# Hybrid vigour and maternal environment in mice. III. Hippocampal mossy fibres and behaviour

By: Douglas Wahlsten, J.M. Lassalle, and B. Bulman-Fleming

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## Abstract:

Inbred BALB/c and C57BL/6 mice as well as their $F_1$ hybrids were reared in either an inbred or hybrid maternal environment prenatally and/or postnatally, and were later tested for several behaviours prior to histological study of the brain at 100 days after birth. Whereas measures of spatial memory showed hybrid vigour or overdominance, measures of hippocampal mossy fibres showed intermediate inheritance. Brain-behaviour correlations within a strain were generally very small, and effects of maternal environment on hippocampal morphology were not significant.

**Key words:** Spatial memory; Open field activity; Inbred strain; Brain-behaviour correlation; Neurogenetics

## Article:

### *Introduction*

Mice of the BALB/c strain are reported to perform poorly on tests involving spatial memory such as an 8-arm radial maze (Lassalle et al., 1990), a water maze (Schwegler et al., 1988) and a Morris submerged platform water maze (Upchurch and Wehner, 1988).

Likewise, these mice are known to have peculiarities of the architecture of the terminal fields of the hippocampal mossy fibres which connect the dentate granule cells with pyramidal neurons in area CA3. Whereas most mice show a large zone of mossy *above* fibres the pyramidal cells (suprapyramidal layer) on their apical dendrites and a smaller zone *below* the pyramidal cells (infrapyramidal layer) on their basilar dendrites, most BALB/c mice have an unusual zone of mossy fibres *in the midst* of the band of pyramidal cell bodies (intrapyramidal layer) in some regions of area CA3 (Barber et al., 1974). One exception may be the BALB/cABom$_f$ strain, which is reported to lack the intrapyramidal mossy fibres (Fredens, 1981). In the Bailey recombinant inbred strains, the BALB/c pattern shows single locus inheritance and $F_1$ hybrids resemble BALB/c, which led Nowakowski (1984) to name a dominant gene "hippocampal lamination defect" *(Hid).* Besides the unusual topographical pattern, BALB/c mice have a relatively small proportion of the total mossy fibre terminal zone in the combined intra- and infrapyramidal layers (Crusio and Schwegler, 1987) compared with C57BL/6 mice.

The question thus arises whether the variation in hippocampal anatomy is related to variations in spatial memory. Brain lesions (Ammassari-Teule and Gozzo, 1982; Reinstein et al., 1983) and injection of drugs (Olton, 1987; van Abeelen and Gerads, 1986) indicate a definite link between hippocampus and spatial behaviour, but the specific role of subtle morphological variations is better studied with correlational methods. The size of the intra- plus infrapyramidal mossy fibre zone (IIP MF) relative to the size of areas CA3 and CA4 has been found to correlate rather highly with several measures of learning and memory (see review in Lipp, et al., 1988) when several inbred strains are compared or a genetically heterogeneous population is sampled. Behavioural consequences of the *Hld* gene itself have not been evaluated, although recombinant inbred strains reveal no major impact on investigatory behaviour (Peeler and Nowakowski, 1987) or two-way avoidance learning (Peeler, 1987).

The present study examined whether the mode of inheritance in hybrid mice was the same for spatial memory and hippocampal morphology, and whether the maternal environment might produce changes in the mossy fibre distributions that would similarly influence behaviour. Hybrid mice formed by crossing two inbred strains sometimes perform better on tests of behaviour than either parent strain (Hyde, 1973), and this hybrid vigour should also be evident in the hippocampus if the variation in behaviour is a direct consequence of variation in anatomy. Furthermore, substantial portions of the variation seen in mouse hippocampus are clearly from non-genetic sources (Crusio et al, 1986; Schwegler et al., 1988), which suggests modest differences in the early environment could alter later anatomy. Inbred mice normally have inbred mothers, and the inbred maternal environment is less favourable for brain growth than a hybrid maternal environment (Bulman-Fleming and Wahlsten, 1988; Bulman-Fleming et al., 1991). The, present study was designed to assess the contribution of pre- and/or postnatal maternal environments to hybrid vigour on tests of brain and behaviour.

Results of portions of this study have been described previously for whole brain size (Bulman-Fleming et al., 1991) and tests of behaviour (Lassalle et al., 1991). This report presents data on hippocampal morphology and correlations with behaviour.

## Methods

Mouse strains, maternal environments and tests of behaviour have been described in detail in prior reports. Briefly, inbred BALB/cWah2 and C57BL/6J mice as well as their reciprocal $F_1$ hybrids were obtained prenatally in either an inbred or $F_1$ hybrid mother using ovarian grafting and then were fostered to either an inbred or $F_1$ hybrid surrogate mother after birth. They were weaned at 21 days and housed with same-sex littermates until the start of behavioural testing at 8 weeks. Following testing for water escape learning, open field activity, spatial object exploration and Olton radial maze learning, they were again housed with littermates for about another 3 weeks.

### *Histology*

At 100 days of age (+ or —1 day), mice were anesthetized with an overdose of sodium pentobarbital and then perfused intracardially using a peristaltic pump running at 18 to 20 ml/min. Solutions in order were a) 45 sec. of 0.9% NaCl as a vascular rinse, b) 1 min. of 0.1% sodium sulfide in phosphate buffer, c) 3 min. of 3% glutaraldehyde fixative, and d) a further 7 min. of 0.1% sodium sulfide. Following this, the brain was removed from the skull, trimmed to a standard configuration, weighed to the nearest mg, stored in 3% glutaraldehyde for 2 hr., and then immersed in 30% sucrose until it sank. Frozen 25 micron sections were cut in the horizontal plane, mounted on glass sides, and stained using the Timm's method to reveal the zinc-bearing mossy fibre terminals (Danscher, 1981). The sections were counterstained lightly with 0.05% thionin in acetate buffer.

### *Morphometry*

For each brain, five consecutive sections of good histological quality nearest the midseptotemporal level of the hippocampus were chosen for measurement using criteria described by Lipp and Schwegler (1982). In each section the outlines of seven regions were drawn with a Leitz Tracing Device on a Dialux microscope and then areas were measured with a digitizing tablet connected to an IBM XT computer running the Bioquant IV program. The regions were a) CA1 (regio superior), b) CA2 and CA3 (regio inferior), c) CA4 (the hilus), d) the granule cell layer of the dentate gyrus, e) the molecular layer of the dentate gyrus, f) the suprapyramidal zone of mossy fibre terminals, and g) the zone of closely packed pyramidal cell bodies below the intrapyramidal layer of mossy fibre terminals in CA3. This latter zone was not seen in many sections, but it was measured if even 3 or 4 cell bodies formed a small cluster below the mossy terminals in CA3. Areas of CA2 and CA3 were combined because the precise boundary between them can only be visualized in Golgi stained tissue (Bayer, 1985).

The area of Timm's staining of the intra- and infrapyramidal mossy fibres (IIP MF) is very difficult to quantify with a digitizing tablet because there are often many small, highly irregular patches of dark stain in CA3. Instead, a video image analysis system (Videtics, Ltd., Waterloo, Ontario) was used to digitize the image from an RCA TC1005 vidicon mounted on a Leitz Laborlux microscope. The system, operating on an IBM XT

computer, converted each pixel in a 1024 × 512 array into one of 64 brightness levels ranging from no light (0) to "white" (63). A technician then determined the threshold brightness that excluded all background staining but included all genuine Timm's staining. The total number of pixels representing mossy terminals in CA3 and CA4 was counted and converted to area, and then a smaller window was specified to count only the pixels representing the IIP MF.

All tracings and measurements were done without knowledge of the strain or environmental condition of the mouse. An average of each measure across the five sections was used for further analysis. In some cases tissue damage made it necessary to base the average on fewer than five sections.

### *Data analysis*

Multiple regression was done with the MGLH program of SYSTAT on an IBM XT computer. Dummy variables were used for prenatal and postnatal maternal environment as well as sex, and effect coding was used to compare the four genetic crosses. First-order interactions among dummy variables and genetic effects were assessed, but no attempt was made to evaluate second- or higher-order interactions because of markedly unequal and sometimes small sample sizes in certain sub-groups.

TABLE 1

Significance of effects, as indicated by values, and proportion of variance attributable to all 4 effects (adjusted $R^2$).

| Measure | Effect | | | | $R^2$ |
|---|---|---|---|---|---|
| | STR | HET | POST | HET × POST | |
| Brain weight [a] | 2.27 * | 3.54 ** | 1.74 | <1 [b] | 0.423 |
| Hippocampus area | 1.24 | 1.25 | <1 | −1.28 | NS [c] |
| CA1 | <1 | 2.45 * | <1 | −2.32 * | NS |
| CA2/3 | 3.19 ** | <1 | <1 | <1 | 0.063 |
| CA4 | −6.81 ** | <1 | 1.88 | <1 | 0.322 |
| Dentate gyrus area | −3.57 ** | <1 | <1 | 1.03 | 0.124 |
| Granule cells | −2.99 ** | <1 | 1.09 | <1 | 0.080 |
| Mol. layer | −3.22 ** | <1 | <1 | 1.35 | 0.105 |
| % of CA2/3 + CA4 | | | | | |
| Total MF | −5.52 ** | <1 | 1.03 | <1 | 0.217 |
| Suprapyr. MF | <1 | 2.81 ** | <1 | −2.18 * | 0.065 |
| IIP MF | −7.84 ** | <1 | <1 | −1.02 | 0.362 |
| Pyr. cells below IIP MF | 10.51 ** | −1.35 | 1.01 | <1 | 0.567 |

[a] Not including cerebellum.
[b] Value less than 1.0 and greater than −1.0.
[c] Overall F test not significant.
* $P < 0.05$.
** $P < 0.01$.

## Results

### *Preliminary analyses and simplifications*

Useful data on the hippocampus were obtained for 107 mice in 32 groups (4 genotypes × 2 sexes × 4 maternal environment combinations), which meant there were only one or two observations in certain conditions. A preliminary analysis of nine measures of the hippocampus revealed that there were no significant differences between reciprocal $F_1$ hybrids or males and females, that no effects of prenatal environment were apparent at 100 days of age, and that interactions involving these variables were either not significant or sporadic and bizarre. Because none of these effects had been predicted to occur, it was concluded that they could be omitted from further statistical analyses. Postnatal environment did not amount to much, either, but it was reasonably expected to influence dentate granule cell projections, which form postnatally, and it clearly affected whole brain size (Bulman-Fleming et al., 1991). Consequently, it was retained in the final regression model, even when not significant. This yielded 6 groups with 107 mice (3 genotypes in inbred or hybrid postnatal maternal environment) and a reasonably large sample in every group.

### *Hybrid vigour and maternal environment*

Significance of variations among the six groups was assessed using 4 terms, each with one degree of freedom, in a multiple regression equation. STR was the strain difference between BALB/c and C57BL/6. NET (for heterosis) contrasted the $F_1$ hybrid group with the mean of the two inbreds (midparent value). POST contrasted inbred

and hybrid postnatal maternal environments. A HET × POST interaction term was included to assess whether hybrid offspring were less sensitive to the difference in postnatal maternal environment, as some theorists have suggested (Hyde, 1973; Palmer and Strobeck, 1986). Results for several measures of the hippocampus were very clear and consistent: the strain difference was often quite large, whereas the HET, POST and HET × POST effects were generally not significant, as shown in Table 1.

### *Mode of inheritance*

Because effects of maternal environment were not detectable with sample sizes used here, further findings can be presented simply for the three genetic groups pooled across treatment conditions. Mean values are shown in Table 2. Mode of inheritance was judged from a Newman-Keuls test of the three group means using $\alpha = 0.05$. OVER denotes overdominance, where the hybrid significantly exceeds both inbred parents. DOM is complete dominance, where the hybrid differs significantly from one parent but not the other. INT is intermediate inheritance, where the hybrid is between the two parents and significantly different from both. N.S. indicates no significant difference among the three groups.

Measures of hippocampal mossy fibre terminals exhibit intermediate inheritance, unlike measures of brain size and spatial memory on the same mice, where hybrid vigour or overdominance is manifested (Lassalle et al., 1989). Frequency distributions of scores for two measures of principal interest are shown in Figure 1. Percent of CA2/3 and CA4 occupied by the IIP MF, an index known to be of considerable relevance to several behaviours (Lipp et al., 1988), provides a picture typical of intermediate inheritance with similar variances in each group (Bartlett chi-squared test $P > 0.50$). About 35% of the total variance derives from genetic differences among the groups. For percent pyramidal cells below the HP MF, an index pertinent to the anatomical anomaly in BALB/c mice described by Barber et al. (1974) and Nowakowski (1984), variances are quite different and distributions are skewed (Bartlett test $P < 0.001$). However, a log transformation eliminates this difficulty (Bartlett test $P > 0.50$), and it yields intermediate inheritance with about 56% of variance coming from genetic differences, which conflicts with the claim by Nowakowski (1984) of complete dominance for *Hld*.

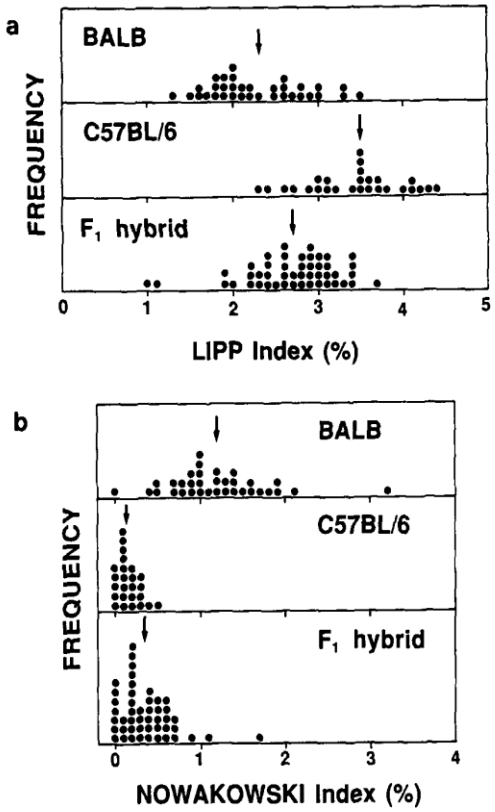


Fig. 1. Frequency distributions of scores for 3 genetic groups. a) Percent of CA2/3+CA4 occupied by intra- and infrapyramidal mossy fibre terminals (IIP MF). b) Percent of CA2/3+CA4 occupied by pyramidal cell bodies below IIP MF.

### *Correlations with behaviour*

Between-group correlation of brain and behaviour in this study is effectively addressed by comparing modes of inheritance. However, the substantial variability observed within a genetically homogeneous group makes non-genetic sources of correlation interesting. A composite estimate for all mice was obtained by standardizing each measure within a genetic group using the z transformation to eliminate group differences in mean and variance. Pearson correlations were calculated between area of hippocampus, area of dentate gyrus and 4 measures of mossy fibres (Table 2), and the following principal measures of behaviour obtained from the same mice (Lassalle et al., 1991): a) average water escape time, b) improvement in water escape time over 4 trials, c) object contacts on the first trial of spatial open field, d) habituation of object contacts (trial 1—trial 2), e) dishabituation when object arrangement was changed (trial 3—trial 2), f) average errors on Olton maze, and g) improvement on Olton maze over 5 trials. Of the 42 correlations, only 5 were significant at the $\alpha = 0.05$ level. For water escape learning, better improvement was associated with a smaller percent of total mossy fibre terminals ($r$ = —0.221, df = 97). For object exploration, larger dishabituation was associated with smaller area of the dentate gyrus ($r$ = —0.242, df = 77) and larger percent pyramidal cells below the IIP MF ($r$ = 0.261, df = 77). For the Olton radial maze, higher average errors were associated with smaller area of hippocampus (r = —0.268, df = 97) and dentate gyrus ($r$ = —0.248, df = 97). These rather modest correlations reveal no consistent relationship between spatial behaviour and any measure of the hippocampal formation within strains. When data were examined separately for each strain, the patterns of results were even less consistent and a small proportion of correlation coefficients was significant. It may be unwise to place much emphasis on correlations with size of the hippocampus or regions within it, because previous studies have found little evidence of such effects but more consistent evidence of the importance of the IIP MF size (see Crusio et al.,1989; Lipp et al., 1988; Lipp et al., 1989). The positive correlation in the present study between spatial memory, as indicated by dishabituation, and the larger extent of pyramidal cells below the IIP MF layer is the first such report in the literature.

TABLE 2

Group means and mode of inheritance for several measures.

| Measure | BALB/c | Strain C57BL/6 | Hybrid | Mode of Inheritance |
|---|---|---|---|---|
| Sample size | 35 | 25 | 47 | |
| Brain weight (mg) [a] | 397 | 391 | 416 | OVER |
| Hippocampus ($mm^2$) | 1.681 | 1.638 | 1.662 | NS |
| CA1 | 0.636 | 0.647 | 0.652 | NS |
| CA2/3 | 0.951 | 0.870 | 0.899 | INT |
| CA4 | 0.095 | 0.120 | 0.110 | INT |
| Dentate gyrus ($mm^2$) | 0.538 | 0.592 | 0.586 | DOM |
| Granule cells | 0.117 | 0.133 | 0.130 | DOM |
| Mol. layer | 0.421 | 0.459 | 0.456 | DOM |
| % of CA2/3 + CA4 | | | | |
| Total MF | 22.5 | 26.1 | 24.2 | INT |
| Suprapyr. MF | 10.8 | 10.6 | 11.2 | NS |
| IIP MF | 2.30 | 3.46 | 2.69 | INT |
| Pyr. cells below IIP MF | 1.20 | 0.16 | 0.35 | INT |
| Log (% Pyr. cells below IIP MF) | 0.065 | −0.635 | −0.423 | INT |

[a] Not including cerebellum.

## Discussion

Highly significant genetic differences were observed for measures of hippocampal mossy fibre terminals (Table 1) as well as spatial behaviour and memory (Lassalle et al., 1991), yet no correlation was observed between these measures of brain and behaviour. The absence of correlation between group means was evident from different modes of inheritance. Measures of mossy fibre terminals showed intermediate inheritance, while measures of spatial memory showed hybrid vigour. This finding does not contradict reports of correlations between the size of the intra- plus infrapyramidal mossy fibre terminal field and various behaviours, because previous studies have emphasized variations among several inbred strains or within a genetically heterogeneous

population, which are sensitive mainly to additive genetic effects. Hybrid vigour or overdominance constitutes a non-additive genetic effect.

The scarcity of substantial correlations within a genetically uniform strain resembles findings of Diaz (1988) for 50 BALB/cAnN mice, where 190 correlations between 38 measures of behaviour and weights of 5 brain regions yielded only 22 significant at the $\alpha = 0.05$ level or better, slightly more than 10%. Perhaps one reason for such disappointing results is the generally low reliability of many tests of mouse behaviour. The expected correlation between a measure of the brain and a measure of behaviour is the correlation between the true values multiplied by the square root of the product of the reliabilities of the two measurements (Rozeboom, 1966). If there is no genetic variance in the population of animals being assessed, test reliability will tend to be rather low and large samples will be required to detect a significant correlation (Wahlsten, 1990). Reliability is especially difficult to determine for tasks where rapid learning is involved, because repeated measurement of the same behavioural state is virtually impossible. It is likely that the low correlations observed in the present study were at least partly a result of small numbers of trials on each task.

Other considerations also restrict the generality of these findings. Only the midseptotemporal region was examined here. Because developmental processes (Gaarskjaer, 1981) and behavioural correlations (C. Wimer et al., 1983) can differ across dorsal-ventral region of the hippocampus, patterns relevant to spatial behaviour may not have been measured. Configuration of the test apparatus and specific procedures can dramatically affect results or alter their interpretation (Olton, 1987; Pico and Davis, 1984), and consequently the magnitude of brain-behaviour correlation probably depends upon the specific apparatus and circumstances of testing, as is the case for motor activity and exploration (Peeler and Nowakowski, 1987).

The fact that 2 to 3 weeks elapsed between the first day of behavioural testing and perfusion was probably of little consequence because the changes in the hippocampus after sexual maturity, although real, are rather modest (R. Wimer et al., 1988). The most characteristic features of the adult anatomy are evident by the age of weaning (Stanfield and Cowan, 1979).

Although the hybrid maternal environment had no discernable impact on mossy fibre terminals in this study, this by no means indicates that the patterns are genetically specified regardless of conditions. There is clearly the potential for plasticity of the mossy fibres postnatally. Destruction of the usual mossy fibre targets, the pyramidal cells in region CA3 of neonatal rats, results in unusual growth of mossy fibres into CA1 (Cook and Crutcher, 1985), and electrical stimulation of the perforant path of adult rats can expand the mossy terminal field into the molecular layer of the dentate gyrus (Sutula et al., 1988). However, consequences of a treatment may be species or strain dependent (van Abeelen and Gerads, 1986). For example, neonatal thyroxine greatly increases the extent of the IIP MF zone and impairs avoidance learning in DBA/2 mice, whereas effects are generally smaller for BALB/c mice (Lipp et al., 1988).

The hybrid maternal environment resulted in generally larger brains for both inbred and hybrid mice (Bulman-Fleming et al., 1989), and brain size itself showed hybrid vigour in both the inbred and hybrid maternal environments. Hippocampal mossy fibre terminals, on the other hand, showed neither hybrid vigour nor modification by maternal environment. The variance in these measures was no less for hybrid than inbred mice, even when pre- and postnatal maternal environments differed substantially.

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