the mean absolute posterior fifth area for the group of nine males in the de Lacoste-Utamsing and Holloway (*24*) study were almost identical to those of this study; all the disparity stems from their group of five females whose posterior fifth ratio score was 0.31 and whose standard errors were large.

27. The results for the one left-handed subject who wrote with an inverted posture (subject 1) support the hypothesis of an association between callosal size and degree of hemispheric specialization. It has been suggested [J. Levy, *Psychol. Bull.* **91**, 589 (1982)] that inverted left-handed writers have greater functional bilateralization, at least for written language, than do left-handed writers with noninverted posture. The callosum of subject 1 was larger than that of any of the other four left-writing females, as well as being the largest of all 30 female subjects. One left-inverted male was available (one of the subjects who had magnetic resonance imaging). His callosal area was not only 5 standard deviations above the mean of the male right-handers, but was the largest of all the non–right-handed males.
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Genetics of Growth Predict Patterns of Brain-Size Evolution

Abstract. *Experimental evidence is presented supporting a developmental model that explains the genetic basis for brain and body size associations. Evolutionary change in body size causes correlated change in brain size because some genes affect both traits. The commonly observed correlation between brain and body size results from genetic variation in growth determinants affecting both traits simultaneously during fetal and early postnatal growth. Later growth reduces brain-body correlation because of changes in the underlying causal components of growth in each trait. Brain-body size evolution shows a different pattern at higher taxonomic levels from that seen within and between closely related species because body-size evolution among higher taxa occurs primarily by change in early portions of growth, which share more genetic growth determinants with brain size.*

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Perhaps the best-documented example of predictable developmental and evolutionary change is the scaling of brain size relative to body size in mammals (*1–5*). Here we report breeding experiments, with rats and mice, that reveal genetic relationships between growth of brain and body sizes. These genetic relationships help to explain commonly observed evolutionary patterns of relative brain size among mammalian species.

Brain size can be predicted by the allometric formula

$$\text{brain size} = a(\text{body size})^b$$

or

$$\log(\text{brain size}) = \log(a) + b \log(\text{body size})$$

where a and b are empirically fitted constants. The allometric coefficient b is the slope of a line in log-log scale. This slope varies among taxonomic levels (Fig. 1). Comparison of adults from different populations of the same or closely related species yields a slope of 0.2 to 0.4, but if adults of distantly related species are compared, a higher slope of up to 0.77 is found (*1–6*). There has so far been no satisfactory explanation for why allometric slopes are higher at higher taxonomic levels. We now present a simple causal model for the increase of brain-body allometric slopes with increased taxonomic level and provide experimental evidence supporting this genetic model.

One explanation for this relation of brain to body size among different taxa is that brain size changes as a side effect during body-size evolution (*1*). Adaptive change in body size occurs because natural selection changes the frequencies of genes affecting body size, some of which also affect brain size. This causes parallel change in brain and body sizes, depending upon the degree of shared genetic variation (pleiotropy). Parallel change in traits not directly selected for is ubiquitous in selection experiments (*7*) and has been demonstrated for brain and body size in rats and mice (*8*). The degree of pleiotropy can be judged from the genetic correlation between traits, as determined by selection or breeding experiments (*7*). The actual ratio of change in brain size per change in body size is predicted by the slope of the genetic regression of brain on body size (*6*). Quantitative genetic theory thus predicts the parallel response of two genetically correlated traits when one is subjected to selection.

When the two traits are logarithmically transformed to represent exponential relationships as linear, as in the allometric formulas presented above, the genetic regression of brain on body size defines an allometric slope along which populations will diverge when selected for different optimal body sizes (*1, 9*). Experiments with rats and mice (*8*) show that selection on body size will yield brain-body allometric slopes in the 0.2 to 0.4 range typical of slopes found when populations of the same or closely related species are compared (*1, 8*). This provides a simple, experimentally verified, genetic explanation of allometric slopes at these lower taxonomic levels: Evolution of body size causes parallel change in brain size because some of the genes that affect body size also affect brain size.

A likely source of genetic correlation between brain and body sizes is genetic variation in shared growth-regulating systems early in life, when both traits are growing rapidly. For example, embryonic somatomedin is a general mitogen affecting growth of many organs, including the brain (*10, 11*). If evolution of body size occurs by change in such systems, corresponding change in brain size is likely.

While this theory accounts for allometric slopes among closely related taxa, it does not explain why slopes are steeper among higher taxa. An equivalent change in body size causes a relatively larger change in brain size at higher taxonomic levels than it does among closely related populations. The question is then why the allometric slope increases, from around 0.4 to nearly 0.8, as we make comparisons higher up the taxonomic scale, going from species to genera, families, and orders (*12*).

A simple genetic explanation for this pattern of increased allometric slopes at higher taxonomic levels is now apparent. Body size can evolve either by change in the frequencies of genes that affect both brain and body size or by change only in the frequencies of those genes that affect

body size alone, and not brain size. The former will cause parallel change in brain size, the latter will not. Here we show that genes affecting both traits generally do so during fetal and early postnatal growth, when both brain and body size are growing rapidly. During subsequent postnatal growth, the brain has already achieved much of its mature size (*13*), so that genes active during later growth can affect body growth but have little effect on brain size. We present evidence that body-size divergence among closely related populations occurs in both early and late components of growth, but that at higher taxonomic levels divergence is progressively more concentrated in the early portions of body growth, which share the greatest pleiotropic gene effects with brain growth. This will cause a more rapid change in brain size, and steeper allometric slopes among higher taxa.

There is thus an important distinction between early growth, during which positive pleiotropic gene effects can influence both brain and body size, versus later growth, during which gene effects influence final body size but have less effect on brain size. These two periods of growth are also distinguished by their histological bases. Early growth is hyperplastic; that is, it occurs mainly by increase in the numbers of cells, intestinal villi, renal nephrons, muscle fibers, pulmonary alveoli, and so forth, while the sizes of these structures change little. Later growth becomes hypertrophic, that is, it occurs mainly by increase in the size of individual cells, villi, nephrons, muscle fibers, pulmonary alveoli, and the like with little change in the numbers of these structures (*14, 15*).

Both hyperplastic and hypertrophic growth increase body size, and both contribute to evolutionary change; but the relative importance of these two types of growth can differ. For example, cell size accounts for 30 to 50 percent of response to artificial selection for body size in mice, indicating a substantial role for the later, hypertrophic, portion of growth (*16, 17*). In contrast with artificial selection, however, major evolutionary divergence occurs primarily in the early, hyperplastic portion of growth. For example, body size differences among distantly related species are almost entirely in the number, rather than sizes, of cells (*16, 18–20*). Cell size also differs, but its contribution at higher taxonomic levels is overshadowed by the far greater differences in cell number. Cells of elephants, for example, are only about twice the size of mouse cells (*20*). The number of cells in these animals must differ by orders of magnitude.

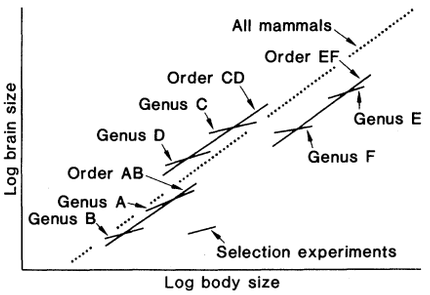

Fig. 1. Allometric relationships among adult mammals. Populations within a species, and the most closely related species within genera, yield allometric coefficients (slopes) of about 0.2 to 0.4, as indicated here for genera A through F. Selection experiments and other genetic studies show that these slopes are expected when direct selection on body size causes correlated change in brain size. Higher taxa, such as orders, or all mammals, yield slopes of 0.6 to 0.8. These are general trends. Considerable variation in slope also exists within taxonomic levels. [Data are from (*1–6, 8, 11*)]

These observations show that although some adaptive change in body size can occur by a general magnification or diminution of both components of growth, major divergence in body size occurs chiefly in the early, hyperplastic, portion of growth. This is probably because natural selection sets narrower functional limits on the sizes of cells, nephrons, muscle fibers, intestinal villi, pulmonary alveoli, and the like than it does on their numbers. Limitations on cell size, for example, may arise from effects of cell size on diffusion and transport rates. Also, cell size is inversely related to metabolic rate (*19–22*). Such physiological correlates may limit the extent to which body size can evolve by change in cell size. Evolution by change in the numbers of cells will not be so limited. Both hyperplastic and hypertrophic growth can thus contribute to body-size divergence, but at higher taxonomic levels the relative contribution of early, hyperplastic growth will be far greater.

Because body size can evolve in these different ways, by change in different components of growth, the parallel change induced in brain size may differ. This will depend upon the timing, during growth, of pleiotropic gene effects. For example, if pleiotropic gene effects influencing these two traits occur mostly in the early portions of body growth, body-size evolution occurring by change in later growth will induce little parallel change in brain size. Evolution occurring by change in early growth, however, will induce greater change in brain size for a given amount of body-size evolution. This will result in steeper allometric slopes among descendant taxa.

To evaluate the timing of pleiotropic gene effects during development of brain and body size, we conducted quantitative genetic experiments with 524 rats and with 1466 mice (*11, 23, 24*). The experimental design provided estimates of genetic variance and covariance for brain size, body size, and body growth during different age intervals (*25*).

Our results show that positive genetic and phenotypic correlations between brain and body size result mainly from prenatal and early postnatal growth. Later periods of growth are negatively correlated with brain size, and generally reduce the initially high correlation. The estimated genetic correlation of 189-day brain weight with age-specific body weight in rats drops from 0.62 at 35 days to 0.15 at 189 days (Table 1). Genetic correlation of body weight with 70-day brain weight in mice drops from 0.64 at 35 days to 0.38 at 70 days (Table 2). Zamenoff *et al.* (*26*) also found that phenotypic brain-body correlations in rats were reduced by postnatal growth.

While these correlations show that positive pleiotropic gene effects on relative brain and body growth occur during prenatal and early postnatal periods, actual allometric slopes are predicted by genetic regression, not correlation. The appropriate genetic regression depends on the mode of body-size evolution. Our model of body-size evolution by extensive change in early growth but little change in later growth corresponds to restricted index selection (*27*). In this model, selection intensities on two correlated traits are adjusted to change one trait (early growth) while the other (later growth) is held constant. The predicted allometric slope is then the partial genetic regression of brain size on body size with later growth held constant. Thus, the predicted slope among closely related populations, where change occurs in all components of growth, is the simple genetic regression of brain on body size, whereas the predicted slope among higher taxa is the partial genetic regression of brain on early growth, with later growth held constant.

Prediction of the slope for higher taxa requires precise knowledge of the genetic variances and covariances of early hyperplastic growth and later hypertrophic growth. These are unknown, but if we use body growth before and after 2 weeks of age as rough estimates of these two components of growth, we obtain predicted slopes consistent with our model: focusing on early growth while holding later growth constant does yield

a steeper genetic regression of brain on body size. For 70-day mice, the genetic regression of brain on body size is 0.37. The partial genetic regression, holding later growth constant (*28*), is 0.47. Standard errors are not available for these predicted slopes, and the direction of the difference is more reliable than the particular value obtained. If we recalculate the partial genetic regression using a range of ±1 standard error of the genetic variance of later growth, we obtain predicted slopes from 0.43 to 0.76. This range agrees well with allometric slopes observed among higher taxa (*1–6*). Higher slopes among higher taxa are predicted by differences in the basis of body-size divergence.

The contrasting allometric slopes for closely related versus distantly related taxa could be described as a difference between micro- and macroevolutionary patterns. Our model, based entirely upon well-established microevolutionary mechanisms, explains patterns at both levels, without invoking special macroevolutionary mechanisms.

As a final point of evidence, we cite an exception that helps prove the rule. The gorilla and the chimpanzee are members of different genera and differ considerably in body size. Nonetheless, the brain-body allometric slope connecting these species is only about 0.34, a low value more typical of conspecific than of intergeneric comparisons (*5*). This low slope results from the unusually small size of the gorilla's brain, relative to the size of its body. Shea (*5*), however, notes that gorilla and chimpanzee neonates are very similar in size, and that body-size divergence between these species has occurred by differences in rates of later postnatal growth, growth that occurs after the brain has achieved most of its mature size. Shea concludes that divergence based on differences in later growth rates has caused only slight parallel divergence in brain size, and that the unusual ontogenetic timing of divergence in these species accounts for the unusually low allometric slope between them. Shea's conclusions for apes are consistent with our own model derived from genetic experiments with rodents.

In conclusion, this developmental model clarifies the underlying nature of brain-body size evolution by describing genetic aspects of brain-size variation in terms of its correlation with underlying components of growth in body size. The perplexing problem of why steeper allometric slopes occur at higher taxonomic levels can be explained by natural selection operating on different portions of growth in body size.

Table 1. Data for rats: genetic and phenotypic correlations (with estimated standard errors) of body weight and of body-weight gain with brain weight.

	189-day brain with gain		189-day brain with weight at end of interval	
Days	Genetic	Phenotypic	Genetic	Phenotypic
Up to 14	0.59 ± 0.12	0.54 ± 0.05	0.59 ± 0.12	0.54 ± 0.05
14–21	−0.32 ± 0.23	−0.13 ± 0.07	0.48 ± 0.14	0.47 ± 0.05
21–28	0.37 ± 0.23	0.13 ± 0.06	0.59 ± 0.13	0.54 ± 0.05
28–35	−0.13 ± 0.24	−0.15 ± 0.06	0.62 ± 0.13	0.54 ± 0.05
35–42	−0.23 ± 0.22	−0.15 ± 0.06	0.58 ± 0.13	0.54 ± 0.05
42–49	−0.46 ± 0.25	−0.12 ± 0.06	0.51 ± 0.14	0.54 ± 0.05
49–70	−0.19 ± 0.22	−0.19 ± 0.06	0.50 ± 0.14	0.54 ± 0.05
70–123	−0.28 ± 0.22	−0.08 ± 0.06	0.42 ± 0.15	0.51 ± 0.05
123–189	−0.71 ± 0.21	−0.13 ± 0.06	0.15 ± 0.19	0.38 ± 0.06

Table 2. Data for mice: genetic and phenotypic correlations (with estimated standard errors) of body weight and body-weight gain with brain weight.

	38-day brain with gain		38-day brain with weight at end of interval	
Days	Genetic	Phenotypic	Genetic	Phenotypic
Up to 14	0.73 ±0.13	0.56 ± 0.05	0.72 ± 0.13	0.56 ± 0.05
14–21	0.46 ±0.21	0.35 ± 0.06	0.72 ± 0.12	0.60 ± 0.04
21–38	−0.74 ±0.14	−0.51 ± 0.05	0.53 ± 0.22	0.49 ± 0.05

	70-day brain with gain		70-day brain with weight		
Days	Genetic	Phenotypic	Day	Genetic	Phenotypic
Up to 14	0.59 ± 0.12	0.39 ± 0.04	14	0.59 ± 0.12	0.39 ± 0.04
14–21	0.73 ± 0.16	0.19 ± 0.04	21	0.68 ± 0.10	0.42 ± 0.04
21–70	−0.56 ± 0.12	−0.32 ± 0.04	28	0.56 ± 0.12	0.42 ± 0.04
			35	0.64 ± 0.14	0.42 ± 0.03
			42	0.44 ± 0.16	0.36 ± 0.04
			49	0.44 ± 0.15	0.38 ± 0.04
			56	0.42 ± 0.15	0.36 ± 0.04
			63	0.43 ± 0.15	0.34 ± 0.04
			70	0.38 ± 0.16	0.34 ± 0.04

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29. We thank J. M. Cheverud, J. F. Crow, W. M. Fitch, W. Goodman, M. A. Hansen, S. Herring, J. Kitchell, L. A. P. Kohn, R. Lande, A. A. Plummer, J. J. Rutledge, and J. Silverstein for comments on the manuscript. Supported by the National Science Foundation (DEB-8109904) and the College of Agricultural and Life Sciences of the University of Wisconsin, Madison. Contribution 2792 from the Laboratory of Genetics, University of Wisconsin, Madison.

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Androgens Prevent Normally Occurring Cell Death in a Sexually Dimorphic Spinal Nucleus

Abstract. *The spinal nucleus of the bulbocavernosus (SNB) contains many more motoneurons in adult male rats than in females. Androgens establish this sex difference during a critical perinatal period, which coincides with normally occurring cell death in the SNB region. Sex differences in SNB motoneuron number arise primarily because motoneuron loss is greater in females than in males during the early postnatal period. Perinatal androgen treatment in females attenuates cell death in the SNB region, reducing motoneuron loss to levels typical of males. The results suggest that steroid hormones determine sex differences in neuron number by regulating normally occurring cell death and that the timing of this cell death may therefore define critical periods for steroid effects on neuron number.*

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Sex differences in the adult vertebrate nervous system can include dramatic dimorphisms in the number and morphology of neurons devoted to various sexually dimorphic behaviors. Gonadal steroids produce many of these sex differences by acting during early "critical" periods to determine the number and size of neurons, as well as their neuritic arborization and biochemical characteristics (*1*). It is generally thought that steroids influence sexual differentiation by acting on developmental events that coincide with these critical periods. Little is known, however, about which developmental events are susceptible to steroid modulation. In this report, we describe the development and androgenic regulation of sex differences in motoneuron number within a rat spinal nucleus. We have found that the critical period during which androgens influence motoneuron number within this nucleus coincides with the period of normally occurring cell death. Moreover, androgens attenuate this cell death, permanently increasing the number of motoneurons retained to adulthood.

The spinal nucleus of the bulbocavernosus (SNB) is a discrete group of motoneurons located in the lumbar spinal cord. Adult male rats have approximately 200 SNB motoneurons innervating two penile muscles—the bulbocavernosus (BC) and levator ani (LA) (*2*)—as well as the anal sphincter (*3*). The LA-BC complex controls penile reflexes important in copulatory behavior (*4*). Adult females have only about 60 SNB motoneurons, and although the LA-BC complex is present in females during early development, these muscles atrophy during the first few weeks of postnatal life (*2, 5*). SNB motoneurons and their target muscles accumulate androgens in adult rats, and the masculinization of this neuromuscular system depends on the presence of androgens around the time of birth (*2, 6*). Males deprived of androgens perinatally have a female number of motoneurons as adults and lack the LA-BC complex. Conversely, females given androgens during an early critical period have an increased number of SNB motoneurons and retain the LA-BC complex to adulthood (*7*).

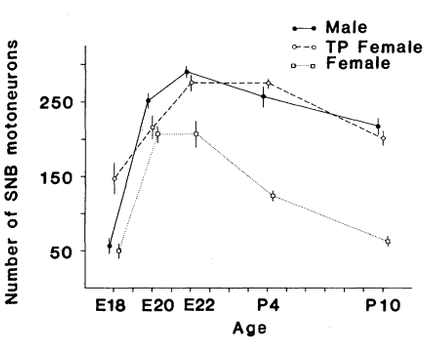

Fig. 1. Counts of SNB motoneurons from E18 through P10 for females (n = 24), TP females (n = 27), and males (n = 23). Points represent means ± standard errors; n = 3 to 7 per data point.

There are several mechanisms by which androgens could regulate SNB motoneuron number. One is that androgens might enhance the proliferation of SNB motoneurons. This possibility is unlikely, since virtually all SNB motoneurons undergo their last mitotic division on day 12 of gestation, before androgens are secreted by the testes and several days before sex differences in circulating androgens are apparent (*8, 9*). Moreover, if females are treated with androgens during the early postnatal period, their masculinized SNB also consists of motoneurons generated on embryonic (E) day 12, well before androgen treatment was begun (*10*). A second possibility is that androgens regulate SNB motoneuron number by influencing cellular migration or differentiation. In this case, androgens could either promote the differentiation of SNB motoneurons or their migration into the SNB region, or prevent their redifferentiation or migration out of the SNB. A final possibility is that androgens enhance the survival of SNB motoneurons during the period of normally occurring motoneuron death. We have focused on the latter two hypotheses in examining SNB ontogeny in males, females, and androgen-treated females during the critical period of androgenic action.

From E16 through E22 (*11*), pregnant Sprague-Dawley rats (Simonsen) either received subcutaneous injections of testosterone propionate (TP) (2 mg/day) dissolved in sesame oil or were left untreated. Pups born to TP-treated dams were cross-fostered to other lactating females and injected subcutaneously with 1 mg of TP on postnatal (P) day 1, P3, and P5. Male, female, and androgen-treated female (TP female) pups were killed with an overdose of pentobarbital sodium and perfused with saline formaldehyde on E18, E20, E22, P4, or P10. Lumbar spinal cords were fixed in Bouin's solu-