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Individual differences in response to novelty, amphetamine-induced activity and drug discrimination in rats

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Individual differences in response to novelty, amphetamine-induced activity and drug discrimination in rats

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Rats were pre-tested in several individual difference screens – novelty-induced activity, novelty-induced place preference, novel-object interaction, and amphetamine-induced activity. Rats that were more sensitive to the locomotor effects of amphetamine were more active in an inescapable novel environment and displayed a greater preference for a novel environment. All animals were then trained to discriminate amphetamine (1 mg/kg) from saline in a two-bar discrimination procedure using food-maintained responding. After acquisition of the discrimination (mean =37 trials), two amphetamine generalization tests (0.0625, 0.125, 0.25, 0.5, 1.0 and 2.0 mg/kg) were conducted. In the second generalization test, rats that were more sensitive to the activating effect of amphetamine were also more sensitive to the discriminative stimulus effects of amphetamine (i.e. lower median effective dose). Moreover, high responders in the novelty-induced activity and novelty-induced place preference screens were more sensitive than low responders to the bar-press suppressant effects of amphetamine in the first generalization test. The relationships are discussed in terms of identifying processes common to the screens (e.g. stress and reward).

Keywords: Activity – *d*-Amphetamine – Dopamine – Operant conditioning – Place preference – Rat

INTRODUCTION

Researchers in the human drug abuse field have sought to identify variables that predict individual differences in drug abuse liability; predictive constructs such as sensation seeking and risk taking are typically examined (e.g., Zuckerman, 1984; Kosten *et al.*, 1994; Wills *et al.*, 1994). Similar research with non-human animals was uncommon until a report by Piazza *et al.* (1989), who found that the activity of rats, as measured by photobeam breaks in an inescapable novel environment, predicted subsequent self-administration of amphetamine (10 μg/infusion). Rats that were more reactive (high responders; HR) acquired and maintained amphetamine self-administration more readily than the less reactive rats (low responders; LR). In the same study, a similar relationship was observed between novelty-induced activity and the acute locomotor activating effects of amphetamine (1.5 mg/kg, intraperitoneally (i.p.)). It was argued that activity induced by novelty and by amphetamine may measure a rat's sensitivity to stress (i.e., a predictive construct). Moreover, the direct relationship between the degree of novelty-induced activity and amphetamine self administration may reflect a shared neural mechanism between stress and amphetamine (see also Antelman *et al.*, 1980; Piazza *et al.*, 1990).

Subsequent individual difference work has found that novelty-induced activity also predicts shock-induced changes in the immune system (Sandi *et al.*, 1992), cocaine- and caffeine-induced activity (Hooks *et al.*, 1992), ethanol self-administration (Gingras and Cools, 1995), amphetamine-conditioned activity to environmental stimuli (Jodogne *et al.*, 1994), and sensitivity to an amphetamine discriminative stimulus (Exner and Clark, 1993). However, reactivity to a novel environment does not predict cocaine- or amphetamine-conditioned place preference (Erb and Parker, 1994; Gong *et al.*, 1996).

The drug discrimination work by Exner and Clark (1993) is directly related to the present experiment. In that study, rats were trained to discriminate amphetamine (0.5 mg/kg) from saline in a food-maintained two-response bar discrimination task. Rats classified as LR for "escape activity" in a novel environment were more sensitive than those classified as HR to the discriminative stimulus effects of amphetamine doses below the training dose. The drug discrimination

paradigm used by Exner and Clark (1993), like the self-administration paradigm used by Piazza *et al.* (1989), is believed to be a good model for assessing the abuse potential of drugs (Overton, 1987; Yanagita, 1987; Kamien *et al.*, 1993). For instance, human subjects will categorize abused drugs in classes that roughly correspond to their pharmacological effects (Preston *et al.*, 1987; Kamien *et al.*, 1993). Moreover, researchers using drug discrimination procedures similar to those described in the present work have found that non-human animals can also classify drugs on the basis of common effects (e.g., Kuhn *et al.*, 1974; Peltier *et al.*, 1996). Identifying individual differences in the drug discrimination paradigm may thus provide insight into the behavioral and/or neural mechanisms that mediate the vast individual differences seen in drug effects in the human population (e.g. deWit *et al.*, 1986; but see Overton, 1987).

The present experiment examined the ability of several individual difference screens to predict subsequent sensitivity of high and low responders to the discriminative stimulus and rate-altering effects of amphetamine. The term "novel" or "novelty" is used to describe many of the screens employed in the present research (see below). This term refers to the fact that stimuli within the screen are unfamiliar (i.e. there is a change in stimulus conditions from previous experience). One obvious example is the novel-object interaction screen. In that screen, an unfamiliar object is introduced into an environment that had been repeatedly experienced without the object.

The individual difference screens employed in the present work were novelty-induced activity, novelty-induced place preference, novel-object interaction, and amphetamine-induced activity. Novelty- and amphetamine-induced activity screens were included because of past research indicating their predictive value as behavioral indices of stress. We included novelty-induced place preference and novel-object interaction screens because these assays may provide good behavioral measures of novelty seeking (Bardo *et al.*, 1996). Given the lack of a predictive relationship between novelty-induced activity and drug place conditioning (e.g., Erb and Parker, 1994), the reader may wonder why novelty-induced place preference was used as a screen. Two main reasons guided our choice. First, the neural processes controlling novelty preference overlap those of abused drugs (for a recent review see Bardo *et al.*, 1996). Second, novelty-induced place preference is a direct measure of the animal's preference for an environment composed of relatively unfamiliar stimuli, in much the same way as novelty-induced activity is a direct measure of locomotor behavior in the presence of unfamiliar stimuli. In contrast, place conditioning is a presumed measure of a learned association between a distinct environment and drug effects.

METHOD

Subjects

Thirty male Sprague–Dawley rats obtained from Harlan Industries (Indianapolis, IN, USA) served as subjects. Rats were housed individually in hanging stainless steel cages. Water was available continuously in the home cage. Rats had free access to food while being screened for individual differences. In the drug discrimination phase, however, access to food was restricted so that each rat was maintained at approximately 80% of its free-feeding weight. The colony room lights were on a 12 h light:dark cycle (lights on at 06.00 h). All phases of the present experiment were conducted during the lighted portion of this cycle.

Apparatus

Individual difference screening. The novelty-induced activity and the novel-object interaction screens were conducted in the white side of a three-compartment chamber. A novelty-induced place preference test employed all three compartments of this chamber. The end compartments had the inside dimensions of $29 \times 23 \times 45$ (l × w × h) cm. The wood walls of one end compartment were painted white; the other end compartment was painted black. The floor of the white compartment was made of wire mesh (13×13 mm) and the litter tray was lined with pine wood shavings. 15 rods (6 mm in diameter) spaced 2 cm apart center-to-center made up the floor of the black compartment. Cedar chips lined the litter tray of the black compartment. The smaller center compartment had inside dimensions of $19 \times 23 \times 45$ cm. Its solid wood walls and floor were painted grey. The solid walls that separated the three compartments were replaced on the preference test day with similarly painted walls that had a 10.5×10.5-cm opening in the bottom center.

Four black boxes, differing from the black compartment just described, were used in the assessment of amphetamine-induced activity. The inside dimensions of each box were $31.5 \times 29 \times 46$ cm. The flooring was 6×6-mm wire mesh with a black liner as bedding.

Drug discrimination. Six Med Associate operant boxes (ENV-001, St Albans, VT, USA) with the inside dimensions of $28 \times 21 \times 20.9$ cm were used. Each box

had stainless steel end walls and a clear Plexiglas ceiling and side walls. The floor comprised 18 metal rods (5 mm diameter) spaced 1.6 cm apart center-to-center. A recessed food tray with a 5 × 4.2 cm opening was located in the bottom center of the front panel. Situated on each side of the food tray was a metal response bar. The center of each bar was mounted 7.3 cm from the grid floor and 4.2 cm from its respective Plexiglas side wall. Centered 6 cm above each response bar was a 28-V cue light 3 cm in diameter. A computer with Med Associate interfacing controlled experimental sessions and collected data. Bar-pressing was maintained by 45 mg sucrose pellets (P.J. Noyes Co., Lancaster, NH, USA).

Procedure

Individual difference screening. On the first day of the experiment all rats were confined for 30 min to the white side of the three-compartment chamber. Activity during this initial confinement provided a measure of novelty-induced activity. Novelty-induced activity was defined as the total number of line crosses and rears made in the 30 min test session. Line crosses were scored by bisecting the chamber and counting the number of times the rat's front paws crossed the line. Rearing was defined as both front paws off the floor. If the rat reared in such a way that its front paws crossed the dividing line, only a rear was scored. On day 2, rats were again confined for 30 min to the white compartment. Day 3 was a test for novelty-induced place preference. Rats were placed in the center grey compartment and given unrestricted access to the black (novel) and the white (familiar) compartments for 15 min. A preference ratio served as the measure of novelty-induced place preference. This preference ratio equalled the time spent in the novel compartment divided by the sum of the time in both the familiar and novel end compartments. For the purpose of scoring duration, we considered the rat to be in a compartment when both front paws were in the compartment.

On day 4, each rat was again restricted to the white side of the three compartment chamber for 30 min. The novel-object interaction screen was conducted on day 5. Positioned in the center of the compartment was a novel object – a red hard plastic ball 4.5 cm in diameter. Each rat was placed into the white compartment with the object for 15 min. There were two measures of novel-object interaction: (1) number of "directed" contacts with the object and (2) the total time spent contacting the object. Directed contacts excluded interactions deemed "accidental" such as the rat backing into the object or its tail contacting the object. After the novel-object screen, rats received three separate days of 30 min exposure to the black locomotor box. On the fourth day, each rat was given an i.p. injection of saline and then placed in the black box. The rat was removed from the box 30 min later, given an i.p. injection of amphetamine (1 mg/kg), and then placed back in the box for an additional 60 min. Activity (line crosses and rears) in these 60 min provided a measure of amphetamine-induced activity. The 4-day test for amphetamine-induced activity was conducted immediately after the novel-object screen for half the rats; the remaining half started the test 5 days after the novel-object screen.

All observations were made from video tapes by several experienced observers who were not informed of the results from the amphetamine generalization phase or any individual difference screen. Reliability of initial observations (data used in analyses) was assessed for each behavior by an independent observer also naive to the performance of individual rats. Overall, there were high correlations between the independent observations of activity ($r = 0.86$, $n = 17$), duration in end compartments ($r = 0.98$, $n = 15$), number of object contacts ($r = 0.82$, $n = 26$), and duration of contacts ($r = 0.96$, $n = 26$).

Barpress training. After the last set of rats completed the amphetamine-induced activity screen, food was removed from the home cages and the rats' weights were slowly decreased to 80% of their free-feeding weights. Once rats reached their 80% weight, magazine training was initiated. Both response bars were mounted in the operant box and a sucrose pellet was automatically delivered if a bar-press occurred while training the rat to eat from the recessed food tray. Shaping of the bar-press was conducted on day 2, when only the left bar was present. For the remainder of the bar-press training phase, the bar mounted in the operant box (left or right) alternated each day. The number of responses required per pellet was incremented to 25 across daily sessions (i.e., fixed ratio 25; FR25). Unless otherwise noted, all daily sessions lasted 15 min. The onset of cue lights signaled the start of the session, and the offset of lights indicated the end of the session. Bar-press training was considered complete when the rat earned 20 pellets in two separate sessions while on an FR25 schedule of reinforcement. One rat failed to make the FR25 criterion and was dropped from the experiment, thus leaving 29 rats for the discrimination training phase.

Discrimination training. For the remainder of the experiment, both response bars were mounted in the

operant box and all experimental sessions were conducted from Monday to Friday. Rats remained in their home cages on Saturday and Sunday, and were fed daily to maintain their 80% body weight. The injection sequence for 14 rats was 2 days of amphetamine followed by 2 days of saline; the remaining 15 rats had the reverse pattern (two saline injections then two amphetamine injections). This injection sequence was maintained throughout the experiment. Both amphetamine (1 mg/kg) and saline injections were given 15 min before the start of the session (cf. Jones *et al.*, 1976). The amphetamine-correct bar for 14 rats was the left bar; the remaining 15 rats had the right bar as the amphetamine-correct bar. For each operant box, the drug-correct bar was also alternated. Every Monday, Wednesday, and Friday, responding on the injection-correct bar was reinforced for the entire 15 min session. On Tuesday and Thursday, however, a 2 min extinction period was in force at the start of the session. By not providing food for the initial 2 min, we could assess the control of the injection solution over FR responding. The FR25 schedule of reinforcement for injection-appropriate responding was reactivated in the remaining 13 min of the Tuesday and Thursday sessions. A rat was said to have acquired the amphetamine/saline discrimination when it completed the first FR on the correct bar for 10 consecutive sessions, and it had four consecutive extinction periods with 80% or more responding on the injection-appropriate bar. When these criteria were met, the rat was shifted to the amphetamine generalization phase. Three rats failed to meet the discrimination criteria after at least 100 sessions and were dropped from the experiment. This exclusion left 26 rats for the amphetamine generalization phase.

Generalization testing. The procedural details of the amphetamine generalization phase were similar to the discrimination phase, except that the Friday session was a 4 min test in which responding on either bar had no consequence (i.e., extinction). Rats were injected i.p. 15 min before that test with either 0.0625, 0.125, 0.25, 0.5, 1.0, or 2.0 mg/kg amphetamine. Each dose was administered according to a randomized block design. After all doses were tested once, each dose was again tested with a randomized block design. Rats that did not respond on the injection-appropriate bar at 80% or more in the Tuesday and Thursday 2 min extinction periods remained in their home cage on Friday. All 26 rats completed their first amphetamine generalization curve; however one rat did not satisfy the discrimination criterion required to complete its second generalization curve.

Drug

d-Amphetamine sulfate (Sigma, St Louis, MO, USA) was dissolved in saline (0.9% NaCl). All injections were i.p. and the dosage calculations were based on the salt form of the drug.

Data analyses

Pearson product-moment correlation coefficients (*r*) were determined between each individual difference screen and the number of trials required to meet the amphetamine/saline discrimination criteria. Similar analyses were used to correlate median effective doses during drug discrimination with each individual difference screen (see below).

As in previous work in this field (e.g., Piazza *et al.*, 1989; Exner and Clark, 1993) each individual difference screen was also subjected to a median-split procedure in which rats were classified as either high (above the median) or low (below the median) responders. If the rat's score was equal to the median, it was eliminated from the analyses. One rat from the novelty-induced place preference screen and three rats from the trials to criteria measure were dropped from the median-split analyses as a result of this exclusion. The two dependent measures from the amphetamine generalization phase were percentage responding on the drug bar and total number of bar-presses on both bars during the 4 min extinction tests. The percentage of drug-appropriate responding was equal to the total number of bar-presses on the amphetamine bar divided by the total number of responses on both bars times 100. Both measures from the amphetamine generalization phase were analysed with a repeated measures analysis of variance (ANOVA). A separate ANOVA was performed with each individual difference screen. The repeated measure was amphetamine dose (0.0625, 0.125, 0.25, 0.5, 1.0, and 2.0 mg/kg) and the between-groups factor was median-split category (HR versus LR). Post-hoc pair-wise F tests were used if there was a significant effect of category or a category-by-dose interaction (see Gaito and Nobrega, 1981). A two-tail rejection region of 0.05 was used for statistical significance.

RESULTS

Individual difference screening

Table I shows the mean and standard error for the HR and the LR on each screen that was subjected to the median-split procedure. Table II shows the correlations among the individual difference screens. There was a significant correlation between

TABLE I. Performance in each individual difference screen[1]

Screen	Category	
	High responders	Low responders
NovAct	139.85 ± 5.90 (n =13)	99.08 ± 2.96 (n =13)
NovPP	0.63 ± 0.005 (n =12)	0.48 ± 0.027(n =13)
TimeObj	165.48 ± 9.33 (n =13)	93.05 ± 4.97 (n =13)
NumObj	67.92 ± 1.33 (n =13)	48.08 ± 2.17 (n =13)
AmpAct	390.08 ± 22.98 (n =13)	225.46 ± 17.29 (n =13)
Criteria	55.00 ± 6.33 (n =12)	19.82 ± 1.64 (n =11)

[1] Values are means (±SEM). Abbreviations: NovAct, novelty-induced activity; NovPP, novelty-induced place preference; TimeObj, time spent contacting novel object; NumObj, number of contacts with novel object; AmpAct, amphetamine-induced activity; Criteria, number of trials to meet amphetamine/saline discrimination.

TABLE II. Correlations between individual difference screens[1]

Screen	Screen				
	NovPP	TimeObj	NumObj	AmpAct	Criteria
NovAct	0.256	0.309	0.300	0.533†	−0.092
NovPP		−0.035	−0.061	0.478†	−0.224
TimeObj			0.612†	0.059	0.308
NumObj				0.150	0.315
AmpAct					−0.317

[1] Abbreviations: NovAct, novelty-induced activity; NovPP, novelty-induced place preference; TimeObj, time spent contacting novel object; NumObj, number of contacts with novel object; AmpAct, amphetamine-induced activity; Criteria, number of trials to meet amphetamine/saline discrimination. †p <0.05.

novelty-induced activity and amphetamine-induced activity. That is, rats that were more active in an inescapable novel environment were more sensitive to the acute locomotor activating effects of amphetamine. There was also a significant correlation between novelty-induced place preference and amphetamine-induced activity. Rats that had a greater preference for the novel compartment displayed higher levels of activity to acute amphetamine exposure. Finally, the correlation between the number of contacts and time spent with the novel object was significant. This relationship denotes that rats that made more contacts with the novel object also spent more time with it.

The individual difference screens that were significantly correlated also had the highest percentage of rats consistently classified as either HR or LR. For example, 24 of the 26 rats (92%) were classified the same (HR or LR) for the object interaction measures (duration and number of contacts). The concordance was not as high for the amphetamine-induced activity versus novelty-induced activity screens (65%; 17 out of 26) or for the amphetamine-induced activity versus novelty-induced place preference screens (72%; 18 out of 25). Interestingly, the consistency of classification between the novelty-induced activity and the novelty-induced place preference screen was also high (68%; 17 out of 25), yet the correlation between the screens was not significant. These latter two screens predicted the rate suppressant effects of amphetamine (see Figs 1 and 2).

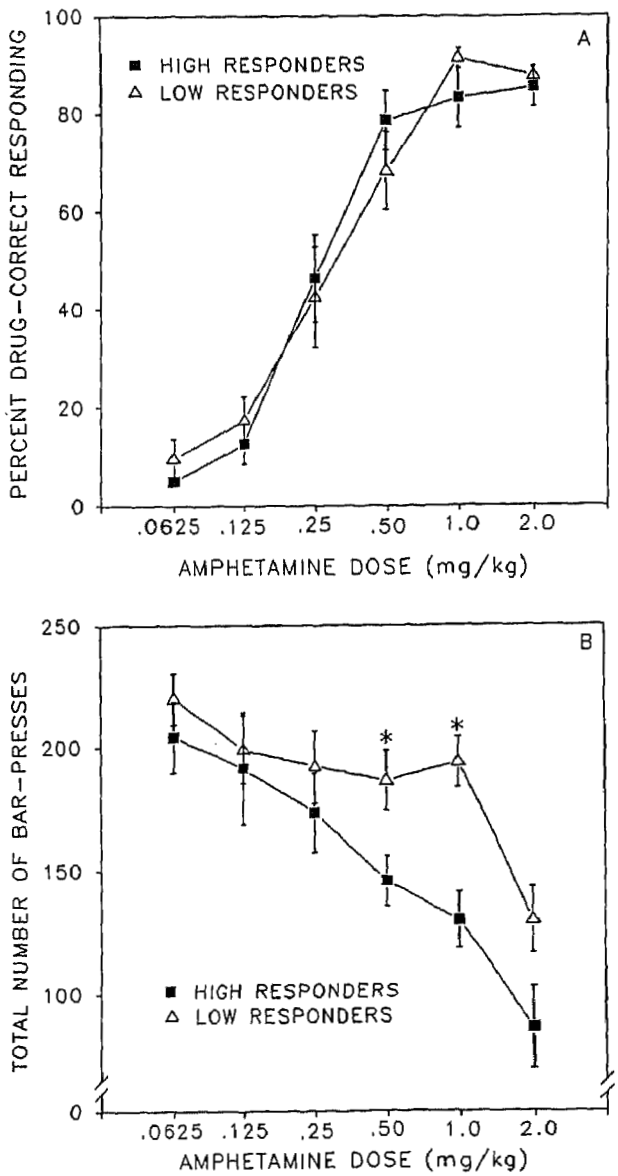

FIG. 1. The percentage of amphetamine-appropriate responding (panel A) and total number of bar-presses (panel B) to each dose of amphetamine tested in the first generalization test. Filled squares denote high responders in the novelty-induced activity screen, whereas empty triangles represent low responders. *Denotes a significant difference (p <0.05) between high and low responders at that dose.

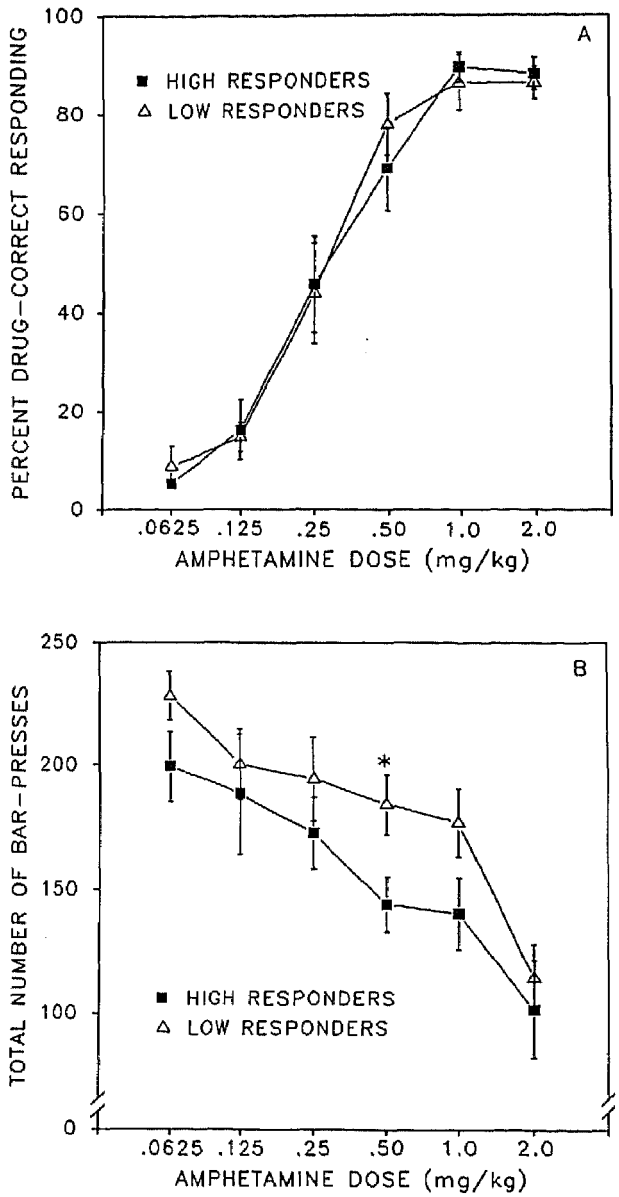

FIG. 2. The percentage of amphetamine-appropriate responding (panel A) and total number of bar-presses (panel B) to each amphetamine dose tested in the first generalization test. Filled squares denote high responders in the novelty-induced place preference screen, whereas empty triangles represent low responders. *Denotes a significant difference ($p < 0.05$) between high and low responders at that dose.

HR versus LR in first generalization test

For the percentage drug-appropriate responding measure, there was a significant main effect of amphetamine dose for all analyses [Fs $\geq$71.67]. This main effect indicated that as the dose of amphetamine increased, so did the percentage of responding on the amphetamine bar. For the total number of bar-presses measure, there was also a significant main effect of dose for all analyses [Fs $\geq$13.00]. This main effect was caused by a decrease in overall responding in the 4 min extinction tests as the dose of amphetamine increased. There was a main effect of category (HR versus LR) for the response rate measure from the novelty-induced activity and place preference screens (see Figs 1 and 2, respectively). No other tests were statistically significant.

Fig. 1(a) shows the percentage of amphetamine-appropriate responding to each dose assessed during the first generalization test. Fig. 1(b) shows the total number of responses on both bars for each dose tested. The distribution of bar-pressing at the training dose (1 mg/kg) and higher was at or above the 80% discrimination criterion for high and low responders. There was no difference in the sensitivity of HR and LR from the novelty-induced activity screen to the discriminative stimulus effects of amphetamine at any dose. However, there was differential sensitivity to the rate-suppressant effects of amphetamine (see Fig. 1(b)). LR were less susceptible to the disruptive effect of amphetamine than HR. Subsequent tests revealed a significant difference between high and low responders at the 0.5 and 1.0 mg/kg doses of amphetamine [Fs(1,23) $\geq$6.81].

Given that the vehicle (saline) was not tested in a Friday generalization test, it was important to provide an assessment of whether HR differed from LR in their baseline level of bar-pressing in the absence of amphetamine. To do this, we conducted a *t*-test with category for novelty-induced activity (HR versus LR) as the unpaired factor; the dependent measure was the sum of the responses for each rat that occurred in the six Tuesday/Thursday saline extinction tests, which immediately preceded each of the generalization tests comprising the data displayed in Fig. 1(b). HR (616 bar-presses $\pm$47.2) did not differ in extinction responding from LR (652 bar-presses $\pm$28.0) after a saline injection [$t < 1$]. The differences in amphetamine-induced bar-press suppression seen at the intermediate amphetamine doses were thus not due to differences in baseline levels of responding.

Because the difference in amphetamine-disrupted responding was seen at the training dose (1 mg/kg), it was of interest to assess whether a similar difference was present during the 2 min amphetamine extinction tests that immediately preceded each of the Tuesday/Thursday generalization tests. HR (419 bar-presses $\pm$29.9) pressed significantly less in extinction than LR (562 bar-presses $\pm$25.9) after an amphetamine injection [$t(24) = 3.63$]. This result corroborates the difference seen in the Friday generalization test at the

1 mg/kg dose of amphetamine (i.e., HR were more sensitive to the response suppressing effects of amphetamine than LR; Fig. 1(b)).

Fig. 2(a) shows the percentage of amphetamine-appropriate bar-pressing for HR and LR in the novelty-induced place preference screen; Fig. 2(b) shows the total number of responses for high and low responders. The results were similar to those described previously in Fig. 1. The percentage of drug-correct responding across test doses was similar regardless of whether rats were classified as HR or LR. However, there was a differential sensitivity to the rate-suppressant effects of amphetamine (see Fig. 2(b)) with HR showing greater response suppression than LR. This difference was statistically significant only at the 0.5 mg/kg dose of amphetamine [$F(1,22) = 6.02$]. As noted earlier, it is important to determine whether the difference in bar-press levels simply reflects a difference in baseline responding. A *t*-test revealed that HR (633 bar-presses ± 51.4) did not differ in extinction responding from LR (641 bar-presses $+28.0$) after a saline injection [$t < 1$]. The difference in bar-pressing between high and low responders cannot thus be attributed to a difference in baselines.

In contrast to the novelty-induced activity screen, a significant difference in amphetamine response suppression was not seen at the training dose (1 mg/kg) when scores were split according to the novelty-induced place preference screen. We assessed whether similar bar-press levels also occurred in the 2 min amphetamine extinction tests that immediately preceded each of the generalization tests. As in the Friday generalization test, there was no difference between HR (492 bar-presses ± 39.9) and LR (482 bar-presses $+31.9$) in the Tuesday/Thursday amphetamine extinction tests [$t < 1$].

HR versus LR in second generalization test

Across all analyses there was a significant main effect of dose for the percentage of drug-appropriate responding measure [Fs ≥ 105.01] and the total number of responses [Fs ≥ 10.07 (data not shown)]. These main effects indicated that the percentage of responding on the amphetamine bar increased with dose, whereas overall responding decreased. On the percentage drug-appropriate responding measure, there was a significant category $\times$ dose interaction for the duration of contact with the novel object. Post-hoc analyses did not reveal any significant pairwise difference at any dose in percentage drug-appropriate responding between HR and LR on this measure. There was, however, a non-significant tendency ($p = 0.069$) at the 0.25 mg/kg amphetamine dose for HR to have a greater percentage of bar-presses on the drug bar (56.5% ± 13.7) than LR (32.5% ± 6.4). On the basis of the amphetamine-induced activity screen, there was a main effect of category for the overall response measure. There were non-significant tendencies for LR to bar-press less at the 0.125 and 0.25 mg/kg doses of amphetamine ($p = 0.061$ and 0.054, respectively) than HR. No other tests were statistically significant.

TABLE III. Correlations between drug discrimination measures and individual difference screens[1]

Drug discrimination measures	ED_{50} test 1		ED_{50} test 2	
Screen	S^D	Bar-press	S^D	Bar-press
NovAct	0.201	0.176	−0.022	0.077
NovPP	−0.196	0.162	−0.256	0.157
TimeObj	0.171	−0.106	−0.180	−0.232
NumObj	0.187	−0.264	−0.309	−0.007
AmpAct	−0.082	0.150	−0.407†	0.060
Criteria	0.055	0.172	0.011	0.307

[1] Abbreviations: NovAct, novelty-induced activity; NovPP, novelty-induced place preference; TimeObj, time spent contacting novel object; NumObj, number of contacts with novel object; AmpAct, amphetamine-induced activity; Criteria, number of trials to meet amphetamine/saline discrimination; ED_{50}, median effective dose; S^D, discriminative stimulus effects of amphetamine. †$p < 0.05$.

ED_{50}s and individual difference screens

A common measure in drug discrimination research is the median effective dose (ED_{50}). For each rat we thus calculated the median effective dose for the discriminative stimulus and the rate suppressant effects of amphetamine in each generalization test. We then used Pearson product-moment correlation tests to determine whether any of the individual difference screens would predict the ED_{50}s. Table III shows these correlations. The only significant correlation was between amphetamine-induced activity and the ED_{50} for the discriminative stimulus effects of amphetamine in the second generalization test. Rats that were more sensitive to the psychomotor effects of amphetamine were more sensitive to the discriminative stimulus effects of amphetamine, as indicated by a lower ED_{50}.

DISCUSSION

Individual difference screening

Rats that were more sensitive to the psychomotor stimulant effects of an acute administration of

amphetamine were also more active in an inescapable novel environment, a finding that replicates research by others (e.g., Piazza *et al.*, 1989; Exner and Clark, 1993). Amphetamine-induced activity was also directly related to the degree of novelty-induced place preference. Those rats that had a greater preference for the novel environment were more sensitive to an acute administration of amphetamine. To our knowledge, this latter result represents the first demonstration that novelty-seeking behavior in a free-choice test predicts amphetamine-induced locomotor behavior. Although amphetamine-induced activity was correlated with novelty-induced activity and place preference, the lack of correlation between novelty-induced activity and novelty-induced place preference suggests that these screens measure different processes. Importantly, the absence of a relationship between preference behavior and locomotor activity in an inescapable novel environment is consistent with the literature. For instance, Erb and Parker (1994) failed to find a relationship between novelty-induced activity and amphetamine-conditioned place preference. Moreover, the degree of activity in an inescapable novel environment does not predict cocaine-conditioned place preference (Gong *et al.*, 1996).

Previous work has suggested that amphetamine-induced activity and novelty-induced activity may involve a common biological process. In particular, these two screens may be related because they both activate mechanisms underlying reactivity to stress. For instance, rats that are more reactive to inescapable novelty also tend to have higher levels of the stress hormone corticosterone before and after experiencing inescapable novelty (Piazza *et al.*, 1989). Exposure to amphetamine can also induce functional changes that are similar to those produced by stress. Piazza *et al.* (1990) found that tail-pinch stress and amphetamine pre-exposure both facilitated subsequent self-administration of a low dose of amphetamine in rats (see also Antelman *et al.*, 1980; Kalivas and Stewart, 1991). Finally, recent work has identified several neural mechanisms that may mediate the relationship between novelty-induced activity and amphetamine-induced activity. Much of this work has examined and implicated the mesolimbic dopamine system (Segal and Kuczenski, 1987; Hooks and Kalivas, 1994; Hooks *et al.*, 1994a; for related work see Higgins *et al.*, 1994; Hooks *et al.*, 1994b).

The significant correlation between amphetamine-induced activity and novelty-induced place preference in the present report suggests that these two screens may also be mediated by some common biological process. One possibility is that novelty, like amphetamine, has appetitive or rewarding properties. Similar to amphetamine, exposure to novelty can engender and/or maintain operant responding (Miles, 1958; Haude and Ray, 1967; May and Beauchamp, 1969). Furthermore, it has been suggested that preference for a novel environment (i.e., novelty-induced place preference) measures an appetitive or rewarding quality of novelty (Bardo *et al.*, 1989; Pierce *et al.*, 1990). One difficulty with this explanation is the lack of correlation between novelty-induced activity and novelty-induced place preference. If behavioral measures of stress, such as novelty-induced activity, can predict the subsequent rewarding effects of amphetamine (Piazza *et al.*, 1989), why does this measure of stress fail to predict the subsequent rewarding effects of novelty? It may be that the neural mechanisms mediating the rewarding effects of novelty are, in part, different from those of amphetamine (cf. Bardo *et al.*, 1989, 1996; Pierce *et al.*, 1990; Erb and Parker, 1994). It would be of interest to determine whether the relationship between amphetamine- and novelty-induced activity or place preference would be altered by experimental manipulation of corticosterone (e.g., repeated pre-exposure).

Drug discrimination

Exner and Clark (1993) found that LR in an inescapable novel environment screen were more sensitive than HR to the discriminative stimulus effects of amphetamine. In contrast, novelty-induced activity in the present work did not predict subsequent sensitivity to the discriminative stimulus effects of amphetamine. Numerous differences in procedural details could explain this discrepancy. For example, Exner and Clark's measure of novelty-induced activity included rears and horizontal locomotor activity (as did our measure). However, their operational definition of horizontal locomotor activity was number of photobeam breaks, whereas our definition was number of line crosses. Moreover, their definition of activity ("escape activity") included measures of ambulation and sniffing directed away from the floor. They used a time-sampling technique across a 1 h period to obtain part of their activity measure, whereas we employed a continuous-observation technique for 30 min (see Altmann, 1974 for a discussion of data resulting from different sampling techniques).

Differences in drug discrimination and generalization testing procedures could also be responsible for the differences between these two experiments. The amphetamine training dose differed (1.0 versus 0.5 mg/kg) as did the final schedule of reinforcement (FR25 versus FR20). Finally, the generalization testing differed. Upon finishing 20 cumulative bar-presses

on one bar, their rats were removed from the testing situation. Our test was a 4 min extinction session that allowed unlimited responding on either bar. Any one or all of these procedural variants could alter the sensitivity of the procedures to the discriminative stimulus effects of amphetamine (Overton, 1979; Colpaert, 1987). Regardless of the explanation, however, this discrepancy highlights the need for more parametric work assessing the importance of procedural variables in detecting individual differences.

Although novelty-induced activity did not predict sensitivity to the discriminative stimulus effects of amphetamine, activity induced by the first injection of amphetamine did. Animals that were more reactive to an acute administration amphetamine, in general, were more sensitive to the discriminative stimulus effects of amphetamine (i.e. lower ED_{50}s) in the second generalization test. This result is in contrast to that of Exner and Clarke (1993) described above, and again emphasizes the need for parametric work in the field of individual differences. The inverse relationship between amphetamine induced activity and ED_{50} in the second generalization test is consistent with the amphetamine individual difference literature. That is, HR to inescapable novelty show greater activity to the first amphetamine injection and acquire amphetamine self-administration more readily (e.g., Piazza *et al.*, 1989). These relationships may reflect greater sensitivity by HR to the psychomotor and the reinforcing effects of amphetamine. The present report adds discriminative stimulus effects to this list. It is not clear why amphetamine-induced activity correlated significantly with the ED_{50} from the second generalization test and not the first test. Perhaps extensive experience with the discrimination procedures was required before the generalization procedures employed in the present work were sufficiently sensitive to detect subtle differences in the median effective dose.

We found differential sensitivity to the response suppressant effects of amphetamine between high and low responders in an inescapable novel environment screen: HR were more sensitive than LR at intermediate amphetamine doses. A similar effect was found using the novelty-induced place preference screen. It was surprising that these two individual difference screens both predicted the rate-suppressant effects of amphetamine, yet were not correlated with each other. This pattern of results suggests that amphetamine may alter on-going behavior (bar-pressing) by more than one mechanism. One possibility is that chronic amphetamine may induce behaviors that compete with bar-pressing through differential activation of the mesolimbic dopamine system. For example, there have been reported differences in dopamine receptor subtype densities in the nucleus accumbens and striatum between HR and LR in the novelty-induced activity screen (Hooks *et al.*, 1994a; see also Segal and Kuczenski, 1987). Similar work has not been done for the novelty-induced place preference screen. Another possibility is that amphetamine could alter attentional processes. It has been shown that the amygdala plays an important role in attentional processes (for review see Gallagher and Holland, 1994). Moreover, selective bilateral lesioning of the amygdala alters the locomotor response to novelty (Burns *et al.*, 1996). Input from the amygdala to the striatum may be changed differentially for high and low responders by the presence of amphetamine in the striatal area (Kalivas and Stewart, 1991; Burns *et al.*, 1996). Further research is clearly needed before choosing between alternative accounts. For instance, to test the attentional hypothesis, one possibility would be to determine individuals' performance on tasks believed to require attention to a stimulus (e.g. latent inhibition; Lubow, 1973), and then correlate these measures with novelty-induced activity, novelty place preference, and amphetamine-induced activity.

Related to this discussion is the finding that amphetamine-induced activity, which was correlated with novelty-induced activity and novelty-induced place preference, did not predict the subsequent rate-suppressant effects of amphetamine. This result suggests that the shared process(es) between amphetamine-induced activity and the other two screens, may not necessarily be the same mechanism responsible for the response-altering effects of amphetamine.

The individual differences detected in the bar-press suppressant effects of amphetamine were transient. The difference between HR and LR was detected across the first amphetamine generalization test, but not across the second test. Perhaps the extensive experience with amphetamine altered the biological processes that initially allowed detection of the individual differences in the response suppressant effects. Consistent with this notion, Piazza *et al.* (1989) found that amphetamine-experienced high and low responders in an inescapable novel environment acquired subsequent amphetamine self-administration at a similar rate. As discussed previously, individual differences in the discriminative stimulus effects of amphetamine were not, however, detected until the second generalization test.

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