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Relation Between Brain and Body Growth in Allied Rats

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ABSTRACT: Cranial volumes were measured from museum specimens of wild-caught and laboratory-born Allied rats from eastern Australia. The relation of these volumes to body weight and body length, and also to age at death in the laboratory-reared sample, was determined. Growth of both brain and body was rapid during the first three postnatal months and slowed markedly over the next month, but appeared to continue at a very slow rate throughout life. In particular, the major surge in brain growth occurred in the first three postnatal weeks. Modified Gompertzian growth functions describe the pattern of growth quite well, though the nature of the data precluded highly sensitive fits. Three features were clear: 1) the rate of slowing of growth was about the same for all variables, 2) growth appeared to continue throughout the life of the animal, and 3) the trajectory of brain growth led that of body growth by about four days. The pattern of growth in Allied rats is similar to that of laboratory rats and probably to those in other murids.

KEY WORDS: Brain, Body size, Allometry, Weight, Length, Rats, Development

INTRODUCTION

Body growth in murid rodents has received substantial study, and brain growth has also received attention. However, the two have not been tracked simultaneously in the same specimens. The weight and external dimensions of the body can readily be monitored throughout postnatal life, but measurement of internal organs usually requires their excision, allowing only one value per specimen for each parameter measured. The ideal solution involves non-invasive methods, such as soft X-ray or CAT or MR scan, but the usual solution has been to sample specimens of different ages in order to estimate growth trajectories. This method was followed in the present study, using age-dated specimens deposited in the Museum of Vertebrate Zoology at Berkeley, CA by J. Mary Taylor (1961) after completing her study of their reproductive biology. Her intent had been to discover why, except for sporadic outbreaks, their numbers remained so low when their reproductive potential seemed so high. In the course of that study, she determined how body weight, body length, and hind foot length changed with age in animals born of wild-caught dams and reared in the laboratory. These plus a separate sample of wild-caught specimens provided the material for the present study.

At issue is the relation between brain size and body size during postnatal growth. Murids are "postnatal brain developers" (Davison and Dobbing, 1968;

[1] The question of the best index of body size was examined by Towe and Mann (1992); they concluded that body weight and length were effectively interchangeable within species. That issue is also re-examined here.

Winick and Noble, 1965). Recent study of myomorph rodents has shown that within a species, adult brain size is roughly proportional to the cube root of body weight (Mann *et al.*, 1988), or proportional to body length (Towe and Mann, 1992)[1]. Hence, the trajectory of postnatal brain growth may parallel that of body growth. In this study, we ask three questions: 1) Do brain growth and body growth run parallel courses? 2) Do brain and body continue to grow at a slow rate throughout life? and 3) Can the observations on laboratory-reared animals be generalized to the wild population?

METHODS

Two different samples of Allied rats (*Rattus assimilis*), wild-caught (W) and laboratory-born and reared (L), were studied. Intact crania were measured from 89 specimens trapped at three widely separated locales in eastern Australia and from 82 specimens born and reared in the laboratory (two additional laboratory-born specimens with mildly damaged crania were also measured). The dams[2] of 70 laboratory-born animals came from Pearl Beach, NSW, 8 came from near Canberra, ACT and 6 from Queensland. Cranial volumes were measured by the shot-displacement method described by Mann *et al.* (1988) and were treated as equal to brain weight (E)[3]. Body weight (P), body length (BL=total length minus tail length) and age at death (A) were taken from the museum specimen tags. All data are stated in cgs units and in days postpartum (pp).

Sample means ($\overline{X}$), standard deviations (SD), standard errors (SE) and coefficients of variation ($CV=\frac{SD}{\overline{X}}$) were calculated on all the variables. Covariation between pairs of variables was estimated by the correlation coefficient (Pearson's r), by least squares regression (a), by reduced major axis (b, calculated by the method of Kermack and Haldane, 1950), and by the ratio of coefficients of variation (B). The latter employs the percentage differences in variance to estimate the covariance slope for pairs of parameters. Kidwell and Chase (1967) found that regressions a and b are quite accurate when the variances are equal (they are close for E and BL, but not for E and P).

Numerous studies have demonstrated that individual body growth curves are polyphasic, requiring a multi-jointed hockey stick function for adequate description. However, broadly scattered, lumped data, with only one point per animal, preclude such a description. Therefore, a Gompertz function (Laird *et al.*, 1965; Laird, 1965) of the form $X(T)=X_o\exp[({}_XG_o/\mu)\,(1-\exp(-\mu t))]$, modified by adding a linear growth term, βt, was used to describe the data (${}_XG_o$ = specific growth rate of variable X at time t_o, and μ =rate of decay of growth rate). In the present study, the variable X signifies E, P or BL. Initial weight, P_o, was taken as the mean of the 8 youngest specimens; their mean age was 20 days pp, so t_o=20 (i.e., when T=0, t=-20 and when T=20, t=0). The same group of specimens defined initial body length, BL_o, at t=20. The method of Barton and Laird (1969) yielded a time-displacement of four days for brain growth ($-\Delta T$=3.95 days); therefore, t_o=16 in the Gompertzian description of brain growth.

The initial specific growth rate, ${}_XG_o$, the starting value for the nonlinear regression, was estimated from the slope of the least squares regression [$X=f(A)$] in the neighborhood of the initial time reference (t_o=20 days pp for P and BL; t_o=16 days pp for E). The rate of decay of growth rate was found through the relation $({}_XG_o/\mu) = \ln(X_a/X_o)$, where X_a is the asymptote of the Gompertz function, attained by day 150 pp. A least squares regression was calculated over days 138-1288 pp for each variable; the value of that function on day 150 pp defined X_a. The values found for μ were rounded to 0.0400 for all three parameters under study. The slope of the least squares regression over days 138-1288 pp defined the coefficient, β, of the linear growth term, βt, required for an adequate description of the observed data.

RESULTS

Laboratory-reared sample. Growth proceeded in two phases: an initial rapid growth, grading into a very slow growth that continued through life. The variation in body weight was three times that for body length and brain weight, reflecting geometric similarity. The youngest animal died on day 16 pp, whereas the oldest exceeded 3.5 years when it died. Average life span of the 53 animals that died during

[2] The dams referred to here are not included among the wild-caught sample, but trapping site data were available for these animals.

[3] We use the terminology employed by most investigators of brain allometry, i.e., E for brain weight and P for body weight.

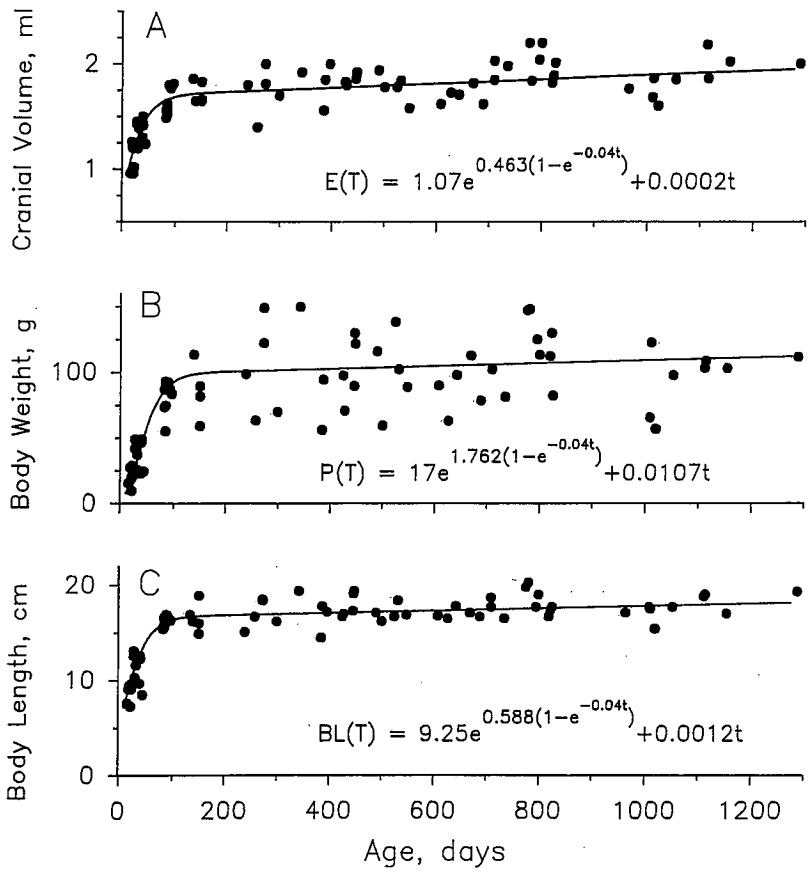

Figure 1. Computed growth trajectories superimposed on the measurements of cranial volume (A), body weight (B) and body length (C). The specific values for the modified Gompertzian function are shown in each graph. Goodness of fit parameters are as follows: A: Coefficient of determination (r^2)=0.741, F ratio (F)=65.685, Degrees of freedom (DF)=69, Fit standard error (FSE)=0.1504; B: r^2=0.616, F=35.285, DF=66, FSE=24.313; C: r^2=0.844, F=124.010, DF=69, FSE=1.329.

Taylor's study was 18.25 months; the remaining animals were killed at various times from day 0.6 to 39 months pp. Even so, significant gaps were left over days 44-82 and 96-133 pp. Also, all specimens from days 82 through 96 derived from Canberra and Queensland stock, whereas all but 5 of the others came from Pearl Beach stock. There are not enough specimens from each location at each age to analyze the effect of trapping site on the parameters studied.

The sample was partitioned into two age groups in order to obtain the values needed for the Gompertz functions: 1) Y (16-44 days pp) and 2) M (138-1288 days pp). The specimens for days 82-96 were not included in the regression analysis, not only because they derived from different stock, but also because they occupied the region of gradual transition from rapid to very slow growth. Seven animals were quite heavy at the time of death, 4 males and 3 females exceeding 175 g. Because their brain weights and body lengths did not differ markedly from those of their neighbors, they were judged to have been obese, and were excluded from the quantitative analysis. They will be described separately.

Does brain growth parallel body growth? Least squares regressions on age for the M group yielded slopes greater than, though statistically not significantly different from, zero. However, an adequate description of growth trajectories required inclusion of these slopes. This can be seen in Fig. 1, which shows the modified Gompertz growth curves super-

TABLE 1.
Slopes (a) derived from least squares regression of X on age (A), along with standard errors of the slopes (SE), correlation values (r), coefficients of alienation (k) and standard errors of the estimate (S_{Xa})

X	a	SE	r	k	S_{Xa}
E	0.00020	0.00008	0.365	0.931	0.16
P	0.0107	0.0141	0.116	0.993	28.51
BL	0.0012	0.0006	0.294	0.956	1.27

imposed on the data. All functions appear to parallel one another quite well, and geometric similarity holds, as the exponent coefficients reveal. That is ${}_{BL}G_o = (1/3)\ {}_pG_o = {}_{p^{1/3}}G_o$. These values approximate ${}_EG_o$. Thus, brain growth parallels growth in body weight and body length, though it is displaced about 4 days in time.

Does growth continue throughout life? The coefficients of the linear growth term, βt, were derived from the linear regressions of X on age; the derived slopes are shown in Table 1, along with other relevant values. It is clear that the slopes did not differ significantly from zero (the low slopes ensure that even a small variation will produce a low correlation), but even simple visual inspection of Fig. 1 reveals the need to use this growth term to adequately describe the data. When normalized, by dividing the regression slope by the value of the unmodified Gompertz function at t=150 days, the slopes were found to be comparable (1.11 : 1.00 : 0.67, respectively). Both brain and body appear to grow throughout life.

Obese animals. The mean weight of the 7 excluded animals was double the value expected from the modified Gompertzian function. On the other hand, the mean for brain weight was 7.7% larger, and that

TABLE 2
Characteristics of the wild-caught (W), and the adult (M) and young (Y) specimens of the laboratory-reared samples.

X	W			M			Y		
	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n
E	1.88	0.19	89	1.84	0.17	47	1.25	0.17	15
P	107.7	38.3	88	102.1	28.4	45	29.5	12.6	15
BL	16.3	2.2	89	17.5	1.3	47	10.2	1.8	15

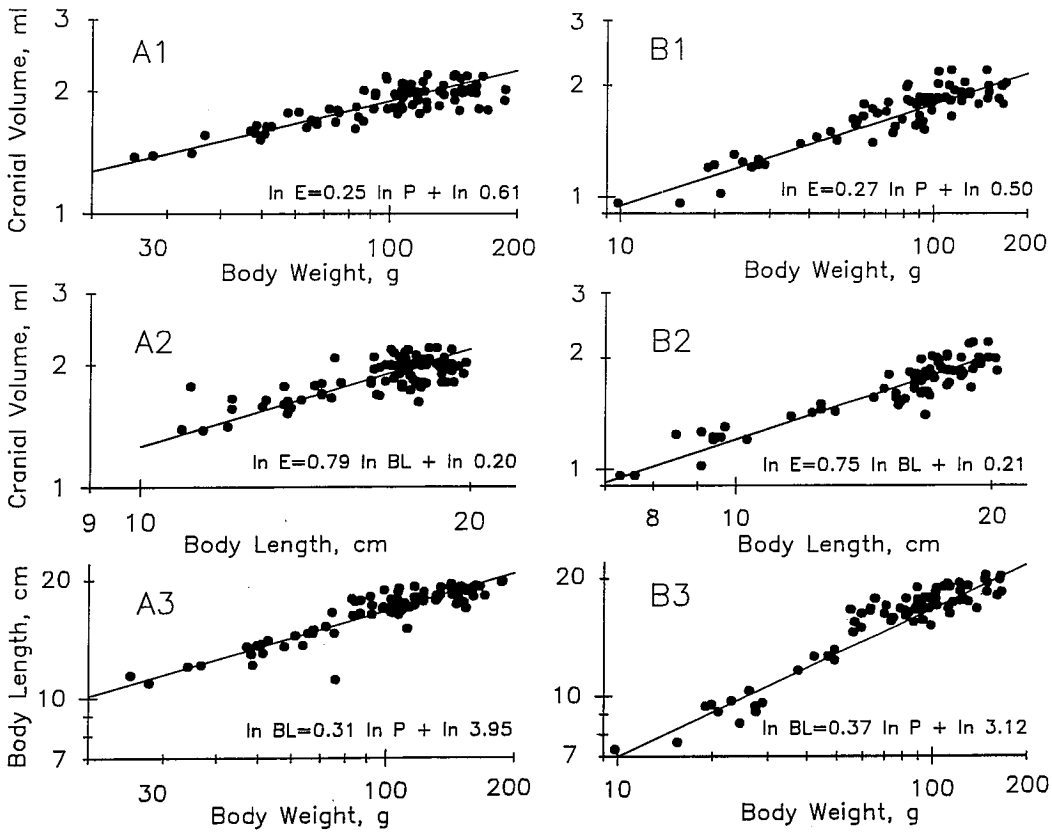

Figure 2. Log-log plots of the data for wild-caught (A) and laboratory-reared (B) animals, showing cranial volume as a function of body weight (1) and body length (2), and body length as a function of body weight (3), with reduced major axes superimposed. The associated equations are shown in each graph.

for body length was 6.9% larger than expected. The mean ratio for body weight/body length was 5.98±0.23 (SE) for the M group, but 11.47±0.49 for the obese animals (this ratio was 2.78±0.18 for the Y group). Adding three marginally obese animals to the obese group yielded a mean P/BL ratio of 10.75±0.21. Thus, though the 7 obese animals differed significantly from the M group, they occupied the tail of a highly skewed distribution. By comparison, the mean P/BL ratio for the wild-caught sample was 6.21±0.18.

Can the results be generalized to wild populations? Table 2 shows that the wild-caught animals (W) were similar to the adult (M) laboratory-reared animals, though they perhaps had relatively shorter bodies. Mean body weight for the M group would have been $\overline{P}$=120.8±48.3 if the obese rats had been included. Fig. 2 plots the relations among the three variables for both wild-caught (Fig. 2A) and laboratory-reared (Fig. 2B) animals. The young specimens in both samples formed direct extensions of the adult relations, so they can be included in any regression analysis with no loss of descriptiveness. The slope of cranial volume on body weight shown in Fig. 2A1 was b=0.248 (B=0.277), and the correlation was r=0.74±0.05 (SE). By comparison, the mean slope and correlation found by Mann *et al.* (1988) for 10 species of *Rattus*, for which at least 15 specimens were measured, were $\overline{b}_{E/P}$=0.280±0.017 (SE) ($\overline{B}_{E/P}$=0.288±0.016) and $\overline{r}_{E:P}$=0.75±0.05 (SE). Thus, the relation between brain weight and body weight for wild-caught Allied rats was similar both to laboratory-reared animals and to other Australasian species. Further, geometric similarity implies a similar generalization for the relation of brain weight to body length.

It is clear from Fig. 2 that power functions can describe the data quite well, even with juveniles pre-

TABLE 3.
Comparison of slopes calculated from Gompertzian function ($G_{y/x}$) with reduced major axis ($b_{y/x}$) and ratio of coefficients of variation ($B_{y/x}$) for both laboratory-reared (L) and wild-caught (W) samples.

Y/X	L			W	
	G	b	B	b	B
E/P	0.263	0.274	0.299	0.247	0.287
E/BL	0.788	0.752	0.814	0.791	0.824
BL/P	0.334	0.366	0.367	0.366	0.349

sent. Table 3 reveals the degree of concordance among the different methods of estimating exponents (slopes). Note that $\frac{S_{E/P}}{S_{E/BL}}=S_{BL/P}$, where S is slope. Thus, if geometric similarity holds, $S_{E/BL}=3S_{E/P}$. These slopes would appear in allometric power functions involving the pairs of parameters. Because the period of rapid brain growth leads that of rapid body weight and length growth, the latter two slopes differ from 1/3 and 1, respectively. There were no sex differences, though the slopes of brain weight on body weight and body length were $b_{E/P}=0.255$ and $b_{E/BL}=0.745$ for males and $b_{E/P}=0.316$ and $b_{E/BL}=0.815$ for females.

DISCUSSION

The altricial murids have short gestation periods and are born with brains only 5-20% of their adult size (Sacher and Staffeldt, 1974). Their brains grow fastest in the first 3 weeks after birth; they are "postnatal brain developers" (Davison and Dobbing, 1968). Not only the murids (Winick and Noble, 1965), but myomorphs in general [e.g., deer mice (King, 1965) and gerbils (Watanabe and Schain, 1980)] belong in this category. By contrast, the precocial caviomorphs [e.g., guinea pigs (Dobbing and Sands, 1970)] are "prenatal brain developers." The Allied rats of the present study attained only 5% of adult body weight and 15% of adult brain weight by the time of birth; the surge in brain growth occurred after birth. How much of this surge is due to cell proliferation and how much to cell growth?

Altman and Das (1965) found a 6-fold increase in number of neurons in the dentate gyrus of lab rats during the first 3 postnatal months, with peak density of precursor cells occurring in the granular layer two weeks after birth. Brizzee and Jacobs (1959) found a 6-fold exponential decline in neuronal density in area 2 of neocortex over the same period, implying a 6-fold increase in cortical volume, if the number of neurons remained constant. Over the same period, the Allied rat brain increased 5-fold, from an estimated 0.28 g at birth to 1.39 g on day 21 pp. By contrast, Dobbing and Sands (1970) found that the major increase in DNA-P of whole brain (which coincides with major brain growth) occurs prior to birth in guinea pigs.

The Allied rat brains grew some 40 mg/day over the first 3 postnatal weeks, close to the 48 mg/day rate for lab rats (Brizzee and Jacobs, 1959). Over the 23 day gestation period, the Allied rat brain grew an average of 12 mg/day, similar to the rate for lab rats

[4] It would be more appropriate to start on embryonic day 11 (Bayer and Altman, 1991), which yields an average growth of 23 mg/day over the 12 days before birth.

(Brizzee and Jacobs, 1959; Sikov and Thomas, 1970)[4]. However, the shapes of growth trajectories for individual animals remain unknown; they probably form polyphasic, rather than smooth, trajectories, much as is seen with body growth. Individual body growth curves of Kangaroo rats (Chew and Butterworth, 1959; Butterworth, 1961) and of pocket mice (Hayden and Gambino, 1966) trace out a sequence of straight line segments; growth rate changes in stairstep fashion with age. However, rodent growth curves are most often portrayed as continuously curving functions (Berg and Harmison, 1957; Dice and Bradley, 1942; Hoffmeister and Getz, 1968; King and Eleftheriou, 1960; Layne, 1966), because the data represent averages on a collection of animals rather than the trajectories of individual animals. The present study was based on one-time-point data for each specimen and thus followed the latter approach. Therefore, although the modified Gompertz functions served well as descriptors and showed that brain growth leads, but closely parallels, growth in body weight and length, they may not properly portray the detailed pattern of individual growth.

Adult growth. An important feature of the data was the apparently steady increase in body weight and length and in cranial volume throughout adult life. Duffy and Sacher (1976) observed a similar steady increase in house mice during the first 20-21 months of life, but a decrease thereafter. Their data on deer mice showed a steady decrease beginning 4-5 months after birth. Chew and Butterworth (1959) reported a similar pattern for Kangaroo rats, the decline beginning about 3 months after birth. This contrasts sharply with the present study, which showed no downturn over three years of life; to the contrary, it seemed to show a steady increase throughout life. Berg and Harmison (1957) parcelled their data from lab rats into two groups, based on the presence or absence of histologically identifiable lesions, and found that the healthy rats grew continuously over 27 months of life, whereas the rats displaying lesions in various body organs showed a steady decrease in body weight, with no change in body length, over 38 months of life (after attaining adult size). It may be significant that in the Taylor data on which the present study was based, the animals that were killed were heavier than those that died at about the same age. The conclusion may be drawn that healthy rats continue to grow at a very slow rate throughout life.

Generality of the results. Because the characteristics of the adult laboratory-reared animals of the present study were similar to those of the wild-caught sample, as well as to other Australasian species (Mann *et al.*, 1988), the findings from laboratory-reared animals may be generalized to wild populations. Such a conclusion has been drawn previously in other rodent studies (Dice, 1949; Hayne, 1950). Mann *et al.* (1988) obtained a mean slope of about 1/3 for cranial volume on body weight among myomorph rodents, the juvenile animals appearing to "extend the brain/body trend for their subspecies," as if, on average, each animal maintained the same brain/body proportions throughout life. This is consistent with the assertion of Riska and Atchley (1985) that brain and body growth in rats and mice are strongly coupled during the first five weeks after birth, though they may be uncoupled thereafter. The latter point would best be tested by following individual brain and body growth into adult life, using periodic CAT scan- or MRI-derived estimates of brain volume.

Brain allometry within demes is of great importance for understanding overall mammalian brain/body allometry. Calculation on the data of King (1965) on deer mice yield $E \alpha BL^{1.03}$ over days 10-30 pp. Because geometric similarity may hold (Towe and Mann, 1992), the data of King and Eleftheriou (1960) on two subspecies of *Peromyscus maniculatus* show near-linearity between brain weight and body length over days 10-30 pp. Though such findings are suggestive, a true ontogenetic study using non-invasive measurements that do not alter the normal course of growth is required to yield accurate relationships. Such a study has yet to be performed.

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