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Individual differences in novelty- and cocaine-induced locomotor activity as predictors of food-reinforced operant behavior in two outbred rat strains

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Abstract

A goal of the current study was to determine if individual differences in cocaine-induced locomotion, which has been shown in outbred Sprague–Dawley (SD) rats to be correlated with differential function of dopamine transporters, were also evident in Long–Evans (LE) rats. Another objective was to determine if differences in locomotion following exposure to novelty or cocaine predicted food-reinforced behavior. Between-strain comparisons of open-field activity revealed similar effects of 10 mg/kg cocaine, although increases in rearing were prominent in LE rats. Both strains exhibited robust individual differences in cocaine-induced locomotion, with nearly identical ambulatory behavior observed in low and high cocaine responders (LCRs and HCRs, respectively) from the two strains. In a cued-discrimination operant task, LE rats learned the contingency in fewer sessions, whereas SD rats obtained more food pellets at fixed ratio 10 and maintained higher progressive ratio (PR) breakpoints. HCRs from both strains also tended to maintain higher PR breakpoints; low and high responders to novelty (LR and HR, respectively) had no consistent differences in food-reinforced behavior. Overall, these studies suggest that wide individual differences in cocaine-induced behavior are common to SD and LE strains and certain differences in food-reinforced behavior are associated with HCRs compared to LCRs.

Keywords: Cocaine; Novelty; Individual differences; Operant behavior; Progressive ratio; Strain differences; Open-field activity

1. Introduction

Initial sensitivity to the effects of cocaine (Schafer and Brown, 1991; Lambert et al., 2006) and numerous other abused drugs (Haertzen et al., 1983; Fergusson et al., 2003) is predictive of the development of long-term use and dependence. Accordingly, a considerable amount of research has been directed at better understanding individual differences in behavioral responses to drugs of abuse and their underlying neurobiological substrates. In humans, for example, individual differences in the mood enhancing and stimulant effects of amphetamine have been linked to specific genetic markers of dopamine system function (Mattay et al., 2003; Veenstra-VanderWeele et al., 2006) and with differences in monoamine transporters (Lott et al., 2005, 2006). A low response to alcohol's motor incoordination and intoxicating effects is associated with an increased risk for alcoholism (Schuckit and Smith, 1996) and allelic variation in the regulatory region of the serotonin transporter gene SLC6A4 (Hinckers et al., 2006).

Studies utilizing animal models have demonstrated robust individual variability in a number of responses to cocaine, including its cardiovascular effects (Branch and Knuepfer, 1994), locomotor-stimulant effects (Sabeti et al., 2002; Gulley et al., 2003; Saka et al., 2004), capacity to produce behavioral sensitization (Mayfield et al., 1992; Pierce et al., 1996), and its ability to reinforce operant behavior (Tornatzky and Miczek, 2000; Mantsch et al., 2001; Panlilio et al., 2003). Experiments designed to assess if individual differences in initial sensitivity to cocaine's locomotor-stimulant effects predict responses to repeated cocaine exposure have revealed that Sprague–Dawley (SD) rats with reduced locomotor responses to 10 mg/kg

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cocaine ("low cocaine responders," or LCRs) exhibit greater locomotor sensitization following seven days of treatment, compared to rats with an initially high locomotor response to the drug ("high cocaine responders", or HCRs; Sabeti et al., 2003). Differences between LCRs and HCRs do not appear to be due to dissimilar reactivity to an inescapable novel environment or to pharmacokinetic factors (Gulley et al., 2003), but instead are related to differences in the function of dopamine transporters in the dorsal striatum and nucleus accumbens (Sabeti et al., 2002, 2003). In particular, cocaine appears to differentially regulate DAT trafficking in the striatum of HCRs, but not LCRs (Briegleb et al., 2004).

It was reported recently that initial sensitivity to cocaine also predicts the extent of conditioned place preference (CPP) to the drug, with LCRs exhibiting a preference for a cocaine-paired environment that was absent in HCRs (Allen et al., 2007). This differential response to the rewarding effects of cocaine might reflect phenotypic differences in behavioral responses to rewards in general, without specificity for drug rewards. A goal of the present study was to address this issue by training rats characterized as LCRs or HCRs in an open-field chamber to lever press for food pellets in a two-lever, cued-discrimination task. Because the open-field in which rats were tested was initially novel, the extent to which responses to inescapable novelty were predictive of behavior in the operant task could also be determined. This was beneficial given the suggestions (Mitchell et al., 2005; Marinelli, 2005) that the well-documented relationship between novelty-induced locomotion and propensity for stimulant self-administration (Piazza et al., 1989) might be related more to differences in learning to respond for a positive reinforcer rather than to individual differences in the reinforcing effects of drugs, per se. Another goal of the present study was to determine if the robust individual differences in the locomotor-stimulant effects of 10 mg/kg cocaine that were described previously for male SD rats (Mayfield et al., 1992; Sabeti et al., 2002; Gulley et al., 2003) would also be evident in another outbred strain, the Long–Evans (LE) rat.

2. Methods

2.1. Animals

The subjects for these studies were outbred, male SD ($n=59$) and LE ($n=58$) rats that were obtained from commercial vendors (Harlan; Indianapolis, IN or Simonsen Laboratories; Gilroy, CA) or bred in our animal facility from stock rats originally obtained from these vendors. Rats were 2.5–3.5 months old at the start of experiments, housed on a 12-h light/dark cycle (lights on at 0800), and maintained with free access to water. Food was available ad libitum until after behavioral characterization in the open-field chamber, when rats were maintained at 85–90% of their free-feeding weight. All animal-use procedures were consistent with the *Principles of Laboratory Animal Care* (NIH Publication no. 85–23) and were approved by the IACUC at the University of Illinois, Urbana-Champaign.

2.2. Open-field activity

Measurement of locomotor activity was done in an open-field activity apparatus consisting of a clear acrylic box (40.6 × 40.6 × 40.6 cm) fitted with a lower ("horizontal") and upper ("vertical") photobeam frame (16 beams per dimension; Coulbourn Instruments; Allentown, PA). The activity chamber was located inside a 76 × 80 × 63 cm sound attenuating cubicle that had a 76 mm speaker mounted on the inside of one wall and two ceiling-mounted white lights (4 W each) that provided dim illumination. Affixed between the two lights was a ceiling-mounted camera. White noise (70 dB) was played continuously through the speakers when rats were in the testing room. Each open-field apparatus was connected to a nearby computer running software (TruScan, v 2.01; Coulbourn Instruments) that recorded both horizontal and vertical beam breaks (500 ms sampling rate).

After they were acclimated to the testing room for at least 30 min, rats were placed in the open-field for a 90-min habituation period. They were then removed from the chamber, injected (i.p.) with either saline (1 ml/kg) or (−) cocaine HCl (10 mg/kg) and returned to the chamber for 60 min. This dose was chosen because previous studies (Sabeti et al., 2002; Gulley et al., 2003) revealed that it produced the widest range of locomotor activation in SD rats. Ambulatory behavior (i.e., locomotion, head movements and sniffing) was recorded as successive horizontal photobeam breaks (i.e., coordinate changes) that were subsequently converted to distance traveled (cm). Rearing behavior was tabulated as number of entries (i.e., photobeam breaks) in the vertical plane.

2.3. Food-reinforced behavior

A subset of animals tested in the open-field for their response to cocaine ($n=20$ SD and 18 LE rats) were maintained at 85% of their free-feeding weight and subsequently trained to lever press for 45-mg food pellets in standard operant chambers (Coulbourn Instruments). The chambers contained two retractable levers located on either side of a central food trough. Above each lever was a white cue light. Rats were first trained in overnight sessions with only one lever extended at a time; they were continuously reinforced (i.e., FR1) for pressing on this lever when the cue light above it was illuminated. Delivery of food pellets was accompanied by an auditory stimulus (the sound of the pellet feeder motor) and illumination of a cue light located within the food trough. After 2–4 of these overnight sessions, rats were allowed daily 1-h sessions in the chambers. In the daily sessions, which were completed between 0900 and 1800 h, both levers were extended but only responses on the active lever (indicated by illumination of the cue above it) were reinforced. Responses on the inactive lever ("incorrect" response) resulted in retraction of both levers and a 15-s timeout period. Rats remained at FR1 until ≤20% of their total responses were on the inactive lever for 5 consecutive sessions. Subsequently, the ratio requirement was increased over several sessions to FR10, where rats remained for 5

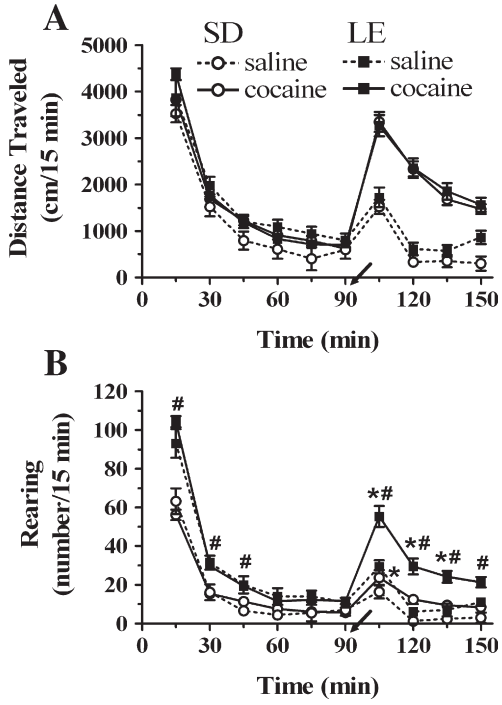

Fig. 1. Cocaine-induced behavior was similar, but not identical, between strains. Mean ambulatory activity (A) and rearing (B) is shown in 15-min bins for the 90 min before and 60 min after injection (arrow denotes injection time) of 10 mg/kg cocaine (n=48 SD and 46 LE rats) or saline (n=11 SD and 12 LE rats). Saline- and cocaine-induced increases in ambulation were very similar between strains, whereas increases in rearing were most prominent in LE rats. For cocaine-injected rats: $^{*}p<0.05$, within strain vs. 90 min; $^{\#}p<0.05$, compared to SD at the indicated time point.

sessions. Lastly, rats were given three operant sessions with a PR schedule of reinforcement. In these sessions, rats were required to perform an increasing number of lever presses on successive trials (1, 2, 4, 6, 9, 12, 15, 20, etc.) according to the following equation: Response requirement (rounded to the nearest integer)=$[5e^{(\text{trial number}\times 0.2)}]-5$ (Richardson and Roberts, 1996). The session terminated 30 min after the rat received its last reinforcement or after 2 h, whichever occurred first.

2.4. Data analysis

Unless otherwise noted, data in the text and figures are presented as mean values±SEM. Measures of ambulatory and rearing behavior in the open-field were summed in 15-min bins. For characterization of rats based on their response to cocaine, animals with horizontal locomotor scores below the distribution median for the 30-min period following cocaine (t=90–120 min) were considered LCRs; those with scores above the median were considered HCRs. For re-characterization based on their response to novelty, these rats were split into low and high responders (LRs and HRs, respectively) if their horizontal locomotor activity scores fell below and above, respectively, the distribution median for the first 30 min the rats spent in the open-field chamber (t=0–30 min). The statistical significance of differences in open-field activity between SD and LE rats was determined with a mixed, two-factor ANOVA (strain×time, with time as the repeated measure). Two-factor ANOVA (strain×type) was used when data from individual strains were separated into groups based on cocaine response (LCR or HCR).

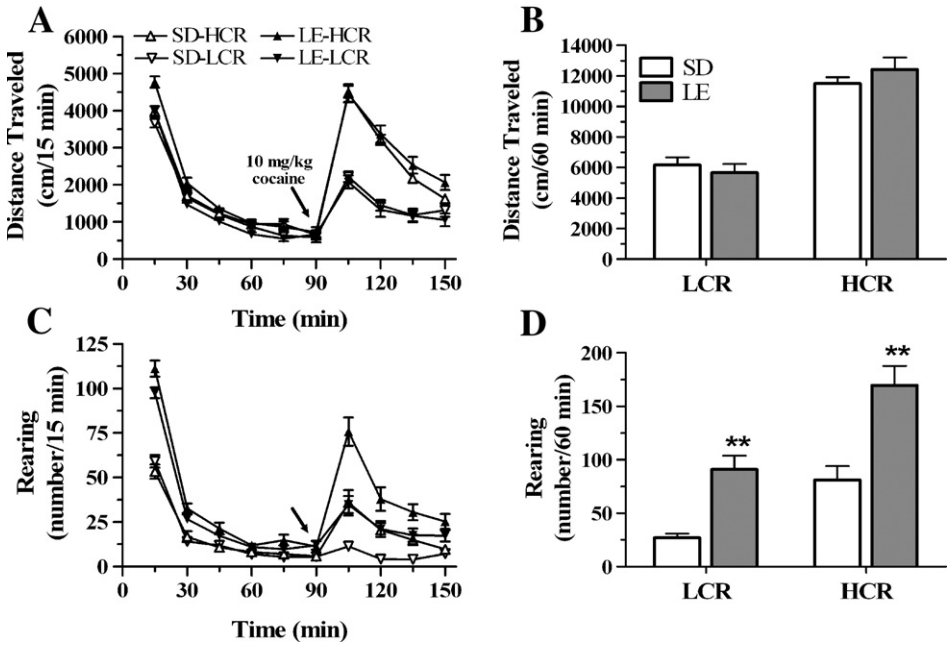

Fig. 2. In both strains, there were pronounced individual differences in cocaine-induced locomotion. Rats (n=48 SD and 46 LE) were classified as LCRs or HCRs based on the locomotor response to cocaine during the first 30 min after injection (see Fig. 1): LCRs were below the median and HCRs were above it (SD median=5730 cm/30 min; LE median=5838 cm/30 min). The time course of open-field activity before and after cocaine injection for LCRs and HCRs in both strains is shown in A and C, and the cumulative response for the entire 60-min period following cocaine is shown in B and D. $^{***}p<0.001$, LCR compared to HCR (collapsed across strain) in panel B; $^{***}p<0.001$, SD compared to LE in panel D.

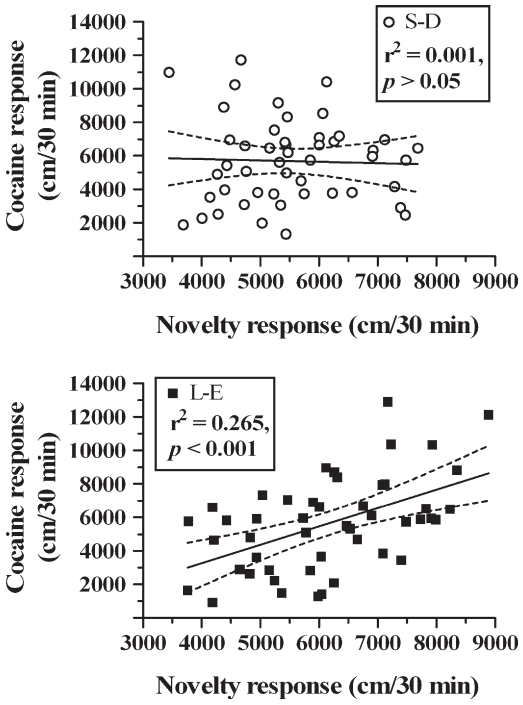

Fig. 3. Locomotor response to cocaine is predicted by response to novelty in LE, but not SD, rats. Values for novelty response are the cumulative distance traveled during the first 30 min rats spent in the open-field chamber; values for cocaine response are the distance traveled during the 30-min following 10 mg/kg cocaine injection. For both strains, the linear regression fit (–) and 95% confidence intervals (- -) are shown. Statistical analysis revealed that the slope of the regression line was significantly different from zero in the LE strain of rats ($F_{1,44}=16.6$, $p<0.001$), but not in the SD strain ($F_{1,46}=0.05$, $p>0.05$).

Where appropriate, post-hoc analyses were performed using Tukey tests.

Multiple dependent measures of food-reinforced behavior were analyzed for potential differences between strains (SD and LE) or characterization type (LCR/HCR or LR/HR). Sessions to criteria was defined as the number of training sessions at FR1 that were necessary for rats to demonstrate five consecutive sessions with ≤20% of their total lever press responses on the incorrect lever. Percent correct was defined as the percentage of total lever press responses that occurred on the active lever. For sessions with a PR schedule of reinforcement, breakpoint was defined as the number of lever presses required for the last successfully completed ratio requirement. Total number of reinforcements obtained at FR1, FR10, and PR schedules was also tabulated. One-way ANOVA was used to determine the statistical significance of strain differences in operant behavior. Two-factor ANOVA (strain × type) was used when data from individual strains were separated into groups based on cocaine (LCR or HCR) or novelty response (LR or HR), with Tukey post-hoc tests used for comparisons between different PR sessions. Pearson correlation was used to evaluate the relationship between PR breakpoint and locomotor activity during response to novelty (first 30 min in the open-field) and cocaine (first 30 min after injection). One SD rat was removed from the study after it completed operant training at FR1 because it stopped lever pressing for food pellets when the ratio requirement was increased to FR10.

2.5. Drugs

(−)-Cocaine HCl was obtained from the National Institute on Drug Abuse (RTI International, Research Triangle Park, NC). It was dissolved in sterile saline (0.9% NaCl) and the dose was calculated as the weight of the salt.

3. Results

3.1. Open-field activity

Fig. 1 shows the time course of locomotor activity in SD and LE rats ($n=48$ and 46, respectively), before and after injection with 10 mg/kg cocaine. Statistical analysis of ambulatory activity (i.e., distance traveled) revealed a significant main effect of time ($F_{9,828}=203$, $p<0.001$), with a non-significant main effect of strain ($p=0.535$) and a non-significant strain × time interaction ($p=0.170$). Analysis of rearing revealed significant main effects (strain: $F_{1,92}=74.4$, $p<0.001$; time: $F_{9,828}=182$, $p<0.001$) and a significant interaction ($F_{9,828}=18.1$, $p<0.001$). The highest levels of locomotor activity were observed when rats were first exposed to the open-field chamber (Fig. 1), and this novelty-induced behavior was most pronounced in LE rats. Post-hoc analysis of rearing behavior revealed strain differences at time points between 15 and 45 min. For the remaining 45 min before injection, rats from both strains exhibited habituation to the environment. Observation of rats during this time revealed that most were resting or sleeping against one side of the chamber during most of this period.

Following injection of 10 mg/kg cocaine, there was a significant and prolonged increase in locomotor activity for the remainder of the test period. Cocaine-induced ambulatory activity was similar in SD and LE rats, but changes in rearing were more pronounced in LE rats (Fig. 1B). For SD rats, significant increases in rearing were only observed during the first 15 min following injection ($t=105$ min) and rearing during the entire post-injection interval was significantly lower than that observed in LE rats. In a separate group of rats given an injection of saline ($n=11$ and 12 for SD and LE rats, respectively), strain differences in novelty-induced activity were observed and were similar to those seen in the cocaine-treated groups. Saline induced a modest increase in activity in both strains, although this was limited primarily to the first 15-min period following injection.

In SD rats, the range and median of cumulative locomotor activity for the 30 min following injection was 1327–11,720 cm and 5730 cm, respectively. The range of cocaine-induced locomotor activation in LE rats was more extreme (923–12,900 cm), although the median was similar (5838 cm). When rats were split into LCRs and HCRs based on each strain's respective distribution median, the resulting time course of the mean distance traveled following cocaine was nearly identical for LCRs and HCRs in the two strains (Fig. 2A). This similarity was also evident in a two-factor ANOVA (strain × type) of cumulative locomotor activity for the 60-min period following cocaine (data

shown in Fig. 2B), which revealed a significant main effect of type ($F_{1,90}=182$, $p<0.001$), a non-significant effect of strain ($p=0.735$), and no interaction ($p=0.220$). However, as shown in Fig. 2C and D, cocaine-induced changes in rearing were more pronounced in HCRs compared to LCRs (type: $F_{1,90}=26.3$, $p<0.001$) and in LE compared to SD rats (strain: $F_{1,90}=34.5$, $p<0.001$). In fact, the mean amount of rearing exhibited by LCRs in the LE strain following cocaine was equal to or slightly higher than that observed in HCRs in the SD strain (Fig. 2D). The type × strain interaction was not significant ($p=0.350$).

A notable feature of the time course data shown in Fig. 2A and C is the apparent relationship between novelty-induced behavior and rats' subsequent responses to cocaine. In particular, LE rats classified as HCRs had higher mean levels of ambulatory activity and rearing during the first 15 min in the open-field chamber compared to LE rats classified as LCRs. This predictive relationship was confirmed by linear regression analysis (Fig. 3), which demonstrated a significant relationship between novelty response and cocaine-induced locomotion. Consistent with a previous report (Gulley et al., 2003), there were no differences in mean novelty response between SD rats classified as LCRs and those classified as HCRs.

3.2. Food-reinforced behavior

A subset of rats tested for their locomotor response to 10 mg/kg cocaine were subsequently maintained at 85% of their free-feeding weight and trained in an operant chamber to lever press for food pellets in a cued-discrimination task. Of the twenty SD rats that underwent training, eleven were classified as LCRs and nine were classified as HCRs; for the eighteen LE rats trained in the task, ten were LCRs and eight were HCRs. When these rats were re-classified based on their novelty response, twelve of the SD rats were LR and the remaining eight were HR. For the eighteen LE rats, seven were LR and eleven were HR.

During the initial stage of training in the cued-discrimination task, rats were required to press an active lever, which was signaled by the illumination of an adjacent cue light, in order to receive a 45-mg food pellet. Responses on the inactive (i.e., non-cued) lever led to a 15-s TO period during which no reinforcements were available. As shown in Fig. 4A and B, rats from both strains learned to discriminate the active from the inactive lever with ~85% or greater accuracy in ~10 or fewer sessions. However, there were significant strain differences in learning, with LE rats reaching the performance criterion in 5.17±0.57 sessions and SD rats reaching it in 8.45±0.71 sessions (strain: $F_{1,36}=12.6$, $p<0.001$). We observed no significant influence of cocaine response (LCR/HCR) on learning the task (p's>0.260 for the main effect of type and the type × strain interaction) and, although the mean sessions to criterion in HRs from both strains were consistently lower than that in LRs, there were also no statistically significant effect of novelty response on learning (type: $p=0.088$; type × strain: $p>0.475$). Similarly, when rats reached the performance

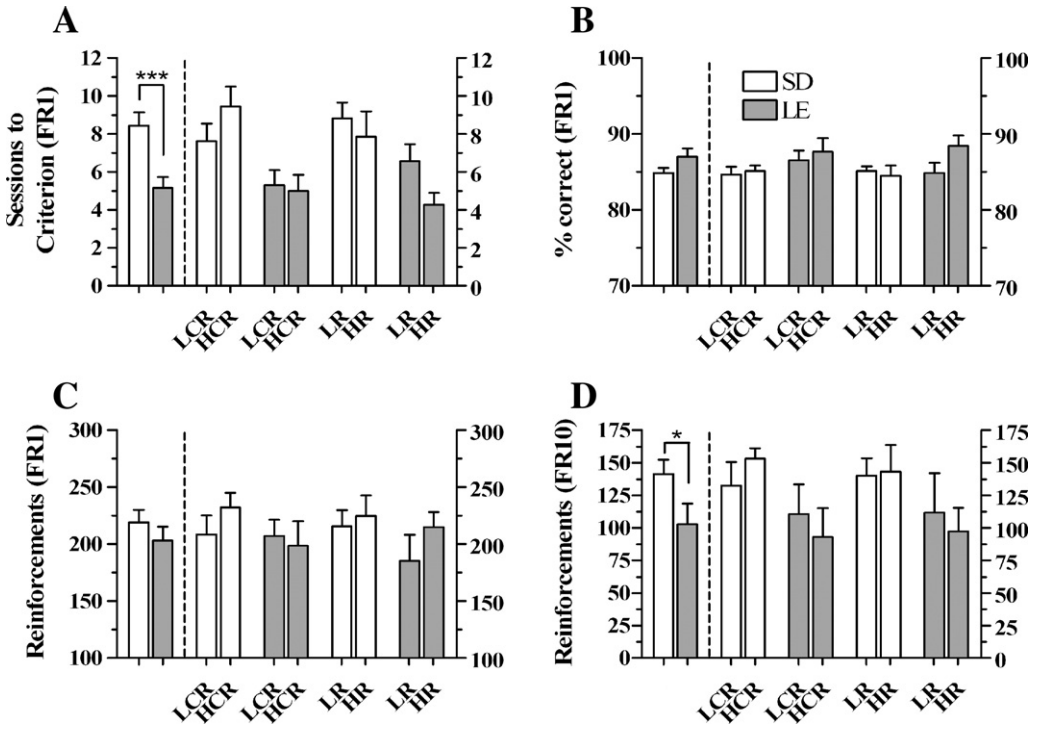

Fig. 4. SD ($n=20$) and LE rats ($n=18$) differed in learning and performance of a cued-discrimination task when reinforcement was given on an FR1 (A–C) or FR10 (D) schedule. Analyses of these data with respect to cocaine (LCR/HCR) and novelty (LR/HR) responses revealed no consistent group differences. (A) SD rats required significantly more training sessions to learn the task compared to LE rats (***$p<0.001$). Criterion performance was demonstrated when ≥80% of a rat's lever press responses occurred on the active lever for five consecutive sessions. Once rats reached criterion, there were no significant differences in the percentage of correct lever presses (B) or the total number of reinforcements obtained (C). When they were required to perform ten lever presses on the active lever to obtain a food pellet (D), SD rats earned significantly more reinforcers during the fifth session of FR10 responding (*$p<0.05$).

criterion, both accuracy (Fig. 4B) and total reinforcements obtained (Fig. 4C) were not significantly different across both strains and in all classification types. Rats were then moved from a continuous reinforcement schedule (FR1) to one requiring 10 lever presses for each food pellet delivery (FR10). As shown in Fig. 4D, LE rats obtained significantly fewer food pellets than SD rats (strain: $F_{1,36}=4.09$, $p=0.051$). There were no consistent, or statistically significant, influences of cocaine- or novelty response on the number of reinforcements at FR10.

In order to assess further potential differences in motivation to obtain food pellets, rats were moved to a PR schedule of reinforcement for the last stage of the experiment. SD rats exhibited higher breakpoints than LE rats (Fig. 5A), with statistical analysis revealing a significant main effects of strain ($F_{1,35}=3.99$, $p=0.053$) and PR session ($F_{2,35}=14.4$, $p<0.001$). The strain × session interaction was not significant ($p=0.447$). When rats were classified based on their response to cocaine, HCRs from both strains tended to achieve higher breakpoints than LCRs during initial sessions at the PR schedule of reinforcement (Fig. 5B and C). For example, during the first session, HCRs from the SD strain achieved mean breakpoints of 164±19.8 lever presses (which corresponds to 17.4±0.56 reinforcements), whereas LCRs achieved mean breakpoints of 90.2±15.5 lever presses (or 13.6±1.30 reinforcements). This LCR/HCR difference in PR breakpoint was statistically significant only during the first sessions in SD rats (Fig. 2B), whereas it was statistically significant in LE rats during the first two sessions (Fig. 2C). Analysis of Pearson correlations between PR breakpoint and locomotor response to cocaine or novelty, which ignores groupings of rats into LCR or HCR, revealed a statistically significant correlation between response to cocaine and BP for SD rats during session 1 and LE rats

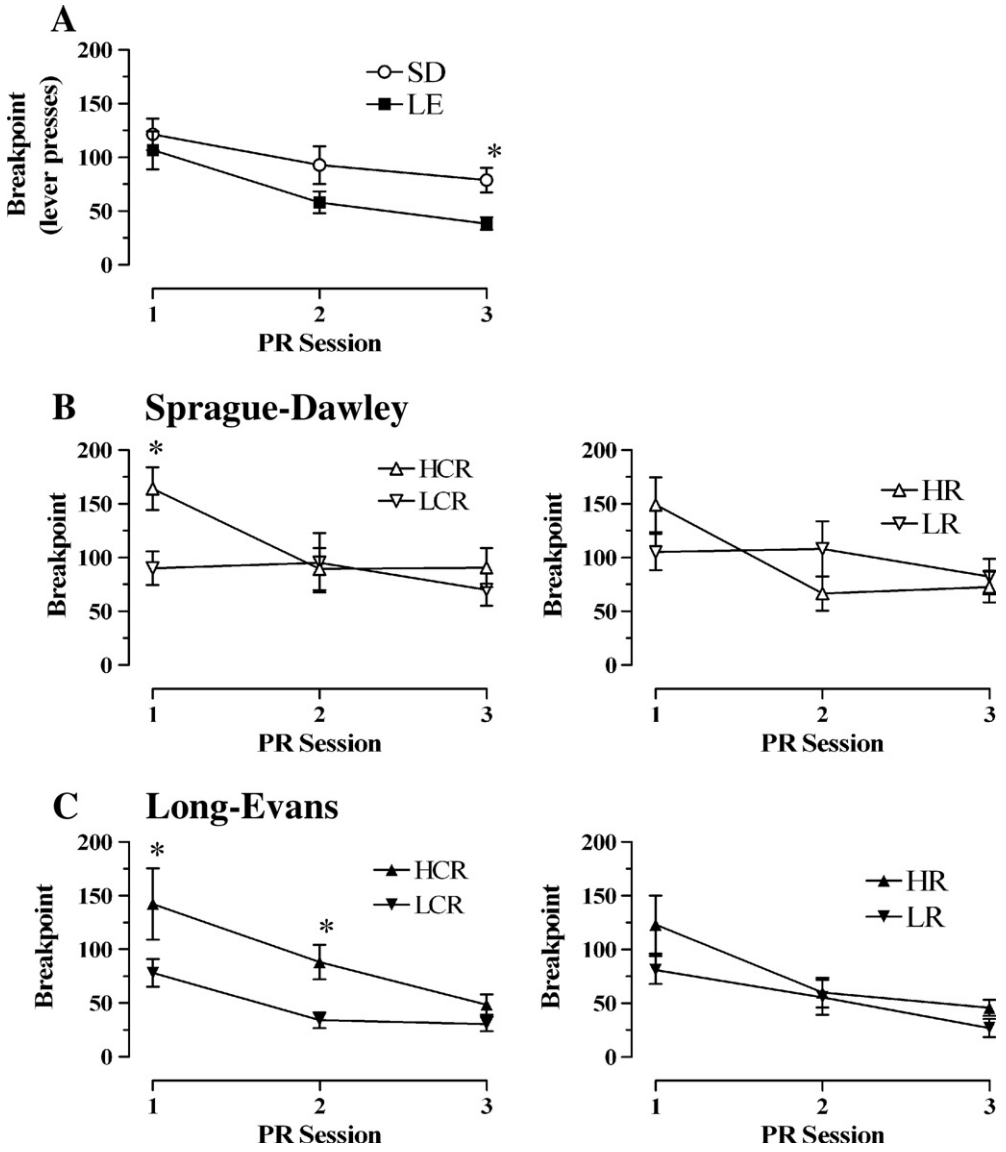

Fig. 5. When they performed the cued-discrimination task on a PR schedule of reinforcement, SD rats maintained higher breakpoints than LE rats at each of the three test sessions (A; *$p<0.05$, compared to LE at session 3). Furthermore, when data were analyzed with respect to cocaine and novelty responses (B and C), HCRs from both strains tended to maintain higher breakpoints. This effect was most prominent for LE rats during sessions 1 and 2 (*$p<0.05$). There were no consistent differences in PR breakpoint between LRs and HRs.

Table 1
Correlations between breakpoint (BP) during the three PR sessions and locomotor behavior measured during the first 30 min rats were in the open-field (novelty) or the first 30 min following injection (cocaine)

Behavior	BP — session 1		BP — session 2		BP — session 3	
	SD	LE	SD	LE	SD	LE
Novelty	0.3338	0.3847	0.1223	0.1795	0.1353	0.1910
Cocaine	0.6705**	0.4520	0.0548	0.4791*	0.3809	0.4992*

*$p<0.05$; **$p<0.01$.

during sessions 2 and 3 (Table 1). There was a trend for significance in the correlation between cocaine response and BP for LE rats during session 1 ($p=0.059$).

4. Discussion

The present study demonstrates that, compared to the behavior measured during the last portion of a 90-min habituation session or to that induced by an injection of saline, a 10 mg/kg dose of cocaine leads to significant increases in open-field locomotor activity in both SD and LE rats. Given that these rat strains are commonly used in studies of cocaine's stimulant effects on behavior, this was not surprising. However, the degree of similarity in cocaine-induced ambulatory activity between these strains was somewhat unexpected given evidence from studies that directly compared SD and LE rats in their responses to other psychostimulant drugs. For example, LE rats consistently displayed greater locomotor stimulation in response to three doses of amphetamine (0.75, 1.5 and 4.5 mg/kg) and apomorphine (0.5, 2.5 and 7.5 mg/kg; Swerdlow et al., 2006). Nicotine, given at a dose of 6 mg/kg/day for up to 10 days via osmotic minipump, produced significantly more locomotor activation in LE rats (Faraday et al., 2003). In contrast to these reports of greater stimulant behavior in LE rats, studies of the behavioral effects of cocaethylene, which is a metabolic product that results from the concurrent use of ethanol and cocaine, indicated more robust locomotor stimulation in SD compared to LE rats (Horowitz et al., 1997). The reason for the apparent discrepancy between some reports in the literature and the effects of cocaine reported here are not clear, although it does not appear to be related to differences in drug effects on rearing (Horowitz et al., 1997; Faraday et al., 2003).

In regards to cocaine's effects on open-field activity, a goal of these experiments was to determine if wide individual variability in responses was evident in both SD and LE rats. Consistent with previous reports (e.g., Gulley et al., 2003), the response of SD rats during the 30-min period following 10 mg/kg cocaine was quite variable, with low responding rats (LCRs) exhibiting approximately 8-fold less distance traveled than those having the highest responses (HCRs). In LE rats, there was a similar wide distribution of cocaine-induced locomotion. Indeed, the post-injection ambulatory activity (i.e., distance traveled) of LCRs and HCRs from the LE strain was nearly indistinguishable from LCRs and HCRs of the SD strain. However, there were noteworthy differences in the responses observed in LE compared to SD rats. For example, cocaine-induced increases in rearing were 3.4- and 2.1-fold greater in LCRs and HCRs, respectively, from the LE strain. In fact, the mean number of rearing episodes in LCRs from the LE strain (90.9 ± 13.1) was higher than those recorded for HCRs of the SD strain (81.2 ± 12.8). Another notable difference between strains was the relationship between initial response in an inescapable novel environment and cocaine-induced locomotion. Overall, LE rats were more active when the open-field chamber was relatively novel (i.e., first 30 min in the open-field), with ambulatory activity and rearing more than 11% and 88% greater, respectively, than SD rats. Similar strain differences in reactivity to novelty were reported previously (van Lier et al., 2003). A correlation analysis revealed a significant, positive relationship between novelty response and the subsequent effect of cocaine on locomotor activity in LE, but not SD, rats.

Taken together, these results suggest that robust individual differences in open-field activity induced by 10 mg/kg cocaine are not a unique characteristic of SD rats. Although some aspect of this variability might be due to random, "experimental error", this finding is significant because previous work in SD rats (Sabeti et al., 2002, 2003; Gulley et al., 2003; Briegleb et al., 2004) suggests that functional differences in dopamine transporters underlie the disparate cocaine responses in LCRs and HCRs. Given the similarity in cocaine-induced locomotion between SD and LE rats, functional differences in dopamine transporters might also be important for the LCR/HCR phenotype in LE rats. This hypothesis requires more empirical evidence, however, given the marked effects of cocaine on rearing in LE compared to SD rats and the relationship between novelty responsiveness and cocaine's effects in LE rats. Furthermore, other known differences in dopamine systems between SD and LE rats could also be contributing to strain differences in these behaviors. Compared to SD rats, for example, LE rats have been reported to have greater activity of the dopamine-synthesis enzyme tyrosine hydroxylase (Park et al., 1990), higher levels of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA; Swerdlow et al., 2005), and greater dopamine-mediated G-protein signaling in the striatum (Swerdlow et al., 2006). The strains also differ in cytochrome P450 enzyme function (Creel et al., 1976), although it is unclear if this leads to differences in brain concentrations of cocaine in SD compared to LE rats.

When a subset of rats tested in the open-field arena was trained in a food-reinforced, cued-discrimination task, we found strain differences in learning and performance. Specifically, LE rats learned the discrimination in fewer sessions compared to SD rats, when food pellets were delivered on a continuous reinforcement schedule (FR1) following a lever press on the active lever (i.e., with its associated cue light illuminated). There were no differences in percent correct responses or total number of food pellets obtained at FR1. However, when the reinforcement schedule was increased to FR10, SD rats performed significantly more lever press responses and thereby obtained more food pellets. This apparent strain difference in motivation to lever press for food pellets was also observed when a PR schedule was used — SD rats obtained higher breakpoints than LE rats. Previous studies that directly

compared learning and performance in these strains also described strain differences, but they tend to be in the opposite direction. For example, LE responded to autoshaping of a lever press response and they learned a two-object discrimination task, whereas SD rats failed to do either one (Andrews et al., 1995). LE rats also learn to self-administer the cannabinoid receptor agonist WIN 55,212-2, when SD rats do not (Deiana et al., 2007). Ultimately, strain differences may be somewhat specific to the task and/or the reinforcer used: SD rats are more accurate in a two-island swim maze task (Andrews et al., 1995) and they learn to drink more ethanol than LE rats (Gauvin et al., 1993).

When the data from the cued-discrimination task were analyzed in terms of cocaine (LCR/HCR) and novelty responses (LR/HR), there were no significant effects of these characteristics on the task when it was performed under FR1 or FR10 schedules of reinforcement. When a PR schedule was utilized, however, HCRs from both strains tended to achieve higher breakpoints than LCRs. This suggests that HCRs were more motivated to continue lever pressing for food pellets and thereby found them relatively more reinforcing than did LCRs. Thus, the hypothesis that significant CPP for intravenous cocaine in LCRs, but not HCRs, is related to phenotypic differences in response to rewards in general (Allen et al., 2007), is unlikely. Instead, it appears to be the case that that LCRs are more responsive to drug rather than non-drug reinforcers. A more direct test of this hypothesis would be a study of cocaine self-administration behavior in rats characterized as LCRs and HCRs.

Response to novelty was not a reliable predictor of learning or performance in the cued-discrimination task, regardless of the reinforcement schedule employed. These findings are at odds somewhat with those using different operant procedures and employing different reinforcers. For example, HR rats from the SD strain acquire sucrose self-administration more rapidly than LR rats, and go on to demonstrate greater self-administration of amphetamine (Klebaur et al., 2001). In addition, SD rats with higher locomotor activity in a novel environment learn to lever press for food pellets in a single-lever, FR1 task at a higher rate than those with low novelty-induced behavior (Mitchell et al., 2005). The relatively greater task demands of the present study may have influenced the results obtained here, but it is noteworthy that the lack of a predictive effect of novelty on operant behavior was relatively consistent across both strains. It is also the case that the current results are in agreement with other studies that suggest differences in drug self-administration behavior between LR and HR rats are specifically related to the differences in reinforcer efficacy between the phenotypes (Piazza et al., 2000). Thus, in general, the results of the current study fail to support the hypothesis that locomotor response to novelty is predictive of a general ability to learn a reinforcement contingency rather than being predictive of responses to drug reward per se (Mitchell et al., 2005; Marinelli, 2005).

In summary, the results of the present study substantiate that the wide range of initial sensitivities to the locomotor-activating effects of cocaine in an open-field arena, which have been detailed for SD rats (Sabeti et al., 2002; Gulley et al., 2003), is also observed in LE rats. Individual differences in ambulatory activity were similar between the strains, but LCRs and HCRs from the LE strain had significantly more cocaine-induced rearing responses than those from the SD strain. Furthermore, response to inescapable novelty reliably predicted response to cocaine in LE, but not SD, rats. Future studies will be necessary to determine how strain differences in neurobiological function, such as in important dopamine system regions like the striatum and nucleus accumbens, contribute to cocaine-induced locomotion compared to rearing in these strains. In light of what is known about the role of dopamine transporters in the differential response of SD rats to cocaine, however, it is plausible that a similar mechanism contributes to the differences in cocaine-induced behavior in LE rats. The findings in rats trained in the two-lever, cued-discrimination task, emphasize that SD and LE rats have different learning and performance capabilities in operant behavior settings and that these are influenced by both the nature of the task and the particular reinforcer employed. They also support the view that the LCR/HCR and LR/HR phenotypes do exhibit differences in some aspects of their response to non-drug reinforcers, but that their differential response to reward in a CPP or operant self-administration context is somewhat specific to particular features of drug rewards. Because food restriction is known to alter the behavioral response to psychostimulant drugs (Carr, 2006) and the function of dopamine transporters (Zhen et al., 2006), future studies will be necessary to determine if the food restriction that was utilized in the cued-discrimination experiments had differential effects on rats exhibiting the LCR/HCR or LR/HR phenotypes.

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