 2 by 2 analysis confirmed that skin conductance reflected differences across categories, (F=3.46, df=3, 84, p 0.05). Post hoc tests indicated that the cocaine slides produced greater skin conductance than the neutral slides (t=2.95, df=84, p 0.01) and the pleasant slides (t=2.32, df=84, p 0.05). No medication effects were observed (Table 1).

Table 1

Data for the Cue-Reactivity Procedure: Motivational and General Measures[a]

Motivational Measures	Cocaine		Neutral		Pleasant		Unpleasant	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Overall mean motivation[b,c,d]	6.74	4.75	2.09	2.49	5.34	5.80	3.25	3.99
N-acetylcysteine								
Craving[b,c,d]	5.81	4.29	1.32	2.41	2.64	4.14	0.86	2.12
Desire to use[b,c,d]	6.19	4.41	1.01	1.66	2.84	4.44	0.97	2.53

Interest[b]	7.85	5.28	2.81	2.61	12.37	5.53	8.24	5.18
Time viewed (seconds)	3.92	1.70	2.86	1.40	3.28	1.97	3.54	1.96
Placebo								
Craving[b,c,d]	7.25	5.27	1.09	2.34	2.21	3.54	0.91	1.79
Desire to use[b,c,d]	8.32	5.13	1.79	3.09	2.65	3.52	1.13	1.92
Interest[b]	9.65	6.03	3.30	3.49	12.21	6.22	6.96	4.44
Time viewed (seconds)[b]	4.86	2.27	2.58	1.33	4.31	2.76	3.40	1.50
General measures								
Pleasantness[c,d]	1.45	4.27	0.56	3.18	5.12	3.51	–4.71	3.14
Arousal[b,d]	9.57	6.33	3.67	4.30	9.51	6.34	6.39	6.10
Dominance[b,c]	13.36	4.91	16.82	3.96	16.37	4.43	14.64	6.36
Maximum heart rate change (bpm)	1.29	2.27	0.71	1.29	0.56	0.81	0.53	0.75
Maximum skin conductance change[b,c,e]	0.03	0.05	0.01	0.03	0.02	0.03	0.03	0.04

Means represent raw unadjusted means (i.e., not estimated marginal means) and standard deviations collected during the procedure. For general measures, means represent overall means across both medical conditions.

Cocaine slides significantly differ from neutral slides.

Cocaine slides significantly differ from pleasant slides.

Cocaine slides significantly differ from unpleasant slides.

Range of corrected values represents maximum change from baseline.

The means for the motivational measures, within each respective medication condition, are presented in Table 1. For motivational measures, correlations were examined within each session, revealing that these measures were highly and significantly associated with each other, although viewing time, a behavioral measure, was less associated with the self-report motivational measures (Table 2). Because all motivational measures were on the same scale (0 to 20), all were initially included in a single linear analysis to maximize the power to detect medication effects. Thus, all four motivational measures (craving, desire to use, interest, and time viewed) for all four slide categories (cocaine, neutral, pleasant, unpleasant) were incorporated into a linear mixed-model analysis with measure, category, medication condition (*N*-acetylcysteine versus placebo) as repeated measures and medication order (*N*-acetylcysteine first versus *N*-acetylcysteine second) as a between-subjects measure. This resulted in a 4 by 4 by

2 by 2 (measure by category by medication condition by medication order) mixed-model analysis. This analysis confirmed that there were indeed significant differences across categories (F=45.63, df=3, 399, p 0.001). The overall mean motivation (i.e., combined craving, desire to use, interest, viewing time) for cocaine slides was greater than neutral slides, t=10.66, pleasant slides, t=3.35, and unpleasant slides, t=8.14, df=399, p 0.01 for all. There was a significant effect for medication condition (F=3.85, df=1, 399, p=0.05); the estimated mean for the *N*-acetylcysteine condition (mean=3.97, SD=4.61) was less than that for placebo (mean=4.57, SD=4.93). The medication-by-category interaction did not reach significance (p=0.12). Because no medication effects were expected for neutral, pleasant, and unpleasant categories, it was reasoned that the inclusion of all three categories could potentially limit the ability to detect a medication-by-slide category interaction. Thus, an analysis that incorporated only cocaine and neutral slides, which produced a 4 by 2 by 2 by 2 (measure by category by medication condition by medication order) mixed-model analysis was performed. It revealed a highly significant effect for medication (F=7.40, df=1, 193, p 0.01), and the medication by category interaction approached significance (p=0.052). Following the initial analysis, separate analyses were performed to determine medication effects on cocaine slides alone, with each motivational measure examined separately. These follow-up analyses were based on methods particular to crossover studies that control for treatment period and sequence assuming no differential carryover effect (8) and used a 2 by 2 study design (medication condition by medication order, see Table 1).

Table 2

Correlations Among Motivational Ratings of Cocaine Users[a]

Variable	All Categories (N=60)	Cocaine Only (N=15)

Rating	1.	2.	3.	4.	1.	2.	3.	4.
1. Craving	—	**0.96**	**0.34**	**0.27**	—	**0.95**	**0.84**	0.47
2. Desire to use	**0.95**	—	0.36	0.24	**0.92**	—	**0.83**	0.36
3. Interest	**0.43**	**0.50**	—	0.16	**0.79**	**0.94**	—	0.26
4. Time viewed	**0.43**	**0.38**	0.26	—	0.18	0.27	0.24	—

Values above the diagonal correspond to session 1; values below the diagonal correspond to session 2. All correlations in bold are p 0.01.

In addition to testing for overall medication effects, exploratory analyses were performed to determine the extent to which cocaine slides differed from the remaining three categories on motivational measures. These follow-up analyses were performed within each medication condition separately for each individual motivational measure with a linear mixed-model analysis that examined for an overall category effect, which was followed up by post hoc t test comparisons (cocaine versus each respective category). Significant differences between cocaine and other categories are indicated in Table 1. For ratings of valence, arousal, dominance, separate 4 by 2 by 2 (category by medication condition by medication order) linear mixed-model analyses were performed, with no medication effects noted. Category effects were noted, however, and are reported in Table 1.

Two final exploratory analyses were performed. The first examined to what extent the motivational measures were related to baseline measures such as total amount of cocaine use and average cocaine per use day (within the 90 days before the study), baseline craving at hospital admission, and recency of last cocaine use before each cue-reactivity session. Only baseline craving at admission was associated with motivational measures, with significant correlations observed for craving and desire to use within the placebo condition (r=0.60 and 0.54, respectively, p 0.05, but not within the *N*-acetylcysteine condition (r=0.41 and 0.28, respectively). The second analysis examined craving before and several hours after the cue reactivity session. There was no change in craving, nor was any medication effect apparent.

References

1

LaRowe SD, Mardikian P, Malcolm R, Myrick H, Kalivas P, McFarland K, Saladin M, McRae A, Brady K: Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. Am J Addict 2006; 15:105–110

2

Sobell LC, Sobell MB, Leo GI, Cancilla A: Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Br J Addiction 1988; 83:393–402

3

Coffey SF, Saladin ME, Drobes D, Brady KT, Dansky BS, Kilpatrick DG: Trauma and substance cue reactivity in individuals with comorbid posttraumatic stress disorder and cocaine or alcohol dependence. Drug Alcohol Depend 2002; 65:115–127

4

Lang PJ, Ohman A, Vaitl D: The International Affective Picture System. Gainesville, University of Florida, Center for Research in Psychophysiology, 1999

5

Lykken DT, Venables PH: Direct measurement of skin conductance: a proposal for standardization. Psychophysiology 1971; 8:656–672

6

Tiffany ST, Carter BL, Singleton EG: Challenges in the manipulation, assessment and interpretation of craving relevant variables. Addiction 2000; 95(suppl 2):S177–S187

7

Bradley MM, Lang PJ: Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. J Behav Ther Exper Psychiatry 1994; 25:49–59

8

Fleiss JL: The Design and Analysis of Clinical Experiments. New York, John Wiley & Sons, 1986