Pharmacology, Biochemistry and Behavior 185 (2019) 172759

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

REM sleep deprivation impairs retrieval, but not reconsolidation, of methamphetamine reward memory in male rats

Kaveh Shahveisi[a], Habibolah Khazaie[a], Vahid Farnia[b], Mehdi Khodamoradi[b,*]

[a] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[b] Substance Abuse Prevention Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO

Keywords:
Methamphetamine
Retrieval
Reconsolidation
REM sleep deprivation
Reward memory

ABSTRACT

Susceptibility to interference can be a result of memory retrieval and reconsolidation. Given the fact that addiction develops through the neural mechanisms of learning and memory, it would not be surprising that a consolidated drug reward memory may also be susceptible to interference following retrieval/reconsolidation. Due to the critical role of sleep in memory consolidation, sleep deprivation (SD) has been shown to impair memory. Therefore, the major objective of this study was to investigate the effect of rapid eye movement (REM) sleep deprivation (RSD) on the retrieval and reconsolidation of methamphetamine (METH) reward memory in male rats. The animals were trained to acquire METH-induced CPP (2 mg/kg, i.p.). METH reward memory was then reactivated/retrieved in the drug-paired chamber during a drug-free (memory reactivation) session. A period of 48-h RSD paradigm using the multiple platform technique resulted in persistent deficits in the retrieval of METH reward memory. Nevertheless, the same protocol of RSD, which was conducted immediately after the memory reactivation, did not affect the reconsolidation of METH reward memory. Additionally, the RSD episode induced a temporary potentiation of METH-induced hyperlocomotion. Our findings would seem to suggest that sleep is involved in the retrieval, but not reconsolidation, of METH reward memory. The results may also demonstrate that RSD mimics the effects of METH on locomotor activity. The results of this study, therefore, support the idea that sleep is involved in the processing of METH reward memory which can be considered for further investigations to manage the relapse associated with drug-related memory.

1. Introduction

Drug addiction, as a chronically relapsing disorder, is characterized by compulsive drug-taking behavior despite adverse consequences (Hyman, 2005; Hyman et al., 2006; Koob and Volkow, 2010, 2016; Leshner, 1997). Methamphetamine (METH), a potent synthetic psychostimulant, is one of the drugs of abuse which dramatically enhances extracellular dopamine, thereby leading to wide-ranging adverse effects on the structure and function of brain, including neuroinflammation, neuronal damage, cognitive deficits, and psychosis (Ghazvini et al., 2016a; Ghazvini et al., 2016b; Hori et al., 2010; Khalifeh et al., 2019; Krasnova and Cadet, 2009; Marshall et al., 2007; McKetin et al., 2010; North et al., 2013; Riddle et al., 2006).

Importantly, it has been well documented that the neurobiology of drug addiction shares similar mechanisms with learning and memory since addiction may develop through a pathological usurpation of the neural circuits of learning and memory (Hyman, 2005; Hyman et al., 2006; Kutlu and Gould, 2016; Madsen et al., 2012). Repeated drug administration may induce an associative memory between the contextual cues and rewarding effects of the drug (Hyman, 2005; Hyman et al., 2006; Kutlu and Gould, 2016; Nestler, 2001; Robbins et al., 2008). Consequently, due to the functional and structural changes in the brain, encountering the cues associated with the prior drug use may promote relapse to drug abuse (Kutlu and Gould, 2016; Weiss, 2005).

A growing literature continues to emphasize that sleep may play a vital role in cognitive processes, particularly in learning and memory (Gais et al., 2006; Maquet, 2001). Hippocampal replay, spontaneous reoccurrence of neural activity in the hippocampus relevant to a recent experience, during deep sleep may play an important role in memory consolidation (Bendor and Wilson, 2012). Thus, it is not surprising that sleep deprivation (SD), including total SD and rapid eye movement (REM) SD (RSD), may result in memory deficits (Cipolli et al., 2013; Fishbein, 1971; Graves et al., 2003; Salari et al., 2015; Smith, 2001; Yoo et al., 2007). A survey of the literature also indicates that SD acts like psychostimulants as both of them enhance dopaminergic neurotransmission and locomotor activity (Berro et al., 2014a; Riviere et al.,

* Corresponding author.
E-mail address: mehdi0khodamoradi@gmail.com (M. Khodamoradi).

https://doi.org/10.1016/j.pbb.2019.172759
Received 19 February 2019; Received in revised form 9 August 2019; Accepted 10 August 2019
Available online 12 August 2019

1999; Van Hulzen and Coenen, 1981).

Sleep has been reported to have a bidirectional relationship with drug addiction (Hasler et al., 2012). Sleep disturbances may lead to relapse since SD, similar to psychostimulants, affects the dopaminergic system of the brain (Berro et al., 2014a) and, therefore, reinforces reactivity of brain reward circuits (Gujar et al., 2011). SD may also postpone the extinction of cocaine reward memory and potentiates the development of amphetamine conditioning (Berro et al., 2014b; Berro et al., 2018). In contrast, the drugs of abuse may affect sleep architecture and, therefore, produce sleep problems, especially insomnia (Angarita et al., 2016; Roehrs and Roth, 2015). On the other hand, however, a piece of evidence indicates that induction of SD during memory reactivation impairs the reconsolidation of morphine reward memory (Shi et al., 2011) which may be due to the fact that an established memory may become labile and susceptible to interference subsequent to retrieval/reactivation (Iordanova et al., 2011; Nader and Einarsson, 2010; Yu et al., 2009). We, therefore, speculated that SD may also affect the retrieval and/or reconsolidation of METH reward memory since reconsolidation following retrieval updates the pre-existing memories and may lead to new learning (Preston and Eichenbaum, 2013; Sara, 2000). It should be emphasized that various memory stages, including reconsolidation and retrieval, may have a different neurobiology (Preston and Eichenbaum, 2013; Sara, 2000). For example, regarding ionotropic glutamate receptors, it seems that retrieval may involve the integrity of AMPA/kainate receptors (Riedel et al., 1999); however, reconsolidation may depend on the NMDA receptors (Steele and Morris, 1999). Furthermore, in contrast to other memory stages, including acquisition and retention which involve only small neuronal ensembles in the hippocampus, retrieval may require large neuronal networks and involve the integrity of at least 70% of the dorsal hippocampus (Moser and Moser, 1998). We, therefore, hypothesized that RSD may have different effects on the retrieval and reconsolidation of METH reward memory. Thus, this study set out with the aim of assessing the effect of RSD on the retrieval and reconsolidation of METH reward memory and METH-induced hyperlocomotion in male rats.

2. Materials and methods

2.1. Subjects

A total number of 133 male Wistar rats (n = 8–10 in each group) weighing 200–250 g served as subjects throughout this study. They were housed four per cage under controlled conditions, including a constant humidity (50 ± 5%), a temperature of 23 ± 1 °C, and a 12/12 h light/dark cycle (lights on at 07:00 h). All behavioral assessments were carried out between 13:00 and 17:00 h. The animals were provided with free access to food and water. All experiments were conducted according to the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Regional Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (Grant No. KUMS.REC.1396.7).

2.2. Apparatus

The conditioned place preference (CPP) apparatus consisted of two identical three-chamber polyvinyl chloride (PVC) boxes as described in previous studies (Carr and White, 1983; Hashemizadeh et al., 2014; Rezayof et al., 2012). The two large conditioning chambers (30 cm × 30 cm × 40 cm) were connected to each other through a small chamber (the start box; 30 cm × 15 cm × 40 cm). Distinct visual and tactile cues were used for each compartment. The walls of the conditioning chambers were covered with visual cues; black-white vertical stripes were used for one compartment and black-white horizontal stripes were used for another compartment. The floor of each conditioning chamber consisted of distinct color and texture features; black-smooth for one chamber and white-grid for another chamber (as visual and tactile cues). The start box was painted neutral purple. The three distinct compartments were separated by two removable guillotine doors. The performance of the animals was video-recorded using a camera installed above the boxes which was connected to a computer. The data were then analyzed offline by experimenters blind to the groups and treatments.

2.3. Conditioned place preference (CPP)

The place preference was carried out based on previous reports (Shi et al., 2011; Voigt et al., 2011a, 2011b; Yu et al., 2009). All behavioral procedures were conducted in a testing room dimly lit with overhead lamps, each containing a 25 W light bulb. Animals were transferred from the colony to the adjacent experimental room ~45 min prior to each experiment. The CPP protocol consisted of four main phases, including Pre–Conditioning or habituation (Pre—C, on day 1), conditioning sessions (over the days 2–9), Post–Conditioning to verify the development of CPP (Post–C, on day 10), and Post–Treatment tests (Post–*t*-tests 1, 2, and 3) to determine the effects of RSD and sleep rebound (SR) on METH reward memory (Post–*t*-tests 1, 2, and 3 on days 13, 14, and 21, respectively; Figs. 1A, 2A, and 3A).

On day 1, the animals underwent a 30-min drug-free Pre–C test to determine their baseline preference. They were placed in the start box and the guillotine doors were immediately removed to allow a free access to the entire box. The place preference was conducted using an unbiased, balanced protocol as those rats which showed a preference > 70% (1260 s) to one compartment during the Pre–C test were excluded for the next sessions (about 2% of the rats were excluded) (Houchi et al., 2005). Conditioning was then carried out every other day interposed by saline administration for a period of 8 days. (+)-Methamphetamine hydrochloride (METH; Catalog No. M8750; Sigma–Aldrich, St. Louis, MO) was dissolved in 0.9% sterile saline and administered intraperitoneally (2 mg/kg, i.p.). Immediately after each METH injection, the animals were confined to the conditioning chamber for a period of 45 min. The conditioning chamber for each rat was assigned randomly and, in alternate sessions, the animals received the same volume of saline and were placed in another chamber. Twenty-four hours after the last conditioning session, the expression of METH was examined during the Post–C test (a 30-min drug-free session on day 10) to confirm the development of CPP. Those animals that did not show an increase in the time spent in the METH-paired chamber during the Post–C test with respect to the same chamber during the Pre–C test by at least 10% (180 s) were discarded for the subsequent analyses (about 1% of the rats were excluded). The CPP scores were calculated as differences between the time spent in the METH-paired chamber and the time spent in the saline-paired chamber (Hashemizadeh et al., 2014; Rezayof et al., 2012; Shi et al., 2011; Voigt et al., 2011a, 2011b; Yu et al., 2009).

2.4. Sleep deprivation

RSD was induced using the modified multiple platform technique as described in previous studies (Hajali et al., 2015; Salari et al., 2015; Zagaar et al., 2012). The RSD apparatus (100 cm long × 60 cm wide × 40 cm high), which was used for the sleep-deprived groups, consisted of 15 circular platforms in three rows with a height of 10 cm and 6 cm in diameter. A similar (wide platform-WP) apparatus was used for the control (WP) groups, with the difference that the platforms were 14 cm in diameter. Thus, in contrast to the RSD apparatus, the animals were able to sleep on the wide platforms without the risk of falling into the water. The WP apparatus, therefore, may minimize the probable effects of the new environmental stress. In both apparatus, the distances between the platforms were such that the animals could jump from one to another. Both the apparatus were filled with water to a height of ~8 cm and, therefore, the surfaces of the platforms were set ~2 cm over

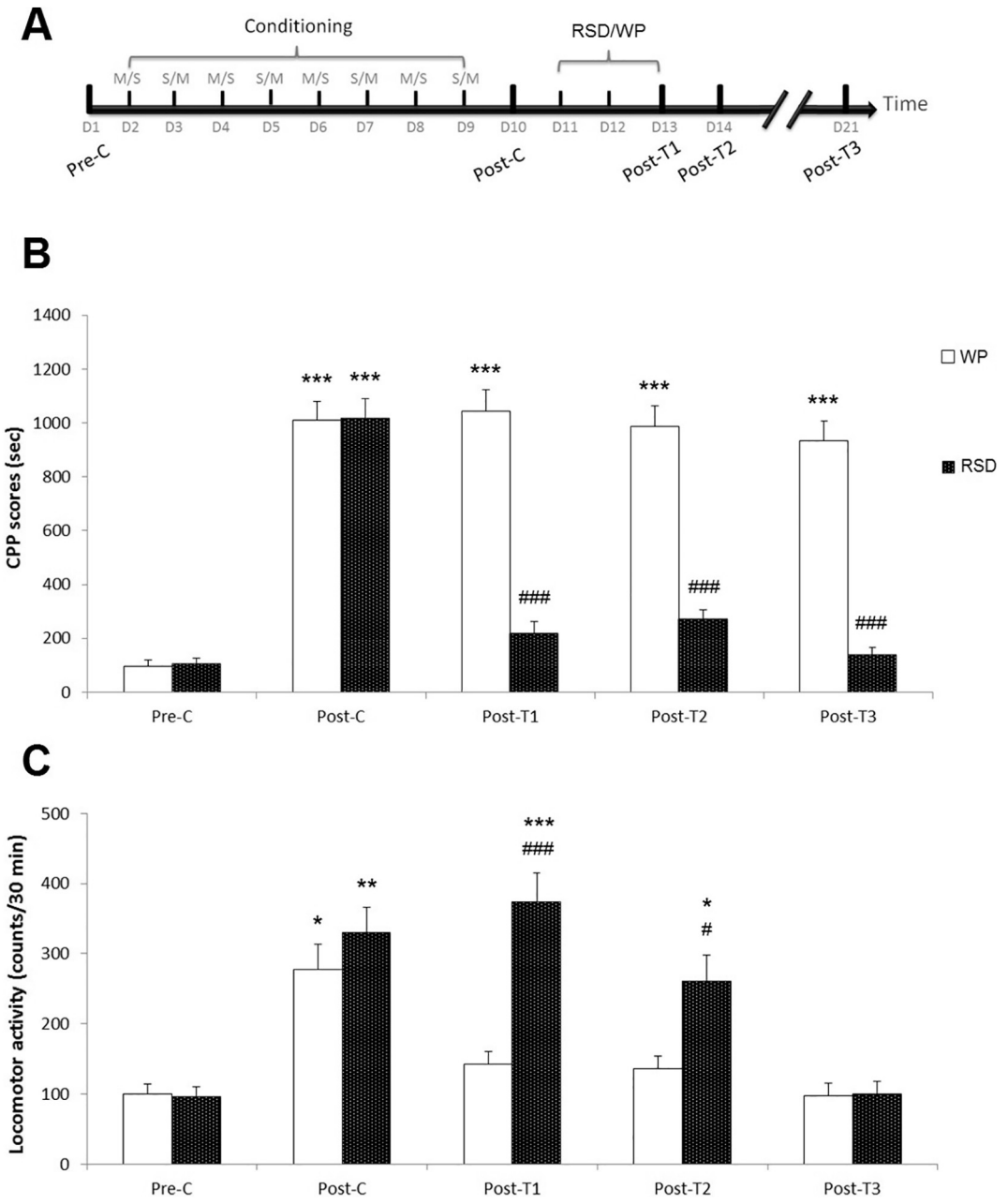

Fig. 1. Effects of RSD on the retrieval of METH reward memory and METH-induced hyperlocomotion during the retrieval experiment. (A) Timeline of the experimental protocol. (B) A period of 48 h RSD in the RSD group induced persistent deficits in the retrieval of the METH reward memory compared with the WP group. (C) Effects of RSD on METH-induced hyperlocomotion during the different phases (test conditions) of the memory retrieval experiment. Analysis of the number of crossings and entries to the large compartments (counts/30 min), as criterions of locomotor activity, revealed that the RSD paradigm (in the RSD group) produced a potentiation of METH-induced hyperlocomotion in the Post–*t*-test 1 than the WP group. The hyperlocomotion induced by METH in the RSD group was also observed after a 24 h period of sleep rebound (in the Post–*t*-test 2), but it was abolished completely when examined one week later (in the Post–*t*-test 3). Data are presented as mean ± S.E.M. (n = 10 rats in each group). $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ vs. the Pre–C test within each group; $\#p < 0.05$ and $\#\#\#p < 0.001$ vs. the WP group within each test condition (the Pre–C test, Post–C test or Post–*t*-tests 1, 2, and 3). Pre–C, Pre–Conditioning test; Post–C, Post–Conditioning test; Post–T, Post–Treatment test; WP, wide platform; RSD, REM sleep deprivation; M, methamphetamine; S, saline; D, day.

the water surface. The cage-mate rats were placed in the same apparatus at the same time (during the induction of RSD) to maintain social stableness. During the 48-h RSD episode, the animals were provided with free access to food and water using pellet baskets and water bottles which were attached to the wire-mesh lids (on the top of the RSD and WP apparatus). Furthermore, the RSD protocol (for 48 h) was conducted under standard conditions, including a 12/12 h light/dark cycle and a temperature of 23 ± 1 °C.

It is worth pointing out that the multiple platform technique has been reported as the best and most common model of RSD as this model considerably reduces immobility stress, forced activity, and isolation stress (Zagaar et al., 2012). It should, however, be noted that, based on previous reports, the multiple platform technique affects both the REM and non-rapid eye movement (NREM) stages of sleep (Machado et al., 2004). Despite the fact that this technique reduces the NREM stage of sleep (−31%) (Machado et al., 2004); nonetheless, this model is the most widely used method to induce REM sleep deprivation in rat (Ashley et al., 2016; Hajali et al., 2015; Karimi-Haghighi and Haghparast, 2018; Salari et al., 2015; Zagaar et al., 2012) since this technique completely abolishes the REM stage of sleep (Machado et al.,

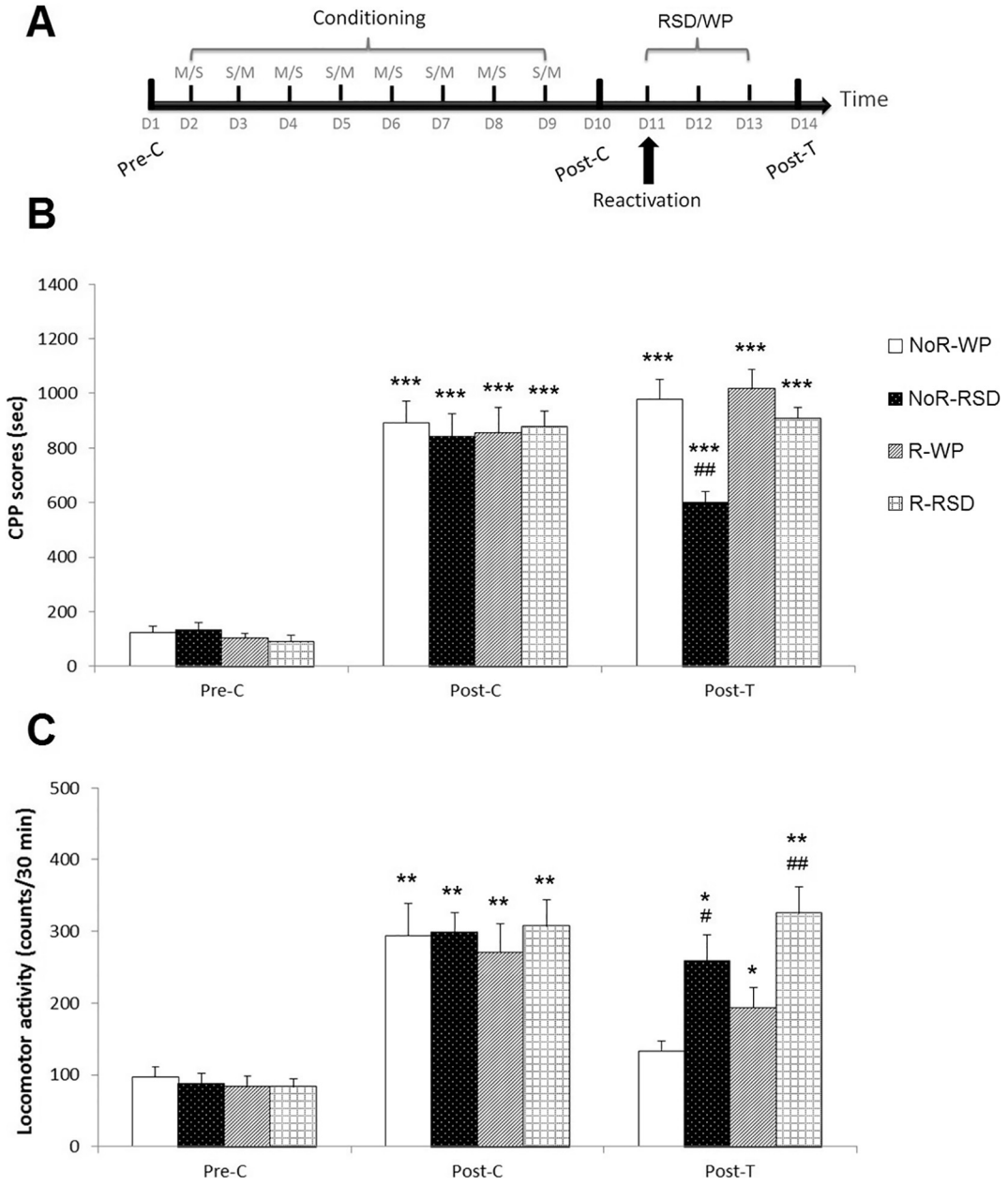

Fig. 2. Effects of RSD on the reconsolidation of METH reward memory and METH-induced hyperlocomotion during the reconsolidation experiment. (A) Timeline of the experimental protocol. (B) A period of 48 h RSD (in the NoR–RSD and R–RSD groups) immediately after memory reactivation did not affect the reconsolidation of METH reward memory during the Post–*t*-test. (C) Effects of RSD on METH-induced hyperlocomotion during the different phases (test conditions) of the memory reconsolidation experiment. Analysis of the number of crossings and entries to the large compartments (counts/30 min), as criterions of locomotor activity, demonstrated a potentiation of the METH-induced hyperlocomotion following RSD induction and memory reactivation (in the NoR–RSD, R–WP, and R–RSD groups) in comparison with the NoR–WP group. Data are presented as mean ± S.E.M. (n = 9–10 rats in each group). $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ vs. the Pre–C test within each group; $\#p < 0.05$ and $\#\#p < 0.01$ vs. any other group within the Post–*t*-test. Pre–C, Pre–Conditioning test; Post–C, Post–Conditioning test; Post–T, Post–Treatment test; WP, wide platform; RSD, REM sleep deprivation; R, reactivation; NoR, no reactivation; M, methamphetamine; S, saline; D, day.

2004).

2.5. Effects of REM sleep deprivation and sleep rebound on the retrieval of METH reward memory

The Pre–C test (habituation), conditioning sessions, and Post–C test were conducted as described above which confirmed the development of CPP. Twenty-four hours after the Post–C test, the animals were randomly assigned into two groups; the WP and RSD groups (n = 10 in each group). The WP and RSD groups were placed in the WP or RSD apparatus, respectively, for a period of 48 h. Immediately after the 48-h episode (in the WP or RSD apparatus), the animals were evaluated for CPP expression during the Post–*t*-test 1 (on day13) to evaluate the retrieval of METH reward memory. Rats were then allowed to sleep undisturbed in their home cages for a period of 24 h. The CPP expression was examined again after the SR period on day 14 during the Post–*t*-test 2. Furthermore, METH-induced CPP was also evaluated one week later (on day 21) during the Post–*t*-test 3 to find out whether the effects of RSD on METH reward memory is persistent or temporary (Fig. 1A).

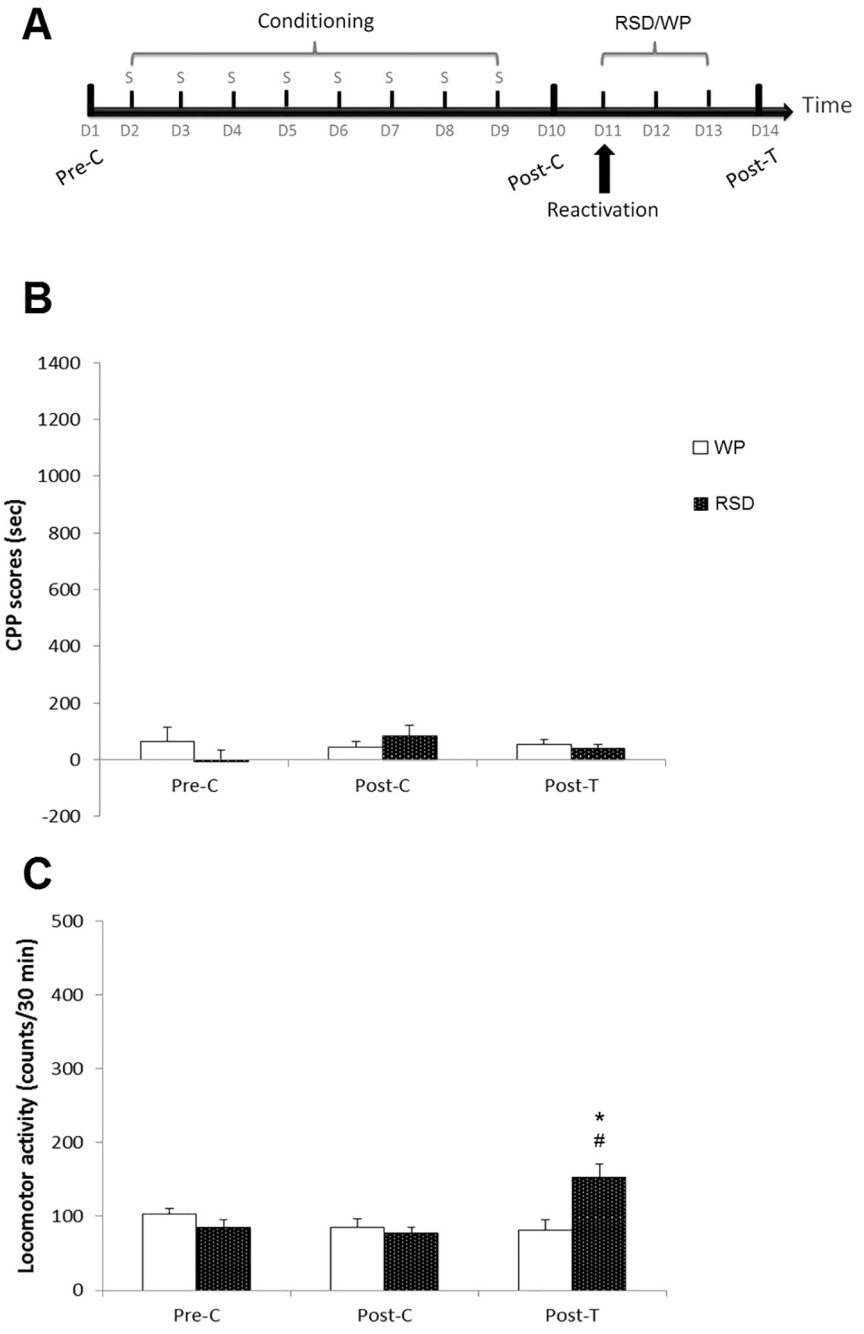

Fig. 3. Effects of RSD on saline place preference and locomotor activity. (A) The experimental timeline. (B) A period of 48 h RSD (in the RSD group) did not produce preference or aversion to the drug-associated compartment as it did not affect saline place preference with respect to the WP group. (C) A period of 48 h RSD resulted in an increased locomotor activity during the Post–*t*-test in the drug-free animals (the RSD group) compared with the WP group. Data are expressed as mean ± S.E.M. (n = 10 rats in each group). $^{*}p < 0.05$ vs. the Pre–C test within group; $\#p < 0.05$ vs. the WP group during the Post–*t*-test. Pre–C, Pre–Conditioning test; Post–C, Post–Conditioning test; Post–T, Post–Treatment test; WP, wide platform; SD, sleep deprivation; S, saline; D, day.

2.6. Effects of REM sleep deprivation on the reconsolidation of METH reward memory

To assess the effects of RSD on memory reconsolidation, the 48-h period of RSD was induced immediately after the reactivation of METH reward memory. For memory reactivation, 24 h after the Post–C test (on day 11), the animals were placed in the METH-paired chamber for a period of 20-min with the guillotine doors closed (Fig. 2A). It has been reported that re-exposure to the drug-paired chamber (without METH administration) may retrieve/reactivate drug reward memory (Shi et al., 2011; Yu et al., 2009).

The Pre–C test, conditioning, and Post–C test were carried out similar to the retrieval experiment. The next day after the Post–C test, the animals were randomly assigned to one of the following treatments (based on the factors reactivation/no reactivation and RSD/WP): (1) no memory reactivation prior to being placed in the WP apparatus (the NoR–WP group; n = 10); (2) no reactivation prior to being placed in the RSD apparatus (the NoR–RSD group; n = 10); (3) reactivation prior to being placed in the WP apparatus (the R–WP group; n = 9); or (4) reactivation prior to being placed in the RSD apparatus (the R–RSD group; n = 10). Thus, immediately after the memory reactivation (or no reactivation) session on day 11, the animals were placed in the WP or RSD apparatus for a period of 48 h and then returned to their home cages. Finally, twenty-four hours following the RSD or WP period, the animals were again evaluated for METH-induced CPP during the Post–*t*-test (on day 14) to assess the reconsolidation of METH reward memory (Fig. 2A).

2.7. Effects of REM sleep deprivation on saline place preference

One may argue that subjecting animals to the RSD or WP paradigm immediately after the memory reactivation session (in the METH-paired

chamber) may have generated a negative associative memory between the context of the METH-paired chamber and the RSD apparatus, and thereby may have interfered with the results. To examine this hypothesis, we conducted the saline place preference experiment. The protocol was the same as the reconsolidation experiment, except that the animals always received saline during the conditioning sessions (Fig. 3A). Twenty-four hours after the Post–C test, the animals were re-exposed to one of the two large compartments (side A or side B). They were immediately divided into two groups; the WP and RSD groups (n = 10 in each group). Thus, immediately following the reactivation session, the animals of the WP and RSD groups were placed in the WP and RSD apparatus, respectively, for a period of 48 h. The next day after the 48 h period of WP/RSD episode, the animals were again evaluated for CPP expression during the Post–*t*-test (Fig. 3A).

2.8. Locomotor activity

2.8.1. Locomotion during the different phases of the CPP paradigm

Locomotor activity was evaluated in the two large compartments during the Pre−C, Post–C, and Post–T (Post–T 1, 2, and 3) tests as reported in previous studies (Hashemizadeh et al., 2014; Rezayof et al., 2012). To do so, the floors of the two conditioning chambers (of the CPP paradigm) were divided into four equal-sized squares. Locomotor activity was defined as the number of crossings and entries from one square to another in the two compartments plus the number of crossings and entries to each chamber during the CPP expression. Thus, the activity of animals was recorded during the different phases of the place preference (in all groups during the retrieval, reconsolidation, and saline experiments) and the data were analyzed offline by experimenters blind to the groups and treatments.

2.8.2. Effects of REM sleep deprivation on locomotion in the open field test

Locomotor activity was also evaluated in the open field test (OFT) as a separate experiment (Abbassian et al., 2016b; Ghotbi Ravandi et al., 2019; Tahamtan et al., 2016) to see if the effects of RSD on CPP expression were not due to hyperlocomotion. The animals were placed in the WP or RSD apparatus for a period of 48 h and they were then, either immediately or 24 h later, examined in the OFT (in separate groups). Thus, the animals were randomly assigned to four groups; the WP-1 and RSD-1 groups (n = 10 in each group) were examined immediately and the WP-2 and RSD-2 groups (n = 9 in each group) were evaluated 24 h after the RSD or WP paradigm for locomotion. A Plexiglas open-field box (40 cm × 40 cm × 40 cm) was used as the apparatus. The floor of the box was divided into 16 equal-sized squares which were defined as the central and peripheral regions. The animals were placed in the middle of the box and their activities were recorded using the Noldus Ethovision video tracking system (Aitken et al., 2017; Noldus et al., 2001) for a period of 5 min. The Ethovision software was installed on a computer with a frame grabber connected to a S-VHS recorder. For every sample the arena was scanned and the positions of the animals were defined using the subtraction mode; the system was tracking spots different than a reference image of the empty arena. After providing a background-scanning of the empty arena, the animals were placed in the box, the arena was scanned, and the background-scanning was subtracted in order to the animals become apparent. A center of gravity was defined for each animal and the rats were then assigned a position in x,y co-ordinates. Such co-ordinates were consequently related to real distances in the arena (Aitken et al., 2017; Noldus et al., 2001). The factors including the total distance moved (TDM) (horizontal activity) and the number of rearings (vertical activity) were measured to assess the effects of RSD on locomotor activity and the factors including the time spent in the central and peripheral squares/regions were measured to evaluate the effects of RSD on anxiety-like behavior (Abbassian et al., 2016b; Tahamtan et al., 2016). Finally, all parameters were exported to Microsoft Excel for further analysis. It is also worth mentioning that the OFT was carried out in the same room under the same conditions as described for the CPP paradigm.

2.9. Effects of REM sleep deprivation on METH consumption using the two-bottle choice (TBC) paradigm

To determine whether the observed effect of RSD on METH reward memory in this study was not due to a reduced motivation for METH, we also examined the effects of RSD on voluntary METH consumption in a separate experiment (Doyle et al., 2015; Hajheidari et al., 2015). All animals received METH (2 mg/kg, ip) for a period of 2 weeks; two injections each day, at 12 h intervals. Afterwards, the animals underwent one week of forced abstinence. The METH-withdrawn rats were then evaluated for METH consumption over an 8-day period in individual cages using the two-bottle choice (TBC) paradigm. All animals were provided with two bottles; one containing water (the control bottle) and the other containing METH in water. The concentration of METH on days 1–4 was 20 mg/l and on days 5–8 was 40 mg/l. Free access to both bottles was limited to 18 h per day to prevent the prevalence of METH-induced anorexia. The positions of the bottles were also changed every day to avoid any learning effect caused by positions of the bottles. The contents of the bottles and the weights of the animals were evaluated every day; between 09:00 and 10:00 h. The animals were randomly assigned to two groups; the WP and RSD groups (n = 8 in each group). The animals were placed in the WP (for the WP group) or RSD (for the SD group) apparatus for a period of 48 h during the last two days of the METH-withdrawal period (the one-week drug-free period) to assess the probable effects of RSD on METH consumption. The daily consumption of METH was defined as mg/kg/18 h. Furthermore, the average METH consumption was determined as mg/kg/18 h and the METH preference ratio was defined as ml METH consumed/total ml consumed from both bottles (Doyle et al., 2015; Hajheidari et al., 2015).

2.10. Statistical analysis

The data were first evaluated using the Shapiro-Wilk or Kolmogorov–Smirnov test which confirmed the normal distribution of data in all groups ($p > 0.05$). All data derived from the CPP paradigm were then analyzed based on two-way or three-way mixed factorial analyses of ANOVA with the within-subjects factor test condition (Pre–C test, Post–C test, and Post–*t*-tests 1, 2, and 3) and the between-subjects factors memory reactivation (reactivation, no reactivation), REM sleep deprivation (WP, RSD), and chamber (side A, side B). The mean differences between the groups during each test condition (Pre–C test, Post–C test or Post–*t*-tests 1, 2, and 3) were analyzed using the independent samples t-test or one-way ANOVA followed by Tukey's post hoc multiple comparison test. The mean differences between the WP and RSD groups in the OFT and TBC paradigms were analyzed using the independent samples *t*-test. The data of the daily TBC paradigm were analyzed according to the mixed ANOVA with the within-subjects factor time (eight days assessment of METH consumption) and the between-subjects factor group/RSD (WP, RSD). All analyses were conducted using SPSS version 16. Data are expressed as mean ± standard error of the mean (S.E.M.) and p values < 0.05 were considered statistically significant.

3. Results

3.1. Effects of REM sleep deprivation and sleep rebound on the retrieval of METH reward memory

Statistical analysis of the CPP scores using the mixed factorial analyses of ANOVA demonstrated significant effects of test condition (Pre–C test, Post–C test, and Post–*t*-tests 1, 2, and 3; $F_{4, 68} = 65.81$, $p < 0.001$), RSD ($F_{1, 17} = 81.2$, $p < 0.001$), and test condition × RSD interaction ($F_{4, 68} = 29.16$, $p < 0.001$), but it revealed no significant

effects of chamber ($F_{1,\ 17} = 0.052$, $p > 0.05$) and test condition × chamber interaction ($F_{4,\ 68} = 0.87$, $p > 0.05$; Fig. 1B). All animals showed a successful conditioning during the Post–C test as they revealed a significant preference for the drug-paired side than the saline-paired side compared with the Pre–C test (habituation) within each group ($p < 0.001$; Fig. 1B). The mean CPP scores of the control WP animals during the Post–*t*-test 1 indicated that there was a sustained significant increase ($p < 0.001$); however, the mean CPP scores of the sleep-deprived animals (RSD group) no longer showed a significant difference compared with the Pre–C test within group ($p > 0.05$; Fig. 1B), indicating a disruptive effect of RSD on METH reward memory. We supposed that the observed memory impairment in the Post–*t*-test 1 was transient and it might be due to sleepiness and fatigue of the animals following the RSD paradigm. Indeed, we hypothesized that enough sleep after the Post–*t*-test 1 may restore the drug-related memory. To examine that hypothesis, following the Post–*t*-test 1, the animals were allowed to sleep undisturbed in their home cages (as sleep rebound - SR) for a period of 24 h and examined again for METH-induced CPP after a period of 24 h (on day 14) during the Post–*t*-test 2. Analysis of the CPP scores during the Post–*t*-test 2 indicated that the WP group demonstrated a sustained increase ($p < 0.001$), but the RSD group showed no significant differences with respect to the Pre–C test within group ($p > 0.05$). Furthermore, the CPP expression was examined one week later (during the Post–*t*-test 3) to determine whether the effects of RSD on METH reward memory are persistent or temporary. The statistical analysis of the Post–*t*-test 3 revealed that the animals of the RSD group, in contrast to the WP group, did not significantly differ in the mean CPP scores than the Pre–C test within group ($p > 0.05$), indicating persistent deficits in METH reward memory (Fig. 1B).

The between-groups analyses indicated that the mean CPP scores were not significantly different between the WP and RSD groups during the Pre–C and Post–C tests (Student's *t*-test, $p > 0.05$); however, during the Post–*t*-tests 1, 2, and 3, the RSD group showed significantly less CPP scores than those for the WP group (Student's *t*-test, $p < 0.001$; Fig. 1B), further demonstrating memory deficits in the RSD group (Fig. 1B).

3.2. Effects of REM sleep deprivation on the reconsolidation of METH reward memory

Analysis of the CPP scores using the Mixed ANOVA showed significant effects of test condition ($F_{2,\ 70} = 202.8$, $p < 0.001$), RSD ($F_{1,\ 35} = 5.73$, $p = 0.022$), and test condition × RSD interaction ($F_{2,\ 70} = 4.9$, $p = 0.01$), but no significant effects of chamber ($F_{1,\ 35} = 0.94$, $p > 0.05$), and test condition × chamber interaction ($F_{2,\ 70} = 1.34$, $p > 0.05$; Fig. 2B). Successful conditioning was observed in all groups during the Post–C test as the animals in all groups showed significant preferences for the METH-paired side than the saline-paired side in comparison with the Pre–C test within each group ($p < 0.001$; Fig. 2B). During the Post–*t*-test, all the four groups, including the NoR–WP (no reactivation – wide platform), NoR–RSD (no reactivation – REM sleep-deprived), R–WP (reactivation – wide platform), and R–RSD (reactivation – REM sleep-deprived) groups, showed a sustained drug reward memory as they revealed significant differences in the mean CPP scores with respect to the Pre–C test within each group ($p < 0.001$; Fig. 2B). Thus, in contrast to the memory retrieval, the reconsolidation of METH reward memory was not affected by the RSD paradigm. Additionally, the between-subjects comparisons of the CPP scores revealed no significant differences between the four (NoR–WP, NoR–RSD, R–WP, and R–RSD) groups during the Pre–C and Post–C tests; nonetheless, the NoR–RSD group showed a significant reduction in comparison with any other group during the Post–*t*-test ($F_{3,\ 35} = 9.57$, $p < 0.001$; Fig. 2B). Thus, the RSD episode in the animals without memory reactivation (in the NoR–RSD group) impaired drug memory compared with other groups during the Post–*t*-test. However, it is worth noting that, during the Post–*t*-test, the CPP scores of the NoR–RSD group still had a significant increase in comparison with the Pre–C test within group ($p < 0.001$). As a result, the reconsolidation of METH reward memory was not affected by RSD, but the reactivation of METH reward memory in the sleep-deprived animals (in the R– RSD group) significantly increased the mean CPP scores than those for the sleep-deprived animals without memory reactivation (in the NoR–RSD group) ($p = 0.005$), indicating an enhancing effect of memory reactivation on drug reward memory (Fig. 2B).

3.3. Effects REM sleep deprivation on saline place preference

Statistical analysis of the CPP scores indicated no significant effects of test condition ($F_{1.38,\ 23.45} = 0.57$, $p > 0.05$), RSD ($F_{1,\ 17} = 0.29$, $p > 0.05$), chamber ($F_{1,\ 17} = 0.97$, $p > 0.05$), test condition × RSD interaction ($F_{1,\ 17} = 0.68$, $p > 0.05$), and test condition × chamber interaction ($F_{1,\ 17} = 0.15$, $p > 0.05$). Furthermore, the between-groups comparisons demonstrated that no significant differences were found in the CPP scores between the two WP and RSD groups during the Pre−C, Post–C, and Post–*t*-tests (Student's *t*-test, $p > 0.05$; Fig. 3B). Thus, the induction of RSD immediately after the memory reactivation session did not induce a negative associative memory between the METH-paired context and RSD paradigm.

3.4. Locomotor activity

3.4.1. Effects of REM sleep deprivation and sleep rebound on METH-induced hyperlocomotion during the memory retrieval experiment

Analysis of the number of crossings and entries (counts/30 min) demonstrated significant effects of test condition ($F_{2.75,\ 46.81} = 33.24$, $p < 0.001$), RSD ($F_{1,\ 17} = 7.22$, $p = 0.016$), and test condition × RSD interaction ($F_{2.75,\ 46.81} = 9.39$, $p < 0.001$), but no significant effects of chamber ($F_{1,\ 17} = 0.014$, $p > 0.05$), and test condition × chamber interaction ($F_{2.75,\ 46.81} = 0.012$, $p > 0.05$; Fig. 1C). The within-subjects analyses of the number of crossings and entries revealed that the animals of the WP group showed a significant difference only during the Post–C test ($p = 0.019$), but not during the Post–*t*-tests 1, 2, and 3 ($p > 0.05$), in comparison with the Pre–C test within group. The RSD group; however, showed significant differences during the Post–C test ($p = 0.002$) and Post–*t*-tests 1 ($p = 0.001$) and 2 ($p = 0.049$), but not during the Post–*t*-test 3 ($p > 0.05$), than the Pre–C test within group (Fig. 1C). Furthermore, the between-subjects analyses of the number of crossings and entries showed no significant differences between the WP and RSD groups during the Pre−C, Post–C tests, and Post-*t*-test 3 (Student's *t*-test, $p > 0.05$); however, the RSD group showed a significant increase than the WP group during the Post–*t*-tests 1 and 2 (Student's *t*-test, $p < 0.001$ and $p < 0.05$, respectively). Thus, the induction of RSD (in the RSD group) resulted in a transient enhancement of the METH-induced hyperlocomotion during the memory retrieval experiment than the control WP group (Fig. 1C).

3.4.2. Effects of REM sleep deprivation on METH-induced hyperlocomotion during the memory reconsolidation experiment

Analysis of the number of crossings and entries revealed significant effects of test condition ($F_{1.61,\ 56.51} = 43.75$, $p < 0.001$), RSD ($F_{1,\ 35} = 7.66$, $p = 0.009$), test condition × RSD interaction ($F_{1.61,\ 56.51} = 4.97$, $p = 0.015$), but no significant effects of chamber ($F_{1,\ 35} = 0.038$, $p > 0.05$) and test condition × chamber interaction ($F_{1.61,\ 56.51} = 0.00$, $p > 0.05$; Fig. 3C). During the Post–C test, all the four (NoR–WP, NoR–RSD, R–WP, and R–RSD) groups showed a significant increase in the number of crossings and entries than the Pre–C test within each group ($p < 0.01$; Fig. 2C). During the Post–*t*-test, except the NoR–WP group (the group without reactivation and RSD), the other three groups, including the NoR–RSD, R–WP, and R–RSD groups, showed a sustained significant increase in the number of crossings and entries compared with the Pre–C test within each group ($p < 0.05$ for

the NoR–RSD and R–WP groups and $p < 0.01$ for the R–RSD group, Fig. 2C). The one-way ANOVA indicated no significant differences between the four groups during the Pre–C and Post–C tests ($p > 0.05$); however, during the Post–*t*-test, the NoR–RSD and R–RSD groups showed a significant increase in number of crossings and entries in comparison with the NoR–WP group ($F_{3, 35} = 6.6$, $p = 0.001$; Fig. 2C). The results, therefore, indicated a potentiation of the METH-induced hyperlocomotion following the induction of RSD and drug memory reactivation (Fig. 2C).

3.4.3. Effects of REM sleep deprivation on locomotion during the saline place preference

The mixed factorial analyses of ANOVA indicated no significant effects of test condition ($F_{1.38, 23.45} = 0.57$, $p > 0.05$), RSD ($F_{1, 17} = 0.29$, $p > 0.05$), chamber ($F_{1, 17} = 0.97$, $p > 0.05$), test condition × RSD interaction ($F_{1, 17} = 0.68$, $p > 0.05$), and test condition × chamber interaction ($F_{1, 17} = 0.15$, $p > 0.05$). During the Post–C test, both the WP and RSD groups did not significantly differ with respect to the Pre–C test within each group ($p > 0.05$); however, the RSD group, but not the WP group, showed a significant increase in the number of crossings and entries during the Post–*t*-test compared with the Pre–C test within group ($p < 0.05$; Fig. 3C). In addition, no significant differences in the number of crossings and entries were observed between the two WP and RSD groups during the Pre–C and Post–C tests (Student's *t*-test, $p < 0.05$); nonetheless, the RSD group showed a significant increase during the Post–*t*-test than the WP group (Student's *t*-test, $p < 0.05$; Fig. 3C). Thus, a 48-h period of RSD resulted in an increased locomotion in the drug-free animals with memory reactivation (the RSD group in the saline place preference experiment).

3.4.4. Effects of REM sleep deprivation on locomotion in the open field task

We conducted the OFT in a separate experiment to find out whether the observed deficits in memory during the retrieval experiment (in the CPP paradigm) were not due to hyperlocomotion and/or anxiety-like behaviors induced by the sleep deprivation protocol. The analyses revealed that, when the OFT was carried out immediately following RSD, the RSD paradigm (in the RSD-1 group) induced an increase in the TDM (horizontal activity) compared with the WP-1 group (Student's *t*-test, $p < 0.05$). Nonetheless, such increase was not observed 24 h after the RSD episode as the RSD-2 group did not significantly differ compared with the control WP-2 group (Student's *t*-test, $p > 0.05$; Fig. 4A). Furthermore, other variables including the number of rearings (vertical activity) (Fig. 4B), and the time spent in the central (Fig. 4C) and peripheral squares (Fig. 4D) (the anxiety factors) were not significantly different between the groups (Student's *t*-test, $p > 0.05$, for all comparisons), neither immediately nor 24 h following the RSD paradigm. Thus, the RSD protocol used in this study only produced a transient effect on locomotion, whereas it did not affect anxiety-like behaviors in male rats.

3.5. Effects of REM sleep deprivation on METH consumption

We also examined whether the effects of RSD on memory were not due to a reduced motivation for METH. The analysis revealed a significant effect of time ($F_{3.65, 51.09} = 3.87$, $p = 0.01$), but no significant effects of group ($F_{1, 14} = 1.435$, $p > 0.05$) and time × group interactions ($F_{3.65, 51.09} = 0.54$, $p > 0.05$). The animals of the WP and RSD groups showed an increase in the daily consumption of METH over a period of 8 days; however, there were no significant differences between the two groups (Fig. 5A). Moreover, analysis of the first (days 1–4) and second (days 5–8) periods indicated no significant differences in the average of METH consumption and METH preference ratio between the WP and RSD groups (Student's *t*-test, $p > 0.05$, for all comparisons; Fig. 5B and C). Therefore, the RSD paradigm did not affect motivation for METH.

4. Discussion

To the best of our knowledge, the current study is the first to emphasize that sleep may play a critical role in METH reward memory as a period of 48-h RSD episode led to persistent deficits in the retrieval of METH reward memory. Nonetheless, the same protocol of RSD, which was carried out immediately after reactivation of METH reward memory, did not affect the reconsolidation of METH reward memory. Additionally, both the RSD paradigm and memory reactivation were associated with a temporary potentiation of the METH-induced hyperlocomotion. Our findings provide a novel insight into the effects of sleep on the processing of METH reward memory and further support the hypothesis that sleep may play a critical role in the processes underlying relapse to METH seeking/taking behavior.

Sleep has been shown to affect the consolidation of declarative and non-declarative memory (Bendor and Wilson, 2012) as a number of studies have shown that both total SD and RSD may result in memory deficits (Fishbein, 1971; Graves et al., 2003; Palchykova et al., 2006; Salari et al., 2015; Smith, 2001; Yoo et al., 2007). Interestingly, it has been reported that a consolidated memory can be modulated during slow-wave sleep via targeting the hippocampal replay (Barnes and Wilson, 2014). Recent evidence also suggests that a consolidated memory can, at least partially, be modified or updated following retrieval and the subsequent reconsolidation processes (Nader and Einarsson, 2010; Preston and Eichenbaum, 2013). De novo protein synthesis due to memory retrieval/reactivation and the subsequent reconsolidation converts the consolidated memory to become susceptible to interference (Iordanova et al., 2011; Nader and Einarsson, 2010; Preston and Eichenbaum, 2013). Since addiction develops through a pathological usurpation of the neural mechanisms of learning and memory (Hyman, 2005; Hyman et al., 2006; Kutlu and Gould, 2016; Madsen et al., 2012), it is not surprising that a consolidated drug reward memory can also be susceptible to interference following retrieval and reconsolidation (Yu et al., 2009). It has been reported that a period of 6-h total SD after memory reactivation impairs the reconsolidation of morphine reward memory in male rats (Shi et al., 2011). It is also stated that acute total SD disrupts the reinstatement of cocaine self-administration in the low drug-taker rats (Puhl et al., 2009). Interestingly, our findings demonstrated that a period of 48-h RSD can impair the retrieval of METH reward memory in male rats. Due to the fact that an established memory may become labile following reactivation, memory retrieval and the subsequent reconsolidation can update, either weakening or strengthening, the memory (Preston and Eichenbaum, 2013; Sara, 2000). Thus, in this study, memory retrieval during the Post-T1 may have updated (disrupted) the METH-reward memory as the animals did not retrieve the METH–context conditioning during the Post-T2 and Post-T3. Therefore, our results, in line with previous evidences, would seem to suggest that RSD and/or modulation of sleep can modify drug reward memory and, thereby alleviate the likelihood of relapse to drug-seeking/taking. Importantly, as mentioned earlier, retrieval may require the integrity of large neuronal networks in the dorsal hippocampus, in contrast to other memory stages (Moser and Moser, 1998; Sara, 2000). This may, in part, account for the findings observed in this study; RSD impaired retrieval, whereas it did not affect reconsolidation of METH reward memory. Furthermore, it has been reported that both REM and NREM stages of sleep are critical for memory processing (Sara, 2000; Stickgold and Walker, 2005). The REM sleep seems to update the cortico-hippocampal transfer of information which is then reinforced during the NREM stage of sleep through bursting activity vital for synaptic plasticity and memory consolidation (Buzsaki, 1998). Drug reward memory may also depend on both REM and NREM stages of sleep as our results and previous reports (Shi et al., 2011) have indicated that it can be impaired by both RSD and total SD. Unfortunately, in this study, we had limitations to measure the time spent asleep by the sleep-deprived and wide platform animals and also the percentage of REM and NREM stages of sleep in both the groups.

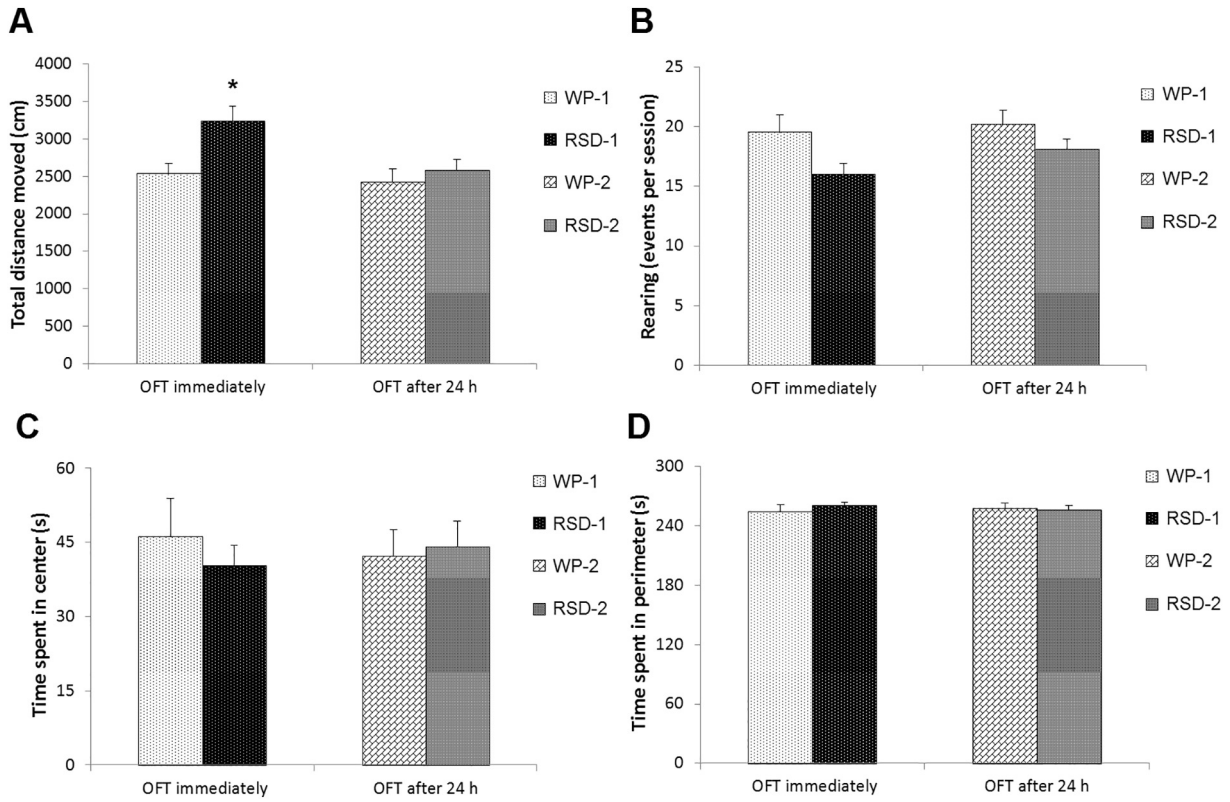

Fig. 4. Effects of SD on locomotor activity in the OFT. (A) Examining TDM immediately after a 48 h period of RSD in the RSD-1 group resulted in a significant increase compared with the WP-1 group; however, such increase was not observed when the TDM was evaluated 24 h following the RSD paradigm (there were no significant differences between the WP-2 and RSD-2 groups). Examining the number of rearings (B) and the time spent in the central (C) and peripheral (D) squares in the OFT indicated that the RSD-1 and RSD-2 groups did not significantly differ in comparison with the WP-1 and WP-2 groups, respectively, neither immediately nor 24 h after the RSD paradigm. Data are expressed as mean ± S.E.M. (n = 9–10 rats in each group). *$p < 0.05$ vs. the WP-1 group. OFT, open field test; TDM, total distance moved; WP, wide platform; RSD, REM sleep deprivation.

However, as mentioned before, Machado et al. (2004) reported that the multiple platform technique not only abolishes the REM stage of sleep, but it also reduces the NREM stage of sleep by 31% in rat. They also reported that the animals in the WP apparatus showed a significant reduction in both REM and NREM sleep (77% and 26%, respectively) (Machado et al., 2004). Thus, the WP apparatus may also reduce the REM and NREM stages of sleep; nonetheless, such reduction may be less than that of the total SD model. Therefore, our and previous findings demonstrate that sleep may play a critical role in drug reward memory, however, the probable differences between the effects of REM and NREM sleep on this regard which should be considered for further research.

On the other hand, however, it has been reported that SD and sleep disturbance may lead to relapse to drug abuse (Berro et al., 2014a; Hasler et al., 2012). It has, for example, been shown that a period of 6-h total SD impairs the extinction of the association between the cocaine effects and contextual cues which may enhance the probability of relapse (Berro et al., 2014b). Sleep deprivation, similar to psychostimulants, may enhance the activity of the dopaminergic system, thereby contributing to relapse to drug-seeking/taking (Berro et al., 2014a; Troncone et al., 1988; Tufik et al., 1978). These rather contradictory results may, in part, be attributable to the differences in the protocols used. Worthy of note here is that, in the retrieval experiment which showed the destructive effects of RSD on METH reward memory, the RSD paradigm was carried out right before the memory retrieval (CPP expression). As mentioned earlier, retrieval makes memory vulnerable to interference and manipulation (Nader and Einarsson, 2010; Preston and Eichenbaum, 2013; Sara, 2000). This seems to be a reasonable explanation for our findings and similar previous ones, indicating the destructive effects of SD on drug reward memory (Shi et al., 2011). Thus, our results, consistent with the claim by Shi et al. (2011) and in contrast to some other reports (Berro et al., 2014a; Berro et al., 2014b), would seem to suggest that SD impairs drug reward memory only when SD occurs during memory retrieval.

Our findings also indicated that RSD transiently potentiates METH-induced hyperlocomotion. This is somewhat interesting since one may argue that RSD, due to the subsequent sleepiness and fatigue of the animals, can lead to a decrease in hyperlocomotion. Nonetheless, our results are consistent with some earlier studies which have reported the enhancing effects of SD on METH-induced hyperlocomotion (Riviere et al., 1999; Van Hulzen and Coenen, 1981). For example, it is reported that a neurotoxic regimen of METH (four injections at 2 h intervals) at lower doses (1.0 or 2.0 mg/kg) attenuates locomotor activity but at higher doses (i.e., 4.0 or 7.5 mg/kg) enhances stereotypic behavior in male rats (Wallace et al., 1999). SD has also been shown to potentiate hyperlocomotion induced by the psychostimulants cocaine and amphetamine (Berro et al., 2014c; Saito et al., 2014). A possible mechanism might be through activation of the dopaminergic system since, as mentioned above, SD seems to mimic the effects of the psychostimulants on the dopaminergic circuits and, therefore, induces supersensitivity of dopamine receptors, aggressiveness, hyperactivity, and stereotypy (Troncone et al., 1988; Tufik, 1981; Tufik et al., 1978). The serotonergic and dopaminergic circuits are thought to be involved in METH-induced hyperlocomotion as it has been indicated that inhibition of the serotonin synthesis, antagonism of the serotonin and dopamine receptors, and blockade of the serotonin and dopamine transporters may lead to a marked reduction in METH-induced hyperlocomotion (Steed et al., 2011). Additionally, SD is thought to increase the density of dopamine D1 (Demontis et al., 1990) and D2 (Nunes Junior et al., 1994) receptors in the mesoaccumbens dopamine system. It has, for

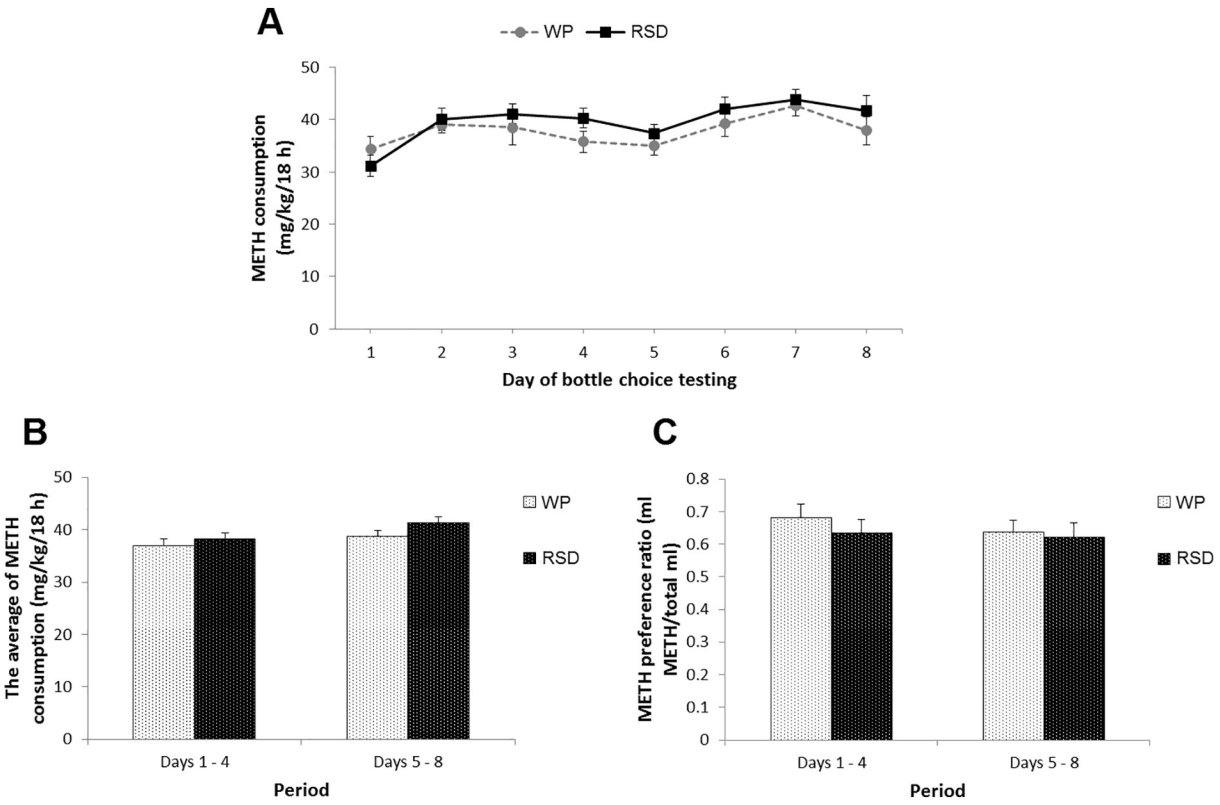

Fig. 5. Effects of RSD on METH consumption. (A) The daily consumption of METH showed an increase over a period of 8 days in both the WP and RSD groups, but the RSD group did not significantly differ in comparison with the WP group. The average of METH consumption (B) and METH preference ratio (C) during the first (days 1–4) and second (days 5–8) periods were also not significantly different between the WP and RSD groups. Data are expressed as mean ± S.E.M. (n = 8 rats in each group). WP, wide platform; RSD, REM sleep deprivation.

example, been demonstrated that one-night SD may enhance the levels of dopamine in the striatum and thalamus regions of the human brain (Volkow et al., 2008). It, therefore, seems reasonable to assume that activation of the dopaminergic system may be involved in the RSD-induced hyperlocomotion observed in the current study; however, the precise mechanisms remain to be elucidated.

It is also worthy to mention that previous studies have investigated the anxiety state of animals following METH administration and induction of SD. It has been estimated that 30.2% of the METH users suffer from anxiety (Salo et al., 2011); however, the anxiogenic-like behaviors following METH administration seems to be time dependent (Miladi-Gorji et al., 2015); METH produces anxiety-like behaviors in the elevated plus-maze at 30 min, but not at 120 min, following its administration in male rats (Miladi-Gorji et al., 2015). Regarding the effects of SD on anxiety, however, there are challenging reports in the literature. In human studies, it has been indicated that SD may lead to anxiety; nonetheless, the animal studies have shown contradictory results as some investigations have shown anxiogenic-like effects of SD and some others have reported no effects of SD on anxiety (Pires et al., 2016; Pires et al., 2015). Regarding our findings in the OFT, which showed no significant effects on anxiety-like behaviors, it should be noted that the cage-mate rats were placed in the same apparatus at the same time (during the induction of RSD) to maintain social stableness which may decrease the anxiety state of animals. Therefore, our findings are consistent with some previous studies. Our results noted that all groups spent approximately 15% of the time in the center of the arena. This may indicate that spending about 15–20% of time in the central zone (in the control groups) seems to be a norm for Wistar rats as some previous studies have reported similar results (Abbassian et al., 2016a; Mohammadi et al., 2019). It should also be noted that the OFT may not model features of anxiety disorders, but it can only be used to assess anxiety-like behaviors in rodents (Prut and Belzung, 2003). Indeed, in case of anxiety, our findings may not be generalized to anxiety disorders and, therefore, evaluation of RSD–induced anxiogenic-like effects may need to be assessed using other methods which is beyond the scope of this study.

Several other important issues should be addressed here. First, METH reward memory was selectively reactivated during the re-exposure to the METH-paired chamber (reactivation session) as RSD in the animals without memory reactivation, in contrast to the animals with memory reactivation, disrupted CPP expression in the Post–*t*-test. Regarding reactivation, it is worth mentioning that the reactivation session was a drug-free trial; however, it should not be considered as extinction because extinction does not happen at one drug-free session. Indeed, the animals showed CPP expression during the Post–*t*-test and, therefore, the reactivation session did not induce extinction of METH–induced CPP. Second, a period of 48-h RSD episode immediately after memory reactivation in the saline-paired chamber did not affect saline place preference which demonstrates that the effect of RSD on memory reconsolidation was not relevant to a negative associative memory between the METH–paired context and the RSD paradigm. Third, one may argue that the disruptive effects of RSD on the retrieval of METH reward memory may be confounded by RSD–induced sleepiness/fatigue in animals. To examine that hypothesis, after the Post–*t*-test 1, the animals were allowed to sleep in their home cages and examined again for CPP expression 24 h or 8 days later (during the Post–*t*-tests 2 and 3, respectively) which demonstrated persistent memory deficits. Fourth, we also examined locomotor activity in a separate experiment using the open field task to see whether the memory retrieval deficits (in the CPP paradigm) were not due to hyperlocomotion and/or stress/anxiety induced by the RSD protocol. The OFT indicated that the RSD paradigm only induced a transient and limited effect on locomotion, whereas it did not produce anxiogenic-like effects in animals. Fifth, and finally, we examined whether the effects of RSD on

memory were not due to a reduced motivation for METH which it also indicated no significant effects of RSD on METH consumption. Therefore, and according to such arguments, the observed effects of RSD on the retrieval of METH reward memory in this study were specific and the experimental conditions did not affect the results. It can, therefore, be suggested that a 48-h episode of REM sleep deprivation may disrupt the retrieval of METH reward memory and induces a transient potentiation of METH-induced hyperlocomotion.

Our findings, in line with some previous studies, indicate that sleep may play an important role in the processing of psychostimulant reward memory; however, due to our limitations, several important questions/issues remain unanswered, including: (1) The probable differences between the effects of RSD and total SD on psychostimulant reward memory; (2) effects of manipulating drug reward memory during both REM and NREM stages of sleep using, for example, pharmacological and electrophysiological techniques; and (3) measuring the time spent asleep by the sleep-deprived vs wide platform animals and their relationship with drug-related memory. Therefore, our findings cannot address such issues; however, this research has thrown up many questions in need of further investigation.

5. Conclusions

Returning to the hypothesis posed at the beginning of this study, it is now possible to state that sleep is involved in the retrieval of methamphetamine reward memory. It should, however, be emphasized that our findings, in line with previous reports, may suggest that RSD impairs drug reward memory only when the RSD episode occurs during drug memory reactivation. Consistent with previous studies, our results may also indicate that RSD induces a transient potentiation of METH-induced hyperlocomotion which may, at least partially, be attributable to the involvement of the dopaminergic neurotransmission. Finally, and importantly, the ethical considerations limit our ability to examine the effects of sleep deprivation in clinical trials; however, the evidence from this and previous studies may suggest that the status and quality of sleep can be targeted for further investigations to manage relapse associated with drug-related memory.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

The authors gratefully acknowledge the Research Council of Kermanshah University of Medical Sciences, Kermanshah, Iran for the financial support (Grant No. KUMS.REC.1396.7).

References

Abbassian, H., Esmaeili, P., Tahamtan, M., Aghaei, I., Vaziri, Z., Sheibani, V., Whalley, B.J., Shabani, M., 2016a. Cannabinoid receptor agonism suppresses tremor, cognition disturbances and anxiety-like behaviors in a rat model of essential tremor. Physiol. Behav. 164 (Pt A), 314–320.

Abbassian, H., Whalley, B.J., Sheibani, V., Shabani, M., 2016b. Cannabinoid type 1 receptor antagonism ameliorates harmaline-induced essential tremor in rat. Br. J. Pharmacol. 173 (22), 3196–3207.

Aitken, P., Zheng, Y., Smith, P.F., 2017. Ethovision analysis of open field behaviour in rats following bilateral vestibular loss. J. Vestib. Res. 27 (2–3), 89–101.

Angarita, G.A., Emadi, N., Hodges, S., Morgan, P.T., 2016. Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. Addict. Sci. Clin. Pract. 11 (1), 9.

Ashley, N.T., Sams, D.W., Brown, A.C., Dumaine, J.E., 2016. Novel environment influences the effect of paradoxical sleep deprivation upon brain and peripheral cytokine gene expression. Neurosci. Lett. 615, 55–59.

Barnes, D.C., Wilson, D.A., 2014. Slow-wave sleep-imposed replay modulates both strength and precision of memory. J. Neurosci. 34 (15), 5134–5142.

Bendor, D., Wilson, M.A., 2012. Biasing the content of hippocampal replay during sleep. Nat. Neurosci. 15 (10), 1439–1444.

Berro, L.F., Frussa-Filho, R., Tufik, S., Andersen, M.L., 2014a. Relationships between sleep and addiction: the role of drug-environment conditioning. Med. Hypotheses 82 (3), 374–376.

Berro, L.F., Hollais, A.W., Patti, C.L., Fukushiro, D.F., Mari-Kawamoto, E., Talhati, F., Costa, J.M., Zanin, K.A., Lopes-Silva, L.B., Ceccon, L.M., Santos, R., Procopio-Souza, R., Trombin, T.F., Yokoyama, T.S., Wuo-Silva, R., Tufik, S., Andersen, M.L., Frussa-Filho, R., 2014b. Sleep deprivation impairs the extinction of cocaine-induced environmental conditioning in mice. Pharmacol. Biochem. Behav. 124, 13–18.

Berro, L.F., Santos, R., Hollais, A.W., Wuo-Silva, R., Fukushiro, D.F., Mari-Kawamoto, E., Costa, J.M., Trombin, T.F., Patti, C.L., Grapiglia, S.B., Tufik, S., Andersen, M.L., Frussa-Filho, R., 2014c. Acute total sleep deprivation potentiates cocaine-induced hyperlocomotion in mice. Neurosci. Lett. 579, 130–133.

Berro, L.F., Tufik, S.B., Frussa-Filho, R., Andersen, M.L., Tufik, S., 2018. Sleep deprivation precipitates the development of amphetamine-induced conditioned place preference in rats. Neurosci. Lett. 671, 29–32.

Buzsaki, G., 1998. Memory consolidation during sleep: a neurophysiological perspective. J. Sleep Res. 7 (Suppl. 1), 17–23.

Carr, G.D., White, N.M., 1983. Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. Life Sci. 33 (25), 2551–2557.

Cipolli, C., Mazzetti, M., Plazzi, G., 2013. Sleep-dependent memory consolidation in patients with sleep disorders. Sleep Med. Rev. 17 (2), 91–103.

Demontis, M.G., Fadda, P., Devoto, P., Martellotta, M.C., Fratta, W., 1990. Sleep deprivation increases dopamine D1 receptor antagonist [3H]SCH 23390 binding and dopamine-stimulated adenylate cyclase in the rat limbic system. Neurosci. Lett. 117 (1–2), 224–227.

Doyle, S.E., Feng, H., Garber, G., Menaker, M., Lynch, W.J., 2015. Effects of circadian disruption on methamphetamine consumption in methamphetamine-exposed rats. Psychopharmacology 232 (12), 2169–2179.

Fishbein, W., 1971. Disruptive effects of rapid eye movement sleep deprivation on long-term memory. Physiol. Behav. 6 (4), 279–282.

Gais, S., Lucas, B., Born, J., 2006. Sleep after learning aids memory recall. Learn. Mem. 13 (3), 259–262.

Ghazvini, H., Khaksari, M., Esmaeilpour, K., Shabani, M., Asadi-Shekaari, M., Khodamoradi, M., Sheibani, V., 2016a. Effects of treatment with estrogen and progesterone on the methamphetamine-induced cognitive impairment in ovariectomized rats. Neurosci. Lett. 619, 60–67.

Ghazvini, H., Shabani, M., Asadi-Shekaari, M., Khalifeh, S., Esmaeilpour, K., Khodamoradi, M., Sheibani, V., 2016b. Estrogen and progesterone replacement therapy prevent methamphetamine-induced synaptic plasticity impairment in ovariectomized rats. Addict. Health. 8 (3), 145–156.

Ghotbi Ravandi, S., Shabani, M., Bashiri, H., Saeedi Goraghani, M., Khodamoradi, M., Nozari, M., 2019. Ameliorating effects of berberine on MK-801-induced cognitive and motor impairments in a neonatal rat model of schizophrenia. Neurosci. Lett. 706, 151–157.

Graves, L.A., Heller, E.A., Pack, A.I., Abel, T., 2003. Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. Learn. Mem. 10 (3), 168–176.

Gujar, N., Yoo, S.S., Hu, P., Walker, M.P., 2011. Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. J. Neurosci. 31 (12), 4466–4474.

Hajali, V., Sheibani, V., Ghazvini, H., Ghadiri, T., Valizadeh, T., Saadati, H., Shabani, M., 2015. Effect of castration on the susceptibility of male rats to the sleep deprivation-induced impairment of behavioral and synaptic plasticity. Neurobiol. Learn. Mem. 123, 140–148.

Hajheidari, S., Miladi-Gorji, H., Bigdeli, I., 2015. Effect of the environmental enrichment on the severity of psychological dependence and voluntary methamphetamine consumption in methamphetamine withdrawn rats. Neurosci. Lett. 584, 151–155.

Hashemizadeh, S., Sardari, M., Rezayof, A., 2014. Basolateral amygdala CB1 cannabinoid receptors mediate nicotine-induced place preference. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 51, 65–71.

Hasler, B.P., Smith, L.J., Cousins, J.C., Bootzin, R.R., 2012. Circadian rhythms, sleep, and substance abuse. Sleep Med. Rev. 16 (1), 67–81.

Hori, N., Kadota, M.T., Watanabe, M., Ito, Y., Akaike, N., Carpenter, D.O., 2010. Neurotoxic effects of methamphetamine on rat hippocampus pyramidal neurons. Cell. Mol. Neurobiol. 30 (6), 849–856.

Houchi, H., Babovic, D., Pierrefiche, O., Ledent, C., Daoust, M., Naassila, M., 2005. CB1 receptor knockout mice display reduced ethanol-induced conditioned place preference and increased striatal dopamine D2 receptors. Neuropsychopharmacology 30 (2), 339–349.

Hyman, S.E., 2005. Addiction: a disease of learning and memory. Am. J. Psychiatry 162 (8), 1414–1422.

Hyman, S.E., Malenka, R.C., Nestler, E.J., 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu. Rev. Neurosci. 29, 565–598.

Iordanova, M.D., Good, M., Honey, R.C., 2011. Retrieval-mediated learning involving episodes requires synaptic plasticity in the hippocampus. J. Neurosci. 31 (19), 7156–7162.

Karimi-Haghighi, S., Haghparast, A., 2018. Cannabidiol inhibits priming-induced reinstatement of methamphetamine in REM sleep deprived rats. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 82, 307–313.

Khalifeh, S., Khodamoradi, M., Hajali, V., Ghazvini, H., Eliasy, L., Kheradmand, A., Farnia, V., Akhtari, J., Shahveisi, K., Ghalehnoei, H., 2019. Naloxone ameliorates spatial memory deficits and hyperthermia induced by a neurotoxic methamphetamine regimen in male rats. Galen Med. J. 8, 1182.

Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. Neuropsychopharmacology 35 (1), 217–238.

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3 (8), 760–773.

Krasnova, I.N., Cadet, J.L., 2009. Methamphetamine toxicity and messengers of death. Brain Res. Rev. 60 (2), 379–407.
Kutlu, M.G., Gould, T.J., 2016. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learn. Mem. 23 (10), 515–533.
Leshner, A.I., 1997. Addiction is a brain disease, and it matters. Science 278 (5335), 45–47.
Machado, R.B., Hipolide, D.C., Benedito-Silva, A.A., Tufik, S., 2004. Sleep deprivation induced by the modified multiple platform technique: quantification of sleep loss and recovery. Brain Res. 1004 (1–2), 45–51.
Madsen, H.B., Brown, R.M., Lawrence, A.J., 2012. Neuroplasticity in addiction: cellular and transcriptional perspectives. Front. Mol. Neurosci. 5, 99.
Maquet, P., 2001. The role of sleep in learning and memory. Science 294 (5544), 1048–1052.
Marshall, J.F., Belcher, A.M., Feinstein, E.M., O'Dell, S.J., 2007. Methamphetamine-induced neural and cognitive changes in rodents. Addiction 102 (Suppl. 1), 61–69.
McKetin, R., Hickey, K., Devlin, K., Lawrence, K., 2010. The risk of psychotic symptoms associated with recreational methamphetamine use. Drug Alcohol Rev 29 (4), 358–363.
Miladi-Gorji, H., Fadaei, A., Bigdeli, I., 2015. Anxiety assessment in methamphetamine-sensitized and withdrawn rats: immediate and delayed effects. Iran. J. Psychiatry 10 (3), 150–157.
Mohammadi, F., Abedini Esfahlani, M., Shabani, M., 2019. Erythropoietin ameliorates harmaline-induced essential tremor and cognition disturbances. Neurosci. Lett. 704, 153–158.
Moser, M.B., Moser, E.I., 1998. Distributed encoding and retrieval of spatial memory in the hippocampus. J. Neurosci. 18 (18), 7535–7542.
Nader, K., Einarsson, E.O., 2010. Memory reconsolidation: an update. Ann. N. Y. Acad. Sci. 1191, 27–41.
Nestler, E.J., 2001. Psychogenomics: opportunities for understanding addiction. J. Neurosci. 21 (21), 8324–8327.
Noldus, L.P., Spink, A.J., Tegelenbosch, R.A., 2001. EthoVision: a versatile video tracking system for automation of behavioral experiments. Behav. Res. Methods Instrum. Comput. 33 (3), 398–414.
North, A., Swant, J., Salvatore, M.F., Gamble-George, J., Prins, P., Butler, B., Mittal, M.K., Heltsley, R., Clark, J.T., Khoshbouei, H., 2013. Chronic methamphetamine exposure produces a delayed, long-lasting memory deficit. Synapse 67 (5), 245–257.
Nunes Junior, G.P., Tufik, S., Nobrega, J.N., 1994. Autoradiographic analysis of D1 and D2 dopaminergic receptors in rat brain after paradoxical sleep deprivation. Brain Res. Bull. 34 (5), 453–456.
Palchykova, S., Winsky-Sommerer, R., Meerlo, P., Durr, R., Tobler, I., 2006. Sleep deprivation impairs object recognition in mice. Neurobiol. Learn. Mem. 85 (3), 263–271.
Pires, G.N., Tufik, S., Andersen, M.L., 2015. Sleep deprivation and anxiety in humans and rodents–translational considerations and hypotheses. Behav. Neurosci. 129 (5), 621–633.
Pires, G.N., Bezerra, A.G., Tufik, S., Andersen, M.L., 2016. Effects of experimental sleep deprivation on anxiety-like behavior in animal research: systematic review and meta-analysis. Neurosci. Biobehav. Rev. 68, 575–589.
Preston, A.R., Eichenbaum, H., 2013. Interplay of hippocampus and prefrontal cortex in memory. Curr. Biol. 23 (17), R764–R773.
Prut, L., Belzung, C., 2003. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. Eur. J. Pharmacol. 463 (1–3), 3–33.
Puhl, M.D., Fang, J., Grigson, P.S., 2009. Acute sleep deprivation increases the rate and efficiency of cocaine self-administration, but not the perceived value of cocaine reward in rats. Pharmacol. Biochem. Behav. 94 (2), 262–270.
Rezayof, A., Ghandipour, M., Nazari-Serenjeh, F., 2012. Effect of co-injection of arachydonilcyclopropylamide and ethanol on conditioned place preference in rats. Physiol. Behav. 107 (3), 301–308.
Riddle, E.L., Fleckenstein, A.E., Hanson, G.R., 2006. Mechanisms of methamphetamine-induced dopaminergic neurotoxicity. AAPS J. 8 (2), E413–E418.
Riedel, G., Micheau, J., Lam, A.G., Roloff, E.L., Martin, S.J., Bridge, H., de Hoz, L., Poeschel, B., McCulloch, J., Morris, R.G., 1999. Reversible neural inactivation reveals hippocampal participation in several memory processes. Nat. Neurosci. 2 (10), 898–905.
Riviere, G.J., Byrnes, K.A., Gentry, W.B., Owens, S.M., 1999. Spontaneous locomotor activity and pharmacokinetics of intravenous methamphetamine and its metabolite amphetamine in the rat. J. Pharmacol. Exp. Ther. 291 (3), 1220–1226.
Robbins, T.W., Ersche, K.D., Everitt, B.J., 2008. Drug addiction and the memory systems of the brain. Ann. N. Y. Acad. Sci. 1141, 1–21.
Roehrs, T.A., Roth, T., 2015. Sleep disturbance in substance use disorders. Psychiatr. Clin. North. Am. 38 (4), 793–803.
Saito, L.P., Fukushiro, D.F., Hollais, A.W., Mari-Kawamoto, E., Costa, J.M., Berro, L.F., Aramini, T.C., Wuo-Silva, R., Andersen, M.L., Tufik, S., Frussa-Filho, R., 2014. Acute total sleep deprivation potentiates amphetamine-induced locomotor-stimulant effects and behavioral sensitization in mice. Pharmacol. Biochem. Behav. 117, 7–16.
Salari, M., Sheibani, V., Saadati, H., Pourrahimi, A., Khaksarihadad, M., Esmaeelpour, K., Khodamoradi, M., 2015. The compensatory effect of regular exercise on long-term memory impairment in sleep deprived female rats. Behav. Process. 119, 50–57.
Salo, R., Flower, K., Kielstein, A., Leamon, M.H., Nordahl, T.E., Galloway, G.P., 2011. Psychiatric comorbidity in methamphetamine dependence. Psychiatry Res. 186 (2–3), 356–361.
Sara, S.J., 2000. Retrieval and reconsolidation: toward a neurobiology of remembering. Learn. Mem. 7 (2), 73–84.
Shi, H.S., Luo, Y.X., Xue, Y.X., Wu, P., Zhu, W.L., Ding, Z.B., Lu, L., 2011. Effects of sleep deprivation on retrieval and reconsolidation of morphine reward memory in rats. Pharmacol. Biochem. Behav. 98 (2), 299–303.
Smith, C., 2001. Sleep states and memory processes in humans: procedural versus declarative memory systems. Sleep Med. Rev. 5 (6), 491–506.
Steed, E., Jones, C.A., McCreary, A.C., 2011. Serotonergic involvement in methamphetamine-induced locomotor activity: a detailed pharmacological study. Behav. Brain Res. 220 (1), 9–19.
Steele, R.J., Morris, R.G., 1999. Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. Hippocampus 9 (2), 118–136.
Stickgold, R., Walker, M.P., 2005. Memory consolidation and reconsolidation: what is the role of sleep? Trends Neurosci. 28 (8), 408–415.
Tahamtan, M., Moosavi, S.M., Sheibani, V., Nayebpour, M., Esmaeili-Mahani, S., Shabani, M., 2016. Erythropoietin attenuates motor impairments induced by bilateral renal ischemia/reperfusion in rats. Fundam. Clin. Pharmacol. 30 (6), 502–510.
Troncone, L.R., Ferreira, T.M., Braz, S., Silveira Filho, N.G., Tufik, S., 1988. Reversal of the increase in apomorphine-induced stereotypy and aggression in REM sleep deprived rats by dopamine agonist pretreatments. Psychopharmacology 94 (1), 79–83.
Tufik, S., 1981. Changes of response to dopaminergic drugs in rats submitted to REM-sleep deprivation. Psychopharmacology 72 (3), 257–260.
Tufik, S., Lindsey, C.J., Carlini, E.A., 1978. Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? Pharmacology 16 (2), 98–105.
Van Hulzen, Z.J., Coenen, A.M., 1981. Paradoxical sleep deprivation and locomotor activity in rats. Physiol. Behav. 27 (4), 741–744.
Voigt, R.M., Herrold, A.A., Napier, T.C., 2011a. Baclofen facilitates the extinction of methamphetamine-induced conditioned place preference in rats. Behav. Neurosci. 125 (2), 261–267.
Voigt, R.M., Herrold, A.A., Riddle, J.L., Napier, T.C., 2011b. Administration of GABA(B) receptor positive allosteric modulators inhibit the expression of previously established methamphetamine-induced conditioned place preference. Behav. Brain Res. 216 (1), 419–423.
Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J., Wong, C., Ma, J., Pradhan, K., Tomasi, D., Thanos, P.K., Ferre, S., Jayne, M., 2008. Sleep deprivation decreases binding of [11C]raclopride to dopamine D2/D3 receptors in the human brain. J. Neurosci. 28 (34), 8454–8461.
Wallace, T.L., Gudelsky, G.A., Vorhees, C.V., 1999. Methamphetamine-induced neurotoxicity alters locomotor activity, stereotypic behavior, and stimulated dopamine release in the rat. J. Neurosci. 19 (20), 9141–9148.
Weiss, F., 2005. Neurobiology of craving, conditioned reward and relapse. Curr. Opin. Pharmacol. 5 (1), 9–19.
Yoo, S.S., Hu, P.T., Gujar, N., Jolesz, F.A., Walker, M.P., 2007. A deficit in the ability to form new human memories without sleep. Nat. Neurosci. 10 (3), 385–392.
Yu, L.L., Wang, X.Y., Zhao, M., Liu, Y., Li, Y.Q., Li, F.Q., Wang, X., Xue, Y.X., Lu, L., 2009. Effects of cannabinoid CB1 receptor antagonist rimonabant in consolidation and reconsolidation of methamphetamine reward memory in mice. Psychopharmacology 204 (2), 203–211.
Zagaar, M., Alhaider, I., Dao, A., Levine, A., Alkarawi, A., Alzubaidy, M., Alkadhi, K., 2012. The beneficial effects of regular exercise on cognition in REM sleep deprivation: behavioral, electrophysiological and molecular evidence. Neurobiol. Dis. 45 (3), 1153–1162.