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Short communication

Exposure to an enriched environment up to middle age allows preservation of spatial memory capabilities in old age

Fanny Fuchs, Brigitte Cosquer, Lorène Penazzi, Chantal Mathis, Christian Kelche, Monique Majchrzak [1], Alexandra Barbelivien [*,1]

Laboratoire de Neurosciences Cognitives et Adaptatives, UMR 7364, CNRS, Université de Strasbourg, Faculté de Psychologie, Neuropôle de Strasbourg, GDR 2905 du CNRS, 12 rue Goethe, 67000 Strasbourg, France

HIGHLIGHTS

- Environmental enrichment until middle age preserves spatial memory of aged rats.
- Enrichment until middle-age is as efficient as whole adult life enrichment to preserve spatial memory of aged rats.
- Enrichment from middle age only mitigates age-related spatial memory decline.

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ABSTRACT

In rats, some cognitive capabilities, like spatial learning and memory, are preserved from age-related decline by whole adult life enriched environment (EE) exposure. However, to which extent late EE contributes to such maintenance remains to be investigated. Here we assessed the impact of late housing condition (e.g., from the age of 18 months) on spatial learning and memory of aged rats (24 months) previously exposed or unexposed to EE from young adulthood. The results showed that late EE was not required for spatial memory maintenance in aged rats previously housed in EE. In contrast, late EE mitigates spatial memory deficit in aged rats previously unexposed to EE. These outcomes suggest that EE exposure up to middle age provides a “reserve”-like advantage which supports an enduring preservation of spatial capabilities in old age.

Alteration of cognitive functions, particularly when memory is concerned, is not a systematic hallmark of physiological aging in both humans and rodents [1,2]. Emphasizing the importance of life experience in the maintenance of cognitive abilities during aging, several studies have shown that whole life enriched environment (EE) exposure mitigates or even prevents age-related decline of cognitive functions displayed by rodents exposed to standard condition (SC) [3–7,but 8]. EE exposure starting much later in life also has beneficial effects on cognitive functions of aged rodents [4,9–12,but 13]. However, aged rats exposed to whole life EE outperform aged rats exposed to EE later in life [4]. The question remains to which extent late EE exposure contributes to improved memory performances of whole life EE exposed subjects. To the best of our knowledge, this has never been investigated before. The aim of the current study was to assess, in a single experiment, the impact of a late EE exposure on spatial memory capabilities in aged rats previously housed in EE or SC. To this end, we used an experimental design in which rats were initially housed either in EE or SC from 2 to 18 months (“Initial” housing condition as first between-subject factor) and then either maintained in their previous housing condition or exposed to the other one from 18 to 24 months (“Late” housing condition as second between-subject factor). The age of 18 months was chosen to either maintain or change housing condition because spatial memory capabilities are declining at this age (e.g., Ref. [14]). Spatial memory of aged rats was assessed in a Morris water maze task, as our previous work showed that whole life EE exposure prevented place learning and memory from age-related decline in this task [6].

Five to six weeks old female Long-Evans rats purchased from Janvier Labs (Le Genest-St.-Isles, France) were housed in large transparent cages ($60 \times 38 \times 20$ cm) in groups of 8 for two weeks,

Abbreviations: SC, standard condition; EE, enriched environment; NK, Newman–Keuls.

* Corresponding author at: LNCA, UMR 7364 CNRS/Université de Strasbourg, 12 rue Goethe, 67000 Strasbourg, France. Fax: +33 368 851 958.
E-mail address: alexandra.barbelivien@unistra.fr (A. Barbelivien).

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then randomly assigned to their initial housing condition, SC or EE, as previously described [6]. In SC, pairs of rats were housed in transparent cages (46 × 26 × 15 cm). In EE, rats were housed in groups of 10–12 in wire-mesh cages (112 × 40 × 40 cm) with various objects (tunnels, toys, chains, etc.) changed five times a week. At the age of 18 months, the rats were assigned to their late housing condition: those housed in SC remained in SC (S/S) or were transferred in EE (S/E) and those housed in EE remained in EE (E/E) or were transferred to SC (E/S). Food and water were provided ad libitum. All rats were housed in the same animal facility with temperature (22 ± 1 °C) and humidity (55 ± 5%) controlled under a 12–12 h light–dark cycle (lights on at 8:00 a.m.). At the age of 24 months, rats were singly housed in transparent cages (42 × 26 × 15 cm) and transferred in another animal facility located near the experimental room. One week later, they were handled for 1 min/day over five consecutive days before the onset of behavioral testing. For the current study, all rats (n = 14 per group) were from the same cohort apart from seven rats of the S/S group which were from a cohort obtained 20 months later. For this group, data obtained were first compared then pooled, as no significant difference between the two cohorts was observed, whatever the variable analyzed. Experimental protocols and animal care were in compliance with the European Community Council Directive (2010/63/UE) and the current project was validated by the local ethical committee (CREMEAS, authorization no. AL/36/43/02/13).

The place learning task was identical to that previously reported in Harati et al. [6]. The rat had to learn to find a hidden platform (diameter 11 cm) located at a fixed position in the center of one quadrant of a pool (diameter 160 cm, height 60 cm) located in an experimental room with many extra-maze cues. A video-tracking system (Noldus, Wageningen, The Netherlands) was used to collect various aspects of the rat's behavior. During each of the five consecutive training days, it received four successive trials having different starting points in a randomized order. For each trial, the rat was given a maximum of 60 s to reach the submerged platform. After 10 s on the platform, the next trial began. When it failed to find the platform within 60 s, the rat was gently guided to it and left there for 10 s. Daily performances were assessed by computing the number of successful trials i.e., trials for which rat located the platform [15] and the distance swum to reach the platform corrected according to the method described by Lindner [16]. Twenty four hours after training, long term memory of the platform location was assess during a single 60-s trial without platform (probe trial). During this trial, several variables reflecting platform search accuracy were collected: the time spent in the quadrant where the platform was located during training (time in the target quadrant), the average distance to a zone covering the area of the platform enlarged by 10-cm (average distance to the annulus), and the number of crossings of this zone (annulus crossings). Swimming speed and thigmotaxis (i.e., the time spent swimming in the 10 cm peripheral part of the pool) were also analyzed. A visible platform task (four consecutive trials with a new platform location) was conducted the next day to assess whether some subjects displayed major motivational and/or sensory-motor bias. One rat of the S/S group failed to find the visible platform, and was thus discarded from all statistical analyses.

Data were subjected to analysis of variance (ANOVA) with "Initial" and "Late" housing condition as between-subject factors and, for training, "Day" as a within-subject factor. The ANOVAs were completed by post hoc comparisons using the Newman–Keuls (NK) multiple range test. For analysis of probe-trial performance, the time spent in the target quadrant was also compared to chance level (15 s) using a Student's t-test. The threshold for rejecting the null hypothesis was 0.05 throughout.

The impact of late EE on spatial learning abilities was assessed by measuring performance improvement during the five days

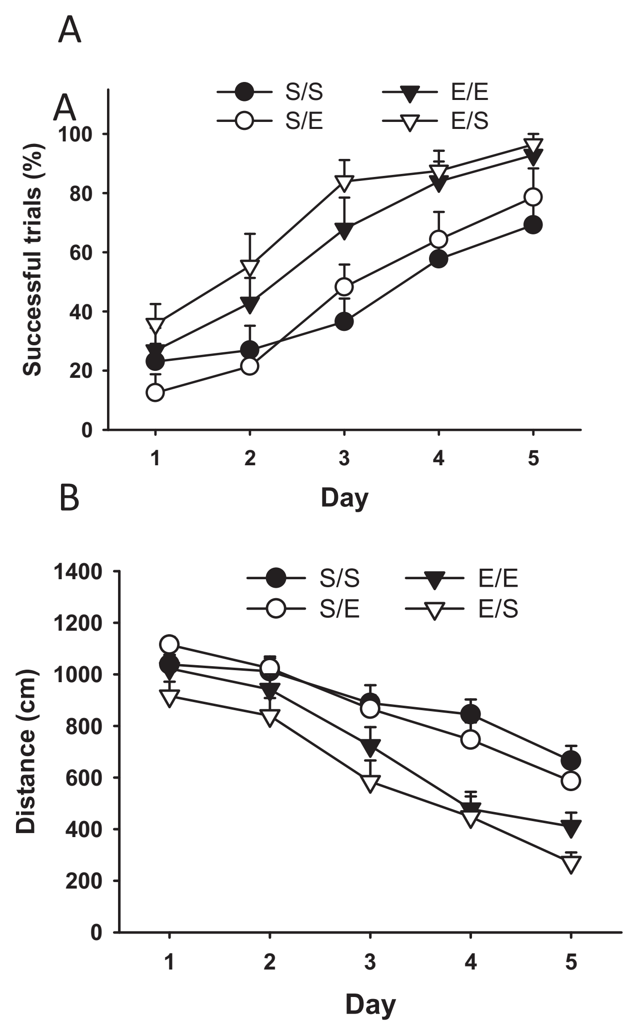

Fig. 1. Performances during the five training days (mean + S.E.M.). (A) Successful trials in percent of total trials. (B) Distance swum to reach the platform (mean of the four successive trials). For statistical description, see text. Group abbreviations are S/S for rats reared until 24 months in SC, S/E for rats reared from 18 to 24 months in EE, E/E for rats reared until 24 months in EE, E/S for rats reared until 18 months in EE.

of water maze training (Fig. 1). The overall number of successful trials (Fig. 1A) was higher in groups housed until 18 months in EE (E/E and E/S) than in those housed until 18 months in SC (S/E and S/S; "Initial", $F1/51 = 17.59$, $p < 0.0001$). In contrast, housing condition after this age failed to affect this performance ("Late", $F1/51 = 0.35$, $p = 0.55$), whatever the previous housing condition ("Initial" X "Late", $F1/21 = 1.07$, $p = 0.32$). Performance improvement throughout training was similar in all groups ("Day", $F4/204 = 73.59$, $p < 0.0001$ with day to day change, $p < 0.01$ at least; but no interaction of "Day" with the other factors: X "Initial", $F4/204 = 1.57$, $p = 0.18$; X "Late", $F4/204 = 1.01$, $p = 0.4$; X "Initial" X "Late", $F4/204 = 0.858$, $p = 0.49$). The analysis of the distance swum to reach the platform (Fig. 1B) confirmed that the rats housed until 18 months in EE (EE and E/S) outperformed those (S/E and S/S) housed until 18 months in SC ("Initial", $F4/204 = 81.92$, $p < 0.0001$; "Day", $F4/204 = 81.92$, $p < 0.001$; "Initial" X "Day" interaction: $F4/204 = 3.92$, $p < 0.01$). These two populations differed significantly from the third to the last day of training (NK, $p < 0.01$ at least). Housing condition from 18 to 24 months had no effect on performances of rats previously housed either in SC or in EE ("Late", $F1/51 = 0.84$, $p = 0.36$; "Late" X "Initial", $F1/51 = 2.02$, $p = 0.16$; "Late" X "Day", $F4/204 = 0.90$, $p = 0.46$; "Late" X "Initial"