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Reactivity to Laboratory Stress Provocation Predicts Relapse to Cocaine

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Abstract

Background—Cocaine dependence is a chronic relapsing disorder characterized by periods of abstinence and high rates of return to drug using behavior. Elevated levels of stress have been associated with relapse to cocaine; however, the nature of this association is not well understood.

Methods—The relationship between reactivity to three human laboratory provocations and relapse to cocaine was investigated. Participants were 53 cocaine-dependent individuals who were admitted for a 2-day inpatient stay during which a psychosocial provocation (i.e., the Trier Social Stress Task), a pharmacological provocation (i.e., administration of 1 µg/kg corticotrophin releasing hormone; CRH), and a drug cue exposure paradigm were completed. Adrenocorticotrophic hormone (ACTH), cortisol, heart rate, and subjective cocaine craving and stress were assessed at baseline and at multiple time points post-task. Participants' cocaine use was monitored for approximately one month following testing.

Results—The majority (72.3%) of participants relapsed to cocaine during the follow-up period. In response to the CRH and drug cue exposure, elevated subjective craving and stress were significant predictors of cocaine use during follow-up. In response to the Trier, attenuated neuroendocrine responses were significant predictors of cocaine use.

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Contributors

Dr. Brady designed the study and wrote the protocol. Drs. McRae and I coordinated the study implementation. Drs. Spratt, Hartwell, and Price assisted with the literature searches and manuscript revisions. Drs. DeSantis, Baker, Saladin, and Moran Santa-Maria and Ms. Simpson managed the analyses and compilation of the figures. Dr. Kreek managed the neuroendocrine assays. I wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

No authors have any conflict of interest to disclose.

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Conclusions—The findings provide further evidence of the ability of laboratory paradigms to predict relapse. The observed associations between stress reactivity and subsequent cocaine use highlight the clinical importance of the findings. Predictors of relapse may vary based on the type of provocation utilized. Interventions aimed at normalizing stress response, as measured using laboratory paradigms, may prove useful in relapse prevention.

Keywords

stress; craving; cocaine; ACTH; cortisol; stress reactivity

1. Introduction

Cocaine dependence is a significant public health problem in the U.S. Recent data from the 2007 National Survey on Drug Use and Health (NSDUH) indicate that, among individuals aged 12 or older, 2.1 million are current cocaine users (SAMHSA, 2008). Furthermore, within the past year almost one million individuals (906,000) are estimated to have initiated cocaine use for the first time (SAMHSA, 2008). Of additional concern is the fact that a significant proportion of cocaine users progress to develop cocaine use disorders (Chen and Anthony, 2004). A recent longitudinal study by Falck and colleagues found that the majority (63%) of crack cocaine users who were followed over 8 years developed cocaine dependence at some time point (Falck, Wang, and Carlson, 2008).

Cocaine dependence is a chronic relapsing disorder characterized by periods of abstinence and high rates of return to drug seeking and drug using behavior (Mendelson and Mello, 1996; O'Brien, Childress, Ehrman, and Robbins, 1998). Relapse rates following treatment for cocaine dependence typically exceed 45% over 6 to 12 months (Hall, Havassy, and Wasserman, 1991; McKay et al., 1998; McKay, Alterman, Rutherford, Cacciola, and McLellan, 1999). A key feature of cocaine dependence and relapse is craving (Childress, McLellan, and O'Brien, 1986; Waldrop et al., 2007), often elicited by drug cues. One study found that elevated levels of craving during treatment predicted poorer treatment response and relapse to cocaine among cocaine-dependent individuals (Kosten, 1992). In a multi-site trial comparing four psychosocial treatments for cocaine dependence ($N = 449$), craving was found to be a significant predictor of subsequent cocaine use in the majority of the treatments (Weiss et al., 2003). Thus, reduction in craving has been proposed an important treatment target and outcome measure (Kosten, 1992).

In addition to craving, stress has also been strongly associated with cocaine use, dependence and relapse (Brady and Sinha, 2005; Kreek and Koob, 1998; Sinha, 2001). Animal studies indicate that exposure to a variety of stressors increases acquisition of cocaine self-administration (Haney, Maccari, Le Moal, Simon, and Piazza, 1995; Kosten, Zhang and Kehoe, 2006; Mantsch et al., 2008; Tidey and Miczek, 1997) and reinstatement of cocaine-seeking behavior after a period of abstinence (Shaham, Erb, and Stewart, 2000). Foot-shock stress and pharmacologic stress have been shown to induce cocaine seeking in rats even after post-stress delays (Erb et al., 2006; Brown and Erb, 2007). Clinical research also demonstrates that psychosocial stress contributes to both drug-seeking behavior and risk of relapse (Brown, Vik, Patterson, Grant, and Schuckit, 1995; Karlsgodt, Lukas, and Elman, 2003).

While both craving and stress appear to be associated with cocaine use and relapse, the nature of these associations is still not well understood. Improved understanding of these associations could significantly aid in the development of more effective interventions and improved treatment outcomes. The goal of this study, therefore, was to prospectively investigate the relationship between reactivity to three laboratory provocations and relapse to cocaine use. Specifically, subjective craving and stress, heart rate and neuroendocrine responses to

psychosocial, pharmacological, and drug cue paradigms among cocaine-dependent individuals were examined as predictors of relapse during the month following testing.

2. Methods

2.1 Participants

Participants were 53 non-treatment seeking, cocaine-dependent individuals (28 men, 25 women). Newspaper and other media advertisements were the primary source of recruitment. Potential participants were first screened by telephone. If eligible, a clinical interview and a history and physical examination were completed. Exclusion criteria included: pregnancy or nursing, BMI ≥ 35 , major medical problems that could affect the HPA axis (e.g., diabetes, HIV, Addison's or Cushing's disease), comorbid psychiatric conditions that could affect HPA functioning (e.g., major depressive disorder, bipolar affective disorders, post-traumatic stress disorder, psychotic disorder), synthetic glucocorticoid or exogenous steroid therapy within one month of testing, or DSM-IV criteria for substance dependence (except caffeine, nicotine, marijuana, or alcohol) within the past 60 days. Individuals who meet criteria for abuse or dependence of other substances had to identify cocaine as their primary drug of choice.

2.2 Substance Use Assessments

The Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, and Williams, 1994) assessed current cocaine dependence and other Axis I psychiatric disorders. The Time-line Follow-Back (Sobell and Sobell, 1992) assessed cocaine use (dollar amount) during the month prior to and after the study.

Participants were informed that the study aimed to investigate the relationship between cocaine dependence, stress reactivity and gender. Participants were informed about all study procedures, including the laboratory stress tasks. IRB-approved written informed consent was obtained before any study procedures occurred. Eligible participants were scheduled for a two-night consecutive hospital stay at the Medical University of South Carolina's (MUSC) General Clinical Research Center (GCRC) following the initial assessment.

2.3 Laboratory Procedures

At least two days of abstinence from alcohol and other substances (except caffeine and nicotine) was required prior to admission to the GCRC. Abstinence was assessed by self-report, breathalyzer (AlcoSensor III, Intoximeters, Inc.) and urine drug screen (Roche Diagnostics). Participants were admitted to the GCRC at approximately 2000h the evening prior to testing to allow for the control of extraneous variables (e.g., sleep, nicotine and caffeine intake, nutrition) that could potentially affect reactivity. Cigarette smokers were provided with a nicotine patch upon admission. Twenty-four hour nicotine replacement therapy was maintained throughout the hospital stay (≥ 20 cigarettes/day = 21 mg; 10-19 cigarettes/day = 14 mg patch; 5-9 cigarettes/day = 7 mg patch).

Participants completed three laboratory stress tasks during the two days of testing in the GCRC: the Trier, CRH administration, and cocaine cue exposure. A standard breakfast was provided at 0830h on both mornings prior to testing. Sedentary activities, such as reading, were then allowed until testing began. At 1150h an indwelling intravenous catheter was inserted in the non-dominant forearm. A standard lunch was provided at 1200h. After lunch, participants were connected to a monitor for intermittent blood pressure and heart rate readings. A 30-minute acclimation period followed the placement of the monitors. The Trier and cue exposure were administered in counterbalanced order at 1400h on either the first or second day of testing.

For the Trier, participants delivered a 5-minute impromptu speech before an audience of 3 research staff members unknown to the participant. Immediately after the speech, participants completed serial subtractions out loud for an additional 5 minutes before the same audience. Paper and writing instruments were prohibited (except during the first 5 minutes when participants prepared to give the speech). Audience members were trained to withhold any verbal or non-verbal reinforcement (e.g., smiling) during the Trier. The Trier was chosen because it has been well-established as a psychosocial stress task that reliably provokes stress (Kirschbaum, Pirke, & Hellhammer, 1993; Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004; Dickerson and Kemeny 2004). For the cue exposure paradigm, participants inspected and handled cocaine-related paraphernalia for 5 minutes and then viewed a 10-minute video of people engaging in cocaine use and related activities. At 1700h on the first day of testing, ovine CRH 1 μ g/kg (Ferring Pharmaceuticals, St. Prex, Switzerland) was administered over 1 minute via IV catheter to directly stimulate the HPA axis. This dose was chosen based on previous research demonstrating HPA-axis stimulation with this amount of CRH (Contoreggi et al., 2003). For each of the 3 stress provocations, subjective craving and stress, heart rate (HR), and blood samples were obtained immediately prior, immediately after, and at multiple time points post-task (5, 15, 30, and 60 minutes). To assess subjective craving and stress, a visual analog scale anchored with adjective modifiers (from 0 = “not at all” to 10 = “extremely”) derived from the Within Session Rating Scale was used (Childress, McLellan, and O’Brien, 1986). Using the Likert scale, participants responded to questions, such as, “How stressed out do you feel right now?” and “How much do you crave cocaine right now?” HR was measured via three electrodes along the participants’ collar bone, bicep, and ribcage.

2.4 Neuroendocrine Assays

Blood samples were collected by GCRC staff in EDTA-prepared tubes and immediately iced. Samples were centrifuged under refrigeration and the serum was frozen at -70°C until assayed. Rockefeller University personnel performed the assays. ACTH was assayed in duplicate using Allegro HS ACTH system that has an intra-assay c.r. of 6% with a sensitivity of 1pg/ml (Nichols Institute Diagnostics). For cortisol, Roche Diagnostics Elecsys 2010 immunoassay analyzer and kits based on electrochemiluminescence competitive immunoassay with a functional sensitivity (lowest reportable concentration) of 8.0 nmol/L (.29 μ g/dL) and intra-assay reproducibility (coefficient of variation, CV) of less than 2% were used.

2.5 Statistical Methods

Relapse was defined as any cocaine use during follow-up. The following measures of cocaine use were assessed for approximately one month (34 days) following the study: 1) an overall indicator of *any* cocaine use, 2) the *average amount* of cocaine used (in dollar amount) per using day, and 3) *time (i.e., number of days) to first use* of cocaine. These three variables served as the dependent variables in separate analyses.

The cues were assessed for potency using Wilcoxon signed-rank tests on the difference between maximum responses versus baseline measure. Mean change from baseline in ACTH, cortisol, and HR served as independent variables in the prediction of follow-up cocaine use. Similarly, median change from baseline was calculated for stress and craving, and a median split (high vs. low) of these measures (0/1) was used as the independent variable. To assess the effects of mean changes in these measures on follow-up use, linear, logistic or proportional hazards regressions were employed, depending on the type of outcome. The effect of neuroendocrine, biological and subjective measures on follow-up cocaine use (a binary outcome) was analyzed using logistic regression. The effect of neuroendocrine, biological and subjective measures on the amount used per using day (a continuous outcome) was analyzed using linear regression. The effect of neuroendocrine, biological and subjective measures on time to first use was analyzed using a proportional hazards regression. This analysis is commonly used to model

time to an event as it accounts for censored or unobserved events (usually because the study ends before the event occurs). For logistic and linear regression, Wald p -values were reported. For time to event analyses, hazard ratios (HR) and corresponding 95% confidence intervals were reported. For time to relapse analyses, we present medians.

Because previous studies have revealed a strong association of pre-study and post-study cocaine use (Paliwal, Hyman and Sinha, 2008), the analogous measure of use for the month before study entry was adjusted for in each analysis (with the exception of the time to first use analysis). In addition, all analyses adjusted for gender and considered the interaction between gender and the mean change variables of interest. Non-significant interactions were removed from the model.

Not all participants had complete data for each manipulation (e.g., due to mechanical error or patients missing an item on the visual analogue scale). Thus, data reported for the three manipulations ranged from 36-48. Where descriptive statistics are presented, they represent frequencies, medians, or the mean $\pm$ standard deviation. P -values less than 0.05 were considered statistically significant findings and p -values less than 0.10 were considered marginally significant.

3. Results

3.1 Demographic and Cocaine Use Information

Table 1 presents the demographic and cocaine use severity characteristics. Race was self-reported by participants and was collected as part of general demographic information. As can be seen, participants used cocaine significantly less often and in less amounts during the follow-up period as compared to the month prior to study entry. For the frequency of use (i.e., percent days using), the mean reduction from pre to post study participation was 11% ($p = 0.0003$) and for the amount of cocaine used per using day, the mean reduction from pre to post study was \$29.33 ($p = 0.0002$). During the follow-up period, 72.3% of participants reported using cocaine at least once. The median time to first use was 4 days.

3.2 Trier Social Stress Task (Trier)

Craving and stress—In response to the Trier, 73.8% of the sample demonstrated a subjective craving response and 85.7% demonstrated a subjective stress response (i.e., a positive mean change from baseline). Baseline and maximum response values for craving and stress are provided in Table 2.

No significant relationships between subjective responses to the Trier and any cocaine use or severity of cocaine used were revealed. Although craving was not a significant predictor of time to relapse, the direction was as expected [$p = 0.25$, HR (95% CI) = 1.56 (0.73, 3.34)]. Median time to relapse was 1 day in individuals with high craving ($n = 21$) in response to the Trier and 3 days in individuals with low craving ($n = 17$).

Neuroendocrine—ACTH and cortisol responses to the Trier were significant predictors of any cocaine use during follow-up [$p = .01$, OR (95% CI) = 1.91 (1.14, 3.20); $p = .02$, OR (95% CI) = 2.01 (1.11, 3.65), respectively]. In addition, ACTH and cortisol responses to the Trier were significant predictors of time to first use [$p = .03$, HR (95% CI) = 0.98 (0.95, 0.99); $p = .04$, HR (95% CI) = 0.98 (0.96, 0.99), respectively]. Figures 1 and 2 illustrate the estimated probability of relapse based on ACTH and cortisol responses to the Trier. The direction of these effects was such that attenuated ACTH and cortisol responses to the Trier were associated with a significantly greater likelihood of using cocaine during the follow-up period and a significantly shorter latency to first use. Regression analyses demonstrated that ACTH

response was a better predictor than cortisol response of any cocaine use during follow up (with removal of cortisol from full model, AUC = 0.88; with removal of ACTH from full model, AUC = 0.80) and shorter time to relapse (with removal of cortisol from full model $-2(LL_T - LL_F) = 1.20$, 1 df; with removal of ACTH from full model $-2(LL_T - LL_F) = 1.27$, 1 df).

Heart rate—HR response to the Trier was not significantly associated with any indices of cocaine use (i.e., any cocaine use, time to first use, average amount used).

3.3 Corticotropin Releasing Hormone (CRH)

Craving and stress—Over half of the sample demonstrated increased craving (56.3%) and stress (62.5%) in response to CRH. See Table 2 for baseline and maximum response values. CRH-induced stress was a significant predictor of any cocaine use during the follow-up period ($p = .05$) and a marginally significant predictor of average amount used per using day ($p = .06$). Higher mean stress in response to CRH was predictive of shorter time to relapse [$p = 0.04$, HR (95% CI) = 2.18 (1.01, 4.74)]. Median time to relapse was 2 days in those with high stress ($n = 21$) response to CRH and 22 days in those with low stress ($n = 22$) (Log Rank P-Value = 0.03) (see Figure 3).

Higher mean craving in response to CRH was also predictive of shorter time to relapse [$p = 0.02$, HR (95% CI) = 2.41 (1.14, 5.11)]. Median time to relapse was 1 day in those with high craving ($n = 20$) and 19 days in those with low craving ($n = 22$). (Log Rank P-Value = 0.01) (see Figure 3). Regression analyses showed that CRH-induced subjective craving was a better predictor than CRH-induced subjective stress of shorter time to relapse (with removal of stress from full model $-2(LL_T - LL_F) = 1.26$, 1 df; with removal of craving from full model $-2(LL_T - LL_F) = 1.43$, 1 df).

Neuroendocrine—There were no significant relationships between ACTH or cortisol response to CRH administration and indices of cocaine use during follow-up.

Heart rate—High baseline HR was significantly associated with more severe cocaine use during follow-up. An increase in HR response to CRH was associated with less severe cocaine use during follow-up ($p = 0.04$).

3.4 Drug Cue Exposure (Cue)

Craving and stress—In response to the cue exposure paradigm, 69.0% of the sample demonstrated increased craving and 60.0% increased stress. See Table 2 for baseline and maximum response values. Higher mean stress in response to the cue was marginally predictive of shorter time to relapse [$p = 0.06$, HR (95% CI) = 1.95 (0.96, 3.95)]. Median time to relapse was 1 day in those with high stress ($n = 25$) and 12 days in those with low stress ($n = 21$) (Log Rank P-Value = 0.04) (see Figure 4).

Cue-induced craving was a significant predictor of time to first use ($p = 0.02$). Individuals with a higher craving response exhibited a significantly shorter time to first use as compared to those with a lower craving response (median time to first use = 1 day versus 21 days, respectively) (Log Rank P-Value = 0.01). Figure 4 illustrates these findings. The hazard ratio for this effect was 2.38 (95% CI = 1.12, 5.07). Similar to the response to CRH, regression analyses showed that cue-induced subjective craving was a better predictor than cue-induced subjective stress of shorter time to relapse (with removal of stress from full model $-2(LL_T - LL_F) = 0.75$, 1 df; with removal of craving from full model $-2(LL_T - LL_F) = 2.81$, 1 df). It is noteworthy that the majority of high cravers to the drug cue (>50%) relapsed the first day following study termination.

Neuroendocrine—Neither ACTH nor cortisol response to the drug cue exposure were significantly associated with any of the follow-up indices of cocaine use.

Heart rate—HR response to the drug cue exposure was not associated significantly with any of the follow-up indices of use (i.e., any cocaine use, time to first use, average amount used).

4. Discussion

This study prospectively examined the relationship between reactivity to three human laboratory paradigms (psychosocial, pharmacologic, and drug cue exposure) and relapse to cocaine use in cocaine-dependent individuals. Controlling for pre-study cocaine use, the findings from the current study demonstrate that reactivity to laboratory paradigms is related to subsequent cocaine use.

A strength of the study is the measurement of multiple indices of response to three different paradigms. All three challenges evoked subjective stress and craving in the majority of cocaine-dependent participants. As would be expected, the psychosocial stressor, which involves uncontrollability and social evaluative threat, evoking a limbic system response (Dickerson and Kemeny, 2004), elicited the highest levels of subjective stress and HR; the pharmacologic stressor, which directly stimulated the HPA axis, evoked the highest levels of ACTH and cortisol response; and the cocaine cue exposure paradigm elicited the highest levels of subjective craving (see Table 2). Notably, this study is among the first to examine the association between response to a pharmacologic provocation (i.e., administration of CRH) and propensity to relapse in cocaine-dependent individuals.

Consistent with previous research in cocaine-dependent individuals (Paliwal, Hyman and Sinha, 2008; Sinha et al., 2006), the majority (72.3%) of participants reported at least one relapse to cocaine during the follow-up period. In spite of the fact that this was a laboratory study and subjects did not receive a treatment intervention, the amount and frequency of cocaine use decreased significantly from pre to post study. As has been found with other studies, exposure to cocaine or drug cues in a laboratory setting did not appear to increase subsequent relapse rates or severity of use (Ehrman et al., 1998; DeSantis, Bandyopadhyay, Back, & Brady, in press). While a robust literature documents that exposure to conditioned drug cues in the environment is relapse-promoting for many individuals with drug use disorders (Childress, 1988; O'Brien, 1998; Volkow, 2006), research studies employing cue exposure paradigms in laboratory settings have not been found to promote increased rates of drug use or relapse. This is likely due to numerous factors that substantially differentiate exposure to drug cues in a laboratory as opposed to in the natural environment, such as, subject selection bias (e.g., individuals who are willing to enroll in a research study may be more motivated to reduce/abstain from using drugs), the fact that inpatient and outpatient laboratory settings ensure that patients are in a safe environment, increased contact with health care providers, and the fact that subjects are not allowed to leave laboratory testing in a state of heightened craving.

Predictors of cocaine use in the month following the laboratory testing varied according to the provocation paradigm employed. In response to the psychosocial stressor (i.e., the Trier), neuroendocrine responses (ACTH in particular) best predicted cocaine use. While the relationship between craving in response to the Trier and cocaine use during the follow-up period was in the expected direction (i.e., increases in craving were positively associated with increases in cocaine use during follow-up), statistical significance was not reached. However, attenuated levels of ACTH and cortisol were associated with a significantly increased likelihood of use and a shorter time to relapse. Thus, individuals who demonstrated a more robust HPA axis response to the challenge demonstrated decreased susceptibility to cocaine use. This has been shown in several previous studies with alcohol-dependent individuals.

Junghanns and colleagues (2003) examined responses to the Trier among 36 alcohol-dependent individuals and 15 controls. Blunted ACTH and cortisol responses were observed among the alcohol-dependent subjects who relapsed to alcohol during a six-week follow-up period. Our group reported similar findings in a study of 63 alcohol-dependent individuals in which attenuated ACTH response to a laboratory stress challenge (i.e., cold pressor task) was associated with increased alcohol use during a one-month follow-up period (Brady et al., 2006). The decrease in HPA axis response to provocation in alcohol dependence has been hypothesized to have important implications for treatment. While some studies have demonstrated that the decreased neuroendocrine response to stress may be a function of alcohol intake (Gianoulakis et al., 2003), abnormalities in stress response may also serve as a risk factor for the development of alcohol dependence and/or relapse. Dai and colleagues (2002) found that individuals at high risk for alcohol dependence based on family history had lower baseline and stress-induced ACTH as compared to individuals at low risk for alcohol dependence. As such, it may be that abnormalities in the response of the HPA axis are associated with both vulnerability to the development of alcohol dependence and relapse.

Sinha and colleagues (2006) studied subjective and HPA axis responses in cocaine-dependent individuals ($N=49$) following exposure to stressful and drug-cue imagery tasks after 2-4 weeks of abstinence. As in the current study, the subjective and HPA axis responses to the stress task were predictive of time to relapse and amount of cocaine use during a 90-day follow-up period. However, the Sinha et al. investigative team found that the cortisol response to stress imagery was positively associated with the amount of cocaine use during follow-up, whereas the present study found a robust relationship between blunted ACTH and cortisol response to the Trier and multiple indices of cocaine use. The discrepancies in findings may be related to differences in sample characteristics as participants in the current study had only 3-5 days of abstinence prior to testing and participants in the Sinha study had been abstinent for 2-4 weeks at the time of testing. Such a blunting of ACTH and cortisol response to the stressor of cocaine itself has been well-documented in rodent models (Mantsch et al., 2000; Zhou et al., 1996). There were also differences in the stress task used that might explain the differences between study findings. Of importance, both studies find meaningful relationships between neuroendocrine and subjective response to stressful stimuli in a laboratory setting and subsequent cocaine use, indicating that these paradigms may be useful in understanding the mechanisms involved in stress-induced relapse. The present study suggests that the findings in alcohol dependence linking blunting of the HPA axis stress response to relapse may be extended to individuals with cocaine dependence.

In response to the pharmacologic stress provocation (i.e., CRH), subjective stress and craving, in particular, were significant predictors of relapse. CRH is thought to play a critical role in the emotional dysregulation associated with cocaine dependence and relapse through actions on both the HPA axis and brain stress systems in the extended amygdala (Koob and Kreek, 2007). Animal models demonstrate that escalation in cocaine intake produces activation of CRH within the prefrontal limbic circuitry which is essential to determining the salience of environmental stressors, suggesting that CRH may play a role in stress-induced relapse (Herman and Cullinan, 1997). A number of the brain sites hypothesized to be important for the behavioral effects of CRH are closely linked to norepinephrine systems including the locus coeruleus, bed nucleus of the stria terminalis and the central nucleus of the amygdala (Valentino, Foote and Page, 1993; Van Bockstaele, Colago and Valentino, 1998). Of interest, there is data suggesting that norepinephrine in these areas stimulates the release of CRH which would imply a powerful “feed-forward” system (Kreek and Koob, 1998) that might be a mechanism for sensitization of the stress response. A publication comparing the acute response to CRH in a control group versus a cocaine-dependent group assessed in this study found a more robust subjective stress response to CRH in cocaine-dependent individuals as compared to the control group, suggesting sensitization of stress response (Brady et al., 2009). This is of

particular interest considering the finding in this study that the level of reported stress and craving following CRH administration was positively associated with the risk of any cocaine use, the severity of use (i.e., amount use per using day) and a shorter latency to first use. These findings suggest that the subjective response to CRH in cocaine-dependent individuals may have a clinically meaningful relationship to relapse.

Higher baseline HR was associated with more severe cocaine use during follow-up. In the study comparing this cocaine-dependent group to a matched control group (Brady et al, 2009), higher heart rate was found in cocaine-dependent women as compared to a control group. Increased baseline heart rate may be indicative of noradrenergic dysfunction and associated with the CRH sensitization, discussed above, in cocaine-dependent individuals. Other investigators have reported dysregulation in noradrenergic function associated with vulnerability to panic attacks during early discontinuation of cocaine use in cocaine-dependent individuals (McDougle et al., 1994). Findings from this study suggest that noradrenergic dysfunction in cocaine-dependent individuals may also be associated with increased cocaine use. The association between higher heart rate response to CRH and less cocaine use during follow-up is likely explained by a ceiling effect, as it is more difficult to detect a HR response in individuals with a high baseline HR. The ACTH and cortisol response to CRH was extremely robust in all study groups, was much higher than the response to either the Trier or cocaine cue, and is likely to represent maximal HPA axis stimulation in the study subjects. As such, the lack of relationship between either the ACTH or cortisol response to CRH and relapse may also be a ceiling effect.

Finally, a drug cue paradigm was explored. Cue-induced stress and craving, in particular, were significantly associated with time to relapse. In contrast, Sinha and colleagues (2006) found no relationship between cocaine cue-induced subjective and HPA axis changes and relapse. These differences may be due to the different laboratory provocations employed (i.e., the current study used paraphernalia and a video drug cue, Sinha et al. used personalized imagery tasks), which have been shown to produce different responses in other studies of addicted individuals (Yu et al., 2007). Previous studies have found that craving is predictive of use during treatment (Flannery et al., 2003; Weiss et al., 2003) and that craving at entry to inpatient treatment is predictive of use following discharge (Paliwal, Hyman and Sinha, 2008). Brain imaging studies demonstrate that cocaine cue-induced craving is associated with increases in dopamine in the dorsal striatum (Volkow et al., 2006) and cue-induced activation is associated with relapse (Kosten et al., 2006). Thus, drug cue craving paradigms might be used to explore interventions designed to decrease relapse to cocaine use.

4.1 Limitations

The current study has several limitations. Although the sample size is comparable to prior investigations, replication with a larger sample will be important to ascertain generalizability. The follow-up period was relatively short and future research may benefit from a longer follow-up assessment phase. It was not feasible to standardize menstrual cycle phase for women, which can impact the HPA axis (Kajantie and Phillips, 2006). Only one dose of CRH was tested in the current study. It may be useful to test higher and lower doses in future research (Schluger et al., 2003). Finally, a no-stress control condition was not employed. Despite these limitations, the current study builds on earlier investigations assessing the relationship between stress- and cue-reactivity and relapse. The study is strengthened by the assessment of a triad of indices of stress reactivity (subjective, physiologic, and neuroendocrine), a well-controlled research environment (the GCRC), and the use of three different stress paradigms.

4.2 Conclusions

In summary, the findings provide further evidence of the ability of laboratory paradigms to predict relapse and, therefore, lend support to the ecological validity of laboratory paradigms

designed to induce craving or stress. The clinical importance of stress and cue reactivity is highlighted in this study by the observed associations between response to provocations in the lab setting and cocaine use outside of the lab setting. Predictors of relapse varied based on the provocation employed. As such, these varying tasks might be used in conjunction to explore the relationship between different relapse precipitants. Further investigations are needed to replicate the current findings and to identify behavioral, pharmacologic, neurofeedback or other interventions that may serve to alter reactivity and decrease relapse.

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Figure 1.

The estimated probability of relapse based on the mean ACTH percent change from baseline in response to the Trier Social Stress Task. The circles represent the mean percent change in ACTH from baseline for relapsers, while the squares represent the mean percent change in ACTH for abstainers. The area within the dashed lines represents the 95% confidence band.

Figure 2.

The estimated probability of relapse based on the mean Cortisol percent change from baseline in response to the Trier Social Stress Task. The circles represent the mean percent change in Cortisol from baseline for relapsers, while the squares represent the mean percent change in Cortisol for abstainers. The area within the dashed lines represents the 95% confidence band.

A) CRH-induced Stress

B) CRH-induced Craving

Figure 3.

Kaplan Meier Survival plot of relapse probability in response to CRH provocation. **A)** CRH-induced stress. **B)** CRH-induced craving.

A) Cue-induced Stress **B) Cue-induced Craving**

Figure 4. Kaplan Meier Survival plot of relapse probability in response to the drug cue exposure paradigm. **A)** Cue-induced stress. **B)** Cue-induced craving.

Table 1
Demographic and Cocaine Use Severity Characteristics (N = 53)

Variable	M(SD)
Age, M(SD)	38.5(10.7)
Gender, % Male	52.8
Education, % Some College	53.9
Employment, % Employed	50.0
Race, % Caucasian ^Δ	51.0
Marital Status, % Married	9.6
Smoking Status, % Smokers	79.3
Average years of cocaine use, M(SD)	13.6(9.3)
Percent days using PRE study, M(SD) [†]	35.1(25.5)
Average amount used per day PRE study, M(SD) ^{††}	65.2(51.3)
Percent days using POST study, M(SD) [‡]	22.4(26.4)
Average amount used per day POST study, M(SD) ^{‡‡}	36.1(34.8)

Note. M(SD) = Mean(Standard Deviation).

^Δ Caucasian group contains two Pacific Islanders. Subjects not included in this category are African American.

[†] Percent days using cocaine during the month prior to study entry.

^{††} Average dollar amount of cocaine used per using day during the month prior to study entry.

[‡] Percent days using cocaine during the month after completion of the laboratory stress tasks.

^{‡‡} Average dollar amount of cocaine used per using day during the month after completion of the laboratory stress tasks.

Table 2
Baseline and Maximum Response to Laboratory Stress Provocation

Variable	Baseline <i>M</i> (SD)	Maximum Response <i>M</i> (SD)
Trier Social Stress Task		
[†] Subjective Craving	2.61 (2.97)	4.07 (3.56)
[†] Subjective Stress	1.73 (2.38)	5.24 (3.21)
^{†*} ACTH	19.05 (5.80)	23.91 (7.97)
^{†*} Cortisol	10.95 (9.54)	12.76 (9.52)
[†] Heart Rate	71.55 (11.81)	79.17 (14.99)
Corticotropin Releasing Hormone (CRH)		
^{†*} Subjective Craving	2.21 (2.95)	2.90 (3.56)
^{†*} Subjective Stress	1.44 (2.16)	2.71 (2.90)
[†] ACTH	17.28 (6.25)	45.38 (27.89)
[†] Cortisol	8.69 (4.76)	21.63 (8.42)
^{†*} Heart Rate	67.03 (11.25)	76.83 (11.24)
Drug Cue Exposure		
^{†*} Subjective Craving	2.44 (2.73)	5.25 (3.35)
^{†*} Subjective Stress	2.19 (2.54)	3.96 (3.25)
[†] ACTH	17.78 (5.74)	22.38 (7.07)
[†] Cortisol	10.07 (5.04)	12.75 (5.17)
[†] Heart Rate	72.14 (9.85)	78.85 (12.84)

* Significant predictors of cocaine use during follow-up

[†] Significant difference between baseline and maximum response, $p < .0001$.