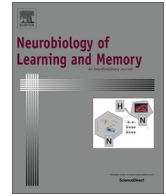




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Age-dependent effects of environmental enrichment on spatial memory and neurochemistry



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ABSTRACT

Although aging and environmental stimulation are well-known to affect cognitive abilities, the question of whether aging effects can be distinguished in already-mature adult rats has not been fully addressed. In the present study, therefore, young and mature adult rats were housed in either enriched or standard conditions (EE or SC) for three months. Open-field (OFT) and radial-maze (RM) behavior, and ex-vivo contents of GABA and glutamate in hippocampus, and of dopamine and DOPAC in ventral striatum (VS) were analyzed and compared between the four groups. In OFT, young rats were more active than mature adults irrespective of the housing condition. Surprisingly, in the RM test, mature adults outperformed young counterparts except for the young-enriched rats, which showed a progressive improvement in RM performance. At the neurochemical level, young EE rats showed higher hippocampal glutamate and GABA concentrations, and DA turnover in VS, which correlated with RM performance. Altogether, the behavioral and cognitive strategies underlying habituation learning and spatial memory seem to be qualitatively different between the two ages analyzed. These results challenge the assumption that mature adult animals are always worse in learning and memory tasks. However, young rats benefited more from the social and physical stimulation provided by the enrichment than mature adult counterparts. The latter effect was evident not just on behavior, but also on brain neurochemistry.

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1. Introduction

Environmental enrichment in rodents has been widely used as a model of experience-dependent plasticity in which mice or rats are housed in large cages where social interaction, object exploration and/or physical exercise are promoted (Van Praag, Kempermann, & Gage, 2000; Simpson & Kelly, 2011; Sampedro-Piquero, Begega, Zancada-Menendez, Cuesta, & Arias, 2013; Solinas, Thiriet, Chauvet, & Jaber, 2010). As a result of sensorimotor and cognitive stimulation, subjects in an enriched condition show enhanced spatial processing capabilities compared with animals housed in standard conditions (Harati et al., 2009). From a cognitive perspective, the latter effect may be attributed to the acquisition of spatial abilities promoted by the complexity of the housing environment, which may enhance procedural strategies, working memory, and reference memory (Leggio et al., 2005). Environmental enrichment

has been shown to affect not only memory processes but also emotional states (Brenes-Sáenz, Rodríguez, & Fornaguera, 2006; Schrijver, Bahr, Weiss, & Würbel, 2002). Thus, improvement in cognitive performance may also derive from a decreased emotional reactivity conferred by coping with the positive, mild stress of being housed in an enriched environment. Thus, reducing the deleterious consequences of impoverished rearing (e.g., in standard laboratory conditions) may facilitate subsequent learning in unfamiliar situations and contexts (Brenes, Rodríguez, & Fornaguera, 2008; Brenes-Sáenz et al., 2006; Schrijver et al., 2002).

Analyzing performance in spatial tasks has proven to be a good method to evaluate learning and memory in rodents (Bird & Burgess, 2008). Spatial cognition is generated by processing a variety of environmental cues, together with ambulation through that environment, allowing the individual to represent its location and movements in space (Bird & Burgess, 2008; Simpson & Kelly, 2011). The eight-arm radial maze (RM) test has been reported to be an appropriate tool to evaluate spatial working and reference memory, based on analyses of different types of errors that the subject commits (Carrillo-Mora, Giordano, & Santamaría, 2009;

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Leggio et al., 2005). Spatial working memory combines the storage of spatial information with central executive function during the time that this information is required to complete a task (Buchsbbaum & D'Esposito, 2008). The rat has to remember the location of food hidden in specific arms of the RM, avoiding previously visited arms that contain no food. Performance on this task indicates that rats have a spatial short-term memory for multiple places that improves its foraging strategy (Dudchenko, Talpos, Young, & Baxter, 2013; Olton, 1979). Spatial reference memory, on the other hand, involves long term memory acquired through a repetition of experiences. It has longer persistence, and greater resistance to interference than working memory (Buchsbbaum & D'Esposito, 2008). In the RM test, working memory allows efficient collection of reinforcers within each session, whereas reference memory is important for performance across multiple trials (Dudchenko et al., 2013).

Spatial working and reference memory have been associated with different brain regions. It is well known that the hippocampus (HPC) has a prominent role in spatial tasks, e.g., creating cognitive maps (Awh & Jonides, 2001; ÓKeefe, 1976, 1979). Moreover, there is evidence for a role of ventral striatum (VS) in learning and memory, specifically associated with motivation and reward (Bowman, Beck, & Luine, 2003; Lucas et al., 2004). A motivated learning process is characterized by the repetition of a rewarding behavior, and it has been linked with an increase in the activity of dopaminergic neurons in the VS (Eagle, Humby, Dunnett, & Robbins, 1999).

Aging has an influence on the decline of spatial functions because of the physiological changes that occur with aging in different brain regions (Carrillo-Mora et al., 2009; Harati et al., 2009). It is known, however, that increasing sensory stimulation that animals receive may counteract the effects of aging on cognitive performance (Simpson & Kelly, 2011). For instance, physical and social environmental enrichment increases neural plasticity (Van Praag et al., 2000), which in turn seems to prevent or delay the negative consequences of aging on learning and memory paradigms (Bennett, McRae, Levy, & Frick, 2006). The duration of environmental enrichment, and the age at which the animal is exposed for the first time to these environmental conditions, vary among studies, and these differences may critically affect the experimental outcome (Bennett et al., 2006; Harburger, Lambert, & Frick, 2007; Leggio et al., 2005; Soffié, Hahn, Terao, & Eclancher, 1999). Although many studies have explored the implications of aging and housing on cognitive abilities (Bennett et al., 2006; Bizon et al., 2009; Harburger et al., 2007), the question of whether aging effects can be distinguished in already-mature adult rats has not been fully addressed. The present study, therefore, investigated the effects of environmental enrichment in both young and mature adult rats on cognitive and neurochemical parameters relevant to spatial memory. In addition to studying memory using a reward-dependent paradigm, we included a non-associative task, the open field test (OFT), in which habituation learning can be easily assessed (Brenes et al., 2008; Simpson & Kelly, 2011). Typically, changes in exploratory activity (i.e., locomotion and rearing) between and within sessions in the OFT have been taken as indicators of such habituation processes (Brenes, Padilla, & Fornaguera, 2009; Brenes et al., 2008). Furthermore, the *ex vivo* contents of glutamate (Glu) and gamma aminobutyric acid (GABA) in the HPC were measured. Glutamatergic and GABAergic transmission have been strongly associated with behavioral and brain plasticity (Simpson & Kelly, 2011), especially in HPC-dependent memory tasks, such as the RM. Considering the prominent role of dopaminergic activity in the VS in instrumental learning and motivation, we also analyzed the contents of dopamine (DA) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) in this brain region.

2. Materials and methods

2.1. Animals and housing conditions

Seventy two male Wistar rats obtained from LEBi Laboratories (University of Costa Rica, San José) were randomly assigned to two groups of thirty six animals each, namely the young and mature adult groups ($n = 3-5$ per cage), which were transported to our colony room at post-natal day 21 (PND 21) and at PND 210 (7 months of age), respectively. After a week of acclimatization, animals in both age groups were then randomly distributed into two different housing conditions ($n = 18$ each): environmental enrichment (EE) and standard control (SC) conditions. All of the rats in the EE group were housed together in a specially designed box (120 cm length \times 70 cm width \times 100 cm height) containing non chewable plastic objects, PVC tubes, food dispensers and water bottles, which were rearranged at least twice a week as previously described by our group (Brenes & Fornaguera, 2008; Brenes et al., 2008; Brenes-Sáenz et al., 2006). SC rats, in contrast, were housed in small groups (3–5 rats per cage) in standard polycarbonate cages (55 cm length \times 33 cm width \times 19.5 cm height). All groups were maintained in their respective housing conditions for three months, with two bedding changes per week, food and water *ad libitum*, under a 12:12 h light–dark schedule (lights on at 6:00 h) in a climate-controlled room with 10 air cycles per hour, temperature at $25.5 \text{ }^\circ\text{C} \pm 1.20 \text{ }^\circ\text{C}$, and 78–87% relative humidity. One hour before behavioral testing, animals were placed in an adjacent dimmed room with red illumination (for OFT and RM test). Animals were tested between 8:00 h and 12:00 h in a pre-determined sequence (one rat of each group randomly assigned during all tests). One week after the last behavioral test, all animals were decapitated and their brains processed for further neurochemical analysis. All experimental procedures were done in accordance with the guidelines of the Costa Rican Ministry of Science and Technology for the Care and Use of Laboratory Animals and were approved by the Institutional Committee for Animal Care and Use of the University of Costa Rica. Particular care was taken to minimize the number of animals used and to reduce their suffering. One animal from the mature adult enriched group had to be discarded because of disease before the behavioral tests started.

2.2. Open field test (OFT)

The open field arena consisted of a black, square wooden chamber (55 cm \times 55 cm \times 40 cm). Single animals were placed in the center of the arena and behavior was scored during a 10-min session. Distance traveled (m) was automatically registered using the video tracking system ANY-maze (version 4.72, Stoelting Co., USA). Frequency and time of rearing behavior (posture sustained with only the hind paws on the floor) was manually scored off-line from video recordings using Etholog 2.25 software (Ottoni, 2000). Between subjects, the arena was cleaned with 70% alcohol solution. The OFT was carried out at three different time points for all animals: (1) one day before starting the housing conditions, as a baseline (OFT-1); (2) three months after housing, before the RM test (OFT-2); and (3) three weeks after OFT-2, one week before sacrifice (OFT-3). Animals were kept in their housing conditions during testing (Fig. 1).

2.3. Radial maze test (RM)

The radial maze procedure was conducted as previously described by Görisch and Schwarting (2006), with few modifications. Our radial maze, made of transparent Plexiglas, consisted of a central platform (46 cm diameter) with eight arms (60 cm long \times 15 cm wide and 30 cm high) radiating outwards. The appa-

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