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Methamphetamine Exposure Delays Formation of Habitual Behavior in Female Rats

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Abstract

Many psychopathologies, including addiction, have been associated with executive dysfunction and changes in behavioral control such as the development of habitual behavior. Psychostimulant drugs, likely due to the effects that these drugs have on dopamine neurotransmission in the striatum, are implicated in accelerating habit formation in male rats. Similar studies in female rats are limited. In this study, female rats received pretreatment of either methamphetamine (METH) or vehicle and were trained to the level of reinforcer-exposures typically associated with habitual behavior and then subjected to reinforcer devaluation. Habit was operationalized as an insensitivity to reinforcer devaluation. Results indicate that female rats pretreated with METH remained goal-directed while the vehicle controls demonstrated habitual behavior. These data suggest that the effect of psychostimulant exposure on habit formation may be sex-dependent, and that female rats may remain goal-directed under the influence of substances that increase dopamine in the striatum.

Keywords: instrumental behavior, habit formation, methamphetamine

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Executive control and its dysfunction are associated with maladaptive behaviors such as addiction. The loss of executive control and development of addiction is thought to coincide with a transition from goal-directed to stimulus-driven behaviors. There are two forms of operant behavior: goal-directed and habitual behavior. In goal-directed behavior, responding is based on the outcome and in particular the value of the outcome. Extensive training or repetitive performance of the behavior results in the formation of an association between the response and contextual stimuli such that the response is triggered automatically in the presence of those cues (Dickinson, 1985). When behavior performance is driven by antecedent stimuli rather than outcome, manipulating outcome value does not influence the responding behavior (Adams, 1982). This type of behavior is considered habitual.

As behaviors become stimulus-driven and habitual rather than goal-directed and purposeful, neural activation shifts from the ventral and dorsomedial striatum (DMS) to the dorsolateral (DLS; Dickinson, 1985; Everitt & Robbins, 2013). Thus, the DMS is believed to govern goal-directed behavior, while the DLS mediates the formation and expression of habitual behavior. Once habit is established, the DLS is thought to inhibit the DMS (Dickinson, 1985; Everitt & Robbins, 2013). This activation shift is reflected by changes in dopamine (DA) transmission with an increase in the DLS and decrease in the DMS (Belin et al., 2013; Everitt & Robbins, 2013). These concurrent changes may play a role in executive dysfunction and maladaptive behaviors such as addiction (Belin et al., 2013).

Sex differences regarding the prevalence and risk of disorders associated with a loss of executive control vary throughout the literature (Bangasser & Valentine, 2014; Becker & Hu, 2008). In the context of drug use and self-administration, several animal studies have noted sex

differences (Bangasser & Valentine, 2014; Becker & Hu, 2008). However, few studies have assessed the development of habitual behavior, and associated mechanisms, in female subjects. In both male and female rats, DA transmission is increased in the DLS upon stimulant administration (Yoest et al., 2018). However, sex differences have also been reported in the organization and modulation of DA circuitry with changes in DA signaling and receptor binding upon estradiol and progesterone administration (Yoest et al., 2018). In male rats, administration of psychostimulants prior to instrumental learning promotes habit formation (Furlong et al., 2018; Nelson & Killcross, 2006; Nordquist et al., 2007), which is hypothesized to be DA-dependent (Nelson & Killcross, 2013). Similar studies have not been conducted in female rats, prior to the work in our lab, leaving the effects of psychostimulants on female habit formation not well understood. This study aims to investigate the effect of methamphetamine (METH) pretreatment on habit formation in female rats.

Habit development is studied through reinforcer devaluation (RD). Beginning with instrumental training, the reinforcer is then devalued with satiety or conditioned taste aversion. Devaluation with satiety is achieved through feeding the animals prior to testing so that they are not motivated to respond for a food reinforcer. Devaluation with conditioned taste aversion is achieved by pairing the food reinforcer with injections of lithium chloride (LiCl), which induces nausea. In studies of habit development, the value of the outcome influences goal-directed behavior such that a decrease in outcome value is accompanied by a decrease in responding for the outcome (Adams & Dickinson, 1981). Stimulus-driven habitual behavior, however, is not sensitive to changes in outcome value (Adams, 1981). Thus, RD does not reduce responding when the behavior has become habitual.

Previous studies in our laboratory have shown that female rats transition from being sensitive to RD following 120 reinforcer-exposures during training, to habitual and insensitive to RD following 160 reinforcers (Schoenberg et al., 2019). To investigate whether METH exposure advanced habit formation in females, which has been demonstrated to be the case in males, female rats were given subthreshold training at 120 reinforcers following METH pretreatment. In this study, the female rats remained goal-directed and were not advanced into habit (Schoenberg et al., in prep). In light of these results, we hypothesize that METH exposure prior to operant training either has no effect on female rat habit formation or has the opposite effect in females compared to males. That is, habit formation may be delayed in female rats rather than accelerated as the literature has demonstrated for male rats. The current study aimed to test this by following the same METH pretreatment regimen as in previous studies, but training females to the level of habitual behavior with 160 reinforcer-exposures.

Methods

Animals

Subjects were thirty-three adult Long Evans intact female rats. Rats were housed in pairs in a colony room maintained at a temperature of 23°C with 12-hour light/dark phase conditions. Rats were habituated to their environment and handled prior to beginning the experiment. In order to motivate rats to earn sucrose (the reinforcer used during operant training), they were fed a restricted diet which maintained their weight at 85% of their free feed weight. Daily vaginal swabs were obtained to confirm free cycling. All procedures for this experiment were approved by the Institutional Animal Care and Use Committee at the University of Vermont.

Drug Pretreatment

Half of the rats were randomly selected to receive drug pretreatment with methamphetamine hydrochloride (METH; Sigma-Aldrich) prior to instrumental learning. Rats were housed such that cage mate pairs were assigned to the same drug pretreatment group. Rats in the METH treatment group received a bodyweight-dependent dose of METH, 2.5 mg/kg via intraperitoneal injection (i.p.), daily for eight days. The Vehicle group received an i.p. injection of 0.9% normal saline of similar volume, daily for eight days. Following a three-day washout period, all rats received a very low dose of METH at 0.3mg/kg to test for sensitization to motor behaviors stereotypical of METH exposure as a proxy measurement for previous drug exposure. Five minutes after the injection, rats were filmed in their home cage for one minute. The videos of the test were scored for these behaviors by experimenters who were blind to the drug pretreatment groups. Prior to the test, several typical motor behaviors associated with methamphetamine administration were identified; these included head-bobbing, torso rotation, and jerky motions, as well as overall enhanced locomotor activity (e.g. traversing the cage). These stereotypic behaviors of METH exposure in female rats were characterized by previous studies in our lab (Schoenberg et al., in prep) with visual observation. Presently we are not aware of published literature characterizing stereotypical motor behaviors in female rats exposed to METH.

Apparatus

Six standard rat operant chambers (Med Associates, St. Albans, VT) were utilized for training and testing. Each rat completed all training and testing in an assigned chamber. Operant chambers contained a light which was on for the duration of each training and testing session. One wall of the chamber included a magazine into which 45-mg sucrose pellets were deposited

via a computer-controlled hopper mechanism. On the same wall was a nose-poke aperture that recorded nose-poke behavior after a break in an infrared beam and prompted sucrose pellet delivery depending on reinforcement schedule and training/testing procedure. Data was collected and recorded with MED-PC software (Med Associates, St. Albans, VT).

Instrumental Magazine Training

Rats began with magazine training consisting of two thirty minute sessions in which sucrose pellet reinforcers were deposited on a random time 60-second (RT-60s) schedule. During magazine training, the nose-poke aperture was not available, thus rats were able to freely learn the value of the sucrose pellet as a positive reinforcer. These training sessions also facilitated rats' familiarity with the training and testing environment.

Nose-poke Acquisition

Rats subsequently underwent two training sessions in which the nose-poke aperture was present, and each performance of a nose-poke was reinforced with a sucrose pellet, ending at 25 pellets per session. This training session supported the association of the nose-poke behavior with earning a sucrose pellet. After completing this training on a continuous reinforcement schedule, rats received four days of training on a variable interval 30-second (VI-30s) schedule. Rats received 40 pellets per session and 160 overall. This training procedure has been shown to facilitate habitual behavior in intact, female Long Evans rats (Schoenberg et al., 2019).

Reinforcer Devaluation

Rats received random assignments to either a reinforcer devalued group or non-devalued group. In each housed pair, one rat was assigned to the devalued group while their counterpart was non-devalued. During the RD procedure, the nose-poke aperture was not available and sucrose pellets were deposited into the magazine at a RT-30s schedule. On odd-numbered days,

rats in the devalued group received sucrose pellets while rats in the non-devalued group did not. Upon termination of these sessions, all rats received an i.p. injection of 0.15M lithium chloride (LiCl) at a dose of 10ml/kg to induce nausea. On even-numbered days, the non-devalued group received the sucrose pellets and the devalued group did not. Sessions ended simultaneously for non-devalued and devalued rat pairs. All rats received i.p. injections of 0.9% normal saline in an equivalent volume to LiCl injections upon individual session termination. This procedure allowed for the controlled pairing of nausea with the sucrose reinforcer in only the devalued group. As the RD procedure continued devalued rats consumed fewer sucrose pellets on each odd-numbered day, so every subsequent even-numbered day, the number of pellets non-devalued rats received was based on the average number consumed the previous odd-numbered day by devalued rats. Prior to reinforcer devaluation, the following criterion was established: full devaluation and conditioned taste aversion was achieved upon zero consumption of delivered sucrose pellets. With this criterion in place, it is possible to interpret responding during the critical test of habit to be indicative of habitual behavior, and not any lingering operant motivation for the sucrose reinforcer. Therefore, this procedure continued until the criterion of zero sucrose pellet consumption by devalued animals was met.

Extinction Test

The day after RD criterion was met, the presence of habitual behavior was evaluated in extinction conditions. Rats were placed in the operant chambers with the nose-poke apertures present and were allowed to nose-poke but did not receive sucrose pellet reinforcement. Response rates (nose-pokes per minute) were recorded across the twelve minute session. It was expected that if animals were goal-directed then devalued animals would respond significantly

less than non-devalued animals. If they were habitual, devalued animals would respond at a rate that is not significantly different from their non-devalued counterparts.

Consumption Test

The day after the extinction test, rats were evaluated for successful reinforcer devaluation through a consumption test. Rats were placed in the operant chamber, without access to the nose-poke aperture. Sucrose pellets were delivered on a RT 30-s schedule until 20 pellets were delivered and pellet consumption was tallied for both rats in both the devalued and non-devalued groups. It was expected that non-devalued rats would consume the sucrose pellets while devalued rats would not.

Reacquisition test

The day after the consumption test, rats were evaluated for reinforcer devaluation through a reacquisition test. Rats were placed in the operant chamber with access to the nose-poke aperture and were allowed to perform the nose-poke response for the sucrose reinforcer on a VI 30-s schedule. Nose-poke rates and pellet consumption were measured. This test lasted for thirty minutes and was intended to assess the association of conditioned taste aversion to the sucrose pellets with the memory of nose-poke responses earning sucrose pellets. Given that only the devalued group was trained for conditioned taste aversion to the sucrose pellets, their nose-poke rates were expected to be lower while the non-devalued group was expected to reacquire the nose-poke behavior.

Results

One animal was an outlier during extinction (z=2.50; Field, 2007) and two animals failed the consumption test; these animals were therefore excluded from analysis.

Sensitization test

Motor behavior counts were blindly tallied for all rats from the sensitization test recordings to verify meth-induced sensitization. Rats that had received METH pretreatment showed higher average behavior counts (M=9.67, SD=5.36) compared to rats in the vehicle pretreatment group (M=5.78, SD=3.15.) An independent samples t-test (t(16)=-1.88, p=.079) showed that this difference was marginally significant.

Nose-poke Acquisition

To evaluate response rates in acquisition, a 4 (session) by 2 (drug pretreatment group: METH or vehicle) by 2 (anticipated devaluation group: devalued or non-devalued) repeated-measures ANOVA was conducted. Mauchly's test revealed a violation of sphericity ($\chi_2(5)$=54.97, p<.001) and Greenhouse-Geisser corrections of degrees of freedom were employed (ε=0.47). A significant within-subject effect of session verified successful acquisition of nose-poking over time (F(1.40, 40.45)=39.41, p<.001), and a lack of significant between-subjects effect of drug pretreatment (F(1,29)=2.12, p=.156) or anticipated devaluation group (F(1,29)=1.14, p=.294), and lack of session by drug pretreatment or devaluation group interactions (F(1.40, 40.45)=0.31, p=.687; F(1.40, 40.45)=0.32, p=.650, respectively) demonstrated that all groups acquired the nose-poke behavior at equal rates (see Figure 1).

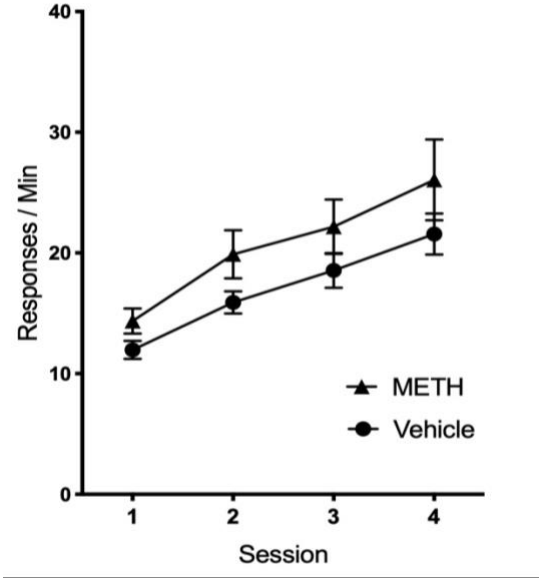

Figure 1. Mean responses per minute for METH and Vehicle groups during acquisition.

Reinforcer Devaluation

During RD, rats in the devalued group reached criteria of zero consumption (see Figure 2). Rats in the non-devalued group behaved as expected and continued to consume sucrose pellets. No difference between drug pre-treatment groups was observed.

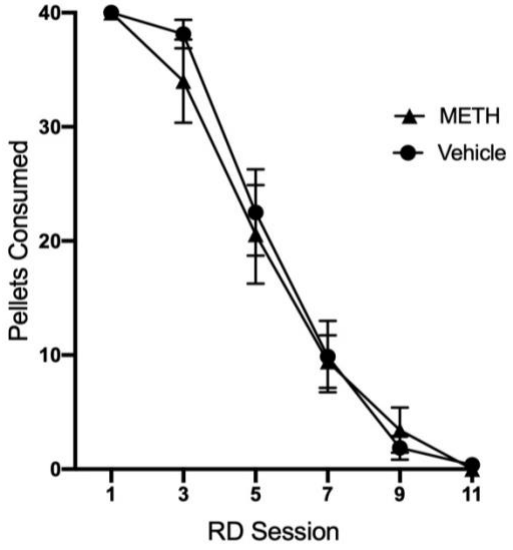

Figure 2. Mean sucrose pellets consumed during RD by devalued rats in both drug pre-treatment groups.

Extinction

To test sensitivity to devaluation, proportion of baseline responding during the extinction test was evaluated in a 2 (drug pretreatment) by 2 (devaluation group) factorial ANOVA. There was a significant main effect of devaluation group ($F(1,29)=8.43$, $p=.007$), and while there was not a significant devaluation group x drug pretreatment group interaction ($F(1,29)=1.43$, $p=.226$), *a priori* planned comparisons between devalued and non-devalued groups within each drug pre-treatment group showed a lack of a statistically significant difference between vehicle devalued and non-devalued response rates ($F(1,29)=1.44$, $p=.240$). However, the METH devalued group responded significantly less than the METH non-devalued group ($F(1,29)=8.27$, $p=.007$; see Figure 3). This suggests that the vehicle pretreated group responded habitually at test, whereas the METH pretreatment group remained goal-directed.

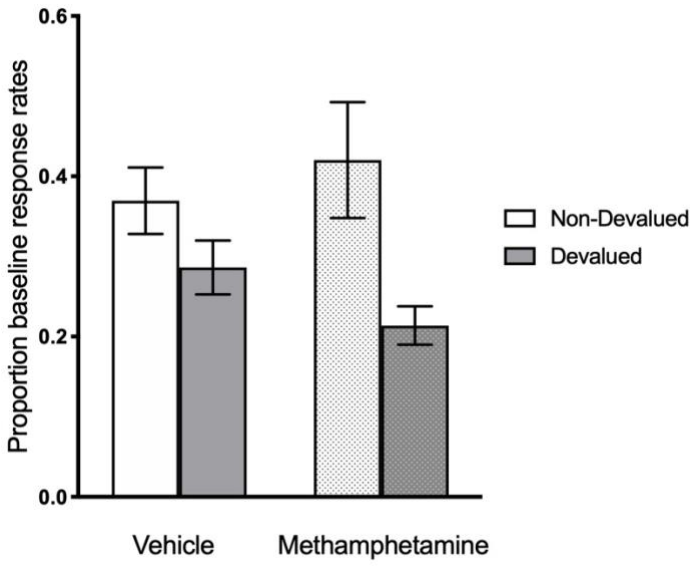

Figure 3. Proportion baseline response rates of devalued and non-devalued rats for both drug pre-treatment groups in extinction conditions.

Consumption

Rats included in analysis behaved as expected in the consumption test. That is, rats in the devalued group consumed on average zero of the sucrose pellets delivered while rats in the non-devalued group consumed all 20 of the sucrose pellets, indicating successful devaluation in the former group.

Reacquisition

Reinforcer devaluation was further assessed in the reacquisition test. Rats in the devalued group did not reacquire to baseline (M=.13, SD=.03) while rats in the non-devalued group did reacquire back to baseline rates of responding (M=1.03, SD=.26). This was verified by factorial ANOVA, which demonstrated a significant main effect of devaluation group ($F(1,29)=171.23$, $p<.001$; see Figure 4). Additionally, no main effect of drug pre-treatment ($F(1,29)=.09$, $p=.76$) or drug pretreatment x devaluation group interaction ($F(1,29)=.16$, $p=.692$) was found. This suggests that drug pretreatment does not affect reacquisition and that reinforcer devaluation significantly affects reacquisition.

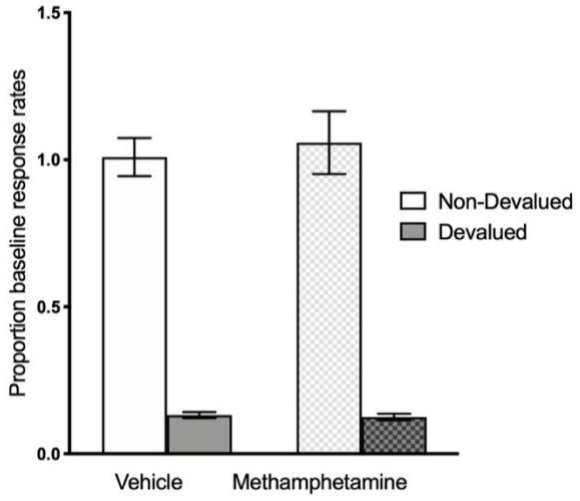

Figure 4. Proportion baseline response rates of devalued and non-devalued rats for both drug pre-treatment groups in reacquisition conditions.

Discussion

The results from this experiment show that exposure to METH, prior to operant training with 160 reinforcers, delays the development of habitual behavior in female rats. Previous experiments demonstrated that female rats, without drug pretreatment, generally exhibited goal-directed behavior at 120 reinforcers and habitual behavior at 160 reinforcers with a transition stage of 120-160 reinforcers (Schoenberg et al., 2019). Thus, as expected, the saline-pretreated females in this study showed habitual responding at 160 reinforcer-exposures, whereas METH pretreated females at the same training level remained goal-directed.

Several studies have demonstrated the relationship between changes in dopaminergic activity and habit formation (Dunovan & Verstynen, 2016; Kravitz et al., 2012; O'Hare et al., 2016). In male rats, psychostimulant-accelerated habit formation is mediated by changes in activation of dopamine receptors and is particularly dependent on the activation of D1 receptors (Nelson & Killcross, 2013). Accelerated habit formation is further augmented by a decrease in D2 receptor activity with a D2 antagonist (Nelson & Killcross, 2013). Similar to a D2 antagonist, repeated psychostimulant exposure has been shown to decrease activity in D2 receptors (Volkow & Baler, 2014). In female rats, an increase in DA transmission and DA receptor changes induced by high levels of estrogen disrupt stimulus response learning mediated by the DLS (Yoest et al., 2018; Shams et al., 2016). METH, which is also known to increase levels of DA, may act via a similar mechanism. Thus, it is possible that the change in DA transmission triggered by METH pretreatment in female rats inhibits DLS function and re-establishes the DMS as the main area of activation, supporting a transition back to goal-directed behavior despite contrasting literature for male rats.

Specific physiological sex differences may contribute the different effect of psychostimulants on habit formation in male and female rats. DA release triggered by amphetamine is dependent on cycling sex hormones in female rats (Yoest et al., 2018). However, we have shown in a previous experiment that cycling estradiol replacement in ovariectomized (OVX) females did not accelerate habit formation independently or when paired with METH pre-exposure (Schoenberg et al., in prep). Interestingly, OVX females show a progressive decrease in the expression of D1 DA receptors (Levesque & Di Paolo, 1990), which, as we described earlier, have been shown to be essential in psychostimulant-accelerated habit formation in male rats ((Nelson & Killcross, 2013). It is possible that the estradiol replacement in OVX rats in Schoenberg et al., (in prep) did not recover D1 DA expression enough to potentiate METH-induced acceleration of habitual behavior. However, this does not account for the lack of METH-induced acceleration of habitual behavior in the intact females of Schoenberg et al., (2019) or the effect of METH in delaying habit formation in the present study, thus sex differences independent of cycling sex hormones may have a significant role. D1 DA receptor expression has also been shown to be higher in male rats than females (Levesque & Di Paolo, 1990). This suggests that the expression of D1 DA receptors in female rats may not be sufficient at baseline to support psychostimulant-accelerated habit formation as it does in males. However, this also does not explain the delaying effect of METH on habit formation in female rats of the present study.

Psychostimulants such as METH may also affect the value of sucrose as a reward. In an experimental context, this could be reflected by an increased rate of responding in acquisition or a delay in reaching criteria for reward devaluation. A study with amphetamine-sensitized male rats found that both habit formation and the motivational value of a sucrose reward were

enhanced but dependent on interval and ratio training schedules, respectively (Dunovan & Verstynen, 2016). Furthermore, this study noted that the reinforcer value may be enhanced in interval training schedules but is not reflected in response rates due to the uncoupling of the response-outcome association. It is possible that METH may enhance the value of a sucrose reward in females to a greater extent than in males, thus causing them to remain goal-directed. Evidence for sex differences in sugar preference and the metabolism of sugar (Butera, 2010; Mauvais-Jarvis, 2015; Vieira-Marques et al., 2017) supports the notion that the value of a sucrose reward, and changes in that value, may be different between males and females.

In studies of habit, female rats have demonstrated a reduced sensitivity to outcome devaluation compared to their male counterparts (Hammerslag & Gulley, 2014; Schoenberg et al., 2019). Additionally, in male rats, pretreatment with the psychostimulant amphetamine has been shown to reduce RD sensitivity and accelerate habit formation at 120 reinforcers, a training level at which males are typically still goal-directed (Nelson & Killcross, 2006). In contrast, we previously found that training to 120 reinforcer-exposures in female rats produced opposite results; pre-exposure to METH had no effect in accelerating habit formation and female rats remained goal-directed (Schoenberg et al., 2019). It would be interesting to evaluate the effect of METH pre-exposure in male rats trained to just below the level of habit formation to determine if METH pre-exposure accelerates habit formation as amphetamine has been shown to do. Future experiments could also evaluate if METH pre-exposure, with training to the level of habit, also keeps males goal-directed as females were in this present study. The results presented here may have significant implications in the context of addictive behaviors in females. It is possible that psychostimulants support goal-directed behavior for a reward such as a drug in females, instead of advancing formation of habitual behavior.

Conclusion

The results of this study show that habit formation is delayed in female rats with pre-exposure to the psychostimulant METH. Training to a specific level of reinforcer-exposures, which in previous studies have demonstrated habitual behavior in female rats, resulted in goal-directed behavior in female rats exposed to METH prior to training. It is possible that exposure to METH, prior to operant training, alters DA transmission in the striatum in such a way that reduces DLS activation and inhibition of the DMS, thus supporting DMS-mediated goal-directed behavior. Future studies should evaluate if the effect of METH pre-exposure demonstrated here in female rats is present in male rats also trained to a level of reinforcer-exposure which typically exhibits habitual behavior. This is an important step in further characterizing potential sex differences in the effect of methamphetamine on habit formation. It would also be interesting to investigate in future studies the effect of METH on DA transmission in the striatum, during operant training, at a receptor level. Lastly, future experiments should evaluate changes in the motivational value of reinforcers in psychostimulant-sensitized female rats.

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