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Community-Dwelling Cocaine-Dependent Men and Women Respond Differently to Social Stressors versus Cocaine Cues

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Summary

There are likely to be gender differences in determinants of relapse to drug use following abstinence in cocaine-dependent individuals. Cocaine-dependent women are more likely to attribute relapse to negative emotional states and interpersonal conflict. Cocaine dependence has also been linked to dysregulation of stress response and the hypothalamic pituitary adrenal (HPA) axis which may differ between genders. Subjective and HPA axis responses to a social evaluative stressor, the Trier Social Stress Test (TRIER), and in vivo cocaine-related cues were examined in the present study.

Results—There were no gender differences in magnitude of craving responses to the TRIER or the CUE. Both genders had a greater craving response to the CUE than to the TRIER, but the magnitude of the difference was greater for men than women ($p=0.04$). Cocaine-dependent subjects, compared to the control group, had significantly higher response throughout the TRIER ($p<0.0001$) and CUE ($p<0.0001$) testing sessions. There were no gender differences and no gender by cocaine interaction for ACTH responses to the TRIER, although women had lower baseline ACTH ($p=0.049$). On the CUE task, in contrast, female cocaine-dependent subjects had a more blunted ACTH response than did the other three groups ($p=0.02$). Female cocaine-dependent subjects also had a lower odds of a positive cortisol response to the TRIER as compared to the other three groups (OR=0.84, 95% CI=[0.02, 1.01]). During the CUE task, cocaine-dependent subjects had overall higher mean cortisol levels ($p=0.0001$), and higher odds of demonstrating a positive cortisol response to the CUE (OR=2.61, 95% CI=[1.11, 6.11]). No gender differences were found in ACTH responses to the CUE. The results are reviewed in the context of the existing literature on gender differences in cocaine dependence and potential implications for treatment are discussed.

Keywords

HPA axis; substance use disorder; gender differences; stress reactivity; cue reactivity; drug craving

Introduction

There are important gender differences in the development and course of substance use disorders (Zilberman, et al., 2003; Hernandez-Avila, et al., 2004). Evidence suggests that

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despite a lower prevalence of cocaine use and abuse, women may actually have an increased vulnerability to some aspects of cocaine dependence. For example, women meet criteria for drug dependence more quickly and enter treatment programs earlier than men (Anglin, et al., 1987; Griffin, et al., 1989; Westermeyer & Boedicker, 2000; Brecht, et al., 2004; Hernandez-Avila, et al., 2004). Cocaine-dependent women also report higher rates of cocaine use and shorter periods of abstinence than cocaine-dependent men (Griffin, et al., 1989). These findings suggest gender differences in cocaine use and dependence with important treatment implications.

Stress and substance-related cues have become widely recognized as triggers for relapse to substance use in substance-dependent individuals (Childress, et al., 1993; Kreek & Koob, 1998). The HPA axis is a key stress response system and has been examined extensively for its involvement in relapse. Proper functioning of the HPA axis is important for managing a cascade of neuroendocrine responses to stress and other stimuli that must be regulated to maintain homeostasis (Koob & Le Moal, 2001). Chronic cocaine use can lead to dysregulation of the HPA axis which may play a role in relapse through effects on stress and reward circuits (Koob & Kreek, 2007). Of interest, stress responses in the laboratory have been demonstrated to be predictive of relapse to cocaine use in cocaine-dependent individuals (Sinha, et al., 2006; Poling, et al., 2007). Studies suggest that women report more frequent drug use in response to negative situations, while men are more likely to report drug use in response to positive events (Waldrop, Back, Verduin, et al., 2007). These gender differences have not been explored in a human laboratory setting.

There are important gender differences in the HPA axis response to laboratory stress paradigms. In general, laboratory stressors provoke a stronger response in men as compared to women (Kudielka & Kirschbaum, 2005); however, this varies by the type of stress paradigm used. In a study that compared men and women's responses to a laboratory-based social rejection task versus a performance-related task, women reacted more strongly to the socially-oriented task and men responded more strongly to the achievement-oriented task (Stroud, et al., 2002). An earlier study by the same group found a stronger response among women to the social stressor, as well (Stroud, et al., 2000).

Drug-related cues in the environment may also be involved in precipitating relapse through associative learning processes in which cues may prime craving and physiological responses that lead to continued drug use (O'Brien, et al., 1990; Childress, et al., 1993). Cue exposure paradigms are another branch of active research in the relapse literature. Drug users report that cues for their drugs of choice are likely to be the impetus for renewed use (Waldrop, Back, Verduin, et al., 2007). In laboratory settings, cocaine cues have been shown to provoke craving, anxiety, and cortisol release in cocaine users (Sinha, et al., 2000; Coffey, et al., 2002; Sinha, et al., 2003); however, studies exploring gender differences in cue reactivity remain few and results are mixed. In at least one study, women reported higher craving to cocaine cues than did men (Robbins, et al., 1999) but another study found that men reported statistically nonsignificant but higher craving to cues (Avants, et al., 1995).

The focus of the present study was to compare subjective and endocrine responses to a cocaine cue exposure and a social stressor paradigm (TRIER) among men and women with and without cocaine dependence. The primary hypotheses were: 1) men would respond more strongly to the cocaine cues than to the TRIER; 2) women would respond more strongly to the TRIER than to the cocaine cues; and 3) cocaine-dependent participants would evidence significant HPA axis dysregulation as compared to a matched control group.

METHODS

Participants

Male and female cocaine users and healthy controls were recruited for the study (N=100). Demographic data are presented in Table 1. Participants were recruited primarily through media advertisements and referrals. Exclusion criteria for all groups included 1) medical conditions that might interfere with safe study participation; 2) history of or current psychotic, bipolar, or eating disorders; 3) steroid or glucocorticoid therapy within one month of study participation; 4) pregnancy, nursing, or reported ineffective means of birth control; 5) body mass index of 35 or higher; and 6) DSM-IV defined substance dependence in past 60 days other than caffeine, nicotine, marijuana, or alcohol. Cocaine users were required to meet criteria for cocaine dependence in the past 60 days. Written informed consent was obtained before any study assessments or procedures were conducted. The study was approved by the Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC).

Assessment

Potential participants were screened by telephone and if preliminary inclusion/exclusion criteria were met, an interview was scheduled. The Structured Clinical Interview for DSM-IV (First, et al., 1994) was used to diagnose current and lifetime psychiatric disorders and substance use disorders. The Time-Line Follow-Back (Sobell & Sobell, 1992) calendar method was used to assess cocaine use for the 90 days prior to the initial study interview and at multiple points throughout the study. A medical history, physical examination, and electrocardiogram were conducted. Female participants provided recent menstrual histories.

Participants who met inclusion and exclusion criteria were scheduled for procedures in the MUSC General Clinical Research Center (GCRC) over a 3-day period during which all laboratory procedures were conducted. Subjects were admitted to an inpatient unit for a two night stay at approximately 2000h on the evening prior to the first study procedure day. This allowed for observation and control of potentially confounding variables such as nicotine, caffeine and illicit substance use. Participants were asked to remain abstinent from alcohol and substances of abuse for at least 48 hrs prior to their hospital admission. Abstinence was assessed through self-report, urine drug screen, and alcohol breath tests. Participants who smoked cigarettes were provided a nicotine patch upon admission in order to minimize the impact of nicotine withdrawal on stress responding (≥ 20 cigarettes/day = 21 mg patch; 10–19 cigarettes/day = 14mg patch; 5–10 cigarettes/day = 7mg patch). Nicotine patches were dispensed in a single dose the evening prior to each study day.

On the morning following the first night of the hospital stay, participants were provided a standard breakfast at 0830h. Vital signs were collected and patients were otherwise left to engage in sedentary activities until escorted to the first testing session. At 1150h, GCRC staff inserted an indwelling intravenous catheter into the forearm of the non-dominant hand. At 1200h, participants were provided a standard lunch. After lunch, participants were connected to heart rate electrodes and an intermittently inflatable blood pressure cuff for recording. Between 1300h and 1600h, participants completed cocaine cue exposure or the Trier Social Stress Task. On the following day, the alternate task was done. Tasks were counterbalanced to manage possible order effects. Because the TRIER was added to the protocol later in the study, sample sizes for the tasks differ. Between 1640h and 1800h, participants completed a CRH challenge procedure. Data from the CRH challenge have been presented in a separate report (Brady, et al., in press).

Between 1300h and 1350h, two baseline assessments of subjective craving, stress, and anxiety were completed using a modified version of the Within Session Rating Scale (Childress, et al.,

1986) (the Craving/Distress/Mood scale) and the State-Trait Anxiety Inventory (Spielberger, et al., 1983). The Craving/Distress/Mood scale is a 100-mm visual 10-point Likert scale anchored with adjectives from “not at all” to “extremely.” Baseline assessments were also collected for physiological data (heart rate and blood pressure) and neuroendocrine data (blood samples for adrenocorticotrophic hormone (ACTH) and cortisol assays).

Neuroendocrine samples, subjective ratings, and physiologic measurements were assessed immediately and at 5, 30, 60 and 120 minutes post-task. Blood samples were collected in EDTA-prepared tubes and immediately placed on ice. Plasma was obtained by centrifugation under refrigeration and the serum sample frozen at -70°C until assayed in duplicate. Allegro HS-ACTH system (Nichols Institute Diagnostics), which has an intra-assay c.r. of 6% with a sensitivity of 1 pg/ml, was used for ACTH assays. Cortisol was assayed using the Roche Diagnostic Elecsys 2010 immunoassay analyzer and kits based on an electrochemiluminescence competitive immunoassay having a functional sensitivity of 0.29 $\mu\text{g/dL}$ and intra-assay reproducibility of less than 2%. MUSC GCRC personnel collected all samples, and Rockefeller University GCRC personnel performed the assays. At the end of the second day, participants were debriefed and compensated for their time. A one-week follow-up appointment was scheduled prior to discharge.

Cue Exposure

The cue exposure task (CUE) combined *in vivo* cocaine cues (three minutes) as well as an audio-visual presentation (seven minutes). Participants listened to a standardized set of instructions that encouraged them to handle the *in vivo* cues (e.g., crack pipe, simulated crack cocaine, lighter). They then viewed a videotape of actors engaging in cocaine-related activities.

Trier Social Stress Test

Participants gave an extemporaneous simulated job talk to a group of three confederates. After the five-minute job talk portion, participants attempted to complete serial subtraction of two-digit numbers from a four-digit number for a total of five minutes. Each time an error was made, the participant was instructed to begin again. Confederates were instructed not to provide any verbal or non-verbal feedback (e.g., smiles, nods) and they made an obvious demonstration of audiotaping the entire performance.

Statistical Methods

All analyses were performed using SAS Version 9.1. Subjective measures (stress and craving) were summarized by calculating area under the curve (AUC) using the trapezoid rule. Experimental group differences in AUC were conducted considering AUC as an outcome in a multiple linear regression. Responders to the CUE and TRIER tasks were participants who had greater than 0% change over baseline measure, which corresponds to a positive AUC. Peak change was calculated as maximum response minus baseline response, and resulting values were collapsed into four groups due to sparse data at the high end of the scale. Cross-task differences in peak change in stress and craving were analyzed using a generalized estimating equations (GEE) approach for repeated ordinal measures in PROC GENMOD (Zeger & Liang, 1986) with gender, task, and gender by task as the factors of interest. Chi Square (χ^2) test statistics for Type III GEE analysis are presented. Spearman's rank correlation coefficients (r_s) were examined to determine the degree of correlation between peak changes in subjective ratings of craving and stress during both the TRIER and the CUE tasks in male and female cocaine-dependent subjects.

Change in neuroendocrine outcomes (cortisol, ACTH) was calculated as the percent change in response over baseline: (max response – baseline response)/baseline response * 100. Percent change was analyzed using a multivariable linear model and transformations were used where

appropriate. All multivariable analyses presented in the paper controlled for smoking status, race, and age where these variables were significant predictors.

Neuroendocrine outcomes were analyzed using covariance pattern models (Brown & Prescott, 2006) to account for repeated longitudinal measurements taken on each subject. To account for non-constant variability among the groups, the estimated covariance matrix was allowed to vary by gender or cocaine status, as appropriate. These analyses were performed in PROC MIXED. Non-normality of the outcomes and residuals was addressed via $\log_{10}$ transformations. Prior to the repeated measures analyses, the effects of gender and cocaine status on each of the baseline responses were assessed via nonparametric Wilcoxon rank-sum tests. Where baseline differences in neuroendocrine measures were found, the baseline measure was included as a covariate in the relevant model. All longitudinal analyses controlled for smoking status, race, and age where these variables were significant predictors of the response variable of interest. Likelihood ratio F -tests for Type III sums of squares are presented.

Where descriptive statistics are presented, they represent the mean $\pm$ standard deviation. P -values less than 0.05 were considered significant findings.

RESULTS

Demographics

In Table 1, demographic and descriptive data by cocaine group and gender are displayed. Study recruitment was designed to equalize groups on gender, age, race, and smoking status. While there were no significant differences in age, race, marital or smoking status, there were significant differences in education and employment, with the cocaine group demonstrating significantly lower educational ($p<0.001$) and employment levels ($p<0.001$).

Subjective Measures

Craving—Thirty-one of 54 (57%) cocaine-dependent subjects and none of the control group had a craving response to the TRIER, while 40 of 52 (77%) cocaine subjects and none of the control subjects exhibited a craving response to the CUE. As a result of this, analyses of craving data were restricted to the cocaine group. Among cocaine-dependent subjects, men and women did not differ on baseline craving (median baseline craving in males = 2, females = 1, $p=0.71$).

There were also no gender differences in AUC ($\chi^2_{(1)}=0.28$, $p=0.60$) for response to either task.

To test for gender differences in subjective reactivity across tasks, as measured by peak change, a subsequent analysis considered the effect of task, gender, and the interaction between task and gender on peak change in subjective craving among cocaine-dependent subjects. There was a significant task by gender interaction implying that while both genders had a greater craving response to the CUE than to the TRIER (with females having greater overall craving response), the differential response in males was even greater than that of females ($\chi^2_{(1)}=4.13$, $p=0.04$). That is, the magnitude of the difference in craving in response to the CUE as compared to the TRIER was greater for men than women (Figure 1a).

Stress—Seventy-three of 85 subjects (86%) had a subjective stress response to the TRIER. AUC analysis (controlling for baseline) demonstrated that cocaine-dependent subjects had significantly higher response throughout the testing session as compared to the control group ($\chi^2_{(1)}=21.46$, $p<0.0001$).

Forty-one of 98 (42%) subjects in the study had a subjective stress response to the cocaine CUE. Baseline stress differed by study group with cocaine-dependent subjects exhibiting

higher subjective levels of stress before presentation of the CUE compared to controls (median = 0 vs. 1.5, $p=0.0003$). AUC analysis indicated that cocaine-dependent subjects also exhibited higher subjective stress throughout the testing session ($\chi^2_{(1)}=19.20$, $p<0.0001$). Caucasian race was not an independent predictor of higher subjective stress in the sample ($\chi^2_{(1)}=3.14$, $p=0.08$).

Cross-task analysis was significant implying that the subjective stress response to the TRIER was greater than the response to the CUE among cocaine-dependent subjects ($\chi^2_{(1)}=13.90$, $p=0.0002$). The plot of mean peak changes in stress (Figure 1b) suggests, but without significant difference found, the opposite of that seen for craving; i.e., there was an apparent but not significant difference in subjective stress response to the TRIER between females versus males (mean peak change = 4.57 and 2.68, respectively; gender by task interaction $\chi^2_{(1)}=1.68$, $p=0.19$).

Correlations among subjective measures—A significant positive correlation was found between peak stress and peak craving in both cocaine-dependent females ($r_s=0.59$, $p=0.0019$) and males ($r_s=0.39$, $p=0.04$) following the CUE exposure. However, this result was found only in cocaine-dependent females ($r_s=0.65$, $p=0.0015$) following the TRIER administration (males: $r_s=0.10$, $p=0.68$, Figure 2).

Neuroendocrine Measures

ACTH—Sixty-one of 74 (82%) subjects exhibited an ACTH response to the TRIER. Women had significantly lower ACTH levels at baseline as compared to men (16.4 ± 6.9 vs. 19.4 ± 6.3 , $p=0.02$). There was no interaction of gender by cocaine in peak change analysis ($\chi^2_{(1)}=2.68$, $p=0.10$).

Seventy-four of 88 subjects (84%) exhibited an ACTH response to the CUE. As with the TRIER, women had significantly lower levels of ACTH at baseline as compared to men (18.4 ± 6.9 vs. 20.5 ± 5.0 , $p=0.049$). African Americans had a smaller peak change in ACTH ($\chi^2_{(1)}=5.22$, $p=0.04$), and a significant gender by cocaine interaction demonstrated that female cocaine-dependent subjects had a more blunted response to the CUE than did the other three groups ($\chi^2_{(1)}=5.22$, $p=0.02$, Figure 3). In the longitudinal analysis controlling for baseline ACTH, females and males exhibited different time courses in ACTH levels as seen by the significant gender by time interaction ($F_{(4,79)}=3.34$, $p=0.01$; Figure 4).

Cortisol—Forty-five of 74 (61%) subjects had a positive cortisol response to the TRIER, and there were no differences in baseline cortisol levels between study groups. Cocaine use and African American race were not significant predictors of a blunted change in cortisol levels ($\chi^2_{(1)}=3.48$, $p=0.06$, and $\chi^2_{(1)}=2.83$, $p=0.09$, respectively) in response to the TRIER task. Consistent with our hypothesis of HPA-axis disruption in female cocaine-dependent subjects, a significant interaction between cocaine and gender demonstrated that female cocaine-dependent subjects had a lower odds of (and are therefore less likely to exhibit) a positive cortisol response to the TRIER (OR = 0.84, 95% CI = [0.02, 1.01]) as compared to the other three groups, as illustrated in the plot of mean cortisol levels over time (Figure 5).

Fifty-four of 92 (59%) subjects exhibited a positive cortisol response to the CUE, and there were no differences in baseline cortisol levels between study groups. While groups did not differ with respect to cortisol response to the CUE, the longitudinal analysis showed that cocaine-dependent subjects had overall higher mean cortisol levels throughout the CUE task ($F_{(1,86)}=16.46$, $p=0.0001$, see Figure 6), and higher odds of demonstrating a positive cortisol response to the CUE (OR = 2.61, 95% CI=[1.11, 6.11]). No gender differences were found.

DISCUSSION

In the present study, subjective and neuroendocrine responses to cocaine cues and a social stress task were compared in cocaine-dependent and control men and women matched on age, race, and smoking status. There were gender differences in the relationships between subjective ratings of craving across the tasks, which are consistent with the observation that social stressors may be more closely associated with relapse for cocaine-dependent women as compared to men. The results of this study also suggest a greater dysregulation of the HPA-axis response in cocaine-dependent women as compared to cocaine-dependent men or healthy men and women.

As would be expected, cocaine-related cues elicited craving responses from both male and female cocaine-dependent subjects. Interestingly, exposure to the cues also increased subjective feelings of stress in these subjects, indicating that exposure to cocaine-related cues is an unpleasant experience. The Trier Social Stress Task also increased subjective stress in these subjects, as would be expected, but it increased reports of cocaine craving as well, indicating that this task is an appropriate model of stress-induced relapse in cocaine-dependent individuals. While both genders had a greater craving response to the cues as compared to the Trier, the differential craving response to the two tasks was significantly greater for men as compared to women, indicating that men may be more motivated by environmental cocaine-related cues as compared to social stressors. This is consistent with the findings of Fox and colleagues (Fox, et al., 2006). The interaction between gender and task could also be considered evidence of an increased effect of social stressors on cocaine craving in cocaine-dependent women compared to men. A lack of gender difference in cue-elicited craving response has been reported elsewhere (Avants, et al., 1995; although see Robbins, et al., 1999; Back, et al., 2005). Previous studies have also reported larger physiological responses but not subjective stress responses to a social stressor in healthy women versus men (Stroud, et al., 2000; Stroud, et al., 2002).

There is ample literature indicating that the stress experienced by cocaine-dependent individuals (intrapersonal, interpersonal, and environmental) contributes to drug use or relapse. In the current study, it is interesting to note that the positive correlation between subjective feelings of stress and cocaine craving are found in both men and women in response to cocaine-related cues, but only for the women in response to the Trier. Therefore, subjective stress and cocaine craving may not be as highly associated for cocaine-dependent men as for cocaine-dependent women. This is further support for the hypothesis that cocaine-dependent women may be more sensitive to interpersonal triggers to cocaine use than are cocaine-dependent men.

HPA-axis functioning is disrupted after prolonged exposure to cocaine, a phenomenon which has been speculated to contribute to continued cocaine use as well as relapse after prolonged abstinence. As in previous studies (Sinha, et al., 1999; Sinha, et al., 2000; Sinha, et al., 2003; Sinha, et al., 2007), the current sample of cocaine-dependent individuals had higher cortisol levels compared to a matched control group and cortisol was elevated in response to cocaine-related cues. Interestingly, although cocaine-dependent women experienced high levels of stress associated with cocaine craving, their neuroendocrine responses were not as robust. Cocaine-dependent females demonstrated a blunted cortisol response to both the TRIER and cocaine-related cues and a blunted ACTH response to the cocaine-related cues when compared to cocaine-dependent males and healthy controls. These findings suggest a more pronounced HPA axis dysfunction in this group. This is consistent with other studies of HPA axis function in individuals with substance use disorders in demonstrating greater dysregulation among women as compared men (Gianoulakis, et al., 2003; Brady, Waldrop, et al., 2006; Back, et al., 2008) (Fox, et al., 2006). In the largest such study available, ACTH and cortisol were measured across respondents in three age groups and at four different levels of alcohol use, ranging from

light users to alcohol-dependent patients in treatment (Gianoulakis, et al., 2003). In every age group, women had lower baseline plasma ACTH than did men. The inverse relationship between alcohol use severity and ACTH was greater in magnitude among women than among men in two of the three age groups (30–44 years and 45–60 years). Cortisol levels did not differ by gender in participants at 30–60 years of age, however, women in the 18- to 29-year-old group had higher cortisol levels than did their male counterparts. The authors hypothesized that female adrenal cortex, compared to that of males, could be more sensitive to ACTH.

A related study examined HPA axis response to a physiological stressor in adults with alcohol dependence, PTSD, or both (Brady, Back, et al., 2006). In that study, women had lower ACTH than did men at all assessment points. In addition, the ACTH response of women with alcohol dependence or PTSD was blunted relative to that of men from the same diagnostic groups. In the same study, women had higher cortisol levels at baseline, but did not differ from men at other time points (Brady, Back, et al., 2006).

In a recent study by Fox and colleagues (Fox, et al., 2006), lower ACTH and cortisol responses were seen in cocaine-dependent women versus men. These findings are consistent in part with those of the present study. Fox et al. (2006) found gender effects in HPA axis responses to both the drug cue and the stressor tasks. The present study also found that cocaine-dependent women were the least likely to have a positive cortisol response to the stressor (Trier), but in contrast to Fox et al. (2006) there were no gender differences on HPA axis responses to the cue.

The results of this study confirm and extend findings reported in the literature concerning possible modest gender differences in factors motivating cocaine use (McKay, et al., 1996; Waldrop, Back, Verduin, et al., 2007), greater HPA axis dysregulation in drug-dependent women as compared to men (Gianoulakis, et al., 2003; Brady, Waldrop, et al., 2006; Back, et al., 2008). The enhanced HPA-axis dysfunction and the more pronounced subjective reaction of cocaine-dependent women to a social stressor in the current study are relevant to the development of gender-specific treatment strategies. Given that cocaine-dependent women often acknowledge using cocaine in response to social and emotional stressors (Waldrop, Back, Brady, et al., 2007), they are likely to be receptive to treatments that could help them to negotiate relationships and modify maladaptive responses to stressors.

Study limitations include the small sample size and baseline group differences on education and employment. Also, we were not able to control for menstrual phase due to scheduling difficulties associated with testing a community-dwelling sample of drug users. In spite of these limitations, there were intriguing differences in response to a social stressor and cocaine cues between cocaine-dependent men and women which have potential implications for treatment.

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Figure 1.

Subjective Reactivity to Trier Stress Task and Cocaine Cues in Cocaine-dependent Subjects: Peak Change from Baseline. A) While both genders had a greater craving response to the cues than the Trier (with women having greater overall craving response), the differential response to the tasks was greater in men than in women ($p=0.04$). B) The change in subjective stress response to the Trier was greater than the response to cocaine cues in all subjects ($p=0.0002$) and females reported a higher (though statistically insignificant) stress response to the Trier than did males.

Figure 2.

Correlations between Subjective Stress and Craving. A significant correlation was found between peak stress and peak craving in both females ($r_s = 0.59$, $p = 0.0019$; A) and males ($r_s = 0.39$, $p = 0.04$; B) in response to cocaine cues. During the Trier Stress Task, a significant correlation was found for females ($r_s = 0.65$, $p = 0.0015$; C), but not males ($r_s = 0.10$, $p = 0.68$; D).

Figure 3.

ACTH Response to Cocaine Cues. Group means of ACTH levels over time indicate that female cocaine-dependent subjects had a more blunted HPA response to the cocaine cues than did the other three groups ($p=0.02$).

Figure 4.

ACTH Response to Cocaine Cues: Male vs. Female. Cocaine- and control-groups were collapsed to show the different time courses of ACTH responses to cocaine cues; the interaction was significant even after controlling for baseline ($p=0.01$).

Figure 5.

Cortisol Response to Trier Stress Task. Group means of cortisol levels over time demonstrate that cocaine-dependent females display blunted HPA response (OR=0.84, 95% CI=[0.02, 1.01]) to a social stressor as compared to cocaine-dependent males and healthy control subjects.

Figure 6.

Cortisol Response to Cocaine Cues. Group means of cortisol levels over time indicate that cocaine-dependent subjects had higher cortisol levels than control subjects throughout the test ($p=0.0001$), as well as a higher likelihood of responding to the cocaine cues.

Table 1

Demographic Characteristics of Participant

Subject Variable	Control Males (n=23)	Control Females (n=24)	Cocaine Dependent Males (n=28)	Cocaine Dependent Females (n=25)	p value
Age, mean (SD)	31.7 (10.3)	39.8 (11.5)	38.0 (11.2)	39.0 (10.4)	NS
Education, % Some College	86	87	67	40	0.001
Employment, % Employed	64	92	59	40	0.001
Race, % Caucasian	70	58	50	50	NS
Marital Status, % Married	14	29	7	12	NS
Smoking Status, % Smokers	65	50	79	80	NS

* NS Indicates not significant ($p \geq 0.05$)