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Developmental structure in brain evolution

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Abstract: How does evolution grow bigger brains? It has been widely assumed that growth of individual structures and functional systems in response to niche-specific cognitive challenges is the most plausible mechanism for brain expansion in mammals. Comparison of multiple regressions on allometric data for 131 mammalian species, however, suggests that for 9 of 11 brain structures taxonomic and body size factors are less important than covariance of these major structures with each other. Which structure grows biggest is largely predicted by a conserved order of neurogenesis that can be derived from the basic axial structure of the developing brain. This conserved order of neurogenesis predicts the relative scaling not only of gross brain regions like the isocortex or mesencephalon, but also the level of detail of individual thalamic nuclei. Special selection of particular areas for specific functions does occur, but it is a minor factor compared to the large-scale covariance of the whole brain. The idea that enlarged isocortex could be a "spandrel," a by-product of structural constraints later adapted for various behaviors, contrasts with approaches to selection of particular brain regions for cognitively advanced uses, as is commonly assumed in the case of hominid brain evolution.

Keywords: allometry; brain size; cortex; development; heterochrony; hominid evolution; limbic system; neurogenesis

1. Introduction

When we speak of brain evolution, what exactly do we imagine to be evolving? This is not a trick question. Natural selection, after all, acts on particular systems and capacities based on differential survival of whole organisms. If some change in brain structure is selected for, how can change be implemented? Such questions arguably have more to do with architectural constraints born of the phylogenetic history of brains than they do with some putative optimal engineering (with *optimal* defined functionally, energetically, or any way the engineer chooses). Based on a legacy of prior change, some patterns of adaptation are more likely to be hit upon by the evolving organism than others. It is our contention here that developmental processes are a primary locus of architectural constraints on brain evolution.

There would seem to be two broad models for how brains change. On the one hand, their parts might be taken to be fundamentally discriminable in function and independently variable. Brain evolution in that case would be a matter of growing a bigger auditory processing system, resource mapper, olfactory system, and so on, with the rest of the system left mostly unchanged. Alternatively, the size of the entire brain might be taken to vary in response to selection of any of its constituent parts. In the latter model, developmentally inspired architectural constraints make part or whole size dissociations inherently less workable responses to selection. (These views are necessarily simplified for the purposes of this introduction.)

Considering just the sensory and motor periphery, the case for special selection looks strong. Sensory systems can vary wildly – consider the ears of the echolocating bats, the eye-shine of nocturnal animals, the near telephoto vision of raptors, or the special chemical communication systems of many rodents. On the motor and sensorimotor side, specializations are no less impressive: prehensile tails and

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trunks, the precision grip of social-grooming primates, the palpating noses of moles. Features of the sensory and motor periphery may diverge quite strikingly in relative size and conformation, in components from the morphological to the biochemical level, and in function.

To what extent is such idiosyncratic organization also a property of the nervous system that organizes the information provided and action afforded by the sensory periphery? If one looks at the mature isocortex, one finds overrepresentation of the fovea in animals with high acuity vision in the striate cortex, overrepresentation of the "acoustic fovea" of bats in their auditory cortex, and disproportionate topographic layout of specializations like vibrissae and fingers in any somatosensory cortex. In these cases, however, there is strong evidence from developmental or adult manipulations that the sensory or motor periphery may impose its form on a "generic" nervous system (Florence et al. 1997; Gilbert et al. 1996; Van der Loos & Welker 1985).

Peripheral to central isomorphisms of the above kind are not the only sort of specialization we could consider, however. Complicated behaviors might have complex and idiosyncratic internal circuitry, from elaborated specialized capacities to single percepts or actions. We have such examples as "the song system" as a coordinated perceptuomotor system; we speak of animals as being "more visual" or "more olfactory." Complex abilities like foraging and food-storing have been shown to relate to hippocampus size and (by implication) the type of cognitive map the hippocampus can support (Jacobs & Spencer 1994). Precocial ungulates without experience (and humans with some experience) recognize a certain pattern of visual stimulation as a cliff and inhibit motion (Gibson & Walk 1960). Human infants recognize a different pattern as a face, orient to it, and reproduce its expressions (Meltzoff 1996). In looking more closely at the structure of brain evolution, we may hope to understand how the general and the specialized can cohabit in a single brain.

The predominant quantitative anatomical and allometric techniques used by evolutionary neurobiologists are differentiative. For example, in most allometric studies, the question typically asked is what part of the brain is largest in an animal with a special behavioral capacity, that is, controlling for general enlargement in brain size. In this article, we wish to turn attention back to the coordination of brain change. We want to look at the relationship of brain evolution to specialized and distributed circuits to get a better methodological idea of what might be involved in controlling for baseline changes in brain sizes. Does the brain have selectable, covarying units from the level of single circuits, structures, functional systems, or anatomical divisions? What is the range of independent variation observed at each one of these levels of analysis?

We will first review some published work on the structure of relative changes in size of gross brain parts, and the close relationship of a highly conserved schedule of neurogenesis and other neurodevelopmental events to this change in brain size. We include consideration of the statistical and methodological issues involved in determining the amount and type of variance accounted for in allometric and developmental data. We will present some new data showing how well the developmental constraint hypothesis works in predicting size changes in the di- and telencephalon, as well as instances where it does not work. Finally, we will make the argument that structural change must often precede functional allocation in the developing brain and explore some implications this has for essential structure-function relationships in cognitive neuroscience and elsewhere.

Even a complete analysis of the adult brain, using the full array of current techniques in neuroscience, will leave unexamined central questions about the essential relationship between structure and function. The study of development promises unique insights into the nature of functional architecture. Likewise, patterns of comparative brain evolution show structure-function links in a different light than that cast by any one species. The problem we concern ourselves with here, then, is establishing the precise developmental substrate on which brain evolution selects. Do the brain and its information-gathering organs divide themselves up in evolution into components, modules, or circuits that can be the independent objects of special selection, either for sensory and motor performance, or for whole coordinated chunks of motivated behavior? Or does selection attack along a broader front, working change by adjusting the parameters of a "standard" developmental program?

The analysis we have done is drawn entirely from information on relative mammalian brain sizes and neurodevelopmental events. There is reason to view mammals as a special case among vertebrates, in that the vast majority of their neurogenesis is confined to very early development and not extended over the life span, as it is in fish, amphibians, birds, and reptiles. On the other hand, issues in space allocation in brains transcend mammals, and the general issue of the segmental structure of the brain and its relationship to neurogenesis should relate to vertebrates generally. In the following discussion, we will take examples and raise issues somewhat more broadly than for mammals alone, though we make no assumptions that the detail of the patterns we see in mammals will apply directly to nonmammalian vertebrates.

2. The structure of variation in mammalian brain size

In the early 1980s, Stephan et al. published their comprehensive volumetric data set for 11 precisely delimited divisions of the brain and for more discrete nuclei and zones for a large sample of insectivores, prosimians, simians, and bats (Baron et al. 1983; 1987; 1988; 1990; Frahm et al. 1982; 1984a; 1984b; Stephan et al. 1981; 1982; 1987; 1988). The strength of this data set is the number of species analyzed, with its information on niche and classes of behavioral specialization, and its comprehensive brain coverage. It has limitations: most of the brain divisions measured subsume multiple functional systems, and the fact that measures are of volumes, which include neurons, their processes, and supporting elements of all kinds, raises secondary problems of how these related elements scale with each other and with brain and body size.

Even so, much has been learned about how brains vary from this valuable source, and it has become a playing field for two opponent approaches to comparative brain structure. One class of analysis has sought to differentiate the size of particular subregions from the overall coordinated enlargement of the brain and map those onto behavioral or niche variables. A second class of analysis has sought to

demonstrate internal covariation and structure in the evolution of brain components. Through all these analyses runs the question of the proper way to handle variance in analyses of data that have an intrinsic structure of relatedness, as all mammalian species (and, indeed, all vertebrates) have with each other.

2.1. "Correcting" for body and brain size: Niche-specific variation

Jerison's (1973; 1991) analysis of the allometric relationship between body size and brain size established many of the core assumptions and analytical methods subsequently used to investigate structural brain evolution. Brain size increases with body size at a characteristic exponential rate. The reason for this well-characterized relationship (Martin 1982) has always remained essentially unexplained, though there have been many intriguing attempts. The neural machinery for controlling muscles and for enervating the sensory surface might reasonably increase with some function of body size. However, in a medium-sized brain like a cat's, the representation of the body surface and the primary motor representation occupies less than a tenth of the surface extent of isocortex, and it is not at all clear (depending upon your model of the brain) why specialized sense organs like eyes and ears should also increase so regularly with body size (and they do – e.g., Hughes 1977).

Why aren't the basic mechanisms of action, memory, communication, and cognition scale-independent? Compare the North American ruby-throated hummingbird, with a brain size of less than a gram, with a baleen whale with a brain in excess of 5,000 grams. Both show a marvelous variety of behaviors. Both sing (the hummingbird adds a courtship dance), defend territories and mates, raise young, and migrate seasonally for long distances. The hummingbird also builds nests and solves some interesting pattern-recognition problems in finding flowers. Uncertainty over the full range of cetacean capabilities notwithstanding, there is really no justifiable metric of behavioral complexity that would account for most of the excess poundage of the whale brain.

Correcting for body weight via the "encephalization quotient" (EQ) does offer some explanatory power. The assumption is essentially that some constant ratio of brain to body size is required for a *basic* behavioral repertoire, and that additional brain may be selected for more specialized or elaborate behaviors or demanding niches. In fact, those animals with high EQs do show a wider range of behavioral complexity. Carnivores have higher EQs than their prey; among prosimians and primates, frugivores beat out folivores, and careful parents outrank the careless. In general, the bottom feeders of each vertebrate radiation stake out the lowest edge of the EQ range (Eisenberg 1981; Gittleman 1994; 1995; Jerison 1973; Stephan et al. 1988).

Stephan and other researchers employing his data set subsequently turned to a finer-grained structural analysis to see if the allometric data would support a closer mapping of behavioral capacities to specialization of brain structures. Do animals with impressive motor skills have larger-than-expected cerebellums, do nocturnal animals have larger olfactory bulbs, and so forth? (Stephan et al. 1988). We might also hope that the reverse analysis will illuminate unsuspected structure-function relationships – maybe all carnivorous animals have larger-than-expected entorhinal cortices, for example, implicating that structure in an unsuspected function.

On the first pass, this type of analysis proved disappointing. (Though researchers might have been more impressed with the correlational structure of the data that they uncovered – for example, in the way Hofman [1989] noted how precisely isocortex volume could be predicted from simple total brain volume.) What are quite obvious are the strong positive correlations of all the individual structure volumes with brain volumes, shown in their least-processed forms in Figures 1A and B (Jolicoeur et al. 1984; Pirlot & Jolicoeur 1982; Stephan & Frahm 1988). This relationship persists even if the overall effect of brain size is removed in any number of ways, from simple ratio to statistical residuals (Finlay & Darlington 1995). What is more clearly revealed is what Stephan termed the "progression index" – that each structure has a characteristic rate of change in size with increase in brain size, with the isocortex the steepest, and basal forebrain and medulla the flattest (Figs. 1C and D). This holds for even recent evolutionary events – brain size regresses overall consequent to domestication across mammalian orders, with the structures with the highest progression indices regressing the most (Kruska 1988). With this strong correlational structure in the data, accounting for around 95% of the variance in this data set (for primates and insectivores, see Sacher 1970; including bats, see Finlay & Darlington 1995), it is not surprising that it is difficult to link variation in any individual structure to niche or behavior-specific variation. For example, contrary to one of the most obvious predictions one might make, researchers found that the cerebellum was relatively larger in the slower-flying (but larger-brained), fruit-eating bats than in the acrobatic (but smaller-brained) insect-eating bats (Stephan et al. 1974).

Successes in the attempt to link more specific brain structures to behavior and niche have been found mostly with respect to the olfactory bulb and associated limbic structures. The variation in the olfactory bulb with respect to total brain size (Figs. 1B and D) is correlated with the volume of a number of other features of the limbic system. The olfactory bulb is smaller overall in simians at any brain size than in prosimians, and both simians and prosimians show a flatter slope of increase of olfactory bulb size with brain size than do insectivores and bats. These lineage descriptions map onto the nocturnal and diurnal niches inhabited by these radiations in a fairly direct way (Barton et al. 1995). Aquatic carnivores such as otters, cetaceans (Oelschlager & Kemp 1998), and semiaquatic insectivores (Bauchot & Stephan 1968; Gittleman 1991) all show reduced olfactory bulb size, so lability in olfactory bulb size is not restricted to the primate lineage.

There are three major grounds for arguing that Figure 1A exaggerates the appearance of high correlation among the sizes of various brain structures. First, the correlations that are visually inferred from Figure 1A are part-whole correlations, since a brain part is plotted against the whole brain. Part-whole correlations are well-known to be exaggerated, often substantially. Second, much of the association visible in Figure 1A may be produced by the correlation of each brain part's size with body size. Third, correlations across species can be exaggerated by treating species as independent units, ignoring the fact that a single evolutionary split, such as the appearance of primates, can affect many species. All these concerns are addressed in section 3.

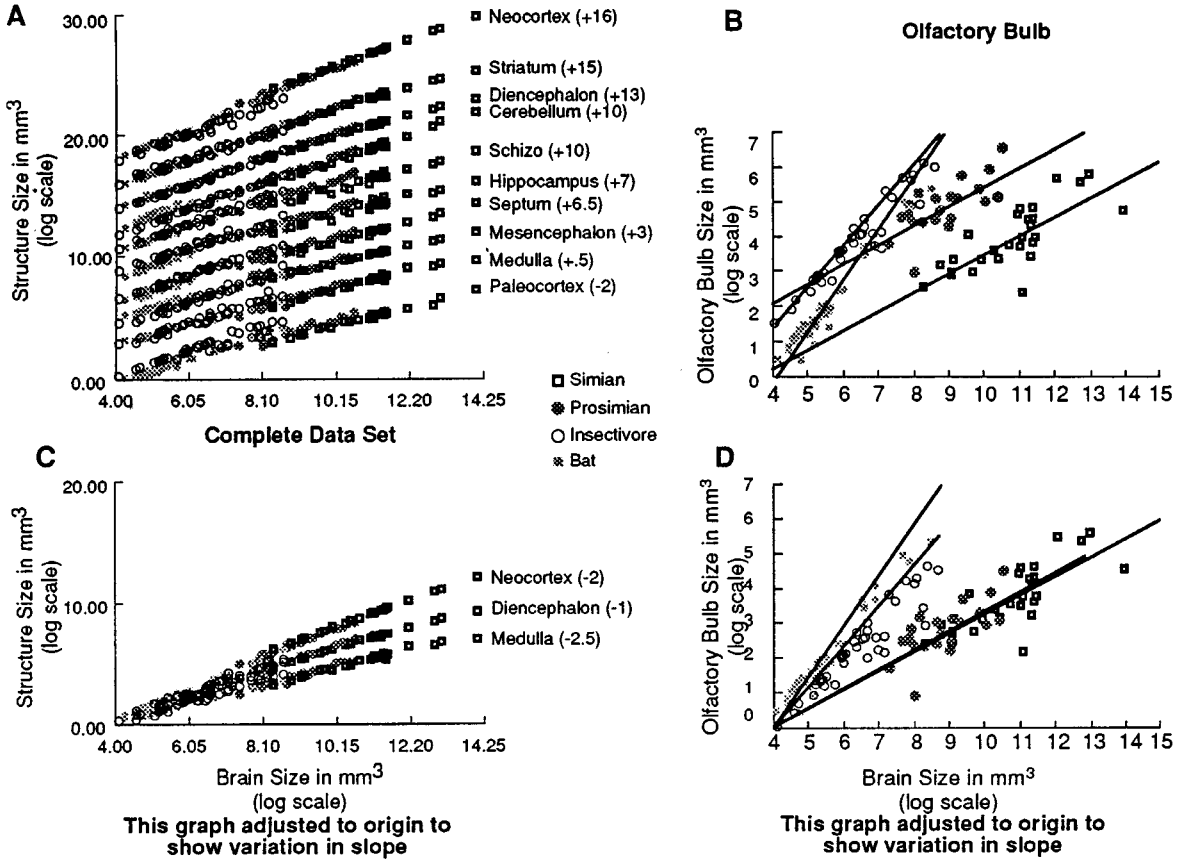

Figure 1. Scaling of brain components on total brain volume. **A:** Scaling of the volumes of brain components against brain size for the collection of bats, insectivores, prosimians, and simians measured by Stephan and colleagues, reprinted (with permission) from Finlay and Darlington (1995). The regression lines for each structure are stepped by the constant indicated in the margin, to separate them for better visualization. All axes on this and other volume/volume regressions are log/log. **B:** Scaling of the olfactory bulb on brain size for the same set of mammals depicted in (A). Note that unlike the other brain parts, both the slope and intercepts differ substantially for each taxonomic group. **C:** Regression lines for the volumes of neocortex, diencephalon, and medulla against total brain volume, this time adjusted with new constants (indicated to the right of the structure name) so as to place each intercept at the origin, so that slopes may be more directly compared. **D**: Replot of graph (B) adjusted to the origin to show more clearly that the increase in olfactory bulb volume for greater brain volume is lower for simians and prosimians compared to insectivores and bats.

2.2. Factor analytic approaches

The importance of the olfactory bulb and associated limbic structures has been demonstrated most clearly in various multivariate approaches to the Stephan work and related data sets. Using factor analysis, several investigators (Finlay & Darlington 1995; Gould 1975; Holloway 1979; Pirlot 1987; Sacher 1970) have found two primary factors, the first associated with brain size, and the second an olfactory bulb factor, loaded not only on the olfactory bulb but on a number of other limbic structures. Similar covariation can be seen in domesticated mammals (Kruska 1988). In stepwise discriminant analysis, these two measures could be used with close to perfect accuracy to discriminate simians, prosimians, and insectivores (Gould 1975). As we will describe in more detail later, a limbic factor also accounts for substantial variation in the structural development of the brain (Clancy et al. 1999). A third factor, accounting for about an order of magnitude less of the variance, and associated variously with body size, the medulla, and the cerebellum, has also been described (Finlay et al. 1998; Fox & Wilczynski 1986; Pirlot 1987; Sacher 1970). The fundamental two-factor structure of allometric brain growth, with the isocortex the most highly loaded component, also tends to associate greater-than-expected isocortex size with various behavioral capacities in primates, such as social group size (Barton 1996; Dunbar & Bever 1998) or tactical deception (Whiten & Byrne 1988).

2.3. Moving closer to functional systems

A fair criticism of all this work is that the units of brain studied are so large and intrinsically multifunctional that it is unsurprising that few direct behavior-to-brain-part links have been made. For that reason, we and a number of other investigators have turned our analysis to explicitly defined functional systems that cut across the parts of brain segmentation used in the overall analysis of Stephan's data. Like other investigators, using the more detailed analyses of Stephan and associates (Baron et al. 1983; 1988; 1987; 1990; Frahm et al. 1982; 1984a; 1984b; Stephan et al. 1981; 1982; 1987;), we have been unable to capture any more of the correlational structure of the data set by defining, for example, all visual system structures, all motor structures, or all auditory structures and seeing if a separate fit for

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those designated structures can improve the variance accounted for (with the sole and striking exception of the limbic factor). The same is true for the component structure of timing of brain development, which we will discuss subsequently (Finlay & Darlington 1995). Put another way, neither comparative structure of adult nor developing brains reveal a covarying unit, distributed across structures, that is the visual system or the motor system. In an elegant analysis of the relationship of dexterity (hooves to hands) to brain structure, Nudo and Masterton (1990) found that the amount of isocortex that was the origin of the corticospinal tract was in fact positively correlated with dexterity, but that that amount in turn was associated with total isocortex size, which accounted for all of the correlation. The result of a recent detailed analysis of the subcortical auditory system (Glendenning & Masterton 1998) was striking for the conservatism it showed in system organization across species, and for the lack of support for overall increase in the relative size of the auditory system in species one might guess to be more auditory.

2.4. Variation in single structures

Considering the dimension of size alone (we will return later to organizational changes in brains), increase in the size of individual structures has often been linked to special behavioral capacities. The size of hippocampus has been linked to range size in mammals (Jacobs & Spencer 1994) and food caching in birds (Sherry et al. 1992). The particular social system of anthropoid apes has been postulated to be associated with relative enlargement of anterior thalamic nuclei (Armstrong et al. 1987). Within the somatosensory representation of the isocortex, the increased size allotted to specialized sensory organs (whether vibrissae, trunks, tongues, or hands) has long been the most notable example of nervous system divergence, in the context of a general mammalian plan for isocortical somatosensory organization (Krubitzer 1995). The sizes of components of the song system in birds have been linked to such variables as repertoire size, though this story presents interesting complexities (Airey 1999; DeVoogd et al. 1993; Nottebohm et al. 1981;). Sex differences (which figure in both of the examples above) are far and away the most fertile area for locating size differences in nuclei associated with a range of behaviors from direct motor control to parental care (Sengelaub 1989). A virtual industry thrives in attempting to link isocortex size, cell density, fissurization patterns, and corpus callosum size with sex differences in cognitive abilities in humans, with ambiguous results (for example, Witelson et al. 1995; reviewed in Bishop & Wahlsten 1997).

One study of special note underscores the importance of knowing the absolute size of a niche-brain effect, which is often not underlined in such studies. Barton (1996) showed consistent covariation in primates between neocortex size and social group size with several other factors controlled. However, the largest difference in neocortex size that Barton observed that could be attributed to social group size was below 3%, although the range in neocortex size in his data set (from *Microcebus murinus* to *Gorilla gorilla*) was over 400:1. That 3% falls in the unaccounted variance we described previously (Finlay & Darlington 1995). For our purposes, the size of the effect is very relevant for understanding what mechanism might produce the observed difference, whether it be an increase in the number of neurons or an increase in dendritic arborization. To show that the effect on size is small is not to discount the effect, but to try to understand its context – for example, experience-related effects on the cortex volume of rats, including social enrichment, are in the 5–10% range (Rosezweig 1972).

The coverage of structures and functions in the sample in the previous paragraph is far from systematic. Overall, though, it is quite clear that while *individual* structures may show behaviorally linked variation, coordinated structural variation in spatially distributed functional systems is rarely greater than the natural coordination of the whole brain. We will further discuss how to integrate these various kinds of variation into a general picture of the development structure of brain change, after consideration of some central issues in statistical analysis of this type of data.

3. Documenting the case for coordination of brain-part sizes

Figure 1A illustrates our claim that, except for the olfactory bulb, major brain structures grow or shrink together in evolution. The analyses in this section are designed to make that point while controlling for three factors that admittedly affect Figure 1A: part-whole correlations, correlation with body size, and the use of species rather than evolutionary lineages as the units of analysis.

In this discussion, we refer to the same data set used by Finlay and Darlington (1995). This is a collection of measures by Heinz Stephan and colleagues of body size and the sizes of 11 brain structures for 131 mammalian species: 40 insectivores, 43 bats, 21 prosimians, and 27 simians, including humans. Whenever we refer here to four "taxonomic groups," we mean those four groups. Of course, these groups represent only a small fraction of all mammalian orders, so any conclusions we draw are subject to later modification.

In our first analysis, we tried to find the simplest or most parsimonious way to accurately predict the sizes of brain structures from other variables. We used three sets of "other" variables: other brain structures, body size, and taxonomy. All predictions were made by simple or multiple regression. All size variables (of the 11 brain structures and body) were used in natural log form. Taxonomy was represented by dummy variables distinguishing among the four taxonomic groups mentioned above.

Since we never predict the size of any structure from the size of the whole brain, we avoid the problem of part-whole correlations. If variation were produced primarily by a structure's association with body size, then body size would contribute. (Later we deal with the criticism that body size tends to contribute less to regressions because of intraspecific variation and measurement error.)

If variation in some structure were produced primarily by the evolutionary splits among our four taxonomic groups, then the taxonomic variables would contribute heavily to the regression. It might be objected that these groupings represent only the grossest taxonomic distinctions among these 131 species, but we respond that this is actually an advantage for "taxonomy" in our analyses, since we measure the contribution of each set of variables in relation to the number of variables in the set. Thus "taxonomy" has the best chance of making a good showing in our analyses if we

represent it by just the few most important taxonomic variables, as we have opted to do. If variables measuring differences among orders, or between simians and prosimians, cannot make an impressive showing in our analysis, it seems clear that more subtle taxonomic variables, measuring differences among families or genuses, will be even less important.

Thus, except for the problem of intraspecific variation in body size, this analysis addresses all three of the issues raised in the final paragraph of section 2.1 and the opening paragraph of this section. We conclude from this analysis that by far the most useful predictors of structure sizes are the sizes of other brain structures. We do not deny that taxonomy and body size add some predictive power, but we argue they are minor factors in comparison to the sizes of other brain structures.

For each regression we computed the familiar MSE, or mean squared error. Perhaps confusingly, MSE is not actually the mean of the squared errors. Rather it is defined as:

$$\text{MSE} = \text{Sum of squared errors}/(\text{sample size} - \text{number of parameters in the regression})$$

The subtraction in the denominator essentially corrects for the fact that the sample sum of squared errors will always decline as new predictors are added to a regression model, even if those predictors are useless in the population. Thus it is reasonable to compare the MSE values of complex models (models with many predictors) to those of simpler models.

Rather than work with MSE itself, we find it more reasonable to work with the standard error of estimate, denoted SEE, and defined as $\text{SEE} = \sqrt{\text{MSE}}$. SEE has the advantage that it is measured in the same units as the dependent variable. When this variable is the natural log of a structure size, then a SEE value of, say, 0.1 means that the structure size is predicted with a typical error of about 10% of the true size.

"Parsimony" is measured by the number of parameters fitted in a regression. This includes one regression slope for each variable in the regression, plus the additive constant.

For each of our 11 brain structures, we predict the structure in seven different ways:

1. From body size alone.
2. From body size, separately by taxonomic group. This is equivalent to using body size, group, and their interaction.
3. From the other 10 brain parts.
4. From the other brain parts plus body size.
5. Same as No. 4, with linear terms added, distinguishing among taxonomic groups.
6. From the other 10 brain parts, separately by taxonomic group. This is equivalent to using 10 terms for brain parts, 3 for group, and 10×3 or 30 for group $\times$ part interactions.
7. From the other brain parts plus body size, separately by family. Again, this is equivalent to a model using interactions.

These seven models are ranked here by complexity, with the most parsimonious first (Fig. 2). Model 1 has just two parameters: the additive constant and the slope for body size. Model 2 has eight: the two just mentioned, for each of four taxonomic groups. Model 3 has 11: 10 slopes plus the additive constant. Model 4 has 12. Model 5 has 15: the same 12 as model 4, plus three for variables distinguishing among taxonomic groups. Model 6 has 44: 11 for each of four groups. Model 7 has 48: 12 for each of four groups.

As mentioned earlier, the subtraction in the denominator of MSE makes it scientifically meaningful to compare the SEE values of complex models with those of simple models. If a more complex model has a smaller SEE value than a simpler model, that is not a statistical artifact but rather suggests that the more complex model is genuinely more accurate.

Even though it is mathematically possible for a more complex model to have a larger SEE value than a simpler model, that almost never happened in this data set, and any such effects were very small. Thus it is generally true that the very best predictions are made by the most complex models. Since the two most complex models differ from simpler models mainly in their inclusion of many interactions involving taxonomic terms, this suggests the existence of evolutionary adaptations specific to particular taxa.

We give two illustrations of this general point. The first concerns the relation between the olfactory bulb and the other structure most closely related to it as measured by correlation in size across species: the paleocortex. These two structures are very highly correlated in size in insectivores and bats, and in a scatterplot the points for the two orders fall essentially on top of each other. But prosimians show both smaller olfactory bulbs than would be predicted from their paleocortex sizes and a lower correlation between the two than is observed in bats or insectivores. Simians show both these tendencies to a much larger degree.

The second illustration concerns body size in bats. When one predicts neocortex size from body size in each of our four taxonomic groups, three of the regression slopes are nearly identical, but the slope for bats is about $1.5 \times$ that of the other groups. This seems to suggest that every additional ounce of weight is more important for a bat than for other orders, or in terms of its relation to the neocortex, every 2% increase in body size is about equal in importance to a 3% increase in other orders. Our faith in this interpretation is increased by the fact that a similar effect is observed when body size is predicted from olfactory bulb size: three of the four within-group regression slopes are almost equal, but the bat slope differs widely, so that a variable of $1.5 \times \log(\text{body size})$ has almost the same regression slope relative to olfactory bulb size as log(body size) has in other orders.

These examples illustrate the ubiquity and complexity of evolutionary adaptation. We have little doubt that many similarly interesting findings still lie hidden in this rich data set. However, we now turn to our original question: When the importance of each group of variables is measured by its contribution to regression fit *per parameter added* to a model, which groups of variables are most important?

The answer to this question appears in Figure 2. Here we show SEE when each of the 11 brain structures is predicted by each of the seven models described above. We have plotted SEE on a logarithmic scale because as SEE gets smaller, each additional 10% drop in SEE shows up as a smaller and smaller change in SEE itself. But each such drop appears equally large when SEE is plotted on a log scale.

Figure 2 is complex and must be taken in doses. The overall picture is that prediction of the olfactory bulb and medulla each follow their own unique patterns, while the remaining nine structures share a single pattern. Temporarily ignoring the olfactory bulb and medulla, as one

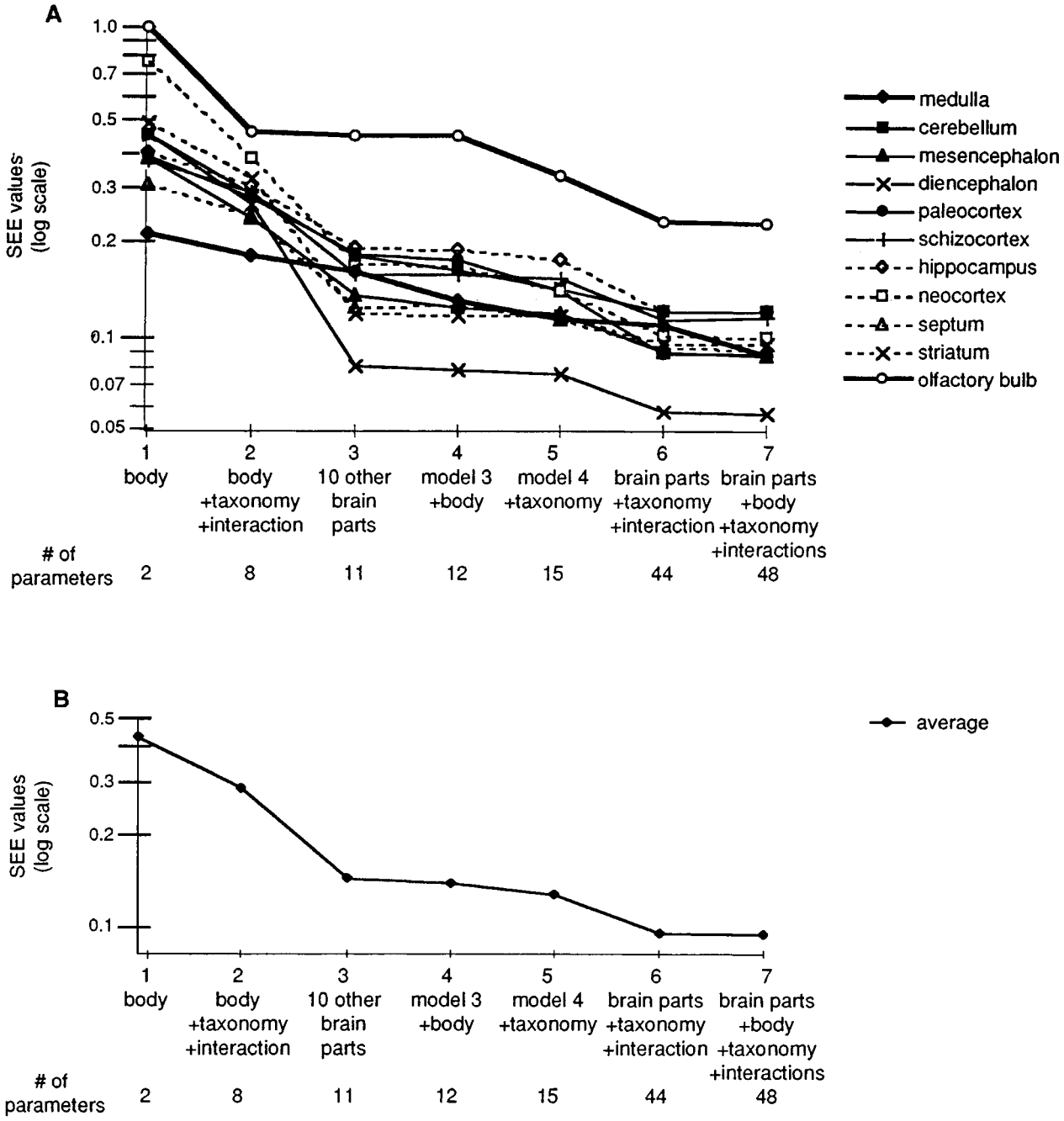

Figure 2. Relative accuracy of seven ways to predict sizes of 11 brain structures. **A:** Seven models are listed along the horizontal axis, in the order of the number of parameters in the model. The text describes the seven models more fully. The olfactory bulb and medulla (heavy lines) each have their own patterns, but the remaining nine lines are all roughly parallel. SEE denotes standard error of estimate; smaller is better. **B:** With medulla and olfactory bulb excluded, we show the average SEE values for the remaining nine brain structures. The graph shows that by far the largest improvement in accuracy comes when moving from model 2 to model 3. We conclude that when model simplicity and accuracy are both considered, the best way to predict the size of any of these nine brain parts is from the sizes of other brain parts, not from body size or taxonomic data.

moves from left to right (that is, from simple models to more complex ones) by far the largest drop in SEE values occurs between models 2 and 3. This is associated with a rather small change in model complexity: from 8 to 11 parameters, or switching from a model using body size, taxonomic group, and their interaction, to a model that completely ignores body size and taxonomic group in favor of other brain structures. As the figure shows, further declines in SEE do occur after model 3, but the only noticeable declines are associated with very large increases in model complexity, as one moves from 11 parameters to 44 or 48 parameters. Thus for these nine structures, model 3 seems to represent by far the best combination of accuracy and parsimony. As mentioned earlier, neither model 3 nor any other model gains any unfair advantage from the use of part-whole correlations, because each brain part is always predicted only from other brain parts.

The olfactory bulb follows a different pattern, in which

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the largest drops in SEE occur in moving from model 1 to 2, from 4 to 5, and from 5 to 6. All three of these moves involve just the addition of taxonomic variables, either as linear terms or as interaction terms. Thus taxonomic variables are clearly most important for the olfactory bulb.

The medulla also has its own pattern. For it, the decline in SEE is not concentrated in just a few parts of the graph; almost every increment in model complexity produces a decline in SEE. This suggests that other brain structures, body size, and taxonomy are all important determinants of medulla size.

3.1. Finding the two best predictors for each structure's size

These points can be illustrated in still another way. We created 10 dummy or indicator variables to represent every possible taxonomic division of our four taxonomic groups. Four of the 10 variables were coded 1 for one of the four groups and 0 for the other three groups. Each of the other six variables was coded 1 for a *pair* of groups – e.g., bats and simians – and 0 for the other two groups (insectivores and prosimians in this case). Thus the 10 variables together represented every possible division among our four groups, whether reasonable or not in an evolutionary sense.

Consider now the problem of predicting logged diencephalon size, across all 131 species, as accurately as possible by regression from just two variables, where the two can be chosen from any of the following: (1) logged body size, (2) the logged sizes of the other 10 brain structures, or (3) the 10 dummy taxonomic variables just described. We predicted logged diencephalon size from every possible pair of these 21 variables, and found it to be predicted most accurately from the logged sizes of the mesencephalon and neocortex.

We performed a similar analysis for every one of the 11 brain structures, finding the best two variables for predicting it from the other 21 variables just described. Even though taxonomic variables constituted essentially half of the pool of variables, a taxonomic variable was selected just once: The paleocortex and simian variables formed the best pair of variables for predicting olfactory bulb size. Body size also appeared only once: Body size and mesencephalon size formed the best pair of variables for predicting medulla size. For every brain structure except medulla and olfactory bulb, the best two-variable prediction was made from the sizes of other brain structures, even though those variables always formed just 10 of the 21 variables in the predictor pool.

3.2. More on body size

It has long been known that mammalian orders show consistent differences in brain size with body size held constant. In our data set, for instance, nonhuman simians have on the average about five times the brain size of insectivores when body size is controlled. But that leaves two questions. First, are such differences caused entirely by large interorder differences in a single brain structure such as the neocortex, or are they caused by a coordinated enlargement of all telencephalic structures, comparable to the coordinated enlargement associated with increased body size within orders? Second, can such a coordinated enlargement, controlling for body size, be observed within orders as well as between orders?

Any attempt to demonstrate such an effect must allow somehow for the well-known fact that the correlation of body size with other structures is reduced because body size is more subject to random individual variation than the sizes of brain structures (Harvey & Krebs 1990). But this argument cannot explain the pattern of correlations mentioned at the end of the previous section, since it cannot explain why body size would so consistently correlate highly with medulla size.

We also addressed the body-size theory, with its random variation corollary, through a two-stage least squares procedure. First we predicted body size, across the 131 species, from the sizes of the 11 brain structures. We took this *estimated* value as a measure of body size with random variation largely removed. This is clearly not a perfect measure of that parameter, but fortunately this measure is biased *against* a positive finding in our subsequent analysis. We then examined the partial correlations among the three telencephalic structures (neocortex, striatum, and diencephalon) with this measure partialed out. Across all 131 species, the lowest of these three partial correlations was .90. When the same partial correlations were computed separately in our four taxonomic groups, the lowest value in each group was: insectivore .91, bat .77, prosimian .88, simian .87. All these values have been rounded *down* to two digits. Thus there is clearly a high association among the sizes of these three structures that cannot be explained by their common association with body size and which exists even within the four taxonomic groups we studied. Like our other analyses, this analysis avoids problems with part-whole correlations. And the claim that these associations are produced by a few evolutionary splits cannot explain why these relations appear so consistently in each of our four taxonomic groups.

3.3. A three-factor model

Given that other brain structures are the most useful predictors for all structures except the medulla and olfactory bulb, can we come up with a plausible model of brain structure based on just those variables? We repeat that one does lose some real predictive power by such simplification, but describing such a model nevertheless appears useful.

We propose a three-factor model of brain structure. Each of these three factors is anchored, and indeed defined, by a single structure or object. In order of importance for predicting the sizes of various brain components, the three factors are a telencephalic factor anchored by the neocortex, a limbic factor anchored by the olfactory bulb, and a somatic factor anchored by body size.

In our model, each factor also has one or two secondary structures. The telencephalic factor has the striatum and diencephalon as secondary structures, the olfactory factor has the paleocortex, and the somatic factor has the medulla. This leaves five structures (hippocampus, cerebellum, schizocortex, septum, and mesencephalon) not clearly identified with any one factor. Even the secondary members of each factor are influenced at least slightly by the other factors. The primary members, by definition, are not so influenced, since the factors are simply defined as those structures.

The utility of the three-factor model is illustrated by some simple statements. In each of our four major taxonomic groups, body size correlates more highly with

medulla size than with any other structure size, and olfactory bulb size correlates more highly with paleocortex size than with any other structure size. Nevertheless, in each group, each of the three telencephalic structures correlates more highly with the other two telencephalic structures than it correlates with either body size or olfactory bulb size.

4. Striking conservation of the order of events in development and its significance for brain evolution

We now turn our attention back to the first observations of Jerison and Stephan, which must rank among the most significant in neuroscience:

1. Increased general "encephalization" is associated with greater behavioral complexity.
2. Enlargement of brain parts is highly coordinated and predictable.
3. Different brain components enlarge with different slopes compared to brain size.

We suggest that these facts argue for a way of viewing brain evolution that does not share the assumptions of the essential nature of structure/function relationships held by most researchers. The effect of the slope of structure enlargement with brain size on the relative sizes of brain parts is massive – the percent of brain mass that is isocortex goes from under 15% in the smallest mammalian brains to over 90% in cetaceans. Just why is the isocortex so systematically and preferentially enlarged? Is it because of some particularly advantageous aspect of its structure, such as its layers or transmitter complements? We might further ask why the enlargement of each and every structure has its own characteristic slope.

There is no doubt that this regular enlargement of the brain carries a cost to the organism, and must confer some benefit; the metabolic rate of brain tissue is nine times higher than the average mass-specific rate of the human body (Aiello & Wheeler 1995). A curious feature of primate evolution is that the basal metabolic rate does not increase as it should with increasing brain mass. To balance the energetic budget, another expensive tissue needed to be sacrificed, and that appears to have been intestinal length. Less elaborated intestines require that higher-quality food be found, which in turn might require greater memory for foraging or coordinated predation. By whatever evolutionary route this enlargement occurred, it suggests that the amount of brain mass is important for terrestrial mammals, and there is every reason to think the brain should be configured optimally for use. (For very large marine mammals, interestingly, the amount of brain tissue produced obligatorily by its relationship to body size may become insignificant compared to body mass, and it may be possible for large cetaceans to carry more brain than they "need.")

The fundamental force driving change in brain size is the number of neurons, coupled with the amount of body the neurons must enervate, directly or indirectly. The somal diameters of some cells, particularly those with long-range connections, varies somewhat with brain size – for example, the pyramidal cells of the cortex of an elephant are a little more than twice as large as those of a mouse. The volume of their connections varies substantially more (Purves 1988). The volume of connections and requirements for supporting glia and vasculature, when they have been studied, can be seen as a regular functions of total neuron number (Murre & Sturdy 1995). We have chosen to concentrate on the factors that control the number of neurons in phylogeny. The number of cells in a structure can increase either via change in the rate at which precursor cells are produced or in the length of time over which they are produced. We have investigated both of these possibilities, beginning with changes in duration, measured by determining the peak of "neuronal birthdays" in the structure or cell group under consideration. Early in the development of the nervous system, each precursor cell located in the ventricular zone divides and produces two daughter cells, each of which can further divide. These symmetric divisions produce precursors whose numbers increase at an exponential rate. The birthday of a neuron is said to occur when a precursor cell divides "asymmetrically" and the resulting cell migrates from its initial position in the ventricular zone of the neural tube to a distant position, where it differentiates into a neuron. The time from conception to the peak of neuronal birthdays in a structure is a measure of the duration of cytogenesis for that particular structure. The longer peak birthday is delayed, the more precursor cells can be produced, which will increase the size of the particular structure. Therefore, if a single structure in the brain were to gain more cells by this method, its peak of neurogenesis would be delayed.

We initially examined data on peak neurogenesis for 51 separate structures or cell groups in seven laboratory animals for which neuronal birth dates were adequately known. Our strategy was to find the simplest possible linear model to capture the alterations of schedules of neurogenesis across species, which ranged in duration of neurogenesis from less than 20 days in the hamster to over a hundred in rhesus; residual variation unaccounted for by this model would be the potential source of variation in brain development that might produce "brain speciation." This model is $Y = \ln(PC \text{ days} - 7) = SP + ST$ (later work increasing the number of species and events altered the constant to 5.37; Darlington et al. 1999). That is, we derived from our data a score for each species (SP) that conveniently represents its duration of neurogenesis, and a score for each structure (ST) that represents the characteristic order of generation of the structures across species. (We found we predicted log of days better than days; the subtraction of the constant essentially finds the true zero for the scale of early neural events, 5–7 days after conception.)

The correlation between observed and predicted Y-values is .988, indicating that the order of neurogenesis is very precisely conserved across the animals we initially examined (four rodents and the possum, cat, and rhesus macaque). This result is of course quite consistent with the prior analyses of extreme conservation of the relative size of brain components, and also with a prior analysis limited to the visual system by Robinson and Dreher (1990). Yet the strength of the relationship is remarkably robust.

4.1. The limbic system

The two-component structure that appears in the analysis of structure sizes – a whole brain factor versus a limbic factor expressed most strongly in simians and prosimians – is reflected in detail in the pattern of neurogenesis. Note in Figure 3A how the slope of increase in size for the two ex-

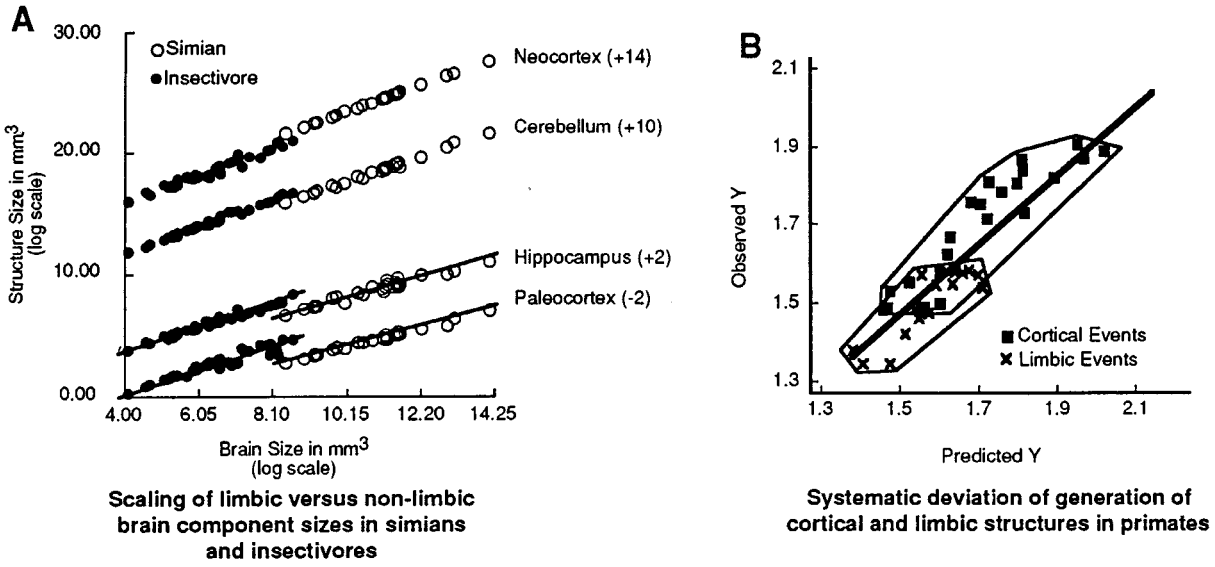

Figure 3. Scaling of cortical and limbic volumes with total brain volume in insectivores and simians compared to relative time of generation. **A:** The regression lines for neocortex and cerebellum are compared to hippocampus and paleocortex for insectivores versus simians to show that simians have a smaller-than-expected volume of limbic structures with respect to brain size, and that the volume of limbic structures increases with a lesser slope with brain volume (taken from Fig. 1A). Regression lines are again stepped arbitrarily to group neocortex and cerebellum together, and hippocampus and paleocortex. **B:** Deviations of the time of neurodevelopmental events in primates for limbic and cortical structures compared to other mammals, including rodents, marsupials, and carnivores (reprinted from Clancy et al., *Developmental Science* 2000). Compared to other mammals, neurodevelopmental events occur systematically earlier for limbic structures in primates and later for isocortical structures. Primate regression residuals are plotted against log-adjusted predicted days (Y) to depict variability in neural events in cortical and limbic areas when using dates predicted by the unadjusted original model.

ample structures of the hippocampus and paleocortex is higher in insectivores and lower in simians, while for isocortex, the pattern is reversed. In our original paper, we noted that the onset dates for neurogenesis of limbic system structures were systematically advanced in the rhesus compared to the rat (Finlay & Darlington 1995). More recently, using an extended data set that includes humans (Clancy et al., in press; Darlington et al. 1999), we found that we consistently overestimated the time of developmental events in the limbic system for primates (in this data set, the rhesus macaque and humans) and underestimated the time of events associated with generation and wiring up of the isocortex (Fig. 3B). Modification of the model for primates produced a better fit (Clancy et al. 1999).

The facts that the one consistent deviation from whole-brain predictability was the limbic system, and that neurogenesis is altered in primates in the predicted manner to produce a smaller limbic system, supports our proposal of the way development can be altered to produce larger or smaller structures. In mammals, the distributed components of the limbic system can all be labeled with a marker protein associated with that system (LAMP, see Levitt 1984). This marker raises the possibility that a single molecular signal might modulate neurogenesis in a number of spatially separated cell groups. No such coordinating molecular marker has ever been found for any other functionally defined system, like the visual, auditory, or motor systems. Nor do these systems show any evidence of coordinated neurogenesis. The isocortex, unlike the limbic system, is not distributed spatially, and the problem of its coordination is less complicated. The terminal neurogenesis of its component neurons might be systematically delayed in primates by a known molecular mechanism, such as later expression of the symmetry-breaking Notch protein (Cepko et al. 1996).

4.2. Late equals large

The most important finding in the comparison of schedules of neurogenesis and brain size is the simple relationship between how structures increase in relation to brain size (the slopes of the curves in Figs. 1A and C) and the order of neurogenesis. Structures whose neurons are born late get disproportionately large as absolute brain size increases. The reason for this can be appreciated in schematic Figure 4. The three events A, B, and C, when transformed from the schedule of the mouse (left) to the schedule of a monkey (center) undergo a nonlinear rearrangement. The neural precursors for the last structure C are in production for about 80 days in the monkey versus 18 in the mouse. Note that this assumes that the onset of precursor production is fairly synchronous across species, and that the rate of neurogenesis is similar in this set of eutherian mammals. Both of these assumptions have empirical support, as we will discuss more fully later.

4.3. Extension of the developmental model to more types of developmental events and more species

Recently, in collaboration with Dunlop, (Darlington et al. 1999), we increased the number of eutherian (placental) species studied from six to nine (including humans), the number of metatherian (marsupial) species from one to six, and the number of developmental events on our scale from

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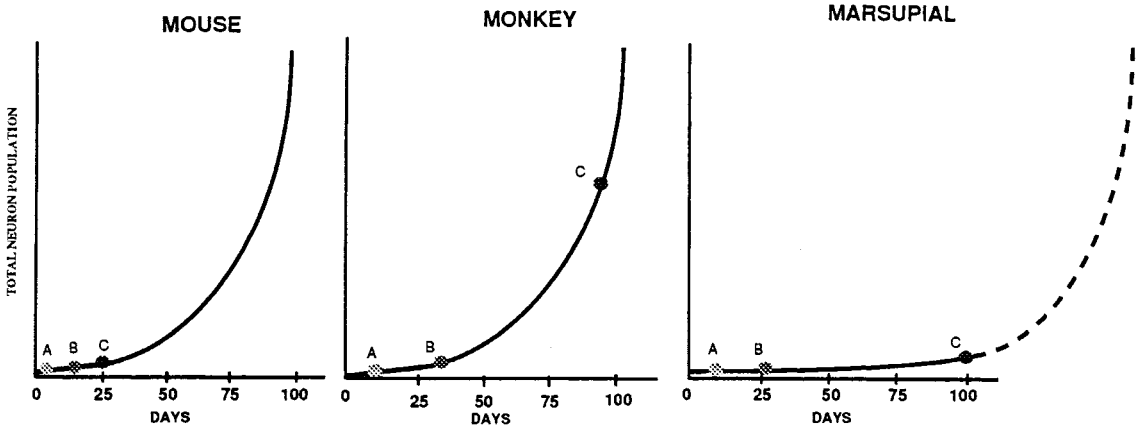

Figure 4. Lengthening of the duration of neurogenesis predictably affects numbers of neurons in comparable structures. (Reprinted from Finlay et al. 1998, *Journal of Comparative Neurology.*) Schematic representation of time of peak neurogenesis of three brain structures A, B, and C for the mouse, monkey, and a marsupial. The mouse and monkey move on the same curve of neuronal production, and the monkey's extended neurogenesis causes late-generated structures to be enlarged predictably. Marsupials have the same event order, producing brains of different sizes, but the pace of neuronal production is slowed overall.

51 to 94. Using data published by Robinson and Dreher (1990), Ashwell et al. (1996), and Dunlop et al. (1997), we expanded the list to include not only neurogenesis, but also other commonly measured events like cell death, axon extension, formation of commisssures, and segregation of overlapping projections. First, we found that there was no difference in the predictability of neurogenesis versus those events associated with forming and refining connections: Both proceeded on the stereotyped plan we had already described for neurogenesis. Second, the rate of neuronal production was characteristically slower in marsupials, which require considerably longer periods of neurogenesis to produce comparably sized brains than do placental mammals (Fig. 4). The event scale derived from eutherian data also works for marsupials, though the latter group exhibits a different relation between scale values and time. The marsupial slowdown is particularly marked for later developmental events. We think it quite likely that slowed development will not only be characteristic of metatherian mammals, but also will be found for single species or related groups with slowed maturation among eutherians.

5. Deep structure in nervous system scaling: From lampreys to language

One conclusion of this work is that big isocortices may be spandrels – by-products of structural constraints for which some use is found later (Gould 1997). The reason that the isocortex gets unusually large and the medulla stays unusually small is that the former is simply produced later by the rules of brain development. None of the intrinsic virtues of isocortex, such as the oft-cited laminar structure or multimodality, caused its disproportionate enlargement.

Why is the order of neurogenesis the way it is? Is it a chance vestige of the sequence of events in early mammalian divergence, or it is orchestrated by something deeper? To address these questions, we made use of a fairly recent recharacterization of the segmental structure of the forebrain: the prosomeric model (Finlay et al. 1998). Here the segmental relationships of the topologically tortuous forebrain (Rubenstein et al. 1994) are found from the the expression of homeobox genes and others. The prosomeric model demonstrates segmentation with respect to the initial neural tube, giving every mature structure a location on the anterior to posterior and dorsal to ventral (or basal to alar) axis of that tube. Everything that arises from a single location on the neural tube is a single point in an analysis of prosomere-based patterns of neurogenesis, which is somewhat different from the cell-group and nucleus-based analysis we have described so far.

For example, for any tangential location in the isocortex, events of interest extend from the first generation of the sub-plate to layers 2–3; for the retina they extend from the first retinal ganglion cells to rods. For some areas of the neural tube, most notably the nuclear regions of the neuraxis, we were less likely to know all the neural progeny of a single neural tube region. Still, we included what was available, albeit with the awareness that total duration of neurogenesis is likely to be underestimated due to missing data for parts of the neuraxis giving rise to diverse nuclei, as in the diencephalon. Figure 5 shows a schematic of the total duration of terminal neurogenesis plotted onto the anterior-posterior and basal-alar axes of the prosomeric model, using combined data from the rat and monkey normalized into a single time frame.

As is clear, there is a strong relationship between the position on the prosomeric axes and duration of neurogenesis: The more alar and anterior, the more protracted neurogenesis is. This bivariate regression accounts for approximately 50% of the total variance, with some interesting exceptions, most notably the cerebellum. The same characterization can be made for the end of neurogenesis, but not for the beginning: Overall, most positions in the neuraxis begin generating neurons at about the same time, but anterior and alar positions contribute neurons much longer. Rephrasing in terms of the cell cycle, the "Q" or quiescent fraction of the cycling population stays lower longer in alar and anterior positions. This allows the precursor pool in these regions to proliferate at a higher rate, producing larger structures as the duration of embryogenesis is extended.

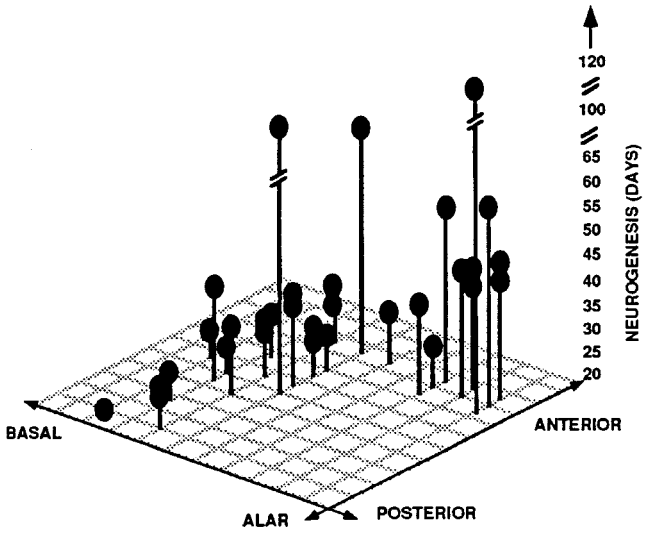

Figure 5. Duration of neurogenesis is predicted by position on the embryonic neural tube. (Reprinted from Finlay et al. 1998 *Journal of Comparative Neurology.*) Termination of neurogenesis by location anterior to posterior and alar to basal in the neural tube organized according to the prosomeric model, combining data from the rat and the monkey. Structures plotted are: (posterior to anterior, basal to alar) Row 1, cranial motor nuclei, cranial sensory nuclei, vestibular nuclei. Row 2, inferior olivary nuclei. Row 3, cochlear nuclei. Row 4, pontine nuclei. Row 5, locus coeruleus, deep cerebellar nuclei, Purkinje cells, granule cells. Row 6, red nucleus, substantia nigra, raphe complex, inferior colliculus, superior colliculus. Row 7, lateral geniculate nucleus, medial geniculate nucleus. Row 8, ventrolateral geniculate nucleus, reticular nuclei. Row 9, amygdala, dentate gyrus, granule cells, CA-1–2. Row 10, globus pallidus, caudoputamen, subplate, and cortical layers 2 – 6. Row 11, anteroventral, anteromedial, and anterodorsal nuclei; suprachiasmatic nucleus; ventroposterolateral and ventrobasal nuclei; retinal structures; magnocellular basal forebrain; preoptic nucleus; nucleus accumbens; subicular structures; septal nuclei; olfactory structures; and entorhinal cortex.

A substantial proportion of the extreme conservation of timing we see in mammalian development (but not all!) may therefore be referred to the basic spatial organization of the two neuraxes. This organization certainly precedes mammals, and, in part, it precedes vertebrates. Language locates itself in the human brain in the progeny of the part of the neuraxis that could have been predicted to become unusually large by its position in the first jawless vertebrates. So, the pattern of duration of neurogenesis we see derives in large part from a very fundamental feature of the intrinsic organization of the embryonic neural plate. We should emphasize that this is not a claim that every vertebrate has the same sequence of neurogenesis – there are in fact some interesting transpositions of this order in different vertebrate radiations, resulting in some quite divergent brain structures. Much, however, is conserved.

6. A closer look at the relationship between birthdays and structure size

The foregoing analysis has taken a broad view of the relationship between birthdate of a structure and its pattern of size change with brain size across species. Our general claim is that if we know the order of neurogenesis of any class of structures in one species, we should be able to predict the pattern of relative change in size of the nuclei for any other set of mammals, whether or not the species are closely related. This should be useful, since there is excellent and systematic knowledge about neurogenesis in the rat from the work of Bayer and Altman (1987). The rat data can be compared to extant allometric data for a variety of other species to see how our predictions hold up on a smaller scale of brain nuclei. Using "found" data to explore this hypothesis is instructive, though differences in nomenclature of neuroanatomical regions used by different investigators makes comparisons somewhat imprecise and precludes much statistical analysis. We will discuss two examples from the neurogenetic and allometric literature we could locate.

6.1. Volumetric reconformation of the amygdala in primates and insectivores compared to generation of the amygdala in the rat

The amygdala is a complex structure with multiple subdivisions. Bayer (1980) has studied the genesis of subdivisions of the amygdala and gradients within those subdivisions in the rat in great detail, while Stephan et al. (1987) have studied changes in the relative volumes of corresponding subdivisions of the amygdala across insectivora and primates. The amygdala shows notable volumetric alteration across brains and can be divided into two regions, the centromedial group versus the corticobasolateral region. The latter increases much more steeply in volume with brain size than the centromedial group – it comprises only 52.4% of the amygdala in insectivores versus 81.1% in *Homo sapiens.* The order of birthdates in the rat predicts this relative enlargement. A weighted mean for the birthdate of these regions was derived from the Bayer data by averaging over nuclei, with each nucleus weighted by its relative volume in the rat. (The same order of neurogenesis is conserved in the monkey, though the manner of data presentation does not permit the semiquantitative analysis done here [Kordower et al. 1992].) For the rat, the mean peak day of neurogenesis for the lesser scaling centromedial group was 14.7, while the mean peak day for the corticobasolateral group was 16.1. This is a large difference, considering that the complete range of all amygdalar birthdays in the rat is embryonic day 13 to 20.

6.2. Changes in the relative volumes of thalamic nuclei in hominoids versus genesis of the same nuclei in the rat

Armstrong has done an extensive quantitative study of the changes in the relative volumes of thalamic nuclei in hominoids. With a sample including two gibbons, one gorilla, one chimpanzee, and three human brains, she looked at which nuclei increased in volume at greater, equal, and lesser rates than the volume of the remaining thalamus (Armstrong 1979a; 1979b; 1980; 1981; Armstrong et al. 1987). The goal of these studies was to map thalamic nucleus volume onto social niche. In this analysis, we ask if the rate of change in volume of the thalamic nuclei can be predicted simply by their relative order of neurogenesis in the rat (Altman & Bayer 1988a; 1988b). A plot of the peak day of neurogenesis in the rat versus the slope of increase of the volume of each nucleus with respect to thalamus size

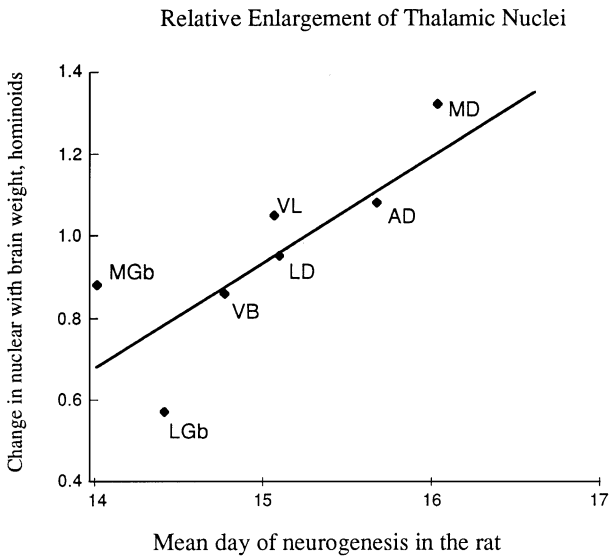

Figure 6. Late equals large: Relative enlargement of thalamic nuclei in anthropoid apes is predicted by the order of neurogenesis of the same nuclei in the rat. Order of generation of thalamic nuclei was derived from the published work of Bayer and Altman. The relative increase in size for the same nuclei with respect to changing thalamic volume was determined from the published work of Armstrong, as cited in the text. MGb, medial geniculate body (primary auditory); LGb, lateral geniculate body (primary visual); VB, ventrobasal nucleus (primary somatosensory); VL, ventrolateral nucleus (motor); AD, anterodorsal nucleus (limbic);MD, mediodorsal (frontal).

for the nuclei studied in both cases is shown in Figure 6. There is a strong positive relationship between the two, with the partial exception of the medial geniculate nucleus, which increases in size at a greater slope than predicted. Because the pulvinar and lateral posterior nuclei appear to derive from different embryonic origins in the rodent, ape, and human, it was necessary to omit those structures from this analysis (Ogren & Rakic 1981; Rakic & Sidman 1969).

Therefore, despite the fact that thalamic nuclei have a much clearer structure-to-function map than larger units like the isocortex or cerebellum, simple order of neurogenesis remains a strong predictor of size. This point is all the more compelling in that it holds across such wildly dissimilar species.

6.3. A caveat about the scaling of layered structures like the retina and isocortex

The relative numbers of cells in individual laminae of layered structures have proven to have a more complicated relationship to birthdate than "late makes large," though they fit the pattern generally. In these cases (Cepko et al. 1996), a single progenitor area in the ventricular zone with multipotent precursor cells gives rise to a region that changes in both its tangential extent and its depth as overall brain size changes. In addition, the rate of cell proliferation and the mechanism that assigns a cell to a *type*, which can be synonymous with layer, may be functionally dissociated (Artavanis-Tsakonas et al. 1999; Cepko 1999). The changing geometry of a layered population is complex, though it can and is being modeled. A full discussion of the processes connecting cell proliferation to cell type is beyond the scope of this review.

The relationship of extended proliferation of an area of the neural tube to the variable size of the resulting structure is thus best applied to whole nuclei or brain divisions that derive from identifiable areas of the neural tube, including the divisions first analyzed in the Stephan data set, or the thalamic nuclei described above.

7. Functional considerations and the structure of brain growth: Return to whales and hummingbirds

In the preceding sections, we have basically described four kinds of growth of the brain that can be statistically distinguished and are supported by both the developmental and allometric literature. The first is the coordination of brain size with body size: The brain enlarges predictably with body size producing no change in EQ, and perhaps little or no increase in behavioral complexity, such as memory capacity, formal problem solving capacity, and the like (tigers vs. housecats). Second, the entire brain may grow while body size is held constant, increasing EQ. This is the type of growth that has been associated with generally enhanced behavioral and cognitive abilities (Jerison 1973). In both of these two cases, the brain appears to grow in the coordinated, predictable, but nonlinear manner we have described with late generated structures increasing in size at a greater rate than early generated ones (though it will be interesting to see if these two patterns may be distinguished in any further ways). The first type of growth may produce size differences of many thousandfold. The smallest shrew brain in our data set is .0584 gram, while a baleen whale has a brain of over 5,000 grams – a ratio of about 100,000 to 1. The second type of growth generally appears to produce ranges of about 10-fold. This not only was the case for the insectivore/primate/bat data set we analyzed, but also seems to be generally true for all the vertebrate radiations (Northcutt 1981). The third type of growth is what we have described for the limbic system, whose size may vary relative to the brain as a whole, even with brain and body size held constant.

The fourth type is the independent variation of individual brain parts, the "unaccounted-for variance" of our model. Including all sources of error, the variation of individual structure size at any particular brain size did not exceed two- to threefold. Deviations in the large collection of auditory nuclei observed across species by Glendenning and Masterton (1998) were of this nature – rather than wholesale enlargement or reduction of auditory nuclei, particular nuclei deviated from the rest in different species. Induced experiential effects on brain weight and cortical thickness fall generally in the range of 5–10% (Rosenzweig 1972) and could account for some of the variation observed in this range. Independent variation of individual brain parts has often been associated with a specific behavioral advantage, like foraging ability (Jacobs & Spence 1994). The *limbic factor* presents a puzzle here. The limbic factor is most often associated with the loss of olfactory ability in principally diurnal primates, but not with any direct behavioral advantage. Since the structures influenced by the limbic factor are decidedly not all olfactory (such as the hippocampus), it would be interesting to determine if there is

any behavioral advantage conferred by other features of a large limbic system. Taking the example of foraging rodents above, one might predict that an insectivore might do better at spatial memory in foraging than a comparably brain-sized small primate.

Our ideas bear some similarity to the views of Aboitiz 1996, though they also differ in certain ways. Aboitiz distinguishes between "passive" and "active" evolutionary brain growth. He suggests that passive growth is associated mainly or entirely with increase in body size, produces little or no increase in processing capacity, and follows a "conservative allometric rule." Active growth is in response to cognitive selection, may affect just one or a few parts of the brain, and increases computational power. He makes other distinctions between the two types of growth that are not germane to the present discussion.

We believe Aboitiz has made an important contribution, but our own views differ from his in at least three ways. First, we agree that a brain part, or the entire brain, may grow as a secondary consequence of some other growth, such as body growth. However, we hold that neural material so added may later be pressed into service – an important feature of a "spandrel" – even if it takes a very long time to do so. The term *adjunct* growth may capture this property more fully than *passive.* Second, we hold that adjunct growth of brain parts is not always adjunct to body growth. Rather, the entire brain may grow in response to evolutionary demand for greater processing power, producing adjunct growth in many individual parts of the brain. Such growth may be associated with some increase in body size but not be adjunct or secondary to that increase. Rather, the causal relation may go the other way – a larger body may be needed to safely carry such a large brain, making body growth secondary to brain growth. Third, we are not as convinced as Aboitiz seems to be of the significance of growth in just one brain part or system (other than the limbic system, which seems to be a special case). There is such variation of individual parts, as we have described above. As we have said before, this is substantial in one sense, but is still trivial in comparison to the many-1,000-fold variation in structure sizes produced by other mechanisms.

We have given here a mechanistic account as to why the brain grows in a coordinated fashion, and why some parts of the brain increase in size at the expense of others. We have no definitive answer as to why this is an advantageous way to organize the brain, but we will offer a speculation.

Why do all sensory systems and brain parts scale so resolutely together? Why do whales and hummingbirds have so similar a range of capacities? Perhaps the answer lies in the distributed nature of sensory processing. If each sensory and cognitive system is a separate module that produces some sort of calculated output, like an *on* or *off* decision, its size does not matter, as long as it influences the circuit. However, in widely distributed systems where many sensory and computed systems are feeding input into a decision, a minority input, in terms of simple volume of connections, might fail to retain any voice. Therefore retinal neuron number must scale with the number of neurons in the skin, or the number of neurons in the cochlea with all the multiple sensory inputs to structures like the superior colliculus, to remain influential in making orienting decisions.

Conversely, functions do migrate within the brain with the changing size of brain parts – the best example of this is the "corticalization" of many functions that are carried out in the midbrain in smaller-brained animals that become dominated by the isocortex in primates. We argue that the development of the brain acts to keep some kind of volumetric parity between sensory and motor components of its input (unless deletion of one is actually desirable, as in the olfactory or limbic system). In contrast, development is noncommittal about the location in the brain where computations should occur and lets those volumes vary widely with respect to each other. Better understanding of these dynamics will only be possible when we know much more about the properties of distributed neural systems.

8. Conclusions and implications: A legacy of evolvability

There are several ways in which the results of this work might seem counterintuitive. The relative metabolic expense of neural tissue would seem to make adjustment of global growth contingencies an inefficient mechanism for increasing the size of particular subsystems. Insofar as the adult brain is functionally differentiated, it seems reasonable to expect selection pressures to act directly upon areas most relevant to adaptive behaviors. Indeed, one might expect the energetic demands of brain tissue preferentially to disentangle the developmental fates of these systems, insofar as organisms with brains that are just big enough, in just the right ways, might bear the advantage of lighter metabolic loads over the globally boosted competition. Gould articulated the present consensus when he argued, "The concept of 'mosaic evolution' . . . refuted the notion of harmonious development by affirming that individual organs could have independent phyletic histories, despite the evident correlation of parts within any organism. Correlations are no more immutable than species themselves" (Gould 1977).

While correlations may not be immutable, they appear to be surprisingly resilient with respect to brain size evolution. Indeed, the model presented here is entirely consistent with a number of important theoretical frameworks of current developmental biology. First, it underlines the relevance of ontogenetic processes to any deeper understanding of how organisms evolve; natural selection does not do its work on some equipotent substrate, but on a complex mechanism with a history of previous change that makes some adaptations more "workable" than others. As Gould also noted, *heterochrony* is a "pervasive phenomenon among evolutionary processes" precisely because it is such a productive mechanism for working disparate changes on the developing organism, from recapitulation (immature descendants resemble adult forms of their ancestors) on the one hand, all the way to paedomorphosis (mature animals resemble their immature ancestors) on the other. As we have seen, heterochrony in the evolution of brain size is manifested in adjustment of a relatively simple nonlinear function – or linear with respect to $Y = \ln(\text{days} - 5.37)$ – that determines the timing of terminal neurogenesis. This adjustment has almost exactly predictable effects along the course of differential growth described by the prosomeric model. Though such nonlinear functions are seldom the first models considered by researchers, they are commonly seen in natural processes and arguably underutilized by students of development (Elman et al. 1996).

Another way of thinking about historical contingencies on evolutionary change is to acknowledge that not only physical and behavioral traits are under selection, but also the processes that produce the traits. Developmental mechanisms that are both robust and flexible are often in the best position to "solve" adaptational problems, with the consequence that evolution tends to conserve those mechanisms. This is the essence of von Baer's explanation for the similarity of embryonic forms treated by Haeckel's *biogenetic law.* More recently, notably in Gerhart and Kirshner (1997), the concept has gone under the term *evolvability,* or the capacity of organisms to transcend ontogenetic constraints by conserving robust and flexible developmental mechanisms. Examples include the near-ubiquity of the *pax-6* transcription factor implicated in development of eyes as structurally disparate as *Drosophila* and human, or the almost endless variations on a theme afforded by the versatility of actin-based cytoskeletons in the evolution of sperm cells. Indeed, evolutionary biologists are becoming increasingly aware that analyzing physical traits atomistically, as independent objects of selection, fails to account for the consequences of the developmental process. McCollum (1999), for instance, presents an account of how the facial morphology of robust australopithecines is affected by alteration of a single key component. In this case, dental morphology is held to have induced wide-ranging effects on the modeling of the entire cranium.

8.1. Cortical enlargement and multiple representations

One of the surprising revelations of recent neuroscience has been the apparent multiplicity and redundancy of sensory and motor representations in isocortex (Kaas 1989). For example, instead of a single cortical map of the visual world, the visual processing system appears to have at least several. These range from the "basic" functions of Brodmann's Area 17 (V1) through the somewhat more integrative representations in Areas 18 and 19, toward the parallel processing facilities of the ventral ("what") and dorsal ("where") streams. Additional processing areas are also suspected, including extrastriate connections that may be responsible for subconscious perception or blindsight, and maps for particular objects, as in suspected object-centered representations in Areas 7a and LIP (Olson & Gettner 1996; Ungerleider & Haxby 1994; Weiskrantz 1996). The persistence of the phantom limb phenomenon in young amputees and even subjects born without particular limbs has been used to argue for multiple and distributed body representations in the iso- and the allocortex, thalamus, and the limbic system that survive local somatosensory reorganization (Melzack et al. 1997). Even emotional affect has been attributed to parallel streams for primary and secondary emotions involving the amygdala and ventromedial areas of the right frontal lobe (Damasio 1994; LeDoux 1995).

What are we to make of nature's penchant for engineering multiple representations based on slightly different processing needs? It is conceivable that each processing stream "grew" its own cortical domain based on the importance of its function to survival – that there existed some early versions of the brain that were, say, good at "what" or "where" visual processing but not both, or perhaps not so good at either until selective pressure expanded the computational resources available to each. It is conceivable, but not plausible. Following our suggestion that structure leads function, it would be our contention that the form of these sensory, motor, and cognitive systems are the result of *competitive recruitment of processing resources from a superabundant pool of cortical neurons made available more or less at the same time.* This superabundance may go some way toward explaining the redundancy of certain representations: In the developing brain, the limiting factor is not space, but the task of solving formidable processing challenges in a finite amount of time. The brain's solution – massively parallel processing – looks very much like the strategy adopted by computer engineers with a complex problem to master (grandmasterlevel chess, realistic modeling of weather) and a multitude of cheap semiconductors to do it with.

8.2. Implications for hominid evolution

If we accept this account, certain deeply entrenched dispositions in most theorizing about human brain evolution may need to be revisited. At the risk of caricature, much speculation on this topic makes the explicit or implicit presumption that some behavioral challenge, such as finding food, using language, learning to manipulate social competitors, and so on, led to functions that took up residence in the 400-gram brains of our australopithecine or early *Homo* ancestors. The imperative to perform these functions better drove the evolution of bigger and better facilities to serve them. The result was presumably a kind of mosaic evolution characterized by differential hypertrophies of the physical subsystems essential to humanness. Indeed, one could infer the behavioral repertoire by taking the relative measure of these hypertrophies: Neanderthal endocasts, for instance, supposedly showed smaller frontal lobes compared to modern human brains of the same size. This appraisal seemed to justify the long-standing judgment of Marcellin Boulle that Neanderthals were capable of only "vegetative or bestial" preoccupations, or more recent claims that these recent ancestors were hampered by "expedient" or "15-minute cultures" marked by poor planning depth (Hayden 1993; Mithen 1996; Noble & Davidson 1996; Stringer & Gamble 1993).

The advent of a *prix fixe* over the old Chinese menu model of brain size evolution alters the scenario. Instead of function dictating the evolution of structure, additional structure preceded enhanced function in hominid brains. To be sure, adaptation has subsequently tailored each subsystem to the processes that tend to take up residence in them. On balance, however, the current model posits a far greater role for exaptation of structure to function in the natural history of the brain.

Based on estimates of endocranial capacity in fossil specimens, the expansion of the hominid brain appears to have proceeded in stepwise fashion from a baseline close to African apes 4–6 million years ago to the modern average around 1,350 grams (Harvey & Krebs 1990). Ambiguities in assigning typical body sizes to ancestral forms, and *Homo habilis* in particular, makes brain/body size ratios fairly speculative. While some within-species variation has been observed over the long career of *Homo erectus,* the most dramatic jumps in mean endocranial capacity occurred first between the australopithecines and the later variants of *H. habilis* (500 to 750 grams) at about 2 million years, and between *H. erectus* and archaic *H. sapiens*

sometime around 400,000 years (about 1,000 to about 1,250 grams).

Based on data presented in a recent review of endocranial capacity and estimated body size for a number of hominid species (Wood & Collard 1999), regression analysis of mean brain volume on body mass alone accounts for some 70% of the variance ($p < 0.001$). By far the largest residual (more than 2.2 standard deviations) is associated with modern humans. If the data for moderns are removed from the set, adjusted R^2 rises to 91.2%. This suggests that the great majority of the brain size increase from australopithecines to Neanderthals is a straightforward function of body mass. Only with the appearance of anatomically modern humans did brain size become somewhat disproportionate.

The advent of lithic technologies around the time of the first growth spurt and of complex tool reduction techniques concurrent with the second have quite naturally been implicated with cognitive enhancements made possible by larger brains. Indeed, the assumption that cognitive function renovated hominid brain structure has become something of a fixture in the paleoanthropological literature (for instance, Deacon 1997; Mithen 1996). Paradoxically, this notion has become yet another way to set humans apart from the rest of the animal kingdom: where evolution is something that happens *to* other organisms, in all the important senses, the author of humanity is itself (cf., for instance, the tradition from Childe 1951 [*man makes himself*] to Kingdon 1993 [*self-made man*]).

The current study suggests that a different emphasis is in order. As all the vaunted capabilities of modern brains are fairly recent developments, their location in isocortex is a straightforward consequence of the fact that that area is the latest brain structure to undergo terminal neurogenesis, and therefore in the best position to provide the additional processing capacity for those functions. The exponential growth of isocortex relative to the rest of the brain is due to its prosomeric location, not to accelerating technological demands "remaking" the brain.

Most important, there is no reason to presume selection pressures for cortically based functions drove brain expansion at all. As we have argued, the brain grows as a covarying whole, increasing in size according to a fairly straightforward log function. It is just as likely, therefore, that pressures for enhanced archicortical, corticoid, or subcortical processing could have triggered the adjustment of global timing constraints that led, incidentally, to much bigger isocortices. Such demands on subcortical processing could have had little or nothing to do with the suite of cognitive traits (language, advanced tool-making) we prefer to think of as distinctly human. The advantage conferred by an enhanced motor control via the basal ganglia, for instance, or a more responsive amygdala in regulating affective function, or a bigger hippocampus for memory of fruiting trees or water, would have done just as well in driving hominid encephalization. The cognitive traits would have been fortuitous by-products, afforded by the "spandrel" of greater isocortical capacity.

This formulation has further implications for our expectations of finding behavioral correlates of bigger brains. One of the current puzzles of paleoanthropology, for instance, is the apparent gap between the appearance of anatomically modern humans some 100,000 years ago and the advent of unequivocally modern behavior. The latter is conservatively marked by new lithic blade industries in Europe around 45,000 years ago (and probably earlier in Africa) and more liberally by the over-water peopling of Australia at around 60,000 years. If function leads structure in brain evolution, then why are modern-looking people with modern-size brains not *acting* modern for some 40,000 years (Klein 1989)?

One answer might be that the archaeological evidence for advanced behavior at deeper time ranges has not been found yet. Alternately, and in accord with our argument here, it is possible that early modern brains reached near-current dimensions for reasons unrelated to modern cognitive functions. Only later, after extra cortical volume had become exapted to the physical correlates of modern behavior, would the full panoply of familiar functions have appeared. We would therefore expect to find evidence for exactly such an anatomical/behavioral gap.

The broad and tight correlations between mass increases all over the brain have implications for primates and every other mammalian order. In moving away from essentialism in our thinking about brain structure and function, we are alive to a wider range of causal scenarios and perhaps to an understanding of brain evolution that goes deeper than a few millimeters of cortex.

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What determines evolutionary brain growth?

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Abstract: Finlay et al. address the importance of developmental constraints in brain size evolution. I discuss some aspects of this view such as the relation of brain size with processing capacity. In particular, I argue that in human evolution there must have been specific selection for increased processing capacity, and as a consequence for increased brain size.

Finlay et al. have made an important contribution by showing that there are significant constraints to the evolutionary development of distinct brain parts. Their article touches some theoretical issues which bear relation to my own work, which I would like to discuss. In a previous paper (Aboitiz 1996), I proposed a modified version of Jerison's (1973) idea that there are two main determinants of brain size: body size and "intelligence." I suggested the existence of two main modes of brain growth in evolution, which nevertheless overlap significantly, making it sometimes difficult to distinguish between them. One of these is passive growth (related

to Jerison's somatic factor); it results from evolutionary increases in body size, and does not necessarily imply higher processing capacity. In passive growth (which Finlay et al. prefer to call "adjunct" growth), the brain increases in size by virtue of genetic and developmental coupling with the rest of the body. This modality is the main determinant of brain size across species. The fact, indicated by Finlay et al., that some brain components correlate better among themselves than with overall body size may imply that these components follow a rather strict schedule of growth, but does not necessarily mean that the cause behind brain growth is other than the increase in body size.

The second modality (active growth, related to Jerison's encephalization factor) results from selection for enhanced processing capacity. In the proposed scenario (Aboitiz 1996), neural (connectional) rearrangements are the main agents to increase processing power in neural circuits. Such rearrangements benefit from increases in brain mass, as the latter facilitate network reorganization by providing increased space for connectional rearrangements and allow increased specificity of synapses. Thus, if there is selection for higher brain capacity, usually there will be also selection for increasing brain mass. However, a larger neuronal number does not *per se* imply network reorganization or increased brain power (passive growth can be an example of this). In active growth, the brain usually grows more than expected for the increase in body size, elevating the encephalization quotient (that is, brain size divided by body size). Humans, with their large brains relative to body size, are an example of this situation.

Finlay et al. argue that sometimes an increase in body size which as a consequence produces increase in brain size may be used to enhance processing capacity. I completely agree with this point, and as mentioned in my article (Aboitiz 1996, p. 241), natural selection may make use of passive growth in order to increase brain power. I also agree with Finlay et al. in that active growth may produce some correlated increase in body size. The case of human brain evolution is an important one in this context. Finlay et al. note that, in hominid history (perhaps excepting anatomically modern humans), increase in body mass is strongly correlated to brain growth. This raises the question of whether the body increased in size secondarily to selection for increased brain mass, or rather if the unusual increase in brain size was a "spandrel," occurring as a consequence of body growth. These two alternatives may not be so different. For example, one possibility is that in hominids there was an especially tight brain/body coupling so that increases in body mass triggered disproportionate increases in brain size (in other species, like the gorilla, changes in body mass produced only moderate amounts of brain growth). However, this unique brain/body coupling in hominids may well have evolved by virtue of selection for increased brain power (and consequently, larger brain size). Thus, this could be an important example of overlap between passive and active growth.

Finlay et al. also argue that the cortical location of our cognitive abilities results because it is the best place where they could reside (as it is the region that expands most for developmental reasons), and that perhaps our cognitive traits are only "spandrels," by-products that occured as a consequence of our developmentally-determined large isocortex. I feel a certain flaw in this line of reasoning, because much evidence suggests that the precursors of our cognitive abilities (such as working memory; Aboitiz & García 1997) resided in the isocortex before the expansion of the brain, rather than residing somewhere else and "choosing" this region among other possible ones because it expanded rapidly. Likewise, if the isocortex is "in the best position to provide additional processing capacity," this might imply that there was some need for this additional capacity. Furthermore, the claim that our brains may be larger than those of other animals by virtue of selection of traits that are not those exclusively human poses the question of why there are not that many animals with such large brains.

Finally, there is one point in which Finlay et al. have challenged my own predictions (which is nevertheless not fundamental for my main proposal). In my original paper (Aboitiz 1996), I suggested that, as opposed to passive growth, in which there should be a close correlation in the growth of different brain parts, in active growth one should observe a sort of mosaic pattern, in which distinct groups of brain components, but not others, tend to increase in size in response to particular processing demands. The data provided by Finlay et al. indicate that there are strong limits to the degree of independent growth of different brain structures. Nevertheless, recent results (Barton & Harvey 2000) suggest that at least in primates and insectivores, there may be correlated variation of some functionally-related brain parts, independent of other brain components. Whether this variability falls within the range allowed by Finlay et al., whether it implies differences in neuronal number, and if it relates to differences in processing capacity, needs to be addressed in future studies. In this sense, one main contribution of Finlay et al. is that these controversies are opening an important avenue of research.

Quantitative neurogenetic perspectives

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Abstract: We comment that covariances between brain divisions may be constraining or facilitating, depending on what is being selected, and that modern quantitative genetic methods provide the tools to discover and manipulate the genetic networks that give rise to the covariances described in the target article.

In our experience, reactions to the work of Finlay et al. have been negative. Horses and horseflies aside (Raff 1996), some biologists and psychologists just do not like constraints. Others become suspicious at the first mention of a principal component. The more keenly minded point out that the mesh of the models and data used by Finlay et al. let escape an important 2–3 fold variation in the size of brain parts typical within species. We suspect, however, that most feel the way we do, bothered that are our dogma has somehow been upended. After all, we *know* that selection targets behaviors, that behaviors are represented discretely in the brain, and that evolution must be mosaic.

This may not be the case, however. *Not yet knowing how brains develop, we do not really know what the units are that selection can target.* We feel this is the important contribution of the work of Finlay et al., beyond the firm grounding of allometry in mechanisms and patterns of neurogenesis. The analysis of Finlay et al. strongly suggests that covariation among the major brain divisions is critically important to mammalian brain evolution. Other than a limbic factor, covariation among brain divisions related to brain size has apparently rarely been pried apart in any substantial way. Of course, what is considered "substantial" is the important crux of what is contended by Finlay et al.; Barton and Harvey (2000) argued recently in the same data set that mosaic evolution is evident and has occurred for functionally and anatomically connected brain divisions. We leave the relative effect size in the Stephan data set of developmental constraint and selectionist positions to the immediate combatants.

From a quantitative genetic perspective, the covariation between traits is also key to evolutionary models. But it is not the *phenotypic* correlation that matters, so much as the *genetic* correlation, or that part of the correlation between traits caused by additive genetic effects. Selection on neural systems will produce evolutionary responses that depend on the genetic (co)variances within and between the brain areas comprising the system (Arnold 1994). Our understanding of brain evolution will benefit by acquiring data on the quantitative genetic architecture of brain systems, particularly those systems with demonstrated behavioral and fitness correlates. With these thoughts in mind, one of the au-

thors (Airey et al. 2000) engaged in a quantitative genetic analysis of the brain system controlling vocal motor patterns (song) in birds.

Airey et al. demonstrated that two structures controlling song behavior (HVC and RA) were heritable, and significantly genetically correlated. Using the heritability quotients for HVC and RA size and the genetic correlation between them, it is possible to calculate the expected changes in HVC and RA size after one generation of selection on HVC. After truncation selection of the 10 males with the largest HVC out of the 100 males Airey measured, a 15% increase in HVC size is expected, along with a correlated increase in RA of 13%. It is important to note that this change in RA size is a correlated response, not directly selected for, but certainly analogous to the kind of developmental structure of concern in the target article. Whether or not this correlated response is constraining or adaptive would depend on whether conjoint or differential evolution of the two structures was being selected. This is an important point not appreciated in the target article; covariations can be constraining or facilitating depending on selection context (Arnold 1992).

Genetic variances and covariances are important parameters in brain evolution, but are not entry points into the networks of genes controlling quantitative differences. More recent advances in quantitative genetics allow neurogeneticists to map the gene loci that underlie genetic variances and covariances for quantitative traits like brain size. Our research group has identified over 30 quantitative trait loci (QTLs) controlling variance in identified cell populations (retina, lateral geniculate, striatum), size of brain regions (olfactory bulbs, hippocampus, cerebellum), and total brain size (Williams 2000). There is nothing stopping a genetic covariance and QTL mapping study in the mouse brain for the major brain divisions used by Finlay et al. in the target article. In fact, we have placed all of the imaged tissue and genetic data necessary for such a study online at the Mouse Brain Library (www.mbl.org). Knowing the genetic variance-covariance (**G**) matrix for the mouse brain would certainly allow useful predictions about what conformations the mouse could be pushed into readily or with difficulty. Marker-assisted selection of controlling QTLs would provide the means to manipulate the mouse brain and test these predictions. Admittedly, the results would be most informative about the genetic architecture of the mouse brain, rather than the mammalian brain. But if there is deep conservation in developmental brain structure we should begin to see it reflected in the recently sequenced mouse and human genomes.

Brain energetics and evolution

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Abstract: The human brain does not use more energy than the smaller brains of animals of comparable corporal weight. Uniquely, human functions localized largely in parts of the human brain that show greatest size increase over other animals may be mediated primarily by nonsynaptic neurotransmission, with reduced energy cost per kilogram of brain. This may affect the energetic constraints on evolution.

The evolutionary changes in brain morphology discussed by Finlay et al. must be accompanied by changes in energetic requirements. A recent upsurge of interest in brain energetics (e.g., Laughlin et al. 1998) has been driven largely by physical anthropologists considering the possibility of energetic constraints on evolution, and exploring where the energy comes from to fuel the large human brain; the studies have been summarized in a *Science* Research News article entitled "Solving the brain's energy crisis" (Gibbons 1998).

The anthropologists are puzzled by the fact that the human brain does not use more energy than the smaller brains of animals of comparable corporal weight (Gibbons 1998). We propose here that the parts of the human brain that show the greatest size increase over other animals, such as prefrontal cortex, may be exactly those parts in which highly nonsynaptic-based functions have their neuronal representation. For those functions, such as music appreciation, space-and-energy expensive synaptic neurotransmission may be largely replaced by nonsynaptic diffusion neurotransmission (NDN).

The manner in which information is carried between brain cells has a great influence on space and energy use by the brain. Calculations of energy expenditure in Hebbian (1949) brain cell assemblies indicate that a fully synaptically connected assembly of 1,000 neurons would expend 100-fold the energy of a fully nonsynaptically connected assembly, and that the metabolic energy increases exponentially with size (Aiello & Bach-y-Rita 2000).

Information in the brain appears to be transmitted both by synaptic connectivity and by NDN. NDN includes the diffusion through the extracellular fluid of neurotransmitters released at points that may be remote from the target cells, with the resulting activation of extrasynaptic receptors. The existence of a large number of receptor sub-types offers the possibility of selective neurotransmission at a distance by NDN. Elsewhere, we (e.g., Bach-y-Rita 1964; 1993; 1995) and others (e.g., Fuxe & Agnati 1991) have discussed the origins of the concept of diffusion neurotransmission and the evidence for high percentages of NDN for certain purposes. These may include mass-sustained functions such as mood, vigilance, and sustained pain (Bach-y-Rita 1991), and are present in both humans and non-humans (NDN mechanisms are also found in invertebrates; cf., Bach-y-Rita 1995).

Assemblies of cells, or neuronal modules, have been postulated to form the basis of many functions of the brain (Edelman 1992; Freeman 1995; Hebb 1949; Sholl 1956). The cells are separated by a significant volume of extracellular space (Nicholson & Phillips 1981), and are connected either by nerve fibers (Hebb 1949 and others consider that each cell in the assembly is connected to other cells synaptically), by the action of neurotransmitters diffusing through the extracellular space, or by a combination of both. Cell-assembly connectivity in these modules is likely to be varying combinations of synaptic and nonsynaptic mechanisms, depending on the specific function.

In previous studies we have explored the diffusion neurotransmission and space and energy saving functional roles of the extracellular space (ECS) and NDN, and the influence of the ECS volume fraction on cell membrane excitability and basal metabolism in an assembly of neurons in the brain (Aiello & Bach-y-Rita 1997; Bach-y-Rita & Aiello 1996). We then calculated that, depending on the extent of the module, synaptic neurocommunication in cell-assemblies might exceed metabolic resources. A medium-size (10,000 neurons) module would require at least 10 joules per liter of brain, based on a calculated cost of an isolated action potential (AP) of $10^{11} - 10^{1}$ molecules of ATP per cm^2 of cell membrane, with an absolute minimum of 10^6 ATP at a node of Ranvier. A circuit model of the cell membrane, based on abrupt changes of Na™ and K™ conductances, was used to emulate the AP and to assess the resulting ionic unbalance. The cost of an AP was equated to the metabolic energy necessary to fuel ATP-based pumps that restore intracellular K (Aiello & Bach-y-Rita 2000).

The sensory input and the motor output components of human activities such as playing a piano concerto are probably highly synaptically organized (although functions such as vision also have many NDN-mediated mechanisms; Bach-y-Rita 1995) and do not differ greatly from comparable functions in nonhumans. However, components of that activity (playing a piano concerto) are specifically human, such as the musicality and artistic components. These probably involve the specifically human isocortical brain structures, and may not require the high-frequency (and en-

ergetically costly) alternating activation-inactivation of synaptic transmission. Although direct evidence is lacking, NDN is consistent with their modes of action.

Mitcheson (1992) suggested that connectivity appears to be minimized in the brain, and Laughlin, et al. (1998) noted: "neurons, neural codes and neural circuits will have evolved to reduce metabolic demands." Concordant with those views, and with a proposed law of conservation of space and energy in the brain (Bach-y-Rita 1996), functions that are highly NDN-mediated may be a basis for the reduced per kilogram energy requirements of human brains in comparison to the brains of animals of comparable size.

Falk (in Gibbons 1998) noted: "We have to attend to the energetics or we're not going to get selection for a bigger brain." We suggest that NDN may play a role in evolution, providing a mechanism to allow the "underlying physical constraints . . . to be overcome to build an oversize brain" (Gibbons 1998).

The coordinated structure of mosaic brain evolution

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Abstract: The opposition set up between co-ordinated and mosaic brain evolution distracts from the fact that the two go hand-in-hand. Here and elsewhere (Barton & Harvey 2000), I show that the patterns of co-ordinated evolutionary change among brain structures fit a mosaic evolution model. The concept of overarching developmental constraints is unnecessary and is not supported by the data.

The components of any adaptive complex, such as the brain, by definition undergo coordinated evolution. To that extent, the idea that brain structures evolved together is uncontroversial. Nevertheless, individual brain components are grouped within functionally differentiated neural systems, upon which natural selection might act independently of evolutionary change in other systems. Finlay et al., however, argue that conservation of developmental programs constrains the independent evolution of neural systems, as follows:

(1) In mammals, the order of neurogenesis and other developmental events is "very precisely conserved."

(2) This conserved developmental program determines how big each structure grows when brain size evolves. Hence, analyses based on functional subdivisions of the brain are "unable to capture any more of the correlational structure of the data set."

(3) The disproportionate expansion of the neocortex in large-brained species is a "spandrel," an allometric effect of its late termination of neurogenesis in the conserved developmental program.

Taking the last first, are enlarged neocortices spandrels? No; the neocortex of primates is about five times larger than that of insectivores, after taking scaling with other brain structures into account (Barton & Harvey 2000). Differences remain even after accounting for relative reduction of olfactory structures in primates. The "spandrel" hypothesis is based on the assumption that neocortex size scales in a nonlinear fashion relative to overall brain size. However, once the effects of taxonomic differences are removed, the scaling of neocortex size is very nearly linear, and the slight nonlinearity that does remain is attributable to the fibre-containing white matter component. As predicted by models of connectivity in relation to brain size (e.g., Zhang & Sejnowski 2000), white matter increases faster than grey matter, whereas grey matter increases proportionately with brain size (Barton & Harvey 2000). Hence, connectional rather than developmental constraints probably explain the slight nonlinearity in the scaling of total neocortex size.

To what extent have functionally defined neural systems evolved independently of general brain size? Much of the correlation between the size of major brain components in the analyses by Finlay et al. is probably due to the fact that, as they note, functional systems cut across these crude subdivisions. Despite the limitations of the Stephan data set, and *contra* the claim of Finlay et al., it turns out that basing analyses on functional systems does, after all, explain more of the variance in structure size. Barton and Harvey (2000) analysed five functional systems in each of two mammalian taxa (primates and insectivores). In every one out of the ten cases, the components of functional systems exhibited significantly correlated evolution after taking variation in a range of other structures *and overall brain size into account.* In 9/10 cases, the partial correlations between functionally linked components were higher than all of those for less directly connected structures. Indeed, in several cases, there were no other significant partial correlations (and where there were, these additional correlations involved structures with further well documented connections, e.g., amygdala components correlated with olfactory structures after accounting for their correlation with each other). Hence, the intercorrelations noted by Finlay et al. seem to be driven by functional connections, not developmental constraints (unless these two influences are so closely related as to render the Finlay et al. model meaningless). It would therefore be justified to turn the Finlay et al. model on its head: once functional interconnections have been taken into account, there is not much variation left that might even in principle be attributable to other constraints, such as conserved development.

Finally, what is the evidence that the schedule of brain development is "very precisely conserved"? The claim is based on an analysis in Finlay and Darlington (1995), which showed a correlation of 0.988 between the dates of peak neurogenesis for 51 structures of seven species and the dates predicted by a model based on all the species. Close examination of the description of this analysis suggests cause for concern on two counts. First, the analysis appears to be circular. Half of the entries in the 51×7 matrix were estimated by extrapolating from the values for the other species. Furthermore, the species contributing data to the model were then used to test the model. Hence, the matrices of predicted and actual values were not derived independently. Second, the analyses were heavily weighted by two structures that finish development late, the retina and neocortex. Comparison of developmental timings indicates conservatism at least to the extent that these two structures tend to develop late in all species. However, the claim of conservatism obviously goes far beyond these two structures. Furthermore, inclusion of multiple data points for these structures, one for each layer, introduces pseudoreplication, and is inconsistent with the allometric analyses, which were based on whole structures. Finally, the retina is not one of the brain structures included in the analysis of volumetric data, and, though late developing, it is not large.

A simpler analysis of the Finlay and Darlington (1995) data, examining the degree to which dates of neurogenesis in one species predict those in another, excluding the retina and collapsing the data for separate neocortical layers to a single mean, does not support the claim of a precisely conserved order of neurogenesis. The distantly related species show either a moderate correlation (rat versus macaque, $r^2 = 0.41$, $df = 14$, $p < 0.01$) or no correlation at all (mouse versus macaque, $r^2 = 0.14$, $df = 10$, $p > 0.05$). As expected, more closely related species (rats and mice) show a stronger correlation ($r^2 = 0.61$, $df = 20$, $p < 0.001$), but even there, much unexplained variance remains. Taken together, it appears that there is some developmental conservatism, but not nearly as much as suggested by Finlay et al., and perhaps no more than might be predicted by the need to preserve some fundamental functional interrelationships.

This leaves just the two examples given to bolster the connection between developmental schedules and structure scaling, the amygdala and thalamic nuclei. First, it is claimed that the late-maturing corticobasolateral nuclei of the amygdala increase in size

disproportionately relative to the earlier-maturing centromedial nuclei. Once again, however, differences in scaling are confused with taxonomic differences in relative size. The corticobasolateral nuclei exhibit similar taxonomic grade shifts as the neocortex, (with which they extensively interconnect) and once these taxonomic effects are taken into account, there is no difference in the scaling of corticobasolateral and centromedial amygdala (Barton & Aggleton 2000). Second, it is claimed that mean day of neurogenesis in the rat predicts the scaling of thalamic nuclei in hominoids. The original data set of three humans, two gibbons, one chimp, and one gorilla cannot, however, be considered a suitable basis for any inferences about scaling, given the conflation of intra- and inter-specific patterns and the lack of account taken of taxonomic effects. Furthermore, the pulvinar and lateral posterior nuclei were omitted from the analysis because they "derive from different embryonic origins in the rodent, ape, and human." The justification for omitting structures that do not fit the assumption of conserved development is not provided.

In conclusion, the major claims of the target article do not stand up to critical scrutiny. Developmental programs are weakly, not precisely conserved, functionally defined systems do evolve independently of the rest of the brain, and expanded neocortices cannot be dismissed as by-products of overall brain expansion. Thus, the classic "mosaic brain evolution" model is alive and well. Finlay and Darlington originally espoused a two-factor model of brain evolution, in which the factors free to vary were overall brain size and the olfactory bulb. They have now moved to a three-factor model. In my view, they are moving in the right direction.

Flaws in evolutionary theory and interpretation

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Abstract: We make three points. First, even if Finlay et al.'s proposed developmental mechanisms hold, there remains great scope for selection on specific brain structures. Second, the positive covariance among the size of brain structures provides far less support for the proposed developmental mechanisms than Finlay et al. acknowledge. Third, even if the proposed mechanisms are the primary size determinants for most brain structures, these structures should not be considered "spandrels."

Understanding brain development is crucial for understanding brain evolution, and Finlay et al. have made a stimulating contribution from the developmental side. Nevertheless, we believe that they have made several mistakes in relating their ideas to evolutionary theory. The first issue we consider is whether, if Finlay et al.'s developmental mechanisms hold, brain structures can undergo selection individually. Finlay et al. argue that because conserved sequences of neurogenesis affect numerous structures, it is nearly impossible for selection to alter the initial number of neurons of any single structure. On an evolutionary level, this means that it is unlikely that a specific socioecological demand could select for an increase in the size of a particular brain structure without altering the size of many other structures. We believe this reasoning is flawed because it overlooks the fact that the number of neurons initially directed toward an area is one of only many factors that ultimately determine its size, organization, and function. Following neurogenesis, interactions between neurons and somatic targets and between neurons and other nonlocal neurons, dramatically affect axonal growth, neuronal survival, and patterns of neural connectivity (Purves et al. 1997). We can imagine, for instance, a subterranean species that evolved a fur covering over the eyes; the "visual areas" of the cortex would receive no visual inputs, and hence would become markedly reduced (or be utilized for new functions). Thus, an adaptation for a loss of visual cortex could occur via a late change in development and this would be perfectly compatible with stasis in (Finlay et al.'s) early mechanisms. Although Finlay et al. allude to this type of change in cortical representation (sect. 1), they apparently do not realize its implications. In fact, one of their stated goals is "establishing *the precise* developmental substrate on which brain evolution selects" (italics added). For orthodox evolutionary biologists, however, there are many possible substrates for selection on the brain; some will permit global changes, some will permit local ones.

We turn next to Finlay et al.'s claim that the strong allometric relationships among the sizes of brain structures provide strong evidence for the existence of the proposed developmental mechanisms. We take issue with this argument because it ignores the fact that these relationships are also consistent with processes other than developmental constraints. First, arguments and models of functional connectivity predict the same general patterns (e.g., Deacon 1997; Ringo 1991; Zhang & Sejnowski 2000). Second, correlated evolution of individually selected traits could also produce these patterns. For example, members of a species that begin living gregariously (perhaps to reduce predation) will experience increased social processing demands; if increased group size leads to greater ranging (because less food is available per patch per individual), the individuals would then face increased spatial memory demands. Although there are several plausible evolutionary scenarios for two or more brain structures to become positively correlated (for another see Deaner et al. 2000), there are none, to our knowledge, suggesting that negative correlations will similarly occur. Furthermore, even the allometric relations of particular brain structures with body size are potentially due to such correlated evolution. For instance, for reasons involving life history, it is expected that improved cognition and larger body size (and the reduced external mortality generally associated with it) will coevolve (Deaner et al., in press); thus, the increasing proportion of neocortex in larger-bodied (and hence larger-brained) animals is explicable without reference to developmental constraints.

Although we do not find Finlay et al.'s model compelling, it may turn out to be correct. Even if it is, though, Finlay et al.'s claim that many brain structures would therefore be "spandrels" is not informative. To understand why, we must start by examining the two ways that Finlay et al. use the term. First, they argue that brain structures would be "spandrels" in the sense of being byproducts of structural constraints (Gould & Lewontin 1979): it would be optimal for only one brain structure to change, but, because of constrained developmental mechanisms, the other structures must "go along for the ride," although ideally they would be unaltered. But, as Finlay et al. recognize, (1) if the unit of selection in the brain is a suite of structures, this is almost certainly because this unit, and the developmental mechanisms that produced it, was favored by natural selection (their sect. 8), and (2) efficient, functional neural processing probably requires that all brain structures respond to the size of other ones in order to "retain any voice" (sect. 7; see references above). Thus, they acknowledge that dramatic hypertrophies in particular brain structures are possible, but that organisms with such phenotypes would have extraordinarily poor fitness. In other words, under Finlay et al.'s model, the brain structures that are termed "spandrels" are not undesirable, neutral, or unavoidable byproducts but rather are *crucial* parts of a large-scale adaptations.

Second, Finlay et al. propose that some brain structures could be "spandrels" in the sense that they are traits that arose for one reason and later were used for a novel function (co-option or exaptation; see Gould & Vrba 1982). Specifically, they suggest that the first anatomically modern humans may have reached their large overall brain sizes because there was selection for hypertrophy of an as yet unidentified subcortical structure that could only be achieved by increasing the size of many other structures, including (much larger) isocortical areas. Fifty thousand years later, these isocortical areas were co-opted for novel cognitive purposes,

leading ultimately to technological break throughs. There is a major problem with this story: if the ecology 100,000 years ago was similar to that 50,000 years ago, why didn't the isocortical areas permit the advantageous cognitive functions to flourish immediately, within the lifetime of the first organism that possessed them? Clearly, after this long delay, some type of developmental process (involving size, organization, etc.) must have occurred to allow this novel type of functioning. And this developmental process, and the change it produced, would most likely be an adaptation. Perhaps, though, Finlay et al. mean that these isocortical areas would be exaptations in the sense that the evolution of their new function or organization was predicated on the ancestral existence of similar structures and developmental processes. Exaptation in this loose sense is ubiquitous, however, because evolutionary theory dictates that every adaptation is this kind of exaptation, for the simple reason that nothing can evolve *de novo* (Dennett 1995).

"Spandrel" is, of course, only a label, and it is fair to ask why we bother criticizing its usage. The general reason is that we are averse to the term, because many authors, including Finlay et al., apparently believe that by labeling structures "spandrels," they have struck a serious blow at the "the adaptationist program." The reality is that good adaptationist reasoning does account for the possibility of developmental constraints, structural byproducts, and cases of co-option. The second, more specific reason we criticized the use of the "spandrel" is to show that even if we accept it as a useful label, upon close examination, few structures actually meet meaningful definitions of the term.

Confounding explanations. . . .

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Abstract: I argue that, while Finlay et al, are correct to suggest that there are developmental regularities (or constraints) acting on brain component evolution, they are incorrect to infer from this that a developmental explanation necessarily implies that structural changes preceded functional use. Developmental and functional (adaptationist) explanations are complementary, not alternatives.

Finlay et al. provide a cogent analysis of the evidence in support of the claim that there are overall structural rules that relate the evolution of brain parts to total brain size, as well as the claim that these relationships arise from regularities in the developmental processes that underpin brain growth. However, they overstep the limits of inference when they infer from these facts the conclusion that "function therefore follows structure." In doing so they confound functional with developmental explanations (see Huxley 1942; Tinbergen 1963).

The issue is this: It is one thing to show that there are developmental constraints on the growth of any organic component (surely this is one of the fundamental tenets that all adaptationists accept?), but it is quite another to claim that evidence for a developmental explanation *ipso facto* excludes a functional (adaptationist) explanation. As biologists have been aware since Aristotle (see Dunbar 1993), developmental and functional explanations are complementary and not alternate explanations. There are developmental *and* energetic constraints on the evolution of larger brains and organisms that need larger brains will only be able to evolve them (and hence occupy the new niches they "seek" to occupy) by first evolving the larger bodies needed to support these larger brains. The fact that we can then show that the size of particular brain components correlates with some behavioural variable does not mean that the behavioural phenomenon developed to fill the gap created by the larger brain component, but rather that only those species for whom the more developed behavioural process was essential went to the trouble of evolving larger brains. If this were not so, there would not be the orderly correlations between particular brain parts and particular cognitive and behavioural functions for which there is now ample evidence; rather, different species of the same taxonomic group would have evolved different functions for the enlarged capacities that they had accidentally acquired and the result would be a random pattern of associations.

This raises two further issues.

Given the sheer cost of neural matter (and Finlay et al. themselves pay due note to this), it is inconceivable that increases in brain size occurred in any lineage merely because they could (as Gouldian exaptations consequent on increases in body size). Even if such a claim were to be sustained, it would merely shift the burden of explanation onto the need for larger bodies. The only way Finlay et al. can then maintain their position is to argue that whatever benefits derived from increased body size outweighed the combined costs of evolving *both* larger bodies *and* larger brains. So what were those advantages? It is, of course, reasonable for Finlay et al. to insist that they do not have to provide an explanation for all components of the evolutionary equation. However, the conventional view already does so (by arguing that brain growth occurred to support specific cognitive faculties, and that larger brains were energetically possible only in larger – or energetically more efficient – bodies). Since the conventional view can already provide a cogent and logically coherent account of how and why the elements in the evolutionary equation relate to each other, should we not expect Finlay et al. to be able to provide at least as complete an answer before asserting that the explanation they have to offer for just one part of the equation is better than anyone else's?

The second point concerns the implied claim that, even when adaptationist correlations between brain component size and some behaviour can be demonstrated, most of the variance in brain part volume can be attributed to total brain size (or body size) rather than to the functional behaviour. However, one should not be misled by statistical artefacts: correlations do not imply causation and we cannot infer that merely because total brain size explains more variance in brain part size it must therefore be the driving variable in this relationship.

Lastly, I feel obliged to make a passing comment on Finlay et al.'s concluding comments on human evolution. It seems that they follow the rather old-fashioned line that tool production and/or ecological problem solving represents the key to understanding human cognitive evolution. This leads them to conclude that the fact that the gaps in the quantal shifts in hominid brain evolution does not necessarily correlate with the observed pattern of ecological or tool-making behaviour is evidence for their claim that structure preceded function. Alas, no. The "social brain" hypothesis (Barton & Dunbar 1997; Dunbar 1998) would also lead us to expect exactly the same lag between brain growth and ecological and tool-making performances.

In summary, I do not wish to undervalue the significance of Finlay et al.'s work on brain developmental regularities – these are surely important features that aid understanding of the evolutionary processes involved – but I would challenge their claim that this evidence necessarily provides an alternative (developmental) explanation for brain evolutionary history that negates more conventional adaptationist (functional) explanations.

D'Arcy Wentworth Thompson, interindividual variation, and postnatal neuronal growth

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Abstract: It is suggested that a connection between neurogenesis and brain part size is unsurprising. It is argued that neurogenesis cannot, however, be the only factor contributing to brain size. Highly individual postnatal experience radically shapes individual brains, leading to dramatic increases in brain size. The role of comparatively coarse statistical techniques in addressing these subtle biological issues is questioned.

Finlay et al. argue that a parsimonious model that predicts brain part size across a large number of mammalian species is based simply on the sizes of other brain parts. Because the duration of neurogenesis could influence the final size of brain structures, they argue that the timing of neurogenesis is important and find a simple log-linear function that determines the timing of terminal neurogenesis. Thus, in answer to the question posed in the first sentence of their abstract, they reply that "evolution grow[s] bigger brains" by tinkering with neurogenesis.

In 1917, D'Arcy Wentworth Thompson published his magnum opus, *On growth and form,* an enlarged and revised second edition appearing in 1942. In this now-classic work, Thompson applied mathematics to the question of form in biology. In particular, he showed that simple scaling laws and transformations can transmute superficially quite different structural forms, one into the other, whether these forms pertain to leaves, shells, skulls, horns, or fish. Modern developmental biology interprets these results as indications of straightforward alterations in the timing of developmental events (see, for example, Gilbert 2000). Delay cell profileration here; prolong cell profileration there: the result can be wildly different-looking organisms. It is not surprising, then, that evolution should act, in part, by exploiting variations in the temporal characteristics of developmental events. Brains, of course, are subject to the same developmental and evolutionary laws and mechanisms as any other part of the body. D'Arcy Wentworth Thompson would thus doubtless accept with perfect equanimity Finlay et al.'s proposal that evolution acts on brains partly by alternating the timing of neurogenesis.

Despite this broad agreement, there are a couple of concerns that should be expressed. First, several studies have demonstrated considerable variation within a species, and even within individual members of a species, in the sizes of particular brain structures. Horton and Hocking (1996b), for example, performed a study of the variability in ocular dominance column periodicity in the striate cortex of six adult macaques (five males and one female), finding that column size and total V1 area can differ significantly between different individuals. Riddle and Purves (1995) performed a related study in the primary somatosensory cortex of 53 adult male rats. They found that the cortical representation of the whisker pad ranges in area from 3.72 to 6.84 mm^2 over their animals. They also examined variations within single animals, finding that representations of the furry buccal pad in the two hemispheres can differ in size by as much as 15%. Subsequent work by Purves and collaborators (Halpern et al. 1999) has demonstrated marked variation in the capacities of 20 humans assessed on a battery of different psychophysical tests, perhaps reflecting two- to three-fold differences in the sizes of the visual cortex, lateral geniculate nucleus (LGN), and optic tract in humans (Andrews et al. 1997). Despite this large intrinsic variability within species, Finlay et al. discuss Armstrong's study (1979a; 1979b; 1980; 1981) of the changes in the relative volumes of hominoid thalamic nuclei, based on just two gibbons, one gorilla, one chimpanzee, and three human brains, and argue that this study further supports their thesis concerning neurogenesis and size. Obviously, such matters need careful consideration.

The second concern relates to the issue of developmental events subsequent to neurogenesis. Finlay et al. briefly allude to this matter, but do not pursue it. Several studies of the postnatal growth of the brain have been performed. For example, Duffy et al. (1998) looked at the growth of the primary visual cortex in 8 macaques, 16 rats, and 24 cats. The surface area of visual cortex in these species increases postnatally by 18, 82, and 132%, respectively. The comparatively small growth of macaque V1 probably reflects the fact that it is "adult-like" at birth (Horton & Hocking 1996a). The 82% growth of rat visual cortex is likely a considerable underestimate, as the youngest rats analysed were at postnatal day 11 (P11), and rat pups undergo very rapid early growth; indeed, the critical period in layer IV of rat barrel cortex is already over, having ended by about P4 (Fox 1992). Riddle et al. (1992) looked at the postnatal growth of rat somatic sensory cortex, paying attention to differences between barrel and inter-barrel cortical growth. Barrel cortex increases in area by between 59% for the hindpaw representation and 104% for the anterior snout representation, with SI increasing in area overall by 93% (assessed over 55 juvenile and 57 adult hemispheres). Inter-barrel cortex increases in area by between 55% (forepaw) and 75% (hindpaw), with an overall 67% increase in SI. All these increases in size are a result of ongoing growth and elaboration of axonal and dendritic arbors, increased vascularisation, and so on, and not neurogenesis. Furthermore, as the rat SI study shows, and as well-known studies in the LGN and striate cortex demonstrate, postnatal growth is strongly influenced by neuronal activity (Purves 1994). This relates to the question of inter-individual variation, because an individual's post-natal neuronal growth will be significantly influenced by its own particular environment, experiences, an so on. Thus, although it is clear that, modulo questions of neuronal size and packing, more neurons make for larger structures (essentially Finlay et al.'s point regarding the order of neurogenesis and brain part size), this cannot, by any means, be the whole story, because it ignores huge amounts of postnatal neuronal growth, which can be strongly affected by highly-individual experience.

These concerns perhaps go some way towards reducing the interest of Finlay et al.'s analysis. To be sure, an attempt at a mechanistic account of the way in which "evolution grow[s] bigger brains" is welcome. But it appears that the statistical techniques used by Finlay et al. (indeed, any such approach) constitute far too blunt a weapon with which to cleave the Gordian knot of brain evolution, development, and function. That all three must be addressed simultaneously is accepted, but it is more likely that detailed genetic, molecular, cellular, physiological, and anatomical techiques will, in time, carefully unpick this particular knot.

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Brain evolution: A matter of constraints and permissions?

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Abtract: The article of Finlay et al. is an excellent example of identifying constraints in the development of the brain, and their implications on brain architecture in evolution. Here we further illustrate the importance of constraints by presenting a few examples of how a small number of biophysical mechanisms or even a single life history parameter can have an enormous impact on brain evolution.

When considering hominid evolution, attempts to understand how evolution produces larger brains is of prime interest. The approach of Finlay et al. is a major contribution to the understanding of constraints on evolutionary changes. The "removal" of constraints al-

lows for evolutionary changes, without positively or "actively" selecting for them. The importance of such an approach has already been highlighted by Whiten (1990) as well as by Finlay (1990) herself in their commentaries on the "radiator" theory (Falk 1990).

As stated by Whiten (1990), positive pressures are necessary for change to take place, but these pressures could have been present in a specie's environment all along, and only becoming operative once a constraint is removed. It is the analysis of the balance between constraints, constraints removal, and positive selection that leads to the understanding of evolutionary changes. Developmental processes as a primary locus of architectural constraints on brain evolution therefore, are of special interest because their removal may result in the emergence of another type of creature.

Constraints on brain evolution operate at all levels. Hofman (1998) recently pointed out that if the brain grows to a point where the bulk of its mass is in the form of connections, then further increases will be unproductive due to the declining capability of neuronal integration and increased conduction time.

In a broad comparative context, two dramatic examples of constraint were highlighted by Allman (1999). Cephalopods (octopus, squids, and cuttlefish), despite a very advanced evolution of their visual system, were not able to evolve a large brain. A constraint on brain evolution in cephalopods is the lack of capacity to manufacture myelin, the insulating material of axons. More space and energy is, therefore, taken up by axons in cephalopods as compared to jawed vertebrates. Another constraint on the evolution of their brain is the oxygen-carrying capacity of their vascular systems. Nervous tissues are highly energy consuming, and the green blood of cephalopods can carry only about one quarter as much oxygen as the red blood cells of vertebrates (Allman 1999).

We would like to point out here a fundamental constraint on brain enlargement in primates. A disproportionate enlargement of the brain size relative to body size is characteristic of the human. Relative brain size (or encephalization) can be expressed by the residual values of individual species relative to a best-fit line between brain size and body size values. Among primates, the highest residual values are found in humans and in capuchin monkeys (*Cebus* sp.). However, why is the human relative brain size value (or encephalization level) not paralleled among primates? Recent studies have stressed the energetic constraints on brain enlargement but a more basic constraint seems to be the body size itself. Sacher (1975) noticed that a brain weight versus body weight ratio of 4% represents the upper limit for adult brain weight versus body weight ratios in all orders of mammals and probably indicates an upper limit of brain metabolism that mammals can support

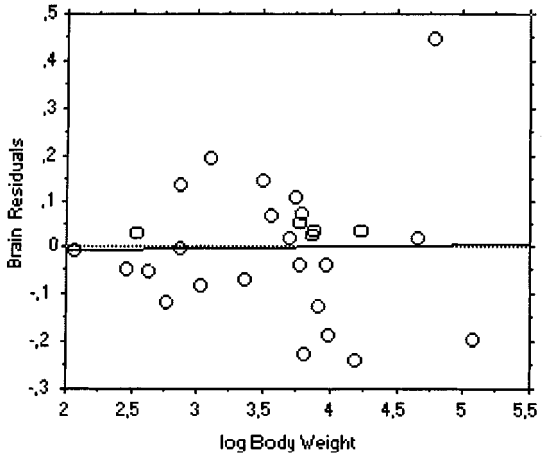

Figure 1 (Gilissen & Simmons). Relationship between brain residuals and body weight (log) for 28 primate species (data from Stephan et al. 1988) (r = 0.016; p = 0.9). Residual values are a measure of "encephalisation." They represent deviations from the best-fit line between brain size and body size.

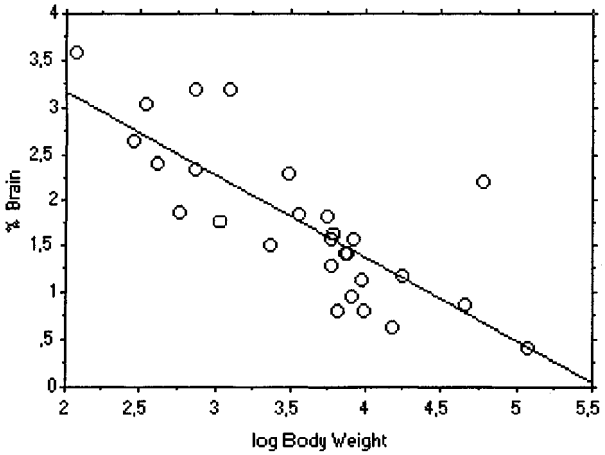

Figure 2 (Gilissen & Simmons). Relationship between percentage of brain tissue and body weight (log) for 28 primate species (data from Stephan et al. 1988) (r = 0.785; p = 0.0001).

(Fig. 3). The actual value of this ratio is 2.0–2.2% in adult humans and 2.2% in *Cebus albifrons.* The expected values of this ratio are, respectively, 0.7 in adult humans and 1.6% in *Cebus albifrons.* If *Cebus albifrons* would have the same level of encephalization as adult humans, the brain weight versus body weight ratio would be 4.3–4.5% in this species and thus would be above the upper limit for adult mammals. It is commonly assumed that residuals are a measure of brain size independent of body size (Fig.1) in contrast with percentages (Fig. 2). However, it appears that body size is a

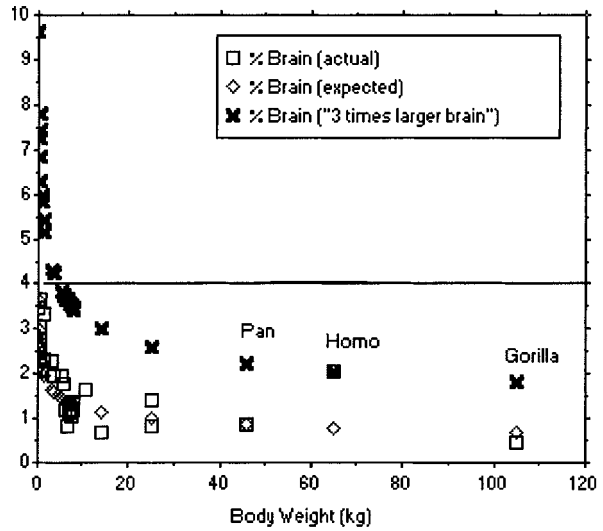

Figure 3 (Gilissen & Simmons). Relationship of the type $y = kx^{-a}$ between percentage of brain tissue and body weight for 28 primate species (data from Stephan et al. 1988). "Pan" is the common chimpanzee. "% Brain (actual)" represents the actual observed value. "% Brain (expected)" represents the value expected from the reduced major axis between brain weight (log) and body weight (log). "% Brain (3 times larger brain)" represents the percentage of brain tissue that would be found in these various primate species if they would have the human level of encephalization, that is, a brain size approximately three times larger than expected for our bod y size. In that case, it appears that the adult brain tissue percentage of several small primates (especially New World monkeys) would represent more than 4% of the body mass. Note that the "% Brain (actual)" value and the "% Brain (3 times larger brain)" value are the same for humans (Homo).

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constraint on relative brain size and that residual values of individual species relative to a best-fit line between brain size and body size values are not independent of body size itself (Fig. 3). This result is important when considering the encephalization level of small New World monkeys.

As a final word, the comparison between the behavioral capabilities of the hummingbird (brain size of less than a gram) and the baleen whale (brain size in excess of 5,000 grams) reminds us of the paradox raised by Barlow in H. J. Jerison (1985). In a heavy brain a high encephalization index might correspond to the addition of many grams of brain tissue, whereas in a light brain the same increase of the index would correspond to the addition of a comparatively small amount of brain tissue. If encephalization is related to intelligence, why does the heavy brain require many times more brain tissue than the light brain to confer the same increase in intelligence?

Clearly, spandrels – by products of structural constraints – requires more attention from evolutionary biologists. The work of Finlay et al. is most welcome.

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Does allometry mask important brain structure residuals relevant to species-specific behavioral evolution?

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Abstract: Despite the ontogenetic allometric size effects that explain much of phyletic variation in brain components, the residuals of some structures indicates that mosaic brain evolution was an important factor in hominid evolution, and that reorganization of the hominid brain may have occurred as early as 3+ MY. Finlay et al.'s allometric technique masks residual variation around allometric trends, and the *patterns* of residuals relevant to species-specific departures from strict allometric trends.

It has been some 25 years since I reviewed Jerison's 1973 book in *Science.* I admire the tenacity with which the allometrists continue to regard brain size as the most salient explanation for behavioral differences among species, whether extant or fossiliferous. In that review (Holloway 1974) I suggested that there was a tendency to reify numbers into a fictional realm, such as "extra cortical neurons" or the fitting of the 0.66 slope to the data without first checking the actual regression figures, something that awaited Martin's (1983) paper, demonstrating an empirical slope of 0.75. At the time of writing that review, I was concerned by Jerison's (p. 81) dismissal of the concept of "reorganization" of brain components as a trivial explanation for even more trivial behavioral phenomena, namely, species-specific behavior. How our symbolic capacities could be regarded as "trivial" surprised me. Plotting numerous graphs of log-log brain-body weight (and brain part volumes, e.g., the hippocampus) relationships completely validate, as does this article by Finlay et al., that there are indeed allometric constraints to brain development operating at ontogenetic levels, and thus having occurred in the phylogenies of most animal groups, hominids included. For this investigator, however, it is the allometric constraints which might be deemed "trivial" (sensu Jerison), and the residuals, or departures from the constraints that are most provocative and nontrivial in analyzing species-specific behavioral repertoires and in particular the paleoneurological evidence for hominid evolution. That was my essential message in the reference that Finlay et al. cites (Holloway 1979), and I tried at that time to make a rapproachment with Jerison which would be holistic regarding both allometric constraints and species-specific departures from those constraints, and I did try factor analysis as one method to demonstrate this. The recent paper in *Nature* by Barton and Harvey (2000) offers a critique of the Finlay et al. study, and demonstrates correctly, I believe, that mosaic evolution did occur among brain components.

I ended my 1979 paper as follows:

> By cathecting on size alone, all evolutionary paradigms become reduced to natural or genetic selection operating on incremental size increases and behavioral efficiency, which always has the underlying implicit structural argument that "intelligence" equals "brain size." Thus, for example, all of hominid evolution becomes "scaling," "allometry," or quantitative increases, whereas these are only *distal* manifestations of something more complex and important. In other words, all of individual variation, the very stuff that evolution works on, is reduced to a single dimension of either small or large. In fact, it is likely that the selection events in any animal's life depend more on the timing of maturational events, epigenesis within the central nervous system (CNS), and everyday events – that is, the "nitty-gritty" life-death "selection walks" – are matters of hierarchical organization, differentiation, and development, of which the outcomes through time can only be measured (thus far) as size increments. We should and can demand richer explanations. (Holloway 1979, p. 85)

I had (and continue to do so at present) used the visual system to illustrate my position regarding *reorganization* as being an important element of human brain evolution. There are at least two good reasons for doing so: (1) the comparative primate volumetric data (e.g., Stephan et al. 1981) shows that the primary visual striate cortex (PVC) in *Homo* is 121% less in volume than expected for a primate of its brain size (the lateral geniculate nucleus is −144% less than expected). These residuals of over 100% should command some attention, despite the small sample sizes within species, and log-log regression lines with very large errors at the extremes. (2) The paleoneurological evidence from brain endocasts occasionally shows details in the posterior cerebral region suggesting that the reduction had occurred at least 3 million years ago. We will never know about the australopithecine hippocampus, basal ganglia, septal, and amygdaloid nuclei, and so on, but we do have a chance to identify and quantify some of the external morphology of the cerebral cortex, as I have tried to show with regard to the lunate sulcus as an anterior boundary of PVC, and cerebral asymmetries in particular (see Holloway 1995 for a theoretical synthesis and Holloway 1996 for a full review).

I am also very skeptical of "spandrel" theories of brain/behavioral evolution as championed here by Finlay et al. That all of our species-specific behavioral attributes such as developing language where arbitrary symbol systems underlie most of our cognition, our emotions, our predispositions toward xenophobia and violence within and against species, our behavioral diversity with regard to intelligence(s), our musicality, and so much more, should simply be epiphenomena of an evolutionary passage (that cannot be tested without time machines) beyond some size rubicon strikes me as implausible. Spandrel theories cannot explain genius, sexual dimorphism of behavior, and brain structures such as the corpus callosum. Neither spandrel or allometric analyses can explain the difference in maternal behavior, between mountain and prairie voles when pups are taken from the nest. Spandrel theories cannot explain the recently demonstrated differences between Australian Aborigines and Caucasians with regard to PVC volumes and perceptual tasks (Klekamp et al. 1994). Take any log-log regression line of mammalian brain-body weights and see which animal's behavior you can predict when they are closely adjacent, for example, whales and cetaceans, or chimpanzee and orangutan, or even various species of *Macaca,* which display differences in temperament and personality. Dog breeds would be yet another example of the failure of allometry to do more than provide an ontogenetic constraint, which while useful, begs the more difficult issues of brain structural variation and behavioral differences. For these, we can only hope that MRI, fMRI, and

PET scans will get us beyond our cathecting on size alone. I am not opposed to allometry at all; it must be a necessary component part of any future holistic theory (or theories) of brain evolution, but I am worried about dismissing evidence which suggests that quantitative shifts in neural systems through time might help us to better understand the conjoint evolution of brain and behavior.

The time when the "Tomte" of evolution was playing with time

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Abstract: Developmental constraints presumably had a major role in channeling evolution. In particular, developmental mechanisms may have coordinated the evolution of neocortex with that of other brain structures. However, the rules determining the differential expansion of different cortical territories remain to be determined as well as the adaptive role of cortical expansion versus that of the structures it is connected to. The high degree of developmental plasticity of neocortex was probably the key to its successful evolution.

Finlay et al. stress the need of thinking of evolution in a developmental perspective, a useful to be remembered truth. Indeed, evolution operates by modifying development. These modifications can produce a viable phenotype only if they can be absorbed by sufficiently flexible (plastic) developmental mechanisms downstream. If not, the modifications are rejected. Indeed, one mystery of evolution is why angels never appeared, except in the early Italian paintings. Wings and arms seem to be alternatives; evolution did not allow both, in spite of their obvious adaptive value. So development constrains evolution and channels it into producing some phenotypic variations, not others. But how does it do it?

The evolution of the neocortex, has attracted much interest since it seems to hold the key to the spectacular peculiarities of the human brain. It was proposed that two developmental mechanisms provide developmental flexibility and hence, in evolutionary terms, *evolvability* of cerebral cortex (Innocenti 1989; 1995; Killackey 1990). The first is the adaptation of cortical structure to the thalamic input. This view is based on evidence of modifiability of cortical structure following manipulations of the thalamic input, and remains valuable although recent studies demonstrate early genetic differences in the developing neocortex, some of which, however, require thalamic input for maintenance (Gitton et al. 1999). The second mechanism is the searching strategy that cortical neurons exhibit in the formation of connections. This mechanism leads to the formation of exuberant dendrites, synapses, and of projection to sites more or less remote from the final target, some of which can be maintained by genetic or epigenetic changes. Here, too, the developmental flexibility has its limits. The formation of connections probably requires some molecular recognition mechanism since cortical axons seem to be targeting from the beginning certain areas and certain locations within an area (Bressoud & Innocenti 1999). Moreover, axons seem to conform to intrinsic geometric rules, which determine their computational peculiarities (Tettoni et al. 1998).

The work of Finlay et al. more directly addresses the channeling issue. Their proposal is simple and elegant: Structures with protracted and delayed neurogenesis are evolutionarily favored, in particular the cerebral cortex. In turn, the expansion of the neocortex results in the emergence of the new capacities this structure confers. The work has several interesting implications.

First, an important cause of phenotypic channeling in evolution is probably the "chaining" of brain modifications in development. One aspect of this chaining is that brain parts cannot change in isolation, instead they all get bigger (or smaller) together, a kind of biological socialism. Why? Finlay et al. are not explicit on this point. One possibility is that that cell proliferation was regulated throughout the whole brain, by modifying ubiquitously the timing of neurogenesis (heterochrony), for example by increasing the period of symmetrical division or by speeding up the cell cycle. However, it is also true that changes in one brain-part affect the development of other parts, often far away, for example by regulating neuronal survival or the selection of axonal and/or dendritic branches and synapses, on grounds of molecular affinities, trophic interactions and activity. So, brain modifiability (plasticity) is essentially global, and this must be so in evolution because it is so in development. Incidentally, as the authors noticed, the coordinated changes of brain parts stress the essentially distributed nature of brain processes, a useful correction of exaggerated neophrenological enthusiasms.

Second, if the brain must change as a whole, how did the cortex manage to increase disproportionately? Finlay has, in the past, set the question in terms of the trophic theory, suggested that the cortex can increase its size without increasing the trophic demands on other structures because the cortical neurons provide their own trophic support through abundant local axon collaterals (Finlay 1989). But does the disproportionate growth of the structures whose neurogensis occurs late apply to neocortex itself? If it were so, the supragranular cortical layers, the latest to be generated should increase disproportionately to the other layers. This seems to be true for some areas, in particular the primary visual cortex, perhaps not for all areas (Kornack & Rakic 1998). Furthermore, there is a clear anterolateral to posteromedial neurogenetic gradient in the cortex (of the rat) and this suggests that the posteromedial areas, notably area 17 should have increased the most. Is this a key to the impressive development of the visual system? However, the rate of cell production might be different for neighboring areas (Dehay et al. 1993) indicating that cell production can be locally regulated in the brain and this local regulation may cause differential expansion of cortical territories. To clarify this issue detailed studies of neuronal production in the whole brain, similar to those pioneered by Caviness et al. (1995) are needed.

The third implication of Finlay et al.'s work is that the relationship between structure and function in evolution is indirect. New structures appear in evolution not because of the functional advantages they confer but as byproducts of developmental changes. In other words, the "Tomte" of evolution (Tomtes are magic gnomes in the Nordic forests, ancestors of Santa Claus) having changed the timing of neuronal proliferation, gets, unexpectedly, an enlarged neocortex and thinks: "What the hell do I do with all this? Let us try to connect it in some way." Rather convincing. But why did the Tomte not just let the extra-neocortex atrophy? There was no developmental constraint here. A cortex deprived of thalamic input in development can degenerate or atrophy, at least in the primary sensory areas (Rakic 1988; Zufferey et al. 1999). Instead the Tomte of evolution reorganized much of cerebral cortex when the latter got bigger. Which rules did he follow then? The behavioral advantage of the newly emerged cortical or cortico-subcortical circuits, or some other development dictated rule? To my mind the issue remains open, but the hypothesis of behavioral advantage at the phenotypic selection stage cannot be easily bypassed. Perhaps this was not the authors' intention either.

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The spandrel may be related to culture not brain function

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Abstract: Finlay et al. describe a method of examining brain evolution, but it has limits that may hinder extrapolation to all vertebrate taxa or the understanding of how brains work. For example, members of different orders have brain and behavioral organization that are fundamentally different. Future investigations should incorporate a phylogenetic approach and more attention to behavior to further test their conclusions.

The employment of complex statistical models and new methods (e.g., character mapping, independent contrasts) can clarify evolutionary patterns of change and enhance our ability to test hypotheses concerning the evolution of the brain. There are limitations in analyzing any interspecific data set, however. These limitations do not necessarily cast doubt upon the conclusions of Finlay et al., but do question whether these patterns are representative of all mammals, or all vertebrates. Related to this note of caution, we would like to make two points, one related to statistical analysis and the second related to behavior.

Stephan et al.'s data is one of the most comprehensive comparative data sets on the anatomy of the mammalian nervous system, but it is not inclusive. Within each order examined, not every extant species has been examined. Only 53 species (Stephan et al. 1991) out of 390+ species of insectivores were examined (13.6%). This suggests that brain-behavior relationships or patterns of brain evolution derived from the data set should be addressed with caution. For example, would the same pattern hold if species representation within each order was constant? A case in point is the Insectivora. The bulk of species within this order are within the family Soricidae (289 spp.) (approx. 74% of total), yet the data set contains 24 soricid species (45%) and most of them represent two genera (*Sorex* and *Crocidura*). Given that there appears to be a skew in the representation of species within the data set, how can we be certain that the observed patterns are representative of the order?

Finlay et al. make an attempt to control for "phylogenetic effects" by employing their taxonomical ranking. Taxonomic ranking has, however, been shown to be more prone to type I error (i.e., false positives) than other comparative methods (Martins & Garland 1991). An additional problem of using taxonomic ranks is the lack of consistency employed by Finlay et al. They have distinguished between two orders and two sub-orders at the same time. If the purpose of taxonomic ranking is to assess whether there are differences in an evolutionary pattern between taxa, it is essential to be consistent. Thus, either remain with order-level rankings or sub-order rankings. For example, for the latter divide Chiroptera into the Megachiroptera ("flying foxes") and the Microchiroptera ("micro-bats"). This is a reasonable division because the neural differences used to differentiate simians from prosimians are similar to those that exist between flying foxes and microbats (Baron et al. 1996; Pettigrew 1986).

In our own analyses, inclusion or exclusion of species pairs resulted in a retention of significance, but a reduction in the amount of variance explained (Iwaniuk et al. 2000). The employment of comparative techniques, on the other hand, can have major effects on the significance of results as well as the amount of variance explained (Harvey & Pagel 1991). Our own research has demonstrated this for the relationships between corticospinal projections and dexterity (Iwaniuk et al. 1999). Previous studies that did not use modern comparative methods were found to have "false positives."

The second reason to use modern comparative methods is that the parameters may be inaccurately estimated with "ahistorical" statistics (Harvey & Pagel 1991; Martins & Garland 1991). This is particularly applicable to Finlay et al.'s comparisons of regression models (Finlay et al.'s Fig. 2). Use of the independent contrasts approach (Felsenstein 1985; Harvey & Pagel 1991) to calculate the regression models could significantly change the standard error of estimate values and would address the "phylogenetic effect" issue raised above.

Given these limitations to the data set, and the limited number of species included in the ontogenetic analysis, it may be premature to extend their theory to hominid evolution. This is especially true if one considers that different clades may vary in the rate of evolution of a trait (Garland 1992).

Related to the theory that structure precedes function, we would also like to address the issue of function. One view of function holds that brains work much the same way, for example, the humming bird versus baleen whale metaphor. Thus, big brains are more likely than small brains to have excess neurons available for cognitive processing. Alternately, the localization function view holds that each region of the brain has a specialized function. Thus, brains of necessity become bigger in order to accommodate new functions. Finlay et al. consider both positions but have not considered a third possibility; that is, that brains do not all work the same way. In order to know how brains work requires better behavioral information.

We illustrate our point with an example. Research from our laboratory shows that rodents are so skilled in the use of their forepaws that their performance in some respects matches that of primates (Whishaw & Miklyaeva 1996). But rodents differ from primates in using olfaction rather than vision to reach (Whishaw & Tomie 1989). This order-related difference is pregnant with consequences. A shift from olfactory guidance of skilled reaching to visual guidance must require a reorganization of the brain. For example, whereas it is proposed that primates control reaching movements using cortically controlled spatial vectors (Georgopoulos et al. 1999), rodent reaching does not require a vectoring system because the target location is always the same, the tip of the nose. Furthermore, the dorsal and ventral streams that mediate hand movements related to object action and object recognition in primates (Milner & Goodale 1995) would not exist as such in rodents. Likely, most cortical regions and their interconnecting pathways in rodent and primate brains will be different to accommodate this order-related difference. The discontinuity in paleocortex size illustrated in Finlay et al.'s Figure 3 may be a manifestation of such reorganization. It is very likely that there are other behavioral changes that might influence not only brain size, but brain organization (e.g., tactile control of skilled movements in Carnivora and language in humans).

Should behavioral differences prove to be central to differences in brain size and organization, this would weaken the hypothesis that structure precedes function. Nevertheless, we agree that the "spandrel" concept might prove to be more useful in explaining how brains acquire culture. All animals are capable of learning and animals with a more complex behavioral repertoire are capable of learning more than animals with a simple behavioral repertoire.

Variability in the sizes of brain parts

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Abstract: Brain parts can scale independently of the whole brain, and an example is given to point out that the authors underestimate variation that can exist in brains of equal size.

Finlay et al. argue that "sensory systems and brain parts scale . . . together" and that "the variation of individual structure size at any particular brain size did not exceed two-to-three fold." While

predictable scaling of brain parts with brain size does seem to be typical, Finlay et al. underestimate the variation that exists in brain parts when brains are approximately of the same size. We include here, for example, photographs of the superior colliculus of a rat and a ground squirrel of nearly the same body and brain size (see Woolsey et al. 1971). We estimate that the superior colliculus is nearly 10 times larger in volume in the ground squirrel than the rat. Such examples demonstrate that brain parts can vary greatly in brains of the same size, and that an overall scaling of parts to the whole does not excessively constrain brain evolution. For brains of the same size, variation in the sizes of parts of 2 or 3 times would seem enough to confer major behavioral advantages, and differences of 10 times would seem to be rarely necessary.

Such observations should not detract from the compelling evidence that given brain parts commonly scale differently with overall brain size, and it remains important to try to understand why this is the case. Given the relative independence of brain parts to brain size in at least some instances, it seems rather speculative to suggest that larger forebrains emerged without adaptive significance in our ancestors, and that early *Homo sapiens* had more neocortex than they could use. Finally, large brains cannot be simply

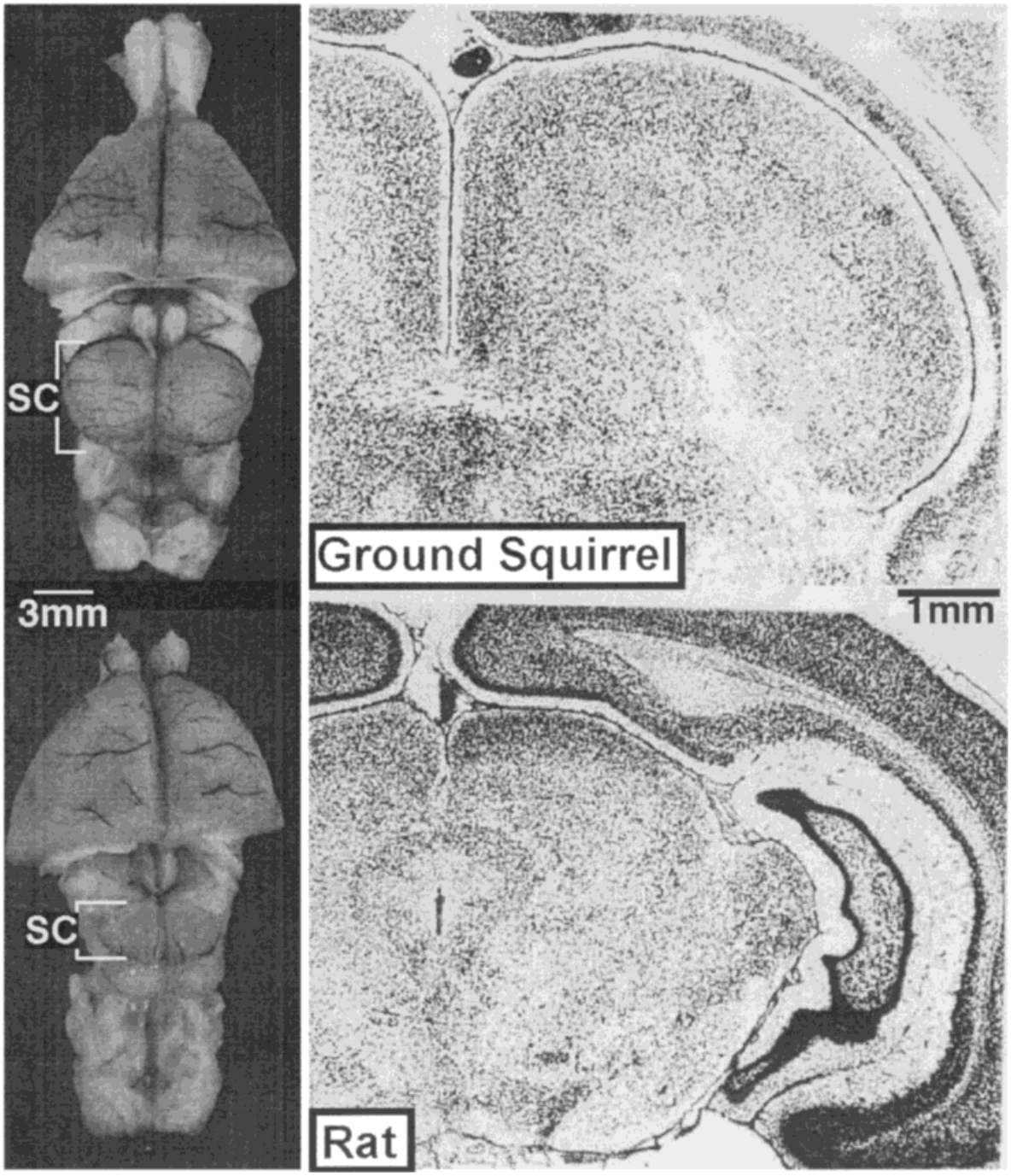

Figure 1 (Kaas & Collins). The left panel shows photographs of dissected whole brains from ground squirrel (top) and laboratory rat (bottom). Cortex has been partially removed caudally to reveal the superior colliculus (SC). The right panel shows coronal sections from each superior colliculus stained for Nissl substance. The photographs have been modified by added text and brackets from the report of Woolsey et al. 1971.

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larger versions of small brains because of scaling problems (see Kaas 2000), and considerations of these problems may help understand common trends in brain evolution.

Hominid brain expansion and reproductive success

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Abstract: Although many aspects of human cognition are likely to be "spandrels" passively affiliated with the primary impetus for hominid brain expansion during the Plio-Pleistocene, that expansion was most likely generated and maintained not by "housekeeping" functions but by improved capacities of reproductive success, especially survivorship.

Novel paradigms often emerge simultaneously in parallel disciplines. The arguments presented by Finlay et al. represent an important example. Their reinterpretation of the underlying basis of mammalian brain expansion echoes similar recent advances in our understanding of other biological structures (Raff 2000). All share two fundamental elements: that subtle fluctuations in developmental sequences provide the primary "raw material" for most evolutionary change, and that the final effects of such changes more often than not encompass more than the "target" adaptations under immediate selection. As an example, the length of the radial neck in the primate forearm has long been argued to vary in a manner that increases the power of forearm flexion by the *m. biceps brachii.* In fact, however, this trait is merely a simple correlate of overall bone length, and has probably not been individually altered in higher primates (Reno et al. 2000). Finlay et al. present arguments for expansion of the isocortex which are almost an exact parallel. Their cogent analysis is exceptionally powerful and likely to transfigure the current view of mammalian brain evolution. However, two of the issues they address concerning hominids require some minor amendment.

First is their view that Plio-Pleistocene expansion of the hominid isocortex was probably an elaboration of some cerebral housekeeping behavior (e.g., "enhanced motor control" or "enhanced memory of fruiting trees or water"). In challenging the "virtual industry" linking specific behaviors to isolated brain substructure, they note that such substructural differences are usually so minor as to negate any validity simply because of the minimal "size of the effect." However, "improvements" in ordinary housekeeping functions of the hominid isocortex are equally improbable as selective agents responsible for its expansion. Hominids rank as the most advanced, K-selected mammals ever to have evolved, and it is implausible that mundane improvements such as the ability to locate food or water could have played a substantial role in their remarkable cerebral advancement, given the dramatically increased *reproductive cost* that accompanies brain expansion. Did early hominids really have a significantly greater capacity in "finding" food or water than highly cerebral chimpanzees which are fully capable of acquiring complex human linguistic functions and to engage in self-cognizant play (Savage-Rumbaugh 1980; 1993)?

As Finlay et al. cogently argue, the largest mammal brains require the longest pre-parturitional maturation. However, they also require the most prolonged periods of post-parturitional development, that is, a corresponding protraction of all subsequent life history phases, including sub-adult dependency, age of sexual maturation, and maximum life potential (Cutler 1976). These systematic delays in "recouping" parental investment impose very high evolutionary costs because they so dramatically depress reproductive rate compared to that of conspecifics, *unless* they can be balanced by proportional reductions in annual mortality. It is therefore unlikely that "simple" house-keeping improvements played a pivotal role in favoring such an increasingly "expensive" isocortex in Plio-Pleistocene hominids.

It is much more likely that early hominid brain expansion was a direct product of behaviors intimately linked to immediate reproductive success. An increase of only 1% in annual *subadult* survivorship would have proved an enormous downstream reproductive advantage, and there are numerous possibilities of improvements in *parenting capacity* which might have contributed to this "goal." Increased indirect involvement by males via provisioning, enhanced maternal attentiveness, and reduced social instability (monogamous pair-bonding and reduced male-male aggression) are some important possibilities among many – all of which may have required more "sophisticated" mate selection by both sexes (Lovejoy 1981; 1994).

Second, some comment is also required about Finlay et al.'s suggestion that most of Plio-Pleistocene brain expansion might be a simple consequence of increased body mass. The willingness of anthropologists to tender "data" so tenuous as to constitute tacit misinformation is truly unfortunate (see White 2000, for discussion). Some relied upon by Finlay et al. (who must be held entirely blameless) are a conspicuous example. Not only are several of the hominid taxa used to make their calculations of dubious validity – their supposed attributes are equally so: there is currently only one specimen for which cranial capacity and body mass can both be *estimated* (KNM-WT-15,000), and there are virtually no current reliable means of associating *postcrania* with crania for any legitimate early hominid species save association by site (which can involve temporal separations of several hundred thousand years). Furthermore, based on the sources they cite, the body mass estimates published by Wood and Collard (1999) were accomplished using a host of entirely different methods, some of which involve the use of orbital area, which is heavily influenced not only by body size but by cranial capacity itself. It is unfortunate that these authors did not properly emphasize the virtual apocryphal nature of these "data." Plio-Pleistocene hominids exhibit dramatic, *morphologically* recognizable expansions in cranial capacity which increasingly distinguish them structurally from living apes. These changes are therefore more likely to reflect true behavioral change than mere increases in body mass.

These minor caveats aside, Finlay et al. are to be congratulated for their pivotal reinterpretation of the evolutionary basis of brain size variation in mammals (including hominids).

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Cetaceans would be an interesting comparison group

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Abstract: One of the mammalian groups absent from the Finlay et al. study is cetaceans (dolphins, whales, and porpoises). Inclusion of cetaceans would be useful for assessing the generalizability of the authors' conclusions. Recent findings suggest dolphins may differ from the general pattern observed by Finlay et al. I encourage Finlay and her colleagues to include developmental neurobiological data on cetaceans, when available.

Finlay et al. provide a major thought-provoking work which will surely stimulate further discussion and empirical testing for a long time. They are to be complimented on their ability to bring together so many facets of mammalian brain evolution, that is, development, phylogeny, allometry, heterochrony, and hominid evolution, and for providing a cohesive framework for interpreting data on brain evolution in mammals.

Finlay et al. included 131 mammalian species in their sample. This is, as they admit, a small fraction of all mammalian orders, leaving intriguing questions about the generality of their findings and interpretations to mammalian groups not included in their analyses, such as carnivores, ungulates, and marine mammals. One of the mammalian orders absent from the Finlay et al. analysis is cetaceans (dolphins, whales, and porpoises), though they are mentioned sporadically throughout the target article and appear to be clearly of interest to the authors. Cetaceans are members of the superorder Ungulata and share a sister-group relationship with artiodactyla, even-toed ungulates. Along with, perhaps, sirenia, cetaceans represent a particularly useful group for testing the generality of the findings and conclusions in the target article. Cetaceans diverged from terrestrial mammals approximately fifty-five million years ago and possess the most derived set of adaptations to a fully aquatic existence of all marine mammals. Brains of species within the suborder Odontoceti (dolphins, porpoises, and toothed whales) are thought to be the most divergent from that of their terrestrial ancestral group, the Mesonychia. There are several characteristics of odontocete brains that make them interesting within the context of the conclusions and hypotheses put forth by Finlay et al. in the target article. Many species of dolphins and porpoises evince a level of encephalization comparable to and exceeding that of living anthropoid primates (Marino 1998). The encephalization level for several species within the Delphinid family is second only to modern humans (Marino 1998). However, the cetacean neocortex possesses a number of divergent features on the level of cortical cytoarchitecture (Glezer et al. 1988), lobular organization (Morgane et al. 1980), and surface morphology (Morgane et al. 1980). The extremely divergent nature of these features from that of other mammalian brains continues to be the centerpoint of active debate about dolphin intelligence. Moreover, the simultaneous occurrence of convergence in relative brain size and divergence in cortical structure between primates and cetaceans suggests that cetacean-primate comparisons would be useful for assessing the generalizability of the hypothesis put forth by Finlay et al. in the target article.

One of the implications of the Finlay et al. findings is that one ought to be able to predict the volume of a given brain structure from the volume of the rest of the brain across species. In other words, one should be able to use the relationship between brain volume (or, more specifically, the total brain minus the target structure) and the target structure in one species to predict the size of that structure in another species. We recently examined whether the size of the cerebellum relative to the rest of the brain could be predicted in dolphins from another highly-encephalized mammalian group, the anthropoid primates (Rilling & Insel 1998). We measured cerebellar volume and the volume of the rest of the brain (total brain minus cerebellum, or noncerebellar brain volume) in a large sample of bottlenose and common dolphin specimens and compared these data with previously published data on anthropoid primates from Rilling and Insel (1998). Our results demonstrated that dolphin cerebella, which average about 15.1% of total brain size, are significantly larger than that of human and nonhuman anthropoid primates after controlling for brain volume (Marino et al. 2000). The average dolphin cerebellum is 17.2, 53.5, and 67.5% larger than the average ape, human, and monkey cerebellum, respectively, after controlling for brain size. We also regressed log cerebellum volume on the log of noncerebellar brain volume for the dolphin and primate samples in order to determine if the primate regression values could predict dolphin cerebellum size. Using this method we found that the average dolphin cerebellum is significantly larger by 15.5, 55.4, and 49.5% than predicted for an ape, monkey, and human of the same noncerebellar brain volume, respectively. Therefore, we could not predict dolphin cerebellum size on the basis of the primate data. Interesting to note, the slopes of the functions relating cerebellar volume to noncerebellar brain volume across the dolphin and primate groups were not significantly different. There was a difference in the elevation of the *y*-intercept once common slopes were fitted across the two groups. However, the fact that the relationship between the cerebellum and the rest of the brain in primates cannot be used to predict cerebellum size in dolphins suggests that there may be something about cetacean brain allometry that does not conform strictly to the general patterns observed by Finlay et al. and that it might be informative to further examine these issues. It is interesting that Finlay et al. found that the cerebellum was an exception to the strong relationship between the position on the prosomeric axes and duration of neurogenesis found in almost all of the other regions of the embryonic neural tube. To add to this, as the authors themselves point out, the fact that the fully aquatic niche allows for a certain amount of decoupling of brain size from body size (presumably because of "aquatic weightlessness") it may be possible for cetacean brain-body allometry to be somewhat different than in other mammals. In our analysis, we found that, relative to body size, the dolphin cerebellum is 149 and 476% larger than predicted for an ape and monkey of the same body size, respectively.

Finlay et al. show that the relationship between the temporal pattern of neurogenesis and brain allometry is broadly predictable. However, our findings and the special circumstances of the cetacean adaptive niche may reveal interesting deviations from this overall pattern. I, therefore, wish to encourage Finlay and her colleagues, as well as others, to undertake the comparison of developmental structure in postmortem brains of cetacean (as well as sirenian) specimens when they become available. These efforts may shed some very valuable light on the generality of their findings and the range of ways in which development shapes brain evolution in mammals.

Changes in perinatal conditions selected for neonatal immaturity

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Abstract: The mechanics of walking restructured the pelvis and narrowed the birth-canal that selected for delays in skeletal ossification. Prolonged phases of fetal maturation increased the mass and volume of the brain relative to adult body-size, as encephalization increased. Thus, bipedal-walking and episodic increases in hominine body size probably triggered selection for neonatal skeletal immaturity that led to encephalization.

The comparative data in Finlay et al. clearly demonstrates that changes in developmental timing underlie encephalization and the parcellation of cortical subsystems in the evolution of mammals. However, their adaptationist explanations for these developmental delays appear seriously flawed. They correctly argue against the possibility that selection pressures for cortically-based adult behavior drove brain expansion; however, they retained a traditional adaptationist model in which natural selection on adult "*archocortical, corticoid, or sub-cortical processing triggered the adjustment of global timing constraints*" (p. 29, emphasis is mine). In their analysis, selection for sub-cortical processes replaced selection for the suite of cognitive traits that we consider distinctly human. Why would selection pressures for enhanced control over the emotions, motor coordination, or a larger memory result in a disproportionate encephalization only in hominines? Why should we accept that selection for sub-cortically controlled behaviors that are presumably adaptive, if not essential, for the survival of most mammals explain the uniqueness of hominine brain growth better than uniquely human skills such as language and tool-making? I do not think that selection for uniquely human cortical or subcortical cognitive functioning can ever satisfactorily explain the delays in fetal development that underlay encephalization (Ragir 2000a; 2000b; 2000c).

Arguments about the evolution of cognitive function tend to ig-

nore the costs of encephalization and delayed postnatal maturation. The energy that is necessary for the growth of a large brain and prolonged juvenile dependency would increase the birth-intervals and depress fertility in those females giving birth to encephalized offspring (Finlay & Darlington 1995; Leonard & Robertson 1992; 1994; 1996; 1997; Little 1989; 1996; Martin 1983; 1985; Ragir 2000a; 2000c; Shea 1989; 1990; 1992). A slow-growing encephalized infant places greater energy-demands on the mother; within-group competition ought to favor the developmental profile that made the fewest demands on female energy during her reproductive life. On the other hand, if a perinatal selective pressure threatened all births, then one might expect a significant reduction in the potential for growth in the whole population rather than just in an encephalized segment. Such a reduction in female fertility might even facilitate the punctuated transformation of a species' developmental profile.

The considerable reproductive advantages of bearing small-brained offspring motivated me to look once more at any universal selection pressures on the perinatal context that could directly affect developmental timing. I believe that the constriction of the anterior-posterior (A-P) dimension of the hominine pelvis was a species-specific trait of that order and that the evolutionary changes in human parturition provide insight not only into the initial shift in australopithicine brain/body proportions but also in encephalization in early Homo and the in late *H. erectus/sapiens* transition (Ragir 1986; 2000b). Although the hominine pelvis widened laterally with each increased adult size, the efficiency and structural demands of bipedal locomotion prevented a comparable increase in the anterior-posterior diameter of the pelvic opening (Abitbol 1987; Ruff 1995). Thus, increases in fetal mass created episodes of selective pressure on parturition and resulted in successive delays in fetal maturation and a disproportionate increase in neonate weight compared with that of the mother.

Since even a small-headed neonate was forced to turn its head to the side to slip through the narrow middle passage between the sacrum and pubis, the shoulders, which tend to follow the head as it turns, were in danger of being caught by this constricted opening (Abitbol 1987; 1990; Leutenegger 1982; 1987; Rosenberg 1992; Rosenberg & Travathan 1996; Trevathan 1992). Thus, skeletally immature neonates and their mothers would be more likely to survive the process. The narrowing of the A-P cross-section of the birth-canal was likely to prolong labor or to block the birth and, thus, to select for less skeletally mature neonates. Delays in skeletal ossification were the result of the progressive prolongation of earlier phases of fetal growth, including crucial phases of neurogenesis. These changes in human fetal maturation resulted in relatively large, boneless neonates able to squeeze through the narrowest dimension of the hominine birth-canal (Leonard & Robertson 1994; Little 1989; Martin 1985; Shea 1990).

There appear to have been at least three significant episodes of encephalization. The initial transition to bipedalism might account for only the first and the least dramatic episode of encephalization among the australopithecines (Aiello & Wood 1994; Falk 1999; Falk et al. 2000; Hartwig- Schwerer 1993). It is difficult to attribute later episodes of encephalization to a terrestrial-bipedalism that emerged millions of years before (Falk et al. 2000; Smith 1992; 1993; Walker & Leaky 1993). These late episodes of encephalization in early Homo and during the *erectus/sapiens* transition may in fact be the result of the sharing of animal foods and detoxification of vegetable foods through pounding, soaking, the consumption of clay, and cooking (Aiello & Wheeler 1995; Kaplan et al 2000; Milton 1999; O'Connell et al 1999; Ragir 2000a, in press).

Adult body size increased with stable, year-round access to high-nutrient foods that probably affected maternal fertility and increased fetal mass. After birth, the percentage of energy available for growth becomes drastically reduced, and despite prolonged juvenile growth and moderately delayed reproductive readiness, increases in the body size of Homo are proportionately less than the combined in utero increases in brain mass and postnatal increases in brain volume. I propose that the delay in skeletal ossification underlies the initial universal shift in brain/body proportions in australopithicines, and that increases in overall hominine size triggered subsequent episodes of encephalization and prolonged postnatal development in early and archaic species of Homo.

Encephalization appears to be the best evidence for a small but significant developmental delay in the australopithecines, and each increase in species size triggered further delays in developmental timing. If encephalization was the result of a commitment to terrestrial bipedalism, then the changes in life history discussed above are independent of and fundamental to the emergence of all unique forms of human behavior.

Allometric departures for the human brain provide insights into hominid brain evolution

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Abstract: Researchers studying primate brain allometry often focus on departures from allometry more than the allometric relationships themselves because only the former reveal what brain regions and behavioral-cognitive abilities were the focus of selection. Allometric departures for the human brain provide insights into hominid brain evolution and cast doubt on the suggestion that the large human cerebral cortex is a "spandrel."

Recently, I was showing a colleague a plot of cerebellar volume against brain volume among anthropoid primates (Fig. 1).

I pointed out that the ape data had a similar slope to the monkey data, but a higher *y*-intercept, implying that apes have larger cerebella for their brain size than monkeys. Meanwhile, a third colleague who knew nothing about brain allometry entered the room to ask my colleague a question. As he was leaving, he glanced down at the graph in my hands and said, "Wow, I wish my data looked that nice." At first, I thought, "How could he possibly make an assessment of these data that quickly?", but then I realized that to someone unfamiliar with the subtleties of this type of analysis, what really caught the eye was the overall strength of the correlation in the data; that is, the consistency with which cerebellar volume increased with brain volume ($r^2 = 0.97$). To him, the grade shift that I was so narrowly focused on looked like inconsequential noise to a very orderly set of data. This off-hand comment ef-

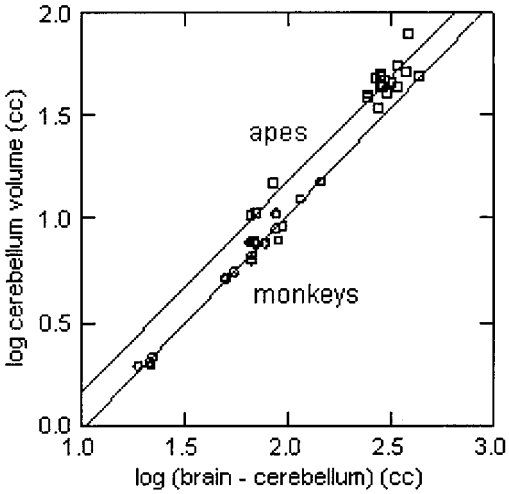

Figure 1 (Rilling).

fectively summarizes the point convincingly driven home by the thorough statistical analysis of Finlay et al. What is truly remarkable when we examine regressions of brain structures on each other (at least for mammals) is the strength of the resulting correlations; the consistently large proportion of the variance that is accounted for.

But if the third colleague had stayed a little longer, I would have told him about the grade shift and why I was excited by it. I would have said that the departure from allometry revealed something about primate brain evolution that a strictly linear relationship could not, namely that hominoid evolution likely involved focused selection for expansion of a specific brain structure; the cerebellum. Furthermore, if we had a clear idea of the functions supported by the cerebellum, we might be able to make some inferences about the type of capacities that were selected for in apes. On the other hand, as the authors emphasize, if growth in all brain structures is perfectly correlated, and structure volumes do not vary independently of each other, then we cannot say anything about the anatomical locus of selection. We do not know which brain structures selection acted on and which were dragged along for the ride; we don't know what is an "arch" and what is a "spandrel." Researchers studying primate brain allometry often focus more on departures from allometry than the allometric trends themselves because the former provide clues with respect to what brain regions and mental operations were selected for. In so doing, however, we often lose sight of the forest for the trees.

Considering this, it is fortunate for our knowledge of hominid brain evolution that the human brain is not simply an allometrically scaled-up version of a nonhuman primate brain. The human cerebellum is smaller than predicted for a nonhuman anthropoid primate with a human-sized brain (Rilling & Insel 1998; Semendeferi & Damasio 2000). Consequently, some other brain region must be larger than predicted by nonhuman primate allometry. Analysis of both post-mortem and in vivo MRI brain data reveal that the human cerebral cortex is larger than predicted by nonhuman primate allometry (Deacon 1988; Rilling & Insel 1999). The human frontal lobe, when defined by cortical surface landmarks, is not disproportionately large for an ape brain of human size (Semendeferi & Damasio 2000). However, although still debated, there are data (Brodmann 1912) showing that when the prefrontal cortex is defined cytoarchitectonically, the volume of the human prefrontal cortex is twice the size predicted for a nonhuman primate of the same neocortical surface area (Passingham 1973). Evidence is also accumulating that the human temporal lobes are disproportionately large for our brain size (Rilling & Seligman 2000; Semendeferi & Damasio 2000), and the latter observation may be related to the expansion of language cortex and associated connections. In this case, the enlarged temporal lobes and the capacity for language are unlikely to be spandrels resulting from selection for some other ability or brain structure. Instead, the adaptive value of language may have driven human brain evolution.

Another criticism of this otherwise superb article is the discussion of human brain evolution, in particular the statement, "Only with the appearance of anatomically modern humans did brain size become somewhat disproportionate." The fact that there is a fairly regular pattern of change in brain size with changes in body size among the sample of hominid taxa considered does not mean that increases in brain size were merely passive responses to selection on body size (Armstrong 1985; Martin & Harvey 1985; Stephan et al. 1988). Artificial selection experiments with mice produce correlations between brain and body size, regardless of which trait is the focus of selection (Lande 1979). The difference is in the steepness of the resulting slopes, with selection on brain size producing slopes of around 0.8, and selection on body size producing much shallower slopes of around 0.4. I calculated an allometric slope of 1.50 for the logarithmic regression of brain size on body size for the sample of hominids referenced by Finlay et al. (Wood & Collard 1999), and Pilbeam and Gould (1974) calculated a brain:body slope of 1.73 for a smaller sample of hominid taxa. As Pilbeam and Gould emphasized, the steepness of this slope almost certainly implies selection on brain size and a correlated, perhaps more passive, increase in body size. Brain:body slopes for non-human anthropoids and mammals are 0.70 and 0.77, respectively (Martin 1996; Stephan et al. 1988). If the hominid data points were compared to one of these two reference lines, then scaling along the hominid curve (with its slope of 1.5) would produce marked increases in encephalization (the distance of the points with respect to the reference line would get larger with increasing body size). What appears to have been altered in hominid evolution is the slope of the scaling relationship between brain and body size, and this in itself is likely an adaptation.

Brain scaling, behavioral ability, and human evolution

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Abstract: The existence of linked regularities in size among brain components across species is, by itself, not a strong argument against the importance of behavioral selection in brain evolution. A careful consideration of hominid brain evolution suggests that brain components can change their scaling relationships over time, and that behavioral selection was likely crucial. The best neuroanatomical index of a given behavioral ability can only be determined empirically, not through comparative analysis of brain anatomy alone.

Finlay et al. make a strong case for linked regularities in size changes among at least some brain components in primates, insectivores, and bats over their evolutionary histories. Their argument that these regularities are a reflection of some basic features of neurogenesis is quite reasonable. However, as they point out, this account is essentially a mechanistic one. The interpretation of these patterns, with respect to what they imply about developmental constraints as well as structure/function relationships, is not particularly clear-cut.

First, it is important to recognize that the existence of scaling regularities among brain components (and between brain and body) is a completely orthogonal question of whether or not the driving force behind brain evolution is behavioral adaptation. Selection on specific behaviors could still logically have been the ultimate cause of any species differences in brain anatomy no matter how closely linked brain components appear to be over evolutionary time.

Second, the lessons of hominid brain evolution make it unclear just how tightly brain components must be connected. There appear to be quite clear differences in the relative proportions of various functional regions of the cerebral cortex between humans and all other primates (e.g., Armstrong 1991; Brodmann 1912). For example, Brodmann's data suggest that humans have about twice the prefrontal cortical surface area that we would predict for primates, based on the overall surface area of their cortex (Deacon 1988; 1997). Holloway (1992) and others have shown (using Stephan et al.'s 1981 data) that the primary visual (striate) cortex in humans is only ~60% as large as predicted from primate brain size scaling relationships. Clearly, some species can significantly change the relative proportions of some components compared to others, and this raises the distinct possibility that natural selection, as opposed to strong developmental constraints, is the explanation for these patterns across species.

The authors' claim that most of hominid brain evolution can be explained as a simple "straightforward function of body mass" is actually very misleading. Their conclusion is based on a regression of brain volume on body mass for hominid estimates (extracted from the literature by Wood & Collard 1999). From this they cal-

culate that greater than 90% of the variability in hominid estimated brain volume can be explained by variation in estimated body mass (if modern humans are excluded). This conclusion, however, completely misrepresents the context (and therefore the significance) of hominid brain evolution, which actually shows clear and consistent trends away from the primate (and mammalian) brain/body relationship. Finlay et al.'s calculation is based solely on estimates from hominid fossil species, and ignores entirely this phylogenetic context. Figure 1 shows the hominid fossil data the authors used in their calculations, along with the primate best fit regression (calculated from Stephan et al.'s 1981 data). One can see that *Australopithecus africanus* estimates are already significantly above primate expectations for their body size (by 199 cc). If further increases in brains size among later hominids were to occur solely in accordance with the empirically derived primate scaling relationship, we would never expect brain sizes to be larger than ~657 cc (i.e., for Neanderthals, the heaviest hominids). In fact, Neanderthal brain sizes are less than 19% as large as one would predict on this basis (actual change from *A. africanus* sized brain was 1,055 cc, predicted change should only have been 200 cc), and modern human brain sizes are less than 10% what we should expect (actual increase: 898 cc, predicted: 89 cc). Thus, in point of fact, only a small proportion of hominid brain size increase can be explained by body size if we take the proper context into account. Finlay et al.'s treatment of the hominid data is completely at odds with their own central focus on broad cross-species comparisons. It also, ironically, is an example of what they specifically caution against: separating human evolutionary processes and patterns from those used to explain other species. To separate hominids from primates the way they do is to suggest that each evolutionary lineage can set its own rules regarding brain/body size relationships, yet this completely undermines the thesis that brain scaling is strongly constrained across broad groups of species.

The discussion of Neanderthal and anatomically modern *Homo sapiens* is also problematic. It is true that these species (assuming they really are different species) do not show obvious behavioral differences for ~40,000 years of temporal and geographic overlap – at least judging from their tool assemblages – and that they also differ in encephalization quotient (EQ). The authors point out that this is consistent with their idea that "big isocortices may be spandrels – byproducts of structural constraints for which some use is found later" (sect. 5). However, Neanderthal appear to have had very large brain sizes in absolute terms (toward the high end of populational variation in modern humans, see Fig. 1 and Holloway 1985). Thus, the authors' explanation first requires us to assume that behavioral capacity is a function of the extent to which a species departs from brain/body scaling relationships (i.e., their EQ). While it is commonly assumed that behavior can only be properly indexed in this way (e.g., Wood & Collard 1999), it does not follow that because brains scale with body size, all relevant behavioral capacities must therefore be a function of deviations from brain/body scaling relationships. Exactly what brain measurement is the best index of any given behavioral attribute is an independent empirical question, not one that can be decided a priori. In fact, there are several studies suggesting that absolute brain size, independent of body size, has important behavioral implications (Beran et al. 1999; Rench 1956; Riddell & Corl 1977; Rumbaugh

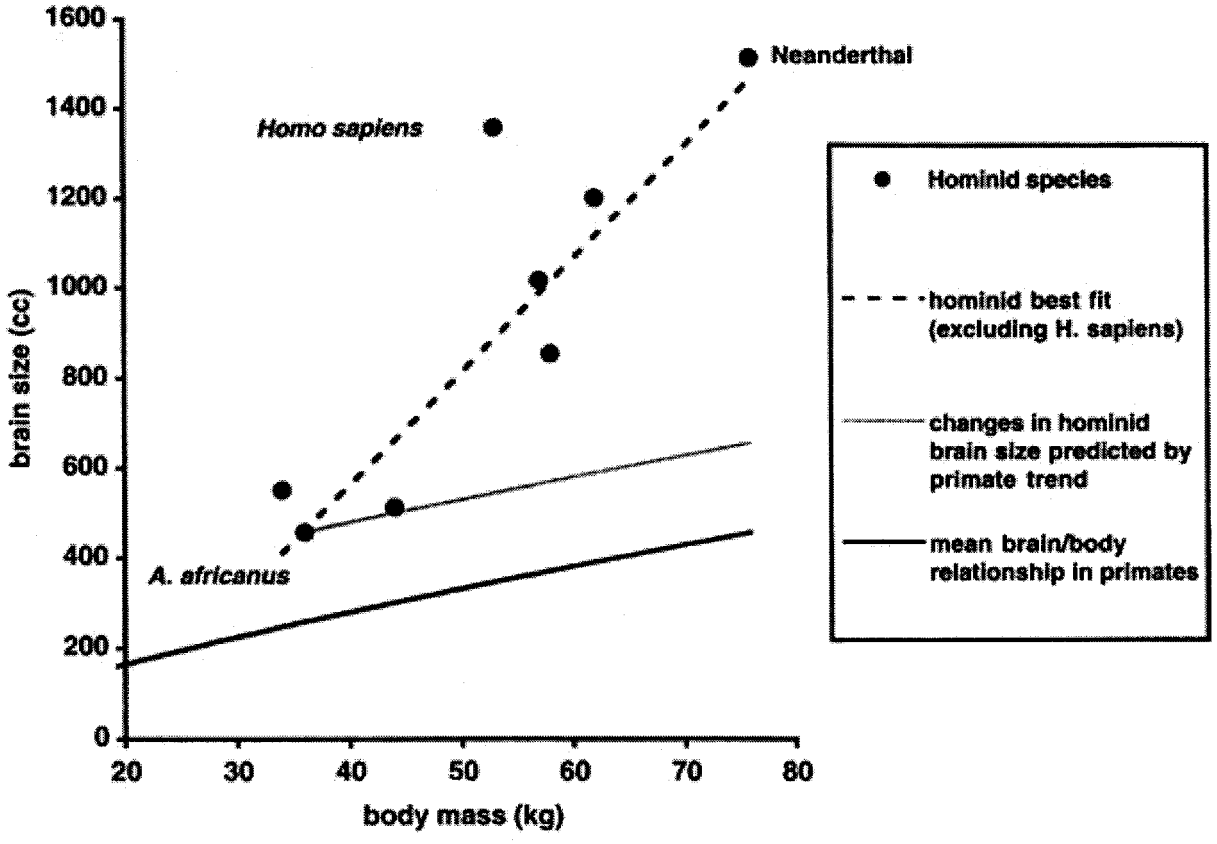

Figure 1 (Schoenemann). Brain size plotted against body mass in hominid species (data from Wood & Collard 1999). Dark solid line represents the best fit (least squares) regression for primates: (brain cc) = .084(body kg)$^{.766}$ (N = 44, r = .97 using log transformed variables; data from Stephan et al. 1981). The gray solid line represents increases in brain size from *A. africanus* that would follow the primate trend. Dotted line represents the relationship reported by Finlay et al. for this data. The extent to which the gray and dotted lines diverge is a measure of how poorly body size predicts brain size evolution in hominids.

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1997). While there are undeniable problems in studying relative abilities across species (Essock-Vitale & Seyfarth 1986; Macphail 1985), lack of unequivocal evidence does not license us to conclude that absolute brain size has no behavioral implications (note that Finlay et al. themselves seem perfectly willing to accept that EQ is behaviorally relevant across species). The authors' comment that "There is really no justifiable metric of behavioral complexity that would account for most of the excess poundage of the whale brain [over that of hummingbirds]." But do we really know enough about whale and hummingbird behavior to legitimately come to this conclusion? Is it really the null hypothesis that, for example, guinea pigs (*Cavia cutler*) are likely to be more behaviorally complex than elephants (*Loxodonta africana*) simply because they have higher encephalization quotients (EQs): .95 versus .63? Guinea pig brains weigh ~3.3 grams, while elephant brains weigh over 5,700 grams (data from Quiring 1950, EQs calculated using Martin's 1981 mammalian brain/body scaling relationship). Is it really likely that this extra ~5,700 grams in elephants has no behavioral implications?

One intriguing possibility is Ringo's (1991) suggestion that the increase in the number of neuronal connections (as estimated from cortical white matter volume) is not sufficient to maintain equal connectivity between all regions. This suggests that a natural by-product of increasing brain size is the increased likelihood of cortical specialization. This, in fact, appears to be the case across species (e.g., Ebbesson 1984; Uylings & Van Eden 1990).

More generally, does the bias for EQs make sense from an evolutionary perspective? As the authors point out, brain tissue is very metabolically expensive (Hofman 1983). It is also highly correlated with maturation time (at least within primates; Harvey & Clutton-Brock 1985). Both of these evolutionary costs operate on absolute amounts of brain tissue – not relative amounts. In the absence of specific benefits accruing to larger brains, a smaller brained animal would necessarily have an adaptive advantage over a larger brained one (Smith 1990). The argument that such adaptive changes would be constrained by a tight linking between brain and body size – making it very difficult for a species to decrease unneeded "excess" brain tissue over time – is belied by the wide variation in brain sizes shown by mammals of the same body size, as the authors themselves point out (see also Schoenemann 1997). The hominid example is a dramatic case in point of the possible disconnect between brain and body size (contrary to the authors' suggestions). If hominid brain size could change so dramatically with respect to body size over the last 2.5 million years, significant deviations from brain/body trends clearly can happen, given the appropriate adaptive environment. The fact that brain and body show tight statistical connections across large groups of species may simply be due to larger bodies allowing for larger brains (perhaps because of metabolic resources; Armstrong 1983; Martin 1981) without strictly requiring them. Selective interactions between and within species would then tend to keep species brain sizes towards the large end. This model is just as consistent with the empirical data as one based on neurogenetic constraints.

However, even if we accept that EQ is the behaviorally relevant variable in the Neanderthal/modern human question, the authors' suggestion requires us to believe that ~2,000 generations (assuming an average time per generation of ~20 years) separate changes in brain structure from their behavioral payoffs. Why would these changes have occurred in the absence of selection? The idea that any significant change in the brain could occur independent of selection for behavioral adaptation is, though possible, just not likely. One can show that adaptive benefits can be extremely weak over evolutionary time and still explain large changes in brain evolution (Schoenemann et al. 2000). Behavioral advantages could have been very subtle (and hence not easy to detect in stone tool assemblages).

Finally, I would take issue with the authors' suggestion that the persistence of behavioral adaptationist views of human evolution are " yet another way to set humans apart from the rest of the animal kingdom" (sect. 8.2). This comment assumes something the authors have not and cannot demonstrate with the data: that brain size differences in other animals have not also been driven by behavioral adaptations. More generally, the implication that human brain evolution is not particularly unique in the natural world is difficult to support empirically. Humans are demonstrably different at a cognitive level precisely because we have more behavioral flexibility. The evolution of the human brain has clearly not led to an increase in the number of hard-wired behavioral reflexes. Thus, it is quite clear, if one actually looks at the behavioral differences between humans and other animals, that humanity has in some nontrivial sense "authored" itself. This is a conclusion based on behavioral data – not brain anatomy data. Anatomy alone cannot determine the significance of behavior.

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Constraint and adaptation in primate brain evolution

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Abstract: Constraint has played a major role in brain evolution, but cannot tell the whole story. In primates, adaptive specialization is suggested by the existence of a covarying visual system, and may explain some residual variation in the constraint model. Adaptation may also appear at the microstructural level and in the globally integrated system of brain, body, life history and behavior.

Before asking questions about *why* brains have evolved as they have, we must understand *how* they have evolved. Finlay et al. have made a major contribution by demonstrating that large-scale covariance associated with conserved developmental timing has dominated mammalian brain-size evolution. In the process, they have successfully addressed major concerns (e.g., Barton 1999; Dunbar 1998) about their previous work (Finlay & Darlington 1995) on the subject. It is not surprising that my own limited analysis of published primate data corroborate the authors' more general findings.

I used the CAIC program of Purvis and Rambaut (1995) to calculate independent contrasts from published (Stephan et al. 1981) volume data for 19 brain structures in 48 primate species. I then assessed covariation in these contrasts by testing for correlation between each of 170 possible pairs of non-overlapping structures and running a principal components analysis of the entire set.

Overall, r^2 values from the pair-wise comparisons were quite high (21% = 0.95, 48% = 0.90). Lower values occurred primarily in comparisons involving olfactory bulb and, to a lesser extent, limbic structures. Interesting to note, visual system structures (striate cortex, lateral geniculate, and optic tract) correlated more highly with each other than with other structures. Principal components analysis of the independent contrasts revealed that two factors accounted for roughly 93% of the observed variance (Table 1). These may be characterized as (1) a "whole-brain factor" loading on all structures except olfactory bulb, and (2) an "olfactory/visual factor" loading positively on olfactory bulb and limbic structures and negatively on visual system structures. Adding body size to the analysis simply introduced a third "somatic" component of variation.

These results closely agree with the three-factor model of Finlay et al., and provide general corroboration for the constraint hypothesis. An important exception, however, is the inclusion of visual system structures in the second factor of variation. This is at odds with the contention of Finlay et al. that there is no "covarying unit, distributed across structures, that is the 'visual system.'"

Table 1. (Stout). *Principle components of brain-size variation in primates*

Structure	Component	
	Whole Brain (83.2% of variance)	Olfactory/Visual (9.5% of variance)
Non-Visual Cortex (neocortex-striate cortex)	0.974	−0.116
Cerebellum	0.975	0.011
Medulla	0.969	0.161
Mesencephalon	0.989	−0.062
Striatum	0.986	−0.066
Schizocortex	0.921	0.346
Hippocampus	0.918	0.312
Thalamus	0.982	−0.081
Hypothalamus	0.981	0.025
Pallidum	0.959	−0.094
Striate Cortex	0.850	−0.466
Optic Tract	0.840	−0.436
Lateral Geniculate	0.892	−0.378
Olfactory Bulb	0.344	0.866
Septum	0.942	0.273
Epithalamus	0.930	0.242
Internal Capsule	0.846	0.003
Vestibular Nuclei	0.923	−0.077

Observation of such a covarying system here provides support for the widespread notion (e.g., Allman 1987; Barton 1999) that visual specialization has played an important role in primate brain evolution. The apparent "trade-off" between olfactory and visual structures seen in the second factor is further suggestive of adaptation.

The fact remains, however, that the vast majority of total variation (83%) is accounted for by the first, "whole-brain," factor. Correlated overall expansion appears to have been the dominant, if not the only, mode of primate brain evolution. As Finlay et al. have also shown, conserved developmental timing probably accounts for much of this overall regularity. Once again, this is corroborated by my own analyses: a multiple regression using the slopes and intercepts of 11 structures regressed on medulla predicts relative developmental timing (event scores from Darlington et al. 1999) with $r^2 = 0.72$ and $p = 0.006$.

What room, if any, does this leave for adaptive specialization? We have already seen that a large proportion of the variation left unexplained by the "whole-brain" factor *is* explained by an "olfactory/visual" factor. Variation in this functionally specific factor most likely reflects adaptive specialization. But what of the variation (7%) that remains even after the second factor is taken into account? Although 7% may not seem like much to be worried about, the extreme range in scale among primates means that even relatively small residuals can equate to striking amounts of absolute variation (Deacon 1990; Finlay & Darlington 1995). Because we do not really understand the relationship between size and function in neural tissue, we cannot say what the functional/adaptive significance of such absolute variation might be.

Of course much of the residual variation may simply reflect measurement error and individual variation. Brain imaging studies of modern primates (e.g., Rilling & Insel 1999; Semendeferi & Damasio 2000) are beginning to reveal just how substantial individual variation can be. In a sample of six chimpanzees, for example, Semendeferi and Damasio (2000) report frontal lobe volumes ranging from 74.1 to 133.4 cm^3 (a difference of 59.3 or 44%). In order to confidently attribute adaptive significance to residual variation, it will probably be necessary to demonstrate strong correlation with some socio-ecological variable such as group size or percent of fruit in the diet.

Adaptive specialization may also be sought in smaller-scale variation not captured by the analysis of large structural divisions (Finlay & Darlington 1995). Adaptive reallocation or reorganization *within* regions may often have been important, as, for example, in the evolution of human neocortex (Deacon 1997; Falk et al. 2000; Holloway 1983; Passingham 1998). In addition, many important adaptations are certain to have occurred at the microstructural level, as is now being documented by researchers including Preuss et al. (2000) and Nimchinsky et al. (1999).

Finally, global brain size change itself can also reflect adaptation. Finlay et al. argue that increased total brain size is one likely response to selection on almost any specific functional capacity, and that this tendency toward "adjunct" growth should foster widespread exaptation of neural tissue. Similar logic applies when brain size is considered in a broader, organismal, context. In any viable organism, the development and expression of such diverse traits as brain size, body size, encephalization, lifespan, range size, diet, reproduction, and social organization are thoroughly integrated. This is reflected in the multiple evolutionary "grades" recognized within the primate order (Dunbar 1998; Kaplan et al. 2000). Each such grade (e.g.,prosimian, anthropoid, hominoid) represents a stable suite of integrated adaptations allowing for pursuit of a similar lifestyle (Brace 1995, p. 70).

In addition to focusing on particular traits like dietary or social complexity, it may prove useful to consider general adaptive complexes or strategies. Whereas some variation is obviously accommodated within any grade, pressures leading to certain particular changes might precipitate a "shift" with widespread and profound implications. It may ultimately be impossible to discern primary causes in such multifaceted and recursive lifestyle shifts, but exploration of the dynamics themselves should prove to be at least as interesting.

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Brain evolution: How constrained is it?

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Abstract: Allometric analyses suggest that there are some developmental constraints on brain evolution. However, when one compares animals of similar body size, these constraints do not appear to be very tight. Moreover, the constraints often differ between taxonomic groups. Therefore, one may ask not only what causes developmental constraints but also how (and why) these constraints might be altered (or circumvented) during the course of evolution.

Traditionally, biologists have been quick to conclude that an owl's large eyes are an adaptation for vision at night and that a hare's large ears are adapted for the detection and localization of sounds. More generally, biologists tend to interpret the hypertrophy of a particular organ as the result of natural selection for the principal function(s) subserved by that organ. They also tend to assume that the size of individual organs can be changed without simultane-

ously affecting the size of many other, functionally unrelated, organs. In other words, biologists tend to believe that natural selection acts in a mosaic fashion, increasing or decreasing the size or utility of a particular organ as it sees fit. Some biologists, however, have pointed out that it may often be impossible to change one part of an organism without simultaneously affecting the development of many other components and that, therefore, the evolutionary process is subject to serious developmental constraints (Gould & Lewontin 1979). Although debates between these two groups of scientists are often contentious (Dennett 1995; Goodwin 1984), I suspect that both perspectives are useful and likely to capture important elements of "the truth."

Finlay et al. have extended this controversy into the realm of evolutionary neurobiology, where the question of developmental constraints had been largely ignored. Previous authors (e.g., Sacher 1970) had noted that the relative proportions of individual brain areas change systematically, and hence predictably, as overall brain size increases, but Finlay and Darlington (1995) were first to note explicitly that this predictability implies the existence of limits on the power of natural selection to change brain regions independently of one another. Moreover, Finlay and Darlington proposed a novel mechanistic explanation for this constraint, namely that some regions enlarge more than others (phylogenetically speaking) because they are born relatively late in development. Since 1995, Finlay and her collaborators have fleshed out several aspects of this hypothesis. They also state more clearly now that developmental constraints may not be "immutable" and that brain evolution may sometimes proceed in a relatively mosaic fashion. Still, I wonder: just how tight are these developmental constraints?

Finlay and Darlington (1995) argued that their model allows for 2.5-fold variations in the size of individual brain regions. Such size differences may not seem large, but human brains are only 2–3 times as large as one would expect for a primate of human body size, and this difference is generally assumed to be important. Moreover, Finlay and Darlington based their model on mammals with a vast range of brain and body sizes, which means that the observed correlations are almost guaranteed to be quite high. Imagine, for example, a mouse with a brain the size of a rabbit's brain. Such a mouse would be grotesquely cerebral and unlikely to be very "fit" in the struggle for existence, even if it were developmentally feasible to build it. I find it more instructive, therefore, to compare the brains of animals with similar body sizes. Tenrecs and squirrel monkeys, for example, have similar body sizes but brains that differ in size by a factor of 9 (Stephan et al. 1981). Looking at individual regions in brains of similar overall size, one can note that *Solenodon paradoxus* and *Cebuella pygmaea* (Stephan et al. 1981) have neocortices that vary in size by a factor of 4 and olfactory bulbs that vary 37-fold. Even more dramatically, hamsters and blind mole rats have similar body weights but dorsal lateral geniculate nuclei that differ in size by a factor of 15 and superior colliculi that vary 38-fold (Cooper et al. 1993). Thus, while I do not doubt that there are some developmental constraints on brain evolution, I suspect that they are not as tight as they appear to be from the analysis presented by Finlay et al.

I also suspect that the developmental constraints themselves are more phylogenetically labile, or "local" (Maynard Smith et al. 1985), than Finlay et al. suggest. Since only mammals were examined, no one knows how well their model applies to non-mammals. Even within mammals, there are significant taxonomic differences in how brains scale with body size and how individual brain regions scale against brain size. Primate brains, for example, are generally 2–3 times larger than insectivore brains of similar body size, and many brain regions scale with much lower slopes in primates than in insectivores (Stephan et al. 1981). Although some might argue that such taxonomic differences negate the existence of developmental constraints, I think that this would be going too far. Instead, I think that one should use such findings to ask how (in terms of mechanisms) developmental constraints can be relaxed or broken and how new constraints are imposed. For example, the finding that human paleocortex is much too large (allometrically speaking) for the size of its principal input structure, the main olfactory bulb (based on Stephan et al. 1981), suggests that human paleocortex (or the olfactory bulb) has been freed from some ancestral developmental constraint. I would love to know what caused the apparent dissolution of this constraint.

Thus, the analysis presented by Finlay et al. raises many exciting new questions about how neural development is related to brain evolution. For example, how might neurogenesis (and neuronal precursor proliferation) be altered in one brain region without affecting the development of other regions? If such mechanisms are limited or do not exist, why? And how might the size of the olfactory bulb (one of the principal factors in the proposed model) influence the size of distant brain regions, if not through direct neuronal connections? Perhaps most intriguing, might some of the developmental constraints have evolved as adaptations for the generation of functionally viable brains? At this point, I come away from the target article with more questions than answers, but I have no doubt that the approach taken by Finlay et al. will be productive and serve as a major stimulus in the ongoing effort to integrate developmental and evolutionary neurobiology. Well done!

Brain allometry: Correlated variation in cytoarchitectonics and neurochemistry?

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Abstract: Brains vary in characters other than size. We should consider whether Finlay et al.'s argument, that developmental shifts responding to selection for change in one area yield correlated changes across the brain, must be extended from size differences to other neural characters responsible for the circuitry or physiological differences distinguishing vertebrate brains.

The most fundamental question in evolutionary neuroscience is: "How do nervous systems differ?" What sets apart the brain of a gorilla from the brain of a camel so that a gorilla acts like a gorilla? Finlay et al. present an answer that, at first encounter, must generate from evolutionary biologists and psychologists the reaction that this cannot be right. It goes against what most of us have come to assume about brain evolution: that individual areas or systems are separable and grow or shrink independently in response to selective pressures, leading to a different neural mosaic in each unique species. On the contrary, argue Finlay et al. on the basis of an impressive statistical analysis, this is more myth than fact when it comes to size, one of the leading experimental metrics of brain differences among mammals and other vertebrates. Within three broad domains, a size increase in one structure is reflected in size increases in others. The major determinate of the size of any one system or area is the size of the brain as a whole. Brain parts are linked: change one for any reason, and you change them all.

We might try to seek refuge from this idea in the fact that brain areas differ in many characteristics of cytoarchitecture and chemoarchitecture, and these in turn are different among vertebrates. Take the mammalian neocortex as an example. Species differ in the number and arrangement of cortical areas (Krubitzer & Huffman 2000) and in the neurochemical and cellular organization of the cortex (Hof et al. 2000). As indicators of circuitry and physiology, differences in cellular arrangement, morphology, and neurochemistry surely must indicate functional differences. Can we regard these differences as the "real" adaptations characterizing brain evolution? Clear differences are apparent in these characters among different brain areas within a species (compare the structure of the primary visual cortex with that of the anterior cingulate cortex, for example), and one sees the potential for the kind

of mosaic evolution leading to independent specialization of areas that one expects to see in neural systems, and that one assumes must underlie the diversification of brains and the behaviors they control. But before we accept this idea, we should think hard about the underlying message of Finlay et al.'s contribution. This is exactly what we believed about size until their careful quantitative analysis showed strong links between the size of any one area and the overall size of the brain. And they have argued that the reason for this resides in developmental processes. Because final form derives from developmental trajectories, and these trajectories link together broad brain areas along a common path, it is difficult to change one specific area without changing many others. We need to consider is if this argument also applies to diversification in other domains.

To my knowledge, no one has ever considered this point. It is difficult for me to imagine how one would construct a rigorous, quantitative analysis of correlated diversification in cyto- or chemo-architectonic characters in the way Finlay et al. have done for size. But a survey of material in a collection of papers on comparative cortex organization across mammals (Preuss 2000) suggests we may want to consider it. Hof et al. (2000) suggest, for example, that primate cortex is characterized by the general feature of having a balance between three types of calcium binding proteins, while ungulate cortex has as its general feature a predominance of calretinin and calbindin neurons over parvalbumin neurons, and additionally a general lack of a distinguishable cortical lamina IV. These are pan-areal features, and, similar to the question raised by Finlay et al. asking why auditory cortex should get bigger because the somatomotor cortex must enlarge to accommodate a bigger body, one should now question why an increase in parvalbumin content in, say, primary visual cortex should be accompanied by an equivalent increase in orbitofrontal cortex. The tendency to increase the number of distinct cortical areas seems similarly to have pan-cortical characteristics. Large brains either tend to have more divisible cortical areas (Krubitzer & Huffman 2000) throughout the cortex, or they have a generally undifferentiated cortex (Glezer et al. 1988). Are there any mammals with, say, highly differentiated parietal lobes but undifferentiated frontal lobes, or vice versa? Why not, unless like size, other brain metrics, associated with growth or not, obey the same kind of overall change rule dictated by some developmental shift as proposed by Finlay et al. for size?

Finlay et al.'s analysis presents a fundamental idea that goes beyond the specific analysis of brain size allometry, that changes in developmental patterns underlying adaptive shifts in one neural character result in similar changes throughout broad regions of the brain. The challenge comes now in determining which of the neural characters separating gorillas from camels result from a selective change directed at one brain area that coincidentally imparted those characteristics throughout the nervous system. Gorillas are more than camels with opposable thumbs. Did they get that way by a multiple, independent changes leading to widespread differences in brain, behavior, and cognition? Or through a key developmental change in response to one selective regime targeting one system, whose effects rippled throughout the brain, causing fundamental differences across its systems, simultaneously providing the substrates for the evolution of the multidimensional differences that distinguish any two species?

Authors' Response

Developmental structure in brain evolution

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Abstract: First, we clarify the central nature of our argument: our attempt is to apportion variation in brain size between developmental constraint, system-specific change, and "mosaic" change, underlining the unexpectedly large role of developmental constraint, but making no case for exclusivity. We consider the special cases of unusual hypertrophy of single structures in single species, regressive nervous systems, and the unusually variable cerebellum raised by the commentators. We defend the description of the cortex (or any developmentally-constrained structure) as a potential spandrel, and weigh the implications of the spandrel concept for the course of human evolution. The empirical and statistical objections raised in the commentary of **Barton** are discussed at length. Finally, we catalogue and comment on the suggestions of new ways to study brain evolution, and new aspects of brain evolution to study.

Rilling comments that a colleague walked into his office, and seeing the nice line produced by .97 correlation of cerebellum size with brain size, wished he could have data so good. His colleague failed to notice the more subtle "grade shift" in cerebellar size between monkeys and apes that had interested Rilling. This incident is analogous to our own initial encounter with brain allometry and evolution, none of us being "allometrists" by initial training (*contra* **Holloway's** apparent impression).

Some time ago, Finlay wanted to explore the question of how spatially distributed functional systems in the brain (like the visual system) could be coordinated in size and connectivity in evolution. In the 1980s, regressive events in development were much under discussion, and one plausible account of system-wide coordination might have been a cascade of alterations of normally-occurring cell death and synapse retraction initiated from a single spot, say the retina or visual thalamus. She undertook a variety of explorations of this hypothesis, with disappointing results. Nothing resembling a cascade of transynaptic effects could ever be seen (Finlay 1992; Xiong & Finlay 1996). **Deaner & van Schaik**, in fact, take us to task for not adequately considering cell death and trophic effects in this paper, but it was not for want of previous effort!

This research program having failed, the next step was to examine coordination and variation in neurogenesis for the purpose of predicting *absolute numbers* of neurons across structures and species (*not* relative or residualized measures, which are irrelevant to understanding the actual mechanics of neurogenesis). Our purpose, that is, was to peer inside the developmental "black box" implicit in the allometrist's dimensionless measures. Unsocialized to allometric custom, and in the business of predicting real numbers of neurons, we were primed to be impressed first by the forest of strikingly robust correlations produced by our

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initial, two-factor model. When we found a further simple relationship between developmental schedules and the pattern of relative expansion of brain regions, the unexpected nature of this result forced us to rethink some basic questions about how functions were distributed in brain tissue, and what the units of selection might be that evolution could operate on. In fact, we were struck by the observation of **Airey & Williams**, noting that most people have a negative initial reaction to our argument, because – "We *know* that selection targets behaviors, that behaviors are represented discretely in the brain, and that evolution must be mosaic." That reaction was ours as well. It is clear, however, that not everyone has rethought with us.

The argument we presented has several components, and different commentators took issue with various aspects, which we will discuss in turn. Since many of the commentators specifically deferred to Barton about the question of mosaic evolution of brain parts, we discuss his comments in particular depth. Finally, many of the commentators went on to propose other ways we might predict brains might evolve, which we summarize at the end.

R1. Overall argument

A number of commentators (**Barton, Deaner & van Schaik, Elliott, Holloway, Kaas & Collins, Stout, Striedter**) assume or imply that we propose a solely constraint- based theory of how brains evolve, or at minimum, overstate the role of developmental constraint in brain evolution. While the new and underlined part of the argument was the observation of predictable, coordinated change attributable to a conserved developmental program in the order of neurogenesis, let us now underline that our proposal about the structure of changes in brains in fact contained three parts. The first was coordinated changes in the relative size of brain components, predicted from the order of mammalian-general neurogenesis. The second was system-specific coordination as we described for the limbic system, produced by *changed* patterns of neurogenesis in specific species. The third was mosaic evolution – a term we would like to reserve for the independent evolution of single brain parts. Bluntly put, our article is about partitioning the variance among these factors, not some simplistic opposition between developmental constraint "versus" mosaic evolution.

Elliott argues the claim that changes in developmental timing produce predictable changes in brain structure is not new and would not surprise D'Arcy Thompson. We also expect it would not, but imagine Thompson would still be interested in what the particular relationships are, which is what we explore. Elliott also brings up the very interesting issue of the relationship of individual variation to species variation. We know very little indeed about individual variation, and he quite correctly notes that there is a disjuncture between the more limited variation seen in data sets like Stephan's and more current data on primate variability by Horton and Hocking (1996a; 1996b), Purves et al. (1994). Most (but not all) of the latter data point to large species differences in allocation of function within the isocortex, which are perhaps examples of the way cortex may epigenetically assume new function. **Stout** also underlines reallocation of function within cortex as a central mechanism of brain change, and we concur. Finally, the comparisons of postnatal growth of the brain in different species compare brains at wildly different stages of maturation (Clancy et al., in press). The studies of enrichment and deprivation effects on brain volumes in a single species (the rat) produce differences in the 5–10 % range, not the 50% range (Rosenzweig 1972).

Holloway chides us for our attention to size and goes on to argue for the importance of "the residuals, or departures from the constraints that are most provocative and nontrivial in analyzing species-specific behavioral repertoires and in particular the paleoneurological evidence for hominid evolution." Holloway may be correct; departures from constraints may be informative. But how we may distinguish constraint-based size changes from residual-based size changes is not clear. Part of the point of our article was to tackle this problem based on analysis of the actual, absolute sizes of developing systems. In so doing, we believe we offer a more comprehensive perspective on the importance of *both* constraints and their exceptions.

R2. Special cases

Others point to special cases we should consider further – **Kaas & Collins** show the particular comparison of the ground squirrel and rat, with the superior colliculus of the ground squirrel exceeding the rat's in volume by nearly a factor of ten, greater than the 2–3 fold residual variation we claimed. A couple of observations are in order. First, the 2–3 fold variation we described was the 95% confidence interval for the large brain divisions in bats, primates, and insectivores described by Stephan. We should expect some structures to lie outside that band, and finding a particular outlier is interesting, but does not negate the statistical description of the other data. Second, a database of more relevance to the claim of Kaas and Collins is the work of Glendenning and Masterton (1998), where the volumes of most typically-identified auditory nuclei are measured in 53 widely disparate species. While an occasional highly disparate volume is seen, such as an unusually large dorsal cochlear nucleus in the feathertailed glider or mountain beaver, or a large inferior colliculus in the kangaroo rat, the striking message of this data set is also the conservation of relative volumes and the lack of obvious relative structural hypertrophy in animals one might guess to be more dependent on their auditory systems, like bats.

Striedter correctly notes that we have not really examined the entire range of naturally occurring variation, noting particularly cases of *regressive sensory systems,* such as the blind mole rat and other fossorial rodents reviewed by Cooper et al. (1993), which show extreme downward variation away from the mean. This is an interesting point, which resonates with one made by Innocenti – if parts of the cortex are not selected for, and are unused, why don't they atrophy? Regressive forms may give us part of the key to reallocation of function in the nervous system. For example, in the blind mole rat, the image-forming functional components of retinas degenerate almost completely, while the superior colliculus regresses but can undergo some reallocation, becoming dominated by the remaining sensory inputs. The visual cortex shows the least regression, demonstrating instead much evidence of reallocation.

There indeed is something interesting about the *cerebellum,* as **Marino** and **Rilling** point out. In cetaceans and pri-

mates, this structure departs systematically from the overall trends we describe; it is the clearly deviant structure in our analysis of the overall relationships of prosomeres to birthdays. It is also one of the last structures to be produced, which may make it accessible to evolutionary alterations. In fact, in nonmammals, elaboration of the cerebellum rather than the telencephalon is often the principal pathway of brain enlargement (see Butler & Hodos 1996). There is much more to be studied here!

R3. Linkages of structures and behaviors in the evolving brain

We return to **Airey & Williams**'s characterization of the received wisdom: "We *know* that selection targets behaviors, that behaviors are represented discretely in the brain and that evolution must be mosaic." **Dunbar** argues that we are suggesting "structural changes preceded functional use." If this is the case, it was not our intention. Certainly, selection must be on behavioral phenotype, in combination with the energetic and other physiological requirements that the brain might have. We do not argue that selection must in some obscure way select solely on structure, leaving function to be set at some later time. **Innocenti** further wonders about the plausibility of uncommitted tissue generated by structural rules, waiting to be played with by hopeful elves in the future.

But behavioral functions and structures may interrelate in a variety of ways in evolving brains. First, if functions are mapped very discretely and fixedly in the brain, and if components enlarge due to a structural rule, then there may in fact be unused brain areas. This may be particularly true, we would argue, in the case of species such as large cetaceans where the added metabolic cost of brain becomes small with respect to body size. Moreover, we might construe "unused" brain tissue as that recruited above some minimal level of activity, redundant in normal operation but perhaps important in times of unusual load. Diamond (1994) has written an illuminating article on this point, pointing out that humans can survive adequately with just one lung, vastly reduced intestinal length, and so on, even when precise metabolic cost seems to be highly defended in evolution (Aiello & Wheeler 1995; Cooper et al. 1993). Second, the conventional view of how functions are represented in the brain may be inappropriately modular. Among the behavioral phenotypes that animals could be selected on, such as foraging ability, migration, mate selection, and so on, very few plausibly suggest a single brain area for their execution. Indeed, the coordination we see in growth of brain parts in fact does evoke the actual nature of distributed behavioral phenotypes in the brain. Finally, it may be a conserved process in the vertebrate lineage for multimodal, expandable areas like the cerebellum and isocortex to be selected as the last produced, conferring "evolvability" on just those lineages with the appropriate order of neurogenesis. Those animals that preferentially expanded, say, their motorneuron pools in response to jitter in maturational length are not the species still with us.

In this regard, we simply disagree with **Dunbar**'s assertion of the primacy of behavioral adaptation on the evolution of whole brain interrelations on the basis of "the orderly correlations between particular brain parts and particular cognitive and behavioural functions." If our thesis were true, he suggests, we should see "different species of the same taxonomic group [evolving] different functions for the enlarged capacities that they had accidentally acquired and the result would be a random pattern of associations." But this would only be true if all brain components are somehow functionally equipotential and that new functions are free to take up residence just anyplace in any species with a bit of "extra" brain. More likely, in accord with a principle Elman et al. have glossed as "architectural innateness," circumstances of configuration, connectivity, and developmental order make certain components consistently better suited to certain kinds of processing than others (Elman et al. 1996). The result of functional exaptation would therefore be similar to that in functional adaptation – a nonrandom pattern of structural-functional correlations between species.

R4. Isocortex: The amazing expanding spandrel?

Our suggestion that "big isocortices may be spandrels – byproducts of structural constraints for which some use is found later." prompted considerable comment. The idea is "not informative," asserts **Deaner & van Schaik**; **Holloway** is "skeptical of 'spandrel' theories of brain/behavioral evolution" in general; **Aboitiz** finds our reasoning "flawed," while **Iwaniuk & Whishaw** suggest the notion of spandrels might best be applied to cultural, not brain evolution. An additional body of commentators (**Dunbar, Innocenti**, **Lovejoy**) are skeptical of the notion that isocortices can get big without some affirmative adaptive benefit derived from their function.

The criticism perhaps dignifies our suggestion with the impression that it is more radical that it really is. First, we wrote that big isocortices "may" and "could be" spandrels. Second, several commentators seem to imply that this possibility means we claim that adaptation had *nothing* to do with the current form and function of hominid isocortex. As we noted, "adaptation has subsequently 'tailored' each subsystem to the processes that tend to take up residence in them. On balance, however, the current model posits *a far greater role* for exaptation of structure to function in the natural history of the brain" (emphasis added). The difference, then, is one of relative emphasis.

If we return to Gould and Lewontin's (i.e., 1979) use of the term "spandrel," it is clear that the coiners had in mind an architectural metaphor for a whole raft of non- and semi-selectionist mechanisms for trait evolution. Like the celebrated spandrels of San Marco's Cathedral in Venice, a trait that emerged as a byproduct of wider developmental constraints is neither an "epiphenomenon" (*contra* **Holloway**) nor "undesirable" nor "neutral" (*contra* **Deaner & van Schaik**). Just as the spandrels in the cathedral may have a derived use that by now appears essential to the building's aesthetic program, an exapted organismal trait might seem indispensable to current behavioral functions.

Gould and Lewontin's argument, however, was not concerned with current function, but with ontology, and with where the most appropriate locus for explanation lies: "the design is so elaborate, harmonious, and purposeful that we are tempted to view it as the starting point of any analysis, as the cause in some sense of the surrounding architecture," they wrote. "But this would invert the proper path of analysis." In our article, we take the position that a pattern of correlated growth in most brain structures is best predicted by

a conserved order of neuronal development, not by particular selective pressures on particular brain components. As Gould and Lewontin hold in their metaphor, we regard "the architectural constraint [as] clearly primary." Specifically, we would regard our model of brain evolution as incorporating elements of the second and the fifth mechanisms in Gould and Lewontin's "partial typology of alternatives to the adaptationist programme": with respect to the initial growth of isocortex, the mechanism may involve "no adaptation and no selection *on the part at issue*" (type 2); with respect to subsequent exaptation to advanced cognitive functions, it also might be said to involve "adaptation and selection, but the adaptation is a secondary utilization of parts present for reasons of architecture, development, or history" (type 5).

Generally, we are not surprised that, as **Stout** notes, "global brain size change can also reflect adaptation," or as **Deaner & von Schaik** observe, "good adaptationist reasoning does account for the possibility of developmental constraints." It is the very essence of what Gould and Lewontin call the Panglossian paradigm that, with enough ingenuity, virtually anything can be rationalized as some sort of adaptation. What is more difficult, it seems, is to acknowledge the limitations of what appears to be a highly conserved explanatory concept.

R5. Barton on mosaics, hyperallometry, and timing

For several years, Robert **Barton** has been a regular critic of this work. His current offering covers three major topics: mosaic evolution, cortical hyperallometry (the notion that as the brain expands, the cortex expands more rapidly than other brain parts), and event timing. Here we take them in that order.

Several commentators cited the discussion of mosaic evolution by Barton and Harvey (2000). That article shows convincingly that even after controlling statistically for the sizes of other brain parts, there are statistically significant correlations between the sizes of closely linked brain structures, including those with major axonal interconnections, such as the lateral geniculate nucleus and the visual cortex, or the two main subdivisions of the amygdala. We would call this "system specific" evolution rather than "mosaic" evolution, since we understand the latter term to refer to evolution of brain parts independent of all other parts. Recall that our interest lies in understanding the developmental mechanism of such an effect, but Barton and Harvey report significance levels from independent contrasts and no absolute magnitudes, so we cannot tell what kind of developmental mechanism we might expect that could produce the effect.

There are three general kinds of processes that could produce correlations of the sort observed, one of those an obligatory measurement artifact. The obligatory artifact is that the increased size of A will also be measured in B, since B will include a substantial volumetric component of projections from neurons originating in A. Second, if the activity of the neurons of A increase, A's own dendritic and axonal volume will increase and could induce greater volume of dendritic and axonal processes in B by well-known activity-dependent trophic processes without increasing the actual number of neurons in B (for example, Purves 1988). Finally, in the class of effect we have been concerned with, the number of neurons, glia or other supporting elements could have been independently selected to be larger in both A and B. It is quite clear that the kind of correlations they report could be entirely produced by either of the first two processes, and could also include some component of independently varying neuron number – it is difficult to say. Size of effect, and also cause of effect, matters.

Barton's position on cortical hyperallometry seems to be that it can be explained by a combination of grade shifts in primates, and hyperallometry of white matter with no increase in cortical neuron number with increasing brain size. Barton and Harvey (2000) found little or no cortical hyperallometry after correcting for these two factors. However, they report detailed results only for the cortex versus the entire rest of the brain, whereas our position is that at least the olfactory bulb, and preferably the entire limbic system, should be subtracted out before calculating the allometric constant. They say they did a second analysis subtracting out the olfactory bulb, but surprisingly report no detailed results.

Zhang and Sejnowski (2000) offer a detailed analysis of white and gray cortical matter in 59 mammals from pygmy shrew to elephant and pilot whale, including human, horse, cow, chimpanzee, sea lion, pig, sheep, fox, cat, rabbit, rat, mouse, 2 bats, and several other cetaceans, insectivores, and primates. They report (Fig. 5, p. 5625) that the log of gray matter increases at .955 times the log of total cortex volume, with r = .9998. Careful visual inspection of their data (their Fig. 2) reveals no visible grade shifts between orders.

We used these results as follows. We defined a nonlimbic "brain core" consisting of the striatum, diencephalon, medulla, and mesencephalon. Within each of our four taxonomic groups we regressed logged neocortex size onto logged "brain core" size. We then multiplied the regression slope by the Zhang and Sejnowski value of .955, to estimate the allometric constant of cortical gray matter against the brain core. We obtained the following values:

1. 1.206 for 26 simians excluding humans
2. 1.145 for 21 prosimians
3. 1.305 for 43 bats
4. 1.064 for 40 insectivores

Including humans would have only raised the first figures. Nevertheless, all of these are noticeably above the value of 1.0 claimed by **Barton**, with most being substantially above.

To get a better feeling for what this means in terms of cortex/braincore ratios, we examined Table 1 of Hofman (1988). For 26 of the 27 species listed there, Hofman gives brain sizes and the amount of white and gray matter in cortex. The 26 species include seven insectivores and four cetaceans. We defined "graybrain" as brain volume minus volume of cortical white matter, and defined "graycortex" as amount of cortical gray matter. For the seven insectivores, the largest value of the graycortex/graybrain ratio was .310. For the four cetaceans, the smallest value of that ratio was .575. Thus, cortical hyperallometry is substantial even when calculations exclude primates and white matter.

Barton seems to have three major criticisms of our work on developmental schedules: that it is "circular," that it depends primarily on the dichotomy between cortical and other events, and that correlations between distantly related species are actually quite small. In this response, we will refer to the very latest values of two figures in our timing model: we now define *Y* as ln(postconceptional days –

4.42), and the multiple correlation R between actual and estimated Y values is now .99000.

There appear to be two parts to the charge of circularity: that the model is tested on the same nine species on which it was derived, and that even within those species it was tested on the same partially-filled data matrix on which it was derived. We completely agree that it would be nice to have more than nine species. And statisticians have long recognized that there is a real problem when a model is tested on the same data used to derive it. Focusing on regression (the method we used), there is a tendency for the computed multiple correlation R to overestimate the true value. However, formulas have been available since the 1930s to correct for this, and today values of "adjusted" R or R^2 are reported by most statistical packages. To keep our argument simple we have not reported adjusted values. But applying the formula to our current R of .9900 yields an adjusted R of .9859 – still very high.

The analyst who wants to deal with this problem even more rigorously can use a still more conservative method, as follows. Delete a single observation from the data set of 362 observations, then predict that one observation from a model derived from the other 361. Repeat that for all 362 observations, so the estimate for any one observation is not based at all on that one observation. For reasons explained by Darlington (1990, p. 161), this method is actually overconservative, yielding a negative correlation between Y, and Y estimated from X, when applied to a sample in which the actual XY correlation is 0. Despite that, in the current data set we find by this method a correlation of .9806 between actual and estimated observations.

Barton's charge that our high correlations depend entirely on the dichotomy between cortical and noncortical events is one of an enormous variety of post hoc hypotheses that one might invent. Since we have published all the data on which our analyses are based, plus a detailed description of our analyses (Darlington et al. 1999), we hope that future hypotheses in this vein might be tested by their originators before they publish their speculations. But to respond to this one charge, we divided our 362 observations into 126 cortical observations and 236 noncortical observations, then computed the correlation between actual and estimated Y-values within each of these subsets. The correlation was .9901 within the noncortical events, and .9896 within the cortical events. Thus, far from explaining all of the original correlation of .9900, the cortical-noncortical dichotomy appears to explain virtually none of it.

Barton raises an interesting question about the correlation between the timing of the same events measured in distantly related species such as rat and macaque. To study this question, we selected the 59 events that had been measured for both these species. We converted the times of these events to $Y = \ln(\text{date} - 4.42)$. The correlation between the two sets of Y-values was 0.8418, where Barton reported a correlation of .64 ($r^2 = .41$) between the timing of the same events in rat and macaque. At least two differences in procedure would give Barton and us different correlations. We used Y-values, while so far as we can tell, Barton used raw dates, which are not linearly related across species. And Barton collapsed all cortical observations together into one composite observation. We could not understand the reason for this, even given Barton's notion that the cortical-noncortical dichotomy would explain our high correlations.

Even with these differences in method, we remain confused. **Barton** reports df = 14 in his correlation. Since df = $N - 2$, this suggests his N was only 16 (a point he never mentioned explicitly). Combining the 23 cortical observations measured in both rat and macaque would lower the 59 observations only to 37, so we are not sure how he reached a sample size of 16. But the bottom line is that when we compute the correlation between Y-transformed event dates in rat and macaque, we find a respectable correlation of 0.84. For reasons explained by Darlington (1990, pp. 209–13), we feel that correlations provide better measures of the size of relationships than squared correlations, so we leave the figure unsquared.

Separate from the scaling of the limbic system and its relationship to neuronal birthdays, we provide two other examples where the order of birth dates studied extensively in one species (the rat) predicts the relative scaling of nuclei in a different set of species (insectivores vs. primates; hominoids). **Barton** claims that the nucleus lateralis posterior and pulvinar were omitted from the analysis because they do not fit the assumption of conserved development, and no justification was provided. In fact, the two citations we provided document the fact that the incommensurability of the rodent lateralis posterior nucleus and the primate pulvinar has been discussed by neuroanatomists for over 40 years (Rakic & Sidman 1961), and that a separate ventricular region of origin for the macaque pulvinar, not homologous with regions seen in the rodent, has been described (Ogren & Rakic 1981). A more interesting point to make from this observation than the one offered is that the primate pulvinar is in fact an excellent specific case of mosaic evolution.

Predicting the scaling of the thalamus in gibbons and gorillas from the order of birthdates in a rat was, in fact, something of a stunt, intended to show the power of the birthday prediction hypothesis: the data are limited, and we made no statistical claims about it for that reason. We invite more elaborated quantitative studies of this question, and are undertaking them ourselves.

R6. Anthropological animadversions

The attempt to throw light on the evolution of hominid brains was hardly necessary to the development of our thesis. Certainly, there is an element of (we hope) goodnatured provocation in our discussion – this was, after all, going to be a "target" article. Nor did the criticisms of a considerable number of commentators come as a surprise. If there is anything close to a sure correlation in social science, it is that hackles rise in direct proportion to proximity to the hominid lineage.

Schoenemann quite correctly criticizes the statement later in the article that "the great majority of the brain size increase from australopithecines to Neanderthals is a straightforward function of body mass." As the commentator rightly notes, it was not the intent of our article to argue for the predictive power of body mass. Rather, that observation was intended as a rhetorical blow against received notions of the "specialness" of hominid brain evolution. Schoenemann and **Rilling**, making a similar point, are amply justified in flagging the inconsistency.

Schoenemann's point that a brain/body mass regression using only fossil hominid data "misrepresents the context

. . . of hominid brain evolution" is also understandable. It does, however, beg the question of what exactly is, as he says, "the proper context" for understanding the hominid pattern? Is the "baseline" best set at the level of the primate order as a whole? At the level of the suborder anthropoidea? Or at the family level, hominidae? The choice of frame can measurably affect how the picture looks.

It is also a bit of an exaggeration to claim, as the commentator does, that "To separate hominids from primates . . . completely undermines the thesis that brain scaling is strongly constrained across broad groups of species." Global constraints in brain scaling and development, as we describe them, should obtain *both* within and between such groups, while the details (residuals associated with particular components in particular species, groups of species, or individuals) can still show two-to three-fold degrees of variation. What **Schoenemann** seems to react against is the inevitable tension inherent in applying a model that does not stress taxonomic distinctions to a question about a very restricted taxonomic group: What about humans?

Dunbar and **Lovejoy** dispute the suggestion that expansion of hominid isocortices could have occurred in an adaptive vacuum. Surely such tissue is too metabolically expensive simply to "hang around," waiting to acquire a function. Both likewise dispute our observation that the archaeological record offers evidence for a behavioral gap between modern-sized brains and modern behaviors. Dunbar suggests that early moderns might have been acting socially modern long before the Upper Palaeolithic, and that we take an "old-fashioned line" in taking development of tool industries as evidence for lagging behavioral capacities. Lovejoy reasonably suspects that nonfossilizable traits such as enhanced parental investment might also have been part of the Life History energetics of modern humans.

In fact, we stand agnostic on exactly what might have triggered the growth of hominid isocortex. Certainly, selective pressure toward **Dunbar**'s "social brain" might have provided the kick, or perhaps it was something else. The essential point is that whatever the trigger, affecting whatever cortical or subcortical system, the rest of the brain was dragged along for the ride. It should be noted, however, that insofar as the advent of art and symboling represent the existence of modern social relations, there still seems to be a substantial gap between the anatomical and behavioral evidence. The question for Dunbar, then, is why, if the "social brain" was fully modern 100,000 or 200,000 years ago, we fail to see significant evidence for modern social rituals (parietal and portable art, deliberate burial, etc.) until far more recently? (But see McBrearty & Brooks 2000 for a different, Africa-centered view.)

Of course, anyone suggesting any kind of evolutionary story is vulnerable to the "why not" objection, as in "if the ecology of 100,000 years ago was similar to that 50,000 years ago, why didn't the isocortical areas permit the advantageous cognitive functions to flourish immediately . . . ?" (**Deaner & van Schaik**), or "why did the Tomte not just let the extra-neocortex atrophy?" (**Innocenti**). The short answer to such questions is "Who knows?" A somewhat longer answer is that Deaner & van Schaik's assumption that the ecologies faced by humans 100,000 years ago and 50,000 years ago were "similar" is demonstrably false, based on worldwide climatic reconstruction and evidence that moderns emigrated into new regions by the latter date, including Europe and Australia. Insofar as changing climates and territories presented new challenges, we might expect to see more pressure to preserve or exapt isocortex to new or enhanced cognitive functions. Nor is the time frame necessarily obvious for the atrophy of cortical overabundance based on relaxed selection, in our view.

R7. Other ways to evolve a brain

A number of commentators offered remarks on our argument, and then went on to suggest further ways that brain evolution might be understood, both in terms of analytical tools to examine size and in terms of kinds of characteristics other than size. We take these suggestions as entirely congenial, because there is no presupposition in our argument that size is "the" way to understand brain evolution. As various commentators expressed in one way or another, an elephant is clearly not just a scaled-up mouse.

Analytic tools of extreme promise are the genetic analyses described by **Airey & Williams**, such as the examination of the heritability of brain traits associated with particular behaviors and the mapping of genetic loci that code for quantitative differences in brains. Returning to our initial statement of the goal of our work, this is a parallel kind of analysis to the kind we have been attempting, where we take naturally-occurring individual differences and induced genetic differences in brain structures in mice, and trace them to the genome. In both cases, we are looking at the intrinsic structure of changes in brain size, and at what factors might control them.

One way of viewing brain evolution, which has often been invoked for human evolution particularly, is where the pressure for and advantage of increased brain size is constant, but some other physiological factor limits the size that a brain can be. **Gilissen & Simmons** make this argument cogently for primates overall, observing that, due to metabolic cost, it appears that brain tissue never reaches more than the relative amount of 4% of body size. Dean Falk's "radiator theory" points out that brain tissue, like a car radiator, must be cooled, and evolution of a more advantageous cooling system may have permitted the larger human brain. **Ragir** argues that the requirements of an immature skull to pass through the changed pelvic dimensions required for bipedal walking could be viewed either as a removal of constraint or pleiotropic effect leading to bigger brains. **Bach-y-Rita & Aiello** argue that reducing the cost of brain metabolism by changing the nature of synaptic transmission is another way to relax a metabolic constraint on brain size. A key part of the latter argument is that "the human brain doesn't use more energy than the smaller brains of animals of comparable corporal weight." However, this provocative claim seems to be based on a misreading of L. Aiello and Wheeler (as reported in Gibbons 1998), who writes instead that "the human brain *and body as a whole* don't use any more energy than smaller brained animals of similar body size" (emphasis added). Gibbons goes on to describe the "expensive tissue hypothesis," which suggests that humans save energy in their gastrointestinal tracts by eating a high quality diet, and the "maternal investment hypothesis," which suggests that for human fetuses and infants extra energy comes through the placenta and breast milk.

Several commentators point out that there is much evidence for remapping of function in the cortex (**Elliott,**

Schoenemann, Stout) as well as wholesale reorganization of behaviors and their substrates (**Iwaniuk & Whishaw).** The cortex has the developmental means for plasticity, as **Innocenti** points out, in the searching behavior of developing cortical axons. Again, we can restate this is the context of "evolvability": we are the descendants of those animals whose expanding cortices had the plasticity to make use of new computational resources.

We end this response by highlighting the suggestion by **Wilczynski,** that it might be very interesting to take the idea of structural constraint and apply it to dimensions of brain variation other than size. This is an idea of immense potential. The catalogue of potential changes in brain organization is vast: transmitters, receptors, changing trophic responses, expression of neuromodulators, cell structure, connectivity, and so on. There has been a tendency to view these more qualitative changes as near random, but that seems highly unlikely. It seems plausible that some classes of changes and elaborations of transmitter and neuromodulator expression are more likely than others. For example, we know that transmitters and neuromodulators are "overexpressed" in the developing brain and reduced to a more limited set in adulthood. Is there some hierarchy to this weeding-out process that might be different in brains of different size of maturational rate?

Science moves from catalogue, to classification, to mechanistic explanation of structure in classificatory schemes. It is time for the advent of the last stage in all the aspects of brain evolution and development.

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Letters "a" and "r" appearing before authors' initials refer to target article and response, respectively.

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