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AGE-DEPENDENT EFFECTS OF ENVIRONMENTAL ENRICHMENT ON BRAIN NETWORKS AND SPATIAL MEMORY IN WISTAR RATS

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Abstract—We assessed the effect of 3 h of environmental enrichment (EE) exposure per day started at different ages (3 and 18 months old) on the performance in a spatial memory task and on brain regions involved in the spatial learning (SPL) process using the principal component analysis (PCA). The animals were tested in the four-arm radial water maze (4-RAWM) for 4 days, with six daily trials. We used cytochrome c oxidase (COx) histochemistry to determine the brain oxidative metabolic changes related to age, SPL and EE. Behavioural results showed that the enriched groups, regardless of their age, achieved better performance in the spatial task. Interestingly, in the case of the distance travelled in the 4-RAWM, the effect of the EE was dependent on the age, so the young enriched group travelled a shorter distance compared to the aged enriched group. Respect to COx histochemistry results, we found that different brain mechanisms are triggered in aged rats to solve the spatial task, compared to young rats. PCA revealed the same brain functional network in both age groups, but the contribution of the brain regions involved in this network was slightly different depending on the age of the rats. Thus, in the aged group, brain regions involved in anxiety-like behaviour, such as the amygdala or the bed nucleus of the stria terminalis had more relevance; whereas in the young enriched group the frontal and the hippocampal subregions had more contribution.
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Key words: environmental enrichment, spatial learning, cytochrome c oxidase, principal component analysis, ageing, Wistar rat.

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Abbreviations: Acb, accumbens nucleus; ANOVA, analysis of variance; BlA, basolateral amygdala; BST, bed nucleus of the stria terminalis; CA1, CA3, hippocampal cornu ammonis; CeA, central amygdala; Cg, cingulate cortex; COx, cytochrome c oxidase; DG, dentate gyrus; EE, environmental enrichment; HPA, hypothalamic–pituitary–adrenal axis; IL, infralimbic cortex; LS, lateral septal nucleus; LTP, long-term potentiation; MANOVA, multivariate ANOVA; MM, medial mammillary nucleus; PC, parietal cortex; PCA, principal component analysis; PL, prelimbic cortex; RAWM, radial water maze; RM ANOVA, ANOVA of repeated measures; RSC, retrosplenial cortex; SPL, spatial learning; SuM, supramammillary nucleus.

INTRODUCTION

Environmental enrichment (EE) is an experimental condition that consists of a combination of enhanced social relations, physical exercise and interactions with stimulating objects (van Praag et al., 2000; Würbel, 2001; Simpson and Kelly, 2011). EE is known to improve spatial memory and learning abilities (Leggio et al., 2005; Petrosini et al., 2009). For example, spatial reference memory is improved in adult rats (Nilsson et al., 1999) and mice (Kempermann et al., 1997; Williams et al., 2001) exposed to 1–3 months of EE relative to isolated or social controls. Other studies have also shown that non-spatial memories, such as object recognition and contextual fear conditioning are enhanced by EE (Rampon et al., 2000; Duffy et al., 2001; Tang et al., 2001). In aged rodents, EE also provides mnemonic benefits reducing the age-related deficits in numerous types of spatial memory tasks (Kempermann et al., 1998; Frick and Fernandez, 2003). These effects are probably due to a wide range of changes in critical brain regions for spatial memory (Leggio et al., 2005; Sale et al., 2009). According to this, EE has been shown to enhance the long-term potentiation (LTP), neurogenesis, dendritic spine growth and neurotrophin expression in the hippocampus (Moser et al., 1994; Ickes et al., 2000; Kempermann, 2002; Landers et al., 2011). Also, neural changes, such as dendritic branching, presynaptic vesicle number and density of dendritic spines are increased in neocortical regions by EE (Greenough et al., 1973; Nakamura et al., 1999; Leggio et al., 2005).

An important factor in the magnitude of these benefits is the age at which the EE condition is applied to the rodents; however, few researches have been carried out to study the effectiveness of EE at different ages. Recent studies suggest that the positive effects of EE on memory and neural function may start at some point in the lifespan (Frick and Fernandez, 2003; Bennett et al., 2006; Rosenzweig and Bennett, 1996). Thus, some studies found that the EE condition improved the spatial memory acquisition in aged rats (Speisman et al., 2013), whereas others did not find these positive effects, suggesting the existence of a critical period for the benefits of EE on cognitive ageing (Freret et al., 2012). On the other hand, it is possible that young animals benefit more from the EE condition because they interact more with the environment and they have

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more brain plasticity (Bouet et al., 2011). This variability of results may be due to the variability of the EE protocols, so the best design is to try to compare the different age groups within the same EE protocol (Simpson and Kelly, 2011).

We consider middle-age as a critical period in which the cognitive decline begins (Bizon et al., 2009) and the animals find it more difficult to solve a spatial allocentric associated task (Begega et al., 2012). Stimulating experiences, such as EE or aerobic exercise (Sampedro-Piquero et al., 2013) could have a high benefit in this age group compared to young rats. The results about the effect of EE during middle-age are contradictory. Freret et al. (2012) point out that EE needs to be initiated before middle-age in order to have a positive effect on cognition. In contrast, Kempermann et al. (1998) found that EE had a positive effect on the performance in the Morris water maze (MWM) in aged animals when EE was initiated during middle-age.

This study was designed to assess the effects of the age at which the animals start an EE protocol (3 and 18 months old) on the performance in a spatial memory task radial water maze (RAWM) and on brain functional networks involved in the spatial memory process. Cytochrome c oxidase (COx) histochemistry (Gonzalez-Lima and Cada, 1994; Gonzalez-Lima and Jones, 1994) was used to map sustained regional changes in neuronal energy metabolism in the different experimental conditions. We used quantitative analysis of COx histochemistry as a reliable marker of neuronal metabolic capacity, because COx activity represents an index of the energy demands after prolonged stimulation of neurons (Villarreal et al., 2002; Mendez-Lopez et al., 2009, 2013; Rubio et al., 2012; Sampedro-Piquero et al., 2013). To understand and differentiate brain networks establishing functional correlations between the brain regions of interest we used principal component analysis (PCA) applied recently in different types of studies, both in humans and animals (Cracchiolo et al., 2007; Salmon et al., 2009; Castilla-Ortega et al., 2010; Meunier et al., 2010; Begega et al., 2012).

EXPERIMENTAL PROCEDURES

Animals

A total of 37 18-month-old (593.5–700.3 g) and 41 3-month-old male Wistar rats (268.7–350.3 g) from the vivarium of the University of Oviedo were used. Subjects were housed in groups. All the animals had access *ad libitum* to food and tap water and were maintained at constant room temperature (20–21 °C), with a relative humidity of 65–70% and artificial light–dark cycle of 12 h (08:00–20:00 h. light/20:00–08:00 h. dark). The procedures and manipulation of the animals used in this study were carried out according to the Directive 86/609/EEC (The Council Directive of the European Community) concerning the protection of animals used for experimental and other scientific purposes. The National legislation, in agreement with this Directive, is defined in Royal Decree N°. 1201/2005. The young rats were 3 months old at the start of the experiment and 5 months old at the beginning of the spatial testing. The aged rats were 18 months old at the start of the experiment and 20 months old at the beginning of the spatial memory testing. All the animals were randomly assigned to eight groups: Young control group (5/CO, $n = 11$), Aged control group (20/CO, $n = 11$), Young spatial learning (SPL) group (5/SPL, $n = 10$), Aged SPL group (20/SPL, $n = 10$), Young EE group (5/EE, $n = 10$), Aged EE group (20/EE, $n = 8$), Young EE + SPL group (5/EE + SPL, $n = 10$) and Aged EE + SPL group (20/EE + SPL, $n = 8$). The CO groups were used as a reference of basal COx activity and consisted of animals without any learning or EE experience. The SPL groups were handled, habituated and trained in the 4-RAWM, like the EE + SPL groups. Finally, the EE groups performed the same EE protocol as the EE + SPL groups.

EE

Young and aged animals were housed separately in large cages of 100 cm × 95 cm × 54 cm (eight aged rats and 10 young rats per cage) for three hours every day (10:00 am/13:00 pm). It has been shown that even a restricted daily exposure to EE condition already produces a positive effect on stress response and cognition (Widman and Rosellini, 1990; Widman et al., 1992; Pereira et al., 2007). We ensured that we always put together in the EE cages the same group of rats and the stimulating objects were similar in the different cages. The rest of the day, the animals submitted to EE were housed in groups of five (young rats), or four (aged rats) rats in standard cages without stimulating objects. In this case, the distribution of the rats in the standard cages was random to ensure that all rats of the same age and experimental condition had lived together and so avoid possible fighting between them in the EE cage. EE cages contained a variety of objects, such as toys, running wheels, ropes, plastic tubes of different diameters, platforms, wooden houses, odorous and sound objects and nesting materials (Diamond, 2001). The configuration of the cages was changed once a week over a period of 2 months and the cages were cleaned twice a week to ensure the welfare of the animals. Video records were not taken throughout the EE condition; however, we observed the animals at different moments for 10 min (at the beginning of the condition, at the middle and at the end) to ensure that all the animals made the same use of the EE elements.

Behavioural procedures

Animals were handled daily for 5 days during 10 min (even the CO and EE groups that did not perform the spatial memory task) in order to avoid stress reactions to subsequent manipulation. One day prior to the spatial task, the SPL and EE + SPL groups received a habituation session in which they were given three trials with the platform using different starting positions in a small square water tank (47 × 75 × 38 cm). We applied a habituation session in order to habituate them to test

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