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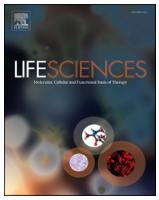

A wide range of Deep Brain Stimulation of the nucleus accumbens shell time independently reduces the extinction period and prevents the reinstatement of methamphetamine-seeking behavior in rats

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ABSTRACT

Methamphetamine (METH) addiction is a significant public health issue, and standard medical therapies are often not curative. Deep Brain Stimulation (DBS) has recently shown the potential to cure addiction by modulating neural activity in specific brain circuits. Recent studies have revealed that the nucleus accumbens shell (NAcSh) could serve as a promising target in treating addiction. Therefore, the present study aimed to investigate the therapeutic effects of NAcSh high- or low-frequency stimulation (HFS or LFS) in the different time points of application on the extinction and reinstatement of the METH-conditioned place preference (CPP). LFS or HFS (10 or 130 Hz, 150–200 μA, 100 μs) was delivered to the NAcSh for 30 min non-simultaneous (in a distinct non-drug environment) or simultaneous (in a drug-paired context) of the drug-free extinction sessions. The obtained results showed that both non-simultaneous and simultaneous treatments by HFS and LFS notably reduced the extinction period of METH-induced CPP. Furthermore, the data indicated that both non-synchronous and synchronous HFS prevented METH-primed reinstatement, while only the LFS synchronized group could block the reinstatement of METH-seeking behavior. The results also demonstrated that HFS was more effective than LFS in attenuating METH-primed reinstatement, and applying HFS synchronous was significantly more effective than HFS non-synchronous in reducing the relapse of drug-seeking. In conclusion, the current study's results suggest that DBS of the NAcSh in a wide range of frequencies (LFS and HFS) could affect addiction-related behaviors. However, it should be considered that the frequency and timing of DBS administration are among the critical determining factors.

1. Introduction

Methamphetamine (METH) is a psychostimulant that is an epidemic health problem [1]. Repeated use of METH results in drug addiction, a chronic relapsing disorder characterized by compulsive drug use and intense cravings [2]. Although various medical treatments (pharmacotherapy, psychotherapy, or rehabilitation) are available, there are no proven treatments for METH addiction, and relapse rates from methamphetamine use are incredibly high [3,4]. Persistent drug-related memories lead to this high rate of relapse [5]. Extinction training (exposure therapy) reduces drug cravings by suppressing drug-related memories. However, the effects are often not permanent [6,7]. Therefore, a vital need exists to develop new therapeutic strategies. Deep Brain Stimulation (DBS) is a safe, minimally invasive, customizable, reversible neuromodulatory procedure approved as standard treatment for mood and movement disorders such as major depressive disorder (MDD), Parkinson's disease (PD), tremor, and dystonia [8,9]. DBS has recently shown the potential to cure addiction by modulating neural activity in specific brain circuits and may help prevent relapse [10,11]. Animal and human studies have demonstrated that applying high- or low-frequency stimulation (HFS or LFS) in different brain areas could reduce cravings or consumption of alcohol, opioids, and cocaine

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[12–14]. However, the target area and stimulation parameters to achieve adequate symptom remission and protection against relapse are controversial [15,16]. For instance, LFS of the dorsal subregions of the ventral striatum (VS) strengthens the morphine extinction memory, whereas HFS of this target impairs drug-related memory extinction [17].

Furthermore, Guercio et al. indicated that HFS in the infralimbic (IL), but not the prelimbic (PL) or anterior cingulate cortex (ACC), selectively blocked cocaine-seeking relapse [18]. Extensive research suggests that METH produces intense and sustained euphoria due to an acute increase in synaptic monoamines, including dopamine, norepinephrine, and serotonin [19]. Its neurobiological basis is generally explained by the mesocorticolimbic system, which includes dopaminergic projections from the ventral tegmental area (VTA to the NAc and prefrontal cortex (PFC), hippocampus, and amygdala [20]. The NAc consists of core (NAcc) and shell (NAcSh) regions that integrate information from cortical and limbic regions to direct behaviors, including motor planning, decision-making, motivation, and reward [21]. Expressly, the NAcSh is a critical region for behavioral stability and shows impaired function after withdrawal from chronic METH use [22,23]. Batra et al. reported that after the establishment of METH self-administration, NAcSh HFS for five consecutive days decreased METH intake in a self-administration model [24]. However, no study has examined the effects of NAcSh DBS on the extinction phase as the basis of exposure-based therapies for addiction and relapse of METH-induced conditioned place preference (CPP). Furthermore, the effects of LFS and HFS on the extinction and reinstatement of METH-seeking behavior have not been previously compared. In addition, the effect of DBS may be affected by the passage of time. Ewing and Grace's local field potential (LFP) recordings showed that DBS's effects decreased after stimulation's cessation. They reported rebound effects in power and coherence after the termination of stimulation [25]. In addition, no previous study has compared the impact of DBS application on METH dependency before and during drug context exposure. Hence, studying the relationship of DBS to addiction-related behaviors with appropriate stimulation targets, time points, and parameters (HFS or LFS) that can potentially improve therapeutic outcomes is necessary. In this study using a CPP procedure and considering the involvement of NAcSh in METH dependency, the encouraging results of DBS application, noting that DBS could exert different effects across different stimulation parameters and time points, LFS and HFS applied to NAcSh non-simultaneously (in a different non-drug environment) and simultaneously (in a drug-paired environment) to extinction sessions to examine the therapeutic effect of DBS on the extinction and priming-induced reinstatement of METH-seeking behavior.

2. Material and methods

2.1. Animals

Forty-six male Wistar rats (Pasteur Institute, Tehran, Iran) weighing between 230 and 270 g were randomly housed, four per cage, and maintained at room temperature (23 °C) under standard conditions. All rats were given ad libitum access to pelleted food and water on a 12-h light/dark cycle. The animals were allowed to acclimatize to the laboratory environment for one week before electrode implantation. All experimental procedures, including operations and behavioral experiments, were performed during the light phase of the cycle. All study protocols were approved and reviewed by the Institutional Research Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1399.006), Tehran, Iran.

2.2. Stereotaxic and electrode implantation surgery

To implant stimulation electrodes, the researchers anesthetized rats with a mixture of ketamine hydrochloride and xylazine (100 mg/kg and 10 mg/kg, body weight) and fixed them in a stereotactic apparatus (Stoelting, USA). Lidocaine (0.2 ml, 20 mg/ml) with epinephrine (12.5 μg/ml) was administered around the scissors to minimize the pain and bleeding. An excision was made in the midline. Bregma, lambda, and their surroundings were cleaned and dried. Two PFA-coated unipolar stainless steel electrodes (inner 0.127 mm each, A-M Systems, Inc.) were twisted together to build bipolar electrodes [26]. The coating was removed at the tips >0.5 mm (the average distance between the two tips was 100 μm) and then implanted bilaterally in the NAcSh in coordinates relative to Bregma: (+1.5 mm anterior to Bregma, ±1 mm mediolateral and 7.7 mm dorsoventral) using the Paxinos and Watson's rat brain atlas [27]. The electrodes were connected to a pin plastic connector. The assembly was secured to the skull with two anchor screws and dental acrylic. After surgery, the rats were housed individually and permitted to recover for about a week before the tests began.

2.3. Drugs

The drug used in the current study was methamphetamine hydrochloride (Baghiyatallah University of Medical Sciences, Tehran, Iran), which was diluted prior to each injection freshly using physiological saline (0.9 % NaCl) and administered at a dose of (0.25 and 1 mg/kg) subcutaneously (sc).

2.4. Conditioned place preference (CPP) apparatus and procedure

Drug reward and addiction-like behavior were measured using an unbiased CPP paradigm. The CPP apparatus is a Plexiglas box with three compartments: two large compartments (large chamber) of the same size (30 × 30 × 40 cm^3) with different black and white stripes in different orientations (horizontal vs. vertical) on the wall and bottom with different textured panels (smooth vs. mesh) to ensure tactile differences. The third compartment is a connector and starter (null part; 30 × 15 × 40 cm^3), with a removable sliding door. The CPP procedure was performed in five phases: pre-conditioning (1 day), 5-day conditioning (acquisition), and post-conditioning (1 day) followed by ten days of extinction sessions and reinstatement phases (1 day) [28]. The Conditioning Score (CS) was taken as an index of preference as time spent in the drug-paired chamber minus time spent in the saline-paired chamber on the test days. CS and total distance traveled by each animal (locomotor activity) were calculated at each stage separately using a video tracking system (the locomotion monitoring device system) and Ethovision software.

2.4.1. Pre-conditioning phase (pre-test)

To adapt the animals to the laboratory environment, they were moved to the experimental room 30 min prior to the initiation of the test. In the pre-test level, each animal was placed separately in the connector (null) box on the first day to determine baseline side preference. The sliding door was removed, the animals were permitted to move freely in all chambers for 10 min, and CS and locomotor activity were calculated. Animals should not prefer either compartment in an unbiased paradigm. Animals spending ≥80 % of the total time in one of the same size compartments were considered biased and excluded (n = 5) from the study [29–32]. The remaining rats were randomly divided into experimental and control groups.

2.4.2. Conditioning phase (acquisition)

The conditioning phase started one day after the pre-test (day 2) and took five days (2–6 days). During these sessions, the animals received METH (1 mg/kg, sc) and were confined for 30 min in a chamber with a closed sliding door in the morning, and after 6 h, they were administered saline (1 ml/kg) and confined to another compartment. The next day, rats received saline in the morning and METH 6 h later [33–35].

2.4.3. Post-conditioning phase (expression)

On the seventh day of the CPP procedure, the expression phase (a

drug-free state) was executed after the acquisition phase. Identical to the pre-test day, the animals were tested on the expression day to determine the CS. It was documented for all groups.

2.4.4. Extinction

On each day of this phase, the rats underwent a 30-min test session (8–17 days). The rats were then placed in the connector part of the CPP apparatus with free access to all chambers, and CS and locomotor activity were recorded and measured daily in the first 10 min of each session. The onset of extinction is considered when the CPP scores show a 50 % reduction during this period compared to the post-conditioning phase's CS as the mean extinction latency (MEL) [36–39].

2.4.5. Reinstatement

One day after the last extinction session, animals were injected with a challenging dose of METH (0.25 mg/kg) [30]. Identical to the pre-and post-conditioning days, the animals were immediately placed in the null part of the CPP box and allowed to explore all three chambers freely. The CS and locomotor activity were calculated.

2.5. Deep Brain Stimulation protocol and experimental design

Constant current stimulation (monophasic square wave pulses) at pulse frequencies of 130 Hz (HFS) or 10 Hz (LFS), a pulse intensity of 150–200 μA, pulse duration of 100 μs similar to those used in previous studies [40,41], was administered to the NAcSh through a cable connected to a current-based stimulator. The pulse intensity was increased stepwise (50 μA increments) to the predicted value.

Following METH conditioning, two sets of the experiment (a total of six groups) were allocated to investigate the effects of two patterns of the NAcSh DBS (LFS and HFS) in different time points (non-simultaneous and simultaneous with extinction sessions) on the extinction and reinstatement of METH-induced CPP. Foremost, to test whether LFS or HFS non-simultaneous to the extinction sessions could affect the extinction period and drug-primed relapse, two separate groups of animals received low-frequency (LFS, 10 Hz, 150–200 μA, 100 μs, n = 6) or high-frequency (HFS, 130 Hz, 150–200 μA, 100 μs, n = 7) stimulation for 30 min non-simultaneous to extinction sessions in a separate non-drug environment. The animals, after 1 h, were put in the CPP box. In the SHAM control group (DBS-off, n = 4), the animals were connected to the external cable and the stimulator for 30 min non-simultaneous to extinction sessions but were not subjected to any electrical pulses. At the end of the extinction period, a priming dose of METH (0.25 mg/kg, sc) was injected to evaluate the relapse of METH-seeking behavior. In another set of experiments to investigate the effect of LFS or HFS simultaneous with the extinction sessions on the extinction and reinstatement of METH CPP, the following two groups received low-frequency (LFS, 10 Hz,150–200 μA, 100 μs, n = 6) or high-frequency (HFS, 130 Hz150–200 μA, 100 μs, n = 7) stimulation for 30 min simultaneous with extinction sessions (corresponding to the duration of each extinction session) in a CPP box (drug-paired environment). In the SHAM control group (DBS-off, n = 4), the rats were similarly connected to the stimulation device during the CPP test but did not undergo electrical stimulation. One day after the last extinction session on the reinstatement day, a priming dose of METH (0.25 mg/kg, sc) was injected to examine the reinstatement of METH-seeking behavior (Fig. 1).

2.6. Verification of electrode placement

At the end of the experiment, the rats were deeply anesthetized with ketamine and xylazine (150:15 mg/kg, intraperitoneal) and transcardially perfused with a 4 % polyformalin solution and saline serum (0.9 %). After sacrifice, brains were removed and fixed in 10 % formalin. The brains were then sliced coronally into 50 μm thickness slices to assess the electrode location (Fig. 2A). An investigator blinded to the animals' behavioral responses determined the location of stimulation electrode placement. Animals with placed electrodes outside the NAcSh area were removed from further data analysis (n = 7; Fig. 2B).

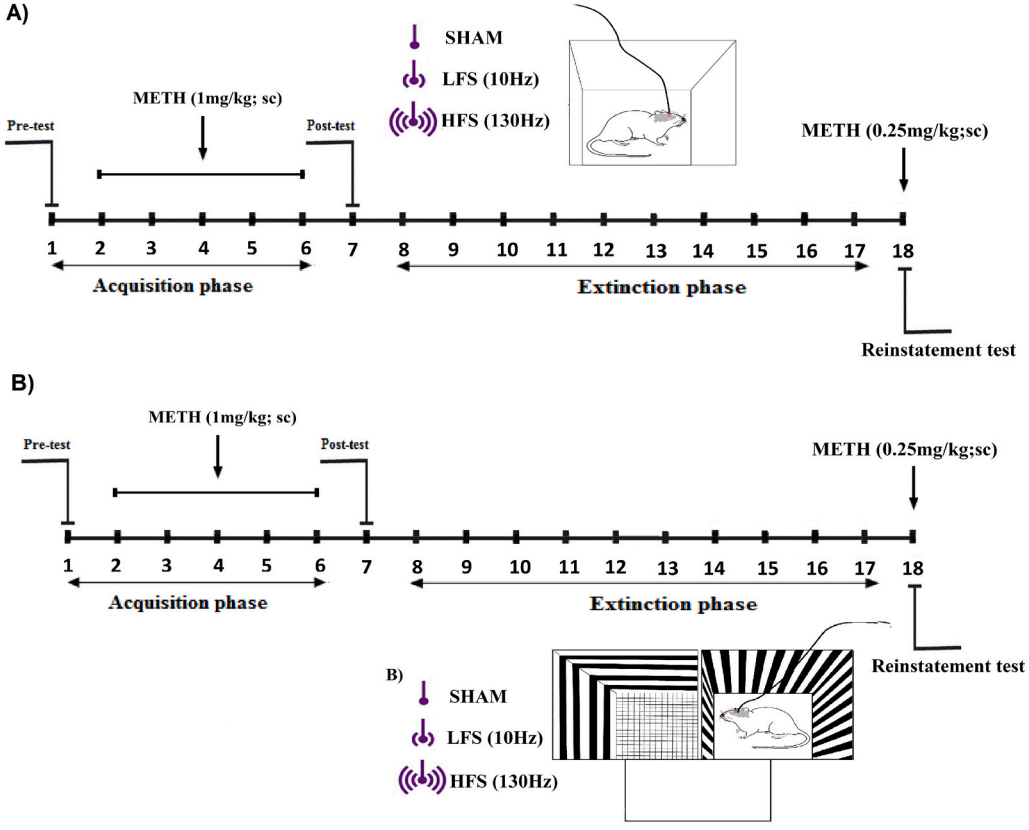

Fig. 1. The graphical scheme shows the experimental protocols. Conditioned place preference (CPP) paradigm: pre-conditioning (pre-test), conditioning (acquisition) phase, post-conditioning day (post-test), extinction phase, reinstatement phase. Following METH conditioning, A) animals received LFS or HFS for 30 min non-simultaneous to extinction sessions in a separate nondrug environment. In the SHAM control (DBS-off) group, the animals were connected to the external cable and the stimulator before extinction sessions but not subjected to any electrical pulses. B) The next three groups received LFS or HFS for 30 min simultaneous with extinction sessions (corresponding to the duration of each extinction session) in a CPP box (drug-paired environment). In the SHAM (DBS-off) group, the rats were similarly connected to the stimulation device during the CPP test but did not undergo electrical stimulation.

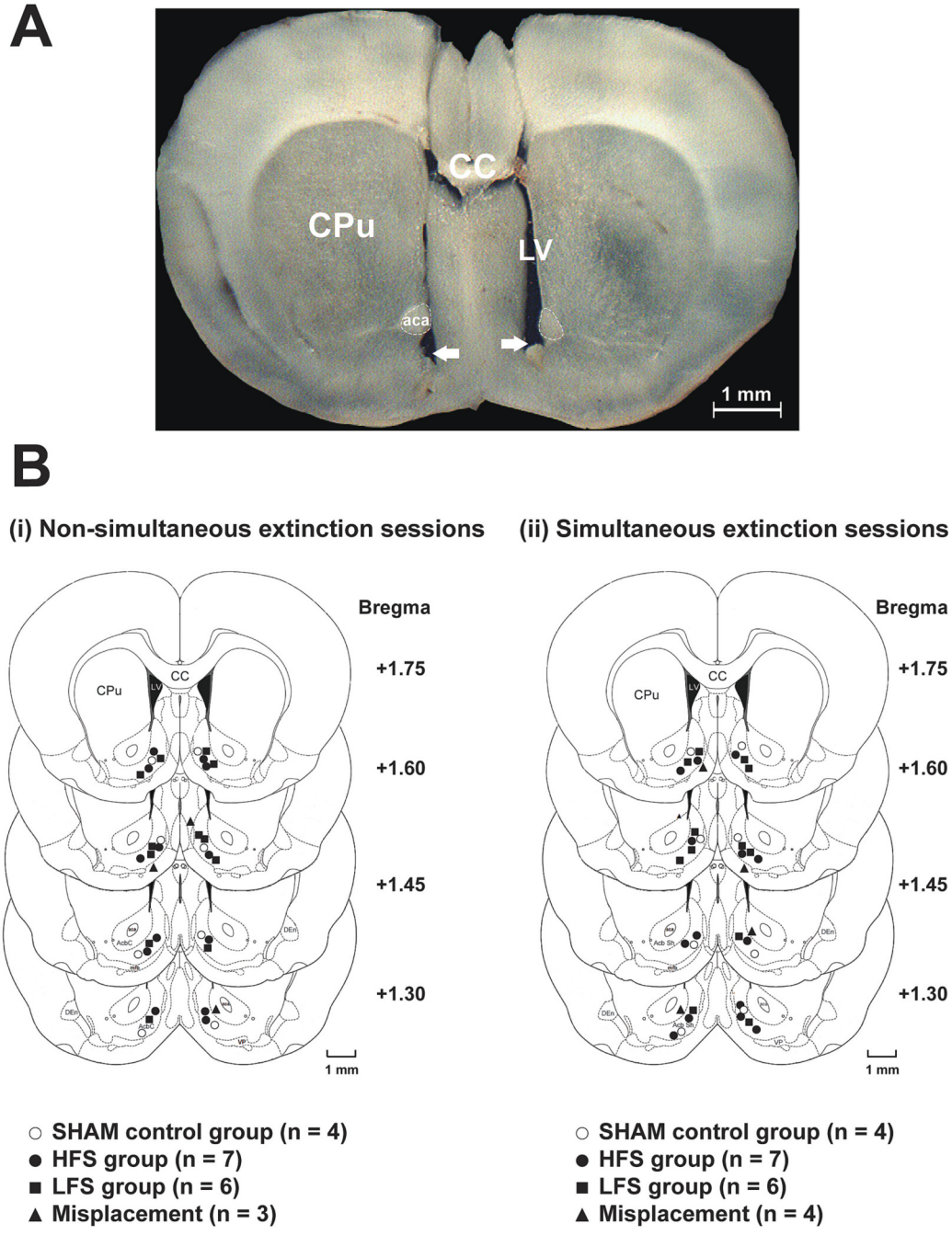

Fig. 2. A) A photomicrograph of representative bilateral electrode placements in the NAcSh (identified by the white arrows). B) The coronal graphic manifestation shows the positions of the electrodes implanted in the NAcSh. i) DBS non-simultaneous to extinction sessions; ii) DBS simultaneous to extinction sessions; (○ SHAM control group); ● high-frequency stimulation (HFS); ■ low-frequency stimulation (LFS); ▲ misplacement. aca, anterior commissure, anterior part; AcbC, accumbens nucleus, Core; AcbSh, accumbens nucleus, shell; cc, corpus callosum; CPu, caudate putamen (striatum); DEn, dorsal endopiriform nucleus; LV, lateral ventricle; mfb, medial forebrain bundle; VP, ventral pallidum.

2.7. Statistics

Data are presented as the mean ± SEM (standard error of the mean). Data were then analyzed and plotted using GraphPad Prism®6.0 software. The paired *t*-test was used to compare data between two dependent groups, and an unpaired Student's *t*-test was used to compare data between two independent groups. Comparisons between experimental and control groups were performed using one-way analysis of variance (ANOVA) followed by multiple comparison tests, Tukey, or Dunnett's test. In addition, a two-way ANOVA followed by Bonferroni's multiple comparisons test was used for comparisons between different stimulation groups at different time points. Differences were statistically considered significant when P was <0.05.

3. Results

It should be emphasized that previous studies reported that a 5-day schedule administration of METH (1 mg/kg, sc) induces a place preference for the METH-paired compartment [42,43]. Furthermore, the unpaired *t*-test between SHAM groups (non-simultaneous vs. simultaneous) did not show any significant difference in MEL [t (6) = 0.3573, P = 0.7331] in the extinction phase. In addition, on reinstatement day, CPP scores had no considerable difference [t (6) = 0.2329, P = 0.8236]. Therefore, the obtained data from these two SHAM groups were merged and randomly selected 6 out of 8 rats for each SHAM group.

3.1. DBS non-simultaneous to the extinction sessions facilitated the extinction phase and inhibited the reinstatement of METH-induced CPP

To test whether LFS or HFS non-simultaneous to the extinction sessions could affect extinction and reinstatement of METH CPP, rats were first trained for five days (conditioning), and after acquiring a preference for methamphetamine, LFS or HFS electrical stimulation (10 or 130 Hz, 150–200 μA, 100 μs) was applied to the NAcSh for 30 min non-synchronize with each daily session in extinction phase (10 days). At the end of the extinction period, a priming dose of methamphetamine (0.25 mg/kg) was administered to reinstate METH-seeking behavior. Fig. 3 illustrates the impact of LFS or HFS on METH extinction and reinstatement in the three experimental groups, including the HFS, LFS, and SHAM groups (the patterns of behavior within individual animals represented for Fig. 3 have been shown in Supplementary Fig. 1). After METH conditioning, the paired *t*-test in all groups exhibited a significant preference for the METH-paired (pre- vs. post-conditioning in the SHAM group: t (5) = 5.717, $P = 0.0023$; HFS: t (6) = 16.21, $P < 0.0001$; LFS: t (5) = 8.529, $P = 0.0004$). During the extinction phase, repeated drug-free exposures to the conditioning context caused gradually eliminated side preference in all experimental groups. Nevertheless, the trends were not the same for all groups.

As shown in Fig. 3A, the repeated measures one-way ANOVA followed by Dunnett's post-hoc analysis [F (12, 77) = 7.190, $P < 0.0001$] showed that in the SHAM group, rats had extinguished their preference for the METH-associated context in the ninth and tenth days of extinction period compared to post-conditioning phase. A paired Student *t*-test [t (5) = 3.021, $P = 0.0294$] revealed that a priming dose of METH significantly reinstated drug-seeking behavior on the reinstatement day compared to the last day of the extinction period. As Fig. 3B showed, in the LFS group, repeated measures one-way ANOVA followed by Dunnett's post-hoc test [F (12, 77) = 4.816, $P < 0.0001$] indicated that preference for the METH compartment significantly reduced in the eighth, ninth and tenth days of extinction period compared to the post-test level. It seems LFS decreased the duration of the extinction period compared to the SHAM group. However, A paired Student *t*-test [t (5) = 3.391, $P = 0.0194$] indicated that LFS failed to block METH priming-induced reinstatement of an extinguished drug-seeking behavior. In the HFS group, repeated measures one-way ANOVA followed by Dunnett's post-hoc analysis [F (12, 90) = 3.583; $P = 0.0003$] confirmed that animals lost their preference for the METH-paired context on the seventh, eighth, ninth, and tenth days of extinction period compared to post-conditioning phase (Fig. 3C). It seems that HFS shortened the duration of extinction period compared to that of SHAM group. Additionally, a paired Student *t*-test [t (6) = 1.441, $P = 0.1995$] indicated that a priming dose of METH could not reinstate drug-seeking behavior compared to the last day of the extinction period. In the next step, for comparing the effect of DBS on shortening the extinction period between experimental groups, the impact of LFS (10 Hz) or HFS (130 Hz) DBS and SHAM control group on the MEL, as a criterion of onset in the extinction of the METH place preference were computed. The one-way ANOVA followed by Tukey's multiple comparisons test [F (2, 18) = 4.687, $P = 0.0250$; Fig. 4A] showed that the daily stimulation of NAcSh (LFS and HFS) for 30 min non-simultaneous to the extinction sessions reduced the MEL compared with the SHAM group. It indicates that DBS non-simultaneous to extinction sessions shorten the extinction period. The result illustrated no significant difference in MEL between LFS and HFS groups. Besides, the One-way ANOVA test followed by Tukey's multiple comparison test showed that NAcSh stimulation by high and low frequency did not affect locomotor activity during the extinction period [F (2, 18) = 0.5601, $P = 0.5820$; Fig. 4B]. In addition, the impact of LFS or HFS non-simultaneous to the extinction sessions on the reinstatement of drug-seeking behavior between experimental groups was compared. One-way ANOVA followed by Tukey's post-hoc test showed no significant difference in the CPP scores between these groups on reinstatement day [F (2, 18) = 2.002, $P = 0.1675$; Fig. 4C]. One-way ANOVA followed by Tukey's multiple comparison test showed no significant differences between groups in locomotor activity on reinstatement day [F (2, 18) = 2/787, $P = 0/0916$; Fig. 4D].

3.2. DBS simultaneous to the CPP test facilitated the extinction phase and inhibited reinstatement of METH-induced CPP

To examine the effect of LFS or HFS simultaneous to the extinction sessions on extinction and drug-primed reinstatement of METH CPP, after the conditioning phase, LFS or HFS electrical stimulation (10 or 130 Hz, 150–200 μA, 100 μs) was delivered to the NAcSh daily simultaneous to extinction period (for 30 min, corresponding to the duration of an extinction session) in the CPP box. A priming dose of METH (0.25 mg/kg) was injected one day after the last extinction session. Fig. 5 shows the impact of LFS or HFS on METH extinction and reinstatement in the three experimental groups, including the HFS, LFS, and SHAM groups (the patterns of behavior within individual animals represented for Fig. 5 have been shown in Supplementary Fig. 2). The paired *t*-test showed that all groups developed a significant side preference for the METH-paired compartment compared to their pre-conditioning levels after the conditioning phase [SHAM: t (5) = 5.682, $P = 0.0024$; HFS: t (5) = 5.810, $P = 0.0011$; LFS: t (5) = 5.768, $P = 0.0022$]. Repeated drug-free exposure to the CPP context during extinction caused a progressive decrease in side preference in all groups. Nevertheless, the trends were different between experimental groups. The repeated measures one-way ANOVA followed by Dunnett's multiple comparison test [F (12, 77) = 6.998, $P < 0.0001$; Fig. 5A] showed that in the SHAM group, on the ninth and tenth days of the extinction period, the rats had extinguished their preference for the METH-associated chamber in comparison with post-test. A paired Student *t*-test [t (5) = 3.302, $P = 0.7455$] indicated that one day after the last extinction session, a challenging dose of METH significantly reinstated drug seeking in animals compared to the last day of the extinction period. As Fig. 5B illustrated, in the LFS group, repeated measures of one-way ANOVA followed by Dunnett's post-hoc test comparison test [F (12, 77) = 3.941, $P = 0.0002$] indicated that in the LFS group, animals had extinguished their preference for the METH-associated context on the sixth, seventh, ninth and tenth days of the extinction phase in comparison with the post-test day. LFS seems to decrease the duration of METH extinction from 9 to 6 days compared to the SHAM group. A paired Student *t*-test [t (5) = 0.2362, $P = 0.8226$] showed LFS inhibited reinstatement of METH-seeking behavior compared to the last day of the extinction period. Fig. 5C illustrated repeated measures of one-way ANOVA followed by Dunnett's post-hoc test comparison test [F (12, 90) = 5.085, $P < 0.0001$] confirmed that in the HFS group, preference for the METH-associated compartment significantly reduced in the eighth, ninth and tenth days of extinction period compared to the post-conditioning phase. It seems HFS shortened the duration of METH extinction compared to the SHAM group. Besides, A paired Student *t*-test [t (6) = 0.4357, $P = 0.6783$] demonstrated that a priming dose of METH could not reinstate drug-seeking behavior compared to the last day of the extinction period. In the following step, the impact of LFS or HFS on the MEL was computed to compare DBS's effect on the shortening of the extinction period. The one-way ANOVA followed by Tukey's multiple comparison test [F (2, 18) = 5.382, $P = 0.0163$; Fig. 6A] showed that the LFS and HFS during the 30-min test session reduced the MEL compared with the SHAM group. It shows that administrating DBS simultaneous to extinction sessions reduces the extinction period. The result indicated no significant difference in MEL between LFS and HFS groups. One-way ANOVA test followed by Tukey's post-hoc test showed no significant differences between experimental groups in locomotor activity during the extinction phase [F (2, 18) = 1.520, $P = 0.2487$; Fig. 6B]. Furthermore, the impact of LFS or HFS on the reinstatement phase was compared. One-way ANOVA test followed by Tukey's multiple comparison test showed no significant differences in the CPP score on reinstatement day [F (2, 18) = 2.386, $P = 0.1239$; Fig. 6C]. However, simultaneous treatment by HFS significantly reduced

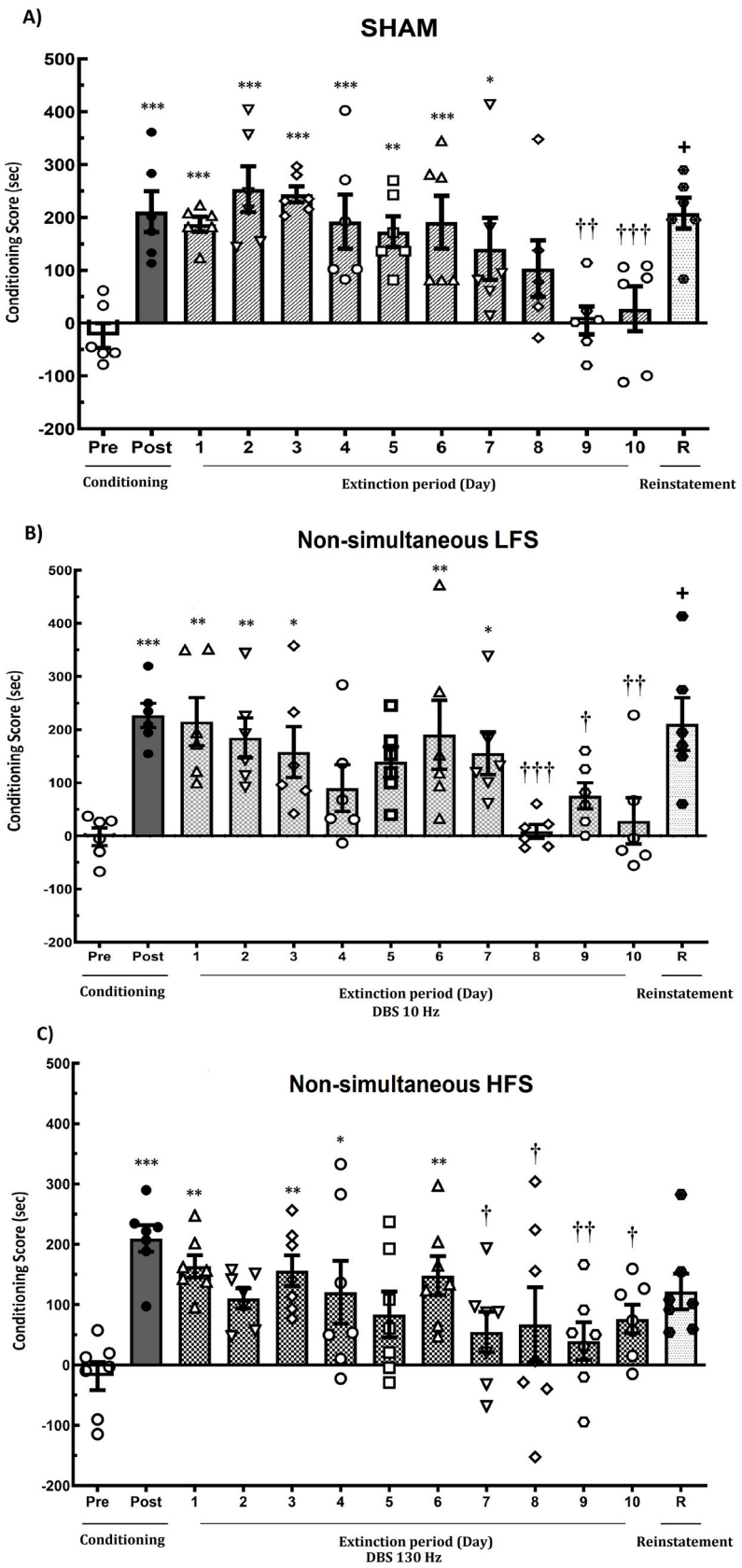

Fig. 3. Effects of NAcSh DBS administering non-simultaneous to the extinction sessions on the extinction and reinstatement of METH-induced CPP in the A) SHAM, B) LFS, and C) HFS groups. Data were expressed as mean ± SEM for 6–7 rats.
*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$; as compared with pre-conditioning CPP score.
†$P < 0.05$, ††$P < 0.01$ and †††$P < 0.001$; as compared with post-conditioning CPP score.
+$P < 0.05$; different from the last extinction day.

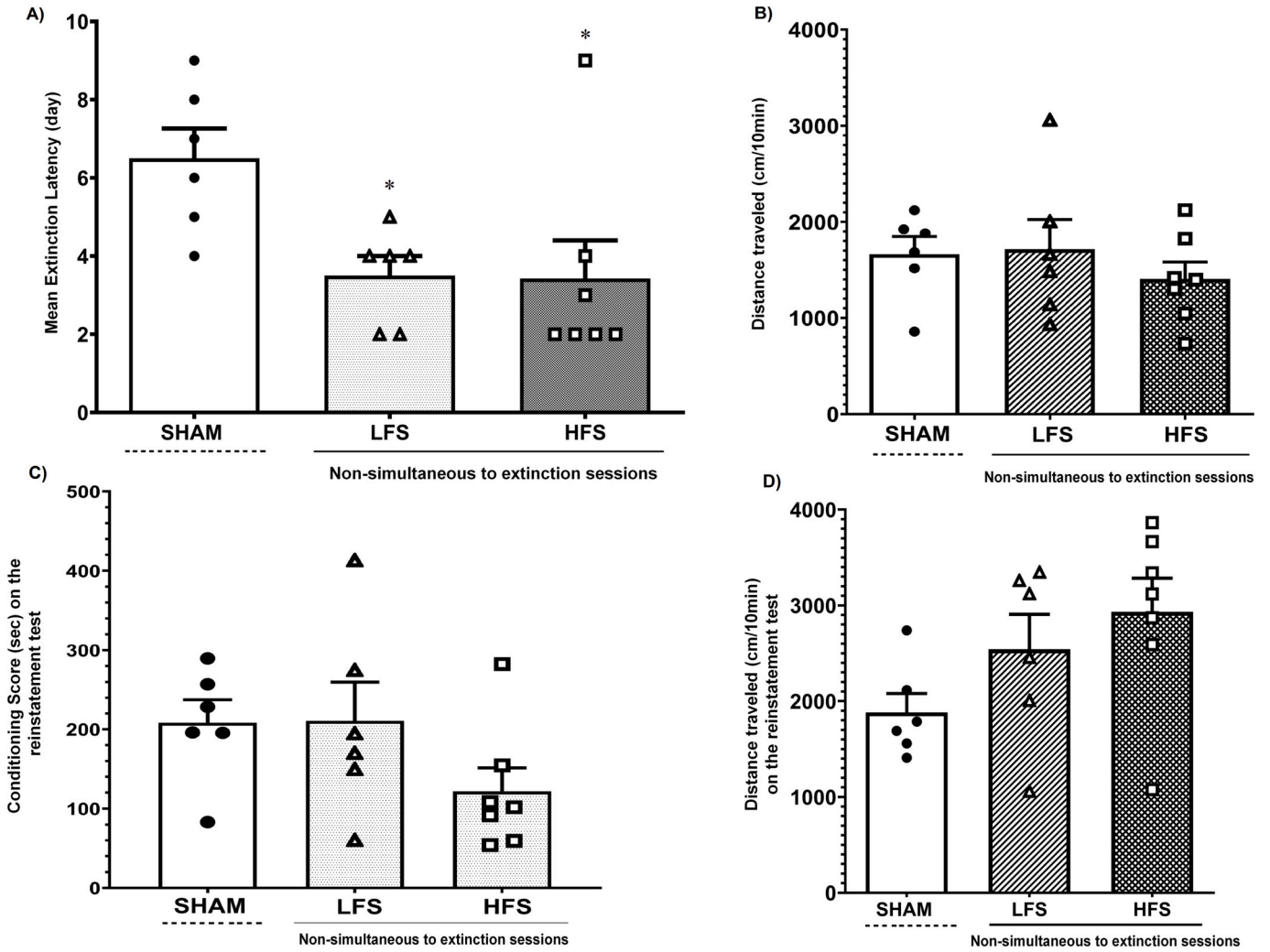

Fig. 4. Effects of 30-min daily stimulation of NAcSh non-simultaneous to the extinction sessions on A) the mean extinction latency, B) locomotor activity during the extinction period, C) the CPP score, and D) locomotor activity on the reinstatement day. Data were expressed as mean ± SEM for 6–7 rats. *$P < 0.05$; as compared with the SHAM control group.

the CPP score on reinstatement day compared to the SHAM control group [$P = 0.0442$]. One-way ANOVA test followed by Tukey's multiple comparison test showed no significant differences in locomotor activity between groups on reinstatement day [F (2, 18) = 2.527, $P = 0.1113$; Fig. 6D].

3.3. Comparing the efficacy of applying DBS non-simultaneous and simultaneous to the extinction sessions on the extinction and reinstatement of METH-induced CPP

To compare the efficacy of synchronized or non-synchronized DBS application to the extinction sessions on the extinction (MEL) and reinstatement of METH place preference (CPP score), a two-way ANOVA followed by Bonferroni's multiple comparisons test was applied. Results regarding the MEL criterion indicated the significant effects of DBS [F (2, 32) = 9.852; $P = 0.0005$] but insignificant effects of time [F (1, 32) = 0.8106; $P = 0.7777$] and DBS × time interaction [Interaction: F (2, 32) = 0.1886; $P = 0.8290$] (Fig. 7A). Furthermore, two-way ANOVA followed by Bonferroni's multiple comparisons test did not show any remarkable effect in applying DBS, non-simultaneous or simultaneous to the extinction sessions on the reinstatement of METH place preference. However, the DBS effect was significant [DBS Factor: F (2, 32) = 3.958; $P = 0.0291$; Time Factor: F (1, 32) = 2.933; $P = 0.0965$; DBS × time Interaction: F (2, 32) = 0.6046; $P = 0.5524$; Fig. 7B].

3.4. Comparing the efficacy of the same DBS frequency non-simultaneous and simultaneous to the extinction sessions on the extinction and reinstatement of METH-induced CPP

To evaluate which HFS- or LFS-DBS protocol (non-simultaneous compared to simultaneous with extinction sessions) is more efficient in accelerating the extinction phase and preventing relapse of METH place preference, we normalized the mean extinction latency and the reinstatement day's CPP scores of each group compared to their SHAM control group. An unpaired Student *t*-test [t (12) = 0.3322, $P = 0.7455$; Fig. 8A] revealed no significant differences between applying HFS simultaneously and non-simultaneously to the extinction sessions on shortening the extinction period. Also, the same result was obtained between the group that received LFS simultaneous and non-simultaneous to extinction sessions [t (10) = 0.5590, $P = 0.5885$; Fig. 8B]. Furthermore, an unpaired Student *t*-test [t (12) = 2.366, $P = 0.0357$; Fig. 8C] revealed that applying HFS simultaneous to the extinction sessions in the CPP box is more effective in reducing METH-induced relapse than administrating HFS non-simultaneously. There was no significant difference between the group that received LFS non-simultaneous and the group that received LFS simultaneous to the extinction session in blocking reinstatement [t (10) = 0.8543, $P = 0.4129$; Fig. 8D].

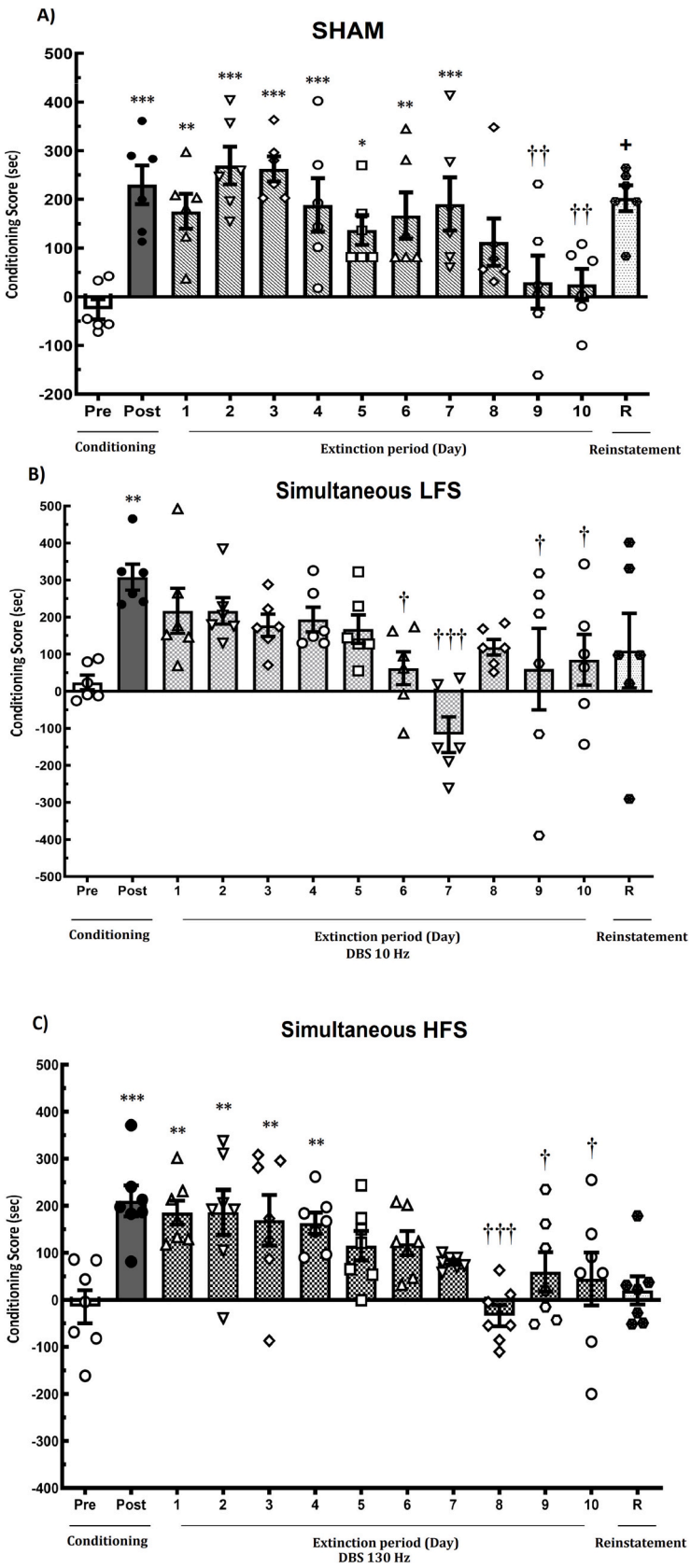

Fig. 5. Effects of DBS application simultaneous to the extinction sessions on the extinction and reinstatement of METH-seeking behavior in the A) SHAM, B) LFS, and C) HFS groups. Data were expressed as mean ± SEM for 6–7 rats.

$^{**}P < 0.01$ and $^{***}P < 0.001$; as compared with pre-conditioning CPP score.

$\dagger P < 0.05$, $\dagger\dagger P < 0.01$ and $\dagger\dagger\dagger P < 0.001$; as compared with post-conditioning CPP score.

$+P < 0.05$; different from the last extinction day.

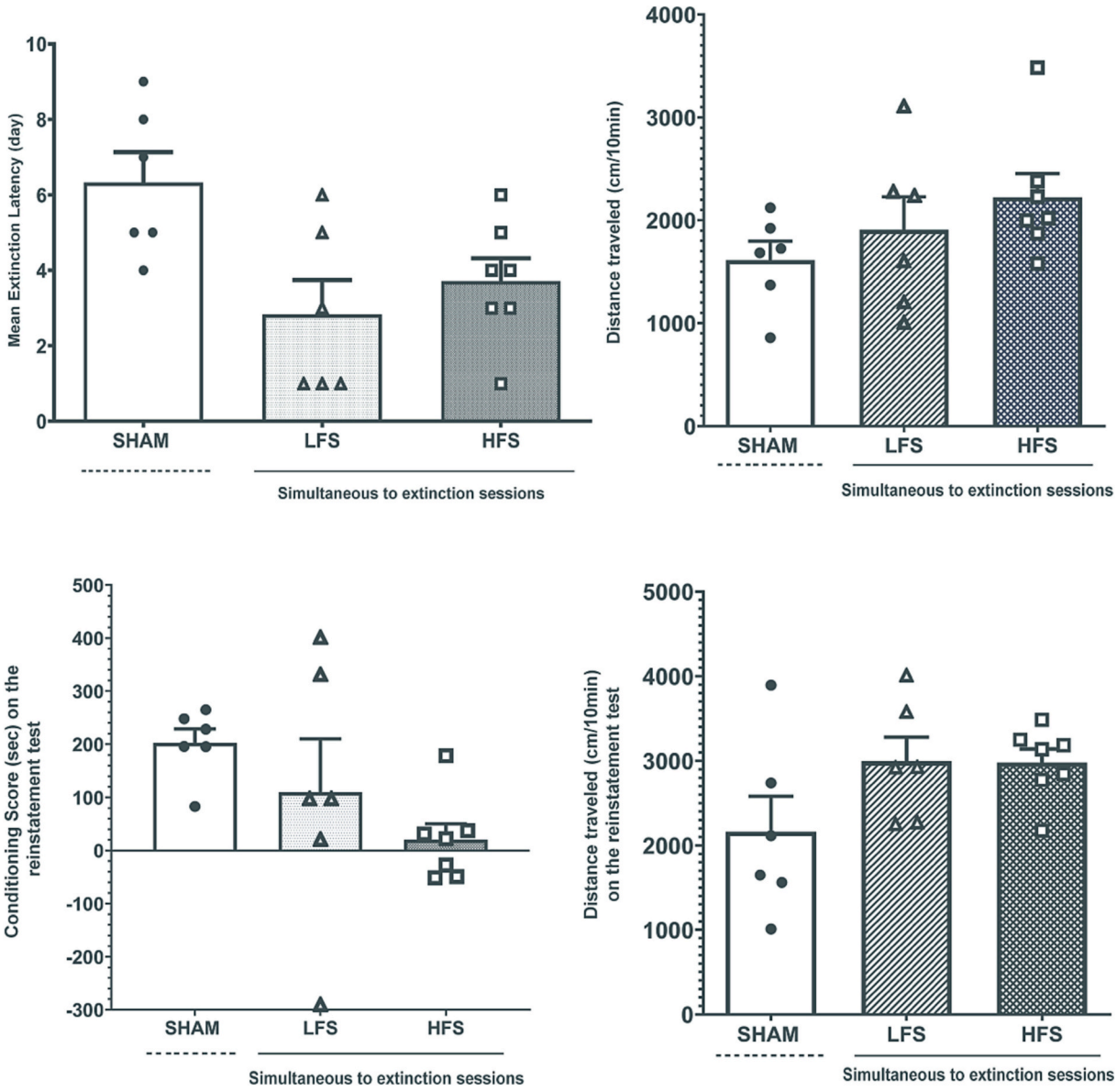

Fig. 6. Effects of daily stimulation of the NAcSh for 30 min simultaneous to the extinction sessions (corresponding to the duration of an extinction session) on A) the mean extinction latency, B) locomotor activity during the extinction period, C) the CPP score, and D) locomotor activity on the reinstatement day. Data were expressed as mean ± SEM for 6–7 rats.
*$P < 0.05$; as compared with the SHAM control group.

4. Discussion

The present study aimed to examine the effect of NAcSh LFS and HFS in different time points (non-simultaneous and simultaneous to drug context exposure) on the extinction and reinstatement of METH-seeking behaviors. The results showed that I. HFS concurrent and asynchrony by extinction sessions facilitated the extinction of METH-induced CPP. II. Both non-synchronous and synchronous HFS prevented METH-primed reinstatement. III. Non-simultaneous and simultaneous treatments by LFS could result in shorter extinction latencies. IV. Only LFS synchronized to the extinction sessions in the CPP box could prevent METH-seeking behavior on the reinstatement day. V. HFS was more effective than LFS in attenuating METH-primed reinstatement. VI. Applying HFS synchronized with extinction sessions in the CPP box was significantly more effective than HFS non-synchronized to these sessions in preventing the relapse of drug-seeking behaviors. VII. DBS in NAcSh had no significant effects on locomotor activity.

Stable and persistent drug-associated memory leads to high relapse rates in addicts. Extinction is a form of learning in which the subject association between the cues and the drug is attenuated by exposure to the cues in the absence of the drug [44]. Consequently, the interrupting of drug memory and enhancement of extinction of drug-associated memory in addicts may suppress drug-seeking behavior and reduce the risk of relapse [45]. The current study's results demonstrated that NAcSh DBS shortens the extinction period and prevents METH-seeking relapse. Consistent with these results, DBS of NAcSh has been shown in order to avoid morphine-seeking behavior and reduce alcohol intake and cocaine-seeking [18,46–48]. Notably, many critical variables exist when considering the therapeutic potential of DBS for drug addiction treatment. For example, HFS of the IL but not the ACC or PL has reduced cocaine seeking [36] selectively. Therefore, the overall results may vary depending on the organization of the neural components in the stimulated region. NAc contains two functionally and anatomically distinct subregions, the NAcc and NAcSh regions. Proposedly, the NAcSh is more

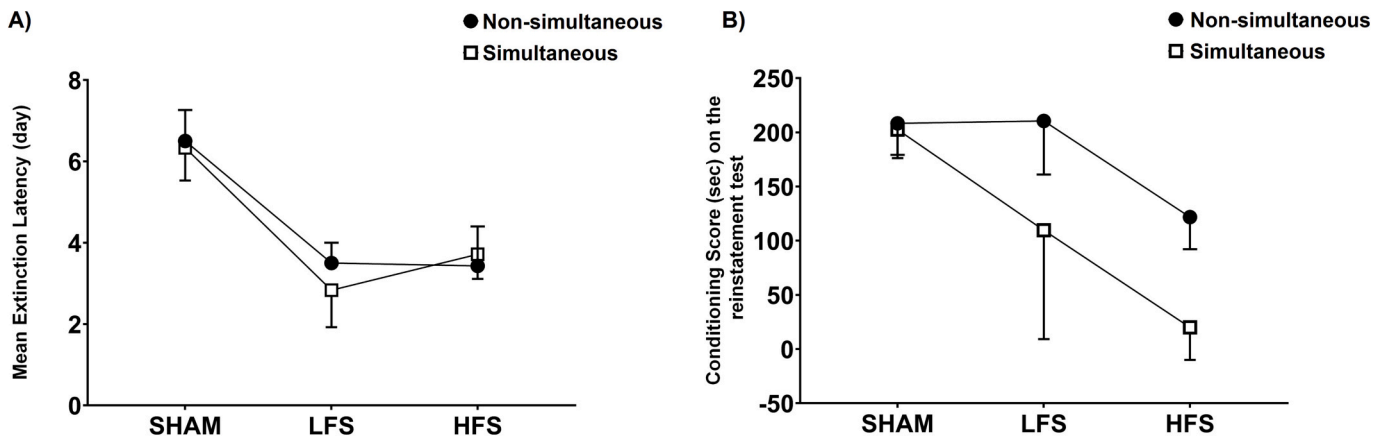

Fig. 7. Comparing the efficacy of applying simultaneous and non-simultaneous NAcSh DBS to the extinction sessions on A) the extinction and B) reinstatement of METH-induced CPP. Data were expressed as mean ± SEM for 6–7 rats.

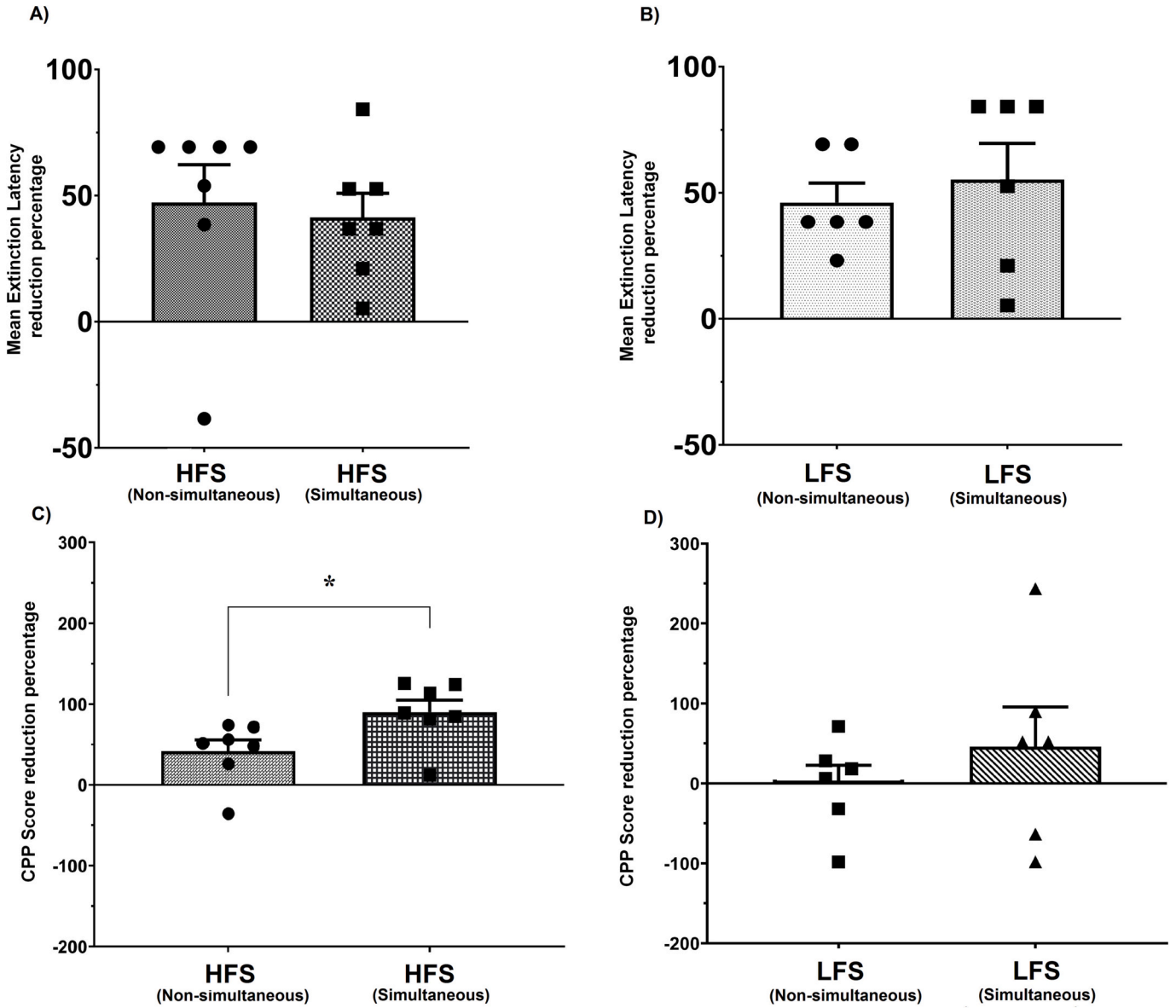

Fig. 8. Comparing the efficacy of the same DBS frequency non-simultaneous and simultaneous to the extinction sessions on A and B) the extinction of METH-induced CPP and C and D) reinstatement of METH-induced CPP. Data were expressed as mean ± SEM for 6–7 rats.
*$P < 0.05$; non-simultaneous compared to simultaneous HFS.

related to the limbic system, while the NAcc acts as an interface between the limbic and motor systems [49,50]. Evidently, the unconditioned dopamine response to cocaine and morphine is remarkably higher in the NAcSh than in the NAcc [51]. The neural network required to mediate the stimulant effects of drugs has been shown to reside within the NAcSh, as the strength of the dopamine response to psychostimulants depends on an intact shell [52].

The mechanism of NAcSh DBS in facilitating extinction and inhibiting relapse could be that DBS dissociates input and output signals and disrupts the abnormal flow of information through the cortico-basal ganglia circulation in pathological conditions ("disruption hypothesis") [53,54]. DBS's effects on brain circuits are not limited to local inhibition or excitation [53,55]. Several studies have indicated that DBS could simultaneously enhance the transmission from the targeted nucleus and activate surrounding fiber pathways, resulting in a complex pattern of inhibitory and excitatory effects [56]. Electrophysiological studies showed that NAc DBS modulated dysfunctional neuronal activity between the orbitofrontal cortex (OFC) and the thalamocortical circuit [57,58]. Vassoler and colleagues showed that DBS of the NAcSh inhibited relapse of drug seeking [59]. In the subsequent study, they showed that NAcSh DBS affected drug-seeking behavior via antidromic activation inhibitory interneurons in the PFC, which plays an essential role in the drug memory extinction, thus normalizing abnormal addiction-related activity in the cortico-accumbal system [60]. Concludingly, the DBS of NAcSh has various effects on the neurons in the cortico-basal ganglia loop and is an essential region in brain networks responsible for motivational behavior control.

After determining the target areas, the crucial factor is the appropriate stimulation parameters with a positive therapeutic effect and minimal side effects. The previous studies on DBS generally use HFS (130–160 Hz). However, several studies have examined the impact of LFS (10–30 Hz). These studies have been associated with positive and sometimes negative results [48,61–63]. Remarkably, despite a similar target, DBS appears to lead to dissimilar clinical outcomes. For example, dorsal-VS LFS enhances morphine extinction memory, whereas HFS of this target impairs the extinction of drug memory [17]. Furthermore, OFC's HFS prevented the development and relapse of morphine CPP, while OFC's LFS did not [40]. These results suggest that the circuits that mediate such key addiction-related behaviors can be disrupted by applying different stimulation intensities. Surprisingly, this research found that HFS and LFS-NAcSh stimulated groups significantly attenuated METH-seeking behavior. These results can be explained by Hu et al. study that showed, in the NAc, a low-frequency range frequency (<50 Hz) dampened neuronal firing in the NAc area similar to high-frequency electrical stimulation (e.g., 130 Hz) [64]. Given the current study results with the previous studies, apparently, both LFS and HFS can produce similar effects on NacSh, which may indicate the promotion of this area as a therapeutic target to cure addiction, as it is effective over a wide range of frequencies.

Last but not least electrophysiological studies have shown that the reversal of DBS effects occurs after cessation of stimulation [25,64]. Concludingly, any adverse or beneficial impact after DBS treatment appears to be transient. The current study showed that synchronized and non-synchronized DBS applications during the extinction period could facilitate the extinction of reward-context memories in both high and low frequencies. Consistent with the present study's results, NAc stimulation has been demonstrated to induce long-term potentiation in cortical interneurons, which may contribute to the long-term impacts of DBS [57,58]. These results imply that the biological effects of DBS are long-term and can continue after the end of the stimulation. In this context, it was shown that HFS during the extinction period could reduce the relapse of METH-seeking behavior more effectively than LFS. Besides, synchronized HFS was accompanied by more efficacy than non-synchronized HFS. It can be concluded that both high and low frequency and timing of DBS administration are critical factors that should be considered for NAcSh DBS, and further studies should be conducted to understand the nature of functional changes before, during, and after DBS to determine the most beneficial timeline for significant reductions in METH dependence.

In conclusion, the present results suggest that NAcSh DBS could affect addiction-related memories across a wide frequency range, accelerates the extinction of drug memory, and attenuates relapse of METH-induced CPP. Proposedly, this region is a therapeutic target for stimulant use disorders because of its effectiveness over a wide range of frequencies. Nonetheless, future studies should design relevant electrophysiological and molecular studies to complement the collected behavioral data to help determine the precise mechanisms for optimal efficacy to develop new, less invasive methods.

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CRediT authorship contribution statement

Abbas Haghparast was responsible for the study concept and design. Kiarash Eskandari contributed to the acquisition of data. Abbas Haghparast and Kiarash Eskandari assisted with data analysis and interpretation of findings. Kiarash Eskandari and Mojdeh Fattahi drafted the manuscript. Abbas Haghparast, Esmail Riahi 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.

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