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Placental invasiveness and brain–body allometry in eutherian mammals

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Abstract

Brain growth is a key trait in the evolution of mammalian life history. Brain development should be mediated by placentation, which determines patterns of resource transfer from mothers to fetal offspring. Eutherian placentation varies in the extent to which a maternal barrier separates fetal tissues from maternal blood. We demonstrate here that more invasive forms of placentation are associated with substantially steeper brain–body allometry, faster prenatal brain growth and slower prenatal body growth. On the basis of the physiological literature we suggest a simple mechanism for these differences: in species with invasive placentation, where the placenta is bathed directly in maternal blood, fatty acids essential for brain development can be readily extracted by the fetus, but in species with less invasive placentation they must be synthesized by the fetus. Hence, with regard to brain–body allometry and prenatal growth patterns, eutherian mammals are structured into distinct groups differing in placental invasiveness.

Introduction

Body size allometry, in which the dimensions of body parts and the values of life-history variables scale across species as a power of body size, has long been the subject of biological study, speculation and controversy (Huxley, 1932; Kleiber, 1932; Brody, 1945; Hunt & Giles, 1956; Gould, 1966, 1971; Stearns, 1980; Martin, 1981; Harvey & Pagel, 1988). A central notion in the study of allometry is that such scaling patterns reflect fundamental constraints on the transfer of energetic resources within living organisms, ultimately affecting development, function and evolution. Biologists have documented interspecific differences in the intercept and slope of allometric log–log plots, and in the deviation of species from an observed allometric scaling relationship, with mammalian brain–body allometry being one of the best studied patterns (Gayon, 2000). Such studies help identify ecological or life-history correlates of variation in the scaling of body size and its components, which have been explained in terms of trade-offs in the allocation of limited energetic resources to different body parts, functions, activities and time periods throughout an animal's life span.

Analysis of the development of energetically expensive tissues (Aiello & Wheeler, 1995; Aiello, 1997; Kaufman, 2003; Isler & van Schaik, 2006) is expected to yield important insights into the origin and evolutionary diversification of animal allometry for two reasons. First, expensive tissues place strong energetic demands on life-history trade-offs over allocation of resources to growth vs. fecundity and other functions. Second, such tissues should mediate strong selective pressures on the proximate mechanisms of resource acquisition during prenatal and infant growth. In terms of its maintenance energy requirements, the brain is the most expensive tissue of the mammalian body, consuming over twenty times the energy of skeletal muscle per unit mass at rest (Siesjö, 1978; Aiello & Wheeler, 1995; Aiello, 1997; Laughlin *et al.*, 1998). The brain is also extremely costly in terms of the structural components that are required for its growth, to such an extent that brain growth may be the main rate-limiting process operating during fetal development (Martin, 1996).

Previous studies have proposed and tested various social and ecological correlates of adult mammalian encephalization patterns, including the nature of mating systems and sexual competition (Pawlowski *et al.*, 1998; Barton, 2006a,b; Pitnick *et al.*, 2006), social group size or

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social complexity (Sawaguchi & Kudo, 1990; Barton, 1996, 1998; Joffe & Dunbar, 1997; Dunbar & Bever, 1998; Pawlowski *et al.*, 1998; Kudo & Dunbar, 2001; Dunbar, 2003; Lindenfors, 2005; Pérez-Barbería & Gordon, 2005; Shultz & Dunbar, 2006a), diet or foraging behaviour (Gittleman, 1986; Mann *et al.*, 1988; Barton, 1996, 1998; Hutcheon *et al.*, 2002; Fish & Lockwood, 2003; Shultz & Dunbar, 2006a), the size or complexity of the behavioural repertoire (Pellis & Iwaniuk, 2002; Reader & Laland, 2002; Changizi, 2003; Byrne & Corp, 2004; Lefebvre *et al.*, 2004; Safi *et al.*, 2005; Ratcliffe *et al.*, 2006), habitat complexity and novelty (Marino *et al.*, 2004; Safi & Dechmann, 2005), the intensity of predation (Shultz & Dunbar, 2006b) and longevity (Allman *et al.*, 1993a,b). Here we adopt a physiological perspective in order to assess how the growth and allometry of developing brains may also be influenced by functional constraints and trade-offs in resource transfer and allocation during the prenatal period.

The anatomical structure of most significance to the developing mammalian fetus is the placenta, which develops from fetal extra-embryonic ectoderm and varies markedly in form and function among eutherians (Mossman, 1987; Carter *et al.*, 2004; Enders & Carter, 2004). The placenta has also been identified as an arena in which genetic conflicts over the rate and magnitude of resource allocation are made manifest (Haig, 1993; Crespi & Semeniuk, 2004). Specifically, more invasive forms of placentation may be associated with enhanced fetal mobilization of maternal resources, and the fetal manipulation of maternal energy budgets by secretion of hormones and other substances into the maternal bloodstream (Petry *et al.*, 2007), potentially resulting in improved resource acquisition by the fetus during pregnancy (Haig, 1993).

Our primary hypothesis is that more invasive forms of placentation are associated with accelerated prenatal brain growth, which may translate into interspecific differences in patterns of brain–body allometry, notably 'grade shifts' (differences in intercept) and changes in allometric slope (which estimates the exponent of the scaling relationship). In order to test this hypothesis we group mammalian species according to their level of placental invasiveness under the standard tripartite classification first developed by Grosser (1909). Placental invasiveness refers to the nature and thickness of the barrier separating maternal blood from fetal tissues. The haemochorial placenta, in which no barrier exists and fetal tissues are in direct contact with maternal blood, is considered the most invasive form. Under endotheliochorial placentation, maternal blood remains enclosed within the endothelium of maternal blood vessels and does not directly bathe the placental surface. Finally the epitheliochorial placenta, in which fetal tissues are separated from maternal blood by a barrier consisting of maternal endothelium, connective tissue and epithelia, is considered the least invasive form (Grosser, 1909; Mossman, 1987). Maximum likelihood reconstructions, which are robust with respect to evolutionary model choice, indicate that the ancestral placental condition of extant eutherians was apparently of an invasive haemochorial form, and the occurrence of less-invasive placentation in extant taxa is the result of 9 to 11 independent evolutionary transitions occurring in Lypotyphla, Primates, Chiroptera, Rodentia, Afrotheria, Edentata and at the common ancestor of Perissodactyla, Artiodactyla, Carnivora and Pholidota (Elliot & Crespi, 2006; Wildman *et al.*, 2006). The taxonomic distribution of eutherian placentation is reviewed in the Supporting Information and described in more detail by Mossman (1987). We use classical and phylogenetic statistical methods to test for differences in the brain–body allometric slope and intercept exhibited by species grouped according to their form of placentation, across mammals as a whole and within a number of focal clades. We further test for differences in prenatal brain and body growth rates between these groups. Finally, we describe physiological mechanisms that may account for our findings.

Materials and methods

Data on brain mass, body mass, litter size and gestation length in 600 eutherian species were obtained from the literature (see Supporting Information). Throughout this article we use female adult body mass data. As our analyses indicate that the extent of sexual size dimorphism correlates positively with overall body size, the relative brain size of large species would be underestimated if male body mass were to contribute towards estimates of average body mass within a species. The use of female data thus minimizes error introduced by the effects of sexual body size dimorphism on estimates of brain–body allometry.

Eutherian species were grouped into three categories on the basis of gross placental morphology; these categories can be ranked in terms of their level of placental invasiveness into the maternal uterine wall: haemochorial > endotheliochorial > epitheliochorial. Our data set and literature sources are available in the Supporting Information. Each placental category contains representatives of diverse mammalian clades. In our data set, the haemochorial category contains species from Afrosoricida, Carnivora, Chiroptera, Cingulata, Erinaceomorpha, Lagomorpha, Macroscelidea, Pilosa, Primates, Rodentia and Soricomorpha ($n = 322$); the endotheliochorial category contains species from Carnivora, Chiroptera, Pilosa, Proboscidea, Rodentia, Scandentia and Soricomorpha ($n = 151$); and the epitheliochorial category contains species from Artiodactyla, Cetacea, Perissodactyla, Primates and Soricomorpha ($n = 127$). Throughout this article we adhere to the taxonomy compiled under the auspices of the American Society of Mammalogists and the Smithsonian Museum of Natural History (Wilson & Reeder, 2005). Average prenatal brain growth rates were calculated by dividing newborn brain mass by

gestation length. Average prenatal body growth rates were calculated by subtracting newborn brain mass from newborn body mass, and dividing by gestation length. Log transformation uses base 10 throughout.

In classic work (i.e. Jerison, 1973), allometric relationships between brain mass and body mass are investigated using ordinary least squares (OLS) regression of the log-transformed species-level data, with a great deal of effort being devoted to identifying the 'correct' mammalian exponent, currently considered to be 0.75 (Harvey & Pagel, 1988). This approach has remained in wide use to the present day, with most functional allometric relationships presented graphically in terms of OLS regression plots (i.e. Hutcheon *et al.*, 2002; Barton, 2006a,b; Burton, 2006; Finarelli, 2008). Two characteristics of comparative biological data may render these classic approaches unsuitable. First, species mean data points are hierarchically autocorrelated due to the existence of phylogenetic relationships between taxa; second, random variation exists is all biological variables, not just the 'dependent' variable of an OLS regression (O'Connor *et al.*, 2007).

A number of alternative approaches, aiming to deal with the first problem, have been devised. Phylogenetic relationships between taxa mean that species mean values cannot be considered independent samples from a single distribution; in our specific case, the clustering of taxa within placental categories may result in biases in the body mass and brain mass characteristic of each placental type, and consequent biases in the results of classical allometry. Felsenstein (1985) argues that the data points of a comparative analysis should be numerical differences in the values of variables between sister nodes on a phylogenetic tree, rather than the absolute values of variables at the terminal tips of the tree. Independent contrasts derived from a cluster of similarly sized, closely related taxa will generate a set of data points clustered around the origin through which a regression line is forced, and so will contribute little to the inference of a regression slope. The slope of a regression based on independent contrasts will then reflect divergence between clustered taxa and exclude the confounding effect of differences in mean value between such clusters within taxonomic groups.

In response to the second problem, a number of authors (Rayner, 1987, Pagel & Harvey, 1988b; Labarbera, 1999) advise the use of major axis or reduced major axis (RMA) rather than OLS regression, as in allometric analysis uncontrolled error variance is not restricted to the dependent variable. Indeed, an impromptu analysis of intraspecific data from Crile & Quiring (1940) indicates that species-level estimates of body mass exhibit more variance than species-level estimates of brain mass even after log-transformation. As the majority of published work on brain–body allometry in mammals reports the results of OLS regression of species mean data points, we begin our analysis using an OLS general linear model. Alongside these results, however, we also present the analysis of independent contrasts under RMA regression. In the case of brain size data, for which explicit measurements of intraspecific variance are generally not available, we choose to use RMA regression because, of the available techniques, it is the least sensitive to assumptions about the error structure in the data (Labarbera, 1999). Our dual analysis of the raw data under OLS and independent contrasts under RMA permits our results to be compared with previous work, while confirming them under a more modern comparative statistical framework. Yet controversy remains over the ideal form of regression for use in comparative analysis, and there exist an array of methods providing best results under different circumstances (Ives *et al.*, 2007; O'Connor *et al.*, 2007).

Our general approach is to identify differences between placental groups in allometric exponent and coefficient by building a linear model and testing for the significance of a placental dummy variable and an interaction term between placental category and body mass respectively. In our Results section we present pairwise comparisons of the three placental categories along with the sample size, the standard error of the difference in exponent between categories and the two-tailed significance tests by which we accept or reject the null hypothesis that placental groups do not differ in allometry.

Analysis of raw data under OLS is accomplished using the general linear model module of SPSS (SPSS Inc, 2006), with the placental dummy variable set as a fixed factor, log brain mass as the dependent variable and log body mass as a covariate. Two placental categories are judged to differ in allometric exponent if the interaction term, body mass × placenta, is a significant component of the model at $P < 0.05$. In the absence of a difference in exponent, two placental categories are judged to differ in allometric coefficient if the binary placental dummy variable is a significant component of the model at $P < 0.05$.

Independent contrasts were based on a recent species-level supertree of the mammals (Bininda-Edmonds *et al.*, 2007), and assembled using the software MESQUITE (Maddison & Maddison, 2005). For the comparison of sister clades differing in placentation, contrasts were generated separately for each clade, categorized by the placentation characteristic of the clade and combined into a single set of contrasts for analysis. In analyses of eutherian mammals as a whole, ancestral placental conditions were inferred by maximum likelihood. Contrasts of ambiguous placentation (in which the statistical significance of ancestral reconstruction was greater than 0.05) were excluded from this data set. Analysis of independent contrasts under RMA is accomplished in SPSS using the nonlinear regression module. The standard bivariate RMA model is defined as $y = ax + b$, where y and x are variables of interest, and a and b are the slope and intercept of the regression line respectively. The loss function, which specifies the manner in which residuals

Table 1 Brain–body allometry in adult mammals (top), newborn mammals (middle) and newborn litters (bottom), under classical regression (left) and regression of independent contrasts (right). Results are presented as pairwise contrasts between placental categories. SE is the standard error of the pairwise difference in slope, whereas *P* is the two-tailed significance of the hypothesis that species with more invasive placentation differ in slope from species with less invasive placentation. Placental invasiveness is ranked: haemochorial > endotheliochorial > epitheliochorial.

	Classical regression				Independent contrasts			
Placentation	*n*	Slope	SE	*P*	*n*	Slope	SE	*P*
Adult allometry								
Haemochorial	318	0.851	0.016	< 0.0001	215	0.690	0.039	0.0248
Endotheliochorial	148	0.758			91	0.602		
Haemochorial	318	0.851	0.021	< 0.0001	215	0.690	0.028	0.0003
Epitheliochorial	124	0.653			94	0.586		
Endotheliochorial	148	0.758	0.018	0.0153	91	0.602	0.036	0.6578
Epitheliochorial	124	0.653			94	0.586		
Newborn allometry								
Haemochorial	55	1.068	0.043	< 0.0001	43	0.882	0.048	0.0224
Endotheliochorial	19	0.830			15	0.769		
Haemochorial	55	1.068	0.083	< 0.0001	43	0.944	0.068	0.0001
Epitheliochorial	33	0.660			28	0.633		
Endotheliochorial	19	0.830	0.034	< 0.0001	15	0.828	0.059	0.0019
Epitheliochorial	33	0.660			28	0.633		
Litter allometry								
Haemochorial	55	0.752	0.045	0.0339	36	0.691	0.111	0.4384
Endotheliochorial	19	0.574			10	0.603		
Haemochorial	55	0.752	0.059	0.0132	36	0.691	0.076	< 0.0001
Epitheliochorial	33	0.602			20	0.516		
Endotheliochorial	19	0.574	0.092	0.7599	10	0.603	0.115	0.4554
Epitheliochorial	33	0.602			20	0.516		

are calculated, is defined as $(y - (ax + b))^2/\text{abs}(a)$. When analysing independent contrasts the regression line must be forced through the origin, hence b is necessarily equal to zero and is removed from the equations. In order to test the significance of a difference in slope between two categories it is necessary to generate a binary dummy variable (equal to zero or one) specifying category membership. The model is then defined as $y = ax + kcx$, where k is the dummy variable and c is the difference in slope between the two categories, and the loss function is defined as $(y - (ax + kcx))^2/\text{abs}(a + kc)$. The mean and standard error of the estimate of c (reported in Tables 1 and 2) are generated by bootstrapping 100 replicates. The regression slopes of each category are considered to differ if c differs significantly from zero in a z-test. In order to assess the accuracy of this method, its estimates of a and c were compared to those produced by Mesquite (Maddison & Maddison, 2005), which can fit RMA regressions but cannot identify significant differences between categories. In every case, the coefficients estimated using spss were identical to those estimated by Mesquite.

Results

Brain–body allometry in adult mammals

Linear regression models were used to explore the relationship between placentation and brain–body allometry. In mammals as a whole, irrespective of placental type, the allometric scaling relationship exhibited a slope of 0.765 (SE = 0.007, $t_{1,587} = 114.305$, $P < 0.001$) and an intercept of −1.257 (SE = 0.022, $t_{1,587} = -58.043$, $P < 0.001$). Each form of placentation is associated with a significant, characteristic departure from this average scaling relationship (Fig. 1). Species with more invasive placentation were found to exhibit steeper allometric slopes than species with less invasive placentation, such that the exponent of the brain–body scaling relationship is highest in the haemochorial category and lowest in the epitheliochorial category. All pairwise differences in allometric slope between eutherian placental categories are statistically significant (Table 1).

By examination of Fig. 1 and statistical comparison it is clear that epitheliochorial species tend to be of larger body size than endotheliochorial species (epitheliochorial mean = 4.472, SE = 0.110; endotheliochorial mean = 2.542, SE = 0.118; $F_{1,269} = 138.419$, $P < 0.001$) and haemochorial species (haemochorial mean = 2.421, SE = 0.063, $F_{1,439} = 278.895$, $P < 0.001$); the difference in mean body mass between haemochorial and endotheliochorial species is not statistically significant ($F_{1,464} = 0.964$, $P = 0.327$). Testing the hypothesis that differences in brain–body allometry are driven by differences in placentation requires us to exclude the possibility that differences in body mass between placental categories are responsible for generating these patterns.

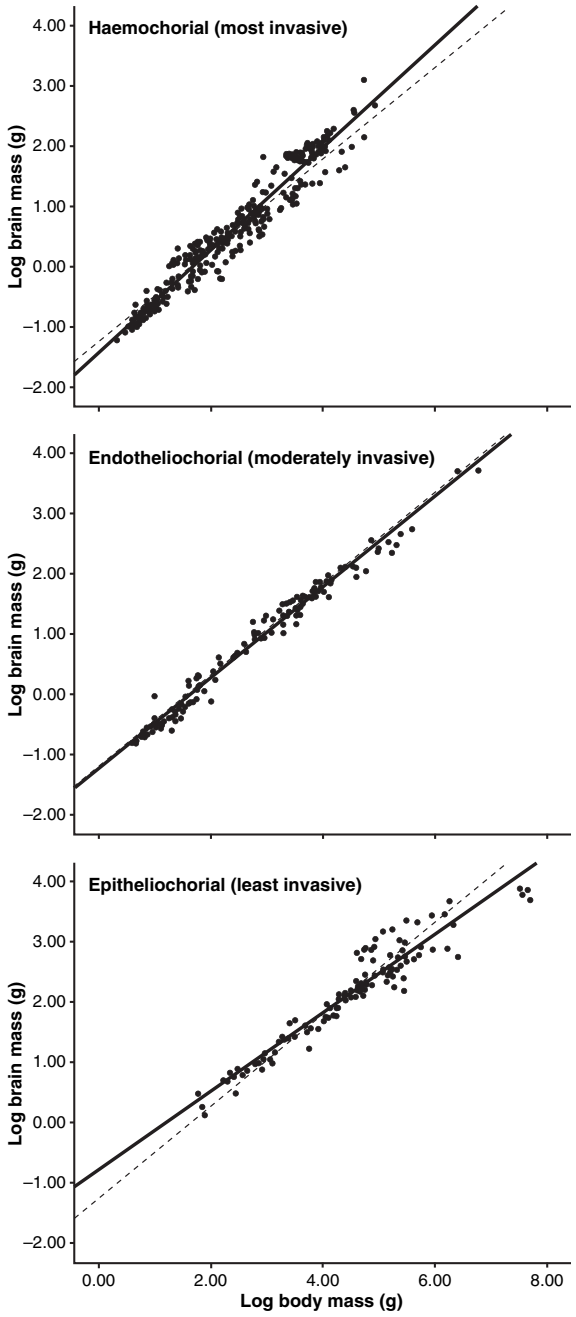

Fig. 1 Brain–body allometry in adult eutherian mammals split by placental invasiveness. More invasive forms of placentation are associated with steeper allometric scaling relationships (solid lines). The allometry of eutherian mammals as a whole, irrespective of placental type, is provided as a basis for comparison between groups (dashed line). The body and brain mass axes of each graph have the same scale.

One approach to this problem is to exclude species of extremely small or large size from the data set, resulting in a subset of 220 species with body mass ranging from 100 g to 6 kg, and exhibiting no significant differences in body mass between placental categories ($F_{2,218} = 2.068$, $P = 0.129$). Placentation was found to exert similar effects in this size-constrained subset as reported above for the complete data set. Thus, species with haemochorial placentation exhibit a steeper allometric slope than species with endotheliochorial placentation ($\beta = 0.985$ vs. 0.706, SE = 0.037, $F_{1,188} = 11.810$, $P = 0.001$), which in turn exhibit a steeper slope than species with epitheliochorial placentation ($\beta = 0.634$, SE = 0.041, $F_{1,74} = 11.974$, $P < 0.001$).

An alternative approach to the problem of systematic variation in body size between placental categories is to use phylogenetically independent contrasts (see Materials and methods). Numerical results of these tests are presented in Table 1 (column labelled 'Independent contrasts'). These results indicate that differences in the slope of the brain–body allometry between the two less invasive placental categories (epitheliochorial and endotheliochorial) may be illusory, driven by the phylogenetic structure of the data set. The brain–body allometry of species with the most invasive (haemochorial) form of placentation, however, was still significantly steeper than that found in either epitheliochorial or endotheliochorial groups.

Together, these results provide evidence that the brain–body allometry of mammals is significantly steeper in species with haemochorial placentation than in species with less invasive forms of placentation. These results are robust with respect to variation in body size between placental categories and are not generated by biases resulting from the phylogenetic nonindependence of species mean brain and body masses.

Brain–body allometry in adult mammals, excluding Primates

It might be suspected that primates in particular are involved in generating the overall patterns described in the previous section. Strepsirhine primates are among the smaller epitheliochorial species, whereas haplorhine primates are among the larger haemochorial species. As both groups are relatively large-brained, strepsirhines may suppress the slope of the epitheliochorial allometry, although haplorhines may inflate the slope of the haemochorial allometry. In order to exclude this possibility we repeated the previous analyses having excluded all primates from our data set. In the classical (nonphylogenetic) regression analysis, haemochorial species exhibited a significantly steeper allometric slope than epitheliochorial species ($\beta = 0.758$ vs. 0.621, $F_{1,318} = 21.284$, $P < 0.001$), as did endotheliochorial species ($\beta = 0.728$ vs. 0.621, $F_{1,240} = 12.988$, $P < 0.001$). However the slope (and intercept) of haemochorial and endotheliochorial species did not differ significantly ($F_{1,373} = 3.424$, $P = 0.065$ and $F_{1,373} = 0.102$, $P = 0.752$ respectively). It should be borne in mind that our previous comparative analyses suggest that the

Table 2 Brain–body allometry in adult mammals from placentally divergent sister clades, under classical regression and independent contrasts. SE is the standard error of the pairwise difference in slope, whereas *P* is the two-tailed significance of the hypothesis that species with more invasive placentation differ in slope from species with less invasive placentation. Placental invasiveness is ranked: haemochorial > endotheliochorial > epitheliochorial.

		Classical regression				Independent contrasts			
Sister clades	Placentation	*n*	Slope	SE	*P*	*n*	Slope	SE	*P*
Haplorrhini	Haemochorial	92	0.776	0.050	0.0105	87	0.779	0.050	0.0479
Strepsirrhini	Epitheliochorial	30	0.646			28	0.669		
Soricidae	Haemochorial	17	0.677	0.041	< 0.0001	16	0.713	0.055	< 0.0001
Talpidae	Nonhaemochorial	6	0.159			5	0.195		
Vespertilionidae	Haemochorial	43	0.796	0.046	< 0.0001	42	0.734	0.053	0.0979
Rhinolophidae	Endotheliochorial	25	0.585			24	0.645		
Vespertilionidae	Haemochorial	43	0.797	0.032	< 0.0001	42	0.734	0.053	0.0044
Hipposideridae	Endotheliochorial	20	0.560			19	0.577		
Microchiroptera	Haemochorial	62	0.815	0.050	0.0003	50	0.739	0.038	0.0059
	Endotheliochorial	49	0.626			46	0.632		
Geomyidae	Haemochorial	9	0.758	0.046	0.0010	8	0.743	0.142	0.1942
Heteromyidae	Endotheliochorial	9	0.576			8	0.550		

apparent steepness of the endotheliochorial allometry may result from phylogenetic nonindependence in our data set. Under analysis of independent contrasts, exclusion of contrasts deriving from primates had no effect on the results of our comparative tests. Haemochorial species continued to exhibit a significantly steeper allometry than endotheliochorial or epitheliochorial species ($\beta = 0.662$ vs. 0.586, SE = 0.043, $P = 0.039$; and 0.662 vs. 0.593, SE = 0.039, $P = 0.038$ respectively). Again, the two groups with less invasive forms of placentation did not differ significantly ($P = 0.425$).

These results confirm that qualitative differences in brain–body allometry between species with haemochorial and nonhaemochorial forms of placentation are not driven by patterns of brain size evolution unique to primates. However, not surprisingly, removal of primates renders these differences slightly less pronounced, as seen by comparing the slopes presented above to those shown in Table 1.

Divergence in adult brain–body allometry between mammalian sister clades

Comparison of brain–body allometry between sister clades which vary in placental morphology is perhaps the most conservative way of testing the hypothesis that species with highly invasive forms of placentation exhibit steeper allometric slopes than species with less invasive forms of placentation. Such tests restrict analysis to a small number of relatively closely related taxa of similar size (thereby reducing the range of body size in which a body size by placental type interaction can make itself apparent). Furthermore, as sister clades are by definition at the same level of 'taxonomic resolution' such tests exclude the potentially confounding effect of taxon-level variation in brain–body allometry (i.e. the fact that brain–body allometry measured at high levels of taxonomic resolution tend to be shallower than when measured at low levels of taxonomic resolution; Pagel & Harvey, 1988a,b). We identified four groups of mammals at or above the ordinal level (Primates, Rodentia, Chiroptera and Lipotyphla) containing species that exhibit more than one form of placentation. Within these groups we identified the most narrowly defined pair of placentally divergent sister clades (no group contained more than one pair) and repeated the analyses using a data set restricted to these taxa. The main numerical results of these tests are provided in Table 2 and illustrated in Fig. 2.

The order Primates is divided into two suborders, Strepsirrhini and Haplorrhini, which exhibit epitheliochorial and haemochorial placentation respectively. Hence, the primates provide a natural sister-taxon comparison for our hypothesis. In our classical analysis of allometry the brain–body allometry of haplorhines is significantly steeper than that of the strepsirhines. This result was confirmed by analysis of independent contrasts. Interestingly, the difference in brain–body allometry in these taxa has previously been identified as a grade shift rather than as a difference in slope (i.e. Kappeler & Pereira, 2003); we attribute this to the fact that previous studies have often concerned themselves with species mean body mass rather than *female* body mass. We suspect that previous reports of a grade shift in the Primates may result from the existence of sexual size dimorphism in many haplorhine primates but its absence in strepsirhine primates (Kappeler, 1996), a tendency that will reduce the inferred allometric slope of the former group relative to the latter group, and cause differences in intercept to play a more significant role in linear regression models.

The taxonomic grouping Eulipotyphla ('Insectivores') consists of solenodons, hedgehogs, shrews and moles. It

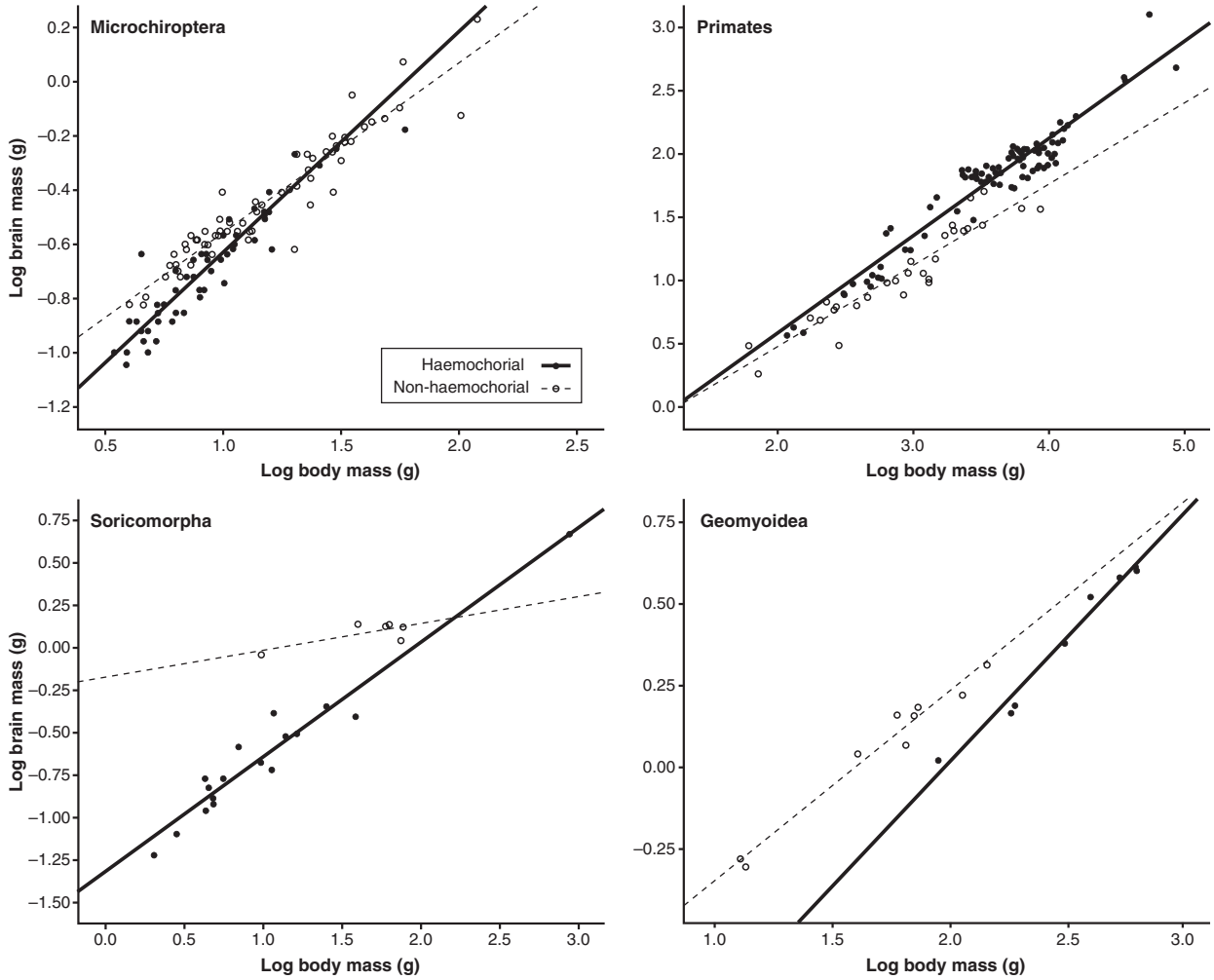

Fig. 2 Adult brain–body allometry in placentally divergent sister clades of mammals. More invasive forms of placentation are associated with steeper allometric scaling relationships (solid lines) than less invasive forms of plantation (dashed lines).

is primarily haemochorial, with less invasive forms of placentation found only among moles and desmans. These taxa are endotheliochorial with the exception of a single species (*Scalopus*) which is epitheliochorial. Within the clade Eulipotyphla, the order Soricomorpha (haemochorial Soricidae + nonhaemochorial Talpidae) forms a phylogenetically robust pair of sister clades for our analysis (Wilson & Reeder, 2005). As the sample size of nonhaemochorial species is low we have grouped the single epitheliochorial species with the endotheliochorial species to form a 'nonhaemochorial' category for this comparison. It was found, however, that inclusion or exclusion of *Scalopus* does not affect the outcome of our tests: haemochorial species consistently exhibit a significantly steeper slope than the nonhaemochorial species.

The bats (Chiroptera) are predominantly haemochorial, but within the non-Pteropods (i.e. 'Microchiroptera') are found species with diverse forms of placentation, further complicated by the fact that placentation in many species is primarily endotheliochorial but involves the development of an accessory haemochorial component towards the end of pregnancy (Rasweiler, 1993). Classification of species whose definitive placenta is wholly haemochorial (i.e. Vespertilionidae) or wholly endotheliochorial (i.e. Rhinolophidae) is trivial. We have classified species whose placenta is primarily endotheliochorial but involves a late accessory haemochorial component (i.e. Hipposideridae) as endotheliochorial. It was found, however, that their exclusion from our tests does not qualitatively affect the statistical results. Chiroptera does not contain any natural placentally divergent sister clades, as nonhaemochorial placentation is scattered throughout the phylogeny. For this reason we analysed Microchiroptera as a whole, then repeated pairwise analyses between the three large families comprising the bulk of our

Chiropteran data set (Table 2). In our tests, species with haemochorial placentation exhibited steeper allometric slopes than species with less invasive forms of placentation, though in two-tailed comparative tests this difference was marginally nonsignificant in one of the three tests (Vespertilionidae vs. Rhinolophidae, $P = 0.098$).

Heteromyidae (kangaroo rats and kangaroo mice) are the only rodent family to exhibit a form of placentation (endotheliochorial) other than haemochorial. Our data set contains insufficient data on brain mass in Heteromyidae ($n = 3$) to conduct a statistical analysis. Instead we have relied upon measurements of the cranial capacity in these species and their relatives, recorded by Hafner & Hafner (1984). The monophyly of Heteromyidae has been considered somewhat uncertain (Alexander & Riddle, 2005). We have therefore restricted our attention to a monophyletic assemblage (*Dipodomys* + *Microdipodops*) whose placentation has been well characterized, and we compared the brain–body allometry of these genera with that of their closest haemochorial relatives, species from the family Geomyidae (pocket gophers). Classical regression analysis indicates that the brain–body allometry of haemochorial species is significantly steeper than that of endotheliochorial species. However, these results are not supported by analysis of independent contrasts (Table 2).

Although the rodent results presented above – which are based on a small sample of cranial capacities rather than brain masses – yield conflicting results, our analyses of brain mass and body mass in primates, bats and insectivores support the hypothesis that the brain–body allometry of mammals is significantly steeper in species with haemochorial placentation than in species with less invasive forms of placentation. These patterns are generally consistent across diverse eutherian taxa, and are robust with respect to variation in brain size and allometry between large-scale and fine-scale taxonomic groupings.

Brain–body allometry in newborn mammals

Relationships between the allometric slopes of newborn mammals with differing forms of placentation were qualitatively identical to those reported for adult mammals, but the differences were more pronounced (Fig. 3). For all placental types, brain–body allometry in newborn mammals was steeper than in adult mammals (Table 1). Interestingly, brain mass attained an isometric relationship with body mass in species with the most invasive (haemochorial) form of placentation, but was negatively allometric in other groups. These differences were also supported by analysis of independent contrasts (Table 1). Data were insufficient to further divide between taxonomic groups within each placental category.

We also analysed the allometric relationship between maternal body mass and the total brain mass of litters

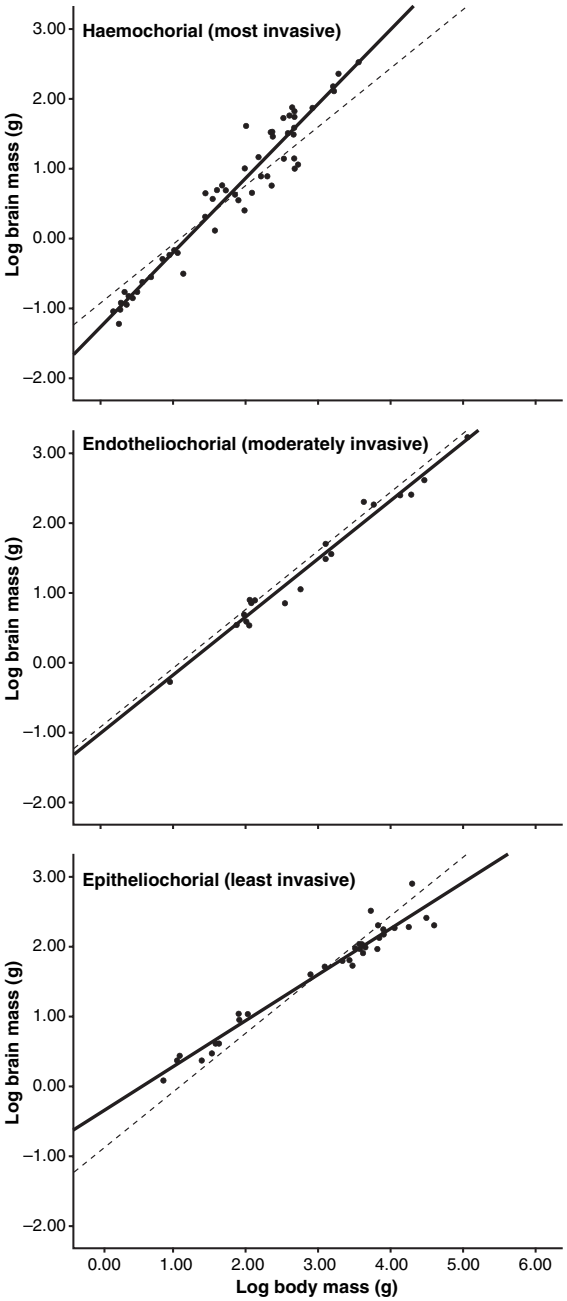

Fig. 3 Brain–body allometry in newborn eutherian mammals split by placental invasiveness. More invasive forms of placentation are associated with steeper allometric scaling relationships (solid lines). The allometry of newborn eutherian mammals as a whole, irrespective of placental type, is provided as a basis for comparison between groups (dashed line). The body and brain mass axes of each graph have the same scale.

(Table 1). Again, the slope of the haemochorial allometry is significantly steeper than that of the endotheliochorial allometry or the epitheliochorial allometry, although the

latter two groups with less invasive placentation did not differ significantly in slope. Differences in slope between the three placental groups were also tested by the analysis of independent contrasts (Table 1), which supports the view that haemochorial species exhibit a significantly steeper slope than epitheliochorial species, but finds that species with endotheliochorial placentation exhibit an intermediate slope that cannot be statistically distinguished from either of the other two groups.

These results indicate that divergence in allometry between haemochorial and nonhaemochorial groups appears to be more pronounced in newborn mammals, consistent with prenatal effects of placentation on growth.

Prenatal growth rates in mammalian litters

As the placenta is involved in mediating the transfer of resources from mother to fetus during prenatal growth, we also examined the relationship between maternal body weight and prenatal growth rates of the brain and body (exclusive of the brain) in eutherian litters. Litter growth rates exhibit an allometric relationship with maternal body mass (Fig. 4). Differences between placental categories in these allometric relationships can most easily be appreciated by contrasting patterns in the most invasive category (haemochorial) with the least invasive category (epitheliochorial), although we also include the results for comparisons involving endotheliochorial species.

The allometric intercepts are significantly higher in haemochorial species than in epitheliochorial species (brain: −2.330 vs. −2.921, SE = 0.061, $F_{1,68} = 633.340$, $P < 0.001$; body: −1.094 vs. −3.018, SE = 0.269, $F_{1,67} = 38.148$, $P < 0.001$). As the slope of the prenatal brain growth rate allometry does not differ between haemochorial and epitheliochorial species ($\beta = 0.445$ vs. 0.491, SE = 0.039, $F_{1,68} = 0.758$, $P = 0.387$), these results demonstrate that haemochorial species exhibit higher prenatal brain growth rates than epitheliochorial species across the entire range of eutherian body weights. However, as the slope of the prenatal body growth rate allometry is significantly lower in haemochorial than in epitheliochorial species (0.415 vs. 0.840, SE = 0.053, $F_{1,67} = 34.257$, $P < 0.001$), haemochorial species exhibit lower prenatal body growth rates than epitheliochorial species in all but the smallest of taxa (Fig. 4). As might be expected, species with moderately invasive (endotheliochorial) placentation exhibit intermediate scaling relationships that are statistically indistinguishable from either of the extremes (intercept: haemochorial vs. endotheliochorial, $F_{1,56} = 0.530$, $P = 0.470$; endotheliochorial vs. epitheliochorial: $F_{1,41} = 1.966$, $P = 0.169$; slope: haemochorial vs. endotheliochorial, $F_{1,56} = 1.591$, $P = 0.213$; endotheliochorial vs. epitheliochorial, $F_{1,41} = 2.257$, $P = 0.141$).

We further compared the slopes of these allometries based on independent contrasts. Species with haemochorial placentation were found to exhibit a significantly higher brain growth rate allometry and a significantly lower body growth rate allometry than species with epitheliochorial placentation (brain: $\beta = 0.517$ vs. 0.324; SE = 0.056, $P = 0.001$; body: $\beta = 0.583$ vs. 0.8, SE = 0.101, $P = 0.036$; $n = 34$ haemochorial and 20 epitheliochorial species). Again, endotheliochorial species ($n = 10$) exhibited intermediate slopes (brain: $\beta = 0.506$; body: $\beta = 0.652$) that were statistically indistinguishable from either of the other groups.

The relationship between prenatal brain and body growth rates within placental categories is also of interest (Fig. 4). In epitheliochorial species the slope of the prenatal brain growth rate allometry is significantly shallower than the slope of the prenatal body growth rate allometry ($F_{1,53} = 43.824$, $P < 0.001$). Hence in species with the least invasive form of placentation, prenatal body growth rate increases more rapidly than prenatal brain growth rate, as a function of maternal body mass. In species with haemochorial placentation, in contrast, the slope of the prenatal brain growth rate allometry does not differ significantly from that of the prenatal body growth rate ($F_{1,83} = 1.886$, $P = 0.173$). Thus in species with the most invasive form of placentation, prenatal brain and body growth rates increase at the same speed, as a function of maternal body mass. Again, species with moderately invasive (endotheliochorial) placentation exhibit an intermediate state, with the prenatal body growth rate allometry steeper than the prenatal brain growth rate allometry but not significantly so ($F_{1,29} = 1.408$, $P = 0.246$). We also tested for the robustness of this pattern by analysing independent contrasts. In haemochorial species the slopes of brain and body growth rate allometries, provided in the previous paragraph, were not found to differ significantly (SE = 0.046, $P = 0.156$), whereas in epitheliochorial species the body growth rate allometry was significantly steeper than the brain growth rate allometry (SE = 0.088, $P < 0.001$). Again, endotheliochorial species exhibited an apparent intermediate condition, the difference between brain and body growth rate allometries apparently being smaller than that found in epitheliochorial species and larger than that found in haemochorial species, but not differing significantly (SE = 0.144, $P = 0.323$).

Are the effects of placentation on allometry specific to the brain?

The results presented above suggest that differences in placental type may underlie differences in mammalian brain–body allometry and patterns of prenatal brain growth. Here we consider the alternative hypothesis that the effects exerted by placentation on allometry are not exclusive to the brain but also influence the development

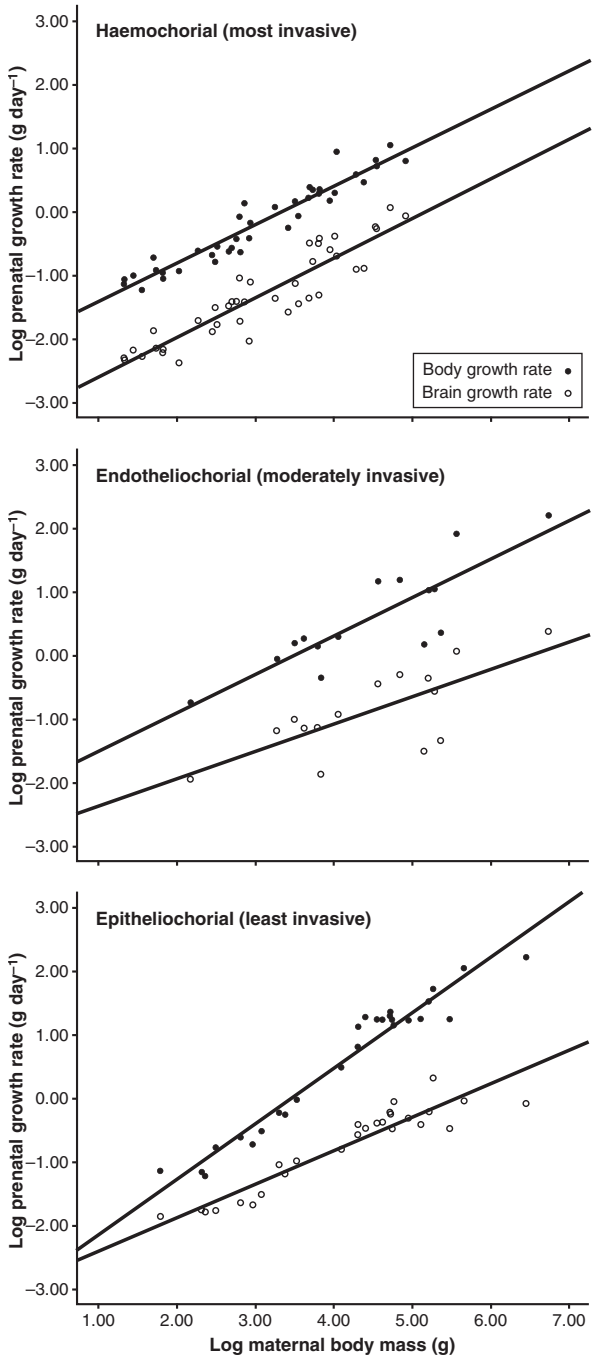

Fig. 4 Litter growth rates in mammalian species with differing forms of placentation. Each chart indicates prenatal brain growth rates (filled circles) and body growth rates exclusive of the brain (open circles). The axes of each graph have the same scale. On average, species with the least invasive (epitheliochorial) form of placentation exhibit significantly lower brain growth rates, at all body sizes, than species with the most invasive (haemochorial) form of placentation. In the former group, maternal resources made available by increases in maternal body mass are allocated disproportionately to body growth (hence the body growth rate correlation is steeper than the brain growth rate correlation) whereas in the latter group, such resources are distributed proportionately to both brain and body (hence the body size/growth rate correlations are parallel). Species with moderately invasive (endotheliochorial) placentation appear to exhibit an intermediate relationship between maternal body mass and litter growth rate.

of other bodily structures. In this case it would be incorrect to propose any special relationship between brain growth and placentation. The results presented in the previous section are not consistent with this alternative view, as haemochorial placentation was found to be associated with relatively high prenatal rates of brain growth but not body growth; however, a pattern might still be found for specific organs other than the brain. In order to test this alternative hypothesis we attempted to identify a placental effect on the allometry of organs and glands other than the brain, using data from a compendium of autopsies on diverse eutherians (Crile and Quiring 1940). We first removed sickly and juvenile individuals and then validated this data set with respect to our initial hypothesis by testing for a placental effect on the brain–body allometry; we found the same pattern described above (haemochorial $\beta = 0.780$, endotheliochorial $\beta = 0.650$, epitheliochorial $\beta = 0.617$, $F_{2,105} = 3.381$, $P = 0.038$). For eight of the remaining nine organs and glands measured in adult animals, placentation was found to play no significant role in determining allometric slopes (thyroid: $F_{2,101} = 0.735$, $P = 0.482$; adrenal gland: $F_{2,108} = 2.683$, $P = 0.073$; heart: $F_{2,99} = 0.418$, $P = 0.660$; liver: $F_{2,95} = 0.732$, $P = 0.484$; kidney: $F_{2,93} = 1.442$, $P = 0.242$; lung: $F_{2,96} = 1.254$, $P = 0.290$; spleen: $F_{2,53} = 0.311$, $P = 0.734$; stomach and intestine: $F_{2,41} = 0.470$, $P = 0.628$). Only in the eyes did we identify a pattern similar to that described for the brain (haemochorial $\beta = 0.970$, endotheliochorial $\beta = 0.537$, epitheliochorial $\beta = 0.330$, $F_{2,74} = 14.959$, $P < 0.001$). Hence, of the 10 organs and glands we examined, the only organ other than the brain to exhibit a placental effect is itself an outgrowth of the brain. Furthermore, the mass of eyes is known to be more tightly correlated with brain mass than with body mass (Burton, 2006), suggesting that variation in eye weight may merely be a result of the brain–eye allometry rather than the result of placental effects on the body–eye allometry.

Discussion

Our analyses indicate that placental invasiveness exerts a pronounced effect on brain–body allometry in eutherian mammals, such that taxa with more invasive forms of placentation exhibit significantly steeper brain–body allometries than taxa with less invasive forms of placentation. Under independent contrasts, species appear to

fall into two groups: species with haemochorial placentation, in which placental tissues are bathed directly in maternal blood, exhibit a significantly steeper brain–body allometry than species with endotheliochorial or epitheliochorial placentation, in which maternal blood is separated from placental tissues by a cellular barrier of maternal origin. These patterns are broadly consistent across both neonate and adult data, across mammals as a whole and between selected sister clades; they are also robust with respect to variation in body mass and phylogenetic structure and the patterns are not found in organs other than the brain and its apparent accessory organ, the eye (Figs 1–3; Tables 1 and 2). These findings indicate that eutherian mammals are structured into two notably different groups with regard to the prenatal underpinnings of brain–body allometry. To the extent that studies of mammalian brain–body allometry, encephalization, and associated life-history traits include sets of taxa that exhibit variation in placental invasiveness, such studies may usefully account for this variation in their design and execution.

We also found that taxa with the most invasive (haemochorial) form of placentation exhibit higher average prenatal brain growth rates, and lower average prenatal body growth rates, than taxa with the least invasive (epitheliochorial) form of placentation. Mathematical models of allometry as a time-independent representation of two growth curves (i.e. that of the brain and that of the body) predict that retardation in the growth of an organ or structure should result in a reduction in the allometric exponent (Vincinius & Mirazon Lahr, 2003). Hence, differences in the slope of the brain–body allometry between placental categories may result in part from different patterns of prenatal brain and body growth. A central pattern identified by our analyses is that prenatal brain growth rates increase more rapidly as a function of maternal body mass in species with highly invasive haemochorial placentation than in species with less invasive placentation. Conversely, prenatal body growth rates (exclusive of the brain) increase more slowly in the former group (Fig. 4). Relatively large reductions in prenatal body growth rate are therefore associated with relatively small increases in prenatal brain growth rate, consistent with the hypothesis that brain tissue is unusually expensive and its growth is traded off against the growth of other bodily structures (Aiello & Wheeler, 1995). However, these findings are not consistent with the hypothesis that mammalian brain growth acts as a pacemaker for bodily growth in general (Sacher & Staffeldt, 1974), as, when grouped by placental type, species with relatively high prenatal brain growth rates tend to exhibit relatively low prenatal body growth rates and vice versa.

Differences in patterns of allometric slope and growth rate between the most invasive and the least invasive placental categories are pronounced and consistent across our various statistical tests. However, results for species with placentation of intermediate endotheliochorial invasiveness are less clear-cut. On the whole, species with endotheliochorial placentation exhibit apparent patterns intermediate between the other two groups, but cannot be distinguished statistically from one or either of them. This lack of statistical difference is especially pronounced in our analysis of growth rate. Apart from the fact that these species constitute the smallest category in our data set, it is also of note that many of the endotheliochorial species in our data set happen to exhibit embryonic diapause (Renfree & Shaw, 2000). This phenomenon may render estimates of gestation length, and hence prenatal growth rates, unreliable. Hence, species with endotheliochorial placentation appear to exhibit much more variable prenatal growth rates than other species (Fig. 4 and Results). These limitations could be alleviated in future work via collection of data from more endotheliochorial species, and by directly assessing the effects of embryonic diapause on prenatal growth trajectories.

One consequence of variation in allometry between placental categories is that estimates of relative brain size relying upon measurement of the departure of species from the global eutherian allometric scaling relationship are likely to be biased when they do not take into account the placental effect. Inspection of Fig. 1 indicates that small haemochorial species will tend to have low encephalization quotients, whereas large haemochorial species will tend to have high encephalization quotients. This pattern is reversed for species with epitheliochorial placentation. The existence of such variation further cautions against the use of encephalization quotients and related measures in studies of mammalian brain size evolution, even within taxonomic groups such as Primates. These considerations also suggest that differences in prenatal brain and body growth between taxa with more invasive vs. less invasive placentation do not mediate any general advantage of invasive placentation with regard to relatively large brain sizes in individuals. Instead, such growth patterns appear to represent one manifestation of differences in the architecture of life-history trade-offs between these two groups, driven in part by differences in the physiological mechanisms of resource transfer from mothers to offspring during prenatal development. Our results also support a more general view that evolutionary transitions in placental structure may be one of the mechanisms by which modifications to the timing and rate of eutherian brain and body growth evolve.

What placental physiological mechanism might be responsible for divergence in brain–body allometry and associated traits between species with more invasive vs. less invasive placentation? One possible explanation is that the more invasive placenta, especially the haemochorial form, is more permeable to energetic or nutritional resources, such as proteins, carbohydrates or fatty acids. Given some increase in maternal body mass

(resulting in an increase in the quantity of circulatory maternal resources), a fetus with an invasive placenta may thus be able to increase placental uptake to a greater extent than a fetus with a noninvasive placenta. Such physiological differences, if they exist, might explain the relatively steep allometric slope found in species with more invasive placentation.

Comparative studies of prenatal nutrition do not indicate any systematic differences in the fetal intake of protein between species with invasive placentation vs. noninvasive placentation. In all mammals studied, the protein composition of fetal carcasses does not differ significantly from that of adults, indicating that fetal protein requirements are not unusually high during growth *in utero* (Young & Hill, 1973). Variation in the rate of protein uptake by fetuses of different species also does not appear to correlate with placental type; both epitheliochorial ruminants and haemochorial primates show similar patterns of protein uptake, in which the transport of acidic amino acids occurs at a low rate (Dierks-Ventling *et al.*, 1971; Steginк *et al.*, 1975; Duée *et al.*, 1987), although the transport of neutral or basic amino acids occurs at a rapid rate but with considerable variation across species within placental types (Lemons *et al.*, 1976; Holzman *et al.*, 1979; Duée *et al.*, 1987). Analysis of fetal proteases further suggests that the chorioallantoic placenta plays a relatively unimportant role in placental transport in comparison with secondary structures such as the yolk sac (Graf & Gossrau, 1985).

In all mammals, maternally derived carbohydrates form the main energy supply for the developing fetus (Père, 2003), and studies of rodents (haemochorial), haplorhines (haemochorial) and artiodactyls (epitheliochorial) suggest that their transfer rates relative to the maternal availability of carbohydrate do not differ systematically between species of different placental type (Leturque *et al.*, 1987). As a result, it appears that absolute levels of energy available to the fetus during gestation – which depend largely upon carbohydrate transfer from mother to fetus – may not be a major constraint on brain growth rate and may not be involved in generating the observed allometric patterns described above. Such a view is consistent with the observation that brain development is relatively spared from the negative consequences of low-energy conditions during gestation (Barbiro-Michaely *et al.*, 2007).

In contrast to studies of fetal protein and carbohydrate nutrition during pregnancy, studies of fatty acids demonstrate a pronounced distinction between species with highly invasive haemochorial vs. less invasive placentation. In studies of pregnancy in species with highly invasive (haemochorial) placentation – including some primates (Portman *et al.*, 1969; Hull & Elphick, 1978; Hendrickse *et al.*, 1985; Haggarty *et al.*, 1997), rodents (Koren & Shafrir, 1964; Hershfield & Nemeth, 1968; Hummel *et al.*, 1975; Thomas & Lowy, 1982, 1983, 1984; Honda *et al.*, 1990) and lagomorphs (Edson *et al.*, 1975; Elphick *et al.*, 1975; Elphick & Hull, 1977a,b; Gilbert *et al.*, 1984; Stephenson *et al.*, 1990) – maternal fatty acids are found to be readily and rapidly transferred to the fetus. Under normal nutritional conditions, the rate of placental transport is responsive to changes in maternal serum lipid concentration, such that fetal fatty acid uptake rate is correlated with maternal serum fatty acid availability (Edson *et al.*, 1975; Elphick & Hull, 1977b; Thomas & Lowy, 1983; Stephenson *et al.*, 1990). Under fasting conditions, the rate of placental transport may increase, and the transfers show signs of selectivity for essential and long-chain fatty acids over nonessential fatty acids. In all cases, fetal levels of serum fatty acid are considerably higher than maternal levels, and in those species whose neonatal body composition has been studied, lipids derived directly from the mother (as opposed to being synthesized by the fetus) constitute a majority of the total lipid content of the carcass (Thomas & Lowy, 1984; Père, 2003).

Nutritional analyses of pregnancy in species with less invasive (epitheliochorial or endotheliochorial) placentation – including bovids (Elphick *et al.*, 1979; Shand & Noble, 1979; Leat & Harrison, 1980), swine (Elphick *et al.*, 1980; Thulin *et al.*, 1989; Père, 2001) – or felines (Elphick & Hull, 1984) – find, in contrast to studies of haemochorial placentation, that the transfer of fatty acids from mother to fetus is minimal or nonexistent. Placental uptake rate is not correlated with maternal serum fatty acid concentration, and there is no evidence of placental selectivity for essential or long-chain fatty acids (Père, 2001, 2003). Fetal serum fatty acid level is as low as 1% of that of the mother, and it appears that only trace amounts of lipid derived directly from the mother (as opposed to being synthesized by the fetus) are present in the neonatal body (Van Duyne *et al.*, 1960; Elphick *et al.*, 1980; Leat & Harrison, 1980; Martin & Hausman, 1981; Thulin *et al.*, 1989).

As noted above, carbohydrate forms the primary energy supply for developing fetuses, with lipid as a secondary source. Lipids are of particular importance to the brain not because of their energetic content but because they perform important structural roles. Lipids constitute around one-half of the dry matter of the mammalian brain, the most structurally and metabolically important being long-chain polyunsaturated derivatives of essential fatty acids, such as docosahexaenoic acid and arachidonic acid (Crawford *et al.*, 1976). Fatty acids required for brain development may be synthesized by the fetal liver or extracted from the mother via the fetally derived placenta. However, the essential fatty acids, being of dietary origin, must follow the latter route (Père, 2003). Research into the transport mechanisms of fatty acids from mother to fetus has been restricted to species with haemochorial placentation, especially primates and rodents. Nevertheless, all the elucidated physiological mechanisms crucially depend upon direct contact between fetal tissues and maternal blood, with mechanisms including diffusion driven by a

concentration gradient in unbound albumin (Stephenson *et al.*, 1993; Hoving *et al.*, 1994; Otto *et al.*, 1997; Patel *et al.*, 1997; Benassayag *et al.*, 1999; Berghaus *et al.*, 2000; Haggarty, 2004), the presence of fetal fatty acid binding/transport proteins, specialized for the transfer of essential fatty acids and their long-chain polyunsaturated derivatives, on the maternal-facing membranes of the placenta (Campbell & Dutta-Roy, 1995; Campbell *et al.*, 1996, 1998; Haggarty *et al.*, 1997; Dutta-Roy, 2000), and secretion of leptin by the placenta into the maternal bloodstream (Hoggard *et al.*, 2001; White *et al.*, 2006). Together, these mechanisms drive selective availability and enrichment of long-chain polyunsaturated fatty acids known to play a central role in brain development, and protect the supply of polyunsaturated fatty acids to the fetal brain during critical periods of growth. The absence of direct contact between maternal blood and fetal tissues in species with epitheliochorial and endotheliochorial placentation thus potentially underlies variation between the two groups in the results of placental perfusion experiments summarized above. As discussed above, physiological differences in the ability of species with different placental types to effect prenatal fatty acid transport from maternal blood to developing fetal brain may underlie variation in the allometric exponent, as fetuses possessing invasive forms of placentation may be better able to mobilize the increased quantity of maternal resources made available by evolutionary increases in maternal body mass. However, our understanding of differences in encephalization between placental categories, evident for example in Fig. 1, is less clear. Among the smallest species with invasive placentation brain size is relatively small. It is of interest that small mammals tend to exhibit a higher degree of long-chain polyunsaturation of cell membrane fats than large mammals, not only in cells of the brain but also in cells from other tissues of the body (Hulbert & Else, 2005). The benefits of invasive placentation might thus be subject to a size-dependent effect. In the smallest species these benefits may not be limited to brain growth, as long-chain polyunsaturated fats become structurally important to tissues other than the brain. Such 'global' benefits of invasive placentation in small mammals may result in an attenuation of the effect of invasive placentation on brain size in smaller species. Differences in encephalization with body size may additionally reflect trade-offs over the allocation of resources to brain growth vs. other life-history traits such as litter size or the overall energetic cost of litter production; of species with body mass less than 1 kg, litters of species with epitheliochorial placentation averaged 1.50 young whereas litters in species with endotheliochorial placentation averaged 2.44 young and litters of species with haemochorial placentation averaged 3.72 young ($F_{2,32} = 4.566$, $P = 0.019$), suggesting the existence of a size-dependent trade-off between productivity and brain mass. Such questions await further examination of a broader set of data on life history and placentation.

Based on the results of the physiological studies described above, we hypothesize that divergence in mammalian brain–body allometry between taxa with highly invasive vs. less invasive placentation may primarily be the result of differences in the ability of species of different placental type to effect prenatal fatty acid transport from maternal blood to developing fetal brain. To the extent that maternal–fetal conflict in this context (Haig, 1993) was involved in the evolution of physiological mechanisms underlying fetal access to maternal fatty acids, and more generally in the evolution of placental form and function (Haig, 1993; Crespi & Semeniuk, 2004), it may also have played a key role in the macroevolution of mammalian brain–body allometry and life history.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Literature sources.

Appendix S2 Eutherian placentation overview.

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