Hybrid vigour and maternal environment in mice. II. Water escape learning, open-field activity and spatial memory

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Abstract:
A combination of ovarian grafting and fostering was used to study the effects of pre- and postnatal maternal factors on adult behaviour. Inbred mice (BALB/c and C57BL/6) and F_1 hybrids were compared to assess differential sensitivity to early maternal effects. In addition to the peculiar behavioural profile of BALB mice, results revealed the existence of a cognitive process in mice and confirmed the greater ability of F_1 mice to adopt efficient escape strategies. Only postnatal maternal factors were shown to exert long lasting effects on behaviour, appearing to affect the general ability to react to a new situation rather than specific psychological functions. F_1 hybrids proved less sensitive to such effects than inbred mice.
Key words: Maternal effect; Ovarian grafting; Fostering; Heterosis; Development; Cognitive process; Behavioural adaptation

Article:
Introduction
Behaviour is considered by modern ethologists (Silverman, 1978; Campan, 1980) an adaptive relationship between the organism and its environment. Behavioural changes constitute, for the subject, the best way to adapt to a changing environment. Behavioural changes can be achieved three ways: 1) Rapid, easily reverting quantitative changes in the expression of a behavioural trait are referred to as behavioural flexibility. 2) Qualitative changes corresponding to switches among alternative behavioural forms or strategies within the individual repertoire can be termed behavioural commutability. The associated shifts between underlying psychological processes are homologous to what neurobiologists call "the vicariousness of pre-existing alter-native strategies" (Paillard, 1972). 3) The third is behavioural plasticity, which involves learning and memory processes, i.e. long lasting behavioural changes correlated with "long lasting modification of the structure connectivity network" (Paillard, 1972). Only variations in behavioural flexibility and behavioural plasticity can be investigated using the methods of behaviour genetics in so far as both of them correspond to variations in the expression of a given phenotype. On the contrary, behavioural commutability assumes the implementation of different underlying processes which would probably imply a control by different series of genes as already hypothesized by Falconer (1972). It corresponds to a kind of genotype by environment interaction which precludes any attempt of analysis by the methods of quantitative genetics (Lassalle, 1986). The behavioural plasticity which is related to learning and individual experience could also play a role in the developmental process and interfere with ontogenetic plasticity which is characterized by sensitive periods. Pre- and postnatal maternal factors could play a major role, along with genotypic factors, in the developmental process, especially in altricial mammals, as already shown by previous results (Wahlsten, 1983; Le Pape and Lassalle, 1981, 1983, 1984, 1986). A combination of ovarian grafting and fostering was used to dissociate the effects of pre- and postnatal maternal factors. Whereas Bulman-Fleming et al. (1991) analysed such effects on body and brain growth, this paper focuses on the effects of genetic and maternal factors on behavioural expression in the young adult.

The aims of the present study were to assess what kind of behavioural changes could be induced by maternal factors in order to identify both the nature of the processes upon which maternal factors exert long lasting effects and the nature of their influences. The sensitivity of inbred and heterozygous animals to early maternal factors was also studied as a kind of genotype by environment interaction. Various experimental situations were chosen or developed to study aspects of behaviour and psychological functions which are either related to the ability to cope with new situations or are thought to be under control of the hippocampus (Vinogradova, 1975; O'Keefe and Nadel, 1978; Olton, 1983).

The water escape situation tests reactions to an unknown stressful situation. Rapid improvement of the escape performance based on reference memory is possible, and the expression of various kinds of escape strategies can be studied (Lassalle et al., 1979). The classic circular openfield assessed activity and the spatial open-field assessed long-term habituation to a set of novel objects introduced in a familiar environment. The reaction of mice to the spatial rearrangement of the objects provided an index of a cognitive process—the long-term memory of a spatial representation. This paradigm was inspired by experiments carried out on other species by Wilz and Bolton (1971) and by Poucet et al. (1986). Mice were also given 5 learning sessions on an Olton radial maze (Olton and Samuelson, 1976). Learning on the radial maze is based on the storage of spatial information in working memory.

Methods
Animals
Mice of the strains BALB/cWah2 (BALB) and C57BL/6J (C57), both highly inbred and genetically homogeneous, and their isogenic reciprocal F_1 crosses (BALB $\times$ C57 and C57 $\times$ BALB) were all bred and raised in the laboratory at the University of Waterloo. Their origins and conditions of rearing are described elsewhere (Wahlsten & Bulman-Fleming, 1987; Bulman-Fleming et al. 1991).

Ovarian grafting
The surgical procedure has been described in detail in Bulman-Fleming and Wahlsten (1988). The females were between 6 and 10 weeks old at the time of surgery. Grafted dams were allowed a minimum of two weeks to recover before mating. A total of 15 BALB, 14 C57, and 30 F_1 (18 BALB $\times$ C57 and 12 C57 $\times$ BALB) were. grafted with inbred ovaries. Where possible, coat color markers were used in order to ensure that offspring were not the result of remnant pieces of the host ovary (see Bulman-Fleming et al. 1991). All mothers underwent the graft operation.

Breeding
Females were introduced into the cage of the male (1-4 females for 1 male), plug-checked twice a day, isolated when visibly pregnant and thereafter checked twice daily until delivery occurred. Grafted dams were mated to either BALB or C57 males, so that each of the 4 resulting genotypes (BALB, C57, BALB $\times$ C57 and C57 $\times$ BALB) experienced a grafted prenatal inbred or hybrid environment. Pups were weighed to the nearest mg as soon after birth as possible and then fostered to an ungrafted lactating dam which had delivered within 48 h of the birth of the litter to be fostered. Weaning occurred 21 days after birth. Mice were weighed to the nearest 0.1 g, and thereafter housed with siblings of the same sex. Mice weighing 5.0 g or less were discarded. In order to avoid the effects of social isolation interfering with later measures, single mice from birth or from weaning were also discarded.

Behavioural testing
When mice were 60 days old, they were given a series of behavioural tests over a period of three weeks: water escape learning, classic open-field testing, habituation and spatial learning in a spatial open-field, and 8-arm radial maze learning. Three days before starting behavioural testing, mice were weighed, tail-marked and placed in a new cage with fresh bedding. Identification tags on the cages were removed and replaced by a single number giving no information about maternal origins of the mice. Three different experimenters were involved in behavioural testing. Each animal was randomly assigned a testing rank order which was kept constant over the three weeks.

Starting on a Monday, 4 water escape learning trials were given at 24 hour intervals in a circular device 70 cm in diameter, lit by a 40 Watt red bulb, 50 cm above the water level (Lassalle et al., 1979). Escape latencies were measured, and the path taken by each animal was recorded.

Starting on the next Monday, mice experienced 4 open-field sessions at 24 h intervals. They were first given a 15 min. classic open-field session in a circular device 45 cm in diameter, of the same type used by Broadhurst (1965) for rats and lit by a 40 Watt red bulb 80 cm above the floor of the device. The floor of the open-field was divided into 6 peripheral and 1 circular central sectors, all of the same area. Behavioural activities were recorded for the first 5 min.

Twenty-four hours later, mice underwent the first spatial open-field session (A). Three different objects (a plastic stork 7 cm in height, a Canadian circular fuse 3 cm in diameter and height, and a screw with its nut 4 cm in height) were placed in the open-field according to one kind of spatial arrangement, (on-line or "V" shape arrangement). Mice were allowed to explore the objects for 15 min. and contacts with the objects were recorded for the first 5 min. Session B was identical to session A. For session C, mice were randomly assigned either to an experimental or a control group: In the control group, the objects remained in the same location as in sessions A and B; whereas in the experimental group, the objects were placed in a new configuration providing a different spatial arrangement ("on-line" turned to a "V" shape or vice-versa). If mice were able to detect a new spatial arrangement of a set of already known objects, this should induce a renewal of the exploratory activity in the experimental group compared to the control group. Dishabituation would then indicate spatial memory. A striped pattern was placed on the wall of the open-field from the classic session on, constituting a local cue which could help mice to detect the new arrangement. Contacts with the objects were observed using a video camera. A contact was counted each time the mouse placed its nose above the grey poly-vinyl chloride disk, 4 cms in diameter, on which the object was glued.

Radial maze learning started on Monday of the 3rd week after 2 training sessions given on Thursday and Friday of the week before. The food deprivation schedule started on Saturday. Mice were maintained at 20 ± 3 weight loss across the experiment. The radial maze was composed of a centre platform, 21 cm in diameter, and 8 arms projecting radially. The arms were 5 cm wide and 50 cm long, surrounded by a 1 cm high wall and terminating in an 8×8 cm platform with an inlaid small cup. The maze was mounted on a tripod, 80 cm high, allowing rotation. The device was placed in a room lit by artificial light (about 450 lux) which provided a variety of potential visual and auditory cues. No confinement to the central platform between choices was used. At the beginning of the learning experiment, each cup was baited with a food pellet (Bailey-strait's egg noodles weighing 15 ± 2 mg). Each mouse was placed on the centre platform and could run to the end of each arm and eat the food reward. Reinforcements were not replaced during the session, so that a maximum of 8 of them could be obtained. The optimal strategy was to choose each arm only once, and not to repeat a choice to any arm, thus getting all the food reinforcements in the minimum number of choices. The learning session ended when 8 correct choices had been completed in a maximum of 16 trials. A mouse was considered to have entered an arm when its head crossed the imaginary line delimiting the entry of the square platform at the end of each arm. Mice were given 5 learning sessions on the Olton radial maze. At the beginning of each learning session, the maze was rotated for random orientation of the arms and each mouse placed on the maze with the head pointing towards an arm number chosen at random.

Data analysis

Data were analysed using either ANOVA or Multiple Regression with the Multiple General Linear Hypothesis program of SYSTAT (Wilkinson, 1986) on an IBM AT computer. Dummy variables were used for prenatal and postnatal environment, and effect coding was used to compare the four genetic crosses. A hierarchical approach was chosen, first testing a large model with several first order interactions. Nonsignificant interactions were then dropped and a simplified model was tested. Effect coding was a follows: the STR (strain) variable contrasts BALB vs C57, HET (heterosis) contrasts hybrids vs. inbreds (midparent value), RECIP (reciprocals) contrasts the two hybrids, PRE contrasts the two prenatal environments (inbred vs hybrid) and POST contrasts postnatal environments. Some interaction terms (HET*POST, HET*SEX) were also included to assess differential effects

of some variables on inbred and hybrid offspring. Orthogonal contrasts were also used for planned comparisons. Because there were no differences between reciprocal F_1 hybrids, they were pooled in a single F_1 group.

Results

Forty-one out of the 59 grafted females gave birth to at least one litter. Ten grafted females had one or more pups derived from host ovarian tissue which had not been removed during the delicate surgical procedure. Mice which could not be unequivocally identified as being of donor ovary origin were destroyed. In total there were 308 mice which were used for behavioural testing.

Water escape learning

Escape performances were analysed using the following indices: the log10 escape latency on each trial (L1 to L4), the mean of the log 10 escape latency over four trials (Mean) and an index of learning (Slope = 3 * L1 + L2 — L3 + 3 * L4). Escape paths were analyzed and allotted to one of three categories: (a) Simple path; mice either followed a straight line from the release point to the landing grid, or followed the walls of the apparatus closely to arrive at the landing grid; (b) Complex path; all other types of paths which allowed the animal to reach the escape grid; (c) Failure; erratic paths with no escape occurring in less than 3 min. Figure 1a shows the variations in escape performances. As can be seen from the STR variable in Table 1, BALB mice displayed longer escape latencies and an inferior learning performance. The HET variable indicated that the F, hybrid escape latency was shorter than the midparent value, the mode of inheritance being complete dominance, not overdominance. No main effect of pre- or postnatal maternal environment was detected. A significant HET*POST interaction (t = 2.80, df = 303, p = 0.006) indicated that rearing by an F_1 adoptive dam improved escape performance in inbred mice on the first trial, but not on subsequent ones. The analysis of escape paths indicated that the proportions of animals using the three categories varied between inbred and hybrid mice from the first to the fourth trial. Values of χ^2 were 9.32, 23.19, 27.97, and 32.2 for trials 1-4 respectively. They were all significant at the p <0.005 level with 2 df. The proportion of mice failing to escape was much lower and close to zero in the F_1 and C57 as compared to BALB. Hybrid mice proved to be more capable of shifting from an erratic to a simpler and more efficient escape strategy. This commutability phenomenon is significant from the second trial onwards. χ^2 values were 12.97, 18.28, and 26.85, respectively, and were all significant at the p < 0.005 level with 1 df. No consistent effect of the maternal environment was detected on behavioural shifts.
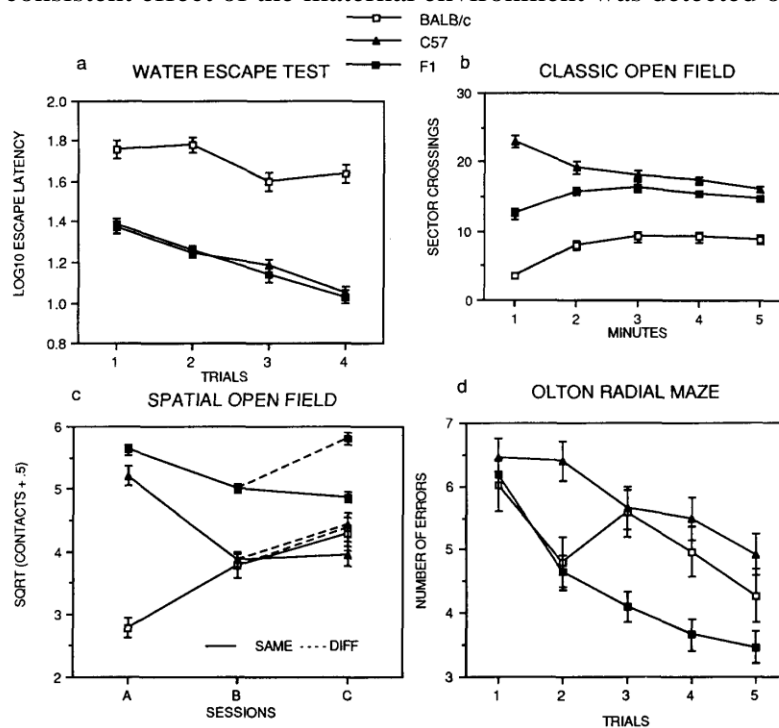

Fig. 1. a) Water escape test—escape latencies for four trials; b) Classic open field—locomotor activity during the first five minutes; c) Spatial open field—exploratory contacts over three sessions; d) Olton radial maze—errors over five trials. Bars indicate one standard error of the mean.

Classic open-field

Figure lb illustrates the variation of level and evolution of locomotor activity in the open open field during the first 5 minutes. The STR variable (Table 1) points out again the behavioural peculiarity of BALB mice which exhibited lower locomotor and rearing activity, longer latency to enter the central sector, and a quite different profile of activity over 5 minutes. When compared to their inbred parents (HET), F_1 hybrids were more active, entered the central sector more quickly and reared and defecated more often. Sex differences appeared in the open-field, females being less active and defecating more than males. The sex factor also interacted with genotype. F_1 females exhibited lower peripheral activity, shorter latencies to enter the central sector and fewer rearings than males, whereas these differences were weaker or even absent in inbreds. Pre- and postnatal maternal factors did not exert any significant main effect but the postnatal environment interacted with both the STR and HET variables; when reared by an F_1 foster mother, BALB mice showed a greater increase of activity over 5 min. than did C57 mice (STR × POST: t = 1.98, df = 294, p = 0.048) and both inbred strains had more defecations than when reared by conspecific mothers, whereas the F_1 animals raised under the two different conditions showed no such differences (HET × POST: t = 2.31, df = 294, p = 0.022).

TABLE 1

Magnitude (t values and significance) of effects of strain difference (STR), heterosis (HET), SEX and postnatal maternal environment (POST). R^2 is the adjusted R^2 for the multiple regression equation, and df is degrees of freedom for error term.

WATER ESCAPE TEST	STR	HET	SEX	POST	R^2	df
Mean log latency	− 13.02 ***	− 9.21 ***	− 1.07	< 1	0.448	303
Change over trials	− 2.35 *	2.51 **	< 1	< 1	0.024	303
First trial latency	7.40 **	− 4.61 ***	< 1	< 1	0.192	303
CLASSIC OPEN-FIELD						
Total peripheral activity	− 16.61 ***	3.99 ***	− 2.68 **	− 1.22	0.492	294
Latency to enter centre	− 14.34 ***	− 3.45 **	1.06	< 1	0.416	294
Change in activity	− 5.89 ***	− 2.70 **	1.82	1.30	0.136	294
Rearing	− 5.33	< 1	< 1	< 1	0.082	294
SQRT (Defecation + 0.5)	7.42 ***	1.07	− 2.75 **	< 1	0.172	294
SPATIAL OPEN-FIELD						
SQRT (Contacts, ses. A)	− 11.89 ***	11.10 ***	< 1	1.48	0.477	293
Habituation (B − A)	− 13.00 ***	3.46 **	< 1	< 1	0.385	293
Habituation (C − B)	1.10	− 1.998 *	< 1	− 2.12 *	0.050	127
Dishabituation(C − B)	< 1	< 1	1.18	1.10	0.000	161
OLTON RADIAL MAZE						
Average errors	− 2.81 **	− 5.74 ***	− 1.24	< 1	0.131	278
Change in errors	< 1	2.41 *	< 1	< 1	0.010	279

* p < 0.05, ** p < 0.01, *** p < 0.001.

Spatial open-field

The number of contacts with the objects in session A (SQRT(total contacts +0.5)) is an index of exploration. Two indices of long term habituation were then computed: Habituation (B-A) is an index of habituation on session B, computed on the whole experimental population, whereas Habituation (C — B) is an index of habituation between the second and third sessions, computed only on the control group (132 subjects) which had three sessions with the objects in the same location. Dishabituation (C — B) quantifies the renewal of exploratory activity after the spatial rearrangement of objects. It was computed on the experimental group (166 subjects). Figure 1c shows the transformed exploratory scores for the three sessions. During the first session BALB mice explored the objects much less than did C57 and hybrids. Table 1 shows that the STR and HET variables explain 47.7% of the total variance of contacts during that session. The habituation performance between the first and second sessions was also characterized by the behavioural peculiarity of BALB. They displayed intense neophobic reactions resulting in a very low level of exploratory activity of the objects for session A which increased during the next session. Habituation between sessions B and C can also be analysed on the control group. The Habituation (C — B) index revealed complex influences acting on that performance. Multiple regression showed a marginally significant heterosis effect and a significant postnatal effect. As can be seen from Figure 2 in the control group (same objects arrangement), inbred mice and mice having experienced the postnatal environment of an F_1 adoptive mother, especially inbred ones, habituated more completely to the set of objects. The analysis of the reaction of mice to the spatial rearrangement of the objects involved a

condition variable according to whether the objects arrangement was different or remained the same as in session B. A global ANOVA on the Dishabituation (C — B) index over the entire experimental sample indicated a highly significant condition effect ($F(1, 296) = 19.723$ $p < 0.0001$), which means that a significant dishabituation took place in the experimental group. The analysis of the dishabituation performance in the experimental group using multiple regression failed to reveal any significant effect of the STR, HET or POST variables. Further analysis using planned comparisons between the various control and experimental groups showed a very significant effect of objects rearrangement in F_1 hybrids ($t = 4.12$, df = 293, $p < 0.001$), a marginally significant one for C57 ($t = 1.32$, df = 293, $0.05 < p < 0.10$) and no effect for BALB/c mice ($t = 0.63$, df = 293, NS).

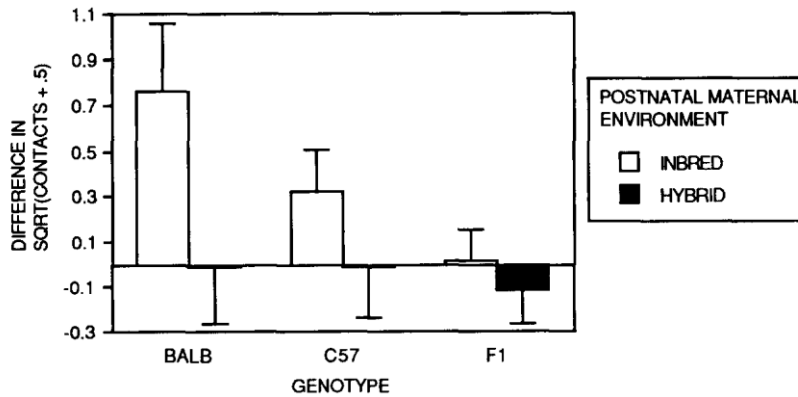

Fig. 2. Habituation (C−B) in the control group. Bars indicate 1 SEM.

Olton radial maze

Various indices related to error numbers, first error rank and an index devoted to the measure of the strength of adjacent choices (the divergence degree) and their changes over sessions, were analysed. Because of the insufficient number of sessions imposed by a very constraining experimental schedule, substantial learning took place only for F_1 hybrids. Figure 1d shows how the decrease in error number over the five trials varied among groups. The multiple regression analysis summarized in Table 1 revealed significant strain and heterosis effects on average performance. No significant effect of pre- or postnatal maternal factors was detected.

Discussion

The use of a new behavioural paradigm gives clear evidence of a cognitive process in mice: the long term memory of the representation of spatial relationships. Results also reveal the numerous behavioural peculiarities of BALB mice, which display low escape performances as well as intense emotional reactivity and neophobic reactions resulting in poor and incomplete exploration of novel objects. There are numerous cases of superiority of F_1 mice over the mid-parent value. Hybrids are more active, display more intense exploratory activity in the classic and spatial open-field, make fewer errors on the Olton radial maze and escape more efficiently from water. F_1 performances exceed both inbred strains on dishabituation in the open field and learning the Olton maze, but the difference from C57 is not significant. These results do not confirm the overdominance phenomenon already demonstrated in the same cross on water escape (Lassalle et al., 1979, Shröder and Sund, 1984), which once again points out the importance of factors such as the age of animals or experimental conditions. Even if they do not escape faster than C57, F_1 hybrids nonetheless display greater ability to shift towards better escape strategies. A combination of ovarian grafting and fostering at birth revealed no prenatal effects on these behavioural measures, whereas postnatal maternal factors sometimes proved to exert long lasting effects. In the multiple regression model, postnatal effects appeared generally as an interaction term with the heterosis or strain effects, which indicated a greater sensitivity of inbred or BALB mice to postnatal maternal factors. Fostering by an F_1 mother from birth to weaning resulted in more efficient escape behaviour of inbreds during the first trial in the water escape test, but not on subsequent ones. In the open-field, it induced also a greater increase in activity over time in BALB and a higher frequency of defecation in both inbred strains. Finally, the postnatal maternal environment provided by an F_1 dam acts as a main effect in the spatial open-field by improving the habituation performance of both inbred and hybrid mice of the control group from the second to the third presentation of the objects. In contrast, it does not exert any influence on either learning

performances in the water-escape and Olton maze learning, or the long term memory of the spatial relationships among a set of objects.

The effects of postnatal maternal factors observed in this study seem to parallel the effects of early handling, which have been shown to reduce fear responses to novelty (Bodnoff et al., 1987), to increase long term potentiation in the hippocampus of the young (Wilson et al., 1986), and to produce an enduring concentration of glucocorticoid receptors in the hippocampus of the rat which results in more rapid recovery from stress (Meaney et al., 1985). Considering the various targets of postnatal factors in this study, it can be concluded tentatively that their effects are essentially nonspecific. They do not appear to influence any of the inferred psychological functions that were studied (spatial learning performance, reference and working memory), whereas they improve the general capability to react efficiently when the animal is faced for the first time with a new stressful situation.

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