Placentation and Maternal Investment in Mammals

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ABSTRACT: The mammalian placenta exhibits striking interspecific morphological variation, yet the implications of such diversity for reproductive strategies and fetal development remain obscure. More invasive hemochorial placentas, in which fetal tissues directly contact the maternal blood supply, are believed to facilitate nutrient transfer, resulting in higher fetal growth rates, and to be a state of relative fetal advantage in the evolution of maternal-offspring conflict. The extent of interdigitation between maternal and fetal tissues has received less attention than invasiveness but is also potentially important because it influences the surface area for exchange. We show that although increased placental invasiveness and interdigitation are both associated with shorter gestations, interdigitation is the key variable. Gestation times associated with highly interdigitated labyrinthine placentas are 44% of those associated with less interdigitated villous and trabecular placentas. There is, however, no relationship between placental traits and neonatal body and brain size. Hence, species with more interdigitated placentas produce neonates of similar body and brain size but in less than half the time. We suggest that the effects of placental interdigitation on growth rates and the way that these are traded off against gestation length may be promising avenues for understanding the evolutionary dynamics of parent-offspring conflict.

Keywords: placenta, parent-offspring conflict, life history, brain evolution, reproductive strategies, gestation.

Introduction

The placenta plays a key role in mammalian reproduction because it regulates the transfer of nutrients and oxygen from mother to offspring and waste products in the opposite direction (Mossman 1987). Despite having this critical and fundamentally similar function in all mammals, the placenta exhibits striking morphological variation (Mossman 1987; Leiser and Kaufmann 1994). The implications of this variation for prenatal maternal investment, in terms of fetal growth rates, offspring size, and gestation length, however, are still mysterious. Commenting on the lack of any obvious pattern in the phylogenetic distribution of placental types, Benirschke and Kauffman (2006, p. 39) remark that this "may even give us the impression that several animals have acquired their respective placental types by chance." Natural selection is unlikely to have been so permissive, however. Here we test hypotheses about the correlated evolution of placental traits, maternal investment, and offspring development using phylogenetic comparative methods.

The chorioallantoic placenta of eutherian mammals develops through the interaction of the chorion, vascularized by the allantoic sac, with maternal uterine tissues during implantation of the conceptus (Mossman 1987; Wooding and Burton 2008). Placental gross morphology varies in the number and position of the exchange areas over the placental surface (shape), in how maternal and fetal tissues are spatially arranged with one another (interdigitation), and in the number of maternal tissue layers separating maternal blood from fetal tissues (invasiveness; Mossman 1987; Leiser and Kaufmann 1994; Wooding and Burton 2008). Placental invasiveness is the trait that has received the most attention regarding a possible impact of placental morphology on offspring prenatal development and maternal investment, particularly in relation to brain growth (Kihlström 1972; Sacher and Staffeldt 1974; Leutenegger 1979; Haig 1993; Crespi and Semeniuk 2004; Elliot and Crespi 2008; Martin 2008). In noninvasive epitheliochorial placentation, three maternal tissue layers (uterine epithelium, connective tissues, and endothelium) constitute a barrier between fetal tissues and maternal blood (Mossman 1987; Leiser and Kaufmann 1994; Wooding and Burton 2008). In more invasive placental types, however, the fetal tissues erode the maternal tissues and gain a more direct access to the maternal bloodstream. In the intermediately invasive endotheliochorial placentation, only the endothelial wall of maternal blood vessels separates fetal tissues and maternal blood, and in the highly invasive hemochorial placentation fetal tissues are bathed in ma-

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ternal blood (Mossman 1987; Leiser and Kaufmann 1994; Wooding and Burton 2008). Haig (1993, p. 501) related placental invasiveness to maternal-fetal conflict, arguing that hemochorial placentation "evolved more than once as a means by which the fetus gained greater access to maternal nutrients." However, recent phylogenetic studies suggest that more invasive placentas (either hemochorial or endotheliochorial) are likely to be the ancestral condition for mammals, with the least invasive epitheliochorial placentation being an evolutionarily derived trait that emerged independently in several lineages (Vogel 2005; Mess and Carter 2006; Wildman et al. 2006; Carter and Mess 2007; Martin 2008; Elliot and Crespi 2009). In a sense, therefore, it is the repeated evolution of less invasive placentas that is demanding of an explanation. Although suggestions have been made about possible correlates of evolutionary changes in placentation (reviewed in Martin 2008), such associations have not been systematically investigated, and as a result the functional consequences of placental variation remain obscure.

Because the more direct contact with maternal blood in more invasive placentas implies easier fetal access to maternal resources, greater invasiveness could potentially lead to a higher rate of transplacental nutrient transfer, which in turn might enhance fetal growth rates (Haeckel 1903; Crespi and Semeniuk 2004; Elliot and Crespi 2008). This might be particularly important for fetal brain growth (e.g., Haig 1993; Crespi and Semeniuk 2004; Elliot and Crespi 2008) because the brain is an expensive organ to grow and maintain (Aiello and Wheeler 1995; Martin 1996; Isler and van Schaik 2006, 2009). This hypothesis predicts that greater invasiveness is associated with increased neonatal brain and/or body size or shorter gestation. Vogel (2005), however, noted that noninvasive epitheliochorial placentas exhibit substantial development of alternative mechanisms of nutrient transfer, such as uterine glands, raising the possibility that invasiveness has little or no impact on nutrient transfer or growth rates.

Two recent studies reevaluated whether and how placental invasiveness plays a role in maternal investment and prenatal development. The hypothesis that relative growth rates are influenced by placental invasiveness predicts a difference in the intercepts (but not the slopes) of fetal growth rates regressed on maternal size by placental type, with increasing invasiveness (epitheliochorial to endotheliochorial to hemochorial) being accompanied by progressively higher intercepts. On the basis of visual inspection of nonphylogenetically controlled plots of relative neonate size in relation to gestation length, Martin (2008) concluded that there is no obvious difference in growth rates between placentation types. Using phylogenetically independent contrasts, Elliot and Crespi (2008) found different slopes for the scaling of brain size and growth rate among different placental types: brain size and growth rates increased more rapidly with maternal size when placentation was highly invasive (hemochorial) than when it was less invasive (eptheliochorial or endotheliochorial) and slopes crossed over at intermediate body sizes. The authors interpreted these findings as reflecting trade-offs between brain growth and litter size, given that small species with highly invasive hemochorial placentation generally produce large litters of less encephalized neonates when compared with larger species with less invasive placentation (Elliot and Crespi 2008). We argue, however, that these results do not provide direct evidence of such trade-offs. On the question of whether placentation influences fetal growth and neonate size rather than the scaling of these variables, Elliot and Crespi (2008) found that brain growth rates of the whole litter were significantly higher in species with hemochorial placentation than in those with epitheliochorial or endotheliochorial placentation. Because growth rates were calculated as ratios of litter body (or brain) mass to gestation length and because this analysis was based on species values (i.e., without controlling for phylogeny), it remains to be determined whether there are significant differences among placental types in neonate size, brain size, and/or gestation length once phylogeny has been taken into account.

An aspect of placental morphology that has been comparatively neglected in the study of placental diversity is the interdigitation of the exchange areas between mother and fetus. This could, in principle, affect nutrient transfer rates because a higher degree of interdigitation increases the surface area for exchange (Wooding and Burton 2008). There are up to five different forms of interdigitation (e.g., Leiser and Kaufmann 1994; Wildman et al. 2006), but most commonly three distinct types are recognized: villous, trabecular, and labyrinthine (Mossman 1987; Mess and Carter 2006). In the simpler villous interdigitation, the fetal tissues branch in villi and form a moplike structure, which is either covered by maternal epithelia in noninvasive epitheliochorial placentas or bathed in maternal blood in highly invasive hemochorial placentas (Mossman 1987; Mess and Carter 2006). In the most complex labyrinthine interdigitation, the villi are highly branched and fused in a weblike structure—the labyrinth—that is bathed in the maternal blood of hemochorial placentas or is in contact with the endothelial walls of maternal blood vessels in the intermediately invasive endotheliochorial placentas (Mossman 1987; Mess and Carter 2006). The trabecular interdigitation of some hemochorial placentas is intermediate between villous and labyrinthine, with the villi branching and fusing at an intermediate degree (Mossman 1987; Mess and Carter 2006). A labyrinthine interdigitation is thought to provide the greatest surface area for exchange and hence is predicted to be associated with greater nu-

trient transfer and fetal growth rates. Indeed, Wildman et al. (2006) argue that this form of interdigitation is metabolically the most expensive for the mother and that interdigitation could explain differences in gestation time among species with highly invasive hemochorial placentation, with labyrinthine placentas being associated with shorter gestations than villous placentas. If increased interdigitation does enhance nutrient transfer rates, it might also be associated with greater neonatal body mass and/or higher neonatal encephalization.

Here we test the hypothesis that placental gross morphology is associated with fetal body and brain growth rates. Specifically, we use phylogenetic generalized least squares (PGLS) models to examine associations between placental traits (invasiveness and interdigitation) and gestation length, between placental traits and neonatal body mass, and between placental traits and neonatal brain mass while controlling for allometric effects. Although fetal growth rates are sometimes calculated as ratios of neonatal brain or body mass on gestation length (e.g., Elliot and Crespi 2008; Martin 2008), ratios cannot reveal whether placentation affects the numerator or the denominator or whether one is traded off against the other, potentially obscuring meaningful patterns. Instead, we examine whether placental traits are associated with each variable separately, using a phylogenetically controlled ANCOVA. For the hypothesis that placental invasiveness favors fetal growth rates, we test predictions that with greater invasiveness (from epitheliochorial to endotheliochorial to hemochorial) (i) gestation length is shorter after controlling for allometry, (ii) neonatal body and/or brain mass is greater after controlling for allometry, and (iii) neonatal body and/or brain mass is greater after controlling for allometry and gestation length. This third model allows testing for differences in growth rates without using ratios. As a corollary, moderately invasive endotheliochorial placentas are predicted to be intermediate between highly invasive hemochorial and noninvasive epitheliochorial placentas in nutrient transfer rates and so in their possible impact on gestation length and neonatal traits. In relation to interdigitation, we test the prediction that after allometric effects are removed, increased interdigitation (villous to trabecular to labyrinthine) is associated with (i) shorter gestation length and/or (ii) larger neonatal brain and/or body mass and (iii) larger neonatal body and/or brain mass after controlling for gestation length. Because neonates vary at birth in their degree of developmental maturity, with altricial offspring being smaller and less encephalized at birth than precocial offspring (Pagel and Harvey 1988), we account for differences in developmental state in all the analyses. Finally, we test Elliot and Crespi's (2008) hypothesis that putative differences in the scaling of brain size with placental invasiveness are due to tradeoffs between offspring brain size and litter size, predicting negative associations between neonatal brain size and litter size, after accounting for allometry, gestation length, and placentation. Furthermore, if litter size explains possible differences in the allometric scaling of neonatal brain size, such differences should disappear once litter size is added to the model.

Methods

Data

We extracted data from the literature on neonatal brain mass (g), neonatal body mass (g), maternal body mass (g), and litter size. Unlike previous studies (e.g., Elliot and Crespi 2008), we excluded time in delayed implantation, as noted by Hayssen et al. (1993), from gestation length (days). Placental invasiveness of the full-term chorioallantoic placenta was classified as epitheliochorial, endotheliochorial, or hemochorial for all species, and, following previous authors (Mossman 1987; Mess and Carter 2006; Elliot and Crespi 2009), placental interdigitation was classified as villous, trabecular, or labyrinthine. Finally, species were considered altricial if neonates were born with the eyes closed and precocial if the eyes were open. Our data set included 109 placental mammals from all major mammalian orders, with three missing data for interdigitation, two for litter size, and one for developmental state. Additional detailed information on the data and the full list of sources are available in the appendix in the online edition of the *American Naturalist*; the data table is available as an Excel file. Continuous variables were $\log_{10}$ transformed to meet assumptions of normality.

Statistical Analysis

Tree topology and branch lengths for the subset of mammals in our data set were extracted from Bininda-Emonds et al.'s (2007) supertree of mammals with updated branch lengths (Bininda-Emonds et al. 2008), using BayesTraits (Pagel et al. 2004). In PGLS models, the phylogeny is converted into a variance-covariance matrix using tree topology and branch lengths (Pagel 1997, 1999; Freckleton et al. 2002; Garland et al. 2005; Lavin et al. 2008). The parameter λ quantifies the phylogenetic signal in the data (Blomberg and Garland 2002) and tests to what extent the phylogeny predicts variation in species trait values (Pagel 1997, 1999; Freckleton et al. 2002); λ potentially varies between 0 (no phylogenetic signal and thus the species can be treated as independent in statistical tests) and 1 (the similarity between species in trait values is proportional to the time of shared evolution; Pagel 1997, 1999; Freckleton et al. 2002). By incorporating λ into the model,

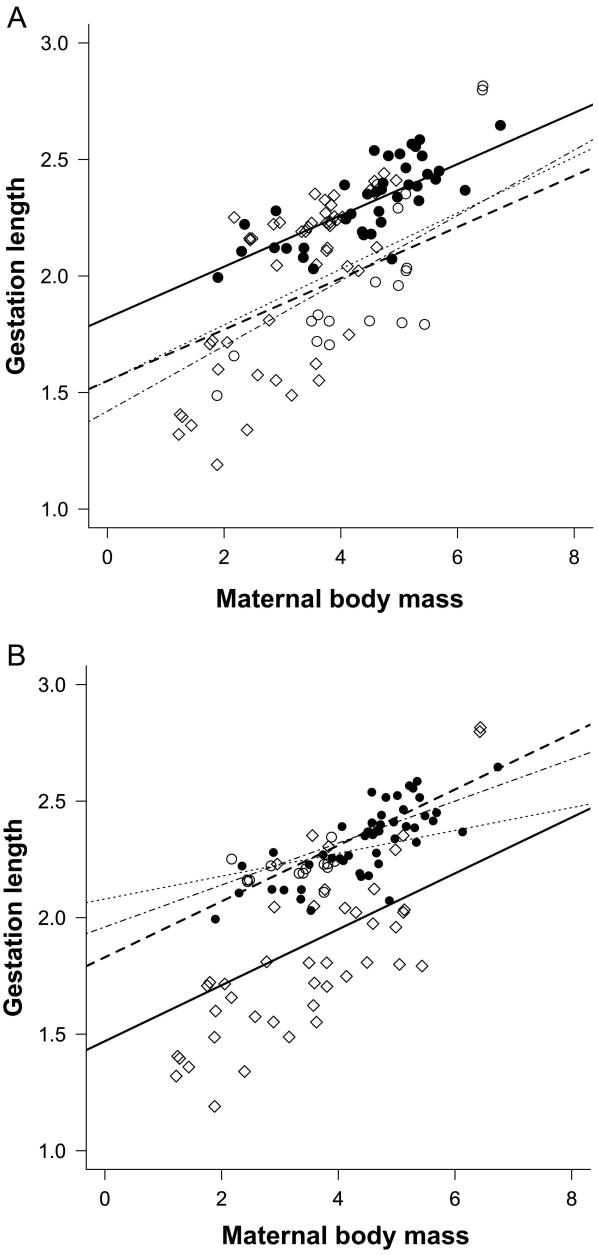

Figure 1: Gestation length on maternal body mass with fit lines by type of placenta. *A*, Fit lines did not differ between hemochorial (*dotted line*) and endotheliochorial (*dot-dashed line*) placentation, but both (*dashed line*) differed significantly from epitheliochorial placentation (*solid line*; see "Results"; table 1). *Filled circles* = noninvasive epitheliochorial placentation; *open circles* = intermediately invasive endotheliochorial placentation; *diamonds* = highly invasive hemochorial placentation. *B*, Fit lines did not differ between villous (*dotted line*) and trabecular (*dot-dashed line*) interdigitation, but both (*dashed line*) differed from labyrinthine interdigitation (*solid line*; see "Results"; table 2). *Filled circles* = villous interdigitation; *open circles* = trabecular interdigitation; *diamonds* = labyrinthine interdigitation.

PGLS offers a more flexible approach relative to other statistical methods, as it can quantify and account for the precise phylogenetic signal in the data rather than imposing an a priori value (e.g., λ is constrained to be equal to 1 in the method of phylogenetically independent contrasts). An additional advantage is that discrete and continuous traits can be studied simultaneously (Lavin et al. 2008). Thus, unlike authors using phylogenetically independent contrasts (e.g., Elliot and Crespi 2008), we could include continuous traits, placentation, and interaction terms in our models; test whether placentation had a significant effect on a given trait; and estimate the strength of such an effect.

We used an ANCOVA within PGLS framework to assess variation in slope and intercept across the three types of placental invasiveness and interdigitation. Allometric effects were accounted for by entering body mass as a predictor in the model. Specifically, we used neonatal body mass to control for allometric influences on neonatal brain mass and maternal body mass for allometric effects on gestation length and neonatal body mass. Gestation length was included in the models for neonatal brain and body mass to test for differences in growth rates; previous studies also showed that neonatal brain and body mass increase with longer gestation (Martin and MacLarnon 1985; Pagel and Harvey 1988). We coded placentation with dummy variables (Quinn and Keough 2002). We used hemochorial placentation in the analyses of invasiveness and villous interdigitation in the analyses of interdigitation as the reference levels against which slopes and intercepts of the other two placental types were assessed. The choice of the reference level does not affect the results (Quinn and Keough 2002), and thus selecting endotheliochorial or epitheliochorial placentation or trabecular or labyrinthine interdigitation as the reference level would have led to identical conclusions. While the dummy variables quantified differences in intercepts, the interaction terms between dummy variables (epitheliochorial and endotheliochorial placentation for invasiveness, trabecular and labyrinthine placentation for interdigitation) and body mass indicated differences in slopes relative to the reference level (i.e., hemochorial placentation; villous interdigitation). This is equivalent to a phylogenetic ANCOVA with slopes free to vary (see also Lavin et al. 2008). The significance of intercepts and slopes can then be tested with *t* statistics, using information on intercept and slope values and associated standard errors. In PGLS, model parameters and λ are found by maximum likelihood (ML), and the phylogeny is incorporated in the error term of the model to account for the species' shared evolutionary history (Pagel 1997, 1999; Freckleton et al. 2002; Lavin et al. 2008). Estimating λ therefore accounts for 1 df.

Under PGLS framework, more complex models are

Table 1: Gestation length and placental invasiveness

	Full model		SSJ model	
Predictor	t_{102}	*P* value	t_{105}	*P* value
Intercept	13.2	<.001	19.0	<.001
Maternal body mass	3.7	<.001	6.7	<.001
Epitheliochorial	2.1	.040	2.9	.004
Endotheliochorial	−.7	.478	…	…
Epitheliochorial × maternal body mass	−.8	.449	…	…
Endotheliochorial × maternal body mass	.5	.639	…	…
Model summary:				
Lh	80.4		79.6	
λ	1.0		1.0	
R^2	.39		.37	

Note: Invasiveness is coded with dummy variables. The full model allows for variation in both intercepts and slopes, so that three slopes and three intercepts are estimated (one slope and one intercept for each type of placenta), with hemochorial placentation as the reference level (see "Methods"). The simplest statistically justifiable (SSJ) model has one slope and two intercepts, one intercept for epitheliochorial placentation and one for endotheliochorial and hemochorial placentation together (which become the new reference level; see "Results"). Lh = log likelihood of the model.

compared to simpler models to investigate whether additional independent variables significantly increase the fit of the model to the data. Nested models, with and without the predictor of interest, are compared using a likelihood ratio (LR) test, with the best-fitting model having the highest log-likelihood (Lh) score, so that

$$\mathrm{LR}_{\mathrm{df}} = -2 \times [\mathrm{Lh}(\text{better-fitting model}) - \mathrm{Lh}(\text{worse-fitting model})].$$

The significance of this difference is evaluated with a χ^2 distribution with degrees of freedom corresponding to the difference in the number of parameters between the two competing models (Pagel 1997, 1999; Quinn and Keough 2002). When placentation was included in the model, we tested for full models with three intercepts and three slopes (one for each type of placenta) and all the simpler models nested within the full models (e.g., models in which only intercepts were free to vary). Here we report the results of the full models and of the simpler models that were statistically justifiable, that is, not overparameterized. All statistical tests were two tailed, with an α level of significance set at 0.05.

Nonnested models can be compared using Akaike Information Criterion (AIC) scores. The AIC score of a model is calculated as [2 × (no. parameters in the model) − 2 × (Lh)]. Differences between AIC scores of two competing models are considered substantial if greater than 2, with the best-fitting model having the lowest AIC score (Burnham and Anderson 2002).

Finally, we evaluated the correlated evolution between placental invasiveness and interdigitation. Given our results, both interdigitation and invasiveness were treated as binary traits in this analysis. We compared the model fit of two alternative nested Markov models of evolution for discrete traits, using ML: an independent model of evolution with four parameters (one backward and one forward rate of transition along the tree for each trait independently) and a dependent model of evolution with eight parameters (a backward and a forward rate of transition for all the four possible combinations of character states along the tree, i.e., 0, 0; 0, 1; 1, 0; 1, 1; Pagel 1994). The dependent model fitted the data better if its log likelihood (Lh(D)) was significantly higher than that of the independent model (Lh(I)) as quantified by an LR test with 4 df (i.e., the difference between the number of parameters between the two competing models) and an α level of significance of 0.05 (Pagel 1994; Pagel et al. 2004).

Results

Gestation Length

A simple allometric model of gestation length on maternal body mass explained 32% of variance in gestation length ($t_{106} = 7.2$, $P < .001$). Once placental invasiveness was added to the model, allowing for differences in both intercepts and slope, this more complex model improved significantly the fit to the data and explained an additional 7% of variance in gestation length (without placentation: Lh = 75.3; with placentation: Lh = 80.4; $R^2 = 0.39$, $\mathrm{LR}_4 = 10.3$, $P = .035$). This model showed that relative gestation length (controlling for allometry) was shorter when placentation was more invasive (hemochorial or endotheliochorial) than when it was noninvasive epitheli-

Table 2: Gestation length and placental interdigitation

	All species				Hemochorial species	
	Full model		SSJ model		SSJ model	
Predictor	t_{99}	*P* value	t_{102}	*P* value	t_{45}	*P* value
Intercept	14.0	<.001	18.2	<.001	11.7	<.001
Maternal body mass	3.2	<.001	6.9	<.001	3.4	.001
Trabecular	.5	.632	…	…	…	…
Labyrinthine	−3.6	<.001	−4.4	<.001	−2.9	.005
Trabecular × maternal body mass	−.5	.589	…	…	…	…
Labyrinthine × maternal body mass	1.7	.093	…	…	…	…
Model summary:						
Lh	83.5		81.4		34.8	
λ	1.0		1.0		1.0	
R^2	.47		.44		.36	

Note: Interdigitation is coded with dummy variables. The full model allows for variation in both intercepts and slopes, so that three slopes and three intercepts are estimated (one slope and one intercept for each type of placenta), with villous interdigitation as reference level (see "Methods"). The simplest statistically justifiable (SSJ) model has one slope and two intercepts, one intercept for labyrinthine interdigitation and one for villous and trabecular interdigitation together (which become the new reference level; see "Results"). Lh = log likelihood of the model.

ochorial (fig. 1*A*). Specifically, the allometric slopes and intercepts did not differ between endotheliochorial and hemochorial placentation, while the intercept of epitheliochorial placentation was significantly higher than the intercepts of the two more invasive placentas, but the slopes did not differ (table 1). Thus, the simplest statistically justifiable model had one slope and two intercepts (one for epitheliochorial placentation and one for hemochorial and endotheliochorial placentation together). This model significantly improved the fit to the data relative to a simple allometric model without placentation ($LR_1 = 8.5$, $P = .003$), and the additional parameters of the full model did not increase the fit further (vs. full model with three intercepts and three slopes: $LR_3 = 1.8$, $P = .616$).

Next we examined the effect of placental interdigitation on gestation length. Interdigitation explained an additional 13% of variance in gestation time relative to a simple allometric model and significantly improved the fit to the data (without interdigitation: Lh = 72.3, $R^2 = 0.34$; with interdigitation: Lh = 83.5, $R^2 = 0.47$; $LR_4 = 22.3$, $P < .001$). As for placental invasiveness, the simplest statistically justifiable model had one slope and two intercepts (vs. full model with three slopes and intercepts: $LR_3 = 4.1$, $P = .246$; table 2). Specifically, villous and trabecular placentas did not differ from one another in intercepts and slopes but had a higher intercept than that of labyrinthine placentas; therefore, they were associated with relatively longer gestation than labyrinthine placentas (fig. 1*B*; table 2). Using regression equations from this last model, we found that in same-sized species, gestation time of labyrinthine placentas was approximately 44% of the duration of that of villous and trabecular placentas. Because hemochorial placentas can be associated with any of the three forms of interdigitation, we replicated these results within the subset of species with hemochorial placentation and used the best statistical model (i.e., two intercepts and one slope). Again, labyrinthine interdigitation was associated with shorter gestation length than villous and trabecular interdigitation after controlling for allometry (table 2).

Finally, we investigated the correlated evolution of invasiveness and interdigitation and then tested for an overall effect of placentation, with both invasiveness and interdigitation as predictors of relative gestation length. Given the above results, we merged endotheliochorial and hemochorial placentation into one state and trabecular and villous interdigitation into one state, so that both invasiveness and interdigitation were binary traits in these analyses. Placental invasiveness and interdigitation were evolutionarily correlated because the dependent model of

Table 3: Gestation length, placental invasiveness, and interdigitation

Predictor	t_{99}	*P* value
Intercept	14.8	<.001
Maternal body mass	6.9	<.001
Invasiveness	−.1	.910
Interdigitation	−3.1	.002

Note: Invasiveness and interdigitation are coded with dummy variables. Given the two best models for invasiveness and interdigitation (tables 1, 2), both traits are treated as binary, so that invasiveness is considered either epitheliochorial or nonepitheliochorial (i.e., hemochorial or endotheliochorial) and interdigitation is either nonlabyrinthine (i.e., villous or trabecular) or labyrinthine. Nonepitheliochorial placentation and nonlabyrinthine placentation are the reference levels.

Table 4: Neonatal body mass and placental invasiveness

	Model 1		Model 2		Model 3		Model 4	
Predictor	t_{102}	*P* value	t_{101}	*P* value	t_{98}	*P* value	t_{99}	*P* value
Intercept	−2.7	.008	−6.5	<.001	−5.3	<.001	−5.4	<.001
Maternal body mass	12.6	<.001	11.7	<.001	11.6	<.001	11.6	<.001
Epitheliochorial	.8	.409	−.3	.801	−.2	.822	−.8	.432
Endotheliochorial	−.6	.576	−.2	.841	−.1	.898	.1	.965
Epitheliochorial × maternal body mass	.1	.890	.6	.545	.5	.584	1.0	.314
Endotheliochorial × maternal body mass	.5	.607	.3	.779	.2	.869	.4	.698
Gestation length	…	…	5.8	<.001	5.0	<.001	3.9	<.001
Litter size	…	…	…	…	−.5	.599	…	…
Developmental state	…	…	…	…	…	…	2.3	.024
Model summary:								
Lh	13.1		28.7		26.9[a]		30.3[b]	
λ	1.0		1.0		.99[a]		1.0[b]	
R^2	.86		.89		.90[a]		.90[b]	

Note: Invasiveness is coded with dummy variables. All models are full models that allow for variation in both intercepts and slopes, so that three slopes and three intercepts are estimated (one slope and one intercepts for each type of placenta), with hemochorial placentation as reference level (see "Methods"). Developmental state is coded as a binary trait (altricial or precocial; see "Methods"). Lh = log likelihood of the model.

[a] For comparison, the model without litter size and same sample of species: Lh = 26.8, λ = 1.0, R^2 = 0.89.

[b] For comparison, the model without developmental state and same sample of species: Lh = 27.6, λ = 0.99, R^2 = 0.89.

evolution provided a better fit to the data than did the independent model of evolution (Lh(I) = −27.9, Lh(D) = −21.6, $LR_4 = 12.6$, $P = .013$). Once invasiveness was entered into the model with interdigitation, only interdigitation retained significance (model Lh = 81.4, λ = 1.0, $R^2 = 0.44$; table 3), and invasiveness did not further improve the fit to the data (vs. model without invasiveness: $LR_1 = 0.02$, $P = .886$).

Neonatal Body Mass

As in previous studies (e.g., Martin and MacLarnon 1985; Pagel and Harvey 1988), neonatal body mass increased with gestation length and maternal body mass, which together explained 89% of the variance in this trait (maternal body mass: $t_{105} = 20.3$, $P < .001$; gestation length: $t_{105} = 6.3$, $P < .001$). Placental invasiveness did not affect neonatal body mass after gestation length and maternal body mass were accounted for, because the more complex model with invasiveness did not significantly improve the fit to the data (without invasiveness: Lh = 28.4; with invasiveness: Lh = 28.7; $LR_4 = 0.5$, $P = .970$) and there was no difference in slope and intercept across placental types (table 4, model 1). Conclusions did not differ when gestation length was excluded from the model (table 4, model 2), nor did they differ when litter size was included in the model (without litter size: Lh = 26.8; with litter size: Lh = 26.9; $LR_1 = 0.2$, $P = .635$), as litter size was not a significant predictor of neonatal body mass after accounting for allometry and gestation length and did not alter the relationship between neonatal body mass and placental invasiveness (table 4, model 3). Finally, although altricial neonates were significantly smaller than precocial neonates and the inclusion of developmental state improved the fit to the data (without developmental state: Lh = 27.6; with developmental state: Lh = 30.3; $LR_1 = 5.5$, $P = .020$), this predictor explained only an additional 1% of variance in neonatal body mass and, importantly, did not alter the conclusions about the (lack of an) effect of placental invasiveness on neonatal body mass (table 4, model 4).

As with placental invasiveness, there was no difference in neonatal body mass across types of placental interdigitation after gestation length and maternal size were accounted for. Interdigitation, in fact, was not a significant predictor of neonatal body mass (table 5, model 1), and its inclusion did not significantly improve the fit to the data (without interdigitation: Lh = 25.5; with interdigitation: Lh = 25.6; $LR_4 = 0.2$, $P = .994$). Again, exclusion of gestation length from the model or inclusion of litter size and developmental state did not alter these conclusions (table 5, models 2–4).

Neonatal Brain Mass

Neonatal brain mass increased with gestation length and neonatal body mass, which together explained 91% of the variance in this trait (neonatal body mass: $t_{105} = 18.5$, $P < .001$; gestation length: $t_{105} = 5.9$, $P < .001$). Placental invasiveness improved the fit to the data when included in a model with gestation length and neonatal body mass, although the variance explained by this model increased by only 1% (without invasiveness: Lh = 47.9; with invasiveness: Lh = 53.1; $LR_4 = 10.4$, $P = .034$). Specifically, while slopes and intercepts of intermediately invasive en-

Table 5: Neonatal body mass and placental interdigitation

	Model 1		Model 2		Model 3		Model 4	
Predictor	t_{99}	*P* value	t_{98}	*P* value	t_{96}	*P* value	t_{97}	*P* value
Intercept	−1.1	.281	−5.3	<.001	−4.5	<.001	−5.4	<.001
Maternal body mass	14.2	<.001	13.8	<.001	13.7	<.001	14.3	<.001
Trabecular	.6	.549	.4	.701	.3	.732	.4	.666
Labyrinthine	−1.5	.135	.3	.761	.3	.770	1.0	.314
Trabecular × maternal body mass	−.7	.482	−.5	.642	−.4	.682	−.5	.607
Labyrinthine × maternal body mass	.7	.512	−.2	.809	−.3	.787	.6	.534
Gestation length	…	…	5.6	<.001	4.9	<.001	4.1	<.001
Litter size	…	…	…	…	−.5	.603	…	…
Developmental state	…	…	…	…	…	…	2.4	.017
Model summary:								
Lh	11.0		25.6		24.8[a]		28.6[b]	
λ	1.0		1.0		1.0[a]		.99[b]	
R^2	.86		.89		.89[a]		.90[b]	

Note: Interdigitation is coded with dummy variables. All models are full models allowing for variation in both intercepts and slopes, so that three slopes and three intercepts are estimated (one slope and one intercept for each type of placenta), with villous interdigitation as reference level (see "Methods"). Developmental state is coded as a binary trait (altricial or precocial; see "Methods"). Lh = log likelihood of the model.

[a] For comparison, the model without litter size and same sample of species: Lh = 24.7, λ = 1.0, R^2 = 0.89.

[b] For comparison, the model without developmental state and same sample of species: Lh = 25.6, λ = 1.0, R^2 = 0.89.

dotheliochorial and highly invasive hemochorial placentation did not differ from one another, epitheliochorial placentation had a lower slope and a higher intercept relative to the other two placental types (table 6, model 1, full model; fig. 2). As a result, fit lines crossed over at an intermediate neonatal body mass (fig. 2). A model in which endotheliochorial and hemochorial placentation were merged into one variable so that two slopes and two intercepts were estimated was therefore the simplest statistically justifiable model (vs. full model: $LR_2 = 0.3$, $P = .860$; table 6, model 1, SSJ model). Results were qualitatively similar if the analysis was conducted without gestation length in the model (table 6, model 2). Developmental state did not improve the fit to the model, as it was not a significant predictor of neonatal encephalization after accounting for gestation length (table 6, model 3).

Similarly, although placental interdigitation improved the fit to the data once included in a model with gestation length and neonatal body mass, interdigitation explained only an additional 1% of variance in neonatal brain mass (without interdigitation: Lh = 44.9; with interdigitation: Lh = 51.3; $LR_4 = 12.7$, $P = .013$). Specifically, slopes and intercepts of the three types of interdigitation differed from one another, and the fit lines crossed over at intermediate neonatal body sizes (table 7, models 1, 2). These results were not influenced by the inclusion in the model of litter size or developmental state, which were nonsignificant predictors of relative neonatal brain mass (table 7, models 3, 4). We then tested whether placental interdigitation or invasiveness better predicted neonatal encephalization. Because the best-fitting model for each placental trait was one with both intercepts and slopes free to vary, an overall model including both interdigitation and invasiveness was overspecified. We thus compared the two best-fitting models (two intercepts and two slopes for invasiveness [see table 6] and three intercepts and three slopes for interdigitation [see table 7]), using AIC scores (interdigitation AIC = −86.5; invasiveness AIC = −88.2). The two models performed equally well because the difference between AIC scores was less than 2.

Trade-Offs between Brain Mass and Litter Size

We tested whether there were trade-offs (predicting negative associations) between neonatal brain mass and litter size that could explain the above differences in neonatal brain scaling with placental invasiveness (Elliot and Crespi 2008). Litter size did not improve the fit to the data once added to the model with neonatal body mass, gestation length, and placentation as predictors of neonatal brain mass (without litter size: Lh = 51.4; with litter size: Lh = 52.3; $LR_1 = 1.8$, $P = .177$); litter size was not significantly correlated with brain mass, and it did not alter the allometric scaling of neonatal brain mass in relation to placentation (table 6, model 4).

Discussion

Although the diversity in mammalian placental structure is widely assumed to reflect differences in maternal investment strategies, there has been little agreement on the precise nature of the link. We provide the first clear demonstration that the evolution of placental structure correlates with differences in gestation length and fetal growth

Table 6: Neonatal brain size and placental invasiveness

	Model 1				Model 2				Model 3		Model 4	
	Full model		SSJ model		Full model		SSJ model		SSJ model		SSJ model	
Predictor	t_{102}	*P* value	t_{104}	*P* value	t_{101}	*P* value	t_{103}	*P* value	t_{101}	*P* value	t_{100}	*P* value
Intercept	−9.1	<.001	−11.5	<.001	−9.2	<.001	−10.2	<.001	−9.3	<.001	−7.4	<.001
Neonatal body mass	16.8	<.001	25.5	<.001	14.3	<.001	18.1	<.001	17.5	<.001	18.1	<.001
Epitheliochorial	3.0	.003	3.6	<.001	2.3	.026	2.5	.012	2.3	.022	2.5	.014
Endotheliochorial	−1.2	.246	…	…	−.5	.604	…	…	…	…	…	…
Epitheliochorial × neonatal body mass	−2.6	.010	−3.7	<.001	−2.42	.017	−3.2	.002	−3.0	.003	−3.1	.002
Endotheliochorial × neonatal body mass	1.1	.271	…	…	.6	.535	…	…	…	…	…	…
Gestation length	…	…	…	…	5.1	<.001	5.3	<.001	4.6	<.001	4.3	<.001
Developmental state	…	…	…	…	…	…	…	…	.3	.773	…	…
Litter size	…	…	…	…	…	…	…	…	…	…	−1.3	.181
Model summary:												
Lh	40.9		40.1		53.1		52.9		51.6[a]		52.3[b]	
λ	.92		.93		.88		.88		.88[a]		.88[b]	
R^2	.90		.90		.92		.92		.92[a]		.93[b]	

Note: Invasiveness is coded with dummy variables. The full model allows for variation in both intercepts and slopes, so that three slopes and three intercepts are estimated (one slope and one intercept for each type of placenta), with hemochorial placentation as reference level (see "Methods"). In the simplest statistically justifiable (SSJ) model, intermediately invasive endotheliochorial and highly invasive hemochorial placentas are merged into one variable, and two intercepts and two slopes are estimated (see "Results"). Developmental state is coded as a binary trait (see "Methods"). Model 4 also tests the hypothesis that there are trade-offs between neonatal brain size and litter size in relation to placental invasiveness. Lh = log likelihood of the model.

[a] For comparison with a model without developmental state but same sample of species: Lh = 51.6, λ = 0.88, R^2 = 0.92.

[b] For comparison with a model without litter size but same sample of species: Lh = 51.4, λ = 0.88, R^2 = 0.92.

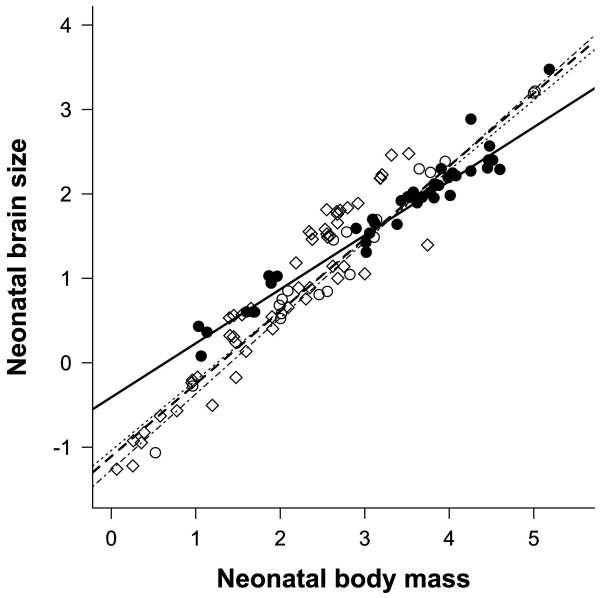

Figure 2: Neonatal brain mass on neonatal body mass with fit lines by type of placenta. Fit lines did not differ between hemochorial (*dotted line*) and endotheliochorial (*dot-dashed line*) placentation, while both (*dashed line*) differed from epitheliochorial placentation (*solid line*; see "Results"; table 6). Albeit significant, placentation explained only an additional 1% of variance in neonatal brain size after controlling for allometry, whether or not gestation length was included in the model (see "Results"; table 6). *Filled circles* = noninvasive epitheliochorial placentation; *open circles* = intermediately invasive endotheliochorial placentation; *diamonds* = highly invasive hemochorial placentation.

rates. Specifically, compared with other placental types, more interdigitated (labyrinthine) and more invasive (hemochorial or endotheliochorial) placentas are associated with shorter gestations, but neonates are of similar body and brain mass. These results remain unchanged once litter size is included in the model. Further, we show that it is interdigitation, rather than invasiveness, that appears to be the critical factor, indicating that the increase in the surface area for exchange has a greater impact on fetal growth rates than does direct fetal access to maternal blood. These findings raise further questions, such as why mechanisms for faster growth and shorter gestation were favored in some lineages rather than others and, if not related to growth rates, what the functional significance of invasiveness is.

As predicted by Wildman et al. (2006), we found that increased placental interdigitation is accompanied by a marked reduction in gestation length after controlling for maternal size, so that relative gestation length associated with labyrinthine placentas is 44% of that associated with villous and trabecular placentas. For example, at a maternal body mass of 10 kg, there is an average gestation length difference of 113 days (89 days in species with labyrinthine placentas vs. 202 days in species with trabecular or villous placentas). Our results are consistent with an early nonphylogenetically controlled study across a small sample of species showing that a higher placental surface area for exchange sustains the growth of a greater volume of fetal (and placental) tissues (Baur 1981). Interdigitation can thus explain why intermediately invasive endotheliochorial placentas—which are generally labyrinthine—appear to have a gestation length similar to that of highly invasive hemochorial placentas when only invasiveness is considered. Note that hemochorial placentation can assume any of the three types of interdigitation and that, consistent with results across all mammals, differences in relative gestation length among species with highly invasive placentas can actually be explained by their degree of interdigitation. We have not found a difference between villous and trabecular forms of interdigitation. While the morphological distinction between labyrinthine and villous patterns is clear, the difference between trabecular and villous interdigitation is, at least in some species, more ambiguous. For example, Mossman (1987, p. 206) classifies the interdigitation of Old World monkeys as "less trabecular and more villous," and other authors (e.g., Leiser and Kaufmann 1994; Wildman et al. 2006) consider suids as having a folded interdigitation (the placenta forms ridgelike folds) rather than villous and describe carnivores as lamellar (the folds are branched) rather than labyrinthine. The exclusion of these species from the analysis, however, does not affect our conclusions.

Correlates of other aspects of placental morphology, particularly at the areas of exchange, would be worth investigating when comparative physiological and morphological data become available. Among these, the blood flow system in the capillaries describing the spatial arrangement of maternal and fetal vessels and direction of the bloodstream, the blood flow rates through the placenta, the number of uterine glands, and the size of the placenta relative to the fetus may be important in determining interspecific differences in nutrient transfer rates (Wooding and Burton 2008; Carter 2009). Given our results, future studies should test whether a labyrinthine interdigitation is indeed energetically more costly for the mother, as suggested by Wildman et al. (2006). Data on maternal investment, offspring developmental traits, and placentation are also necessary for a larger sample of species in orders less well represented in our analyses (e.g., bats and several rodent families).

We confirm Elliot and Crespi's (2008) finding that placental invasiveness influences the scaling of neonatal brain mass on neonatal body mass. However, our analysis reveals that the impact of placentation (both invasiveness and interdigitation) on neonatal brain mass scaling is minimal.

Table 7: Neonatal brain size and placental interdigitation

	Model 1		Model 2		Model 3		Model 4	
Predictor	t_{99}	*P* value	t_{98}	*P* value	t_{96}	*P* value	t_{97}	*P* value
Intercept	−2.1	.035	−5.4	<.001	−4.2	<.001	−5.4	<.001
Neonatal body mass	14.3	<.001	12.7	<.001	12.7	<.001	12.6	<.001
Trabecular	−2.6	.012	−3.1	<.001	−2.8	.005	−3.1	.003
Labyrinthine	−4.2	<.001	−2.6	.002	−2.6	.010	−2.3	.024
Trabecular × neonatal body mass	2.6	.010	3.2	.002	2.9	.004	3.2	.002
Labyrinthine × neonatal body mass	3.2	.002	2.3	.023	2.3	.022	2.2	.033
Gestation length	…	…	4.9	<.001	3.9	<.001	4.5	<.001
Litter size	…	…	…	…	−1.2	.227	…	…
Developmental state	…	…	…	…	…	…	.1	.902
Model summary:								
Lh	40.1		51.3		51.3[a]		51.2[b]	
λ	.90		.86		.87[a]		.87[b]	
R^2	.91		.93		.93[a]		.93[b]	

Note: Interdigitation is coded with dummy variables. All models are full models allowing for variation in both intercepts and slopes, so that three slopes and three intercepts are estimated (one slope and one intercept for each type of placenta), with villous interdigitation as reference level (see "Methods"). Lh = log likelihood of the model.

[a] For comparison, the model without litter size; Lh = 50.5, λ = 0.86, R^2 = 0.93.

[b] For comparison, the model without developmental state; Lh = 51.2, λ = 0.86, R^2 = 0.93.

Our results do not support the hypothesis that placentation (higher invasiveness and/or interdigitation) is associated with greater neonatal encephalization. Elliot and Crespi (2008) suggest that the difference in the scaling of neonatal brain mass reflects life-history trade-offs between offspring size and number that vary along the range of mammalian body sizes. We find no evidence in support of this hypothesis because litter size is unrelated to brain mass after accounting for allometry, gestation length, and placentation and its inclusion in the model does not alter the observed scaling pattern. This indicates that although offspring size and number are negatively associated (e.g., Read and Harvey 1989; Bielby et al. 2007), a larger litter does not directly reduce prenatal maternal investment in each offspring's brain size; that is, the negative effects of an increase in litter size on neonatal brain size are indirect and caused by the reduction in neonatal body mass when litter size increases. Unlike Elliot and Crespi (2008), we show that intermediately invasive and highly invasive placentas perform similarly. This discrepancy may reflect the fact that we correct for preimplantation time from total gestation length in species with delayed implantation or diapause to better capture the actual time during which the placenta sustains fetal growth. Because most species with delayed implantation also have endotheliochorial placentation, previous results are likely to be an artifact of inflated gestation length when time in delayed implantation is not accounted for. Although our results do not support the hypothesis that placental invasiveness and interdigitation are linked to neonatal encephalization, other aspects of placental morphology might impact neonatal brain growth. Moreover, variation in adult brain mass and structure across species reflects species differences in both prenatal and postnatal growth (Leigh 2004).

The placenta is believed to be a major site for the evolutionary arms race between maternal and paternal genes over maternal allocation of resources to the developing offspring (Haig 1993; Crespi and Semeniuk 2004; Pollux et al. 2009). Several studies have shown that imprinted genes are particularly important in this context, with expressed genes of paternal origin promoting placental and fetal growth beyond the optimum for maternal interests, and expressed genes of maternal origin acting antagonistically to paternally expressed genes and generally restricting placental and fetal growth (see reviews in Riek et al. 2003; Crespi and Semeniuk 2004; Angiolini et al. 2006; Petry et al. 2007; Vrana 2007; Bressan et al. 2009; Ng et al. 2010). The highly invasive hemochorial placentation has therefore been interpreted as an evolutionary condition of fetal (hence paternal gene) advantage, compared with the noninvasive epitheliochorial placentation (Haig 1993; Crespi and Semeniuk 2004). Our results, however, do not support a direct link between placental invasiveness and fetal growth, suggesting that variability in invasiveness requires a different explanation. Instead, the degree of placental interdigitation appears to be more directly related to fetal growth and hence potentially a factor in maternal-offspring conflict. The fact that faster growth rates associated with interdigitated placentas result in shorter gestations, rather than larger neonates, suggests that conflict hypotheses must explicitly incorporate the interaction between growth rates and gestation length. For example, there could be an arms race between paternal genes that increase interdigitation and nutrient transfer and maternal

genes that shorten gestation length. In support of this idea, gestation length is reduced where sibling competition, which exacerbates maternal-offspring conflict, is more intense (Stockley and Parker 2002). Maternal-offspring conflict theory predicts that larger litters and greater levels of female promiscuity, which increase sibling competition due to the lower relatedness among littermates and so selection on paternally expressed genes, should lead to greater maternal-offspring conflict and be associated with the evolution of placental morphologies promoting nutrient transfer (Trivers 1974; Haig 1993; Vrana 2007; Pollux et al. 2009; Zeh and Zeh 2000).

Our study sheds light on the relationship between placental gross morphology and maternal investment in mammals and highlights effects on gestation length rather than on neonatal size or encephalization. After maternal body mass and gestation length have been controlled for, placentation is unrelated to neonatal body or brain mass. Nevertheless, both the latter variables do show considerable variation across mammals and correlate with gestation length (Martin and MacLarnon 1985; Pagel and Harvey 1988; this study). In our analyses, about 50% of the variation in gestation length remains unexplained after taking placental morphology and allometry into account. We conclude that changes in placental morphology affect gestation length while the size of the neonate remains relatively constant, and we suggest that changing gestation length independently of placentation affects size and encephalization of the neonate. Interestingly, while placentation is unrelated to neonate size, it appears to be strongly related to altriciality: at least among the species in our data set, altriciality is found exclusively in species with a labyrinthine placenta, belonging to nine mammalian orders. An association between altriciality and labyrinthine interdigitation, together with a lack of any association between neonate size and placentation, would suggest that neonate size and developmental state are partially dissociable. Hence, there may be a limit on the extent to which faster growth can be accompanied by speeded-up maturation of the central nervous and other physiological systems associated with developmental state. Altriciality might thus be a cost of enhanced nutrient transfer, faster growth in mass, and shorter gestations. Given such a cost, we suggest that ecological selection pressures acting on gestation length may have been an important factor in the evolution of placentation. For example, selection to produce multiple litters in seasonal environments may have favored the evolution and/or the maintenance of more "efficient" placentas in small mammals, which in turn would have exacerbated maternal-offspring conflict.

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