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Early Experience and Incentive Relativity in Adulthood

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Human and animal studies have shown the long-lasting impact of early life experience on the development of individual differences in stress responsiveness in later life. Despite the numerous works that evaluate the effect of early experience on different behavioral paradigms, which for the most part are related to aversive situations, there are few studies that assess the effects on the unexpected downshift or omission of rewards. The purpose of this article is to review several independent lines of research into how frustration responses during adulthood may be influenced by early experience. Few articles have been found on the subject and in most cases the results were negative or controversial. However, recent research suggests that the response to frustration or euphoria in adults may be modulated by early experience.

Human and animal studies have shown the long-lasting impact of early life experience on the development of individual differences in stress responsiveness in later life. This phenomenon underlies the interplay between genes and the environment. These studies address (1) the effects of early environment on later stress phenotypes, (2) the role of genetic factors in modulating the outcome of environmental influences, and (3) the role of nonshared environmental experience in the outcome of gene × environment interactions (Claessens et al., 2011). Early studies contributed to the notion that the consequences of early life stress exposure are invariantly deleterious. These consequences are achieved through the action of specific environmental cues acting at a specific time during development, that result in permanent alterations in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (e.g., Andrews & Matthews 2004; De Kloet, Sibug, Helmerhorst & Schmidt, 2005; Matthews, 2002; Meaney, Szyf, & Seckl, 2007; Seckl, 2008). This research shows that the stress of early parental loss, neglect, or abuse produces enhanced fear and anxiety, increased anhedonia, impaired cognition, abnormal brain neurochemistry and neurobiology, and alterations in baseline activity as well as stress reactivity of the HPA axis (e.g., Maestripieri, Lindell, Ayala, Gold, & Higley, 2005; Pryce et al., 2005; Rosenblum, Forger, Noland, Trost, & Coplan, 2001; Stevens, Leckman, Coplan, & Suomi, 2009; Suomi, 1997). However, other research has shown that environmental influences in early life do not always lead to disease or increased vulnerability. There is evidence that early life stress exposure produces a diverse range of developmental outcomes, including resilience to subsequent stressors encountered in

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adulthood. For example, childhood stress has been linked to attenuated increases in salivary cortisol responses to the Trier Social Stress Test, a protocol in which the subjects have to deliver a free speech and perform mental arithmetic in front of an audience (Gunnar & Donzella, 2002) and lower cerebrospinal fluid levels of corticotropin releasing factor in healthy adults (e.g., Carpenter et al., 2004). Moreover, stress during childhood diminished cardiovascular responses during stressful laboratory tests, such as mental arithmetic task, videogame performance and hand submersion in ice water (e.g., Boyce & Chesterman, 1990). Prior stressful experience also diminishes emotional distress in day-care settings and hospital admissions (e.g., Holmes, 1935; Stacey, Dearden, Pill, & Robinson, 1970), and men and women are found to cope better with stressful events such as spousal loss, major accidents, illness, and work stress if they previously experienced and successfully coped with stressors in childhood (e.g., Forest, 1991; Khoshaba & Maddi, 1999). When early life exposure to stress is examined across a continuum, adults exposed to moderate levels of early life stress exhibit lower levels of state anxiety (Edge et al., 2009) and more resilient cardiovascular responses to a stressful motivated performance task, compared to individuals exposed to either low or high levels of early life stress (Parker & Maestripieri, 2011). These empirical studies suggest that exposure to early life stress may be best conceptualized as a quadratic, rather than linear, function. The outcome of early experience is not necessarily deterministic nor can it be evaluated as positive or negative. Several environmental, cognitive, and genetic inputs are involved in an intricate manner in the modulation of the outcome of early experience on adulthood (Claessens et al., 2011).

Animal models used to study the effects of early experience on stress expression during adult life in rodents include such experimental manipulations as handling, electric shock, exposure to hot or cold temperatures, maternal separation, mild chronic stress and acute stress, and litter size. Typically, behavioral and psychobiological responses are evaluated in adulthood in different tests consisting of the administration of moderate or intense aversive stimuli, such as the exposure to a novel context (e.g., Levine, Haltmeyer, Karas, & Denenberg, 1967) or to avoidance tasks (e.g., Denenberg, 1967), among others.

The majority of studies evaluate the effect of early experience on behavioral paradigms related to aversive situations; only a few studies assess the effects of early experience on the unexpected downshift or omission of rewards. These effects are known as paradoxical reward effects (Amsel, 1992), surprising reward omissions (Papini & Dudley, 1997), or incentive relativity (Flaherty, 1996). A frustration response occurs when an expected appetitive reinforcer is not presented or is reduced in magnitude or quality, even though there are signals for its impending presentation. Different procedures are employed to produce frustration responses, including the total elimination of a reward (extinction), a change of a preferred reward for a less preferred one (contrast effects), a reduction of the reinforcement rate, or an introduction of an impediment or barrier to reach the reward (e.g., Hull, 1943). Although these methods do not apply aversive stimuli, numerous investigations show that these protocols instigate behavioral and neurophysiological responses similar to reactions prompted by the presentation or anticipation of aversive events. Gray (1987) and Gray and McNaughton (2000) stated that both types of experience activate the same brain structures, and different authors have proposed that surprising reward omission is a source of anxiety, stress and psychological pain (e.g., Mustaca, 2013; Papini & Dudley, 1997; Papini, Wood, Daniel, & Norris, 2006).

Based on the above theories and evidence, it could be inferred that situations involving a decrease or loss of positive reinforcers during early childhood might alter adult behavior. However, if early experience affects the stress response, then it should also affect the adjustment to frustrating situations. The purpose of this article is to present several independent lines of research on the influence of early experience on frustration responses. A series of studies related to pharmacological and environmental treatments during infancy and adolescence and their influence on incentive relativity are included, together with designs that evaluate the effect of total or partial reward devaluation (i.e., extinction and negative contrast), random presentation of rewards and extinction (i.e., partial reinforcement), and surprising reward upshift (i.e., positive contrast), either in instrumental or consummatory procedures.

Research on the effects of early experiences on incentive relativity in adulthood has both theoretical and applied implications. From a theoretical level, the evaluation of theories that propose a motivational equivalence between psychological and physiological stress responses caused by aversive stimuli, devaluation or omission of appetitive stimuli can be performed. Moreover, compared to those using aversive conditioning, frustration models have a higher ecological validity. Most stressful events in human lives are related to incentive devaluation or incentive loss (e.g., death of relatives, unemployment; Scully, Tosi, & Banning, 2000). From an applied level, psychological treatments aimed at reducing wasteful consumption of appetitive reinforcers such as food or drugs of abuse usually fail because of frustration responses that subjects experience during the abrupt reduction or elimination of an expected reinforcement. Understanding the mechanisms by which early experiences modulate frustration reactions could contribute to the development of more effective treatments to prevent relapse.

Neonatal Clomipramine and Consummatory Successive Negative Contrast

Neonatal administration of clomipramine (CLI) produces physiological, neuroendocrine, and behavioral abnormalities in rats when they reach adulthood, which are similar to those observed in animal models of depression (Justel, Bentosela, Mustaca, & Ruetti, 2011). This pharmacological manipulation consists in the subcutaneous administration of CLI (15 mg/kg, dissolved in 0.9% saline solution), twice a day, at 08:00 and 20:00 h in rats from postnatal day (PND) 8 to 21. Newborn rats treated with CLI show a decrease in weight (Hansen & Mikkelsen, 1988; Maciag et al., 2006); a decrease in their pleasure-seeking behavior (Vogel, Neill, Kors, & Hagler, 1990); are less aggressive (Martínez-González, Prospero-García, Mihailescu, & Drucker-Colın, 2002); show a lower increase of plasma corticosterone levels during exposure to the stressor, faster return to basal levels, and a reduction in serotoninergic activity (Hansel & Mikkelsen, 1988); and display increased immobility in a forced-swim test, a widely used procedure to assess depressive behaviors (e.g., Bhagya, Srikumar, Taju, & Shankaranarayana Rao, 2008). This background suggests that CLI rats might show an attenuated frustration response. Only one experiment has tested this hypothesis. Ruetti, Burgueño, Justel, Pirola, and Mustaca (2013) evaluated CLI rats in a consummatory successive negative contrast (cSNC) situation. These rats receive daily access to 32% sucrose (preshift phase) and then they are shifted to 4% sucrose (postshift). Compared to unshifted animals that always received access to 4% sucrose, downshifted rats exhibited a sharp suppression of consummatory behavior, followed by a recovery during the next 2-4 trials (Flaherty, 1996). Results were in accordance with the hypothesis: CLI rats showed a cSNC effect only during the first downshift trial, whereas vehicle rats (VEH, subcutaneously administration of saline solution) showed this effect on two post-shift trials, which indicates a faster recovery of CLI animals. Amsel´s theory (1992) suggests that the initial rejection of the 4% solution is triggered by a state of primary frustration induced by the discrepancy between the expectation of a 32% reward acquired during the pre-shift trials and the actual 4% reward encountered on the first post-shift trial. This emotional reaction is hedonically aversive and it induces rejection with minimal or no conflict, serving as an unconditioned stimulus for the acquisition of secondary frustration through Pavlovian conditioning (i.e., pairings of stimuli present at the time of reward downshift with the internal state of primary frustration). Once acquired, secondary frustration plays its role as the avoidance component of the conflict induced at full strength during the second postshift trial. On the basis of Amsel´s theory (1992), the results suggest that both CLI and VEH rats showed a similar response pattern when they face to the downshift solution (unconditioned response). By contrast, the secondary frustration could be attenuated because of a diminished expectative in the CLI rats. Moreover, most of studies have found a significant increase in blood plasma corticosterone in the second post-shift test but not the first one, which coincides with the fact that CLI animals showed a lower increase in plasma corticosterone levels during the exposure to the stressor, and a faster return to basal levels (e.g., Bonilla-Jaime, Retana-Márquez, Vázquez-Palacios, & Velázquez-Moctezuma, 2003). For these reasons the authors concluded that the result may be

accounted for by an alteration of the HPA axis, a serotonergic system deficit, a low expectation formation during the pre-shift phase, or by a combination of some of all these factors.

Litter Size and the Frustration Effect

Litter size (i.e., the number of litter siblings) has previously been shown to strongly affect early growth in many small and social mammal species including laboratory rats. Some studies indicate that the effects of litter size also involve stress reactions, although the results were more modest compared to other treatments. For example, Rödel, Meyer, Prager, Stefanski, and Hudson (2010) found, in young Long–Evans rats, a negative correlation between serum corticosterone concentrations and litter size during PND 17 and on PND 33 after a10-min test in an elevated plus maze. The authors suggested two main explanations, not necessarily mutually exclusive: delayed maturation of the HPA axis in the typically lower body-mass pups of large litters. However, pups encountering greater competition for maternal resources adjust to this presumably more stressful developmental environment by down-regulating responsiveness of the HPA axis. Spencer and Tilbrook (2009) found that these differences were higher in females than in males. Wistar rats raised in small litters (4 vs. 16) have greater access to their mothers' milk and weigh more in adulthood than those raised in large litters. Compared to males, females from small litters show enhanced exploratory behavior and reduced anxiety in the elevated plus maze, (i.e., they enter open arms more often), and enhanced central response to restraint stress, including greater activation of the paraventricular nucleus of the hypothalamus and paraventricular nucleus of the thalamus.

We found only one experiment on the effect of litter size on frustration. Amsel and Penick (1962) evaluated the influence of early experience and training on the frustration effect to test the associative theory proposed by Lawson and Marx (1958) and Marx (1956) regarding the frustration effect. The authors reported that the frustration effect in a double-runway situation did not vary as a function of the litter size during rearing. Nevertheless, this result should be taken with caution because Amsel and Penick did not report the sex of the animals. Considering that later experiments have shown that the influence of the litter size on stress is sex-dependent, the lack of a positive result in Amsel and Penick's study could be due to the used of males.

Early Handling and Frustration

Levine (1957) challenged the dominant theory that early life stress invariably contributes to the development of emotional instability. He exposed neonatal rat pups to daily handling sessions, which consisted of brief maternal separation periods (less than 15 min) between PND 1 and 21 (early handling, EH). This manipulation differs from transient isolation from the mother and siblings or maternal separation (MS), which consists of prolonged periods of daily maternal absence ranging from 1 to 24 h. The outcome of these manipulations was unexpected at the time. Levine, and then others, found that early handling (EH) induced long-lasting changes in the adult phenotype, such as HPA axis hypo-responsiveness (e.g., Levine, 2005; Meaney & Aitken, 1985; Meerlo, Horvath, Nag, Bohus, & Koolhaas, 1999), reduced emotionality (Meerlo et al. 1999), and increased cognitive performance (Kosten, Lee, & Kim, 2007), as compared to nonhandled (NH) rats raised in undisturbed laboratory conditions. Compared to normally reared controls, stimulated rats have higher activity levels and lower defecation scores in an open field (Denenberg & Morton, 1962), shorter latencies in an emergence from home-cage test (Williams & Wells, 1970), a lower adrenal response to stress (Levine et al., 1967), and learn a shock avoidance response faster (Levine, 1957). These findings have demonstrated that, in some instances, exposure to moderate stress in early life appeared to be beneficial for the infant by promoting a greater ability to adapt to psychological and physiological stressors in adulthood (Levine, 1957). This same principle also serves as the basis for the stress inoculation-induced resilience theory developed later (Levine & Mody 2003; Lyons, Kim, Schatzberg, & Levine, 1998; Lyons, Martel, Levine, Risch, & Schatzberg, 1999). One interpretation of these results has been that stimulation in infancy reduces

emotional reactivity in adulthood (Denenberg, 1967). Using other experimental designs, it was shown that maternal care changed when pups were returned after handling, which leads to the maternal mediation hypothesis on the handling effects observed in adulthood. Nevertheless, a review on experimental results has suggested that variation in active maternal care could be understood as an epiphenomenon rather than as a causal factor in developmental plasticity of HPA axis and low fear responses in EH rats (Macrí & Würbel, 2006).

This evidence suggests that handling might attenuate responses to surprising reward changes. If contrast effects resulted from emotional processes, then animals known to differ in emotional reactivity should behave differently when exposed to frustration. Four studies assessing the EH effect on contrast procedures have been reported. Daly and Rosenberg (1973) evaluated infant male Wistar rats that were either removed from the nest each day (EH) or left undisturbed (NH) in instrumental extinction with or without shock (Experiment1), and in instrumental successive negative contrast (iSNC) employing a runway (Experiment 2). Handling consisted of removing the pups from the nest on a daily basis during the first 20 days after birth and isolating each one for 3 min in individual cages. At the end of the 3-min interval, pups were returned to the nest. The control rats were left completely undisturbed until weaning. In Experiment 1, one handled and one nonhandled groups were given extinction training with no shock (NS), whereas the other two groups were given extinction training plus shock (S) in the goalbox. Two control groups, one handled and one nonhandled, were given runway training with no food reinforcement (0) to determine if baseline running speeds were affected by the handling variable. In instrumental acquisition and extinction, reinforced rats ran faster than nonreinforced rats. Handled rats ran faster than nonhandled rats during the initial trials of runway acquisition, irrespective of the reinforcement condition. During extinction all groups showed decreases in speed of running, but the shocked group's speed decreased faster than the nonshocked group's, and differences between handled and nonhandled groups were larger for shocked than for nonshocked groups. Handled subjects ran faster in all segments of the alley despite the fact that they received more shocks. Nonhandled rats stopped running sooner than handled rats when shock was introduced in the goalbox, but there were small differences between handled and nonhandled rats when given extinction training without shock. Instead, responses on iCSN showed no differences between handled and nonhandled rats in the magnitude of the depression effect after an incentive shift. These results suggest that the handling procedure diminished the suppressive effect of punishment on extinction, but not incentive devaluation. Taken together, these results do not support theories of analogy between incentive devaluation and application of aversive stimuli.

Fagen and Rycek (1980) examined the effects of EH using male and female Long-Evans hooded rats on the response to positive and negative contrast effects in the sucrose-licking paradigm and in open field testing. For handled litters, the mother was removed from the cage and the pups were individually placed into wooden compartments for 3 min daily between PND 2 and 22. Approximately on PND 101, they were given alternating 1-min access periods to two bottles containing either 32 % or 4% sucrose solutions. Measures of lick rate and latency to switch bottles revealed that both EH and NH rats exhibited contrast effects of equal magnitudes. The open-field test showed that, although both infantile treatment groups were equally active, NH rats defecated and urinated more on each of the four open-field days than EH rats. The experimental design employed in this work was simultaneous contrast, which involves sensory adaptation mechanisms (Flaherty, 1996). Therefore, early handling will most likely not have an effect on this type of response as it is not modulated by emotional processes.

Meinrath and Flaherty (1987) handled preweanling male Sprague-Dawley rat pups during 3 min daily from PND 2 to15. The subjects were subsequently evaluated during adulthood in open field, cSNC, and neophobia tests. They observed that EH rats reared and ambulated more, and defecated less than NH subjects (i.e., EH rats exhibited lower emotionality than NH rats). However, the handling manipulation had no effect on the size of the cSNC effect after a shift from 32% to 4% sucrose and did not influence sucrose neophobia in two different test situations.

Finally, de la Torre et al. (2008, unpublished work) tested handled and nonhandled rats in the elevated plus maze, cSNC, and iSNC. They reported that nonhandled rats were more fearful than their handled counterparts in the elevated plus maze. In iSNC, no significant differences were found between handled and nonhandled rats. In cSNC, no contrast effect was exhibited in either group during the first block of two postshift trials. Instead, in the second block (i.e., postshift Trials 3 and 4) only NH rats showed a negative contrast effect. It should be noted that (1) usually, the cSNC effect is observed with greater intensity in the first two postshift trials (Flaherty, 1996), but in this work there was no evidence of the effect on such trials (first block of 2 trials); and (2) as the difference between the EH and NH groups emerged in the second block (postshift Trials 3 and 4), EH might affect the recovery from the negative contrast. In any case, there are misgivings regarding this interpretation because, given the lack of negative contrast in the first two trials, how can it be argued that early handling accelerates recovery from cSNC? In sum, this is a positive result that could indicate some influence of early handling on cSNC, but it should be replicated with more animals and better measurements.

In conclusion, the EH manipulation does not seem to produce an alteration on the adult animal's response in situations involving surprising reward changes. The only study reporting positive results using cSNC should be replicated because there was no contrast effect in the first two devaluation trials, which thus contradicts the results obtained in earlier investigations into cSNC.

Chronic Random Neonatal Stress and Frustration

Sharing the basic thinking behind the early handling approach, some authors found that infant rats isolated during short periods of time from their litters and exposed to moderate and random aversive stimuli exhibited less emotionality in adulthood when subject to moderate or intense stressors (Toth, Avital, Leshem, Richter-Levin, & Braun, 2008). One of the procedures of chronic random neonatal stress (CRNS) consists of unpredictable and repeated stimulation from PND 2 to 15. Pups are daily separated from their mothers (between 6 and 10 h) and different stimuli are presented, including white noise, cold–heat exposure, handling, moderate electric shocks, and tail pinch (Ruetti, González, Justel,Torrecilla, & Mustaca, 2010). González, Rodríguez, Cabrera, and Fóscolo (1991) evaluated adult rats subjected to CRNS, handling, or controls in tests that involved exposure to aversive stimuli. Animals exposed to CRNS showed an attenuated increase in prolactin and corticosterone, and an improvement in a forced-swimming test, compared to EH and control conditions. However, EH was a less effective treatment than CRNS to reduce the behavioral deficit observed in the forced swimming test due to unpredictable electric shocks during the estrous cycle of female rats (González Jatuff, Rodríguez Echandía, Cabrera & Fóscolo, 1991). Considering that frustration triggers emotional states similar to those generated by aversive stimuli, it was hypothesized that CRNS might also modulate the emotional reaction produced by devaluation or omission of an expected reward. Ruetti et al. (2010) evaluated rats exposed to CRNS in cSNC and consummatory extinction (cE) situations. The latter consists of measuring the approach response to an empty tube after acquisition of the consummatory response to an appetitive solution (32% sucrose). Rats exposed to CRNS showed an attenuated cSNC effect and a faster cE (significant decrease in the time of contact with the feeder compared to the no CRNS group). These results suggest that previous research on the handling treatment was probably not strong enough to affect the animals´ frustration responses.

Maternal Separation and Negative and Positive Contrast Effects

Maternal separation (MS) consists of prolonged periods of maternal absence each ranging from 1 to 24 h during the early period of life. The reported effects of MS on adulthood appear to be less consistent

compared to the effects of early handling, probably because of the substantial variety of different experimental procedures across different laboratories in terms of duration, frequency, age of onset of the separation, and the choice of control group (e.g., Lehmann, Russig, Feldon, & Pryce, 2002; Rosenfeld, Wetmore, & Levine, 1992). Nevertheless, MS appears to "program" the functioning of the HPA axis. This manipulation was reported to yield a more severe outcome, opposing the effects of early handling and chronic random neonatal stress, including HPA hyper-responsiveness following stress (Plotsky & Meaney, 1993), increased emotionality (Kalinichev, Easterling, Plotsky, & Holtzman, 2002a), altered sensitivity to opioids (Kalinichev, Easterling, & Holtzman, 2002b), and impaired cognitive performance (Levine, 2005). However, two opposite behavioral phenotypes may result from similar neonatal MS protocols. One is characterized by hyperactive/impulsive behaviors in the open-field and defensive withdrawal tests (e.g., Arnold & Siviy, 2002; Braun, Kremz, Wetzel, Wagner, & Peoggel, 2003; Colorado, Shumake, Conejo, Gonzalez-Pardo, & Gonzalez-Lima, 2006; Kaneko, Riley, & Ehlers 1994). The other phenotype expresses hypoactive/anxiety-like behaviors in open-field, defensive withdrawal, and elevated plus-maze tests (e.g., Huot, Thrivikraman, Meaney, & Plotsky, 2001; Janus, 1987; Matthews & Robbins, 2003). The reason of these conflicting results are still unknown, nevertheless it was proposed that it is presumable related to genetic variations in the outcome of environmental influences (see Claessens et al., 2011).

Only one article on the effects of MS on frustration responses was found. Matthews, Wilkinson, and Robbins (1996) studied the effects of repeated MS of preweanling rats on responses to both primary and conditioned incentives in mature rats. The procedure consisted of separating pups on ten occasions spaced randomly between PND 5 and 20. On PND 21 the animals were housed in pairs by gender. When assessed during adulthood, it was observed that MS animals showed enhanced weight gain, a reduction in the immediate exploratory locomotor response to novelty in both sexes, and a decrease of locomotor responsivity to compound cues predictive of food reward in females (Experiment 1). When responding to different sucrose solutions, MS rats did not exhibit changes in either consummatory behavior or sucrose preference. In Experiment 2, the animals were evaluated in positive and negative contrasts. In each session of negative contrast, the animals had access to a 15% sugar solution for 2 min, and then to a 2% sugar solution for 2 min. In sessions of positive contrast, the animals had access to a 2% sugar solution for 2 min, and then to a 15% sugar solution for 2 min. The licking rate was measured every minute. The sessions were conducted 24-h apart. Before evaluating contrast effects, rats were given 3-min access to a 15% sugar solution (when measuring negative contrast) or 3-min access to a 2% sugar solution (when assessing positive contrast). The authors found that MS rats displayed increased negative contrast and attenuated positive contrast as compared to animals with no MS. The method used does not rule out that these differences may be due to carryover or sensory contrast. Therefore, even though the findings are interesting, they should be replicated to eliminate such confounding variable.

Social Isolation in Adolescence and Incentive Relativity

Many behavioral and neurophysiological changes occur during adolescence. These include an increased focus on peer-directed social interactions, novelty seeking and the pursuit of new sensations (see Spear, 2000), changes in the use of appetitive reinforces like food (e.g., Neumark-Sztainer et al., 2006) or drugs of abuse (e.g., Chen & Jacobson, 2012; Cuenya, 2006) and close proximity to incentive situations (see Ernst, Romeo, & Andersen, 2009). In rats, as in other species, adolescence is characterized by behavioral and neurochemical changes from PND 20 to 55 (Spear, 2000). During this period, there is an increase in social interaction and play behaviors with peers (Vanderschuren, Niesink, & Van Ree, 1996), in novelty-seeking and exploratory behaviors (Douglas, Varlinskaya, & Spear, 2003), in the release of gonadal hormones (Sisk & Foster, 2004), and in changes in mesolimbic dopamine function (Wahlstrom, Collins, White, & Luciana, 2010).

The social isolation procedure during adolescence in rats consists usually in socially isolating animals for a specific period of time with as little manipulation as possible. However, subjects keep visual, auditory, and olfactory contact with their littermates in the room (Weiss, Domeney, Heidbreder, Moreau, & Feldon, 2001). The behavioral and neuroendocrinological changes produced as a result of adolescent isolation are mainly observed when the treatment is applied from the first day of weaning until PND 30. Within the wide range of alterations noted during adulthood figure a decrease in social interactions; an impairment of inhibitory mechanisms and sensorimotor gating, shown in low latent inhibition and prepulse inhibition; hyperresponsivity to novel environments; cognitive inflexibility; dopaminergic hyperactivity in the nucleus accumbens (NAc); and glutamatergic and dopaminergic hypoactivity in the prefrontal cortex (Fone & Porkess, 2008). Other studies have shown that adolescent isolation produced alterations in the consumption of appetitive reinforcers during adulthood, like hyperphagia (Jahng, Yoo, Ryu, & Lee, 2012), increased preference for sucrose solutions (Hong et al., 2012), and changes in responsivity to food novelty (Hall, Humby, Wilkinson, & Robbins, 1997).

The impact of social isolation during adolescence on contrast effects has hardly been investigated. Shanab and Ralph (1979) compared adult male rats that were group-housed or isolated from weaning to adulthood in an iSNC situation and in an instrumental partial reinforcement extinction effect (iPREE) situation, using a runway. They found that housing conditions had no effect on the iSNC, but that only isolated animals showed the iPREE, which the authors interpreted as the expression of a higher level of emotionality or anxiety under such conditions. However, the study does not make a distinction between the specific effect of adolescent isolation and the possible effect of adult isolation. Adult isolation is also considered a stressor generating alterations in mammals, although its effects cannot be matched to social isolation since each one produces different patterns of deleterious consequences (Morgan & Tromborg, 2007). Cuenya, Fosacheca, Mustaca, and Kamenetzky (2011, 2012) showed that isolation in adulthood, from PND 60 to testing, did not affect the expression of cSNC, partial reinforcement effect on cSNC, or consummatory successive positive contrast (cSPC). These results suggest that the findings reported by Shanab and Ralph (1979) could be explained by the specific isolation during adolescence. In any case, the kind of design employed by Shanab et al. does not allow testing of this hypothesis.

Hall et al. (1997) showed a study with the same methodological problem. The authors compared adult male *Lister* hooded rats reared in isolation after weaning for eight weeks with rats housed always in groups, in connection with the consumption of sucrose solutions of different concentrations (0.7%, 2.1%, 7%, 21%, and 34%) presented in an ascending and descending order during 5-min trials. The authors concluded that the consummatory positive contrast was increased in isolated animals, while no differences were noted in the negative contrast. The study has yet another problem. Consumption trials were run every 25 min instead of every 24 h, as in standard incentive contrast procedures (e.g., Cuenya et al., 2011; Cuenya et al., 2012), so that differences might be due to a sensory after effect and not to a violation of expectation recovered through a memory process. Finally, the design used did not feature groups receiving the same incentive value throughout the training so as to determine the contrast effect. Therefore, these results do not allow for conclusive interpretations on how social isolation in adolescence affects the animals' response to shifts in reinforcements.

Finally, Cuenya, Kamenetzky, Tassone, and Mustaca (2010) assessed the effect of adolescent isolation in male Wistar rats on elevated plus maze responses, cSNC, cSPC, and cE. The animals were submitted to a period of social isolation from PND 21 to 36. From PND 37 until the end of the experiment, they remained grouped in their home cages, even when evaluated during adulthood. Adolescent isolation generated higher levels of locomotor activity, without affecting anxiety on the elevated plus maze. It also enhanced response to a surprising increase in reinforcement during adulthood, both when going from 0% to a 32% sucrose solution (Experiment 1), and from 4% to 32% (Experiment 2), showing a greater positive contrast, as in the work by Hall et al. (1997). At the same time, it was noted that the treatment did not alter either anxiety levels in adulthood or responses to incentive omission or devaluation in cSNC and cE, just as was reported for the iSNC by Shanab and Ralph (1979). The study, however, was devoid of methodological limitations that characterized

previous studies, allowing us to identify adolescence as a period in which, if certain chronic stressors such as isolation occur, long-lasting effects on responses to surprising reward change can be generated.

Conclusions

There is evidence that exposure to stress in early life produces a diverse range of developmental outcomes, including resilience to subsequent stressors encountered in adulthood. There are numerous investigations that analyze the neurobiological and behavioral effects of early experience on adulthood by means of procedures that apply aversive stimuli of varying intensity. However, the effects of early experience on adult behavior when exposed to surprising upshifts or omissions of appetitive reinforcers have hardly been investigated. Table 1 summarizes the research work that evaluated the impact of early experience on incentive relativity.

Table 1. *Early experience and frustration in rats.*

Early treatment	Procedure	Result	Reference
Neonatal clomipramine	cSNC	faster recovery	Ruetti et al. (2013)
Perinatal asphyxia	ID	minor devaluation	Galeano et al. (2011)
Litter size	Double runway	no effect	Amsel & Pennick (1962)
Early handling	iSNC (runway)	no effect	Daly & Rosenberg (1973)
Early handling	Simultaneous positive and negative contrast	no effect	Fagen & Rycek (1980)
Early handling	cSNC	no effect	Meinrath & Flaherty (1987)
Early handling	iSNC (runway)	no effect	De la Torre et al. (2008, unpublished)
Early handling	cSNC	small contrast effect (?)	De la Torre et al. (2008, unpublished)
Chronic random neonatal stress	cSNC	small contrast effect	Ruetti et al. (2010)
Chronic random neonatal stress	cE	facilitated extinction	Ruetti et al. (2010)
Maternal separation	cSPC	small positive contrast (?)	Mattews et al. (1996)
Maternal separation	cSNC	enhanced negative contrast (?)	Mattews et al. (1996)
Adolescent isolation	iPREE	no iPREE in grouped rats (?)	Shanab & Ralph (1979)
Adolescent isolation	iSNC	no effect (?)	Shanab & Ralph (1979)
Adolescent isolation	cSPC	enhanced positive contrast (?)	Hall et al. (1997)
Adolescent isolation	cSNC	no effect (?)	Hall et al. (1997)
Adolescent isolation	cSPC	enhanced positive contrast	Cuenya et al. (2010)
Adolescent isolation	cSNC	no effect	Cuenya et al. (2010)
Adolescent isolation	cE	no effect	Cuenya et al. (2010)

Note. Early experiences and frustration in rats. "?": controversial methods or results; cSNC: Consummatory Successive Negative Contrast; cSPC: consummatory Successive Positive Contrast; iSNC: instrumental Successive Negative Contrast; ID: Incentive devaluation; iPREE: instrumental Partial Reinforcement Extinction Effect; cE: consummatory Extinction.

There are only 12 papers with 19 studies on incentive relativity, of which seven had some methodological problems or lack of information that hinders proper interpretation, six obtained a negative result, and only five had positive results. It should be noted that negative results obtained in early work during the 1960s could be the reason for abandoning this line of research. Flaherty (1996), an author who contributed significantly to the study of incentive relativity, suggested based on negative results on the effects of early handling on cSNC that "the lack of usefulness of emotionality as a general concept does not exclude the

possibility that a particular emotion might be involved in contrast." (p. 90).

The hypotheses guiding these experiments were based on theories of emotional frustration that confirm the existence of a neurobiological and functional equivalence between the presentation of aversive stimuli and the devaluation of appetitive reinforcers (e.g., Amsel, 1992; Gray, 1987; Konorsky, 1964). Evidence accumulated over the years has supported these theories. The effect of the devaluation of appetitive reinforcers is modulated by genetic factors (Cuenya et al., 2012), by anxiolytic and analgesic drugs (Justel, Ruetti, Bentosela, Mustaca, & Papini, 2012; Pellegrini, Wood, Daniel, & Papini, 2005), by the application of aversive stimuli prior to reward devaluation (Ortega, Daniel, Davis, Fuchs, & Papini, 2011), by exposure to anxiolytic behaviors before devaluation (Freidin, Kamenetzky, & Mustaca, 2005), by pharmacological manipulations of emotional memory (Bentosela, Ruetti, Muzio, Mustaca, & Papini, 2006), by partial reinforcement (Cuenya et al., 2011; Pellegrini, Muzio, Mustaca, & Papini, 2004), and by exposure to open-field testing prior to reinforcement devaluation (Justel, Pautassi, & Mustaca, 2014), among other manipulations. It is possible that the parameters needed to obtain positive results have yet to be identified. This has been suggested in recent work by Ruetti et al. (2010) and Galeano et al. (2011), who found an attenuation of cSNC and a facilitation of cE in rats exposed to chronic random neonatal stress, an attenuation of cSNC in rats subjected to neonatal clomipramine treatment, and higher consumption in perinatal asphyxia rats. Moreover, the effects of early experience also seem to affect positive contrast, which is difficult to observe. There is at least one paper that reported a stronger positive contrast effect in animals exposed to adolescent isolation (Cuenya et al., 2010). The latter finding may encourage further research into the relationship between early experience and the response of adult animals to the surprising upshift or omission of appetitive reinforcers.

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