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Gender and stimulus difference in cue-induced responses in abstinent heroin users

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Abstract

Background: Environmental stimuli associated with drug taking have been known to elicit drug craving and increase the likelihood of relapse, and sex differences have been observed in the development of drug addiction and relapse to drug taking. Differential cue paradigms (drug-related imagery scripts and drug-related paraphernalia) have been used to investigate cue-induced drug craving. However, there is little research on the possible gender differences in responses to drug cues in heroin-dependent individuals. This study examined whether two different stimuli, drug-related imagery scripts and drug-related paraphernalia, produce similar or different patterns of cue reactivity in heroin-dependent men and women.
Methods: In the laboratory sessions, 26 male and 23 female heroin-dependent subjects were exposed to script-guided imagery of heroin-related cue situations and to heroin-related paraphernalia (e.g., needles, syringes, spoons, cigarette filters, and aluminum foil). Heroin craving, subjective anxiety, emotion state ratings, and cardiovascular changes were assessed.
Results: Significant increases in heroin craving were seen with drug-imagery scripts or drug paraphernalia but not with neutral-relaxing imagery or neutral-item handling. In addition, drug imagery and paraphernalia produced significant increases in subjective anxiety, negative emotions, systolic and diastolic blood pressure, and heart rate, as well as decreases in positive emotion. Paraphernalia exposure was somewhat more effective than imagery scripts in inducing heroin craving, primarily reflecting a lower response to imagery scripts among men. Most other dependent measures also differed by gender, and each gender difference occurred with imagery scripts only or with paraphernalia only.
Conclusions: The present results indicate that heroin-imagery scripts and heroin paraphernalia each induce heroin craving and emotional and cardiovascular changes, but that the changes show a complex pattern of gender differences that may need to be taken into account in future laboratory studies.

Keywords: Heroin abuse; Cue reactivity; Craving; Gender difference; Cue paradigm

1. Introduction

Drug addiction is characterized by high rates of relapse and long-lasting vulnerability to drug-taking behaviors (Mendelson and Mello, 1996; O'Brien, 1997). Drug-associated environmental cues are among the factors that have been shown to reinstate drug-seeking and drug-taking in laboratory animals and to induce drug craving in humans (Lu et al., 2003; See, 2002; Shaham et al., 2003; Sinha et al., 2000). Drugs for which cues can increase subjective craving and autonomic arousal in humans include cocaine (Ehrman et al., 1992; Foltin and Haney, 2000), methamphetamine (Newton et al., 2006), opiates (Childress et al., 1994; O'Brien et al., 1992), nicotine (Chiamulera, 2005), and alcohol (Drummond et al., 1990).

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Different studies have used different types of drug-associated cues. For example, imagery-based drug-related cues have been developed by having subjects identify a recent situation that was a trigger for subsequent drug use (e.g. buying drugs, being at a bar, or watching others use drugs) (Lang et al., 1980; Sinha et al., 2000; Tiffany and Drobes, 1990). Such cues have been demonstrated to elicit drug craving and physical responses (Sinha et al., 2000; Tiffany and Drobes, 1990). Alternatively, subjects may be given the opportunity to handle drug-related paraphernalia, such as needles, syringes, spoons, cigarette filters, or aluminum foil; this, too, produces a strong urge to use drug, which may be associated with conditioned drug-like or drug-opposite effects (Childress et al., 1993; Powell, 1995; Robbins et al., 1999; Satel et al., 1995).

Evidence is accumulating that the physiology and epidemiology of drug abuse differ somewhat between males and females (Carroll et al., 2004; Lynch et al., 2002). Females appear to be more vulnerable than males to the reinforcing effects of psychostimulants, opiate, and nicotine during many phases of the addiction process. In human studies, it is reported that women substance users typically begin using substances later than do men, but they demonstrate an accelerated transition from casual, controlled use to uncontrolled, "binge" patterns of use (Kosten et al., 1996; Lynch et al., 2002; Westermeyer and Boedicker, 2000). Also, female drug users are more likely to report subjective distress before and after the onset of drug abuse, whereas male abusers often report depression after use of substances (Brady and Randall, 1999; Kosten et al., 1993; Sinha and Rounsaville, 2002). Of particular relevance to the present study is that female cocaine addicts were more likely to report increased craving in response to cues than males (Robbins et al., 1999). However, there is little known on the gender effect of cue response in heroin addicts. Such differences, if not accounted for, may be partly responsible for difficulties in translating laboratory findings (Lu et al., 2003; O'Brien, 2005; Shaham et al., 2003) into the development of effective anti-craving and relapse-prevention medications (O'Brien, 2005; Vocci et al., 2005).

The purpose of the present paper is to examine whether heroin-dependent men and women show similar responses to different heroin-related cues. All subjects were participating in inpatient treatment and had abstained from heroin and other drugs for at least 3 weeks. All were exposed to the same set of laboratory stimuli. Stimuli included heroin-related paraphernalia (e.g., syringes, spoons, cigarette filters, and aluminum foil) and drug-related imagery. Self-reported levels of heroin craving and general emotional states were assessed before and after each exposure to the cues. Physiological recording of heart rate and blood pressure occurred continuously throughout the cue-exposure session.

2. Materials and methods

2.1. Subjects

Forty-nine heroin-dependent individuals (26 men and 23 women) age 21–45 years, who had recently begun inpatient treatment in the Addiction Treatment Center of Tangshan Ankan Hospital, Tangshan city, China, were recruited to be in the study. All subjects were interviewed using the Structured Clinical Interview for DSM-IV (SCID-I, (First and Pincus, 1999) and met criteria for current heroin dependence. Subjects were ineligible if they met criteria for a psychotic disorder or mental retardation or if they reported current suicidal or homicidal ideation. 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 provided written informed consent, in which they were told that the purpose of the study was to examine the effects of drug-related situations on their body, mood, and craving.

2.2. Procedures

2.2.1. Development sessions for imagery scripts

In a session prior to the experimental session, imagery scripts for drug cues situations were developed based on previous reports (Lang et al., 1980, 1983; Sinha et al., 1999, 1992; Tiffany and Drobes, 1990). Each subject identified a recent situation that included heroin-related cues (e.g. buying heroin, meeting a drug-using peer, getting a call from a drug dealer, watching others preparing and using); the script was developed from the specific description of each situation and was used as an example of a trigger for subsequent heroin use. The scripts included information on the specific stimuli (including physical and interpersonal context and verbal/cognitive attributions regarding the people and environments involved) and on the subject's response (including psychological and bodily sensations) (Lang et al., 1980; Miller, 1991; Sinha et al., 1999, 1992). Neutral-imagery scripts were developed that depicted experiences such as walking in the park, reading on a Sunday afternoon, or going to the beach. Subjects were asked if these scenes were neutral drug-free situations, and no subjects endorsed these scenes as triggers.

2.2.2. Imagery vividness

After the imagery period for each imagery condition, subjects made an additional rating on a 10-point visual analog scale for how "clearly and vividly" they were able to imagine the situation (1="not at all clear"; 10="perfectly

Table 1
Sample characteristics

Demographic variable	Men (n=26)	Women (n=23)	p-value
Age (y)	28.4 (6.2)	26.9 (5.5)	n.s.
Education (y)	10.8 (2.4)	12.5 (3.5)	n.s.
Full time employment (%)	26.9	43.4	n.s.
Currently married (%)	30.7	65.2	<0.05
Total number of years of heroin use	6.9 (3.7)	6.2 (3.8)	n.s.
Average frequency of heroin use per week	3.4 (2.6)	2.8 (2.4)	n.s.
Average amount of heroin use per week ($)	$98.1 (84.5)	$82 (88.1)	n.s.
Route of administration (IV,%)	76.9	86.9	n.s.

Data are presented as % or mean (SD). n.s., not significant, $p>0.05$.

Table 2
Schedule of assessments for cue exposure conditions

−0.05 min	Subject arrived in laboratory room; Psychophysiological setup
Neutral/cue imagery (condition 1)	
0:00 min	Baseline period: on-line heart rate and anxiety ratings; craving and DES ratings
0:05 min	Neutral image period: on-line heart rate and anxiety ratings; craving and DES ratings
0:10 min	5-min relaxation period
0:15 min	Baseline period: on-line heart rate and anxiety ratings; craving and DES ratings
0:20 min	Cue image period: on-line heart rate and anxiety ratings; craving and DES ratings
0:25 min	10-min recovery period
Neutral/cue paraphernalia (condition 2)	
0:00 min	Baseline period: on-line heart rate and anxiety ratings; craving and DES ratings
0:05 min	Neutral item period: on-line heart rate and anxiety ratings; craving and DES ratings
0:10 min	5-min relaxation period
0:15 min	Baseline period: on-line heart rate and anxiety ratings; craving and DES ratings
0:20 min	Paraphernalia period: on-line heart rate and anxiety ratings; craving and DES ratings
0:25 min	10-min recovery period

clear-as if it were happening now"). This rating served as a manipulation check. Mean vividness ratings were 7.18 (SD=2.21) and 7.49 (SD=2.42) for heroin cue imagery, and 7.25 (SD=1.98) and 7.56 (SD=2.21) for neutral imagery in male and female subjects, respectively. No significant differences were found between the vividness ratings by condition or by gender.

2.2.3. Exposure to heroin-associated paraphernalia

All subjects participated in another session that included two conditions: a neutral-item situation and a paraphernalia situation. In the neutral-item situation, subjects watched and then handled a pencil, a drinking cup, a sheet of paper, and a stethoscope; in the paraphernalia situation, subjects watched and then handled spoons, cigarette filters, aluminum foil, and syringes.

2.3. Assessments

2.3.1. Heroin craving

Heroin craving was assessed using a 10-point visual analog scale (VAS) on which subjects rated their "desire for using heroin"; where 1 was anchored at "not at all" and 10 was anchored at "extremely high." Anxiety was also measured using a similarly anchored 10-point VAS for "anxious, tense, and/or jittery." Craving and anxiety ratings were obtained at baseline and immediately after exposure to neutral or cue stimuli.

2.3.2. Emotional states

An abbreviated 30-item version of the Differential Emotion Scale (DES) (Izard, 1992; Izard et al., 1993; Sinha et al., 1999, 1992) was used to measure specific positive and negative emotional states at each time point. The DES requires the subject to rate the extent to which each of 30 items describes the way he or she presently feels, on a scale of 1 to 5. The 30 items were: 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,

Table 3
Overall effect of cues (*p* values)

Effect	Craving and anxiety[a]		Emotions[b]					Cardiovascular		
	Heroin craving	Anxiety	Joy (decrease)	Sadness	Anger	Neutral (decrease)	Fear	Heart rate	Systolic BP	Diastolic BP
CueVsNeutral	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)	0.0001 (C>N)
CueType	0.0364 (P>I)	n.s.	n.s.	0.0022 (I>P)	0.0002 (P>I)	n.s.	0.0191 (I>P)	n.s.	0.0133 (I>P)	n.s.
CueVsNeutral * Cuetype	0.0356 (P>I)	n.s.	n.s.	0.0021 (I>P)	n.s.	n.s.	n.s.	0.0305 (I>P)	n.s.	n.s.
Sex	0.014 (F>M)	n.s.	n.s.	0.0015 (F>M)	0.0108 (M>F)	n.s.	n.s.	0.0526 (F>M)	n.s.	n.s.
CueVsNeutral * Sex	n.s.	n.s.	0.0087 (F>M)	0.0031 (F>M)	0.0001 (M>F)	n.s.	n.s.	n.s.	n.s.	0.0061 (F>M)
CueType * Sex	n.s.	n.s.	n.s.	0.0004	0.0468	0.0009	n.s.	n.s.	n.s.	n.s.
CueVsNeutral * CueType * Sex	n.s.	n.s.	n.s.	0.0107	0.0103	0.0003	n.s.	n.s.	0.0472	n.s.
Sex (within drug imagery)	0.0001 (F>M)	n.t.	n.s.	0.0001 (F>M)	n.s.	0.0207 (M>F)	n.t.	0.0242 (F>M)	0.0001 (F>M)	n.s.
Sex (within drug paraphernalia)	n.s.	n.t.	0.0002 (F>M)	n.s.	0.0001 (M>F)	0.0004 (F>M)	n.t.	n.s.	n.s.	0.0211 (F>M)
Sex (within neutral imagery)	n.s.	n.t.	n.s.	n.s.	n.s.	n.s.	n.t.	n.s.	n.s.	n.s.
Sex (within neutral paraphernalia)	n.s.	n.t.	n.s.	n.s.	n.s.	n.s.	n.t.	n.s.	n.s.	n.s.

M — male; F — female; C — heroin cue; N — neutral cue; I — imagery; P — paraphernalia; n.s. — not significant; n.t. — not tested.
[a] Visual Analog Scales.
[b] 30-item Differential Emotion Scales.

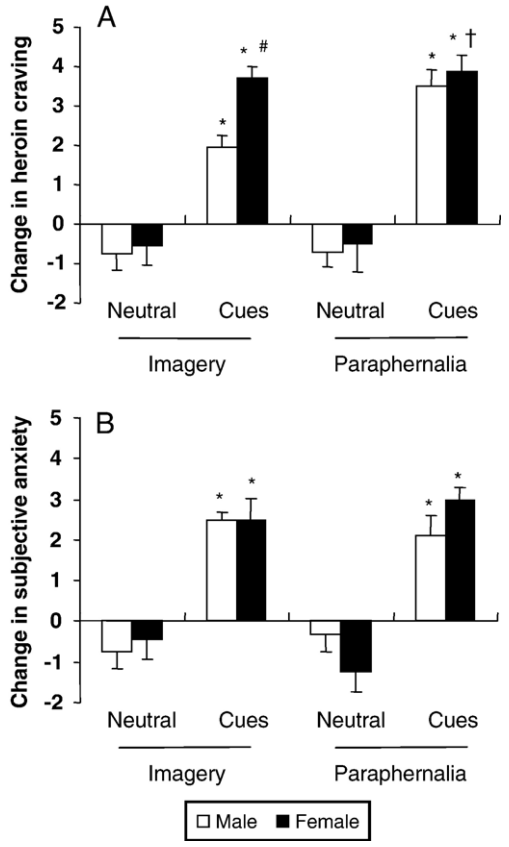

Fig. 1. Mean change from baseline to imagery stimuli (neutral or cue) and paraphernalia stimuli (neutral or cue). A) Heroin craving; B) Subjective anxiety. *$P<0.05$ with neutral cue responses in same stimuli type; $^{\dagger}P<0.05$ with imagery cue responses; $^{\#}P<0.05$ with cue responses in male subjects.

lonely, comfortable, frightened, energized, upset, and delighted. Five items were taken to define each of six emotional states: fear, anger, joy, sadness and neutral/relaxed. The sum of the ratings for the five defining items generated the scores for each emotional state; thus, possible scores for each state ranged from 5 to 25. The time taken to complete the DES was 1–2 min.

2.3.3. Cardiovascular measures

Acquisition and on-line analysis were accomplished with a Grass Model 7 polygraph and data-acquisition software. Heart rate was derived from the electrocardiograph (EKG) signal obtained by attaching chloride silver electrodes to the subject's abdomen. Blood pressure was measured on line by an SD-700 monitor (IBS Corporation, Mass., USA). Pulse was measured continuously with a sensor attached to the subject's finger and connected to an SD-700 monitor.

2.4. Laboratory session

Subjects arrived for the laboratory session at 8:00–9:00 a.m. After providing urine to confirm drug-free status, subjects were prepared for EKG recordings and blood pressure measurement. Subjects were then seated in a comfortable chair and asked to relax for a few minutes; they were instructed to clear their minds of any worrying thoughts and to focus on deep breathing. Then the subjects underwent heroin-related cue conditions: imagery or paraphernalia (Table 2). Each subject was presented with the two different cue stimuli and their neutral stimuli (Table 2). The order of cue stimuli was counterbalanced. The procedure for each cue condition followed the same timeline: a 5-min baseline, a 5-min neutral condition, another 5-min baseline, a 5-min cue presentation, and a 10-min recovery period.

At the beginning of each (neutral and cue) imagery condition, subjects were given the following instructions: "You are hearing a situation being described to you. Please keep closing your eyes and your task is just to imagine yourself in the situation being described, as if it were happening to you right now. You can allow yourself to become completely involved in the situation, by involving your mind and body in actually doing what is being described. Continue imagining

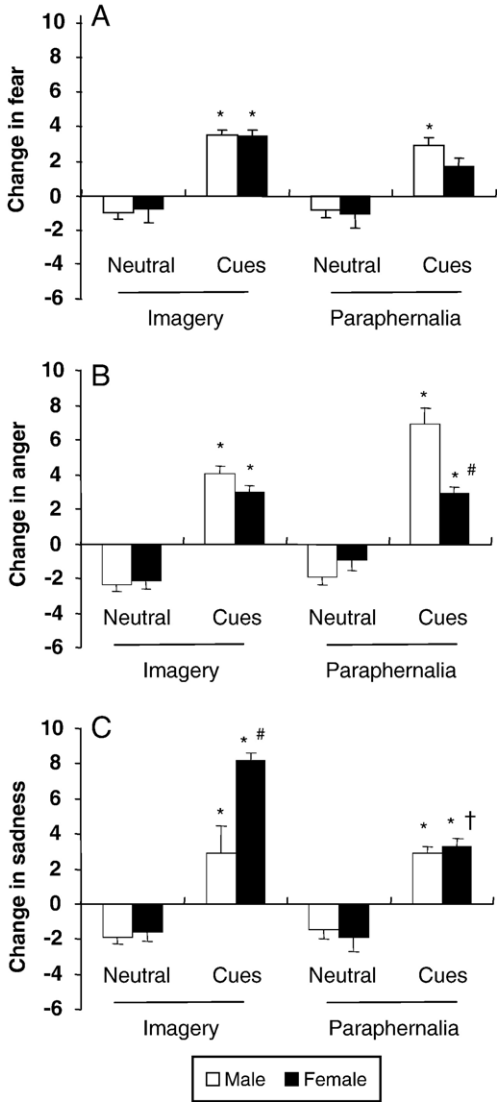

Fig. 2. Mean change of negative emotion scale rating from baseline to imagery stimuli (neutral or cue) and paraphernalia stimuli (neutral or cue). A) Fear rating; B) Anger rating; C) Sadness rating. *$P<0.05$ with neutral cue responses in same stimuli type; $^{\dagger}P<0.05$ with imagery cue responses; $^{\#}P<0.05$ with cue responses in male subjects.

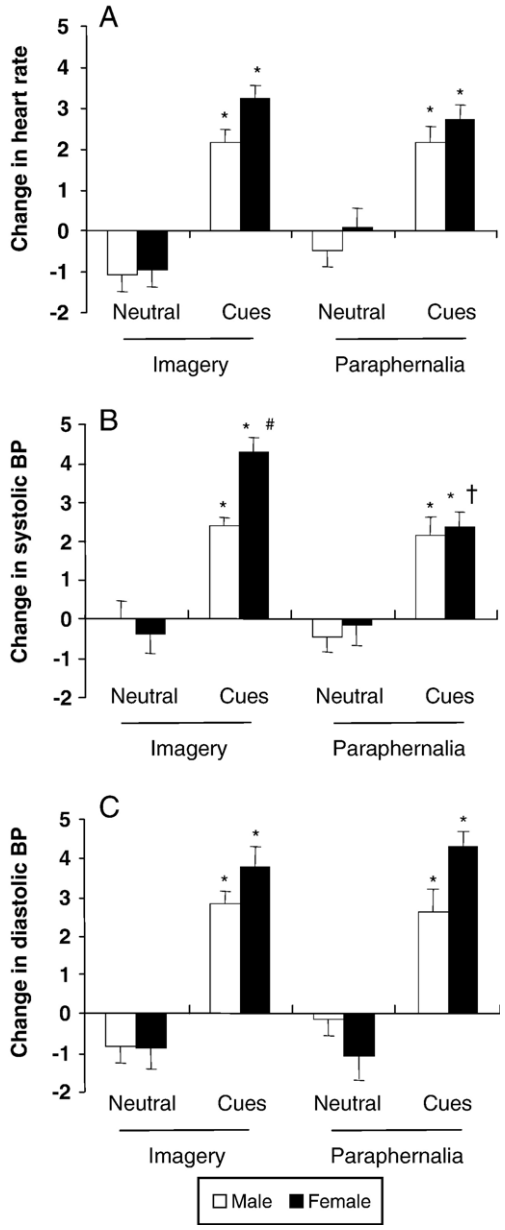

Fig. 3. Mean change of cardiovascular measures from baseline to imagery stimuli (neutral or cue) and paraphernalia stimuli (neutral or cue). A) Heart rate; B) Systolic blood pressure (BP); C) Diastolic blood pressure. *$P<0.05$ with neutral cue responses in same stimuli type; $^{\dagger}P<0.05$ with imagery cue responses; $^{\#}P<0.05$ with cue responses in male subjects.

until you are asked to stop" (Sinha et al., 2000; Tiffany and Drobes, 1990). Subjects then listened to the script.

Following each of the baselines and each cue condition, subjects completed ratings for heroin craving, subjective anxiety, and emotion. Physiological changes were monitored and recorded at the same time. After the first cue condition, subjects underwent the 10-min recovery period with instructions to relax and focus on deep breathing. The second cue condition was not initiated until subjects exhibited baseline levels of anxiety and heart rate. The second cue condition then followed the same timeline as the first. Table 2 outlines the schedule of assessments within each cue condition.

3. Data analysis

Reactivity to cues was assessed using change scores from baseline for craving ratings, anxiety ratings, emotion ratings, and cardiovascular measurements. Change scores were used instead of absolute raw scores based on previous studies of cue reactivity (Berger et al., 1996; Robbins and Ehrman, 1992; Sinha et al., 2000). Each dependent measure was analyzed by analysis of variance (ANOVA) with one between-subjects factor (gender) and two within-subjects factors (stimulus type: imagery vs. paraphernalia; cues: neutral vs. drug). All possible interactions were tested; a differential effect of stimulus type was inferred only when the interaction of stimulus type and cues (neutral vs. drug) was significant. When gender was significant as a main effect or interaction, follow-up ANOVAs were conducted to examine gender differences within each of the four cue conditions (neutral imagery, neutral paraphernalia, drug imagery, and drug paraphernalia) (Each follow-up ANOVA had one between-subjects factor, sex; we used ANOVAs rather than *t*-tests simply to maintain consistency in the presentation of results.) All analyses were done in the GLM procedure in SAS 8.0. Statistical significance was accepted at $p \leq 0.05$.

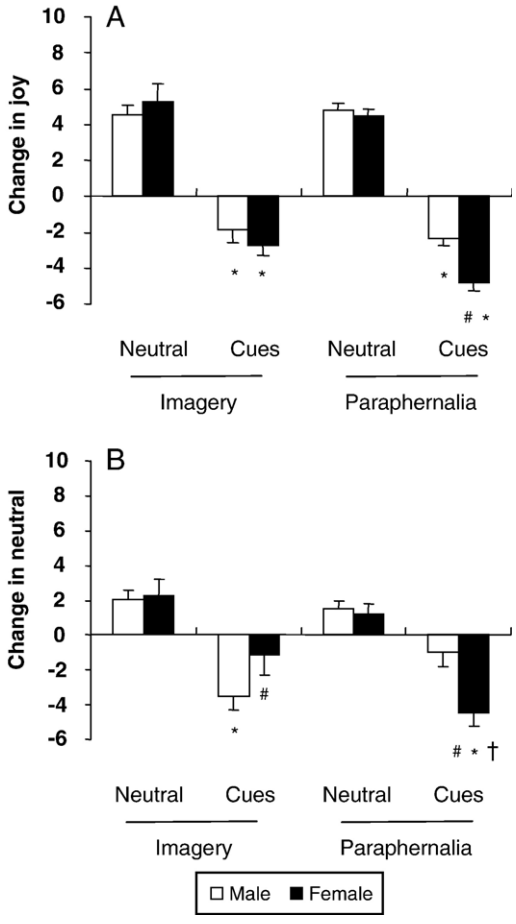

Fig. 4. Mean change of positive emotion scale rating from baseline to imagery stimuli (neutral or cue) and paraphernalia stimuli (neutral or cue). A) Joy rating; B) Neutral rating. *$P<0.05$ with neutral cue responses in same stimuli type; $^{\dagger}P<0.05$ with imagery cue responses; $^{\#}P<0.05$ with cue responses in male subjects.

4. Results

4.1. Overall effect of cues

Both imagery and paraphernalia cues were effective; for every dependent measure (heroin craving, anxiety, five emotion ratings, and three cardiovascular measures), the main effect of Cue vs. Neutral was significant (Table 3).

4.2. Imagery cues vs. paraphernalia cues

For heroin craving, paraphernalia cues were somewhat more effective than imagery cues [CueVsNeutral × CueType: $F(1,47)=4.68$, $p=.036$; Table 3; Fig. 1A]. Inspection of Fig. 1A suggests that this was attributable to low responsiveness to imagery among males, though the relevant interaction was not statistically significant [Sex × CueVsNeutral × CueType: $F(1,47)=3.17$, $p=.08$].

For sadness [CueVsNeutral × CueType: $F(1,47)=10.59$, $p=.002$] and heart rate [CueVsNeutral × CueType: $F(1,47)=4.98$, $p<.031$], imagery cues were somewhat more effective than paraphernalia cues (Table 3; Figs. 2C and 3A). For the other seven dependent measures, the two stimulus types were not differentially effective in the sample as a whole. However, the two stimulus types were often differentially effective within each gender, as described below.

4.3. Gender differences

For almost every dependent measure on which there was a gender difference, the difference occurred for imagery only or for paraphernalia only.

Men showed stronger responses than women on only one dependent measure: anger [paraphernalia only; $F(1,47)=19.61$, $p=.0001$; Fig. 2B]. Women showed stronger responses than men on six dependent measures: heroin craving [imagery only; $F(1,47)=21.65$, $p=.0001$; Fig. 1A], sadness [imagery only; $F(1,47)=17.04$, $p=.0001$; Fig. 2C], systolic blood pressure [imagery only; $F(1,47)=21.31$, $p=.0001$; Fig. 3B], heart rate [imagery only; $F(1,47)=5.43$, $p=.024$; Fig. 3A], diastolic blood pressure [paraphernalia only; $F(1,47)=5.69$, $p=.021$; Fig. 3C], and decreased joy [paraphernalia only; $F(1,47)=15.72$, $p=.0002$; Fig. 4A].

For decreases in ratings of neutral emotion, the direction of the gender difference varied with the cue type; men responded more strongly to imagery [$F(1,47)=5.73$, $p=.021$] and woman responded more strongly to paraphernalia [$F(1,47)=14.43$, $p=.0004$; Fig. 4B].

Ratings of fear and anxiety did not differ by gender.

5. Discussion

We found that heroin craving was significantly increased by exposure to drug imagery or drug paraphernalia but not neutral imagery or neutral items. In addition, imagery and paraphernalia produced significant increases in subjective anxiety, negative emotions, systolic and diastolic blood pressure, and heart rate, as well as decreases in positive and neutral emotions. We also found that imagery and paraphernalia induce different pattern of responses, and that women tended to respond more strongly on most measures.

Our findings are consistent with those of previous studies in which increases in drug craving and physiological reactivity were produced by different types of drug-related cues, including drug paraphernalia (either in vivo or on videotape) or drug-related imagery (Chiamulera, 2005; Drobes and Tiffany, 1997; Robbins and Ehrman, 1992; Sinha et al., 2000; Tiffany and Drobes, 1990). Several previous studies with opiate-dependent subjects have reported that craving is accompanied by dysphoric mood states and/or increased subjective anxiety (Childress et al., 1994; Powell et al., 1992).

Contemporary versions of withdrawal-based theories of addiction emphasize the role of classical conditioning in the elicitation of withdrawal-like reactions. It has been theorized that, following repeated pairings with the abused drug, previously neutral stimuli acquire incentive-motivational properties through a process of associative learning (O'Brien et al., 1992; Stewart et al., 1984). When exposed to previously drug-paired stimuli, drug abusers report intense subjective craving and autonomic arousal (Ehrman et al., 1992; Grant et al., 1996; Sinha et al., 2000). Dysphoric mood states and/or increased subjective anxiety may co-occur with drug craving (Childress et al., 1994; Lu et al., 2005; Wikler, 1973). For example, the negative affective state of opiate withdrawal dramatically motivate compulsive heroin-seeking behavior and opiate abuse (Baker et al., 2004; Koob and Le Moal, 2001); subjective anxiety has been linked to cocaine craving associated with exposure to cocaine-associated cues (Bauer and Kranzler, 1994; Berger et al., 1996). Our findings of increased negative emotion in response to heroin cues are consistent with these reports and further indicate that the negative affectivity induced by heroin-cue exposure is comparable to heroin craving produced by cue exposure in heroin-abstinent individuals (Wikler, 1973). Drug craving often precedes drug seeking and may cause abstinent individuals to relapse to prior patterns of drug use (Gawin, 1989), although the relationship between craving and relapse remains disputed (Tiffany and Carter, 1998; Tiffany and Drobes, 1990).

In our study, drug cues also increased heart rate and blood pressure. Cardiovascular changes in response to psychological stimuli are well documented among normal subjects (Lovallo et al., 1990; Mason, 1975). Increases in heart rate and blood pressure have been consistently reported in cue-reactivity studies in drug-dependent individuals (Carter and Tiffany, 1999; Sinha et al., 1999, 2000). Similarly, cue-induced craving for cocaine is accompanied by increases in adrenocorticotrophic hormone, cortisol, prolactin, and norepinephrine, and these increases may be associated with the subjective anxiety associated with craving (Sinha et al., 2006, 2003).

Gender differences in drug dependence have been reported in terms of epidemiology, acute biological response to drug administration, patterns of use, and progression and health consequences of drug dependence (see Lynch et al., 2002 for a review). It has been difficult to interpret these findings because

they may be due to sociocultural factors or due to biological differences between woman and men. A small body of work has evaluated the influence of gender on cue reactivity in drug-dependent individuals, and this work has produced conflicting results. Some investigators have found that women were more likely than men to report increased craving in response to cocaine-associated cues (Lynch et al., 2002; Robbins et al., 1999). But other investigators found a higher reactivity in males (Sterling et al., 2004) or no gender difference in reports of cravings (Avants et al., 1995; Fox et al., 2006) or skin-conductance response (Negrete and Emil, 1992; Robbins et al., 1999; Sterling et al., 2004). Similarly, in tobacco smokers, no gender effect was seen in ratings of craving following exposure to tobacco-associated cues (Franklin et al., 2004; Niaura et al., 1998). In alcohol-dependent individuals, there was no gender differences in reactivity to beverage cues alone, but a greater urge reactivity in response to experimentally induced negative moods in women than in men (Monti et al., 1993). Based on these preliminary findings, it has been proposed that negative mood situations may place women at a higher risk for relapse than men (Monti et al., 1993). Here, we found a significant effect of gender on some aspects of cue reactivity. Presentation of heroin-associated imagery scripts produced more heroin craving, sadness, and cardiovascular changes in women than in men. These results suggest that women may be more reactive than men to drug-associated imagery. Presentation of heroin-associated paraphernalia did not produce a gender difference in craving, though it did produce more anger in men than in women (and greater decreases in joy and increases in diastolic blood pressure in women than in men). This set of findings suggests that men and women differ in cue responsiveness in complex ways.

It is not yet possible to determine the relative roles of sociocultural and biological factors underlying the gender differences we observed. The possibility that biological factors play at least some role is supported by the preclinical finding that female rats responded more robustly to nicotine-associated stimuli than their male counterparts (Chaudhri et al., 2005). On the other hand, the few conditioned place preference (CPP) studies performed with female rats have not suggested any such sex difference (Bardo et al., 1995; Schechter, 1992; Schindler et al., 2002). Further studies evaluating effect of opiates in such paradigms are needed to address this issue.

This present study has several limitations. First, the number of subjects is small. Second, the subjects had been abstinent from heroin for at least three weeks; it is not known how the results would generalize to individuals actively abusing opiates. Third, we did not attempt to control for menstrual cycle, which may affect cue reactivity in women (Franklin et al., 2004).

With those caveats, our results suggest that some psychological and physiological responses to heroin-associated stimuli may be greater in females than in males and that this gender effect may depend on the type of cue being used. In particular, imagery scripts induced less heroin craving in men than in women, despite the absence of a significant gender difference in self-reported imagery vividness. If this finding is replicated, it may suggest that investigators wishing to induce heroin craving in male research participants should choose paraphernalia cues over imagery scripts. Further characterization of gender differences in cue-elicited craving may also help target treatment interventions intended to prevent relapse.

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