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The effect of partial reinforcement on instrumental successive negative contrast in inbred Roman High- (RHA-I) and Low- (RLA-I) Avoidance rats

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ABSTRACT

Frustration is an emotional response that can be induced by the sudden devaluation of a reinforcer in the presence of greater reinforcement expectancies (*e.g.* instrumental successive negative contrast, iSNC). This emotional response seems to be similar to anxiety and can be attenuated by previous experiences of reward loss (*e.g.* partial reinforcement, PR, as opposed to continuous reinforcement, CR). In this study we used iSNC and PR procedures in order to compare the performance of two strains of rats psychogenetically selected on the basis of their emotional reactivity: the inbred Roman High- (RHA-I, low anxiety) and Low- (RLA-I, high anxiety) Avoidance rats. Animals were exposed to a straight alley, where they were changed from 12 pellets in the preshift phase (presented in 100% of trials—CR *vs.* 50% of trials—PR) to 2 pellets in the postshift phase, or exposed to 2 pellets throughout the training. The results indicated that the iSNC only appeared in RLA-I rats exposed to CR, as opposed to RLA-I animals exposed to PR and to RHA-I rats exposed to PR or CR. These data seem to support the implication of emotional responses in both iSNC and PR situations, and indicate that the behavioral reactivity to reward loss experiences is modulated by genetic variables.

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1. Introduction

The Roman High- (RHA/Verh) and Low- (RLA/Verh) Avoidance rats, derived from Wistar rats, were initially selected and bred on the basis of their good (RHA/Verh) *vs.* poor (RLA/Verh) acquisition of the two-way active (shuttle box) avoidance response [1]. Two inbred strains (RHA-I and RLA-I, respectively), derived from those outbred rat lines in 1993, are maintained at the Autonomous University of Barcelona since 1997 [2]. As a result of this selection, clear behavioral differences have been found in both outbred and inbred RHA and RLA rats in a variety of anxiety/fear tests, including the Vogel test, open-field, light–dark box, elevated zero-maze, fear conditioning, hole-board, one-way avoidance and fear-potentiated acoustic startle, among others [3–8]. In addition, some studies have found a greater tendency to novelty seeking and impulsivity in the RHA in comparison to RLA rats [9–11]. Strain/line-based divergences have also been observed in neuroendocrine indexes of anxiety, such as a higher activation of the HPA axis in RLA than RHA rats [see 12 for review], as well as neurochemical and neuroanatomical differences in brain structures related to fear and anxiety, such as hippocampus, amygdala, cortex, and nucleus accumbens [7,3]. Finally, a recent microarray study has enabled to detect 14 up-regulated and 24 down-regulated genes in RLA-I *vs.* RHA-I rats. These genes are functionally related to neurological processes, including 5 genes implicated in behavior/brain-related functions that are divergent in Roman rats [13]. This evidence suggests that the Roman rats constitute a valid experimental approach to explore the genetic basis of emotions induced by stressful and anxiety-provoking events.

Recent research conducted in our laboratory suggests that the RHA-I/RLA-I behavioral differences repeatedly obtained in fear/anxiety/stress tests are also observed when they are exposed to experiences of reward loss. The psychobiological consequences of loss of reinforcement have been systematically studied in the laboratory through the use of animal tests in which the omission or reduction of an expected appetitive reinforcer is used as an aversive event that triggers an emotional arousal reaction called frustration [14,15], disappointment [16] or anxiety [17,18]. These models include instrumental and consummatory successive negative contrast effects (iSNC, cSNC), extinction, the partial reinforcement extinction effect (PREE) and the magnitude of the reinforcement extinction effect (MREE), among others [19]. It was shown that female RLA-I rats exhibited appetitive and aversive iSNC [20,21] and PREE effects that were not observed in RHA-I rats [22]. Moreover, RHA-I animals showed increased

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resistance to the extinction of an appetitive instrumental response compared to Wistar and RLA-I rats [23]. Finally, when Roman rats were exposed to a consummatory task, RLA-I rats exhibited a longer cSNC effect in comparison to RHA-I rats [24].

The present experiment was designed to study for the first time the performance of the Roman rat strains in an additional reward-loss phenomenon, the partial reinforcement contrast effect (PRCE). It is important to underline here that the PRCE phenomenon has not been compared thus far neither between the Roman rat strains nor between any other pair of psychogenetically selected rat strains differing in their proneness to anxiety or frustration. Successive negative contrast (SNC) refers to a temporary reduction in responding to a smaller reward observed in animals previously exposed to a larger reward, compared to the responding observed in a control group always exposed to the smaller reward [25]. PRCE is defined as a reduced SNC observed after training with partial reinforcement as compared to continuous reinforcement [25,26]. Groups of food-deprived RHA-I and RLA-I animals were exposed to a straight alley where they were partially or continuously reinforced with 12 pellets (contrast groups), or continuously reinforced with 2 pellets (control groups) during the preshift phase. In the postshift phase the reward was downshifted in contrast groups and all the groups received 2 pellets. According to the abovementioned previous results, obtained in different reward loss procedures, it was hypothesized that the more anxious RLA-I rats should show more robust behavioral effects induced by frustration (iSNC and PRCE), than the less anxious RHA-I rats.

2. Material and methods

2.1. Subjects

Thirty-six 90-day-old male rats (18 RHA-I, 18 RLA-I), weighing 320–375 g at the beginning of the experiment, served as subjects. The inbred RHA-I and RLA-I rats are currently bred and reared at the Autonomous University of Barcelona (A.F.-T; A.T.). Animals were housed in pairs in plastic cages and deprived to 80–90% of *ad lib* feeding weight, with free access to water. This level of deprivation was maintained throughout the duration of the experiment by post training supplementary food administered approximately 30 min after the end of the experimental session. Room temperature was kept at about 20 °C. Animals were maintained under a 12-h light/12-h dark cycle with lights on at 8:00 a.m. All testing sessions were performed between 9:00 a.m. and 14:00 p.m. The experiment was carried out according to E.U. guidelines on the use of animals for research (86/609/EU).

2.2. Apparatus

The test apparatus were two identical straight 120 cm × 11 cm × 14 cm runways divided into three sections separated by cardboard guillotine doors. The start sections measured 20 cm, the running sections measured 80 cm; and the goal sections measured 20 cm. The walls and floor of the runways were made of painted wood (green) and two guillotine doors separated the start and goal sections from the running sections when closed. The entire lengths of the runways were covered by clear Plexiglas lids. The food reward was 45-mg pellets (formula P; Research Diets, Inc., Noyes Precision Pellets, Lancaster, NH). Pellets were placed on the floor at the distal end of the goal box. Time to run through the runway was manually registered by using a chronometer. Trials began as soon as the start door was raised, and the chronometer was stopped when the rat entered the goal section with its four paws.

2.3. Procedure

The procedure used was similar to the one previously described by Flaherty et al. [27] and Gómez et al. [22]. Rats were moved from the colony to an adjacent experimental room in sets of eighteen and in their own home-cages. The floor of the apparatus was vacuumed and wiped down with 5% ethanol solution after every set of rats finished its session. The experiment was conducted in three phases: pretraining, preshift, and postshift phases.

2.3.1. Pretraining

Three habituation days to the apparatus preceded training. On the first day, rats were placed in the start box with both doors open and given five 1-min access periods to the entire runway spaced ≈20 min apart. On the following day, rats were given two 2-min access periods, followed by two goal-box feedings (the animal was confined to the goal box and given the appropriate number of pellets) and an additional trial in which the pellets were spread throughout the runway. For the continuous and partial reinforcement groups (HC12-2, HP12-2, LC12-2 and LP12-2) the preshift reward was 12 pellets, and for the control groups (H2-2 and L2-2) the reward was set at 2 pellets (H and L refer to RHA-I and RLA-I strains, and C and P refer to continuous and partial reinforcement, respectively). Each group was composed by 6 animals. The last habituation day consisted of three goal-box feedings spaced ≈20 min apart. Subjects were given a maximum of 30 s to consume the food reward and were then removed from the goal box. Twelve Noyes pellets were placed in the home cage 30 min after the third habituation session along with their daily ration of lab chow.

2.3.2. Preshift phase

Training began on the fourth day. Each animal was placed in the start box with the start box door closed and the goal box door opened. The start box door was then opened and the rat was allowed to run down the runway to obtain the food reward. HC12-2 and LC12-2 received 12 pellets in each trial, while HP12-2 and LP12-2 had an unpredictable alternation between reinforced with 12 pellets trials and nonreinforced trials. The sequence of reinforced and nonreinforced trials was randomly arranged by using those Gellermann's sequences [28] with a similar number of RN and NR transitions. Control groups (H2-2 and L2-2) received 2 pellets per trial. A maximum time of 20 s was allowed for the rat to complete the trial. If the rat did not reach the goal box before 20 s had elapsed, it was gently pushed down the runway by the experimenter and 20 s was assigned as the latency for that trial. When the rat reached the goal box, the goal box door was quietly closed by the experimenter and a stopwatch was started. The rat was given a maximum of 30 s to consume the food reward. As soon as the rat had finished eating or 30 s had elapsed, it was removed from the goal box and placed back in its home cage. The rats were kept in the home-cage between trials. Each rat underwent six trials per day/session, and the preshift phase lasted 5 days.

2.3.3. Postshift phase

On the first trial of the postshift phase, the rats receiving 12 pellets (continuous or partial) were shifted to 2 pellets. The rats receiving 2 pellet remained at that level. The postshift phase lasted 6 days, and each daily session was composed by 6 trials.

2.4. Dependent variable

The time (1 s) spent to run from the start section to the goal section of the straight alley was manually recorded and used as dependent variable.

2.5. Statistical analysis

The mean values in each experimental session were subjected to a three factor analysis of variance, with Strain (RLA *vs.* RHA), Reinforcement (12 pellets continuous *vs.* 12 pellets partial *vs.* 2 pellet) and

Session (5 in preshift phase, 6 in postshift phase) as factors, adjusting analysis by Greenhouse–Geisser correction. Separate ANOVAS were conducted for preshift and postshift data, respectively. Where appropriate, post-hoc comparisons were made by using Tukey *post hoc* test. For all statistical analyses, alpha was set at .05.

3. Results

3.1. Preshift phase

A 2 (Strain) × 3 (Reinforcement) × 5 (Session) analysis conducted with data from the preshift phase ANOVA found a significant main effect of Session, $F(2.48, 73.43)$: 81.32, $p<.001$, Reinforcement, $F(2, 30)$: 4.17, $p<.03$, and Strain, $F(1, 30)$: 14.63, $p<.01$. The Strain × Session interaction was also significant, $F(2.44, 73.43)$: 8.88, $p<.001$ (data shown in Fig. 1). No other effect or interaction was significant.

Subsequent analysis conducted to explore the Strain × Session interaction found that the simple effect of Strain was significant on sessions 1, 2 and 3, smallest $F(1, 30)$: 4.88, $p<.04$, with worse performance in RLA-I than in RHA-I rats. When the strains were separately analyzed, a simple effect of Session was found in both RHA-I, $F(1.83, 27.5)$: 30.99, $p<.001$, and RLA-I animals, $F(2.15, 32.31)$: 52.06, $p<.001$, indicating that, although the running performance was worse in RLA-I rats than in RHA-I rats throughout training, both strains seemed to improve their performance across days.

3.2. Postshift phase

A 2 (Strain) × 3 (Reinforcement) × 6 (Session) ANOVA conducted with the postshift data found a significant main effect of Strain, $F(1, 30)$: 24.57, $p<.001$, Reinforcement, $F(2, 30)$: 3.94, $p<.04$, and Session, $F(3.08, 92.48)$: 7.53, $p<.001$. The interactions Reinforcement × Session, $F(6.16, 92.48)$: 4.42, $p<.001$, Strain × Session, $F(3.08, 92.48)$: 3.79, $p<.02$, and Reinforcement × Strain × Session, $F(6.16, 92.48)$: 2.34, $p<.04$ were also significant (see Fig. 1). In order to explore the source of this triple interaction, the Reinforcement × Session interaction was analyzed on each strain. This analysis enabled us to separately study the iSNC (12-2C *vs.* 2-2) and the PRCE (12-2P *vs.* 12-2C) effects in RHA-I and RLA-I rats, respectively. In RLA-I rats, a main effect of Session, $F(2.72, 40.91)$: 6.09, $p<.01$, and a Session × Reinforcement interaction were obtained, $F(5.45, 40.91)$: 3.67, $p<.01$. The analysis of this interaction revealed that the simple effect of reinforcement in RLA-I rats was significant on session 2, $F(2, 15)$: 5.46, $p<.02$, and session 3, $F(2, 15)$: 5.44, $p<.02$. Post-hoc comparisons found that, on session 2, LC12-2 rats run significantly slower than LP12-2 animals, $p<.02$, and presented a tendency to run slower than L2-2 rats, $p<.07$. On session 3, the group LC12-2 showed higher response latencies as compared to the group L2-2, $p<.02$. LP12-2 and L2-2 groups did not significantly differ on these sessions, $ps>.44$. As opposed to the results obtained in RLA-I rats, in RHA-I only a Session effect was obtained, $F(2.62, 39.3)$: 3.26, $p<.04$. These results indicate that the iSNC effect and the PRCE effect were evident in the more emotional RLA-I strain, as opposed to the less emotional RHA-I strain.

4. Discussion

The aim of the present study was to explore for the first time the presence of between-strain (RHA-I *vs.* RLA-I) differences in the PRCE (partial reinforcement contrast effect), *i.e.* whether the iSNC effect can be attenuated by a chronic experience of frustration induced by partial reinforcement. The results indicated that the iSNC effect was only observed in the more anxious RLA-I strain. Such an effect, *i.e.* the iSNC, was observed in female RLA-I rats in a previous study [20], thus the present iSNC results extend the phenomenon to males of that rat strain. Most importantly for our main objective, the present study provides the first evidence showing that this iSNC effect is not observed when RLA-I animals are previously exposed to a chronic experience of frustration induced by partial reinforcement, which for the first time demonstrates the PRCE phenomenon in the more anxious RLA-I rat strain. That is to say, in frustration-prone (RLA-I) rats, a previous frustrating experience is able to counteract the effects of a new frustrating (iSNC) situation/experience. The demonstration that the PRCE appears only in the RLA-I strain has the importance of completing the picture of that strain as a valid animal model of frustration, as RLA-I rats (but not the RHA-I strain) show a remarkable sensitivity to a wide variety of frustration-related procedures, such as the extinction of an appetitive instrumental learning, the iSNC, the cSNC and the PREE [20,22,23]. By contrast, the PRCE did not appear in the RHA-I strain (similar to what was previously observed in the abovementioned frustration procedures/phenomena), as the latencies of the running response showed by the RHA-I groups during the postshift phase were similar, regardless of the reinforcement schedule (partial *vs.* continuous) or the amount of reward (12 *vs.* 2 pellets) received on the preshift phase.

The RHA-RLA performance differences observed during the preshift phase of the present study agree with performance divergences previously obtained in our laboratory using female rats and a similar instrumental runway task, in which SNC, extinction and PREE were induced [23,22,20]. These strain differences consistently appeared regardless of the magnitude of the presented reinforcer (12 pellets, 2 pellets or 1 pellet) and the reinforcement schedule used

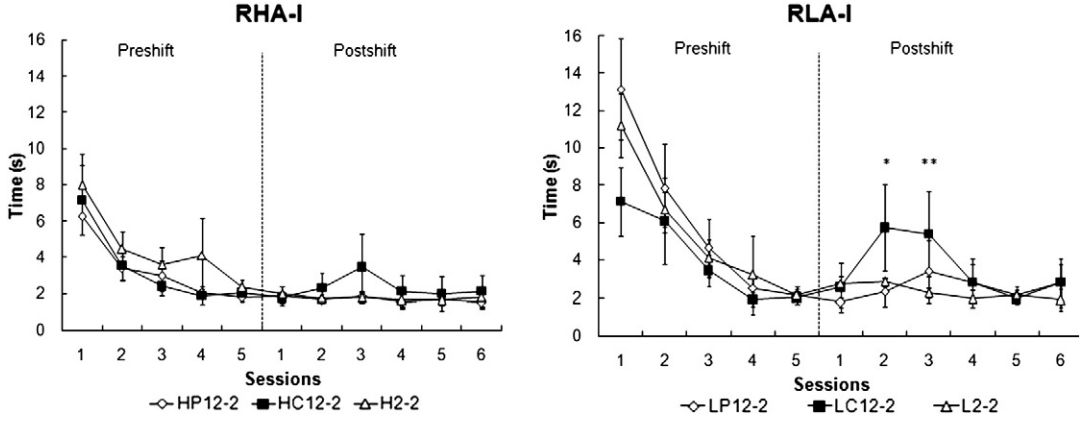

Fig. 1. Mean latency (s) to reach the goal box in RLA-I rats (right panel) and RHA-I rats (left panel) per session, each session was composed by six trials. Bars denote standard error of the mean. *: Low 12-2C *vs.* low 12-2P. **: Low 12-2C *vs.* low 2-2. $p<.05$.

(continuous *vs.* partial). These divergences could be dependent on RHA-I/RLA-I differences observed in the mesolimbic dopaminergic transmission that seem to modulate their response to the reinforcing properties of natural and artificial rewards [see 29 for review].

With regard to the results obtained during the postshift phase, it was observed that the sudden reduction in the amount of reward received by animals (from 12 pellets to 2 pellets) significantly impaired the running response and induced an iSNC effect only in the more anxious RLA-I rats exposed to continuous reinforcement in preshift phase, as opposed to RLA-I rats exposed to partial reinforcement and the less anxious RHA-I animals receiving partial or continuous reinforcement before the reward downshift. These data on iSNC extend to males the results previously reported with female Roman rats and indicate that the between-strain behavioral differences observed in a variety of animal models of anxiety can also be consistently observed in instrumental reward loss situations [20,21,23,24]. According to this view, several lines of evidence have demonstrated that the surprising reduction or omission in the magnitude of an expected reward triggers an aversive emotional response of frustration or disappointment similar to a fear/anxiety state [18]. The results obtained in the present study can be considered as an additional support for this hypothesis, given that the more anxious/fearful RLA-I rats showed an iSNC effect that was not observed in the less anxious/fearful RHA-I animals.

The absence of iSNC effect observed in RLA-I rats exposed to partial reinforcement in the preshift phase, as well as the absence of performance differences between RHA-I and RLA-I rats trained under partial reinforcement can also be discussed within this context. Behavioral persistence that is observed after an experience of partial reinforcement (such as the PREE or the PRCE induced in the present study) refers to the fact that any sort of reward inconsistency tends to induce behavioral persistence [26,30,19,15]. Although several theories have been proposed to account for this effect, most of them have considered that partial reinforced phenomena are closely related to emotional mechanisms [14], given that (i) previous experience of partial reinforcement can increase subsequent behavioral resistance to other frustrative non-reward situations such as the cSNC, this effect being attenuated by the administration of the anxiolytic drug chlordiazepoxide [25] and ethanol [30]; (ii) the lesion of the septo-hippocampal system abolishes the PREE [31,32]; (iii) the chronic administration of anxiolytic GABAergic compounds in both acquisition and extinction phases tends to decrease persistence in partially reinforced subjects, abolishing the PREE in spaced-trial procedures [see 17,33, for review]; and (iv) differences in extinction resistance after partial reinforcement were obtained in female RLA-I and RHA-I rats, the former showing a PREE that was not observed in the latter. The results obtained in the present study could be considered as an additional support for the emotional nature of the PRCE. Thus, according to the frustration theory proposed by Amsel [14], when a response is nonrewarded in the presence of reward expectancy (as occurring in the nonreinforced trials of the partial reinforcement preshift phase) an aversive internal state of primary frustration is induced. The pairing of initially neutral contextual stimuli with this emotional reaction would enable these stimuli to trigger an expectancy of frustration, called secondary frustration. The occurrence of a reinforced trial in the presence of this secondary frustration would increase the tolerance to frustration through a counterconditioning process, enabling the response persistence observed during the partial reinforcement postshift phase, as opposed to response impairment observed during the continuous reinforcement postshift phase [15,25]. Within this context, it could be hypothesized that RLA-I rats exhibited greater frustration reactions during the nonrewarded trials of the preshift phase, and therefore a stronger counterconditioning of the secondary frustration that could prevent the occurrence of the iSNC during the postshift phase. These emotion-mediated phenomena were absent in the less anxious RHA-I strain, preventing the occurrence of the iSNC and its abolition by partial reinforcement [22].

Although the present results can be explained in terms of between-strain differences in anxiety, alternative explanations cannot be completely ruled out within this context. Firstly, some authors have found evidence suggesting the implication of memory processes, rather than emotional mechanisms, in the reward omission related phenomena [34,35]. From this point of view, it could be argued that the faster running response observed in RHA-I rats in comparison to RLA-I rats could be dependent on higher memory capacities in the former strain with respect to the latter. However, RLA (both outbred and inbred) rats have been shown to be superior to their RHA counterparts in a variety of spatial and working memory tasks [36–38], making difficult to explain the results obtained in the present study on the basis of between-strain cognitive differences. Alternatively, it has been repeatedly found that, as opposed to the freezing response usually observed in RLA-I rats, RHA-I animals tend to show higher levels of locomotor activity and novelty seeking responses when coping with challenging and novel situations [9,10], as well as higher behavioral indexes of impulsivity [11]. Although these divergences could alternatively explain the faster runway behavior observed on RHA-I rats in comparison to the RLA-I rats, previous results obtained in our laboratory indicate that the strain differences observed in the speed of the running response can be abolished by exposing animals to partial reinforcement, as opposed to continuous reinforcement, suggesting the implication of emotional/frustration mechanisms in the between-strain differences observed in this instrumental task [22].

5. Conclusions

In summary, the present results suggest that experiences of frustrative inconsistent reinforcement can reduce subsequent emotional reactions derived from reward downshift. These attenuating effects of frustration seem to be observed only in those organisms particularly reactive to these stressful events (*e.g.* RLA-I rats as opposed to RHA-I rats), indicating that the individual vulnerability to develop behavioral, emotional and physiological disorders induced by reward loss is modulated by genetic variables.

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