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Partial Reinforcement Reduces Vulnerability to Anti-anxiety Self-medication During Appetitive Extinction

Lidia Manzo[1], M. José Gómez[1], José E. Callejas-Aguilera[1], Alberto Fernández-Teruel[2], Mauricio R. Papini[3] & Carmen Torres[1]

[1]Department of Psychology, University of Jaén, Spain
[2]Department of Psychiatry & Forensic Medicine, Autonomous University of Barcelona, Spain [3]Department of Psychology, Texas Christian University, USA

Inbred rats from the Roman low-avoidance strain (RLA-I), but not from the Roman high-avoidance strain (RHA-I) increased preference for ethanol after being exposed to sessions of appetitive extinction (Manzo et al., 2014). RLA-I rats have shown greater sensitivity than RHA-I rats to a variety of anxiogenic situations, including those involving reward loss. Such increased fluid preference did not occur after acquisition (reinforced) sessions or in control groups with postsession access to water, rather than ethanol. Because ethanol has anxiolytic properties in tasks involving reward loss, oral consumption after extinction sessions was interpreted as anti-anxiety or emotional self-medication (ESM). The present research was an attempt to reduce or eliminate the ESM effect in RLA-I rats by giving them 50% partial reinforcement training during the acquisition of an instrumental response, a treatment known to induce resilience to loss-induced anxiety. As expected, partially reinforced RLA-I rats showed a higher resistance to extinction in comparison to continuously reinforced animals, displaying lower ethanol consumption than continuously reinforced rats during the postsession preference test. Partial and continuous control groups receiving water during the preference tests showed no changes in preference. These results suggest that exposure to reward uncertainty typical of partial reinforcement training can reduce ESM in rats genetically selected for high levels of anxiety.

Research on the mechanisms underlying substance use disorders (SUDs; APA, 2013) shows that stress is a strong predictor of drug consumption and abuse (Hassanbeigi, Askari, Hassanbeigi, & Pourmovahed, 2013). Emotionally painful experiences promote drug consumption. Thus, individuals exposed to physical or psychological abuse, natural catastrophes, death of a love one, job loss, family and economical problems, chronic pain, etc., show higher rates of alcohol, benzodiazepine, and illicit-drug abuse than matched controls (Duffing, Greiner, Mathias, & Dougherty, 2014; Egli, Koob, & Edwards, 2012; Gordon, 2002; Konopka, Pełka-Wysiecka, Grzywacz, & Samochowiec, 2013; Spanagel, Noori, & Heilig, 2014). This clinical evidence has been

Please send correspondence to Dr. Carmen Torres, Department of Psychology, Department of Psychology, University of Jaén, Campus Lagunillas, 23071, Spain. Tel: +34 953212292, Fax: +34 953211881 (Email: mctorres@ujaen.es). https://doi.org/10.46867/ijcp.2015.28.00.07

frequently explained in terms of the emotional self-medication (ESM) hypothesis, which argues that drug taking contributes to coping with and reducing painful and threatening emotions (Khantzian, 1985, 2013). From this perspective, the onset, progression, and/or relapse into an SUD depend on the reinforcing reduction of an aversive emotional state (Blume, Schmaling, & Marlatt, 2000).

ESM behaviors have also been observed in nonhuman animals (Torres & Papini, in press). In such studies, individuals exposed to stimuli inducing acute or chronic stress (e.g., inescapable electric foot shock, social stress, forced swimming, restrain, physical pain), show higher consumption of psychoactive drugs simultaneously or subsequently presented (Becker, Lopez, & Doremus-Fitzwater, 2011; Spanagel et al., 2014). Recent studies have extended this experimental approach to situations involving reward loss, a source of frustration and psychological pain that has been overlooked in studies on stress and anxiety despite its clinical relevance (Papini, Fuchs, & Torres, 2015). The impact of reward loss on the voluntary consumption of anxiolytic drugs was investigated in two recent studies that followed the same methodology. Animals were exposed each day to two tasks in tandem: An induction task designed to trigger frustration followed by a preference test given animals a choice between an anxiolytic solution and water. In one study (Manzo et al., 2014), animals with extreme divergence in emotional reactivity and anxiety, inbred strains of Roman High- and Low-Avoidance (RHA-I, RLA-I) rats (Torres & Sabariego, 2014), were exposed to two induction tasks involving acquisition and extinction sessions. Immediately after each session, rats were exposed to an ethanol-water, two-bottle preference test. The main finding was that the more anxious RLA-I rats showed greater preference for ethanol than the less anxious RHA-I rats selectively after nonreward (extinction sessions). Controls given access to water showed no changes in consumption after extinction sessions. A second study (Manzo, Donaire, Sabariego, Papini, & Torres, 2015) tested the effects of reward loss on the consumption of ethanol and of the benzodiazepine anxiolytic chlordiazepoxide in Wistar rats exposed to a preference test. Again, the main results indicated that Wistar rats showed increased preference for these anxiolytics selectively in tests given after reward downshift sessions. These results suggest that reward loss can induce an increased preference for substances that are independently known to reduce anxiety in reward-loss situations (Becker & Flaherty, 1982, 1983; Kamenetzky, Mustaca, & Papini, 2008) and to have addictive potential (Tan, Rudolph, & Luzcher, 2011).

The present experiment was designed to determine whether extended partial reinforcement (PR) training, rather than continuous reinforcement (CR) training, attenuates the effects of reward omission on post-session ethanol consumption in emotionally reactive RLA-I rats. PR experience (that is, the quasi-random alternation between reinforced, R, and nonreinforced, N, trials) is known to attenuate the disruptive effects of subsequent reward loss during extinction trials, relative to animals receiving CR training (Amsel, 1992). This effect, called the partial reinforcement extinction effect (PREE), can be conceptualized as a treatment for developing resilience to loss-induced anxiety (Papini, Wood, Daniel, & Norris, 2006). The PREE has been observed in RLA-I rats, but not in RHA-I rats (Gómez et al., 2008), therefore, the present experiment included only RLA-I rats. A substantial amount of research shows that RLA-I rats score highly in a variety of tests indexing anxiety and stress compared to RHA-I rats (Escorihuela et al., 1999; Papini et al., 2015; Torres & Sabariego, 2014; Steimer & Driscoll, 2003). This experiment aims at determining whether a history of PR can compensate, at least partially, for vulnerability to anxiety in a rat strain subjected to

psychogenetic selection for poor performance in an active avoidance task since the late 1960s (Broadhurst & Bignami, 1965). Based on this information, we made the following predictions: (1) RLA-I rats would show evidence of the PREE independently of the type of preference test administered after runway sessions; (2) RLA-I animals receiving PR training during acquisition would exhibit a lower preference for ethanol over water after extinction sessions than RLA-I animals receiving CR training; and (3) groups receiving PR and CR training, but given access to water after these sessions, would not exhibit any changes in preference.

Method

Subjects

Twenty-six male RLA-I rats, about 120 days old at the start of the experiment, obtained from the Autonomous University of Barcelona, were used. Their ad libitum weights ranged from 306 to 425 g. Animals were individually housed in polycarbonate cages with water continuously available and deprived to 82% (range 80%-84%) of their ad libitum weight. They were maintained at the target deprivation weight by daily feedings of lab chow approximately 30 min after each experimental session. Room temperature was kept around 20 ºC. Animals were maintained under a 12:12 h cycle, with lights on at 08:00 h. All testing sessions were performed between 09:00 and 16:00 h. The experiment followed the European Union directive guidelines for the use of animals in research (2010/63/EU) and Spanish Law (6/2013; R.D. 53/2013).

Apparatus

The induction task was administered in two wooden runways painted green and measuring 120x11x14 cm (LxWxH). Each runway was divided into a start (20 cm), central (80 cm), and goal boxes (20 cm). Guillotine doors operated manually separated these compartments. Response latencies (in seconds) were measured with a manual chronometer (Extech, Madrid, Spain). The chronometer was started when the guillotine door in the start box was raised and was stopped when the rat had its four legs inside the goal box.

The preference test was administered in the animal's home cage (32x30x15 cm, LxWxH). Two 50-ml bottles were introduced side by side through the metallic lid. For two groups, one bottle contained tap water and the other 2% ethanol. For two other groups, both bottles contained tap water. Fluid consumption was determined by weighing each bottle before and after the 2-h preference test with a digital scale (Cobos, JT-300C, Barcelona, Spain). The 2% ethanol solution was prepared by mixing 62.5 ml of 96% alcohol (Panreac, Castellar del Vallés, Spain) for every 2,937.5 ml of tap water. The 2% ethanol concentration was selected because a previous study showed preference of ethanol over water in RLA-I rats (Manzo et al., 2012). Daily animal weights were recorded with a Baxtran scale (model BS3, Girona, Spain).

Procedure

Rats were randomly assigned to one of four conditions depending on the acquisition training in the induction task (PR, CR) and the preference test (E: ethanol-water; W: water-water): PR/E (n = 7), CR/E (n = 7), PR/W (n = 6), and CR/W (n = 6). The groups included in this experiment were run simultaneously, but the results for the two groups that received CR training (Groups CR/E and CR/W) were published before in Manzo et al. (2014).

Induction task. Rats were taken from the colony room to the experimental room in squads of 13 animals. Animals were run two at a time. This yielded an inter-trial interval of approximately 15 min throughout the experiment. The floor of the runway was vacuumed and wiped with 5% ethanol solution after every squad finished its session.

Days 1-3 involved habituation to the runway. Each session had five 1-min trials. No food was administered in the first habituation session; 12 pellets per trial were placed in the goal box during the

second habituation session; and 12 pellets per trial were scattered about the floor during the third habituation session.

Acquisition training was administered on Days 4-13 (10 sessions, 6 trials/session). For partial reinforcement groups (PR/E and PR/W), 12 pellets were administered on R trials. On N trials, the rat was left in the goal box for 30 s and was then returned to its home cage until the next trial. Thus, the time spent in the goal box on R and N trials was approximately the same. The sequence of R and N trials was determined by Gellermann (1933) sequences with a similar number of RN and NR transitions. For continuously reinforced groups (CR/E and CR/W), 12 pellets were administered in the goal box on every acquisition trial. A maximum time of 20 s was allowed for the rat to complete the trial. If a rat did not reach the goal box before 20 s, it was gently guided by the experimenter to the goal, allowed to experience the R or N outcome scheduled for that trial, and given a 20-s running time. When the rat reached the goal box, the goal-box door was quietly closed and a second stopwatch was started to measure a maximum of 30 s to eat the food or stay in the empty goal box. After either eating was finished eating or the 30 s elapsed, the rat was removed from the goal-box and placed back into its home cage. The number of pellets left uneaten, if any, was recorded.

On Days 14-20, all rats received seven 6-trial extinction sessions. Extinction and acquisition sessions were equal to N trials in partially reinforced groups.

Preference test. Immediately after each session of instrumental training in the runway, animals were placed back in their home cage with two bottles. For two groups (CR/E and PR/E), one bottle contained tap water and the other contained 2% ethanol. For two other groups (CR/W and PR/W), both bottles contained tap water. Each preference test lasted 2 h and the amount of fluid consumed from each bottle was registered. The position of the ethanol bottle was switched daily to minimize position preferences. The dependent variable was a preference index calculated as follows: consumption (ml) of the target bottle (whether ethanol or water) divided by total consumption (ml) for the entire postsession preference test.

Statistical analysis. The dependent variables (latency in the induction task; preference in the preference test) were subjected to conventional analysis of variance with an alpha set at the 0.05 level. Whenever appropriate, significant interactions were analyzed using the error term derived from the main analysis. Pairwise comparisons were computed with the LSD test. All statistics were run with the IBM SPSS statistics package (V. 21). For brevity, only significant effects are reported below in detail.

Results

Induction Tasks

Ad libitum weights did not differ across groups. A Schedule (PR, CR) x Ethanol (E, W) analysis of initial weights indicated that none of the factors or their interaction were significant, Fs < 1. Figure 1 presents the main results of the experiment. The results for the runway induction task are presented on the left column, separately for groups that received ethanol (top) or water (bottom) immediately after these runway sessions. Inspection of this figure shows that, regardless the subsequent access to water-water vs. water-ethanol in the preference test, CR animals extinguished faster than PR animals during the induction task. In addition, CR rats showed greater preference for ethanol over water than PR animals, whereas these differences were not obtained in CR and PR groups exposed only to water during the preference test. Statistical analyses confirmed these observations. Because acquisition data did not meet the sphericity assumption, Greenhouse-Geisser corrections are reported for these analyses. A Schedule (PR, CR) x Ethanol (E, W) x Session (1-10) analysis indicated a significant triple interaction, $F(9, 198) = 6.64$, $p < 0.003$. In addition, the main effect of session was significant, $F(9, 198) = 67.59$, $p < 0.001$. Pairwise tests were calculated to determine the source of the triple interaction. These tests indicated isolated differences between

groups. For example, whereas Groups PR/E and CR/E did not differ in any of the session, *p*s > 0.05, PR/W and CR/W differed in Session 1, $F(1, 22) = 4.95$, $p < 0.04$. Additionally, whereas Groups PR/E and PR/W did not differ in any of the session, *p*s > 0.07, Groups CR/E and CR/W differed on Session 1, $F(1, 22) = 8.45$, $p < 0.009$. Thus, although the triple interaction was significant, the source of the difference appeared to be relatively isolated pairwise differences.

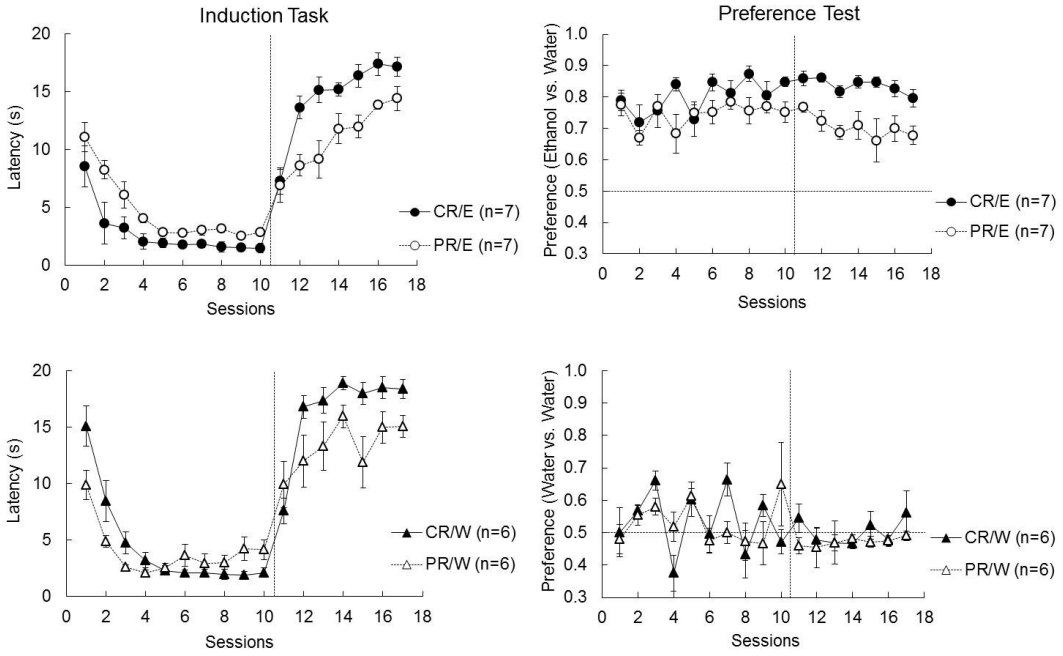

Figure 1. The left panels show the performance in the induction task (runway) during acquisition and extinction in terms of latency (s) to reach the goal box. Groups received partial reinforcement (PR) or continuous reinforcement (CR) training during acquisition, and had access to ethanol (E, top) or water (W, bottom) immediately after these runway sessions. The right panels show the results of the preference test in terms of a preference score (see text for formula). Measurements taken after acquisition sessions and after extinction sessions in the runway are shown separately for groups receiving either ethanol-water (top) or water-water (bottom) during the two-bottle preference test. The results from groups receiving CR had been published before and are here reproduced with permission from Manzo et al. (2014). Anti-anxiety self-medication induced by incentive loss in rats, *Physiology & Behavior, 123,* 86-92, Elsevier.

Figure 1 also shows the results of extinction. In both pairs of groups, animals receiving continuous reinforcement extinguished faster than animals receiving training under partial reinforcement—the PREE effect. Extinction data failed the sphericity assumption, so Greenhouse-Geisser corrections are reported here. A similar statistical analysis restricted to extinction sessions supported this conclusion in terms of a significant schedule by session effect, $F(6, 132) = 3.46$, $p < 0.02$. Also significant were the simple effects of schedule and sessions, *F*s > 6.87, *p*s < 0.002. Pairwise LSD tests indicated that latencies for PR and CR groups were significantly different on Sessions 12, 13, 15, 16, and 17, *F*s(1, 22) > 4.96, *p*s < 0.04. Thus, there was no evidence that the post-session preference test affected performance in the runway; rather, instrumental behavior was a function of the schedule of acquisition training.

Preference Test

Figure 1, right column, shows the results of the preference test separately for groups given access to ethanol-water (top) and water-water (bottom). Clearly, whereas preference differed among groups given access to ethanol, there were no systematic differences in groups given access to water. Greenhouse-Geisser corrections were used for acquisition data. A Schedule (PR, CR) x Ethanol (E, W) x Session (1-10) analysis indicated again a triple interaction, $F(9, 198) = 3.34$, $p < 0.009$. There were also significant effects for the Ethanol x Session interaction and Ethanol main effects, Fs > 4.05, ps < 0.001. The source of the triple interaction was determined by two pairwise comparisons. First, in PR groups, preference for ethanol over water was significant on Sessions 1-9, Fs(1, 22) > 4.93, ps < 0.04, whereas in CR groups, preference for ethanol over water was significant on Sessions 1-2 and 4-10, Fs(1, 22) > 4.46, ps < 0.05. Second, in ethanol groups, preference for ethanol was greater in CR than in PR animals only on Session 4, $F(1, 22) = 5.86$, $p < 0.03$, whereas in water groups, preference was greater in CR than PR animals only on Session 7, $F(1, 22) = 8.77$, $p < 0.008$.

A similar analysis for extinction sessions yielded a significant Schedule x Ethanol interaction, $F(1, 22) = 7.65$, $p < 0.02$. There were also significant main effects for Schedule and Ethanol, Fs(1, 22) > 20.40, ps < 0.001. Pairwise LSD tests revealed that the difference between PR and CR groups was significant in their preference for ethanol, $F(1, 22) = 28.73$, $p < 0.001$, but not in terms of water, $F(1, 22) = 1.43$, $p > 0.24$. In both PR and CR groups, preference for ethanol was higher than water, Fs > 81.51, ps < 0.001.

Discussion

The present experiment was designed to determine whether PR training can attenuate the impact of reward omission on postsession ethanol preference in anxiety-prone RLA-I rats. The results confirmed the predictions outlined in the introduction and can be summarized as follows: (1) RLA-I rats partially reinforced during acquisition showed increased resistance to extinction in comparison to continuously reinforced RLA rats—the PREE. This effect occurred regardless of whether rats had post-session access to ethanol or water during the preference task. The presence of the PREE confirms previous results (Gómez et al., 2008). (2) RLA-I rats exposed to CR during the acquisition phase exhibited a higher preference for ethanol over water after extinction sessions than animals exposed to PR. (3) No differences in preference were found between continuously vs. partially reinforced groups exposed only to water during the preference test. Most importantly, the reduction in ethanol preference after partial reinforcement training shows that despite extensive selective breeding leading to an anxiety-prone phenotype with documented differences in gene expression (Torres & Sabariego, 2014), ESM can still be affected in adult animals by experiential factors such as exposure to reward uncertainty.

The PREE has been seen as a paradoxical form of learning and explanations in terms of emotional processes have been proposed. For example, Amsel (1992) suggested that the PREE occurs because animals trained under PR conditions learn to persist in the face of frustration. Thus, during the initial acquisition trials, animals develop expectancy for reward and experience an emotional reaction of frustration when this expectancy is violated during N trials. An anticipatory form of this reaction then develops under the control of contextual cues, inducing a hesitation (conflict) to

enter the goal box associated with reward loss. Once anticipatory frustration is repeatedly followed by food reinforcement (as it occur during PR training), the disrupting effects of frustration on goal approach tend to be reduced, thus facilitating behavioral persistence during extinction trials. Frustration and its counterconditioning are absent in the case of continuously reinforced responses. The fact that the PREE and related effects have been observed only in the more emotionally reactive RLA-I strain, as opposed to the less reactive RHA-I strain, provides support for an emotional component in situations involving reward loss (Cuenya et al., 2012; Gómez et al., 2008). The present results support this conclusion, suggesting, additionally, that reward uncertainty can reduce the impact of reward loss on ESM.

The fact that ethanol preference was higher in RLA-I rats exposed to CR than in those exposed to PR, can be understood within this theoretical framework. In contrast to extinction after PR, extinction after CR would have led to increased levels of frustration, thus promoting preference for ethanol over water because of the anxiolytic properties of this drug in reward loss situations (Flaherty, 1996). This ESM account is also consistent with the absence of differences between CR and PR groups exposed only to water, which does not have anxiolytic properties.

Three aspects of the present results deserve additional comments. First, reward loss procedures can be useful tools to study how animals react and adjust to emotionally arousing events by changing the consumption of substances with anxiolytic properties (Torres & Papini, in press). The ability for ESM has been shown in animal models of stress and addiction involving the presentation of aversive stimuli (e.g., Becker et al., 2011), rather the removal of appetitive stimuli. Reward loss has been neglected as a source of negative emotion despite survey and clinical evidence suggesting that this experimental manipulation would model more closely events linked to SUDs in humans (Konopka et al., 2013; Torres & Papini, in press). Second, the use of animals that are highly reactive to reward loss enables an analysis of the way genetic factors and environmental conditions combine to determine individual differences in ESM. Finally, the reduced consumption of ethanol observed in PR rats in comparison to CR rats has some clinical implications. For example, the risk for addiction via ESM in anxiety-prone individuals could be reduced by training coping strategies and tolerance to reward loss. Such a behavioral intervention could potentially protect against drug abuse and misuse.

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References

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. 5th ed. American Psychiatric Publishing, Arlington, VA.

Amsel, A. (1992). *Frustration theory*. Cambridge University Press, Cambridge, UK.

Becker, H. C., & Flaherty, C.F. (1982). Influence of ethanol on contrast in consummatory behavior. *Psychopharmacology, 77*, 253-258.
Becker, H. C., & Flaherty, C. F. (1983). Chlordiazepoxide and ethanol additively reduce gustatory negative contrast. *Psychopharmacology, 80*, 35-37.
Becker, H. C., Lopez, M. F., & Doremus-Fitzwater, T. L. (2011). Effects of stress on alcohol drinking: A review of animal studies. *Psychopharmacology, 218*, 131-156.
Blume, A.W., Schmaling, K. B., & Marlatt, G. A. (2000). Revisiting the self-medication hypothesis from a behavioral perspective. *Cognitive and Behavioral Practice, 7*, 379-384.
Broadhurst, P. L., & Bignami, G. (1965). Correlative effects of psychogenetic selection: a study of the roman high and low avoidance strains of rats. *Behavior Research Therapy, 3,* 273-280.
Cuenya, L., Sabariego, M., Donaire, R., Fernández-Teruel, A., Tobeña, A., Gómez, M.J., Mustaca, A. E., & Torres, C. (2012). The effect of partial reinforcement on instrumental successive negative contrast in inbred Roman High- (RHA-I) and Low- (RLA-I) Avoidance rats. *Physiology & Behavior, 105*, 1112-1116.
Duffing, T. M., Greiner, S. G., Mathias, C. W., & Dougherty, D. M. (2014). Stress, substance abuse, and addiction. *Current Topics in Behavioral Neurosciences, 18,* 237-263.
Egli, M., Koob, G. F., & Edwards, S. (2012). Alcohol dependence as a chronic pain disorder. *Neuroscience & Biobehavioral Reviews, 36*, 2179-2192.
Escorihuela, R. M., Fernández-Teruel, A., Gil, L., Aguilar, R., Tobeña, A., & Driscoll, P. (1999). Inbred roman high- and low-avoidance rats: Differences in anxiety, novelty-seeking, and shuttlebox behaviors. *Physiology & Behavior, 67*, 19-26.
Flaherty, C. F. (1996). *Incentive relativity*. Cambridge University Press, Cambridge, UK.
Gellermann, L. W. (1933). Chance orders of alternating stimuli in visual discrimination experiments. *Journal of Genetic Psychology, 42*, 206-208.
Gómez, M. J., de la Torre, L., Callejas-Aguilera, J. E., Lerma-Cabrera, J. M., Rosas, J. M., Escarabajal, M. D., Agüero, A., Tobeña, A., Fernández-Teruel, A., & Torres, C. (2008). The partial reinforcement extinction effect (PREE) in female Roman high- (RHA-I) and low-avoidance (RLA-I) rats. *Behavioural Brain Research, 194*, 187-192.
Gordon, H. W. (2002). Early environmental stress and biological vulnerability to drug abuse. *Psychoneuroendocrinology, 27*, 115-126.
Hassanbeigi, A., Askari, J., Hassanbeigi, D., & Pourmovahed, Z. (2013). The relationship between stress and addiction. *Procedia – Social and Behavioral Sciences*, *84*, 1333–1340.
Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*, 1259-64.
Khantzian, E. J. (2013). Addiction as a self-regulation disorder and the role of self-medication. *Addiction, 108,* 668-74.
Kamenetzky, G. V., Mustaca, A. E., & Papini, M. R. (2008). An analysis of the anxiolytic effects of ethanol on consummatory successive negative contrast. *Avances en Psicología Latinoamericana*, *26*, 135-144.
Konopka, A., Pełka-Wysiecka, J., Grzywacz, A., & Samochowiec, J. (2013). Psychosocial characteristics of benzodiazepine addicts compared to not addicted benzodiazepine users. *Progress in Neuropsychopharmacology and Biological Psychiatry, 40*, 229–35.
Manzo, L., Gómez, M. J., Callejas-Aguilera, J., Fernández-Teruel, A., Papini, M. R., & Torres, C. (2012). Oral ethanol self-administration in inbred Roman high- and low-

avoidance rats: Gradual versus abrupt ethanol presentation. *Physiology & Behavior, 108*, 1-5.
Manzo, L., Gómez, M. J., Callejas-Aguilera, J. E., Fernández-Teruel, A., Papini, M. R., & Torres, C. (2014). Anti-anxiety self-medication induced by incentive loss in rats. *Physiology & Behavior, 123*, 86-92.
Manzo, L., Donaire, R., Sabariego, M., Papini, M. R., & Torres, C. (2015). Anti-anxiety self-medication: Oral consumption of chlordiazepoxide and ethanol after reward devaluation. *Behavioural Brain Research, 278*, 90-97.
Papini, M. R., Fuchs, P. N., & Torres, C. (2015). Behavioral neuroscience of psychological pain. *Neuroscience & Biobehavioral Reviews, 48*, 53-69.
Papini, M. R., Wood, M., Daniel, A. M., & Norris, J. N. (2006). Reward loss as psychological pain. *International Journal of Psychology and Psychological Therapy, 6*, 189-213.
Spanagel, R., Noori, H. R., & Heilig, M. (2014). Stress and alcohol interactions: Animal studies and clinical significance. *Trends in Neuroscience, 37*, 219-227.
Steimer, T., & Driscoll, P. (2003). Divergent stress responses and coping styles in psychogenetically selected Roman high-(RHA) and low-(RLA) avoidance rats: behavioural, neuroendocrine and developmental aspects. *Stress, 6*, 87-100.
Tan, K. R., Rudolph, U., & Lüscher, C. (2011). Hooked on benzodiazepines: $GABA_A$ receptor subtypes and addiction. *Trends in Neurosciences, 34*, 188-97.
Torres, C. & Papini, M.R. (in press). Emotional self-medication and addiction. In *The Neuropathology of Drug Addictions and Substance Misuse*
Torres, C., & Sabariego, M. (2014). Incentive relativity: Gene-environment interactions. *International Journal of Comparative Psychology, 27*, 446-458.

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