Response to Corticotropin-Releasing Hormone Infusion in Cocaine-Dependent Individuals

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Context: Corticotropin-releasing hormone (CRH), through the hypothalamic pituitary adrenal axis and other brain stress systems, is involved in the emotional dysregulation associated with cocaine dependence. Little is known about the response of cocaine-dependent individuals to CRH administration.

Objective: The primary objective was to examine the hypothalamic-pituitary-adrenal axis and the subjective and physiologic response to CRH in cocaine-dependent individuals and controls.

Design: A case-control study.

Setting: Subjects were admitted to a General Clinical Research Center for testing and abstinence was verified with a urine drug screening.

Participants: Participants were male controls (n=23), female controls (n=24), cocaine-dependent men (n=28), and cocaine-dependent women (n=25). Individuals with dependence on other substances (except caffeine or nicotine) or with major depression, posttraumatic stress disorder, bipolar disorder, or psychotic or eating disorders were excluded.

Intervention: Subjects received 1 µg/kg of CRH intravenously.

Main Outcome Measures: Primary outcomes included plasma corticotropin levels, cortisol levels, and heart rate and subjective measurements.

Results: Cocaine-dependent individuals exhibited higher stress (P<.001) and craving for CRH compared with controls. A positive correlation (r_s=0.51; P<.001) between stress and craving was found in cocaine-dependent subjects. Intravenous CRH elevated heart rates in all groups; however, cocaine-dependent women demonstrated a significantly higher heart rate at all time points (P=.05). Women had higher cortisol responses to CRH (P=.03). No effect of cocaine status was observed. The corticotropin response to CRH was independent of sex and cocaine dependence. Cortisol and corticotropin were positively correlated in the controls and cocaine-dependent men, but not in cocaine-dependent women (r_s=0.199; P=.4).

Conclusions: There is an increased subjective and heart rate response to CRH and a relationship between stress and craving in cocaine-dependent individuals. The lack of difference in hypothalamic pituitary adrenal axis response between the cocaine-dependent and control groups suggests that the heart rate and subjective responses in the cocaine group may be mediated by sensitization of nonhypothalamic stress-responsive CRH systems.

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It has been postulated that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, brain reward, and corticotropin-releasing hormone (CRH)–involved stress systems is a critical part of the allostatic changes associated with the transition from drug use to dependence as the organism attempts to maintain reward function stability through changes in reward and stress system neurocircuitry. The corticotropin-releasing hormone 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. The HPA axis is activated during binge cocaine use and contributes to the activation of the brain reward systems. Chronic cocaine use is associated with attenuation of the HPA response in animal models and in the clinical laboratory setting. Interestingly, there are CRH receptors within the processive lim-
bic circuitry that are essential in determining the salience of environmental stressors, suggesting that CRH may play a role in stress-induced relapse. Animal models demonstrate that escalation in cocaine intake produces activation of CRH in the extended amygdala that is particularly evident during withdrawal and may play a prominent role in the maintenance of cocaine self-administration. In animal models of relapse, administration of CRH or exposure to a variety of stressors facilitates reinstatement of self-administration of drugs of abuse, and this effect is blocked by CRH antagonists.

There are important sex differences in stress response and HPA axis function that may play a role in sex differences in relapse. Women consume cocaine using more addictive routes and progress from occasional drug use to dependence faster than men. In addition, cocaine-dependent women have more affective and anxiety disorders compared with men, and these comorbidities are associated with HPA axis and stress response dysregulation. The brain circuitry (including the amygdala and hippocampus) underlying cognitive processing of stress is sexually dimorphic in both humans and laboratory animals. In addition to circuitry differences, hormonal regulation contributes to sexual dimorphism in stress responses with both estrogen and progesterone acting as potent modulators of HPA axis stress regulation.

The primary focus of the present study was to investigate the role of the HPA axis in the physiologic and subjective response to a CRH infusion in cocaine-dependent men and women compared with a matched control group. Because this study is a part of a larger grant focused on sex differences in substance use disorders, sex differences in response were studied.

### METHODS

**SUBJECTS**

The sample consisted of 100 participants. Demographic characteristics are presented in the Table. Subjects were recruited primarily via media advertisements over a 48-month period. Data for the present study were drawn from a larger study on sex differences in stress and cue reactivity among cocaine-dependent and control participants. Written informed consent was obtained before study assessments were administered. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and received institutional review board approval. General exclusion criteria included (1) current major depression and posttraumatic stress disorder; (2) a history of or current medical conditions that might interfere with safe conduct of the study or affect HPA activity; (3) a history of or current psychotic, eating, or bipolar affective disorders; (4) synthetic glucocorticoid or exogenous steroid therapy within 1 month of testing; (5) current benzodiazepine, antipsychotic, β-blocker, and other medication use that might interfere with HPA axis activity or psychophysiological measurement; (6) pregnancy, nursing, or ineffective means of birth control; (7) a body mass index (calculated as weight in kilograms divided by height in meters squared) of 35 or more; or (8) DSM-IV criteria for substance dependence except caffeine, nicotine, or marijuana within the past 60 days.

**ASSESSMENT**

Subjects meeting preliminary screening criteria were evaluated for study eligibility with the Structured Clinical Interview for DSM-IV, which permits accurate diagnosis of lifetime and current psychiatric disorders using DSM-IV criteria. Substance use in the 90 days prior to study enrollment and throughout the study period was assessed using the Time-Line Follow-Back. A medical history and physical examination, including electrocardiogram, were completed to assess medical exclusions. Menstrual history was obtained for female subjects. While we attempted to schedule all female subjects for testing during the luteal phase of the menstrual cycle, this was not feasible. Delaying the scheduling of testing, particularly for cocaine-dependent women, led to a drop-out rate that made it impossible to complete the study in a reasonable time frame. Following baseline assessments, participants were scheduled to complete the laboratory procedure.

**CRH ADMINISTRATION**

All laboratory procedures were conducted at the General Clinical Research Center of the Medical University of South Carolina. Subjects were admitted to an inpatient hospital unit at approximately 10:00 pm prior to testing to control extraneous variables that could affect stress reactivity (eg, nutrition, caffeine intake, sleep, nicotine use). Subjects were required to abstain from alcohol or other substances (except nicotine and caffeine) for a minimum of 3 days prior to testing. Abstinence was assessed using self-report, urine drug screening (Roche Diagnostics, Indianapolis, Indiana), and breathalyzer tests (AlcoSensor III; Intoximeters Inc, St Louis, Missouri).
Missouri). Subjects dependent on nicotine (n=66) were provided with a nicotine patch.

On the morning following admission, subjects were provided a standard breakfast at 8:30 AM. They were allowed to engage in sedentary activities on the unit (eg, reading magazines, watching television) until testing. At 11:50 AM, an indwelling intravenous catheter was inserted in the forearm of the nondominant hand. At 12:00 PM, subjects were given a standard lunch. Following lunch, the participants were connected to electrodes for heart rate and to an intermittently inflatable blood pressure cuff. Between 1:40 and 2:00 PM, the subjects completed additional testing procedures. Specifically, subjects were exposed either to cocaine-related paraphernalia for a period of approximately 10 minutes or they completed the Trier Social Stress Task. Data from these tasks will be presented in a separate article. Neuroendocrine, physiologic, and subjective outcomes returned to baseline levels within 20 minutes of the Trier. Subjects were allowed a rest period prior to CRH administration.

Beginning at 4:40 PM, 2 baseline assessments of subjective, heart rate, and neuroendocrine parameters were obtained 10 minutes apart to provide a stable baseline index for challenge response comparisons. Presession subjective scales included the Craving/Distress/Mood Scale, a modification of the Within Session Rating Scale designed to rapidly assess craving and other mood feeling states (including stress) during the test session. This 100-mm visual 10-point Likert scale is anchored with adjectival modifiers (“not at all” to “extremely”). This scale was also used at each of the posttask assessment time points.

At 5:00 PM, CRH (1 µg/kg to a maximum dose of 100 µg [Ferring Pharmaceuticals, St Prex, Switzerland]) was administered via intravenous push over a 1-minute period. Immediately following CRH administration, subjective ratings and heart rate measurements were obtained and blood was collected for neuroendocrine assay (corticotropin and cortisol). Neuroendocrine samples, subjective ratings, and physiologic measurements were further assessed at 5-, 30-, 60-, and 120-minute intervals after administration. 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. The Allegro HS-ACTH system (Nichols Institute Diagnostics, San Clemente, California), which has an intra-assay coefficient of variation of 6% with a sensitivity of 1 pg/mL, was used for corticotropin 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 µg/dl. (to convert to nanomoles per liter, multiply by 27.588) and intra-assay reproducibility of less than 2%. General Clinical Research Center personnel collected all samples, and Rockefeller University personnel performed the assay. The heart rate was recorded via 3 electrodes along the bottom of the participant’s ribcage, bicep, and collar bone.

Following completion of data collection, subjects remained in the hospital overnight and completed additional tasks the following day. The subjects were debriefed and compensated for their participation prior to discharge from the General Clinical Research Center.

### STATISTICAL ANALYSIS

Subjective measures (stress and craving) were summarized by calculating the area under the curve using the trapezoidal rule. Experimental group differences in median area under the curve were conducted using the nonparametric Kruskal-Wallis test.

Physiological (heart rate) and neuroendocrine (corticotropin and cortisol) outcomes were analyzed using covariance pattern models to account for repeated longitudinal measurements taken for each subject. To account for nonconstant variability among the groups, the estimated covariance matrix was allowed to vary by sex or cocaine use status, as appropriate. These analyses were performed via the mixed procedure (SAS/STAT software, Version 9.1.3 of the SAS System for Windows; SAS Institute Inc, Cary, North Carolina). Nonnormality of the outcomes and residuals was addressed via log transformations. Prior to the repeated-measures analyses, the effects of sex and cocaine use status on each of the baseline responses were assessed via nonparametric Wilcoxon rank sum tests. Where baseline differences in physiological or neuroendocrine measures were found, the baseline measure was included as a covariate in that model. All longitudinal analyses controlled for smoking status, race, and age.

The peak changes in subjective, physiological, and neuroendocrine outcomes were calculated as the percentage of change in response over baseline: (maximum response – baseline response) / baseline response × 100. The peak change was analyzed using a multivariable linear model and transformations were used where appropriate. In multivariable analysis, the covariates (smoking status, race, and age) were controlled for when possible. Confounding was suspected. For multiple comparisons that were not part of the hypothesis a priori, the Bonferroni correction was used.

To test our hypothesis of HPA dysregulation, we examined the Spearman rank correlation coefficients (r) of peak change in physiological, neuroendocrine, and subjective outcomes by experimental group. Where descriptive statistics are presented, they represent the mean (standard error of the mean). P < .05 was considered significant.

### RESULTS

#### SUBJECT DEMOGRAPHIC AND DESCRIPTIVE DATA

In the Table, subject demographic and descriptive data by cocaine use status and sex are displayed. While there were no significant differences in age, race, or marital or smoking status, there were significant differences in education and employment, with the cocaine group demonstrating significantly lower educational (P < .001) and employment levels (P < .001). Four female controls and 2 cocaine-dependent women met the criteria for social phobia or generalized anxiety disorder. Two cocaine-dependent men and 1 cocaine-dependent woman met the criteria for marijuana dependence.

#### SUBJECTIVE MEASURES

While some of the control subjects reported an increase in subjective stress following CRH administration (12 of 45 subjects), both the number of responders (21 of 48) and the magnitude of the subjective stress response was significantly higher in the cocaine-dependent individuals than in the control group (Figure 1A). This response was significantly more robust in the cocaine group as measured across all time points by the area under the curve (P < .001). There were no sex differences in this response. Cocaine-dependent subjects also experienced cravings after CRH administration while, as would be expected, the control group subjects did not (Figure 1B).
A significant correlation was found between peak stress and peak craving in cocaine-dependent individuals \((r_s=0.511; P<.001)\) (Figure 2).

HEART RATE

Heart rate was increased following CRH administration across all groups \((F_{4,90}=6.37; P<.001)\) (Figure 3A). There was a significant difference in baseline heart rate between men and women \((P<.001)\), with women demonstrating a higher heart rate response to CRH compared with men \((71.5 [9.5] \text{ vs } 64.4 [9.9] \text{ beats per minute})\). As a result, baseline heart rate was included as a covariate in the subsequent analysis. Cocaine-dependent women had significantly higher heart rates over the course of the study compared with the other 3 groups \((F_{1,88}=3.87; P=.05)\) (Figure 3A). A peak change analysis for CRH heart rate responders was conducted. Responders were defined as having a greater than 0% change over the baseline heart rate. There were 87 responders (male controls, \(n=22\); female controls, \(n=19\); cocaine-dependent men, \(n=26\); cocaine-dependent women, \(n=20\)). In a multivariable analysis of responders, cocaine use was an independent marginal predictor of higher heart rate response \((\chi^2=3.66; P=.06)\) (Figure 3B).

CORTICOTROPIN

Corticotropin levels were increased across all groups following CRH administration \((F_{5,91}=2.63; P=.04)\) (Figure 4A). Women exhibited significantly lower baseline corticotropin levels than men \((16.29 [6.19] \text{ pg/mL } \times 0.022 \text{ vs } 20.49 [7.35] \text{ pg/mL}; P=.003)\), so baseline corticotropin level was included as a covariate in subsequent analyses. No group × time or sex × time interactions were found for corticotropin response. The peak change in corticotropin was analyzed using a linear model with a log10 transformation of peak change. A marginally significant cocaine × sex interaction \((\chi^2=3.43; P=.06)\) was found, indicating a greater peak change in corticotropin levels following CRH administration in cocaine-dependent men compared with cocaine-dependent women.

CORTISOL

Cortisol levels were increased in all groups following CRH administration \((F_{5,61}=118.99; P<.001)\) (Figure 4B). A group × time interaction was not observed, indicating that the cortisol response to CRH infusion in cocaine-dependent individuals was similar to that of the control group. A significant sex × time interaction \((F_{5,61}=2.71; P=.03)\) in cortisol response was found, indicating that the time course of the cortisol response differed between men and women. Both cocaine-dependent and control women have a higher cortisol level at all time points following CRH administration compared with men, with elevated levels persisting at the 120-minute time point (Figure 4B). An analysis of peak change in cortisol demonstrated a main effect of sex \((\chi^2=4.97; P=.03)\).

CORTICOTROPIN AND CORTISOL PEAK CHANGE CORRELATIONS

A significant positive correlation was observed between peak change in corticotropin and cortisol in male con-
controls ($r_s=0.797; P<.001$), female controls ($r_s=0.412; P=.05$), and cocaine-dependent men ($r_s=0.523; P<.005$). However, there was no association between corticotropin and cortisol in cocaine-dependent women ($r_s=0.199; P=.4$) (Figure 5).

**PAST AND FUTURE COCAINE USE AS PREDICTORS OF RESPONSE**

The percentage of days that cocaine was used in the 30 days before the start of the study and in the 30 days following were analyzed to determine any relationship to subjective craving and stress or heart rate, corticotropin response, and cortisol response. Subjects reported using cocaine 35% of the 30 days prior to the study and 18% of the 30 days following. There were no sex differences in the percentage of days using cocaine either before or after study participation. After adjusting for age, the percentage of days subjects used cocaine in the 30 days prior to the study was a significant predictor of the peak change in cortisol ($P=.01$), stress ($P=.01$), and craving ($P<.001$). The percentage of days using cocaine in the 30 days following the study was a significant predictor of the peak change in stress ($P<.03$), while a trend ($P<.1$) was observed for the peak changes in craving and cortisol. No sex differences were found in these relationships.

In the present study, the subjective, physiologic, and HPA axis responses to CRH in cocaine-dependent men and women were compared with those of a control group matched for sex, age, race, and smoking status. The differences between the cocaine and control groups in the subjective and heart rate response to CRH were striking. Both the number of responders and the magnitude of the subjective stress response to CRH in the cocaine-dependent individuals were significantly higher than in the control group across all time points. As previously discussed, with acute cocaine use, there is activation of the HPA axis. With prolonged use, there may be downregulation of the HPA response but activation of CRH systems in limbic...
circuitry, particularly the extended amygdala, that have been implicated in the behavioral responses to stressors. 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 central nucleus of the amygdala. Of interest, there is data suggesting that norepinephrine release in these areas stimulates the release of CRH, which would imply a powerful “feed-forward” system that might be a mechanism for sensitization of the stress response. The difference in the heart rate response to CRH between the cocaine-dependent and control groups also provides support to the idea that CRH stimulation in the cocaine-dependent group may have been acting through preferential sensitization of CRH-linked noradrenergic systems in the locus coeruleus, which regulate the heart rate response to stress. Importantly, the CRH-noradrenergic interaction has been hypothesized as one of the mechanisms contributing to allostatic development of addiction. 

Figure 5. Hypothalamic pituitary adrenal dysregulation in cocaine-dependent women. Correlation between the peak changes in plasma cortisol and plasma corticotropin levels in response to corticotropin-releasing hormone administration in male controls (A), female controls (B), cocaine-dependent men (C), and cocaine-dependent women (D). Data were analyzed using Spearman rank correlation coefficients (r_s). P < .05 denotes a significance correlation between the peak change in corticotropin and peak change in cortisol. To convert corticotropin to picomoles per liter, multiply by 0.22; to convert cortisol to nanomoles per liter, multiply by 27.588.

A substantial number of cocaine-dependent subjects (16 of 48) reported craving cocaine following CRH administration, and the correlation between craving and stress was high, emphasizing the importance of the stress-relapse connection on a neurobiologic and subjective level for cocaine-dependent individuals. In an interesting series of studies, Sinha and colleagues reported that stress imagery and cocaine cues produce craving, anxiety, HPA axis, and sympatho-adreno-medullary responses that are similar to the arousal produced by cocaine itself in cocaine-dependent individuals. In the current study, CRH administration may have produced responses similar to those experienced with cocaine administration for some cocaine-dependent individuals. Sinha and colleagues also found a good correlation between drug cue- and stress imagery-induced stress and craving, and that greater stress-induced, but not drug cue-induced craving was associated with shorter time to cocaine relapse after a laboratory session. They also found that both cortisol and cortico-
tropin peak response were positively associated with the amount of cocaine used per occasion in the 90-day period following study participation, but not associated with time to relapse or frequency of relapse. In the present study, the number of days using cocaine prior to and following study participation were predictive of peak stress and craving responses following CRH administration. A positive association was also found between peak cortisol change and the amount of cocaine use before study participation ($P < .01$) and a trend toward a relationship between cortisol change and cocaine use after study participation ($P < .08$). Together, these studies support the predictive validity of responses in laboratory paradigms designed to induce craving or stress and substance use in real-life situations. In addition, these findings provide support for a positive relationship between HPA axis response and propensity to use cocaine. In contrast, several recent studies suggest that a blunted HPA axis response in alcohol dependence is predictive of relapse. However, the effect of chronic alcohol use on HPA axis function differs from that of chronic cocaine use and the fact that there is a relationship between HPA response and propensity to relapse in both disorders, regardless of the direction of change, might be the more important issue.

There was surprisingly little difference between the cocaine and control groups in the corticotropin and cortisol response to CRH. While several studies have described HPA axis dysregulation in cocaine-dependent individuals, others have noted no abnormalities in basal cortisol during early abstinence in cocaine-dependent individuals. A previous study comparing the HPA axis response to CRH (1.0 µg/kg) in a group of polysubstance-abusing subjects with controls found a lower cortisol and corticotropin response in the methadone-maintained group compared with the polusubstance group; however, this study included a heterogeneous group of individuals with substance use disorders including cocaine, alcohol, heroin, and marijuana dependence, while the population sampled in the current study primarily had cocaine dependence only. There are no other studies that we are aware of investigating the response to CRH in individuals with primary cocaine dependence, and the effect of dependence on a variety of substances could explain the discrepancy in the findings between studies. The dose of CRH used may be a factor. In a study comparing 2 doses of CRH in methadone-maintained vs control subjects, no between-group difference in corticotropin response was found following low-dose CRH (0.5 µg/kg), but there was a greater corticotropin response in the methadone-maintained group following high-dose CRH (2.0 µg/kg) compared with the control group. In the present study, only 1 dose of CRH was explored (1.0 µg/kg), so it is possible that differences would have been found if a broader range of CRH dosing had been explored.

Sex differences in the activity of the HPA axis under basal conditions and in response to various challenges have been reported. In humans, basal cortisol levels are similar between men and women, but basal corticotropin is significantly higher in men. A number of studies have found higher total plasma cortisol response to various challenge paradigms in women compared with men; however, this may reflect sex differences in the cortisol-binding protein rather than higher free cortisol. The general sex findings of the present study are consistent with these studies. While there were no profound differences between the cocaine and control groups in the corticotropin and cortisol response to CRH, there is some suggestion of greater disruption in cocaine-dependent women compared with cocaine-dependent men. There was a trend toward lower corticotropin response in cocaine-dependent women compared with all other groups. Despite the blunted corticotropin response, the cortisol response in cocaine-dependent women was robust and did not decrease during the 120-minute follow-up period. Consistent with this finding, peak plasma corticotropin was positively correlated with the peak plasma cortisol in the cocaine-dependent men and in both control groups, but not in cocaine-dependent women. The correlation between the corticotropin and cortisol response in a well-regulated HPA axis response should be high, and the lack of correlation in cocaine-dependent women suggests dysregulation of the response. In addition, cocaine-dependent women demonstrated the greatest increase in heart rate and a prolonged heart rate response following CRH infusion compared with all other groups. Taken together, these findings suggest greater sensitivity to the toxic effects of cocaine in women compared with men. This is consistent with other studies demonstrating greater HPA dysregulation with chronic substance use in women compared with men. Gianoulakis and colleagues investigated the effect of chronic alcohol consumption on HPA axis activity as a function of alcohol intake, age, and sex and found lower plasma corticotropin levels in heavy drinkers, which was more pronounced in women than in men. In a subanalysis of data from the control group in the current study, female smokers evidenced a blunted cortisol response to CRH compared with nonsmokers, whereas smoking status did not affect cortisol response in men. An increased vulnerability of women to adverse medical and psychosocial consequences of substance use has been well documented, and women have been shown to advance more rapidly than men from initial to regular use. These clinical differences may be related to increased sensitivity to the toxic effects of substances of abuse.

There are a number of significant study limitations. There were unanticipated baseline differences in employment and educational status. However, important baseline variables such as age, sex, race, and smoking status were controlled for, and it is unlikely that employment or educational status affected the primary study measures. The measurement points after CRH administration were limited and only 1 dose of CRH was tested, so some group differences might have been missed. In addition, it was not feasible to standardize the menstrual cycle phase for women at the time of testing. Adding a saline infusion to serve as a control condition would have improved the study design, as it is possible that the subjective response to CRH in the cocaine group was a placebo response. However, we would have expected a similar placebo response in men who received saline. This placebo response was not absent in women, and it is possible that the observed differences were due to the placebo effect.

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response in control subjects. In addition, there was a difference in the heart rate response to CRH between the cocaine and control groups, and peak stress and peak craving were correlated with the percentage of days using cocaine before and after the study. These findings make it less likely that the subjective response to CRH in the cocaine group was a placebo response.

Despite these limitations, there were a number of intriguing findings. Cocaine-dependent subjects had a greater subjective and heart rate response without substantial difference in corticotropic and cortisol response to CRH infusion. This may indicate differential stimulation of pathways in the extended amygdala and locus coeruleus by CRH in cocaine-dependent individuals. The robust relationship between stress and craving supports the role of stress in relapse in the clinical setting. Consistent with other studies, cocaine-dependent women appeared to be more sensitive to the toxic effects of chronic use, as evidenced by greater HPA axis dysregulation. Finally, the relationship between the amount of cocaine use and stress/craving and cortisol response in the laboratory supports the validity of these laboratory paradigms in studying the neurobiologic underpinnings of relapse in individuals with substance use disorders.

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