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Assessing the relationship between latent inhibition and the partial reinforcement extinction effect in autoshaping with rats

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Abstract

Results from a variety of independently run experiments suggest that latent inhibition (LI) and the partial reinforcement extinction effect (PREE) share underlying mechanisms. Experiment 1 tested this LI=PREE hypothesis by training the same set of rats in situations involving both nonreinforced preexposure to the conditioned stimulus (LI stage) and partial reinforcement training (PREE stage). Control groups were also included to assess both LI and the PREE. The results demonstrated a significant, but negative correlation between the size of the LI effect and that of the PREE. Experiment 2 extended this analysis to the effects on LI and the PREE of the anxiolytic benzodiazepine chlordiazepoxide (5 mg/kg, i.p.). Whereas chlordiazepoxide had no effect on LI, it delayed the onset of the PREE. No evidence in support of the LI=PREE hypothesis was obtained when these two learning phenomena were compared within the same experiment and under the same general conditions of training.
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In a typical latent inhibition (LI) experiment based on a between-subject design, one group receives a phase of nonreinforced preexposure to the training context and the conditioned stimulus (CS-), whereas another group is also placed into the apparatus, but receives no presentations of the CS (for a discussion of control conditions, see Boughner et al., 2004). In the second phase, both groups receive Pavlovian training in which the CS is paired with an unconditioned stimulus (US). During the second phase, preexposed animals respond significantly below the level of nonpreexposed animals and this difference in responding defines LI (Lubow, 1989; Lubow and Moore, 1959).

According to conditioned attention theory (Lubow, 1989), when the CS is followed by no consequence, the animal learns to ignore the stimulus. During subsequent CS–US pairings, the animal fails to attend to the CS and associative learning is retarded relative to the context control condition. Whereas not all theories explain LI as an attentional deficit (e.g., Bouton, 1993; Stout and Miller, 2007; Wagner, 1976), the view that LI is an example of learned inattention has gained in acceptance (Lubow, 1997). According to this view, LI reflects the operation of an adaptive mechanism for processing stimuli since, normally, ignoring a stimulus that was irrelevant in the past is beneficial. LI is an interesting phenomenon partly because of the possibility that it can serve as an animal model for some aspects of schizophrenia. The first studies to provide the link between LI and schizophrenia reported that the systemic administration of low doses of the indirect dopamine agonist amphetamine, a drug known to have psychotomimetic effects similar to some symptoms of schizophrenia, prevented the development of LI (Solomon and Staton, 1982; Solomon et al., 1981; Weiner et al., 1981). In these experiments, the disruption of LI was caused by increased levels of responding to the CS in preexposed animals. Later, this finding has been replicated and extended to various situations using diverse parameters (see Moser et al., 2000). Furthermore, training parameters that do not typically yield evidence of LI (e.g., after a limited number of CS-preexposures) produce such evidence if animals are treated with the dopamine antagonist haloperidol (Feldon and Weiner, 1991;

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Weiner and Feldon, 1987; Weiner et al., 1987a,b). Haloperidol is an antipsychotic often used in the treatment of schizophrenia. Direct support for the relationship between LI and schizophrenia was provided by the finding that acute schizophrenics exhibit a disruption of LI, whereas chronic schizophrenics who have been on neuroleptic treatment for at least 8 weeks show normal LI levels (Baruch et al., 1988; Gray et al., 1992).

In addition to LI, other phenomena have generated interest as possible animal models of schizophrenia, including blocking and the partial reinforcement extinction effect (PREE; e.g., Gray et al., 1999; Hemsley, 1993). Blocking is produced by a procedure in which one element of a compound CS paired with a US is novel whereas the other was previously paired with the US (Kamin, 1969). Blocking is observed when, despite repeated pairings, the novel CS produces little evidence of conditioned responding. It has been suggested that LI and blocking are produced by the same process of learning to ignore irrelevant stimuli (e.g., Oades and Sartory, 1997). For this reason, it was expected that LI and blocking would show similar sensitivity to dopaminergic manipulations. Indeed, subsequent research confirmed that the administration of amphetamine disrupts both LI and blocking (Jones et al., 1997; Weiner et al., 1988).

The empirical similarities between LI and blocking are somewhat unsurprising given their similar theoretical treatments. The same cannot be said for LI and the PREE which have shown some empirical similarities, but have received dissimilar theoretical treatments (see Amsel, 1992; Capaldi, 1994). The PREE is defined as increased resistance to extinction following partial reinforcement training relative to extinction after continuous reinforcement. PREE experiments generally involve a between-subject design with two groups. The continuously reinforced (CRF) group is given training in which a stimulus or response is reinforced on every trial, whereas the partially reinforced (PRF) group receives reinforcement on only a fraction of the trials (typically 50% of the trials in a pseudorandom order). All animals are then given extinction training in which the reinforcer is withheld. The PREE is defined by a retardation of extinction in the PRF group relative to the CRF group. Gray et al. (1991) first suggested that the PREE may also be a good model for schizophrenia, primarily because manipulations that affect LI also affect the PREE. Amphetamine, which was shown to disrupt LI (Moser et al., 2000), also disrupts the PREE when long intertrial intervals (ITIs) are used (Feldon and Weiner, 1992; Weiner et al., 1985, 1987a,b). For example, Weiner et al. (1985) gave either amphetamine (1.5 mg/kg) or saline 15 min prior to each acquisition session to CRF and PRF groups running in a straight alley. The acquisition phase lasted for 15 days at one trial/day. All animals were then shifted to extinction. In extinction, when rats received only saline injections, saline-treated rats showed the PREE, but the effect was eliminated in amphetamine-treated rats. The PREE was eliminated because of increased persistence in the CRF group and decreased persistence in the PRF group. In contrast, Gray et al. (2002) found that a single dose of amphetamine had no effect on the PREE in normal human participants. More research is necessary to determine whether amphetamine modulates human performance under some conditions.

Research has also shown that both LI and the PREE are disrupted in rats with lesions in the nucleus accumbens (Tai et al., 1995, 1991; Weiner et al., 1996). For the PREE, Tai et al. (1991) administered either electrolytic lesions of the nucleus accumbens or a sham operation, and then trained rats under either CRF or PRF in a straight alley for 8 sessions, at 6 trials/session. Over the course of extinction (an additional 8 sessions of 6 trials each), sham-operated rats showed the PREE, lesioned rats exhibited no apparent PREE. Again, the disruption of the PREE after accumbens lesions was caused by decreased persistence in the PRF condition and increased persistence in the CRF condition.

A common neural mechanism underlying both LI and the PREE may relate to the mesolimbic dopaminergic system (Gray et al., 1995, 1997), a projection from the ventral tegmental area to the nucleus accumbens. However, most of the relevant evidence for this hypothesis has been derived from LI studies (e.g., Solomon and Staton, 1982; Weiner et al., 1988). The septo-hippocampal system also seems to be important. Lesions to the hippocampus eliminate both LI (Ackil et al., 1969; Kaye and Pearce, 1987) and the PREE (Rawlins et al., 1980; Sinden et al., 1988). Moreover, lesions of the dorsal septal area disrupt LI and the PREE (Feldon and Gray, 1979; Weiss et al., 1974), whereas lesions of the medial septal area enhance both phenomena (Feldon and Gray, 1979; Turgeon et al., 2001).

Other manipulations have also shown parallels between LI and the PREE. Both phenomena are eliminated by the benzodiazepine anxiolytic chlordiazepoxide (Feldon and Gray, 1981; Feldon and Weiner, 1989; LaCroix et al., 2000; McNaughton, 1984), and by chronic administration of the angiotensin-converting-enzyme-inhibitor ceronapril, presumably by indirectly increasing dopamine in the nucleus accumbens (Weiner et al., 1994). Both LI and the PREE can also be disrupted by manipulations of early rearing experience. Male rats that are not handled by the experimenter prior to weaning show an absence of both LI and the PREE when assessed during adulthood (Feldon et al., 1990; Feldon and Weiner, 1988).

Whereas not all experiments have provided support for this LI=PREE hypothesis (e.g., fimbria-fornix lesions disrupt the PREE but not LI; Weiner et al., 1998; Feldon et al., 1985), the body of research cited above suggests that these two learning phenomena may share at least some neural mechanisms. Two experiments were designed as further tests of the LI=PREE hypothesis. They did so by using an approach that takes advantage of individual differences in rats' performance in each of the tasks. According to the LI=PREE hypothesis, if the same rats are given both LI and PREE training, then an individual's performance in one should correlate with its performance in the other. Experiment 1 was designed to assess whether rats that show especially strong suppression of behavior after CS-preexposure also show enhanced resistance to extinction after PRF training. Similarly, rats that show large disruption of performance after CS-preexposure caused by a pharmacological manipulation should also show large disruptions of extinction after PRF training caused by the same drug. Experiment 2 was designed to assess this possibility using the benzodiazepine anxiolytic chlordiazepoxide.

1. Experiment 1

Experiment 1 tested the LI=PREE hypothesis using a novel approach involving the testing of both learning phenomena in the same organisms. This approach allows for a comparison of the effects in terms of group differences and also exploits individual differences in performance. The former analysis is common in studies of animal learning and it involves typical experimental designs (e.g., analysis of variance). The latter analysis is less typical of animal learning studies and it exploits the universal fact that individuals differ in their behavioral adjustments to almost any type of situation. Such variability is common to most biologically relevant traits and, although usually neglected in animal learning studies, it also embodies potentially relevant information for an understanding of behavioral plasticity (West-Eberhard, 2003). Accordingly, the same rats received training in both CS-preexposure and PRF, and the individual's performance in each was compared. Flaherty et al. (1998) used a similar approach to assess the relationship between four animal models of anxiety. All rats were tested in consummatory successive negative contrast, open-field activity, elevated plus-maze, and contextual fear conditioning. Flaherty et al. (1998) concluded that models that produced correlated behavioral outcomes were probably measuring the same underlying variable. Experiment 1 applied this rationale to test the LI=PREE hypothesis. Based on this hypothesis, it was expected that rats that showed strong suppression of behavior after CS-preexposure and during CS–US pairings would also show more resistance to extinction after acquisition training with PRF. Control groups were included to assess both LI and the PREE.

2. Method

2.1. Subjects

The subjects were 32 male, experimentally naïve Wistar rats. They were approximately 90 days old at the beginning of the experiment. Their ad libitum weights ranged between 350 and 450 g, and they were maintained at 85% of this weight by limiting daily access to food throughout the experiment. Animals were housed in individual wire-bottom cages with water available at all times and were kept in a 12:12 h light:dark cycle (lights from 07:00 to 19:00 h). Training sessions were administered in the middle portion of the light cycle (between 12:00 and 17:00 h).

2.2. Apparatus

Four standard operant chambers (MED Associates) each enclosed in a sound-attenuating chamber were used for this experiment. Boxes were altered to form two distinct contexts, referred to as *X* and *Y*, and distinguished in terms of olfactory and tactile cues (see Boughner and Papini, 2006a). The boxes were 20.1 cm wide, 28 cm long, and 20.5 cm high. For context *X*, the floor of the boxes consisted of a grid floor made with stainless steel bars, 0.4 cm in diameter and spaced 1.6 cm apart. Underneath the grid floor was a pan filled with corncob bedding, which presumably provided a distinct odor. The food cup was located on the front wall of the chamber, 2 cm above the floor. Two retractable levers were located 1 cm to the right and left of the feeder, and 6 cm above the floor. Pellet dispensers delivered 45 mg Noyes pellets (rodent formula AI). The sound-attenuating chambers were equipped with a light (GE 1820) that provided diffuse illumination, a speaker that administered white noise, and a fan for air circulation. Background masking noise (speaker and fan) registered 75 dB (SPL, scale C). Context *Y* was set up in the same boxes as context *X*, but altered to make it distinct. A smooth porcelain tile was laid over the grid floor to provide different tactile stimulation. Moreover, the corncob bedding was removed and replaced by two drops of peppermint oil (Humco 100% oil). Previous research shows that rats readily discriminate between these contexts (Boughner and Papini, 2006a). A computer located in an adjacent room controlled session events and recorded the number of lever presses.

2.3. Procedure

Prior to training, rats received two 20-minute sessions of habituation to the context. On the third day, rats were randomly assigned to one of four groups. Group names reflect the procedure administered during the LI stage (either nonreinforced preexposure to the CS and training context, LI, or nonreinforced preexposure to a different context, Con), followed by a slash and then the procedure given during the PREE stage (either continuous reinforcement, CR, or partial reinforcement, PR).

The LI stage was divided into two phases: preexposure and autoshaping. During the preexposure phase, Groups LI/PR and LI/CR received 12 sessions with 10 trials/session in context *X*. On each trial, the left lever (the CS) was presented for 10 s with no consequences. The average intertrial interval was 90 s (range: 60–120 s). Groups Con/PR and Con/CR received an equivalent amount of contextual exposure, but in the nontarget context *Y*. Contexts were not counterbalanced because previous research demonstrated similar conditioning effects in each of these two contexts (Boughner and Papini, 2006a, Experiment 1). During these sessions, the house light was turned on at the start of the session and off at the end of the session, but no other programmed events occurred.

Starting on the day following preexposure, all rats received 10 sessions of autoshaping training, with 10 trials/session. In autoshaping, the right lever (the CS) was presented for 10 s and followed by the response-independent delivery of one food pellet (the US). Intertrial intervals were the same as during CS-preexposure. All rats received this training in context *X*.

The PREE stage started the day following the last autoshaping session of the LI stage and it involved two phases: acquisition and extinction. All training in the PREE stage took place in context *X*. In acquisition, Groups LI/PR and Con/PR received 15 sessions, at 10 trials/session, in which the right lever (the CS) was presented for 10 s and followed by the response-independent delivery of 5 food pellets (the US) on a random half of the trials. Pellets were delivered in rapid succession at a rate of one every 0.2 s. These changes in the lever (right vs. left) and

number of pellets (1 vs. 5) between the LI and PREE stages were introduced in an attempt to reduce stimulus generalization across the autoshaping and acquisition phases. On the other half of the trials, the lever was presented as described before, but no pellets were delivered. The average intertrial interval was 60 s (range: 45–75 s), while the interreinforcement interval was 120 s on average (range: 90–150 s). Groups LI/CR and Con/CR received the same treatment as their PR counterparts, except that nonreinforced trials were omitted. Each of the 10 trials/session ended with the delivery of 5 pellets. Thus, the intertrial and interreinforcement intervals averaged 120 s (range: 90–150 s). PR and CR groups were matched by the number and temporal distribution of USs during acquisition training. The sequence of reinforced and nonreinforced trials for the PR groups was determined prior to the session by randomly choosing from a series of sequences from Gellermann (1933).

After the last session of acquisition, all rats were switched to extinction. This consisted of the same number and distribution of trials, and the same general training parameters as described above for the CR groups, but all the USs were omitted. A total of 10 extinction sessions were administered.

Responses recorded on each trial were transformed to responses/min and subjected to two types of analyses. Conventional analysis of variance (ANOVA) was used to determine group effects in each of the two stages of the experiment, the LI and PREE states. In addition, Pearson's product–moment correlations were calculated on measures of LI and the PREE. In all cases, an alpha value equal or smaller than 0.05 was set and, where appropriate, two-tailed tests were used for statistical inference. For brevity, p values were omitted in the text.

3. Results

3.1. Assessing LI and the PREE

In Fig. 1, the top panel presents the results of the LI portion of the experiment, whereas the bottom panel presents the results of the PREE portion of the experiment. Because of the sequential nature of the four phases of this experiment, when the animals reached the PREE portion they had different LI experience: either exposure to the CS and context, or just to the context. Consequently, the results of the PREE phase were analyzed taking into account the treatment received in the previous phases.

During the CS-preexposure phase, the somewhat intermediate levels of initial responding habituated rapidly to a very low asymptotic level. As in other similar experiments, lever-contact responses do not entirely disappear under nonreinforced conditions (Boughner and Papini, 2006b). A mixed-model ANOVA revealed significant levels of response habituation across sessions, $F(11, 165)=13.06$. During the autoshaping phase, nonreinforced CS-preexposure led to less responding than that observed in a group preexposed only to a nontarget context. A Group by Session ANOVA revealed a significant difference across groups, $F(1, 30)=8.25$, that confirms the presence of LI. There was also a significant increase in responding across sessions, $F(9, 270)=33.50$, but the group by session interaction did not reach significant levels, $F<1$.

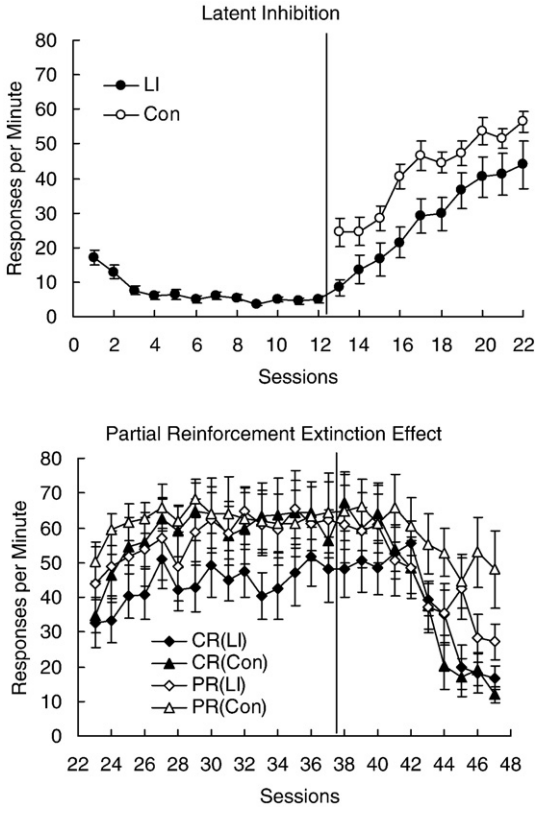

Fig. 1. The top panel shows the results of the latent inhibition phase for groups receiving CS-preexposure in the target context (LI) or exposure to a nontarget context (Con) and later trained in an autoshaping situation. Following the previous training, rats were trained in either continuous (CR) or partial reinforcement (PR) in an autoshaping situation and then given extinction training (bottom panel). The CSs were different levers in the LI and PREE phases of the experiment. The results of the PREE portion of the experiment are presented as a function of prior nonreinforced preexposure to the CS (LI) or to the control condition (Con).

Fig. 1, bottom panel, shows that responding for the partially reinforced rats during the acquisition phase was consistently lower for the group that received CR training and had previously received nonreinforced preexposure to the CS. Although different levers were used in the LI and PREE portions of this experiment, considerable generalization of LI was expected. In extinction, there was evidence of higher response level in the two PR groups than in the two CR groups, consistent with the presence of a PREE. A mixed-model ANOVA was calculated for each phase with the current reinforcement treatment (CR vs. PR), the previous treatment (LI vs. Con) and sessions as the factors. For the acquisition phase, there was a significant increase in responding across sessions, $F(14, 392)=6.62$, but none of the other interactions, Fs <1, or main effects, Fs <1.71, achieved significance. Thus, although visually inferior, there was no statistical evidence that nonreinforced preexposure to a similar CS in phase 1 reduced responding to the CS used in phase 3 of this experiment.

For the extinction phase, the same design revealed a significant interaction between the schedule of reinforcement (CR vs. PR) and sessions, $F(9, 252)=2.70$, and between schedule, CS-

preexposure, and session, $F(9, 252)=2.51$. The first is consistent with the presence of the PREE, whereas the second suggests that the PREE was weaker in the groups that had previously received nonreinforced preexposure to the CS. The extinction effect was also significant, $F(9, 252)=26.16$. The interaction between schedule and CS-preexposure was nonsignificant, $F<1$, as was the main effect of CS-preexposure, $F(1, 28)=1.22$. The main effect of schedule approached, but did not achieve significance, $F(1, 28)=3.77$, $p=0.062$.

3.2. Correlational analyses

Two types of correlational analyses were calculated on the data. First, the sizes of LI and PREE were estimated according to a procedure described below and the scores correlated in rats that had experienced nonreinforced CS-preexposure and either partial or continuous reinforcement training. To make the relationship between these two phenomena easier to understand, the data were converted into two variables that transformed the response rate of each individual animal in the experimental group relative to the overall response rate obtained for their corresponding control group. Thus, each rat provided a measure of "LI-size" and of "PREE-size" that could then be correlated. LI-size was defined as the mean response rate for all 10 sessions of acquisition in the two control groups that did not receive CS-preexposure (Groups Con/PR and Con/CR) divided by the sum of that mean plus the average individual response rate over the 10 autoshaping sessions of the rats that had received CS-preexposure (Groups LI/PR and LI/CR). Thus if an individual rat had a mean of 10 responses/min over the course of acquisition training and the control rats averaged 50 responses/min, the LI-size score for that rat was equal to $50/(10+50)=0.83$. Notice that the higher the ratio, the greater the suppression of behavior, and thus the larger the size of the LI effect.

To calculate PREE-size, the individual average extinction responding of partially reinforced rats (Groups LI/PR and Con/PR) was divided by the sum of that response rate plus the mean for extinction performance in the continuously reinforced rats (Groups LI/CR and Con/CR). In this case, the greater the PREE-size, the slower extinction progressed for that rat and, therefore, the greater the size of the PREE. If the PREE and LI share a common mechanism, a significant positive correlation should be found for these two measures, namely, the greater the suppression observed after nonreinforced CS-preexposure (relative to exposure to a nontarget context), the greater the persistence observed during extinction after partial reinforcement training (relative to extinction after continuous reinforcement training).

As shown in Fig. 2, top panel, the size of these two effects was actually opposite to the prediction derived from the LI=PREE hypothesis. The correlation between the two variables was negative and significant, $r(6)=-0.74$. This negative correlation suggests that the mechanisms underlying LI and the PREE work against each other, at least in the autoshaping situation with rats. To determine whether the relationship was specific to the partial reinforcement condition, a similar analysis was performed using extinction after continuous reinforcement as the experimental condition, compared to extinction after partial reinforcement as the control condition. The data come from Group LI/CR and portray a sort of CREE effect (i.e., extinction after continuous reinforcement relative to partial reinforcement training). As shown in Fig. 2, bottom panel, there was no detectable relationship between LI and the CREE, $r(6)=0.19$.

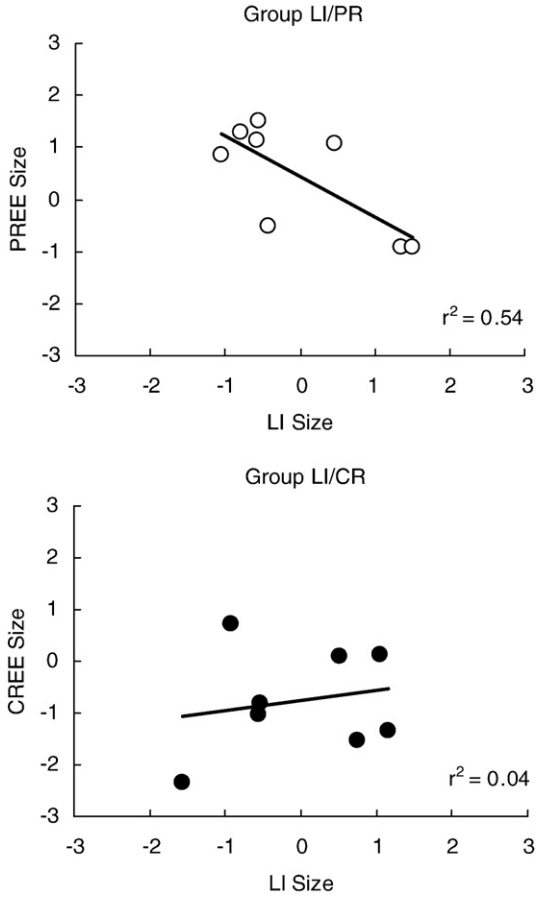

Fig. 2. The top panel shows the correlation between PREE-size and LI-size in a group that received both CS-preexposure and partial reinforcement training. The bottom panel shows a similar calculation for a group receiving CS-preexposure and continuous reinforcement training. See text for details.

Second, the rate of behavioral change was estimated according to a procedure applied by Boughner and Papini (2006b) to LI data. Briefly, when the response rates across autoshaping sessions in individual rats are transformed to cumulative scores, the resulting functions are remarkably linear, as shown in Fig. 3 for group averages. A linear equation of the form $Y=a+bX$ is then obtained for each rat and the b parameter (slope) used for correlational analyses. This approach provides an assessment of the relationship between rates of behavioral accumulation during specific phases of training, across animals. Thus, a rat that shows substantial autoshaping retardation after CS-preexposure (few responses) and slow extinction after PR training (many responses) should produce a low b for LI and a high b for PREE. When all scores are compared, the critical comparison for Group LI/PR should yield a negative correlation.

Table 1 shows the average coefficients of determination obtained for individual linear fits. Only one average falls below

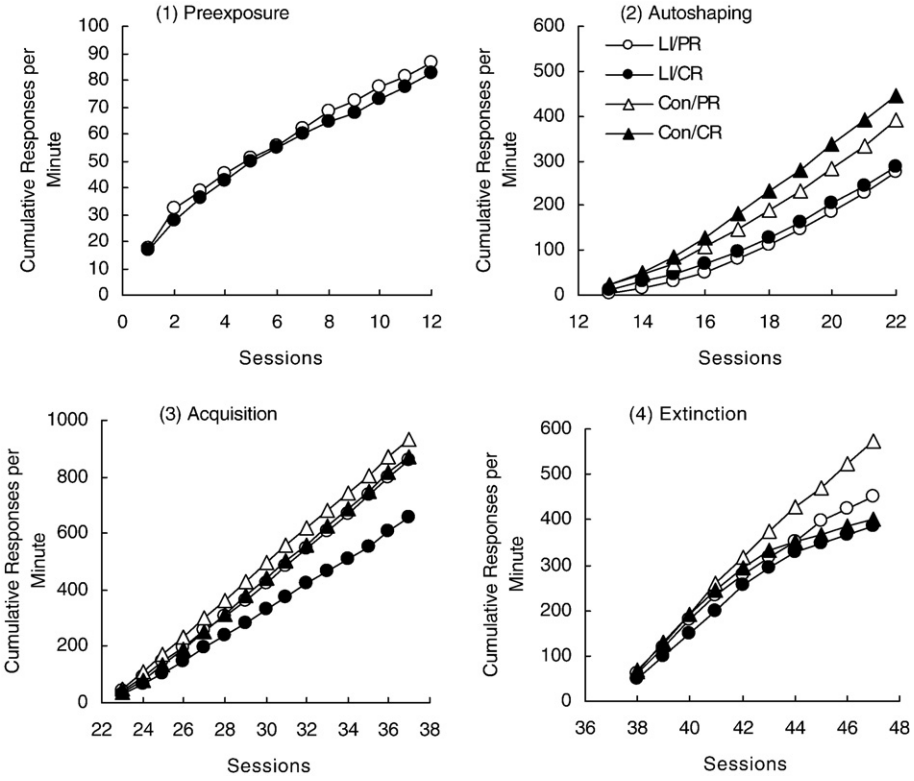

Fig. 3. Cumulative response rate functions for each group and phase of training show remarkably linear changes in behavior. Linearity is also characteristic of the performance of individual animals.

0.9 (Group LI/PR, autoshaping) due to an animal that showed poor acquisition of the lever-contact response, yielding an $r^2=0.45$. Excluding this animal, the average increases to 0.94. Table 2 presents the univariate coefficients of correlation for pairs of phases in each group separately. The main result is signaled by the intersection of the two rectangles, that is, the correlation in the rates of change between autoshaping and extinction in Group LI/PR. The coefficient is positive and relatively high, $r(6)=0.599$, but falls short of significance. The positive sign of the correlation suggest that a low response accumulation during acquisition after CS-preexposure (slow acquisition, as it is expected for a strong LI effect) was correlated with a low response accumulation during extinction after PR training (fast extinction, as expected of a weak PREE). The correlation coefficient drops to $r(5)=0.457$ if the rat with a poor linear fit is removed from the sample, so the lack of significance is not attributable to this single rat. This result provides no support for the LI=PREE hypothesis.

Table 1
Coefficients of determination for each group and phase in the cumulative response rate analyses

	LI/PR	LI/CR	X/PR	X/CR
Preexposure	0.94	0.97	–	–
Autoshaping	0.88	0.95	0.98	0.99
Acquisition	0.99	0.99	0.99	0.99
Extinction	0.97	0.94	0.99	0.91

The coefficient of determination is equal to r^2, where r is Pearson's coefficient of correlation.

Only three correlations were significant in Table 2. Group LI/PR showed a significant positive correlation in the autoshaping vs. acquisition comparison, $r(6)=0.787$. Low response accumulation in autoshaping after CS-preexposure was correlated with low response accumulation in acquisition under PR (Group LI/PR); notice, however, that the same did not occur under CR (Group LI/CR). This correlation suggests a common mechanism operating across the two treatments involving nonreinforced presentations of the CS–LI and PR. Group LI/PR also showed a significant positive correlation in the acquisition vs. extinction comparison, $r(6)=0.938$, again highlighting the correspondence between procedures involving CS-preexposure. The analogous correlation for Group LI/CR was also positive, but nonsignificant, $r(6)=0.458$. The third significant correlation

Table 2
Correlations across training phases for rate of change

	LI/PR	LI/CR	X/PR	X/CR
Preexposure vs. Autoshaping	0.642	−0.020	–	–
Preexposure vs. Acquisition	0.328	−0.433	–	–
Preexposure vs. Extinction	0.156	−0.507	–	–
Autoshaping vs. Acquisition	0.787*	−0.180	0.373	−0.103
Autoshaping vs. Extinction	0.599	−0.180	0.382	0.658
Acquisition vs. Extinction	0.938**	0.458	0.882**	−0.002

Rates of change were indexed by regression analysis. Session response rates were transformed to cumulative rates across sessions, a linear regression fit was calculated for each rat in each training phase, and the b parameter of the linear equation ($Y=a+bX$) computed for each rat and training phase used in these correlational analyses. For all coefficients of correlation, $df=6$. $r_{(6,\ 0.05,\ \text{two-tailed})}=0.707$. *, $p<0.05$. **, $p<0.01$.

in Table 2 occurred for Group Con/PR in the acquisition vs. extinction comparison, $r(6)=0.882$. This correlation suggests that poor acquisition under PR was associated with fast extinction in the subsequent phase, again reflecting a correspondence between conditions involving CS-trials.

Whereas these results do not provide support for the LI=PREE hypothesis, they do suggest that there is a connection between CS-training and partial reinforcement training. This connection may be appreciated more clearly in Fig. 4, which represents the rats in Groups LI/PR and LI/CR segregated according to their performance in the autoshaping phase into low (*L*) and high (*H*) performers using a median split procedure (*n*s=4). Autoshaping performance was selected as a reference point because it was the first phase of training shared by all the groups. The average response rate for the entire 10 sessions of autoshaping was computed and rats were rank ordered according to this average. The four rats with the lowest average response rate were then assigned to the *L* subgroup, whereas the four with the highest average were assigned to the *H* subgroup. The question of interest is how *L* and *H* autoshaping responders performed in the training phases that preceded and followed autoshaping. Group by Session ANOVAs were calculated for each phase (the group effect of each analysis is emphasized for brevity).

Fig. 4, top panel, shows the performance of the *L* and *H* subgroups in the partial reinforcement condition (Group LI/PR), as well as that of their control condition, Group Con/PR. Not surprisingly, the median split procedure successfully segregated the subgroups in autoshaping, creating a significant difference between them, $F(1, 6)=40.37$. *L* and *H* subgroups did not differ during preexposure, $F(1, 6)=1.05$. Most interestingly, the *H* and *L* subgroups remained essentially unchanged during the acquisition phase, while undergoing partial reinforcement training. In this case, *L* was significantly below *H*, $F(1, 6)=15.94$, and below Group Con/PR, $F(1, 10)=4.96$, whereas *H* and Con/PR did not differ from each other, $F(1, 10)=3.05$. *L* also performed significantly below *H* and Con/PR during extinction, Fs>5.26, whereas *H* and Con/PR did not differ from each other, $F<1$.

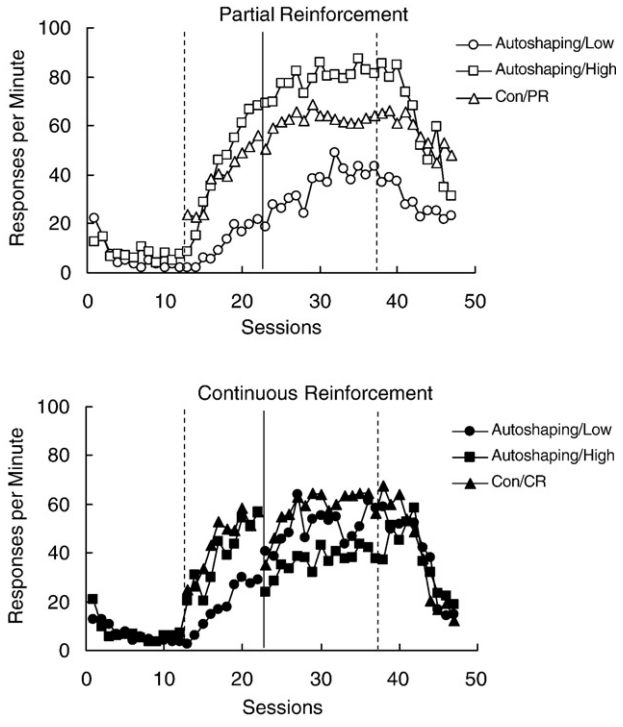

Fig. 4. Groups receiving partial (top panel) or continuous reinforcement (bottom panel) during the third phase were segregated into high and low responders during the second phase of training. The respective control group was included for comparison.

Fig. 4, bottom panel, shows a different distribution of group scores for rats exposed to continuous reinforcement training (Group LI/CR), relative to their control (Group Con/CR). Again, the median split procedure produce significantly different group performance during the autoshaping phase, $F(1, 6)=24.63$. *L* and *H* subgroups did not differ, however, during the CS-preexposure phase, $F<1$, the acquisition phase under continuous reinforcement, $F(1, 6)=1.03$, or the extinction phase, $F<1$. If anything, the high responders in autoshaping actually exhibited a tendency (albeit a nonsignificant one) to perform below the level of the low autoshaping responders during the continuous reinforcement phase of training. Low responders also performed significantly below Group Con/CR during autoshaping, $F(1, 10)=18.63$, although these groups were not different during subsequent acquisition under continuous reinforcement or extinction, Fs<1. In turn, high autoshaping responders were not different from Group Con/CR during autoshaping, $F<1$, or in any of the other two phases, acquisition and extinction, Fs<3.24.

In conclusion, Experiment 1 shows that while LI and the PREE were not related, nonreinforced preexposure to the CS and partial reinforcement training were correlated to distinct levels of responding in specific rats. Individual differences in autoshaping performance after CS-experience were directly related to performance during partial reinforcement, while bearing no detectable relationship to performance under continuous reinforcement.

4. Experiment 2

Experiment 1 provided evidence that LI and the PREE are based upon different mechanisms. The two phenomena were not correlated in a manner consistent with the LI=PREE hypothesis. The experiment did, however, identify a relationship of responding that suggested that autoshaping performance was correlated across various procedures and parameters. In addition, Experiment 1 provided a framework for studying LI and the PREE by showing that they can be obtained in the same rats and within a single experiment. Therefore, comparisons across experiments with different rats trained at different times and under different conditions are not required. Experiment 2 utilized the same basic design used in the previous experiment to study the effects of the benzodiazepine anxiolytic chlordiazepoxide (CDP) on both LI and the PREE. While testing the effect of CDP on LI and the PREE is not novel, testing its effect within the same experiment and in the same group of rats is a novel procedure.

As mentioned above, CDP eliminates both LI and the PREE. For example, Feldon and Gray (1981; Experiment 2) administered a 5 mg/kg dose (i.p.) prior to every session of runway acquisition in a PREE design. During the acquisition phase, continuously reinforced rats received 16 trials, at one trial/day, in which running resulted in the delivery of 20 pellets, whereas partially reinforced rats were reinforced in a random half of the trials. Extinction trials were similar to acquisition trials, except that the reward was omitted and saline was administered before each trial. Feldon and Gray (1981) found evidence of the PREE in rats treated with saline during acquisition, but no evidence of the PREE in rats tested with CDP during acquisition. PREE disruption was caused almost entirely by decreased persistence in the partial reinforcement group.

LI is also disrupted when CDP is administered prior to CS-preexposure. Feldon and Weiner (1989) preexposed rats to either 0 or 40 presentations of a tone CS after either CDP (5.0 mg/kg, i.p.) or saline treatment. In a subsequent acquisition phase in which the CS was paired with shock US, saline groups showed evidence of LI, whereas the CDP groups responded to the CS at the same level, whether or not they received CS-preexposure. The disruption of LI was caused by increased responding in the preexposed rats and not by a depression of performance in the controls.

The LI=PREE hypothesis suggests that any variable that affects one of the two phenomena, should affect the other in the same direction because the underlying mechanisms are the same. Thus, just as CDP was shown independently to affect both LI and the PREE, Experiment 2 should produce confirming results when the manipulation is implemented within the same experiment and group of subjects.

5. Method

5.1. Subjects and apparatus

The subjects were 64 male, experimentally naïve Wistar rats. They were approximately 90 days old at the beginning of the experiment. Housing and maintenance were the same as in Experiment 1. The same apparatus was also used, including the same arrangements of the two contexts.

5.2. Drugs

Chlordiazepoxide (Sigma Chemicals, USA) was dissolved into sterile isotonic saline (0.9%) to a concentration of 5.0 mg/ml. Both CDP and saline were administered at a 1.0 ml/kg volume by i.p. route. All injections were given 20 min before the start of the session (e.g., Feldon and Gray, 1981).

5.3. Procedure

Rats were randomly assigned to one of eight groups ($n=8$). Group names refer to the procedure administered during the LI stage, the procedure given during the PREE stage, and the drug condition (e.g., LI/CR/Sal, Con/PR/CDP, etc.). For the groups assigned to the saline conditions, the training conditions were exactly the same as in Experiment 1, except that an injection of saline was administered before each session. For the groups assigned to the CDP conditions, the training conditions were also the same, except that CDP was administered before each session as specified above. Injections were administered before every session for two reasons, namely, to avoid state dependency and to avoid possible withdrawal symptoms that could arise if CDP were withdrawn at some stage of training.

6. Results and discussion

Early during the CS-preexposure phase, one rat died in Group LI/CR/CDP. The data from this animal were excluded from all the analyses (thus, $n=7$ for this group).

6.1. Assessing drug effects on LI

Fig. 5 shows the results of Experiment 2 for the LI phase. During this phase, rats had not yet received partial and continuous reinforcement training. Thus, the design can be represented as a 2×2 with Preexposure (Con, LI) and Drug (Sal, CDP) as the between-subject factors, and Sessions as the repeated-measure factor. Three of the four groups thus formed (Con/Sal, LI/Sal, and Con/CDP) has 16 rats each, whereas Group LI/CDP had 15 rats.

A Drug by Session (1–12) for the preexposure phase indicated a significant interaction effect, $F(11, 319)=5.91$. There were also significant main effects for drug, $F(1, 29)=40.76$, and session, $F(11, 319)=6.08$. Thus, CDP administration reduced response rate relative to the saline condition, especially during the first training session. The significant session effect indicates the long-term habituation of the orienting response to the lever CS. The significant interaction reveals that CDP disrupted this habituation process by lowering the initial response to the lever CS.

Fig. 5 also shows the results of the autoshaping phase that tested for LI. As in Experiment 1, there was a clear indication that CS-preexposure reduced response rate relative to the control condition. However, LI was present in both CDP and saline conditions and did not appear to be affected by the drug treatment. A Preexposure by Drug by Session (13–22) analysis revealed a significant effect of preexposure, $F(1, 59)=18.48$,

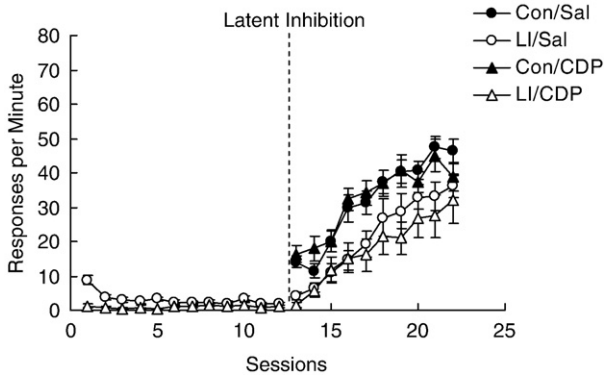

Fig. 5. Effects of CDP on lever-pressing performance during the preexposure and autoshaping phases of training. Groups received either CS-preexposure (LI) or exposure to a nontarget context (Con).

which confirms the presence of LI. The acquisition effect across sessions was also significant, $F(9, 531)=67.41$. No other factors or interactions were significant, Fs<1.49. The lack of a significant CDP main effect or of any interaction involving CDP indicates that CDP had no detectable influence on LI.

6.2. Assessing drug effects on the PREE

The results from the PREE phase are presented in Fig. 6 separately for groups that received the CS-preexposure (bottom panel) or no preexposure treatment (top panel) during the LI phase of the experiment. A Schedule (PR, CR) by Drug (Sal, CDP) by Preexposure (Con, LI) by Session (1–15) analysis for the acquisition sessions indicated only a significant acquisition effect, $F(14, 770)=22.15$. None of the other main effects of interactions reached significance, Fs<1.99.

Fig. 6 also shows the extinction performance of all the groups. A PREE is apparent in all the groups, independently of the drug and LI treatment. Although the PREE was evident in groups treated with CDP, it developed more slowly than in the corresponding saline control groups. A Schedule by Drug by Preexposure by Session (16–25) analysis provided the following results. The retardation of the PREE by CDP-treated groups was detected in terms of an interaction between schedule, drug, and sessions, $F(9, 495)=2.33$. There were also significant interactions between schedule and sessions, $F(9, 495)=9.37$ and drug and sessions, $F(9, 495)=2.88$. There was also a significant main effect of preexposure, $F(1, 55)=7.82$. All the other effects were nonsignificant, Fs<1, except for an interaction between schedule, preexposure, and sessions, $F(9, 495)=2.41$, indicating that the PREE was stronger in rats that had received CS-preexposure than in preexposure controls.

In conclusion, Experiment 2 replicated the effects of CDP on the PREE, but failed to detect any effect of CDP on LI. Although the reasons for the lack of an effect of CDP on LI in the autoshaping situation are unclear, the results indicate that LI and the PREE responded differentially to CDP treatment under the same conditions of training.

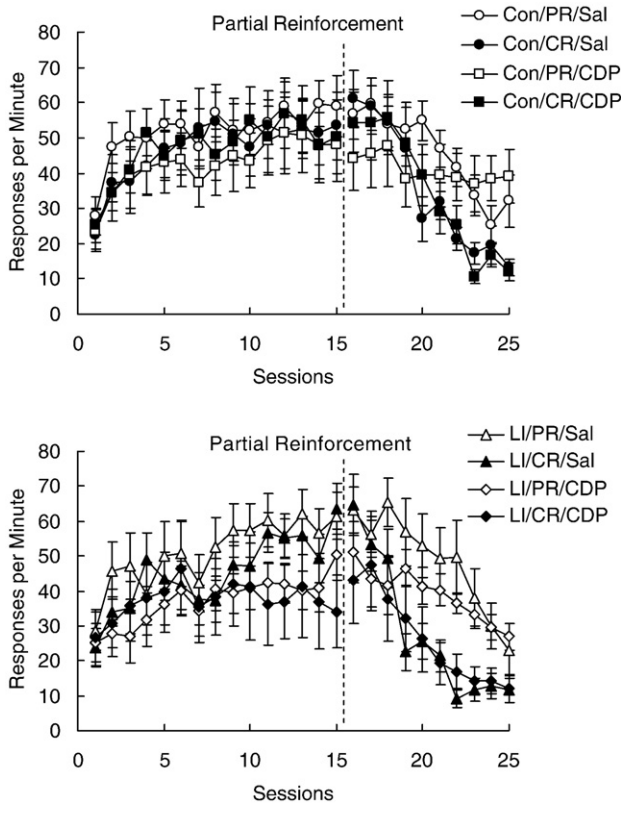

Fig. 6. Effects of CDP on lever-pressing performance during acquisition under partial reinforcement (PR) or continuous reinforcement (PR), segregated according to whether they had received CS-preexposure (LI; bottom panel) or exposure to a nontarget context (Con; top panel).

7. General discussion

Both LI and the PREE are readily observed in the autoshaping preparation with rats (Boughner and Papini, 2006a,b; Boughner et al., 2004) and can be induced in the same animals, in sequential fashion, as shown in the present experiments. This feature opened the way for an empirical testing of the LI=PREE hypothesis advanced on the basis of analogous results obtained in separate experiments (Gray and McNaughton, 2000). The present procedure tested this hypothesis under the same conditions and in the same animals, thus providing a more direct assessment. The data thus obtained provided no support for the LI=PREE hypothesis. Experiment 1 approached the problem from an individual-difference perspective, asking whether the strength of LI and the PREE were correlated when both effects were produced in the same animals and under similar conditions of training. Individual differences did not correlate in a manner consistent with shared mechanisms. Experiment 2 approached the problem from a pharmacological perspective, asking whether the same drug, CDP, would disrupt both behavioral phenomena in a similar manner and in the same animals. CDP retarded the emergence of the PREE, but had no effect on LI, even though it reduced lever-pressing performance during the preexposure phase. This result demonstrates that LI and the PREE can be dissociated pharmacologically, at least in the autoshaping preparation.

These conclusions must be tempered by some considerations. For example, the design of both experiments is open to the criticism that the order of training phases was not counterbalanced. Thus, rats were trained first in the LI design and then on the PREE design. Lack of counterbalance implies that LI and PREE were not completely independent. As Fig. 6 shows, extinction performance was influenced by prior preexposure training during the initial phase. It is plausible that LI could also be influenced by prior partial reinforcement training. One problem with counterbalancing the sequence in this particular case is that CS-preexposure would not be accomplished in a relatively neutral context and to a relatively neutral CS, as it was the case in these experiments. The potential for contextual conditioning from a prior phase of continuous or partial reinforcement would introduce the possibility that an eventual retardation of acquisition would reflect contextual blocking on the target CS, rather than LI (see Boughner et al., 2004). If the

degree of dependency between these two effects would have been high, one would expect a variety of spurious correlations that were, in fact, not observed.

During the CS-preexposure phase, administration of CDP clearly reduced unconditioned lever pressing relative to the saline controls. This result is consistent with at least two other reported findings. First, CDP has been found to reduce novelty-induced behavior, such as rearing responses in a novel environment (Cole, 1983; Iwahara and Sakama, 1972; Nieto and Posadas-Andrews, 1984). Unconditioned lever pressing may be viewed as a novelty-induced response that habituates with continued exposure to the lever (Boughner and Papini, 2006b). This potential effect of CDP cannot explain all the results obtained in Experiment 2. For example, the lower terminal levels in the autoshaping and acquisition phases in rats receiving CDP treatment cannot be attributed to a novelty-related factor because at this point rats had received extensive exposure to the lever. Similarly, lower terminal levels in CDP-treated rats cannot be attributed to drug-induced motor impairment (Lorivel and Hilber, 2006) because that was not obvious during early acquisition and extinction sessions, despite extensive previous drug administration. If CDP disrupted motor performance, a consistent reduction in autoshaping performance should have been observed across all phases.

CDP had no detectable effect on LI in the autoshaping situation. Rats preexposed to the CS responded at lower levels than control rats whether they had received CDP or saline treatment. This lack of effect cannot be attributed to an ineffective drug dose or an insensitive dependent variable because CDP had significant effects during CS-preexposure and extinction. Furthermore, the fact that CDP affected preexposure, but not autoshaping, adds to the evidence that LI is not a simple consequence of preexposure performance interfering with autoshaping performance (see Boughner and Papini, 2006a,b). These results were at variance with those reported for other training preparations in which CDP was found to disrupt LI (e.g., Feldon and Weiner, 1989). At least three factors can account for these disparate results. First, it is possible that the disruption of LI after CDP treatment reported in other studies is not a true disruption. In one study (Feldon and Weiner, 1989), LI was said to be disrupted when CDP was administered during both CS-preexposure and acquisition, as done in the present experiment. However, for reasons that were not clear, both groups receiving CDP administration, whether given CS-preexposure or not, exhibited low levels of conditioned responding. Thus, Feldon and Weiner's results may reflect an effect of CDP on conditioning, rather than on LI. This result is not entirely surprising if one considers that the anxiolytic properties of CDP may have affected fear conditioning in the conditioned suppression preparation used by Feldon and Weiner (1989). In the only other study reporting disruptive effects of CDP on LI, the drug was administered only during the CS-preexposure phase (LaCroix et al., 2000). Such a disruptive effect may be interpreted as a byproduct of state dependency. LI is known to be debilitated by a change in external context (e.g., Hall and Channell, 1985) and state-dependent learning is known to act at least in part by creating an internal context equivalent to the role played by external contextual cues in conditioning (e.g., Maes and Vossen, 1997). Thus, if CDP administered during preexposure created an internal context, then discontinuing the drug during acquisition training may have modified this internal context, thus reducing LI. It is then possible that the apparent effect of CDP on LI reported in previous studies may be explained in terms of state-dependent learning. In Experiment 2, CDP was administered before each session, in both CS-preexposure and acquisition, thus eliminating state dependency as a potential factor. Furthermore, normal levels of conditioning were observed in these groups, in comparison with other experiments carried out under similar conditions (e.g., present Experiment 1; Boughner and Papini, 2006a,b; Boughner et al., 2004). Thus, the absence of a CDP effect on LI in the present experiment sheds doubt on the interpretations advanced to explain the results of previous experiments (Feldon and Weiner, 1989; LaCroix et al., 2000).

The fact that CDP had no effect on LI may be a result specific to the autoshaping situation. Rat autoshaping is not commonly used in LI or PREE experiments (see Boughner and Papini, 2006a,b; Boughner et al., 2004), although the effects were readily observed and there are no theoretical reasons to anticipate that these phenomena would be any different than in more typical training situations. CDP may, in fact, reduce attention to a novel stimulus during CS-preexposure, as it happened in Experiment 2, and therefore disrupt LI. However, it might be argued that in the autoshaping situation the effects of CDP are exhibited by behaviors other than lever pressing. Available evidence suggests that different responses recorded concurrently can be differentially sensitive to the effects of CS-preexposure. For example, Boughner and Papini (2003) reported that CS-preexposure caused deficits in sign tracking (orientation toward a light CS) but not in goal tracking (orientation toward the US site). Thus, it is possible that the effects of CDP on acquisition after CS-preexposure are obscured by other factors that influence lever-pressing responses.

Comparisons across experiments are also complicated by the use of different control conditions in the two experiments in which CDP was administered throughout both phases of training (i.e., present Experiment 2; Feldon and Weiner, 1989). In Feldon and Weiner's experiment, acquisition in a group preexposed to the CS was compared to acquisition in a group preexposed to the training context. Boughner et al. (2004) demonstrated that, under certain conditions, preexposure to the context actually facilitates conditioning to the CS during acquisition. Such facilitation is eliminated when the preexposure context is different from the acquisition context, as used in the present experiment. Thus, the use of a context control may inflate the evidence for LI obtained in the saline conditions by Feldon and Weiner (1989).

The results of the extinction phase were similar to those reported by Feldon and Gray (1981) for a condition in which CDP was administered before both acquisition and extinction trials, as in the present experiment. In both studies, CDP increased resistance to extinction in CRF and PRF rats. The presence of a significant Schedule by Drug by Session interaction in the present Experiment 2 indicated that the time course for the appearance of

the PREE was delayed in the CDP groups, relative to the saline groups. In summary, Experiment 2 produced the expected results in terms of the effects of CDP on the PREE, but not in terms of its effects on LI.

Finally, consider the potential value of the individual-difference approach utilized in Experiment 1. Correlational analyses could be valuable tools for testing theories claiming that LI or the PREE shares some underlying mechanism with any other learning phenomenon, while simultaneously minimizing the number of animals used to demonstrate such correlations. The rationale for this technique lies in the universal rule that all behavioral effects exhibit variability across individuals caused by differences in genetic background, experience, and their complex interaction during ontogeny (Papini, 2002a). This technique is common in some areas of psychology (e.g., intelligence testing), but rarely used in animal learning, although theoretical claims of fundamental similarities among learning phenomena are common in the literature (for one example, see Daly and Daly, 1982). In the particular case studied here, comparisons among independently ran experiments, often involving drastically different parameters of training and dependent measures, suggested a mechanistic link between LI and the PREE. In contrast, the present approach disconfirmed such a view without being open to any of the problems associated with drawing conclusions from different studies. This individual-difference technique could now be extended to testing links with other learning phenomena. For example, it has been claimed that LI shares important mechanistic similarities with blocking (e.g., Hemsley, 1993) and prepulse inhibition (e.g., Gray et al., 1999). Similar links have been postulated between the PREE and other effects involving incentive shifts (e.g., Amsel, 1992; Daly and Daly, 1982). Of course, detecting a significant correlation between two learning phenomena does not itself prove that the underlying mechanisms are the same. Similar behavioral effects could be the result of different underlying mechanisms (Papini, 2002b). But once a correlation is detected, the same individual-difference technique may be applied to clarify the issue of homology vs. homoplasy of learning mechanisms across learning phenomena by studying the influence of a common independent variable on two or more learning phenomena in the same organisms, as done in Experiment 2 with CDP.

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