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Dissociation of Novelty- and Cocaine-Conditioned Locomotor Activity From Cocaine Place Conditioning

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KOSTEN, T. A. AND M. J. D. MISERENDINO. *Dissociation of novelty- and cocaine-conditioned locomotor activity from cocaine place conditioning.* **60**(4) 785–791, 1998.—High locomotor response to novelty is associated with ease of drug self-administration but does not predict greater place-conditioning effects of drugs. Yet, the latter reflects context conditioning and high responders (HR), compared to low responders (LR), show greater conditioned locomotor effects. Conditioned locomotor effects may occur in place conditioning, perhaps confounding its measure. To examine whether conditioned locomotor effects occur in place conditioning, the present study classified rats as HR vs. LR by using approximately the two extreme 15% percentiles of the distributions. The place conditioning and locomotor sensitizing effects of cocaine were tested. In Experiment 1, HR rats exhibited more crossings between compartments but did not differ from LR rats in cocaine place conditioning. Further, both groups showed increased crossings at test compared to baseline, indicative of a conditioned locomotor effect. In Experiment 2, HR rats showed greater acute locomotor activation to cocaine, whereas LR rats tend to show greater locomotor sensitization. Finally, in Experiment 3, HR rats showed habituation in locomotor responses, whereas LR rats did not. Results of these studies suggest that inherent and conditioned locomotor activity levels are dissociated from place-conditioning effects. © 1998 Elsevier Science Inc.

Cocaine Individual differences Novelty response Conditioned place preference Context conditioning Habituation Locomotor sensitization Reward Outbred rats

THE ability of psychoactive drugs, such as cocaine, to stimulate locomotor activity and their capacity to be positively reinforcing share common neural components in the mesolimbic dopamine (DA) system (34). This system has also been related to locomotor response in a "novel" environment (15,17,21,25). Novelty responses predict the acute locomotor effects of psychoactive drugs (8,10,13,14,21,24) and the ease of acquisition of amphetamine self-administration (23,24). Specifically, rats that are high responders (HR) to novelty show enhanced behavioral effects compared to rats that are low responders (LR). Yet, novelty responses do not predict degree of place conditioning (9,12), and results from studies of locomotor sensitization, or the enhanced responding that occurs with repeated drug exposure (19,28), have been inconsistent (10,13,14,21).

The lack of association between novelty responses and place-conditioning effects is puzzling because such studies often show concordance with self-administration studies (5). Moreover, place conditioning (5), as well as locomotor sensitization (26,31), involves context conditioning, effects found to be greater in HR rats (16,18), which would further predict differences between HR and LR rats. However, conditioned locomotor effects are usually not found in place conditioning studies with rats [e.g., (27,29)], although these have been demonstrated with mice (7). This may be due to the insensitivity of locomotor measures assessed typically (i.e., numbers of crossings between sides) or to the use of outbred rats that show large variability in inherent locomotor activity levels. That inherent or conditioned locomotor activity influences measures of place conditioning has been suggested by research in which rats were limited in their opportunity to move during place-conditioning training (32,33). Furthermore, outcome measures of place conditioning (30) and locomotor sensitization (11) have also been suggested to be influenced by

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habituation to novelty effects. That is, the usual preference for novel vs. familiar environments (2,3) that decreases with repeated exposure may not occur when rats are under drug effects. Sparing habituation to novelty through drug administration would also predict larger place-conditioning effects in HR rats because these rats show greater habituation (24).

Thus, by employing rats that differ in novelty locomotor responses, the present study assessed whether conditioned locomotor activity occurs during place conditioning. The locomotor sensitization effects of cocaine as well as habituation to novelty were also examined by employing groups of rats exhibiting extreme differences in locomotor response. Specifically, rats representing approximately the highest 15% and lowest 15% response levels were used because we showed previously that these groups show the greatest differences in several biochemical characteristics of the mesolimbic DA system (21). The place-conditioning effects of cocaine were examined in Experiment 1, acute and sensitized locomotor responses to cocaine were assessed in Experiment 2, and habituation of novelty locomotor responses were tested in Experiment 3.

GENERAL METHOD

Animals and Housing

Male, outbred Sprague–Dawley rats (CAMM, Wayne, NJ) weighing about 200–250 g at the start of the experiment were employed as subjects in the present study. Rats were group housed (three per cage) in hanging, wire-mesh cages in a temperature-controlled colony room with a 12 L:12 D cycle (lights on at 0700 h). Food (Purina chow) and tap water were available ad lib. All behavioral procedures were performed between 0900 and 1300 h, 5 days per week. The procedures were approved by the institutional Animal Care and Use Committee in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and the facilities were accredited by the American Association of Laboratory Animal Care.

Novelty Response Groups

Rats were purchased in groups of 40 on four occasions, in groups of 22 on two occasions, and in a group of 52 on one occasion. Rats were screened for ambulatory, horizontal locomotor activity in a circular locomotor apparatus. The design of this apparatus was based on Piazza et al. (23) and described previously (20,21). Briefly, it featured a concentric design such that rats moved between two circular walls with the larger circle measuring 26″ in diameter and the smaller circle measuring 22″ in diameter. There were four sets of photocell light beams located at four 90° intervals. The number of light beam interruptions was tabulated automatically during 30-min sessions and was used as the measure of locomotor response to novelty (23).

On the occasions when 40 rats were screened, the six rats showing the greatest amount of locomotor activity were classified as high responders (HR) and the six rats showing the least amount of locomotor activity were classified as low responders (LR) and employed in the present experiments. On the occasions when 32 rats were screened, the four rats showing the greatest amount of locomotor activity were classified as HR and the four rats showing the least amount of locomotor activity were classified as LR. On the occasion when 52 rats were screened, the seven rats showing the greatest amount of locomotor activity were classified as HR and the seven rats showing the least amount of locomotor activity were classified as LR. No other rats from these screenings were employed in the present studies. In all cases, these extreme responses represent approximately the highest and lowest 15 percentiles of the total groups screened.

Drug

Cocaine HCl was obtained from the National Institute on Drug Abuse (Research Triangle Park, NC). Drug was dissolved in isotonic saline and administered IP in a volume of 1 ml/kg at one of the following doses: 0 (saline), 10, or 15 mg/kg.

EXPERIMENT 1: NOVELTY RESPONSE AND COCAINE PLACE CONDITIONING

This study examined whether locomotor response to novelty was associated with differences in the place conditioning effects of cocaine and investigated whether conditioned locomotor responses occur in this procedure. This latter effect may have been masked in previous studies because of the large individual variability of locomotor activity in outbred rats. Further, because locomotor response to novelty is associated with differences in habituation to novelty (24), this study provides a test of the role of novelty and its habituation in place conditioning. Two recent studies have failed to find a relationship between novelty response and the place conditioning effects of amphetamine (9) or cocaine (12).

Method

Subjects. Three sets of six HR and six LR rats were obtained from three of the screenings of 40 rats each. One set each of HR and LR rats was assigned to one of the following cocaine dose training groups: 0, 10, or 15 mg/kg.

Apparatus. The place conditioning apparatus used was a gray, wooden box with internal dimensions of 25″ long × 7″ wide × 13″ high. As described previously, the place-conditioning apparatus consisted of two conditioning sides (12.5″ × 7″) that provided distinct visual and tactile cues (20). The two sides were divided by a guillotine door that was removed on baseline and test days and remained in place on conditioning trials to confine the animal to the appropriate conditioning side. On one side of the apparatus, a set of six infrared sensors were located equidistantly along the side of the wall about 2″ above the floor. Information on time spent on this side (and by subtraction, time spent on the other side) as well as number of crossings between sides were tabulated automatically and relayed to an event recorder.

Procedure. On the first day, the animal was placed into the center of the conditioning apparatus with the door removed. Times spent on each side and number of crossings between sides were recorded for 30 min during this baseline session. There were four cocaine and four saline training days all of which began immediately after the injections and were 15 min in length. On cocaine training days, the guillotine door was in place and the animal was injected IP with cocaine and confined to the side of the apparatus on which it had spent less time on the baseline session. On alternate days, the animal was injected (IP) with saline and confined to the other side of the apparatus. This procedure has been shown to be valid (4). On the test day, the door was removed from the place-conditioning apparatus and the animal was again placed into the center of the apparatus with time spent on each side and number of crossings between sides recorded for 30 min. Both the baseline and test sessions were conducted without drug administration.

Data analyses. Times spent on the cocaine-paired side on the baseline and test days were analyzed using a 2 × 3 × 2

ANOVA with novelty response group and cocaine dose training group as between subjects factors and session as a repeated measure factor. Increased time spent on the cocaine-paired side on the test session, compared to the baseline session, in the groups administered cocaine would indicate a cocaine-conditioned place preference. The number of crossings made between sides were also analyzed using a 2 × 3 × 2 ANOVA (same factors). These data were used as an indicator of activity and, because no cocaine was administered during either the baseline or test session, increases in this measure on the test session would reflect conditioned effects.

Results

Rats for all three cocaine dose groups were screened in squads of 40 and six each were assigned to the high and to the low novelty response groups. As seen in Table 1, the mean (± SEM) locomotor responses in these screening sessions do not differ between the three HR groups nor between the three LR groups (ps > 0.10). Thus, rats assigned to their respective novelty response groups for the three cocaine dose training groups are not statistically different from each other.

Times spent on the cocaine-paired side during the baseline, or precocaine exposure session, and during the test, or postcocaine exposure session, are presented in Fig. 1A by cocaine dose training group and by novelty response group. Groups administered 0 mg/kg cocaine (i.e., vehicle) during training spend similar amounts of time on the cocaine-paired side during both of these sessions. Groups administered 10 or 15 mg/kg cocaine spend more time on the cocaine-paired side during the test session compared to the baseline session. These statements are supported by the significant dose effect, $F(2, 30) = 3.28$; $p = 0.05$, the significant session type effect, $F(1, 30) = 21.92$; $p < 0.0001$, and the significant dose × session type interaction effect, $F(2, 30) = 5.66$; $p < 0.01$. Further, there is no significant effect of dose for the baseline session, but there is a significant dose effect for the test session, $F(2, 30) = 5.09$; $p < 0.01$. These data indicate that cocaine supports conditioned place preference. However, there is no effect of novelty response group on times spent on the cocaine-paired side overall or when either session is analyzed individually (ps > 0.10), as seen in Fig. 1A.

The number of crossings made between sides during the baseline, or precocaine exposure session, and during the test, or postcocaine exposure session, are presented in Fig. 1B by cocaine dose training group and by novelty response group. Groups administered 0 mg/kg cocaine during training show similar numbers of crossings during both sessions whereas, groups administered 10 or 15 mg/kg cocaine show increased numbers of crossings during the test session compared to the baseline session. These statements are supported by the significant dose effect, $F(2, 30) = 5.16$; $p < 0.01$, the significant session type effect, $F(1, 30) = 4.07$; $p = 0.05$, and the trend for a significant interaction of dose × session type, $F(2, 30) = 3.08$; $p = 0.06$. Further, there is no significant effect of dose for the baseline session, but there is a significant dose effect for the test session, $F(2, 30) = 5.52$; $p, < 0.01$. These data suggest that the cocaine exposure given during place conditioning training increases activity levels, as measured by numbers of crossings between sides.

There is a significant effect of novelty response group on numbers of crossings, which is in contrast to the lack of this effect on cocaine place conditioning. Consistent with their assignments to locomotor response groups, HR rats exhibit greater numbers of crossings between sides compared to LR rats, as seen in Fig. 1B. These statements are supported by the

TABLE 1

MEAN (± SEM) TOTAL LOCOMOTOR ACTIVITY COUNTS DURING 30 MIN SCREENING TEST FOR NOVELTY RESPONSE GROUPS (ns = 6) AND TOTAL SAMPLES (ns = 40) BY COCAINE DOSE (mg/kg) TRAINING GROUP

Cocaine Dose	HR Groups	LR Groups	Total Sample
0	636.1 ± 12.2	245.8 ± 14.7	424.6 ± 20.0
10	611.2 ± 23.0	295.2 ± 18.6	459.6 ± 16.0
15	632.3 ± 12.2	295.1 ± 16.5	447.4 ± 17.3

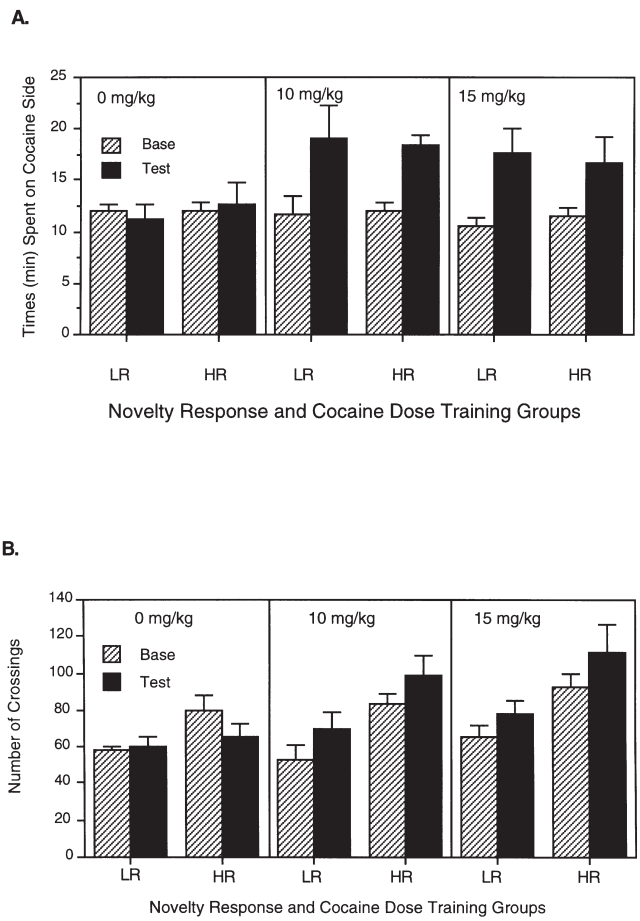

FIG. 1. Three sets of rats assigned to novelty response groups (high responders: HR and low responders; LR) were trained with one dose of cocaine (0, 10, or 15 mg/kg; n = 6/group) in a place-conditioning procedure. Panel A presents minutes spent on the cocaine-paired side during the 30-min baseline session (base; hatched bars) and during the 30-min test session (closed bars) by novelty response group and cocaine dose training group. Cocaine supported place-conditioning with no novelty group differences seen. Panel B presents the number of crossings made between compartments during the baseline session (base; hatched bars) and during the test session (closed bars) by novelty response and cocaine dose training group. Compared to LR, HR rats showed significantly greater numbers of crossings overall. Both groups exhibit a greater number of crossings on the test session compared to the baseline session.

significant novelty response group effect, $F(1, 30) = 20.39$; $p < 0.0001$ overall and by this significant effect on both baseline, $F(1, 30) = 23.78$; $p < 0.0001$, and test, $F(1, 30) = 7.53$; $p < 0.01$, sessions. Both novelty response groups show increased numbers of crossings after cocaine exposure, as seen in Fig. 2B, consistent with the lack of significance seen for the novelty response group × session type interaction.

EXPERIMENT 2: NOVELTY RESPONSE AND COCAINE LOCOMOTOR SENSITIZATION

This study examined whether locomotor response to novelty was associated with differences in the acute locomotor activating effect of cocaine and to the sensitization of this effect. This experiment was performed to determine whether our procedure for classifying rats into HR and LR groups was comparable to that used in previous studies, which did show that novelty response predicts acute locomotor response to psychoactive drugs (8,10,12,14,21,23). A second purpose was to examine further the suggested effect from Experiment 1 in which novelty response group was associated with differences in activity overall, as measured by numbers of crossings in a shuttlebox apparatus, but not with the differential effects of cocaine of increasing this level. Using a similar cocaine dose and exposure regimen, one set of HR and LR rats received four cocaine exposures prior to the locomotor activity test with cocaine (15 mg/kg) while another set of HR and LR rats received four saline exposures prior to this test. The dose of cocaine chosen for this study was based on Experiment 1 and on observations in our laboratory that this dose reliably induces locomotor sensitization to cocaine after four, daily cocaine exposures.

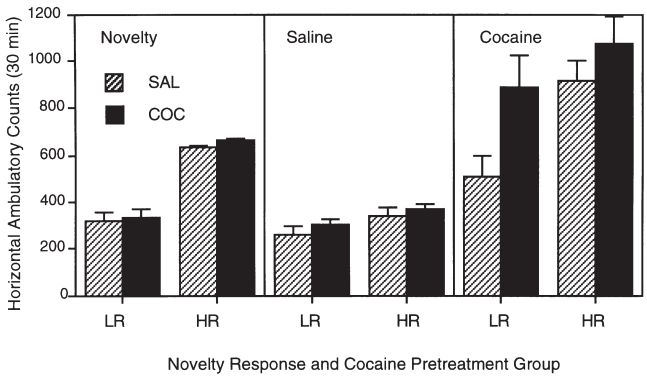

FIG. 2. Two sets of rats were assessed for novelty locomotor response during the novelty test session (30 min). Rats were classified into novelty response groups, High responders (HR) and low responders (LR), and assigned to one of two treatment groups, COC ($n = 8$ each) or SAL ($n = 6$ each). All rats received saline injections on the saline test session and were assessed for locomotor activity during a 30-min session. Next, COC groups (closed bars) were administered four IP cocaine injections (15 mg/kg) once per day while the SAL groups (hatched bars) were administered IP saline injections during this time. On the following cocaine test session day, all rats received IP cocaine injections (15 mg/kg) and were assessed for locomotor activity for 30 min. This figure presents horizontal, ambulatory activity counts by novelty response and cocaine treatment groups on the novelty, saline, and cocaine test sessions. Cocaine increased locomotor activity to a greater extent in HR rats compared to LR rats. The COC groups showed greater activation compared to the SAL groups, indicating locomotor sensitization occurred. However, there was no novelty response group difference in locomotor sensitization to cocaine.

Method

Subjects. Two sets of four HR and four LR rats were obtained from two screenings of 32 rats and assigned to the cocaine (COC) treatment group (i.e., *n*s = 8/novelty response group). One set of six HR and six LR rats was obtained from one of the screenings of 40 rats each and assigned to the saline (SAL) treatment group. Data from the SAL treatment groups will provide an index of the effect of novelty response group on the acute locomotor activating effects of cocaine. Comparisons of these data to those obtained from the COC treatment groups will provide an index of the effects of novelty response group on sensitization to the locomotor activating effects of cocaine.

Apparatus. The same locomotor apparatus used in the novelty response screening session was used for this experiment.

Procedure. On the day after screening for novelty response (day 1), rats were given saline injections and placed in the locomotor apparatus for 30 min on three consecutive days (days 2–4). Three days later, on day 7, HR and LR rats in the COC treatment groups were injected with cocaine (15 mg/kg, IP) and placed in the locomotor apparatus for 30 min. HR and LR rats in the SAL treatment groups were injected with saline and placed in the locomotor apparatus for 30 min. This schedule was repeated daily for three more sessions (days 8–10). On day 11, all rats in both treatment groups received cocaine injections (15 mg/kg, IP) and placed in the locomotor apparatus.

Data analysis. Total number of light beam interruptions over the 30-min sessions was used as a measure of horizontal, ambulatory activity. Data from the novelty screening session (day 1), the last saline administration day (day 4), and the cocaine administration test session (day 11) will be presented. Because rats were assigned to novelty response group (HR or LR) based on their response in the novelty screening sessions, data from this session will not be used in the analyses of locomotor sensitization to cocaine. Data from the saline and cocaine sessions were analyzed using a $2 \times 2 \times 2$ ANOVA with novelty response group and cocaine treatment group as between subjects factors and session as a repeated measure factor.

Results

As seen in the left panel of Fig. 2, there were no differences in novelty locomotor responses between treatment groups (i.e., the two HR groups did not differ statistically from each other nor did the two LR groups; *p*s > 0.10). Further, the activity levels seen in these novelty response groups are similar to those found in Experiment 1, as seen in Table 1. Thus, rats assigned to their respective novelty response groups for this experiment were likely comparable to those tested in the previous experiment.

Figure 2 presents locomotor activity data from the saline administration session and from the cocaine test session by novelty response and cocaine treatment group. Prior to the cocaine session, the COC treatment groups had received four cocaine administrations and were placed in the locomotor apparatus, whereas the SAL treatment groups had received four saline administrations. Comparison of locomotor activity on the saline session to that seen on the cocaine session reveals that acute cocaine administration increases locomotor activity and that this effect is enhanced by prior cocaine treatment. These statements are supported by the significant Session effect, $F(1, 24) = 69.56$; $p < 0.0001$, the significant cocaine treat-

ment group effect, $F(1, 24) = 7.13$; $p < 0.02$, and the trend for a significant interaction of these effects, $F(1, 24) = 3.42$; $p < 0.08$, Further, there is no significant effect of cocaine treatment group for the saline session ($p > 0.10$), but this effect is significant for the cocaine session, $F(1, 30) = 5.29$; $p < 0.05$. As seen in Fig. 2, the COC treatment groups showed greater locomotor activity compared to the SAL treatment groups on the cocaine session. Thus, the cocaine dose and treatment procedure used in this experiment does result in the expected results of enhanced locomotor activity with acute cocaine administration and with the sensitization of this effect with repeated cocaine administration.

There is a significant effect of novelty response group on locomotor activity. As seen in Fig. 2, HR rats exhibit higher levels of locomotor activity compared to LR rats, an effect that tends to be greater on the cocaine session. These statements are supported by the significant novelty response group effect, $F(1, 24) = 10.42$; $p < 0.005$, and the trend for a significant interaction of novelty response group × session type, $F(1, 24) = 3.45$; $p < 0.08$. The novelty response group × cocaine treatment group interaction and the interaction of these effects with session failed to reach significance ($ps > 0.10$). However, inspection of Fig. 2 suggests that LR rats show a greater effect of cocaine treatment on locomotor activity than HR rats. This is supported by the significant cocaine treatment group effect for LR rats, $t(10) = 2.23$; $p < 0.05$, and by the lack of this effect for HR rats ($p > 0.10$).

EXPERIMENT 3: HABITUATION OF LOCOMOTOR RESPONSE TO NOVELTY

Habituation to novelty has been suggested to influence outcome measures of place conditioning (30) and locomotor sensitization (11), although other research does not support this contention (1,22). And, rats that differ in novelty locomotor responses differ in the habituation of this response; HR rats show greater habituation than LR rats (24). Yet, the results of Experiment 1 and previous research (9,12) show that HR and LR rats do not differ in the place-conditioning effects of drugs. This experiment seeks to replicate this habituation effect in order to determine whether our procedure for classifying rats into HR and LR groups was comparable to that used in previous studies in which novelty response groups differ in habituation of these responses (24). Locomotor responses were assessed over three sessions, including the novelty screening session, with each session separated by 10 days. This 10 day period was chosen because it approximates the number of total training and test sessions in the previous two experiments.

Method

Subjects. Seven HR and seven LR rats obtained from one screening of 52 rats were used.

Procedure. Rats were screened for novelty response in the locomotor apparatus for 30 min on the first session and assigned to novelty response groups. Locomotor activity was measured 10 days after the screening test and again 10 days after the test session in 30 min sessions.

Data analysis. Total number of light beam interruptions over the 30-min sessions was used as a measure of horizontal, ambulatory activity. Data were analyzed using two separate three-way ANOVA with session as a repeated-measure factor. Novelty response groups were analyzed separately because rats were classified into groups based on locomotor activity measures.

Results

Figure 3 presents the locomotor activity for HR and LR rats on the novelty and two test sessions. As seen in Fig. 3, HR rats show higher locomotor activity compared to LR rats, which is to be expected because they were assigned to a novelty response group based on activity levels shown on Test session 1. HR rats show a decrease in activity levels across sessions, as supported by the significant Session effect, $F(2, 33) = 8.28$; $p < 0.005$. In contrast, LR rats do not show a decrease in activity levels across sessions ($p > 0.10$). Thus, HR rats habituate to novelty and LR rats do not, a finding to be expected given their classification to groups based on novelty locomotor responses.

DISCUSSION

The results of the present study show that novelty locomotor response is associated with the habituation of locomotor responses and with the acute locomotor activating effects of cocaine, but not with the place conditioning effects or with the locomotor sensitizing effects of cocaine. The lack of novelty response group effects in place-conditioning and locomotor sensitization cannot be attributed to failures to show these behavioral effects of cocaine in the present study. These results replicate previous research that categorized novelty locomotor response groups based on a median split and extend it to groups classified by extreme response differences (e.g., the highest and lowest 15%) in the present study. This study also shows that number of crossings between sides of the place-conditioning apparatus, which differ by novelty response group, increases after cocaine training. The latter effect, which did not differ by novelty response group, suggests that conditioned activation occurs in place conditioning and that this effect is dissociated from measures of conditioned place preference.

Habituation of locomotor responses with repeated exposures to the apparatus is seen for HR, but not LR, rats similar to a previous study (24). The lack of habituation in LR rats is not surprising, because their level of response is low initially. Novelty locomotor response is also associated with the acute locomotor activating effects of cocaine, consistent with previous research (8,10,12,14,21,23), but there are no group differ-

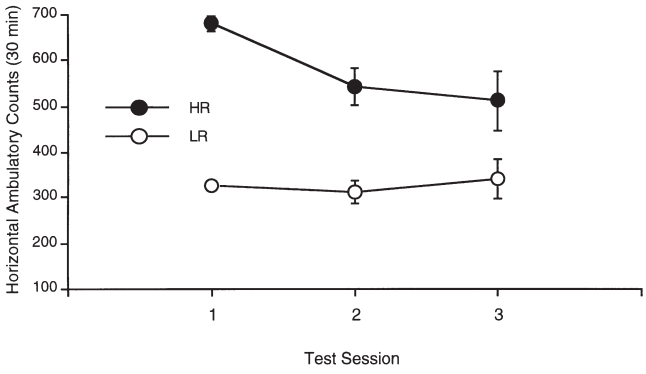

FIG. 3. Rats were assessed for novelty locomotor response during the 30-min novelty (test session 1) and assigned to novelty response groups: high responders (HR; closed circles) and low responders (LR; open circles). Locomotor activity was assessed in two subsequent sessions that occurred 10 days apart. Locomotor activity decreased over session (i.e., habituation occurred) for HR rats, but not for LR rats.

ences in the sensitization of this effect in the present study. Previous research has not consistently shown novelty response group differences in locomotor sensitization (10,13,14) even though repeated drug administration abolishes these group differences in acquisition of amphetamine self-administration (23). The lack of novelty group differences in cocaine locomotor sensitization may reflect a "ceiling" effect for HR rats in that the high level of locomotor activity seen with acute cocaine administration cannot be enhanced by repeated cocaine exposure. Indeed, when data from each novelty response group are analyzed separately, LR rats show sensitized responses, whereas HR rats do not.

Novelty locomotor response is not associated with differences in cocaine place conditioning in the present study, consistent with previous place conditioning studies with amphetamine (9) and cocaine (12). The negative findings with place conditioning is at odds with studies on acquisition of drug self-administration (23,24), but this may reflect procedural differences. First, acquisition of self-administration studies typically utilize low doses (23,24) and the cocaine doses (10 and 15 mg/kg) used in the present study are moderately high. However, no novelty response group difference is seen with lower doses (9,12). Second, novelty response group differences may have occurred if fewer than four cocaine administrations were used as this number is sufficient to abolish group differences in acquisition of self-administration (23). Yet, Erb and Parker (9) report that with one drug administration, LR rats tend to show greater place conditioning than HR rats. Third, repeated exposure to cocaine or to the context in which cocaine was administered may have masked a potential difference between HR and LR rats (6). Fourth, if novelty response group differences are seen only when threshold doses are used then the lack of group differences in place conditioning may reflect that this procedure does not show a robust dose response relationship. Indeed, there are no differences in the degree of place conditioning seen with the doses used in the present study or in the Gong et al. (12) study. Finally, the discrepant findings between self-administration and place conditioning may reflect differences in response requirements: self-administration requires rats to perform a response to obtain the drug injection, whereas this requirement does not exist for place conditioning.

Compared to LR rats, HR rats show greater numbers of crossings between compartments in the shuttlebox-shaped, place conditioning apparatus, consistent with locomotor activity levels assessed in the circular locomotor apparatus. Novelty response groups do not differ in this measure in the Gong et al. (12) study, perhaps because that study categorized rats based on a median split. Numbers of crossings increased with cocaine training and, because no cocaine was administered on the baseline, precocaine exposure or on the postcocaine exposure tests, this suggests that the increased responses reflect a conditioned effect. Thus, the data from the present study suggest that inherent and conditioned activity responses, as measured by number of crossings in the place conditioning procedure, are dissociated from measures of place preference (i.e., time spent in the drug-paired compartment). Further, this demonstration of a dissociation between inherent- and cocaine-conditioned activity from place conditioning is in contrast to results from previous place conditioning studies using other procedures for manipulating activity levels (32,33). These earlier studies report that place conditioning is compromised either by restraining the animal during conditioning (32) or by decreasing the size of the conditioning environment (33) even though conditioned increases in activity levels are seen. The utilization of LR and HR rats in the present study avoids the potential of stress effects that may have occurred in these other studies and appears to have permitted the demonstration of conditioned activity increases in a place-conditioning procedure with rats. Previous research using rats has not shown this effect [e.g., (27)], although it has been seen for mice (7), probably due to the large variability incurred by employing outbred rats.

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