



Biofeedback combined with cue-exposure as a treatment for heroin addicts



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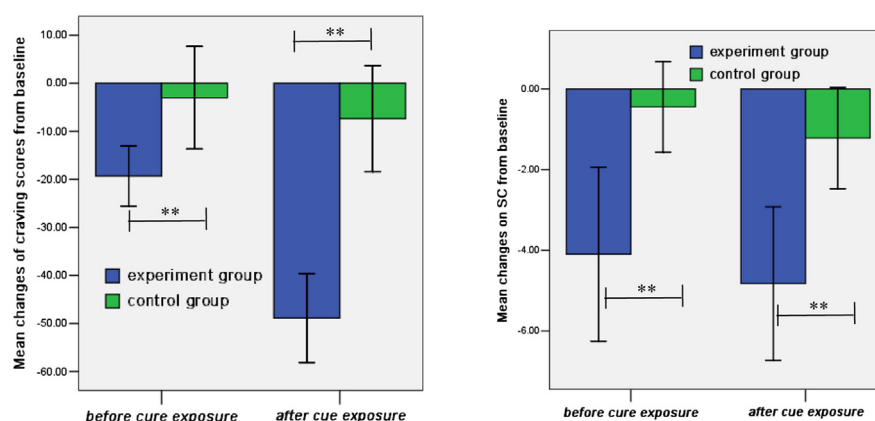
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HIGHLIGHTS

- Heroindependents were randomly assigned to usual treatment with or without CET combined with BT.
- Craving, skin conductance (SC), and muscle electromyography (MEG) were recorded.
- After treatment, the craving, SC and MEG in experiment group were lower than control group.
- Experimental group had a greater decrease in craving, SC, and MEG from baseline after the treatment.
- CET combined with BT is effective in reducing craving in heroin dependents.

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of this study was to test if cue-exposure therapy (CET) combined with biofeedback therapy (BT) could decrease craving and physiological reactivity to drug-related cues in heroin dependents. Forty-five participants were randomly assigned to usual rehabilitation with or without CET combined with BT. Craving was assessed by a 100-point visual analog scale (VAS). Skin conductance (SC) and muscle electromyography (MEG) were recorded using a biofeedback device. After 2 months of treatment, both the pre-cue exposure craving and the post-cue exposure craving, SC, and MEG were lower in the experimental group than in the control group. Compared to the control group, the experimental group had a greater decrease in craving, SC, and MEG from baseline after the treatment. The results suggest that CET combined with BT treatment is effective in reducing craving and physiological reactivity in heroin dependents and could be used as a component of heroin-dependence rehabilitation.

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1. Introduction

Heroin remains a dominant drug of abuse in China, and high treatment dropout and relapse rates are one of the most prominent

problems in treatment sites [1]. One of the reasons for relapse is that drug-related cues can evoke strong reactions, such as craving and other physiological measurements, in drug dependents [2–5].

The concept of craving has been regarded as the central character of addiction behavior, and craving also can be seen as a final common pathway expression of motivation for relapse [5,6]. Drug-related cue induced craving has been demonstrated repeatedly. The link between these drug-related cues and craving is thought to be activated by

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drug-related memories and conditioned responses, that is these cues have come to elicit craving through a history of repeated pairing with the drug [7]. Research shows that cue reactions may exist for a long period. Our previous research also indicates that cue-induced craving and physiological reactions are still present after more than one year of abstinence in heroin dependents [8]. Therefore, it is important to address cue-induced craving through psychosocial intervention.

With the realization that cue-induced craving promotes relapse, clinicians have developed interventions to decrease the frequency or intensity of cue-induced craving. Several studies have found that craving can be survived without lapsing when subjects apply coping mechanisms to get through the situation, and cognitive and behavioral interventions appear to be successful in this regard, including positive self-talk and relaxation techniques [9–12]. Because cue-induced cravings are thought to be the result of conditional stimuli, the most logical treatment for cue-induced craving is to extinguish the conditional response by repeatedly exposing a drug user to the stimuli associated with the addiction in the absence of the drug. Cue exposure therapies (CETs) have been used with alcohol and drug abusers after effectiveness was demonstrated for phobic disorder and obsessive–compulsive disorder [13,14]. Several studies have showed that CET could be effective in decreasing craving; however, its effectiveness on decreasing physiology measurements was not proved consistently, and a number of smaller evaluations of CET indicated that it is not effective at promoting abstinence—dropout and relapse rates were significantly higher in the CET group compared to the control group [15,16]. In addition to the methodological limitations of the studies, the absence of offering additional tools to improve the effects of CET, such as relaxation exercises and biofeedback treatment, is another possible reason that the results are in the unexpected direction.

Biofeedback, which was developed in the late 1960s, has been widely used in physical and psychological therapy [17,18]. It is often aimed at changing habitual reactions to stress that can cause physical and mental health problems. Patients use the biofeedback machine as a kind of sixth sense that allows them to “see” or “hear” activity inside their bodies. One commonly used type of machine picks up electrical signals in the body and translates these signals into a form that patients can detect. Then patients are asked to do relaxation exercises under the instruction of a therapist to try to slow down the electrical signal. Relaxation is a key component in the biofeedback treatment (BT) of many behavior disorders [19]. Many studies have documented that BT is effective in decreasing several physiological measurements, such as heart rate, skin conductance (SC), and muscle electromyography (MEG) [17,18,20]. There have been several studies showing that biofeedback training is an effective treatment for decreasing drug craving [21–24].

From the existing research, some researchers have suggested that CET should only be performed if clients can be simultaneously offered additional tools to learn how to cope with drug-related high-risk situations, rather than merely exposing them to these risks [22]. Since the effectiveness of CET on diminishing the physiology measurements was not confirmed, and biofeedback designed to train patients on how to relax and change physiological measurements has been effective, we speculated that CET combined with biofeedback will be helpful in decreasing the craving and physiological measurements of abstinent heroin dependents.

In this randomized control trial, we divided abstinent heroin dependents into either a CET combined with BT group or a control group. We hypothesized that CET combined with BT would reduce the degree of objective physiological response as well as subjective craving for heroin after repeated exposure to drug-related cues in a video.

2. Materials and methods

2.1. Participants

A total of 45 heroin dependents who showed increased craving after being exposed to heroin-use related cues were recruited from two

compulsory drug rehabilitation centers in Shanghai. Overall, 72 individuals were invited and assessed for eligibility, among whom 26 individuals were excluded and 46 agreed to participate, signed informed consent forms, and were randomized into two groups, a combined CET and BT group (CET + BT group) and a control group (Fig. 1). In the CET + BT group, there were 23 participants (12 females). In the control group, there were 22 participants (12 females, 1 female participant dropped out before the experiment ended). All subjects were interviewed using the SCID-I by trained psychiatrists and met the criteria for heroin dependence according to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [25]. Subjects with other Axis I psychiatric diagnoses were excluded from the study. Urine samples were obtained and screened for opiate use before the patients were sent to the drug rehabilitation center. The research protocol was approved by the Ethic Committee of the Shanghai Mental Health Center and each subject signed the informed consent form approved by the institution's IRB. Participants received a 20 RMB gift card (about 3 U.S. dollars) for their time and effort.

2.2. Procedures

Prior to being recruited into the study, the heroin-dependent patients had resided in a locked inpatient drug rehabilitation center with no access to heroin or any other drugs for a period of time. The participants were screened from another study which sought to understand the characteristics of the psychological and physiological reactions to heroin-use related cues. The heroin-dependent patients who showed increased craving after being exposed to heroin-use cues were interviewed by a trained research fellow. The fellows explained to the potential participants the aim and the process of the study and invited them to participate. Those who provided informed consent were randomized into usual rehabilitation with (experimental group, $n = 23$) or without (control group, $n = 22$) BT combined with CET. The participants were interviewed to complete demographic, drug history, and diagnostic assessments. Within 3 days of the recruitment interview, a cue-exposure experiment was conducted to obtain baseline craving and physiological measurements for both before and after cue exposure. The cue-exposure experiment was conducted by a therapist who has specific training on BT and CET. All participants were assessed by biofeedback machine during the cue-exposure process, and craving for heroin, SC, and MEG were measured before and after the cue exposure. Participants who were assigned to the experimental group were then given an appointment for the first CET + BT session. Participants who were assigned to the control group were informed that another assessment would be carried out two months later.

2.3. Interventions

The control group received the routine treatment program, which mainly included labor, exercises, legal education, unstructured group and individual counseling, and social skills training. The experimental group received the same routine program as the control group, plus a CET combined with BT program. The CET + BT program was carried out in groups of 3–4 participants. The program comprised 12 sessions of 1–2 sessions per week for eight weeks. The duration of each session of CET + BT was 60 min. The content of the sessions is described in Table 1.

2.4. Measures

2.4.1. Clinical assessment

All subjects were screened using the patient edition of the Structured Clinical Interview for DSM-IV Axis I disorders to ensure that they did not have a current anxiety, mood, or psychotic disorder. Diagnoses of DSM-IV opiate dependence were also established by DSM-IV.

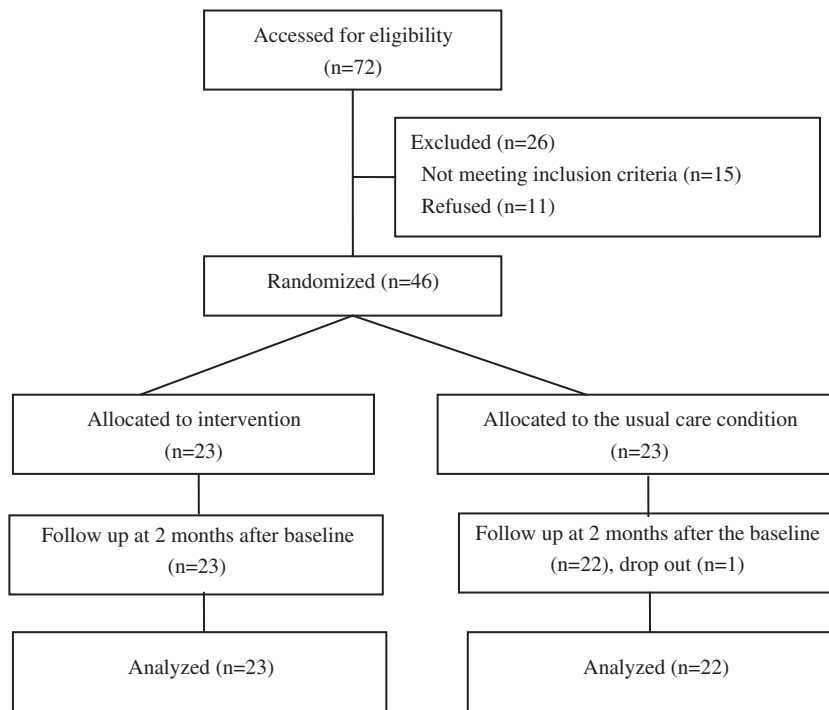


Fig. 1. Flow diagram of participants through the trial.

2.4.2. Demographic and drug use history

Demographic information (age, years of education, marital status, etc.) and drug use history (age at onset of drug use, frequency and amount of current daily use, history of previous treatment, etc.) were collected by a self-completion form developed for the study.

2.4.3. Craving for heroin

Craving for heroin was assessed by a 100-point visual analog scale (VAS) that participants marked as “0” for “not at all” to “100” for “extremely high” in response to the question, “How much do you feel the urge to use heroin?” Craving ratings were obtained at the end of the baseline period and immediately after the cue-exposure period, when patients watch a heroin related videotape. The cravings both before and after the heroin-use related cue exposure were assessed at the baseline of the study and 2 months after the 12 sessions of CET + BT ended.

2.4.4. Physiological measurements

Physiological measurements included skin conductance (SC) and muscle electromyography (MEG) both before and after the heroin-use related cue exposure. A multichannel biofeedback device (Thought Technology Ltd., Canada, VBFB3000) was used to monitor physiological reactions including SC and MEG. The physiological measurements were recorded at several time points at baseline and during the cue-exposure

period. The mean value of each physiological measurement at each period was used for the study. The physiological measurements were recorded at baseline and 2 months after the 12 sessions of CET + BT treatment ended.

2.5. Cue exposure experiment laboratory session

All participants received two laboratory sessions (at baseline and again at 2 months after the CET + BT ended). The heroin-use related cue was about the process of a middle-aged heroin-dependent man smoking or injecting heroin; each video lasted 3 min. During the laboratory session, a smoking heroin use video and an injection heroin use video were exposed to smoking and injection heroin dependents, respectively. In the morning of each laboratory day, each participant was brought into the testing room and seated in a comfortable chair, and sensors were attached to the patient and connected to a multichannel biofeedback device.

The laboratory procedure was based on the following format: a 5-min baseline period, a 3-min cue-exposure period, and a 10-min recovery period. During the baseline period, participants were given instructions to relax for 5 min and focus on deep breathing as light music was played to clear their minds of any worrying thoughts. After the baseline period, participants were shown the cue exposure (heroin-related videotape). During the recovery period, the participants were again instructed to relax for 10 min. Cravings and physiological

Table 1

The main content of CET + BT sessions.

| | |
|----------------|--|
| Sessions 1–2 | The procedure of experiment was introduced. Then the addicts were taught how to feel the feeling of strain and relaxation and how to identify the signal of biofeedback. Finally, the participants were taught to do relaxation exercise and biofeedback therapy to calm down and decrease physiological measurements (SC). |
| Sessions 3–6 | The participants were gradually exposed to a drug-related video. The following instructions were given to the participants before the CET: “You will see a video about heroin use; after the video, please close your eyes and imagine yourself in the situation you watched, as if it were happening to you. Continue to imagine until we ask you to stop”. Finally, the biofeedback therapy and relaxation exercise were provided to all the participants to decrease the craving and physiological reactions. |
| Sessions 7–9 | Watching a drug-related video, presenting simple stimuli (tinfoil, cigarette lighter, pipe, heroin simulacrum). Addicts were asked to depict how to use heroin and the high feeling after the using, then biofeedback therapy and relaxation exercise were given. |
| Sessions 10–12 | Role plays were conducted in pairs to imitate the process of heroin use. After that, feedback therapy and relaxation exercise were given to all the participants. |

measures including SC and MEG were obtained before the cue-exposure session and also immediately after the cue presentation. Physiological measures were monitored using a multichannel biofeedback device. Participants were allowed to leave when their physiological measures had returned to baseline levels.

2.6. Data analysis

The Statistical Package for Social Sciences 15.0 was used to do the data analysis. Demographic and clinical characteristics of the two heroin-dependent groups were assessed using independent *t*-tests or chi-square tests. Different independent *t*-tests were used to analyze craving and physiological measures assessed both before and after the cue exposure at baseline and post-CET + BT exposure between the experiment group and the control group. Different paired *t*-tests were used to analyze changes on craving and physiological measures from baseline in both groups, respectively. Different mixed-design ANOVAs (2 × 2) were conducted to examine the differences post-treatment on craving and physiological measures, with time of assessment (baseline, post-treatment) as repeated measures and group as a between-subjects factor. The significant level was 0.05, two-tailed.

3. Results

3.1. Characteristics of the participants

The characteristics of participants in the study are summarized in Table 2. The participants had a mean age of 34.0(10.1) years. Almost half (48.9%) of them were never married; 60% of them had less than a high school education. The mean age of first drug use was 22.6(7.8), and they had used heroin for an average of 7.1(3.8) years. The majority (82.2%) of the participants used drugs by injection. They had been abstinent from heroin for 333.4(45.8) days when recruited for the study. There were no statistical differences between the two groups ($p > 0.05$).

3.2. Craving and physiological measurements at baseline for the experimental and control groups

Table 3 shows craving and physiological measurements both before and after the cue exposure at baseline for the experimental and control groups. The participants reported a mean craving score of 23.78 ± 18.62 before the cue exposure and reported a mean craving score of 49.78 ± 23.18 after the cue exposure ($p < 0.001$). Different independent *t*-test results showed that cravings, SC, and MEG both before and after the cue exposure were not different between the experimental

and control groups ($p > 0.05$). The craving scores, SC, and MEG increased significantly after the cue exposure in both groups ($p < 0.01$).

3.3. Craving and physiological measurements after intervention

Table 4 shows cravings and physiological measurements for both groups before and after the cue exposure when the CET + BT was ended. Compared to the control group, the experimental group had lower craving scores, MEG, and SC both before and after the cue exposure ($p < 0.05$). Paired *t*-tests showed that craving scores and MEG increased significantly after the cue exposure in control groups ($p < 0.05$), but changes on SC were not significantly different ($p = 0.53$). For the experimental group, no significant changes were found on craving scores, SC, and MEG after the cue exposure ($p > 0.05$).

3.4. Changes in craving and physiological measurements after CET + BT

In order to observe the effects of CET + BT on reducing craving and physiological measurements, different repeated-measures ANOVA tests were conducted to compare the changes in craving scores, MEG, and SC at post-intervention from baseline between the experimental and control groups. Results from repeated-measures ANOVA tests showed that the time effect (changes from baseline measurements to post-intervention) was significant on craving before [$F(1,43) = 14.31, (p < 0.001)$] and after the cue exposure [$F(1,43) = 66.15, (p < 0.001)$], on SC before [$F(1,43) = 15.58, (p < 0.001)$] and after the cue exposure [$F(1,43) = 29.63, (p < 0.001)$], and on MEG before [$F(1,43) = 5.79, (p = 0.02)$] and after the cue exposure [$F(1,43) = 5.54, (p = 0.023)$].

For the experimental group, the cravings, SC, and MEG both before and after the cue exposure were significantly lower compared to baseline ($p < 0.01$). On the other hand, no significant changes were found for cravings, SC, and MEG both before and after the cue exposure for the control group ($p > 0.05$). In sum, only the experimental group showed decreased craving and physiological measurements compared to baseline; the control group did not have such changes.

Compared to the control group, the experimental group showed greater decreases in heroin craving and SC both before and after the cue exposure from baseline ($p < 0.01$) (see Figs. 2 and 3). But the changes on MEG were not significant between the two groups ($p > 0.05$).

4. Discussion

The results show that, prior to the CET + BT, baseline cue reactions measured by subjective craving and objective physiological measurements (SC and MEG) are still present among abstinent heroin-dependent patients after several months of resident rehabilitation. This is consistent with another study that found that heroin-related cues can

Table 2
Characteristics and drug use history of experiment and control groups.

| | Experiment (n = 23) | Control (n = 22) | Total (n = 45) | p-Value |
|---------------------------------------|------------------------|---------------------|-------------------|---------|
| Age (years) | 32.9(8.7) | 36.4(8.6) | 34.0(10.1) | 0.199 |
| Gender (male), n(%) | 11(47.8) | 10(45.4) | 21(45.7) | 0.758 |
| Education n(%) | | | | 0.478 |
| | Junior school | 13(59.1) | 27(60.0) | |
| | High school | 9(39.1) | 17(37.8) | |
| | College/university | 0(0) | 1(2.2) | |
| Marital status n(%) | | | | 0.192 |
| | Married/remarried | 5(21.7) | 14(31.1) | |
| | Divorced/separated | 4(17.4) | 5(22.7) | |
| | Never married | 14(60.9) | 22(48.9) | |
| Drug use method n(%) | | | | 0.892 |
| | Injection | 19(82.7) | 37(82.2) | |
| | Smoking | 4(17.3) | 8(17.8) | |
| Times of drug use treatment | 7.6(8.5) | 6.1(4.5) | 6.8(6.9) | 0.457 |
| Age of first use of drug (years) | 21.7(7.7) | 24.4(6.2) | 22.6(7.8) | 0.207 |
| Average years of heroin use (years) | 6.7(3.4) | 7.4(4.0) | 7.1(3.8) | 0.362 |
| Abstinent from last heroin use (days) | 341.1(38.4) | 324.9(52.5) | 333.4(45.8) | 0.108 |
| Frequency of daily use in the past | 4.1(1.7) | 3.5(1.1) | 3.8(1.4) | 0.188 |
| Amount of daily drug use (g) | 0.98(0.94) | 0.90(0.48) | 0.94(0.75) | 0.709 |

Table 3
Cravings and physiological reactions at baseline by groups.

| | | Experiment group (n = 23) | Control group (n = 22) | Total (n = 45) | P1 | P2 | P3 |
|-----------------|------------|------------------------------|---------------------------|-------------------|------|--------|--------|
| Craving (mm) | Before cue | 22.09 (15.24) | 25.55 (21.85) | 23.78 (18.62) | 0.54 | <0.001 | <0.001 |
| | After cue | 53.35 (22.38) | 46.05 (23.93) | 49.78 (23.18) | 0.30 | | |
| MEG (uV) | Before cue | 12.07 (5.12) | 13.98 (9.07) | 13.00 (7.30) | 0.39 | 0.007 | <0.001 |
| | After cue | 14.36 (6.49) | 15.78 (10.24) | 15.06 (8.46) | 0.58 | | |
| SC (uS) | Before cue | 6.46 (4.37) | 5.06 (2.88) | 5.78 (3.74) | 0.21 | 0.003 | <0.001 |
| | After cue | 7.24 (4.07) | 5.70 (2.60) | 6.49 (3.48) | 0.14 | | |

P1: compared between two groups; P2: compared before and after the cue exposure in the experiment group; P3: compared before and after the cue exposure in the control group.

induce robust craving and physiological reactions [8,9,26]. Given that subjects in their resocialization phase are likely to be confronted with these stimuli soon after treatment discharge, interventions that reduce cue reactivity should be an important component of relapse prevention.

To our best knowledge, this is the first randomized study to evaluate whether CET combine with BT can reduce craving and physiology responses to drug-use cues for heroin dependents. The results showed that, after 8 weeks of CET + BT, the craving, SC, and MEG did not change after the cue exposure in the experimental group; however, the control group still showed increased craving and MEG after the cue exposure. These findings indicated that the cue responses measured by craving, SC, and MEG were diminished in the experimental group, but the cue response (measured by craving and MEG) still exists in the control group. These results confirm our hypothesis that CET + BT is effective in diminishing the craving and physiology responses to cue exposure in heroin dependents. Furthermore, our study shows that, after 2 months of the CET + BT, compared to the control group, the craving, SC, and MEG both before and after heroin-related cue exposure were lower in the experimental group, and the experimental group showed a greater decrease in craving and SC both before and after the cue exposure. It indicates that CET + BT can decrease the level of craving, SC, and MEG both before and after the cue exposure.

CET has been applied to the treatment of addictions for a variety of substances, including cigarettes, alcohol, and illicit drugs [4,5]. However, the effect of only CET is not consistent, but research has shown that combining CET with another intervention such as cognitive behavior therapy (CBT) and other skill training was more effective [9,10]. The CET in this study consists of gradual and repeated exposure to drug-related stimuli in order to extinguish associated responses. In addition to the CET, in order to help patients cope with their cue-induced responses, we added BT as a means of helping patients to relax and control their SC response. The results confirmed that CET + BT was effective in diminishing cue reactivity and decreasing the level of craving, SC, and MEG in abstinent heroin dependents. The findings have important clinical applications, since craving is considered one of the main factors responsible for relapse after drug cessation, SC or MEG represent the arousal level of the autonomic nervous system, and high levels of autonomic nervous arousal leads to more sensitivity to stress. Therefore, a lower level of craving, SC, and MEG should be favorable in preventing relapse. CET + BT could be considered as a new alternative treatment in the process of drug abuse rehabilitation.

Although there are several meaningful findings in this study, some limitations should be mentioned. First, the sample of drug users was recruited from a drug rehabilitation center and therefore may not be representative of other treatment sites, including voluntary treatment sites and community rehabilitation sites. Second, the sample size is relatively small. Third, information about the time patients spent in rehabilitation is uncertain, which may be a potential bias on the results. However, previous study has demonstrated that there were no differences of cue-induced craving and physiological reactions between the recently and the long-abstinent patients [8], so we speculated that the time variable does not affect the accuracy of the results. Finally, there were no follow-up data to evaluate the long-term effect of CET + BT on relapse after the patients were discharged from the rehabilitation center. Despite these limitations, our study demonstrates that CET combined with BT can reduce heroin dependents' craving and physiological measures for drug-related cues, and therefore this is an efficient intervention method in drug abuse treatment sites in the future. Future research is needed to study the effectiveness of CET combined with BT with a large sample and in different treatment sites. In addition, the long-term effect of this treatment should be explored in future studies.

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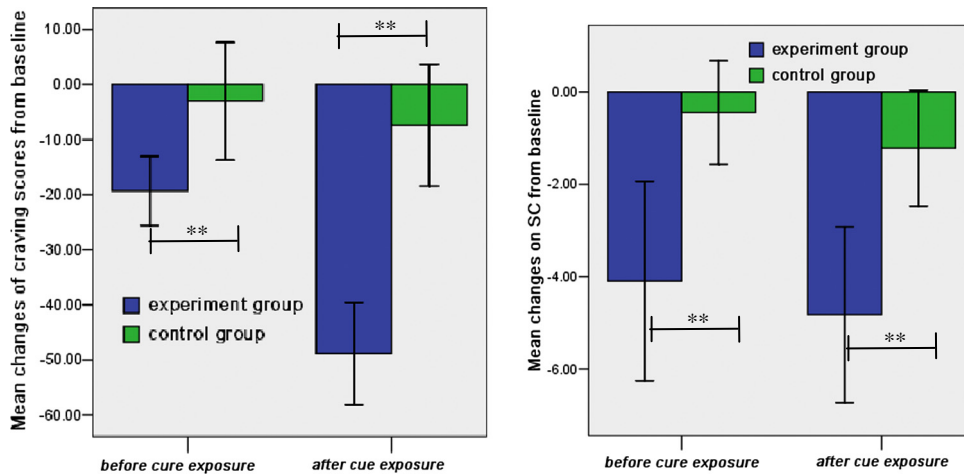
Contributors

Min Zhao conceptualized and designed the study; Chenglu Fan and Jiang Du conducted the cue exposure experiments and collected the data. Jiang Du and Min Zhao prepared the manuscript. Haifeng Jiang, Hanhui Chen, Haiming Sun, and Xu Li collected the clinical data. All authors contributed to the editing of the manuscript and all have approved the final manuscript.

Table 4
Cravings and physiological measurements after intervention by groups.

| | | Experiment group (n = 23) | Control group (n = 22) | P1 | P2 | P3 |
|-----------------|---------------------|------------------------------|---------------------------|--------|------|--------|
| Craving (mm) | Before cue exposure | 2.78 (6.00) | 22.55 (20.03) | <0.001 | 0.12 | <0.001 |
| | After cue exposure | 4.48 (7.57) | 38.68 (22.80) | <0.001 | | |
| MEG (uV) | Before cue exposure | 8.56 (4.21) | 12.06 (5.17) | 0.017 | 0.70 | 0.03 |
| | After cue exposure | 8.67 (4.35) | 14.79 (5.86) | <0.001 | | |
| SC (uS) | Before cue exposure | 2.37 (1.57) | 4.61 (2.24) | <0.001 | 0.86 | 0.53 |
| | After cue exposure | 2.41 (1.44) | 4.49 (2.59) | 0.002 | | |

P1: compared between two groups; P2: compared before and after the cue exposure in the experiment group; P3: compared before and after the cue exposure in the control group.



Figs. 2–3. Craving and physiological measurement changes in two groups. Note: **group differences, $p < 0.01$.

Conflict of interest

The authors have no conflicts of interest to report.

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