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Individual differences in rats' reactivity to novelty and the unconditioned and conditioned locomotor effects of methamphetamine

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Abstract

Rat's reactivity to inescapable novelty can predict the subsequent psychomotor effects of many stimulants. This relation has not been examined for methamphetamine. Experiment 1 assessed the locomotor effects of methamphetamine (0.0625–1.0 mg/kg). On average, acute administration of methamphetamine (0.25, 0.5, and 1 mg/kg) had a stimulant effect on activity; locomotor sensitization was seen after repeated administration of 0.5 and 1 mg/kg. In a subsequent drug-free test, rats that had the locomotor chamber paired with 0.25, 0.5, or 1 mg/kg methamphetamine on eight separate occasions were more active than controls—conditioned hyperactivity. Experiment 2 used the 0.5-mg/kg dose to examine whether forced novelty exposure (novelty-induced activity) or free-choice novelty (approach to novel environment or object interaction) was predictive of methamphetamine's psychomotor effects. Only reactivity to inescapable novelty was systematically correlated with methamphetamine-induced activity. Rats more reactive to novelty [high responders (HR)] were more active to the acute and chronic methamphetamine challenge. Furthermore, these HR showed more conditioned hyperactivity than low responders (LR). Although acute methamphetamine did not have a stimulant effect in LR, only the LR displayed locomotor sensitization after chronic methamphetamine. This research extends the predictive variable of reactivity to inescapable novelty to methamphetamine's conditioned and unconditioned locomotor effects.

Keywords: Activity; Associative learning; Context conditioning; Drug abuse; Individual differences; Locomotor stimulant; Methamphetamine; Novelty; Object interaction; Rat; Sensitization

1. Introduction

In the last 15 years, the drug abuse field has seen a significant increase in research with nonhuman animals attempting to identify variables that predict individual differences in reactivity to abused drugs. This increase in interest followed a report by Piazza et al. (1989) in which activity induced by confined exposure to a novel environment was related to rats' sensitivity to the acute psychomotor stimulant effects of D-amphetamine sulfate (1.5 mg/kg) and the acquisition of amphetamine self-administration (10 μg per infusion). That is, rats more reactive to the inescapable novel environment were more active when challenged with amphetamine and more readily self-administered amphetamine. This predictive relation between reactivity to inescapable novelty and subsequent behavioral effects of abused drugs has been observed across many laboratories, with many different drugs of abuse, and with several different measures of a drug's effect. For example, in rodents, novelty-induced activity also predicts later activity induced by caffeine, cocaine, ethanol, and morphine (Deroche et al., 1993; Gingras and Cools, 1996; Hooks et al., 1992), sensitivity to the discriminative stimulus effects of amphetamine (Exner and Clark, 1993), amphetamine-conditioned hyperactivity and conditioned taste avoidance (Jodogne et al., 1994; Kunin et al., 2001), ethanol self-administration (Gingras and Cools, 1995; Nadal et al., 2002), and nicotine enhancement of a T-maze visual discrimination (Besheer and Bevins, 2000). This predictive relation between novelty-induced activity and the behavioral effects of drugs is not universal. The most notable exception is the lack of relation between reactivity to inescapable novelty and the ability of drugs, such as morphine, cocaine,

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and amphetamine, to condition a place preference (Erb and Parker, 1994; Gong et al., 1996; Xigeng et al., 2003).

(+)-Methamphetamine hydrochloride is a potent locomotor stimulant and these stimulant effects tend to increase (i.e., sensitize) with repeated exposure to the drug (Dews, 1953; Fujiwara et al., 1987; Itzhak, 1997). The ability of novelty-induced activity to predict these unconditioned locomotor effects of methamphetamine has not been investigated. Accordingly, one goal of the present research was to determine whether reactivity to inescapable novelty was correlated with the initial (acute) and chronic locomotor-activating effects of methamphetamine. The individual difference research with amphetamine suggests that rats more reactive to a novel environment should be more sensitive to the locomotor-activating effects of amphetamine (cf. Bevins et al., 1997; Hooks et al., 1991). Interestingly, if stimulant drug administration (e.g., amphetamine or nicotine) reliably occurs in the presence of a distinct environment, then that environment (context) can acquire through associative (Pavlovian) learning processes the ability to evoke increases in activity above controls even in the absence of any drug (Bevins et al., 2001; Palmatier et al., 2003; Stewart, 1992; Wise and Leeb, 1993). This cue-evoked increase in activity likely reflects a conditioned association between the context and the locomotor-activating effects of the drug (e.g., Stewart, 1992). Acquisition of amphetamine- and food-conditioned hyperactivity to environmental cues is positively correlated with novelty-induced activity (Hooks et al., 1994b; Jodogne et al., 1994). Thus, another goal of the present research was to determine whether reactivity to inescapable novelty predicted methamphetamine-conditioned hyperactivity controlled by a distinct environment (context).

The main focus of this report was on reactivity to an inescapable novel environment as an individual difference screen given its ability to predict sensitivity to the psychomotor effects of stimulant drugs. However, there is an interesting distinction in the individual differences literature between "forced" exposure to novelty and "free-choice" exposure to novelty. Forced exposure to novelty, such as the inescapable environment, is thought to evoke physiological responses associated with stress. Indeed, much published research is consistent with this notion. For example, confined exposure to a novel environment increases plasma levels of corticosterone (Oitzl et al., 1997). Furthermore, the greater this increase in corticosterone, the more active the rat is in the inescapable novel environment (Piazza et al., 1989). Presumably, the positive correlation between reactivity to forced exposure to novelty and the locomotor-activating effect of stimulants reflects at least partial overlap in the neurobiological processes mediating stress (for a review, see Piazza and LeMoal, 1996). In contrast, situations that allow the rat to choose whether to approach or avoid novelty seem to measure some other process besides stress sensitivity (e.g., sensation seeking; see Bardo et al., 1996, for a review). Interestingly, these free-choice tasks (e.g., novel object interaction) predict the ability of amphetamine and morphine to condition a place preference (Klebaur and Bardo, 1999; Robinet et al., 1998; Xigeng et al., 2003). As noted earlier, forced exposure to novelty does not consistently predict place conditioning effects (Erb and Parker, 1994; Gong et al., 1996; Xigeng et al., 2003). Conversely, the forced exposure, but not free-choice exposure, predicts locomotor activity and drug self-administration (e.g., Gingras and Cools, 1995; Klebaur et al., 2001; Nadal et al., 2002; Piazza et al., 1989). This brief review suggests that behavior in a forced, but not free-choice, novelty task will predict rats' sensitivity to the locomotor effects of methamphetamine. Accordingly, we also screened rats on two free-choice tasks—approach to a novel environment and interaction with a novel object.

Before we could assess individual difference in sensitivity to methamphetamine, we first had to conduct an experiment identifying a dose of methamphetamine that (1) has acute stimulant effects on locomotor activity, (2) produces locomotor sensitization following chronic administration, and (3) engenders a hyperactive conditioned response to contextual cues. To accomplish this task, the first experiment in this report assessed the unconditioned and conditioned locomotor effects of a wide range of methamphetamine doses (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg). Then, in the second experiment, a separate set of rats was screened for individual differences before treatment with one of the doses of methamphetamine (i.e., 0.5 mg/kg).

2. Materials and methods

2.1. Subjects

The subjects were 73 experimentally naive male Sprague–Dawley rats, 200–224 g on arrival, from Harlan (Indianapolis, IN). They were housed individually in plastic tubs lined with aspen shavings. Rats had free access to water and food in the home cage. All experimental sessions were conducted during the light portion of a 12-h light/dark cycle (lights on approximately 0630 h). Experimental protocols were approved by the University of Nebraska-Lincoln IACUC and followed the *Principles of laboratory animal care* (NIH publication No. 85-23, revised 1985).

2.2. Drug

(+)-Methamphetamine hydrochloride (Sigma/RBI, St. Louis, MO) was mixed in saline (0.9% NaCl) at a concentration of 1 mg/ml and injected intraperitoneally at a volume of 1 ml/kg. Doses are reported in the salt form.

2.3. Activity chambers

Located in a room separate from the animal colony were eight circular chambers made from white PVC pipe. The inside diameter of each chamber was 30.5 cm; the top edge of the chamber was 45 cm from the wire-mesh floor. Each

chamber was equipped with two infrared emitter/detector units mounted 4 cm above the floor, such that they divided the chamber into four equal sections. Each beam break was sent to an interface and then recorded by a personal computer. Activity was defined as the number of infrared beam breaks in the session. General room illumination was provided by fluorescent ceiling lights and a continuous 80-dB white noise served to mask external sounds.

2.4. Experiment 1: Methamphetamine dose–effect function

2.4.1. Conditioning

Rats were assigned to one of six groups ($n = 7–8$ per group). Five of the groups received the locomotor chamber repeatedly paired with methamphetamine − 0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg. Rats in the sixth group served as an unpaired control group and did not experience methamphetamine in the presence of the chamber (i.e., injected with saline). Thus, once daily for eight consecutive days, each rat was injected with its assigned solution and then placed in the chamber for 30 min. To control for exposure to methamphetamine, rats in the unpaired control group ($n = 8$) were divided into four pairs. Each rat in a pair received an injection of methamphetamine (0.125, 0.25, 0.5, or 1.0 mg/kg) in the home cage about 4 h after removal from the locomotor chamber. Because activity for the pairs of rats did not differ, Ps $\geq .717$, we pooled them into one control for analyses and display in figures. To control for injection experience, rats in the other groups received a saline injection in the home cage.

2.4.2. Drug-free test

To assess whether the chamber (context) acquired the ability to evoke a conditioned increase in activity by virtue of being paired with methamphetamine, 24 h after the last conditioning trial (Day 9), each rat was injected with saline and placed in the chamber for 30 min (i.e., drug-free test).

2.4.3. Data analyses

The activity data during conditioning was first analyzed using a two-way mixed factorial analysis of variance (ANOVA). The between-groups factor was methamphetamine dose [0.0 (unpaired), 0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg] and the within-subject repeated measure was conditioning trial (1 to 8). A one-way ANOVA was used for activity data during the drug-free test. Dunnett's multiple comparison tests were used to determine whether methamphetamine-paired groups differed from the unpaired control group. Statistical significance was set at a two-tailed α of .05 for all tests.

2.5. Experiment 2: Individual differences

2.5.1. Novelty-induced activity (inescapable environment)

Rats' ($n = 30$) initial reactivity to an inescapable novel environment was measured by placing each rat in a circular chamber for 30 min. The primary dependent measure in the correlation matrix was the total number of beam breaks in the 30-min session (see Table 2).

2.5.2. Novelty approach (unfamiliar environment)

This individual difference screen started 4 to 6 days after measuring novelty-induced activity. Two similar three-compartment wood chambers, housed in a room different from the activity chambers, were used to index approach to an unfamiliar environment. One end compartment, $31 \times 24 \times 45.5$ cm ($L \times W \times H$), had white walls and a mesh floor with pine chips lining the litter tray. The other similar-sized end compartment had black walls and a rod floor with newspaper lining the litter tray. A smaller middle compartment ($15 \times 24 \times 45.5$ cm) with gray walls and an aluminum floor separated the end compartments. The experimental room was illuminated with fluorescent lights and a white-noise generator provided an 80-dB masking noise. Rats were first familiarized with the black compartment for 10 min. On the following day, the solid center walls were lifted 11 cm, such that when each rat was placed in the center gray area, it could freely explore each end compartment for the 10-min test. An 8-mm camera mounted above the chambers recorded the test sessions. These tapes were later used to observe time in each end compartment and number of compartment entries. A rat was considered in a compartment when both front paws were located in that compartment (cf. Bevins et al., 2002). The primary dependent measures in the correlation matrix were time and number of entries into the novel (white) environment. We purposefully did not have the novel environment be black with mesh flooring for half the rats because this could have biased behavior in this screen, such that individual differences might have been due to differences in approach tendencies to the environment features rather than to differences in approach tendencies to a novel environment.

2.5.3. Novelty approach (unfamiliar object)

The day following the last test for approach to the novel environment was a 2-min test of novel–object interaction. Rats were placed against the outside wall of the white end compartment; located against the outside wall of the black end compartment was the novel object—a paint roller (7.5 cm long, 4 cm diameter) attached to a plastic scouring pad (9 cm diameter). The main dependent measures in the correlation matrix were time spent interacting with the object and the number of contacts. Object interaction was scored from video tapes. Only "directed" contacts with nose or front paws were scored as object interaction. This definition precludes such behaviors as standing on the object looking upward (rearing) or brushing the object with tail or side (cf. Bevins et al., 2002).

2.5.4. Methamphetamine challenge (conditioning and testing)

Following the novel–object test, rats were randomly assigned to either the paired or unpaired group ($n = 15$/

group). All paired rats had 0.5 mg/kg methamphetamine paired with the chamber; rats in the unpaired group had saline injected intraperitoneally immediately before placement in the activity chamber. All other procedural details for conditioning and testing were similar to Experiment 1 except all rats in the unpaired group received 0.5 mg/kg of methamphetamine in the home cage about 4 h after exposure to the chambers. The first conditioning trial occurred 3 days after the last individual difference screen.

2.5.5. Data analyses

To confirm that random assignment of rats to paired and unpaired groups resulted in no systematic differences, performance on each individual differences measure was compared using pairwise *t* tests. Activity across conditioning trials employed a two-way ANOVA with group (paired versus unpaired) as one factor and trial (1 to 8) as the repeated measure. A pairwise *t* test was used to compare activity on the test for locomotor conditioning.

2.5.6. Individual differences

We first conducted Pearson's correlations using the measures from the individual differences screens and locomotor activity on Trial 1 (acute), Trial 8 (chronic), and drug-free test (conditioned activity) separately in paired and unpaired rats. An individual difference screen that systematically predicted methamphetamine activity was subjected to more detailed analysis. As described in the Results section, the only screen that prompted additional analysis was activity induced by the inescapable novel environment. Accordingly, for each condition, we converted the total number of beam breaks during the 30-min exposure to the novel chamber to a *z* score (cf. Bevins and Besheer, 2001). A *z* score was calculated using the following formula: ((individual's value − group mean)/standard deviation for the group) (Hoel, 1960). Rats with positive *z* scores (upper portion of the activity distribution) were classified as high responders (HR); rats with negative *z* scores were deemed low responders (LR). We then examined HR and LR on Trial 1, Trial 8, and the conditioning test in two ways. First, activity for paired and unpaired HR (and separately for LR) was compared with *t* tests to determine whether, relative to saline, there was differential sensitivity to the unconditioned and conditioned locomotor effects of methamphetamine. Second, activity on these days (Trials 1 and 8, and test) was converted to *z* scores before statistically comparing the paired and unpaired conditions separately for rats classified as HR and LR on inescapable activity. By normalizing the activity data with a *z*-score conversion before this analysis (i.e., all distributions had a mean of 0 and a standard deviation of 1), we could determine whether HR and LR on novelty-induced activity changed their relative position in the distribution across experimental treatment. Notably, *z* scores are less susceptible to rate-dependency effects because a methamphetamine-treated rat with 800 activity counts can be in the same relative position in the distribution as a saline-treated rat with 300 counts. Thus, comparing *z* scores allowed us to determine whether LR on inescapable novelty remained in the lower portion of the distribution although this subset of rats displayed a greater degree of sensitization than HR. That is, will HR remain HR and will LR remain LR? If so, HR, on average, will have a positive *z* score and LR will have a negative *z* score. Note that nonsystematic changes in relative position in the distribution will result in an average *z* score around 0 (see Bevins and Besheer, 2001, for further discussion of this approach).

3. Results

3.1. Experiment 1: Methamphetamine dose–effect function

Fig. 1A shows the activity counts for each group across the eight conditioning trials. There was a main effect of dose, $F(5,37) = 22.80$, $P < .001$. Although the main effect of trial was not significant, $F(7,259) = 1.57$, $P = .143$, there was a significant Trial × Dose interaction, $F(35,259) = 2.71$, $P < .001$. Post hoc Dunnett *t* tests comparing the overall activity levels across each methamphetamine-treated group to the unpaired control revealed that overall activity levels were higher in rats treated with 0.25, 0.5, and 1.0 mg/kg methamphetamine, $Ps \leq .001$. The significant interaction suggests that activity differentially changed across groups. To determine the source of the interaction and limit the number of statistical contrasts, we calculated a difference score between activity on Trial 1 and Trial 8 for each rat (see Fig. 1B) and then determined whether each group differed significantly from a hypothetical value of 0 (i.e., no change in activity from first to last trial). The difference score for the unpaired group and the two lower doses of methamphetamine was significantly below 0, indicating a decrease in general activity by the eighth trial, $ts \geq 3.24$, $Ps \leq .018$. Rats treated daily with the two highest doses of methamphetamine (0.5 and 1.0 mg/kg) were significantly above 0, $ts \geq 2.81$, $Ps \leq .031$, suggesting that the locomotor-activating effects of methamphetamine sensitized by the last conditioning trial.

Fig. 1C displays the activity data from the drug-free test for conditioning. There was a significant main effect of dose, $F(5,37) = 10.35$, $P < .001$. Relative to the unpaired controls, there was significantly more activity in the groups that were conditioned with the 0.25-, 0.5-, and 1.0-mg/kg doses of methamphetamine, $Ps < .007$.

3.2. Experiment 2: Individual differences

Fig. 2A shows the activity counts for the paired and unpaired group across the eight conditioning trials. There was a main effect of group, $F(1,28) = 90.14$, $P < .001$, indicating more activity in the 0.5-mg/kg methamphetamine-treated rats (paired group). Although the main effect of trial was not significant, $F(7,196) = 1.31$, $P = .248$, there

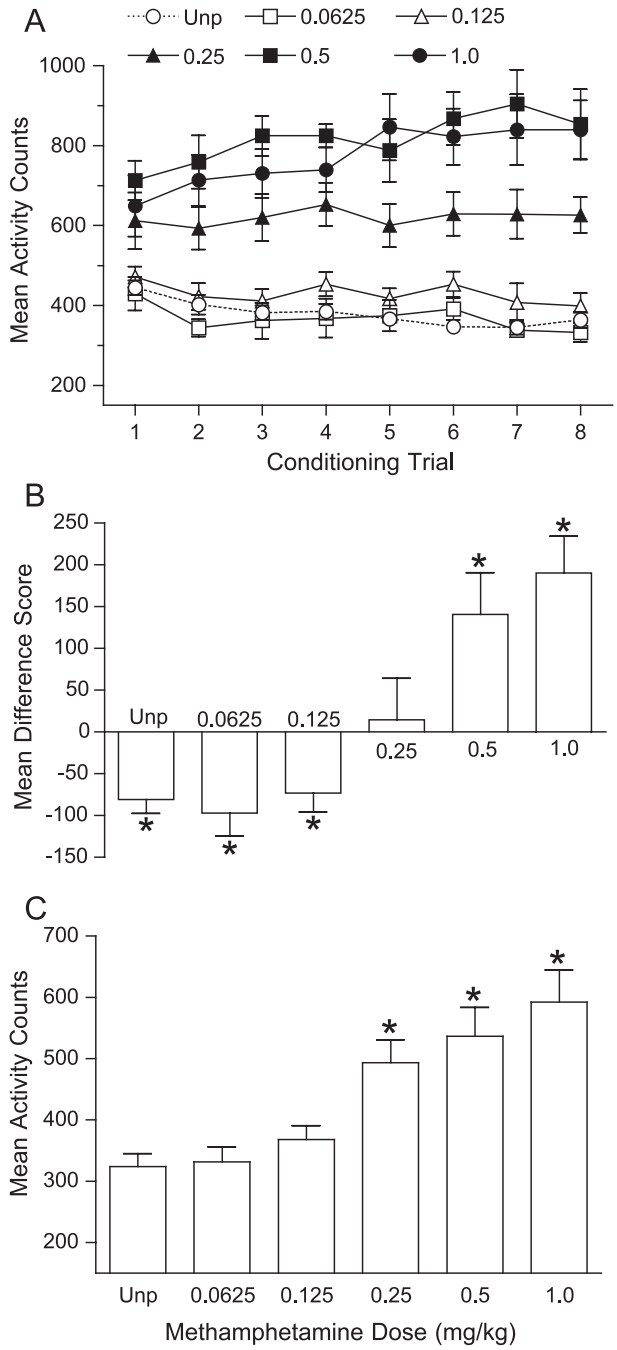

Fig. 1. Panel A displays the mean activity counts (±1 S.E.M.) across conditioning trials for each methamphetamine dose and the unpaired (Unp) controls in Experiment 1 (*n*s = 7 to 8). Panel B shows the average difference between the first and last conditioning trial for each group. Asterisks (*) denote a significant difference ($P \leq .05$) from a hypothetical value of 0. Panel C displays the mean activity counts for the drug-free test for conditioning. Asterisks (*) denote a significant difference from the unpaired control.

was a significant Trial × Dose interaction, $F(7,196) = 9.69$, $P < .001$. The significant interaction suggests that activity differentially changed across groups. Indeed, the difference score between activity on Trial 1 and Trial 8 for the unpaired group (-146 ± 22) was significantly below 0, $t(14) = 6.75$, $P \leq .001$, indicating a decrease in activity by Trial 8. The difference score for the paired group (144 ± 44) was significantly above 0, $t(14) = 3.24$, $P = .006$, suggesting that the locomotor-activating effects of methamphetamine sensitized by the last conditioning trial. Fig. 2B shows the activity data from the test for conditioning. There was significantly more activity in the paired group than in the unpaired group, $t(28) = 5.17$, $P < .001$, replicating the methamphetamine-conditioned hyperactivity of Experiment 1.

Given that novelty-induced activity, novel environment approach, and novel–object interaction were assessed before any experimental manipulations, it is not surprising that performance for groups paired and unpaired on each individual difference screen did not differ statistically (see Table 1 for descriptive statistics and *t*-test results). Table 2 shows the correlation between each individual difference screen and the acute, chronic, and conditioned (test) methamphetamine activity. For paired and unpaired rats, there was a significant positive correlation between number of contacts with the object and the total time spent interacting with the object. That is, as directed contacts increased, so did the

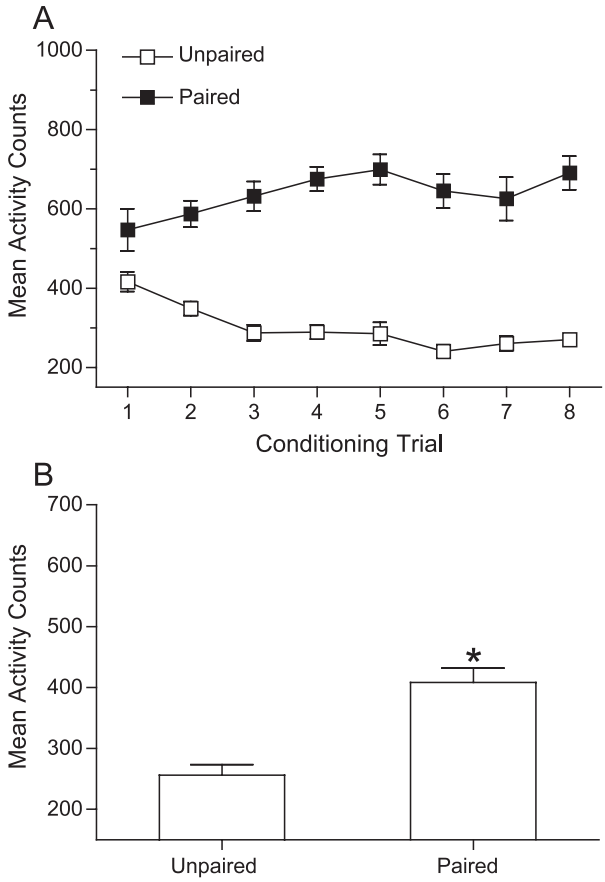

Fig. 2. Panel A displays the mean activity counts (±1 S.E.M.) across methamphetamine (0.5 mg/kg) conditioning trials for the paired and unpaired groups of Experiment 2 ($n = 15$ per group). Panel B shows the average number of activity counts for the drug-free test for conditioning. Asterisk (*) denotes a significant difference ($P \leq .05$) from the unpaired control.

Table 1
Descriptive statistics for Experiment 2 behavioral screens

Screen	Group	Mean (±1 S.E.M.)	*t* Value	*P* value
Novel act	Unpaired	483 (±25)	0.473	.640
	Paired	466 (±27)		
Enviro time	Unpaired	164 (±10)	0.786	.438
	Paired	174 (±9)		
Enviro entry	Unpaired	11.2 (±0.6)	1.779	.086
	Paired	12.6 (±0.5)		
Obj time	Unpaired	32.9 (±2.2)	1.549	.133
	Paired	37.6 (±2.1)		
Obj contact	Unpaired	10.7 (±0.7)	1.030	.312
	Paired	11.8 (±0.7)		

Novel act = novelty-induced activity; Enviro = novel environment; Obj = novel object.

total duration of object interaction. Interestingly, a similar correlation did not exist between number of entries into novel environment and total time spent in that environment.

For the unpaired group, there were no systematic correlations across the conditioning and test phases. The two significant correlations that occurred involved the novel environment screen. However, the correlations were in the opposite direction. That is, time spent in the novel environment was positively correlated with test-day activity, yet number of entries into the novel environment was negatively correlated with activity on the first conditioning session (acute). Given the chance of a Type I error is 1 in 20, we are hesitant to overinterpret these two nonsystematic correlations. In contrast, for the paired group, activity induced by an inescapable novel environment was systematically and significantly correlated with methamphetamine-induced activity (acute and chronic), as well as with conditioned activity evoked by the environment on the test day. That is, those rats more reactive to inescapable novelty were also more sensitive to the unconditioned and conditioned locomotor-activating effects of methamphetamine. Furthermore, acute and chronic (sensitized) activity induced by methamphetamine was positively correlated with each other and with test-day activity. The only other significant correlation was between contacts with the object and chronic methamphetamine-induced activity. A similar positive correlation was not seen for acute or test-day activity levels.

Given the systematic nature of the correlations between novelty-induced activity and the conditioned and unconditioned effects of methamphetamine (0.5 mg/kg) in the paired group, we followed up these correlations with the *z*-score split of HR and LR described in the Materials and methods section. For comparison purposes, a similar split was conducted on the unpaired group. Rats in the upper portion of the distribution (positive *z* score) for novelty-induced activity were classified as HR (paired group $n=7$; unpaired group $n=6$), whereas rats in the lower portion of the distribution (negative *z* score) were designated LR (paired group $n=8$; unpaired group $n=9$). Fig. 3A shows acute, chronic, and test session activity counts for HR (left half) and LR (right half). Paired rats classified as HR were consistently more active than their comparable unpaired control, $ts(11)\geq 2.76$, $Ps\leq .019$. Paired rats classified as LR were more active than its unpaired control after repeated treatment with methamphetamine, $t(15)=7.05$, $P<.001$, and on the test day, $t(15)=2.74$, $P=.015$. Thus, in contrast to the HR, LR were not sensitive to the acute locomotor-activating effects of methamphetamine. Visual comparison of acute and chronic activity for HR and LR treated with methamphetamine suggests that only the LR showed locomotor sensitization. Indeed, eight of eight rats classified as LR displayed an increase in activity from Trial 1 to Trial 8, $P=.003$, and had an average difference score (195 ± 34)

Table 2
Pearson's correlations (*r*) among the behavioral screens of Experiment 2

	Enviro time	Enviro entry	Obj time	Obj contact	Acute	Chronic	Test
Unpaired							
Novel act	−.165	.189	−.025	−.151	.252	.466	−.173
Enviro time	–	.281	.168	.306	−.182	−.074	.537*
Enviro entry	–	–	−.320	−.053	−.570*	−.024	.377
Obj time	–	–	–	.781**	.183	−.219	−.468
Obj contact	–	–	–	–	.195	−.070	−.077
Acute	–	–	–	–	–	.521	−.144
Chronic	–	–	–	–	–	–	−.104
Paired							
Novel act	−.130	.361	.183	.294	.637*	.657**	.654**
Enviro time	–	−.323	−.119	−.351	−.338	−.348	−.289
Enviro entry	–	–	.510	.192	−.064	.378	.356
Obj time	–	–	–	.598*	−.111	.314	.082
Obj contact	–	–	–	–	.311	.543*	.244
Acute	–	–	–	–	–	.592*	.548*
Chronic	–	–	–	–	–	–	.869**

Novel act = novelty-induced activity; Enviro = novel environment; Obj = novel object.
* $P\leq .05$.
** $P\leq .01$.

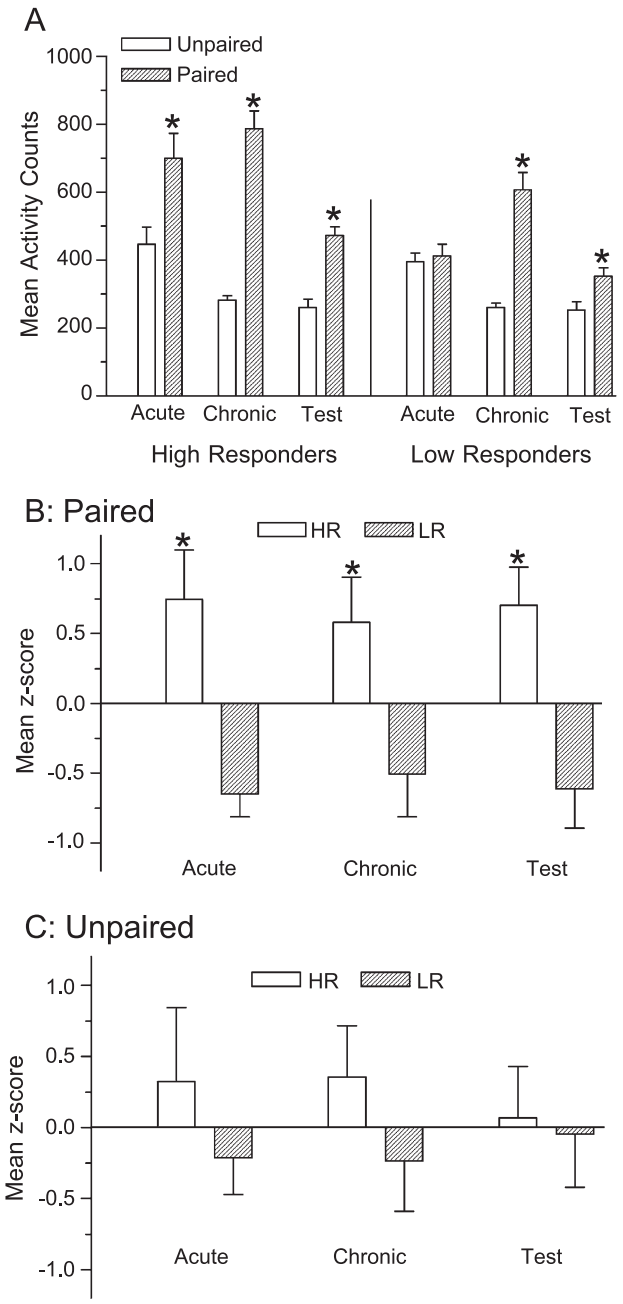

Fig. 3. Panel A shows the mean activity counts (+1 S.E.M.) after the first (acute) and eighth (chronic) administration of methamphetamine (0.5 mg/kg ip), and the activity from the drug-free test for rats classified as HR or LR based on reactivity to inescapable novelty. Asterisks (*) denote a significant difference ($P \leq .05$) from its comparable unpaired control. Panels B and C show the mean z-score values for HR and LR for the paired and unpaired conditions, respectively, from the acute, chronic, and test day of Experiment 2. Asterisks (*) denote a significant difference ($P \leq .05$) from the comparable LR.

significantly above 0, $t(7) = 5.68$, $P < .001$. However, only four of the seven rats classified as HR displayed an increase in methamphetamine-induced activity, $P = .273$. Furthermore, the difference in activity from Trial 1 to Trial 8 for these HR (86 ± 85) did not differ significantly from 0, $t(6) = 1.01$, $P = .352$.

For the paired group (see Fig. 3B), HR remained in the upper portion of the distribution on the first exposure to methamphetamine (acute), on the eighth exposure (chronic), and on the test for conditioning. This observation was supported by a significant difference between HR and LR at each measure, $ts(13) \geq 2.44$, $Ps \leq .03$. Thus, paired HR remained HR and paired LR remained LR regardless of the observation that LR were the only rats to display statistically significant sensitization to the locomotor effects of methamphetamine. A similar outcome was not observed for the unpaired group (Fig. 3C). The mean z scores for HR and LR was around 0, regardless, and the groups did not differ statistically on any trial, $ts(13) \leq 1.13$, $Ps \geq .278$. This pattern indicates that a subset of rats that were in the upper end of the distribution on inescapable novel activity moved to the lower end of the distribution on Sessions 1 (acute) and 8 (chronic), and on the test day; vise versa was true for LR.

4. General discussion

In the present report, we found that acute administration of methamphetamine (0.25, 0.5, and 1 mg/kg) had a stimulant effect on rats' general activity. Furthermore, locomotor sensitization occurred after repeated administration at the two higher doses. These findings replicate previously published research (Dews, 1953; Fujiwara et al., 1987; Wang and McGinty, 1995). If these stimulant effects are reliably paired with environmental stimuli, then those stimuli can come to evoke increases in activity. For example, Itzhak (1997) treated mice with 1 mg/kg ip methamphetamine for 5 days; on Days 1 and 5, mice were familiarized with the chamber for 30 min before an injection of methamphetamine and measurement of activity in that chamber; remaining injections occurred in the home cage. Controls received vehicle injections and comparable chamber exposure. Subsequently, the conditioning test occurred following 30 min of chamber familiarization. In this test, all mice were injected with saline. Methamphetamine-treated mice were more active following the injection than controls. Itzhak (1997) took this difference as evidence for methamphetamine-conditioned hyperactivity. Unfortunately, the stimuli controlling the locomotor-activating effect of methamphetamine were not clearly specified, but the most likely possibility is the injection protocol. Alternatively, because controls were not equally exposed to methamphetamine in an unpaired fashion, group differences might reflect a nonspecific effect of drug exposure.

Regardless, in the present report, we found that 0.25, 0.5, or 1 mg/kg methamphetamine paired on eight separate occasions with a distinct context (circular locomotor chamber) produced evidence for conditioned hyperactivity. That is, paired rats at these doses were more active than the unpaired control in a drug-free test. This result extends the demonstration of methamphetamine-conditioned hyperac-

tivity by Itzhak (1997) to very different conditioning parameters (e.g., dose, trial duration, number of conditioning trials, etc.) that avoid an account based on nonspecific effects altering activity in controls. On this latter point, we included an unpaired control that received equal exposure to methamphetamine (0.5 mg/kg in Experiment 2), but never in a temporally contiguous manner with the chamber cues (Pavlov, 1927).

Similar to other stimulants, such as amphetamine, cocaine, and caffeine (Deroche et al., 1993; Gingras and Cools, 1996; Hooks et al., 1992; Piazza et al., 1989), reactivity to an inescapable novel environment predicted rats' sensitivity to the locomotor effects of methamphetamine. As indicated by significant positive correlations, rats more reactive to inescapable novelty were, in general, more active to acute and chronic treatment with methamphetamine and displayed greater environment-evoked (conditioned) hyperactivity during the drug-free test. In contrast to the inescapable novelty screen, none of the free-choice screens with novelty (object interaction and approach to novel environment) systematically predicted rats' sensitivity to the behavioral-activating effects of methamphetamine. Similar to previous work, this dissociation suggests that the ability of inescapable novelty to serve as a predictive construct likely reflects its relation to the behavioral and neurobiological process of stress reactivity rather than novelty seeking (cf. Bardo et al., 1996; Dellu et al., 1996; Klebaur and Bardo, 1999; Piazza and LeMoal, 1996). Given that our primary focus was on the ability of inescapable novelty to predict the psychomotor effects of methamphetamine, we conducted this individual difference screen before any of the free-choice screens. Thus, there is the possibility that exposure to inescapable novelty had some effect on all the following screens, such that they did not correlate with methamphetamine-induced activity.

To further examine the significant correlations between inescapable novelty and the stimulant effects of methamphetamine, each rat's activity level in the inescapable novel environment was converted to a *z* score. Notably, rats in the upper portion of the distribution (positive *z* score) on inescapable activity remained HR to an acute challenge of methamphetamine. This means the LR remained in the lower portion of the distribution. However, LR that received an acute challenge of methamphetamine had similar activity levels to their respective unpaired control; HR were more active than controls. This pattern of results has some features in common with D-amphetamine. For example, Piazza et al. (1989) found that HR were more active than LR to an acute challenge of 1.5 mg/kg amphetamine. Bevins et al. (1997) found a similar result with 1 mg/kg (see also Hooks et al., 1991, with 0.5 mg/kg but not with 1 or 1.5 mg/kg amphetamine). In addition, in the present study, we found a lack of an acute response to methamphetamine in LR; a similar pattern was not reported in a study with amphetamine (0.5 mg/kg) that included the appropriate comparison condition for evaluating the degree of behavioral activation (Jodogne et al., 1994).

HR remained more active than LR after repeated treatment with 0.5 mg/kg methamphetamine. This result is especially interesting, considering that only LR displayed evidence of behavioral sensitization after chronic methamphetamine treatment. Piazza et al. (1989) reported sensitization only in LR treated with 1.5 mg/kg of amphetamine on four separate occasions. However, in that study, activity after repeated amphetamine treatment was comparable in HR and LR. Hooks et al. (1991) also found no difference in HR and LR after chronic exposure to 1.5 mg/kg amphetamine (up to nine administrations); notably though, in this study, there was no difference in acute activity, so sensitization was similar at the 1.5-mg/kg dose of amphetamine. In contrast, in this same paper, Hooks et al. (1991) reported that HR, but not LR, showed sensitization to a 1-mg/kg dose of amphetamine—a pattern opposite from Piazza et al. (1989) with 1.5 mg/kg amphetamine and from the present study with 0.5 mg/kg methamphetamine. Finally, in the drug-free test for conditioning in the present study, HR and LR were more active than comparable unpaired controls indicating that the environmental cues that compose the activity chamber entered into an association with the locomotor-activating effects of methamphetamine. Notably, HR displayed more methamphetamine-conditioned hyperactivity than LR. Jodogne et al. (1994) found a somewhat similar pattern with amphetamine (0.5 mg/kg), except only the HR displayed statistically significant evidence of conditioned hyperactivity.

Determining predictors of individual vulnerability to drugs of abuse might help practitioners tailor better prevention and intervention strategies (Donohew et al., 1990). At present, research with other drugs has begun to elucidate the neurobiological processes underlying the correlation between reactivity to inescapable novelty and the locomotor effects of these drugs. To our knowledge, the present report reflects the first paper examining the relation between the behavioral-activating effects of methamphetamine and forced exposure to novelty. Thus, conclusions as to whether the predictive relation between inescapable novelty and the behavioral-activating effects of methamphetamine reflect overlapping processes within, say, the hypothalamic–pituitary–adrenal axis and/or the mesocorticolimbic system (cf. Dellu et al., 1996; Hooks et al., 1994a; Piazza and LeMoal, 1996; van Oosten and Cools, 2002) would be too speculative at this point. However, there is clear evidence that both systems are involved in the effects of methamphetamine (e.g., Baumann et al., 2002; Brady et al., 2003; Kabbaj et al., 2003; Lowy and Novotney, 1994; Wang and McGinty, 1995). Moreover, whether the differences between methamphetamine and D-amphetamine described earlier simply reflect the procedural variations that exist across the studies (e.g., dose, apparatus design, etc.) or differences in underlying process(es) will have to await further systematic research.

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