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Differential Effects of an Early Housing Manipulation on Cocaine-Induced Activity and Self-Administration in Laboratory Rats

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BOYLE, A. E., K. GILL, B. R. SMITH AND Z. AMIT. *Differential effects of an early housing manipulation on cocaine-induced activity and self-administration in laboratory rats.* PHARMACOL BIOCHEM BEHAV **39**(2) 269–274, 1991.—Several reports in the literature suggested that environmental influences which are reflected in the social housing conditions of the rat may play a role in the expression of individual differences in drug self-administration. The present experiments were performed in order to further examine the effects of early housing manipulations, as reflected by grouped or isolation housing, on cocaine-induced behavioral responding. The first study examined the effects of this manipulation on the locomotor stimulant properties of cocaine. The results suggested that grouped housing produced a significantly greater increase in cocaine-induced locomotion than was observed in animals housed in isolation. Experiment 2 examined the effects of housing manipulations on the self-administration of cocaine under a continuous reinforcement schedule. Differences in the rate of cocaine self-administration were only observed at the lowest dose tested. Responding at all other doses was equivalent, including the optimal dose for both groups, suggesting that the housing manipulations failed to affect the reinforcing efficacy of cocaine. The present investigation suggests that, while the early housing manipulation produced a differential sensitivity in rats to the stimulant properties of cocaine, the same manipulation failed to alter the sensitivity of rats to the reinforcing properties of cocaine as assessed through self-administration.

Housing Cocaine Self-administration Locomotion

THE manipulation of the early housing environment has been demonstrated to modify the basic behavioral and neurochemical mode of functioning of the laboratory rat (3,5). One line of research in this area has attempted to demonstrate a role for specific environmental influences in the expression of individual differences in drug self-administration (1, 2, 4, 14, 20).

In animals, the role of environmental influences in drug self-administration has often been examined through the manipulation of the social housing conditions. Investigations of this type have typically incorporated designs which have manipulated the relative degree of physical interaction permitted between subjects. The most common approach taken employed a design that contrasted the behavioral effects of being housed in isolation with those of being housed in groups (23).

It has been reported that such an early housing manipulation altered the propensity of rats to self-administer cocaine intravenously (20). Specifically, grouped subjects failed to reliably self-administer cocaine and, as a result, were described as being insensitive to the reinforcing properties of cocaine. Isolation-housed subjects, on the other hand, exhibited a robust self-administration of this drug. As a result, the authors concluded that housing manipulations play a major role in mediating the expression of individual differences in self-administration and, by implication, of cocaine reinforcement (20).

The demonstration of the enhanced sensitivity of isolated rats to the effects of cocaine (20), however, was in contrast to other reports examining the effects of housing by using alternate paradigms and other drugs. It has been suggested that housing manipulations produced an enhanced sensitivity to the effects of cocaine in grouped-housed subjects, when assessed through conditioned place preference (19) and oral self-administration (10) paradigms. In addition, it has been reported that housing manipulations failed to affect amphetamine-induced behavioral responding as expressed through self-administration (21), conditioned place preference (19) and locomotor (16,21) paradigms. In contrast to these negative findings on the effects of amphetamine, there has been a report that isolation housing enhanced the interaction of amphetamine exposure and food-related reward stimuli (12). From the foregoing, it would appear that, while housing manipulations have a limited effect on amphetamine-induced behavioral responding, the effects of housing on cocaine-induced behavioral responding remain contradictory.

Recently, an attempt to further assess the extent to which housing manipulations influenced the propensity of animals to self-administer cocaine as well as other drugs of abuse has been reported (4). It was demonstrated that both isolated and group-

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housed subjects readily acquired the operant response for self-administration of cocaine, although the acquisition of heroin self-administration was delayed in grouped subjects. Furthermore, they found that housing manipulations failed to produce differences in the optimal rates of heroin self-administration. The authors concluded that isolation housing was not a prerequisite of IV cocaine self-administration and, further, that the underlying reinforcement mechanisms were not influenced by environmental conditions (4). These conclusions were inconsistent with those previously reported concerning the differential effects of housing on cocaine self-administration (20).

The failure to demonstrate an effect of housing (4) may be confounded by methodological issues. Specifically, in that study (4), older rats were used. Older rats have been shown to be less susceptible to the effects of housing manipulations (17). In addition, the specific housing manipulation used was of a shorter duration than is typically used in the related housing literature (9,18–20).

It would appear that the effects of housing manipulations on the expression of individual differences in the self-administration of cocaine have been equivocal. The present investigation attempted to overcome the difficulties presented by the previous research by evaluating the effects of housing on cocaine-induced behavioral responding through the application of a consistent manipulation of housing and the testing of animals in multiple behavioral situations. The effects of early housing manipulations on cocaine-induced locomotor activity and stereotypy were assessed through the use of an open-field paradigm. In addition, the same early housing manipulation's effect on the propensity to self-administer cocaine under a continuous reinforcement schedule was also examined.

EXPERIMENT 1

METHOD

Subjects

Sixty male Long-Evans rats (Charles River, Canada) obtained at weaning (21 days of age) were used. The subjects were housed in hanging stainless steel cages either in isolation (cage size = 20 × 25 × 18 cm) or in groups of four (cage size = 41 × 25 × 18 cm) for six weeks postweaning. Food and water were freely available at all times except during testing. Subjects were maintained in a colony under reverse-cycle lighting (off at 0900, on at 2100), and all testing occurred within four hours of the onset of the dark cycle.

Apparatus

Open-field boxes (45.7 × 45.7 × 39.4 cm) were used to assess horizontal locomotor activity. Each open-field box was painted black and illuminated with dim red lighting. There were four sets of light sources and photocells located 3.8 cm above the chamber floor. The light sources were arranged such that one pair of light beams crossed the other pair perpendicularly, dividing the chamber into 9 equal sectors. Interruptions of the light beams were automatically registered on a control panel in an adjacent room.

Procedure

Following the termination of the six-week housing period, subjects (63 days of age) were placed in the open-field chambers for a 50-minute habituation session on the day before drug testing. They were then randomly assigned to one of five drug conditions. During test sessions, all animals were placed in the boxes for a 50-minute recording of baseline activity. Following this, they were removed, given an intraperitoneal (IP) injection of cocaine HCl (0, 2.5, 5, 10 or 20 mg/kg dissolved in a constant volume of physiological saline) and returned to their chambers for an additional 50-minute period. Locomotor scores were recorded for the duration of the pre- and postinjection periods.

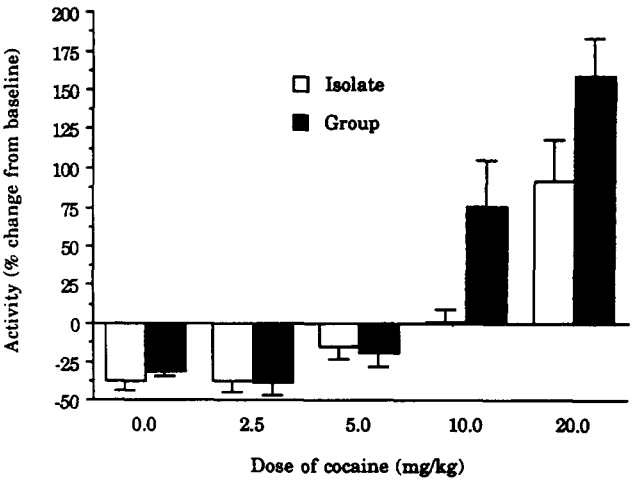

FIG. 1. The effect of differential housing on cocaine-induced locomotor activation as represented by percent change from baseline activity for isolated and grouped housed subjects (n = 6/group). Vertical lines represent the S.E.M.

RESULTS

A two-way ANOVA (group and dose) conducted on the baseline activity scores revealed a significant main effect for housing, $F(1,70) = 8.19$, $p < 0.006$. The isolated subjects exhibited significantly higher levels of baseline locomotor activity. Consequently, all later analyses were based on the transformation of the data to a percent change from baseline to eliminate initial differences in activity. The percent change in activity was calculated using the cumulative activity scores for the 50-minute period prior to and following drug treatment.

Figure 1 shows the percent change from baseline activity scores for grouped and isolated subjects following cocaine injections. A two-way ANOVA yielded a significant 2-way interaction between housing and dose, $F(4,70) = 2.94$, $p < 0.04$. An analysis of simple main effects revealed that the grouped subjects exhibited a significantly greater increase in locomotion in response to cocaine at 10 mg/kg, $F(1,70) = 10.93$, $p < 0.002$, and 20 mg/kg, $F(1,70) = 8.89$, $p < 0.004$. The differences between the two groups at 0, 2.5 and 5 mg/kg cocaine were not significant.

These findings suggested that the manipulation of early environmental housing may influence the sensitivity of rats to the locomotor-activating effects of cocaine. Group-housed subjects exhibited significantly greater levels of locomotor activation following cocaine treatment than did subjects housed under isolation conditions. The inconsistency between the present observations and those previously reported for amphetamine-induced locomotion (12,21) may be interpreted as support for the proposal that the effects of housing manipulations may be specific for certain drugs (4).

The following experiment was conducted in order to determine the influence of possible cocaine-induced stereotypy in the enhanced activation observed in group-housed animals from Experiment 1.

EXPERIMENT 1A

METHOD

Subjects

Twenty male Long-Evans rats (Charles River, Canada) obtained at weaning (21 days of age) were used as subjects. The subjects were housed in either isolation or groups of four, for six weeks postweaning. Subjects were maintained under conditions identical to those of Experiment 1.

Apparatus

Subjects were tested for locomotion and stereotypy in Plexiglas open-field observation boxes (40 × 40 × 35 cm). The behavioral responses of the rats were recorded using an 8-mm video camcorder. Lighting conditions throughout the testing period consisted of the minimum level of white light necessary for the video recording. The video tape recordings were later used for analysis.

Procedure

Following the six-week housing period, the subjects (63 days of age) were placed in open-field chambers for a 50-minute habituation session on the day before drug testing. On the day of drug testing, subjects were placed in the open-field boxes for 20 minutes. Following this interval, the subjects were removed, given an injection (IP) of 10 or 20 mg/kg of cocaine HCl and placed back into the chambers for an additional 20 minutes. Video recordings were made of both pre- and postinjection periods. The duration of the test period was selected on the basis of the observation in Experiment 1 that the expression of locomotor activation was largely limited to the initial 20-minute time period.

The video tapes were scored with respect to the cumulative number of line crossings for the 20-minute sessions and the incidence of stereotypy. The rats were required to move all four paws from one quadrant to another in order for a line crossing to have been scored. Stereotypic behavior was measured using a time-sampling technique which consisted of observing the subjects for a 1-minute period every 10 minutes during the 20-minute sessions. Stereotypy was rated on a scale from 0 to 6: 0—asleep or stationary, 1—actively locomoting, 2—predominantly active with bursts of stereotyped sniffing or rearing, 3—stereotyped sniffing along a fixed path, 4—stereotyped sniffing or rearing in one location, 5—stereotyped behavior in one location with bursts of gnawing or licking, and 6—continual gnawing or licking in one location (7).

RESULTS

The baseline activity scores for the isolated and grouped subjects were analyzed. The results, as in Experiment 1, showed that there were significant differences, $F(1,56) = 18.74$, $p<0.01$, in baseline activity rates between grouped and isolated subjects for the 20-minute period prior to injection. All subsequent analyses were based upon the transformation of scores to a percent change from baseline.

The percent change from baseline locomotion scores for the 20-minute (postinjection) sessions are presented in Fig. 2. A two-way analysis of variance with repeated measures yielded a significant main effect for housing, $F(1,16) = 12.04$, $p<0.004$, and dose, $F(1,16) = 17.27$, $p<0.0008$. The results suggested that grouped subjects exhibited significantly greater changes in locomotor activity at both doses tested. These data are consistent with those observed in Experiment 1. The interaction between housing and dose was not significant.

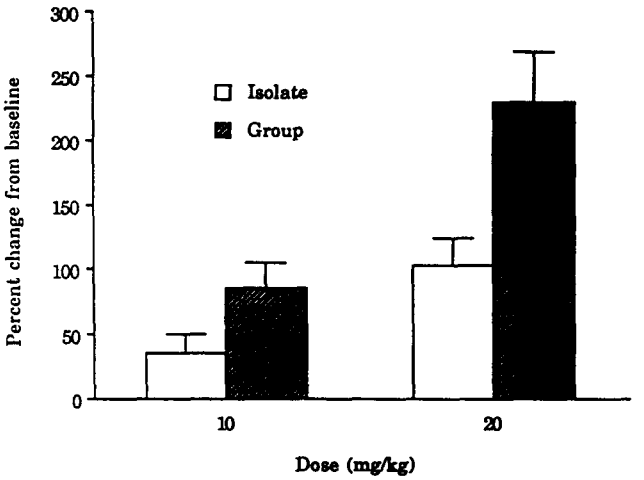

FIG. 2. The percent change from baseline locomotion scores for the 20-minute (postinjection) session following cocaine treatment (n = 5/group). Vertical lines represent the S.E.M.

Table 1 summarizes the stereotypy ratings for the isolated and grouped subjects. There were no significant differences between the two groups in the expression of cocaine-induced stereotypy. The differential levels of activation observed in the two groups appear not to be a result of enhanced stereotypy.

The findings of Experiment 1, indicating an enhanced sensitivity of group-housed subjects to the stimulant effects of cocaine, are in contrast to a previous report which indicated that group-housing induced a diminished sensitivity to the reinforcing properties of cocaine, as evidenced by the failure of grouped subjects to self-administer the drug (20). It has been suggested that the direction of alterations following manipulation of the behavioral response to stimulant drugs is similar (21,25). On the basis of these reports, it was expected that the enhanced sensitivity to the stimulant properties of cocaine brought about via the housing manipulation should be similarly reflected in a self-administration paradigm examining the reinforcing efficacy of this drug.

It is possible that the failure of grouped subjects to self-administer cocaine in a previous study (20) may reflect an inhibition of the ability to acquire the operant response, as opposed to

TABLE 1

EFFECTS OF HOUSING ON COCAINE-INDUCED STEREOTYPY

		Baseline		Test	
	Dose	10	20	10	20
Isolates	10	1	1	1	1
	20	1	1	2.6	1.2
Group	10	1	1	2	1.2
	20	1	1	2.4	1.4

Stereotypy was rated on a scale from 0 to 6: 0—asleep or stationary, 3—stereotyped sniffing along a fixed path, 6—continual gnawing or licking in one location.

a diminished sensitivity to the reinforcing properties of the drug. The subjects in this study (20) were initially presented with a large dose of cocaine and subsequently presented with doses of descending concentration. Therefore, the inhibition of the acquisition process may reflect the influence of the grouped subjects' increased sensitivity (as observed in Experiment 1) to the stimulant or, perhaps, aversive properties of cocaine on learning processes.

The following experiment, therefore, examined the effects of early housing manipulations on the self-administration of cocaine. In contrast to the procedure used previously (20), an ascending sequence of doses was used in this experiment, in order to minimize the potential for an inhibition of the acquisition process of the grouped-housed subjects as a result of the observed enhanced sensitivity to the stimulant properties of cocaine (Experiment 1).

EXPERIMENT 2

METHOD

Subjects

Thirty-two male Long-Evans rats (Charles River, Canada) obtained at weaning (21 days of age) were used as subjects. The subjects were housed in either isolation or groups of four for six weeks postweaning. Subjects were maintained under conditions identical to those of Experiment 1.

Apparatus

Ralph Gerbrands Company Model C operant conditioning chambers equipped with a lever mounted 6 cm from the floor were used. Suspended above each box was a polyethylene tube attached to a flow-through swivel (6) which served to connect the animal to an infusion pump (Model A, Type 17, 1-rpm motor from Razel Scientific Instruments Inc.). Each depression of the lever activated both a cue light and the pump, which delivered 0.1 ml (over 9 seconds) of a cocaine HCl solution (prepared daily in a 0.9% saline solution) or saline control solution (0.9%). All operant responses were recorded on a chart recorder.

Procedure

Each rat was implanted with a chronically indwelling catheter. A catheter [Dow silastic i.d. = 0.020; o.d. = 0.037 (24)] was implanted into the jugular vein of the rat. The catheter was passed subcutaneously to the skull, where it was secured with stainless steel screws and dental acrylic. Subjects recovered over a five-day period during which they received daily infusions through the catheter (1 ml) of a saline/penicillin solution. The daily infusions were performed in order to maintain the patency of the catheter and minimize the loss of subjects due to infection.

Following recovery, subjects were randomly assigned to either drug or saline conditions, and testing in the self-administration chambers was initiated. Testing occurred during daily three-hour sessions within the first four hours following the onset of the dark cycle. Each session was initiated with a noncontingent administration of a priming infusion of cocaine or saline solution. The subjects receiving infusions of drugs initially received 0.04 mg/kg/infusion of cocaine solution for 5 consecutive days. Subjects were subsequently exposed to doses of 0.08, 0.16, 0.32, and 0.64 mg/kg/infusion. Each dose was presented for a period of five days.

RESULTS

One subject was withdrawn from the study due to a leak in the catheter. Thirty-one subjects completed the study. Figure 3 shows the mean number of responses for grouped and isolated subjects self-administering cocaine or saline. The data are expressed as the mean cumulative number of responses for the 5 trials at each individual dose.

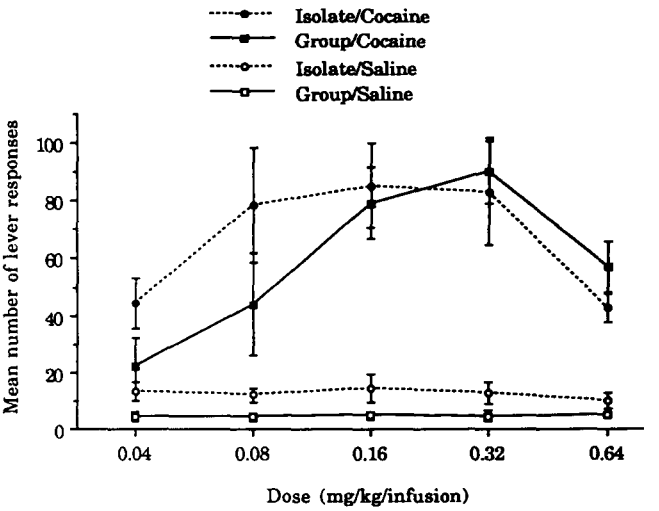

FIG. 3. The mean number of responses for grouped and isolated subjects self-administering cocaine or saline under continuous reinforcement (n = 8/group). The data are expressed as the mean cumulative number of responses for the 5 trials at each individual dose. Vertical lines represent the S.E.M.

An analysis of variance (with repeated measures) yielded a significant three-way interaction for housing, dose and drug (cocaine or saline), $F(4,108) = 2.5$, $p<0.04$. The main effect for the housing variable was not significant.

Post hoc analysis (Tukey) of the marginal means indicated that both the grouped and isolated subjects self-administering cocaine maintained operant rates significantly greater ($p<0.01$) than those subjects self-administering saline.

On the basis of a significant 3-way interaction, an examination of the simple main effects and simple interaction effects was performed (13). When these were calculated, holding the variable dose constant, the results indicated that, for the 0.08 to 0.32 mg/kg/infusion doses, there were no significant simple main effects for housing or housing-by-drug simple interactions. However, at the lowest dose tested, a significant simple main effect for housing (0.04 mg/kg/infusion), $F(1,27) = 5.65$, $p<0.03$, was obtained. On the basis of the significant simple main effect of housing obtained at this dose (0.04 mg/kg/infusion), a post hoc analysis (Tukey) was performed. The results indicated that, at the 0.04 dose, isolated rats exhibited significantly greater rates of cocaine self-administration ($p<0.05$) than did the grouped subjects. Simple interactions for housing and drug at each of the other doses tested did not reach significance.

Further, results indicated that, when the simple main and simple interaction effects were calculated holding the drug variable constant, there was a significant main effect of dose for cocaine, $F(4,108) = 5.21$, $p<0.0007$, but not saline. Post hoc (Tukey) analysis suggested that there was a dose-dependent effect of cocaine on self-administration behavior independent of housing condition. The optimal dose resulting in the highest rates of responding for cocaine was not different between the two housing conditions. Saline controls maintained consistent operant rates over the 5 trial periods.

The present experiment demonstrated that social isolation was not a prerequisite for cocaine IV self-administration. The results show that both grouped and isolated subjects self-administered

cocaine. The pattern of responding indicated that grouped subjects exhibited significantly lower rates of cocaine self-administration only at the lowest dose tested. This finding would suggest that the acquisition of cocaine self-administration by the grouped animals was attenuated by this manipulation in comparison to the isolated animals. However, in light of the comparable levels of self-administration achieved by both groups over all but the lowest dose of cocaine, and the fact that both groups exhibited optimal rates of responding at equivalent doses, the present findings suggest that the early housing manipulation did not appear to influence the reinforcing efficacy of cocaine.

GENERAL DISCUSSION

The results obtained in the present investigation demonstrated that early housing manipulations influenced the sensitivity of rats to the locomotor-activating effects of cocaine while failing to affect its reinforcing efficacy as measured by rates of self-administration. In Experiment 1, it was shown that, at doses that produce locomotor activation, rats who were housed in groups following weaning exhibited significantly greater cocaine-induced locomotor activation as compared to subjects housed in isolation. The data on the increased sensitivity of grouped subjects to the activating effects of cocaine were inconsistent with the reports indicating that housing manipulations failed to influence amphetamine-induced locomotion (16,21). It is suggested that this discrepancy may reflect a failure on the part of earlier studies to account for differential baseline activity levels in the assessment of drug-induced activation. Consideration of the baseline levels of activity was justified on the basis of results described in the present study and others (10,15) which demonstrated that group-housed subjects exhibit significantly lower baseline rates of locomotor activity in open-field paradigms.

The differential effects of housing on cocaine and amphetamine-induced locomotion, however, may also be interpreted as an indication that the effects of the present housing manipulation may have a differential action on the mediators of cocaine- and amphetamine-induced behavior. Further support for the concept of housing specificity is provided by the report that housing manipulations differentially influenced place preference for cocaine and amphetamine (19).

In contrast to the findings of Experiment 1, early housing manipulations failed to alter the reinforcing efficacy of cocaine as assessed through cocaine self-administration in rats. The results of Experiment 2 showed that both isolation- and group-housed subjects readily self-administered cocaine in a dose-dependent manner. Furthermore, the dose of cocaine at which the maximum rate of responding was attained was comparable in both groups. While the reinforcing properties of cocaine were not influenced by the housing manipulations, it was observed that acquisition of self-administration by grouped subjects was attenuated. It is suggested that the enhanced sensitivity of the grouped subjects to the locomotor-activating effects of cocaine (Experiment 1) may have interacted with the novelty of the environment to inhibit the initial acquisition of the operant response.

The results of Experiment 2, however, are in contrast to a previous report (20) suggesting that group-housed rats may be insensitive to the reinforcing effects of cocaine as evidenced by their failure to self-administer this drug. This reported failure to observe self-administration in grouped subjects (20) may be a result of an attenuated process of acquisition, as opposed to a reflection of differential effects upon motivational processes. The findings of the present study suggest that the acquisition of self-administration by the grouped subjects may have been attenuated due to the enhanced stimulant effects of cocaine. The presentation of a large initial dose of cocaine to grouped subjects which were naive to the operant paradigm (20) may act to potentiate this attenuation and would, therefore, necessitate a longer period for the acquisition of cocaine self-administration to become evident.

The series of results obtained from the present investigation demonstrated that early housing manipulations influenced the sensitivity of grouped rats to the locomotor-activating effects of cocaine while failing to affect its reinforcing efficacy as measured by the expression of self-administration. The present findings appear to be inconsistent with a suggestion that the stimulant and reinforcing properties of cocaine are homologous (25). On the basis of this notion, the enhanced sensitivity to the stimulant properties of cocaine seen in the group-housed animals should have been similarly reflected in the self-administration paradigm. The only effect of this housing manipulation seen was to attenuate the acquisition of self-administration of cocaine in grouped rats relative to isolated rats.

The early housing manipulation used in the present series of experiments produced conflicting results, with respect to their effects on cocaine-induced locomotion and self-administration. While the findings suggested that housing manipulations induced a differential sensitivity to the locomotor-activating effects of cocaine, the manipulation did not appear to play a significant role in the expression of individual differences in the liability to self-administer cocaine IV. Furthermore, it is evident from the literature that the influence of early housing manipulations on drug-induced behavioral responding is inconsistent across species and paradigms (8, 15, 22). It would appear, therefore, that an early housing manipulation that involves the simple comparison of grouped versus isolated subjects may not be an appropriate model for the investigation of the effects of environmental influences on drug-induced behavioral responding.

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