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# Enriched environment (EE): immediate and long term effects on spatial memory

# Enriquecimento ambiental (EA): Efeitos imediatos e a longo prazo sobre a memória espacial

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**Abstract**

Environmental factors seem to play an important role in terms of mental and functional/behavioral plasticity, either in humans or other animals. The application of different methods in terms of environmental enrichment generates long-term physiological and behavioral effects. This research verified the immediate and long-term effects of environmental conditions through the application of environmental enrichment (EE) protocol on the spatial memory of mice. At the 70$^{th}$ day of their lives, animals were tested on Morris' Labyrinth (ML) and it was observed that the group subjected to EE had a better performance locating the submerged platform at the ML than the group not subjected to EE. After completing 120 days of life, without being submitted to EE, both groups were retested at ML and, was featured that, although the average time of the group not subjected to EE had been twice than in the group subjected to EE, this difference was not statistically significant. The data indicates that EE improves the performance in terms of spatial memory, an effect that, despite decreasing when the subject is no longer submitted to EE, lasts for long terms.

**Keywords:** environmental enrichment, plasticity, memory, aging.

**Resumo**

Fatores ambientais parecem desempenhar um papel muito importante em termos de plasticidade cerebral e funcional/comportamental, tanto em seres humanos como em outros animais. A aplicação de diferentes métodos em termos de enriquecimento ambiental geram efeitos fisiológicos e comportamentais a longo prazo. Neste estudo foram verificados os efeitos imediatos e a longo prazo de condições ambientais mediante a aplicação de um protocolo de enriquecimento ambiental (EA) sobre a memória espacial em ratos. Ao completar 70 dias de vida os animais foram testados no Labirinto de Morris (LA) e foi observado que o grupo de animais submetido ao protocolo de EA teve melhor desempenho para localizar a plataforma submersa no LA do que o grupo não submetido a EA. Após completarem 120 dias de vida e, sem mais serem submetidos a EA, os dois grupos foram novamente testados no LM e, foi constado que, embora o tempo médio do grupo não submetido a EA tenha sido o dobro do tempo do grupo submetido a EA, essa diferença não foi estatisticamente significante. Os dados indicam que o EA favorece o desempenho em termos de memória espacial, efeito este que, no entanto, apesar de diminuir quando os sujeitos não mais são submetidos a EA, perdura por longo prazo.

**Palavras-chave:** enriquecimento ambiental, plasticidade, memória, envelhecimento.

## Introduction

The body works as a whole in a dynamic relation with the environment (Goldstein, 1935, 1995). According to Bueno (1997) the reactions caused by stimuli are determined not by the physical particularities of the situation, but by behavioral biological laws because he proposes that, for the body, the stimulus is not limited to the externally defined physical characteristics. For Bueno (1997, p. 166), the stimulus "involved in 'causal texture' of organism-environment relationship is not specified only by a physical characteristic defined externally, but as part of a processing." This stimulus-environment relationship not only contributes to the development of behaviors that ensure the adaptation, but also shapes the neural circuit of the body. In a dynamic sense, when it is adapting to the environment or modifying the environment, the organism changes its own structure. Considering these assumptions, this research aims to investigate the immediate and long-term effects of environmental conditions through the application of an environmental enrichment (EE) protocol on the spatial memory of mice.

## Plasticity, memory and aging

Literature about the relationship between plasticity and aging has indicated that the plasticity of the nervous system and cognition are impaired during normal aging. Cognitive functions that depend on the medial temporal lobe and prefrontal cortex, such as learning, memory and executive function, show considerable decline with aging. Thus, functions related to these areas are vulnerable during the aging process (Burke & Barnes, 2006). It is noticeable that during the aging process there is reduced density especially in the prefrontal and parietal cortex. Moreover,

these regions show an activity increased during this phase. For Greenwood (2007) the adult brain is plastic, that is, during the aging process changes also occur in terms of cortical representation. Thus, the cognitive aging reflects not only the loss, but also adaptation to the loss. In other words, cognitive aging brings changes in terms of processing strategies. For Mora, Seovia and Arco (2007), the neural plasticity is still present in the brain over the aging. These authors suggest that aging is a physiological process that occurs asynchronously in different brain areas. According to them, the rate of this process in different cortical areas is modulated by environmental factors. Thereby they postulate that EE has effects, especially in neurogenesis and extracellular concentrations of glutamate and GABA, and the hippocampus, on concentrations of dopamine, acetylcholine, glutamate and GABA.

A long time ago, Bromley (1958) stated that with aging there is a decrease in memory processing. According to him, there is a reduction in terms of encoding, maintenance and retrieval of new information after a certain time interval. More recently, reviewing the literature about the subject, Light, Prull, LaVoie and Healy (2000) conclude that there is strong evidence that the recall declines with age. Salthouse (1993, 1995, 1996) suggests that cognitive aging effects can be explained by the reduction in processing speed, characteristic of aging. The author also suggests that there is evidence that the decline of memory would be separable from a more general decline in age-related cognitive function (Salthouse, 2000; Salthouse, 1999). Similarly, Park *et al*. (2002) observed that, during normal aging, there is a continuous decline in tasks that involve processing speed, working memory, and long-term memory. Moreover they observe that the verbal knowledge increases in all stages of the

life cycle and there is little differentiation in cognitive architecture.

Regarding spatial memory, Smith and Park (1990) found a lower performance in elderly individuals. Also regarding spatial memory, Denney, Dew and Kihlström (1992) observed that subjects had difficulties in screen quadrant recall tasks in which a word had previously been presented. With respect to the route, faces and images memory, the worst performance was observed in the elderly in urban routes memory (Lipman & Caplan, 1992), faces memory (Crook & Larrabee, 1992) and for complex scenes memory (Frieske & Park, 1993).

Studies carried out by Craik and Byrd (1982), Craik, Byrd, and Swanson (1987) and Craik (2005) outline three factors as determinants in the performance of episodic memory in the elderly: real decline in episodic memory itself; individual processing capacity, and level of environmental support provided during the recall. Regarding environmental support volume, Craik, Byrd, and Swanson (1987) concluded that when there are external cues, the damage caused by age are slightly lower when provided evoking stimuli, and even lower under recognition conditions where are provided clues. An interesting feature of the effects of age on memory recognition is that older people seem to have a much better performance in the recognition of the occurrence of an item than about the context where the memory occurred (Park & Puglisi, 1985; Chalfonte & Johnson, 1996).

Despite the lower efficiency of encoding and retrieval processes, Perlmutter *et al*. (1981) claim that the contents of our minds (our knowledge base) may continue to increase. Kramer and colleagues (2004) indicate, from an extensive literature review, that factors such as formal and informal education, leisure activities, intellectual engagement and physical activity act as a protective factor in relation to age-related cognitive decline. Thus, environmental influences

act on cognition and brain plasticity during adulthood.

**The effects of environmental enrichment (EE)**

Current studies in different fields of neuroscience have indicated that environmental factors appear to play a very important role in brain and behavioral plasticity, both in human and nonhuman animals (Cymerblit-Sabba *et al*., 2013; Moodie *et al*., 2013; Vazquez-Sanroman *et al*., 2013; Qiu *et al*., 2012; Bouet *et al*., 2011; Ali *et al*., 2009).

EE can be defined as a combination of social interaction, physical exercise and continued exposure to learning opportunities that, according to Krech, Rosenzweig, and Bennett (1963), can alter the structure and function of the rodents' encephalon. According to the literature, the EE has been reported as being related to housing conditions in boxes or exploratory cameras, where there is a facilitation of sensory, cognitive and motor stimulation (Rosenzweig, Krech, & Bennet, 1961, 2004).

The literature points to different types of research protocols for stimulation by EE. Generally, there are variations in box sizes, composition, duration, social complexity, stimuli by objects, and frequency of objects exchange. Some studies use the permanent maintenance of the animals in the enriched environment after an ischemic event, while others also use the previous stimulation (Biernaskie & Corbett, 2001). Still, there are studies that use the continued maintenance in the environment, while others use a stimulating protocol for a certain period of the day (Rampon *et al*, 2000a 2000b; Frick & Fernandes, 2003; Gobbo & O'Mara, 2004). The variety of EE stimulation protocols may hinder discussion and comparison of the effects of environmental enrichment on various aspects (Bennett *et al*, 2005).

Research conducted by the application of different environmental enrichment protocols (EE) pointed to significant improvements in the adaptation of captive animals to new situations. In general, these studies demonstrated improvements in cognition and emotion aspects. Some studies showed that animals submitted to EE in which there were devices which stimulated action, such as wheels and mazes, developed, more slowly, some pathologies, than animals that have not passed through EE, suggesting that the environment can be decisive in behavior and expression of some organic amendments (Pappas *et al*., 1992; Woodcock & Richardson, 2000; Tang *et al*, 2001; Pritchard *et al*., 2007; Zimmerberg, 2013). Other researches emphasizing the aspect of neural plasticity demonstrated that animals of different species show changes in the structure of the nervous system when experiencing changed environments; including significant changes in areas related to spatial memory consolidation (Renner & Rosenzweig, 1987; Rosenzweig, 1996).

It is generally agreed that the EE can generate neurochemical changes (Rosenzweig, 1996; Rosenzweig & Bennett, 1996). For example, Diamond, Krech, and Rosenzweig (1964) showed that the cortex of animals submitted to EE have greater thickness, compared to animals living in standard conditions. This cortical effect can occur by several factors, among them increased neuronal soma, number and length of dendrites and the number of dendritic spines.

More recently, Gobbo and O'Mara (2004) showed that the brain-derived neurotrophic factor (BDNF) had their levels increased in mice submitted to EE, compared to those that lived in standard conditions. It is important to note that the neurotrophic factor BDNF control intra- and intercellular signaling pathways that form neuronal circuits during development and regulate plasticity and neuronal survival, axonal growth and

neurotransmission in adult brain (Mattson, Maudsley, & Martin, 2004). BDNF has been proposed as an important factor related to the neuroprotective effects of EE. It is well established in the literature that there is an increase in BDNF levels after a stimulation period of enriched environment (Nithianantharajah & Hannan, 2006). The hippocampal neurogenesis has been associated with BDNF levels (Rossi *et al*., 2006). There is also evidence of the interaction of EE's protective effects in relation to oxidative stress. One study showed improvement in cognitive and motor functions of old mice by EE with the reduction of oxidative stress (Fernandez *et al*., 2004). Research has reported increased levels of synaptophysin (SBS), protein present in synaptic vesicles and neuronal differentiation marker, along with memory recall in elderly mice kept in an enriched environment (Frick & Fernandez, 2003). The SNF is a presynaptic calcium-binding protein localized in the presynaptic membrane vesicles containing neurotransmitters. Decreases in SNF levels have been associated with cognitive impairment due to aging and also neuropathological frames (Liu, Erikson, & Brun, 1996). Nakamura, Kobayashi, Ohashi, and Ando (1999) showed that the density of synaptic vesicles in the prefrontal cortex of mice gradually decreased with aging, but remained unchanged during senescence and that the EE exposure restored the age-related decline in the quantity of SNF, that is, the data suggest that there was a change of content of synaptic vesicles but without altering synaptic density. Thus, the EE may contribute to the occurrence of synaptic reinforcement. Steiner and collaborators (2005), using the experimental model of Parkinson's disease, found clues that EE, associated with the physical exercise, increases cellular plasticity. Will, Galani, Keiche, and Rosenzweig (2004) also reported that the EE associated with exercise and training

influenced the compensatory functional recovery process. Segovia *et al*. (2005), through research on animal model of brain injury, found that EE promoted increased neurotransmitter synthesis.

EE models developed for the study of mature central nervous system (CNS) plasticity after injury is a form of continuous stimulation that not only allows voluntary movement, but may also generate tactile and proprioceptive stimulation, essential to the animal's recovery. Thus, voluntary exercise, through exposure to EE, provides incentives to encourage voluntary movement early. The hypothesis of these studies is that these stimuli influence the nerve regeneration process, accelerating the maturation of the regenerated fibers. The results could suggest new alternatives for rehabilitation after peripheral nerve injury (Rosenzweig, Krech, & Bennet, 1961, 2004; Will, Galani, Keiche, & Rosenzweig, 2004). The compensatory functional recovery involves mechanisms aiming to restore the whole function or partially lost function due to an injury, both central and peripheral. The SNC reacts to exposure to new experiences through the formation of new circuits, balance neural turnover and the neuroprotective effect. These events reflect in structures beyond the CNS, providing improvement in motor and sensory deficits caused by brain lesions (Passineau, Green, & Dietrich, 2001; Will, Galani, Keiche, & Rosenzweig, 2004).

In general, we can say that EE provides opportunity for new sensory-motor experiences that improve the amount of integration between the central and peripheral nervous system. Animals exposed to EE are able to acquire new skills faster than the others. Furthermore, they become habituated quickly, changing its motor behavior. An attempt to reduce habituation is to replace or change, periodically, environmental devices that serve as a source of stimulation. Thus, the animals would be constantly under the

influence of new stimuli, and could remain for longer periods of time in these environments without habituation interfering with locomotion (Mello, Benetti, Cammarota, & Izquierdo, 2008).

Studies in mammalian and other species have shown that we can use EE to understand memories consolidation and learning facilitating in humans (Bailey & Kandel, 1993). To understand the consolidation of long-term memories in animal models, spatial memory processing has been investigated, which involves the ability to encode, store and retrieve information about spatial locations, settings or routes (Soares, Andrade, & Goulart, 2012; Kessels, Haan *et al*., 2001; Kessels, Hendriks *et al*., 2004). It is this function that allows remembering the location of objects or finding their way into the environment.

It is important to note that the hippocampal system is essential for spatial memory consolidation process of rodents (Eichenbaum, 2002) and primates (Brasted, Bussey, & Murray, 2003). According to the theory of cognitive mapping, the hippocampus encodes spatial relationships in the form of an allocentric cognitive map (centered in the world), which means that the representation is formed based on information of absolute location in our environment (both distance and direction), independent of the observer (Burgess, Maguire, & O'keefe, 2002). Thus, the memory space would have its operation based on this map (Xavier, 1993).

One of the most widely used assessment tools for spatial memory consolidation and learning has been the water-maze or Morris water maze (MWM) (Rossato *et al*., 2006). This (LAM) model, developed in 1982 by Richard Morris, had the initial aim of verifying evidence that spatial memory was different from other forms of associative learning (Morris, Garrud, Rawlins, & O'keefe, 1982). In practice, LAM mice have to learn to find and climb a platform (escape platform),

submerged in a tank with water. It should be noted that the water temperature and its variations are among the factors affecting the animal's motivation to climb the platform (Morris, 1984). Although animals cannot see, hear or feel the platform odor, they quickly learn, after some training, to swim towards the platform using the shortest path. For this purpose they use visual cues to / from the room to find the platform. As parameters to measure the performance of animals in LAM the following criteria were used: 1) Latency: time for the animal to find the platform; 2) Walked Space: distance traveled by the animal until he finds the platform, and 3) Average speed: relationship between the distance and latency (D'hooge & De Deyn, 2001).

**Mice and human ages**

In relation to mice age as compared to human animals' age, it is important to consider that mice exhibit faster growth during childhood. Sexual maturity occurs at about 6 weeks of age, whereas human puberty occurs around 12-13 years old (Krinke, Kaufmann, Mahrous & Schaetti 2000; Quinn, 2005). As adults, each month in mice corresponds to approximately 2.5 years in humans. Mice initiate menopause at 15-18 months of age, while human animals between 48 and 55 years old (Rat Behavior and Biology, 2012). According to Quinn (2005), the lab mouse, in an ideal environment, lives on average three years. If not properly handled, it tends to experience less than a year (Quinn, 2005; Rat Behavior and Biology, 2012). Experimental studies in mice indicate, in general, the following correspondence: 1 day of a mouse's life represents 30 days of life in human animal (Peckham, 1979; Gittes, 1986; Klee, Hoover, Mitchell, & Rink, 1990; Hayward, Zavanelli, & Furano, 1997). We also emphasize that there is no defined standard and simple pattern to make comparisons between mice and humans ages. The comparison results

may vary depending on the analyzed period of development - childhood, adolescence, adulthood, and so on - and the factors studied - cognition, obesity, sexual development, and so on (Gittes, 1986; Hayward, Zavanelli & Furano, 1997; Verneau , Catzeflis, & Furano, 1997; Quinn, 2005).

In terms of brain aging, Schaie (1989) notes that not all animals of the same age have the same neuronal loss rates. This indicates a large variation between animals in terms of neuronal loss with age, even considering proportional development tracks. Morterá & Herculano-Houzel (2012), studying the cellular composition of the brain in a group of *wistar* rats of different ages (1, 60, 90, 120, 150, 360 and 660 days), that is, from childhood through adolescence, adult age and elderly, concluded that the neuronal loss process starts in the late teens, namely around 90 days of age. The results indicated that between 1 and 2-3 months of age (adolescence) a large increase in the number of neurons occurs and that, after this phase, neuronal losses happen progressively and widely. Such losses become more evident between 12 and 22 months of age (Morterá & Herculano-Houzel, 2012).

## Materials and Methods

In this research 16 *wistar* males rats (*Rattus Norvegicus Albinus*) from the Biotério Central of Unesp from Botucatu SP were used. The subjects were randomly divided into 2 equally sized groups: experimental (EG) and control (CG) and arranged into standard polypropylene boxes in groups of 4 mice per box. The experiment started after the weaning, when the animals were 40 days of life. The subjects of CG were kept in their standard polypropylene boxes without any EE. The subjects of EG, after the 40th day of life, were submitted to EE protocol for 30 consecutive days. This protocol consisted to submit the EG subjects to EE for 2

hours/day, starting at 18:30, respecting the circadian cycle of rats. For the EE two open fields of 1.50 meters in diameter were used, arranged in an external environment outside the animal maintenance room where the subjects of experimental and control groups were kept at an average temperature of 22 celcius in standard polypropylene boxes in groups of 4 animals per box. In the open fields used for EE different objects were placed, from factory and manufactured by the researchers (Figure 1).

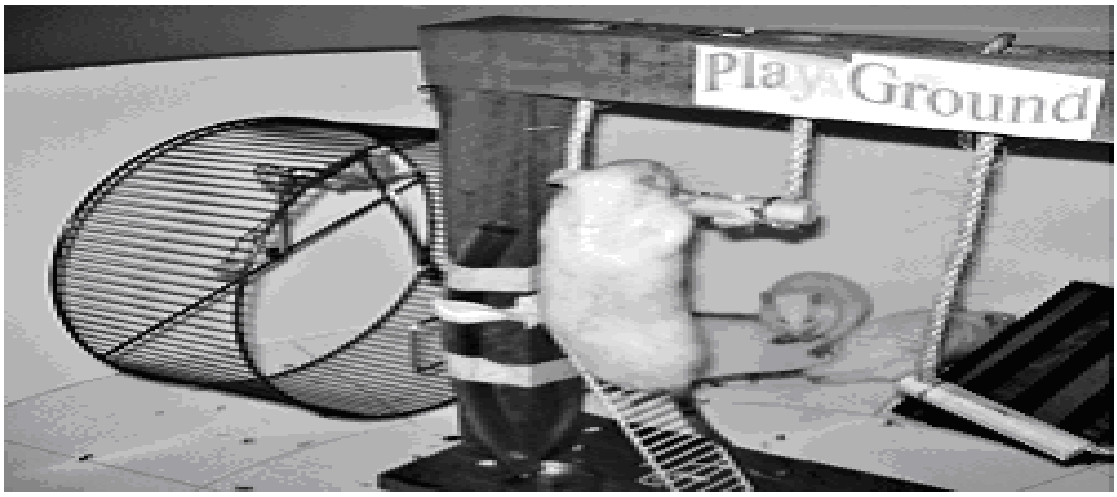


Figura 1: EA em campo aberto

**Figure 1**: EE in open field.

Some objects, called "toys" by the researchers, produced sound when moved. In each field there were 4 animals. Toys and members of each group were changed periodically. Other situations posed challenges for obtaining food, such as climbing on a platform, going through a "tunnel", touching a suspended object, and so on. In EE, sunflower seeds were used, as reinforce elements, and also administered to the control group during the experimental sessions. The EG and CG subjects were deprived of food 12 hours a day before the experimental sessions.

At the end of a 30 days, when the animals completed 70 days of life, the subjects from both groups underwent the test of LAM, as the following protocol: 1) Training: the subjects of the EG and CG were distributed by chance, randomized by order within the group (animal lottery). Each subject was individually placed in LAM with the muzzle facing the edge of the pool. At this moment a timer was triggered, starting at 90s, time in which the subject should find and climb the platform. Animals that failed to climb to the platform in an interval of 90s were kept in LAM for another 30s. The subjects who still have not found the platform were placed in there during 30 seconds and then removed from the LAM. After being removed from the LAM, subjects were dried with absorbent cloth towel and placed into separate boxes from other animals that have not undergone the training. Every 2 and half minutes new subjects were placed into the LAM for training, sequentially until the eighth animal. Five consecutive sessions were held. In each of these, subjects in the experimental and control groups were placed in different position in LAM, but always with the muzzle facing the edge and at an equidistant point of it. 2) Test: After 24 hours of training, animals in a single session were submitted again to the LAM and the latency time for the subjects of the EG and CG find the platform within 90 seconds was measured. After the test, all subjects were kept in the maintenance room in its polypropylene boxes with food and water available *ad libitum*; but without any stimulation or extra-daily activity until they reached 120 days. The test in LAM was repeated when the animals completed 120 days. The tests in LAM were filmed with a digital camera for later deliberation about the performance of the subjects. Data was statistically analyzed with t-Student's test for independent groups, adopting the 5% level of probability to reject the null hypothesis. The experiment followed the current legislation and the

standards established by the Brazilian College of Animal Experimentation (COBEA) that defines the principles of laboratory animal care (Guimarães; Mázaro, 2004; Institute of Laboratory Animals Resources, Commission on Life Sciences, National Research Council, 2003).

## Results and Discussion

The data indicate that, at 5 training sessions in LAM, when the animals completed 70 days, no statistically significant differences were observed between the EG, submitted to EE and the CG, not subjected to EE (Figures 2 and 3).

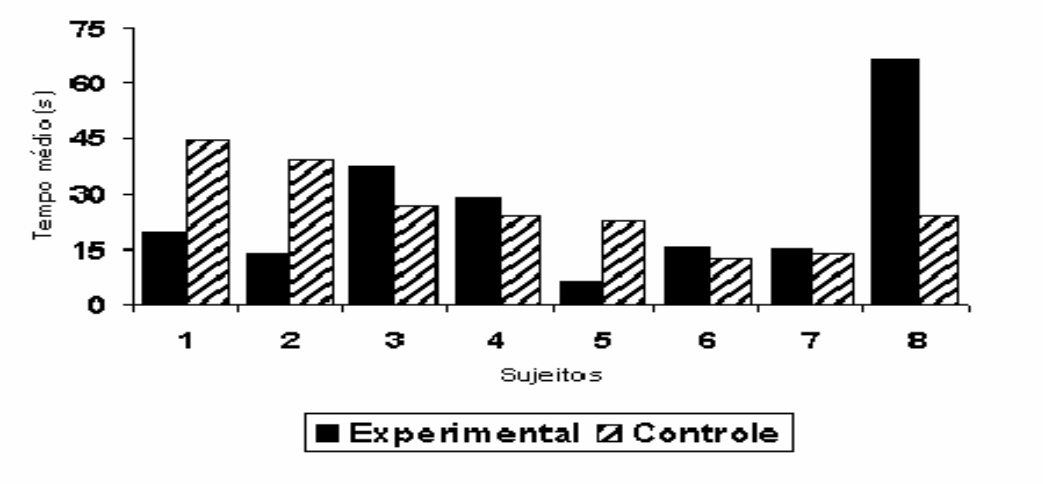


**Figura 2: Média do tempo, em segundos, de cada sujeito do GE e do GC durante o treino no LAM.**

**Figure 2**: Average time, in seconds, of each subject in the experimental and control groups during training at LAM.

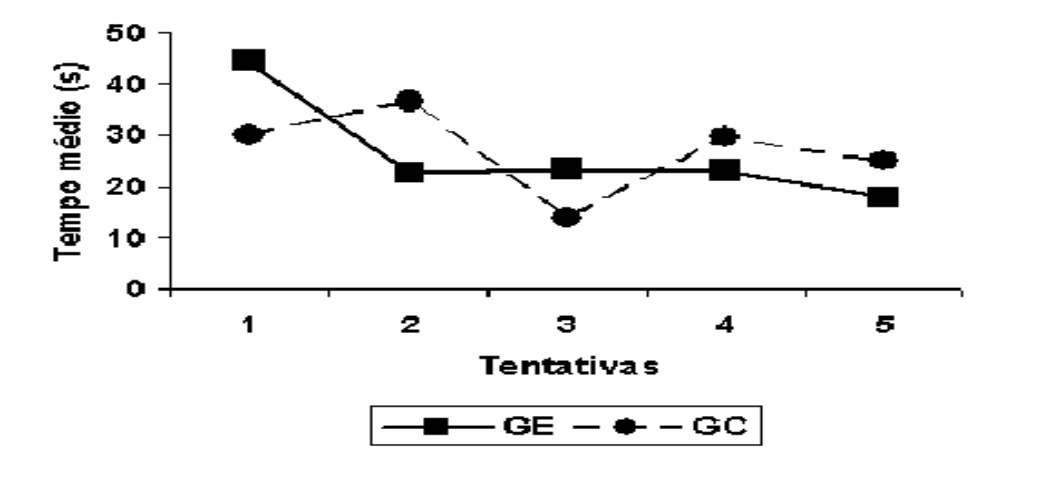


**Figura 3: Tempo médio, em segundos, do GE e GC em tentativas - treino no LAM.**

**Figure 3**: Average time, in seconds, of experimental and control groups in attempts - training at LAM.

The results obtained in the first phase of the experiment, when the subjects completed 70 days of life, indicated that the subjects of EG performed better in LAM. In other words, animals subjected to EE were faster in finding the submerged platform in the maze than the CG, not subjected to EE ($t = 2.4$, $df = 11$, $p = 0.035$) (Figures 4 and 5).

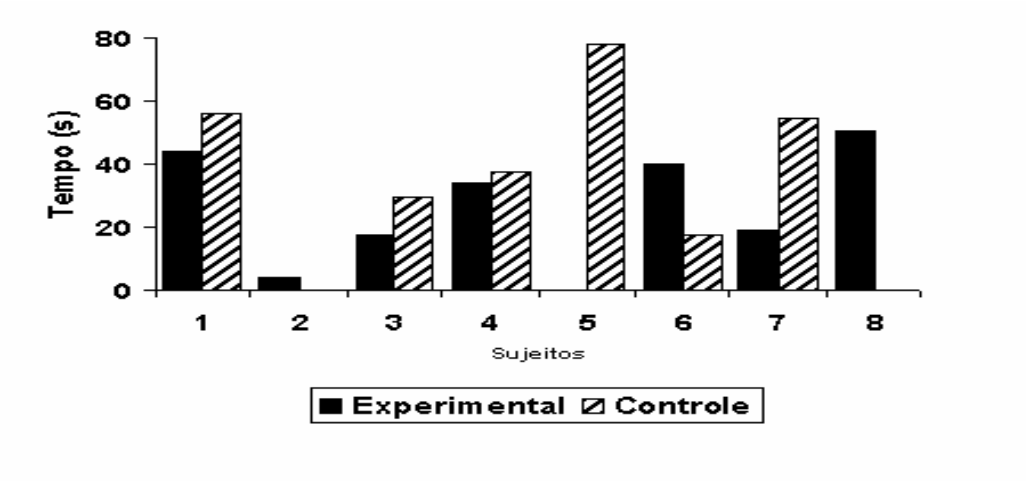


**Figura 4: Tempo, em segundos, de cada sujeito dos GE e GC no teste do LAM.**

**Figure 4** – Time, in seconds, of each subject from EG and CG in the test at LAM.

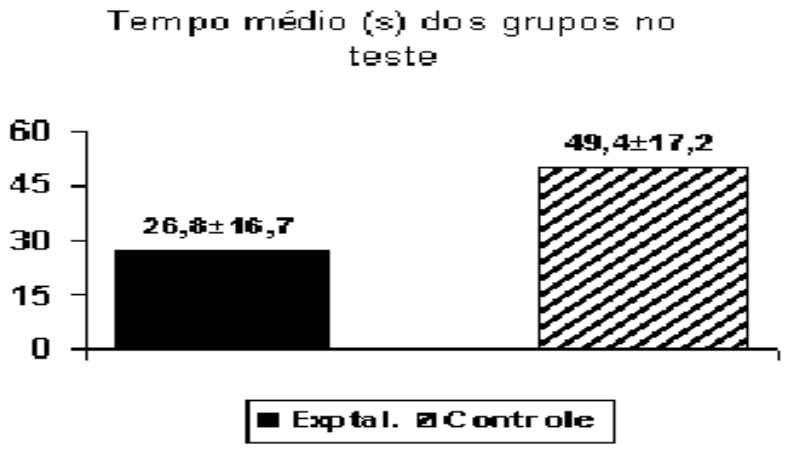


**Figura 5: Tempo médio do GE e GC no LAM.**

**Figure 5**: Average time from EG and CG at LAM.

In the second phase of the experiment, after the animals had completed 120 days, the test at LAM indicated that, although the average time to locate the submerged platform from CG (25.1 ± 16.3 sec.) had been twice the EG time (12.6 ± 11,2 sec.), this difference was not statistically significant ($t = 1.7$, $df = 13$, $p = 0.105$).

Before starting the discussion of the results we would like to point out that the evaluation of memory in the elderly is not easy because, in addition to relying on experimental condition (Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991), the exclusive use of correlational methods is due to the fact that many physical and intellectual abilities decline together as the body ages, making it difficult to assign a causative role to one over and above the other (Soares, Coelho, & Carvalho, 2012; Baddeley, Anderson, & Eysenck , 2009).

The data allows us to state that the EE promotes performance in terms of spatial memory, an effect which, despite decrease when subjects are no longer subject to EE, lasts for a long term, encouraging further research on neural plasticity and behavioral in senescence period. Although the research did not hold in physiological and histological results, and although the subjects were not tested during aging, the data from this study corroborates findings indicating that memory processing decreases with aging (Bromley, 1958; Light, Prull, La Voie & Healy, 2000), including in spatial memory processing (Denney, Dew, & Kihlstrom, 1992; Lipman & Caplan, 1992). This statement is based on the data indicating that mental functions such as memory, are associated with certain brain areas such as medial temporal and parietal lobes and prefrontal cortex (Burke & Barnes, 2006; Greenwood, 2007), particularly affected by aging (Liu, Erikson, & Brun, 1996; Nakamura, Kobayashi, Ohashi, & Ando, 1999) and in Morterá and Herculaneum-Houzel (2012) observations, indicating that neuronal loss, characteristic of aging in humans, begin in *wistar* rats approximately at 90 days.

The decrease in performance at LAM in the second stage of the experiment can be attributed to the reduction in terms of processing speed related to cerebral aging, as suggested by Salthouse (1993, 1995, 1996, 1999, 2000) and Park *et al*. (2002). However, despite

the reduction in performance and despite the subjects no longer be submitted to EE, the results point to the benefits of EE, as already indicated in the scientific literature, especially in Rosenzweig and colleague's works (Rosenzweig, 1996, Rosenzweig, Krech & Bennet, 1961, 2004; Diamond, Krech & Rosenzweig, 1964; Renner & Rosenzweig, 1987; Rosenzweig & Bennett, 1996; Will, Galani, Keiche, & Rosenzweig, 2004), as well as in other studies with different approaches (Pappas *et al*., 1992; Richardson & Woodcock, 2000; Biernaskie & Corbett, 2001; Tang *et al*., 2001; Fernandez *et al*., 2004; Globbo & O'Mara, 2004; Segovia *et al*., 2005; Nithianantharajah & Hannan, 2006; Pritchard *et al*., 2007; Zimmerberg, 2013). Thus, the data also indicates that environmental influences act on cognition and brain plasticity in adulthood and that the EE can function as a protective factor in age-related cognitive decline. Therefore, factors such as formal and informal education, leisure activities, intellectual engagement and physical activity throughout life are shown essential in terms of cognitive performance.

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