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ORIGINAL INVESTIGATION

Psychosocial stress after reactivation of drug-related memory impairs later recall in abstinent heroin addicts

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Abstract
Introduction Stress and stress hormone are known to play important roles in modulating different stages of memory including reconsolidation. In a previous study, we found that treatment with stress or corticosterone after a single memory reactivation disrupted reconsolidation of a drug-related memory in rats. Here we presumed that stress after memory reactivation can effectively inhibit drug-related memory by disrupting its reconsolidation in abstinent heroin addicts.
Materials and methods In the present study, 21 abstinent heroin addicts learned a word list (containing ten neutral, ten heroin-related negative, and ten heroin-related positive words) on day 1; retrieval of a word list (learned 24 h earlier) was made on day 2; and immediately after retrieval, they were exposed to either a standardized psychosocial laboratory stressor (Trier Social Stress Test) or a control condition in a crossover manner. On day 3, free recall of the word list and other psychological and physical responses were assessed.
Results The stressor induced a significant increase in salivary free cortisol and a decrease in mood. Memory recall was significantly impaired after the stress condition. Follow-up analysis revealed that heroin-related negative and positive words (i.e., heroin-related words) were affected, whereas no effect was observed for neutral words. No changes were detected for cued recall, working memory, or attention. Stress after drug-related memory retrieval significantly decreased its subsequent recall, likely through impaired drug-related memory reconsolidation process.
Conclusion Reconsolidation blockade may thus provide a potential therapeutic strategy for the prevention of relapse in drug addiction.

Keywords Stress · Glucocorticoids · Heroin-related memory · Reconsolidation

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Introduction

A pathological usurpation of neural processes that normally serve reward-related learning and memory has been thought to underlie the progress of drug addiction (Berger et al. 1989; Hyman and Malenka 2001; Robbins and Everitt 1999, 2002; White 1996). Maladaptive memories associated with the effects of drugs of abuse is possible to result in relapse to drug-seeking and -taking behaviors that are often found in drug-dependent patients. Nonetheless, previously formed memories are susceptible to disruption immediately after recall due to a necessity for reconsolidation. According to current reconsolidation theories, reactivation of a consolidated memory renders it once again vulnerable to amnestic treatment (Campbell et al. 1968), and the so-called reconsolidation of this old memory requires de novo protein synthesis (Amorapanth et al. 2000; Aoki et al. 2003). Notably, repeated relapse induced by drug-related cues is likely to be influenced by memory reconsolidation in which a consolidated memory could again return to a labile state after retrieval (Lewis et al. 1968; Misanin et al. 1968; Nader 2003; Nader et al. 2000b; Przybyslawski and Sara 1997; Sara 2000a, b).

Ample evidence of animal studies has demonstrated that the reconsolidation of memory is subjective to various behavioral and pharmacological manipulations. The process of reconsolidation can be profoundly affected by amnesic effects induced by the administration of blockers, such as the protein synthesis inhibitors or β-blockers (Nader et al. 2000a; Przybyslawski et al. 1999), or also by the learning of a new memory (Boccia et al. 2005; Walker et al. 2003), after the presentation of a reminder. Using the task of conditioned place preference, various substrates in the brain, including Zif268 antisense oligodeoxynucleotides, β-adrenoceptor, and glutamate receptors have been demonstrated to play an integrated role in modulating the reconsolidation of drug-conditioned memory (Bernardi et al. 2006; Kreek and Koob 1998; Lee et al. 2006; Popik et al. 2006). Miller and Marshall (2005) showed that reconsolidation of cocaine-conditioned place preference (CPP) can be disrupted by interfering in the molecular processes within the nucleus accumbens core.

The importance of stress and stress hormone in the different stages of memory processes including reconsolidation has been implicated in the literature (Diamond et al. 1996; Loscertales et al. 1998; Newcomer et al. 1994, 1999; Roozendaal 2002). Stress and glucocorticoids enhance (Loscertales et al. 1998; Roozendaal 2002) as well as impair (Diamond et al. 1996; Newcomer et al. 1994, 1999) memory consolidation, and memory retrieval is usually impaired (de Quervain et al. 1998; Kuhlmann et al. 2005b). Moreover, in our recent study, we found that treatment with stress or corticosterone after a single memory reactivation blocks reconsolidation of a drug-related memory in rats. However, little is known regarding the effects of stress on reconsolidation of drug-related memories in human. So, we presumed that stress after memory reactivation can effectively inhibit drug-related memory by disrupting its reconsolidation in abstinent heroin addicts.

The current research was designed to investigate the amnesic effect on heroin-related memory by psychosocial stress immediately after heroin-related memory retrieval in abstinent heroin addicts. A wide range of psychological and physical responses were assessed to examine the effects of psychological stress on drug-related memory reconsolidation.

Materials and methods

Participants

The study was conducted according to human research guidelines and was approved by the Peking University Research Ethics Board. Informed consent was obtained from all subjects before testing, who were compensated for taking part in the study. Prior to enrollment, participants underwent thorough physical and psychiatric evaluations, including medical-history interview, physical examination, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV), and clinical laboratory tests (including electrocardiogram, blood chemistry, and urinalysis). Participants met DSM-IV criteria for heroin dependence. Exclusion criteria were: current DSM-IV diagnosis of any affective, anxiety, or psychotic disorder and current dependence on any substance besides heroin and nicotine (assessed by urine test and self-report). Twenty-one male inpatient abstinent heroin addicts between 24 and 45 years of age (mean±SE; 31.4±1.3) were recruited from Addiction Treatment Center of Beijing Ankang Hospital, Beijing, China. They had a mean lifetime history of regular heroin use of 7.1±0.8 (mean±SE) years and average heroin use 0.6±0.1 (mean±SE) g/day. Upon enrollment, they reported having been abstinent 3.9±0.3 (mean±SE) months. Urine drug screens were conducted three times per week.

Demographic characteristics of the participants are summarized in Table 1.

Procedure

This was a crossover study, consisting of a total of six sessions per participant, with each session occurring on a separate day. An interval of 4 weeks separated the first three sessions from the second three. On day 1, participants arrived in the morning (9:30–10:30 A.M.) and learned a list of 30 words (ten heroin-related positive words, ten heroin-related negative words, and ten neutral words; for details, see below). Participants were initially given 2 min to learn the words and subsequently asked to write down the words they were able to recall. The same learning trial was immediately repeated once (Kuhlmann et al. 2005b).

On day 2, participants filled out a mood questionnaire upon arrival in the morning. Thirty minutes later, participants were asked to write down the words they had learned on the previous day. Immediately, they were challenged with the

Table 1 Demographic characteristics of participants

Characteristic	Mean±SEM/*N* (%)
Age	31.4±1.3
Years of education	9.2±0.5
Dose used (g/day)	0.6±0.1
Duration of heroin use (years)	7.1±0.8
Months since last heroin use	3.9±0.3
Marital status/*N* (%)	
Married or cohabiting	9/42.9
Separated or divorced	2/9.5
Never married	10/47.6

Trier Social Stress Test (TSST; Kirschbaum et al. 1993) or underwent a control condition for 15 min. After that, participants filled out the same mood questionnaire again. Cortisol, heart rate, and blood pressure were measured before TSST or control condition (0 min), immediately afterward (+20 min), and 10 min later (+30 min).

On day 3, participants arrived at the laboratory in the morning at the same time, and participants were asked to write down the words they had learned on day 1. Cued recall was assessed immediately after free recall by randomly presenting part of the word on a piece of paper, with instructions to complete the word with the previously learned words. Finally, attention and working memory were assessed.

After 4 weeks, participants returned for days 4, 5, and 6, during which the same procedures were repeated with the alternate condition (TSST or control) counterbalanced among participants.

Task battery

TSST task The TSST is a well-established paradigm to produce a significant hypothalamic–pituitary–adrenal response to stressful events in a clinical setting (Dickerson and Kemeny 2004; Kirschbaum et al. 1993; Kuhlmann et al. 2005b). The TSST began with a 2-min preparation period followed by 5 min of public speaking (a simulated job interview focusing on personal strengths and weaknesses) in front of a group of staff (containing one man and one woman wearing formal coats). Immediately following the 5 min of speaking, the participants were asked to do mental arithmetic (i.e., counting backward from 2,308 by 13) aloud in front of staff for 5 min (Dickerson and Kemeny 2004; Kuhlmann et al. 2005b; Mason 1968). In addition, the subjects are videotaped. The control condition consisted of a 5-min chat with a tester (about a movie or a book) and 5 min of rest. The challenges were given immediately after retrieval of words, but the subjects were not informed in advance.

Memory for words Two parallel Chinese word lists were used in the current study. They were presented to participants on paper. The word list contained ten heroin-related positive words (e.g., heroin, syringe), ten heroin-related negative words (e.g., withdrawal, diarrhea), and ten neutral words (table, refrigerator). In a pilot study, 100 abstinent heroin patients (who did not participate in the present study) rated the emotional valence of the words on a seven-point scale ranging from negative (1) over neutral (4) to positive (7) (Kuhlmann et al. 2005a). Positive heroin words received an average rating of 6.48±0.42 (mean± SD), range 5.0–7.0; negative heroin words received an average rating of 1.23±0.28 (mean±SD), range 1.0–1.9, while neutral nondrug words received an average rating of 4.39±0.38 (mean±SD), range 3.6–5.2. This difference was significant ($F_{(2,198)}$=5,635.55, p<0.001; post hoc t test, all p<0.01). This word list was used to test the effect of psychosocial stress on the reconsolidation of heroin-related words in abstinent heroin addicts.

Working memory (digit-span test) This task was used to assess working memory in all participants. Several series of digits of increasing length were read to the participants, who were required to repeat each series. Each set length was tested twice. A forward and a backward condition were used. Participants earned one point for each correctly repeated set (Wechsler 1987).

d2 test of attention/psychomotor speed From a series of the letters d and p, with one or two lines above and/or below each letter, the participants were asked to mark the d's with two lines as quickly and accurately as possible. A summary test score was calculated using the number of correctly marked d's minus the number of errors (Brickenkamp 1994).

Mood assessment Participants completed an adjective checklist containing 32 words to assess bad versus good mood (16 items), alertness versus fatigue (eight items), and calmness versus restlessness (eight items). On a scale of 0 to 5, participants had to rate how much each word matched their current state (Kuhlmann et al. 2005a; Steyer et al. 1994).

Cortisol, blood pressure, and heart rate assessment

Saliva was collected using Salivette collection devices (Sarstedt, Nümbrecht, Germany). Free cortisol levels were measured using a commercially available immunoassay (Immuno-Biological Laboratories, Furui Company, Beijing, China). Interassay and intra-assay variations were <15%. Blood pressure was measured with a 9062D monitor (Baozhong Biotechnology Company, China). Heart rate was measured continuously with a sensor attached to the participant's finger (Shi et al. 2007).

Statistical analysis

Repeated measures analyses of variance (ANOVAs) with the within-subjects factors Challenge (stress and control) and Valence (positive, negative, and neutral) were used to compare word free recall on days 3 and 6. Repeated measures ANOVAs with the within-subjects factors Challenge (stress and control) and Time (0, +20, +30 min) were used to analyze cortisol levels, systolic pressure, diastolic pressure, and heart rate. Repeated measures ANOVAs with the within-subjects factors Challenge (stress and control) and Time (pre-challenge and post-challenge) were used to analyze subjective ratings. Post hoc pairwise comparisons

were done with Fisher's least significant difference. Other cognitive measures (cued recall, working memory, and attention) were analyzed by paired *t* tests. *p* values less than or equal to 0.05 were considered statistically significant. The analyses were performed with SPSS 13.0.

Results

The effect of psychosocial stress on heroin-related word memory reconsolidation

The stress challenge significantly affected reconsolidation of the words in abstinent heroin users (the main effect of Challenge, $F_{(2,40)}=6.29$; $p<0.05$, interaction of challenge by valence, $F_{(2,40)}=5.27$; $p<0.05$). Post hoc analysis revealed that the stress condition reduced recall of heroin-related positive words ($t_{(20)}=3.52$, $p<0.05$) and heroin-related negative words ($t_{(20)}=5.06$, $p<0.01$) but not neutral words ($t_{(20)}=0.45$, $p>0.10$; Fig. 1).

Salivary cortisol levels

As expected, the stress challenge significantly increased salivary cortisol concentrations (main effect of Challenge, $F_{(2,40)}=10.06$, $p<0.01$; interaction of Challenge by Time, $F_{(2,40)}=8.86$, $p<0.05$). Post hoc *t* tests between the stress and control conditions showed significantly higher cortisol concentrations at +30 min ($t_{(20)}=-5.263$, $p<0.01$; Fig. 2).

Blood pressure and heart rate measures

The stress condition (compared to the control condition) significantly increased systolic pressure (main effect of Challenge, $F_{(2,40)}=6.81$, $p<0.01$; interaction of Challenge by Time, $F_{(2,40)}=5.03$, $p<0.05$), diastolic pressure (main effect of Challenge, $F_{(2,40)}=3.14$, $p<0.05$) and heart rate (main effect of Challenge, $F_{(2,40)}=25.4$, $p<0.01$); interaction of Challenge by Time, $F_{(2,40)}=18.83$, $p<0.01$). Post hoc *t* tests showed that significant differences were at +20 min (all *p* values <0.05, Fig. 3a–c).

Other cognitive measures

The stress challenge had no effect on measures of cued recall, working memory, or attention (all *p* values >0.10; Table 2).

Subjective ratings

A significant Challenge by Time interaction was observed only for calm versus restlessness ($F_{(1,20)}=8.72$, $p<0.05$), reflecting a decrease in calm after the TSST (confirmed by a paired *t* test, $p<0.05$). For the other two scales, there was no Challenge by Time interaction (all *p* values >0.10; data not shown; Table 2).

Discussion

We found that acute stress immediately after the word list retrieval impairs recall of drug-related positive and negative but not neutral words in abstinent heroin addicts (Table 3 and Fig. 1). The impaired recall of drug-related words is consistent with the hypothesis that the process of reconsolidation of drug-related memory can be profoundly affected by amnesic effects induced by stress after the presentation of a reminder in abstinent heroin addicts.

Numerous studies have demonstrated that stress plays an important but complex role in learning and memory. Stress or glucocorticoids have shown an inverse U-shaped dose–response relationship with consolidation (Lupien and

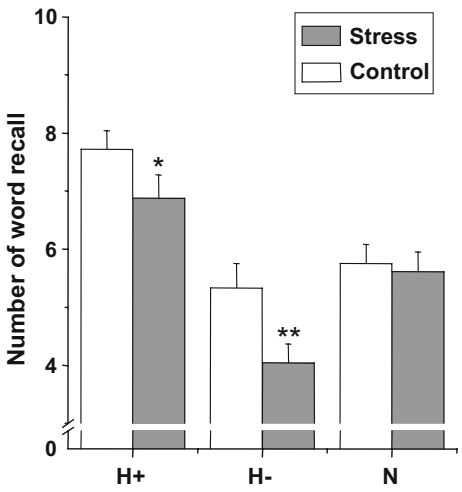

Fig. 1 Recall of words on day 3 or 6. Results are expressed as number of word recalls. *Error bars* represent SE. *H+* heroin-related positive words, *H−* heroin-related negative words, *N* neutral words. *$p<0.05$, **$p<0.01$ differences in post hoc *t* tests. For additional statistical analysis, see "Results"

Condition	Day 1, 4	Day 2, 5	Day3, 6
Control	Learning	Retrieval + C	Testing
Stress	Learning	Retrieval + S	Testing

C, Control;S, Stress

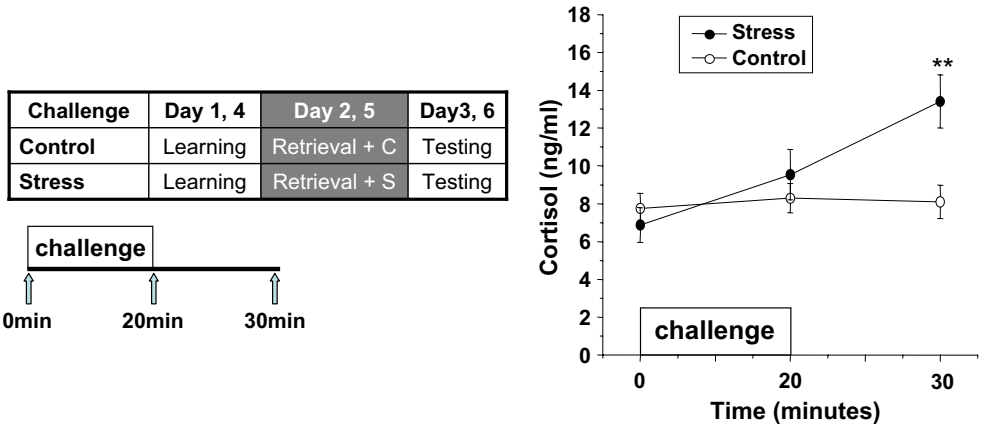

Fig. 2 Salivary cortisol concentrations. "*Challenge*" refers to stress versus control condition (for details, see "Materials and methods." $^{**}p<0.01$ in post hoc *t* tests. *Error bars* represent SE

McEwen 1997; Sandi et al. 1997; Roozendaal et al. 1999) and an inhibitory effect on retrieval (de Quervain et al. 1998; Roozendaal et al. 2002). In humans, acute stress or glucocorticoid administration has beneficial or detrimental effects, depending on several modulatory variables (Lupien and Lepage 2001; Wolf 2003). The previous studies have found a significant negative effect of acute stress or glucocorticoids on delayed memory retrieval in humans (Buss et al. 2004; de Quervain et al. 2000, 2003; Kuhlmann et al. 2005a; Payne et al. 2002; Wolf et al. 2001). Emotionally arousing words were more affected by stress than neutral words (Kuhlmann et al. 2005b). Moreover, moderate cortisol elevations in response to stress, most likely in combination with activation of the autonomous nervous system, can lead to negative effects on retrieval that are similar to those seen with oral cortisol treatment. Only a few groups have studied the effects of stress or glucocorticoids on reconsolidation of memory. Maroun and Akirav (2008) provided the first evidence that stress might have an inhibitory effect on the reconsolidation of memory. They found that, in habituated (low arousal level) and nonhabituated (high arousal level) rats, exposure to an out-of-context stressor impaired long-term reconsolidation of objective recognition memory (Maroun and Akirav 2008). In our recent study, morphine CPP was blocked in rats that received a cold-water stress or corticosterone after a single-trial reactivation by disrupting reconsolidation of morphine reward memory (Wang et al. 2008). In this study, we found that stress after drug-related memory retrieval significantly decreased its subsequent recall through impaired drug-related memory reconsolidation process, a result consistent with the previous studies that stress impairs reconsolidation of recognition memory (Maroun and Akirav 2008; Wang et al. 2008).

Two previous studies have observed enhanced consolidation of emotionally arousing material when compared with neutral material after cortisol or stress treatment (Buchanan and Lovallo 2001; Cahill et al. 2003). However,

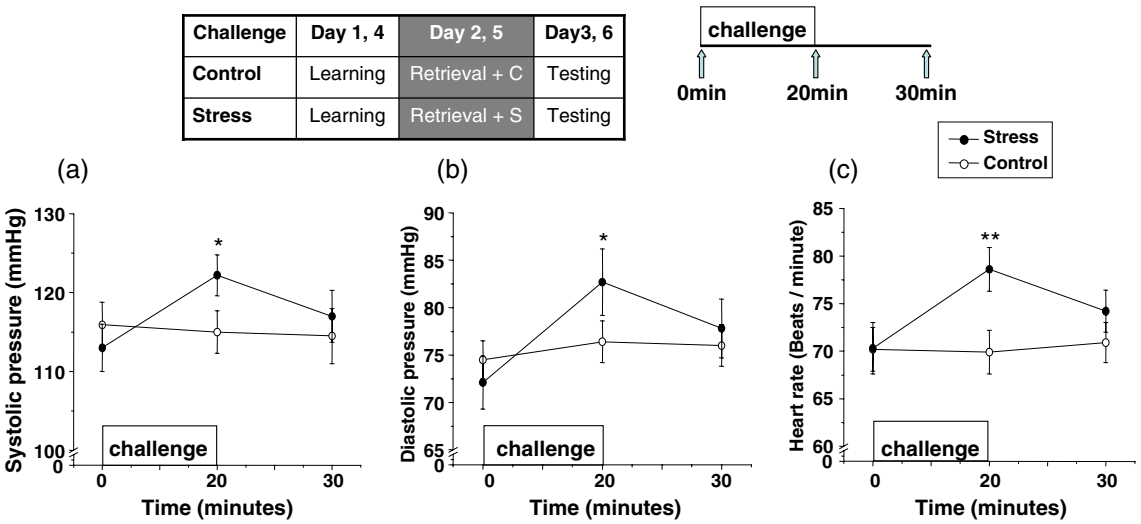

Fig. 3 Systolic pressure (**a**), diastolic pressure (**b**), and heart rate (**c**) in response to the stress or the control condition in participants with heroin dependence. "*Challenge*" refers to stress versus control condition (for details, see "Materials and methods"). $^{*}p<0.05$ and $^{**}p<0.01$ versus control in post hoc *t* tests. *Error bars* represent SE

Table 2 Results of the working memory, attention test, and the mood scale

	Control condition	Stress condition
Digital-span forward	8.62±0.27	8.95±0.23
Digital-span backward	5.81±0.31	6.09±0.27
Attention test	209.28±7.48	194.71±10.25
Calmness versus restlessness mood (before challenge)	3.29±0.29	3.58±0.33
Calmness versus restlessness mood (after challenge)	3.42±0.27	2.73±0.28*

All results are mean±SE. For statistical analysis, see "Results"
*$p<0.05$ differences in paired t tests

our present study found stress impaired heroin-related emotional word reconsolidation when compared with neutral words. Thus, the beneficial and detrimental effects of stress might be depend on whether stress was given after drug-related memory acquisition or after reactivation. The knowledge accumulated so far indicates that reconsolidation of a reactivated memory and consolidation of an initial learning are characterized by distinctive features (Alberini 2005). First, they involve different brain areas and circuits. Consolidation appears to require several areas that are not essential for reconsolidation, and reconsolidation might involve mostly modulatory systems. Second, consolidation and reconsolidation also differ in their temporal dynamics.

The previous finding documented that the interference following reactivation specifically disrupted subsequent reconsolidation rather than immediately reversing prior learning (Walker et al. 2003). In that study, the subjects were required to rehearse the materials learned on day 1 immediately before giving the interference on day 2. However, when retested again on the material on day 3, the material recall was decreased significantly. To confirm that inference following reactivation specifically disrupted subsequent reconsolidation rather than immediately reversing prior learning, another group of subjects was retested again directly after the interference on day 2 rather than on day 3 and showed no decrease compared to the earlier test (Walker et al. 2003). Taken together with previous findings, our results indicated that brief periods of recall of drug-related material return the memory to labile state, rendering it once again vulnerable to interference from stress and in need of reconsolidation.

A large body of evidences has demonstrated that drug-related memory can be prevented by inhibition of its reconsolidation (Bernardi et al. 2006; Kreek and Koob 1998; Lee et al. 2006; Miller and Marshall 2005; Popik et al. 2006). Memory consolidation and reactivation-induced memory "lability" appear to be dependent on some overlapping molecular mechanisms such as *N*-methyl-D-aspartate (NMDA) receptor activation, β-adrenergic receptor activation, and cyclic adenosine monophosphate response element-binding protein activation, whereas some manipulations can affect one process and not the other (Bourtchuladze et al. 1994; Cahill et al. 2000; Debiec and Ledoux 2004; Kida et al. 2002; Lee et al. 2004; McGaugh 2002; McGaugh and Roozendaal 2002; Przybyslawski et al. 1999; Przybyslawski and Sara 1997; Sara 2000a). Systemic NMDA antagonist MK-801 after memory reactivation can reduce the expression of amphetamine-CPP (Sadler et al. 2007). Zif268 ASO can induce blockade of drug memory reconsolidation and impair the maintenance of cocaine-seeking behavior (Baran et al. 2005; Bellani et al. 2006). In our current study as well as in previous studies (Wang et al. 2008), we found that stress or glucocorticoids also can block the drug-related memory reconsolidation.

An important conceptual advance in the past decade has been the process of drug addiction that is a pathological

Table 3 Numbers of word recall for the three categories separately

	Control condition			Stress condition		
	H+	H−	*N*	H+	H−	*N*
First learning trail on day 1	5.26±0.39	3.57±0.33	4.01±0.34	5.43±0.36	3.85±0.44	4.10±0.37
Second learning trial on day 1	7.91±0.31	6.09±0.44	6.40±0.38	7.95±0.39	5.96±0.43	6.37±0.42
Recall of words on day 2	7.50±0.36	5.23±0.49	5.58±0.49	7.43±0.39	5.02±0.36	5.01±0.49
Cued recall on day 3	9.13±0.39	7.50±0.41	7.67±0.35	9.04±0.27	7.24±0.42	7.43±0.28

All results are mean±SE. For statistical analysis, see "Results." There are no significant differences between control and stress condition for all variances.

usurpation of neural processes that normally serve reward-related learning and memory (Hyman and Malenka 2001; Robbins and Everitt 1999). Maladaptive memories associated with the effects of drugs of abuse are possible to result in priming motivation to drug seeking. Primed motivation to engage in addictive behavior has been linked with increased "incentive salience" of target reinforcers (Robinson and Berridge 1993, 2001). From a cognitive science perspective, salience involves selective activation of concepts related to the target reinforcer in memory (Volkow et al. 2002). Such activation should be measurable in terms of recall of drug-relevant versus drug-irrelevant concepts (Zack and Poulos 2004). Therefore, in the present study, we used memory recall for previously learned words including drug-relevant and -irrelevant ones to investigate the effect of stress on heroin-related material memory in abstinent heroin addicts.

The finding of our study is that heroin-related words appear to be more affected by stress than neutral words. A probable mechanism of our finding is that post-reactivation stress inhibiting reconsolidation of the reactivated drug-related memory may act by cortisol, but neutral material is not involved in the impairment effect of cortisol. Stress and stress hormones have important roles in susceptibility to and maintenance of drug dependence. Patients with heroin dependence have been shown to have higher circulating levels of cortisol and altered hypothalamic–pituitary axis activity (Day et al. 1997; Kreek and Koob 1998) which might actually lead to persistent, pathologically strong, drug-related memories in addicts. Another probable interpretation of our findings is that the recall of emotionally arousing words appears to be more affected by stress than recall of neutral words if both word categories are presented within one word list. In this study, we found the arousing rating of these heroin-related words were significantly higher than that of neutral words. Previous studies have observed that there was significant enhancement or impairment effect of cortisol or stress on emotionally arousing material when compared with neutral material (Buchanan and Lovallo 2001; Cahill 2003; Kuhlmann et al. 2005a, b). In our study, the effects of cortisol were similar for positive as well as negative heroin-related memory, which suggests that emotional arousal rather than valence is the crucial aspect of the observed interactions. Pharmacological functional magnetic resonance imaging studies have shown that this effect of glucocorticoids on emotional arousal materials is dependent on β-adrenergic activation in the amygdala (Strange and Dolan 2004; van Stegeren et al. 2005). Amygdala is a critical brain site that mediates memory consolidation and reconsolidation (Debiec and LeDoux 2006; Doyere et al. 2007; Hellemans et al. 2006; Jin et al. 2007; Lee et al. 2005; Maroun and Akirav 2008; McGaugh 2002, 2004; McIntyre et al. 2003; Milekic and Alberini 2002; Nathan et al. 2004; Pare 2003). However, the role of the amygdala in heroin-related memory reconsolidation is not as well understood. In our previous studies, infusion of microinjection of RU28362 (a glucocorticoid receptor (GR) agonist) into the basolateral amygdala (BLA), disrupted reconsolidation of morphine reward memory (Wang et al. 2008). BLA may be a critical brain region involved in integrating the influences of stress or glucocorticoids on drug-related memory.

In addicted individuals, heroin "highs" are inexorably followed by a severe opiate withdrawal syndrome composed of somatic signs and negative affective states, such as dysphoria and depressed mood (O'Brien 1996). The negative affective states of opiate withdrawal dramatically motivate compulsive heroin-seeking behavior and opiate abuse (Baker et al. 2004; Koob and Le Moal 2001). The heroin-related negative words used in this study were almost withdrawal syndrome- and negative affective states-related ones, so the inhibition effect of stress on heroin-related negative word reconsolidation was also prospectively useful for therapy.

Interestingly, the inhibited effect of stress or stress hormone on subsequent drug-related memory recall is inconsistent with its effect on relapse (Shaham 1996; Shaham et al. 2000). The stress effects are modulated by whether the stress is administered before or after drug-related memory reactivation. In our study, administration of stress after retrieval test inhibits reconsolidation of drug-related memory.

The limitation of our study is whether the effect of stress on reconsolidation is specific for heroin-related words or would have also occurred for other emotional words as well. In the present study, the main purpose is to examine the effect of stress on reconsolidation of heroin-related emotional memory. Another limitation is that we did not assess heroin craving, so we do not know whether the mnemonic and physiological effects of the stressor were correlated with a decrease in craving (as we suspect they were). We can state, however, that the effects of the stressor were not so generalized as to change overall cognitive function (e.g., cued recall, attention, and working memory).

In conclusion, stress after drug-related memory retrieval significantly decreased its subsequent recall, likely through impaired the drug-related memory reconsolidation process. These studies provide a model for a therapeutic approach in the treatment of pathological drug-related memories in human research and suggest future experiments designed to explore the specific neurobiological mechanisms of this effect.

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