



## Effects of partial reinforcement on autoshaping in inbred Roman high- and low-avoidance rats

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### ABSTRACT

Individuals trained under partial reinforcement (PR) typically show a greater resistance to extinction than individuals exposed to continuous reinforcement (CR). This phenomenon is referred to as the PR extinction effect (PREE) and is interpreted as a consequence of uncertainty-induced frustration counterconditioning. In this study, we assessed the effects of PR and CR in acquisition and extinction in two strains of rats, the inbred Roman high- and low-avoidance (RHA and RLA, respectively) rats. These two strains mainly differ in the expression of anxiety, the RLA rats showing more anxiety-related behaviors (hence, more sensitive to frustration) than the RHA rats. At a neurobiological level, mild stress is known to elevate corticosterone in RLA rats and dopamine in RHA rats. We tested four groups of rats (RHA/CR, RHA/PR, RLA/CR, and RLA/PR) in two successive acquisition-extinction phases to try to consolidate the behavioral effects. Animals received training in a Pavlovian autoshaping procedure with retractable levers as the conditioned stimulus, food pellets as the unconditioned stimulus, and lever presses as the conditioned response. In Phase 1, we observed a PREE in lever pressing in both strains, but this effect was larger and longer lasting in RHA/PR than in RLA/PR rats. In Phase 2, reacquisition was fast and the PREE persisted in both strains, although the two PR groups no longer differed in lever pressing. The results are discussed in terms of frustration theory and of uncertainty-induced sensitization of dopaminergic neurons.

### 1. Introduction

Autoshaping in rats is a Pavlovian procedure in which the brief presentation of a retractable lever acts as the conditioned stimulus (CS) for the response-independent delivery of a reinforcer, typically food (the unconditioned stimulus, US). Two phenotypes quickly emerge among rats during acquisition training: “sign trackers” approach and interact with the lever [43], whereas “goal trackers” approach and inspect the food dish during the CS [8]. A third category of individuals, referred to as “ambivalent,” track both the sign and the goal during CS presentation (e.g., [51]).

In most autoshaping studies, animals are trained under continuous reinforcement (CR), that is, each lever CS presentation is followed by food delivery. However, under partial reinforcement (PR), lever CS presentations are randomly followed by food or no food, a procedure

often leading to higher asymptotic lever pressing in the PR than in the CR condition. This is referred to as the partial reinforcement *acquisition* effect (PRAE; e.g., [5, 37, 56, 66, 76]). After acquisition, extinction sessions in which the CS is no longer followed by food typically show greater persistence of responding in PR than in CR individuals. This phenomenon is known as the partial reinforcement *extinction* effect (PREE; e.g., [10, 42, 59, 63]).

Frustration theory can explain these two effects in a variety of training situations [2], including autoshaping in rats [10, 13, 23, 37, 56, 58, 74]. According to frustration theory, unexpected reward omissions have motivational and associative effects that generate opposing influences on behavior. Unexpected reward omissions during PR training induce a negative emotion (called primary frustration, an unconditioned response) that can be anticipated (secondary frustration, a conditioned response). These emotional responses also have the

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capacity to increase motivation for responding (e.g., [23]), explaining the invigoration of sign tracking in acquisition under PR, but not CR. Thus, the PRAE has been taken to reflect the increased activation resulting from the motivational properties of secondary frustration and uncertainty that characterizes PR training. Alternatively, the PREE results from the counterconditioning of secondary frustration, a mechanism activated when secondary frustration is followed by reward. Counterconditioning replaces the associative tendency of secondary frustration to induce avoidance responses for a tendency to induce approach responding. This results in increased persistence of approach during extinction trials, compared to the rapid disruption of approach behavior after a shift from CR acquisition to extinction [2].

An alternative view, the incentive hope hypothesis, interprets the PRAE as an indication that animals behave *as if* they hoped for the reliability of the CS on the ongoing trial under PR training [3]. Like frustration theory, this view relies on the assumption that uncertainty is aversive (notably increasing the levels of circulating glucocorticoids; e.g., [14, 49]). But contrary to frustration, the incentive hope hypothesis suggests that the response invigoration that follows PR training is also related to increased incentive salience—a dopamine-dependent process [7]. Indeed, there is strong evidence that food uncertainty triggers the release of dopamine in the brain reward system (e.g., [41]), an effect possibly mediated by glucocorticoids [4]. Thus, both the stress and motivational systems are assumed to contribute to the PRAE [4]. Taken separately, glucocorticoids and dopamine are less likely to produce a PRAE than if combined together. Although the incentive hope hypothesis does not account for the PREE, the ability of dopamine neurons to be sensitized to reward uncertainty [50, 81] could promote a greater resistance to extinction after PR vs. CR training. This hypothesis has not been tested in rat autoshaping, but it is consistent with reduced persistence in runway extinction after both PR and CR acquisition (without PREE disruption) following treatment with the dopamine antagonist haloperidol [28, 29].

Contrasting these two theories by using traditional laboratory rat strains (e.g., Sprague-Dawley or Wistar rats) is not revealing because they make mostly similar predictions. Alternatively, using strains of rats with differential patterns of behavior and neurobiology in response to stress and reward enables a comparison between frustration and incentive hope theories. The present study therefore compared the performance of inbred Roman high- and low-avoidance rats (RHA and RLA, respectively) in an autoshaping task involving CR vs. PR training.

RHA and RLA lines were initially selected and bred for their rapid (RHA) vs. slow (RLA) acquisition of the two-way active avoidance response in a shuttle box. This selection led to extreme differences in the emotional responses displayed in stress and anxiety situations (higher in RLA rats), as well as in novelty seeking, impulsivity, and sensitivity to reward (higher in RHA rats). Compared to RHA rats, RLA rats exhibit more anxiety and are less proactive in coping with aversive conditions ([21, 30, 71]; see [33]). Given their high anxiety levels, RLA rats are also more susceptible to frustration than RHA rats, as revealed by their stronger behavioral avoidance of a reward suddenly reduced in amount or in concentration [18, 38, 67, 75]. In the same vein, previous studies comparing the performance of RHA and RLA rats in an instrumental task involving PR vs. CR showed increased resistance to reward omission and devaluation in the more anxious RLA strain, but no evidence of strain differences during acquisition under PR vs. CR conditions [18, 39]. On the other hand, RHA rats display more impulsive behaviors [52], cognitive impairments [65], increased novelty seeking [17, 48], and enhanced vulnerability to drug abuse [35].

These strain differences in behavior are related to a divergence in neurobiological markers of stress. For example, although similar corticosterone levels are recorded in both strains in the absence of stress and under high stress conditions (e.g., ether exposure, foot shock, and immobilization), those levels are higher in RLA than in RHA rats after mild stress conditions, such as exposure to an open field [6, 11, 31, 78]. In RLA rats, stressors cause immediate augmentation of heart rate and

more defecation compared with RHA rats [20], which reflects higher levels of corticosterone [32]. By contrast, mild stress, anxiogenic drugs, natural reinforcers (e.g. palatable food, sexual behavior), and drugs of abuse (e.g., amphetamine, cocaine, morphine, or alcohol) results in a stronger activation of dopamine function (i.e. dopamine release) in reward-related brain regions in RHA rats compared to RLA rats [20, 33–35]. Collectively, these findings indicate that RHA rats have a more robust mesolimbic dopaminergic functional tone than their RLA counterparts (see [33]). This enhanced dopaminergic activity in RHA rats relates to their increased novelty/incentive/reward-seeking and impulsive profile and to their enhanced vulnerability to both psychostimulant-induced (and morphine-induced) sensitization and drug addiction relative to RLA rats (e.g., [27, 35, 77]; see [33]).

Frustration theory assumes that uncertainty induces negative emotion and promotes the release of stress hormones, whereas the incentive hope hypothesis links uncertainty to incentive salience and enhanced glucocorticoid-induced dopaminergic function. Based on the behavioral and neurobiological differences between RHA and RLA rats described above, frustration theory would predict the occurrence of a stronger PRAE in RLA rats, while the incentive hope hypothesis would be more compatible with a stronger PRAE in RHA rats. In extinction, frustration theory predicts a larger PREE in RLA rats than in RHA rats. The incentive hope hypothesis does not make specific predictions for the PREE. However, if its prediction that uncertainty processing requires dopamine is correct, uncertainty-induced sensitization of dopamine neurons might cause a higher behavioral persistence after PR in RHA than in RLA rats, while the response of rats exposed to CR training (not sensitized) should extinguish at the same rate in both strains.

## 2. Materials and methods

### 2.1. Subjects

Twenty male, inbred RHA rats and twenty male, inbred RLA rats from colonies in the Autonomous University of Barcelona served as subjects. Animals were housed in pairs in transparent polycarbonate cages (33.7 × 55.7 × 19.5 cm) with minimal enrichment (one red-tinted polycarbonate tunnel per cage) at the animal facility of UNED (Universidad Nacional de Educación a Distancia, Madrid, Spain). The housing room was maintained under a 12-h light/dark cycle (lights on at 08:00 h), with constant temperature (21 ± 2 °C) and relative humidity (55%). Rats were food deprived gradually until reaching 81–84% of their *ad libitum* body weight (342.8 g ± 18 g), measured over 3 days. Rats were weighed daily before the start of experimental sessions and were fed at least 20 min after the end of the sessions. All animal care procedures were in accordance with the European Union Council Directive 2010/6 and the Spanish Royal Decree 53/2013 for minimizing stress and discomfort in animals, and were approved by UNED bioethics committee.

### 2.2. Apparatus

Rats were trained in eight LI-836 (Leticia Instruments, Barcelona, Spain) conditioning chambers (29 × 24.5 × 35.5 cm), enclosed in soundproof wooden cabinets equipped with a ventilation system and a small observation window at the front. The front panel of each conditioning chamber was made of aluminum; the left wall and the roof were made of transparent polycarbonate; the other two walls were made of black polycarbonate. The floor consisted of 12 metallic rods located above a removable sawdust tray. A food dispenser allowed the automatic delivery of 45-mg precision pellets (Bio-Serv, Frenchtown, NJ, USA) in an aperture in the front of the chamber wall, located 3.7 cm above the floor level, between the two retractable levers of the panel. Only one lever, set at minimum effort, was operational during the experimental sessions. Magazine entries were measured by means of a photocell beam located at the entrance of the aperture. During

experimental sessions, chambers were indirectly lit by a 25-W light bulb placed in the soundproof wooden cabinets. Inside each chamber, a fan produced masking background noise (approximately 60 dB). Lever presses and magazine entries were recorded using MED-PC-IV software in a Windows-7 environment.

### 2.3. Procedure

Rats were randomly assigned to four groups (RHA/CR, RLA/CR, RHA/PR, and RLA/PR;  $n = 10$  in each group). Phase 1 started with food deprivation as described previously. Autoshaping training involved 14 acquisition sessions followed by 7 extinction sessions. Each session included 30 trials separated by a variable intertrial interval averaging 90 s (range: 60–120 s). For CR groups, on each trial, a lever was extended and then retracted 10 s later, and 5 food pellets were delivered at a rate of 1 pellet per 0.2 s immediately after the lever was retracted. For PR groups, the presentation of the 10-s lever was randomly followed by either 5 food pellets or nothing on 50% of the trials. Extinction started the day following the last acquisition session and lasted 7 sessions. Extinction training involved the same conditions described for acquisition, except that no food was delivered at the end of any of the lever presentations.

To consolidate the results obtained during Phase 1 and possibly reveal uncertainty-induced sensitization effects, an “incubation” phase of 4 weeks was imposed for all rats. During this period, animals remained in their home cage, no training was administered, and food was freely available. Phase 2 started following incubation. Animals were food deprived again for a week and then re-trained in acquisition and extinction using the same procedure described above. Phase 2 involved 7 acquisition session and 5 extinction sessions. Apart from these changes, rats experienced the same housing and experimental conditions as during Phase 1.

The dependent variables were lever presses per trial and magazine entries per trial – two behaviors measured during lever insertion and before pellet delivery. Both behaviors were considered to determine how the expression of sign tracking altered goal tracking, or vice versa, as their possibly strong interdependence should lead to symmetrical patterns of responses (i.e., one could decrease when the other increases, and vice versa; e.g., [57, 61]). These two behaviors are known to depend on distinct psychological processes (sign tracking is less “cognitive” than goal tracking, e.g. [68]) and are statistically analyzed separately in the autoshaping literature. Mixed-model analyses of variance (ANOVAs) were computed using Statistica 13 and IBM SPSS Statistics 24. Planned comparisons were derived from the main ANOVAs to identify the source of significant interactions. An alpha level equal or lower than 0.05 was used in all statistical tests.

## 3. Results

### 3.1. Phase 1

#### 3.1.1. Acquisition

A three-way ANOVA (Strain  $\times$  Reinforcement  $\times$  Session) for lever pressing revealed a main effect of session,  $F(13, 468) = 30.14$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.45$ , where the gradual increase in performance suggested that the rats properly learned the task (Fig. 1, top). This effect was significant in each of the four groups,  $F_s(1, 36) > 13.50$ ,  $ps < 0.001$ . There was also a near-significant Session  $\times$  Reinforcement interaction,  $F(13, 468) = 1.74$ ,  $p = 0.050$ ,  $\eta_p^2 = 0.05$ , as PR groups had a propensity to respond more than CR groups, especially starting on session 5. All other comparisons were nonsignificant.

With respect to magazine entries (Fig. 1, bottom), the same three-way ANOVA showed a main effect of reinforcement,  $F(1, 36) = 4.38$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.11$ , although the CR and PR treatments,  $F_s(1, 36) < 4.04$ ,  $ps > 0.05$ , and the session effects,  $F(13, 468) = 1.58$ ,  $p = 0.09$ ,  $\eta_p^2 = 0.04$ , were nonsignificant. The Reinforcement  $\times$  Session

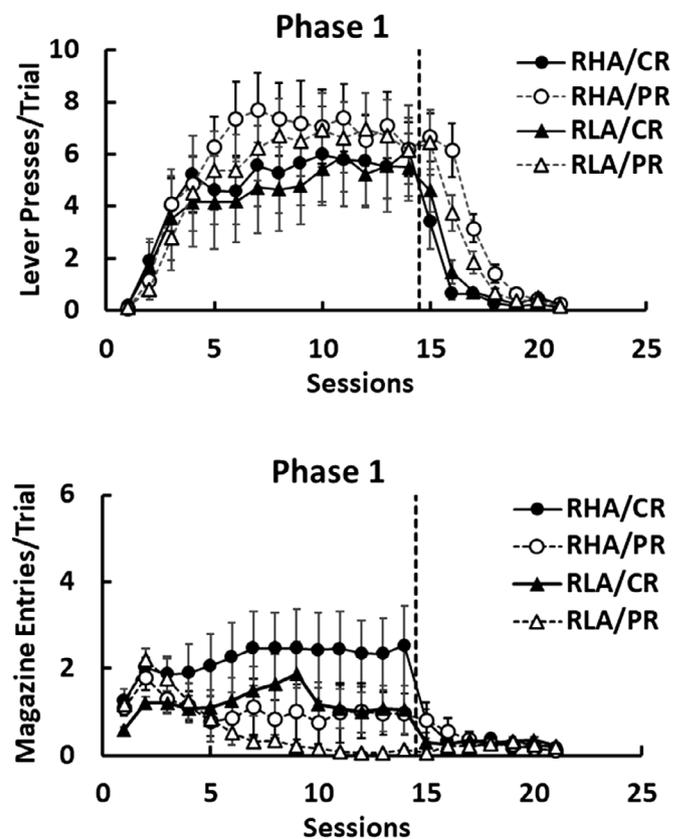


Fig. 1. Acquisition (sessions 1–14) and extinction (sessions 15–21) performance during Phase 1 for lever presses (top) and magazine entries (bottom). Means (SEMs) are plotted.

interaction was significant,  $F(1, 36) = 3.93$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.10$ . Of note, the number of anticipatory magazine entries was very low in RLA/PR rats, starting on session 7 and throughout the end of training. All other comparisons were nonsignificant.

#### 3.1.2. Extinction

During extinction, lever pressing decreased in the four groups, but at different rates (Fig. 1, top). A three-way ANOVA indicated a main effect of session,  $F(6, 216) = 83.19$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.70$ , a main effect of reinforcement,  $F(1, 36) = 18.05$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.33$ , and a Session  $\times$  Reinforcement interaction,  $F(6, 216) = 12.89$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.26$ . This interaction is consistent with a PREE. Visual inspection of extinction (Fig. 1, top) indicates that the PREE appeared to be larger in RHA rats than in RLA rats, an impression consistent with a marginally nonsignificant Strain  $\times$  Reinforcement interaction,  $F(1, 36) = 3.19$ ,  $p > 0.08$ ,  $\eta_p^2 = 0.08$ . Planned comparisons indicated that RHA/PR rats lever pressed more than RHA/CR rats on sessions 15–19,  $F_s(1, 36) \geq 5.052$ ,  $ps \leq 0.031$ . RLA/PR rats responded above RLA/CR rats only on sessions 16–17,  $F_s(1, 36) \geq 4.696$ ,  $ps \leq 0.037$ . The source of this difference was a distinct PR performance in RHA and RLA rats, with RHA/PR rats lever pressing more than RLA/PR rats on sessions 16, 17, and 18,  $F_s(1, 36) > 6.30$ ,  $ps < 0.02$ . RHA/CR and RLA/CR rats, however, exhibited similar rates of lever pressing on each extinction session,  $ps > 0.16$ . Thus, the PREE appeared stronger and longer lasting in terms of lever pressing in RHA rats than in RLA rats.

Magazine entries were also altered by the extinction procedure, although to a lesser extent (Fig. 1, bottom). Statistical analyses revealed a main effect of session,  $F(6, 216) = 2.82$ ,  $p < 0.02$ ,  $\eta_p^2 = 0.07$ , and a Strain  $\times$  Session interaction,  $F(6, 216) = 4.61$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.11$ . There was a significant effect of session in each group,  $F_s(1, 36) > 6.98$ ,  $ps < 0.02$ . Of note, the RLA/PR individuals exhibited an unusual

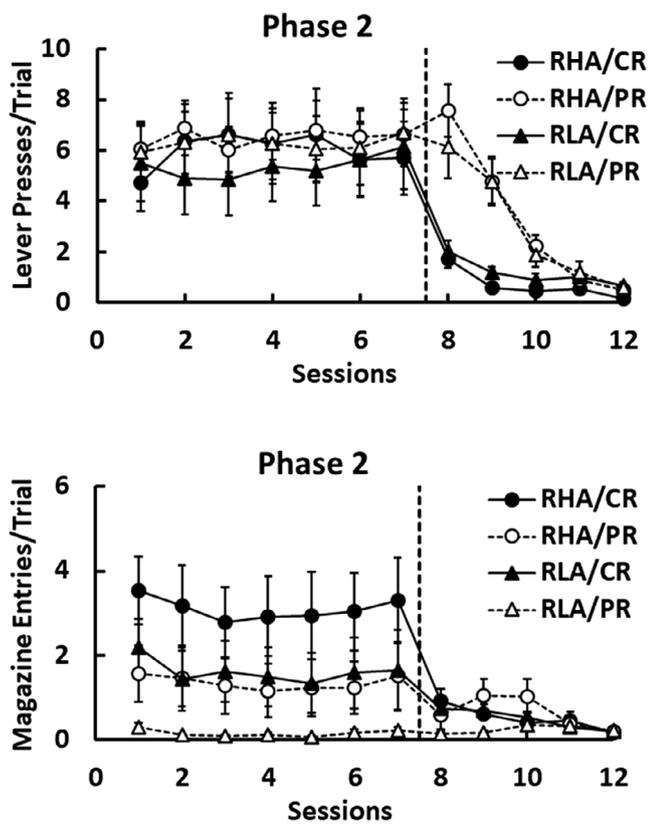


Fig. 2. Acquisition (sessions 1–7) and extinction (sessions 8–12) performance during Phase 2 for lever presses (top) and magazine entries (bottom). Means (SEMs) are plotted.

pattern of responses (with an apparent increase between sessions 15–19). However, none of these changes were statistically significant, 15–19:  $p > 0.36$ ; 19–21:  $p > 0.11$ . A significantly higher response rate was found in RHA/PR relative to RLA/PR rats on session 15,  $F(1, 36) = 4.17$ ,  $p < 0.05$ , but no other significant effects between- or within-strain relative to reinforcement conditions were found.

### 3.2. Phase 2

#### 3.2.1. Reacquisition

Reacquisition was fast, as the rats from each group responded at their asymptotic level of lever-pressing performance as soon as the first session (Fig. 2, top). Lever pressing was similar in each group. A three-way ANOVA yielded nonsignificant effects for all factors and interactions,  $F_s < 1.06$ ,  $p_s > 0.18$ ,  $\eta_p^2_s < 0.04$ .

The effects of reacquisition on magazine entries were also modest (Fig. 2, bottom). Nevertheless, we obtained significant effects of Session,  $F(6, 216) = 2.86$ ,  $p < 0.02$ ,  $\eta_p^2 = 0.07$ , and of Reinforcement,  $F(1, 36) = 5.78$ ,  $p < 0.03$ ,  $\eta_p^2 = 0.14$ . Specifically, RHA/CR and RLA/CR rats showed a significant decrease in magazine entries (between sessions 1–3 for the former, and between sessions 1–2 for the latter;  $F_s(1, 36) > 8.33$ ,  $p_s < 0.006$ , followed by a nonsignificant increase in the subsequent sessions,  $F_s(1, 36) < 2.41$ ,  $p_s > 0.13$ . With respect to reinforcement, the CR and PR conditions differed significantly only on session 1 in both RHA,  $F(1, 36) = 4.97$ ,  $p < 0.04$ , and RLA rats,  $F(1, 36) = 4.62$ ,  $p < 0.04$ . All other comparisons were nonsignificant.

#### 3.2.2. Extinction

A three-way ANOVA for lever pressing revealed significant effects of Session,  $F(4, 144) = 72.95$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.67$ , and of Reinforcement,  $F(1, 36) = 26.63$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.42$ , as well as a significant Session  $\times$  Reinforcement interaction,  $F(4, 144) = 34.90$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.49$ .

Across the extinction sessions, there was a decrease in lever pressing in all groups,  $F_s(1, 36) > 7.79$ ,  $p_s < 0.008$ , except in group RHA/CR, where a nonsignificant effect was found (Fig. 2, top). The response rates to the PR and the CR conditions differed significantly in both strains on session 8,  $F_s(1, 36) > 11.46$ ,  $p_s < 0.002$ , and session 9,  $F_s(1, 36) > 14.78$ ,  $p_s < 0.001$ , but remained significant only in the RHA strain on session 10,  $F(1, 36) = 12.56$ ,  $p < 0.001$ . Of note, RLA/CR rats pressed the lever more than the RHA/CR rats on session 12,  $F(1, 36) = 6.86$ ,  $p < 0.02$ .

Magazine entries showed a significant effect of Session,  $F(4, 144) = 6.56$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.15$ , a Session  $\times$  Reinforcement interaction,  $F(4, 144) = 2.93$ ,  $p < 0.03$ ,  $\eta_p^2 = 0.07$ , and a Session  $\times$  Reinforcement  $\times$  Strain interaction,  $F(4, 144) = 2.58$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.07$ .

A comparison of Figs. 1 and 2 (top) and their corresponding statistical analyses suggest that Phase 2 training eliminated the PRAE and also the differential PREE across strains that had been observed in Phase 1.

## 4. Discussion

There was more consistency between animals in their sign tracking than in their goal tracking. Therefore, this discussion centers on the results obtained with sign tracking. In Phase 1, the four groups were just slightly distinguishable during acquisition, showing no strong evidence of a PRAE. By contrast, a greater resistance to extinction was obtained after acquisition under PR than under CR training. Moreover, there was evidence that this PREE was stronger and longer in RHA rats than RLA rats. This is the opposite of what was observed in a runway instrumental task involving training with PR vs. CR, where only the RLA strain exhibited the PREE [18, 39]. In Phase 2, reacquisition was fast and nondifferential, as rats from all groups pressed the lever similarly throughout the seven sessions. So, the interruption between Phases 1 and 2 did not cause any forgetting of the task or play a role of incubation to differentiate responding between PR and CR groups, as initially expected. Finally, the strain effect on the PREE vanished. For both strains, extinction was faster after CR than after PR training.

The significant reinforcement by session effect during acquisition, Phase 1, suggested but did not demonstrate the possibility of a PRAE. None of several analyses designed to identify the source of this interaction produced significant differences between animals from either strain or both strains combined trained under CR vs. PR. Therefore, there was no evidence that the source of the reinforcement by session interaction was the difference between groups that received CR vs. PR training. In this experiment, lever pressing during acquisition was sufficiently variable to prevent the detection of a schedule effect. Such response variability was reduced in extinction, thus leading to significant schedule effects. Therefore, the PREE was more reliable than the PRAE in the present experiment.

The reasons for the absence of a clear PRAE in this experiment were unclear. The PRAE in rat autoshaping has in some cases failed to be observed (e.g., [10]). In addition, the expectation was that there would be a strain difference in the PRAE. The absence of a strain effect in the PRAE contradicts both frustration theory and the incentive hope hypothesis (see references in Introduction). Frustration theory led to the expectation that the PRAE would be stronger in the RLA strain than in the RHA strain because the former is known to be more reactive to reward omission than the latter. This prediction was supported by prior results in the runway situation cited above.

As for the incentive hope hypothesis, a stronger PRAE was predicted in the RHA strain than in the RLA strain, because the former is known to be more sensitive to reward than the latter. However, it is unclear whether the conditions for the occurrence of incentive hope were met in these rat strains. Incentive hope posits that the PRAE results from glucocorticoid-induced dopamine release [4], so that glucocorticoids (a determinant of stress and anxiety) or dopamine (a determinant of

incentive salience) *taken separately* should be insufficient for the PRAE to emerge. Given that under mild stress (e.g., reward uncertainty), RLA rats produce more glucocorticoids, but less dopamine, than RHA rats (e.g., [6, 11, 31, 78]), the conditions for incentive hope may not have been met in the RLA strain. The reverse pattern applies to RHA rats: they release more dopamine, but less glucocorticoids, under mild stress (e.g., [11, 20, 31, 33, 34, 78]). The conditions for incentive hope are probably also not met in the RHA strain—the extra dopamine does not stem from an activation of the glucocorticoid system, which is assumed to be necessary to invest more effort in the search of an uncertain reward. We did not directly measure the levels of corticosterone and dopamine in this study, so this interpretation must be taken with caution. However, if reward uncertainty had similar effects to environmental novelty (a source of mild stress) in RLA and RHA rats, the incentive hope hypothesis should logically predict no PRAE between the two reinforcement conditions in these strains. A PRAE is more likely to occur in “normal” rats, designed by natural selection to respond more vigorously to uncertain events through optimal glucocorticoid-induced dopamine release.

The absence of strain differences during acquisition resembles previous studies showing similar levels of lever pressing during the acquisition of an appetitive operant task [16]. Interference caused by divergent strain characteristics could alternatively underlie the lack of results obtained during acquisition training, including differential levels of incentive motivation for the reward. In this respect, RHA rats tend to exhibit higher levels of anticipatory and consummatory responses to natural rewards (e.g., regular and palatable food, sucrose solutions, sexually receptive female rats, etc.), although these results can be variable [36, 38, 47, 67]. In addition, both strains differ in metabolic processes. For instance, under some conditions, RLA rats show enhanced sensitivity to obesity induced by a fat-rich diet, and disruption in glucose homeostasis and in some associated compensatory behaviors [9, 26]. Such differential metabolic responses to dietary changes across strains could affect reward motivation during acquisition, an issue that needs to be addressed in further studies.

In extinction, our results are in accordance with decades of research showing that animals trained under PR are more resistant to extinction than animals trained under CR. The PREE is thought to be the expression of frustration counterconditioning, which can only develop after PR training [2]. However, frustration theory predicts that the PREE should be more pronounced in RLA than in RHA rats, a prediction consistent with runway data [18, 39], but opposed by the present results with the autoshaping procedure. It seems unlikely that the present results reflect increased frustration in RHA relative to RLA rats [12]. Decreased negative emotion in both conditioned and unconditioned procedures and increased behavioral disinhibition in conflict situations in RHA (vs. RLA) rats are among the most consistent findings throughout the literature (e.g., [21, 22, 24, 33, 45, 46, 64, 70, 71]). The incentive hope hypothesis makes no predictions about the PREE, but it has implications that may be relevant in that context. Incentive hope explains why dopamine is involved during PR training. Moreover, training under various conditions of reward uncertainty sensitizes dopamine neurons similarly to drugs of abuse, such as amphetamine [50, 81]. Thus, it is possible that the PREE in autoshaping is a consequence of uncertainty-induced sensitization of dopamine neurons. If correct, this would explain why the hyperdopaminergic RHA rats (with high density of dopamine D1 receptors and high functional effectiveness of dopaminergic activity in their brain; see [33]) showed a stronger and longer-lasting PREE than RLA rats. Repeated exposure to reward uncertainty during acquisition could lead to sensitization of dopamine pathways more readily in RHA than in RLA rats. This would also explain the increased lever pressing observed in RHA rats during extinction of an unpredictable instrumental variable-interval 15-s procedure [15, 16]. As for the CR rats from both strains, they extinguished lever pressing quite fast and at the same rates because they were not exposed to (and hence, not sensitized by) uncertainty.

The stronger and longer PREE in RHA compared with RLA rats during Phase 1 disappeared during Phase 2. One explanation that is coherent with the previous interpretation is to suggest that there was a ceiling effect of dopaminergic sensitization in RHA, but not in RLA rats, so Phase 1 promoted the highest propensity of RHA rats to release this neurotransmitter in response to reward uncertainty. In Phase 2, the RLA rats would simply have caught up with RHA rats. Accordingly, RLA/PR rats increased responding on session 2 of Phase 2 relative to Phase 1. However, this interpretation may appear problematic because, in Phase 2, the RHA/PR rats responded like RLA/PR rats in Phase 1, that is, they did not maintain responding but decreased it on sessions 2 and 3. More research on the effects of repeated extinction on dopamine release in rat autoshaping is needed to clarify this question.

The traditional incentive salience view would suggest that RHA rats “want” rewards more than RLA rats, and should therefore be more impulsive and more inflexible in extinction. Under certainty, it has indeed been shown that sign trackers, which naturally release more dopamine, are more resistant to extinction and to reward devaluation than goal trackers, which release less dopamine [1, 53, 54]. This finding is in accordance with the increased resistance to extinction observed in RHA rats after CR in comparison with RLA rats [39]. The problem with this interpretation is that we obtained a greater resistance to extinction in PR rats, but not in CR rats—of which the RHA/CR rats should be at least as impulsive and inflexible as their PR counterparts. So, an interaction between dopamine release and reward uncertainty can be suspected. Since Skinner's [69] initial insight, animal and human studies of gambling have contributed to establishing a link between reward uncertainty, dopamine, and the continuation of betting behavior despite nonreinforcement (e.g., [50, 81]). For example, in a computerized human gambling task, high-frequency gamblers were shown to respond more in extinction than low-frequency gamblers when trained under partial reinforcement, but not when trained under continuous reinforcement [44].

Both increased and decreased DA activity have been related to impulsivity [19], questioning a singular unidirectional involvement of DA in this behavioral trait. The relationship between monoamine levels and impulsivity seems to depend on the particular impulsive behavior evaluated [80]. With respect to the between-strain differences in the functioning of DA systems, these differences are more clearly identified after different challenges/treatments, being far less consistent in their directionality when evaluated under baseline conditions (see [35]). Interestingly, RHA rats show lower dopamine D2 auto-receptor density in the substantia nigra and ventral tegmental area, and lower density of postsynaptic dopamine D2/D3 receptor density in the striatum and nucleus accumbens than RLA rats [77]. These findings are considered as compensatory responses and, taken together, support the view that the functional tone of the mesolimbic dopaminergic system is especially intense in impulsive sensation seekers (such as in RHAs relative to RLA rats; see [33]).

There is inconsistent evidence for the role of dopamine in the PREE. On the one hand, the results from runway studies were often inconsistent because of considerable methodological variations across experiments. Many of these studies were based on the blockade of dopamine D2 receptors by means of the antagonist haloperidol, showing both increases and decreases in the magnitude of the PREE [25, 28, 29, 62]. Drugs of abuse that increase dopamine release (including cocaine, amphetamine, and nicotine) also affected the PREE in an inconclusive way [40, 55, 79]. On the other hand, electrolytic lesions of the nucleus accumbens, a major reward-related region of the brain, abolished the PREE [72], thus suggesting an involvement of dopamine in this phenomenon. As a behavioral phenomenon, the PREE may be based on different mechanisms in different training situations and different species (see [73]). The results presented here in the autoshaping situation indicate that the more intense functional tone of the mesolimbic dopaminergic system that characterizes the RHA, as opposed to RLA, could underlie the stronger PREE observed in the former strain

compared with the latter. The use of a manipulable signal in auto-shaping may tilt the balance away from the GABAergic function found to be important in the runway and consummatory procedures (see [60]), toward a dopaminergic function. RHA rats have been considered a valid genetic model to investigate the neural basis of impulsivity, novelty seeking, and vulnerability to drug addiction, among other dopamine-dependent behavioral traits [33]. In fact, the enhanced impulsivity/reward seeking profile of RHA rats has been proposed to explain their higher lever press responding under uncertainty during acquisition and extinction of a variable-interval training with food reinforcement [15, 16, 77]. Future studies will determine the usefulness of RHA rats to analyze additional patterns of behavioral persistence associated with pathological conditions, such as gambling. In particular, characterizing how the dopaminergic system interacts with the HPA axis in the auto-shaping procedure might help understand their respective contribution to CS-directed behavior under partial reinforcement.

### Declaration of Competing Interest

The authors declare no conflicts of interest.

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