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Incentive Relativity: Gene-Environment Interactions

Carmen Torres & Marta Sabariego
Department of Psychology, University of Jaén, Spain

Reward loss experiences are among the main sources of emotional stress that humans face throughout their lives. In the animal laboratory, it has been repeatedly shown that the unexpected omission or devaluation of a reinforcer triggers a physiological, cognitive, and behavioral state called frustration. This state involves emotional mechanisms that resemble those unleashed by the presentation of other aversive stimuli, inducing similar stress responses through the activation of brain circuits involved in fear and anxiety. Although this hypothesis has been supported by behavioral, pharmacological, hormonal, and neurobiological evidence, only a few studies have focused on the neurogenetic basis of frustration in animals. This review focuses on the gene-environment interactions that determine the emotional response under conditions of reward loss. Behavioral and genetic correlates of frustration are reviewed in two strains of animals selected on the basis of extreme differences in active avoidance learning: inbred Roman High- (RHA-I) and Roman Low-Avoidance (RLA-I) rats. The review shows the usefulness of Roman strains for neurogenetic research and sets out unsolved questions regarding gene-environment interactions underlying behavior induced by incentive loss.

In everyday speech it is common to talk about the loss of a loved one in terms of painful feelings. We now know that this is more than poetic license or semantic metaphor: pain that accompanies grief and loss shares commonalities with the affective state linked to physical pain (Panksepp, 2005). Physical pain usually implies a somatosensorial event (or its anticipation) that signals a potential body injury, having a protective function that helps organisms to escape or avoid environmental conditions that threaten their physical integrity (Panksepp, 2011).

Response to a reinforcer is affected by prior experience with different reward values of that reward, a phenomenon known as incentive relativity (Flahety, 1996). Incentive relativity triggers psychological pain when the comparison between present and past rewards results in incentive loss (Justel, Mustaca, Boccia, & Ruetti, 2014). The function of psychological pain is to break an attachment with a physical or social object and to facilitate a switch from responses that no longer yield incentives to a search mode for discovering alternative resources (Papini, 2003; Papini, Wood, Daniel, & Norris, 2006).

In spite of their differences, both physical and reward loss-related pain seem to share some type of activity in brain affective systems related to fear, stress, and anxiety, as a large body of evidence suggests (Flaherty, 1996; Gray, 1987). In spite of its similarity, the reactions to reward downshift are not experienced in the same way when using some manipulations of incentive value (Judice-Daher, Tavares, & Bueno, 2011). Likewise reinforcement downshift effects are not the same for all the subjects, indicating that the vulnerability to develop psychophysiological disorders induced by reward loss can result from complex interactions between genetic and environmental variables (Cuenya et al., 2012).

Please send correspondence to Dr. Torres, Department of Psychology, University of Jaen, Campus Lagunillas s/n Jaén 23071, Spain. (Email: mctorres@ujaen.es)

This paper reviews the psychobiological basis of reward loss, considering particularly the successive negative contrast, appetitive extinction, partial reinforcement extinction, and partial reinforcement contrast procedures, and focusing on psychogenetic studies conducted in nonhuman animals. Subsequently, we review the genetic basis of frustration, with special attention devoted to studies conducted with animals selected on the basis of extreme differences in emotional reactivity. Psychobiological differences between Roman High- and Roman Low-Avoidance rats are subsequently described, including a detailed revision of strain differences obtained in animal tests of reward loss and their genetic correlates. The main conclusions derived from this research line are also mentioned.

Animal Models of Reward Loss

Incentives have absolute and relative value (Flaherty, 1996). For example, the magnitude of a current reward determines its absolute value, whereas this magnitude in comparison to the magnitudes of previously received rewards refers to the current reward's relative value. Animal models provide a useful approach to study incentive relativity and its emotional consequences from a psychobiological perspective because they enable a careful manipulation of genetic and environmental variables, and a systematic recording of the behavioral, hormonal, and neural responses. Studies with nonhuman animals can shed light on the causes of emotional disorders induced by psychological pain and suggest possible therapeutic interventions.

A large body of evidence from the animal laboratory indicates that downshifting the quality or quantity of a previously presented appetitive reinforcer triggers a physiological, cognitive, and behavioral state called frustration (Amsel, 1992), disappointment (Flaherty, 1996), or psychological pain (Papini et al., 2006). Successive negative contrast (SNC), appetitive extinction, the partial reinforcement extinction effect (PREE), and the partial reinforcement contrast effect (PRCE), constitute some animal tests of reward downshift extensively used to explore the psychobiological basis of frustration. We review next the research on SNC and cover the other effects in a subsequent section on Roman rat strains (see below).

SNC has been traditionally considered in discussions of animal models of anxiety (Gray, 1987). SNC is defined as a suppression of responding to a smaller reward observed in an experimental group previously exposed to a larger reward, compared to the response observed in a control group always exposed to the smaller reward (Pellegrini, Muzio, Mustaca, & Papini, 2004). There are two basic procedures to study SNC. One of them involves instrumental behavior (iSNC), that is, behavior that reflects the effect in anticipation of the goal event, and the other involves consummatory behavior (cSNC), that is, changes in the consumption of the reward (Flaherty, 1996).

Although terminologically confusing, it has been proposed that the emotional state induced by downshifting an expected reward involves mechanisms similar to those induced by the presentation of aversive stimuli (e.g., punishment, physical pain, novelty, etc.; Dantzer, 1987), inducing stress responses through the activation of brain circuits that regulate fear and anxiety. Several lines of research support that fear and frustration are similar functional states. First, fear and frustration have comparable behavioral features, including an initial increase in response strength, aggression, agitation, ultrasonic vocalizations, anxiety-like responses, escape, immobilization, and search behavior, among others (Huston, de Souza Silva, Komorowski, Schulz, & Topic, 2013; Papini & Dudley, 1997). Second, fear and frustration responses are affected by similar pharmacological agents. For example, both iSNC and cSNC can be attenuated or abolished by anxiolytics such as benzodiazepines, ethanol, and barbiturates, which also attenuate fear induced by physical pain (Flaherty, 1996; Gray, 1987). A series of pharmacological experiments also connect selective and nonselective opioid-receptor drugs with incentive loss (Daniel, Ortega, & Papini, 2009; Papini, 2009; Papini & Ortega, 2011). Third, experimental situations involving devaluation or omission of an expected reinforcer induce hypothalamic-pituitary-adrenal axis activation, increasing plasma levels of stress hormones such as ACTH and corticosterone (Kawasaki & Iwasaki, 1997; Mitchell & Flaherty, 1998; Pecoraro, de Jong, & Dallman, 2009).

Lesion studies also suggest similarities between the emotional states induced by physical and psychological pain. Both fear and frustration can be influenced by damaging brain areas involved in emotion, including the hippocampus (Flaherty, Coppotelli, Tsu, & Otto, 1998), septum (Flaherty, Powell, & Hamilton, 1979), amygdala (Liao & Chuang, 2003; Salinas, Packard, & McGaugh, 1993), nucleus accumbens (Leszczuk & Flaherty, 2000; Judice-Daher & Bueno, 2013a), ventrolateral orbital cortex (Ortega, Glueck, Uhelski, Fuchs, & Papini, 2013), anterior cingulate cortex (Ortega, Uhelski, Fuchs, & Papini, 2011), and medial prefrontal cortex (Pecoraro, De Jong, Ginsberg, & Dallman, 2008), among others. However, there are also some studies that do not fully support these data. In this regard, Judice-Daher, Tavares, and Bueno (2012) found that basolateral and medial amygdala lesioned rats were more sensitive to reward loss. Nevertheless they also showed that the basolateral complex is involved in incentive processes relative to omission of different reinforcement magnitudes. In addition, these authors reported some data opposite to the hypothesis that the orbitofrontal cortex is included in the neural substrates related to reward loss modulation (Judice-Daher & Bueno, 2013b). Overall, these data suggest a role of emotional behavior in reward loss situations, suggesting that a complex neurochemical and neurophysiological network underlies judgments of incentive relativity, their emotional correlates, and its translation into behavior.

Genetic Basis of Frustration

The connection between emotions induced by reward loss (frustration) and physical pain (fear, anxiety) has been additionally supported by the use of strains of rats selectively bred on the basis of their differences in the behavioral trait known as *emotional reactivity*, *fearfulness*, or *anxiety*. This trait is defined as a pattern of behavior that differs between individuals, but is relatively constant within subjects over time and situations related to fear and anxiety (e.g., reactivity to novelty, avoidance learning). Selective breeding based on this behavioral trait has shed light on the psychogenetic basis of individuality (Pawlak, Ho, & Schwarting, 2008), and has also provided insights on gene-environment interactions with respect to incentive relativity (see Cuenya, Gómez, Sabariego, Mustaca, & Torres, 2011).

Brush et al. (1985) selectively bred two strains of rats that differed in active avoidance behavior: the Syracuse Low-Avoidance (SLA) and Syracuse High-Avoidance (SHA) rats. When tested in the cSNC paradigm, SLA rats showed larger cSNC than SHA rats (Flaherty & Rowan, 1989). The Maudsley reactive (MR) and Maudsley nonreactive (MNRA) rats, originally selected on the basis of number of defecations registered in an open field, have been widely characterized as differing in emotional reactivity (Broadhurst, 1975; Gray, 1987), including frustration tests. Unexpectedly, the reactive animals showed a reliably smaller cSNC compared to the nonreactive animals (Rowan & Flaherty, 1991). This result could relate to the inconsistent differences these strains show in anxiety tests such as the elevated plus-maze and the two-way active avoidance task (Broadhurst, 1975).

Reward devaluation-related effects have also been studied in the Okamoto lines that includes the spontaneously hypertensive rats (SHR) and their control counterparts (Wistar-Kyoto, WKY). Regarding the anxiety levels exhibited by these strains of rats, the results are conflicting and seem to depend on the procedures and measures used for assessing anxiety levels. Bentosela and Mustaca (2005) found that SHR rats responded more intensely after unexpected reward devaluation, showing a longer lasting cSNC effect than the WKY animals.

The genetic basis of frustration has also been studied by selecting and breeding rats on the basis of their differences in the size of the cSNC effect. Flaherty, Krauss, Rowan, and Grigson (1994) selectively bred Sprague-Dawley rats showing either large or small cSNC. The selective breeding conducted for seven generations produced two lines differing in degree of reactivity to reduction in sucrose concentration. However, the response to the selective pressure applied by parental selection was reliable only in the *large contrast* line. Moreover, the selection was apparently restricted to a specific type of emotional behavior and of

incentive relativity (cSNC), given that animals did not differ in anticipatory contrast, open-field defecations and thigmotaxis, response to midazolam, or in response to the absolute rewarding value of sucrose or cocaine (Flaherty et al., 1994).

More recently, Ortega, Norris, López-Seal, Ramos, and Papini (2014) selectively bred Long-Evans rats on the basis of differences (high vs. low) in their recovery rates from cSNC; they also included a line of randomly mated rats as controls. Whereas cSNC was reduced in the high line, low and random lines did not differ across generations. In addition, high rats failed to show increased persistence in extinction after training with partial reinforcement, as opposed to the PREE obtained in low and random lines. The high and low lines did not differ from the random line with respect to water intake, sucrose sensitivity, activity in the open-field, or in response to sucrose solutions before the downshift. Additional experiments with animals from the sixth generation showed that high infant rats exhibited increased vocalizations in a mother-infant separation test, whereas high adult rats showed less sensitivity to the effects of the opioid-receptor antagonist naloxone on reward downshift, in both cases relative to low and random rats. The latter result suggests a connection between physical and psychological pain (Ortega et al., 2014).

Finally, the genetic basis of reward loss-induced responses has been extensively studied in Roman High- (RHA) and Roman Low- Avoidance (RLA) rats. These strains were selected for their good (RHA) vs. poor (RLA) ability to acquire a two-way active avoidance response (Driscoll & Bättig, 1982). As a result of this psychogenetic selection, both outbred and inbred lines of Roman rats differ in their emotional reactivity in a variety of anxiety-inducing situations, including those downshifting the magnitude of an expected reward.

Roman High- and Roman Low- Avoidance rats

Individual differences in physiology and behavior have been repeatedly found in animals and humans. These differences seem to critically influence the organism's adaptive capacity for coping with challenging situations, this individual reactivity being dependent upon environmental as well as genetic factors (Steimer & Driscoll, 2005). One behavioral difference extensively investigated in rodents is the capability for avoiding an aversive stimulus. In this context, differences in avoidance of foot shock have been repeatedly reported between strain of rats and between animals of the same strain obtained as result of a psychogenetic selection procedure. Psychogenetic selection refers to selective breeding based on divergence in a particular type of behavior (Martin & Baettig, 1980). The Swiss sublines of Roman Low-Avoidance (RLA/Verh) and Roman High-Avoidance (RHA/Verh) rat lines are an example of strains of rats developed on the basis of this psychogenetic selection procedure. The two Swiss rat lines were originally outbred, but some of them were continued as inbred (RHA-I/RLA-I) starting in 1993 at the Autonomous University of Barcelona (Escorihuela et al., 1999). As a consequence of this selection, both outbred and inbred RLA rats are characterized by more pronounced anxious reactions to novel, conflicting, and threatening situations, less impulsivity and novelty-seeking behaviors, and a blunted response to addictive drugs compared with their RHA counterparts (see Driscoll, Fernández-Teruel, Corda, Giorgi, & Steimer, 2009). For example, RLA rats exhibit greater shock-induced drinking suppression in the Vogel conflict test in comparison to RHA rats (Ferré et al., 1995). Similar results (more behavioral inhibition in RLA rats vs. RHA rats) are found when the animals are exposed to anxiogenic situations related to novelty and exploration, such as the open field, the hole board, and the light/dark box (e.g., Fernández-Teruel et al., 1992; Fernández-Teruel, Escorihuela, Castellano, González, & Tobeña, 1997; Manzo, Gómez, Callejas-Aguilera, Donaire et al., 2014). In addition, RLA rats show higher rates of unconditioned and conditioned fear responses (e.g., defecation, freezing, grooming, startle response, and passive avoidance) than RHA rats (Escorihuela et al., 1999; López-Aumatell et al., 2009). However, there are contradictory results when using other tests of anxiety, such as the elevated plus-maze, the successive alley, and the mobility test, given that the expected greater tendency of RHA rats to explore open and novel spaces is not always observed (Donaire, Sabariego, Cano et al., 2013, unpublished results; Escorihuela et al., 1999).

In addition to these behavioral differences, several neuroendocrine studies have found increased hormonal and physiological reactivity in RLA rats compared to RHA rats, both at rest and in response to threatening situations. Specifically, both outbred and inbred RLA rats exhibit increased stress responses (e.g., higher levels of ACTH, corticosterone, and prolactin) and adopt a more passive coping style when facing new environmental situations (Carrasco et al., 2008; Díaz-Morán et al., 2012; Steimer & Driscoll, 2003, 2005). By contrast, RHA rats show a greater tendency to sensation seeking, drug self-administration, and impulsivity (Coppens, de Boer, Steimer, & Koolhaas, 2013; Giorgi, Piras, & Corda, 2007; Manzo et al., 2012; Manzo, Gómez, Callejas-Aguilera, Donaire et al., 2014; Moreno et al., 2010).

Moreover, strain neuroanatomical and functional differences have been observed in brain structures associated with emotion and motivation, such as the amygdala, hippocampus, nucleus accumbens, and prefrontal cortex (Driscoll et al., 2009). These divergences are accompanied by neurochemical and molecular differences that affect neurotransmitter systems such as dopamine, serotonin, GABA, glutamate, acetylcholine, and neuropeptides (D'Angio, Serrano, Driscoll, & Scatton, 1988; Guitart-Masip, Johansson, Fernández-Teruel, Tobeña & Giménez-Llort., 2008; Piras, Piludu, Giorgi, & Corda, 2014), among others. Overall, these strain neurobiological differences could underlie the strain behavioral divergences described above, with a special emphasis in the differential functional properties of their mesothelencephalic dopaminergic systems (Driscoll et al., 2009; Sanna et al., 2013; Sanna et al., 2014).

Roman Rats and Frustration Responses

Our research group has recently extended the behavioral phenotyping of inbred Roman rats to responses induced by incentive loss, supporting theories that account for these responses on the basis of emotional mechanisms (Amsel, 1992; Flaherty, 1996; Papini, 2006). This line of research has found that the more fearful/anxious RLA-I strain showed increased aversive and appetitive iSNC effects as compared to the less fearful/anxious RHA-I strain. For example, an impairment of the instrumental response (running) was observed in RLA-I (but not in RHA-I) rats, when animals were downshifted from 12 to 2 food pellets presented in the goal box of a straight alley (Cuenya et al., 2012; Rosas et al., 2007; Sabariego et al., 2013). Similar results were found by decreasing the time spent in the safe compartment (from 30 s to 1 s) of a one-way avoidance box (Donaire, Sabariego, Gómez, Fernández-Teruel, & Torres, 2013; Torres et al., 2005). These RHA-I/RLA-I differences were also obtained during the extinction of a previously learned appetitive instrumental response, such as runway behavior, with the RLA-I strain showing a faster extinction rate than the RHA-I strain (Gómez, de la Torre et al., 2009). Strain differences were also found in the cSNC situation: the RLA-I strain showed a slower recovery from the consummatory suppression induced by downshifting animals from 22% sucrose in the preshift phase to 4% sucrose in the postshift phase (Gómez, Escarabajal et al., 2009).

These results indicate that RHA-I and RLA-I rats can be valid animal models for the study of negative emotions induced by the unexpected devaluation/omission of an expected reward. According to this view, whereas RHA-I rats prefer ethanol over water at low concentrations under resting environmental conditions (Manzo et al., 2012), when these strains were exposed to frustrating situations involving reward loss (consummatory and instrumental appetitive extinction), it was the more anxious RLA-I strain that showed greater preference for and consumption of 2% ethanol (Manzo, Gómez, Callejas-Aguilera, Fernández-Teruel et al., 2014).

Behavioral differences between Roman rats have also been described in environmental conditions involving repeated (chronic) experience of reward loss. These experiences can immunize animals when coping with subsequent lack of reward situations, triggering behavioral persistence and resistance to frustration (Amsel, 1992; Papini, 2006). The PREE, for example, evaluates whether the extinction of a previously learned response can be attenuated by a chronic experience of frustration induced by partial reinforcement (i.e., random, unpredictable rewarding and nonrewarding response outcomes). Although the Roman lines showed

divergence in their extinction rate under continuous reinforcement conditions (Gómez, de la Torre et al., 2009), these strain differences disappeared when animals were exposed to partial reinforcement in the acquisition phase (Gómez et al., 2008). Interestingly, strain differences in ethanol consumption were not obtained after partial reinforcement (Manzo et al., in preparation), as opposed to continuous reinforcement (Manzo, Gómez, Callejas-Aguilera, Fernández-Teruel et al., 2014).

Finally, the PRCE constitutes an alternative experimental situation involving repeated/chronic frustration. This phenomenon is defined as a reduced SNC effect after training with partial reinforcement compared to continuous reinforcement during the preshift phase (Pellegrini et al., 2004). Cuenya et al. (2012) found that the unexpected reduction in the amount of a reward presented in the goal box of a straight alley (12-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 the preshift phase. This impairment was not observed in RLA-I rats exposed to partial reinforcement, or in RHA-I animals receiving partial or continuous reinforcement before the reward downshift.

Genetic Correlates of Frustration in Roman Rats

The results obtained by our research group in frustration paradigms have extended the behavioral phenotyping of Roman rats. In addition, our results experimentally support theories that account for reward-loss effects on the basis of emotional mechanisms, suggesting that these phenomena are under genetic control. To further explore this possibility, the next step was to analyze differential gene-expression profiles in the brain of Roman rats. To this aim, we used microarray and real-time reverse transcription polymerase chain reaction (qRT-PCR) techniques to identify strain differences in brain gene expression that would correlate with frustration responses.

Microarray is an analytical technique that allows for genomic analysis with speed and precision. The expression of tens of thousands of genes can be simultaneously explored, thus allowing for a complete genome-wide analysis of the differences in the gene expression taking place between two different biological conditions. This technique is widely used in biomedical research to detect altered gene expression of particular genes in a given disease when compared to healthy controls. The obtained results are generally validated by using qRT-PCR techniques that amplify those genes found to be differentially up-regulated or down-regulated among biological or environmental situations (see Lee & Saeed, 2007).

In studies conducted with Roman rats, we expected to find differences in the expression of genes functionally linked to negative emotions (e.g., Mei et al., 2005; Wang et al., 2003), and in genes previously shown to be differentially expressed in these strains (Zhang, Amstein, Shen, Brush, & Gershenfeld, 2005). In addition, we also expected new genes to be differentially expressed in these strains. The nomination of unsuspected genes as candidate genes underlying frustration-mediated processes can be facilitated by the use of this assumption-free approach of gene expression profiling.

Three microarray experiments have been conducted thus far. In the first (Sabariego et al., 2011), whole-brain samples of Roman rats maintained under resting conditions were used. We identified a considerable number of genes as differentially expressed between the two Roman strains: 14 upregulated and 24 downregulated genes in RLA-I rats compared to their RHA-I counterparts. Among the list of differentially expressed genes, five functionally relevant genes were selected and validated by qRT-PCR: EPHX2, PRL, CAMKK2, CRHBP, and HOMER3. These genes have been repeatedly linked to biobehavioral traits shown to be divergent in RHA-I vs. RLA-I rats, including fearfulness and hedonism (EPHX2), hormonal reactivity to stress (PRL, CRHBP), aversive learning (CAMKK2), and brain plasticity phenomena related to drug seeking behavior and neuropsychiatric disorders (HOMER3).

In the second experiment, Sabariego et al. (2013) extended the results described above by analyzing strain differences in hippocampal gene expression after an aversive experience involving reward downshift (iSNC). Food-deprived Roman male rats were exposed to a reduction in the amount of solid food presented in the goal of a straight alley (from 12 pellets in preshift trials to 2 pellets in postshift trials). The iSNC effect appeared only in RLA-I rats (higher response latencies in the 12-2 group as compared to the 2-2 control group in postshift trials). Two hybridized microarrays for the detection of differential gene expression were conducted. The former compared the hippocampal genetic expression in the RLA-I contrast group (12-2) vs. the RLA-I control group (2-2), whereas the second compared gene expression profiles of the RLA-I contrast group (12-2) vs. the RHA-I contrast group (12-2). Three genes were detected as up-regulated and five were down-regulated in the RLA-I contrast group compared to the RLA-I control group. Moreover, 10 genes were up-regulated in the RLA-I contrast group in comparison to the RHA-I contrast group. Seven of these genes were selected as candidates for qRT-PCR validation, according to their extreme strain differences in expression levels (PSORS1, SLC45A3, and NANOS1) or their behavior/brain-related functions (THAP1, RGSL2H, PKD2L1, and TAAR2). The gene expression tendency was validated for the selected genes, with the exception of RGSL2H and SLC45A3. Some of the validated genes have been related to neurobehavioral processes known to be divergent in Roman rats, including neuropsychiatric disorders (e.g., schizophrenia, affective disorders, anxiety, and drug abuse: TAAR2), fear memory (THAP1), taste sensitivity (PKD2L1), and hippocampal development (NANOS1). None of the genes found have been associated before with anxiety or frustration states (except for the RGSL2H gene, which was not validated in the present study), but direct comparison with previous work is precluded because of methodological differences (see Sabariego et al., 2013).

Finally, in the third study, Sabariego et al. (in preparation) extended this research line to an experimental condition involving reward inconsistence: the PREE. As reviewed above, this paradoxical learning effect constitutes an experimental example of response-outcome uncertainty during acquisition that results in an increased, rather than in a decreased, behavioral persistence during extinction (Pellegrini et al., 2004). Given that training with partial reinforcement abolished strain differences in extinction rate obtained after continuous reinforcement (Gómez et al., 2008), we expected to identify genetic correlates that could underlie the impact of this experience on the behavior of Roman rats. To this aim, animals were continuously or partially reinforced with a 12 pellets presented in the goal box of a straight alley, and then exposed to an extinction phase in which this reward was omitted. In agreement with previous studies (Gómez et al., 2008; Gómez, de la Torre et al., 2009), RHA-I rats continuously reinforced during acquisition exhibited more resistance to extinction than their RLA-I counterparts, these strain differences being absent in partially reinforced groups. Differences among groups were accompanied by hippocampal divergence in the expression of genes with relevant neurobehavioral functions, including those related to protein kinase cascades (GH1, SH3RF1, F10, TLR3, ZEB2, PRKCD, IL22RA2, KL, CHRNA3), signal transduction (SHOX2, GH1, F10, TLR3, ZEB2, PRRX2, PRKCD, LECT1, SOX17, ADIPOQ, KL, CHRNA3), phosphorylation (GH1, ITLN1, ZEB2, PRKCD, IL22RA2, ADIPOQ), cell communication (SHOX2, GH1, F10, TLR3, ZEB2, PRRX2, PRKCD, LECT1, SOX17, ADIPOQ, SHOX2, GH1, ADIPOQ), learning/memory processes (Kcnj13, EPHX2), addiction (Vcsa2, Phkg1, SNCG, Gpr35), and neuropsychiatric disorders (C1qtnf3, Ms4a7, SNCG, Birc6, Gpr35, SNCG, EPHX2, SNCG). Further studies with RT-PCR will enable us to validate these preliminary results, therefore extending the neurogenetic study of Roman rats to persistence behavioral phenomena induced by repeated incentive loss experiences (Torres et al., 2013, unpublished results).

Concluding Remarks

This article reviewed the behavioral and genetic correlates of frustration in two strains of animals selected on the basis of extreme differences in active avoidance learning. Roman strains were found to exhibit correlated differences in situations inducing fear and anxiety, with RLA-I rats showing higher emotional reactivity than RHA-I rats. Our research group has extended the behavioral phenotyping of Roman rats to

reward loss/frustrating situations, including both acute (e.g., iSNC, cSNC, appetitive extinction) and chronic frustration-related phenomena (PREE, PRCE). Several conclusions can be derived from the results reviewed here. First, individual differences in reactivity to incentive loss seem to depend on genetic influences, given that the more anxious RLA-I strain consistently show greater frustration responses compared to the less anxious RHA-I strain. Second, reward loss-related responses are modulated not only by genetic influences, but also by environmental variables, as the studies conducted with partial reinforcement training suggest. Thus, whereas acute reward loss events could increase the risk for the onset of emotional disorders in genetically prone subjects, repeated incentive loss experiences could increase its resilience to frustration, approaching the behavioral profiles of genetically different individuals. Based on the reviewed evidence, we postulate that genetic differences in the initial response to reward loss can be modulated by experiential factors, such as experience with repeated frustrating events. Consistent with this hypothesis, some of the behavioral differences observed in Roman rats can be abolished by exposing animals to early handling or environmental enrichment, a result mainly due to an enduring reduction of fearfulness (see Fernández-Teruel et al., 2002). Future studies should examine the suitability of these assumptions and the extent to which these results relate to the apparently opposite results derived from studies conducted with extinction paradigms (Huston et al., 2013).

Finally, although microarray techniques are not exempt from experimental, procedural, technical, and statistical limitations (Pratsch, Wellhausen, & Seitz, 2014; Yang, Parrish, & Brock, 2014), they provide a promising approach to identifying differential gene expression profiles linked to complex behavioral traits. Accordingly, complementary behavioral and genetic studies in Roman rats may help shed light on the relationship between genotype, temperament traits, environmental events, and neural mechanisms underlying the vulnerability or resistance to reward-loss experience in humans. Advances in genetics and molecular biology will definitely improve our understanding of the biological basis of behavior in incentive relativity situations.

References

Amsel, A. (1992). *Frustration theory: An analysis of dispositional learning and memory.* Cambridge, UK: Cambridge University Press.

Bentosela, M., & Mustaca, A. E. (2005). Efectos del contraste sucesivo negativo consumatorio en ratas hipertensas: ¿Una cuestión de memoria? *Suma Psicológica, 12*, 87-100.

Broadhurst, P. (1975). The Maudsley reactive and nonreactive strains of rats: A survey. *Behavior Genetics, 5*, 299-319. doi: 10.1007/BF01073201

Brush, F. R., Baron, S., Froehlich, J. C., Ison, J. R., Pellegrino, L. J., Phillips, D. S., Sakellaris, P. C., & Williams, V. N. (1985). Genetic differences in avoidance learning by *Rattus norvegicus*: Escape/avoidance responding, sensitivity to electric shock, discrimination learning, and open-field behavior. *Journal of Comparative Psychology, 99*, 60-73. doi: 10.1037/0735-7036.99.1.60

Carrasco, J., Márquez, C., Nadal, R., Tobeña, A., Fernández-Teruel, A., & Armario, A. (2008). Characterization of central and peripheral components of the hypothalamus–pituitary–adrenal axis in the inbred roman rat strains. *Psychoneuroendocrinology, 33*, 437-445. doi: 10.1016/j.psyneuen. 2008.01.001

Coppens, C. M., de Boer, S. F., Steimer, T., & Koolhaas, J. M. (2013). Correlated behavioral traits in rats of the Roman selection lines. *Behavior Genetics, 43*, 220-226. doi: 10.1007/s10519-013-9588-8

Cuenya, L., Gómez, M. J., Sabariego, M., Mustaca, A. E., & Torres, C. (2011). Relatividad de los incentivos: Aportes de los estudios con líneas endocriadas. In M. C. Richaud, & V. Lemos (Eds.), *Psicología y otras ciencias del comportamiento. Compendio de investigaciones actuales. Vol 1.* (Buenos Aires: CIIPME-CONICET ed.).

Cuenya, L., Sabariego, M., Donaire, R., Fernández-Teruel, A., Tobeña, A., Gómez, M. J., Mustaca, A., & 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. doi: 10.1016/j.physbeh.2011.12.006

D'Angio, M., Serrano, A., Driscoll, P., & Scatton, B. (1988). Stressful environmental stimuli increase extracellular DOPAC levels in the prefrontal cortex of hypoemotional (Roman high-avoidance) but not hyperemotional (Roman low-avoidance) rats. An in vivo voltammetric study. *Brain Research, 451*, 237-247. doi:10.1016/0006-8993(88)90768-8

Daniel, A. M., Ortega, L. A., & Papini, M. R. (2009). Role of the opioid system in incentive downshift situations. *Neurobiology of Learning & Memory, 92*, 439-450. doi: 10.1016/j.nlm.2009.06.003

Dantzer, R. (1987). Behavioral analysis of anxiolytic drug action. In A. J. Greenshaw, & C. T. Dourish (Eds.), *Experimental Psychopharmacology* (pp. 263-297). Clifton, NJ: Human Press.

Díaz-Morán, S., Palència, M., Mont-Cardona, C., Cañete, T., Blázquez, G., Martínez-Membrives, E., López-Aumatell, R., Tobeña, A., & Fernández-Teruel, A. (2012). Coping style and stress hormone responses in genetically heterogeneous rats: Comparison with the roman rat strains. *Behavioural Brain Research, 228*, 203-210. doi: 10.1016/j.bbr.2011.12.002

Donaire, R., Sabariego, M., Cano, F. J., Márquez, I., Fernández-Teruel, A. & Torres, C. (2013, unpublished). Behavioral profile of Roman High- (RHA-I) and Low-Avoidance (RLA-I) rats in the successive alley test for anxiety. *XXV Congress of the Spanish Society of Comparative Psychology* (San Sebastián, Spain).

Donaire, R., Sabariego, M., Gómez, M. J., Fernández-Teruel, A., & Torres, C. (2013). Learning in the one-way avoidance task: Male-female differences in genetically selected strains. *Revista Argentina de Ciencias del Comportamiento, 52*, 40-46.

Driscoll, P., & Bättig, K. (1982). *Behavioral, emotional and neurochemical profiles of rats selected for extreme differences in active, two-way avoidance performance*. Amsterdam: Elsevier.

Driscoll, P., Fernández-Teruel, A., Corda, M. G., Giorgi, O., & Steimer, T. (2009). Some guidelines for defining personality differences in rats. In K. Yong-Kyu (Ed.), *Handbook of Behavior Genetics* (pp. 281-300). New York, NY: Springer.

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. doi:10.1016/S0031-9384(99)00064-5

Fernández-Teruel, A., Escorihuela, R. M., Castellano, B., González, B., & Tobeña, A. (1997). Neonatal handling and environmental enrichment effects on emotionality, Novelty/Reward seeking, and age-related cognitive and hippocampal impairments: Focus on the Roman rat lines. *Behavior Genetics, 27*, 513-526. doi:10.1023/A:1021400830503

Fernández-Teruel, A., Escorihuela, R. M., Núñez, J. F., Gomà, M., Driscoll, P., & Tobeña, A. (1992). Early stimulation effects on novelty-induced behavior in two psychogenetically-selected rat lines with divergent emotionality profiles. *Neuroscience Letters, 137*, 185-188. doi:10.1016/0304-3940(92)90400-2

Fernández-Teruel, A., Giménez-Llort, L., Escorihuela, R. M., Gil, L., Aguilar, R., Steimer, T. & Tobeña. A. (2002). Early-life handling stimulation and environmental enrichment. Are some of their effects mediated by similar neural mechanisms? *Pharmacology, Biochemistry & Behavior, 73*, 233-245. doi:10.1016/S0091-3057(02)00787-6

Ferré, P., Fernández-Teruel, A., Escorihuela, R. M., Driscoll, P., Corda, M. G., Giorgi, O., & Tobeña, A. (1995). Behavior of the Roman/Verh high- and low-avoidance rat lines in anxiety tests: Relationship with defecation and self-grooming. *Physiology & Behavior, 58*, 1209-1213. doi:10.1016/S0091-3057(02)00787-6

Flaherty, C. F. (1996). *Incentive relativity*. New York: Cambridge University Press.

Flaherty, C. F., Coppotelli, C., Hsu, D., & Otto, T. (1998). Excitotoxic lesions of the hippocampus disrupt runway but not consummatory contrast. *Behavioural Brain Research, 93*, 1-9. doi:10.1016/S0166-4328(97)00138-1

Flaherty, C. F., Krauss, K. L., Rowan, G. A., & Grigson, P. S. (1994). Selective breeding for negative contrast in consummatory behavior. *Journal of Experimental Psychology: Animal Behavior Processes*, *20*, 3-19. doi: 10.1037/0097-7403.20.1.3

Flaherty, C. F., Powell, G. & Hamilton, L. W. (1979). Septal lesion, sex, and incentive shift effects on open field behavior of rats. *Physiology & Behavior, 22,* 903-909. doi:10.1016/0031-9384(79)90335-4

Flaherty, C. F., & Rowan, G. A. (1989). Rats (*Rattus norvegicus*) selectively bred to differ in avoidance behavior also differ in response to novelty stress, in glycemic conditioning, and in reward contrast. *Behavioral & Neural Biology, 51*, 145-164. doi:10.1016/S0163-1047(89)90782-6

Giorgi, O., Piras, G., & Corda, M. G. (2007). The psychogenetically selected roman high- and low-avoidance rat lines: A model to study the individual vulnerability to drug addiction. *Neuroscience & Biobehavioral Reviews, 31*, 148-163. doi:10.1038/npp.2008.43

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. doi:10.1016/j.bbr.2008.07.009

Gómez, M. J., de la Torre, L., Callejas-Aguilera, J. E., Rosas, J. M., Escarabajal, M. D., Agüero, AA., Tobeña, A., Fernándezá-Teruel, A., & Torres, C. (2009). Differences in extinction of an appetitive instrumental response in female inbred Roman high- (RHA-I) and low- (RLA-I) avoidance rats. *Psicológica, 30*, 181-188.

Gómez, M. J., Escarabajal, M. D., de la Torre, L., Tobeña, A., Fernández-Teruel, A., & Torres, C. (2009). Consummatory successive negative and anticipatory contrast effects in inbred Roman rats. *Physiology & Behavior, 97*, 374-380. doi:10.1016/j.physbeh.2009.03.003

Gray, J. A. (1987). *The psychology of fear and stress* Cambridge, UK: Cambridge University Press.

Guitart-Masip, M., Johansson, B., Fernández-Teruel, A., Tobeña, A., & Giménez-Llort, L. (2008). Divergent effect of the selective D3 receptor agonist pd-128,907 on locomotor activity in Roman high-and low-avoidance rats: Relationship to NGFI-A gene expression in the Calleja islands. *Psychopharmacology, 196*(1), 39-49. doi: 10.1007/s00213-007-0925-6

Huston, J. P., de Souza Silva, M. A., Komorowski, M., Schulz, D., & Topic, B (2013). Animal models of extinction-induced depression: Loss of reward and its consequences. *Neuroscience & Biobehavioral Reviews, 37*, 2059–2070. doi: 10.1016/j.neubiorev.2013.02.016

Judice-Daher, D. M., Tavares, R. F., & Bueno, J. L. O. (2011). Influence of the reinforcement magnitude on omission effects. *Behavioural Processes*, *88*, 60-62. doi: 10.1016/j.beproc.2011.06.010.

Judice-Daher, D. M., Tavares, R. F., & Bueno, J. L. O. (2012). Involvement of the basolateral complex and central nucleus of amygdala in the omission effects of different magnitude of reinforcement. *Behavioural Brain Research, 233,* 149-156. doi: 10.1016/j.bbr.2012.04.046

Judice-Daher, D. M., & Bueno, J. L. O. (2013a). Lesions of the nucleus accumbens disrupt reinforcement omission effects in rats. *Behavioural Brain Research, 252*, 439-443. doi: 10.1016/j.bbr.2013.06.028

Judice-Daher, D. M., & Bueno, J. L. O. (2013b). Lesions of the orbitofrontal cortex do not affect the reinforcement omission effect in rats. *Psychology & Neuroscience, 6*, 391-396. doi: 10.3922/j.psns.2013.3.17

Justel, N., Mustaca, A., Boccia, M., & Ruetti, E. (2014). Incentive relativity in middle aged rats. *Neuroscience Letters, 559*, 122-126. doi: 10.1016/j.neulet.2013.11.053

Kawasaki, K., & Iwasaki, T. (1997). Corticosterone levels during extinction of runway response in rats. *Life Sciences, 61*, 1721-1728. doi:10.1016/S0024-3205(97)00778-9

Lee, N. H., & Saeed, Al (2007). Microarrays: an overview. *Methods in molecular biology, 353*, 265-300. doi:10.1385/1-59745-229-7:265

Leszczuk, M. H., & Flaherty, C. F. (2000). Lesions of nucleus accumbens reduce instrumental but not consummatory negative contrast in rats. *Behavioural Brain Research, 116*, 61-79. doi:10.1016/S0166-4328(00)00265-5

Liao, R. M., & Chuang, F. J. (2003). Differential effects of diazepam infused into the amygdala and hippocampus on negative contrast. *Pharmacology Biochemistry & Behavior, 74*, 953-960. doi:10.1016/S0091-3057(03)00023-6

López-Aumatell, R., Blázquez, G., Gil, L., Aguilar, R., Cañete, T., Giménez-Llort, L., Tobeña, A., & Fernández-Teruel, A. (2009). The Roman high-and-low-avoidance rat strains differ in fear potentiated startle and classical aversive conditioning. *Psicothema, 21*, 27-32.

Manzo, L., Gómez, M. J., Callejas-Aguilera, J. E., 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. doi: 10.1016/j.physbeh.2012.07.002

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. doi: 10.1016/j.physbeh.2013.10.002

Manzo, L., Gómez, M. J., Callejas-Aguilera, J. E., Donaire, R., Sabariego, M., Fernández-Teruel, A., Cañete, A., Blázquez, G., Papini, M. R., & Torres, C. (2014). Relationship between ethanol preference and sensation/novelty seeking. *Physiology & Behavior, 133,* 53-60. doi: 10.1016/j.physbeh.2014.05.003

Martin, J. R., & Bättig, K. (1980). Exploratory behaviour of rats at oestrus. *Animal Behaviour, 28*, 900-905. doi:10.1016/S0003-3472(80)80151-5

Mei, B., Li, C., Dong, S., Jiang, C. H., Wang, H., & Hu, Y. (2005). Distinct gene expression profiles in hippocampus and amygdala after fear conditioning. *Brain Research Bulletin, 67*, 1-12. doi:10.1016/j.brainresbull.2005.03.023

Mitchell, C., & Flaherty, C. F. (1998). Temporal dynamics of corticosterone elevation in successive negative contrast. *Physiology & Behavior, 64*, 287-292. doi: 10.1016/S0031-9384(98)00072-9

Moreno, M., Cardona, D., Gómez, M. J., Sánchez-Sante, F., Tobeña, A., Fernández-Teruel, A., Campa, L., Suñol, C., Escarabajal, M. D., Torres, C., & Flores, P. (2010). Impulsivity characterization in the Roman high- and low- avoidance rat strains: Behavioral and neurochemical differences. *Neuropsychopharmacology,* 35:1198-1208. doi: 10.1038/npp.2009.224

Ortega, L. A., Glueck, A. C., Uhelski, M., Fuchs, P. N., & Papini, M. R. (2013). Role of the ventrolateral orbital cortex and medial prefrontal cortex in incentive downshift situations. *Behavioural Brain Research*, *244,* 120-129. doi: 10.1016/j.bbr.2013.01.029

Ortega, L. A., Norris, J. N., López-Seal, M. F., Ramos, T. & Papini, M. R. (2014). Correlates of recovery from incentive downshift: A preliminary selective breeding study. *International Journal of Comparative Psychology, 27*, 18-44.

Ortega, L. A., Uhelski, M., Fuchs, P. N., & Papini, M. R. (2011). Impairment of recovery from incentive downshift after lesions of the anterior cingulate cortex: Emotional or cognitive deficits? *Behavioral Neuroscience, 125*, 988-995. doi: 10.1037/a0025769

Panksepp, J. (2005). Social support and pain: How does the brain feel the ache of a broken heart? *Journal of Cancer Pain & Symptom Palliation, 1*(1), 59-65.

Panksepp, J. (2011). The neurobiology of social loss in animals: Some keys to the puzzle of psychic pain in humans. In G. MacDonald & L. A. Jensen-Campbell, A. Lauri (Eds.), *Social pain: Neuropsychological and health implications of loss and exclusion*. Washington, DC: American Psychological Association.

Papini, M. R. (2003). Comparative psychology of surprising nonreward. *Brain, Behavior & Evolution, 62*, 83-95. doi: 10.1037/a0029207

Papini, M. R. (2006). Role of surprising nonreward in associative learning. *Japanese Journal of Animal Psychology, 56*, 35-54.

Papini, M. R. (2009). Role of opioid receptors in incentive contrast. *International Journal of Comparative Psychology, 22*, 170-187.

Papini, M. R., & Dudley, R. T. (1997). Consequences of surprising reward omissions. *Review of General Psychology, 1*, 175-197.

Papini, M. R., & Ortega, L. A. (2011). Endogenous opioids, opioid receptors, and incentive processes. In V. R. Preedy, R. R. Watson, & C. R. Martin (Eds.), *Handbook of behavior, food, and nutrition* (pp. 1011-1019). New York, NY: Springer.

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.

Pawlak, C. R., Ho, Y. J., & Schwarting, R. K. (2008). Animal models of human psychopathology based on individual differences in novelty-seeking and anxiety. *Neuroscience & Biobehavioral Reviews, 32*, 1544-1568. doi: 10.1016/j.neubiorev.2008.06.007

Pecoraro, N., de Jong, H., & Dallman, M. R. (2009). An unexpected reduction in sucrose concentration activates the HPA axis on successive post shift days without attenuation by discriminative contextual stimuli. *Physiology & Behavior, 96*, 651-661. doi: 10.1016/j.physbeh.2008.12.018

Pecoraro, N., De Jong, H., Ginsberg, A. B., & Dallman, M. F. (2008). Lesions of the medial prefrontal cortex enhance the early phase of psychogenic fever to unexpected sucrose concentration reductions, promote recovery from negative contrast and enhance spontaneous recovery of sucrose-entrained anticipatory activity. *Neuroscience, 153*, 901-917. doi: 10.1016/j.neuroscience.2008.03.043

Pellegrini, S., Muzio, R. N., Mustaca, A. E., & Papini, M. R. (2004). Successive negative contrast after partial reinforcement in the consummatory behavior of rats. *Learning & Motivation, 35*, 303-321. doi:10.1016/j.lmot.2004.04.001

Piras, G., Piludu, M. A., Giorgi, O., & Corda, M. G. (2014). Effects of chronic antidepressant treatments in a putative genetic model of vulnerability (Roman low-avoidance rats) and resistance (Roman high-avoidance rats) to stress-induced depression. *Psychopharmacology, 231,* 43-53. doi: 10.1007/s00213-013-3205-7

Pratsch, K., Wellhausen, R., & Harald Seitz, H. (2014). Advances in the quantification of protein microarrays. *Current Opinion in Chemical Biology*, *18*,16–20. doi: 10.1016/j.cbpa.2013.10.024

Rosas, J. M., Callejas-Aguilera, J. E., Escarabajal, M. D., Gómez, M. J., de la Torre, L., Agüero, A. A. Tobeña, A., Fernández-Teruel, A., Torres, C. (2007). Successive negative contrast effect in instrumental runway behaviour: A study with Roman high- (RHA) and Roman low- (RLA) avoidance rats. *Behavioural Brain Research, 185*, 1-8. doi:10.1016/j.bbr.2007.07.027

Rowan, G. A., & Flaherty, C. F. (1991). Behavior of Maudsley reactive and nonreactive rats (*Rattus norvegicus*) in three consummatory contrast paradigms. *Journal of Comparative Psychology, 105*, 115-124. doi:10.1037//0735-7036.105.2.115

Sabariego, M., Gómez, M. J., Morón, I., Torres, C., Fernández-Teruel, A., Tobeña, A., Cañete, T., Martínez-Conejero, J. A., Horcajadas, J. A., & Esteban, F. J. (2011). Differential gene expression between inbred Roman high- (RHA-I) and low- (RLA-I) avoidance rats. *Neuroscience Letters, 504*, 265-270. doi: 10.1016/j.neulet.2011.09.044

Sabariego, M., Morón, I., Gómez, M. J., Donaire, R., Tobeña, A., Fernández-Teruel, A., Martínez-Conejero, J. A., Esteban, F. J., & Torres, C. (2013). Incentive loss and hippocampal gene expression in inbred Roman high-(RHA-I) and Roman low- (RLA-I) avoidance rats. *Behavioural Brain Research, 257*, 62-70. doi: 10.1016/j.bbr.2013.09.025

Salinas, J., Packard, M. G., & McGaugh, J. L. (1993). Amygdala modulates memory for changes in reward magnitude: reversible post-training inactivation with lidocaine attenuates the response to a reduction in reward. *Behavioural Brain Research, 59,* 153-159. doi:10.1016/0166-4328(93)90162-J

Sanna, F., Corda, M. G., Melis, M. R., Piludu, M. A., Giorgi, O., & Argiolas A. (2014). Male Roman high and low avoidance rats show different patterns of copulatory behavior: Comparison with Sprague Dawley rats. *Physiology & Behavior*, *127*, 27-36. doi: 10.1016/j.physbeh.2014.01.002

Sanna, F., Corda, M. G., Melis, M. R., Piludu, M. A., Löber, S., Hübner, H., Gmeiner, P., Argiolas, A., & Giorgi, O. (2013). Dopamine agonist-induced penile erection and yawning: A comparative study in outbred Roman high- and low-avoidance rats. *Pharmacology, Biochemistry & Behavior, 109*, 59-66. doi: 10.1016/j.pbb.2013.05.002

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. doi:10.1080/1025389031000111320

Steimer, T., & Driscoll, P. (2005). Inter-individual vs line/strain differences in psychogenetically selected Roman high-(RHA) and low-(RLA) avoidance rats: Neuroendocrine and behavioural aspects. *Neuroscience & Biobehavioral Reviews, 29*, 99-112. doi:10.1016/j.neubiorev.2004.07.002

Torres, C., Cándido, A., Escarabajal, M. D., de la Torre, L., Maldonado, A., Tobeña, A., & Fernández-Teruel, A. (2005). Successive negative contrast in one-way avoidance learning in female roman rats. *Physiology & Behavior, 85*, 377-382. doi: 10.1016/j.physbeh.2005.02.023

Torres, C., Sabariego, M., Morón, M., Gómez, M. J., Donaire, R., Cano, F. J., Fernández-Teruel, A., Esteban, F. J. (2013, unpublished presentation). Partial reinforcement extinction effect and hippocampal gene expression in Roman high- and low avoidance rats strains. *43rd Anual Meeting of the Society for Neuroscience* (San Diego, USA).

Wang, H., Zhu, Y., Wong, P., Farook, J., Teo, A., Lee, L., & Moochhala, S. (2003). cDNA *microarray* analysis of gene expression in anxious PVG and SD rats after cat-freezing test. *Experimental Brain Research, 149*, 413-421. doi:10.1007/s00221-002-1369-1

Yang, D., Parrish, R. S., & Brock, G. N. (2014). Empirical evaluation of consistency and accuracy of methods to detect differentially expressed genes based on microarray data. *Computers in Biology & Medicine*, *46*, 1–10. doi: 10.1016/j.compbiomed.2013.12.002

Zhang, S., Amstein, T., Shen, J., Brush, F., & Gershenfeld, H. (2005). Molecular correlates of emotional learning using genetically selected rat lines. *Genes, Brain & Behavior, 4*, 99-109. doi: 10.1111/j.1601-183X.2004.00099.x

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