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Diurnal variation in cue-induced responses among protracted abstinent heroin users

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ABSTRACT

Objectives: The physiological and psychological responses to drug cue exposure have been assessed in substance abusers. However, there is no study to demonstrate whether the responses to drug cue exposure are diurnal dependence. The present study was to examine whether there was a variation in drug-related cue reactivity across the diurnal cycle among recently abstinent opiate addicts.
Methods: Four groups of 20 abstinent heroin dependent patients (n=80) were exposed to both neutral and drug-related videos at four separate times during the day: 8:00, 12:00, 16:00, and 20:00 h. Physiological and psychological responses, including heart rate, blood pressure, heroin craving, and subjective anxiety were assessed before and after each cue exposure.
Results: Drug cue significantly increased craving ratings compared to neutral cues across all the four separate times of day. Drug cue-induced craving was greater in the morning (8:00 am) than noon (12:00 pm), but was similar to evening assessments (8 pm). Drug cues also significantly increased anxiety, which positively correlated with cue-induced craving. Drug cues increased heart rate, systolic and diastolic blood pressures, which were not correlated with cue-induced craving or anxiety. However, no time effects were found on the three physiological measures.
Conclusions: Cue-induced craving could be profoundly affected by the time points of cue exposure, using cue-reactivity paradigm. The relative sensitivity of morning and evening assessments of drug craving suggests a need for replication and further research on mechanisms contributing to these diurnal variations.

1. Introduction

Drug dependent patients show specific physical and psychological responses to drug-related stimuli, so called cue reactivity. Cue reactivity is a conditioning effect, in which drug-related cues associated with prior use of drugs become conditioned stimuli which, in turn, elicit conditioned responses. Wikler (1948) observed "conditioned withdrawal" in abstinent opiate abusers who exhibited symptoms of opiate withdrawal when talking about drugs or returning to environments previously associated with drug taking. Since Wikler's initial findings, early cue-reactivity studies have demonstrated a wide range of conditioned physical responses, such as associating an auditory tone/odor as a conditioned stimulus with naloxone injection (O'Brien, 1975; O'Brien et al., 1976) or exposing participants directly to drug-related cues (Glautier and Drummond, 1994; Sideroff and Jarvik, 1980). Conditioning of psychological reactions in drug abusers can also be produced experimentally (Childress et al., 1986; Glautier and Drummond, 1994; Monti et al., 1993; Powell et al., 1993). These conditioned responses can trigger relapse to drug seeking and taking (see reviews, Childress et al., 1993; Rohsenow et al., 1990; Sinha and Li, 2007). In order to extinguish or minimize such learned associations patients have been repeatedly exposed to drug-related cues while preventing drug taking and seeking (Childress et al., 1986; Franken et al., 1999; Marissen et al., 2007; O'Brien et al., 1990).

The cue-reactivity procedure assesses physiological and psychological responses before and after exposure to a wide range of drug-related cues including sight of drug paraphernalia (Yu et al., 2007), imaginary of craving (Weinstein et al., 1997), drug-related pictures (Waters et al., 2003), words or sentences and videos (Ooteman et al., 2006; Upadhyaya et al., 2004). Physiological responses often include heart rate, salivation, body temperature, skin conductance, blood pressure, and withdrawal symptoms (Carter and Tiffany, 1999; LaRowe et al., 2007). The most commonly collected psychological measures are craving, urge to use, drug-induced arousal, mood swings, and anxiety (Fox et al., 2007; Fox et al., 2005). In order to better understand the neurobiology of cue reactivity and develop pharmacotherapeutic agents for preventing relapse to drug dependence, cue-reactivity studies have integrated brain imaging (Kosten et al., 2006; Volkow et al., 2007), pharmacological manipulations (Ooteman et al.,

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2007; Smelson et al., 2004), acute tryptophan depletion (Petrakis et al., 2002; Petrakis et al., 2001), induction of psychological stress (Fox et al., 2007; Sinha et al., 2003), and behavioral or cognitive tasks (Havermans et al., 2003; Sayette and Hufford, 1994).

Although the cue-reactivity paradigm can reliably induce conditioned responses, several methodological confounders may influence the outcomes of cue reactivity (Carter and Tiffany, 1999; Glautier and Drummond, 1994). First, cues presented earlier in a sequence can induce a stronger cue response than those presented later in the sequence (McCusker and Brown, 1991; Monti et al., 1987). Second, abstinence from drug use also results in a non-specific enhancement in urge reporting, regardless of the presence of cues (Drobes and Tiffany, 1997). Third, lack of a neutral stimulus as a control condition can limit interpreting the specificity of cue-reactivity (Carter and Tiffany, 1999; Glautier and Drummond, 1994).

An uninvestigated potential confound is time of day for assessment. The vast majority of cue-reactivity studies are conducted in the morning. While morning is the time of peak levels for several hormones such as cortisol, which can be altered by both abused drugs and cue-induced craving, other data suggest that the urge to use drugs may peak later in the day. For example, opioid overdoses are brought in to emergency departments most often in the evening hours (Gallerani et al., 2001; Manfredini et al., 1994; Raymond et al., 1992). Thus, craving or urge to drug use may be greater late in the day leading to opioid overdose. However, variation in craving to drug-related cues has not been examined for a circadian or diurnal pattern using a cue-reactivity paradigm. Thus, we designed a study comparing cue-reactivity responses during four different times of the day. Four groups of abstinent heroin-dependent patients were recruited and given cue exposure at 8:00, 12:00, 16:00, and 20:00 h. Psychological (craving and anxiety) and physiological reactions (heart rate and blood pressure) were assessed before and after neutral or drug-related cues in abstinent heroin addicts. We hypothesized that cues-induced psychological and physiological response in substances abusers is affected by the time point of the cue exposure.

2. Materials and methods

2.1. Participants

Eighty male heroin-dependent patients between 20 and 45 years old were recruited from an inpatient treatment center of Beijing Ankang Hospital, Beijing, China. All participants were strictly required to follow a 24-hour daily regime in which daily activity (i.e. meals, sleeping, doing exercise and entertainment) was carried out at specific time each day. The description of their activities at specific time points is as follows: 8:00 and 12:00 is 20 min after breakfast and lunch respectively and all participants were resting. Patients were watching TV at both 16:00 and 20:00. During their stay in rehabilitation center, only one cigarette was permitted after each meal every day. Access to alcohol and illicit drugs is completely prohibited, during the entire period of stay in rehabilitation center. All these ensured that all participants were abstinent from drugs. On the previous day of experiment, participants were not permitted to smoke from 18:00 until the completion of the experiment in the next day.

All participants met DSM-IV criteria for heroin dependence upon admission and had been abstinent from heroin for about four months when they entered experiment for cue paradigm (Table 1). Those who initially diagnosed with DSM-IV criteria for dependence on another psychoactive substance were excluded. In addition, those who were currently on medications for physiological or psychological disorders, and anyone who needs to use other prescribed drugs were excluded from the study. All participants gave written informed consent. The study was approved by Human Investigation Committee of the Peking University School of Medicine. The demographic and substance-abuse characteristics of the participants are summarized in Table 1 and no significant differences were found across four groups.

Table 1
Characteristics of heroin abusers

	Group 1 (8:00) (n=20)	Group 2 (12:00) (n=20)	Group 3 (16:00) (n=20)	Group 4 (24:00) (n=20)
Age (years)	33.7 (6.85)	33.1 (5.75)	34 (7.23)	33.8 (6.62)
Years of education	9.45 (3.36)	9.30 (2.96)	8.85 (3.90)	8.30 (3.16)
Years of regular heroin use	7.76 (4.29)	6.91 (5.77)	7.42 (4.58)	7.71 (4.41)
Amount of heroin use per day (g)	0.85 (0.47)	0.88 (0.61)	0.71 (0.67)	0.73 (0.47)
Duration of abstinence (month)	4.42 (1.50)	4.24 (1.23)	4.06 (1.27)	3.97 (1.25)

Data are presented as mean (±SD). No significant differences were found for all demographic measures.

2.2. Experimental procedure

The participants were randomly divided into four groups and exposed to the same neutral and heroin films at four times of day, 8:00, 12:00, 16:00, and 20:00 h. Neutral cues consisted of natural scenery including trees and flowers, while heroin cues consisted of a film of drug users injecting and smoking heroin (Shi et al., 2007; Yu et al., 2007). Each cue was presented for 5 min. Two sessions, neutral and heroin cue exposure, were conducted in one experimental day. The session of neutral cue exposure was completed before that of heroin cue exposure with a 10 min resting period between. This fixed order was chosen to prevent a "carry-over" effect from drug-related cues to neutral cues (Weinstein et al., 1997). During each cue-exposure session, baseline psychological and physiological responses (see below) were obtained 5 min before cue exposure. Participants were subsequently provided headphones and asked to watch a neutral and subsequently a heroin-related video followed by assessment of the same psychological and physiological responses (Shi et al., 2007; Yu et al., 2007; Zhong et al., 2006).

2.3. Assessments

Heroin craving and anxiety were measured at baseline and immediately following cue exposure using a visual analogue scale starting at 0 (none at all) to 10 (more than ever) (Sinha et al., 2003).

A 9062D Monitor (Baozhong biotechnology Company, Beijing, China) measured systolic and diastolic blood pressure using an arm cuff and heart rate using a pulse sensor attached to the subject's finger. Cardiovascular responses for 5 participants were not obtained, due to monitor failure.

2.4. Data analysis

One-way analysis of variance (ANOVAs) was used to compare differences of the demographic characteristics (age, year of education, years of regular heroin use, amount of heroin use/day, and duration of abstinence) among the four groups. Reactivity to cues was assessed using change scores from baseline (Berger et al., 1996; Robbins and Ehrman, 1992; Sinha et al., 2000). Each dependent measure was analyzed by two-way ANOVA with one between-subjects factor (time of day) and one within-subject factor (stimulus type: neutral vs. heroin-related videos). LSD post-hoc was used. Spearman correlations assessed the association between cue-induced heroin craving and anxiety, as well as cardiovascular responses.

3. Results

3.1. Craving and anxiety

Table 2 shows the rating scores for heroin craving and anxiety at the baseline; no significant differences for rating scores of craving and anxiety were found among the four separate times of day at pre-exposure to neutral or heroin-related cues (p>0.05) (Table 2).

Table 2
Rating scores of psychological and physiological measures at baseline

	Group 1 (8:00)		Group 2 (12:00)		Group 3 (16:00)		Group 4 (20:00)	
	Baseline 1	Baseline 2	Baseline 1	Baseline 2	Baseline 1	Baseline 2	Baseline 1	Baseline 2
Craving	1.9±0.22	1.7±0.24	1.6±0.21	1.4±0.21	1.4±0.23	1.5±0.18	1.7±0.32	1.7±0.32
Anxiety	1.0±0.06	0.9±0.07	1.0±0.0	0.9±0.06	1.1±0.08	1.2±0.1	1.1±0.12	1.1±0.12
HR	80.4±1.9	78.7±1.8	84.3±2.0	82.2±1.9	71.0±2.3*	70.5±2.5*	74.8±1.5*	72.2±1.6*
SP	115.3±2.6	113.7±3.2	121.9±3.2	116.5±2.9	120.3±4.2	119.0±3.3	126.5±4.5	123.6±4.7
DP	74.8±2.7	72.0±2.3	76.6±2.5	76.1±2.6	80.8±3.0	82.1±2.3	83.4±2.7	82.7±2.6

Data are presented as mean (±SEM). Baseline1: pre-exposure to neutral films; Baseline 2: pre-exposure to heroin-related films; HR: heart rate; SP: systolic blood pressure; DP: diastolic blood pressure.
$p<0.05$, compared with group 1 at each baseline.

Fig. 1A shows changes of craving ratings for neutral or heroin-related cue exposure at four separate times of day. Overall, participants reported greater craving to heroin-related cues than neutral cues in a time-dependent fashion [time of day: $F_{(3,\ 76)}=4.55$, $p<0.05$; stimuli type: $F_{(1,\ 76)}=97.56$, $p<0.01$; interaction: $F_{(3,\ 76)}=3.27$, $p<0.05$]. Post-hoc testing found no significant difference in craving ratings to neutral stimuli in the four groups ($p>0.05$). However, compared to 12:00 (noon), participants reported significantly higher levels of craving to drug-related cues at 8:00 and 20:00 ($p<0.05$), indicating that craving ratings to drug-related cues were greater not only in the morning, but also in the evening compared to the noon.

Fig. 1B shows anxiety ratings for neutral and drug-related cues. Consistent with self-reports of craving, higher anxiety was reported for heroin cues than neutral stimuli [stimuli type: $F_{(1,\ 76)}=28.71$, $p<.0001$]. Time of day did not reach statistical significance [$F_{(3,\ 76)}=2.0$, $p=0.12$], indicating that there were no significant differences in anxiety ratings at the four separate times of day. And no interactions were found.

3.2. Cardiovascular measures

Table 2 also shows the three cardiovascular measures at baseline; no significant differences for SP and DP were found among the four separate times of day at pre-exposure to neutral or pre-exposure to heroin-related cues ($p>0.05$) (Table 2). However significant differences were found for HR among the four separate times of day at pre-exposure to neutral cues [$F_{(3,\ 71)}=9.25$, $p<0.01$] or heroin-related cues [$F_{(3,\ 71)}=7.48$, $p<0.01$]; HR were lower at 16;00 and 20:00 than at 8:00 and 12:00, which is consistent with the findings in health subjects (Recordati and Zanchetti, 2008).

Fig. 2 shows changes of the three cardiovascular measures in response to neutral and drug-related cues at the four times of day. The participants showed significantly higher HR, SP and DP to heroin cues than to neutral stimuli [Stimuli type: HR: $F_{(1,\ 71)}=17.68$, $p<0.001$; SP: $F_{(1,\ 71)}=26.09$, $p<0.001$; DP: $F_{(1,\ 71)}=11.82$, $p<0.001$]. However, time of day had no significant effect on HR, SP and DP responses [time of day: HR: $F_{(3,\ 71)}=0.70$, $p=0.56$; SP: $F_{(3,\ 71)}=0.49$, $p=0.69$; DP: $F_{(3,\ 71)}=0.80$, $p=0.50$]. Also no significant for interactions of stimuli type and time of day were found in three cardiovascular responses [interaction: HR: $F_{(3,\ 71)}=0.01$, $p=0.99$; SP: $F_{(3,\ 71)}=0.66$, $p=0.58$; DP: $F_{(3,\ 71)}=1.5$, $p=0.22$].

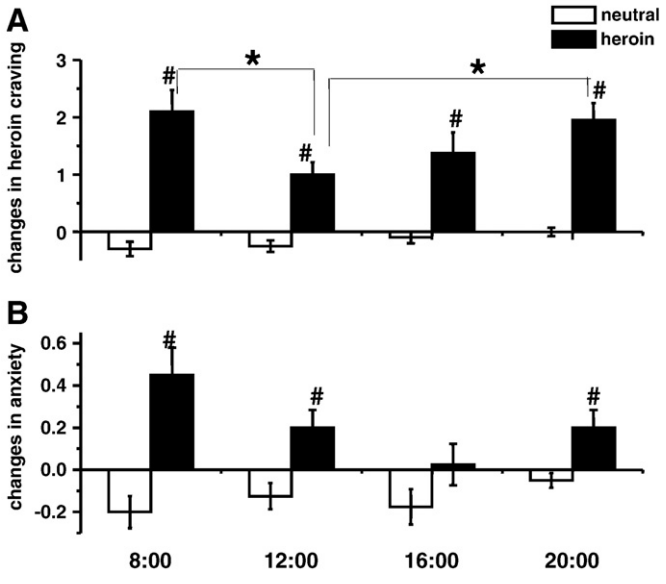

Fig. 1. Changes in craving (A) and anxiety (B) in response to neutral and drug cues. A. Drug cues significantly enhanced craving in time-dependently, with 8 am and 8 pm (20:00 h) values significantly higher than noon (12:00 h) values; B. Drug cues significantly increased anxiety ratings except at 16:00 h. # $p<0.05$, comparing changes in craving score or anxiety score in neutral video condition within the same time group; *$p<0.01$, comparing with the changes in craving score at noon. Data are presented as mean±SEM.

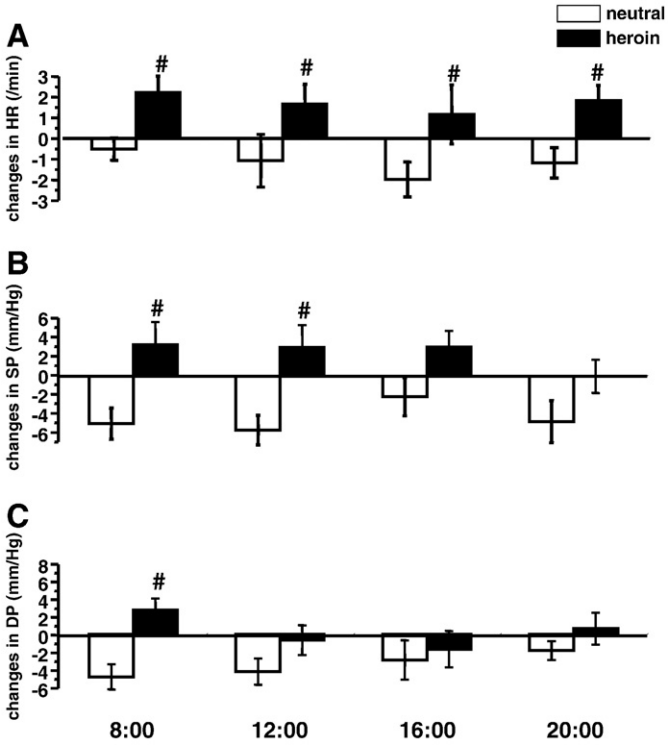

Fig. 2. Changes in cardiovascular measures from baseline in response to neutral and drug cues. A. heart rate (HR); drug cues significantly increased changes of HR at 8:00, 12:00, 16:00 and 20:00 h; B. systolic pressure (SP); drug cues significantly increased changes of SP at 8:00 and 12:00 h; C. diastolic pressure (DP); drug cues significantly increased changes of DP at 8:00 h. # $p<0.05$, comparing with the changes in HR, SP or DP to neutral cues within the same time of day. Data are presented as mean±SEM.

3.3. Correlation between changes of craving or anxiety and cardiovascular measures

Change of heroin craving was not associated with changes in SP, DP or HR ($r=0.02$, $p=0.84$; $r=0.16$, $p=0.6$; $r=0.08$, $p=0.50$ for SP, DP and HR, respectively). Also, no significant correlations were found between changes in anxiety and changes in SP, DP or HR ($r=0.06$, $p=0.63$; $r=0.14$, $p=0.22$; $r=0.10$ $p=0.38$ for SP, DP and HR, respectively). However, cue-induced craving and anxiety were significantly correlated ($r=0.23$, $p=0.04$).

4. Discussion

The current study demonstrated that heroin-related cues induced significant increases in psychological and physiological reactions such as heroin craving, anxiety, HR, DP and SP in protracted abstinent heroin abusers. Furthermore, heroin craving was significantly affected by the time of day for cue exposure with the greatest responses during the morning and evening. Since the vast majority of the cue-reactivity studies are conducted in the morning, clinical experience has perhaps led to this selection of a time of day as the most sensitive time for detecting drug cue-induced craving (Fox et al., 2007). This time of day might be predicted based on diurnal variations in hormone levels, particularly since the highest cortisol and hypothalamo-pituitary-adrenal activity occurs in the morning (Wilhelm et al., 2007). Although we found these expected greater craving responses in the morning than in the noon, surprisingly the evening responses were as great as the morning responses. However, neither the anxiety reports nor the cardiovascular responses to drug cues showed this second evening peak perhaps reflecting their closer tie to diurnal rhythms of the hormonal systems. The greater evening craving response to heroin cues may be consistent with the clinical reports that overdoses with opiates are more frequent later in the day (Gallerani et al., 2001; Manfredini et al., 1994; Raymond et al., 1992). The pathophysiology for this peak of overdoses and possibly peak in craving may provide a lead for future investigations of this unexpected finding, if replicated in subsequent studies.

Variations in craving responses to drug-related cues based on the time of day may reflect a circadian rhythm interaction with craving as a protracted, behavioral effect of opioid withdrawal (Vitaterna et al., 2001). Acute opioid effects such as morphine-induced analgesia (Frederickson et al., 1977) and feeding responses (Bhakthavatsalam and Leibowitz, 1986), as well as drug reinforcement and drug-seeking behaviors such as self-administered heroin and conditioned place preference to morphine are diurnally regulated (Negus et al., 1995; Smith et al., 2006; Tahsili-Fahadan et al., 2005). Humans exhibit diurnal variations in response to analgesia and sedation from morphine (Citron et al., 1992; Graves et al., 1983). As previously noted even opioid overdose has a circadian rhythm (Gallerani et al., 2001; Manfredini et al., 1994; Raymond et al., 1992).

Our present findings suggested a relative disassociation between the physiological and psychological responses to the heroin cues. First was a marginal difference between the morning and afternoon for the increase in heart rate and blood pressure compared to a more robust difference in cue-induced craving. Second, the craving response was alone and not supported by the physiological or anxiety ratings in showing a second evening peak in the heroin cue-induced responses. Overall, many cue-reactivity studies in addiction research have shown relatively large effect sizes for self reported craving and small effect sizes for physiological responses (Carter and Tiffany, 1999). These reviewers suggest that physiological responses can be influenced by many other manipulations unrelated to drug cues, while craving ratings are likely to be more cue-specific. Thus, future examination of this diurnal variation in drug cue-induced responses appears warranted and might include within patient designs and consider patients who are just after detoxification or earlier in protracted withdrawal than the average of 4 months since last heroin use in this population.

Several limitations of the present study might be addressed in a replication. First, the times of day for cue exposure were at 8:00, 12:00, 16:00, and 20:00, which did not cover an entire period of 24 h. This restricted time range reflected our needing to maintain the participants' regular daily regime in the rehabilitation center, and we could not conduct the experiment late at night or very early in the morning. Second, we used four separate groups for each time of day rather than an ideal within-subject design with cue-induced responses assessed in one group of participants across four times of day. For this first study we were concerned about habituation and the sensitivity of cue-induced responses following repeated exposure. Nevertheless, we found differences by time of day in spite of the relatively larger variation among time points that occurs with an across-groups design. Third, it remained undetermined whether the daily activities of the participants would have profound influences on the diurnal effects observed. Given the fact that participants all follow a 24-hour regime strictly in present study, it's thought that if any, their daily activities have marginal effect on the present findings. Lastly, the nicotine withdrawal periods (range of 14 to 26 h) of the four group participants were not identical, which may be also the limitation in our findings and should be better controlled in future studies.

Future studies can address all of these limitations and perhaps find stronger associations between diurnal variation and these subjective and physiological measures.

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