

Genetic Variation in the Development of Mouse Brain and Behavior: Evidence from the Middle Postnatal Period

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Abstract:

Six inbred strains and 3 F₂ hybrid crosses of mice were assessed for developmental status at 32 days after conception (about 13 days after birth). Phenotypes measured included body weight, brain weight, maturity of 14 reflexive behaviors, myelination of 80 fiber tracts, and thickness of the external granular layer of the cerebellum. All measures of brain and behavior showed a similar pattern of results: hybrids were generally more advanced than either of their inbred parent strains; differences among inbred strains were large, but differences among hybrid crosses were quite small. Acceleration of F₂ mice compared to their homozygous relatives ranged from .5 to 2.4 days mean difference. Developmental ages of inbred litters ranged from 28.7 to 32.2 days, whereas hybrid litters ranged from 31.5 to 32.7 days.

Article:

One of the most remarkable features of the development of brain and behavior is the great predictability of daily changes. Although this observation is not a surprising outcome in a longitudinal study of the same individual, a similarly precise trend observed in separate naive litters of mice tested at successive ages (Wahlsten, 1974a) indicates that well-regulated processes underlie ontogeny. The causes of this impressive regulation should therefore be of primary concern to those interested in developmental psychobiology. A great deal of attention has been devoted to the study of environmental influences such as nutrition and experience on early development, but, apart from the voluminous research on single-gene effects in development (Sidman, Green, & Appel, 1965), little work has been done with genetic influences on the emergence of brain and behavior in viable strains. Significant genetic influences on the ontogeny of simple reflexes have been reported for mouse strains studied during both the prenatal (Henrikson, Wallace, & Vaughn, 1973) and the postnatal phases of growth (Fuller & Geils, 1973; Fuller & Herman, 1974; McClearn, Wilson, & Meredith, 1970). Studies of nervous system development have also found the genotype of the subject to be of considerable importance for phenotypes such as brain weight (Fuller & Geils, 1972), major forebrain fiber tracts (Wahlsten, 1974b), and caudal nerve conduction velocity (Hegmann & White, 1973). Parallel research into development of external morphology in mice has revealed comparable genetic differences during the preimplantation period (McLaren & Bowman, 1973), the fetal period (Wahlsten, 1974b; Wainwright, 1974), and the neonatal period (Garrard, Harrison, & Weiner, 1974). The work with morphological growth suggests that measures of reflex or neural ontogeny may show genetic differences because the rate of development of the whole organism is strongly affected by genotype.

The present study was designed to extend these various findings to a wider range of measurable phenotypes and a greater variety of genotypes. Particular attention was given to differences between hybrid crosses and their inbred parent strains. In preparation for this experiment, a time scale for postnatal development was devised to enable the developmental age of a mouse to be calculated by a comparison of its maturity to that of a standardized series of B6D2F₂ hybrid mice (Wahlsten, 1974a). The time scale thus allowed a precise determination, in fractions of a day, of the differences in rates of development among different mouse strains.

Because the scale incorporated measures of many behaviors and brain regions, it also indicated the overall developmental status of the mouse and, hence, had greater generality than a scale based on a single phenotype.

This paper reports the developmental ages of 6 inbred and 3 F₂ hybrid groups of mice, all tested at 32 days after conception. Each hybrid group was derived from 2 of the inbred strains. Thus the inbred mice were homozygous at every locus, whereas F₂ hybrid mice were heterozygous at many of the loci where the parent strains possessed different alleles. The F₂ mice were studied instead of F₁ mice in order that they would have the benefit of hybrid vigor in their own genetic makeup as well as in their maternal environment. In this respect the study was intended to ascertain the greatest extent of differences in developmental rates which could be expected in normal mouse development. Only if sufficiently large genetic effects were detected would subsequent analyses of maternal effects and nutrition be considered fruitful.

Method

Subjects

All parent mice (*Mus musculus*) were procured from The Jackson Laboratory, Bar Harbor, Maine, at an age of 7 weeks, and were maintained in standard plastic mouse cages with free access to tap water and dry food under a 12-hr light: 12-hr dark schedule. Mice arrived and were mated in replications of 2 inbred strains and their F₁ hybrid at weekly intervals. Groups were as follows:

- (1) A/J, BALB/cJ, and CAF₁/J (BALB/c female x A male);
- (2) A/HeJ, C57L/J, and LAF₁/J (C57L female x A/He male);
- (3) C57BL/6J, DBA/2J, and B6D2F₁/J (C57BL/6 female x DBA/2 male).

At least 9 females of each strain were mated in an attempt to obtain at least 3 litters for testing; where 9 females were insufficient, additional females were procured.

Breeding

One male and 1 virgin female mouse of the same strain were mated in a standard cage at approximately 60 days of age. The female was examined for the presence of a vaginal plug at least twice each day. The pair was maintained together for at least 3 weeks unless a vaginal plug and subsequent pregnancy were detected. The chronological age of the litter was taken from the midpoint of the interval between detection of a plug and a previous plug check (0 days, 0 hr). The female was isolated as soon as definite signs of pregnancy were apparent; thereafter, she and her litter were left undisturbed until testing.

Testing

Each entire litter was tested at 32.0 days following conception (about 13 days after birth). Each mouse was given a standard battery of 14 reflex tests described previously (Wahlsten, 1974a) and then weighed. The series of behavioral tests was originally modified from Fox (1965); minor changes were made from the time scale standardization study (Wahlsten, 1974a). Each mouse was assigned a score on each test ranging from 0 (no response) to 1.0 (mature or adult form). Criteria for assigning fractional scores are available from the author upon request.

Tests in the order administered were as follows:

- (1) Righting reflex. Does subject (S) return rapidly to its feet when placed on its back?
- (2) Cliff aversion. Does S withdraw from the edge of a flat surface when its snout and forepaws are placed over the precipice?

- (3) Forelimb grasp reflex. Does S grasp strongly the barrel of an 18-gauge needle when it is touched to the palm of each forepaw?
- (4) Hindlimb grasp reflex. Same as forelimb test, but with hindpaw.
- (5) Vibrissa placing reflex. Does S place its forepaw onto a cotton swab which is stroked across its vibrissae?
- (6) Level screen test. Can S hold onto a piece of 288-mesh aluminium screen when it is dragged across it horizontally by the tail?
- (7) Vertical screen test. Can S hold onto the screen when it is placed vertically?
- (8) Screen climbing test. Can S climb up the vertical screen using both fore- and hindlimbs?
- (9) Pole grasp. Can S grasp the shaft (2.5 mm) of a cotton swab firmly with both fore- and hindpaws?
- (10) Forelimb stick grasp. Can S grip firmly a 9.5-mm wooden stick with forepaws?
- (11) Hindlimb stick grasp. Same as (10), but with hindpaws.
- (12) Eyes open. Are both eyes fully open?
- (13) Visual placing reflex. Does S extend its forelimbs when it is lowered rapidly towards a flat surface?
- (14) Auditory startle response. Does S show a whole-body startle response when a loud snap of fingers occurs less than 15 cm away?

The first 8 mice in each litter were perfused intracardially with 10% formalin immediately following testing. The brains were extracted and weighed to the nearest mg. Several brains were studied histologically. They were encased in gelatin and sectioned sagittally at 25 μ m. Alternate sections were stained with Sudan Black B for myelin and thionin for Nissl substance. Within 10 days of staining, the sections of each brain were assessed for myelin staining intensity of 80 different fiber tracts at 40X magnification. The thickness of the external granular layer (E.G.L.) of the cerebellum was measured at 10 sites with an ocular microscale at 1000X magnification. All details of testing and brain evaluation were described in a previous report (Wahlsten, 1974a).

The major variables assessed in this study were thus body weight, brain weight, mean reflex score on 14 tests, mean myelin intensity for 80 tracts, and mean thickness of the E.G.L. at 10 different sites.

Results

At least 3 litters were obtained for all groups except BALB/c. A total of 36 BALB/c matings were attempted, 25 of which resulted in a detectable vaginal plug. From these 25 plugs, 7 litters were delivered; 5 of these succumbed because of poor maternal care, 1 "litter" consisted of a single pitifully neglected mouse, and 1 litter was quite healthy at testing. Hence, the data presented herein for BALB/c mice cannot be considered truly representative of that strain.

The gestation length was generally longer in smaller litters ($r = -.72$); the relationship was observed among F₂ litters ($r = -.76$) and inbred litters ($r = -.45$) considered separately. The mean litter size of inbreds (5.2) was smaller than that of F₂'s (8.5), and the inbred mean gestation length (19.6 days) was longer than that of F₂'s (18.7 days).

In the statistical analyses of major variables, 1-way unweighted means analysis of variance was used unless otherwise indicated. The extent of differences between the 9 groups was expressed by estimated ω^2 , were an indication of the proportion of the total variance which could be attributed to between-group differences (Hays, 1963). Because group sizes were unequal for some phenotypes, the value of ω^2 should not be interpreted too strongly. Comparisons among the 9 groups were then done in order to answer major questions about genetic effects. The sum-of-squares between groups was partitioned into 3 components, and the percent of the total attributable to each component is given in Table 1. One component arose from differences among the 6 inbred strains ($df = 5$); another resulted from differences among the 3 hybrid groups ($df = 2$); the last comparison reflected the difference between the 3 hybrids and the 6 inbreds ($df = 1$).

TABLE 1. Statistical Summary of Differences Between 9 Genotype Groups for Several Phenotypes.

| Phenotype | Total | Estimated ω^2 | Percent of Between-Group Sum of Squares | | | Between-Groups Variance (days ²) | Median Within-Litter Variance (days ²) |
|-------------------|-------|----------------------|---|---------------|--------------------|--|--|
| | | | Among Inbreds | Among Hybrids | Hybrids vs Inbreds | | |
| Body weight | 249 | .25 | 36.8 | .5 | 62.7 | — | — |
| Brain weight | 230 | .43 | 57.5 | 1.7 | 40.8 | — | — |
| Behavioral age | 249 | .69 | 51.1 | 1.0 | 47.9 | 31.95 | .145 |
| Myelination age | 106 | .37 | 43.9 | 4.2 | 51.9 | 7.84 | .312 |
| E. G. L. age | 111 | .42 | 59.7 | 12.0 | 28.3 | 5.83 | .294 |
| Developmental age | 106 | .60 | 45.7 | 4.8 | 49.5 | 8.48 | .114 |

Separate analyses of variance were used to evaluate differences between litters of a single genetic group. Mean-squares between litters are given in Table 2 for all groups except BALB/c. Measures on all litters were available only for body weight, brain weight, and behavioral age.

TABLE 2. Between-Litter Variance in Three Phenotypes for Several Mouse Strains.

| Group | Litters | Body Weight (g ²) | Brain Weight (g ²) | Behavioral Age (days ²) |
|--------------------|---------|-------------------------------|--------------------------------|-------------------------------------|
| Inbred: | | | | |
| A | 5 | 8.89 ^a | .00222 ^a | 3.75 ^a |
| A/He | 4 | .29 | .00148 ^a | .61 ^a |
| C57L | 3 | 3.57 ^a | .00631 ^a | 7.48 ^a |
| C57BL/6 | 3 | 2.81 ^a | .00859 ^a | 3.47 |
| DBA/2 | 4 | .35 | .00050 ^a | .47 |
| Hybrid: | | | | |
| CAF ₂ | 5 | 9.56 | .00497 ^a | 1.25 ^a |
| LAF ₂ | 5 | 2.19 ^a | .00019 | .90 ^a |
| B6D2F ₂ | 6 | 12.73 ^a | .00026 | 1.51 ^a |

^a $p < .01$.

Body Weight

Large differences in body weight between litters of the same age and genotype were observed (Table 2); only for A/He and DBA/2 were the differences not significant. The mean body weight of a litter was highly correlated with litter size for F₂ groups ($r = -.84$), but the correlation was small for inbreds ($r = .05$). Mean body weight of F₂ mice (6.9 g) was significantly greater than that of inbred mice (5.7 g) in spite of much larger F₂ litters (Table 1).

Brain Weight

Between-litter variation within a genotype was highly significant except for LAF₂ and B6D2F₂ (Table 2). A high correlation with body weight was evident for certain groups (A, CAF₂, C57L, C57BL/6), but brain weight was remarkably homogeneous despite large variations in body weight for LAF₂ and B6D2F₂. Correlations

between body weight and brain weight of individual mice within a litter revealed a similarly variable pattern of results. Brain weight differences among the 9 genotypes revealed large effects of hybrid vigor as well as large differences among inbreds (Table 2).

Developmental age was not calculated using brain weights for 2 reasons: (1) the various genetic groups studied herein were known to achieve different adult brain weights (Roderick, Wimer, Wimer, and Schwartzkroin, 1973), which prevented the use of a single scale to compare the groups; and (2) brain weight was known to vary much less predictably from day-to-day than were other phenotypes such as behavior and brain myelination (Wahlsten, 1974a). A preliminary analysis of the present data in terms of percent of adult brain weight for each strain also revealed substantial between-litter variation.

Behavior

Behavioral age was determined for each mouse from its mean score on the 14 reflex tests. The score was substituted into a quadratic regression equation to obtain the behavioral age with respect to a B6D2F₂ standard population. The derived age represented the age at which a litter of B6D2F₂ mice would exhibit the same behavioral score. The equation employed was $Y = 24A0 + 11.14X - 1.09 X^2$ (X , a behavioral score ranging from 0 to 1.0), which was fit to the data from a series of 10 litters of B6D2F₂ mice tested 1 litter per day from 27-36 days after conception; the goodness of fit was $r^2 = .99$. The coefficients, slightly different than those in the time scale standardization study (Wahlsten, 1974a), were based on a replication of 10 B6D2F₂ litters using response score criteria identical to those of the present study.

The mean behavioral age for the 9 groups is shown in Figure 1. Differences between genotypes revealed large hybrid vigor and among-inbreds effects. In all 3 instances the F₂ behavioral age significantly exceeded that of its most advanced inbred parent strain. The impressively large value of ω^2 may have been exaggerated somewhat because behavioral testing was done by the author who knew the genotype of each litter. Such bias undoubtedly did tend to minimize difference within a litter tested within a short period of time. A consistent difference between A/He and DBA/2, however, could not reasonably have resulted from experimenter bias, in that testing was done at all times of the day and night over a period of 2 months. The large difference between DBA/2 and C57BL/6 was actually opposite to that expected by the experimenter on the basis of previous reports (Hegmann & White, 1973; Wainwright, 1974).

Highly significant differences were found between litters within all groups except DBA/2. Even within groups such as A/He or LAF₂, the seemingly small mean differences were significant, primarily because of large numbers of subjects and small within-litter variance. For groups with small mean differences between litters, no correlations with body weight were apparent. This outcome was especially dramatic for the F₂ groups, where tight clustering of behavioral ages appeared in contrast to the very wide range of body weights of the various litters. This suggested that the level of nutrition beyond the minimum adequate amount may have had little influence on the rate of behavioral development. Litters in groups such as C57L and C57BL/6 may have, in fact, differed in overall developmental rate quite apart from nutritional causes, because body weight and behavioral age varied so consistently between litters, whereas litter sizes were nearly equal.

Myelination

Sudan staining intensity was assessed for several brains of at least 2 litters per genotype, except BALB/c. Subjects per genotype ranged from 9 for BALB/c to 13 for CAF₂. Mean myelin staining intensity of 80 fiber tracts was calculated for each subject on a scale ranging from 0 (no myelin evident) to 3.0 (intense, adult-like staining). This score was then put into the equation $Y = 25.86 + 2.46X + .68X^2$ to obtain myelination age with respect to the B6D2F₂ standard series.

Genotype differences (Fig. 1) resulted in large hybrid vigor and among inbreds effects. The F₂ mean exceeded the most advanced inbred parent for all comparisons except B6D2F₂ vs DBA/2. Because all assessment of myelin intensity was done with a double-blind procedure, group differences and the moderate ω^2 were not subject to experimenter bias.

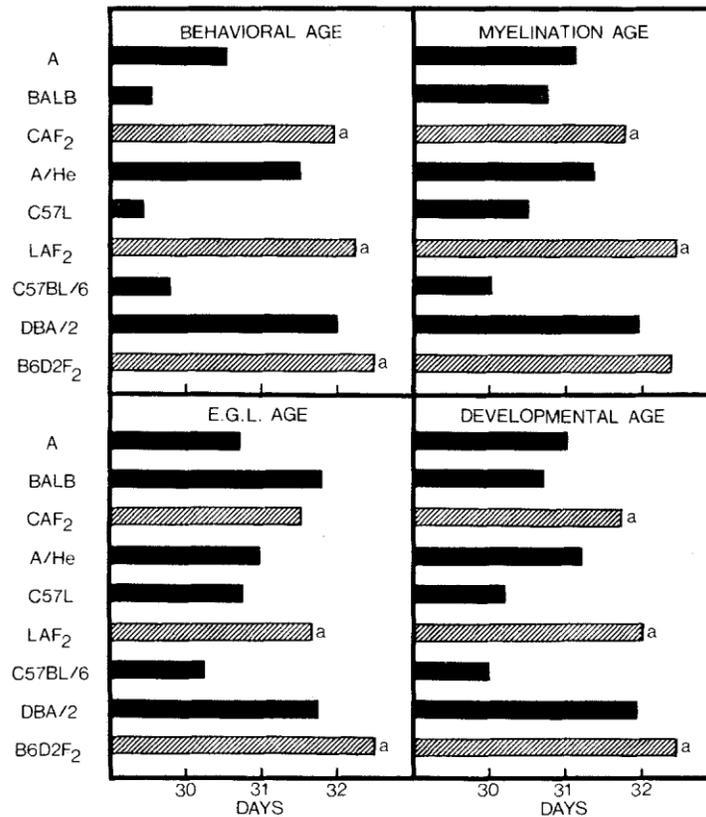


Fig. 1. Mean ages of 6 inbred and 3 F₂ hybrid groups estimated from behavioral performance on 14 reflex tests, myelination of 80 fiber tracts, and thickness of the external granular layer (E.G.L.) of the cerebellum. Mean developmental age represents the average of the 3 other ages for each mouse. Instances where the F₂ mean age significantly ($p < .05$) exceeded the most advanced inbred parent are indicated by the letter *a*.

Myelination age revealed significant between-litter differences only for C57BL/6 and C57L. Of course, the test had much less power than that for behavioral age because fewer mice were measured from fewer litters. E.G. L.

Mean thickness of the E.G.L. of the cerebellum was measured in pm for each subject and entered into the equation $Y = 35.66 - .54X + .01X^2$.

Results revealed significant genetic differences (Fig. 1, Table 1). A smaller percent of between-genotype variation was attributable to hybrid vigor than for other variables and, as a consequence, more of it could be ascribed to among-inbreds effects. The LAF₂ and B6D2F₂ groups significantly exceeded their most advanced parent strain. The BALB/c mice appeared to be relatively precocial in E.G.L. disappearance compared with their status for other variables. The B6D2F₂ hybrids were significantly ahead of both LAF₂ and CAF₂ hybrids. Thus, the E.G.L. ages revealed a pattern of differences unlike that for either myelination or behavioral ages. The E.G.L. thickness was also assessed with a double-blind procedure. Hence, this finding cannot be attributed to either histological artifact or experimenter bias.

Developmental Age

Ages of mice based upon behavior, myelination, and the E.G.L. in all 3 cases revealed: (1) F₂ hybrids were significantly more advanced than their inbred parent strains; (2) large differences existed among the 6 inbred strains; and (3) differences among the 3 hybrids were generally not significant. The extent of between-genotype differences in age was much greater for behavioral age than for myelination or E.G.L. ages, as indicated by the variance between groups (Table 1). Moreover, the precise rank orderings of genotypes were different for the 3 kinds of age, and thus a measure of overall developmental age was needed. Accordingly, the developmental age of each mouse in the present study was defined as the arithmetic mean of ages derived from behavior, myelination, and E.G.L. These developmental ages (Fig. 1) exhibited highly reliable differences between

genotypes ($\omega^2 = .60$). Fully half of the between-genotypes effect could be attributed to hybrid vigor. Differences among inbreds were also large, but the differences among hybrids accounted for barely 5% of between-group variance. All F₂ vs high-parent comparisons were significant. The F₂ hybrid mean ages ranged from 31.7 -32.4 days, whereas inbred mean ages ranged from 30.0 - 31.9 days. When individual litters were considered, developmental ages at 32.0 days of chronological age ranged from 28.7 days for C57BL/6 Litter 1 and 29.1 days for C57L Litter 1 to 32.7 days for B6D2F₂ Litter 3. Thus, genetic variation in developmental age was a highly reliable phenomenon; differences at 32 days gestation age were commonly greater than 1 day and were sometimes as large as 3 or 4 days.

Discussion

This study has demonstrated that when both the mother mouse and her offspring possess considerable genetic heterozygosity, the offspring are more mature in both brain and behavior at 32 days following conception than are closely related mice of the same chronological age but of inbred, homozygous genetic constitution. Acceleration of F₂ mice compared to their homozygous relatives ranged from .5-2.4 days mean difference. The range of developmental ages for inbred litters was from 28.7-32.2 days, whereas F₂ litters ranged from 31.5-32.7 days. Thus, F₂ mice clustered closely around a developmental age of 32 days, whereas inbreds varied widely.

Developmental age, being an average of 3 independent scores, should be primarily sensitive to variation in development status of the whole mouse. A mouse in B6D2F₂ Litter 2 with a developmental age of 30.8 days, for example, had the lowest score of any other mouse in that group for behavior, myelination, and E.G.L., in spite of the fact that its body and brain weights were above the group mean. Hence, the retardation of its neural maturation must have been genuine.

Effects arising because of heterozygosity of the developing mouse itself cannot be distinguished from those attributable to a superior environment provided by a heterozygous mother in this study. Previous research has suggested that both effects are probably important (Hegmann & White, 1973; McLaren & Bowman, 1973; Rutledge, Robinson, Eisen, & Legates, 1972; Wainwright, 1974). Their relative contributions can be compared in future research by using reciprocal crosses or reciprocal backcrosses.

Some of the F₂-inbred differences observed herein may have reflected different nutritional levels, but the nutritional variations must have been conservative in this study. After all, F₂ mothers actually had much larger litters; if litter sizes had all been restricted to 4 or 5 mice, genetic differences would probably have been greater. Clearly, inbred mice did not lag behind F₂ mice simply because of nutritional restriction. Brain and behavior of inbred mice generally lagged behind those of F₂ mice having similarly low body weight. Total confirmation of these assertions, of course, must await studies of experimental nutritional restriction in both inbreds and hybrids, because neural development of inbred mice may be more sensitive to nutritional effects than that of hybrids.

The presence of genetic variation in developmental rate above and beyond nutritional factors should enable the causes of stable ontogeny to be investigated further. Environmental manipulations alone can reveal the presence of highly buffered processes, such as the precise timing of the growth spurt of the rat brain in spite of wide nutritional variation (Dobbing & Sands, 1971), but they are not likely to reveal why an event does in fact occur at a particular time. Indeed, the timing of developmental spurts and lags is just as interesting as the overall rate of development (see also Epstein, 1974; Wohlwill, 1970). Genetic variation in the temporal profile of development has been revealed in a study of behavioral ontogeny in human twins (Wilson, 1972). The present data also suggest the genetic determination of spurts and lags. The DBA/2 mice were advanced at 32 days compared to C57BL/6, and they were nearly equal to the F₂ hybrids derived from the 2 inbred strains. In contrast, C57BL/6 mice are well ahead of DBA/2 at 16 days after conception, and both strains are retarded compared with their F₂ hybrid (Wahlsten, 1974b; Wainwright, 1974). A developmental "spurt" is also evident at 32 days in B6D2F₂ mice, for they consistently score about 32.5 days. This occurred in the original time scale

study (Wahlsten, 1974a) and in the present study. Obviously, a smooth quadratic curve is only an approximation of the undulating pattern of development, even for a healthy hybrid.

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