



Neonatal maturity as the key to understanding brain size evolution in homeothermic vertebrates

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What parameters determine brain size? This question is of particular interest for humans because our large brains confer outstanding cognitive abilities. The answer has long been sought in comparative analyses of brain size relative to body size (herein termed ‘brain size’) in our fellow homeothermic vertebrates – namely other mammals and birds [1–3]. Unfortunately, brain size is an idiosyncratic trait corresponding to a seemingly miscellaneous collection of traits ranging from gestation length to deception behaviour [4]. Some order can be established by attributing brain size correlates to categories of constraint (‘what traits permit or limit increased brain sizes?’) and selection (‘what traits select for increased brain sizes?’) [5]. Even so, the vast number of potential correlates has led to a plethora of (frequently mutually exclusive) hypotheses regarding avian and mammalian brain size evolution [6]. This confusion has

recently prompted calls for better integration of brain size correlates [4, 7]. In this article we argue that the latest advances in the field of brain size constraints, combined with modern techniques for tracing brain development, put an integrated framework of brain size evolution within our reach.

Constraints on brain size

The evolution of large brains is generally considered to be constrained by the cost of brain growth and/or brain maintenance. Growth costs relate to the energy supply available to the growing brain, which can be met through increases in maternal energy investment. For example, larger brains may be achieved through increased gestation/lactation times or decreased offspring number [8–12]. In addition,

basal metabolic rate (BMR) – a proxy of metabolic turnover – is often suggested as a constraint on brain size in placental mammals, although this relationship and its specific pathway have been heavily debated [10, 12, 13]. It has been argued that increased metabolic rates (or tradeoffs with other metabolically demanding tissues [14, 15]) are required because brain size is constrained by the metabolic ‘running costs’ of larger brains [14, 16]; others have suggested that higher metabolic rates increase maternal investment efficiency [10, 11]; and lastly, a recent study has argued that increased BMR caters to both development and maintenance [9].

Patterns of brain size evolution across and within mammalian clades

Several studies have attempted to provide a global explanation for brain size constraints across all mammalian species, but the topic has remained contentious [9, 17]. Isler and Van Schaik [9] recently provided an important contribution by demonstrating that the costs of increased brain sizes are defrayed differently in altricially (immature-born) versus precocially (mature-born) developing placentals. Specifically, altricial placentals differ from precocial ones in that they lack a correlation between brain size and gestation length. In addition, the costs of increased brain size are compensated by decreased litter

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Abbreviations:

BMR, basal metabolic rate; **NMH**, neonatal maturity hypothesis.

sizes in altricial placentals. We recently contributed to this debate by evaluating data on marsupials, which have been long neglected but are highly relevant as they represent the most altricial mammalian radiation [18]. We showed that, similar to altricial placentals, both litter size and lactation times correlate with marsupial brain size. However, our results also revealed a crucial difference: no correlation between brain size and BMR was detected in marsupials. Marsupials are not smaller-brained than placentals, but they do have lower BMRs, which conflicts with the hypothesis that BMR constrains brain size due to maintenance requirements [19].

In agreement with work on mammalian subclasses, studies within ordinal-level or less-inclusive clades of placental mammals show that closely-related species vary in development-related brain size correlates. For example, a recently published study on lemurs and lorises was one of the first studies to test hypotheses of brain size constraints on developmental data [20]. Interestingly, while the data strongly supported the significant correlation between BMR and brain size found in studies across primate species [21], lemurs and lorises differed in how they provide the energetic requirements for brain growth. Specifically, data from the largest-brained lemur suggested that increased metabolic turnover and a tradeoff between brain growth and intestinal growth facilitate the growth of a larger brain. Correspondingly, the results suggested that varying pre-natal growth rates determine differences in brain size within lemurs, contradicting previous assertions that brain growth rates are relatively constant across mammals [6, 22; but see 23]. Brain size correlates for lorises support an alternative strategy of longer gestation and lactation periods, rather than sacrificing the development of other tissues. This diversity of developmental strategies for brain size increase may explain why studies in Primates have found ambiguous support for a brain/intestine tradeoff [24].

In contrast to Primates, carnivorans fail to show any significant correlation between brain size and metabolic rate [17, 21]. In fact, across the order, there is support only for a positive relationship of brain mass with neonatal mass and a

negative relationship with litter size. The correlation between brain size and neonate mass, but not gestation length, corresponds with previous studies suggesting that larger-brained species must produce larger-bodied offspring [9]. As in lemurs, this suggests that variation in growth rate is a factor in carnivoran brain size evolution, although further developmental data are needed to explicitly test this hypothesis. Subclade-specific patterns within Carnivora also suggest that general patterns oversimplify the relationship between brain size and life history. For example, gestation length can correlate positively, negatively, or not at all with brain size in different carnivoran clades. Similarly, a study of bats showed another distinctive reproductive strategy in which gestation time, but not BMR, correlated with brain size [25]. In contrast, a small-scale study of a large-brained and precocial clade, toothed whales, did not support a relationship between brain size and gestation length [26], defying predictions for precocial mammals [9].

One of the most consistent correlates of mammalian brain size is litter size [9, 17, 18], supporting suggestions that litter size increases the metabolic burden on females [27]. However, double-sized litters do not correspond to half-size brains, which points towards a compensatory mechanism in brain size development. Studies in mammals have shown that maternal starvation affects other tissues more than the brain ('brain sparing') [28], and it is possible that similar mechanisms are in place across species. Again, the current lack of developmental data impedes explicit testing of this relationship.

The complex relationships among brain size, metabolic rate, life history and potential tissue tradeoffs are perhaps not surprising given that brain size has increased, and in some cases decreased, independently in many clades [29]. Furthermore, mammalian orders differ in neuronal density [30], which may also relate to differences in the relative amount of energy resources devoted to brain function [31]. General patterns of brain growth relating to neonatal maturity, maternal investment, and, in placentals, metabolic rate, are evident and well supported across higher clades. However, the examples

discussed here demonstrate that taxon-level effects and observed variation in growth rates and brain structure [32] must be considered when applying large-scale trends to more specific hypotheses concerning less-inclusive clades.

Avian brain size evolution and the structural basis of constraints on brain size

It appears evident that the most universal constraint on avian and mammalian brain size is the energy required to fuel brain growth. However, understanding the biological processes underlying the statistical correlations and the observed variation across clades remains a challenge. The pre-eminent role of the precocial/altricial distinction suggests that this could be best achieved by matching patterns of brain size evolution with data on brain development. Avian brain size evolution provides a clue because altricial birds are larger-brained than precocial birds [3, 33, 34]. This has been explained in different ways, but we find what could be termed the 'neonatal maturity hypothesis' (NMH) particularly appealing. It suggests that early independence of the hatchling requires increased structural maturity of the brain. This extensive 'wiring' may not be amenable to extensive post-hatching growth, thereby restricting brain size in precocial birds [8, 35]. This sounds mechanistically plausible, but considering that altricial and precocial mammals do not differ systematically in brain size [2, 18], how does this hypothesis relate to mammals? We suggest that the unique trait of extended placentation allows placental mammals a longer and more intense growth period in the sheltered environment of the uterus, so that postnatal growth periods become less important for the achievement of increased brain sizes [18]. The highly altricial marsupials instead rely on extensive lactation periods for growth of the initially immature neonatal brain. In contrast, avian maternal investment in prenatal brain size growth can only occur through yolk provisioning [2], and thus there is limited scope for compensating for the constraints on post-hatching brain growth in precocial birds [18].

Testing the 'Neonatal maturity hypothesis' in mammals

The NMH provides a unifying explanation for the evolution of mammalian brain size constraints and is consistent with the available developmental data. For example, the NMH predicts that a tendency towards increased brain growth in utero should be discernible with increasing precociality. This applies to placentals versus marsupials, and is consistent with the fact that gestation correlates with brain size in precocial, but not altricial, placentals [9]. Another tenet of the NMH, that placentals 'speed-grow' their offspring's brains during gestation to varying degrees, is also supported by data showing that mammalian brain growth rates tend to be higher in utero [36, 37] and differ according to placental type [23]. The NMH also predicts that, if there are no differences in prenatal brain growth rates, precocial placental mammals should be smaller-brained than altricial ones. In the only investigation to address this [26], using a small-scale dataset of toothed whales and primates, Marino [26] indeed found evidence for a negative correlation between neonatal brain maturity (measured as neonatal brain size as a proportion of adult brain size) and relative brain size. It is nevertheless possible that the NMH only coincidentally fits the few data currently available, and the model presented here may need to be extended to accommodate the many reproductive traits acting on different stages of development, as well as the exceptions to the general patterns across mammals (e.g. toothed whales). As noted above, very few studies have comprehensively traced mammalian brain growth from fetus to adult [36, 38], despite the recognized importance of the interaction between brain growth and reproductive mode for brain size evolution [9, 11, 18]. Instead, most data on mammalian brain growth [2, 33, 39] are extrapolated from a placental neonatal brain size dataset published in 1974 [22].

Additional data on brain growth will also provide opportunities for more rigorous analyses of trends in brain evolution. For example, to improve on the useful but oversimplified altricial/

precocial dichotomy, brain growth data can be used to generate continuous proxies of neonatal brain maturity, which will be more amenable to quantitative analysis. An additional issue is that size measures may not correspond consistently to structural maturity, which is important to establish in testing the neonatal NMH. One promising avenue includes direct measures of cellular brain maturity for greater resolution of structural developmental as it relates to brain size evolution [3]. The tools for relatively straightforward investigations already exist; it is possible, for example, to quantify the cellular composition of the brain [40] or to summarize markers of structural maturity from histological sections [41–43], MRI, or CT scanning using tissue stains [44].

Implications for studies on brain size selection

In addition to providing an explanation for how large brains are possible, a better understanding of the interaction between brain size and development could also clarify the purpose of larger brain size. This is because many presumed selection factors for increased brain size are related to complex social interactions, which are thought to require increased cognitive abilities and hence larger brains [5, 29]. However, social complexity also has reproductive advantages (e.g. with respect to pair-bonding [45] or allomaternal care [9]) and is thus potentially confounded with the 'constraints' aspect of brain size evolution. This has been elegantly demonstrated in a recent study on birds by Shultz and Dunbar [34], who concluded that the evolution of biparental care systems allows for increased altriciality, which in turn permits the evolution of larger brains. This contradicts the notion that pair-bonding, which frequently coincides with biparental care systems, selects for larger brain sizes as a cognitively complex trait [5, 46, 47]. The integration of basic developmental information therefore shows that some social traits may be at least partly incidental to selection for increased brain sizes by other factors (e.g. display of novel behaviours or predation pressures [48]). The distinction between selecting versus

constraining factors will be considerably more accurate once more precise predictions can be made on the requirements of the growing brain in clades with different reproductive traits. We therefore expect that by giving brain development centre stage, we will soon be able to respond to the challenge of providing a comprehensive explanatory framework for brain size evolution in homeothermic vertebrates.

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