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Short-term but not long-term exposure to an enriched environment reduces unconditioned fear responses but not conditioned fear responses

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Abstract. Environmental enrichment (EE) has been shown to produce beneficial effects in animal models of a wide variety of neurological and psychiatric disorders. EE exhibits antidepressant function; reduces anxiety, improves spatial learning and memory impairment. EE can reduce sensitivity to loss of reward by reducing frustration-like emotional states and facilitates the extinction of conditioned fear. However, some studies related to the emotional effects of EE present controversial results such as reduction or increase in anxiety. The time of exposure to an enriched environment seems to be an important factor in the behavioral responses presented by animals subjected to aversive stimuli. The present study compared the effects of two and four week exposure to EE with young adult Wistar rats under the same conditions and protocol on fear behavioral parameters in the face of footshock (unconditioned fear) and on re-exposure to an environment after electrical shock pairing (conditioned fear). We showed that the EE with a duration of two weeks reduced the freezing response of the animals in an unconditioned fear situation, that is, with the aversive stimulus present in the environment, however, did not influence the same behavior in a conditioned fear situation. In addition, the short-term EE developed the locomotor and exploratory activity, identified by the high rearing behavior, which may also suggest a low level of anxiety in these animals. We can conclude that EE changes the unconditioned fear responses of young adult rats. In addition, the duration of EE interferes differently, being two weeks of treatment with EE sufficient to cause improvement in coping with unconditioned aversive situations. We suggest that the emotional benefits resulting from the welfare provided by EE can be abolished by the longer duration of this treatment, due to the already known effect of tolerance to lasting or abundant rewards.
Keywords: Environment; Memory; Emotion; Fear; Conditioning; Rats.

Introduction

Research has shown brain and behavioral neuroplastic changes in rodents submitted to environmental enrichment (EE). The enriched environment provides visual, motor, somatosensory, cognitive stimuli, in addition to favoring social relationships. It is believed that EE promotes plasticity in the hippocampus and cerebral cortex by providing an increase in neurotrophin levels (Ickes et al., 2000; Rossi et al., 2006), in cell proliferation (Kempermann; Kuhn; Gage, 1997; Faherty; Kerleya; Smeyne, 2003), in the dendritic branches and synaptogenesis (Faherty; Kerleya; Smeyne, 2003; Moser; Trommald; Andersen, 1994). EE causes histone acetylation and chromatin remodeling, regulating DNA activity and protein synthesis (Fischer et al., 2007; Pizzorusso; Berardi; Maffei, 2007).

EE has been shown to produce beneficial effects in animal models of a wide variety of neurological and psychiatric disorders, such as: Huntington's disease, Alzheimer's disease, Parkinson's disease (PD), stroke, traumatic brain injury, epilepsy, multiple sclerosis, depression, Schizophrenia and autistic spectrum disorders (Campêlo et al., 2017, Folweiler et al., 2017, Jungling et al., 2017, Leary et al., 2017, Shilpa et al., 2017, for review Nithianantharajah; Hannan, 2014).

EE exhibits antidepressant function in the CIS (chronic immobilization stress) model; reduces anxiety, improves spatial learning and memory impairment, restores hippocampal hypotrophy and the expression of BDNF, VEGF, GFRF, and GR (glucocorticoid receptors). Thus, EE improves cognitive deficits induced by stress, modulating the neurotrophic factors, astrocytes and glucocorticoid receptors in the hippocampus, frontal cortex and amygdala (Shilpa et al., 2017).

One study showed that EE can reduce sensitivity to loss of reward by reducing frustration-like emotional states and disappointment in rats (Burman et al., 2008).

On the other hand, considering that a significant loss produces a high degree of stress and compromises well-being in humans, and that current models of rodent stress involve the application of physical or psychologically aversive stimuli, but do

not address the concept of loss , a group of researchers developed a model of significant loss for rodents, involving the removal of long-term exposure to compensatory enriched environment. Removal of EE produces a behavioral and physiological phenotype with characteristics similar to depression, including helplessness, hypothalamic-pituitary-adrenocortical axis dysregulation, increased food intake and weight gain; and this phenotype was prevented by antidepressant treatment (Smith et al., 2017).

Emotions are automatic behavioral and cognitive responses, triggered when the brain detects a significant, positive or negative stimulus. Fear is the emotion best studied because it is so important for the survival of animals, and because of the availability of excellent experimental protocols (for review Blanchard et al., 2008; Brandão et al., 2003; Grupe, Nitschke, 2013, Ledoux, 2000; Ledoux, 2014; Tovote; Fadok; Luthi, 2015).

To develop innovative strategies to alleviate anxiety and depression disorders, neuroscientists are studying the substrates and neural mechanisms underlying fear and anxiety in animal models of normal and pathological brain function. One study showed that animals exposed to EE for two weeks had the extinction of conditioned fear facilitated (Lach et al., 2015). In this sense, considering that EE generates effects on emotional and motivational responses (Burman et al, 2008; Goes; Antunes; Teixeira-Silva, 2015; Lach et al., 2015), it is possible that environmental manipulation capable of bringing positive effects on emotional behavior, may favor the recovery of these disorders.

However, some studies related to the emotional effects of EE present controversial results such as reduction (Goes; Antunes; Teixeira-Silva, 2015) or increase in anxiety (Van De Weerd et al., 1994). These divergences of results can be related to the diversity in the variables that constitute the EE, emphasizing the need for a better understanding of these factors and their effects (Xie et al., 2013). The time of exposure to an enriched environment seems to be an important factor in the behavioral responses presented by animals subjected to aversive stimuli (Leger et al., 2015).

In many species, a common pattern of fear responses includes withdrawal (avoidance or escape) from the danger, somatomotor immobility (freezing), a host of autonomic adjustments, such as changes in arterial pressure and heart rate as well as the release of stress hormones and hypoalgesia (Blanchard and Blanchard 1972; Iwata and LeDoux 1988). A good example of an aversive event that elicits these behavioral and physiological responses is footshock (Antoniadis; McDonald, 2001). When rats are presented to environments containing recurrent footshock stimuli, they exhibit behaviors with a high degree of aversivity (Curzon; Rustay; Browman, 2009).

Therefore, in the present study we opted to compare the effects of two and four week exposure to EE with young adult Wistar rats under the same conditions and protocol on fear behavioral parameters in the face of footshock (unconditioned fear) and on re-exposure to an environment after electrical shock pairing (conditioned fear).The results presented in this paper are from the training and the testing phase of a contextual fear conditioning test, as previously done (Antoniadis; McDonald, 2001).

Methods

Animals

Thirty-six male Wistar rats (300 to 500g) were used. They were 3 months old at the beginning of fear conditioning protocol. All animals were maintained in a room with 12h light-dark cycle and controlled temperature (20 ± 2ºC). Food and water were available ad libitum. Animals used in this study were handled in accordance with the Brazilian law (Law Number 11.794) for the use of animals in research, and all procedures were approved by the local ethics committee. All efforts were made to minimize animal pain, suffering or discomfort.

Housing conditions

Animals were randomly divided in three groups (n = 12): control (CTR); short-term environmental enrichment (EE2), kept under enriched conditions for two weeks; and long-term environmental enrichment (EE4), kept for four weeks. CTR rats were maintained in polypropylene cages (40 cm x 33 cm x 17 cm, 4 rats per cage) with sawdust bedding. Rats from EE group were continuously stimulated by the exposure to an environment consisting of plastic cage (55 cm x 38 cm x 30 cm, 6 rats per cage) provided with various objects of different shapes, sizes, colors, texture and materials (wood, plastic, metal, glass, cardboard) such as tunnels, colorful toys, light protected sites, nesting material, ramps and running wheels. Most of the objects and their location were renewed twice a week.

Experimental design

Animals from EE2 group were placed in enriched environment at 76 days old, and those from EE4 group were transferred at 62 days old. Rats were submitted to contextual fear conditioning test at 90 days old. Rats remained in EE until the end of the behavioral experiment. Animals were handled daily for 5 min during five days before the beginning of the behavioral test (Fig. 1A).

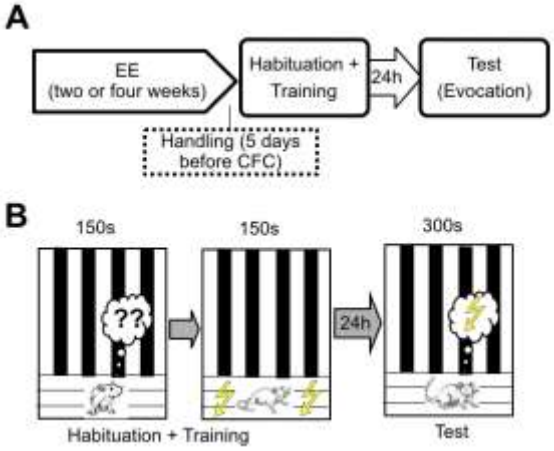

Figure. 1. Schematic representation of the experimental design. (A) Experimental outline. Animals were exposed to enriched environment for 2 or 4 weeks before the behavioral test begun until the end of the experiment. Animals were handled for 5 days before the beginning of the behavioral experiments. Animals were submitted to the behavioral task, composed by 2 moments intercalated for 24 h each. (B) Schematic illustration of the behavioral experiment. After 150 s of the habituation in the chamber, six sequential 0.3 mA footshock (2s each and 28s of interval each) was applied during training (conditioning) session and submitted to one 300 s evocation (Test) session in the same chamber (24 h of interval). EE: Enriched environment; CFC: Contextual fear conditioning.

Contextual fear conditioning

Contextual fear conditioning test (CFC) was used to assess unconditioned fear responses (Training session) and conditioned fear responses (Test session). Animals were subjected to Pavlovian conditioning. The floor of the conditioning chamber (22 x 22 x 25 cm) consisted of stainless steel bars throw which footshocks were delivered from a current source. The unconditioned stimulus (US) was electric footshocks and the conditioned stimulus (CS) was the apparatus internal environment (Ribeiro et al., 2010) whose internal walls consisted of stripes with alternating colors, black and white. The test was divided into two moments (five minutes each) performed sequentially at 24-hour intervals: Habituation + Training and Test (Fig.1B). In the Habituation + Conditioning (Training) phase, the animal was placed in the apparatus and after 150 seconds of habituation it received the first electric footshocks, initiating the conditioning (Fig.1B). In this stage, was realized a schedule of six 0.3 mA electric shocks (2s each) and intervals (28s) (Ribeiro et al., 2010). After 24 hours, animals were reintroduced into the apparatus, where they remained for five minutes without electric shock stimuli (Ribeiro et al., 2010). The apparatus was cleansed with 5% ethanol solution before the next animal was introduced. The phases of the behavioral test were recorded for later acquisition of number of ambulation, number of rearings behavior (standing on the hind legs) and the freezing time percentage, being the freezing defined by total immobility of the rat, except for the respiratory movements (Curzon; Rustay; Browman, 2009). The videos were submitted to evaluation of the animals behaviors using the ANY-maze program (Stoelting, USA).

Data analysis

To evaluate if there was conditioning, the means of freezing time percentages of the same group in habituation stage and test session was compared using a paired t test. One-way ANOVA followed by Tukey's post hoc test evaluated the freezing time percentages, number of ambulatory and rearing behavior counts in training session (coping with unconditioned aversive stimulus) and test session (conditioned fear expression). Results are expressed as mean ± S.E.M. and $p < 0.05$ was considered to reflect significant differences. Statistical analysis of data and graphing were done by Graph Pad Prism version 7.0 software

Ethical Principles

This study was submitted to the Ethics Committee on Animal Research of Federal University of Sergipe and was approved within the principles ethics and law.

Results and discussion

1. Effects of short- and long-term environmental enrichment on unconditioned fear responses

The EE influenced the defensive behavior of the experimental animals elicited by aversive stimulus (electric shock) present in the environment. Through the evaluation of the parameter freezing time in the training phase of the CFC, we identified significant effects of this treatment [one-way ANOVA; $F(2.33) = 19.65$; $p < 0.001$]. The Turkey's post-test showed that EE2 group presented a lower freezing time when compared to CTR [$p < 0.001$] and EE4 [$p < 0.001$)](Fig. 2).

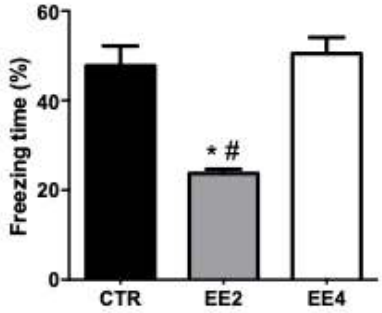

Figure. 2. Effects of short- and long-term enriched environment in the unconditioned freezing response. Data are expressed as mean ± S.E.M. n = 12/group. *p < 0,05 when compared to CTR; **#**p < 0,05 when compared to EE4. One-way ANOVA followed by Tukey's post-test. CTR: Control; EE2: Enriched environment for 2 weeks (short-term); EE4: Enriched environment for 4 weeks (long-term).

Regarding rearing behavior in CFC training, we detected a significant effect of EE treatment [one-way ANOVA; F (2.33) = 45.24; p <0.001]. The Tukey post-test showed that the EE2 group performed a greater number of rearings behavior than the CTR [p <0.001] and the EE4 [p <0.001] (Fig. 3A). However, there was no statistically significant effect in relation to the ambulation behavior [One-way ANOVA; F (2, 33) = 0.04; p = 0.963] (Fig. 3B).

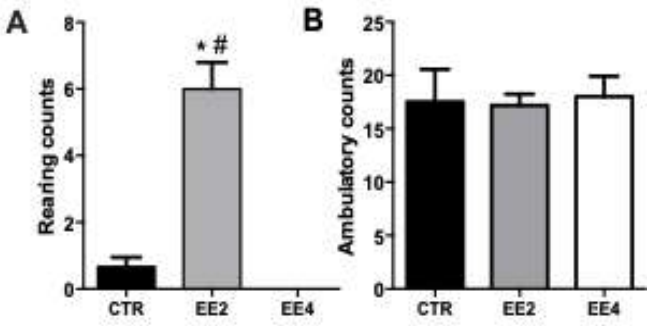

Figure 3. Effects of short- and long-term enriched environment in the number of rearing and ambulation behavior during aversive stimulation. Data are expressed as mean ± S.E.M. n = 12/group. *p < 0,05 when compared to CTR; **#**p < 0,05 when compared to EE4. One-way ANOVA followed by Tukey's post-test. CTR: Control; EE2: Enriched environment for 2 weeks (short-term); EE4: Enriched environment for 4 weeks (long-term).

2. Effects of short- and long-term environmental enrichment on conditioned fear responses

Paired t test revealed the efficacy of the conditioning proposed by CFC to the three groups [Ctr: t = 12.64, p <0.001, Habitation= 2.40$\pm$0.38, Test= 56.70$\pm$4.62; EE2: t = 15.10, p <0.001, Habitation= 0.11$\pm$0.34, Test= 63.89$\pm$4.24; EE4: t = 17,93, p <0.001, Habitation= 3.59$\pm$1.01, Test= 66.62$\pm$3.40].

We evaluated the expression of the conditioned fear responses by comparing the groups in the test session, and no significant difference was found between the means [ANOVA de uma via; F (2, 33) = 1.55; p = 0.228] (Fig. 4).

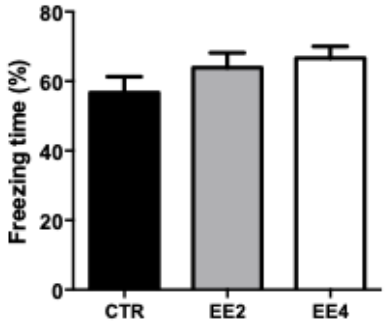

Figure 4. Effects of short- and long-term enriched environment in the conditioned freezing response. Data are expressed as mean ± S.E.M. n = 12/group. One-way ANOVA followed by Tukey's post-test. CTR: Control; EE2: Enriched environment for 2 weeks (short-term); EE4: Enriched environment for 4 weeks (long-term).

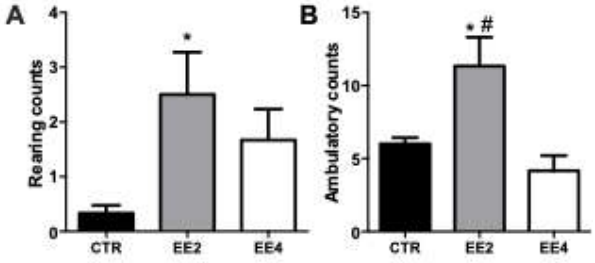

Figure 5. Effects of short- and long-term enriched environment in the number of rearing and ambulation behavior during the test session. Data are expressed as mean ± S.E.M. n = 12/group. *p < 0,05 when compared to CTR; #p < 0,05 when compared to EE4. One-way ANOVA followed by Tukey's post-test. CTR: Control, EE2: Enriched environment for 2 weeks (short-term), EE4: Enriched environment for 4 weeks (long-term).

The present study aimed to analyze the effects of EE on defensive behavior in conditioned and unconditioned fear situations. We showed that the EE with a duration of two weeks altered the defensive response of the animals in an unconditioned fear situation, that is, with the aversive stimulus present in the environment (Fig. 2), however, did not influence the same behavior in a conditioned fear situation (Fig. 4).

In rodents, freezing is a defensive response with high adaptive value and is usually performed in aversive situations related to fear and anxiety, involving conditioning or not (Vianna; Landeira-Fernandez; Brandão, 2001). The short-term EE leads to a lower expression of the unconditioned fear response to the footshocks triggered in the apparatus, it showed a shorter freezing time (Fig. 2). It may suggest a favoring effect in coping with fear when submitted to short-duration EE but not found when EE treatment has a long-duration.

In addition, the short-term EE developed the locomotor and exploratory activity, identified by the high rearing behavior (Fig. 3), which may also suggest a low level of anxiety in these animals. Shilpa et al. (2017) showed that daily exposures to EE for two weeks increase the number of rearing. On the other hand, studies involving EE with longer duration, two months (Ronzoni et al., 2016) or 12 months (Del Arco et al., 2007), show a reduction in the performance of this behavior.

The rearing is considered a spontaneous, motor and exploratory, vertical activity (Lacerda, 2006). Futhermore, there is an important discussion about the influence of anxiety on this behavior (Boergen-Lacerda; Souza-Formigoni, 2000). Pawlak and Schwarting (2002) showed that animals that present high exploratory activity in the open field are more responsive to novelty (they explore more new objects) and do not present alterations in sensitivity to psychostimulants, evidencing the separation between search for novelty and susceptibility to abuse of drugs. In addition, studies have shown that animals classified with low levels of anxiety present higher exploration behavior (Landgraf; Wigger, 2002; Steimer; Driscoll, 2005). Besides that, another study showed that novelty and avoidance of damage are independent behavioral parameters (Ray; Hansen, 2004).

Therefore, it is possible that the greater exploratory activity of the short-term EE is indicative of reduction in the anxiety-related responses.

Science highlights two main patterns of coping styles or reaction to stressful conditions. In the case of rodents, we distinguish between proactive and reactive coping, which refer to patterns of alternative responses in response to stable challenges over time or in various situations (Koolhaas et al., 1999; Copens, Boer, Koolhaas, 2010). Animals with a proactive coping style are characterized by a greater motivation to take risks in the face of potential dangers and to look for novelties (David et al., 2004; Steimer; Driscoll, 2005). Reward-seeking and exploration provide evolutionary advantage, widen the spectrum of available rewards, and thus improve the chances of survival, reproduction and gene propagation (Schultz, 2015).

In this sense, it can be seen that the short-term EE can generate important emotional effects that alter the motivated behavior of the animals in the presence of aversive stimulus, reducing the freezing behavior and improving the exploratory behavior (Fig. 2 and 3). It suggests that short-term EE changes the coping style of animals, making them more proactive.

Steimer and Driscoll (2003) showed that rats of the Roman strain can be selected in high (RHA) or low (RLA) avoidance animals for good or poor performance in the active avoidance test, and are classified with proactive and reactive psychobiological profiles, respectively. According to these authors, RHA rats adopt active coping styles and are less sensitive to stress, additionally they show little anxiety in novel situations and tend to be novelty- and reward-seekers.

Expression of conditioned fear was assessed in a session after 24 hours of conditioning. We identified that the animals of the three groups formed aversive memory, as there was a significant increase in the freezing time presented in the evocation session when compared to the time presented in the habituation session. We observed

that the animals of the three groups were able to recover memory in a similar way, there was no significant difference in the freezing times expressed by the groups in the test session (Fig. 4).

Freezing can arise in response to conditioned fear and can last from seconds to minutes, depending on the intensity of the aversive stimulus, the number of presentations, and the degree of learning attained (Curzon; Rustay; Browman, 2009). The persistence of memories of disturbing experiences has an adaptive value because it increases the likelihood of recall of information about warning or traumatic events at moments when such memories may be decisive for survival. On the other hand, the flexibility of memory through several forms of forgetting and distortion also allows the brain to adapt to the physical and social environment (Kandel et al., 2014). A characteristic difficulty of many psychological disorders, such as anxiety and depression, is the inadequate cognitive interpretation of situations and events (Phelps; Ledoux, 2005). This highlights the importance of aversive memory extinction.

One study showed that animals exposed to EE for two weeks had the extinction of conditioned fear facilitated (Lach et al., 2015). Considering that in our study only the short-term EE altered the unconditioned fear response, it would be interesting to carry out research to assess whether the beneficial effect of the short-term EE identified by Lach and collaborators (2015) is also evidenced with long-term EE.

Interestingly, animals of the short-term EE group showed higher locomotor and exploratory activity in the CFC test session (Fig. 5). Therefore, it is possible that in addition to the emotional benefits that the short-term EE brought in coping with unconditioned aversive situations, it may also happen after conditioning, as evidenced by increased locomotor and exploratory activity. The long-term EE did not have the same effect in this behavior. One research identified that three weeks EE generated anxiolytic-like emotional effects and improved passive avoidance (aversive memory) performance, however, a five-week EE did not provide these effects, although both benefited the memory of recognition of objects (Leger et al, 2015), showing beneficial emotional effects only in the short-term treated animals.

Coppens; Boer and Koolhaas (2010) argue that coping variations are related to different levels of dopamine in the mesocorticolimbic system, so possibly the early stage EE (short-term EE) causes changes in dopamine release or sensitivity in the via the mesocorticolimbic.

Possibly, the persistence of EE (as presented with four weeks EE) results in tolerance to the emotionally competent stimuli of EE, considering that this treatment can generate rewards stimuli, since as discussed by Burman et al. (2008) EE provides well-being. Although rewards stimuli provide benefits, tolerance to these stimuli may occur to avoid over-searching (Spruijt; Bos; Pijlman, 2001). However, this result does not mean that EE persistence does not continue to promote other cognitive enhancements, other than emotional.

Conclusion

We can conclude that EE changes the unconditioned fear responses of young adult rats. In addition, the duration of EE interferes differently, being two weeks of treatment with EE sufficient to cause improvement in coping with unconditioned aversive situations.

In addition, we suggest that the emotional benefits resulting from the welfare provided by EE can be abolished by the longer duration of this treatment, due to the already known effect of tolerance to lasting or abundant rewards.

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