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Phenotypic variation in sensorimotor performance among eleven inbred rat strains

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Biesiadecki, Brandon J., Paul H. Brand, Lauren G. Koch, Patricia J. Metting, and Steven L. Britton. Phenotypic variation in sensorimotor performance among eleven inbred rat strains. *Am. J. Physiol.* 276 (*Regulatory Integrative Comp. Physiol.* 45): R1383–R1389, 1999.—As a first step toward identifying the genes that determine sensorimotor ability (motor coordination) we subjected 11 inbred strains of rats to three different tests for this trait. Rats were tested at 13 wk of age to determine how long they could remain on *1*) a rotating cylinder as the velocity of rotation increased every 5 s (1-direction rotation test), *2*) a rotating cylinder that reversed direction every 5 s and increased velocity every 10 s (2-direction rotation test), and *3*) a platform that was tilted 2° every 5 s from 22 to 47° (tilt test). On all three tests, rats of the PVG strain demonstrated the greatest sensorimotor ability. In contrast, rats of the MNS strain were most often represented among the group of strains that demonstrated the lowest performance on all tests. Considering all three tests, there was a 3- to 13-fold range in sensorimotor performance between the highest and lowest strains. This large divergence between the highest and lowest strains provides a genetic model that can be used to identify intermediate phenotypes and quantitative trait loci that contribute to sensorimotor ability.

coordination; cosegregation analysis; heritability; genetic model

RECENT DEVELOPMENTS in theory and technology have made possible the identification of the genetic components of variations in complex traits (6). Genetic models have proven to be the critical substrate for dissecting the genetic origin of allelic variations that are determinants of the differences in complex traits that are by definition polygenic (17). A somewhat ideal model can be created by selectively breeding for the low and high states of the trait of interest over many generations. Such selective breeding concentrates genes for the extremes of the trait in divergent lines. Once maximal divergence is attained, the low and high selected lines can be inbred to create strains that have minimal genetic variation, thereby optimizing the genomic analysis for differences between the strains (9, 16).

Another useful path is to identify wide differences for a trait of interest in already available inbred strains. Numerous inbred strains have been developed that were not first selectively bred for a specific trait. Like populations of individuals, these inbred strains can demonstrate wide variation for a given trait and thus serve as models to explore the cause of this variation.

A long-term goal of our laboratory is to define the genetic basis for the variation in physical performance within species of mammals. Physical performance is often separated into the components of strength, endurance, and sensorimotor ability. Although these are interrelated traits, the allelic variations that determine each of these individually defined components may indeed have discrete and unique genetic substrates.

The goal of this work was to evaluate the degree of variation in sensorimotor ability among 11 inbred strains of rats. If sufficient and consistent variation exists, then the strains with high and low sensorimotor ability can be used as a model to determine the genetic basis of the phenotypic differences. Our results demonstrate a consistent, striking variation in sensorimotor ability among the strains of rats evaluated. The PVG strain demonstrated the greatest sensorimotor ability, and the COP and MNS strains demonstrated the least. When evaluated by gender, the magnitude of the difference in sensorimotor performance between the low and high strains ranged from 3- to 13-fold on the three operationally defined tests of sensorimotor ability. These wide differences suggest that the PVG, COP, and MNS strains can be utilized as models to explore the genetic basis of variation in sensorimotor ability.

METHODS

Six male and six female rats from 11 inbred strains were evaluated at 13 wk of age by three tests of sensorimotor ability. At this age, the neurological processes involved in the control of movement are well developed (2). These strains include seven strains purchased from Harlan Sprague Dawley (Indianapolis, IN) received at 7–8 wk of age and four strains obtained from colonies maintained by John Rapp at the Medical College of Ohio (Toledo, OH). The seven strains obtained from Harlan Sprague Dawley were ACI/SegHsd, AUG/OlaHsd, BUF/NHsd, COP/Hsd, DA/OlaHsd, F344/NHsd, and PVG/OlaHsd. The strains obtained from Dr. John Rapp were the LEW, WKY, SR/Jr, and MNS. Animals were housed two rats per cage; only rats of the same gender, age, and strain were housed together. The rats were housed on a 12:12-h light-dark cycle with the light cycle occurring from 6:00 AM to 6:00 PM. Food and water were available ad libitum.

Protocol

All rats were tested daily for 5 consecutive days between the hours of 12:00 PM and 3:00 PM. The sensorimotor tests used, and the order in which they were applied, were *1*) a one-direction rotation test, *2*) a two-direction rotation test, and *3*) a tilt test. The order in which the animals were tested was random from day to day but was consistent for all three tests on any given day.

One-Direction Rotation Test

For this test a device was built based on the rotating rod apparatus originally described by Dunham and Miya (5). This device consisted of a hard plastic cylinder (7.9 cm in diameter and 15 cm long) with concentric 53-cm-diameter circular plastic sides attached to prevent the rat from climbing off the cylinder laterally. The cylinder was connected to a variable-speed reversible motor, allowing the speed and direction of rotation of the cylinder to be changed. The rat was placed on the cylinder with the long axis of its body parallel to the long axis of the cylinder while the cylinder was rotating in the counterclockwise direction at 0.60 rpm. The velocity of rotation of the cylinder was then increased 1.3 rpm every 5 s to a maximum of 26 rpm at 100 s. The time interval between placing the rat on the cylinder and the moment when the rat was no longer able to remain on the cylinder and fell 50 cm into a padded box was recorded as a measure of sensorimotor ability.

Two-Direction Rotation Test

The same apparatus as described for the one-direction rotation test was used in the two-direction rotation test. The rat was placed on the cylinder as described in *One-Direction Rotation Test* while the cylinder was rotating counterclockwise at 0.6 rpm. The direction of rotation of the cylinder was alternated every 5 s, and the velocity of rotation was increased every 10 s by 1.3 rpm to a maximum of 26 rpm at 200 s. The time from when the rat was released on the cylinder until it fell 50 cm into the padded box was recorded as the second measure of sensorimotor ability.

Tilt Test

Each rat was evaluated for its ability to remain on an inclined platform, in a modified version of the test described by Murphy et al. (15). The platform consisted of the side of a rectangular stainless steel pan (24 cm wide × 30 cm long × 15 cm deep) that was set at an initial angle of 22° to the horizontal. At the start of the test the rat was placed in the pan on the side set at 22°, with the long axis of its body parallel to the open edge of the pan. The angle of the pan was then increased by 2° every 5 s to a maximum of 47° at 75 s. The time from when the rat was placed in the pan until it fell into a padded box was recorded as the third measure of sensorimotor ability.

For all three tests, if the rat failed to remain on the cylinder or on the inclined side of the pan for at least 5 s, the rat was allowed two more attempts. If after three attempts the rat failed to remain on the cylinder or the inclined pan for at least 5 s, a score of zero was recorded. In all tests, only 7% of the trials resulted in a score of zero.

Data Analyses

For each rat, the single best performance out of the five daily trials for each test was used as the measure most closely associated with the genetic component of sensorimotor ability. This idea of estimating the genetic component from the best performance, rather than (for example) the average of all trials, has two origins. *1*) The environment can have an infinite negative influence on performance (i.e., a detrimental environment can take the performance to 0). Factors such as subtle differences in housing or daily handling could cause a genetically superior rat to perform below its maximal ability on a given day. *2*) However, the environment can have only a finite positive influence on sensorimotor performance. That is, environmental influences cannot cause a rat to perform

above its genetically determined upper limit of ability. Thus the rat's best performance comes closest to the genetically determined upper limit of its ability. Because our goal was to look for genetically determined differences in phenotypes between inbred strains, we used the best performance rather than the average.

The mean value of the best performances was calculated for each strain, and, for each sensorimotor test, the data were analyzed by a two-way ANOVA with strain and gender as the independent variables. If the difference between strains was significant, then the strain with the lowest mean value was compared with all other strains by the post hoc Dunnett test at a 5% significance level. To test for gender effects, differences between strains were compared by the Bonferroni test. To determine if any learning effect occurred during testing, a regression analysis was carried out comparing performance for each of the tests to trial (day) number for the 5 consecutive days of testing. Data are presented as means ± SE.

RESULTS

One-Direction Rotation Test

Females. The two-way ANOVA indicated that differences between strains was significant ($P < 0.0001$). Figure 1*A* shows the means of the best performance for the females on the one-direction rotation test for all 11 strains. The PVG females remained on the cylinder for the longest time (91 ± 6 s), whereas the DA females remained for the shortest time (30 ± 6 s), resulting in a threefold difference. The Dunnett post hoc test was used to identify strains whose mean performance times were significantly greater than that of the lowest-performing strain. Results of the Dunnett test indicate that the PVG, BUF, WKY, F344, and ACI strains remained on the cylinder for a significantly longer time than the DA strain, the lowest-performing strain ($P < 0.05$; Fig. 1*A*).

Males. Figure 1*B* shows the means of the best performance for the males on the one-direction rotation test for all strains. The PVG males ranked highest on the one-direction rotation test by remaining on the cylinder for 81 ± 10 s, whereas the MNS males ranked lowest, remaining on the cylinder for 8 ± 3 s, a 10-fold difference between the strains. In the males, the PVG, BUF, SR/Jr, ACI, AUG, WKY, and F344 strains remained on the cylinder for a significantly longer time than the MNS strain ($P < 0.05$; Fig. 1*B*).

The ANOVA also indicated that, on the one-direction rotation test, differences between genders were significant ($P < 0.0001$) as was the gender-strain interaction ($P = 0.038$). Table 1 compares the mean values of the best performance for each strain on the one-direction rotation test for males versus females. Data are ranked by strain from highest to lowest performance for the females. For the one-direction rotation test, in two strains there was a significant gender difference; in both strains, the females performed better than the males (WKY, $P = 0.0013$; MNS, $P < 0.005$).

Two-Direction Rotation Test

Females. Figure 2*A* shows the best performance on the two-direction rotation test for the females of each
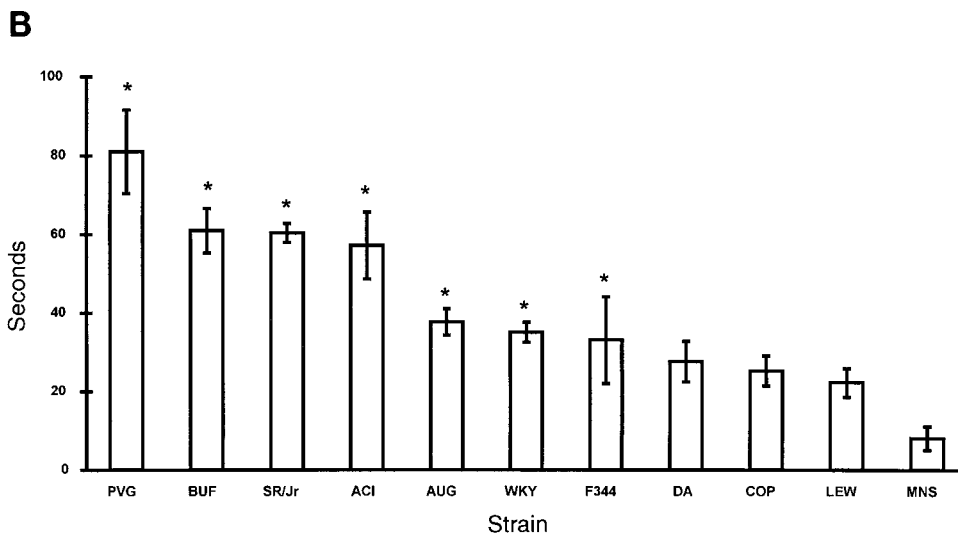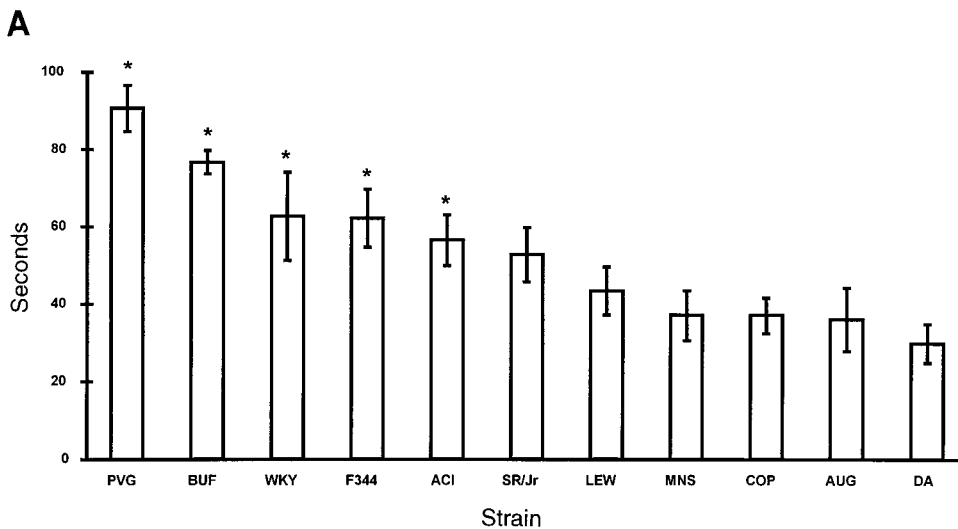
Fig. 1. No. of seconds each strain was able to remain on the cylinder in the one-direction rotation test. Mean of the best performance for each strain ± SE is shown. *A*, females; *B*, males. *Strains in which performance was significantly greater than that of the lowest-performing strain.

strain; differences between strains were significant (ANOVA, $P < 0.0001$). The female PVG rats remained on the cylinder the longest (156 ± 13 s), whereas the COP females remained on the cylinder for the shortest time (34 ± 4 s), representing a 4.6-fold difference in performance. For the females, the PVG, BUF, SR/Jr, F344, WKY, and LEW strains remained on the cylinder significantly longer than the COP strain ($P < 0.05$; Fig. 2A).

Males. Figure 2B shows the best performance on the two-direction rotation test for the males of each strain.

Table 1. *Comparison of females and males in three tests of sensorimotor ability*

	One-Direction Test			Two-Direction Test			Tilt Test	
Strain	Females	Males	Strain	Females	Males	Strain	Females	Males
PVG	91 ± 6	81 ± 11	PVG	156 ± 13	128 ± 9	PVG	76 ± 2	63 ± 3
BUF	77 ± 3	61 ± 6	BUF	142 ± 8*	98 ± 12	F344	73 ± 1	57 ± 7
WKY	63 ± 6*	35 ± 3	SR/Jr	103 ± 12	96 ± 12	LEW	70 ± 2*	52 ± 3
F344	62 ± 7	33 ± 11	F344	102 ± 17	52 ± 16	BUF	59 ± 1	59 ± 3
ACI	57 ± 8	57 ± 9	WKY	79 ± 6	69 ± 3	AUG	49 ± 4	41 ± 6
SR/Jr	54 ± 11	61 ± 3	LEW	74 ± 12	33 ± 5	SR/Jr	47 ± 7	37 ± 5
LEW	43 ± 8	22 ± 4	ACI	65 ± 13	81 ± 15	DA	43 ± 5	47 ± 3
AUG	36 ± 6	37 ± 3	MNS	52 ± 7*	10 ± 5	ACI	42 ± 2	48 ± 6
DA	30 ± 6	28 ± 5	AUG	44 ± 7	57 ± 10	WKY	40 ± 2	38 ± 3
MNS	37 ± 5*	8 ± 3	DA	42 ± 8	34 ± 9	COP	31 ± 4	30 ± 3
COP	37 ± 5	25 ± 4	COP	36 ± 4	26 ± 3	MNS	22 ± 6	18 ± 5

Data are the means of the best performances in each strain ± SE. Asterisks indicate a significant difference between females and males (Bonferroni, $P < 0.05$).
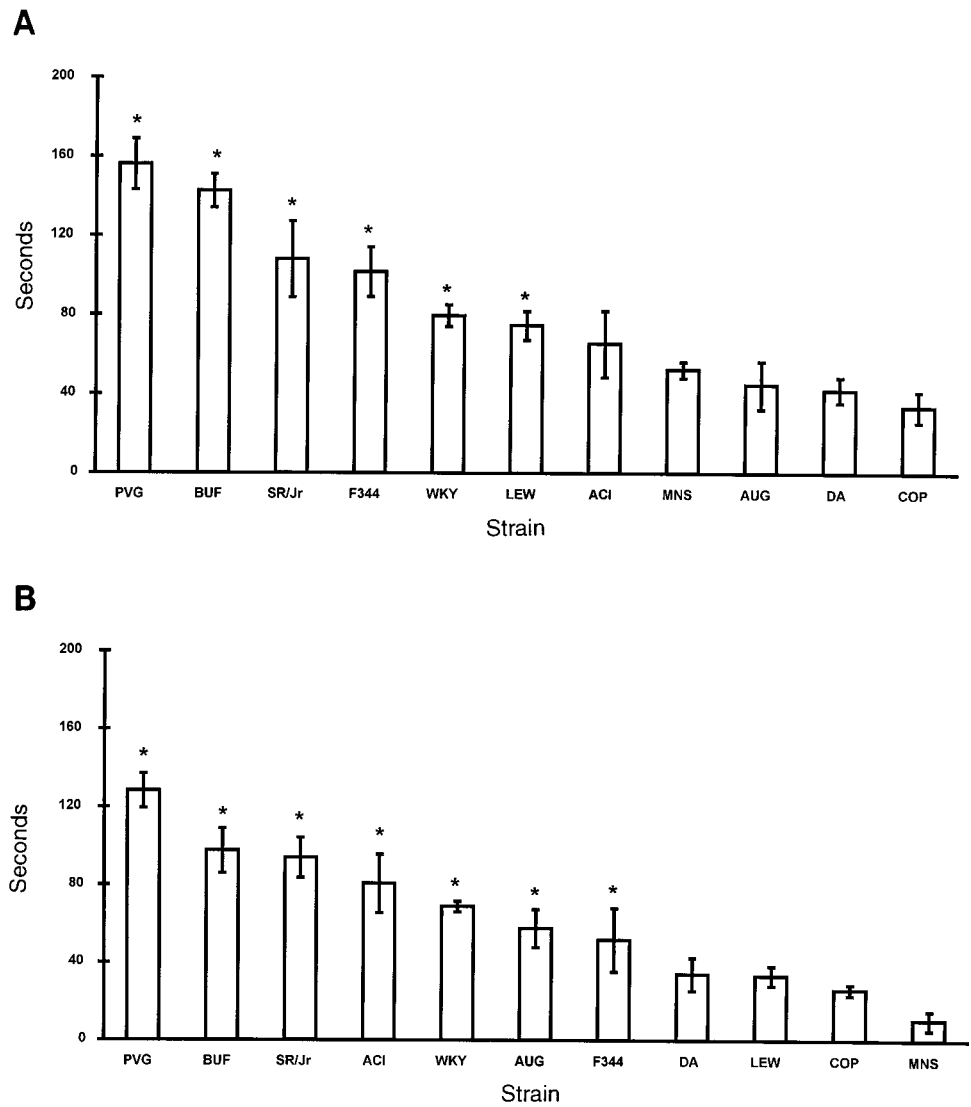
A

B

Fig. 2. No. of seconds each strain was able to remain on the cylinder for the two-direction rotation test. *A*, females; *B*, males. *Strains in which performance was significantly greater than that of the lowest-performing strain.

The PVG males exhibited the highest performance by remaining on the cylinder for 128 ± 9 s, whereas the MNS males were the lowest performers, remaining on the cylinder for only 10 ± 5 s, a 13-fold difference. For the males, the PVG, BUF, SR/Jr, ACI, WKY, AUG, and F344 strains remained on the cylinder significantly longer than the MNS strain ($P < 0.05$; Fig. 2*B*).

For the two-direction rotation test, in addition to significant strain differences, differences between the genders were significant ($P < 0.0001$) as was the gender-strain interaction ($P = 0.008$). Table 1 compares the mean values for the best performance on the two-direction rotation test for males versus females. In 2 of the 11 strains (BUF and MNS), the females remained on the cylinder longer than the males ($P < 0.005$).

Tilt Test

Females. Again, differences in performance between strains on the tilt test were significant ($P < 0.0001$). Figure 3*A* shows the best performance on the tilt test for the females. The PVG females remained on the platform for the longest time (76 ± 2 s), whereas the MNS females remained for the shortest time (22 ± 6 s), a 3.5-fold difference. The strains that remained on the platform significantly longer than the MNS were the PVG, F344, LEW, BUF, SR/Jr, AUG, DA, ACI, and WKY ($P < 0.05$; Fig. 3*A*).

Males. Figure 3*B* shows the best performance for the males on the tilt test. The PVG males scored highest on the tilt test, remaining on the platform for 64 ± 3 s, whereas the MNS males scored lowest, remaining on the platform for 19 ± 5 s, a 3.4-fold difference. The strains that remained on the platform significantly longer than the MNS were the PVG, BUF, F344, LEW, ACI, DA, AUG, and WKY ($P < 0.05$; Fig. 3*B*).

For the tilt test, similar to the other sensorimotor tests, differences between the genders were significant ($P < 0.0001$) as was the gender-strain interaction ($P = 0.025$). Table 1 compares the mean values for the best performance on the tilt test for males versus females. In 1 of the 11 strains (LEW), the females remained on the platform significantly longer than the males ($P < 0.005$).
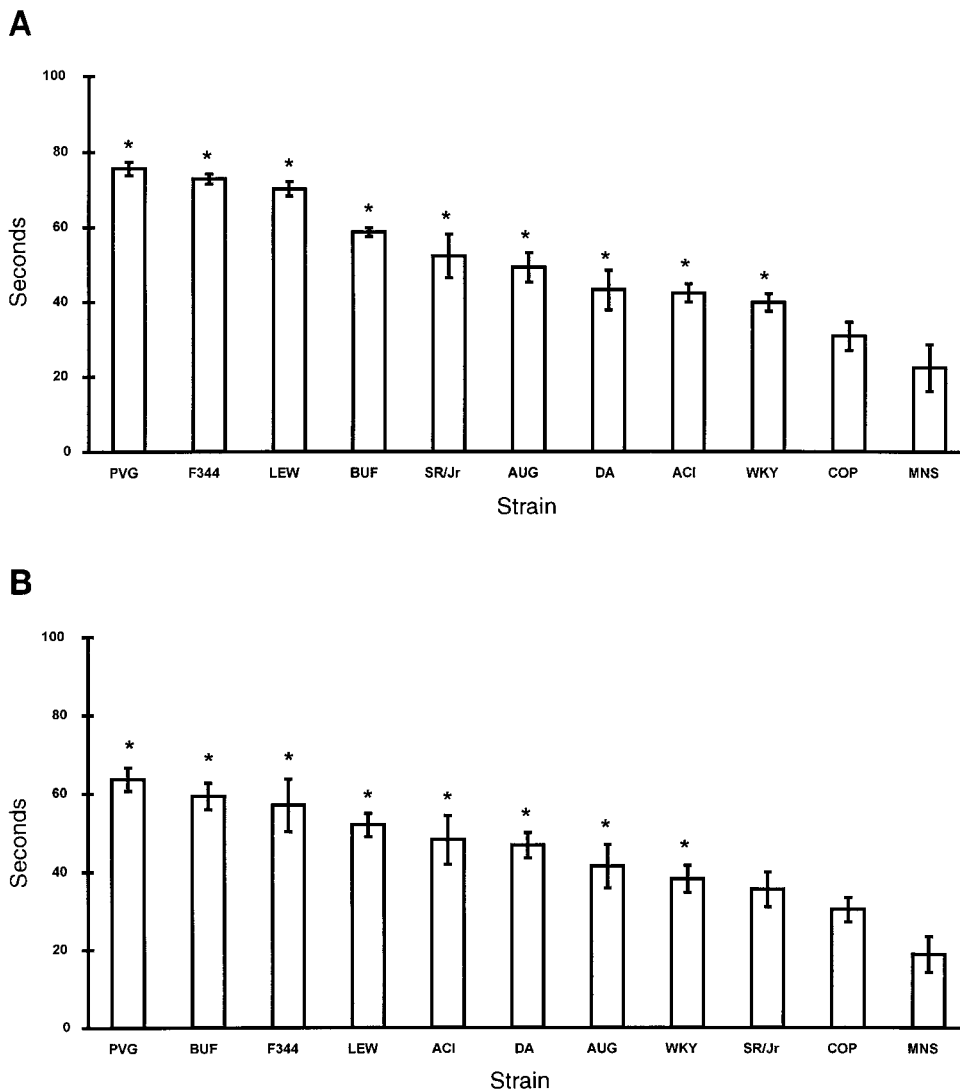
A

B

Fig. 3. No. of seconds each strain was able to remain on the platform for the tilt test. *A*, females; *B*, males. *Strains in which performance was significantly greater than that of the lowest-performing strain.

Learning Effects

A regression analysis was performed for each strain, for the males and females separately, comparing performance on each test to the trial (day) number (Table 2). A significant positive correlation was taken to indicate that a learning effect had occurred. Examination of the data in Table 2 indicates that the learning effect, as judged by the value of R^2, is greatest for the one-direction rotation test and least for the tilt test. There is no clear relationship between the absolute performance of the various strains and the magnitude of the learning effect.

DISCUSSION

The complexity of evaluating coordination in conscious animals carries with it the necessity of using an operational test. Sensorimotor ability (motor coordination) was measured as the total time each rat was able to either remain on a rotating cylinder as the velocity and/or direction of rotation was increased or the time it was able to remain on an inclined platform as the angle of inclination was progressively increased. We observed 3- to 13-fold differences between the highest and lowest performance in individual strains for these tests of sensorimotor ability. In all three tests, in both genders, the highest-performing strain contained no animals whose performance overlapped the performance of rats in the lowest strain. The PVG strain was consistently the highest ranking strain for both the females and males for all three tests, and the COP and MNS strains were consistently in the lowest ranking group. The consistency of ranking observed between the PVG and COP or MNS strains in the three tests suggests that the major factor determining performance was similar for all the tests. Presumably, this common factor is sensorimotor ability. Our goal was to evaluate the aggregate of traits that contribute to the performance of complex sensorimotor tasks. It is axiomatic that many individual traits contribute to a rat's ability to perform on these tests, such as differences in coordination, strength, fear, anxiety, tractability, intelligence, motivation, and subtle anatomic variations. In conscious animals these traits are inextricably intertwined and cannot be evaluated as purely independent events. There were no

Table 2. *Learning effect*

	Females				Males		
Strain	R^2	P	Slope	Strain	R^2	P	Slope
One-direction rotation							
MNS	0.540	0.000	0.121	ACI	0.439	0.000	0.162
WKY	0.463	0.000	0.178	SR/Jr	0.419	0.000	0.161
CPHG	0.369	0.000	0.105	BUF	0.303	0.002	0.133
ACI	0.332	0.001	0.117	WKY	0.300	0.002	0.073
BUF	0.304	0.002	0.141	DA	0.238	0.006	0.060
PVG	0.289	0.002	0.184	LEW	0.206	0.012	0.054
F344	0.193	0.015	0.108	AUG	0.203	0.013	0.070
AUG	0.191	0.016	0.072	CPHG	0.127	0.054	0.047
LEW	0.133	0.048	0.076	F344	0.125	0.055	0.072
SR/Jr	0.101	0.173	0.085	MNS	0.086	0.115	0.017
DA	0.025	0.408	0.024	PVG	0.056	0.210	0.086
Two-direction rotation							
MNS	0.538	0.000	0.172	WKY	0.542	0.000	0.179
AUG	0.317	0.001	0.105	MNS	0.203	0.012	0.041
DA	0.263	0.004	0.095	LEW	0.199	0.013	0.075
BUF	0.251	0.005	0.257	AUG	0.185	0.018	0.122
WKY	0.086	0.115	0.080	SR/Jr	0.138	0.043	0.155
LEW	0.053	0.220	0.084	PVG	0.116	0.065	0.144
SR/Jr	0.047	0.358	0.088	DA	0.115	0.067	0.067
ACI	0.006	0.677	−0.026	BUF	0.051	0.239	0.087
PVG	0.002	0.815	0.021	ACI	0.049	0.239	0.078
F344	0.002	0.817	0.020	COP	0.037	0.308	0.026
COP	0.002	0.838	0.006	F344	0.024	0.415	0.057
Tilt test							
COP	0.235	0.007	−0.056	MNS	0.343	0.001	0.056
ACI	0.227	0.008	−0.067	BUF	0.115	0.066	−0.068
MNS	0.156	0.031	0.048	ACI	0.062	0.185	−0.041
F344	0.109	0.075	0.107	DA	0.039	0.293	0.031
PVG	0.101	0.086	−0.041	LEW	0.035	0.321	0.028
AUG	0.093	0.101	−0.047	SR/Jr	0.017	0.496	0.019
WKY	0.062	0.183	0.027	PVG	0.011	0.584	0.019
BUF	0.031	0.354	−0.022	COP	0.005	0.717	0.007
SR/Jr	0.026	0.493	0.023	WKY	0.004	0.753	0.008
LEW	0.023	0.249	0.027	F344	0.002	0.829	−0.013
DA	0.003	0.758	0.009	AUG	0.000	0.921	0.003

Square of correlation coefficient, *P* value, and slope for relationship between performance on a test and trial for 5 consecutive daily trials.

notable differences in the appearance or behavior of the various strains that could contribute to the differences in performance on our tests. Other factors that could influence performance are differences between strains in the timing of the diurnal activity cycle and in learning ability. We tested all strains at approximately the same time of day. However, it is possible that one or more strains could have been tested at a less than optimal time for their peak activity, which could have degraded their performance. Also, some strains (or one gender) may learn or adapt more readily to the one- and two-direction rotation test than other strains (Table 2), resulting in improved performance. Such a difference between strains in learning on sensorimotor tests would of itself be a valuable phenotype to identify. Nevertheless, it seems likely that sensorimotor ability will be at least one of the major traits that separate the strains on the tests we selected. Variants of the tests we employed have been previously used to evaluate sensorimotor deficits in rats (2–5, 18, 19).

Although a vast literature has developed dealing with the physiological aspects of sensorimotor ability

(8, 11), the genetic components causing the differences between high and low sensorimotor ability have yet to be identified. It appears that genetic variance accounts for a significant portion of the range observed in sensorimotor ability between individuals (7, 13, 14). Simple additive models of heredity plus environment have been utilized to estimate the genetic contribution to variance in human sensorimotor ability in monozygotic and dizygotic twins. Although the assumptions of twin studies are often not completely fulfilled or verifiable (9), it has been estimated that the interindividual variance in sensorimotor ability between pairs of monozygotic and dizygotic twins is ~46% genetically determined (12, 20).

Sensorimotor ability, or coordination, includes all processes that affect the brain's ability to synchronize the function of interrelated muscles. Determination of the genes responsible for sensorimotor ability would provide for a better understanding of the mechanisms responsible for controlling synchronized muscle movement and balance. In humans, the primary area of motor planning occurs in the cerebral cortex, with the basal ganglia contributing by converting the intention to move into action and by controlling posture (12). In rodents the cerebral cortex is believed to be especially important in controlling the forelimbs and less important in control of the predominantly ambulatory hindlimbs (1, 20). In both humans and rodents, synchronization of muscle movement occurs primarily in the cerebellum. A major function of the cerebellum is to receive somatosensory information on the position of the body, compare this information with a desired motion, and then compensate for any discrepancies by smoothing and coordinating ongoing movements. In the rat, lesions of the inferior olivary complex (the source of all climbing fiber input into the cerebellum), cerebellectomy, and myelectomy of the spinal cord between C-7 and T-1 have been shown to greatly reduce performance on tasks requiring a high degree of synchronized movement (2, 18, 19). Rats in which the cerebellum or inferior olivary complex has been destroyed are unable to substantially improve in their ability to perform complex sensorimotor tasks over time (19). This evidence suggests that likely places to look for differences in the nervous system between rat strains with high and low sensorimotor ability are in the inferior olivary nucleus, the cerebellum, or the pathway between the cerebellum and the motor neurons. Conventional neurophysiological analysis of the pathways controlling coordinated muscle movements, including the use of lesion and electrical stimulation studies, is a formidable task. The analysis of the genetic basis of strain-specific differences in sensorimotor ability should provide a complementary route to determine the mechanisms underlying this phenotype.

The large divergence observed (as much as 13-fold) between highest- and lowest-performing strains in the three tests of sensorimotor ability suggests that these strains provide a suitable substrate for the identification of the genes associated with the extremes of sensorimotor ability. The identification of the genes

responsible for a given phenotype utilizing inbred strains that differ widely in expression of that phenotype is based on two widely held principles of biology: *1*) genes cause traits and not vice versa and *2*), in a segregating F_2 population, genes that cause a given trait (such as sensorimotor ability) will remain associated with that trait, and other genes will segregate randomly relative to the trait. The path and criteria to identify the genetic basis of complex traits in inbred rat models has been developed by Rapp (17). As a beginning point to dissecting the genes and mechanisms responsible for sensorimotor ability, we report wide divergence in sensorimotor ability between the PVG and COP or MNS inbred rat strains. This divergence provides a substrate to begin a genetic analysis of this complex, high level phenotype in the rat.

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