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Individual Differences in Novelty Seeking on the Playground Maze Predict Amphetamine Conditioned Place Preference

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KLEBAUR, J. E. AND M. T. BARDO. *Individual differences in novelty seeking on the playground maze predict amphetamine conditioned place preference.* PHARMACOL BIOCHEM BEHAV **63**(1) 131–136, 1999.—Previous research has shown that a rat's level of activity in a novel environment can predict the strength of amphetamine-induced locomotor behavior and self-administration, but not amphetamine-conditioned place preference. The increase in activity observed when a rat is exposed to an inescapable novel environment may reflect escape behavior due to stress. To assess approach to novelty in a free-choice test, we examined the ability of a new test, the playground maze, to predict individual differences in response to amphetamine (1 or 3 mg/kg). Using the playground maze to categorize rats as either high or low novelty seekers, it was found that individual differences in novelty seeking did not predict amphetamine-induced changes in locomotor activity following either a single or repeated injections. However, high novelty seekers showed greater amphetamine-conditioned place preference than low novelty seekers. These results provide support for the hypothesis that novelty seeking and drug reward are neuropharmacologically related. ©1999 Elsevier Science Inc.

Amphetamine Novelty seeking Individual differences Conditioned place preference Locomotor activity

IT is commonly known that a large number of drugs are abused in today's society. The reasons for drug abuse are many, including the pharmacological profile of the drug, marketing factors, and sociocultural factors (1). One other reason relates to individual differences in personality traits. Zuckerman (22) has labeled one personality trait as sensation seeking, based on the Sensation Seeking Scale (SSS). Sensation seeking is defined as the need for varied, novel, and complex sensations and experiences, and the willingness to take risks for the sake of such experiences (22). Studies involving humans have shown a correlation between scores on SSS and high-risk behavior, including drug use behavior. For example, in a national survey of young males, those who reported moderate to heavy drinking were more likely to score high on risk-taking/impulsivity and SSS (5). In another study, individuals who scored high on scales assessing SSS also used drugs such as marijuana, cocaine, or amphetamine more often (19).

Similarities to the human personality trait of sensation seeking have been researched in animals. For example, Piazza, Deminiere, Le Moal, and Simon (14) have identified behavioral characteristics in rats that may be similar to features of sensation seeking in humans. These investigators exposed a random sample of rats individually to a novel open-field environment. Based on their locomotor response in the novel environment, each rat was categorized as either a high responder (HR) or low responder (LR) using a median split based upon the entire sample. Following this, rats were tested for acquisition of amphetamine self-administration. HR rats acquired self-administration more readily than LR rats, suggesting that individual differences in vulnerability to drug abuse may be predicted from the behavioral response in a novel environment.

In addition to drug self-administration, drug reward can be measured using a classical conditioning paradigm known as conditioned place preference (CPP). In a study by Erb and Parker (6), rats were divided into HR and LR groups based on activity level in a novel chamber and then were given place conditioning trials with amphetamine (1–10 mg/kg). Although amphetamine CPP was consistently demonstrated, there were no differences in the strength of amphetamine CPP between HR and LR rats. These results suggest that the novelty-related individual differences in amphetamine self-administration paradigm do not generalize to amphetamine CPP.

Although the work on amphetamine self-administration in

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HR and LR rats is consistent with the notion that sensation seeking and drug abuse may be linked, categorization of rats into HR and LR groups has been based on forced exposure to an inescapable novel environment. Previous work has shown that HR rats have a more prolonged secretion of corticosterone than LR rats when exposed to a novel environment (15); thus, this test more likely reflects a stress response rather than a true exploratory response. Perhaps a better animal analogue of the sensation-seeking trait in humans is a test in which animals are allowed free-choice access to both novel and familiar stimuli such that approach to novelty (i.e., novelty seeking) can be quantified.

The place preference paradigm has been shown to be sensitive to individual differences in reactivity to novelty. In one recent study, rats were first classified into high or low novelty-seeking groups based on novelty place preference in a free-choice test (17). Rats were then assessed for amphetamine CPP. High novelty seekers showed a greater magnitude of amphetamine CPP than low novelty seekers. However, one problem with this study is that the place-preference apparatus was used to assess both novelty seeking and amphetamine CPP. Thus, experience with the novelty-induced place-preference apparatus may have influenced amphetamine CPP. A better way to assess the ability of individual differences in response to novelty to predict amphetamine reward may be to use a separate apparatus for each measure.

Other than the place preference test, a number of tests have been used to quantify a free-choice approach to novelty in animals. Some tests involve exposing animals to discrete environmental changes by placing a novel stimulus into a familiar environment or allowing access to a novel area adjacent to a familiar one (3,4,7,11,21). Other tests of novelty seeking require an animal to make an operant response for access to a novel stimulus or environment (18). More recently, Nicholls, Springham, and Mellanby (13) designed a new test of novelty seeking, referred to as the "playground maze." In this test, rats are exposed to different objects on a maze. A novel object is then substituted for one of the familiar objects. Rats spend more time with the novel object than the familiar objects. This test can measure novelty seeking and locomotion separately, as well as providing a graded response to the novel object.

The major purpose of the present study was to examine the relationship between novelty seeking on the playground maze and response to amphetamine in the CPP paradigm. We chose doses of amphetamine (1 or 3 mg/kg) similar to Erb and Parker (6). However, in contrast to Erb and Parker (6), we did not use 10 mg/kg amphetamine, as this dose has been reported to produce a place aversion (2).

EXPERIMENT 1

The purpose of Experiment 1 was to determine if individual differences in novelty seeking on the playground maze could be demonstrated in our laboratory. This experiment used a modified procedure of the playground maze based on the work of Nicholls, Springham, and Mellanby (13).

Method

Subjects. Naive, male Sprague–Dawley rats ($n = 8$), 200–225 g, were used. Rats were individually housed in hanging wire mesh cages with food and water available continuously. Animals were handled in the colony room for 3 days prior to the start of the experiment.

Apparatus. The playground maze was a circular platform made from 3/4″ plywood painted flat black. The maze was 100 cm in diameter, and was raised 55 cm above the floor. Eight hard plastic objects were secured to the maze with velcro 20 cm from the edge equally spaced from each other. The objects were a yellow block ($6 \times 6 \times 6$ cm), a purple razor ($6 \times 10 \times 5$ cm), a pink rabbit (about $7.5 \times 9 \times 6.5$ cm), a green monster (about $9 \times 7.5 \times 6.5$ cm), a Fisher-Price man (about $5 \times 9.5 \times 5$ cm), a baker man (about $8.5 \times 12 \times 7$ cm), a purple dinosaur (about $5 \times 7 \times 6.5$ cm), and a miniature capital building (about $7.5 \times 7.5 \times 4$ cm). The novel object used on the test day was an orange tiger (about $4.5 \times 4.5 \times 8.5$ cm). A video camera was suspended from the ceiling above the maze to record a rat's behavior on the familiarization days and test day.

Procedure. Rats were habituated to the playground maze for 3 min on each of 3 consecutive days. On these familiarization trials, each rat was initially placed in the middle of the maze facing away from the experimenter. The position of the objects was kept constant for all rats on a single familiarization day, but was changed on a daily basis to prevent a position bias. Objects were wiped down with isopropyl alcohol after each trial. The experimenter remained in the room during the familiarization trials.

On the day after the last familiarization trial, rats were tested for their approach to a novel object placed on the maze. For this test, rats were placed on the playground maze for another 3 min familiarization trial (trial 4) and then were removed and placed back in their cage while remaining in the room for 1 min. During this time, one object was removed and replaced by the novel object; the position of the novel object varied among the rats. For the novelty-seeking test, rats were placed back in the maze facing away from the novel object and were allowed to explore the maze for 3 min.

Observation and data analysis. The behavior of each rat on the familiarization days and test day was video taped for subsequent analysis. The dependent measures were: 1) the duration of time spent in a circular area, 14 cm in diameter, around each object; and 2) the number of entries into each circular object area. A rat was considered in the object area when its head was in the circular area. On the familiarization days, the duration and the number of entries were analyzed separately in a 4×8 ANOVA with familiarization day and object as within-subject factors. On the test day, the duration in the novel object area was compared to the duration in the familiar object area using a paired *t*-test. For this test, the duration (seconds) spent by each rat in each of the seven familiar object areas was summed and divided by seven to get the average duration (seconds) in the familiar object area. The number of entries was compared in the same manner. A novelty preference score was also calculated from the following formula: duration (seconds) in novel object area minus the average duration (seconds) in the seven familiar object areas.

Results

There was a significant object $\times$ day interaction for duration spent in each object area across the four familiarization trials, $F(21, 224) = 2.81, p < 0.0001$. Subsequent simple effects analyses indicated significant differences in duration spent in the different object areas on Day 1, $F(7, 56) = 2.98, p < 0.01$ and on Day 2, $F(7, 56) = 4.86, p < 0.0002$ but not on Days 3 or 4. However, multiple comparison analyses using Tukey's HSD *t*-tests on Days 1 and 2 showed that there was no consistent object preference nor any location bias.

There was also a significant object $\times$ day interaction for

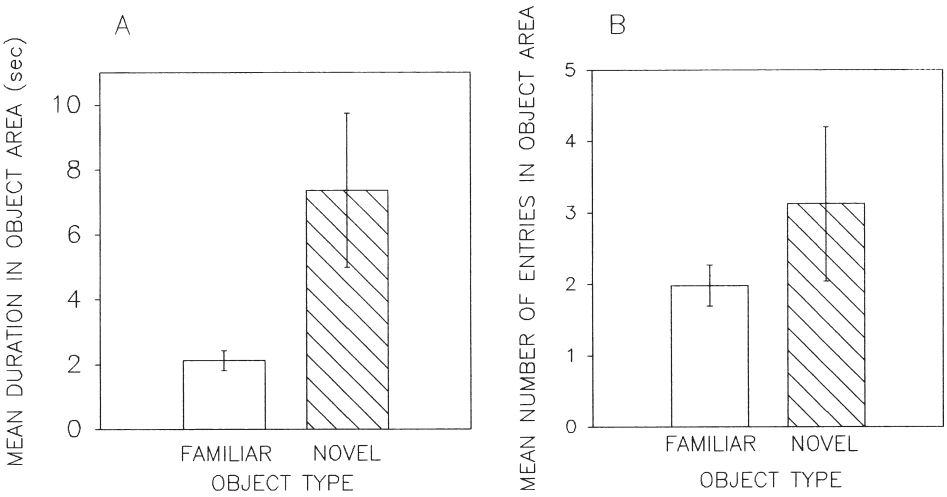

FIG. 1. Mean duration (seconds ± SEM) in familiar and novel object areas (A) on the test day. Mean number of entries (seconds ± SEM) into the familiar and novel object areas (B).

the mean number of entries in each object area across the four familiarization trials, $F(21, 224) = 2.81$, $p < 0.0001$. Subsequent simple effects analyses revealed that there were significant differences in the different object area entries on Day 1, $F(7, 56) = 2.47$, $p < 0.03$, and on Day 2, $F(7, 56) = 4.58$, $p < 0.0004$, but not on Days 3 or 4. Again, multiple comparison analyses using Tukey's HSD *t*-tests on Days 1 and 2 showed that there was no consistent object preference nor any location bias.

The mean duration of time spent in the novel object area versus the familiar object area on the test day is shown in Fig. 1A. The effect of object type (novel vs. familiar) approached significance, $t(7) = 2.24$, $p < 0.06$. As can be seen, there was substantial variation in the amount of time rats spent with the novel object. Entry data is shown in Fig. 1B. There was no significant difference in the number of entries into the novel object area and the familiar object area, $t(7) = 1.26$, $p = 0.25$.

Figure 2 shows the novelty preference score for each individual animal. Again, there was substantial variation in an individual rat's preference for the novel object. These individual differences indicate that the playground maze may be useful for predicting differences in the strength in amphetamine CPP.

EXPERIMENT 2

The purpose of Experiment 2 was to determine if individual differences in novelty seeking on the playground maze could predict differences in sensitivity to the locomotor stimulant and rewarding effects of amphetamine in the CPP paradigm. It was predicted that high novelty seekers would be more sensitive to the rewarding effects of amphetamine (1 or 3 mg/kg) as measured by CPP.

Method

Subjects. Naive male Sprague–Dawley rats ($n = 66$), 200–225 g, were used. Rats were individually housed in hanging wire mesh cages with food and water available continuously. Animals were handled in the colony room for 3 days prior to the start of the experiment.

Apparatus. The playground maze, as described in Experiment 1, was used to assess novelty seeking. The familiar and novel objects remained the same as in Experiment 1.

The apparatus used for assessing locomotor activity and CPP consisted of a rectangular wooden chamber that had three compartments separated by removable walls. The two end compartments measured 24 × 30 × 45 cm high and the center compartment measured 24 × 10 × 45 cm high. One end compartment had white walls, a wire mesh floor, and pine bedding. The other end compartment had black walls, a grid floor, and cedar bedding. The middle compartment had gray

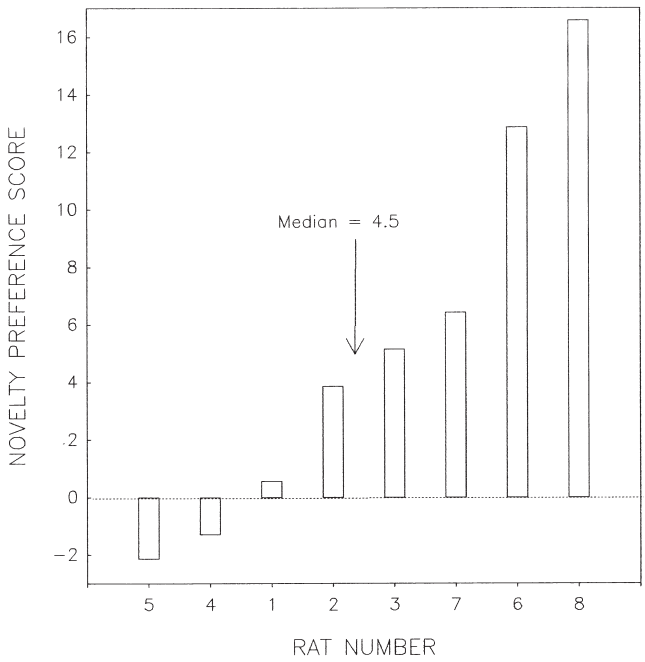

FIG. 2. Novelty preference score for individual rats on test day in Experiment 1.

walls and a solid wood floor. The solid walls could be replaced with similar walls that contained a 10 × 10-cm opening allowing rats access to all compartments. A video camera was suspended from the ceiling to record a rat's behavior.

Procedure

Novelty seeking. Rats were tested on the playground maze as described in Experiment 1, except the length of the habituation and test trials was 5 min rather than 3 min. Rats were classified as high or low novelty seekers based on a median split of their duration with the novel object on the playground maze. Data for six rats from the novelty-seeking screen were equal to the median and, therefore, these rats were excluded from the conditioned place preference procedure.

Conditioned place preference. Rats were assigned to one of three different treatment conditions (0, 1, or 3 mg/kg amphetamine) such that for each condition one half of the rats were high novelty seekers and the other half were low novelty seekers.

The place preference procedure required 9 days. On the first 8 days, each rat was confined on one of the two end compartments for 30 min. The compartment alternated from day to day, giving a total of four exposures to each compartment. For each rat, drug treatment (i.e., 0, 1, or 3 mg/kg amphetamine) was paired with exposure to the white compartment, whereas on alternate days saline treatment was paired with exposure to the black compartment. Drug treatment was paired with the white compartment to condition against the rat's slight preference for the black compartment (16). Within each group, one half of the rats started their conditioning regime exposed to the white compartment and the remainder to the black compartment. The control group received saline on both white and black compartment exposure days. During conditioning, rats were injected subcutaneously with either amphetamine or saline immediately before placement into a compartment. On the day after the last conditioning trial, rats were given a preference test by being allowed free access to all compartments for 15 min.

Drugs. Amphetamine sulfate was prepared at concentrations of 1 and 3 mg/ml in a saline solution and injected subcutaneously at doses of 1 or 3 mg/kg in a volume of 1 ml/kg body weight. Injections of saline (0.9% NaCl) were also in a volume of 1 ml/kg body weight.

Observations and data analysis. The behavior of each rat on Conditioning Days 1 and 4, as well as on the test day, was video taped for subsequent analysis. The dependent measures were: 1) the number of horizontal line crosses in the white compartment on Conditioning Days 1 and 4 (defined by both front paws crossing a line drawn on the video monitor screen that bisected the compartment parallel to the partitioning walls); 2) the number of rears in the white compartment on Conditioning Days 1 and 4 (defined by both front paws off of the floor, excluding grooming movements); and 3) the duration spent in each end compartment on test day (defined by duration that both front paws remained in the compartment). The number of line crosses and rears during the last 20 min of the conditioning trial on both days were analyzed separately in a 2 × 3 × 2 ANOVA with novelty seeking (high or low) and dose of amphetamine (0, 1, or 3 mg/kg) as between-subjects factors and conditioning day (1 or 4) as a within-subject factor. The mean duration in the amphetamine-paired compartment was analyzed in a 2 × 3 ANOVA with novelty seeking (high or low) and dose of amphetamine (0, 1, or 3 mg/kg) as between-subjects factors. Tukey–Kramer's *t*-tests were subsequently used to determine if high novelty seekers and low novelty seekers differed from each other.

Results

Line crosses during the last 20 min on Conditioning Days 1 and 4 are presented in Fig. 3. Only the last 20 min of the 30-min conditioning trial were analyzed because brain levels of amphetamine during the first 10 min of the conditioning trial would be minimal. There was no significant interaction between conditioning day, dose, and novelty seeking, $F(2, 53) = 0.27$, $p = 0.7665$, or a significant interaction between conditioning day and novelty seeking, $F(1, 53) = 0.06$, $p = 0.8146$. However, there was a significant interaction between conditioning day and dose, $F(2, 53) = 16.04$, $p < 0.0001$, as well as a significant main effect of dose, $F(2, 53) = 26.62$, $p < 0.0001$. Tukey–Kramer's *t*-tests showed that on Conditioning Day 1, amphetamine increased the number of line crosses compared to saline controls at both the 1 mg/kg, $t(53) = 5.99$, $p < 0.05$, and 3 mg/kg, $t(53) = 5.62$, $p < 0.05$ doses. On Conditioning Day 4, amphetamine produced an inverted U-shaped curve, with 1 mg/kg amphetamine increasing horizontal activity more than 3 mg/kg amphetamine. At the 1 mg/kg dose, there was no significant change in activity from Conditioning Day 1 to day 4, $t(53) = 0.31$, $p > 0.05$, indicating behavioral sensitization was not obtained. At 3 mg/kg, there was a significant decrease in activity across conditioning days, $t(53) = 4.81$, $p < 0.05$.

Rears during the last 20 min on Conditioning Days 1 and 4 are presented in Fig. 4. There was no significant interaction between conditioning day, dose, and novelty seeking, $F(2, 53) = 1.06$, $p = 0.3547$, or a significant interaction between conditioning day and novelty seeking, $F(1, 53) = 0.02$, $p = 0.90$. However, there was a significant interaction between conditioning day and dose, $F(2, 53) = 18.42$, $p < .0001$, as well as a significant main effect of dose, $F(2, 53) = 10.86$, $p < .0001$. Tukey–Kramer's *t*-tests showed that on Conditioning Day 1, amphetamine increased the number of rears compared to saline controls at both the 1 mg/kg, $t(53) = 16.72$, $p < 0.05$ and 3

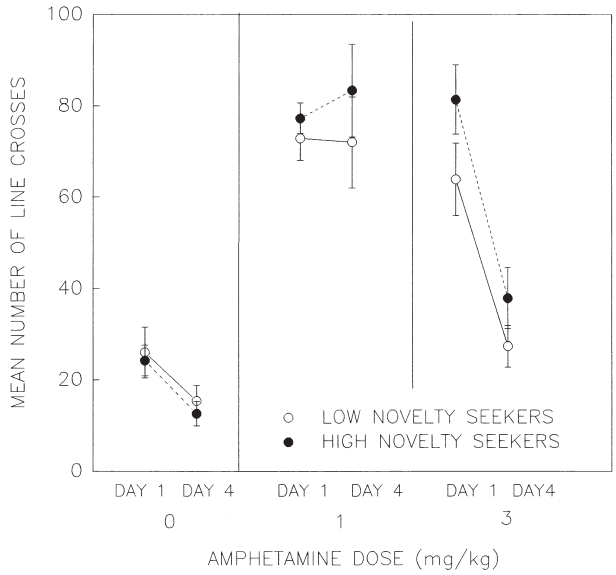

FIG. 3. Mean number of lines crosses (number ± SEM) on Conditioning Days 1 and 4 for high and low novelty seekers in Experiment 2.

mg/kg doses, $t(53) = 16.19$, $p < 0.05$. On Conditioning Day 4, amphetamine produced an inverted U-shaped curve, with 1 mg/kg amphetamine increasing vertical activity more than 3 mg/kg amphetamine. At the 1 mg/kg dose, there was no significant change in activity from Conditioning Day 1 to day 4, $t(53) = 2.45$, $p > 0.05$, indicating behavioral sensitization was not obtained. At 3 mg/kg, there was a significant decrease in activity across conditioning days, $t(53) = 13.75$, $p < 0.05$.

The mean duration spent in the amphetamine-paired compartment during the preference test for high and low novelty seekers is shown in Fig. 5. The main effect of novelty seeking was not significant, $F(2, 55) = 3.31$, $p = 0.0742$. However, there was a significant main effect of dose, $F(2, 55) = 36.07$, $p < 0.0001$, as well as a significant interaction between novelty seeking (high or low) and dose, $F(2, 55) = 3.29$, $p < 0.05$. Tukey–Kramer's *t*-tests showed that both low and high novelty seekers spent more time in the drug-paired white compartment as the dose of amphetamine increased. However, at the 1 mg/kg dose of amphetamine, high and low novelty seekers differed in response to amphetamine. At this dose, high novelty seekers showed greater amphetamine CPP than low novelty seekers.

DISCUSSION

As previously described, Nicholls, Springham, and Mellanby (13) first used the playground maze to assess novelty seeking. In that study, rats were first familiarized with eight different objects on a maze and then a novel object was substituted for one of the familiar objects. Rats showed a significant novelty effect, spending more time with the novel object than the familiar objects. Using a similar procedure, we found that there were differences in both the duration and number of approaches directed at the eight different objects on the initial familiarization trials. Across familiarization trials, however, there was no consistent object preference, nor was there any location bias on the apparatus. When subsequently tested with a novel object in the stimulus array, rats tended to spend more time with the novel object, although this effect did not reach statistical significance. Importantly, there was a range of individual differences in novelty seeking on the test day, with some rats showing no preference for the novel object and others showing a clear preference.

In a subsequent experiment, the playground maze was used to predict differences in sensitivity to the locomotor stimulant and rewarding properties of amphetamine in a CPP paradigm. Following acute amphetamine, locomotor activity increased at both doses of amphetamine (1 or 3 mg/kg) when compared to saline controls. However, behavioral sensitization to the locomotor stimulant effect of repeated injections of amphetamine did not occur for either horizontal or vertical activity at the 1 mg/kg dose. Behavioral sensitization also was not obtained at the highest dose of amphetamine tested (3 mg/kg). To the contrary, repeated administrations of 3 mg/kg amphetamine actually reduced both line crosses and rears. This latter finding may reflect sensitization to responses such as sniffing or stereotypic behaviors that are incompatible with line crossing and rearing behaviors. Sensitization of stereotypic behaviors following repeated amphetamine injections has been described previously by others (12,20).

When rats were classified as either high or low novelty seekers, there were no differences between the groups in sensitivity to the locomotor stimulant effect of amphetamine. This contrasts with previous work showing that HR rats are more sensitive than LR rats to the acute locomotor stimulant effect of amphetamine (9). One possible explanation for this apparent discrepancy is that the screening procedures involved in Hooks et al. (9) and the present study were different. Hooks et al. (9) classified rats as HR or LR based on activity in an inescapable novel environment. In the present study, rats were screened on the playground maze, a test that allowed us to assess free-choice approach to novelty. Therefore, individual differences in response to inescapable novelty and free-choice novelty do not appear to be equivalent predictors of a rats locomotor response to amphetamine. Alternatively, because Hooks et al. (9) did not differentiate be-

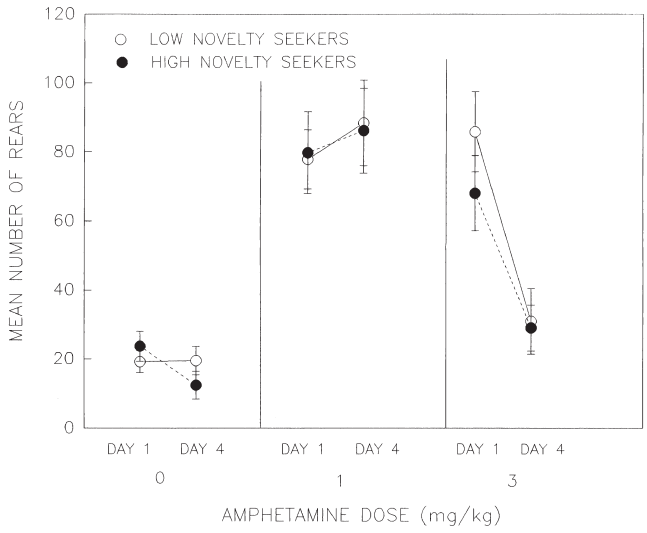

FIG. 4. Mean number of rears (number ± SEM) on Conditioning Days 1 and 4 for high and low novelty seekers in Experiment 2.

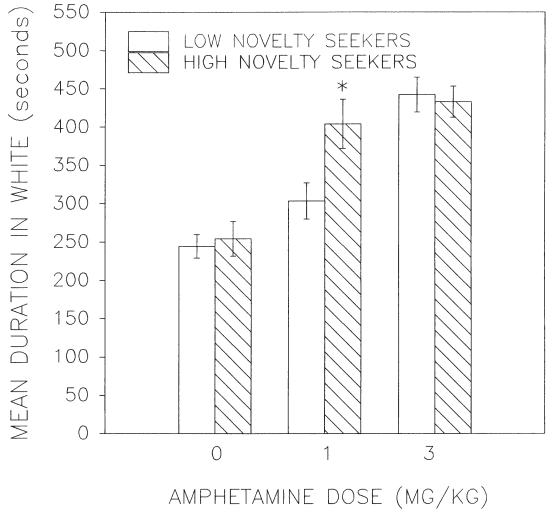

FIG. 5. Mean duration (seconds ± SEM) in amphetamine-paired white compartment for high and low novelty seekers on test day in Experiment 2. Asterisk (*) indicates a significant between subject difference between high and low novelty seekers, $p < 0.05$.

tween horizontal and vertical activity, it is possible that the inconsistent results obtained in that study and the present study may reflect differences in the dependent measures.

As expected, amphetamine induced a preference for the drug-paired compartment at both the 1 and 3 mg/kg doses. More important, however, high and low novelty seekers differed in response to the rewarding effects of amphetamine (1 mg/kg). At this dose, high novelty seekers were more sensitive than low novelty seekers to amphetamine CPP. These results contrast with a previous study by Erb and Parker (6), who found that HR or LR rats in an inescapable novel environment did not differ in amphetamine CPP and Gong et al. (8), who found that HR and LR rats did not differ in cocaine CPP. The most likely explanation for the difference in results obtained between these previous studies and the present study relates to differences in the screening procedures used to quantify individual responses to novelty. Specifically, it appears that a free choice approach to novelty, but not inescapable exposure to novelty, predicts amphetamine CPP. Alternatively, other procedural differences may play a role because the previous studies used a within-subject CPP procedure and the present study used a between-subject CPP procedure. In any case, further research is needed to determine if individual differences in novelty seeking on the playground maze also predicts amphetamine self-administration or predicts CPP to other drugs of abuse.

Although there are many reasons why individuals use drugs, one of these reasons has been tied to the sensation seeking trait proposed by Zuckerman (22). Much research shows that individuals who score high on SSS tend to take more risk in several aspects of their lives (5,10,19). There is also strong evidence for a biological basis for sensation seeking (23). Despite this research, however, there is presently no direct evidence to indicate whether differences in the brain exist between high and low sensation seekers. The present work indicates that an animal model of novelty seeking, as assessed on the playground maze (13), may be useful to examine the neural mechanisms of this trait.

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