



## Short communication

## Early environmental cues affect object recognition memory in adult female but not male C57BL/6 mice

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## ABSTRACT

We studied the effects of variations in maternal environment on maternal behaviour and offspring memory in mice by exposing lactating C57BL/6J dams to predator cues and/or environmental enrichment. At 10 weeks of age, object recognition memory in the offspring was assessed. The presence of enrichment in the maternal environment had no effect on offspring memory. In contrast, female offspring of dams that were not exposed to predator cues displayed a significant preference for the novel object ( $p=0.05$ ) and a significantly higher preference score (PS) than female offspring of dams that were exposed to predator cues ( $F=4.23$ ,  $p=0.05$ ) indicating an impairment in object recognition memory in the latter. Conversely, there was no evidence of object recognition memory in male offspring, except for males of dams exposed to predator cues without shelter ( $p=0.03$ ). These effects can be explained by an interaction between variations in maternal care and the stressfulness of the rearing conditions since a regression analysis revealed an inverse relationship between the level of licking–grooming and the PS, but only in female offspring reared by dams exposed to the predator cues ( $\beta=-0.96$ ,  $p=0.001$ ). The present findings thus provide some evidence that early rearing conditions may affect cognitive abilities of mice. The data also suggest that these effects may be sex-specific, and that females may be more sensitive to early environmental variations than males.

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## 1. Article outline

The characteristics of the postnatal environment affect the neural systems that regulate emotional and neuroendocrine responses to stress in several mammalian species (humans [12]; non-human primates [22]; rats [19]). Studies in rodents suggest a predominant role of maternal care in this process [13,19], even if recent evidence shows that other factors must contribute, such as environmental stress [7–9,15–17,24]. Other studies in rats and mice suggest an influence of the early life conditions on the developing hippocampus that may account for individual differences in cognitive function in adult life. Thus, low levels of maternal care or early maternal separation were associated with lower performance in tests of spatial learning and object recognition and with increased age-related learning impairments [2–4,11,14]. Recent evidence indicates that these effects occur when the adult offspring are tested under low stress conditions, whereas under stressful test conditions, low levels of maternal care resulted in enhanced hippocampal-dependent learning in the adult offspring [6].

In the biparental California mouse (*Peromyscus californicus*), Bredy et al. showed that changes in parental care, induced by environmental conditions (presence or absence of the father, neonatal handling), alter spatial learning and memory in the adult offspring in a sex-specific manner [5]. The aim of the present experiment, was to study the effects of early environmental and maternal cues on hippocampus-dependent cognitive abilities in a common inbred strain of mouse.

Forty adult multiparous female C57BL/6 mice derived from animals obtained from Harlan-Winkelmann (Germany) were used. Few days before delivery, dams were randomly allocated to four treatment groups ( $n=10$  per group) and placed in special cage systems until postnatal day (PND) 14. They were inspected once daily (at 1630h) for delivery, and day of birth was designated as PND 0. Litters were not culled and the dams and their litters were left undisturbed until PND 14 when they were moved to standard Makrolon type III cages. At PND 21, offspring were weaned into same-sex groups of 2–3 littermates in Makrolon type III cages with sawdust as bedding and a red polycarbonate house (Mouse house, Techniplast, Italy) as shelter. Offspring were left undisturbed until testing except for a weekly cage change. The experiment was run in six successive replicates. All replicates were conducted under the same conditions.

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### 1.1. Early postnatal environment variations

The experimental cage system consisted of a nest cage (NC) with solid floor and sawdust and a foraging cage (FC) with grid floor connected by a tunnel. To further increase the attractiveness of the NC for nesting, the walls and top of the rear part of the NC were covered. Food and water were provided ad libitum in the FC. The condition in the FC was determined by two factors according to a  $2 \times 2$  factorial design, with factor 1 depending on the presence or absence of rat odour (feces), and factor 2 depending on the presence or absence of shelters (MouseHouse, Techniplast, Italy, and a polycarbonate tube, 89 mm  $\times$  89 mm  $\times$  77 mm, Lillico, England). The four treatments were defined as follows:  $ro^-s^-$  group: No rat odour ( $ro^-$ ) and no shelter ( $s^-$ ) was present in the FC.  $ro^-s^+$  group: No rat odour ( $ro^-$ ), but shelter ( $s^+$ ) was present in the FC.  $ro^+s^-$  group: Rat odour ( $ro^+$ ), but no shelter ( $s^-$ ) was present in the FC. Rat odour was introduced in the FC by placing rat feces underneath the grid floor. The feces were replaced everyday by fresh feces taken from rat cages within the animal facility. Replacement of feces was conducted without manipulating the cage system to minimize disturbance.  $ro^+s^+$  group: Rat odour ( $ro^+$ ) and shelter ( $s^+$ ) were present in the FC.

### 1.2. Maternal behaviour

The behaviour of each dam was recorded for seven 32-min observation sessions every day from PND 1 to PND 13. On each scan, the occurrence of active nursing (AN), licking–grooming (LG) and other nursing posture was recorded (see Refs. [7,8] for a detailed description of the method).

### 1.3. Object recognition test (ORT)

When the litters composition allowed it, one male and one female of each dam were tested at 10 weeks of age in the ORT (8 pups in each group for each sex resulting in a total of 64 offspring). Animals were tested individually in a familiar arena (50 cm  $\times$  50 cm  $\times$  40 cm). The test consisted of two trials, each of 10 min, with an inter-trial interval of 15 min. During the first trial animals were exposed to two similar unfamiliar objects (A1 and A2). On the second trial, the objects were replaced by a triplicate of the familiar object (A3) and a novel object (N). Both objects and object location were counterbalanced in order to remove object and location preference effects. A camera mounted above the arena recorded each trial and was connected to a video-recorder and the video tracking system EthoVision (Noldus IT, Netherlands) for analysis. The total time spent exploring the objects in both trials and the time spent exploring the objects A3 and N during the second trial were recorded. Exploration of an object was defined as directing the nose towards an object at a distance of less than 1 cm and/or touching the object with the nose and/or paws. Sitting on the objects was not considered as exploratory behaviour [10].

### 1.4. Statistics

In the object recognition test, mice with a total exploration time of less than 5 s in either trial 1 or 2 were excluded from the analysis [1]. Across the four groups and both sexes, 11 animals failed to reach the 5 s exploration criteria. Thus, following group sizes remained: males:  $ro^-s^- = 6$ ;  $ro^-s^+ = 6$ ;  $ro^+s^- = 7$ ;  $ro^+s^+ = 7$ ; females:  $ro^-s^- = 7$ ;  $ro^-s^+ = 6$ ;  $ro^+s^- = 7$ ;  $ro^+s^+ = 7$ . We analysed the absolute difference in time investigating N vs. A3 as well as a preference score (PS) (calculated as: exploration time of N (s)/total exploration time of A3 + N (s)). Males and females were analysed separately. All variables were found to be normally distributed according to the Kolmogorov–Smirnov test. Three analyses were performed: (1)

Differences between postnatal conditions were analysed by a two-way ANOVA with presence or absence of shelter and rat odour as between subjects factors. (2) Object recognition memory was tested for each group using a paired *t*-test calculating differences between the experimental preference score and the chance level of 0.5. (3) The relationship between measures of maternal behaviour (LG and AN) and offspring PS and total exploration time of the objects was assessed by regression analysis for each group and each sex. Differences were considered significant at  $p \leq 0.05$ .

## 2. Results

No effect of the postnatal condition in the total time spent exploring the objects was found. In males, there were no main effects of rat odour ( $F_{1,22} = 0.74, p > 0.1$ ) or shelter ( $F_{1,22} = 0.91, p > 0.1$ ) on PS (Fig. 1) or on the absolute difference in time investigating N vs. A3 (data not shown –  $F_{1,22} = 0.13, p > 0.1$  and  $F_{1,22} = 0.03, p > 0.1$ , respectively). However, males reared by dams exposed to rat odour without shelters ( $ro^+s^-$ ) showed a PS significantly above chance ( $p = 0.03$ ; Fig. 1). In females, the presence or absence of shelter in the dams' environment did not affect the PS ( $F_{1,23} = 0.04, p > 0.1$ ) or the absolute difference in time investigating N vs. A3 ( $F_{1,23} = 0.27, p > 0.1$ ). But, a significant effect of the presence of the rat odour in the maternal environment was found in the absolute difference in time investigating N vs. A3 (data not shown –  $F_{1,23} = 3.665, p = 0.034$ ); females of dams exposed to rat odour tend to show a lower PS compared to females of dams that were not exposed to rat odour ( $F_{1,23} = 4.23, p = 0.05$ ; Fig. 1). Furthermore, females reared by dams exposed to rat odour showed a PS that was not significantly different from chance, while the PS of females reared by dams that were not exposed to rat odour was significantly above chance ( $p = 0.05$ ; Fig. 1).

Our previous work has already shown that the total level of nursing was not influenced by the presence or absence of these two factors (shelter and rat odour). However, the presence of rat odour induced higher levels of active nursing and licking/grooming, while the presence of shelter did not affect nursing style (see Ref. [8] for a detailed analysis of the results).

In males, there was no significant relationship between the level of LG or AN and measures of object exploration in the ORT (Fig. 2). In females reared by dams exposed to the rat odour, an inverse relationship was found between the level of LG received during the 1st week of lactation and the PS ( $ro^+s^+$ :  $\beta = -0.76, p = 0.07$ ;  $ro^+s^-$ :  $\beta = -0.96, p = 0.001$ ; Fig. 2). No relationship between the total time of exploration during the second trial and the level of LG during the 1st week of lactation was found.

The present results show that male and female C57BL/6J mice react differently to specific aspects of the environment and to environment-dependent variations in maternal behaviour, resulting in individual differences in object memory in adulthood.

The presence of shelters, which could be considered as enrichment, did not affect object recognition memory in the offspring. Previous studies in rats have shown that postweaning environmental enrichment affects positively spatial learning and object recognition [3,20,21]. However, in the present experiment, enrichment was used during the preweaning period and only the mothers were directly exposed to the enriched cage while offspring remained in the unenriched nest cage. Furthermore, the style or level of nursing, that could have mediated any effect of the environmental enrichment on the offspring, was unaffected by the presence of the shelters. Therefore, it is not necessarily surprising to note the absence of a shelter effect on the cognitive abilities of the offspring.

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