Life Sciences 322 (2023) 121613

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Distinct suppressing effects of deep brain stimulation in the orbitofrontal cortex on the development, extinction, and reinstatement of methamphetamine-seeking behaviors

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ARTICLE INFO

Keywords:
Reward
Methamphetamine
Orbitofrontal cortex
Deep brain stimulation
Conditioned place preference
Rat

ABSTRACT

Aims: The orbitofrontal cortex (OFC) is implicated in compulsive drug-seeking and relapse, the characteristics that result in addiction treatment failure. Structural and functional impairments within the OFC have been detected in many substance use disorders (SUDs). Deep brain stimulation (DBS) is proposed as a promising therapeutic option in treating SUDs. Therefore, the present study aimed to investigate the potential efficacy of DBS application on the various stages of the methamphetamine-conditioned place preference (CPP) paradigm in rats.

Main methods: Electrodes were implanted unilaterally in the rat's right OFC. DBS in the form of high- or low-frequency stimulation (HFS: 130 Hz, LFS: 13 Hz) was applied during the 5-day conditioning phase (a daily 30-min session) or extinction period (30-min session, daily, ten days) of methamphetamine-induced CPP in two separate sets of experiments. Following extinction, place preference was reinstated by injecting a priming dose of methamphetamine (0.25 mg/kg).

Key findings: The HFS and LFS significantly decreased the methamphetamine place preference when applied over the conditioning period. In the extinction experiment, only HFS could remarkably accelerate the extinction of reward-context associations and even reduce the methamphetamine-induced reinstatement of seeking behaviors.

Significance: Conclusively, DBS administration in the OFC demonstrated some positive results, including suppressing effects on the development, maintenance, and relapse of methamphetamine-seeking behavior. These findings encourage conducting more preclinical studies to strongly suggest a wide range of DBS applications in cortical areas such as OFC as an efficient treatment modality for psychostimulant use disorder.

1. Introduction

Methamphetamine use is a remarkable public health concern in the United States and worldwide [1] and is second to cannabis as the most widely abused illicit drug globally [2]. Repeated intake of methamphetamine increases the risk of drug addiction, a chronically relapsing brain disorder distinguished by compulsive drug-taking, inability to limit intake, and severe drug cravings [3]. No pharmacological treatment is explicitly addressed to methamphetamine addiction, and behavioral therapy is accompanied by poor long-term recovery and relapse [4]. Therefore, many methamphetamine users relapse following the treatment, and novel approaches to managing methamphetamine addiction are urgently needed.

Deep brain stimulation (DBS) is an adjustable, reversible, non-destructive neurosurgical procedure delivering electrical pulses to some brain areas using implanted electrodes [5]. DBS is an approved treatment for movement disorders and is also under active investigation for other pathological states, such as major depressive disorder (MDD) and Alzheimer's disease [6]. Recently, preclinical and clinical studies have proposed that DBS has the potential to prevent relapse and improve

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https://doi.org/10.1016/j.lfs.2023.121613
Received 11 January 2023; Received in revised form 10 March 2023; Accepted 18 March 2023
Available online 21 March 2023

outcomes for those addicted to methamphetamine [7–12]. The development of drug addiction is linked with functional alterations in the reward circuitry, within which the nucleus accumbens (NAc) is anatomically positioned as a crucial interface between motivational salience and behavioral output [13]. In this way, the most common target of DBS for addiction treatment has been the NAc, a fundamental structure in the mesolimbic reward pathway [14]. Although the NAc is the most widely used brain area for DBS administration [11,15], therapeutic effects have been reported by targeting other brain structures at the level of preclinical investigations [16–18].

Brain mapping studies have indicated that neuronal activity in the orbitofrontal cortex (OFC), a brain area thought to promote the ability to control behavior in proportion to likely outcomes or consequences, is changed in drug users. The OFC is involved in compulsive drug-seeking and relapse, the significant characteristics of addiction that couldn't be attributed to the neural substrate responsible for the acute rewarding features of drugs [19,20]. Fakhrieh-Asl et al. have recently shown that DBS administration in the OFC could effectively inhibit morphine-conditioned place preference (CPP), facilitates the extinction of morphine place preference, and prevents morphine-induced reinstatement of drug-seeking in rats [21]. So, it seems that OFC is a potential therapeutic target to treat some addictive responses through neuromodulation approaches such as DBS. However, further investigations are needed to assess the efficiency of DBS in addiction treatment regarding various drugs of abuse, such as psychostimulants.

DBS application as a treatment modality for psychostimulant dependence in the NAc, lateral habenula and anterior limb of the internal capsule has been investigated in human and animal studies, and it has been shown encouraging findings, including a decrease in drug intake, craving, and relapse [9,22–25]. Considering the role of OFC in addictive behaviors and the positive results of Fakhrieh-Asl et al. study [21], we aimed in this present study to investigate the potential therapeutic effects of DBS administration in the OFC on different stages of methamphetamine-induced CPP to further evaluate the ability for DBS to treat psychostimulant dependency in rats.

2. Method & materials

2.1. Animals

Ninety-four male Wistar rats weighing 220–280 g (Institute of Pasteur, Tehran, Iran) were maintained and randomly housed in equal and standard conditions, including a temperature-controlled animal room (23 ± 1 °C), 12-hour light-dark cycle with food and water ad libitum. All the investigations were conducted under the Guide for the Care and Use of Laboratory Animals (NIH Publication; 8th edition, revised 2011) and approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1399.147), Tehran, Iran.

2.2. Drugs

Methamphetamine Hydrochloride was diluted in sterile normal saline (0.9 % NaCl) and injected subcutaneously (sc) at the dose of 1 mg/kg over the conditioning phase and 0.25 mg/kg prior to the reinstatement phase according to the former studies [26,27].

2.3. Surgical procedure

Animals were anesthetized via intraperitoneal injection of a mixture of Ketamine (100 mg/kg) and Xylazine (10 mg/kg) and fixed in a stereotaxic apparatus (Stoelting, USA). After a midline incision over the scalp, the skull was cleaned to locate the bregma landmark and target the concerned areas. Following the skull drilling, bipolar stimulating electrodes (stainless steel, PFA-insulated wire with 127-μm bare diameter; A-M Systems, Inc.) were unilaterally implanted into the rat's right OFC (AP = +4 mm; ML = 2.5 mm; DV = 5 mm) according to the rat brain atlas [28] and secured with screws and acrylic cement. Then, rats were recovered for 5–7 days to start behavioral procedures.

2.4. Stimulation procedure

Monophasic square pulses were generated and delivered to the rat's OFC through a current-based stimulator with a built-in isolation circuit (Behineh Sazan Fannavari Salamat Co.). The stimulation parameters were selected based on the clinical and preclinical studies discovering the therapeutic role of DBS in substance use disorder (SUD) treatment (frequency: 130 or 13 Hz, current intensity: 150–200 μA, pulse duration: 100 μs) [21,29,30]. The current intensity was increased slowly by 30–50 μA steps to reach the target value. In Sham-DBS groups, animals were similarly connected to the stimulator, but didn't receive any electrical stimulation.

2.5. Conditioned place preference paradigm

An unbiased CPP paradigm was applied in the present study to evaluate the rewarding effects of methamphetamine as an addictive drug. We used Plexiglas three-compartment CPP boxes consisting of two main symmetric chambers (30 × 30 × 40 cm), different in visual (vertical vs. horizontal inner wall stripes) and tactile characteristics (rough vs. smooth floors), connecting through the third smaller compartment via a sliding door. To conduct the CPP procedure, one of the equal-sized compartments should be paired with a reward (methamphetamine), and the other have to remain reward-free (saline). Animals were brought to the lab and habituated to handling by the experimenter, subcutaneous injection of saline, stimulator cable attachment, and CPP environment, one day before the initiation of the CPP procedure.

The CPP paradigm consists of five stages and begins with the pre-conditioning phase in which animals are free to explore all parts of the box for 10 min to determine their baseline side preference. During the conditioning phase, rats were administered alternatively methamphetamine and saline and restricted to the methamphetamine- and saline-paired compartments for 30 min with a six-hour interval for two sessions in a day over five consecutive days. In addition, the drug-paired compartment was counterbalanced across the animals. The post-conditioning stage, was quite similar to the pre-conditioning phase, including 10 min of freely moving between three compartments and monitoring the rats' behaviors by recording the time spent in each compartment and locomotor activity through the video-tracking system and Ethovision software (version 7). Side preference or CPP score was calculated by the difference in time (s) between the time spent in the methamphetamine compartment and the time spent in the saline compartment. Locomotor activity was considered the traveled distance (cm/10 or 30 min) in the CPP box.

Following the acquisition and expression of methamphetamine-induced place preference, animals were subjected to a 10-day extinction period with daily 30-min sessions, no methamphetamine injection, and unrestricted access to all compartments of the CPP box to slowly extinguish the previously formed context-reward associations. The “extinction latency” was considered by the number of days required to reach a 50 % decrease in side preference concerning the post-conditioning phase as a criterion for each rat to evaluate the maintenance of reinforcing effects of methamphetamine.

Subsequent to the last day of extinction, methamphetamine place preference was reinstated by administering an ineffective dose of methamphetamine (0.25 mg/kg, sc) and placing the animals in the CPP box for 10 min to explore all the compartments freely. It should be noted that the rat's behavior was recorded and analyzed throughout the extinction and reinstatement phases as well.

2.6. Experimental design

2.6.1. Investigating the effects of DBS administration in the OFC during the acquisition of methamphetamine place preference

In order to recognize the effects of DBS application in the OFC during the conditioning period on the acquisition of methamphetamine or saline place preference, six groups of animals (n = 10–11/group) were used. Four groups that received high-frequency stimulation (HFS: 130 Hz, 150–200 μA, 100 μs) or low-frequency stimulation (LFS: 13 Hz, 150–200 μA, 100 μs) for 30 min in a separate environment than the CPP box before methamphetamine or saline conditioning sessions (Saline-HFS, Saline-LFS, Meth-HFS, and Meth-LFS groups). In two other groups, animals were connected to the stimulator for 30 min. Still, they didn't receive any electrical stimulation before methamphetamine (Meth-Sham) or saline (Saline-Sham) injections over the conditioning period (Fig. 1A). Consequently, after the conditioning phase, six groups of animals were tested on the post-conditioning day to show their place preference. It should be noted that in Saline-DBS and Saline-Sham groups, animals received only saline before each conditioning session and, HFS, LFS or sham stimulation was administered before injecting saline and limiting to one of the equal-sized compartments as a reward-paired compartment to exclusively assess the effects of applying DBS in the OFC during the saline conditioning period. Furthermore, in Meth-DBS and Meth-Sham groups animals were subjected to both saline and methamphetamine daily sessions during the conditioning period and, HFS, LFS or sham stimulation were applied before injecting methamphetamine and confining to the methamphetamine compartment.

2.6.2. Investigating the effects of DBS administration in the OFC during the extinction phase of methamphetamine CPP on the extinction and reinstatement of drug-seeking behaviors

In the second experiment, to investigate the effects of administering DBS during the extinction period on the maintenance of methamphetamine-rewarding characteristics, especially the mean extinction latency (MEL) and methamphetamine-induced reinstatement of drug-seeking, animals were divided into three groups (n = 10–11/group) after the acquisition and expression of methamphetamine CPP; A Sham-DBS group that animals were just connected to the stimulator without electrical stimulation, and two other groups, HFS (130 Hz, 150–200 μA, 100 μs) and LFS (13 Hz, 150–200 μA,100 μs) groups in which animals were daily stimulated in high- or low-frequencies for 30 min before conducting extinction sessions in an environment separate than CPP box (Fig. 1B). Following the last day of extinction, methamphetamine-induced reinstatement of place preference was undertaken to assess the lasting effects of DBS administration during the extinction phase.

2.7. Histological procedures

Following the termination of behavioral studies, rats were deeply anesthetized by an intraperitoneal administration of Ketamine and Xylazine mixture and transcardially perfused with 10 % paraformaldehyde. The brains were extracted and maintained in a 10 % paraformaldehyde solution. The 50-μm thick coronal sections were prepared at the level of OFC to verify the electrode position under light microscopy by an investigator blind to the treatment conditions. Rats with electrodes outside the OFC were omitted from further data analyses (9 animals, Fig. 2).

2.8. Statistical analysis

Data were expressed as mean ± SEM (standard error of the mean) and analyzed by GraphPad Prism® software (version 8.0). A two-way repeated measure analysis of variance (ANOVA) followed by the post-hoc Tukey's multiple comparisons test was performed to compare the CPP scores between the conditioning groups in the pre- and post-

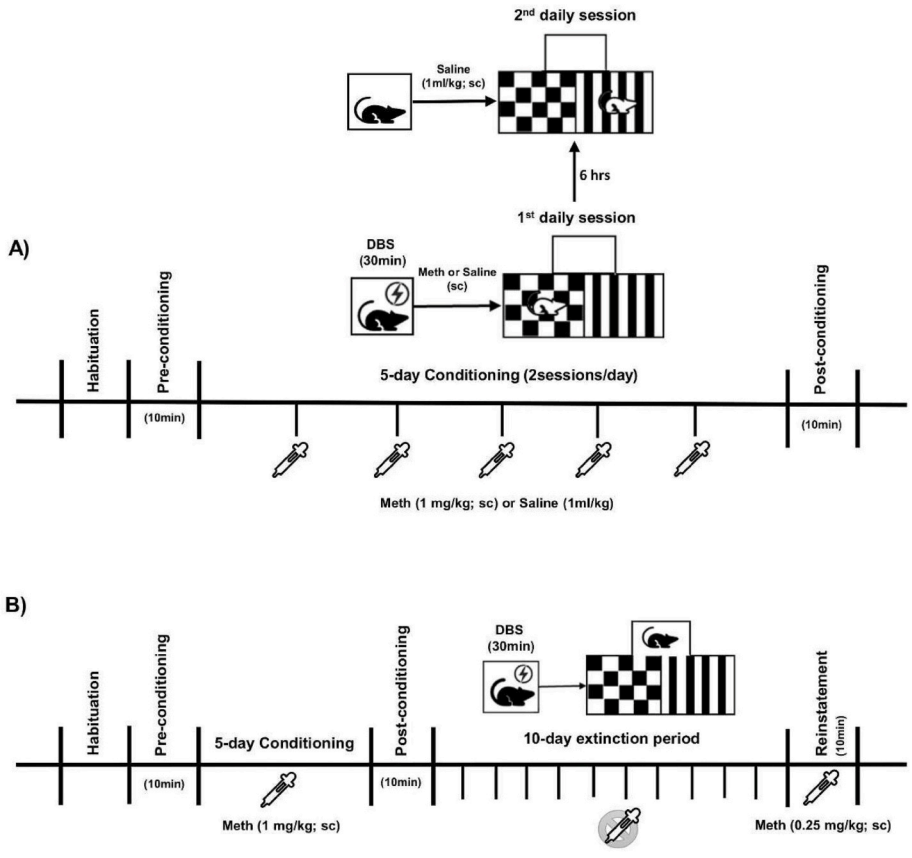

Fig. 1. Schematic design of experiments. (A) Animals in the acquisition experiment received HFS (130 Hz, 150–200 μA, 100 μs), LFS (13 Hz, 150–200 μA, 100 μs), or sham stimulation in the OFC for 30 min before injecting methamphetamine or saline and limiting to the drug-paired compartment. (B) In the extinction experiment, animals were administered HFS (130 Hz, 150–200 μA, 100 μs), LFS (13 Hz, 150–200 μA, 100 μs), or sham stimulation in the OFC for 30 min before conducting daily extinction sessions for ten consecutive days.

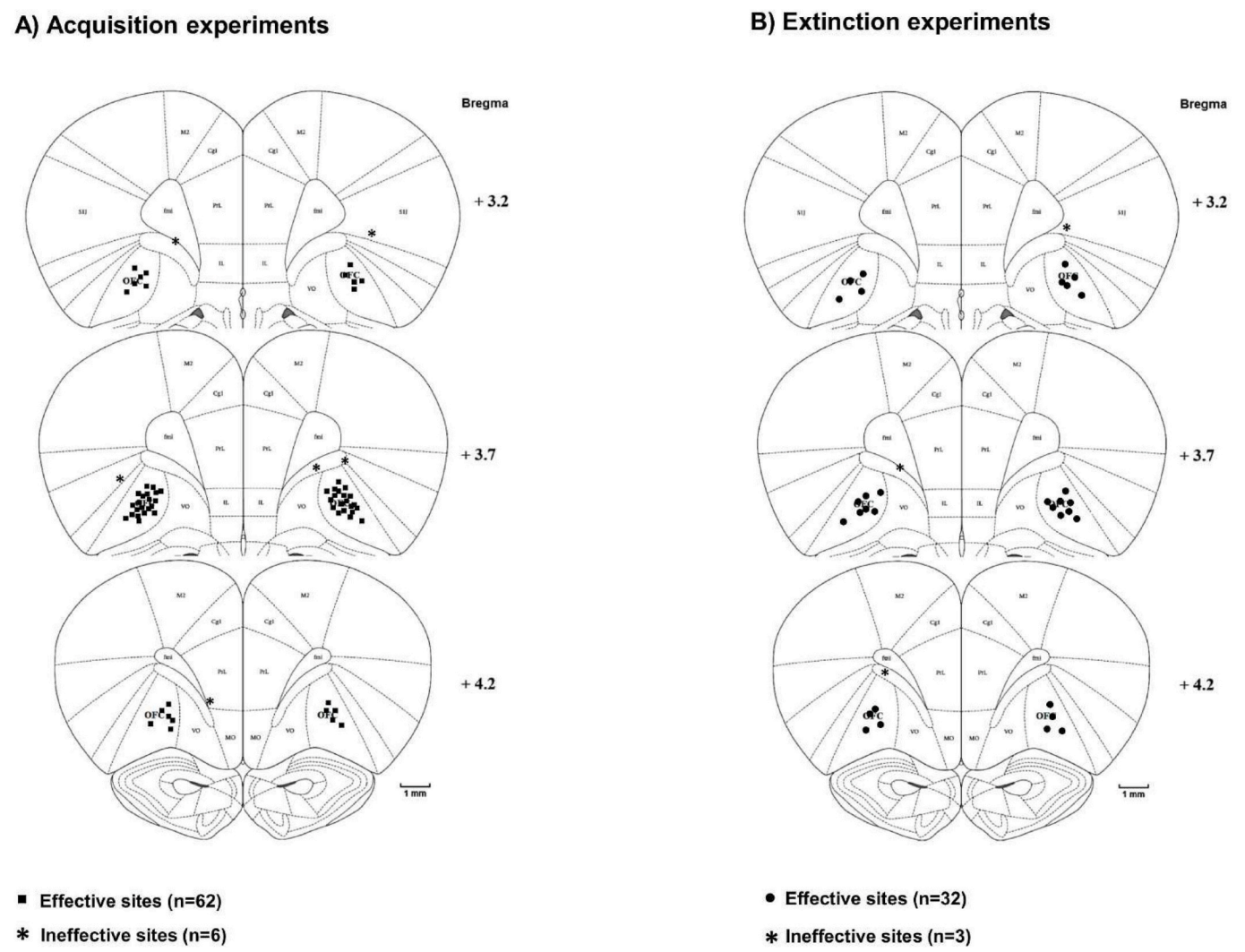

Fig. 2. Effective (circles and squares) and ineffective (asterisks) sites of electrode implantation in the OFC in (A) acquisition experiment and (B) extinction experiment. Generally, 103 rats entered the study, and nine were removed from subsequent behavioral data analysis due to misplacement.

conditioning phases. An ordinary one-way ANOVA followed by the post-hoc Tukey's multiple comparisons test was applied to compare the MELs and CPP scores on the reinstatement day among the extinction groups. In addition, a one-way repeated measure ANOVA followed by Dunnett's multiple comparisons test was used to assess the behavior of animals within the groups in the extinction experiment. Moreover, a paired Student *t*-test was performed to compare the CPP scores of animals between the last day of extinction and reinstatement day. P-values less than 0.05 ($P < 0.05$) were considered statistically significant.

3. Results

3.1. Effects of DBS administration on the acquisition of methamphetamine place preference

To assess the effects of DBS administration on the reward-associated learning induced by methamphetamine, electrical stimulation of the OFC in the form of HFS or LFS was applied 30 min before the injection of methamphetamine or saline during the 5-day acquisition phase of the CPP paradigm. A two-way repeated measure ANOVA followed by the post-hoc Tukey's multiple comparisons test [Phase: $F(1,57) = 0.87$, $P = 0.35$; DBS: $F(5,57) = 6.22$, $P = 0.0001$; interaction: $F(5,57) = 7.98$, $P < 0.0001$; Fig. 3A] revealed no significant difference among the groups regarding the pre-conditioning phase but a significant difference between CPP scores of Saline-Sham and Meth-Sham groups in the post-conditioning phase, indicating that methamphetamine as an addictive drug induces significant side preference ($P < 0.0001$). Nonetheless, there was no significant difference in CPP scores between Saline-HFS and Saline-LFS groups with Saline-Sham animals in the post-conditioning CPP scores meaning that OFC DBS alone couldn't produce any side preference ($P > 0.05$). In addition, both HFS ($P < 0.0001$) and LFS ($P < 0.0001$) could considerably reduce the development of methamphetamine place preference in comparison to the Sham-Meth group, which didn't receive any electrical stimulation. Furthermore, there was no significant difference between the groups concerning the locomotor activity in the pre- and post-conditioning tests [Phase: $F(1,57) = 0.72$, $P > 0.05$; DBS: $F(5,57) = 1.16$, $P > 0.05$; interaction: $F(5,57) = 1.59$, $P > 0.05$; Fig. 3B].

3.2. Effects of DBS administration during the extinction phase on the maintenance and relapse of methamphetamine rewarding features

In the next experiment, to test the effects of DBS application in the OFC on the maintenance of reward-context associations and methamphetamine-induced reinstatement of drug-seeking, HFS or LFS was applied before each daily extinction session (30 min/day for 10 days). A repeated measured one-way ANOVA followed by post-hoc Dunnett's multiple comparisons test was performed to analyze the

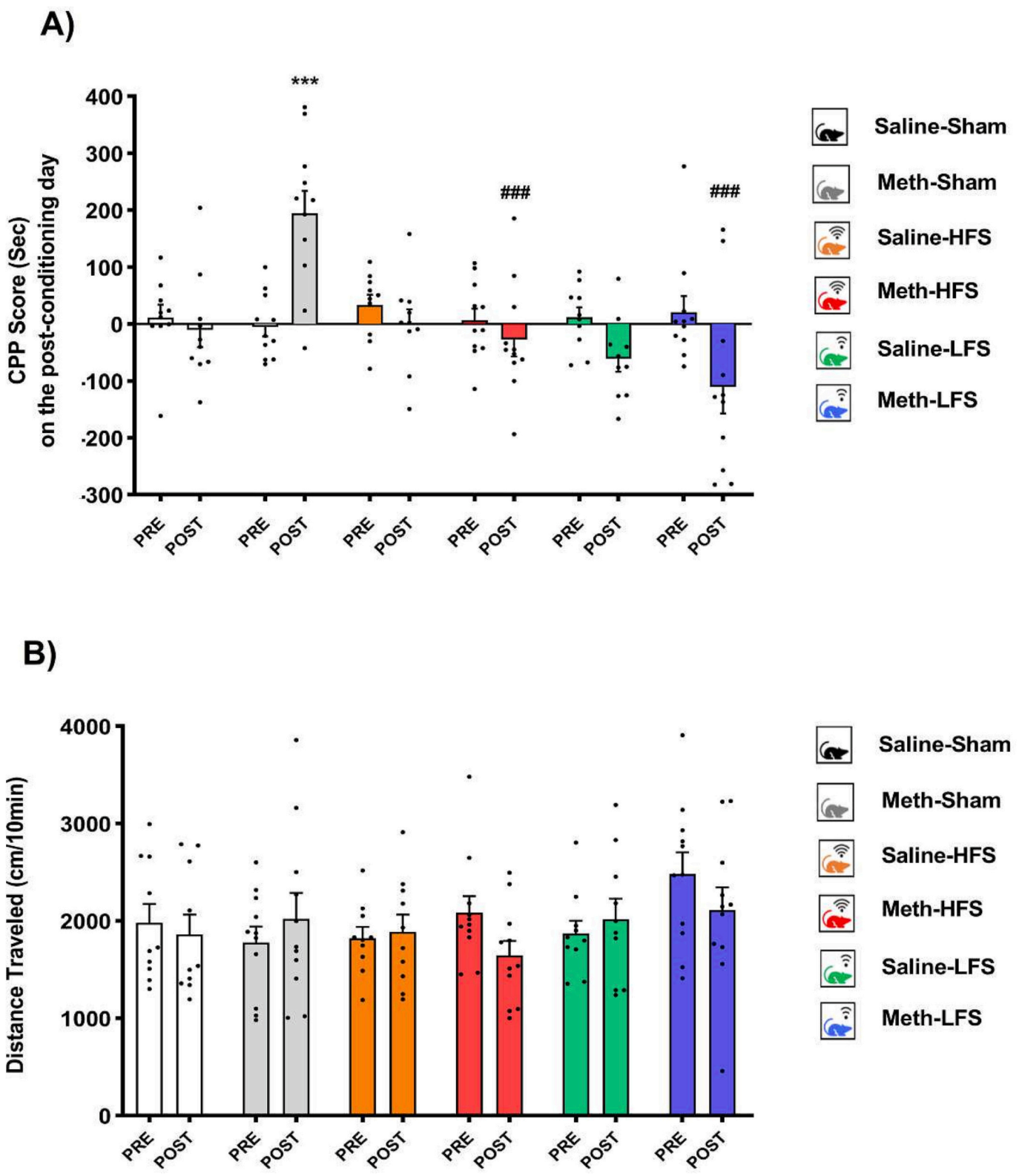

Fig. 3. The effects of DBS administration in the OFC during the acquisition of methamphetamine place preference. (A) The conditioning scores (s) of all six groups in the acquisition experiment are indicated on the pre- and post-conditioning phases (n = 10–11/group). HFS and LFS application during the conditioning period remarkably reduced the development of methamphetamine-induced CPP. (B) The locomotor activity of all groups in this experiment. Data represent mean ± SEM.
***P < 0.001compared to the Saline-Sham group post-conditioning CPP scores.
###P < 0.001 compared to the Meth-Sham group post-conditioning CPP scores.

behavior of animals within each group (Sham and DBS groups) throughout the CPP paradigm. Generally, it was shown that after the conditioning phase, the place preference of animals in all three groups increases in the post-conditioning test compared to the level of the pre-conditioning test and begins to reduce gradually during the extinction phase. Results showed that there was a significant difference between the CPP scores of the post-conditioning test with the pre-conditioning test and extinction days (days 8–10) in the Sham-DBS group [$F(12,142) = 9.03$; $P < 0.0001$; Fig. 4A]. The same trend of changes in CPP scores was detected in the HFS [$F(12,129) = 10.21$; $P < 0.0001$; Fig. 4B] and LFS [$F(12,142) = 6.58$; $P < 0.0001$; Fig. 4C] treated animals. Statistically significant differences in place preference were detected between the post-conditioning and the pre-conditioning tests and the last few days of the extinction period (days 6–10 for HFS and days 8–10 for LFS groups).

In addition, a paired Student *t*-test between the CPP scores for each of the three groups on the last day of the extinction period (day 10) and reinstatement day was conducted to assess the effects of two types of DBS or Sham-DBS on the reinstatement of drug-seeking behaviors when were applied during the extinction period. Significant differences were detected for Sham-DBS [$t(10) = 3.83$; $P = 0.003$; Fig. 4A] and LFS [$t(10) = 2.88$; $P = 0.016$; Fig. 4C] groups, meaning that a priming dose of methamphetamine reinstated drug-seeking behavior. However, there was no remarkable difference for the HFS group indicating that high-frequency DBS has prevented the relapse of drug-seeking behavior [$t(9) = 0.42$; $P = 0.68$; Fig. 4B].

3.3. Effects of DBS administration during the extinction phase on the mean extinction latency and reinstatement of methamphetamine-seeking behavior

To evaluate the effects of DBS application during the extinction phase on the extinction of methamphetamine place preference, we computed mean extinction latency (MEL) for each group and, an ordinary one-way ANOVA Followed by post-hoc Tukey's multiple comparisons test was performed to indicate the statistical differences between the groups [$F(2,31) = 6.50$; $P < 0.01$; Fig. 5A]. It was shown that MEL in the HFS group was significantly lower than that in the Sham-DBS group ($P < 0.01$), and there was no notable difference between LFS and Sham-DBS groups ($P > 0.05$) as well. In addition, no significant difference in the locomotor activity of animals in these three groups was found [$F(2,31) = 0.23$; $P = 0.78$; Fig. 5B].

In the next step, we investigated the lasting effects of DBS administration during the extinction period on the methamphetamine-induced reinstatement of drug-seeking behavior following the last day of the extinction period through an ordinary one-way ANOVA followed by post-hoc Tukey's multiple comparisons test [$F(2,31) = 5.31$; $P < 0.05$; Fig. 6A]. Results indicated a remarkable difference between side preferences of animals in HFS group with Sham-DBS and LFS ($P < 0.05$) groups in the reinstatement day, indicating that HFS could significantly prevent the relapse of preference for methamphetamine context. Furthermore, the locomotor activity of animals in these three groups was not significantly different on the reinstatement phase [$F(2,31) = 1.35$; $P = 0.27$; Fig. 6B].

4. Discussion

The present study supported the potential therapeutic effects of targeting OFC through DBS in treating psychostimulant dependence. We showed that DBS administration in both high- and low-frequency patterns during the acquisition of methamphetamine place preference could effectively decrease the expression of drug-seeking behavior. At the same time, OFC electrical stimulation (HFS or LFS) alone could not produce any place preference. In the extinction experiment, HFS application in the OFC over the extinction phase could remarkably attenuate the maintenance of the reinforcing effects of methamphetamine. In other words, HFS accelerated the extinction of previously formed drug-context associations and even declined the reinstatement of drug-seeking behavior when applied in a separate context before exposure to drug paired environment. In comparison, none of the aforementioned effects after HFS were observed significantly following LFS administration during the extinction period. These positive effects of DBS in the OFC on suppression of reward-related behaviors were in agreement with findings from other studies indicating that DBS administration in other areas of the brain reward system such as NAc, subthalamic nucleus (STN), insula, and lateral hypothalamus results in a remarkable decrease in various drug-seeking and drug-taking behaviors [18,30–34]. Neuromodulation therapy for SUD aims to restore regular brain activity in target regions to attenuate addictive behaviors [35]. Many hypotheses have been suggested for the mechanisms by which DBS acts. Prevailing theories have concentrated on stimulation-induced disruption of pathological brain circuit activity [36]. It is suggested that DBS dissociates input and output signals in the targeted nucleus and disrupts the abnormal flow of information via the cortico-basal ganglia circuit in pathological situations ("disruption hypothesis") [37]. The stimulation-induced disruptions occur at the ionic, protein, cellular and network levels to produce improvements in symptoms. Although it is currently ambiguous which of the wide-ranging impacts of DBS are essential and adequate to generate therapeutic outcomes, it is obvious that high-frequency trains of pulses produce responses that are fundamentally different from LFS [38]. For example, HFS has been indicated to induce depolarization blockade due to activation of local interneurons [39,40], as well as synaptic depression associated with neurotransmitter depletion and inhibition [40]. In contrast to HFS, LFS has been

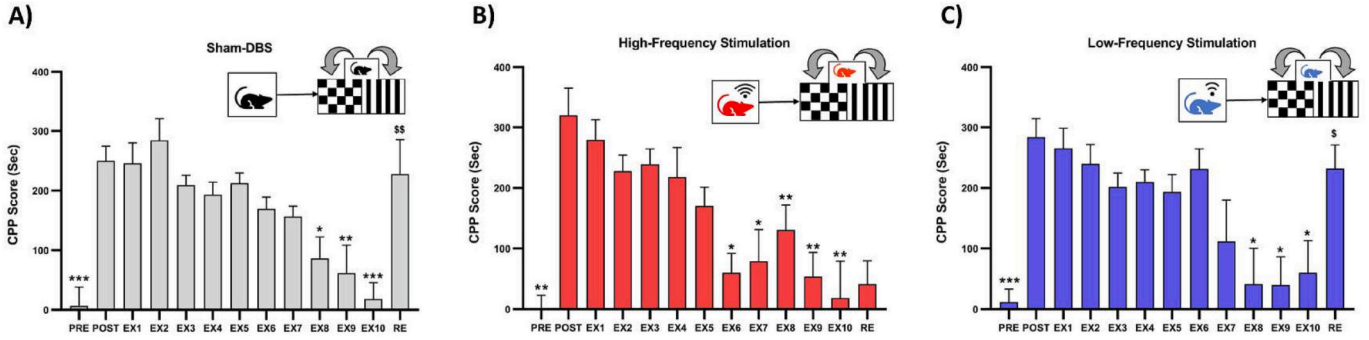

Fig. 4. Effects of DBS administration in the OFC during the extinction phase on the extinction and reinstatement of drug-seeking behavior within each group (n = 10–11/group). Methamphetamine conditioning caused significant place preference in all three groups, and a gradual decline in methamphetamine side preference could be seen in all three groups. (A) Sham-DBS group. (B) LFS group. (C) HFS group.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared to post-conditioning day.
$^{\$}P < 0.05$, $^{\$\$}P < 0.01$ compared to the last day of extinction.

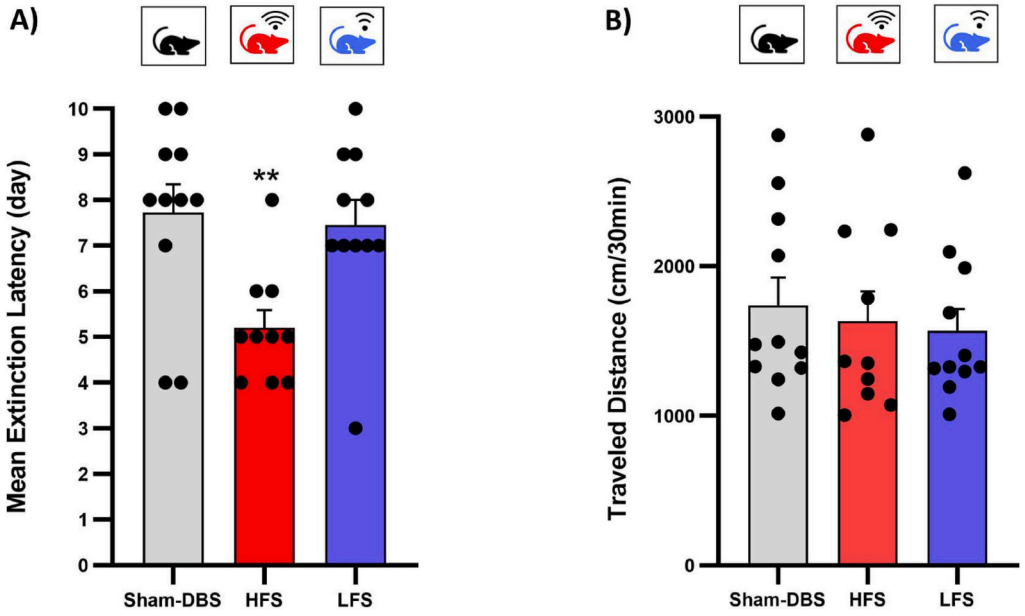

Fig. 5. Effects of OFC DBS administration during the extinction phase on the mean extinction latency (day). (A) High-frequency DBS of OFC in the extinction period significantly reduced mean extinction latency and facilitated the extinction of methamphetamine place preference. (B) The locomotor activity of all groups in this experiment. Data represent mean ± SEM.
**P < 0.01 compared to the Sham-DBS group.

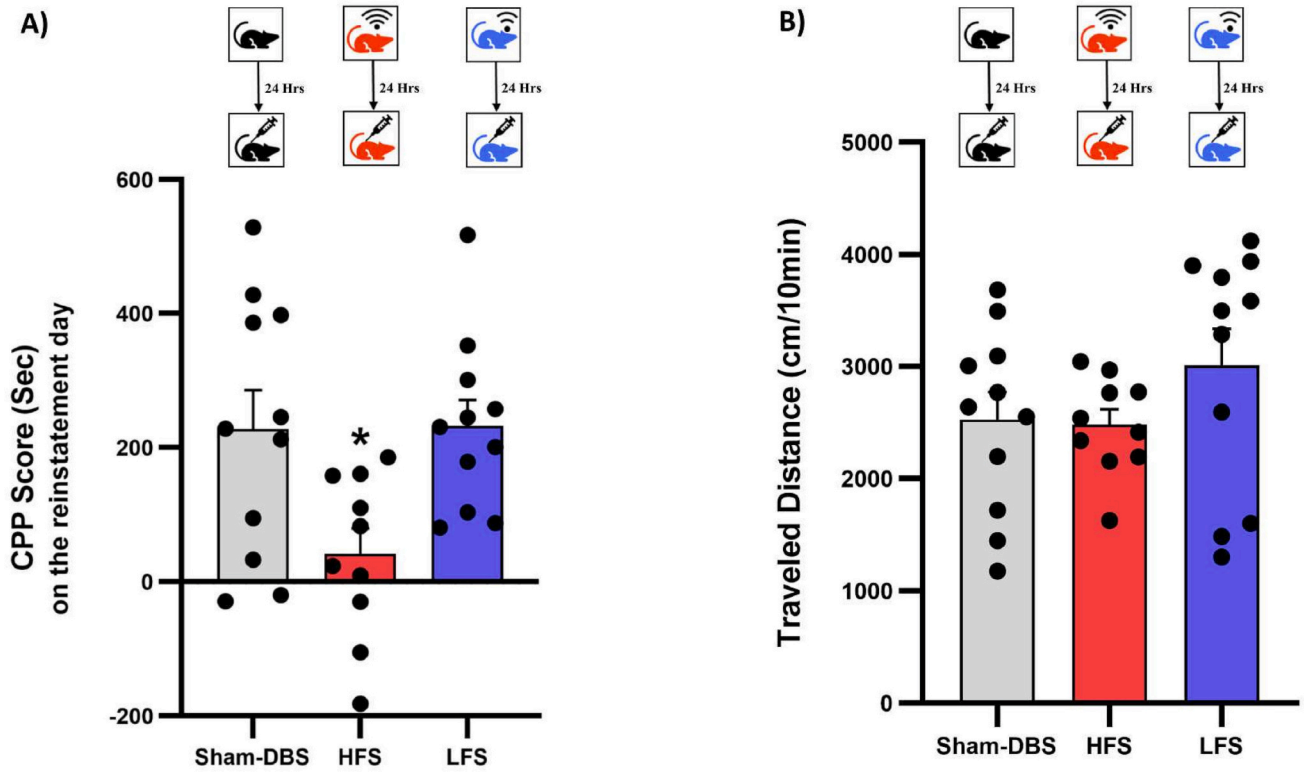

Fig. 6. Effects of DBS application in the OFC during the extinction phase on the methamphetamine-induced reinstatement of drug-seeking behavior. (A) CPP scores (s) of three extinction groups are shown in the reinstatement phase. High-frequency stimulation in the OFC significantly decreased the reinstatement of methamphetamine place preference when applied during the extinction period. (B) Locomotor activity of animals on the reinstatement phase.
*P < 0.05 compared to the Sham-DBS group.

associated with distal activation rather than distal inhibition [41]. Consistent with this idea, Vassoler et al. showed that HFS of the NAc shell attenuates cocaine reinstatement and antidromically stimulates axon terminals, which finally activates GABAergic interneurons in cortical regions that send projections to the shell [9]. But in another study by Martínez-Rivera et al., 2016 it was suggested that LFS in the dorsal region of the ventral striatum acts through activating infralimbic pyramidal neurons, rather than activating infralimbic inhibitory interneurons and improve extinction memory of morphine-context associations [30].

The OFC is a region that is neuroanatomically linked with brain structures implicated in the reinforcing and rewarding effects of drugs of abuse, such as NAc, ventral tegmental area, amygdala, cingulate gurus, and hippocampus. This makes the OFC not only a direct target for the

effects of drugs of abuse but also a region that could integrate information from different limbic areas and, because of its reciprocal connections, a region that in turn, could also modulate the response of these limbic brain areas to drug administration [42]. Although the primary symptoms and neuropsychological profiles of MDD, obsessive-compulsive disorder (OCD), and SUDs differ, common orbitofrontal-striatal impairments have been detected across these conditions. For instance, neuroimaging studies investigating MDD, OCD, and SUDs have indicated decreased gray matter volume in the OFC and associated subcortical areas, such as the ventral striatum and amygdala [43]. It has been revealed that repetitive transcranial magnetic stimulation (rTMS) over the right OFC may lead to some efficacy in the treatment of resistant OCD patients and a decrease in glucose metabolism of bilateral OFC [44]. In another study, a patient suffering from major depression showed remarkable improvement following treatment with OFC rTMS after not responding to conventional rTMS (over dorsolateral prefrontal cortex and dorsomedial prefrontal cortex) used in MDD. In addition, neuroimaging findings of this study revealed declines in functional connectivity from OFC to NAc and other nodes of the orbitofrontal cortico-striato-thalamo-cortical loop [45]. More interestingly, Rao et al. [46] applied DBS in epileptic subjects and indicated that lateral OFC stimulation enhances mood state in subjects with depression symptoms. These effects may be mediated through a combination of local and network-level changes in neural activity [46]. Eventually, based on this encouraging evidence, the present study targeted the OFC to assess the potential positive effects of DBS application in different phases of methamphetamine-induced CPP. In the context of targeting OFC to treat substance dependency, there was only one animal study indicating that, unlike the high-frequency DBS, low-frequency DBS administration in the OFC inside the CPP apparatus was not able to block morphine place preference, impaired the process of extinguishing previous drug-context memories and couldn't prevent the relapse of morphine-seeking behavior [21]. While in the present study, LFS administration in the OFC could prevent the acquisition of methamphetamine CPP with no significant effects on the animal's behavior when applied during the extinction period. These discrepancies could be attributed to the different drugs of abuse (opioids vs. psychostimulants) and the environment that DBS was applied (inside vs. outside of the CPP apparatus). It should be considered that usually, HFS and LFS exert opposite effects at the level of behavior, as has been expressed in some studies [21,30,31,47]. However, Hamilton et al. indicated that both HFS and LFS application in the NAc during the withdrawal period could effectively reduce the reinstatement of cocaine-seeking in a self-administration paradigm [48]. It seems that more investigations considering different types of abused drugs, reward models and targeting various brain areas with different patterns of stimulation are crucial to resolve these disagreements.

The OFC seems to play an essential role in the ability of drug-paired cues to promote cocaine-seeking [19]. It has been suggested that drug-induced adaptations in the OFC may underlie the enhancement of the motivational effects of drugs and drug-related cues over time [20]. These results are in agreement with findings from imaging studies indicating strong activation of the OFC by the presentation of drug-associated cues [42]. Lesions or reversible inactivation of the OFC may decrease cue-induced drug-seeking because of a failure to normally activate information regarding the expected value of the drug [49]. The results considering the inhibition of methamphetamine-seeking behavior in the post-conditioning phase following HFS or LFS administration in the OFC over the conditioning period may be the result of interfering with assigning high motivational value to contextual cues paired with methamphetamine reward experience leading to no significant preference to drug paired context in the expression of methamphetamine place preference.

The OFC is crucially involved in reversal learning, and chronic exposure to psychostimulants such as cocaine in monkeys and rats results in reversal learning deficits similar to animals with OFC damage [20,50,51]. This reversal learning impairment is associated with a failure of OFC neurons to update the expected outcomes appropriately [52]. Extinction of previously formed drug-context associations is a kind of reversal learning in which drug paired environment is no longer accompanied by reward, and animals begin the devaluation process of contextual cues. Based on present results, high-frequency DBS in the OFC facilitated the process of devaluation when applied in the extinction period.

Although the orbitofrontal cortex has been indicated to be involved in the reinstatement of drug-seeking following various triggers such as stress, context, and cue [53–55], it appears not to be involved directly in the drug-priming-induced reinstatement of drug-seeking behavior [54,55]. Interestingly, Fakhrieh-Asl [21] and our results demonstrated that HFS administration in the OFC throughout the extinction phase could notably reduce the morphine and methamphetamine priming-induced reinstatement of drug-seeking behavior, indicating that DBS exerts its effects not only at the site of stimulation but also through effects on the OFC-associated circuits. In this context, DBS was initially thought to inhibit local neurons because its therapeutic effects in the STN were similar to the effects of lesions in this structure [56]. However, the discharge frequency of globus pallidus neurons was significantly increased when DBS was applied to the STN of monkeys, proposing that DBS is capable of affecting regions connected to the target site [57].

5. Conclusion

In summary, DBS is emerging as a novel treatment modality for psychiatric disorders, including SUDs. Its success critically depends on target selection and stimulation parameters. But it must be considered that DBS is an invasive neuromodulatory approach along with the risk of intracranial hemorrhage (1.9 % to 4.1 % of cases), and permanent neurological issues (approximately 2 %). Nonsurgical neuromodulatory techniques such as repetitive transcranial magnetic stimulation are at a considerable advantage in this regard, as they do not need invasive intervention and, therefore, avoid many intraoperative and post-operative side effects of DBS [58]. The present findings suggest that high-frequency DBS in the OFC is effective in preventing drug-reward memory formation, facilitating the extinction of drug-context associations, and inhibiting the relapse of drug-seeking behaviors. More investigations in this area are required to discover the mechanism of actions by which DBS exerts its effects in different brain areas with varying patterns of stimulation to could strongly propose DBS as a practical neuromodulatory approach for treating substance dependency.

CRediT authorship contribution statement

Abbas Haghparast was responsible for the study concept and design. Mojdeh Fattahi performed data collection. Kiarash Eskandari, Mojdeh Fattahi, and Esmail Riahi assisted with data analysis and interpretation of findings. Mojdeh Fattahi wrote the first draft of the manuscript. Abbas Haghparast and Reza Khosrowabadi provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

This article has been extracted from the Ph.D. thesis written by Mrs. Mojdeh Fattahi at the Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences. This project was also supported by the Vice-Chancellor for Research & Technology of Shahid Beheshti University of Medical Sciences (Grant No. 99-26180-1399/11/13), Tehran, Iran.

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