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ORIGINAL INVESTIGATION

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Psychological stress, drug-related cues and cocaine craving

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Abstract *Rationale:* While several environmental situations may produce cocaine craving, there is little research on whether patterns of drug cue reactivity are similar across different environmental situations. *Objective:* This study examined whether two different environmental situations, psychological stress and drug cues, produce similar or varying patterns of cue reactivity in 20 cocaine dependent individuals. *Methods:* All subjects participated in a single laboratory session and were exposed to stress, drug cues and neutral-relaxing imagery conditions. Cocaine and alcohol craving, emotion state ratings, subjective anxiety, heart rate and salivary cortisol measures were assessed. *Results:* Significant increases in cocaine and alcohol craving were observed with stress and drug cues imagery but not with neutral-relaxing imagery. In addition, stress and drug cues situations produced similar increases in subjective anxiety, heart rate and salivary cortisol levels. Significant increases in negative emotion ratings and decreases in positive emotion ratings were found for stress and drug cues conditions as compared to the neutral condition. *Conclusions:* The findings indicate that a similar and comparable pattern of cue reactivity is induced by stress and drug cue manipulations. Furthermore, the comparable increases in subjective anxiety and negative affect observed with stress-induced and drug cue-induced craving provides support for the negative reinforcement model of drug craving and relapse. The negative affectivity co-occurring with the craving state appears to be an important target in the development of new treatments for cocaine dependence.

Key words Cocaine abuse · Psychological stress · Cue reactivity · Craving · Emotion · HPA activation

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Introduction

Several studies have shown that cocaine craving can be successfully induced in the laboratory by exposing subjects to cocaine cues. These cue reactivity studies have primarily used exposure to drug-related paraphernalia as the method for craving induction (Ehrmann et al. 1992; Childress et al. 1993; Margolin et al. 1994; Berger et al. 1996). Exceptions to the above studies are those that used erotic stimuli (Bauer and Kranzler 1994) and stress cues for induction of cocaine craving (Sinha et al. 1999). One of the main purposes of these studies has been reliably to produce cocaine cue reactivity in the context of the above manipulations.

A second focus of this line of research has been to use the cue reactivity method to test medications that may block/attenuate cocaine craving in the laboratory (Dackis et al. 1987; Gawin et al. 1989; Kosten 1992; Robbins et al. 1992). However, these efforts have not been entirely successful, in that pharmacological agents shown to attenuate cocaine craving in the laboratory have not proven to be efficacious treatments for cocaine addiction (Kosten 1992; Robbins et al. 1992). There are several possible reasons for the failure to develop an effective anti-craving medication for cocaine addiction, thus far. First, while previous studies have screened agents that act on the dopaminergic system, it is likely that more than one neurobiological system may be involved in cocaine craving and compulsive drug use. Second, it is also possible that different types of environmental cues may activate different neurobiological systems, thus producing varying patterns of cue reactivity associated with different environmental cues. For example, while exposure to drug cues may produce a craving state associated with the positively reinforcing properties of cocaine, craving associated with psychological stress may be linked to the negatively reinforcing and self-medicating properties of compulsive cocaine use. If a consistent and stable pattern of cue reactivity were observed under different environmental cue manipulations, then blocking or attenuation of cocaine craving would be an important pharmacologi-

cal treatment target for cocaine dependence. If on the other hand, cue reactivity varied as a function of different environmental cues, efforts to target cocaine craving by specific medications development may not be a useful treatment strategy.

Thus, the present study examined whether two different cue manipulations, i.e. stress and drug cues, produce consistent and similar patterns of cue reactivity. Psychological stress was selected because drug abusers identify stress and negative affect as frequent reasons for drug use and relapse (Bradley et al. 1989; Wallace et al. 1989). Laboratory studies have shown that psychological stress or mood induction in substance abusing populations can successfully induce drug craving (Litt et al. 1990; Childress et al. 1994; Rubonis et al. 1994; Maude-Griffin and Tiffany 1996; Cooney et al. 1997; Sinha et al. 1999). Drug abusers also identify triggers in the environment such as people, places and things associated with drug use as common reasons for drug use (Childress et al. 1993). Cocaine craving has been induced in the laboratory most frequently by exposure to drug-related cues either by watching videotapes/films or in-vivo exposure to cocaine paraphernalia (Robbins et al. 1992; Childress et al. 1993; Bauer and Kranzler 1994; Margolin et al. 1994; Berger et al. 1996). Therefore, exposure to non-stress, drug-cues was used as the contrasting condition. A third condition using neutral-relaxing cues was included as a control for the induction method. The specific hypothesis was that in contrast to neutral-relaxing cues, exposure to stress and drug cues will produce comparable patterns of cue reactivity as assessed via self-report of craving, anxiety, emotional state, heart rate and salivary cortisol.

Table 1 Sample characteristics

Subject variable	Cocaine dependent ss (*n*=20)
Caucasian	60%
Age*	33.3 (6.08)
Male	90%
High school education	85%
Full time employment	40%
Currently married	45%
Alcohol dependence	79%
Alcohol use (drinks/week)*	43.73 (53.47)
Average frequency of cocaine use per week*	3.34 (2.12)
Average amount of cocaine use per week*	$137 (87.40)
Route of administration	90% freebase

* Values represent means and standard deviations

Table 2 Schedule of assessments for imagery conditions

2:45 p.m.	Subject arrived; urine and BAC check Psychophysiological setup
Stress/drug cues (condition 1)	
3:00 p.m.	Baseline period; on-line heart rate and anxiety ratings
3:05 p.m.	Craving and DES ratings; cortisol samples
3:10 p.m.	Image period; on-line heart rate and anxiety ratings
3:15 p.m.	Craving and DES ratings; cortisol samples
3:20 p.m.	Recovery period; on-line heart rate and anxiety ratings
3:25 p.m.	Craving and DES ratings; cortisol samples
3:30 p.m.	10-min relaxation period
Neutral imagery condition (condition 2)	
3:40 p.m.	Schedule as in condition 1
Stress/drug cues (condition 3)	
4:20 p.m.	Schedule as in condition 1

Materials and methods

Subjects

Twenty cocaine dependent individuals (18 men and two women) ages 21–55 years, who recently entered treatment for cocaine dependence at an outpatient substance abuse treatment facility, were recruited to be in the study. All subjects were interviewed using the Structured Clinical Interview for DSM-IV (SCID-I; First et al. 1995) and met criteria for current cocaine dependence. Subjects were ineligible if they met criteria for a psychotic disorder, mental retardation, or reported current suicidal or homicidal ideation, and/or reported a past or present history of opiate use. Subjects were also ineligible if they were currently on medications for psychiatric or cardiovascular problems. The demographic and substance use characteristics of the sample are presented in Table 1. All subjects participated voluntarily in the study, and were paid for their participation. Informed consent, in which subjects were told that the purpose of the study was to examine the effects of stressful situations and non-stressful drug related situations on their body, mood and craving, was obtained for all subjects. In addition, the Yale Human Investigation Committee approved the study protocol.

Study design

Drug craving was induced using imagery-based induction procedures shown to be effective in previous cue reactivity studies (Tiffany and Drobes 1990; Tiffany and Haekeneworth 1991; Maude-Griffin and Tiffany 1996; Drobes and Tiffany 1997; Sinha et al. 1999). All subjects participated in a single 2-h laboratory session that included three imagery conditions: a neutral-relaxing imagery, stress imagery and a drug cue imagery condition. Each imagery condition was presented in 30-min blocks with a 10-min relaxation period between conditions. The neutral-relaxing imagery was always presented as the second condition, while the stress and drug cues imagery were presented as either the first or last condition, with the order of the stress and drug cues imagery counterbalanced across subjects. The subject was not informed of the order of imagery conditions. Table 2 presents the schedule of assessments for each imagery condition, and the time points at which physiological and subjective assessments were conducted.

Procedures

Imagery script development session

In a session prior to the experimental session, imagery scripts were developed for the stress and drug cues situations using the scene development questionnaire (adapted from Miller et al. 1987; Sinha et al. 1992). The *stress imagery script* was developed by having subjects identify a recent stressful experience they had personally experienced as “most stressful”. “Most stressful” was determined by having the subjects rate the perceived stress experienced by them on a 10-point Likert scale where 1=“not at all stressful” and 10=“the most stress they have felt recently in their

life". Only situations rated as 8 or above on this scale were accepted as appropriate for script development. Stressful situations related to drug use, such as being arrested for possession of drugs or being caught in a police chase, were not allowed. Examples of acceptable stressful situations include breakup with significant other, a verbal argument with a significant other or family member or unemployment-related stress, such as being fired or laid off from work. The *drug cues script* was developed by having subjects identify a recent situation that included cocaine-related cues and was a trigger for subsequent cocaine use (e.g. buying cocaine, being at a bar, watching others smoke crack and drink alcohol). Drug related situations that were associated with negative affect or psychological distress were not allowed, i.e. when subjects went to a bar after a fight, or feeling depressed and called a drug using buddy. A *neutral-relaxing script* was developed from a standard commonly experienced relaxing summer beach scene. Subjects were asked if the beach scene was a neutral drug-free situation, and no subjects endorsed the relaxing beach scene as a trigger situation. The scripts were developed by obtaining specific stimulus and response details, including specific physical and interpersonal context details, verbal/cognitive attributions regarding the people involved, including themselves, and physiological and bodily sensations that the subject experienced in the situation. A script for imagery induction was developed from the specific description of each situation. The script development procedures were based on methods developed by Lang and his colleagues (Lang et al. 1980, 1983; Miller et al. 1987), and further adapted in our previous studies (Sinha et al. 1992, 1999; Sinha and Parsons 1996).

Laboratory session

Subjects arrived for the laboratory session at 3:00 p.m. After obtaining confirmation of alcohol and drug-free state via urine toxicology (EZ Kit, test for opiates, cocaine, amphetamines and barbiturates) and breathalyzer tests, subjects were prepared for electrocardiograph (EKG) recordings. Subjects were then seated in a comfortable chair and asked to relax for a few minutes. Instructions to clear their mind of any worry thoughts and to focus on deep breathing were provided. The experimental procedure was based on the following format: a 5-min *baseline*, a 5-min *image*, and a 5-min *recovery* period during which subjects were asked to stop the imagery and remain seated quietly. After the baseline period, subjects were given the following instructions for imagery: "You will soon hear a situation being described to you. Your task is to close your eyes and imagine yourself in the situation being described, 'as if' it were happening right now. Allow yourself to become completely involved in the situation, by involving your mind and body in actually doing what is being described. Continue imagining until you are asked to stop". Subjects then listened to the script and participated in the image period for a period of 5 min. Following each of the baseline, image and recovery periods, subjects completed ratings for cocaine and alcohol craving, emotion ratings and provided one salivary cortisol sample for each time period. After each imagery condition, subjects were given a 10-min break with instructions to relax and focus on deep breathing. Physiological recordings were monitored during this time and the next imagery condition was not initiated until subjects exhibited baseline levels of anxiety and heart rate. The second and third imagery conditions followed the procedures described above. Table 2 outlines the schedule of assessments within each imagery condition.

Manipulation check for imagery vividness

After the image period in each imagery condition, subjects made an additional rating on a 10-point visual analog scale (with 1=not at all clear, and 10=perfectly clear image) for how "clearly and vividly" they were able to imagine the situation. Average vividness ratings were 8.35 (0.92) for stress imagery, 8.65 (0.67) for neutral imagery and 8.84 (0.84) for drug-related cues imagery with no significant differences between the three conditions.

Assessments

Craving

Cocaine craving was assessed using a 10-point visual analog scale (VAS) where 1 was anchored at "not at all" and 10 was anchored at "extremely high", and subjects rated their "desire for using cocaine" along this scale. As a majority of subjects were also abusing alcohol, an additional 10-point VAS was used for assessing alcohol craving and subjects rated their "desire for an alcoholic drink".

Emotion state ratings

An abbreviated 30-item version of the Differential Emotion Scale (DES; Izard 1972) used in previous laboratory studies to assess emotional states (Schwartz and Weinberger 1980; Sinha et al. 1992, 1999; Sinha and Parsons 1996) was included to measure specific positive and negative emotional states at each time point. The DES requires the subject to rate on a single 5-point Likert scale the extent to which various emotional words describe the way he/she felt at the present time. The following items from the original scale were included: pleasant, downhearted, irritated, distressed, alert, fearful, hostile, at ease, happy, attentive, annoyed, relaxed, joyful, active, jittery, mad, enthusiastic, scared, aroused, discouraged, calm, disgusted, afraid, excited, lonely, comfortable, frightened, energized, upset and delighted. Five items were attributed to each of the fear, anger, joy, sadness, neutral/relaxed and physical action states. The sum of the ratings for the five defining items generated the scores for each emotional state (scores ranging from minimum of 5 to a maximum of 25). The time taken to complete the DES was 1–2 min.

Continuous ratings of anxiety were obtained by using a rating dial instrument with ten divisions anchored by extremely calm (1) and extremely tense/anxious (10). Subjects were instructed to keep their dominant hand on the dial and to adjust it freely so that it always reflected their current level of tension. The rating dial was connected to the computer system to obtain on-line continuous anxiety ratings. The anxiety dial has been successfully used in previous stress studies (Levenson et al. 1987; Sinha et al. 1998) and similar devices have been used in other laboratory studies assessing moment-to-moment changes in mood states. In general, continuous ratings are considered more sensitive in assessing subjective state than paper and pencil ratings administered after the experimental manipulation (Lukas and Mendelson 1988).

Heart rate

Acquisition and on-line analysis was accomplished using a system consisting of a Grass Model 7 polygraph, a 386/25 Mhz IBM compatible PC and data acquisition software. Heart rate was derived from the electrocardiograph (EKG) signal obtained by attaching chloride silver electrodes on the subject's abdomen. Heart rate data for one subject was missing due to equipment malfunctioning.

Salivary cortisol

Salivary cortisol represents a simple non-invasive measure of hypothalamic-pituitary-adrenal (HPA) axis activity, which is reliable, stable and highly correlated with plasma cortisol (Kahn et al. 1988; Kirschbaum and Hellhammer 1994). The salivary cortisol assessments were conducted by collecting saliva samples using the salivette kit (Sarstedt, Inc.). A cotton roll insert from the salivette kit was placed in the subject's mouth for approximately 2–3 min at the assigned timepoints. Once the cotton was thoroughly saturated, it was collected in the upper part of the salivette tube and stored in a freezer until the time of analysis. Cortisol assays were conducted using commercial cortisol RIA kits (Diagnostic Products Corporation, Inc.) with modified assay sensitivity and di-

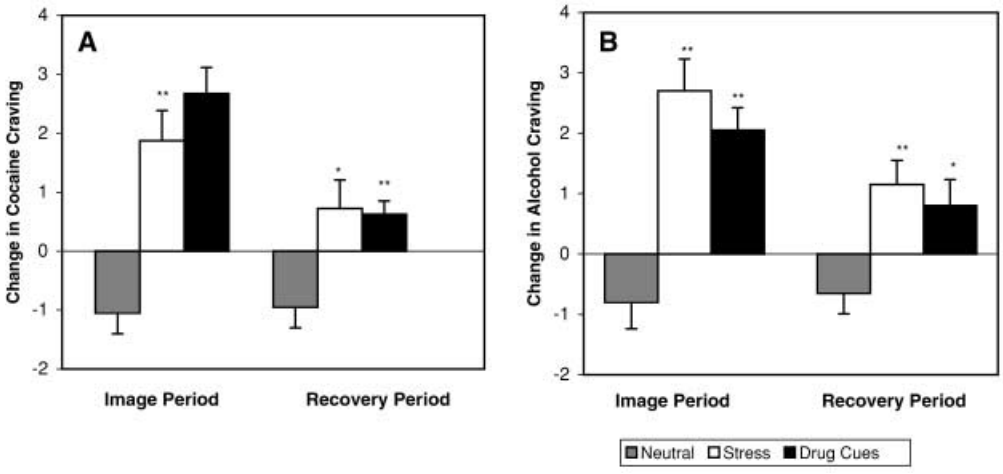

Fig. 1A–B Mean change in craving (and SE) from baseline to image and recovery periods for each the stress, drug cues and neutral imagery conditions. **A** Cocaine craving; **B** alcohol craving

lution procedures provided by Diagnostic Products Corporation, Inc. Four of the 20 subjects produced inadequate amounts of saliva to accurately measure cortisol levels; thus generating missing values for certain time-points. Therefore only 16 subjects were included in the analysis of cortisol data.

Data analysis

Online heart rate recordings and continuous subjective anxiety ratings were averaged across each minute per recording period, for each imagery condition.

Assessment of baseline differences

As each imagery condition had a separate baseline period, baseline differences between imagery conditions were first examined. One way repeated measures ANOVAs were conducted for each dependent measure. The only dependent measure with trend towards significance was for baseline alcohol craving scores [$F(2,38)=2.10$, $P<0.13$]. Baseline alcohol craving scores for the neutral condition was higher than the baseline alcohol craving score for the stress and drug cues condition.

Cue reactivity differences

Cue reactivity was assessed using change scores from baseline to the image and recovery period for *each* imagery condition for heart rate, craving ratings, emotion state ratings and cortisol measures. Change scores were used instead of absolute raw scores for purposes of consistency with previously published cue reactivity studies (Robbins et al. 1992; Ehrman et al. 1992; Berger et al. 1996; Sinha et al. 1999). A 3 (imagery type: stress, drug cues versus neutral)×2 (time-period: image and recovery change) repeated measures analysis of variance (ANOVA) procedure was conducted on change scores for each dependent measure. Significant main effects were further analyzed by post-hoc comparisons to examine differences between levels within a factor, and simple effects analyses were conducted to examine the source of any significant interactions.

Results

Cocaine and alcohol craving

Cocaine craving produced main effects for imagery condition [$F(2,38)=14.16$, $P<0.0001$], and time period [$F(1,19)=21.26$, $P<0.0002$] and a significant imagery×time period interaction [$F(2,38)=7.26$, $P<0.004$]. Results for alcohol craving also produced effects similar to cocaine craving, with main effects for imagery condition [$F(2,38)=11.95$, $P<0.0003$], time period [$F(1,19)=22.9$, $P<0.0001$], and a significant imagery×time period interaction [$F(2.38)=5.77$, $P<0.007$]. Simple effects analyses revealed significant increases in cocaine ($P<0.0005$ for image; $P<0.02$ for recovery) and alcohol ($P<0.0003$ for image; $P<0.01$ for recovery) craving for stress cues and drug cues imagery (cocaine craving: $P<0.0001$ for image; $P<0.002$ for recovery; alcohol craving: $P<0.0002$ for image; $P<0.02$ for recovery) conditions as compared to neutral imagery (see Fig. 1A, B). The significant interactions resulted from a decrease in craving scores for stress and drug cues imagery from the image period to the recovery period, but no change in craving across time period for the neutral imagery condition.

Subjective anxiety

Significant main effects of imagery condition [$F(2,38)=26.05$, $P<0.0001$] and time period [$F(1,19)=9.57$, $P<0.006$] and a significant imagery×time period interaction [$F(2,38)=5.06$, $P<0.02$] was observed. Anxiety increased during the stress (image period: $P<0.0001$; recovery period: $P<0.03$) and drug cues (image period: $P<0.0001$; recovery period: $P<0.001$) conditions and was significantly different from anxiety ratings during the neutral condition. As expected, there was significantly greater increase in anxiety during the image period as compared to the recovery period resulting in a time period main effect. Further, this was true for the stress and drug cues conditions but not for the neutral imagery condition, resulting in a significant interaction between imagery condition and time period (see Fig. 2A).

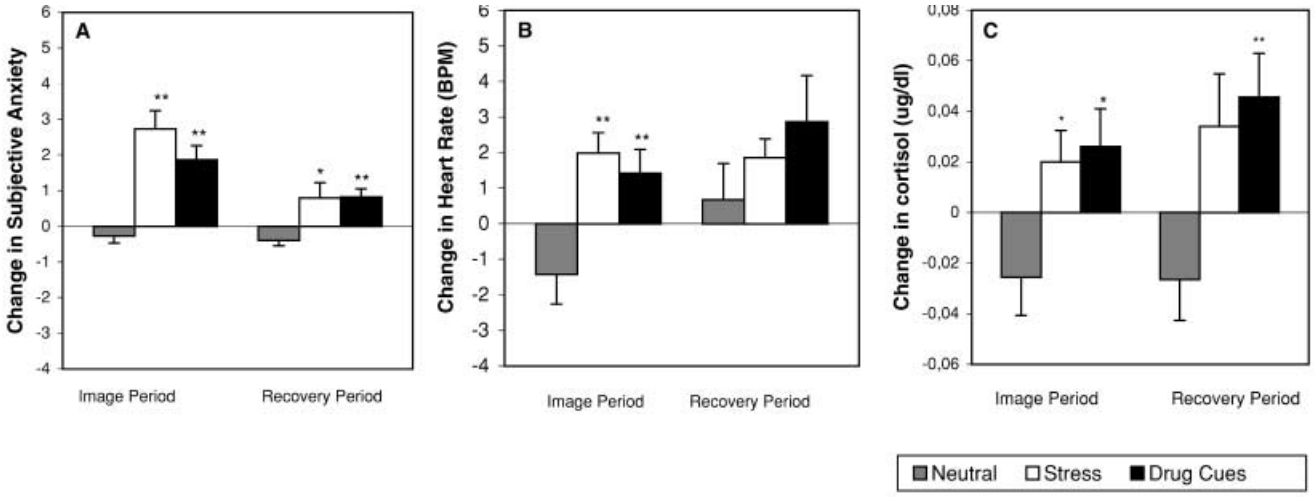

Fig. 2A–C Mean change (and SE) from baseline to image and recovery periods for each of the stress, drug cues and neutral-relaxing imagery conditions. **A** Subjective anxiety; **B** heart rate; **C** salivary cortisol

Heart rate

A significant main effect of imagery condition [$F(2,36)=4.37$, $P<0.02$] and a trend toward significance for time period [$F(1,18)=3.00$, $P<0.10$] were observed. Post-hoc comparisons revealed significant increases in heart rate for stress and drug cues imagery as compared to the overall decrease in heart rate during the neutral imagery condition (see Fig. 2B).

Salivary cortisol

A significant main effect of imagery condition was found for change in salivary cortisol [$F(2,30)=5.30$, $P<0.01$]. Post-hoc comparisons revealed a decrease in cortisol found with neutral imagery, which was significantly different from the increases in cortisol observed for stress (image: $P<0.04$; recovery: $P<0.08$) and drug cues (image: $P<0.05$; recovery: $P<0.01$) imagery conditions (see Fig. 2C).

DES ratings

Figure 3A–F illustrates changes in emotion ratings for each of the three imagery conditions, which resulted in several significant effects.

Positive emotion ratings

Joy and neutral ratings decreased for the stress and drug cues conditions, but increased for neutral imagery resulting in a significant main effect of imagery condition [Joy: $F(2,38)=10.9$, $P<0.0002$; Neutral: $F(2,38)=5.13$, $P<0.01$]. Furthermore, significant imagery×time period interactions were also observed [Joy: $F(2,38)=8.27$, $P<0.001$; Neutral: $F(2,38)=10.15$, $P<0.0008$]. The interactions resulted from decreased joy and neutral-relaxed emotion ratings with stress and drug cues exposure, with no significant change in these ratings across time period. However, although these ratings increased for the neutral imagery condition, the positive emotion state was not maintained in the recovery period (see Fig. 3A, B).

Negative emotion ratings

A similar pattern of results was observed for fear, anger and sadness (see Fig. 3C–E). A significant main effect of imagery condition was obtained for fear [$F(2,38)=9.84$, $P<0.0005$], anger [$F(2,38)=11.43$, $P<0.0003$] and sadness [$F(2,38)=9.31$, $P<0.001$]. Significant main effects of time period were also obtained for fear [$F(1,19)=9.71$, $P<0.006$], anger [$F(1,19)=9.44$, $P<0.006$] and sadness [$F(1,19)=13.14$, $P<0.002$], as were significant imagery×time period interactions for fear [$F(2,38)=7.22$,$P<0.003$], anger [$F(2,38)=12.86$, $P<0.0001$] and sadness [$F(2,38)=8.55$, $P<0.002$]. For fear ratings, simple effects analysis revealed that fear ratings were increased during stress ($P<0.0005$) and drug cues ($P<0.003$) image period which were significantly different from the decrease in fear ratings seen during the neutral image period. During the recovery period, decreased fear ratings for neutral imagery remained significantly different from the increased fear ratings for stress imagery but not for drug cues imagery ($P<0.05$). For anger and sadness ratings the simple effects analyses were similar. Marked increases were observed in anger and sadness ratings for the stress image period, which was significantly different from the increases in these ratings during drug cues image period (anger: $P<0.007$; sadness: $P<0.01$), which in turn was significantly different from the reductions in anger ($P<0.005$) and sadness ($P<0.009$) ratings for the neutral image period. During the recovery period, while there were no significant differences in anger ratings between the three imagery conditions, there was a trend toward significance in the difference between sadness ratings

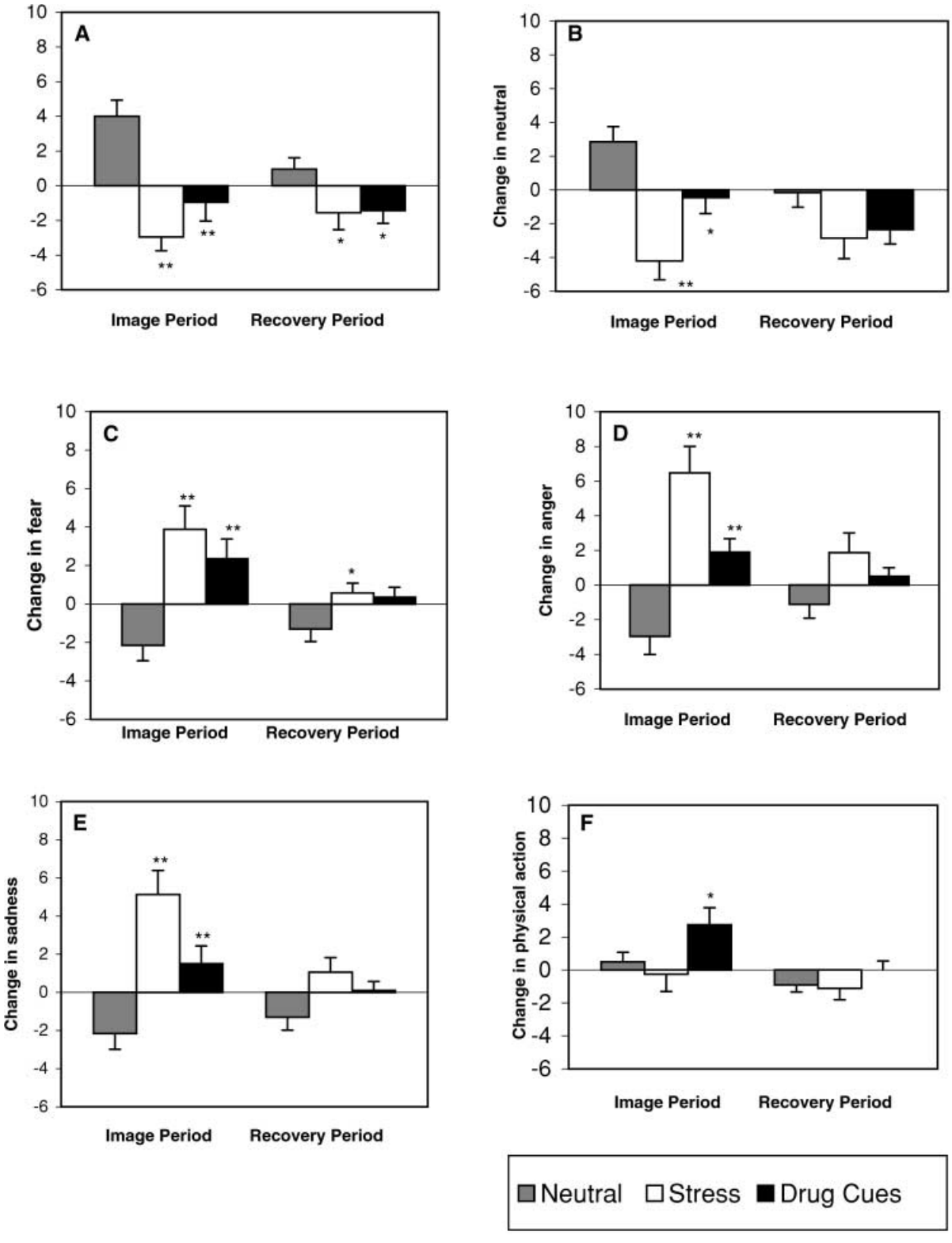

Fig. 3A–F Mean change in differential emotion scale (DES) ratings (and SE) from baseline to image and recovery periods for each of the stress, drug cues and neutral conditions are presented. **A** Joy ratings; **B** neutral-relaxed ratings; **C** fear ratings; **D** anger ratings; **E** sadness ratings; **F** physical action ratings

for the stress imagery as compared to neutral imagery ($P<0.06$).

Finally, we examined the ratings for physical action that assesses the subject's perception of their preparedness for physical action. Interestingly, there was a significant main effect of imagery condition [$F(2,38)=3.53$,

$P<0.04$] and time period [$F(1,19)=7.33$, $P<0.01$]. Post-hoc comparisons indicated a significant increase in physical action ratings for the drug cues image period as compared to the stress and neutral image periods ($P<0.05$), but not during the recovery period (see Fig. 3F).

Discussion

This study examined whether psychological stress-induced craving and drug cues-induced craving produced similar or different patterns of cue reactivity in cocaine dependent individuals. The findings supported our hypothesis that psychological stress-induced and drug cue-induced craving produced similar patterns of psychobiological activation as measured by subjective-emotional ratings, autonomic arousal and HPA activation. The findings suggest that a comparable cocaine craving state is generated across two different cue manipulations, and that it appears useful to target the drug craving state in future studies that use this methodology to screen new anti-craving agents in the treatment of cocaine dependence.

The results indicated similar increases in craving with stress and drug cue situations when compared to the neutral-relaxing situation (see Fig. 1A, B). Concomitant with increases in drug craving were increases in subjective anxiety and negative emotions, along with reductions in positive emotions for the stress and drug cues imagery as compared to neutral imagery. Although anxiety and emotion ratings were assessed at slightly different points for each time period, i.e. anxiety using the rating dial during each time period and emotion ratings using paper and pencil immediately following each time period, the findings were consistent with each other. This pattern of emotion and anxiety ratings suggests an anxiety and negative affect component to the cocaine craving state. To the extent that increases in negative affectivity co-occur with the craving state across different types of environmental cues, it may be an important aspect of the motivational state that promotes drug-seeking behavior, in the absence of drug itself. These findings support the negative reinforcement models of drug craving and relapse (Wikler 1972; Siegel 1983), which suggest that craving and relapse are more likely to occur in environmental situations that induce a withdrawal-like state or a state opposite in direction to the pharmacological effects of the drug. It is possible however, that availability of drug itself is a significant factor in expression of the positive hedonic component of craving, and in the absence of drug, the anxiogenic and negative affect component of craving is more prominently manifested.

Several previous studies with opiate addicts (Powell et al. 1992; Childress et al. 1994) and alcoholics (McCusker and Brown 1991; Rubonis et al. 1994) have reported dysphoric mood states and/or increased subjective anxiety co-occurring with drug craving. Indeed, craving has often been associated with the negative reinforcement of withdrawal symptoms (Wikler 1972; Kosten 1992; Childress et al. 1994). While in the case of cocaine, craving has been linked to the positive reinforcement or euphoria associated with cocaine's effects (Kosten 1992), there is evidence of increased subjective anxiety associated with cocaine cue-induced craving (Bauer and Kranzler 1994; Berger et al. 1996). In addition, chronic use of cocaine itself is known to induce anxiety symptoms (Anthony et al. 1989), and acute and chronic cocaine administration are known to result in anxiogenic-like behavioral responses in animal studies (Ettenberg and Geist, 1991; Yang et al. 1992). Our findings are consistent with these reports and further indicate that the negative affectivity induced by drug cue-induced craving is comparable to that produced by the stress-induced craving state in cocaine dependent individuals.

The data also showed comparable increases in heart rate and salivary cortisol for stress and drug cues as compared to neutral-relaxing cues. Heart rate and cortisol increases in response to psychological stress are well documented in the literature among normal volunteers (Mason 1968; Frankenhauser 1980; Meyerhoff et al. 1988; Lovallo et al. 1990), and in our previous study of cocaine dependent individuals (Sinha et al. 1999). Heart rate increases have also been consistently reported in cue reactivity studies (Carter and Tiffany 1999). Similar to our findings, Berger et al. (1996) reported increases in cortisol with drug cue-induced craving, and linked the cortisol increases to the subjective anxiety associated with cocaine craving. Findings from preclinical studies suggest an important role of CRF and corticosterone in stress-induced drug seeking and in psychostimulant self-administration (Goeders 1997; Shaham et al. 1997). Most recently, two preclinical studies have shown that a non-peptide CRF antagonist significantly attenuated both stress-induced drug seeking (Shaham et al. 1998) and IV cocaine self-administration in laboratory animals (Goeders and Guerin 1998). Cortisol increases seen with both stress-induced and drug cue-induced craving in this study is consistent with the above preclinical data showing that the CRF/HPA systems are involved in psychostimulant self-administration. Pharmacological manipulation of the CRF/HPA axis in future human studies to examine whether this system may be specifically involved in cocaine craving and compulsive cocaine use appears warranted.

In conclusion, the above findings support our hypothesis that different environmental cues produce similar patterns of cue reactivity, and further suggest that the negative affect component of the drug craving state may be an important target in the treatment of cocaine dependence. However, several aspects of the study design may limit the generalizability of these findings. First, while the stress and drug cues scripts were personalized, the neutral cue script was based on a standard commonly experienced situation. Second, only one situation for each condition was presented, and therefore the responses across different stress and drug cue situations remains unknown. Third, cue conditions were only partially

counterbalanced in this study, in that the order of stress and drug cues was counterbalanced but the neutral cues was not. Fourth, while we found robust increases in craving which is consistent with previous cue reactivity studies, craving ratings were obtained using a single-item visual analog scale, rather than a multi-item craving scale. Finally, a large proportion of the cocaine dependent sample was dependent on alcohol as well. While a strong association between alcoholism and cocaine abuse has been previously documented (Helzer and Pryzbeck 1988; Regier et al. 1990; Carroll et al. 1993), it is possible that cocaine abusers without alcoholism may show a different subjective-emotional response associated with drug craving. Clearly, future studies that include different subgroups of cocaine abusers, and control for the above design limitations are needed to further understand the negative affect and anxiogenic component of the drug craving state.

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References

Anthony JC, Tien AY, Petronis KR (1989) Epidemiologic evidence on cocaine use and panic attacks. Am J Epidemiol 129: 543–549

Bauer LO, Kranzler HR (1994) Electroencephalographic activity and mood in cocaine-dependent outpatients: effects of cocaine cue exposure. Soc Biol Psychiatry 36:189–197

Berger SP, Hall S, Mickalian J, Reid MS et al. (1996) Haloperidol antagonism of cue-elicited cocaine craving. Lancet 347:504–508

Bradley BP, Phillips G, Green L, Gossop M (1989) Circumstances surrounding the initial lapse to opiate use following detoxification. Br J Psychiatry 154:354–359

Carroll KM, Rounsaville BJ, Bryant KJ (1993) Alcoholism in treatment seeking cocaine abusers: clinical and prognostic significance. J Stud Alcohol 54:199–208

Carter BL, Tiffany ST (1999) Meta-analysis of cue reactivity in addiction research. Addiction 94:327–340

Childress AR, Hole AV, Ehrman RN, Robbins SJ, McLellan AT, O'Brien CP (1993) Cue reactivity and cue reactivity interventions in drug dependence. NIDA Res Monogr 137:73–95

Childress AR, Ehrman R, McLellan AT, MacRae J, Natalie M, O'Brien CP (1994) Can induced moods trigger drug-related responses in opiate abuse patients? J Subst Abuse Treat 11:17–23

Cooney NL, Litt MD, Morse PA, Bauer LO (1997) Alcohol cue reactivity, negative mood reactivity and relapse in treated alcoholics. J Abnorm Psychol 106:243–250

Dackis CA, Gold MS, Sweeney DR et al. (1987) Single-dose bromocriptine reverses cocaine craving. Psychiatry Res 20:261–264

Drobes DJ, Tiffany ST (1997) Induction of smoking urge through imaginal and in vivo procedures: physiological and self-report manifestations. J Abnorm Psychol 106:15–25

Ehrman RN, Robbins SJ, Childress AR, O'Brien CP (1992) Conditioned responses to cocaine-related stimuli in cocaine abuse patients. Psychopharmacology 107:523–529

Ettenberg A, Geist TD (1991) Animal model for investigating the anxiogenic effects of self-administered cocaine. Psychopharmacology 103:455–461

First MB, Spitzer RL, Gibbon M, Williams JB (1995) Structured clinical interview for DSM-IV, patient edition. American Psychiatric Press, Washington D.C.

Frankenhauser M (1980) Psychobiological aspects of life stress. In: Levine S, Ursin H (eds) Coping and health. Plenum Press, New York, pp 203–223

Gawin FH, Morgan CR, Kosten TK (1989) Double-blind evaluation of the effect of acute amantadine on cocaine craving. Psychopharmacology 97:402–405

Goeders NE (1997) A neuroendocrine role in cocaine reinforcement. Psychoneuroendocrinology 22:237–259

Goeders NE, Guerin GF (1998) Effects of CP-154,526 on intravenous cocaine self-administration in rats. Paper presented at the Annual Meetings of the College of Problems on Drug Dependence, June 13–18, Scottsdale, Arizona

Helzer J, Pryzbeck T (1988) The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. J Stud Alcohol 49:219–224

Izard CE (1972) Patterns of emotions: a new analysis of anxiety and depression. Academic Press, New York

Kahn JP, Rubinow DR, Davis CL, Kling M, Post RM (1988) Salivary cortisol: a practical method for evaluation of adrenal function. Biol Psychiatry 23:335–349

Kirschbaum C, Hellhammer DH (1994) Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19:313–33

Kosten TR (1992) Can cocaine craving be a medication development outcome? Drug craving and relapse in opioid and cocaine dependence. Am J Addict 1:230–239

Lang PJ, Kozak MJ, Miller GA, Levin DN, McLean A (1980) Emotional imagery: conceptual structure and pattern of somatovisceral response. Psychophysiology 17:179–192

Lang PJ, Levin DN, Miller GA, Kozak MJ (1983) Fear behavior, fear imagery, and the psychophysiology of emotion: the problem of affective response integration. J Abnorm Psychol 92: 276–306

Levenson RW, Oyama ON, Meek PS (1987) Greater reinforcement from alcohol for those at risk: parental risk, personality risk, and sex. J Abnorm Psychol 96:242–253

Litt MD, Cooney NL, Kadden RM, Gaupp L (1990) Reactivity to alcohol cues and induced moods in alcoholics. Addict Behav 15:137–146

Lovallo WL, Pincomb GA, Brackett DJ, Wilson MF (1990) Heart rate reactivity as a predictor of neuroendocrine responses to aversive and appetitive challenges. Psychosom Med 52:17–26

Lukas SE, Mendelson JH (1988) Electroencephalographic activity and plasma ACTH during ethanol-induced euphoria. Biol Psychiatry 23:141–148

Margolin A, Avants SK, Kosten TR (1994) Cue-elicited cocaine craving and autogenic relaxation: association with treatment outcome. J Subst Abuse Treat 11:549–552

Mason JW (1968) A review of psychoneuroendocrine research on the pituitary-adrenal cortical system. Psychosom Med 30:576–607

Maude-Griffin PM, Tiffany ST (1996) Production of smoking urges through imagery: the impact of affect and smoking abstinence. Exp Clin Psychopharmacol 4:198–208

McCusker CG, Brown K (1991) The cue-responsivity phenomenon in dependent drinkers: "personality" vulnerability and anxiety as intervening variables. Br J Addict 86:905–912

Meyerhoff JL, Oleshansky MA, Mougey EH (1988) Psychologic stress increases plasma levels of prolactin, cortisol, and POMC-derived peptides in man. Psychosom Med 50:295–303

Miller GA, Levin DN, Kozak MJ, Cook EW, McLean A, Lang PJ (1987) Individual differences in imagery and the psychophysiology of emotion. Cognit Emot 1:367–390

Powell J, Bradley B, Gray J (1992) Classical conditioning and cognitive determinants of subjective craving for opiates: an investigation of their relative contributions. Br J Addict 87: 1133–1144

Regier DA, Farmer ME, Rae DS, Lockey BZ, Keith SJ, Judd LL, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug use: results from the Epidemiologic Catchment Area (ECA). JAMA 264:2511–2518

Robbins SJ, Ehrman RN, Childress AR, O'Brien CP (1992) Using cue reactivity to screen medications for cocaine abuse: a test of amantadine hydrochloride. Addict Behav 17:491–499

Rubonis AV, Colby SM, Monti PM, Rohsenow DJ, Gulliver SB, Sirota AD (1994) Alcohol cue reactivity and mood induction in male and female alcoholics. J Stud Alcohol 53:487–494

Schwartz GE, Weinberger DA (1980) Patterns of emotional responses to affective situations: relations among happiness, sadness, anger, fear, depression and anxiety. Motiv Emot 4: 175–191

Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J (1997) Corticosterone does not contribute to relapse to heroin-seeking in rats induced by footshock stress or priming injections of heroin. J Neurosci 17:2605–2614

Shaham Y, Erb S, Leung S, Buczek Y, Stewart J (1998) CP-154-526, a selective non-peptide antagonist of the corticotrophin-releasing factor receptor attenuates stress-induced relapse to drug seeking in cocaine- and heroin-trained rats. Psychopharmacology 137:184–190

Siegel S (1983) Classical conditioning, drug tolerance and drug dependence. In: Israel Y, Glaser F, Kalant H, Popham R, Schmidt W, Smart M (eds) Research advances in alcohol and drug problems (vol 7). Plenum Press, New York, pp 207–246

Sinha R, Parsons OA (1996) Multivariate response patterning of fear and anger. Cognit Emot 10:173–198

Sinha R, Lovallo WR, Parsons OA (1992) Cardiovascular differentiation of emotions. Psychosom Med 54:422–435

Sinha R, Robinson J, O'Malley SS (1998) Stress response dampening: effects of gender and family history of alcoholism and anxiety. Psychopharmacology 137:311–320

Sinha R, Catapano D, O'Malley SS (1999) Stress-induced craving and stress response in cocaine dependent individuals. Psychopharmacology 142:343–351

Tiffany ST, Drobes DJ (1990) Imagery and smoking urges:the manipulation of affective content. Addict Behav 15:531–539

Tiffany ST, Haekenewerth DM (1991) The production of smoking urges through an imagery manipulation: psychophysiological and verbal manifestations. Addict Behav 16:389–400

Wallace BC (1989) Psychological and environmental determinants of relapse in crack cocaine smokers. J Subst Abuse Treat 6:95–106

Wikler A (1972) Sources of reinforcement for drug using behavior: a theoretical formulation. Pharmacology and the future of man. Proceedings of the 5th International Congress of Pharmacology 1:18–30

Yang XM, Gorman AL, Dunn AJ, Goeders NE (1992) Anxiogenic effects of acute and chronic cocaine administration: neurochemical and behavioral studies. Pharmacol Biochem Behav 41:643–650