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Mediational Role of Hormones in Incentive Contrast

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Frustration can be defined as an emotional state generated by the omission or devaluation in the quantity or quality of an expected reward. Thus, reactivity to a reward is affected by prior experience with the different values of that reward, a phenomenon known as incentive relativity, which can be studied by different paradigms to induce frustration. In this article we focus on successive negative contrast, involving a reward downshift, and in extinction, involving complete reward omission. We discuss the role of neuroendocrine mechanisms in these phenomena, specifically analyzing the action of monoamines, adrenal hormones, and sexual hormones. Incentive contrast could be utilized as a model of clinical psychopathologies in which emotions and cognitions are assessed. We show its utility using evidence from hormonal studies of incentive contrast.

Imagine a kid was told he/she would be given a carbonated, highly sugared beverage after successfully completing homework, yet only receives a reward of artificially sweetened green tea. Just like in this fictitious example, many of the unpleasant, aversive situations that people face every day involve losing an expected reward or receiving a lessened, devalued reward. The ensuing frustration, disappointment, or psychological pain (Mustaca & Papini, 2005; Papini, Wood, Daniel & Norris, 2006) can be considered a product of positive expected consequences that were not realized (Papini, 2006; Tinklepaugh, 1928). The analysis of reward expectancies of specific incentive values is, therefore, key to understanding the frustration process. A corollary is that the incentive value attributed to stimuli and situations is not absolute, but relative, and is shaped by previous learning experiences, biological factors, and genetic factors (Flaherty, 1996).

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Frustration can be defined as an emotional state generated by the omission or devaluation in the quantity or quality of an expected reward (Amsel, 1992). Evidence shows that frustration has emotional, behavioral, neuroendocrine, and physiological correlates similar to those observed after the presentation or anticipation of typical aversive stimuli, such as exteroceptive nociceptive stimulation (Gray, 1987; Konorsky, 1964). In this article, we focus on the neuroendocrinal underpinnings of frustration behavior in animals, mainly rodents, although it is important to highlight that there are studies with others species (see Papini, 2003).

There are multiple experimental procedures to induce frustration in animals. Here the emphasis is on successive negative contrast (SNC) and extinction. In the consummatory SNC (cSNC) situation, animals undergo daily sessions (preshift phase) in which they receive access to a high magnitude reward (e.g., 32% sucrose). This is followed by a second phase (devaluation or postshift phase) in which the value of the reinforcer is abruptly and significantly reduced (e.g., 4% sucrose). The acceptance of the reinforcer in the experimental, downshifted animals is compared against control (unshifted) animals that are always exposed to the small-magnitude reward (Flaherty, 1996). Downshifted animals exhibit reduced acceptance of the devalued reinforcer and this apparent conditioned avoidance is taken as an index of frustration (Flaherty, 1996). The difference between the groups gradually subsides in three or four sessions as experimental animals end up consuming as much of the lesser reinforcer as controls. Downshifted rats also exhibit changes in behaviors such as ambulation or rearing which last between two and four trials.

Similar processes occur in instrumental SNC (iSNC) situations. In this procedure, animals usually run through a straight alley to access a highly appetitive reward (e.g., 12 food pellets) or to a relatively poor reward (e.g., 4 food pellets). During the postshift phase all subjects have access to the less preferred reward. Typically, downshifted animals take longer to run through the straight alley than unshifted animals (e.g., Bentosela, Muzio, & Mustaca, 2001).

In an extinction procedure, a reward that was readily available (e.g., access to a 32% sucrose solution) is suddenly and completely omitted. Rats abruptly suppress the approach behavior to the empty sipper tube (consummatory extinction, cE) or take longer to traverse the alley to the chamber where the reward used to be (instrumental extinction, iE; Domjan, 2010; Flaherty, 1990; Mustaca, Freidin, & Papini, 2002).

Historically, several theories offered explanations of behavior observed in situations involving reward omission or devaluation (Amsel, 1958; Capaldi, 1971; Elliott, 1928; Gray, 1987; Helson, 1964). Flaherty (1982) published one of the first systematic reviews on the topic. Research conducted over the past few decades has helped discard some theories, while strengthening others. These theories have been classified in terms of their reliance on emotional processes, cognitive processes, or a combination of both. Among those focused on emotional variables, Amsel's (1958, 1962, 1992) and Gray's theories (1987) have been the most influential.

According to Amsel´s theory, the absence of an expected reward generates an internal aversive state called *primary frustration*. The stimuli associated with this state acquire the ability to generate in later trials a conditioned expectation of primary frustration, called *secondary frustration*. This theory suggests that two factors explain the suppression of behavior during incentive downshift. First, the violation of expectancy during the first postshift trial generates an aversive unconditioned response of primary frustration, which is associated with the contextual stimuli present in that trial through Pavlovian conditioning. Second, exposure to contextual stimuli during the second shift trial reactivates two types of memories: that of the reward received in the preshift phase and the memory of primary frustration. These expectations result in an approach-avoidance conflict: approach to the solution that is appetitive in its absolute value, but avoidance due to the comparison with the reward previously received.

Gray's bidimensional defense theory or behavioral inhibition theory also explained frustration behavior by emphasizing the role of emotional factors (Gray, 1987; Gray & McNaughton, 2000; McNaughton & Corr, 2004). The theory proposes a functional equivalence between fear and frustration. Both fear and frustration are emotional states activated by the experience of pain and reward omission, respectively. The ability of any given stimulus to activate these states requires conditioning, which is why they are understood as internal states or representations. If we follow Amsel's tenets, the equation should be that fear is a conditioned state analogous to secondary frustration, and pain is an unconditioned state analogous to primary frustration (Papini et al., 2006).

In the procedures outlined in this article, animals are not exposed to explicit aversive stimuli (like in the fear conditioning paradigm, in which animals receive nociceptive stimulation). Instead, rats experience a downshift in the magnitude of expected rewards. This experimental model provides a window for the assessment of emotional memory, anxiety, depression, and stress (Justel, Ruetti, Bentosela, Mustaca, & Papini, 2012a; Justel, Ruetti, Mustaca, & Papini, 2012b; Justel, Pautassi, & Mustaca, 2014; Ruetti, Burgueño, Justel, Pirola, & Mustaca, 2013; Ruetti & Justel, 2010). Incentive contrast could be utilized as an experimental model of psychopathology to assess the modulatory role of emotion and cognition on behavior; and here we intend to show its utility using evidence from hormonal studies of incentive contrast (Bentosela, Ruetti, Muzio, Mustaca, & Papini, 2006; Justel et al., 2012a, b; Ruetti, Justel, Mustaca, & Papini, 2009).

Adrenal Hormones

Adrenal hormones (e.g., glucocorticoids) are released in situations that involve strong emotional stimulation. Reports indicate that these hormones, notably corticosterone (cortisol in humans), modulate the consolidation of associative memories (Justel et al., 2013; Ruetti et al., 2009) in animals and humans.

One method to assess the role of hormones on incentive relativity is to study hormonal changes after the occurrence of SNC or extinction (Flaherty, Becker, & Pohorecky, 1985; Mitchell & Flaherty, 1998). A second approach is to evaluate frustration processes after agonists or antagonists administered either before or after the downshift that affect hormonal activity, such as dexamethasone or astressin B, respectively (Justel, Psyrdellis, & Ruetti, 2013; McArthur, McHale, Dalley, Buckingham, & Gillies, 2005; Ruetti, Justel, & Bentosela, 2009; Vulliemoz, Xiao, Xia-Zhang, Rivier, & Ferin, 2007). A third alternative involves conducting lesions in target places of the brain, through chemical or electrolytic means, while animals undergo a frustration procedure. Changes in behavior, compared to controls given sham lesions, are taken as an index of a mediational role of the injured area (e.g., Nonkes & Homberg, 2013).

In early work, plasma corticosterone (CORT) levels were measured after downshift trials in the cSNC procedure. The hypothesis was that frustrated rats would exhibit an enhanced adrenal response. The initial findings indicated that CORT was elevated in downshifted animals during the second, but not during the first, postshift trial (Flaherty et al., 1985; Mitchell & Flaherty, 1998). More recent data, however, indicated an increase in CORT and in adrenocorticotropic hormone (ACTH) levels after the first and second downshift trials (Pecoraro, de Jong, & Dallman, 2009). This apparent discrepancy could relate to procedural differences. Mitchell and Flaherty (1998) measured CORT levels immediately after each trial, whereas Pecoraro's team (2009) inserted a 10-min gap between the end of the trial and blood collection. The latter procedure may have had better detection sensitivity by allowing time for plasma CORT levels to rise.

The data seem to be more consistent in the case of extinction procedures. It has been reported that during appetitive extinction there is an increase in plasmatic levels of CORT (Coover, Goldman, & Levine, 1971; de Boer, de Beun, Slangen, & van der Gugten, 1990; Kawasaki & Iwasaki, 1997).

A valuable source to understand the relationship between stress, emotion, and memory is provided by human studies in which participants are submitted to stressful situations while exposed to verbal or visual, emotional, or neutral stimuli. Memory for these stimuli is then assessed. Cahill, Gorski, and Le (2003) studied the interaction between stress hormones and emotional activation induced by the learning experience. The participants watched neutral and emotional images while experienced a stressful or control situation (immersion of the arm in cold or warm water respectively). One week later, participants who received the stressor, but not those in control conditions, showed better recognition of the emotional pictures than the neutral ones. Buchanan and Lovallo (2001) assessed the possibility that this memory facilitating effect was caused by cortisol release. Participants watched neutral and emotional images followed by administration of cortisol. It was found that those treated with cortisol exhibited better recognition of the emotional photos than those treated with the vehicle. Moreover, the expectative of receiving a stressor is also effective to elevate the activation of hormones (Justel et al., 2013; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2008; Weymar, Bradley, Hamm, & Lang, 2013).

It is thus expected that stress exposure before devaluation or CORT administration after the devaluation of appetitive reinforcers in cSNC (or extinction) results in an enhanced expression and persistence of the aversive memory. Consistent with this hypothesis, animals exposed to restraint stress that elevated CORT levels subsequently exhibited increase cSNC compared to nonstressed controls (Ortega et al., 2013).

Bentosela et al. (2006) found that systemic administration of CORT after the first trial of incentive downshift generated a stronger and longer lasting cSNC effect, in comparison to animals that received the vehicle. The expression of this effect requires a minimum discrepancy between the pre- and postshift concentrations of the sucrose solution. Specifically, the effect of CORT on cSNC was observed in animals downshifted from 32% to 4% sucrose, but not in those downshifted from 8% to 4% sucrose (Ruetti et al., 2009). These results indicate that CORT serves to magnify a situation that already possesses a significant emotional tone. Likewise, the systemic administration of CORT during the first extinction trial results in faster extinction, both in consummatory (Ruetti et al., 2009) and in operant paradigms (Garrud, Gray, & de Wied, 1974; Hennessy, Cohen, & Rosen, 1973; Tomie, Tirado, Yu, & Pohorecky, 2004). Similar results are found with the synthetic corticoid dexamethasone (Zorawsky & Killcross, 2002). This drug is clinically used to treat adrenal insufficiency and to reduce inflammation (Galofré, 2009).

Monoamines

Noradrenaline (or norepinephrine, NA) is a catecholamine released in stressful situations and is involved, among other functions, in attention, learning, and homeostasis maintenance (McGaugh & Roozendaal, 2002, 2009). Noradrenergic agents can be used in the treatment of depression and attention deficit disorder.

Systemic administration of the prototypical adrenergic agonist clonidine before the second downshift trial did not affect incentive downshift (Flaherty, Grigson, & Demetrikopoulos, 1987). A more recent study, however, observed that intra-amygdala infusions of the adrenergic antagonist propranolol before downshift trials diminished the iSNC effect (Salinas, Intrioni-Collinson, Dalmaz, & McGaugh, 1997). Propranolol is a nonselective β-adrenergic antagonist used for the treatment of anxiety disorders.

The effects of propranolol during operant extinction seem to depend on the time of administration of the antagonist. Propranolol facilitated extinction when applied during acquisition (Marsland, Salmon, Terry, & Stanford, 1990). However, animals given propranolol after acquiring stable responding exhibited increased resistance to extinction (Salmon, Tsaltas, & Gray, 1989). These effects seemed to be fairly specific to the adrenergic system, since administration of a serotonin and noradrenaline synthesis inhibitor (demetilmipramine, DMI) had no effect on extinction. Rats suddenly withdrawn from chronic treatment with

DMI, however, exhibited increased resistance to extinction in a runway and after continuously reinforced lever pressing (Willner, Montgomery, & Bird, 1981). The interpretation was that chronic DMI administration is likely to mimic the treatment given to depressed patients and may have induced deficits in the dorsal noradrenergic bundle. This deficit does not seem to alter reactivity to the reinforcer per se, as consummatory extinction was preserved (Cohen & Gothard, 2011).

The modulatory action of propranolol and the β-adrenergic system on memory was analyzed in several studies with human participants (see Chamberlain & Robbins, 2013). It seems that this system is involved in the enhanced encoding of information during emotional events. The administration of the β-adrenergic antagonist propranolol or lesions of the amygdala specifically affected the long term recall of emotional information (Cahill, Prins, Weber, & McGaugh, 1994). Similarly, these agents disrupted performance during the downshift trials of iSNC, when emotional components are predominant (Salinas, Parent, & McGaugh, 1996; Salinas et al., 1997).

Dopamine (DA), a hormone and neurotransmitter of the catecholamine family, is involved in learning, mood, motivation, and reward, among other functions (Abraham, Neve, & Lattal, 2014). DA also acts as a sympathomimetic promoting an increase in heart rate and blood pressure (Berridge & Robinson, 1998). Appetitive stimuli with a wide range of incentive value activate the dopaminergic system and result in augmented extracellular DA concentration (Phillips, Vacca, & Ahn, 2008), whereas aversive stimuli are more likely to reduce the tone of this system (Tobler, Fiorilo, & Schultz, 2005). This regulation is achieved in concert with other neurotransmitter systems. Ethanol administration, for instance, activates mesocorticolimbic DA neurons via μ opioid-receptor mechanisms. Activation of μ receptors inhibits GABA interneurons that normally function to inhibit DA neurons. This "inhibition of inhibition" results in greater activation of DA neurons (Xiao, Zhang, Krnjevic, & Ye, 2007). However, aversive stimulation causes the release of dynorphin, which activates κ opioid receptors thus reducing dopamine activity (Pautassi, Nizhnikov, Acevedo, & Spear, 2012).

Genn, Ahn, and Phillips (2004) reported a decrease flux of DA in the nucleus accumbens in rats after incentive downshift in comparison to animals that had been exposed to an unshifted condition. This result is important because it supports the hypothesis that SNC is analogous to preparations that employ standard aversive stimulation, such as fear conditioning. Administration of sulpiride, an antipsychotic with high DA-receptor affinity, reduces cSNC when administered prior to the downshift (Genn, Barr, & Phillips, 2002). The effect found in Genn et al.'s (2002) study has the caveat, however, of losing significance at lower doses. Moreover, other studies have provided conflicting data on the role of dopamine on frustration, as neither chlorpromazine nor haloperidol (neuroleptics that antagonize DA receptors) affected cSNC when administered before the first or second trial of incentive downshift (Flaherty, Becker, Checke, Rowan, & Grigson, 1992).

Kurylo and Tanguay (2003) assessed operant extinction in an appetitive procedure, in which access to water was contingent on head dipping. Animals administered quinpirole (QNP), a DA_2 receptor agonist, during acquisition and extinction exhibited greater resistance to extinction in comparison with untreated animals or animals given QNP only during the acquisition phase (Kurylo & Tanguay, 2003). Conversely, administration of the DA antagonist haloperidol facilitated extinction in an operant appetitive task (Phillips & Fibiger, 1979).

DA transmission within cortical and subcortical structures is involved in the processing of emotionally relevant information. Evidence from clinical, genetic, behavioral, and electrophysiological experiments indicates a critical role for the DA in the processing, encoding and expression of emotional memories (Berridge & Robinson, 1998; Hoogman et al., 2013; Lauzon & Laviolette, 2010). DA release in the left amygdala, left medial temporal lobe, and left inferior frontal gyrus was reported in human participants exposed to sets of emotional, but not neutral, words (Badgaiyan, Fischman, & Alpert, 2009).

Serotonin is a monoamine involved in the regulation of mood, sleep, and emotions. Several drugs that regulate its action are used in the treatment of anxiety disorders and depression, such as fluoxetine, paroxetine, or sertraline (Hjorth et al., 2000). The claim that SNC can be considered an experimental model of anxiety has prompted the use of serotoninergic agonists in this preparation. cSNC, however, was insensitive to acute or chronic administration of buspirone and gepirone, administered before the first or second downshift trial (Flaherty et al., 1990). The use of antagonists yielded conflicting results. Ketanserine and ritanserine had no effect on incentive downshift, yet both cinanserine and cyproheptadine proved effective to reduce contrast when administered before the second shift trial (Becker, 1986; Grigson & Flaherty, 1991).

It has been observed that the administration of serotonin-synthesis inhibitors during the acquisition or extinction of an operant task increases resistance to extinction (Beninger & Phillips, 1979; Egan, Earley, & Leonard, 1979; Komorowski et al., 2012). This is congruent with data gathered in animals genetically altered to not express serotonin receptors. Like their normal counterparts given serotonin synthesis inhibitors, these knock-out mice exhibit increased resistance to extinction in operant procedures (Nonkes & Homberg, 2013).

Sexual Hormones

Testosterone (T) is a steroid sexual hormone produced by the gonads (Justel, Bentosela, & Mustaca, 2009) that has been observed to exert anxiolytic effects in aversive conditioning procedures (Fernández-Guasti, Roldán-Roldán, & Saldivar, 1989). The increase in T after sexual activity decreases anxiety levels in several species (Justel, Bentosela, & Ruetti, 2010). Sexual behavior attenuates frustration in rats undergoing a cSNC procedure (Freidin, Kamenetzky, & Mustaca, 2005). Specifically, male rats that ejaculated immediately before the second, but not before the first, downshift trial showed an attenuated cSNC effect. Sexually-satiated animals exhibited greater acceptance of the devalued sucrose solution than animals without the sexual experience. A follow-up study found attenuation of cSNC in males that were exposed to receptive females but did not have the possibility to ejaculate (Cuello, Freidin, & Mustaca, 2010). This suggested that mere exposure to sexually-arousing stimulation, such as estrous female odor, is sufficient to attenuate cSNC, an effect possibly related to the anxiolytic effects of T (Cuello et al., 2010).

Following this line of thought, it could be hypothesized that the anxiolytic effect of sexual behavior on frustration may relate to an increase in T levels following exposure to female estrous pheromones or after ejaculation (Justel et al., 2009, 2010). Congruent with this observation, it has been found that T, either endogenous or exogenous and after acute (Aikey, Nyby, Anmuth, & James, 2002; Frye & Edinger, 2004) or chronic manipulations (e.g., Bing et al., 1998; Bitran, Kellog, & Hilvers, 1993; Fernández-Guasti & Martínez-Mota, 2005), altered behavioral performance in paradigms that employ aversive stimuli. An intriguing study reported that chronic, but not acute, T administration had an anxiolytic effect in cSNC. Specifically, animals given injections of the hormone throughout cSNC exhibited an attenuated cSNC effect and faster recovery in comparison with animals that received the vehicle (Justel et al., 2012a).

Analogous results were found in consummatory extinction. Chronic, but not acute, administration of the androgen resulted in faster extinction (Justel et al., 2012a). These results were associated with decreased anxiety in an open field test. These results provided support for the hypothesis that an increase in T levels is involved in the anxiolytic effect of sexual behavior (Justel et al., 2012a).

As with rodents, T is used in human studies to ameliorate stress, anxiety, and depression symptoms (Enter, Spinhoven, & Roelofs, 2014; Hermans et al., 2007). Some studies also suggest that the level of this hormone is associated with memory enhancement (Ackermann et al., 2012; Davison et al., 2012). Intriguingly, women show more anxiety and depression symptoms, which can be reversed with the administration of the gonadal hormone (Giltay et al., 2012; McHenry, Carrier, Hull, & Kabbaj, 2014).

The complex interaction between activation of the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis is exemplified by situations in which unconditioned or conditioned aversive stimuli occurs in close temporal contiguity with sexual behavior. The effect of stress on sexual behavior depends on the nature, intensity, and, in some conditions, duration of the stress stimulus; it can produce a deficit, an enhancement, or even no change in subsequent sexual performance. Males exposed to stress may exhibit suppression of T secretion, spermatogenesis, and libido (Collu, Gibb, & Ducharme, 1984; Rabin, Gold, Margioris, & Chrousos, 1988). D'Aquila, Brain, and Willner (1994) showed that male rats reared in isolation and exposed to chronic mild unpredictable stress (i.e., unpredictable food, water deprivation, overnight illumination, 45º cage tilt, periods of paired housing, periods in a soiled cage, and confinement in a smaller cage) exhibited decreased mounting. However, tail pinch, tail shock, and flank shock stimulate and enhance sexual behavior in male rats (Caggiula, 1972; Caggiula & Eibergen, 1969).

To our knowledge, there has been only one attempt to analyze the effect of incentive devaluation upon sexual behavior in male rats. Freidin and Mustaca (2004) found deficits in sexual behavior of animals subjected to consummatory extinction. These animals showed lower copulatory efficiency rates and greater latency to ejaculation, following termination of the first and second extinction trial, respectively. These alterations may involve the action of several hormones secreted during stressful situations, such as corticotrophin releasing factor (MacLusky, Naftolin, & Leranth, 1988) and glucocorticoids, on hypothalamic-pituitary-gonadal axis function (e.g., Doerr & Pirke, 1976).

Final Comments

In this article, we discussed the effect of hormones in experimental procedures that induce frustration in rats. The results indicate that adrenal hormones increase after the downshift or omission of a reward (Flaherty et al., 1985; Mitchell & Flaherty, 1998; Pecoraro et al., 2009). The administration of adrenal hormones, in turn, produces a more intense contrast and a faster extinction (Bentosela et al., 2006; Ruetti et al., 2009).

With regard to noradrenaline, it was reported that the administration of noradrenaline receptors antagonist decreased frustration (Salinas et al., 1997). During extinction, agonism and antagonism of the NA system seem to exert opposite effect depending on the time of administration (Marsland et al., 1990; Salmon et al., 1989). Regarding dopamine, Tobler et al. (2005) observed a decrease in DA functionality after incentive downshift, whereas reward downshift was correlated with a decrease of this monoamine in the nucleus accumbens (Genn et al., 2004). Moreover, dopamine agonists increased resistance to extinction while the antagonists decreased it (Kurylo & Tanguay, 2003). The effects of serotonin in cSNC have been inconsistent and more information is needed to ascertain its role (Becker, 1986; Grigson & Flaherty, 1991). During extinction, in turn, the administration of serotonin-receptor inhibitors results in greater resistance to extinction (Beninger & Phillips, 1979; Egan et al., 1979; Komorowski et al., 2012).

Sexual hormones seem to exert a dramatic, calming effect upon frustration. Greater T levels, derived from ejaculation, exposure to a receptive female, or exogenous administration, result in diminished frustration and faster extinction (Cuello et al., 2010; Freidin et al., 2005; Justel et al., 2012a, 2012b). Conversely, sexual behavior is negatively affected by incentive devaluation, a result suggesting an interaction between stress hormones and the hypothalamic-pituitary-gonadal system.

Throughout this review, efforts were made to establish connections between preclinical (animal) studies and clinical research. Basic research set the basis for the development of applied studies. It is only through the development of true partnerships between researchers and clinicians that mental health treatments can achieve an optimal level of success. Clinical research on emotional and anxiety disorders features great ecological validity but faces the difficulty of correctly identifying the etiology and mechanisms of these

disorders. The vast majorities of these highly valuable clinical studies are correlational and exhibit relatively poor experimental control (Kamentezky & Mustaca, 2004; Papini et al., 2006). Animal models allow for optimal experimental control, as well as the possibility to manipulate environmental, psychological, physiological, genetic, or neurophysiological variables. These models also treat psychopathologies as behavioral processes, whose mechanisms could be scientifically studied (Hunziker & Pérez Acosta, 2001). Clearly, extrapolation from basic to applied science is not automatic, but requires careful testing and gradual accumulation of knowledge. The use of animal models is highly relevant to this process (Kamenetzky & Mustaca, 2004).

It is important to highlight that, across the procedures outlined in the present work, animals are not exposed to explicit aversive stimuli (like in fear conditioning or taste aversion paradigms, in which animals receive nociceptive or sickness-inducing stimulation, respectively; Papini et al., 2006). Instead, rats experience downshifts in the magnitude of expected rewards. The induction of experimental frustration provides a naturalistic approach to study emotional memory, anxiety, depression, and stress, among others domains of animal cognition. Experimental frustration has, however, important limitations. For instance, it is more complicated to implement than other paradigms (e.g., fear conditioning) because the establishment of an expectative of magnitude reinforcement can only be achieved after substantial exposure to the reinforcer. Furthermore, more research is needed to validate the use of experimental frustration as a model of anxiety. For instance, it has been observed that serotoninergic agents modulate conditioned fear (Burghardt & Bauer, 2013) and fear-related behaviors after social defeat (Bader, Carboni, Burleson, & Cooper, 2014), yet they are not fully effective in experimental frustration paradigms (Flaherty et al., 1990). Researchers interested in using frustration paradigms, however, can look forward to important advantages: ethical constraints are mostly avoided due to the use of innocuous stimuli (instead of, for instance, electric shock or social defeat) and the magnitude of the unconditioned stimuli can be carefully controlled.

The studies reviewed are also relevant for applied science. The adversities faced by humans in their everyday endeavors most often involve reduction or loss of appetitive rewards (e.g., death of loved ones, unemployment, divorce, social exclusion, etc.). Situations that involved actual exposure to prototypical aversive stimulation (e.g., physical pain, chronic pain) are probably less common. The development of coping strategies and resilience to disappointments is essential to a proper adjustment to the social environment. Experimental frustration could be a valuable model, on a par to the widely used fear conditioning preparations, to expand our knowledge on the mechanisms involved in the effects of stress.

The research about the role of the hormones on frustration provides partial support for the hypothesis of an overlap (at least in terms of neuroendocrine mechanisms) between prototypical aversive stimuli and stimuli implicated in the partial or complete omission of appetitive rewards. Under this theoretical umbrella, the frustration model becomes a useful model of anxiety and psychological pain (Mustaca, 2013; Papini et al., 2006).

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