

Open-Field Behavior of House Mice Selectively Bred for High Voluntary Wheel-Running

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Open-field behavioral assays are commonly used to test both locomotor activity and emotionality in rodents. We performed open-field tests on house mice (*Mus domesticus*) from four replicate lines genetically selected for high voluntary wheel-running for 22 generations and from four replicate random-bred control lines. Individual mice were recorded by video camera for 3 min in a 1-m² open-field arena on 2 consecutive days. Mice from selected lines showed no statistical differences from control mice with respect to distance traveled, defecation, time spent in the interior, or average distance from the center of the arena during the trial. Thus, we found little evidence that open-field behavior, as traditionally defined, is genetically correlated with wheel-running behavior. This result is a useful converse test of classical studies that report no increased wheel-running in mice selected for increased open-field activity. However, mice from selected lines turned less in their travel paths than did control-line mice, and females from selected lines had slower travel times (longer latencies) to reach the wall. We discuss these results in the context of the historical open-field test and newly defined measures of open-field activity.

KEY WORDS: Correlated response; emotionality; exercise; open-field activity; selective breeding; wheel-running.

INTRODUCTION

C. S. Hall (1934, 1936) originally proposed that measuring aspects of rat behavior in a contained arena would indicate the emotional reactivity of the subjects. Specifically, he suggested that both the number of fecal boli deposited by individuals and their activity patterns mapped directly onto variation in the levels of fear and emotional reactivity; large numbers of boli and little activity indicated a fearful individual. Subsequently, the “open-field” test has been developed into an often-used indicator of emotionality (e.g., Belzung, 1999;

Crawley, 1999), although not without criticism (Archer, 1973, 1975; Walsh and Cummins, 1976) and a call for standardization and verification of methods (Weiss and Greenberg, 1998). Many reports have validated open-field tests as useful measures of emotional reactivity [(Blizard, 1981; van der Staay *et al.*, 1990); e.g., reviewed by Sandnabba (1996) for Turku aggressive mice]; others have not found differences in open-field activity despite differences in other anxiety measures [e.g., MHC-congenic mice (Brown *et al.*, 1999)]. Nevertheless, the open-field test remains a standard behavioral assay reported in the literature (e.g., Crabbe *et al.*, 1999).

Open-field defecation and activity have proven to be traits that can be genetically modified by selective breeding in both rats (e.g., Broadhurst, 1957; Blizard, 1981) and mice. In a long-term, replicated artificial selection experiment with mice, DeFries *et al.* (1970, 1974, 1978) were able both to increase and decrease open-field activity and to demonstrate a correlated response in deposition of fecal boli. At the 30th

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generation of selection, mice selected for low activity deposited many boli (ca. 10 per 3-min trial), whereas mice selected for high activity deposited few fecal boli (ca. two per 3-min trial). DeFries *et al.* (1970) also examined the “situational generality” of selection for open-field activity after 10 generations, by testing for correlated changes in other measures of activity. High- and low-selected lines had corresponding high and low activity scores in other box-like and brightly illuminated apparatuses. However, high- and low-activity lines did not differ in their voluntary wheel-running behavior measured on 2 nonconsecutive days, presumably under normal light/dark cycle conditions. Additionally, the low-activity lines became 100% albino, whereas the high-activity lines lost the albino phenotype. The implications of this correlated evolution in coat color remain unclear (DeFries *et al.*, 1974).

Here we report on open-field tests of mice from four replicate lines that have been subjected to 22 generations of within-family selection for increased voluntary wheel-running (Swallow *et al.*, 1998; Koteja *et al.*, 1999). These mice now run approximately three times farther (total revolutions) per day than do mice from the four randomly bred control lines, primarily by increases in the number of revolutions run per minute. This result is true for both sexes, but the divergence in average running speed between selected and control lines is somewhat greater for females (e.g., see Rhodes *et al.*, 2000; Koteja and Garland, 2001). Furthermore, females run more total revolutions than do males in both the selected and the control lines. We test several hypotheses relating to the evolved differences in wheel-running behavior. Specifically, we test whether mice from lines selected for high wheel-running exhibit (i) higher activity and lower defecation in the open field (based on the extreme divergence in wheel activity and the putative negative genetic correlation between open-field activity and defecation); (ii) less turning behavior in the open field (based on the fact that wheel-running occurs primarily in a straight line); and (iii) a sex difference, with females being more active in the open field than males (based on a similar pattern in wheel-running). We report both traditional indices (distance traveled, fecal boli) and newly recognized indices of open-field activity including thigmotaxis (wall-hugging), latency of entry into the wall zone, time spent in the interior, and movement path “roughness” (*sensu* Krebs-Thomson *et al.*, 1998; Paulus *et al.*, 1998; see van der Staay *et al.*, 1990; Crawley, 1999; Belzung, 1999). Mice that travel little (and defecate often) or that hurry to the wall zone, spend little time in the interior, or tend to travel without turns are classified as less exploratory and more emotionally reactive.

MATERIALS AND METHODS

Subjects. The mice (*Mus domesticus*) used in this study were offspring from generation 22 (S_{22}) of an ongoing laboratory selection experiment on voluntary wheel-running behavior (the base population was the Hsd:ICR strain, which is fixed for albinism). The design employs eight lines of mice, four selected lines and four lines bred randomly as controls (see Fig. 1). Each line is maintained with 10 families per generation. Breeders are chosen based on the average revolutions run on days 5 and 6 of a 6-day test at approximately 6–8 weeks of age. Although revolutions are monitored continuously over days 5 and 6 (i.e., for 48 h), voluntary activity occurs primarily during the dark phase (unpublished data). Substantial response to selection has occurred (Fig. 1) (see Swallow *et al.*, 1998; Koteja *et al.*, 1999); by the 17th generation, mice from selected lines were running approximately 150% more revolutions than control mice (Rhodes *et al.*, 2000), and an apparent selection plateau may have been reached. Routinely, mice are housed in same-sex groups of four per cage (except during breeding and wheel-running measurements) and maintained on a 12-h light/12-h dark cycle (lights on at 0800 h), which is also maintained during the wheel-running trials.

For the open-field measurements, one male and one female were randomly chosen from each of 10 families within each of the eight lines (age at time of testing ranged from 60 to 78 days; mean = 69.6 days). These 160 S_{22} mice were split randomly into three measurement batches, and open-field trials were conducted on 6 days (2 consecutive days per batch; 1200–1700 h) in June 1999, following the 6-day wheel-running test. Although the selection protocol involves revolutions on days 5 and 6, here we report data from days 1 and 2 of the wheel test to facilitate comparison with studies by DeFries *et al.* (1970).

Open-Field Arena and Testing Protocol. We used a 100 × 100-cm arena with 45-cm-high walls constructed of five pieces of black Trovicel plastic held together with duct tape on the outside. The Polytrack video system and corresponding Chromotrack software (v4.02b; both by San Diego Instruments, Inc., San Diego, CA) were used to collect, digitize, and analyze data. A video camera was placed 245 cm above the arena to record trials, and the tracking software noted the location of the mouse every 0.055 s for 180 s. We defined a minimum displacement of 2.5 cm to constitute a change in location, a minimum angle of 30° to constitute a turn, and a 3-cm-wide wall zone.

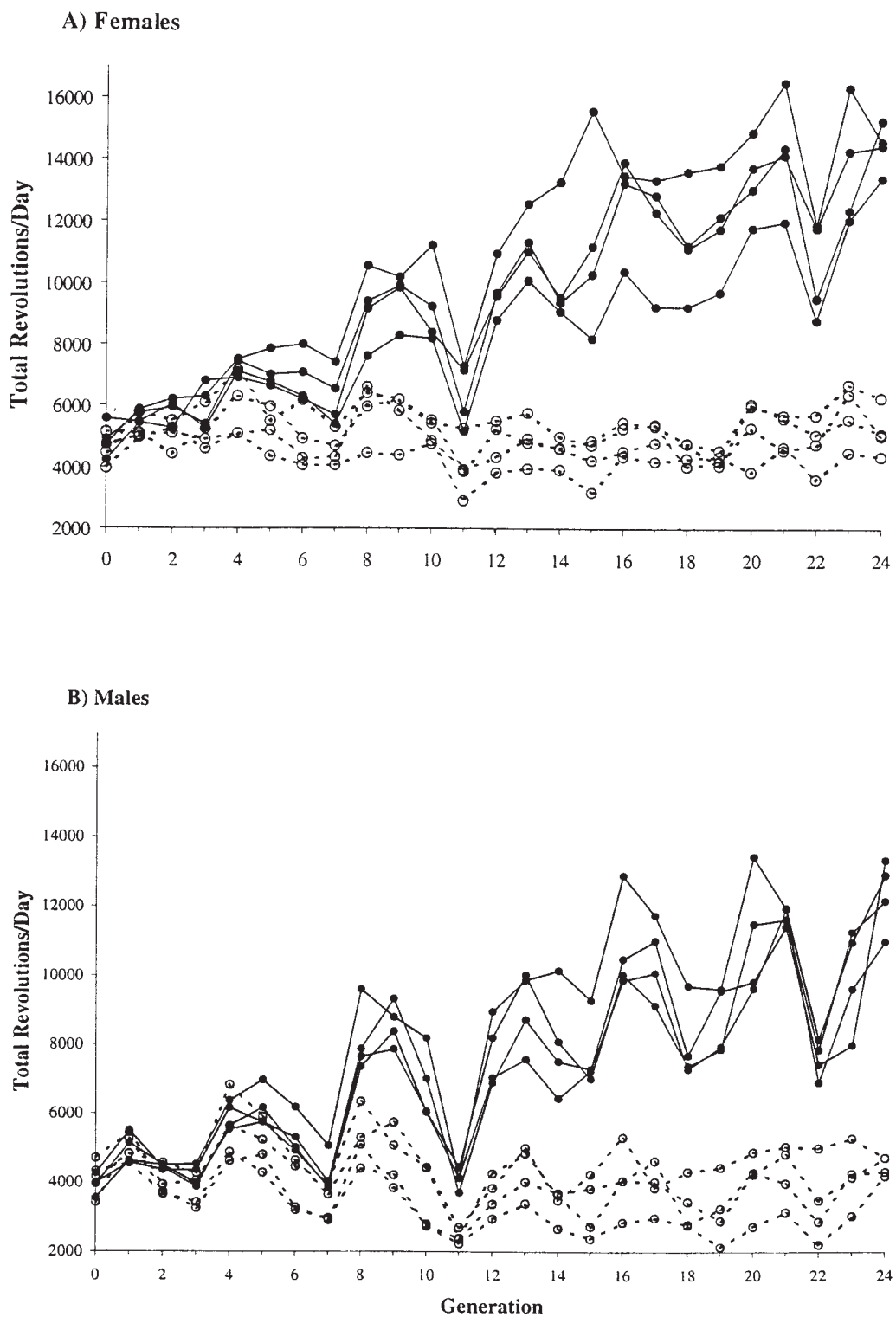


Fig. 1. (A) Female and (B) male wheel-running (revolutions/day) for selected and randombred control lines (four each) averaged over days 5 and 6 of a 6-day trial for generations 1–24. Solid lines and filled circles are selected mice; dashed lines and open circles are control mice.

Trials were 3 min in duration and were performed in a dimly lit room (5 lux on the floor of the testing arena) to optimize digitization and because mice are active and perform voluntary wheel-running during the dark half of their light/dark cycle. Within a measurement day, the order of mice was assigned randomly, and the time of day was noted for use as a statistical covariate. At the start of each trial, a mouse was grasped by the tail and placed in the center of the arena. The arena floor was wiped with a moist sponge (water only) between trials and allowed to dry before the next trial, as is standard protocol in open-field testing. Each mouse was weighed after its first trial. In addition to the computer-recorded variables, we recorded the number of fecal boli and urine pools deposited on the arena floor.

Analysis. We analyzed all day 1 and day 2 dependent variables separately with nested mixed-model analysis of covariance, applying the repeated-measures option to test additionally for differences between day 1 and day 2 (PROC GLM in SAS, v6.12; SAS Institute, Inc., Cary, NC). Selection history (selected vs. control) was a fixed effect, and line nested within selection history was a random effect (i.e., four selected lines and four control lines). In addition, we analyzed an individual's maximum travel distance and minimum latency to enter the wall zone over the 2-day trial. Our previous studies on these mice have indicated various behavioral differences between males and females (e.g., Swallow *et al.*, 1998; Koteja *et al.*, 1999; Carter *et al.*, 2000; Rhodes *et al.*, 2000); therefore, males and females were analyzed separately. We included several covariates in our analysis: body mass (g), age (days), z^2 -transformed age, time of day, and z^2 -transformed time of day. To analyze the repeatability of behaviors within individuals, we calculated Pearson correlation coefficients for values on days 1 and 2.

RESULTS

Nested Analysis of Covariance. The p values from the full-model ANCOVA for the main effect of selection history and the replicate effect (line nested with selection history) are reported in Table I, along with least-square means and pooled standard errors for each dependent variable. None of the age or time-of-day covariates were significantly correlated with any dependent variable; body mass was significant only in the analysis of wheel-running and female latency. We focus here on differences between selection and control lines.

Mice from selection lines weighed less than controls (see also Swallow *et al.*, 1999) and ran signifi-

cantly more on running wheels for both females and males. However, neither open-field travel distance nor defecation differed between mice from selection and mice from control lines on either day. (Table I). Because the defecation data are counts with a positively skewed distribution centered near zero (e.g., 75% of animals did not defecate during the 3-min trial on day 1), we also analyzed defecation as a nominal response variable. When we analyzed the presence or absence of boli with nominal logistic analysis (line nested within selection history), we again found no differences between mice from selection and mice from control lines in defecation ($p > \chi^2 > .30$ in all tests). Thus, the two measures associated with traditional open-field assays (defecation and activity) did not differ between individuals from our selection and individuals from our control groups. Unlike previous studies of open-field behavior, (transformed) fecal boli and travel distance were uncorrelated ($p > .20$ in all cases). Furthermore, when we tested for a correlation between these two variables using the residuals from a full-model analysis of covariance (i.e., after correcting for line, age, and time-of-day variation), the correlation was still non-significant ($p > .15$ in all cases).

Latency of entry to the wall zone was shorter for control females than for females from selection lines on day 1 (Table I). However, the minimum latency in the 2-day trial was not different between selection and control mice. Likewise, time spent in the interior versus the wall zone did not differ between mice from selection and mice from control lines on either day (range: 83–107 s spent in the interior in a 180-s trial) for either males or females. Average distance from the center of the arena during the trial was similar between control and selection mice and was also similar for males and females (Table I; range = 44.3–47.0 cm).

Both male and female control mice turned significantly more in their travel paths than did mice from selection lines on at least 1 of the trial days, which indicates that control mice had a greater degree of roughness in their travel paths. And although control mice turned more than selection-line mice, the total number of movements did not differ between the two groups (Table I) (e.g., day 1: control males = 921 movements, selection males = 906; control females = 977, selection females = 1,018).

Days 1 and 2: Differences and Repeatability. For comparison of the mean trait values between day 1 and day 2, we report the significance level for the repeated effect (Table II); interactions between it and other effects, e.g., selection history, were never statistically

Table I. Least-Square Means (LSmean), Pooled Standard Error (SE), and *F*-Test Significance Levels for Selection History and Replicate Line from Analyses of Covariance Correcting for the Time and Age at Which the Test was Performed

Dependent variable (units)	Females					Males				
	Control LS mean	Both (SE)	Selected LSmean	<i>p</i> value		Control LS mean	Both (SE)	Selected LSmean	<i>p</i> value	
				Selection history	Line				Selection history	Line
Wheel-running (revs/day) ^a	3195	(548)	5772	.03	.02	2358	(328)	3873	.02	.03
Body mass (g)	26.2	(0.37)	23.1	.0009	.12	33.3	(0.65)	29.5	.006	.002
SQRT defecation ^b (boli)										
Day 1	0.68	(0.23)	0.30	.30	.0001	0.54	(0.25)	0.60	.88	.0006
Day 2	0.64	(0.20)	0.24	.20	.003	0.85	(0.28)	0.75	.81	.0002
Maximum travel distance (cm)	3106	(157)	3,436	.19	.44	2830	(121)	2701	.48	.26
Travel distance, day 1(cm)	2804	(109)	2,969	.33	.69	2628	(148)	2574	.81	.24
Travel distance, day 2(cm)	2892	(158)	3,166	.27	.52	2419	(141)	2217	.36	.18
LN shortest latency(s) ^c	1.02	(0.21)	1.55	.16	.62	1.71	(0.16)	1.71	.99	.74
LN latency, day 1	2.11	(0.16)	2.93	.03	.91	2.62	(0.19)	2.90	.36	.52
LN latency, day 2	1.52	(0.19)	1.50	.96	.44	2.09	(0.18)	1.79	.29	.39
LN interior time (s)										
Day 1	4.55	(0.07)	4.62	.52	.09	4.67	(0.05)	4.60	.38	.10
Day 2	4.42	(0.06)	4.43	.36	.26	4.56	(0.06)	4.44	.20	.52
Avg. center distance (cm)										
Day 1	46.0	(0.8)	44.3	.22	.44	43.9	(1.0)	45.7	.25	.34
Day 2	46.4	(0.6)	46.5	.94	.65	45.0	(0.88)	47.0	.16	.55
Left turns (number)										
Day 1	132	(8.5)	123	.48	.19	132	(3.4)	114	.008	.49
Day 2	118	(3.7)	103	.03	.54	117	(3.4)	97	.004	.54
Right turns (number)										
Day 1	140	(2.7)	124	.008	.80	146	(1.9)	127	.0001	.98
Day 2	131	(5.7)	114	.08	.18	137	(4.4)	108	.003	.63
Straight lines (number)										
Day 1	706	(31)	771	.19	.74	643	(44)	664	.74	.25
Day 2	752	(49)	870	.15	.44	593	(43)	583	.87	.22
Movements (number)										
Day 1	977	(35)	1,018	.44	.68	921	(46)	906	.82	.26
Day 2	1002	(47)	1,087	.25	.56	848	(45)	788	.39	.22

^a Days 1 and 2 of a 6-day wheel-running trial measured 1 week prior to the open-field test. Analysis includes body mass as a covariate.

^b Female latency to move to wall-zone analysis includes body mass as a covariate.

^c Transformations are SQRT = square root, and LN = natural logarithm.

Table II. Comparison of Replicate Trials Within Individuals (Pearson *r*) and Across Days (Repeated-Measures *F* Statistic)^a

Dependent variable	Females			Males		
	Repeatability Pearson <i>r</i>	Repeated measures		Repeatability Pearson <i>r</i>	Repeated measures	
		<i>F</i> _{df1,df2} (<i>p</i>)	Conclusion		<i>F</i> _{df1,df2} (<i>p</i>)	Conclusion
SQRT (fecal boli)	-.04	.28 _{1,69} (.60)	Day 1 = day 2	-.02	5.64 _{1,68} (.02)	Day 1 < day 2
Travel distance (cm)	.58	2.01 _{1,68} (.16)	Day 1 = day 2	.42	8.18 _{1,66} (.006)	Day 1 > day 2
LN (latency)	.04	25.7 _{1,68} (.0001)	Day 1 > day 2	.19	26.5 _{1,64} (.0001)	Day 1 > day 2
LN (interior)	.58	29.2 _{1,69} (.0001)	Day 1 > day 2	.51	3.50 _{1,66} (.0005)	Day 1 > day 2
Center distance	.65	7.76 _{1,68} (.007)	Day 1 < day 2	.84	12.2 _{1,66} (.0009)	Day 1 < day 2
Left turns	.28	10.8 _{1,69} (.002)	Day 1 > day 2	.35	24.7 _{1,66} (.0001)	Day 1 > day 2
Right turns	.26	8.83 _{1,69} (.004)	Day 1 > day 2	.18	8.75 _{1,66} (.004)	Day 1 > day 2
Straight lines	.59	5.98 _{1,69} (.017)	Day 1 < day 2	.48	5.13 _{1,66} (.027)	Day 1 < day 2
Total movements	.59	2.17 _{1,69} (.14)	Day 1 = day 2	.43	9.21 _{1,66} (.003)	Day 1 > day 2

^aSignificant ($p < .05$) Pearson *r* coefficients appear in boldface and indicate that values were positively correlated within individuals across days 1 and 2. A significant *F* statistic implies that the day 1 mean was significantly different from the day 2 mean (direction indicated under Conclusion).

significant. For most variables, the mean trait value changed between day 1 and day 2 (excepting female defecation, travel distance, and total number of movements). Consistent with a previous report on the base population (Friedman *et al.*, 1992), males traveled significantly farther and defecated less on day 1 than on day 2 (Table II). Both males and females approached the wall zone sooner and spent less time in the interior on day 2; thus, the average distance from the center was longer on the second day of the trial (Table II). Additionally, males and females turned more on day 1 than on day 2.

We tested for consistency within individuals with a Pearson correlation of scores on days 1 and 2 (Table II). For most traits, individuals showed statistically significant consistency in relative behavior on days 1 and 2, with the exceptions being defecation, latency, and right turns. For example, individual females tended to keep their same relative order on both days, such that individuals that moved earliest to the wall zone on day 1 also did so on day 2.

DISCUSSION

Historically, open-field defecation and activity have been used to assess the “fearfulness” or “emotional reactivity” of rodents (Hall, 1934, 1936; Broadhurst, 1957; DeFries *et al.*, 1970, 1974, 1978; Blizard, 1981; reviewed by Boissy, 1995; Weiss and Greenberg, 1998). In our study, we found no differences in either open-field activity or defecation between mice from lines that had undergone selection for increased voluntary wheel-

running activity and mice from random-bred control lines. Thus, despite large differences in wheel-running behavior measured over 48 h (Fig. 1), the situational generality (*sensu* DeFries *et al.*, 1970) of increased activity in shorter assays has not evolved in a correlated fashion. This result is in agreement with other studies that have tested both open-field activity and voluntary activity on running wheels (e.g., DeFries *et al.*, 1970; Dishman *et al.*, 1988; Friedman *et al.*, 1992). Specifically, in the DeFries lines, average daily wheel-running distances were 2.7, 1.6, and 2.0 km for high-selected, control, and low-selected groups, respectively, for mice approximately 90 days old (wheel circumference = 47.85 cm). Mice used in our study averaged 5.4 and 3.1 km/day for selected and control mice, respectively, for mice approximately 70 days old (values computed for days 1 and 2 of the 6-day wheel exposure and averaged for males and females). Differences in ages and wheel size notwithstanding, our selection experiment and that of DeFries and colleagues are consistent in indicating no genetic correlation between open-field activity and voluntary wheel-running. Similarly, across 12 species of murid rodents, the correlation between open-field activity and wheel-running is .36 (two-tailed $p > .2$), and the correlation between open-field defecation and wheel-running is .44 ($p > .1$) [computed using mean values reported by Wilson *et al.* (1976), Webster *et al.* (1979), and Dewsbury (1980)]. Thus, all studies to date support the view that voluntary exercise on running wheels and locomotor behavior in a (novel) open-field environment are neither genetically related nor controlled by similar environmental factors.

Control-line males and females performed significantly more right and left turns in their open-field traversing than did mice from the selected lines. This observation is perhaps unsurprising, given that wheel activity presumably comprises mainly straight-line running. Nonetheless, differences in turning behavior are of interest because, in recent literature, straight-line movements are associated with less exploratory behavior (e.g., Krebs-Thomas *et al.*, 1998; Paulus *et al.*, 1998).

Despite the similarity between control and selected mice in most measures, males and females consistently differed in all aspects of their activity in the open-field arena, as do male and female control and selected mice in measures of wheel-running. Overall, females defecated less and traveled greater distances than males. This result is consistent with sex differences in wheel-running within both the selected and the control treatments. By the 24th generation (Fig. 1), selected-line females and males were running approximately 16.2 and 13.9 km per 24-h test period, respectively; for control lines, the corresponding values are 5.8 and 5.0 km. These data suggest that females are generally more active than males, irrespective of selection history. The ultimate reasons for this activity difference are unknown but may reflect differences in parental care and/or foraging strategies in nature (see also Perrigo and Bronson, 1985; references cited by Sherwin, 1998).

Perhaps the most surprising result from this study was the lack of a negative correlation between open-field defecation and activity, particularly given the reports of DeFries and colleagues and the report of a negative correlation in the base (preselection) population of males in a 15-min open-field trial (Friedman *et al.*, 1992). In general, evidence from wild murid rodents is less clear in terms of what our a priori expectation should be regarding correlated responses in the present selection experiment. Dewsbury and colleagues (Wilson *et al.*, 1976; Webster *et al.*, 1979; Dewsbury, 1980) performed open-field tests on 20 species of captive-reared, wild murid rodents. The correlation between number of squares entered (a measure of distance moved) and number of defecations varied widely, ranging from $-.43$ to $.49$, and was not statistically significant for any of the 20 species. Moreover, the cross-species correlation using mean values reported by Wilson *et al.* (1976) and Webster *et al.* (1979) is also not statistically significant ($r = -.22$, $df = 18$, $p > .2$). Hence, the lack of a correlated response in our selection experiment seems more consistent with patterns observed within and among species of nondomesticated

rodents, rather than those observed in other studies of laboratory mice and rats. Several methodological factors may also account for differences or similarities of results across studies, including variation in size of arena, substrate texture, length of observation period, mechanism of scoring activity, illumination, and time within photoperiod cycle (e.g., see Dixon and Van Mayeda, 1986; Blizard and Bailey, 1979; reviewed by Weiss and Greenberg, 1998).

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