



## Research paper

# Effects of environmental enrichment during induction of methamphetamine dependence on the behavioral withdrawal symptoms in rats



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## HIGHLIGHTS

- METH-induced behavioral withdrawal symptoms include stereotypic behaviors, depression and anxiety.
- The 14 days of environmental enrichment during induction of METH dependence reduces METH-induced stereotypic behaviors and rearing in rats.
- The 14 days of environmental enrichment during induction of METH dependence reduces depression in METH withdrawn rats.

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## ABSTRACT

This study was designed to examine the effect of environmental enrichment during METH administration on the behavioral withdrawal symptoms after drug abstinence in rats. Rats reared in standard (SE) or enriched environment (EE) during induction of METH dependence with bi-daily injections of METH (2 mg/kg, at 12-h. intervals) for 14 days. Then, rats were evaluated for behavioral withdrawal symptoms, and also for anxiety (elevated plus maze-EPM) and depression (Forced swim test-FST) over a ten day period of abstinence. The results showed that stereotypic behaviors score and the number of rearing were significantly lower in METH/EE rats compared to the SE group during 1–4 days. Also, The METH/EE group exhibited more weight gain during 6–10 days of abstinence. The METH/EE rats exhibited lower levels of immobility after METH abstinence than control group in the FST. EE had no effect on anxiety-like behavior. This study showed that exposure to EE diminished the severity of withdrawal symptoms and depressive-like behavior during spontaneous withdrawal from METH.

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## 1. Introduction

Methamphetamine (METH) is a potent psychostimulant for dependence [23] with neurotoxic properties [7]. METH dependence is associated with a number of withdrawal symptoms after METH cessation including depression and anxiety after 2–3 days of abstinence in human [19] and animal models of anxiety using the EPM [22] and depression using the FST [24], stereotyped behavior, locomotor activity such as vertical rearing behavior in rats [10] and weight loss in humane [9]. The acute withdrawal symptoms last 7–10 days, and chronic phase associated with neurotoxicity effects may persist for several months. The severity of withdrawal signs

are related to the dosage and duration of methamphetamine use [7]. Stereotypies is defined as repetitive and invariant behavior patterns with no obvious goal or function [29], include head and forelimb movement and oral behavior such as repetitive chewing [1]. Stereotyped behaviors are associated with an imbalance in serotonergic and dopaminergic axis [2]. These signs might be due to METH-induced dependence and neurotoxicity [20], which causes the depletion of presynaptic monoamine stores and down-regulation of receptors [7]. Thus, the reversal or prevention of METH-induced dependence and neurotoxicity could be a useful method for the treatment of METH dependence and withdrawal. In previous studies, environmental enrichment (EE) has shown rewarding effects [30] and useful results in animal models of drug addiction [27]. The EE consists of a big cage which covered with fiber and physical stimuli, which stimulate exploration behavior in laboratory animals [26]. In our previous study, we have

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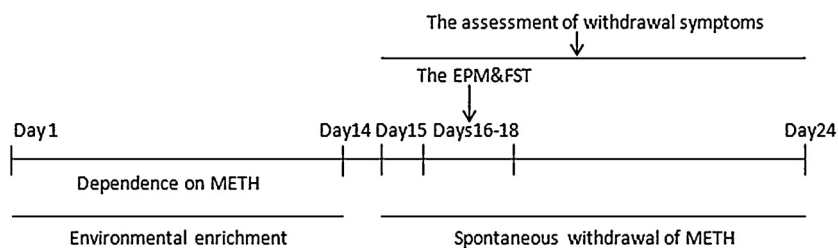


Fig. 1. Timeline of experiment (see Section 2 for details).

found that 30 days of exposure to enriched environment during METH withdrawal is associated with a decrease in anxiety and depression in METH withdrawn and intact rats [11]. It has been shown that enriched environment could improve neurotransmitters activity after drug abuse [12,31], also ameliorate stereotyped behaviors [29]. Thus, a more important question would be whether EE could blunt the deleterious effects of chronic administration of METH during dependency. Therefore, the aim of this study was to investigate whether exposure to EE during induction of METH dependence would attenuate behavioral withdrawal symptoms in rats. In previous studies, 10 and 14 days of exposure to the enriched environment reduced depressive symptoms [14] and cognitive deficits [17], respectively. Thus, with regard to the 14-days period to induce the development of methamphetamine dependence, we examined the effects of 14 days of environmental enrichment during induction of METH dependence.

## 2. Material and method

Male wistar rats ( $210 \pm 10$  g) were housed in a 12-h light/dark cycle at  $22\text{--}24^\circ\text{C}$ , with food and water ad libitum. All of the experimental procedures were conducted in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize the number of animals and their suffering. Methamphetamine hydrochloride (Sigma-Aldrich, M 8750) was dissolved in 0.9% saline. The rats were chronically treated with subcutaneous injections of METH (2 mg/kg), twice per day at 12 h intervals, for 14 days, as described previously [11]. Control rats were similarly injected with saline. Rats were placed in their home cages (standard or enriched environment) for 14 days during induction of METH dependence ( $n=7\text{--}8$  rats per cage). The standard environment (SE) consisted of standard plastic cages ( $42 \times 34 \times 15$  cm). The enriched environment (EE) was consisted of large cages ( $96 \times 49 \times 38$  cm), and the animals could play by plastic tunnels, rope, swing, balls, ramp, ladder, shelters, step, cube and running wheel, which were cleaned and changed every 2–3 days to stimulate exploratory behavior in rats [11].

Rats were divided into four groups ( $n=7\text{--}8$  per group): saline-standard environment (Sal/SE), saline-enriched environment (Sal/EE), METH-standard environment (METH/SE), and METH-enriched environment (METH/EE). The EE groups were allowed to freely exercise, play and explore their environment during induction of METH dependence (14 days). Then, all rats were transferred to standard cages on day 15. From day 15 to 24, stereotypic behavior, locomotor activity and body weight were recorded daily for 10 days in METH ( $n=7\text{--}8$  per group) and saline ( $n=4$  per group) groups. Also, on days 16–18 all animals were tested on the EPM and FST, respectively, 30 min after spontaneous behavioral testing during METH spontaneous withdrawal (see Fig. 1).

Spontaneous behavioral activity (stereotypy and locomotion) was recorded with a video imaging system as described previously [13]. Each rat was first placed in Plexiglas cylinder ( $45 \times 30$  cm) for a 10 min habituation period, and spontaneous behavioral

activity was recorded over the next 20 min. The stereotypic movements scored during METH spontaneous withdrawal for 10 days using the following scales; 0 = sleeping, 1 = resting with open eyes but not moving, 2 = active (grooming and exploratory behaviors), 3 = stereotypy including oral (chewing, licking or biting), focused sniffing, and repetitive head and paw movements. The number of vertical movements (rearing) was also recorded in the locomotor activity test at the same time. After each test the floor of the box was cleaned. The body weight of each rat was monitored daily over 10 days, and a change in body weight was calculated days before and after.

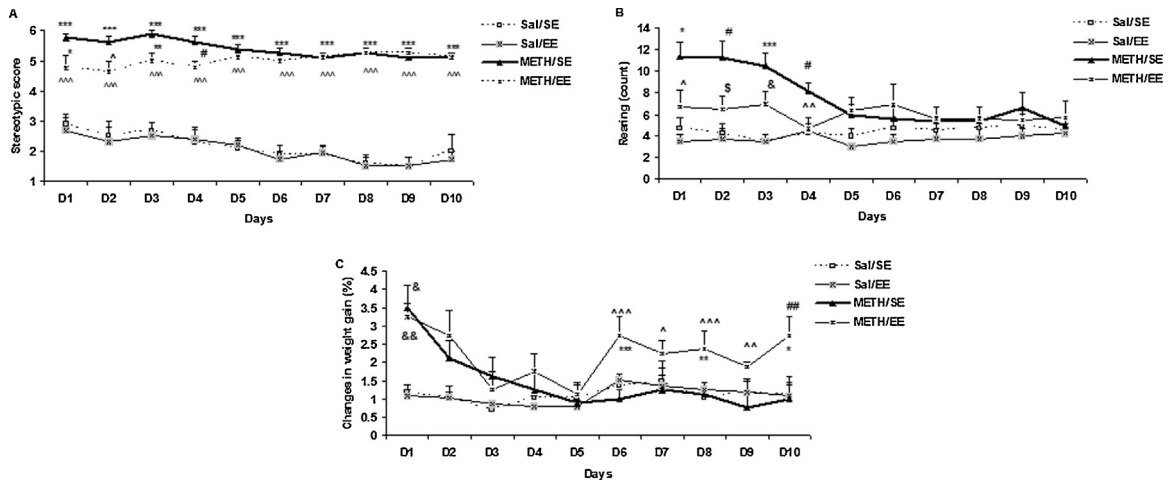
To assess the level of anxiety, the rats were individually placed in the center of the elevated plus maze (EPM) with two open ( $50 \times 10$  cm, with a ledge of 5 mm) and closed ( $50 \times 10 \times 40$  cm) arms, and a central platform ( $10 \times 10$  cm), and allowed to explore the apparatus for 5 min [21]. Time spent in, and entries into open and closed arms were measured during each 5 min test. In addition, the total number of arm entries was used as relative index of general activity. The apparatus was cleaned after each trial with water. Two days after METH cessation, on day 16, the rats were assessed by the EPM test (see Fig. 1).

The FST is a test of behavioral despair for rodents that used to assess the depressive-like activity. The test is carried out in a Plexiglas cylinder with a diameter of 20 cm, a height of 45, and the cylinder is filled with water  $25^\circ\text{C}$  to a height of 30 cm. Animals are forced to swim in two trials, the first trial lasts 15 min, and followed 24 h later by a 5 min test. The following factors are evaluated: swimming time, escaping time (toward the cylinder wall), immobility time (floating in the water, do only necessary movements to keep its head above water) [11]. On the test day, swimming sessions were videotaped from a lateral angle using a Nikon Camcorder, and behavioral assessments were accomplished by observers blind for experimental groups. For each rat, water was exchanged. After each session, the rats were immediately removed from water, and dried with a towel in a heated room before being returned to their home cages. The FST conducted on days 17–18 during METH spontaneous withdrawal (see Fig. 1).

The data expressed as the mean  $\pm$  standard error of the mean (S.E.M.). Data of spontaneous behavioral activity were analyzed with a  $4 \times 10$  (group  $\times$  day) two-way analysis of variance for repeated measures. Analysis of anxiety and depression was performed with the fixed factors treatment (saline and METH) and housing condition (SE and EE) by using two-way analyses of variance (ANOVA). Post-hoc analyses were included Tukey's test and using Bonferroni adjustments for multiple comparisons as required. Statistical differences were considered significant at  $P < 0.05$ .

## 3. Results

The results of stereotype behaviors are shown in Fig. 2A. Two-way ANOVA with repeated measures revealed a significant effect of day ( $F_{9, 171} = 2.25$ ,  $P = 0.021$ ), a significant effect of group ( $F_{3, 19} = 313.43$ ,  $P = 0.0001$ ) and a significant interaction between



**Fig. 2.** Effect of EE on spontaneous behavioral activity in METH rats during METH spontaneous withdrawal. (A) The stereotypic behaviors. (B) The number of rearing. (C) The percentage of weight gain. Stereotypic behavior score and the number of rearing significantly decreased in METH/EE rats after drug cessation compared to the SE group on days 1–4. Stereotypic behavior score in METH rats was more than saline groups on days 1–10. Also, METH/EE rats showed more weight gain during spontaneous drug withdrawal on days 6–10. Data are expressed as Mean  $\pm$  SEM. In (A)  $^{\wedge} P=0.043$ ,  $^{\sim} P=0.033$   $^{**} P=0.004$ ,  $^{\#} P=0.05$  vs. METH/SE group.  $^{***} P=0.0001$  vs. Sal/SE group.  $^{****} P=0.0001$  vs. Sal/EE group. In (B)  $^{\wedge} P=0.016$ ,  $^{\S} P=0.014$ ,  $^{\&} P=0.023$ ,  $^{\sim} P=0.01$  vs. METH/SE group.  $^{\ast} P=0.029$ ,  $^{\#} P=0.019$ ,  $^{***} P=0.003$ ,  $^{\#} P=0.018$  vs. Sal/SE group. In (C)  $^{***} P=0.0001$ ,  $^{\wedge} P=0.034$ ,  $^{**} P=0.003$ ,  $^{##} P=0.001$  vs. METH/SE group.  $^{\S} P=0.026$ ,  $^{***} P=0.0001$ ,  $^{**} P=0.002$ ,  $^{\ast} P=0.007$  vs. Sal/SE group.  $^{SS} P=0.004$  vs. Sal/EE group.

day and group ( $F_{27, 171} = 2.53$ ,  $P=0.003$ ). Between group comparisons indicate that stereotypic score in METH/SE and METH/EE rats were more and less than Sal/SE and Sal/EE groups on days 1–10, respectively (both,  $P=0.0001$ ). Also, stereotypic score in METH/SE group was more than METH/EE group on day 1 ( $P=0.029$ ), day 2 ( $P=0.033$ ), day 3 ( $P=0.004$ ) and day 4 ( $P=0.05$ ) (Fig. 2A).

Spontaneous locomotor activity and exploratory behavior such as number of vertical movements (rearing) are shown in Fig. 2B. The analysis of variance with repeated measurement for the number of rearing showed no significant effect of day ( $F_{9, 171} = 1.52$ ,  $P=0.144$ ), and significant effect of group ( $F_{3, 19} = 4.95$ ,  $P=0.01$ ), and significant interaction between factors (group  $\times$  day) ( $F_{27, 171} = 1.63$ ,  $P=0.033$ ). The number of rearing in METH/SE rats was more than Sal/SE group on day 1 ( $P=0.029$ ), day 2 ( $P=0.019$ ), day 3 ( $P=0.003$ ) and day 4 ( $P=0.018$ ). Also, the number of rearing was less in METH/EE rats than METH/SE rats on days 1–4 (all,  $P<0.05$ ) (Fig. 2B).

Two-way ANOVA with repeated measures for the percentage of weight gain immediately upon METH cessation showed a significant effect of day ( $F_{9, 171} = 3$ ,  $P=0.002$ ), a significant effect of group ( $F_{3, 19} = 23.48$ ,  $P=0.0001$ ) and a significant interaction between day and group ( $F_{27, 171} = 1.85$ ,  $P=0.01$ ). Between group comparisons indicate that the percent of weight gain were more in METH/SE and METH/EE rats on the first day of withdrawal than Sal/SE and Sal/EE groups, respectively ( $P=0.026$ ,  $P=0.004$ ). The METH/EE rats gained more weight than METH/SE rats on days 6–10 (all,  $P<0.05$ ). Also, there was a significant difference between METH/EE and Sal/EE rats on day 6, 8 and 10 (all,  $P=0.0001$ ) (Fig. 2C).

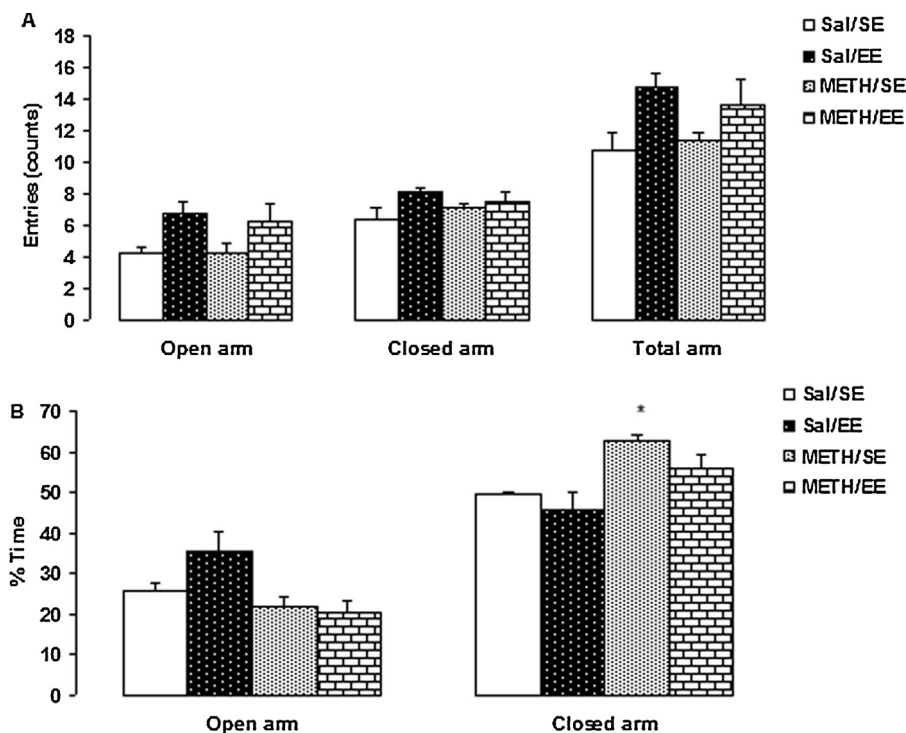
The results of the elevated plus maze (EPM) are illustrated in Fig. 3. Two-way ANOVA revealed no significant effect of treatment, group, and interaction between treatment and housing (all,  $P>0.05$ ) for open and closed arm entries, the number of total arm entries and time spent on the open arms. Also, two-way ANOVA revealed a significant effect of treatment ( $F_{1, 27} = 15.1$ ,  $P<0.001$ ) and housing ( $F_{3, 27} = 3.5$ ,  $P<0.05$ ) for closed arm time. Pair-wise Bonferroni comparisons (adjusted alpha = 0.025) revealed that the time spent on the closed arms was significantly more in the METH/SE group than the Sal/SE group ( $P=0.012$ ) (Fig. 3B).

Results of the forced swim test are shown in Fig. 4. Two-way ANOVA revealed a significant effect of housing ( $F_{3, 27} = 64.19$ ,  $P=0.0001$ ), and treatment ( $F_{1, 27} = 12.69$ ,  $P=0.001$ ), and significant interaction between both factors ( $F_{3, 27} = 56.31$ ,  $P=0.0001$ )

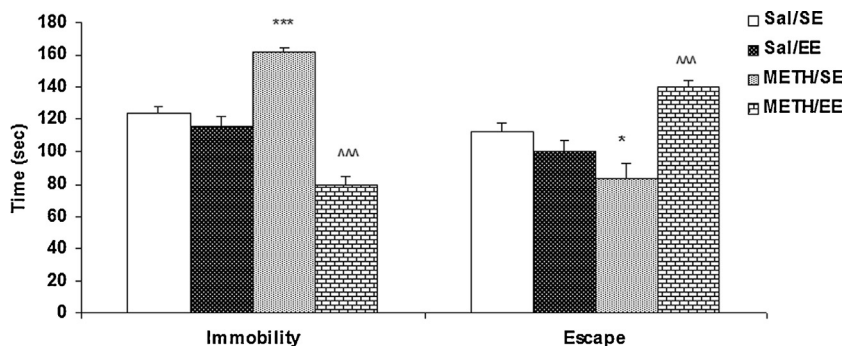
in immobility time. Also, two-way ANOVA for the escape time indicated a significant effect of group ( $F_{3, 27} = 10.9$ ,  $P=0.003$ ), and treatment ( $F_{1, 27} = 4.51$ ,  $P=0.05$ ), and significant interaction between treatment and housing ( $F_{3, 27} = 9.4$ ,  $P=0.005$ ). Comparison between groups revealed that the immobility and escape time in METH/SE rats were more and less than Sal/SE group, respectively ( $P=0.0001$ ,  $P=0.034$ ). Also, the immobility and escape time in METH/EE rats were less and more than METH/SE group, respectively (both  $P=0.0001$ ). There was no significant difference in swimming time between groups, ( $P>0.05$ ) (data not shown).

#### 4. Discussion

In present experiment, rats reared under enriched environmental conditions during induction of METH dependence showed more weight gain and greater decrease in behavioral withdrawal symptoms (stereotypic behaviors and vertical rearing numbers) during spontaneous withdrawal. Interestingly, the effect of EE on the stereotypic behaviors, locomotor activity appeared on day 4 of withdrawal, while weight gain was seen on day 6 after withdrawal, indicating a more operant effect of the EE in METH rats. Given that there was no significant difference between the two saline groups in behavioral withdrawal symptoms. No study with the same nature has been conducted thus far. In this experiment, the number of rearing was higher in METH/SE group, which is coincident with a previous study that repeated administration of psychostimulants enhanced the motor effects of these drugs [3,4,18]. In line with our study, past studies have shown that exposure to EE resulted in a substantial reduction in the development of stereotypic behavior following environmental restriction, which were associated with increased dendritic spine density of the motor cortex and the striatum [29] and increased expression of nerve growth factor and brain-derived neurotrophic factor in rats [15]. Although METH/EE rats showed a further decline in the stereotypic behavior during the first 4 days of withdrawal than METH/SE rats. However, the METH rats exhibited intense stereotypic behavior than the saline rats. This finding indicates that higher stereotyped behavior during withdrawal of METH may be due to dopaminergic depletion [7]. METH elicited an augmented stereotypic response and a decrease in the levels of dopamine in the caudate nucleus [32]. While, EE improved the neuronal dysfunction due to



**Fig. 3.** Effect of EE on anxiety-like behavior during spontaneous METH withdrawal in rats. (A) The number of entries and (B) the time spent into open and closed arms. There was no significant difference between groups in the number of entries into open and closed arms and also the time spent into open arms ( $P > 0.05$ ). The time spent on the closed arms was significantly higher in the METH/SE group than the Sal/SE group. Data are expressed as Mean  $\pm$  SEM. \*  $P = 0.012$  vs. Sal/SE group.



**Fig. 4.** Effect of EE on depressive-like behavior during spontaneous METH withdrawal in rats. The METH/EE group showed less immobility and more escape time than METH/SE group. Also METH/SE group showed higher immobility and less escape time than Sal/SE. Data are expressed as Mean  $\pm$  SEM. \*\*\*  $P = 0.0001$ , vs. Sal/SE group. \*\*  $P = 0.0001$  vs. METH/SE, \*  $P = 0.034$ , vs. Sal/SE group.

disruption of dopamine and serotonin [28]. These modifications induced by the EE may influence stereotyped and depressive-like behaviors in enriched rats [5,28].

In present study, enriched housing also reduced depressive-like behavior after 2–3 days of abstinence. Whereas, in our previous study, enriched environments during a 30-day abstinence period decreased anxiety and depressive-like behavior [11]. It may be explained in part, by increased serotonin concentration [17] and Brain-derived neurotrophic factor (BDNF) expression in reared animals in the EE [6].

However, in this study, EE had no effect on anxiety-like behavior after METH cessation. It is possible that 14 days of housing in enriched cages was insufficient to produce anxiolytic effect. Another interesting finding was losing weight coincide with spontaneous METH withdrawal in METH/SE rats. More weight gain in the METH/EE group from 6 to 10 days of withdrawal could be interpreted as a positive treatment outcome. Weight loss after METH withdrawal in METH/SE group may be due to an increase

in energy metabolism, and decreased appetite, induced by depressive outcomes such as anhedonia and fatigue [8,16]. In contrast, no difference was observed between EE and control rats in weight gain after amphetamine [25]. It may be due to age of exposure to EE in rats, which in our study was approximately 12 weeks after birth. However, in a previous study [25] the younger rats (approximately 6 weeks of age) were still growing, that both groups showed an equal weight gain.

## 5. Conclusion

These results show that the enriched environment during induction of METH dependence can decrease METH-induced locomotor activity (rearing), stereotypy and depressive-like behavior during spontaneous METH withdrawal. Our findings may have a potential therapeutic application by shortening the period of abstinence and prevention of relapse to METH.

## Conflict of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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