Wheel running behavior is impaired by both surgical section and genetic absence of the mouse corpus callosum

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Schalomon, P. M., and Wahlsten, D. (2002).Wheel running behavior is impaired by both surgical section and genetic absence of the mouse corpus callosum. *Brain Research Bulletin*, 57: 27-33.

Abstract:
Mice lacking a corpus callosum (CC) often show little or no deficit on tests of behavior. This paper reports that on highly complex bimanual motor tasks, deficits can be found. The speed of running on a wheel with irregularly spaced rungs is reduced by both hereditary absence of the CC in 129 × BALB/c recombinant mice and surgical section of the CC in genetically normal B6D2F$_2$ mice. The effect of CC absence appears on measures most closely related to speed, no influence exists on the amount of running over a period of 5 days. Motor behavior on a notched balance beam, on the other hand, shows clear superiority of the hybrid mice but no relation with reduced size of the CC, whether it was produced by genotype or surgery. The effect of absent CC is task dependent, but it is not obscured by developmental compensation in the recombinant mice.
Key Words: Recombinant inbred strains, Hippocampal commissure, Balance beam, Motor coordination, Task difficulty.

Article:

INTRODUCTION

The corpus callosum (CC) that interconnects the cerebral hemispheres of placental mammals is one of the most striking anatomical structures in the forebrain, and lack of the CC is a neuropathological feature in mice [35]. Nevertheless, a surprising range of behavioral functions shows little or no change when the CC is absent. Typically, fewer than half the mice in inbred strains such as BALB/c and 129 have no CC [35], a condition termed incomplete penetrance, and this within-strain non-genetic variation provides an excellent test of CC function. No relation of CC size in these strains is apparent with paw preference scores [7,13,27], the speed of running on a wheel [3], or performance on several common behavioral tasks [17,34], although some indication exists that mouse strains with a high frequency of absent CC also show deficits on a notched balance beam [21].

These results are not totally conclusive because the strains in question also show a number of behavioral peculiarities that are unrelated to the effects of an absent CC [2,18,20,26], and it remains possible that effects of absent CC may depend on the strain background, just as CC absence does [22]. The present paper addresses this limitation by utilizing several recombinant inbred lines created from the 129 and BALB/c strains, so that genes responsible for absence of the CC would not likely be spuriously correlated with genes relevant for abnormal behavior.

The literature on humans lacking the CC points to mild, language-related deficits in intelligence and rhyming [10,24], and it suggests that deficits are most likely to appear on motor tasks, in which pressure exists to perform at high speed [14,23]. In this paper, we report that CC-related deficits in high-speed wheel running indeed appear when the task is rendered more difficult by removing several rungs from the wheel.

The interpretation of behavioral test results from acallosal mice is challenging because usually no compelling reason exists to believe that the behaviors in question rely heavily on interhemispheric communication. It is also possible that as with human CC agenesis [9,11,19,29], developmental plasticity creates or pre-serves alternative

pathways between the hemispheres when the CC fails to form. It therefore is difficult to distinguish between behaviors that are not related at all to CC function and those that normally are CC-dependent but fail to show this when the CC is absent before birth. To address this problem, we devised a surgical procedure for sectioning the CC of normal adult mice [25], and surgery is used in this paper to assess whether the behavioral tests are impaired in genetically normal mice.

MATERIALS AND METHODS

Mice

B6D2F_1/J mice were obtained from the Jackson Laboratory, Bar Harbor, ME, USA, and mated to obtain B6D2F_2/J offspring. Recombinant inbred (RI) lines were obtained from the progenitors 129/ReJ and BALB/cWah1 by randomly mating pairs from the F_2 hybrid generation and then inbreeding by brother-sister mating thereafter. The RI mice used in this study were from generations 4 to 8 of inbreeding and therefore possessed considerable heterozygosity [12]. They were from five different RI lines; one line almost always had a normal CC, two lines almost always had no CC, and two lines were highly variable; thus, mice with normal CC came from three RI lines, whereas mice with no or small CC came from four RI lines. Mice were weaned at 21 or 22 days after birth and then were housed with same-sex littermates until testing. They were allowed free access to local tap water and Wayne Rodent Blox 8604. The colony room was on a 12-h light/12-h dark cycle with lights off at 1800 h. Ages of mice at testing ranged from 49 to 77 d, the average age being close to 60 d for all groups. Approximately equal numbers of males and females were used.

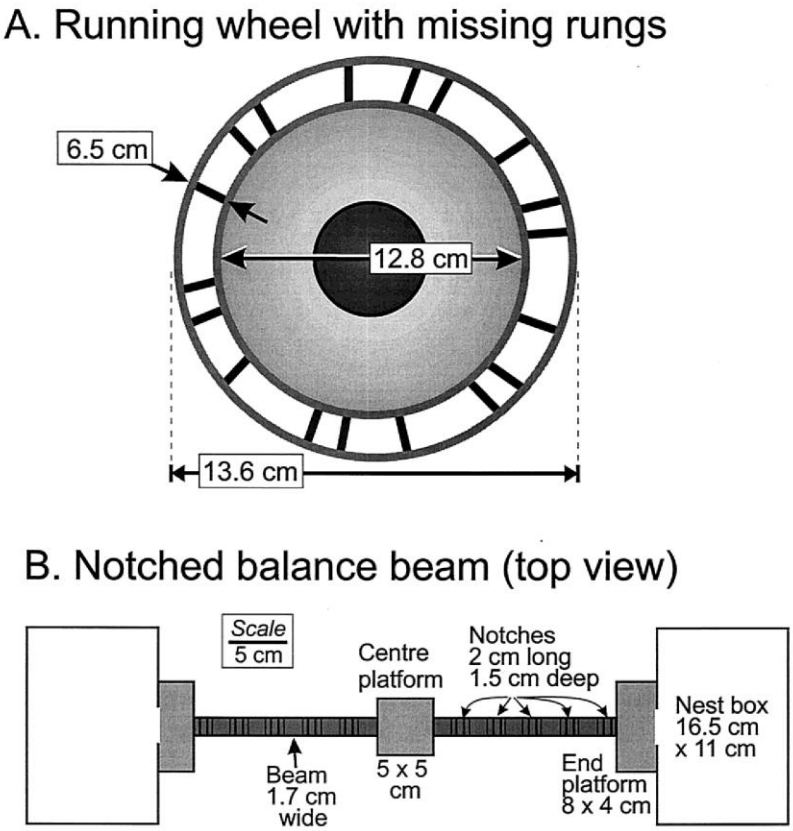

FIG. 1. (A) The plastic running wheel with half its rungs removed in a pattern of 0, 1, and 2 rungs missing in succession. The same kind of wheel but with all 36 rungs intact in a previous study [3] revealed no difference between mice with no corpus callosum (CC) and normal CC. (B) The notched balance beam modeled after an earlier version [21] but with the addition of nest boxes at either end to provide motivation for crossing from the center platform. Mice rarely fell from the beam but frequently had a hind foot slip down.

Surgery

The procedure for sectioning of the mouse CC has been described in detail elsewhere [25]. B6D2F_2 mice were anesthetized with isoflurane, and the CC was sectioned with a fine (0.5-mm) hook-shaped knife inserted via a small slot in the skull about 0.5 mm lateral to midline. Equal numbers of mice had the cut placed to the left or the right of midline. This surgical method involved very little loss of blood and resulted in a severing of 90% of CC axons in most cases. Sham surgery involved the same anesthesia and drilling of the slot in the skull, except

that the knife was inserted dorsal to the CC and usually severed few CC axons while resulting in a similar pattern of extracallosal damage. Unoperated B6D2F_2 controls were also used for behavioral testing.

Behavioral Test Apparatus

Running wheels were very similar to those used in a previous study in this laboratory, where no effect was found in mice with a genetically caused absence of the CC [3]. In order to render the task more difficult, half of the rungs were removed from a "Fritz Plastic Playwheel" (Fritz Pet Products, Dallas, TX, USA) in an irregular pattern in this study (see Fig. 1A). The wheel was mounted in a plastic box (32 × 32 × 30 cm) with a metal nest box (15 × 12 × 10 cm) available through the wall opposite the running wheel. The time of each one-third turn of the wheel was registered by photocells that sent data to a computer [33]. A mouse lived in the wheel test box continuously for 5 days and had free access to the usual water and laboratory chow at all times. All running was entirely voluntary and could occur at any time of the day or night, although most activity was observed during the dark phase. The experimenter visited the mouse during testing only briefly each day at the end of the light cycle to clean the cage floor and provide fresh water and food, as required.

The notched balance beam was a copy of the apparatus first built in the laboratory of H.-P. Lipp at the University of Zürich [21], who generously sent his device to our laboratory. Our copy was machined from aluminum according to the dimensions shown in Fig. 1B. The apparatus was suspended 66 cm above a table and 50 cm from a wall, and the movements of the mouse were recorded with a video camera at a distance of 1 m and at the same level as the beam. The front, top, and back surfaces of the beam were covered with masking tape to provide a consistent grip for all animals [15]. A thin, U-shaped strip of aluminum could be placed over the notches in the beam to make ambulation a little easier. Illumination of the apparatus from a 7.5-W red light bulb and dimmed fluorescent lights provided about 5 Lux.

Procedures

Separate groups of mice were used for the running wheel and the balance beam tests. Those used on the running wheel were brought to the testing room and allowed 3 d in their group cage to adapt to a 12:12 light cycle in which lights went off at 1200 h rather than 1800 h. Each mouse was then placed individually into a wheel chamber and allowed to live there for 5 days with minimal disturbance.

The balance beam testing was done in the same room and with the same adaptation and lighting conditions as the running wheels, but no wheels were in operation during beam testing. All testing occurred during the first 2 h of the dark phase. Each mouse was tested on the beam for 5 min on each of 2 successive days, with the aluminum strip in place to cover the notches on the first day and then removed to expose the notches on the second day. The trial began when a mouse was placed gently onto the center platform. If it did not make at least three crossings of the beam between the center platform and one of the end platforms during 5 min, it was allowed an additional 2 min on the apparatus. The experimenter remained 3 m from the apparatus and intervened only if the mouse fell from the apparatus or remained in a nest box for 30 s; in which cases, the mouse was gently returned to the center platform.

Histology

Within 24 h of the end of behavioral testing, each mouse was anesthetized with an overdose of pentobarbital sodium (120 mg/ kg) and perfused intracardially with saline followed by neutral 4% paraformaldehyde in phosphate buffer. Brains were removed from the skull and allowed at least 1 further week in fixative, and then weighed. Each brain was bisected at the midsagittal plane and stained en bloc with gold chloride for myelin [4,28], and then commissure areas were measured with the JAVA image analysis program from Jandel Scientific (San Rafael, CA, USA). To assess the extent of transection of the CC during surgery, brains of B6D2F_2 mice in both the surgery and sham surgery groups were sectioned coronally at 60 μm throughout the rostrocaudal extent of the CC, and every fourth section was stained with gold chloride. The cross-sectional area of the portion of the CC that was not transected by the knife was estimated by determining the percent-age of uncut CC axons from the approximately 16 serial sections and then multiplying this by the average area for the B6D2F_2 mice that had no surgery.

RESULTS

Preliminary analysis revealed only one difference among a large number of measures between unoperated B6D2F$_2$ mice and sham surgery mice, and the sham and unoperated groups were therefore combined for further analysis. Additionally, no differences were detected between behaviors of pigmented and albino mice of comparable genetic backgrounds, and coat colors were also combined for analysis. As observed previously in genetically abnormal mice [36], the CC area showed a bimodal distribution with very few animals in the range from 0.3 to 0.6 mm^2. The distribution was similar in B6D2F$_2$ mice because a small portion of CC axons was sometimes severed in the sham surgery group and a few axons in the complete surgery condition escaped the knife. Thus, for purposes of analysis, both the RI and B6D2F$_2$ groups were dichotomized, with any animal having CC area of 0.7 mm^2 or more being considered normal, and this yielded four separate groups for a 2 × 2 Analysis of Variance (ANOVA). Each ANOVA used repeated measures, the kind and number of repeated measures depending on the specific behavioral test. Group differences detected with the dichotomy were examined further with multiple regression methods that treated CC size as a continuous variable. The criterion of significance was set at $\alpha = .05$ for tests of the central predictions, and $\alpha = .01$ for other effects.

TABLE 1

RUNNING WHEEL BEHAVIOR FOR FOUR GROUPS OF MICE (MEAN ± SD)

Measure	Day	B6D2F$_2$ with normal CC $n = 25$	B6D2F$_2$ with deficient CC $n = 45$	RI with normal CC $n = 10$	RI with deficient CC $n = 25$
Rotations in 24 h	2	9121 ± 5156	10729 ± 5045	5873 ± 3510	4680 ± 4602
	3	12751 ± 5857	13525 ± 5858	7323 ± 4188	5337 ± 4762
	4	15729 ± 7417	15969 ± 7076	9596 ± 6904	7130 ± 4913
	5	18302 ± 9330	18081 ± 7713	9550 ± 7181	9158 ± 5192
Minimum time (ms) for 1/3 rotation	2	171 ± 69	218 ± 25	206 ± 32	232 ± 65
	3	157 ± 63	205 ± 26	206 ± 24	242 ± 89
	4	151 ± 62	195 ± 27	195 ± 28	210 ± 64
	5	146 ± 58	186 ± 28	189 ± 24	197 ± 52
Modal time (ms) for 1/3 rotation	2	293 ± 82	346 ± 74	294 ± 30	415 ± 163
	3	262 ± 71	312 ± 58	289 ± 35	408 ± 175
	4	244 ± 67	284 ± 54	274 ± 44	358 ± 154
	5	229 ± 76	271 ± 54	262 ± 37	310 ± 103
Bouts of running lasting 10 or more seconds	2	255 ± 174	309 ± 166	143 ± 65	129 ± 170
	3	384 ± 191	399 ± 177	229 ± 133	222 ± 472
	4	440 ± 183	479 ± 189	287 ± 228	185 ± 180
	5	505 ± 202	540 ± 178	283 ± 210	258 ± 185

CC, corpus callosum; SD = standard deviation; RI, recombinant inbred.

Running Behavior

Numerous indicators of running behavior were derived from the computerized wheels and subjected to repeated measures analysis, as described previously [3]. Mice in all groups improved their performance substantially over days, and the B6D2F$_2$ mice were generally superior to the RI mice, but generally no significant sex differences were found. Behavior tended to be highly variable on the first day when mice encountered the wheels for the first time and just began to run. Formal statistical analysis was therefore done on days 2 to 5. Several measures are summarized in Table 1. The size of the CC showed no relation with the total number of rotations of the wheel during a 24-h period (Table 1) in either the B6D2F$_2$ or RI mice, whereas measures of peak running speed revealed that a deficit in the CC was associated with poorer running ($F = 8.1$, $p < 0.001$). In both the B6D2F$_2$ and RI groups, mice with very small or absent CC achieved slower maximum running speeds, as indicated by the minimum time required for one-third rotation of the wheel and especially by the modal time for one-third rotation. Despite the generally slower speed of acallosal than of normal mice, they had similar numbers of bouts of continuous running that lasted 10 or more seconds.

Measures that appeared to show an effect of dichotomized CC size were analyzed further with multiple regression using CC size as a continuous measure. Genetic group (B6D2F$_2$ versus RI) was effect coded (+ 1/2, — 1/2), whereas CC area was centered by taking the difference from the overall group mean CC size [4]. The third term in the regression equation was the interaction coded as the product of group and centered CC area. Dependent measures were averaged over the 4 test days. These methods resulted in almost perfect independence (tolerance > 0.96) of the genetic group, CC size, and group × CC size interactions in the regression equation. For modal rotation time, B6D2F$_2$ mice ran faster than did RI mice ($t(99) = 3.89$, $p = 0.0002$), and the

progressive increase of CC size led to an increase in rotation speed ($t(99) = 4.09$, $p = 0.00009$), but the interaction was not significant ($p = 0.27$, two-tailed). As indicated in Fig. 2, the CC size effect was also significant when each genetic group was considered separately. This result was especially important because we predicted that modal speed in particular would show the clearest effect of deficient CC.

Balance Beam Behavior

A variety of indicators of behavior on the balance beam was observed on both days of testing, including the number of crossings from the center platform to an end platform (half crossings of the beam), cage entries, frequency of falls to the table from the beam and the platforms, frequency of long inactivity (>30 s) in the nest box, and frequency of slips from the beam with the hind foot. Slips with the fore foot were not usually seen unless the animal fell from the beam. Data were scored only for mice having three or more beam crossings (six half-crossings) on both test days, and consequently, the results for 36 inactive mice were not used for analysis. According to previous work with the notched balance beam [21], hind foot slips were expected to be most sensitive to absence of the CC.

Results for the $B6D2F_2$ and RI mice with normal and deficient CC are summarized in Table 2. Mice in all four groups were considerably more active on the second day, despite the exposure to the more difficult, notched surface on the second day, and $B6D2F_2$ mice generally made fewer slips off the beam than did RI mice. They made more hind foot slips on the notched than on the smooth surface, but the hind foot slips per crossing of the beam were very similar on the 2 days for the $B6D2F_2$ mice and only slightly more common for the RI mice. A preliminary statistical analysis examined sex and group effects for all measures, and no sex differences significant even at $p = 0.05$ were seen. Group differences were apparent only for hind foot slips off the beam on both days. Because a moderate correlation occurred between activity, as indicated by half-crossings of the beam, and hind foot slips, the ratio of hind foot slips to half-crossings was also calculated, and the analysis showed no sex difference but a large group effect. Also, a strong correlation occurred ($r(117) = 0.63$) between the ratio on the 2 d, which indicates that the ratio was reasonably reliable.

Multiple regression analysis of the ratio of hind foot slips to half-crossings used strain coded as (+ 1/2, — 1/2) and centered CC area, as was done for wheel running. The analysis yielded clear evidence that $B6D2F_2$ mice were superior to RI mice on day 1 with the smooth beam ($t(115) = 5.7$, $p < 0.00001$) and day 2 with the notched beam ($t(1\ 15) = 8.7$, $p < 0.\ 0000\ 1$), but no relation with CC size or interaction between group and CC size was apparent (all $p > 0.2$, two-tailed), as indicated in Fig. 2.

DISCUSSION

A deficit in voluntary running speed on an irregular wheel was apparent for animals having deficient CC resulting from both surgical section in normal hybrid mice and genetic abnormalities in recombinant inbred mice, whereas no CC-related deficit was apparent on the notched balance beam. The wheel and the beam are both sensitive to motor coordination deficits, but the kind and degree of deficits differ to some extent. One obvious distinction that we believe may be relevant to the present results is speed of movement. On the balance beam, mice must carefully place one foot and then the next in order to avoid a fall. For the most active mice that were continually moving along the beam between the nest boxes, 25 half-crossings of a 25-cm length of beam and platform were made in 5 min, which amounted to an average speed of about 2 cm/s. Most mice moved much slower than 2 cm/s. For the running wheel, on the other hand, peak speeds of less than 200 ms per one-third rotation of the wheel were commonly observed, which amounted to 2 revolutions/s of a wheel having a circumference of 41 cm, equivalent to a peak speed of 82 cm/s, about 40 times faster than on the notched beam.

To confirm the speed hypothesis, testing on additional kinds of apparatus involving different speeds of movement will be necessary. It is known that genetic effects are sometimes evident on specific kinds of motor coordination tasks but not others [5,6,16]; hence, the domain of motor coordination is differentiated and complex. If this is true for genetic defects, it is also likely to be true for anatomical defects. Running and grasping a beam with the opposing force of opposite limbs also differ in topography as well as speed, and further tests of the speed hypothesis will benefit from a series of tasks that is made to vary only along the speed

dimension. One task that might be used is the rotarod, in which speed is systematically increased to determine the maximum running speed of subjects [5,20,30]. This task may be useful for testing CC-deficient mice, provided that a means can be found to prevent subjects from wrapping around the rotating rod to circumvent running.

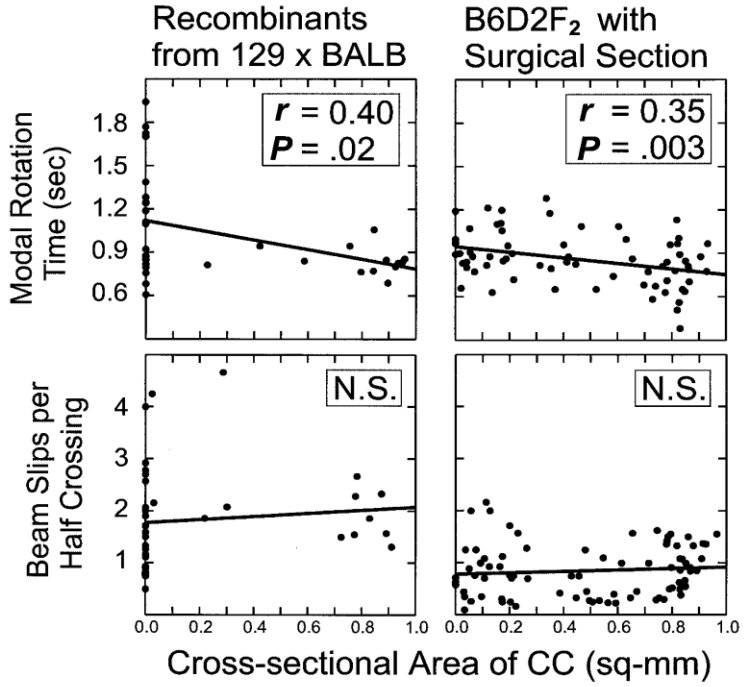

FIG. 2. Scatterplots of individual data and straight lines of best fit relating cross-sectional area of the corpus callosum (CC) at the mid-sagittal plane to two measures of motor coordination for two groups of mice. The recombinant inbred mice often had no CC for genetic reasons, whereas the $B6D2F_2$ mice with no or small CC resulted from surgical section. In both groups of mice, wheel running, indexed by modal time for one rotation, was slower for those with no or small CC, whereas no significant relation with CC size was observed for either group on the balance beam.

The size of surgical and genetic effects on the two kinds of tests may also be evaluated with statistical criteria [31,32]. One convenient index compares the difference between group means with standard deviations within groups ($d = (M_1 — M_2)/s$). On the wheel, modal running speed was $d = 0.83$ standard deviation higher for the $B6D2F_2$ hybrids than for the RI mice and $d = 1.2$ standard deviation higher for mice with an intact CC. On the balance beam, hind foot slips per half-crossing were $d = 1.1$ and $d = 1.7$ standard deviations higher for the $B6D2F_2$ hybrids than for the RI mice on days 1 (smooth beam) and day 2 (notched beam), respectively, but the nonsignificant CC size effect was about $d = 0.3$ standard deviation for total CC absence versus normal CC. With $n = 50$ mice in each of two groups, the 90% confidence interval for the true CC effect size would be $(-0.04 < \delta < 0.63)$. Thus, the present data do not conclusively prove the absence of any CC effect, but they certainly show that any effect on the balance beam is likely to be small. The sample size issue is challenging when group by treatment interactions are of interest, because much larger samples are usually needed to detect interac-tions than are main effects with the same level of statistical power [8,31,32]. This poses a problem for our running wheel results (Fig. 2), in which large main effects of strain and CC size were detected but the strain × CC size interaction was not significant. Looking more closely at Fig. 2, it appears to the eye that hybrid and RI mice with normal CC size had very similar running speeds, whereas the acallosal RI mice were considerably slower than were CC sectioned hybrid mice. Nevertheless, the multiple regression tells us that the hypothesis of interaction is not supported. Considerably larger samples than studied here will be needed to resolve the matter.

The large within-group variability in running speed of acallosal RI mice (Fig. 2) was clearly present within two of the RI lines, where modal speeds among acallosals within each line ranged from 0.75 to 1.8 rotations per second. One of the RI lines, however, had no acallosal mice with modal speeds in excess of 1.2 rotations per second. Thus, the large variability arose from both within-line and between-line sources, the latter perhaps involving a genetic difference between lines that was unrelated to CC maldevelopment. This also raises the possibility of an epistatic interaction between genes pertinent to both absent CC and motor coordination, and the

genetic background of the lines. Much larger samples would be required to confirm this kind of effect, in view of the modest brain-behavior correlation reported here. The large variability in running speed of acallosals was not apparent in other measures of running, such as total rotations. For slips on the balance beam, the apparently greater variability in acallosal mice arose from only two animals in one RI line, a line in which five other acallosals had less than three slips per half-crossing, which is comparable to performance by hybrid mice.

TABLE 2

BALANCE BEAM BEHAVIOR FOR FOUR GROUPS OF MICE (MEAN ± SD)

Measure	Day	B6D2F$_2$ with normal CC n = 32	B6D2F$_2$ with deficient CC n = 49	RI with normal CC n = 8	RI with deficient CC n = 30
Half-crossing of beam	1	5.28 ± 3.39	5.53 ± 3.78	4.12 ± 0.83	6.23 ± 3.42
	2	8.62 ± 4.98	9.61 ± 5.21	6.50 ± 3.46	9.70 ± 6.92
Cage entries	1	4.96 ± 1.53	4.51 ± 1.63	4.50 ± 2.51	4.80 ± 2.88
	2	4.78 ± 2.21	4.51 ± 2.32	2.62 ± 2.26	4.50 ± 2.82
Hind foot slips off beam	1	3.31 ± 2.02	2.53 ± 1.87	6.12 ± 2.30	6.87 ± 4.09
	2	5.59 ± 3.00	4.88 ± 2.56	11.12 ± 5.72	13.70 ± 6.09
Falls from beam	1	<1	<1	<1	<1
	2	<1	<1	0	<1
Hind foot slips per half-crossing	1	0.72 ± 0.46	0.60 ± 0.54	1.59 ± 0.84	1.44 ± 1.13
	2	0.75 ± 0.42	0.67 ± 0.50	1.77 ± 0.45	1.79 ± 1.00

CC, corpus callosum; SD = standard deviation; RI, recombinant inbred.

Although B6D2F$_2$ hybrid mice were definitely superior to RI mice on both tests, it would be premature to conclude that this happened because of greater heterozygosity in the F$_2$ mice. One group was derived from C57BL/6J and DBA/2J, and the other came from 129/ReJ and BALB/cWah1. Inbred strains differ among themselves on many tests of motor coordination [1,20,30], and the differing alleles of these strains might have influenced our results. This matter could be addressed in future work by comparing F$_2$ mice with RI lines derived from the same F$_2$ population, so that the groups would differ only in the degree of heterozygosity.

The F$_2$ mice in the present study were used because they were known to be free from any CC defects and were expected to show good motor coordination when the CC was intact. If a robust deficit in motor behavior results from CC section, it should have been apparent with the F$_2$ mice, and indeed a deficit was seen on the running wheels. Having established one definite effect of CC section, it was then easier to interpret data from the RI mice with hereditary absence of the CC. In our study, these animals also suffered a deficit in wheel running. Hence, for this particular motor behavior, developmental compensation did not spare mice with congenital CC absence. Exposure to running wheels earlier in life may ameliorate the deficit in acallosal mice, but it is also possible that the deficit would be even more severe at younger ages, as has been observed with the visual system [19].

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