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Biological interpretations of the biphasic model of ontogenetic brain–body allometry: a reply to Packard

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Allometry is a description of organismal growth. Historically, a simple power law has been used most widely to describe the rate of growth in phenotypic traits relative to the rate of growth in overall size. However, the validity of this standard practice has repeatedly been criticized. In an accompanying opinion piece, Packard reanalysed data from a recent study on brain–body ontogenetic allometry and claimed that the biphasic growth model suggested in that study was an artefact of logarithmic transformation. Based on the model selection, Packard proposed alternative hypotheses for brain–body ontogenetic allometry. Here, I examine the validity of these models by comparing empirical data on body sizes at two critical neurodevelopmental events in mammals, i.e. at birth and at the time of the peak rate of brain growth, with statistically inferred body sizes that are supposed to characterize neurodevelopmental processes. These analyses support the existence of two distinct phases of brain growth and provide weak support for Packard's uniphasic model of brain growth. This study demonstrates the importance of considering alternative models in studies of allometry, but also highlights that such models need to respect the biological theoretical context of allometry.

ADDITIONAL KEYWORDS: brain size evolution – developmental constraints – measurement theory.

INTRODUCTION

Allometry is a description of the covariation between traits and the overall size of organisms. Julian S. Huxley (1932) introduced allometry as a relationship between a trait, Y, and overall body size, X, in the form of a power law, $Y = aX^b$. This equation is usually expressed as the linear relationship on a logarithmic scale as $\log(Y) = \log(a) + b\log(X)$. The theoretical context of this model is that if a trait and overall size are under common growth regulation, the model approximates a linear relationship between trait size and overall size. The fit of this formula to many morphological, physiological and life-history traits (Gould, 1966; McMahon & Bonner, 1983; Schmidt-Nielsen, 1984; Peters, 1986; Calder, 1996) suggests that the growth of traits may often share developmental and genetic factors with overall size. Understanding the causes and consequences of these factors is the central goal of allometry studies (e.g. Gould, 1977).

Despite its popularity, the use of Huxley's power equation has repeatedly been criticized (Smith, 1980; Stumpf & Porter, 2012). The main issue is that, because allometry is a phenomenological model, there is no guarantee that the model represents the underlying biological processes. In recent years, this debate has been invigorated by a research group led by G. C. Packard in a series of replies to primary studies of allometry (e.g. Packard, 2009, 2018). Briefly, Packard's arguments are as follows: (1) the first step in studies of allometry is to describe the observation as accurately as possible, and a simple power function is not always the best model in this respect; (2) because the linear arithmetic scale is the scale of interest, allometry should always be expressed on this scale regardless of the context of the data and the study; and (3) graphical presentation on the original scale often eliminates the apparent multimodal distribution on the logarithmic scale. In a series of responses to Packard's opinion (Kerkhoff & Enquist, 2009; Cawley & Janacek, 2010; Xiao *et al.*, 2011; Ballantyne, 2013; Glazier, 2013; Mascaro *et al.*, 2014; Lemaître *et al.*, 2015; Pélabon *et al.*, 2018), opponents claim that: (1) because

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allometry is a study of developmental processes, statistical validation cannot precede the formulation of a biological hypothesis concerning these processes; (2) there are good biological and statistical reasons to consider that the error structure in allometric studies is multiplicative, which validates the use of a standard allometric model and the logarithmic scale; and (3) the visual inspection of data structure can, at best, provide a weak qualitative support for Packard's contention.

The article by Packard (2019) is a sequel to this line of discussion fed by the group (Packard, 2009, 2018). This time, Packard argues that the biphasic model of brain–body ontogenetic allometry, suggested by several investigators (Count, 1947; Deacon, 1990; Halley, 2016; Tsuboi *et al.*, 2018), is an artefact of logarithmic transformation, and therefore, the model is invalid. Based on the model selection performed on the original gram scale, the author found support for multiple-parameter power functions over a simple model of allometry. According to these models, Packard proposes alternative modes of vertebrate brain development.

The biphasic model of brain–body allometry has its roots in evolutionary and developmental neurobiology. Among numerous hypotheses concerning the evolution of vertebrate brain size (Jerison, 1973; Striedter, 2005), one of the most widely appreciated ideas is that the life-history traits at early stages of life predict adult relative brain size (brain size controlling for the effect of body size). For instance, relative brain size is explained by the mode of development (Martin, 1983), gestation length (Barton & Capellini, 2011) or neonatal size (Sacher & Staffeldt, 1974; Barton & Capellini, 2011) in mammals and by the egg size (Isler & van Schaik, 2006), incubation time (Isler & van Schaik, 2006) and developmental mode (Iwaniuk & Nelson, 2003) in birds. There is growing evidence that this pattern holds for teleost fishes (egg diameter and duration of parental care: Tsuboi *et al.*, 2015, 2017), amphibians (egg diameter: Liao *et al.*, 2016) and cartilaginous fishes (reproductive mode: Mull *et al.*, 2011). These empirical patterns imply that early and late brain development are qualitatively different and that early development has disproportionally more influence on relative brain size than later development. This hypothesis is corroborated by the presence of two distinct phases in brain development, whereby growth in the number of cells precedes growth in cell size (Caviness *et al.*, 1995; Finlay & Darlington, 1995). It is these biological insights, not the visual perception of data (e.g. Packard, 2019), that motivated researchers of vertebrate brain–body allometry to use the biphasic growth model. The overall context of our debate is such that Packard (2019) challenges biologically driven ideas from a purely statistical point of view.

In this article, I will focus upon two specific points. One is the issue of the interpretation of parameters of allometry models in biological contexts. The second concerns the treatment of the materials and arguments that Packard (2019) retrieved from the literature.

MATERIAL AND METHODS

Biological interpretations of allometry models

In the standard allometry model, $\log(Y) = \log(a) + b\log(X)$, the exponent '$b$' represents a parameter that determines the rate of growth in a trait relative to the rate of growth in the body overall. Given that this parameter may reflect the magnitude and direction of developmental and genetic constraints (Lande, 1979; Voje *et al.*, 2014), b has been the subject of considerable research effort with the aim of understanding the role of constraints in trait evolution (Gould, 1975, 1977; Voje & Hansen, 2013; Halley, 2016; Tsuboi *et al.*, 2016, 2018).

In the context of brain–body ontogenetic allometry, the intercept '$\log(a)$' represents the predicted brain size at 1 g body mass, which corresponds approximately to the timing at which neural tissue becomes differentiated from somatic tissue (Deacon, 1990). It is upon these theoretical underpinnings that ontogenetic and static allometries are explored to test the idea that evolution of brain size might be bounded to follow the developmental trajectory (Count, 1947; Gould, 1975; Deacon, 1990; Halley, 2016; Halley, 2017; Tsuboi *et al.*, 2018). The reason for choosing a simple power equation plotted on the logarithmic scale is to ensure a match between the biological theoretical context (allometry as a quantity that characterizes the magnitude of genetic and developmental constraints) and the property of interest (the allometric exponent, b). Criticizing the choice of scale based on statistical fit is therefore nonsensical, because statistical inference is meaningful if and only if the statistical model contains the subject of research.

The Packard's multiple-parameter power equation relates a trait, Y, to overall body size, X, in the general form of $Y = Y_0 + aX^b$. Packard (2019) pointed out that Huxley (1932) mentioned this model as 'the most inclusive' formula, but Huxley also suggested that 'Y_0 will often be negligible where heterogony (e.g. allometry) is marked; and where heterogony is not marked, b will be so close to unity that Scammon's formula (e.g. $Y = Y_0 + aX$) will approximately apply' (Huxley, 1932: pp. 241; notes in parentheses are given by the author). Hence, Huxley recognized this model, but clearly stated that its utility would be limited empirically. The major problem of this model is that

it is not fully representational (*sensu* Wolman, 2006; Houle *et al.*, 2011), because the interpretation of model parameters (Y_0, a and b) is scale dependent. On the original scale, this model is the standard allometry model, in which a trait and the overall body start their growth at different times. On the logarithmic scale, this model could be interpreted as a description of growth in which the growth rate of a trait depends on size. Therefore, unlike the standard allometry model, the biological meaning of the multiple-parameter power equation is not interchangeable across scales. The issue of biological interpretation and scale dependence of the three-parameters power function is presented with more details by Sartori & Ball (2009).

If we set aside the representational issue of the multiple-parameter equations for the sake of our debate, there are three potential models of the ontogenetic brain–body allometry (Fig. 1): (1) the biphasic growth model, in which the ontogenetic trajectory is biphasic, with a steep slope at the beginning followed by a shallow slope that continues to the adult phase; (2) the decelerating rate model, in which the brain initially grows fast relative to the growth of the body overall, but the rate decreases as development proceeds; and (3) the differential timing model, in which the ontogenetic trajectory follows a single multiplicative process, but growth of the body overall precedes growth of the brain. Note that the exponential equation, yet a another allometry model proposed by Packard (2019), is not considered here because it does not allow biologically meaningful interpretations of model parameters. In the following sections, I evaluate the validity of these developmental models by examining the relationship between the body mass at statistically inferred breakpoints and the body mass at two critical developmental events in mammalian ontogeny: at birth (Deacon, 1990) and at the peak rate of brain growth (Halley, 2017).

Data collection, analysis and prediction

I collected neonatal body mass data for 21 species of placental mammals from Halley (2016). The data for brain mass and body mass from fetal to adult stages are taken from Tsuboi *et al.* (2018) and supplemented by data from Halley (2016). The breakpoint between the rapid growth phase and the slow growth phase was estimated as described by Tsuboi *et al.* (2018). I retained the brain mass at the peak growth velocity from Halley (2017) and estimated the corresponding body mass using the rapid growth phase regressions of each species. The body mass at the onset of neurogenesis (i.e. Y_0 in the multiple-parameter power function) was taken from estimates shown by Packard (2019). All data were $\log_{10}$-transformed before analyses.

To evaluate the biphasic growth model and the decelerating rate model, I regressed the body mass at the breakpoint of broken-stick models against neonatal body mass or against body mass at the highest rate of brain growth, using ordinary least squares regression. If the biphasic growth model reflects real neurodevelopmental processes, the empirical data of body sizes at these events should match with the statistically inferred body sizes at the breakpoint (i.e. the regression should follow a one-to-one relationship). Given that the rate of brain growth changes continuously (Halley, 2017), an examination of a correlation between the breakpoint and the point of peak velocity would test the validity of a decelerating rate model. Alternatively, the biphasic growth model would be supported if the correlation between the breakpoint and neonatal body mass is

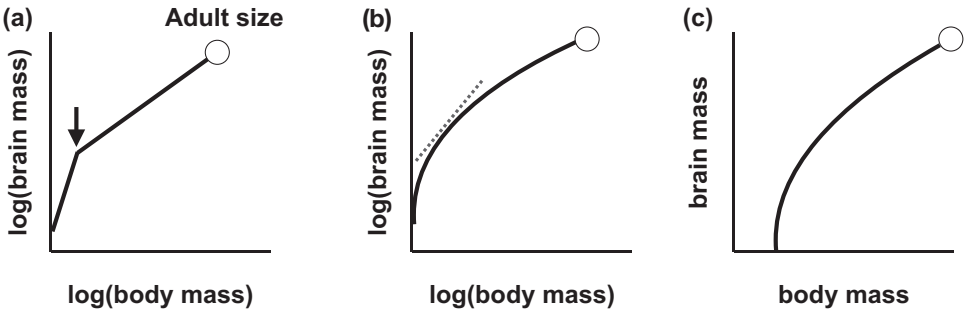

Figure 1. Schematic illustration of three potential models of brain–body ontogenetic allometry. A, in the biphasic growth model, the brain grows initially with a steep slope, followed by a shallow slope that continues until the adult size is attained (open circle). The arrow denotes the breakpoint between two developmental phases. B, in the decelerating rate model, the rate of brain growth relative to the rate of body growth decreases as body size increases. The dotted line denotes the range over which the greatest change in growth rate occurs. C, in the differential timing model, the ontogenetic trajectory follows a single multiplicative process, but growth of the body overall precedes growth of the brain. Note the difference in types of scales.

close to a one-to-one relationship, because birth is an abrupt event.

To evaluate the differential timing model, I compared the statistically inferred body mass at the onset of neurogenesis (Y_0) with the body mass of the smallest individuals in the dataset. The differential timing model would gain support if the smallest individuals observed were larger than Y_0. To facilitate interpretation, I calculated the relative error (percentage error) as the absolute difference between the empirically derived mass and the statistically inferred mass in proportion to the empirical value.

All statistical analyses were performed in R v.3.6.0 (R Core Team, 2019).

RESULTS

Evaluation of models

The body mass at the breakpoint, neonatal body mass and the body mass at the peak velocity of brain growth for 21 species of placental mammals are presented in Table 1. The bivariate regressions revealed that both the neonatal body mass and the body mass at the peak velocity were tightly correlated with the body mass at the breakpoint between the rapid growth phase and the slow growth phase (Fig. 2). A comparison of the ordinary least squares regression and a one-to-one relationship indicated that the shift between the rapid growth phase and the slow growth phase occurred consistently after the rate of brain growth had reached its peak (intercept ± SE: 0.68 ± 0.16) and after birth (0.53 ± 0.18). Estimated slopes (± SE) were 0.82 (± 0.06) with neonatal body mass and 0.92 (± 0.07) with the body mass at the peak velocity of brain development. The discrepancy of these estimates from unity was driven primarily by poor matches between empirical and statistically inferred values in the rabbit and rodents (415–602% relative error). The statistically inferred breakpoint and the body masses at two developmental events were tightly correlated (R^2; neonatal body mass, 95.1%; and body mass at peak brain development, 91.6%), but the relative error was generally high (mean; neonatal body mass, 156%; and body mass at peak brain development, 166%). Overall, these observations suggest that the breakpoints in brain–body allometric slopes are likely to reflect an underlying developmental event in early mammalian ontogeny, but exactly what causes the shift in allometric slopes remains to be elucidated.

Next, I evaluated the differential timing model by comparing the estimated body size at the onset of brain growth from models reported by Packard (2019) with empirical observations (Table 2). Similar to the other two models examined earlier, the statistically inferred body masses and the body masses of the smallest individual in each species were strongly correlated (R^2 = 99.8%; Fig. 2), but the precision of this prediction was low (mean relative error = 134%). A critical observation against the differential timing model is that, in all but one species (*Cyprinus carpio*), the smallest individuals in the dataset had already developed brains at body sizes at which the model suggests they should not yet have grown brains. Although it cannot be precluded that the mismatch is caused by imprecision in statistical inferences owing to the paucity of relevant data, it is known that neurodevelopment is one of the earliest events in mammalian ontogeny (Clancy *et al.*, 2001). This means that, even when Y_0 of the differential timing model, $Y = Y_0 + aX^b$, is non-zero, this value should be very small. In such a case, the model effectively boils down to the standard power equation, $Y = aX^b$. Thus, the differential timing model is either plainly unrealistic from a biological point of view or redundant, in that the model can be approximated well by the standard power equation.

Taken together, the statistically inferred breakpoints in brain developments are largely congruent with birth and the rate of brain growth, but not with the idea that organs start their growth at different times. This suggests that the breakpoint in ontogenetic brain–body allometric slope is likely to exists, although the mode of transition (either discrete or continuous) remains an open question. One plausible statistical model for the deceleration rate model, which I did not consider here, is a quadratic allometry model (Lemaître *et al.*, 2014; Tidière *et al.*, 2017). Based on this, the biphasic growth model by means of a broken-stick model of standard allometry and the decelerating rate model by means of a quadratic allometry model are, tentatively, the two likely models for brain–body ontogenetic allometry.

DISCUSSION

Aside from the lack of connection to biological theory, Packard's contention is problematic in the use of data and arguments taken from the literature. For example, according to Packard (2019), Ngwenya *et al.* (2013) and Lisney *et al.* (2017) are relevant to our debate, but a closer look at the data used in these studies reveals that they lack observations from the prenatal stage. Given that the biphasic allometry proposed by Tsuboi *et al.* (2018) and Halley (2016) depends crucially on prenatal allometry, these studies are not relevant to our debate. Likewise, Packard (2019) refers to several studies (e.g. Smith, 1980; Menge *et al.*, 2018) to deliver an impression that $\log_{10}$-transformation

Table 1. Body mass at the breakpoint between the rapid growth phase and the slow growth phase, at birth and at the peak velocitiy of brain growth for 21 species of placental mammals

Species	Breakpoint (g; mean ± SEM)	Neonatal body mass (g)		Body mass at the peak velocity of brain growth (g)	
		Empirical value	Percentage error	Empirical value	Percentage error
Artiodactyla					
Bos taurus	20 090 ± 2551	25 000	20	13 627	47
Ovis aries	1552.4 ± 324.0	3000	48	1258.8	23
Sus scrofa	1006.9 ± 92.9	1040.9	3	1121.8	10
Cetacea					
Phocaena phocaena	16 368 ± 2116	6750	142	–	–
Stenella coeruleoalba	12 302 ± 1106	16 100	24	–	–
Lagomorpha					
Oryctolagus cuniculus	350.8 ± 67.4	52	575	141.4	148
Primate					
Callithrix jacchus	33.6 ± 14.5	28	20	12.49	169
Homo sapiens	9099.1 ± 314.3	3660	148	2110.1	331
Macaca fascicularis	360.6 ± 112.1	326.2	11	–	–
Macaca nemestrina	385.4 ± 20.4	473	185	–	–
Macaca mulatta	442.6 ± 17.3	534.9	17	220.7	101
Pan troglodytes	5164.2 ± 488.3	1560	231	–	–
Papio ssp.	1267.7 ± 172.7	544	133	–	–
Pongo ssp.	4017.9 ± 819.7	1500	168	–	–
Saimiri sciureus	287.1 ± 31.8	109.7	162	–	–
Sapajus apella	193.2 ± 38.1	210.4	8	–	–
Trachypithecus cristatus	211.3 ± 27.3	391	46	–	–
Rodentia					
Cavia porcellus	128.8 ± 24.2	98.72	30	18.33	602
Mesocricetus auratus	10.40 ± 0.62	1.8	478	–	–
Mus musculus	6.95 ± 0.16	1.35	415	4.11	69
Rattus rattus	35.89 ± 2.56	5.191	591	13.75	161
		Mean	156	Mean	166
		Median	48	Median	124

Relative error (percentage error) represents the absolute difference between the breakpoint and the empirical value in proportion to the empirical value.

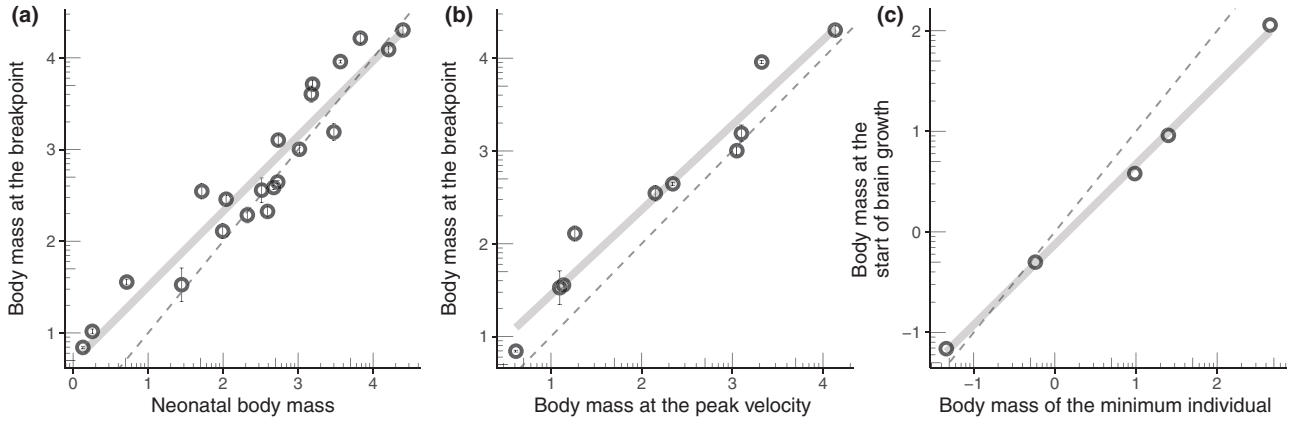

Figure 2. Plots showing the relationship between statistically inferred body mass and empirical body mass for: A, body mass at the breakpoint between the rapid growth phase and the slow growth phase and neonatal body mass (ordinary least squares regression estimates: intercept ± SE = 0.68 ± 0.16, slope ± SE = 0.82 ± 0.06, R^2 = 91.6%); B, body mass at the rapid growth phase–slow growth phase breakpoint and body mass at the peak of brain growth (intercept ± SE = 0.53 ± 0.18, slope ± SE = 0.92 ± 0.07, R^2 = 95.1%); and C, body mass at the start of brain growth and body mass of the smallest individual of the species in our dataset (intercept ± SE = −0.13 ± 0.03, slope ± SE = 0.80 ± 0.02, R^2 = 99.8%). The continuous grey line shows the ordinary least squares regression between two variables, and dashed black lines show the one-to-one relationship. Error bars indicate the standard error. Units of all axes are $\log_{10}$(grams).

Table 2. Summary of the estimated body mass at the onset of brain growth and observed fetal body mass at which brain mass was measured

Species	Model	Body mass at the onset of brain growth inferred from the model (g)	Body mass of the smallest individual (g)	Percentage error
Cyprinus carpio	$Y = 0.04X^{0.45} - 0.01$	0.046	0.069	33
Gallus gallus	$Y = 0.42X^{0.28} - 0.36$	0.576	0.5	15
Macropus giganteus	$Y = 11.19X^{0.20} - 21.31$	25.04	9.12	175
Oryctolagus cuniculus	$Y = 2.84X^{0.20} - 4.47$	9.658	3.8	154
Stenella coerulealba	$Y = 325.26X^{0.14} - 746.74$	448.8	114	294
			Mean	134.2
			Median	154

Species name and estimated model parameters are also provided. The relative error (percentage error) represents the absolute difference between the body mass at the onset of brain growth and the empirical value in proportion to the empirical value.

is problematic regardless of the context. However, those studies did not make such a radical claim. A clear demonstration of this is that Smith (1980) stated 'the point is not that there is anything inappropriate about logarithmic transformations … the argument presented here is that the exclusive and uncritical use of log-log transformation has lead to misinterpretations' (p. 99). This is essentially the argument recently brought forward by Menge *et al.* (2018), in the context of ecology. These oversights indicate that the argument of Packard (2019) needs to be viewed with caution.

CONCLUDING REMARKS

The important message illustrated by Packard (2019) is that allometry is a phenomenological model and that the validity of its underlying theory should not be taken for granted (Savageau, 1979; Stumpf & Porter, 2012). In this light, the developmental models proposed by Packard are, by themselves, viable hypotheses, but they are of little practical use owing to the lack of connection to biological processes. In biological sciences, the choice of statistical model cannot be determined by statistical criteria alone (Riska, 1991; Wolman, 2006; Smith, 2009; Houle *et al.*, 2011). This

is where I fail to agree with the purported advice of Packard (2019) on analyses of allometry in general, and the reason why the biphasic growth model remains to be a sound hypothesis for brain–body ontogenetic allometry despite potential issues.

The strength of the biphasic growth model lies in its clear biological interpretability, in that the slope at each segment represents the coefficient of relative growth in the original Huxleian sense, and the breakpoint between segments represents the body size at shifts in development. This is the core value that makes this model suitable for testing biological hypotheses, such as developmental and genetic constraints. In this study, I have given some evidence that the biphasic model provides a decent approximation of underlying brain developmental processes. However, this practice also revealed that the decelerating rate model could be a viable alternative to the biphasic growth model. A rigorous examination of these and other alternative developmental models is essential to advance our understanding of brain–body allometry. However, in doing so, one must respect the biological theoretical context of allometry (Houle *et al.*, 2011).

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