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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.
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1. 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 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 and 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 and 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 and 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 and 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 et al., 2007b). 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 and 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 et al., 2007b). In laboratory settings, cocaine cues have been shown to provoke craving, anxiety, and cortisol release in cocaine users (Sinha et al., 2000, 2003; Coffey et al., 2002); 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.

2. Methods

2.1. 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 1 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).

Table 1 Demographic characteristics of participants.

Subject variable	Control males ($n = 23$)	Control females ($n = 24$)	Cocaine-dependent males ($n = 28$)	Cocaine-dependent females ($n = 25$)	p value
Age, mean (S.D.)	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 ($p \geq 0.05$).