SHORT TITLE: PREVENTING RESPONSE RECOVERY

Spacing Extinction Sessions as a Behavioral Technique for Preventing Relapse in an Animal Model of Voluntary Actions

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Abstract

Instrumental extinction has been proposed as a model for understanding the suppression of problematic voluntary actions. Consequently, it has been suggested that response recovery after extinction could model relapse. Four experiments with rats used a free operant procedure to explore the impact of spacing extinction sessions on spontaneous recovery, renewal, reinstatement, and rapid reacquisition of extinguished lever-pressing. Initially, in all experiments, hungry rats were trained to perform two responses (R1 and R2) for food. Then, all responses underwent extinction. For R1, rats experienced a longer intersession interval (72h) than for R2 (24h). During the final restoration test, it was observed that using spaced extinction sessions reduced spontaneous recovery, renewal, and reinstatement. However, implementing a longer intersession interval throughout extinction exposure did not slow the rate of reacquisition of operant responses. The present findings suggest that in most cases extinction is more enduring when the extinction sessions are spaced. Since expanding the intersession interval during extinction might be interpreted as conducting extinction in multiple temporal contexts, the overall pattern of results was explained based on contextual modulation.

Key words: Operant Conditioning, Rats, Relapse, Response Recovery Effects, Spacing extinction sessions.

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1. Introduction

It has been noted that many human diseases are caused by voluntary and learned behaviors, such as drinking, inactivity and overeating high-calorie foods (Harrington, 2008; Schroeder, 2007; Schulze et al., 2004). The laboratory model to study how voluntary and goal-directed actions are influenced by their outcomes is instrumental conditioning (Dickinson & Balleine, 1993, 1994). Because of the clinical relevance for suppressing problematic actions, many behavioral scientists have been interested in the decrease of the original learned behavior produced by withholding the reinforcer (i. e., extinction; Rescorla, 2001). Although during extinction a decline in the strength of the behavior is observed, several phenomena indicate that this behavioral change is difficult to sustain, making the extinguished behavior likely to return (relapse, Bouton, 2014).

There are at least four phenomena that show a response recovery from extinction. For example, in the renewal effect (Bouton, Todd, Vurbic & Winterbauer, 2011; Nakajima, Tanaka, Urushihara & Imada, 2000) an extinguished behavior reappears by simply testing the subject outside the extinction context (e. g., therapist's office). In spontaneous recovery (Rescorla, 1997, 2004), the mere passage of time produces a return of the extinguished response (e.g., relapsing after a long period of abstinence). Reinstatement (Baker, Steinwald & Bouton, 1991; Rescorla & Skucy, 1969) occurs because of a mere exposure to the outcome after extinction (e.g., sipping a soda may begin overdrinking again). Finally, the return of responding can be very fast (Ricker, & Bouton, 1996; Todd, Winterbauer & Bouton, 2012) when the response-outcome contingency is resumed after extinction (e.g., consuming beer again after a period of abstinence).

Because those phenomena show that the impact of extinction treatment is labile and an eliminated behavior is likely to reappear under several circumstances, some authors have proposed them as laboratory models for understanding lapse and relapse of unhealthy voluntary behaviors (Bouton, Winterbauer & Vurbic, 2011; Crombag, Bossert, Koya & Shaham, 2008; Kelley, Liddon, Ribeiro, Greif & Podlesnik, 2015; Marchant, Li & Shaham, 2013).

Although it seems that renewal, spontaneous recovery, reinstatement, and rapid reacquisition are products of different causes, one theoretical perspective assumes that despite the methodological differences those effects could be explained by the same mechanism (Todd, Vurbic & Bouton, 2014). Bouton (1993, 2004) proposed that extinction is not unlearning, rather during extinction subjects learn to inhibit a previously trained response (see also Rescorla, 1993; Todd, 2013). Moreover, this new learning is highly specific to context (extinction performance is restricted to the extinction context). Thus, Bouton proposes that response recovery effects might be understood as the loss of extinction performance produced by changes in the context (e. g., Bouton, 2011), whether contextual change is given by the external context (renewal), the temporal context (spontaneous recovery) or the associative value of the context (reinstatement and rapid reacquisition; see Bouton, 1993, 2010).

According to this line of reasoning, behavioral strategies that facilitate retrieval of the extinction learning outside the extinction context should prevent response recovery. One factor that has been shown to enhance long-term retention of learning is expanding or spacing practice (e. g., Schmidt & Bjork, 1992). Given that extinction is also learning, spacing extinction sessions might be used as a strategy to thwart relapsing. Rowe and Craske (1998) reported results consistent with that idea using spider fearful students. They

found that participants that experienced spaced exposure sessions (i. e., controlled presentations of a tarantula spaced over 4 days) demonstrated less return of fear at a 1-month follow-up assessment compared to participants in a massed exposure condition (i. e., exposures conducted consecutively on the same day). The findings of Rowe and Craske (1998; see also Tsao & Craske, 2000) show that spacing extinction sessions is effective in reducing spontaneous recovery of fear. Given that no other study has continued to evaluate the effect of spacing extinction sessions, to date, it is unknown whether such manipulation also attenuates spontaneous recovery of instrumental responses. Furthermore, the effect of using spaced extinction sessions on the rest of response recovery effects is unexplored. Thus, the aim of the present experimental series was to evaluate the impact of using spaced extinction sessions on spontaneous recovery (Experiment 1), renewal (Experiment 2), reinstatement (Experiment 3) and rapid reacquisition (Experiment 4) of instrumental responses.

2. Experiment 1

Experiment 1 studied whether spacing extinction sessions could attenuate the spontaneous recovery of extinguished lever-pressing. Rats were trained to perform two different responses (R1 and R2) for food (outcome, O). Then, both responses underwent extinction. During extinction, the intersession interval for R2 (24h) was shorter than for R1 (72h). Finally, Recovery Test occurred 5 days after Extinction Test (see the experimental design in the first row of Table 1). If spacing extinction sessions is effective in reducing spontaneous recovery, less responding should be observed in R1.

Insert Table 1 about here

2.1 Method

2.1.1 Subjects

A group of 16 four-month-old experimentally naïve female Wistar rats weighting in average 297 g were used. Rats were individually housed in methacrylate cages (21 x 24 x 46 cm, *height* x *width* x depth*)* inside a room maintained on a 12-12 hr light dark cycle (07:00 onset and 19:00 offset of lights). The temperature of the colony room ranged between 20 – 25°C, while the humidity value was 45-60 %. They were maintained with ad libitum access to water but were food-deprived to 83% of their initial body weight throughout the experiment.

2.1.2 Apparatus

Eight identical chambers manufactured by MED Associates (model ENV-008) measuring 29 x 22 x 24 cm, (*H* x *W* x *D)* were used.The side walls and ceiling were made of clear acrylic plastic, while the front and rear walls were made of stainless steel. The floor of the chamber consisted of sixteen 0.5-cm diameter stainless steel rods spaced 1.5 cm apart. A recessed 5 cm x 5 cm food magazine in which 45 mg Noyes A/I pellets could be delivered was centered on the front wall. Each chamber had two retractable levers, whichwere positioned to the right and to the left of the food tray. A 28 Vdc bulb was placed 4.2 cm above each lever which served as a general house light. The chambers were connected to a PC that controlled and recorded the events.

Four chambers provided the *Vinegar-Rod* context which consisted of vinegar scent provided with a dish containing 5 ml of White vinegar (Clemente Jacques, Sabormex S.A. de C.V., México, DF) placed outside each chamber near the front wall. The floor consisted of sixteen 0.5 cm diameter stainless steel rods spaced 1.5 cm apart. Four additional chambers provided the *Windex-Sandpaper* context. The floor was covered with a sandpaper

sheet (number 10). The distinct odor was provided by 5 ml of Windex (S. C. Johnson and Son, S. A. de C.V. Mexico) placed outside each chamber near the front wall. Scents were refreshed daily. Contexts were counterbalanced as A and B across rats.

2.1.3 Procedure

The present experimental protocol was approved by the Ethical Committee of the Faculty of Psychology of the National University of Mexico. All the experiments reported here used an experimental arrangement similar to Bernal-Gamboa, Gámez and Nieto (2017; see also Todd, 2013) because this kind of design controls the associative values of all responses through equated histories of reinforcement and nonreinforcement, providing more information about the possible mechanisms underlying the spaced extinction sessions effect.

Pre-exposure. Sessions were conducted on successive days at the same time each day. On day 1, half of the rats were first exposed to Context A, and then experienced Context B. For the other half, the opposite was true. Sessions were separated by approximately 1 hr. During those sessions, approximately 30 food pellets were delivered at a variable time (VT) 30s schedule. No levers were presented. Each session lasted 15 min.

Acquisition. The next five days, rats were trained in two daily sessions to press both levers for food on a variable interval (VI) 30 s schedule. Only one lever was available in a particular context. Contexts and responses were counterbalanced. Thus, for five days R1 (left or right lever) was trained in Context A, while R2 (left or right lever) was trained in Context B. Sessions were separated by approximately 3 hours. For half of the rats, context A was always experienced first, whereas for the other half context A was experienced at the second session of the day. Each session lasted 30 min.

Extinction. All rats received three extinction sessions for each response. No pellets were delivered. R1 underwent extinction in Context A and R2 in Context B. Each session lasted 30 min. Because the intersession interval for R1 was 72 h, whereas for R2 was 24 h, extinction for R1 started four days before R2's extinction (e. g., extinction for R1 started on Monday and finished on Sunday, whereas extinction for R2 started on Friday and finished on Sunday). This arrangement ensured that both responses received Extinction Test and Recovery Test the same day.

Extinction Test. Immediately after the last extinction session finished (the third extinction session for each response), rats received a 10 min test in the same context as the previous days for R1 and R2. No pellets were delivered. The order of testing responses were fully counterbalanced. Rats did not remain in the chambers, they were returned to their homecages. As in the previous phases, only one lever was available for each context.

Recovery Test. For the next four days, rats remained on their homecages and their weight were controlled. On the next day, rats received another two-10 min sessions. R1 was tested in context A while R2 in context B. No pellets were delivered. Only one lever was available for each context. The order of testing responses were fully counterbalanced. Each session was separated by 60 min.

2.1.4 Statistical Analysis

For all experiments presented here, mean responses per minute were compared using analyses of variance (ANOVA). The rejection criterion was set at $p<.05$, and effect sizes were reported using partial eta-squared (η_p^2). Moreover, 90% confidence intervals for the effect sizes were calculated and reported for each analysis.

2.2 Results and Discussion

Figure 1 shows the mean response per minute for both responses during acquisition (left panel) and extinction (right panel). A 2 (Response) x 5 (Session) ANOVA conducted with the data from acquisition confirmed that both responses were acquired similarly by all rats and that the responding increased as acquisition progressed, only finding a significant main effect of Session, $F(4, 60) = 123.41$, $p < .0001$, $\eta_p^2 = .89$ [CI: .84,.91]. The main effect of Response and all related interactions including this factor did not reach significance, *Fs<1*, showing that there was no difference in acquisition between R1 and R2.

A 2 (Response) x 3 (Session) ANOVA conducted on the extinction data only found a significant main effect of Session, $F(2, 30) = 77.27$, $p < .0001$, $\eta_p^2 = .84$ [CI: .72,.88]. More importantly, the main effect of response and all related interactions including this factor did not reach significance, Fs < 1, indicating that extinction proceeds similarly for both responses.

Insert Figure 1 about here

Figure 2 shows the mean responses per minute for both test sessions. A 2 (Response) x 2 (Test) ANOVA conducted with the data from Test found a significant main effect of Response, $F(1, 15) = 32.70$, $p < .0001$, $\eta_p^2 = .69$ [CI: .39, .79]. Analysis also found a significant main effect of Test, $F(1, 15) = 110.50$, $p < .0001$, $\eta_p^2 = .88$ [CI: .74, .92]. Moreover, the Response x Test interaction was also significant $F(1, 15) = 50.64$, $p < .0001$, $\eta_p^2 = .77$ [CI: .53, .85]. Subsequent analyses conducted to explore this interaction found that the simple effect of Test was significant for R1, $F(1, 15) = 9.00$, $p = .009$, $\eta_p^2 = .37$ [CI: .06,

214 .58], and for R2, $F(1, 15) = 143.15$, $p < .0001$, $\eta_p^2 = .90$ [CI: .79, .94], showing that rats
215 perform higher levels of both responses when they were tested after five days (Recovery
216 Test) than in Extinction Test, indicating spontaneous recovery of R1 and R2. Moreover, the
217 simple effect of Response was not significant for Extinction Test, $F < 1$, showing that
218 extinction took place in both responses in a similar way. The primary data for the present
219 experiment are the results that show that the simple effect of Response was significant for
220 Recovery Test, $F(1, 15) = 124.18$, $p < .0001$, $\eta_p^2 = .89$ [CI: .76, .93], demonstrating that rats
221 showed lower levels of spontaneous recovery when they received spaced extinction
222 sessions.
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224 Insert Figure 2 about here
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227 The present results extended the findings of Rowe and Craske (1998) to a situation
228 involving instrumental responses. Furthermore, the present data is, to the best of our
229 knowledge, the first demonstration of reduction of spontaneous recovery of instrumental
230 behavior by spacing the extinction sessions.
231
232 **3. Experiment 2**
233 The results from Experiment 1 show that spontaneous recovery of instrumental responses
234 was reduced by spacing the extinction sessions. Since it has been suggested that
235 spontaneous recovery and other response recovery effects (e. g., renewal) share a common
236 mechanism, one hypothesis might be that all response recovery effects should be affected in

a similar manner by the same treatments. Thus, Experiment 2 intended to assess whether a similar effect could be found in an ABA renewal design. In this experiment, hungry rats were trained to perform two instrumental responses (R1 in Context A and R2 in Context B). Responding was then extinguished in the alternative context (R1 in Context B and R2 in Context A). Rats received a spaced extinction session for R1with an intersession interval of 72 h, whereas for R2 rats experienced an intersession interval of 24 h. Finally, both responses were tested in their original Contexts (see the experimental design in the second row of Table 1). If using a spaced extinction procedure attenuates renewal, then R1 should show less response recovery.

3.1 Method

3.1.1 Subjects

Sixteen four-month-old experimentally naïve female Wistar rats weighing in average 302 g were used. Rats were maintained in the same conditions as Experiment 1.

3.1.2 Apparatus

The same apparatus as in Experiment 1 was used.

3.1.3 Procedure

Except as noted, the same procedure as in Experiment 1 was used.

Extinction. This session was conducted in the same manner as in the previous experiment. However, unlike in Experiment 1, each response underwent extinction in the alternative context (R1 in Context B; R2 in Context A). Context and responses were counterbalanced. Each session lasted 30 min.

Extinction Test. These sessions were conducted in the same manner as in Experiment 1.

Recovery Test. On the day after the extinction test, rats were tested two times. Both responses were tested in their original contexts. The order of response testing were fully counterbalanced, as in Experiment 1. Both sessions lasted 10 min. No pellets were delivered.

3.2 Results and Discussion

The left panel of Figure 3 depicts the mean response per minute for R1 and R2 throughout acquisition, while the right panel shows extinction performance for both responses. A 2 (Response) x 5 (Session) ANOVA conducted with the data from acquisition confirmed that both responses were acquired similarly by all rats and that the responding increased as acquisition progressed, only finding a significant main effect of Session, $F(4, 60) = 44.72$, $p < .0001$, $\eta_p^2 = .75$ [CI: .63, .79]. The main effect of the response and all related interactions including this factor did not reach significance, Fs < 1, showing that there was no difference in acquisition between R1 and R2.

A 2 (Response) x 3 (Session) ANOVA conducted on the extinction data only found a significant main effect of Session, $F(2, 30) = 41.25$, $p < .0001$, $\eta_p^2 = .73$ [CI: .56, .80]. Given that neither the main effect of Response, $F(1, 15) = 1.61$, $p = .22$, nor the Response x Session interaction, $F<1$, reached significance, ANOVA confirmed that R1 and R2 were extinguished in a similar manner.

Insert Figure 3 about here

Figure 4 shows the mean responses per minute for R1 and R2 during Extinction Test and Recovery Test. A 2 (Response) x 2 (Test) ANOVA found a significant main effect of Response, $F(1, 15) = 6.47$, $p = .02$, $\eta_p^2 = .30$ [CI: .03, .52], and a significant main effect of Test, $F(1, 15) = 71.20$, $p < .0001$, $\eta_p^2 = .83$ [CI: .63, .88]. In addition, the Response x Test interaction was also significant $F(1, 15) = 7.26$, $p = .01$, $\eta_p^2 = .33$ [CI: .04, .54]. Subsequent analyses to explore this interaction showed the simple effect of Test was significant in R1, $F(1, 15) = 14.55$, $p = .002$, $\eta_p^2 = .49$ [CI: .15, .66], and in R2, $F(1, 15) = 82.65$, $p < .0001$, $\eta_p^2 = .85$ [CI: .67, .90], indicating ABA renewal of both responses because rats show higher levels of lever-pressing in the original context. The simple effect of Response was not significant in Extinction Test, $F < 1$, indicating a similar extinction of both responses, as we stated above. Furthermore, the simple effect of Response was significant only in the Recovery Test, $F(1, 15) = 6.96$, $p = .01$, $\eta_p^2 = .32$ [CI: .03, .53], confirming that response retrieval was lower for R1, that is, rats performed lower levels of renewal when they received a longer intersession interval during extinction. To our knowledge, this is the first report that shows a reduction of ABA renewal of operant behavior produced by spacing extinction sessions.

Insert Figure 4 about here

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4. Experiment 3

Previous experiments have supported the benefits of using spaced extinction sessions to reduce spontaneous recovery and renewal of operant responses. Given that reinstatement is

also considered a context effect (Todd et al., 2012), Experiment 3 studied the impact of spacing extinction sessions on reinstatement of instrumental behavior. The rats' behavior was trained and extinguished using the same procedure as in Experiment 1. However, Recovery Test took place after rats were re-exposed to the food (see third row of Table 1). Thus, if spacing extinction sessions also reduces reinstatement, then rats should show lower responding for R1.

4.1 Method

4.1.1 Subjects

A group of 16 three-month-old experimentally naïve female Wistar rats weighing in average 290 g were used. Rats were maintained in the same conditions as Experiment 1.

4.1.2 Apparatus

The same apparatus as in previous experiments were used.

4.1.3 Procedure

Except as noted, the same procedure as in Experiment 1 was used.

*Extinction Test.*This session was conducted in the same manner as in the previous experiment. After the extinction test, a re-exposure to the outcome was conducted. Rats received two 15 min sessions with no levers,one session in Context A and another in Context B (counterbalanced). Free pellets were delivered using a VT 30s schedule.

Recovery Test. One day after the corresponding re-exposure session, rats received two 10 min sessions. Testing for R1 was conducted in Context A, while testing for R2 took place in Context B. Each session was separated by 60 min. The order of response testing was fully counterbalanced, just as in Experiment 2.

4.2 Results and Discussion

Figure 5 shows the mean responses per minute for both R1 and R2 during acquisition (left panel) and extinction (right panel). A 2 (Response) x 5 (Session) ANOVA conducted with the data from acquisition confirmed that both responses were acquired similarly by all rats and that the responding increased as acquisition progressed. The main effect of Session, $F(4, 60) = 60.17$, $p < .0001$, $\eta_p^2 = .80$ [CI: .71, .84], and the Response x Session interaction were significant, $F(4, 60) = 4.74$, $p = .002$, $\eta_p^2 = .24$ [CI: .06, .34], while the main effect of Response was not, $F < 1$. Analyses conducted to explore the Response x Session interaction show that the simple effect of Session was significant in both R1, $F(4, 60) = 44.44$, $p < .0001$, $\eta_p^2 = .75$ [CI: .63, .79], and R2, $F(4, 60) = 37.31$, $p < .0001$, $\eta_p^2 = .71$ [CI: .59, .76], indicating that rats acquired R1 and R2 in the same manner. The interaction found a simple effect of Response which was significant in Session 1, $F(1, 15) = 13.10$, $p = .03$, $\eta_p^2 = .47$ [CI: .13, .64], but the rest of the acquisition sessions were similar for both responses, largest $F(1, 15) = 2.12$, $p = .17$.

A 2 (Response) x 3 (Session) ANOVA conducted on the extinction data only found a significant main effect of Session, $F(2, 30) = 49.67$, $p < .0001$, $\eta_p^2 = .77$ [CI: .61, .83]. Given that the main effect of Response and the Response x Session interaction were not significant, largest $F(1, 15) = 1.73$, $p = .21$, the analyses confirmed that extinction proceeded similarly for both responses.

Insert Figure 5 about here

Figure 6 depicts the mean responses per minute for both tests. A 2 (Response) x 2 (Test) ANOVA found a significant main effect of Response, $F(1, 15) = 54.78$, $p < .0001$, $\eta_p^2 = .78$ [CI: .55, .86], and a significant main effect of Test, $F(1, 15) = 238.61$, $p < .0001$, $\eta_p^2 = .94$ [CI: .87, .96]. The ANOVA also found that the Response x Test interaction did reach significance $F(1, 15) = 44.43$, $p < .0001$, $\eta_p^2 = .75$ [CI: .49, .83]. We conducted subsequent analyses to explore the Response x Test interaction and we found that the simple effect of Test was significant in both R1, $F(1, 15) = 33.30$, $p < .0001$, $\eta_p^2 = .69$ [CI: .39, .79], and R2, $F(1, 15) = 175.35$, $p < .0001$, $\eta_p^2 = .92$ [CI: .82, .95], indicating higher levels of lever-pressing when rats received the Recovery Test. Hence, reinstatement for R1 and R2 was observed. The primary data for the present experiment are the results that show that the simple effect of Response was significant in the Recovery Test, $F(1, 15) = 117.80$, $p < .0001$, $\eta_p^2 = .89$ [CI: .75, .92], but not in the Extinction Test, $F<1$, showing that rats did perform lower levels of reinstatement when they received spaced extinction sessions. The present results extended our previous findings to a situation involving reinstatement. Additionally, as far as we know this is the first report in the field of instrumental learning that shows the benefits of spacing extinction sessions on reducing reinstatement.

Insert Figure 6 about here

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5. Experiment 4

So far, our findings show that spacing the extinction sessions promote less recovery of instrumental actions. In addition, results from the first three experiments are consistent with

Bouton's perspective about the mechanism underlying the response recovery effects. Therefore, Experiment 4 examined whether spacing extinction sessions also thwarts rapid reacquisition. Rats were trained to press two levers for food in two different contexts (R1 in Context A; R2 in Context B). Both responses were extinguished in the same context used in the previous phase (R1 in Context A; R2 in Context B). However, R1 received a longer intersession interval than R2 (72h vs. 24h). In the final test, both responses were reinforced again (see last row of Table 1). Thus, if using a spaced extinction treatment had any impact on reacquisition, then rats should show a slower response restoration for R1.

5.1 Method

5.1.1 Subjects

Sixteen three-month-old experimentally naïve female Wistar rats weighing in average 294 g were used. Rats were maintained in the same conditions as Experiment 3.

5.1.2 Apparatus

We used the same apparatus as in previous experiments.

5.1.3 Procedure

Except as noted, the same procedure as in Experiment 3 was used.

Recovery Test. On the day after the extinction test, rats received two 10 min test sessions. Testing for R1 was conducted in Context A. Testing for R2 took place in Context B. Both responses were reinforcedby a VI-30s schedule. Each session was separated by 60 min. The order of response testing was fully counterbalanced, as in Experiment 3.

5.2 Results and Discussion

The left panel of Figure 7 depicts the mean response per minute for both responses throughout acquisition, while the right panel shows the extinction performance for R1 and

R2. A 2 (Response) x 5 (Session) ANOVA conducted with the data from acquisition confirmed that both responses were acquired similarly by all rats and that responding increased as acquisition progressed by only finding a significant main effect of Session, $F(4, 60) = 58.98$, $p < .0001$, $\eta_p^2 = .80$ [CI: .70, .83]. The main effect of Response and the Response x Session interaction did not reach significance, largest $F(4, 60) = 1.98$, $p = .11$, showing that there was no difference in acquisition between R1 and R2.

A 2 (Response) x 3 (Session) ANOVA conducted on the extinction data only found a significant main effect of Session, $F(2, 30) = 20.33$, $p < .0001$, $\eta_p^2 = .57$ [CI: .34, .68]. The main effect of Response and the Response x Session interaction were not significant, Fs < 1, showing that there was no difference in extinction between R1 and R2.

Insert Figure 7 about here

Figure 8 shows the mean responses per minute for R1 and R2 during Extinction Test and Recovery Test. A 2 (Response) x 2 (Test) ANOVA only found a significant main effect of Test, $F(1, 15) = 894.30$, $p < .0001$, $\eta_p^2 = .98$ [CI: .96, .99]. The main effect of Response and the Response x Test interaction were not significant, Fs < 1, indicating that rats show rapid reacquisition for both responses in a similar manner.

The results of the present experiment show that spacing extinction sessions did not have any impact on rapid reacquisition of instrumental behaviors.

Insert Figure 8 about here

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424 **6. General Discussion**

425 The present experimental series was conducted to explore the impact of using a
426 spaced extinction sessions treatment on the response recovery effects of instrumental
427 behavior in rats. The within-subject design used in all the experiments reported here
428 allowed a direct comparison between two instrumental actions. The response recovery
429 effects were demonstrated by the return of the extinguished R2. Moreover, the effectiveness
430 of using a longer intersession interval during extinction was supported, as it reduced the
431 recovery of R1. Note that the benefits of spacing extinction sessions were shown in
432 spontaneous recovery, renewal, and reinstatement but not in rapid reacquisition.

433 Previous studies with humans have reported that spacing extinction sessions
434 attenuate spontaneous recovery of fear with anxious public speakers (Tsao & Craske, 2000)
435 and spider-fearful students (Rowe & Craske, 1998). Our findings in Experiment 1 extended
436 the efficacy of spaced extinction sessions to a situation that involves response restoration of
437 instrumental actions. In addition, a longer intersession interval during extinction is able to
438 attenuate two other sources of instrumental relapse: ABA renewal and reinstatement. These
439 findings are consistent with Bouton's theoretical perspective about context-specificity of
440 extinction learning (Bouton, 2002). This view explains renewal, spontaneous recovery and
441 reinstatement as failures to retrieve extinction information outside extinction context
442 (whether the context is external, temporal or associative). Spacing extinction sessions
443 overcome this retrieval failure by making the extinction context more similar to the test

444 context (i. e., spacing extinction sessions might result in multiple *temporal* contexts;
445 Bouton, 1993, 2002, 2010).

446 Similarly, the effectiveness of spaced extinction sessions could also be explained
447 under the contemporary approach of exposure therapy (Craske et al, 2008; Craske, Treanor,
448 Conway, Zbozinek & Vervliet, 2014). According to Craske et al. (2014) spacing extinction
449 sessions involves variable exposure (diversifying the practice of the to-be-learned material).
450 This so-called variability might enhance accessibility and retrievability of extinction
451 learning because spacing extinction sessions allows to pair extinction learning with more
452 retrieval cues (see also, Craske, Liao, Brown & Vervliet, 2012).

453 Reduction of response recovery in the first three experiments suggests that, despite
454 methodological differences between spontaneous recovery, renewal and reinstatement,
455 these sources of relapse share a common mechanism (Bouton, 2014; see also Bouton &
456 Swartzentruber, 1991). These findings are consistent with recent data obtained in
457 instrumental learning that demonstrated that presenting an extinction reminder during
458 testing can attenuate renewal (Nieto, Uengoer & Bernal-Gamboa, 2017; Willcocks &
459 McNally, 2014), spontaneous recovery, and reinstatement (Bernal-Gamboa et al., 2017).
460 Altogether, the results obtained support Bouton's proposal because both strategies (spaced
461 extinction sessions and an extinction reminder) involve enhancing the recovery of
462 extinction learning in a context different from the extinction context (therapeutic setting).

463 In contrast with Experiments 1-3, our last experiment shows that spacing extinction
464 sessions has no effect on retraining. Using a longer intersession interval during extinction
465 did not slow or reduce the rate of reacquisition. Note that other authors have also reported
466 the persistence of reacquisition in instrumental learning. For example, in a drug-self
467 administration paradigm with rats, Willcocks and McNally (2014, Experiment 3) observed

that an extinction reminder does not affect reacquisition of extinguished alcohol seeking. Although it has been suggested that reacquisition is less sensitive to contextual manipulations (e. g., Willcocks & McNally, 2011), literature is mixed because other studies have shown slower reacquisition by manipulating contextual stimuli (e. g., Todd et al., 2012; Woods & Bouton, 2007). However, before we accept that spacing the extinction sessions has no impact on reacquisition, is important to note that contrary to the other three response recovery effects, reacquisition might be obscured by responding that occurs after the animal contacts the reinforcement contingency. Therefore, a finer-grained analysis may reveal an effect of spaced extinction on reacquisition. Future studies should focus on using a more sensitive comparison by analyzing responding in shorter periods of time within the test session. Nevertheless, given that reacquisition is the laboratory model to understand the rapid transition from lapse to relapse, it is necessary to conduct more research in order to fully understand the mechanisms underlying reacquisition of instrumental actions.

It worth to mention the parallelisms between the present findings and the data reported using a similar procedure in Pavlovian preparations: the spacing of extinction trials. For example, Urcelay, Wheeler and Miller (2009) reported that longer intertrial intervals during extinction attenuates both renewal and spontaneous recovery in a fear conditioning paradigm. Moreover, Moody, Sunsay & Bouton (2006, Experiment 5b) found that extending the extinction trials was effective in reducing reinstatement in appetitive conditioning. However, it is important to note that reports in Pavlovian learning also showed that the spacing of extinction trials does not have any impact on spontaneous recovery (Cain, Blouin, & Barad, 2003; Moody, et al., 2006, Experiment 1-5a) nor reinstatement (Moody et al., 2006, Experiment 4b). As noted elsewhere the mixed results might be due to parametric differences. Nevertheless, the mechanisms underlying

492 expanding the extinction trials are far from clear (e. g., Laborda, McConnell & Miller,
493 2011).

494 Although the effects of implementing longer intervals between extinction trials and
495 extinction sessions may share a common mechanism, a methodological difference between
496 these treatments could hinder the explanation based on a single mechanism for both. Note
497 that using the extinction trial procedure involves that the subject receives more exposure to
498 the apparatus than the use of the spacing extinction sessions (i.e., subjects experienced the
499 intersession interval outside the apparatus). Thus, more research is mandatory in order to
500 fully understand these behavioral treatments.

501 The overall results might have some relevance for clinical practice. Although it may
502 be easier to relate exposure therapy to aversive Pavlovian learning (e. g. fear), it is
503 important to highlight that this technique has been effectively used to diminishing addictive
504 behaviors (instrumental learning; see Conklin, 2006; Conklin & Tiffany, 2002). Since, we
505 present here experiments that show that different sources of voluntary but unhealthy
506 behaviors could be understood as contextual-dependent retrieval effects, the development
507 of treatments that promote remembrance of therapeutic abilities (extinction learning)
508 beyond the therapist's office (extinction context) should reduce the propensity for
509 unwanted action restoration (i. e., smoking). Spacing extinction sessions (which might be
510 translated as longer intervals between therapeutic exercises) may help prevent clinical
511 treatment from becoming too routinary (e. g., more restricted to a particular context). In
512 addition, longer intervals between clinical sessions might enhance the salience of the
513 therapeutic technique and thereby enhance recalling in the future.

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References

Baker, A. G., Steinwald, H., & Bouton, M. E. (1991). Contextual conditioning and reinstatement of extinguished instrumental responding. *The Quarterly Journal of Experimental Psychology, 43,* 199-218, http://dx.doi.org/10.1080/14640749108401267

Bernal-Gamboa, R., Gámez, A. M., & Nieto, J. (2017). Reducing spontaneous recovery and reinstatement of operant performance through extinction-cues. *Behavioural Processes, 135,* 1-7. http://dx.doi.org/10.1016/j.beproc.2016.11.010

Bouton, M.E. (1993). Context, time, and memory retrieval in the interference paradigms of pavlovian learning. *Psychological Bulletin, 114,* 80–99, http://dx.doi.org/10.1037/0033-2909.114.1.80

Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry, 52*, 976–986, http://dx.doi.org/10.1016/S0006-3223(02)01546-9

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning & Memory, 11,* 485-494, http://dx.doi.org/10.1101/lm.78804

Bouton, M.E. (2010). The multiple forms of context in associative learning. In: Mesquita, B., Feldman Barret, L., Smith, E. (Eds.), *The mind in context*. The Guilford Press, New York, pp. 233-258.

Bouton, M. E. (2011). Learning and the persistence of appetite: Extinction and the motivation to eat and overeat. *Physiology & Behavior, 103,* 51–58. http://dx.doi.org/10.1016/j.physbeh.2010.11.025

538 Bouton, M.E. (2014). Why behavior change is difficult to sustain. *Preventive Medicine, 68,*
539 29-36. http://dx.doi.org/36. 10.1016/j.ypmed.2014.06.010
540 Bouton, M. E., & Swartzentruber, D. (1991). Sources of relapse after extinction in
541 Pavlovian and Instrumental Learning. *Clinical Psychology Review, 11,* 123-140.
542 http://dx.doi.org/10.1016/0272-7358(91)90091-8
543 Bouton, M. E., Todd, T. P., Vurbic, D., & Winterbauer, N. E. (2011). Renewal after the
544 extinction of free operant behavior. *Learning & Behavior, 39*, 57-67.
545 http://dx.doi.org/10.3758/s13420-011-0018-6
546 Bouton, M.E., Winterbauer, N.E., & Vurbic, D. (2011). Context and extinction:
547 mechanisms of relapse in drug self-administration. In: Haselgrove, M., Hogarth, L.
548 (Eds.), (pp.103-133). *Clinical Application of Learning Theory*. East Sussex:
549 Psychology Press.
550 Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowsi, J., Chowdhury, N., & Baker,
551 A.(2008). Optimizing inhibitory learning during exposure therapy. *Behaviour*
552 *Research and Therapy, 46*, 5-27, http://dx.doi.org/10.1016/j.brat.2007.10.003
553 Craske, M. G., Liao, B., Brown, L., & Verliet, B. (2012). Role of inhibition in exposure
554 therapy. *Journal of Experimental Psychopathology, 3*, 322-345.
555 http://dx.doi.org/10.5127/jep.026511
556 Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014).
557 Maximizing exposure therapy: An inhibitory learning approach. *Behaviour*
558 *Research and Therapy, 58*, 10-23. http://dx.doi.org/10.1016/j.brat.2014.04.006
559 Crombag, H., Bossert, J.M., Koya, E. & Shaham, Y. (2008). Context-induced relapse to
560 drug seeking: A review. *Philosophical Transactions of The Royal Society B*
561 *Biological Sciences, 363,* 3233-3243. http://dx.doi.org/10.1098/rstb.2008.0090

562 Dickinson, A., & Balleine, B. (1993). Actions and responses: the dual psychology of
563 behaviour. In N. Eilan & R. A. McCarthy (Eds.), *Spatial representation: problems*
564 *in philosophy and psychology* (pp. 277–293). Malden: Blackwell.
565 Dickinson, A., & Balleine, B. (1994). Motivational control of goal-directed action. *Animal*
566 *Learning & Behavior, 22,* 1–18
567 Harrington, S. (2008). The role of sugar-sweetened beverage consumption in adolescent
568 obesity: a review of the literature. *The Journal of School Nursing, 24*, 3-12.
569 http://dx.doi.org/10.1177/10598405080240010201
570 Kelley, M. E., Liddon, C. J., Ribeiro, A., Greif, A. E., & Podlesnik, C. A. (2015). Basic and
571 translational evaluation of renewal of operant responding. *Journal of Applied*
572 *Behavioral Analysis, 48*, 390-401. http://dx.doi.org/10.1002/jaba.209
573 Marchant, N. J., Li, X., & Shaham, Y. (2013). Recent developments in animal models of
574 drug relapse. *Current Opinion in Neurobiology. 23,* 675-683,
575 http://dx.doi.org/10.1016/j.conb.2013.01.003
576 Nakajima, S., Tanaka, S., Urushihara, K., & Imada, H. (2000). Renewal of extinguished
577 lever-press responses upon return to the training context. *Learning and Motivation,*
578 *31,* 416–431. http://dx.doi.org/10.1006/lmot.2000.1064
579 Nieto, J., Uengoer, M., & Bernal-Gamboa, R. (2017). A reminder of extinction reduces
580 relapse in an animal model of voluntary behavior. *Learning & Memory, 24*, 76–80.
581 http://dx.doi.org/10.1101/lm.044495.116
582 Rescorla, R. A. (1993). Inhibitory associations between S and R in extinction. *Animal*
583 *Learning and Behavior, 21,* 327–336, http://dx.doi.org/10.3758/BF03197998

584 Rescorla, R. A. (1997). Spontaneous recovery of instrumental discriminative responding.
585 *Animal Learning and Behavior, 25*, 485 -497.
586 http://dx.doi.org/10.3758/BF03209854
587 Rescorla R.A. (2001). Experimental extinction. In: Mowrer R.R., Klein S.B. (Eds.)
588 *Handbook of contemporary learning theories.* (pp. 119–154). Erlbaum; Mahwah,
589 NJ.
590 Rescorla, R. A. (2004). Spontaneous recovery. *Learning & Memory, 11*, 501-509.
591 http://dx.doi.org/10.1101/lm.77504
592 Rescorla, R.A., & Skucy, J.C. (1969). Effect of response-independent reinforcers during
593 extinction. *Journal of Comparative and Physiological Psychology, 67*, 381-389.
594 http://dx.doi.org/10.1037/h0026793
595 Ricker, S. T., & Bouton, M. E. (1996). Reacquisition following extinction in appetitive
596 conditioning. *Animal Learning and Behavior, 24,*423–436.
597 Rowe, M. K., & Craske, M. G. (1998). Effects of an expanding-spaced vs massed exposure
598 schedule on fear reduction and return of fear. *Behaviour Research and Therapy, 36,*
599 701–717.
600 Schmidt, R. A. & Bjork, R. A. (1992). New conceptualizations of practice: Common
601 principles in three paradigms suggest new concepts for training. *Psychological*
602 *Science. 3,* 207-217.
603 Schroeder, S. A. (2007). We can do better-Improving the health of American people. *The*
604 *New England Journal of Medicine, 357,* 1221-1228.
605 http://dx.doi.org/10.1056/NEJMsa073350

606 Schulze, M. B., Manson, J. E., Ludwig, D. S., Colditz, G. A., Stampfer, M. J., Willett, W.
607 C., & Hu, F. B. (2004). Sugar-Sweetened Beverages, Weight Gain, and Incidence of
608 Type 2 Diabetes in Young and Middle-Aged Women. *JAMA, 292*, 927-934.
609 Todd, T. P.(2013). Mechanisms of renewal after the extinction of instrumental behavior.
610 *Journal of Experimental Psychology: Animal Behavior Processes, 39,* 193-207.
611 http://dx.doi.org/10.1037/a0032236
612 Todd, T. P., Vurbic, D., & Bouton, M. E. (2014). Behavioral and neurobiological
613 mechanisms of extinction in Pavlovian and instrumental learning. *Neurobiology of*
614 *Learning & Memory, 108,* 52-64, http://dx.doi.org/10.1016/j.nlm.2013.08.012
615 Todd, T. P., Winterbauer, N. E., & Bouton, M. E. (2012). Contextual control of appetite:
616 Renewal of inhibited food-seeking behavior in sated rats after extinction. *Appetite,*
617 *58*, 484–489. http://dx.doi.org/10.1016/j.appet.2011.12.006
618 Tsao, J. C. I., & Craske, M. G. (2000). Timing of treatment and return of fear: effects of
619 massed, uniform, and expanding spaced exposure schedules. *Behavior Therapy, 31,*
620 479-497. http://dx.doi.org/10.1016/S0005-7894(00)80026-X
621 Willcocks, A. L., & McNally, G. P. (2011). The role of context in re-acquisition of
622 extinguished alcoholic beer-seeking. *Behavioral Neuroscience, 125,* 541–550.
623 http://dx.doi.org/10.1037/a0024100
624 Willcocks, A. L., & McNally, G. P. (2014). An extinction retrieval cue attenuates renewal
625 but not reacquisition of alcohol seeking. *Behavioral Neuroscience, 128*, 83-91,
626 http://dx.doi.org/10.1037/a0035595
627 Woods, A. M., & Bouton, M. E. (2007). Occasional reinforced responses during extinction
628 can slow the rate of reacquisition of an operant response. *Learning and Motivation,*
629 *38*, 56-74. http://dx.doi.org/10.1016/j.lmot.2006.07.003

Table 1

Experimental Designs

Experiment	Acquisition	Extinction	Extinction Test	Recovery Test
1 Spontaneous Recovery	A: R1-O B: R2-O	A: sR1- B: R2-	A: R1- B: R2-	A: R1- B: R2-
2 Renewal	A: R1-O B: R2-O	B: sR1- A: R2-	B: R1- A: R2-	A: R1- B: R2-
3 Reinstatement	A: R1-O B: R2-O	A: sR1- B: R2-	A: R1- B: R2-	A: R1- B: R2-
4 Rapid Reacquisition	A: R1-O B: R2-O	A: sR1- B: R2-	A: R1- B: R2-	A: R1-O B: R2-O

Note. A and B are two different contexts. R1 and R2 refer to pressing left or right lever counterbalanced. "R1-O" and "R2-O" means that pressing the lever was reinforced. "R1-" and "R2-" means that pressing the lever was not reinforced. "s" means that rats received a spaced extinction sessions procedure. For all experiments, Extinction Test took place immediately after the last extinction session. For Experiment 1, the Recovery Test took place five days later than Extinction Test. For Experiment 2, rats experienced the Recovery Test in the original context. For rats in Experiment 3, Recovery Test was conducted after rats received a single session of free delivery food. In Experiment 4, during Recovery Test rats were reinforced for pressing both levers.

Figure 1

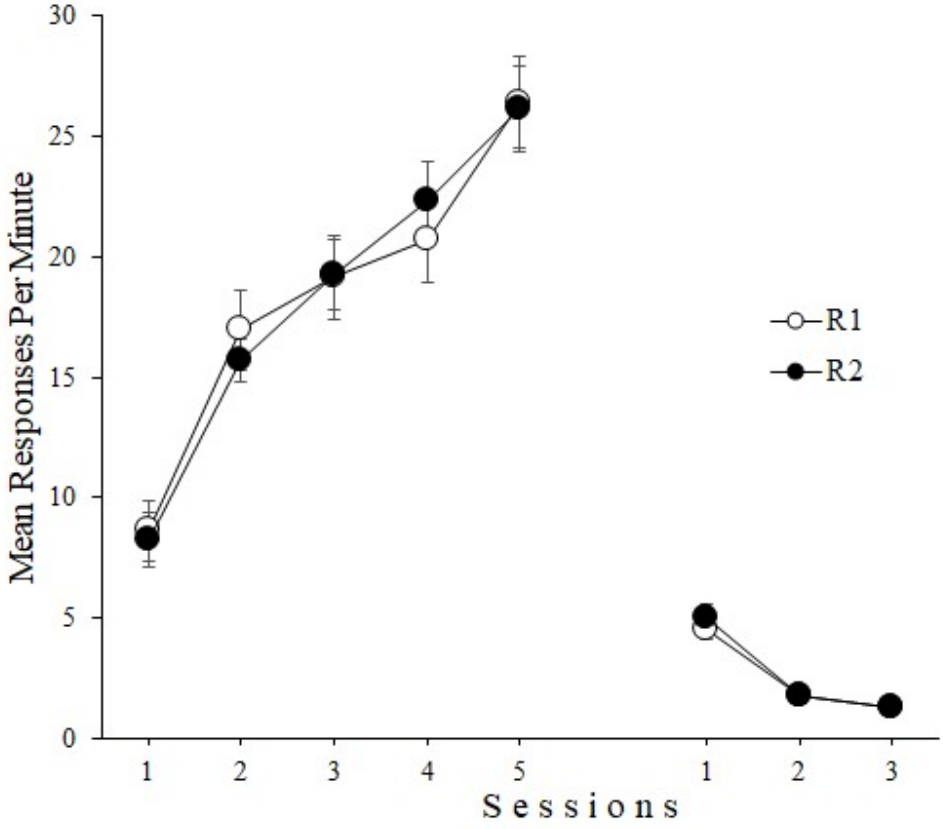


Figure 1. Mean responding of R1 and R2 during acquisition and extinction in Experiment 1. Error bars denote standard errors of the mean.

Figure 2

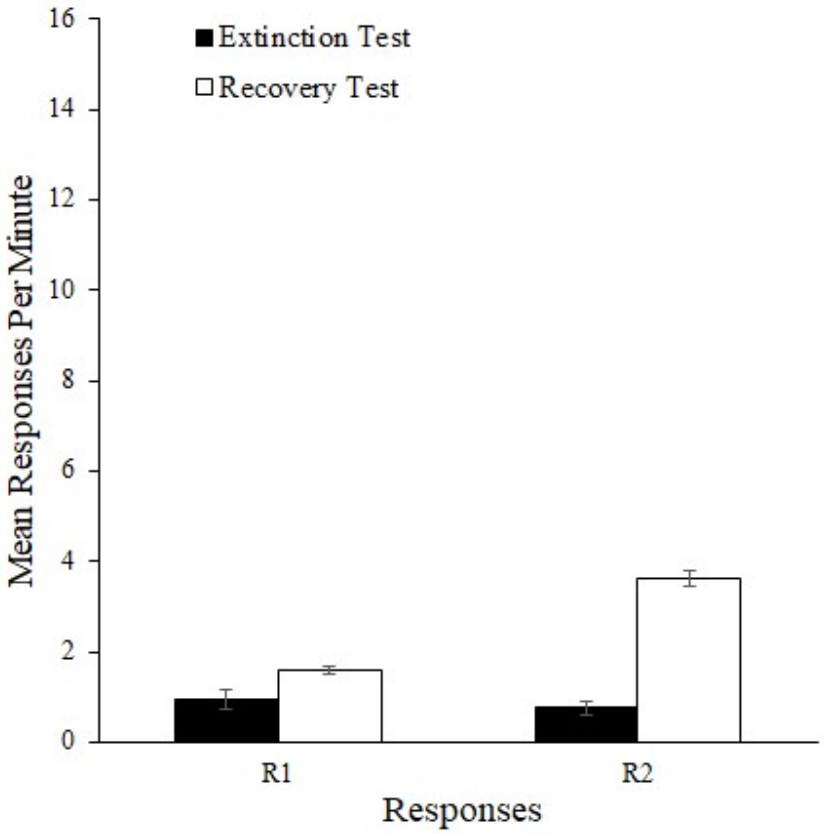


Figure 2. Mean responding of R1 and R2 during the testing sessions in Experiment 1. Error bars denote standard errors of the mean.

Figure 3

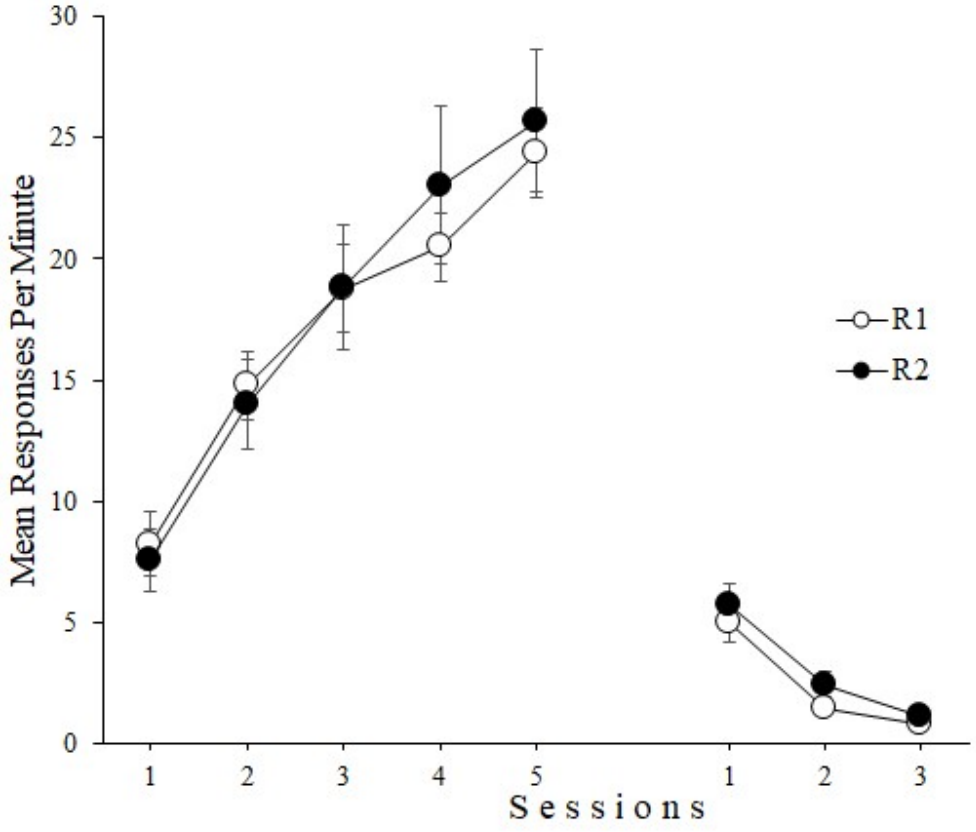


Figure 3. Mean responding of R1 and R2 during both acquisition and extinction phases in Experiment 2. Error bars denote standard errors of the mean.

Figure 4

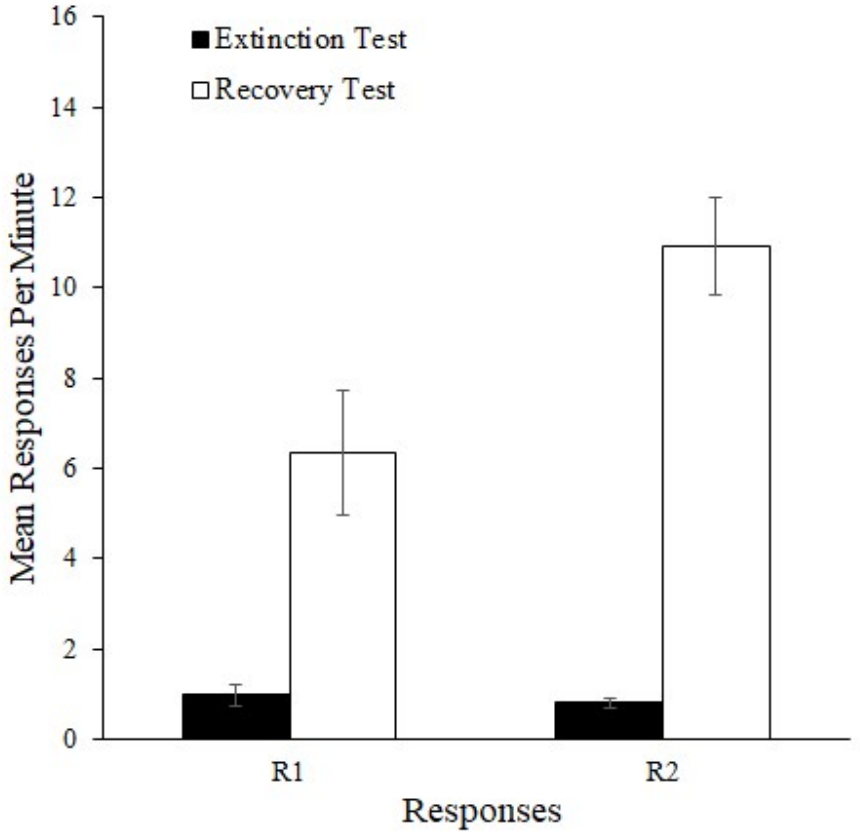


Figure 4. Mean responding of R1 and R2 during the testing sessions in Experiment 2. Error bars denote standard errors of the mean.

Figure 5

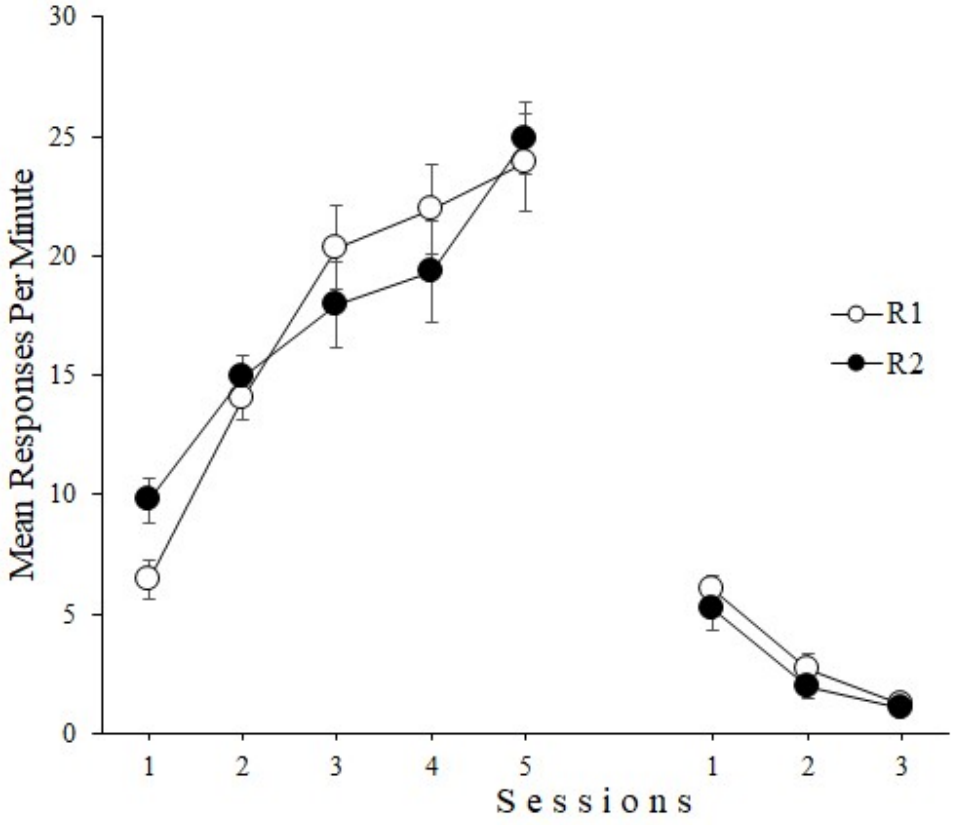


Figure 5. Mean responding of R1 and R2 during acquisition and extinction in Experiment 3. Error bars denote standard errors of the mean.

Figure 6

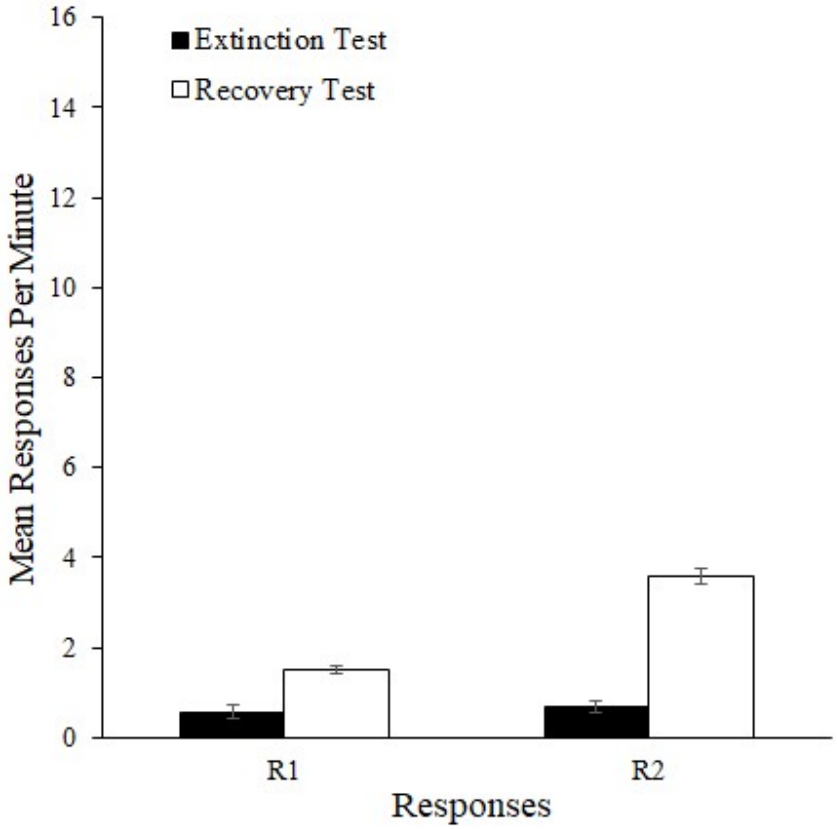


Figure 6. Mean responding of R1 and R2 during the testing sessions in Experiment 3. Error bars denote standard errors of the mean.

Figure 7

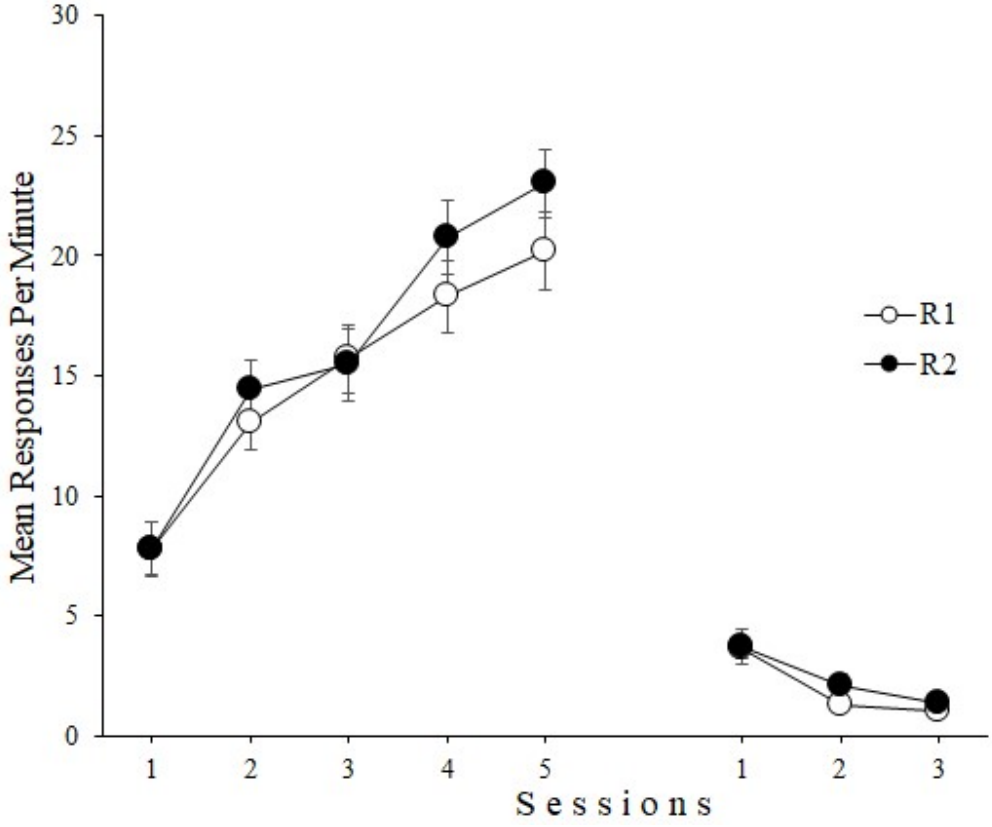
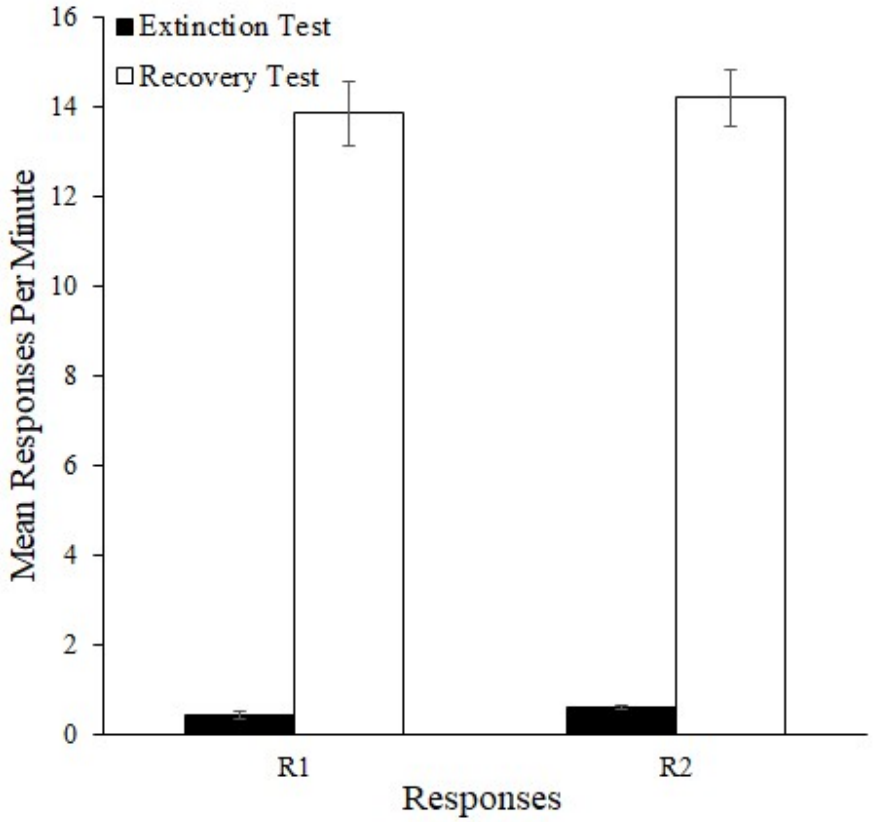


Figure 7. Mean responding of R1 and R2 during both acquisition and extinction phases in Experiment 4. Error bars denote standard errors of the mean.

730 **Figure 8**



731

732 **Figure 8**. Mean responding of R1 and R2 during the testing sessions in Experiment 4. Error

733 bars denote standard errors of the mean.

734