before implantation, since the intrauterine transfer of 22 carrier blastocysts that had developed in vivo resulted in the birth of 17 progeny. The method described here can also be used to introduce donor nuclei obtained from later-stage embryonic cells into enucleated zygotes (*7*). This procedure may therefore aid in further defining the possible developmental restriction of nuclei during mammalian embryogenesis. In addition, reciprocal pronuclear transplantations between genetically distinct one-celled embryos may be used to define the degree to which maternally inherited cytoplasmic components persist.

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Relative Brain Size and Metabolism in Mammals

Abstract. *Comparisons of the relation between brain and body weights among extant mammals show that brain sizes have not increased as much as body sizes. Interspecific increases in brain and body size appear to occur at the same rate, however, when the amount of available energy is taken into account. After this adjustment, brains of primates are slightly larger than expected from the overall mammalian data, but primates also use a larger proportion of their total energy reserves for their brains. Analyses of relative brain size must take into account the requirements that the metabolically active brain has for the body.*

For the past 50 years the relation of brain to body weights among different mammalian taxonomic groups has been thought to scale allometrically at 0.67 (*1, 2*), but recent expansion of the data base led to estimates of the slope being approximately 0.75 (*3*). The newer and larger sets of points may have disproportionately increased the numbers of small mammals with relatively small brains and this alone could produce a steeper slope (*4*). Although the reason for the discrepancy between the slopes is not known, the mammalian data sets appear regular and contain certain consistent deviations; anthropoids (*1–3, 5*), pinnipeds, and odontocetes (*5*) are highly encephalized and frugivorous bats are more encephalized than insectivorous ones (*6*), a situation that may have parallels among primates (*7*).

The causal factors controlling brain to body-weight scaling are not known, but it has been conjectured that the scaling reflects the functions of the brain for analyzing sensory information and controlling motor output (*2, 8*). The brain controls the body's actions but also needs the body for its energy supply. The brain is metabolically very active and demands a large supply of oxygen and glucose, as much during sleep (*9–11*) as during increased mental activity (*9, 11*). Regulation of cerebral homeostasis permits small perturbations in the delivery of oxygen and glucose, but decreased availability of oxygen or glucose are associated with pathological states such as coma (*9, 10, 12*). The metabolic relation between the brain and body has received attention (*3, 13, 14*), but its role in relative brain size has not been adequately analyzed (*15*). It is proposed here that the size of the brain will be constrained both by the size of the system delivering oxygen and glucose and by the rate at which energy can be expended on supporting the brain's constantly high metabolic demands. Body weight is a first approximation of the size of the storage and delivery systems for glucose and oxygen, and the organism's basal (standard) metabolic rate (BMR) estimates the amount of available oxygen and energy per unit time (*16*).

In this study brain weights of 93 adult mammalian species were collected from the literature (*1–3, 6, 13, 17*) and analyzed allometrically in terms of both body weight and body mass times the metabolic rate. These adjusted body weights parallel the animal's caloric expenditure. Only species that had brain weights, body weights, and BMR's (in cubic centimeters of O_2 per 100 g per minute) were used. If the studies in which the species-specific brain weight and BMR were determined used individuals of a species whose body weights differed by more than 10 percent, the BMR was adjusted (*13*). Rates of total brain metabolism measured with the Kety-Schmidt technique were also taken from the literature (*13*). Linear regressions and principal axes were used to study the relation among the logarithmically transformed data. Comparisons of intercepts or adjusted group means are based on analyses of covariance ($N - 3$ degrees of freedom) and reported as t-tests (Table 1).

The overall picture of the regression of brain weights against body weights resembles other mouse-to-elephant curves (Fig. 1). The relation is best described by the linear regression equation $\log E = -1.28 + 0.76 \log S$ [$r = .976$, 95 percent confidence limits of the slope (cls) = 0.743 to 0.779], where E = brain weight and S = body weight; (slope of the principal axis = 0.761). The slope from these data is very close to recent estimates (*3*) and higher than the 0.67 slopes reported earlier (*1, 2, 5*). Although primates ($\log E = -1.11 + 0.81 \log S$; 95 percent cls = 0.693 to 0.927; $r = .973$) have larger relative brains compared to all other mammals ($\log E = -1.29 + 0.74 \log S$; 95 percent cls = 0.707 to 0.776; $r = .983$), the pinnipeds and odontocetes have relatively big brains with values overlapping those of large anthropoids (*18*). Furthermore, the pinnipeds and odontocetes have larger relative brain sizes than do terrestrial ungulates (artiodactyls, perissodactyls, and elephant). Frugivorous bats have bigger brains per body weight (*19*) than insectivorous bats, corroborating earlier reports (*6, 7*) (Table 1). Because only one insectivorous primate, *Galago demidovii* (*20*), was included in this sample, statistical analyses were not run on dietary differences among primates.

For this mammalian sample, the amount of O_2 consumed per body weight is described by the equation $\log \text{BMR} = 0.84 - 0.269 \log S$ (95 percent cls = −0.292 to −0.248; $r = -.93$; principal axis slope = −0.270), and the slope is close to the predicted −0.25 one (*21*). The unexplained variance for BMR to body weight is higher than that for brain to body weight, reflecting either an increase in measurement error or a larger biological variation. Several taxonomic deviations from the overall trend occur here too. Primates (log BMR = 0.60 −

0.217 log S; 95 percent cls = −0.30 to −0.13; r = .83) do not differ significantly from the mammalian trend, but seals and toothed whales (log BMR = 1.40 − 0.332 log S; 95 percent cls = −0.469 to −0.195) have higher BMR's for their body size than do the large anthropoids or terrestrial ungulates. As expected (*21*), insectivorous bats have lower BMR's than frugivorous bats (Table 1).

The regression of brain weight on body weight adjusted for BMR is described by the equation, mammalian log E = −2.11 + 1.026 log (S × BMR) (95 percent cls = 0.97 to 1.08; r = .97; principal axis slope = 1.027). Primates (log E = −1.69 + 1.02 log (S × BMR); 95 percent cls = 0.88 to 1.16; r = 0.975) maintain a higher adjusted relative brain size than other mammals (*18*). If BMR is controlled, the odontocete and pinniped relative brain sizes are shifted farther away from the anthropoids (but not significantly at an .05 level) and closer to the terrestrial ungulate values, from which they can no longer be separated at an .05 level. The adjusted relative brain sizes of frugivorous bats completely overlap those of insectivorous bats (*19*) (Fig. 2 and Table 1).

Whereas the unexplained variance for BMR to body weight is large, combining BMR with body weight produces little scatter and a correlation that is as strong as brain to body weight. Additionally, the ratio of brain weight to body weight (E/S) is highly correlated with BMR according to a Spearman rank correlation (r = .785; P < .0001), particularly after primates are excluded (r = .868). Most importantly, the slope for brain to adjusted body weight is not significantly different from isometry (Fig. 2)—that is, among extant mammals an increase in brain size keeps pace with the increase in body size when the size is adjusted for the availability of energy.

Given the general isometry of brain and adjusted body size, how does the primate brain, and in particular the large human brain, support its metabolic de-

Table 1. Intercepts and comparisons of relative brain sizes and basal metabolic rates among various taxonomic groups of mammals. The intercepts have not been logarithmically transformed. Abbreviations; S, body weight; BMR, basal metabolic rate.

Group	Number of species	Brain to S			BMR to S			Brain to (BMR × S)		
		Intercept	t	P	Intercept	t	P	Intercept	t	P
All mammals	93	0.053			7.001			0.008		
Nonprimate mammals	78	0.051	6.3	< .0001	7.199	1.5	.12	0.007	2.2	.03*
Primates	15	0.077			3.983			0.021		
Large anthropoids (*18*)	5	0.004	0.3	.781	2.425	3.3	.01*	0.002	1.7	.13
Seals, toothed whales	6	1.938	7.1	< .0001	38.825	3.6	.003	0.191	2.0	.06
Terrestrial ungulates	11	0.056			2.889			0.025		
Frugivorous bats	8	0.698†	4.0	.002	12.466	2.6	.02*	0.049	1.7	.11
Insectivorous bats	6	0.481†			8.785			0.001		

*Bonferroni's test for multiple comparisons (*23*) suggest that only P values less than .0042 be definitely accepted as significantly different statistically. †Adjusted group means are used because slopes are not parallel.

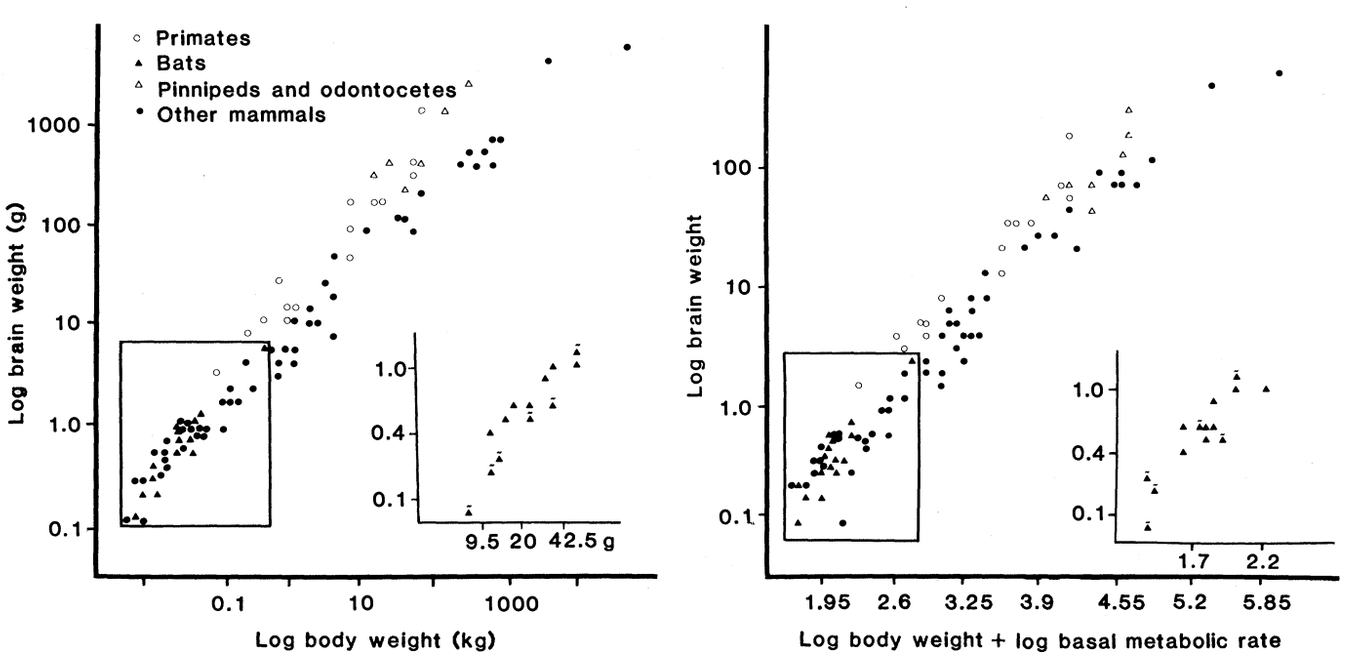

Fig. 1 (left). Logarithmic plot of brain and body weights among 93 mammals. The slope, 0.761, is one of negative allometry. Primates, pinnipeds, and odontocetes have slightly larger brains for their body size than do most other mammals. A cetacean point is the one closest to the human value, the highest primate point. Insectivorous bats, identified with superscripts (~), have smaller relative brain sizes than do the frugivorous bats. Because of the numerous small mammals, the bats are shown separately. Three points are superimposed. Fig. 2 (right). Logarithmic plot of the regression of relative brain weight against body weight adjusted for its metabolic rate. The slope, 1.03, describing the association between these two parameters among all mammals is not significantly different from isometry. Brains of primates are relatively larger than those of other mammals after the adjustment. Relative brain sizes of insectivorous bats cannot be distinguished from those of the frugivores. Several points are superimposed.

mand? The decrease of cerebral metabolic rate accompanying increments in brain size (slope = −0.13) (*13*) is too small to suggest a constancy in overall energy demands by larger brains. Mammals differ, however, in the relative amount of energy used by the brain. Primate brains, as represented by *Macaca mulatta* and *Homo sapiens*, use a relatively higher proportion of their body metabolism (9 and 20 percent, respectively) (*22*) than do the nonprimate brains of rat, cat, and dog (4 to 6 percent) (*13*). These proportions correlate significantly with the species-specific deviations of both adjusted and unadjusted relative brain size (r = .986 and .98; respectively, $P < .01$)—that is, the proportion of available energy directed toward the brain accounts for much of the observed deviations in relative brain size. A major primate adaptation appears to have been the allocation of a larger proportion of the body's energy supply for the brain. An analysis of the brain's energetics is necessary for a better understanding of the relation of brain to body.

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Pimozide Blocks Establishment But Not Expression of Amphetamine-Produced Environment-Specific Conditioning

Abstract. *Animals with a history of receiving daily injections of +-amphetamine in a specific environment showed a placebo effect (enhanced activity) when injected with saline and placed there; control animals with similar but dissociated drug histories and experience with the test chamber failed to show the effect. The dopamine receptor blocker pimozide antagonized the establishment of conditioning. However, the same dose of pimozide, when given to previously conditioned animals on the placebo test day, failed to antagonize the expression of conditioned activity. Thus, during conditioning dopaminergic neurons mediated a change that subsequently influenced behavior even when dopaminergic systems were blocked. Although schizophrenia may be related to hyperfunctioning of dopamine, neuroleptic drugs, which block dopamine receptors on their first administration, do not have therapeutic effects for a number of days. The results of the pimozide experiments may resolve this paradox.*

Chronic abuse of psychomotor stimulant drugs such as +-amphetamine and cocaine can lead to schizophrenia-like behavior in humans (*1*). Because the stimulant effects are mediated by dopaminergic neurons in the brain (*2*), dopaminergic hyperfunctioning has been suggested as a cause of schizophrenia (*3*). A number of animal studies have shown that these stimulant effects can become conditioned to environmental stimuli associated with the drug state (*4*). We now show that although a dopamine antagonist blocks the establishment of this effect, once conditioning has occurred the same drug fails to block its expression. This finding raises the possibility that during conditioning, dopaminergic neurons mediate a change that can subsequently influence behavior even when dopaminergic systems are blocked.

Experimentally naïve male Wistar rats (250 to 300 g) were housed individually in a climatically controlled colony room kept on a 12-hour light-dark cycle. Food and water were freely available.

Experiments were conducted at the same time each day seven days a week.