Evolution and Scaling in Mammalian Brains

Thesis by

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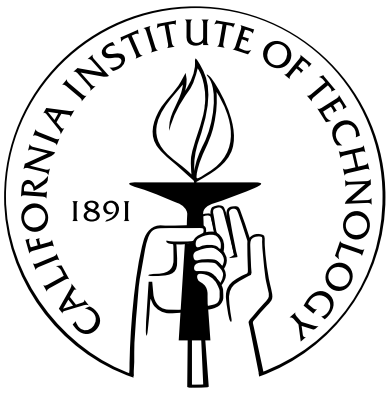

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Abstract

Here I look at three stages in the evolutionary development of mammalian brains. Chapter one addresses how connectivity in neocortex scales with brain size. This is of evolutionary interest because it helps define the basic mammalian condition. Neocortical white matter increases disproportionately in large brains. This might reflect increases in the number of connections per neuron. It might also reflect scaling in axon diameter. I compare these hypotheses by examining white matter-gray matter scaling in cerebellum. Because the white matter of cerebellum lacks cortico-cortical connections, the connectivity theory predicts that cerebellar white matter should not hyperscale relative to gray matter. I have measured white matter and gray matter volume in a large sample of mammals and I find that cerebellar white matter does not hyperscale. This supports the proposition that neocortical hyperscaling reflects an increase in the number of connections per neuron in large brains.

In chapter two I use independent contrasts analysis to examine the scaling of frontal cortex in a large sample of mammals. I find significant differences in scaling between primates and carnivores. Primate frontal cortex hyperscales relative to the rest of neocortex and the rest of the brain, and the primate slope is significantly greater than that for carnivores. This suggests that there are substantial differences in frontal cortex structure and development between the two groups. Combined with with anatomical differences, it suggests that primates have evolved a number of unique adaptations in frontal cortex.

Chapter three examines the evolution of brain size in anthropoid primates. Living anthropoids have larger brains than strepsirrhines. What about early anthropoid fossils? I measure brain size in the early anthropoid *Parapithecus grangeri* using

computed tomography. I find that relative to the living anthropoids, *Parapithecus* had a small brain for its body size. Thus large brains did not develop at the same time as a number of other anthropoid adaptations.

Contents

Chapter 1

Introduction

How did the human brain come to be the way it is? There are striking behavioral differences between humans and other primates, something which is made particularly interesting by the fact that we are very closely related to the African great apes. The human-chimp divergence is thought to have occurred on the order of 5-8 million years ago (Kumar and Hedges, 1998; Brunet et al., 2002). This is a very short time in evolutionary terms. Large complex animals have existed for over 500 million years, mammals for roughly 200 million.

The large behavioral differences which mark humans must have arisen in a short time. A common inference from this is that some very important changes happened in the human brain in the last 5-8 million years. In fact there is only one known neurobiological difference which could plausibly explain the behavioral differences: brain size. Others surely exist, but our methods are not yet subtle enough yet to have found them.

In the attraction to the chimp-human difference, there is an assumption that the latest changes must have been the most important. This leads us to neglect the long train of evolutionary changes in mammalian brains before the human chimp divergence. But without these you also could not have a human brain. In this thesis I will look at three important steps in the evolution of mammalian brains over the last 200 million years. These predate the chimp-human divergence. They are the early evolution and subsequent expansion of the neocortex, the specialization of frontal cortex in early primates, and the brain expansion in anthropoid primates.

The neocortex is present in all mammals from egg laying monotremes to placental primates. This implies that it was present in the last common ancestor of these groups, an animal that lived around the time of the earliest mammals (Carroll, 1988). At the time reptiles filled the large land vertebrate niches, and early mammals were small. This means that at the time of its evolution neocortex was subject to a set of constraints peculiar to small brains.

When the dinosaurs died out mammals began to fill large vertebrate niches. Their brains expanded with their bodies, and this introduced new evolutionary challenges. When brains increase in size in evolution, their various parts do not simply increase proportionally. For structural reasons the relative sizes of some parts change. In chapter one I focus on one such case, the scaling of neocortical white matter with gray matter.

Neocortical gray matter contains neuron bodies and dendrites, while white matter contains the axons of long range connections. As has been known for some time, in larger brained mammals the white matter of neocortex increases disproportionally relative to gray matter (Frahm et al., 1982). There are different theories as to why this is. One idea is that the number of long range cortico-cortical connections per neuron increases in larger brains (Frahm et al., 1982). An alternative possibility is that the average diameter of axons increases (Changizi, 2001). Here I compare these hypotheses indirectly.

The cerebellum is a laminar structure which like neocortex possesses a white matter layer. Unlike neocortex, it does not have long range cortico-cortical connections in white matter. If the connectivity theory of neocortical white matter hyperscaling is correct, we would expect that cerebellar white matter should not hyperscale. In contrast, if the axon diameter theory is correct there is no reason to expect a difference between neocortex and cerebellum, and we would expect to see white matter hyperscaling in cerebellum. I measured white matter and gray matter volumes in a large sample of mammals. I find that the white matter of cerebellum does not hyperscale, supporting the connectivity theory.

It seems that larger mammalian brains have more cortico-cortical white matter

connections per neuron. The implication of this is that to some extent it matters what proportion of the total neocortical network a given neuron is talking to. When you increase the number of neurons in a network while holding the number of connections per neuron constant, the result is that any given neuron talks to a smaller proportion of the network. The fact that connections per neuron grows in a larger neocortex implies that for the neocortical network, percent interconnected matters.

In chapter two we move forward to the time of the origin of primates. Molecular work on the timing of mammalian diversification has recently shown that the earliest primates probably existed before the cretaceous-tertiary boundary (Springer et al., 2003). We have no fossil primates from this period, so what we know about these early primates is based on inferences from living species and later fossils. Comparative studies of the neocortex in living mammals have shown a number of differences between primates and other mammals (e.g. primates have more visual areas than most mammals (Kaas and Preuss, 2003)). The traditional method of identifying such differences is quite time consuming. It involves doing electrophysiology in a number of primate and non-primate mammal species. Here I have adopted a different approach. Instead of studying a small cortical area intensively, I have measured the volume of a large region.

The region I have examined is frontal cortex which in humans is thought to be involved in executive functions such as planning and social reasoning (Damasio and Anderson, 1993). Frontal cortex is defined as neocortex anterior to the motor-somatosensory cortex border. This border is easily identified in a wide range of mammals. I have measured the volume of frontal cortex in two orders of mammals, primates and carnivores.

I find that in primates, the fraction of cortex devoted to frontal cortex increases systematically as a function of brain size. There appears to be something about the way frontal cortex is structured in primates that requires a primate with a large brain to have a disproportionately large frontal cortex. The carnivores in contrast show no systematic increase in frontal cortex proportion with size. This suggests that there are significant differences in frontal cortex structure between the two groups. Taken

together with anatomical evidence it supports the idea that primates have evolved some unique adaptations in frontal cortex. The scaling relationship I found in primate frontal cortex appears to be true in all groups of primates. This suggests that the unique adaptations in modern primate frontal cortex were present in the last common ancestor of living primates.

In chapter three we move the historical narrative forward again, this time to the evolution of early anthropoid primates. A brain body plot for the living primates reveals that anthropoids have much larger brains than other primates. This is in fact the most striking feature of such a plot, excepting the large human outlier.

One thing we would like to know about this expansion is when it happened. Fossils give us the best means of addressing this because they allow us to examine nodes on the phylogenetic tree which living animals do not tell us about. Here I present a CT study of the cranium of a fossil anthropoid primate *Parapithecus grangeri*.

I find that *P. grangeri* had a small brain relative to its body size. This is interesting for several reasons. First, together with other data Simons (1993) it supports the proposition that all anthropoids at this time had small brains. That suggests that in subsequent primate evolution, brain expansion happened independently in several lineages. Second, the fact that *P. grangeri* had a small brain shows that not all anthropoid characteristics evolved at once. In the past some workers have spoken of an anthropoid suite of adaptations which evolved at the time of origin of anthropoids. *P. grangeri*'s small brain shows us that this was not the case.

This thesis is a small tour of developments in mammalian brain evolution over the last 200 million years. I deal with the early evolution of the neocortex, the specialization of frontal cortex in early primates, and brain expansion in anthropoids. The result of all this is a monkey. Monkeys, big, intelligent, social creatures that they are, are a long way from the small insectivorous mammals of the Cretaceous. Understanding the details of those changes is an important part of understanding how humans came to be as we are.

Chapter 2

The scaling of white matter to gray matter in cerebellum and neocortex

2.1 Introduction

As brain size increases, the amount of white matter in neocortex increases disproportionately relative to gray matter (Schlenska, 1974; Frahm et al., 1982; Rilling and Insel, 1999; Zhang and Sejnowski, 2000). This has been interpreted in several ways.

One view is that variation in the relative volume of gray and white matter corresponds to variation in the number of neocortical units (these could be neurons, or perhaps columns), and the number of connections between them (Frahm et al., 1982). In Frahm et al. (1982)'s view, the hyperscaling of white matter reflects an increase in the number of connections per unit. The ideal way to test this would be to measure the number of white matter fibers directly. However, such direct measurements are not possible.

Another interpretation is that the hyperscaling of white matter reflects changes in the diameter of axons, with larger brains having thicker axons (Changizi, 2001). It is difficult to measure axon thickness in white matter generally. However there are several recent studies on axon diameter in the corpus callosum. Those studies found that average axon diameter does scale up with brain size (Olivares et al. (2001) and Harrison et al. (2002)). If such increases also exist in neocortical white matter

outside the corpus callosum, they could explain white matter hyperscaling. However, it is hard to be confident of this based on measurements only from corpus callosum, which represents an atypical population of white matter fibers.

Here, we compare these two hypothesis indirectly by examining white matter-gray matter scaling in the cerebellum. The cerebellum is the second most prominent laminar structure in the mammalian brain. It is similar to neocortex in its possession of an underlying layer of white matter. But the constituents which make up that white matter differ in the two structures. In the neocortex, much of the white matter consists of axons projecting between neocortical regions. In the cerebellum, there are thought to be no cortico-cortical projections (Braitenberg et al., 1997). The connectivity theory of white matter hyperscaling thus has a specific prediction regarding scaling in cerebellum: white matter should not hyperscale relative to gray matter in the cerebellum.

What prediction does the axon diameter theory of white matter scaling make? Very few measurements have been made of the diameter of axons in the cerebellum.[1] There is however no reason to suppose that systematic differences exist in the scaling of fiber diameter in neocortex and cerebellum. In the absence of such differences, the theory predicts that scaling in cerebellum should be like that in neocortex.

The two theories therefore make different predictions. There are however few published data on white and gray matter volume in the cerebellum. Sultan, citing measurements in human and rat, suggested that the proportion of white matter in the cerebellum is nearly constant (Sultan, 2002; Andersen et al., 1992; Korbo et al., 1993). Here we have measured cerebellar white and gray matter volume in a large set of mammals. For purposes of comparison, we have also measured neocortical values in the same group.

[1]Only two to our knowledge (Wu et al., 1999; Shinoda et al., 1992).

2.2 Materials and Methods

We analyzed 45 mammalian species from 8 orders. These included 21 primates, 10 carnivores, 5 rodents, 3 xenarthra, 2 artiodactyls, 2 marsupials, as well as a perissodactyl and a hyrax. All brains were prepared at the Laboratory of Neurophysiology at the University of Wisconsin Madison and kept in the Comparative Mammalian Brain collection there. All were embedded in celloidin, sectioned exhaustively, and stained with thionin. For more details see, for example, Campos and Welker (1976).

For each brain we took a systematic random sample of 40 or more slices. We scanned these on a standard office flatbed scanner (Epson Expression 800), at 800 dpi. We then roughly aligned the resulting images so as to make them easier to work with.

We used a combination of semi-automatic and manual image segmentation tools in the Amira software package to segment the images. We calculated the coefficient of error (CE) of our measurements using the method of Gundersen et al. (1999). For the measurements presented here, the largest CE was 0.019.

Tissue shrinkage resulting from celloidin embedding has two effects on volume measurements of the type we are making. First, the overall size of the brain may decrease substantially. Second, white matter and gray matter may shrink differently.

To correct for the effect of shrinkage on the overall size of the brains, we used pictures which were taken of the brains before sectioning. These were done from standard views at standard distances, and always included a ruler. By comparing various measurements on these pictures with our scanned images, we were able to make estimates of slice dimensions before celloidin embedding.

This technique makes a gross correction for overall shrinkage, but still leaves us with a second problem. Gray and white matter shrink differently in celloidin. [2]

Because we are interested in measuring a scaling exponent, differential shrinkage would not be a problem if it were consistent in different brains. That is, if the amount of shrinkage in gray and white matter differed by a fixed proportion, this would would

[2]The same is true of paraffin (Kretschmann et al., 1982).

change the intercept but not the slope of the regression line of the log-transformed data. If however, the ratio of shrinkage in the two tissues varied systematically with brain size, then this would introduce a bias into estimates of the scaling exponent.

To address this problem, we examined two celloidin shrinkage studies from the University of Wisconsin brain collection. In these studies, one hemisphere of a brain had been cut frozen, and the other embedded in celloidin. Neither study included a cerebellum. Both brains were in the 10–15 cc range. In the beaver brain we found that neocortical gray matter shrank to 39% of its original volume, and white matter to 38%. In the capybara brain, gray matter shrank 34%, and white matter 41%. Earlier examination of a larger number of such studies did not reveal any clear or simple dependence of shrinkage on other factors. (W. Welker pers comm.)

We do not believe that shrinkage ratios in these brains vary systematically with brain size. However, as this factor could bias our result, we have considered what effect it might have on the estimated slopes. The values above come from neocortex, but they also probably give a general indication for the possible range of shrinkage in the cerebellum. We took two hypothetical data points from around the minimum and maximum values for our data set. We then "shrank" the white and gray matter to either 30% or 40%, so as to systematically bias the result with size. We found that this could bias the resulting slope by up to 0.09. The magnitude of this is too small to account for our results unless neocortex and cerebellum were affected in opposite directions which is very unlikely.

Our scaling exponents were calculated using the method of independent contrasts which allowed us to remove the effects of phylogeny (Felsenstein, 1985). We used the Ape package for R for this (Paradis et al., 2004). Phylogenies and dates come from the literature (Murphy et al., 2001; Springer et al., 2003; Douady et al., 2002; Bininda-Emonds et al., 1999; Purvis, 1995; Kumar and Hedges, 1998). In cases of soft polytomies, we separated uncertain nodes with branches of length zero and reduced the degrees of freedom correspondingly in our statistical analysis (Purvis and Garland, 1993). The 95% confidence intervals we report have been calculated with these minimum degrees of freedom, and so represent the maximum range. We used regres-

sion forced through the origin to calculate slopes, and followed the recommendations of Garland et al. (1992) and Harvey and Pagel (1991) to ensure that the requirements for regression were met. Regression coefficients we present were calculated using a robust line fitting method, iterated re-weighted least squares (Huber, 1981).

2.3 Results

We present our volume measurements for neocortex and cerebellum in Table A.1. Total brain size in our sample varies over more than two orders of magnitude making the data suitable for looking at scaling relationships. We find that white matter gray matter scaling differs significantly in cerebellum and neocortex. As can be seen in Figure 2.1, the regression line for cerebellum has a shallower slope. This can also be seen in the scaling exponents we calculated for white matter contrasts on gray matter contrasts. For cerebellum the exponent is 1.03 (95% int. 0.95-1.11). White matter scaling in the cerebellum is essentially isometric. In comparison, the scaling exponent for neocortex is 1.20 (95% int. 1.09-1.31), which is significantly greater than 1.

2.4 Discussion

White matter gray matter scaling differs in cerebellum and neocortex. In neocortex white matter hyperscales relative to gray matter; in cerebellum it does not.

This scaling difference correlates with the presence or absence of cortico-cortical connections. It suggests that white matter hyperscaling in neocortex is dependent in some way on the presence of such connections. In particular, it probably reflects an increasing number of connections per unit as neocortex size increases.

Ringo (1991) introduced some useful terminology. He called the percentage of neurons that a given neuron connects to the "percentage interconnected", and the simple number of connections per neuron the number of "absolute connections". Frahm et al. (1982) pointed out that in a maximally connected network the number of connections scales with the number of neurons with an exponent of 2. In fact, this is true of any

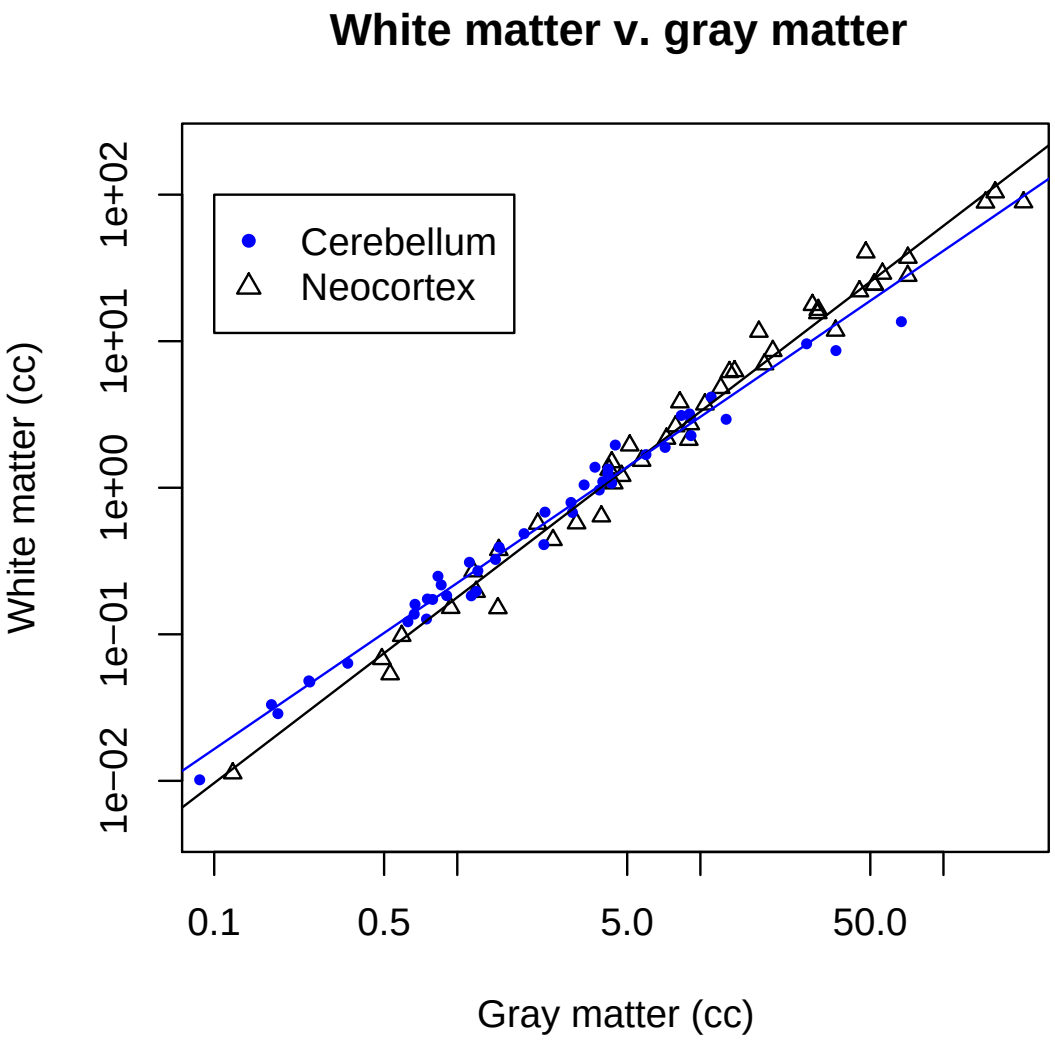

Figure 2.1: Log–log plot of white matter and gray matter for both neocortex and cerebellum. Also included are regression lines for the two structures.

network where the percentage interconnected is fixed. In a different network where the absolute number of connections (per neuron) is fixed, the exponent would be 1. In general, an exponent of less than 2 indicates that the percentage interconnected declines as the number of neurons increases.

The white matter-gray matter exponent for neocortex is 1.20. This suggests that as neocortex size increases, the percentage interconnected decreases, but the absolute number of connections per neuron increases. This could be seen as a compromise between the ideal of maintaining a constant percentage interconnected, and the physiological impossibility of producing that many axons as a brain gets large.

The popular concept of a small world network could help explain how this compromise is made. As it turns out, a very small number of random connections are enough to significantly lower the characteristic path length of a network (network diameter) (Watts and Strogatz, 1998). In the context of a neocortical network this could be manifested as a small number of long range axonal connections. Perhaps large neocortices are more small worldy. In a large neocortex long range communication could be handled less by direct long range connections and more via intermediate neurons, themselves connected to a few long range connections.

Figure 2.2 shows network diameter as we move from a locally connected network to a random network, as in Watts and Strogatz (1998). Network diameter is the average number of nodes (neurons) you must pass through to get from one randomly chosen node to another. We have calculated network diameter for N=100 and N=200 neurons varying the number of connections per neuron at N=200. The range of values for k (connections per neuron) was chosen to correspond to exponents of roughly 1-1.8 in the scaling of connections vs. neurons. As one would expect, increasing the number of neurons increases network diameter. For low values of p, even increasing k by a lot doesn't overcome this. But, as you raise p, making the network more small worldy, networks with higher k actually cross below the baseline. There is an interaction between p and k, meaning that if your goal is to increase the number of neurons and keep network diameter low, it makes sense to play with both of these parameters.

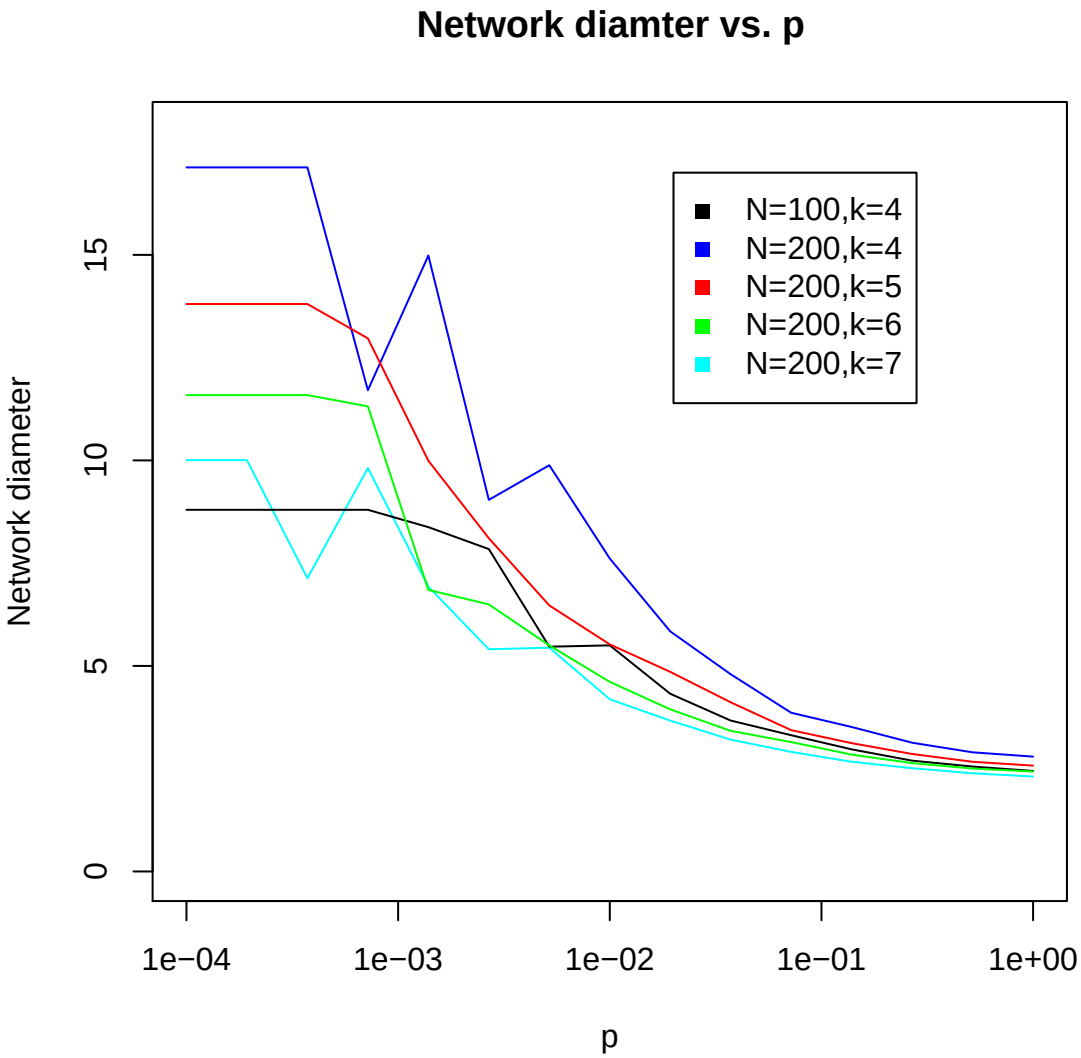

Figure 2.2: This plot is based on Watts and Strogatz (1998). They studied network diameter as locally connected networks were converted to randomly connected networks. The parameter p gives the probability that a given connection switches from local to random connectivity. Here we show the network diameter vs. p for networks of different size, with different numbers of connections per neuron. N=number of neurons, k = connections per neuron.

A second point we can take away from the plot is that for an even more random network (values of p¡0.01), k has very little effect on network diameter. That is, neuron number can increase without increasing network diameter by much. One might have thought that a relatively low exponent like 1.2 is surprising. What this shows is that for a network with lots of long range connections, a large exponent is not necessary.

If this is the case, why would the number of white matter connections need to increase at all in a large brain? Perhaps there are certain functions for which indirect connectivity via an intermediary neuron is not advantageous. (Remember, network diameter is measuring connectivity though other neurons). This could be true for computations where timing is very important and adding the noise of an additional synapse would be a disadvantage. In these cases direct axonal connections might be preferable.

The difference between neocortex and cerebellum probably reflects fundamental differences in the kinds of computation performed by each structure (Sultan, 2002). Cerebellum appears to aid other brain regions by performing certain specialized computations. Neocortex in contrast is responsible for a much more general integration of inputs in order to guide behavior. Such integration may require large numbers of connections between its different parts.

2.5 Acknowledgements

We would like to thank Wally Welker, who provided access to the Wisconsin brain collection, as well as Inge Siggelkow for assistance there. Pietro Perona made important suggestions regarding the relevance of the small world network idea, and kindly provided several programs for measuring network diameter. We would also like to thank Sam Wang for several stimulating discussions and for comments and suggestions on a draft of this paper. This work was supported by NIH EY11759 and NIH GM07737.

Chapter 3

The scaling of frontal cortex in primates and carnivores

3.1 Introduction

Comparative neuroanatomists have long been interested in the relationship between size and brain structure. Early work focused on how the brain scales with the body, and how gross morphological characteristics such as cortical folding change with size (Baillarger, 1845; Dubois, 1913). More recently emphasis has been put on the scaling of various brain structures with each other and with overall brain size (Frahm et al., 1982; Haug, 1987; Finlay and Darlington, 1995; Stevens, 2001).

The scaling of frontal cortex presents an interesting case. From the beginning, workers have been drawn to this region because of the supposition that volume increases occurred in the line leading to humans. Brodmann's *regio frontalis* consisted of frontal cortex minus areas 4 and 6 and parts of the cingulate. He described a "progressive" expansion of this region in the primate line going from prosimians to humans, and argued that primates more closely related to humans have a disproportionally larger *regio frontalis* (Brodmann, 1912). But primates more closely related to humans also have larger brains. The disproportionate expansion of the frontal region could be due to allometric scaling only.

Von Bonin explicitly argued that frontal cortex hyperscales with brain size, and man has "precisely the frontal lobe which he deserves by virtue of the overall size

of his brain" (Von Bonin, 1947). A number of subsequent workers used allometric lines as a kind of standard for comparing whether human frontal cortex is bigger or smaller than one would expect for a similarly sized primate (Uylings and VanEden, 1990; Semendeferi et al., 2002; Passingham, 2002). However, neither Von Bonin nor later workers had adequate data or methods to establish whether frontal cortex hyperscaling is a regular and systematic relationship with size, or simply an artifact of grade differences. As was originally pointed out by Felsenstein (1985), the phylogenetic structure of a sample of species can make it appear that there is a systematic relationship between two variables where none exists.

To make the distinction between a series of grade shifts and systematic allometry one must apply a method such as independent contrasts which can factor out the effects of phylogeny (Felsenstein, 1985). In addition, one must have data from a phylogenetically wide sample of species. Here we examine the scaling of frontal cortex in a large sample of mammals which includes broad representation in two orders, primates and carnivores. We analyze the resulting data using the method of independent contrasts.

3.2 Materials and Methods

3.2.1 Brains

We examined brains from a total of 55 mammalian species in 8 orders. The majority of these are located at the comparative brain collection at the University of Wisconsin, Madison. Brains were embedded in celloidin and stained with thionin.[1] We took a systematic random sample from each brain. That is, slices were chosen at a regular sampling interval with the position in the first interval randomized. We used 40 or more slices per brain, digitizing these with a standard office flatbed scanner (Epson Expression 800) at 800 dpi. In cases where a slice we needed was missing, we took an adjacent slice or a slice from a corresponding fiber series. In several cases where

[1]Our *Daubentonia madagascariensis* measurement was based on a T2 weighted MRI in conjunction with nissl stained frozen sections from the same brain.

no suitable substitute was available, we interpolated between adjacent slices in our series to obtain volume measurements. The digital images were roughly aligned for convenience, and analyzed using the Amira software package. Coefficients of error for our volume measurements were less than 0.03, using the method of Gundersen et al. (1999). A table of our raw measurements is available in the supplementary information.

3.2.2 Demarcation of Boundaries

Frontal cortex is neocortex anterior to the motor-somatosensory border. Except for the borders of primate V1 this is the most recognizable and reliable cytoarchitectonic border in the neocortex (Brodmann, 1994). Several notable features of the cytoarchitecture change here. Motor cortex has large Betz cells in layer 5. In addition, it lacks a granular layer 4 which is present in somatosensory cortex. Included in the supplementary information are several photomicrographs of motor cortex and its border with somatosensory cortex. The motor-somatosensory border is also a landmark which has been identified electrophysiologically in a number of species. We referred to this work where available: *Hylobates* and *Pan* (Welt, 1962), *Allouatta* (Vogt and Vogt, 1907), *Aotus* (Stepniewska et al., 1993), *Perodicticus* (Fitzpatrick et al., 1982), *Otolemur* (Fogassi et al., 1994), *Galago* (Sur et al., 1980), *Nycticebus* (Sanides and Krishnamurti, 1967), *Procyon* (Welker and Seidenstein, 1959), and *Dasypus* (Royce et al., 1975). We also referred to several cytoarchitectonic studies for *Lemur* and *Potos* (Brodmann, 1994), and *Choloepus* (Gerebtzoff and Goffart, 1966). We were able to identify the motor-somatosensory border in 43 species of mammals including 25 primates and 15 carnivores, and we used its position and trajectory to divide cortex in two. On the lateral side in primates we followed its trajectory until it intersected the sylvian fissure. We then followed the sylvian forward, counting everything anterior of where the sylvian disappears as frontal cortex. In carnivores on the lateral side we followed the trajectory of the motor-somatosensory border until it reached the coronal sulcus. We followed the coronal until it disappeared or until we reached the

level of the cruciate sulcus, whichever came first. We counted everything anterior to that as frontal cortex. In the three other mammals there were not limiting sulci of this type, and we simply followed the trajectory of the motor somatosensory border all the way to the edge of neocortex. Medially in all mammals we followed the trajectory of the motor-somatosensory border though the cingulate down to the level of the corpus callosum. We identified the borders of neocortex in our sample using well known cytoarchitectonic criteria.

3.2.3 Shrinkage

Celloidin embedding causes shrinkage. We corrected for overall shrinkage using pictures taken of the brains before embedding. These were from standard views and included a scale bar. By comparing various measurements on these pictures with our scanned images, we were able to make estimates of slice dimensions before celloidin embedding. In *Homo sapiens* and *Propithecus verreauxi* no pre-sectioning picture was available. In these cases we scaled our measurements so that whole brain volumes would match those measured by Stephan et al. (1981).

A second issue relates to differential shrinkage of various structures. Our frontal cortex scaling results have been presented as comparisons between two regions of neocortical gray matter. If gray matter in different regions of cortex shrinks differently, it would present a problem for us. We therefore examined two celloidin shrinkage studies, a beaver and a capybara, from the Wisconsin collection. One hemisphere of these brains was sectioned frozen while the other was sectioned after being embedded in celloidin. We measured shrinkage in the celloidin hemisphere relative to that in the frozen one. We did not feel we could identify the motor-somatosensory border reliably in these two rodent brains, so we used the caudal end of the corpus callosum as a landmark. We used it to divide the cortex into two parts. In the beaver, we found that gray matter caudal to the corpus callosum shrank to 39.6 % of its original volume in the celloidin hemisphere. In our other, rostral division of beaver neocortex, gray matter shrank to 39.1 % of its original volume. In the capybara, the values

were 33.7 % and 32.1 % for caudal and rostral divisions, respectively. In both brains, the amount of shrinkage found in the two divisions of neocortex was very similar. We conclude that differential shrinkage of neocortical gray matter within the same brain is not a significant problem for our analysis. We also looked at scaling between neocortical gray matter and the subcortical brain, i.e. whole brain minus neocortical gray and white. In the shrinkage studies we looked at the shrinkage of the rest of the brain, which is whole brain minus neocortex and cerebellum, which is missing in these studies. Rest of brain shrank to 43.2 % and 40.7 % of its original volume in the beaver and capybara respectively. These values differ somewhat from the values for neocortical gray matter. But they do not differ by enough to account for our results, even if they varied systematically with brain size, which they almost certainly do not.

3.2.4 Data Analysis

Data analysis was performed in the R language (Ihaka and Gentleman, 1996). To calculate independent contrasts we used the Ape package for R applied to log transformed volume data (Felsenstein, 1985; Paradis et al., 2004). Phylogenies and dates come from the literature (Murphy et al., 2001; Springer et al., 2003; Douady et al., 2002; Bininda-Emonds et al., 1999; Purvis, 1995; Kumar and Hedges, 1998), and a copy of the tree we used is available in the supplementary information. In cases of soft polytomies, we separated uncertain nodes with branches of length zero and reduced the degrees of freedom correspondingly in our statistical analysis (Purvis and Garland, 1993). The 95% confidence intervals we report have been calculated with these minimum degrees of freedom, and so represent the maximum range. We used regression forced through the origin to calculate slopes, and followed the recommendations of Garland et al. (1992) and Harvey and Pagel (1991) to ensure that the requirements for regression were met. Regression coefficients we present were calculated using least squares. Because our variables were log transformed volumes of brain structures, regressions were highly significant with high coefficients of determination(>0.93) making it unlikely that the choice of line fitting method affected the results significantly.

We also applied a robust line fitting method, iterated re-weighted least squares (Huber, 1981), and found that this did not change the results. To determine whether scaling exponents in two groups were significantly different, we regressed their contrasts together and compared the residuals for each group with a t-test (Barton and Harvey, 2000).

We wanted to ensure that our observed hyperscaling relationships are not due to the confounding effect of several categorical variables: diet, activity pattern, and social structure. To do this, we used a simple method that involves performing independent contrasts separately on each category. For example, if we wish to know whether the apparent hyperscaling between frontal gray volume and rest of cortex volume is actually caused by the confounding effect of activity level we can do the following. We perform independent contrasts on frontal cortex and rest of cortex for nocturnal and diurnal primates separately. We can regress the results for nocturnal and diurnal separately as well, and if the hyperscaling persists, be confident that activity pattern is not affecting the scaling relationship. But this has the disadvantage of dividing the data into parts and reducing the sample size used in any individual regression. Instead, we can take the contrasts which were calculated separately for nocturnal and diurnal primates and regress them through the origin together. As long as the phylogenies for nocturnal and diurnal primates are drawn from the same underlying phylogeny and have been treated in the same way (e.g., put through the same transformations on branch lengths) this will give a valid result. Again if the hyperscaling persists, we can conclude that it is not due to the confounding influence of activity level.

To test whether group size is related to relative frontal cortex size, we calculated the ratio of frontal cortex to rest of cortex. We performed Pearson's correlation between this ratio and log group size. We also calculated the residuals of frontal cortex contrasts on rest of cortex contrasts and regressed these against group size contrasts.

Our group size numbers were population group size from Wrangham et al. (1993). Our categories for diet, activity and social structure in primates were based on Rowe

Table 3.1: Independent contrasts results. Slopes and 95% confidence intervals for regression through the origin of independent contrasts of frontal cortex gray matter, rest of cortex gray matter and subcortical brain. Data for all mammals and for primate total neocortex consists of our own data combined with that of Frahm et al. (1982).

	Structures compared	Slope	95% int.	# Contr.
Primates	frontal neog v. rest of neog	1.18	1.06-1.30	24
	frontal neog v. subcort brain	1.38	1.22-1.53	24
	rest of neog v. subcort brain	1.13	0.98-1.28	24
	total neog v. subcort brain	1.10	1.01-1.18	37
Carnivores	frontal neog v. rest of neog	0.94	0.82-1.07	14
	frontal neog v. subcort brain	1.13	0.98-1.27	14
	rest of neog v. subcort brain	1.17	1.03-1.31	14
	total neog v. subcort brain	1.14	1.02-1.26	14
All Mammals	total neog v. subcort brain	1.17	1.11-1.24	93

(1996). For diet we divided the primates into 3 groups, insect eaters, leaf eaters, and those who eat primarily high quality food of limited availability: fruit, gums, and seeds. For social structure we used 6 groups: monogamous, fission fusion, troop, solitary, harem, and human.

3.3 Results

We find significant differences in frontal cortex scaling between primates and carnivores (Figure 3.1 A). In primates the slope of frontal gray matter contrasts on rest of cortex contrasts is 1.18 and the 95% confidence interval is 1.06 to 1.30 (Table 3.1 gives a summary of independent contrasts results). The lower bound of the primate 95% confidence interval is greater than one and the scaling is therefore significantly greater than isometric. Figure 3.1 B illustrates primate hyperscaling in a different way.

The scaling exponent for carnivore frontal cortex contrasts vs. rest of cortex contrasts is significantly less than for primates ($p = 0.03$, $t = 2.22$, $df = 35$). The carnivores show no tendency toward frontal cortex hyperscaling (Figure 3.1 C). Their exponent is 0.94 (95% int. 0.82-1.07), which is not significantly different from isometric scaling.

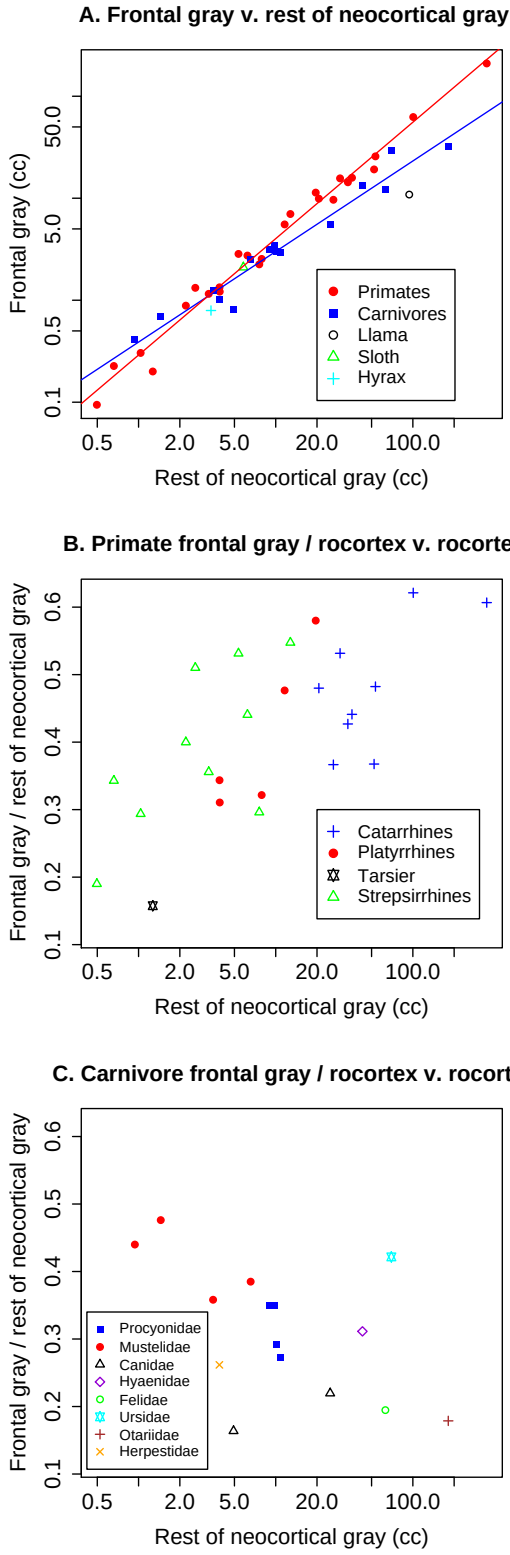

Figure 3.1: Frontal cortex scaling. (A) Log-log plot of frontal gray matter volume vs. rest of cortex gray matter volume for primates, carnivores, and other mammals. Included are least squares regression lines for primates (red) and carnivores (blue). Plots B and C take the form of a ratio on the y axis, plotted against its own denominator on a logarithmic x axis. (B) Ratio of primate frontal gray matter volume to rest of neocortical gray matter volume plotted against rest of neocortical gray matter volume. (C) Same as B but showing carnivores.

We see that primates and carnivores differ in how these two regions of cortex scale with each other. Does this result primarily from differences in frontal cortex, rest of cortex, or both? We can examine this by looking at the scaling of the cortical regions with the subcortical brain. Table 3.1 makes it clear that the scaling exponent for rest of cortex vs. the subcortical brain does not differ significantly in primates and carnivores. But the exponent for frontal cortex vs. subcortical brain does differ in the two groups. Table 3.1 also shows that, consistent with previous claims, neocortex as a whole scales up relative to the rest of the brain in mammals (Frahm et al., 1982; Hofman, 1989). Taken separately, primates and carnivores show neocortex vs. subcortical brain scaling trends similar to the rest of mammals and to each other. Thus primates and carnivores show similar scaling relationships for neocortex as a whole and for the non-frontal parts of it. But frontal cortex scaling in the two groups differs significantly.

Figure 3.1 B hints at the possibility of grade differences within primates. For a given volume of rest of cortex, strepsirrhines seem to have a larger frontal cortex than haplorhines. To demonstrate that this is a grade difference we would want to show that strepsirrhines and haplorhines have the same scaling exponent. In our sample their exponents are not significantly different ($p = 0.38$, $t = 0.91$, $df = 22$) though this may reflect our small sample size for the individual primate groups. In any event Figure 3.1 B shows that where their cortex sizes overlap, strepsirrhines tend to have a larger frontal cortex than haplorhines.

We also examine whether the allometric scaling of frontal cortex in primates can be accounted for by confounding relationships with the ecological variables diet, activity pattern and social structure. When we calculate the scaling exponents for frontal vs. rest of cortex contrasts separately for each category within a variable (e.g., nocturnal and diurnal within activity pattern) and regress them together, we find that hyperscaling persists in all three variables (activity pattern: 1.18, 95% int. 1.05-1.30; diet: 1.11, 95% int. 0.99-1.24; social structure: 1.20 95% int. 1.01-1.40). For all three the slope remains high, and for two, social structure and activity pattern, the 95% confidence interval still excludes 1. In fact in many cases there is strong hyperscaling

even within single categories (e.g nocturnal primates 1.33, 95% int. 1.11-1.56).

We compared the ratio of frontal gray over rest of cortex to log group size for 9 primates and 8 carnivores. Pearson's correlation between these two quantities was not significant ($p>0.3$). We also calculated the residuals for a regression of frontal cortex contrasts on rest of cortex contrasts. We regressed these against groups size contrasts, again finding no relationship. This suggests that group size and relative frontal cortex size are not related.

3.4 Discussion

We have provided evidence for significant differences between primates and carnivores in frontal cortex scaling. In primates frontal cortex hyperscales relative to the rest of cortex. In carnivores it does not. This suggests important differences in the development and composition of frontal cortex in the two groups, and supports the claim that primate frontal cortex differs from that of other mammals (Preuss, 1995).

In addition, our use of the method of independent contrasts demonstrates that the hyperscaling of primate frontal cortex is a regular and systematic relationship with size. It is not due to a series of grade shifts in the line leading to humans.

Our results also provide some new context for old arguments. Much interest has focused on the question of whether humans have an unusually large frontal cortex compared to other primates. Semendeferi et al. showed that frontal cortex occupies about the same proportion of total cortex in humans as it does in the great apes (Semendeferi et al., 2002). Figure 3.1 B shows the ratio of frontal to rest of cortex for the wider range of primates in our data set. Ratios of frontal to rest of cortex for individual species can be found in Table B.1. Note that catarrhines are not the only group where species with a high frontal cortex proportion have evolved. Such species have also evolved independently in platyrrhines (e.g., the spider monkey) and strepsirrhines (e.g., the aye aye). This is broadly consistent with the proposition that humans are not special with regard to the portion of their cortex devoted to frontal cortex. Indeed the presence of a hypermetric scaling relationship in primate frontal

cortex only serves to reinforce the point.

In addition our data suggests that there may be a grade difference between strepsirrhines and haplorhines, with haplorhines actually having a smaller frontal cortex for a given rest of cortex size. This appears to turn on its head Brodmann's notion of a progressive expansion of frontal cortex in the line leading to humans.

Our results also shed some light on an *Aegyptopithecus zeuxis* endocast described by Simons (1993). *Aegyptopithecus* is an early catarrhine from the Oligocene of Egypt. On this endocast (DUPC 5401) we examined the position of the central sulcus. The sulcus is about 40% of the way back as you move along the top of the brain from the frontal to the occipital pole. In comparison, in a 3D reconstruction we made of the brain of the living mandrill, the sulcus is about 50% of the way back. The ratio of frontal cortex to rest of cortex in the mandrill is at the bottom of the range among catarrhines in our sample. This shows that the central sulcus in *Aegyptopithecus* was placed relatively far forward, and implies that the animal had a small frontal cortex compared with living catarrhines. *Aegyptopithecus* had a brain volume of about 27 cc (Simons, 1993), which is also below the range of living catarrhines. The small brain volume likely explains the relatively small frontal cortex. With its small brain *Aegyptopithecus* represents an element of catarrhine variation which no longer exists today.

The difference in scaling between primates and carnivores is striking. Perhaps the most general conclusion to be drawn is that there are important differences between the two orders in the molecular regulation of cortical development. We discuss possible explanations for the scaling difference below, several of which do not have an immediate connection with development. Even in these cases however, the ultimate mechanisms behind the difference must be the mechanisms of development.

Now let us consider several possible explanations for the scaling difference. In other parts of the brain, allometry has been argued to be the result of a fixed order of neurogenesis which causes later developing structures to become disproportionately large (Finlay and Darlington, 1995). This theory was intended to explain scaling differences between structures (e.g., why does neocortex scale up and hippocampus

scale down). It was based on the suggestion that mammals share a rigid developmental program in which the order of development for different structures does not change. Clearly the theory as originally specified does not explain our data, where we find that a single structure scales differently within two mammalian orders. One might propose that primates and carnivores have a different rigid developmental program in cortex. To explain our scaling data, primates would need to have a gradient of neurogenesis which moved from posterior to anterior. But this is inconsistent with the known facts. In mammals which have been examined so far, including primates, anterior areas of neocortex complete neurogenesis before posterior areas do (Rakic, 1988; Sanderson and Weller, 1990; Bayer and Altman, 1991).

Another possible explanation is that the apparent relationship with size in primates is actually driven by some other variable which is itself correlated with size. In primates, ecological variables such as diet, activity pattern and social structure are related to body size. Primate frontal cortex might contain structures, absent in carnivores, whose relative size correlates with such variables. This would make it appear that relative frontal cortex size is correlated with absolute size in primates. We calculated scaling exponents so as to remove the effect of the categorical variables diet, activity pattern and social structure. Our results suggest that the scaling of frontal cortex is not due to confounding with these variables.

A third alternative follows from a more functional explanation for scaling. In other contexts biologists think of scaling in functional terms, for example the relationship between bone thickness and body weight (Schmidt-Nielsen, 1984). In the brain too, certain scaling phenomena have been explained functionally. White matter hyperscales relative to gray matter in neocortex and cerebellum, though to different degrees (Frahm et al., 1982; Bush and Allman, 2003). This has been seen as a consequence of the need to maintain connectivity as brain size increases or as a reflection of systematic changes in axon diameter.

Perhaps a more relevant example can be found in the hyperscaling of V1 relative to LGN which provides all of V1's input. Stevens pointed out that this might be a reflection of the information the two structures represent (Stevens, 2001). In V1

a number of features are represented explicitly which are implicit in LGN. Edge orientation is an example. As retinal and LGN resolution increase, the resolution of edge orientation ought to increase too. The result is that the total number of cells involved in representing edge orientation will increase disproportionately with size (Stevens, 2001).

Sensory information is repeatedly transformed in the brain, eventually finding its way back into the world as behavior. Perhaps the situation described for V1 and LGN is not uncommon. The case of primate frontal cortex could be seen in this light. Perhaps primates have evolved machinery in their frontal cortex which is absent in carnivores. This machinery, because of the nature of the circuits it uses and the information it represents, increases disproportionately with size.

3.5 Acknowledgements

We would like to thank Wally Welker and Inge Siggelkow for access to the Wisconsin brain collection. We would also like to thank Eric Ahrens for kindly providing MR data, and Elwyn Simons for providing an *Aegyptopithecus zeuxis* endocast. Rizvan Mamet made suggestions on the analysis, and Wulf Haubensak provided German translation help. This work was supported by NIH EY11759, and the W.M. Keck Foundation Fund for Discovery in Basic Medical Research at the California Institute of Technology.

Chapter 4

Endocranial volume in *Parapithecus grangeri*

4.1 Introduction

Among living primates, substantial brain size differences exist between anthropoids and strepsirrhines (Stephan et al., 1981). At a given body weight, an anthropoid brain is on the order of two times larger than that of a strepsirrhine. One theory of brain expansion in anthropoids relates it to the development of the visual system (Barton, 1998). Anthropoids have high acuity vision compared to strepsirrhines. However, because all living anthropoids have large brains and high acuity vision, comparative studies are not that informative about the relationship between these two characteristics.

It is therefore of particular interest to study brain size and the relative development of sensory structures in early anthropoid fossils. The discovery of a nearly complete skull (DPC 18651) of the species *Parapithecus grangeri* affords us this opportunity. The Parapithecidae are widely regarded as a sister group to the living anthropoids (Kay and Fleagle, 1988; Ross et al., 1998; Simons, 2001). As such, they may retain primitive features which have been lost in the living anthropoids. DPC 18651 was embedded in a hard sandstone which preserved its shape. This sandstone fills the endocranial cavity, and the posterior part of the orbital cavity, obscuring the optic foramina. In order to examine these features, we performed an X-ray computed

tomography (CT) scan of the fossil.

4.2 Methods

Imaging was performed at the high-resolution CT facility at the University of Texas at Austin, using the ultra high-resolution subsystem with 1024 detectors. (Scanner built by Bio-Imaging Research, Inc., Lincolnshire, Illinois). Slices were acquired perpendicular to the Frankfort plane, in roughly coronal orientation. The following scanning parameters were used: 120 kV; .2 mA; slice thickness 0.048 mm; field of view 45.5 mm. Images were reconstructed with a Laks convolution filter into 16 bit images, 1024 x 1024 x 1334 matrix, with voxel dimensions of .044 x .044 x .048 mm. These parameters give the ability to resolve objects on the order of .12 mm. Subsequent analysis was performed on a Linux workstation running Amira software (TGS, Inc. San Diego CA).

The position of interfaces between materials was calculated using the half maximum height (HMH) technique which sets the threshold halfway between the CT values on each side of an interface (Baxter and Sorenson, 1981; Spoor et al., 1993). Figure 4.1 shows a coronal slice, and a plot of the CT values along a line passing through it. These values were used to determine the midpoint between the bone and matrix intensity levels. The threshold was then set at the midpoint, as shown in Figure 4.1 C.

After determining HMH values, we used semi-manual image segmentation tools to segment out the endocranial cavity and the olfactory fossa. We determined the caudal end of the fossa based on the curvature of the surrounding endocranial cavity and on the structure of more lateral parts of the fossa itself. We then calculated volumes for the brain and olfactory bulb from these segmentations.

All visual information from the eyes reaches the brain via the optic nerve. The optic nerve passes though the optic foramen and the cross sectional area of the nerve can be well approximated by the size of the foramen. This offers us a means for looking at acuity in fossil primates. Kirk and Kay (2004) have measured optic foramen area

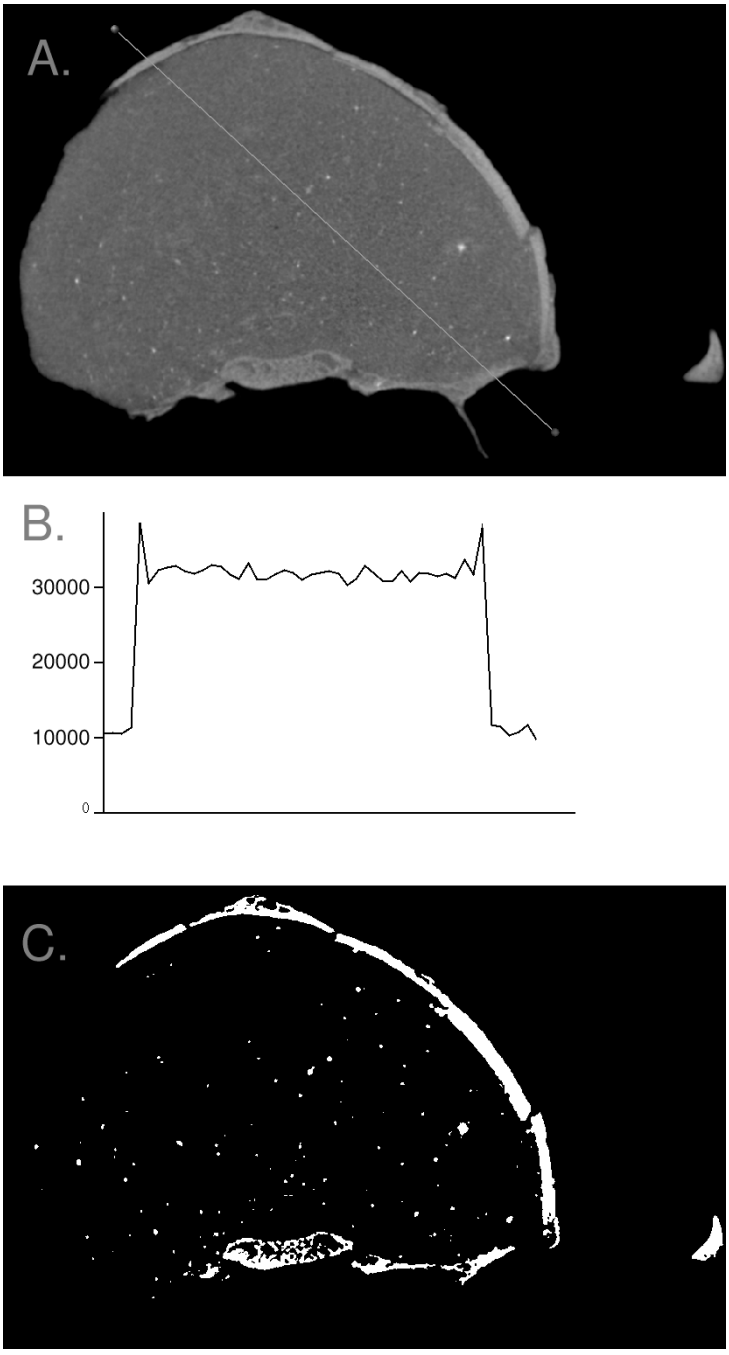

Figure 4.1: A. A coronal slice through the middle of the cranium. B. This graph represents the CT intensity values along the probe line which is visible in A. C. The slice from A. thresholded at the HMH value.

in a large number of living primates. When we plot their cross section data against a measure of size we find that the living anthropoid primates have larger foramina than other primates

Figure 4.2 shows how we measured the cross section of the optic foramen in the CT data. We aimed to make our measurements comparable to the data for living animals collected by Kirk and Kay (this volume), who made measurements from the external (orbital) perspective. The plane of the optic foramen does not match the plane that the scans were taken in. We made our foramen measurements by resampling the data so that the plane of the foramen coincided with one of the orthogonal planes of the data set. We did this by first making a crude surface of the foramina. This was used to determine how much the data set should be rotated for the right and left foramina respectively. The resampling was then done using a lanczos filter. The surface area of each foramen was estimated from the resulting cross section, thresholded at the HMH level.

4.3 Results

The scans have good contrast between matrix and bone. In our 16 bit images, bone and matrix CT values typically differ by around 5000 CT units. This can be seen in the plot in Figure 4.1 which represents the values through a region in the middle of the skull. It is also true in the areas around the optic foramen and olfactory bulb. Imaging artifacts are confined to a small amount of beam hardening around some of the thicker bones, too small to significantly effect our measurements.

The resolution of the scans is more than adequate to measure small structures such as the olfactory bulb and optic foramen. The optic foramen has linear dimensions an order of magnitude larger than the 0.12 mm resolution of these scans.

Figure 4.1 A illustrates another feature of DPC 18651. In some regions the bones of the braincase have been worn away exposing the matrix of the endocranial cavity. However, based on the symmetry of the endocranial space in the images it is clear that very little endocranial matrix was lost, so this should not have a significant effect

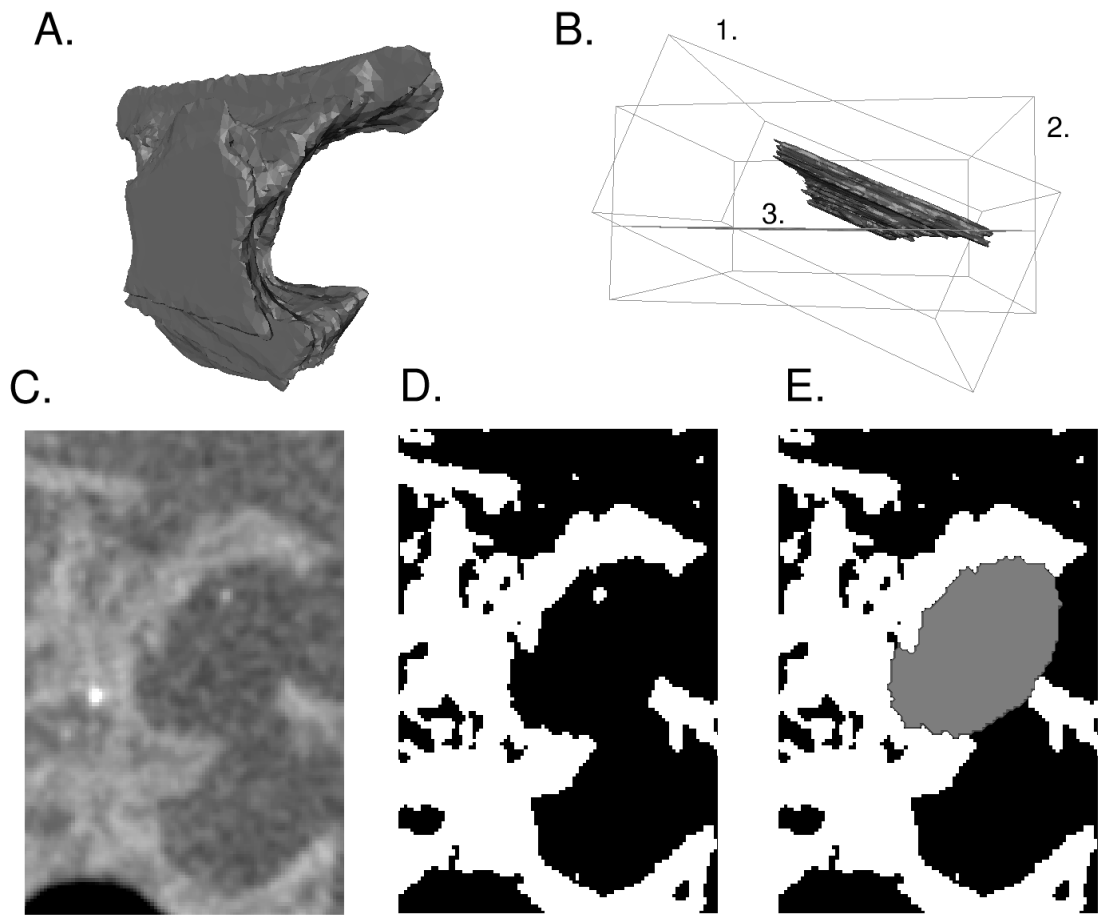

Figure 4.2: Illustration of measurement of left optic foramen. A. Crude surface of the bone around the optic foramen. B. Surface viewed from above. Bounding boxes show the rotated data set relative to the original data set. 1. Bounding box of original data set. 2. Bounding box of rotated data set. 3. Slice through the new data set which now lies in the plane of the foramen. C. View of the left optic foramen in new rotated data set. D. Left optic foramen thresholded at HMH level. E. Left optic foramen showing extent of surface area measure. The superior orbital fissure is visible below the optic foramen.

on measurements of endocranial volume.

Fig 4.3 shows a computer-generated surface of the skull of DPC 18651. In the bottom image the skull has been made transparent revealing the endocranial surface.

Our measurement of the brain volume of *P. grangeri* is 11,400 mm^3. In Figure 4.4 we present a log brain size log body mass plot, which includes a number of living species. For *P. grangeri* we use body mass estimates from post-cranial material Simons (this volume), and also from teeth (Kay and Simons, 1980; Gingerich et al., 1982; Conroy, 1987). As the figure makes clear, *P. grangeri* had a small brain, even relative to the smallest estimate of body mass.

Our measure of *P. grangeri* olfactory bulb volume is 75.0 mm^3. Figure 4.5 shows log olfactory bulb volume plotted against log brain volume for a number of living primates and *P. grangeri*. The value for *P. grangeri* lies closer to the strepsirrhines, but also falls withing the 95% prediction interval for a new observation among living anthropoids.

We also measured the cross-sectional area of the optic foramen in *P. grangeri* to be 3.46 mm^2. In Figure 4.6 we show this area plotted against skull length for *P. grangeri* and a large sample of primates. The value for *P. grangeri* can be seen to be intermediate to both anthropoids and strepsirrhines.

4.4 Discussion

Our results show that *P. grangeri* had a small brain for its body mass. In Figure 4.4 we can see that even with the smallest available estimates of body mass, *P. grangeri* had a brain size more in line with the living strepsirrhines than the living anthropoids. This is consistent with results for *Aegyptopithecus zeuxis* in Simons (1993). It seems likely that the last common ancestor of *P. grangeri* and the living anthropoids retained the relatively small brain of its ancestors.

It is worth noting that body mass estimates for *P. grangeri* based on teeth and skull dimensions have probably been overestimates. Figure 4.4 shows data for several large insectivores plotted alongside *P. grangeri* and the primates. If *P. grangeri* had

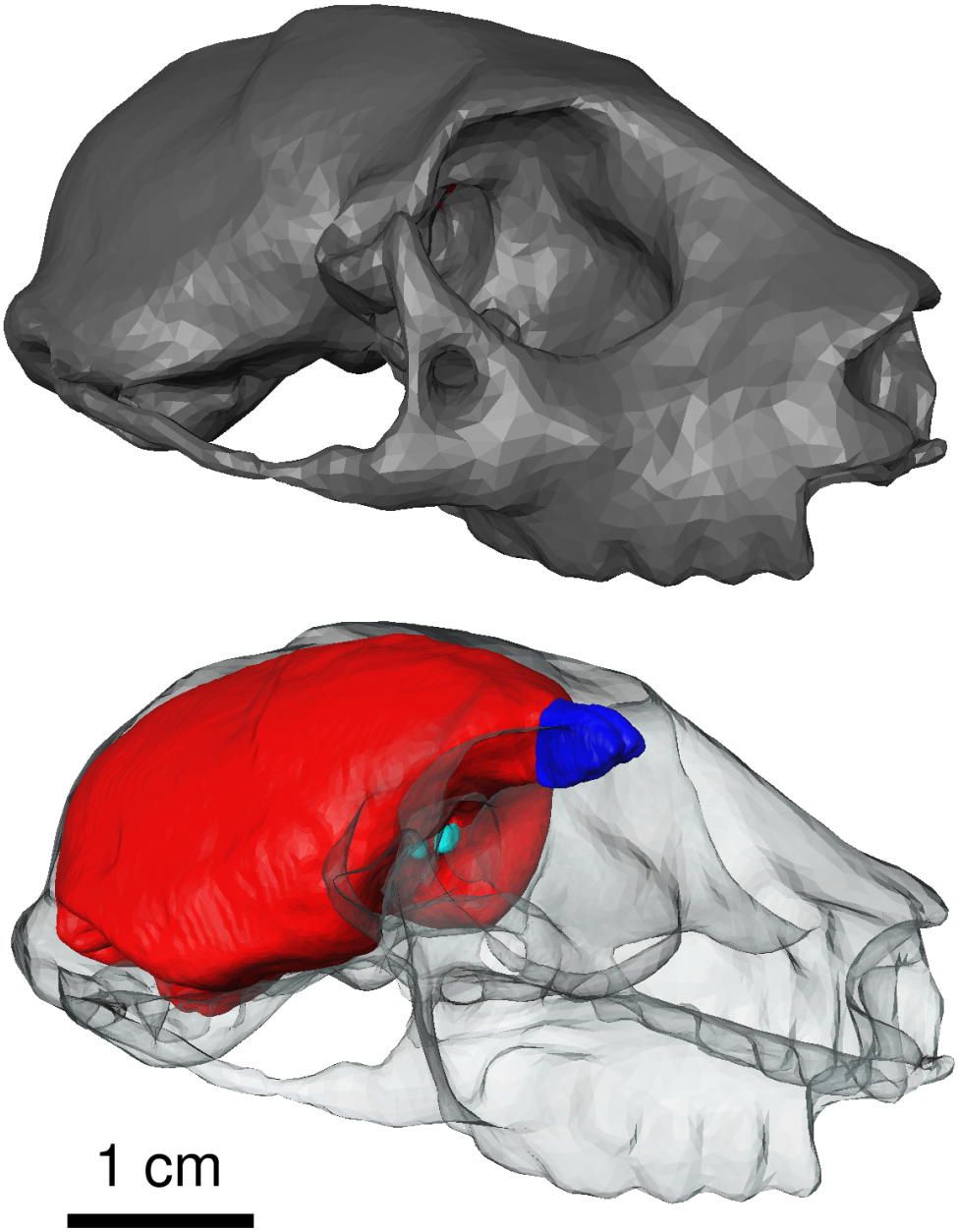

Figure 4.3: Surfaces of *P. grangeri* skull and braincase. The lower image shows the skull rendered transparent revealing the endocranial cavity. Dark blue represents the olfactory bulbs and light blue represents the optic nerves.

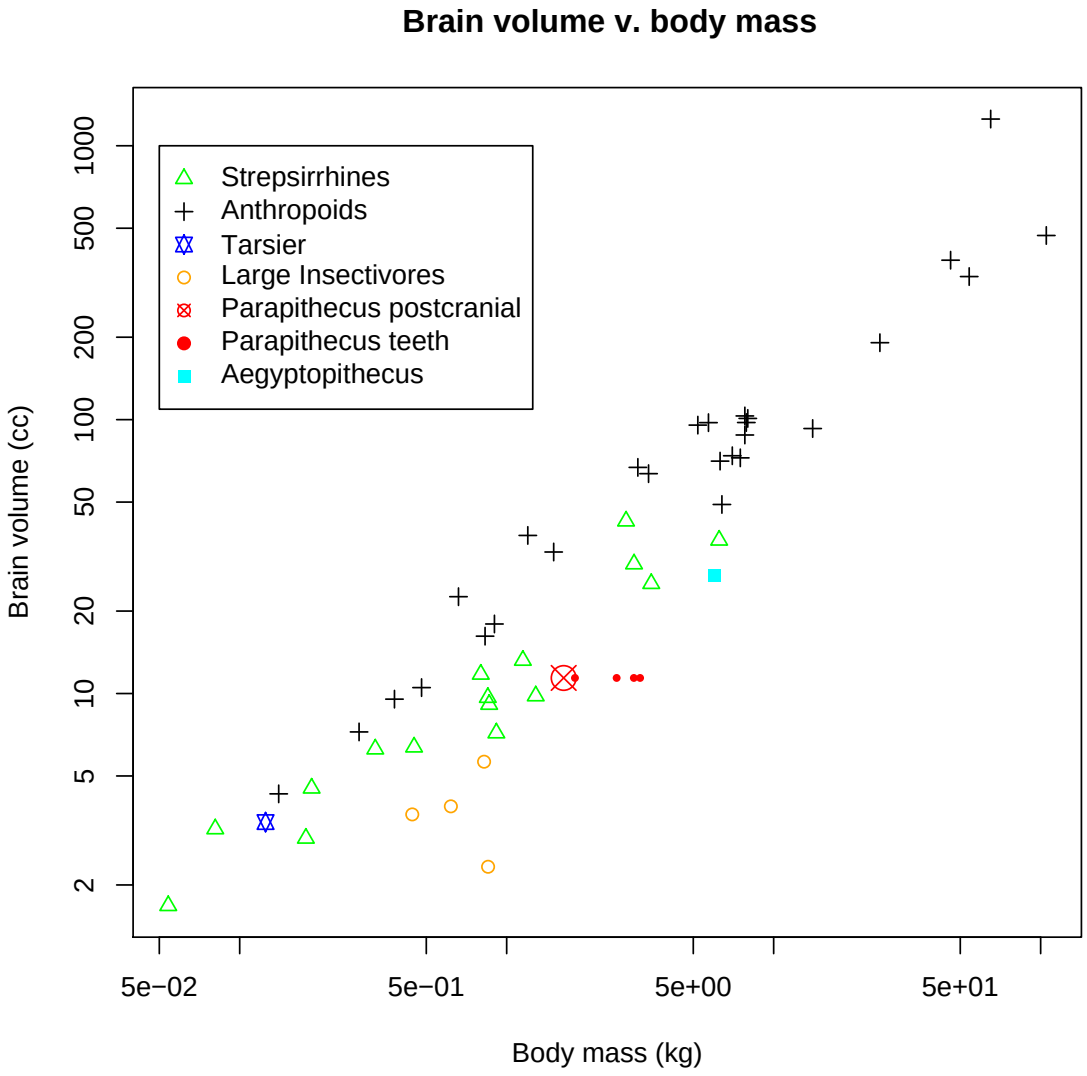

Figure 4.4: Brain volume plotted against body mass on logarithmic axes for *P. grangeri* and a collection of primate species. We use body mass estimates for *P. grangeri* from post-cranial material (Simons this volume) and from teeth Kay and Simons (1980); Gingerich et al. (1982); Conroy (1987). Also plotted is data for *Aegyptopithecus zeuxis* from Simons (1993), and four large insectivores from Stephan et al. (1981, 1991).

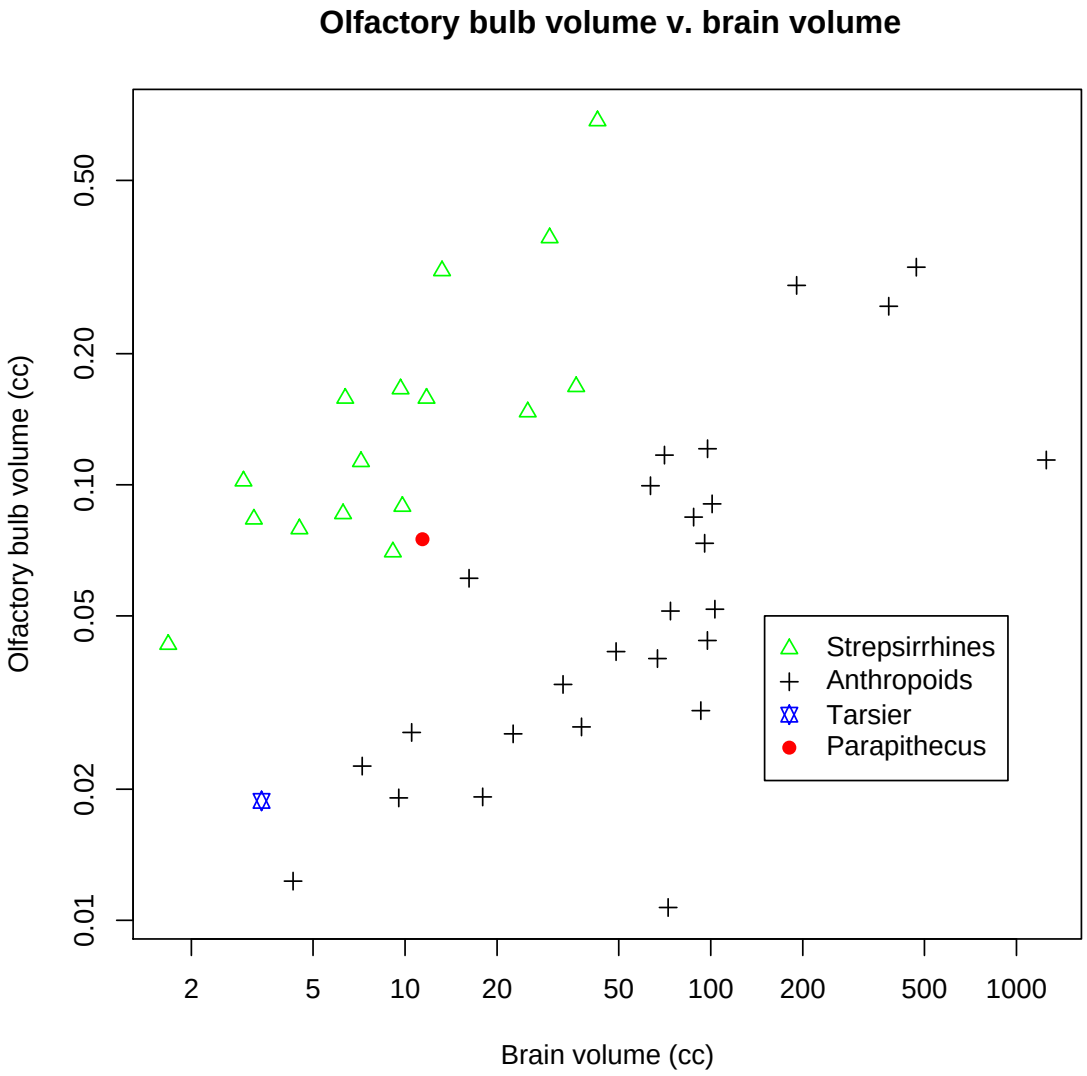

Figure 4.5: Olfactory bulb volume plotted against brain volume on logarithmic axes for a number of living species and *P. grangeri*. Data from living species are from Baron et al. (1983).

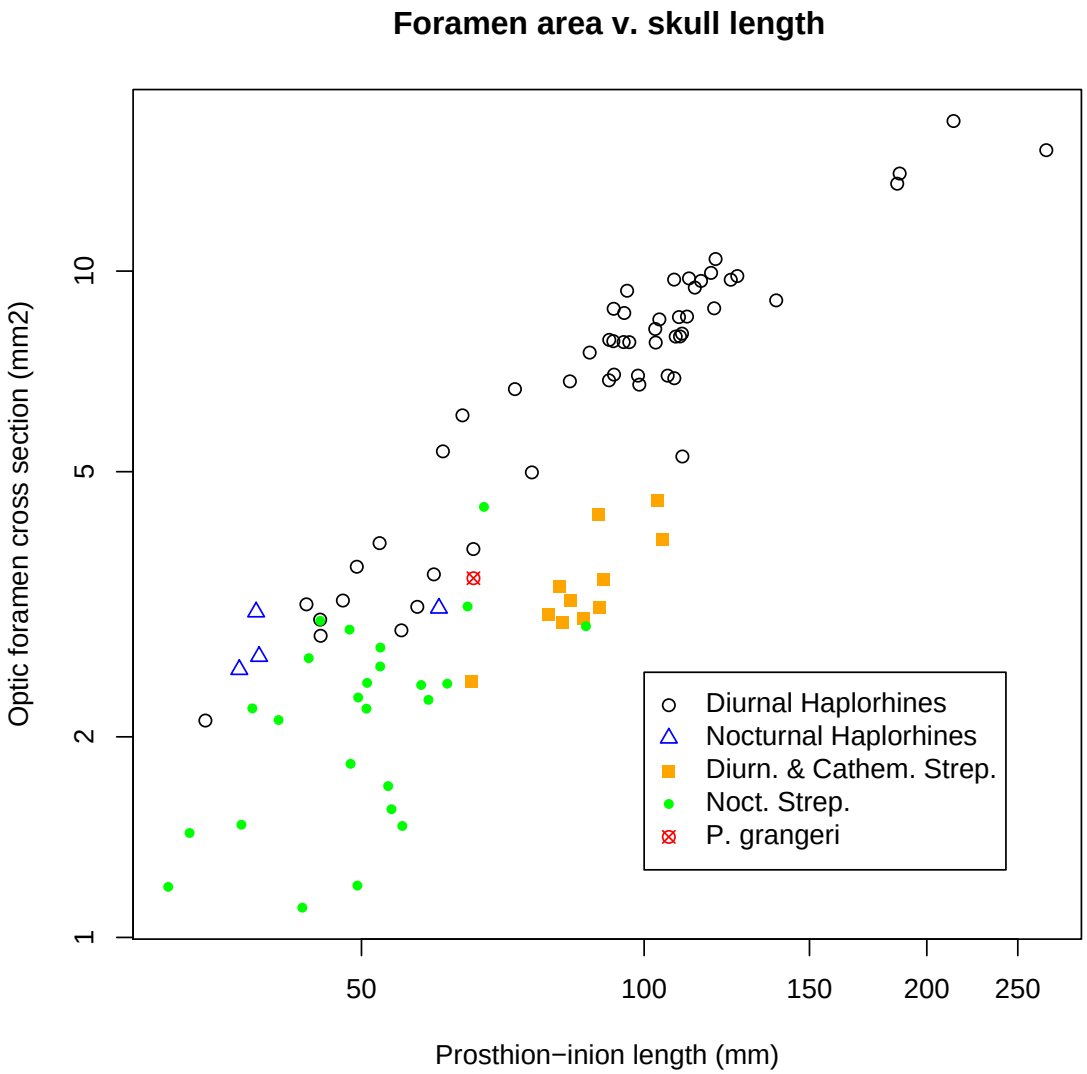

Figure 4.6: Optic foramen area plotted against skull length for *P. grangeri* and living primates. Living primate data is from Kirk and Kay, this volume.

a body mass around 3 kg, which is one value taken from the literature, then it had a brain relatively smaller than a number of living insectivores. Supporting the idea that previous estimates have been too high, Simons (this volume) provides body size estimates based on two tibiae and a humerus. All three are smaller than published values based on cranial measurements.

Figure 4.5 shows that the olfactory bulb of *P. grangeri* is similar in size to what one finds at the bottom end of the strepsirrhine range. However, because it also falls within the 95% prediction interval for anthropoids, it is not possible to say that *P. grangeri* has a significantly larger olfactory bulb than we would expect for a living anthropoid.

Our examination of the optic foramen of *P. grangeri* was also inconclusive. Its value is intermediate to that for living anthropoids and strepsirrines, and could fit with either statistically.

These results emphasize the fact that the so called anthropoid 'suite' of adaptations did not arise at once. *P. grangeri*'s brain retains the ancestral condition in overall size and olfactory bulb size. In other characteristics of its biology however- for example the structure of its skull and diurnal lifestyle-*P. grangeri* was similar to todays anthropoids. Thus it is wrong to think of the whole collection of unique anthropoid characters as reflecting a single adaptive complex.

4.5 Acknowledgements

We would like to thank Christopher Kirk and Richard Kay for kindly sharing their most recent OFI data set with us. We would also like to thank Matthew Colbert for assistance with the CT, Kevin Berney for help with the analysis, and one anonymous reviewer. This research was supported by NIH grant EY11759, the Keck Discovery Fund, and the Frank V. Hixon Fund.

Appendix A

White matter scaling supplemental information

Species	CerWhite	CerGray	NeoWhite	NeoGray
Hylobates Lar	2.93	12.77	21.92	45.12
Pan troglodytes	8.63	36.11	103.77	163.18
Cercocebus torquatus	1.96	4.47	40.36	47.92
Cercopithecus nictitans	0.97	3.84	11.81	35.99
Macaca mulatta	1.38	3.68	16.35	30.54
Mandrillus sphinx	1.89	7.16	27.93	71.30
Papio hamadryas	2.98	9.14	37.12	71.40
Semnopithecus entellus	2.27	9.15	24.26	51.85
Alouatta palliata	1.05	3.32	11.61	17.41
Aotus trivirgatus	0.17	0.75	1.49	4.32
Ateles sp.	1.68	5.97	17.68	28.90
Callicebus sp.	0.25	0.83	1.94	5.12
Saimiri sciureus	0.39	1.49	3.70	10.44
Tarsius syricta	0.05	0.25	0.15	1.47
Eulemur mongoz	0.49	1.88	3.83	8.23
Galago senegalensis	0.06	0.35	0.19	1.20
Lemur catta	0.41	2.27	2.12	8.96
Microcebus murinus	0.03	0.17	0.10	0.59
Nycticebus coucang	0.20	1.20	1.07	4.40
Otolemur crassicaudatus	0.13	0.75	0.57	3.10
Perodicticus Potto	0.18	1.14	0.64	3.91
Odocoileus virginianus	4.16	11.08	24.38	51.96
Tayassu tajacu	1.25	4.17	6.96	18.36
Marmosa mitis	0.01	0.09	0.01	0.12
Didelphis marsupialis	0.16	0.67	0.15	0.94
Myrmecophaga tridactyla	3.19	9.02	8.58	19.86
Tamandua tatradactyla	0.68	2.98	2.16	7.25
Choloepus didactylis	0.68	2.30	2.63	7.91
Procavia capensis	0.31	1.12	1.33	4.21
Equus burchelli	9.60	27.35	88.36	148.88
Applodontia rufa	0.14	0.67	0.38	1.48
Chinchilla laniger	0.17	0.79	0.27	1.16
Myoxus glis	0.05	0.25	0.07	0.49
Rattus norvegicus	0.03	0.18	0.05	0.53
Sciurus carolinensis	0.18	0.90	0.44	2.48
Ailurus fulgens	1.10	3.97	6.25	13.82
Canis latrans	1.34	4.17	15.54	30.42
Crocuta crocuta	3.12	8.34	28.90	56.10
Galictis vitatus	0.32	1.44	2.72	9.09
Mustela putorius	0.12	0.63	0.57	2.14
Mustela vison	0.22	0.86	1.21	4.75
Nasui narica	0.79	2.94	4.80	12.13
Potos flavus	1.07	4.32	6.16	13.17
Vulpes zerda	0.27	1.21	1.53	5.73
Zalophus californianus	13.59	67.12	88.71	213.49

Table A.1: White matter and gray matter volumes in neocortex and cerebellum for 45 mammals (cm^3).

Appendix B

Supplemental information for the scaling of frontal cortex in primates and carnivores

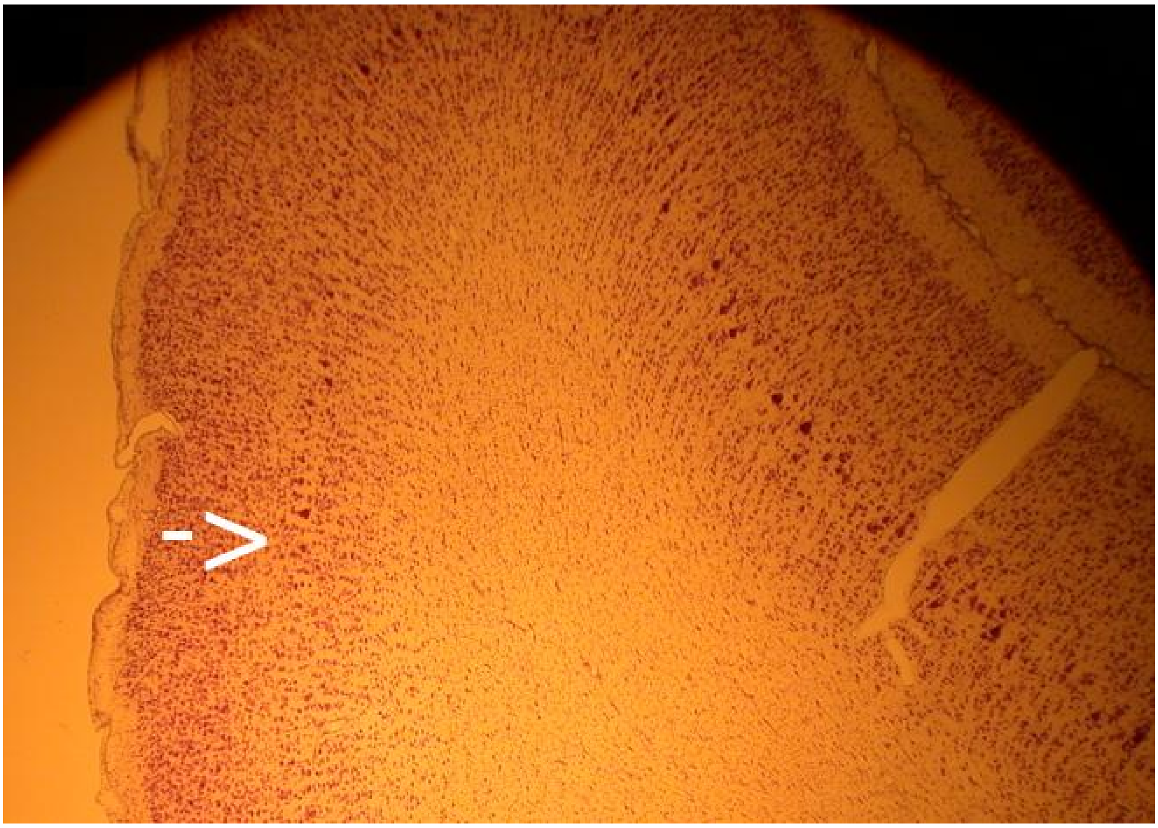

Figure B.1: Kinkajou (*Potos flavus*) motor-somatosensory cortex border.

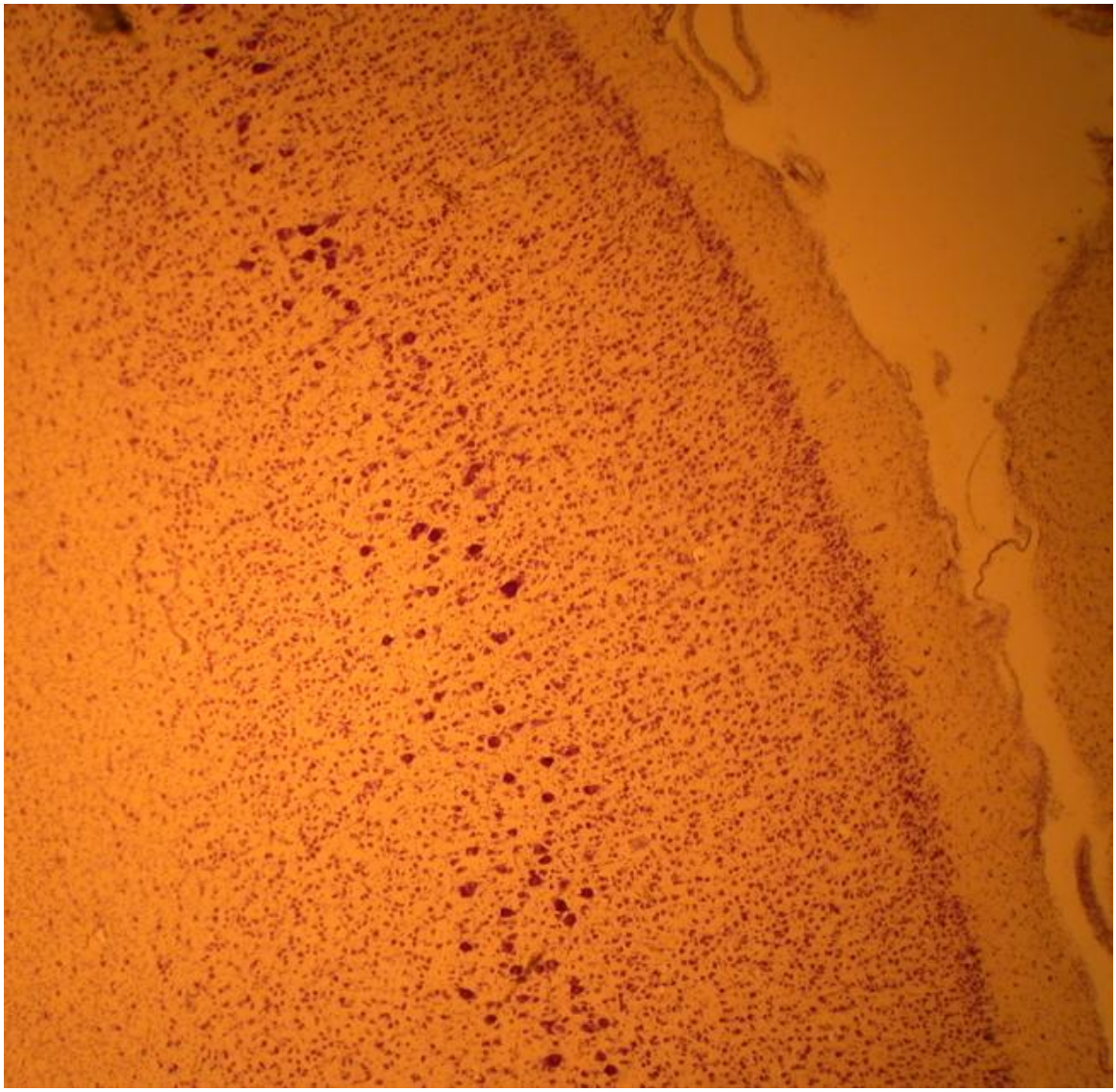

Figure B.2: Lion (*Panthera leo*) motor cortex.

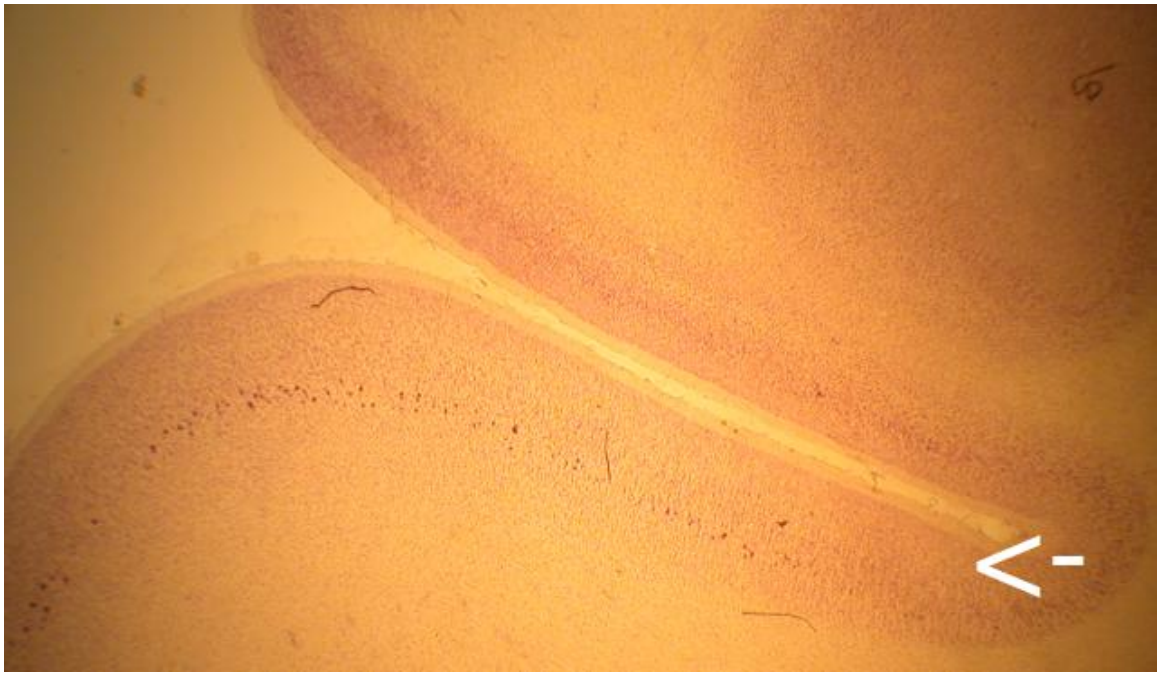

Figure B.3: Chimpanzee (*Pan troglodytes*) motor-somatosensory cortex border.

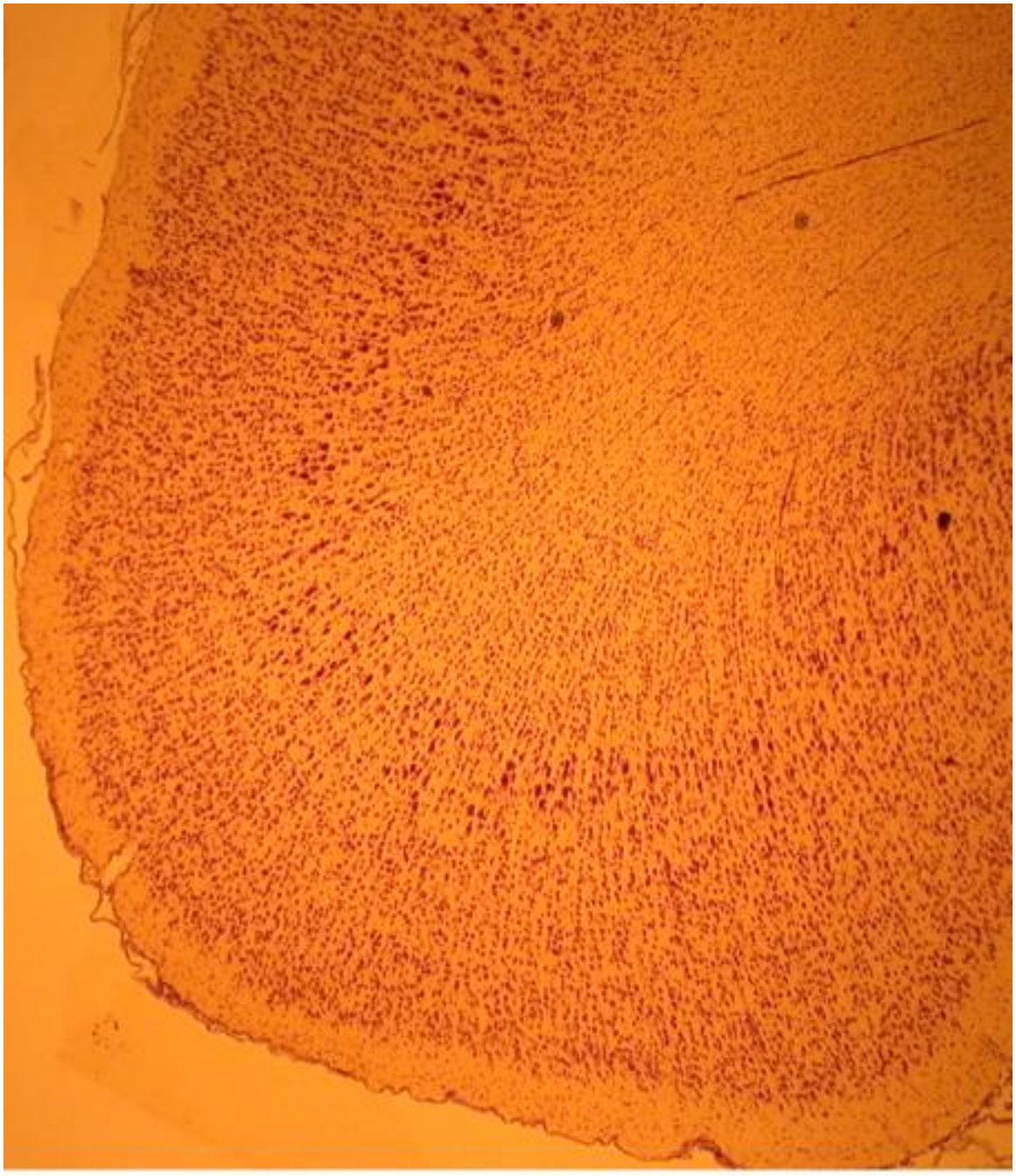

Figure B.4: Loris (*Nycticebus coucang*) motor cortex.

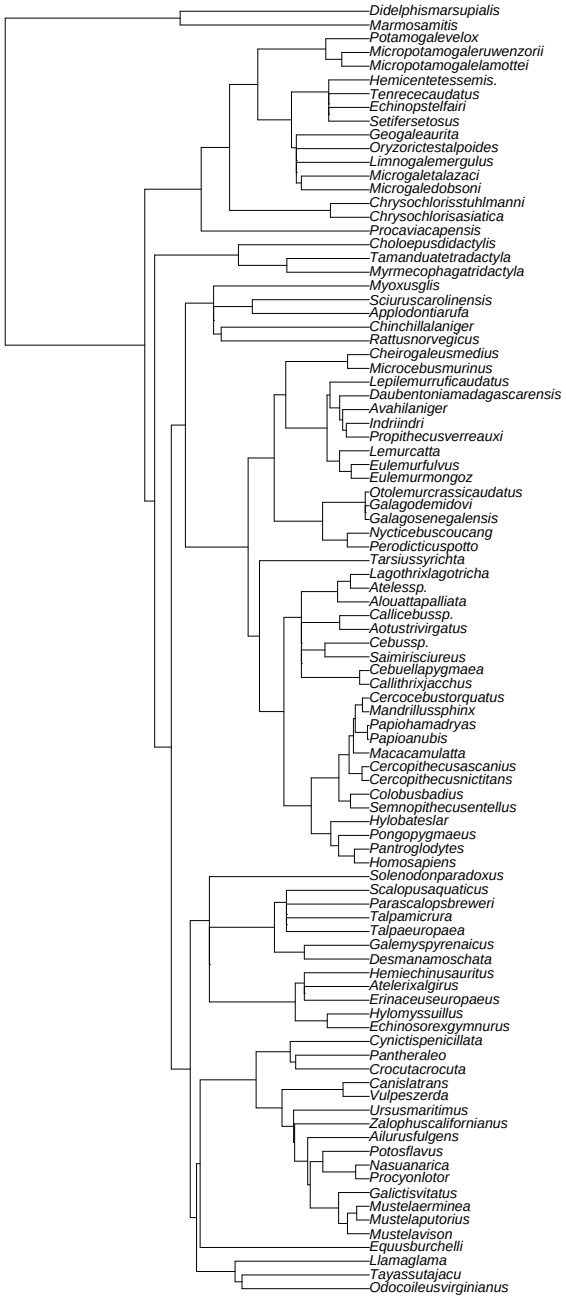

Figure B.5: Phylogenetic tree used to compute independent contrasts for whole neocortex data (combining our measurements with those of Frahm et al. Frahm et al. (1982)). It was taken from the literature Murphy et al. (2001); Springer et al. (2003); Douady et al. (2002); Bininda-Emonds et al. (1999); Purvis (1995); Kumar and Hedges (1998).

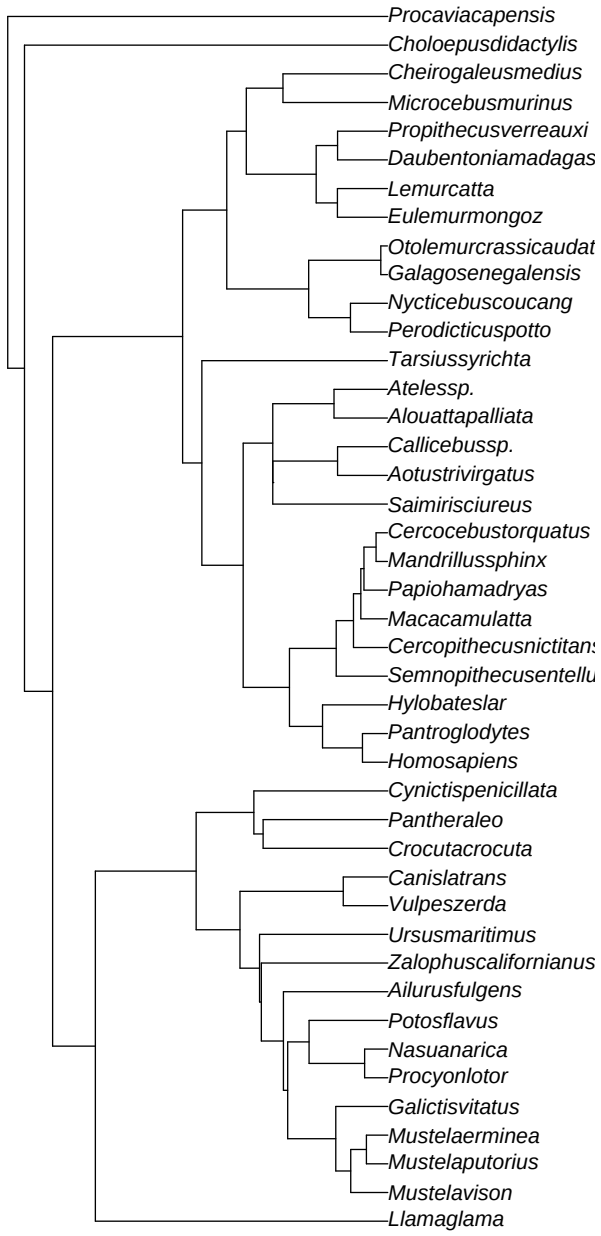

Figure B.6: Phylogenetic tree of species for which we have frontal cortex data. It is a subset of the species shown in Figure B.5, and is of course taken from the same sources.

	FrG	RoG	FrRat	WhBr	NeoG	NeoW	Act	Diet	Gr	Grsz
Hylobates Lar	15.66	29.46	0.53	101.28	45.12	20.5	D	FGS	M	3.5
Pan troglodytes	62.52	100.65	0.62	364.14	163.18	103.77	D	FGS	FF	28
Homo Sapiens	209.7	345.66	0.61	1251.85	555.36	422.48	D	NA	Hs	NA
Cercocebus torquatus	14.34	33.58	0.43	117.08	47.92	40.36	D	FGS	T	NA
Cercopithecus nictitans	9.66	26.34	0.37	64.74	35.99	11.81	D	FGS	H	20
Macaca mulatta	9.9	20.63	0.48	65.76	30.54	16.35	D	NA	T	NA
Mandrillus sphinx	19.17	52.16	0.37	127.61	71.33	27.93	D	FGS	T	NA
Papio hamadryas	25.74	53.36	0.48	159.11	79.1	39.68	D	NA	FF	68
Semnopithecus entellus	15.87	35.98	0.44	107.54	51.85	24.26	D	L	NA	19
Alouatta palliata	5.54	11.62	0.48	43.52	17.15	11.41	D	L	T	12.3
Aotus trivirgatus	1.34	3.89	0.34	11.42	5.23	1.74	N	FGS	M	NA
Ateles sp.	11.35	19.58	0.58	72.41	30.93	17.95	D	FGS	FF	NA
Callicebus sp.	1.21	3.91	0.31	11.90	5.12	1.94	D	FGS	M	NA
Saimiri sciureus	2.54	7.9	0.32	21.22	10.44	3.7	D	I	T	42
Tarsius syrichta	0.2	1.27	0.16	3.06	1.47	0.15	N	I	NA	NA
Eulemur mongoz	2.84	5.35	0.53	22.24	8.2	3.83	C	NA	NA	2.6
Galago senegalensis	0.3	1.04	0.29	3.58	1.34	0.23	N	I	S	NA
Lemur catta	2.74	6.22	0.44	21.00	8.96	2.12	D	FGS	T	18
Microcebus murinus	0.09	0.5	0.18	1.65	0.59	0.1	N	I	S	NA
Nycticebus coucang	1.16	3.25	0.36	11.27	4.4	1.07	N	FGS	S	NA
Otolemur crassicaudatus	0.88	2.21	0.40	7.11	3.1	0.57	N	FGS	S	NA
Perodicticus Potto	1.32	2.59	0.51	10.16	3.91	0.64	N	FGS	S	NA
Propithecus verreauxi	2.25	7.59	0.30	25.19	9.84	2.35	D	NA	NA	NA
Daubentonia madagascariensis	7.0	12.79	0.55	41.07	19.79	4.28	N	FGS	S	NA
Cheirogaleus medius	0.23	0.66	0.35	2.63	0.89	0.13	N	FGS	S	NA
Odocoileus virginianus	NA	NA	NA	140.74	51.96	24.38	NA	NA	NA	NA
Tayassu tajacu	NA	NA	NA	48.28	18.36	6.96	NA	NA	NA	NA
Llama glama	10.87	94.08	0.12	281.27	104.95	58.67	NA	NA	NA	NA
Marmosa mitis	NA	NA	NA	0.77	0.12	0.01	NA	NA	NA	NA
Didelphis marsupialis	NA	NA	NA	5.89	0.94	0.15	NA	NA	NA	NA
Myrmecophaga tridactyla	NA	NA	NA	78.04	19.86	8.58	NA	NA	NA	NA
Tamandua tetradactyla	NA	NA	NA	24.64	7.25	2.16	NA	NA	NA	NA
Choloepus didactylis	2.1	5.81	0.36	25.56	7.91	2.63	NA	NA	NA	NA
Procavia capensis	0.79	3.37	0.23	12.68	4.17	1.33	NA	NA	NA	NA
Equus burchelli	NA	NA	NA	371.75	148.88	88.36	NA	NA	NA	NA
Applodontia rufa	NA	NA	NA	5.60	1.48	0.38	NA	NA	NA	NA
Chinchilla laniger	NA	NA	NA	5.15	1.16	0.27	NA	NA	NA	NA
Myoxus glis	NA	NA	NA	2.00	0.49	0.07	NA	NA	NA	NA
Rattus norvegicus	NA	NA	NA	1.69	0.53	0.05	NA	NA	NA	NA
Sciurus carolinensis	NA	NA	NA	7.70	2.48	0.44	NA	NA	NA	NA
Ailurus fulgens	2.96	10.86	0.27	36.62	13.82	6.25	NA	NA	NA	1
Canis latrans	5.48	24.94	0.22	73.16	30.42	15.55	NA	NA	NA	5
Crocuta crocuta	13.36	42.91	0.31	134.31	56.27	28.93	NA	NA	NA	55
Galictis vitatus	2.53	6.57	0.39	19.36	9.09	2.72	NA	NA	NA	NA
Mustela putorius	0.69	1.45	0.48	5.88	2.14	0.57	NA	NA	NA	NA
Mustela vison	1.25	3.49	0.36	11.00	4.75	1.21	NA	NA	NA	NA
Mustela erminea	0.41	0.94	0.44	3.89	1.35	0.23	NA	NA	NA	1
Nasua narica	3.15	8.98	0.35	30.19	12.13	4.8	NA	NA	NA	10
Panthera leo	12.27	63.03	0.19	192.64	75.3	45.79	NA	NA	NA	8.7
Potos flavus	3.41	9.76	0.35	38.24	13.17	6.16	NA	NA	NA	NA
Procyon lotor	2.97	10.21	0.29	34.10	13.18	5.51	NA	NA	NA	1
Ursus maritimus	29.38	69.69	0.42	281.00	99.07	73.01	NA	NA	NA	1
Vulpes zerda	0.81	4.93	0.16	13.32	5.73	1.53	NA	NA	NA	NA
Zalophus californianus	32.4	181.26	0.18	455.70	213.66	88.72	NA	NA	NA	NA
Cynictis penicillata	1.02	3.88	0.26	14.23	4.9	2.02	NA	NA	NA	NA

Table B.1: Volumes for cortical regions for 55 species of mammals (cm^3). Also included are several ecological variables. FrG=frontal neocortical gray matter; RoG=rest of neocortical gray matter; FrRat=FrG/RoG; WhBr=whole brain; NeoG=total neocortical gray matter; NeoW=neocortical white matter; Act=activity pattern (N=nocturnal, C=cathemeral, D=diurnal); Diet: (FGS=fruit gum or seeds; L=leaves; I=insects); Gr= group category (M=monogamous; FF=fission fusion; Hs=human; T=troop; S=solitary;); Grsz=group size. Group size numbers were population group size from Wrangham et al. Wrangham et al. (1993). Categories for diet, activity and social group in primates were based on Rowe Rowe (1996).

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