PLACENTAL MORPHOLOGY AND THE CELLULAR BRAIN IN MAMMALIAN EVOLUTION

by

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I, *Eric Lewitus* confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

– *Harpo*

A major focus of evolutionary neurobiology has been on whether different regions of the eutherian brain evolve in concert, and how free the brain is to evolve independently of body plans. Since the eutherian brain is loosely modularized, such that one region is rarely isolated for specialization at the expense of others, but the design of modularization itself can be adapted by tweaking developmental programs, the degree to which brain regions must evolve in concert and can evolve independently may carry a deep phylogenetic signal. Using data collected from preserved brain tissue of 37 primate, 21 carnivore, and 15 other eutherian species (spanning 11 orders), I examined the phylogenetic level at which the proliferation of neurons and glia in the primary visual cortex and hippocampus proper, as well as granular layer volumes of the dentate gyrus and cerebellum, may be constrained by conserved developmental programs. In doing so, I was able to test for cellular signatures of (1) evolutionary changes in metabolic activity, (2) phylogenetic divergences, (3) specializations in behavior, and (4) developmental constraints. The degree to which disparate brain regions evolve in concert is shown to be generally conserved in *Eutheria*, although a derived ability to evolve regions independently is observed along the primate lineage. Using a separate dataset on placental and life-histroy character states, a comprehensive comparative phylogenetic approach was used to resolve relationships among five aspects of placental structure and to identify syndromes of placental morphology with life-history variables. My results support two discrete biological phenotypes of placental morphology and life-history, which are shown to have an evolutionary affect on allocortical, but not neocortical, brain organization. I have provided a new perspective on exploring how developmental constraints – acting both within and without the brain – may affect brain organization at the cellular level, and the extent to which those constraints have been adapted along certain eutherian lineages.

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INTRODUCTION

Since brain size is subject to significant heritability (Thompson *et al* 2001; Geschwind *et al*. 2002; Wright *et al*. 2002; reviewed in Winterer & Goldman 2003), hypothetical selective pressures directing brain evolution in hominins have included hunting (Washburn & Lancaster 1968; Calvin 1983), tool-making (Tobias 1981; Reader & Laland 2002; Stout *et al* 2008) and long-distance running (Bramble & Lieberman 2004), and in other mammals have been extended more generally to activity period (Barton 1996), social group size (Joffe & Dunbar 1997), diet (Eisenberg & Wilson 1978; Clutton-Brock & Harvey 1980; Hutcheon *et al* 2002), and tactical deception (Byrne & Corp 2004). However, while the study of brain size variation remains integral to the study of mammalian brain evolution, it may also be useful to ask the following: What changes in internal reorganization have resulted from or effected massive increases in brain size? And what other biological systems have constrained evolutionary variation in the brain?

Evidence for major phyletic differences in the cellular organization of mammalian brains has increased with advancing comparative histological studies. Phylogenetic signals in the cellular density of cortical columns and in the morphology and biochemistry of neuronal phenotypes have been reported in rodents (Celio 1990; Beaulieu 1993; Skoglund *et al* 1996b), bats and Eulitophyla (Valverde 1986), cetaceans (Garey *et al* 1985; Haug 1987; Hof *et al* 1992, 2007), carnivores (Peters & Yilmaz 1993), and primates (Zilles *et al* 1986; Peters & Yilmaz 1991; Preuss & Goldman-Rakic 1991; Preuss *et al* 1992;; Hof *et al* 2001). Further studies have reported differentiated expressions of calcium-binding proteins in different taxa (Glezer *et al* 1992; Preuss & Kaas 1996; del Rio & DeFelipe 1997; Preuss 2001), qualitative and quantitative differences in cortical projection layers in primates (Preuss 2001), species-specific quantities of von Economo neurons (Nimchinsky *et al* 1999; Vogt *et al* 1995; Butti *et al* 2009; Hakeem *et al* 2009), and diversity of cellular scaling relationships in different mammalian orders (Herculano-Houzel *et al* 2007; Azevedo *et al* 2009; Herculano-Houzel 2010). Additionally, the configuration of structural and functional topographical maps that compose the mammalian brain (Kaas 1982; Passingham *et al* 2002), although ostensibly conserved at a cursory level, show many examples of phylogenetic proliferation, addition, and segregation (Ramon-Moliner & Nauta 1966; Lende 1969; Kaas 1982, 1987; Butler 1994; Krubitzer 1995; Northcutt & Kaas 1995; Catania *et al* 1999a; Zeki 2003). While homologous features exist across mammalian brains (e.g., the basic arrangement of cortical laminae), universal modular architecture does not exist, and the argument

to consider brain size as an index of general functional capacity common to all mammals, therefore, lacks support.

Recent studies have shown that neuronal densities in hominoids vary independently of overall brain size (Sherwood & Hof 2008), that features of cortical microstructure in homologous regions display phylogenetic diversity both across and within mammalian orders (Semendeferi *et al* 1998; Hutsler *et al* 2005), and that subtle modifications in neural microstructure or gene expression may considerably impact behavior in the absence of brain size variation (Hammock & Young 2005; Sherwood *et al* 2008). These studies demonstrate that interspecific variation in factors underlying brain size variation (e.g., cellular density, degree of dendritic arborization, and cell soma size) may better reflect evolutionary adaptations within lineages. And while it is clear that some species are behaviorally adapted to certain practices or faculties, and that certain brain areas are devoted to mediating quite specific behaviors, it is not clear whether quantitative adaptation particular to one region will *prima facie* affect the rest of the brain, or even whether one region can evolve independently of functionally unrelated regions. The assumption that conserved neurogenetic scheduling in the mammalian brain constrains the concerted evolution of different brain regions may not be satisfactorily tested using gross morphology, as it has been historically (Huxley 1863; Darwin 1871; Le Gros Clark 1959; Jerison 1973; Finlay & Darlington 1995; Barton 1996; Joffe & Dunbar 1997; Pawlowski *et al* 1998; Byrne & Corp 2004; also see Healy & Rowe 2007).

The implication that glial cells may regulate the generation of new neurons (Song *et al* 2002; Horner & Palmer 2003; Nedergaard *et al* 2003), influence the development and synaptogenesis of those neurons (Pfrieger & Barres 1997; Kang *et al* 1998; Haydon 2001; Ullian *et al* 2001), monitor neurometabolic interactions at the synaptic cleft (Laming *et al* 2000; Hertz *et al* 2001), generally be required for dense synaptic networks to achieve advanced degrees of local modulation and control and to bypass axonal size constraints in increasingly larger brains, suggests an evolutionary role for a relative increase in glial cells in larger-brained species. However, the rate of this relative increase is unknown and its expression in specific brain regions has only begun to be tested.

Using data collected from preserved brain tissue, the current study compared neuronal and glial cell densities in the primary visual cortex (V1) and subfields of the hippocampus proper (CA1-3), volumetric estimates of the granule cell and molecular layers of the dentate gyrus, and volumetric estimates of the granule cell layer of the cerebellum in 37 primate species, 21 carnivore species, and 15 other mammalian species (spanning seven orders). The aim of the study was to examine phyletic

diversity in the quantitative histological organization of homologous cortical areas and establish cellular signatures of (1) evolutionary changes in metabolic activity, (2) phylogenetic divergences, (3) specializations in behavior, and (4) developmental constraints. Using a separate dataset on placental and life-history character states, collected from the literature, phylogenetic methods were employed for ancestral reconstruction, mutational mapping, and association analysis to resolve associations between five aspects of placental structure and to identify combinations, or syndromes, of placental morphology. Twenty life-history characters were mapped onto the eutherian phylogeny to examine how they may have influenced, over evolutionary time, the multivariate diversification of placental structures. The two datasets were used to provide evidence for an evolutionary relationship between elements of placentation and levels of glia and neurons in the mammalian brain.

I provide evidence for cellular signatures of phylogenetic divergences in primates and carnivores that are better explained by placental characteristics and behavioral specializations than overall or regional brain size. I show that conserved organization and functionality in the hippocampus has not completely safeguarded its cellular composition during mammalian evolution, and that a strong association between cellular composition of the hippocampus and model of placentation indicates a cirtical evolutionary role for prenatal development in the maintenance and evolution of neurogenetic scheduling. Finally, I provide evidence for the presence of tight developmental constraints controlling the proliferation of different cell types in disparate regions of the mammalian brain, but also for an adaptation on those constraints along the primate lineage. I propose that the human neocortex conforms to the cellular scaling rules of Old and New World monkeys and that any adaptation to modularity at the cellular level may necessarily carry a deep phylogenetic signal.

CHAPTER 1
CELLULAR PROCESSES (HOW THE BRAIN EVOLVES)

Neurogenesis and cortical expansion

Cortical size is determined in an individual before any neuronal connections are established. Post-mitotic cells, guided along the so-called scaffolding of radial glia, migrate from their origin in the ventricular and subventricular zones to the developing cortical plate (Rakic 1972, 1974, 1981), where arrays of cells, generated near each other and at the same time, form radial columns (Kornack & Rakic 1995). Thus, the cortex is made. The number of neurons in the cortex is approximately determined by the number of progenitor cells, the duration of cell-division cycles, and the number of successive cell-cycles during neurogenesis. The extended duration of cell-division in macaques compared to mice, for example, results in more successive rounds of cell division during neurogenesis and, therefore, more cortical neurons in macaques than in mice (Kornack & Rakic 1998; Kornack 2000; Rakic 2000). Since progenitor cells divide symmetrically (i.e., each progenitor cell produces two progenitor cells), the population of progenitor cells increases exponentially, so even a small increase in the number of cell divisions (i.e., a prolongation of the cell-division phase) can result in significant surface enlargement of the cerebral cortex. Alterations in the duration of neurogenesis, however, which is asymmetrical and begins after the population of radial columns has largely been established, only affect the number of neurons in each column (i.e., cortical thickness) (Algan & Rakic 1997). It is generally agreed that cortical expansion is a result of increased surface area rather than cortical thickness (Caviness *et al* 1995; Rakic 2007). Programmed cell death (apoptosis) is also an important factor in determining cortical size. When the genes needed for a cell to die (i.e., caspase 3 and 9) are inactivated in a mouse embryo, apoptosis is reduced, an atypically large population of progenitor cells is established, and the surface area of the cortical plate is increased (with convolutions) (Kuida *et al* 1996, 1998). Although the mouse embryo dies before parturition when caspase 3 and 9 are artificially inactivated, the observed reductions in apoptosis and changes in the timing of cell-cycles, which could produce novel cortical features liable to natural selection, are indicated as potential elements of evolutionary cortical expansion (see Fish *et al* 2008).

The extraordinary neocorticalization in primates has been attributed to the expansion of a subpopulation of progenitor cells in the outer subventricular zone (OSVZ). In mammals, basal progenitor cells, a type of cell that emerges from the division of the more common apical progenitor cells, migrate basally and retract their apical process before mitosis (Haubensak *et al* 2004; Miyata *et*

al 2004; Noctor *et al* 2004; Gotz & Huttner 2005; Kriegstein *et al* 2006; Farkas & Huttner 2008; Pontious *et al* 2008). Since they have no processes, basal progenitor cells are unpolarized and divide symmetrically – 90% of the time into neurons, 10% into basal progenitor cells (Noctor *et al* 2004; Wu *et al* 2005; Attardo *et al* 2008). As these cells divide, they accumulate along a secondary proliferative zone (Fig. 1), the subventricular zone (SVZ). In primates, the SVZ has increased in size in relation to other mammals (Cheung *et al*. 2007), but may have also evolved two morphologically distinct layers: the inner SVZ (ISVZ), which contains mammalian-typical basal progenitor cells; and the OSVZ, which is considerably thicker than the inner layer and contains elongated, radially aligned nuclei with basal processes that can reach the pial surface. The radial morphology and expression of progenitor markers (e.g., Pax6 and Sox2) in primate OSVZ cells suggest a close relation with apical progenitor cells in the ventricular zone (Smart *et al* 2002; Kriegstein *et al* 2006), but it is a point of contention whether OSVZ cells are like or unlike epithelial cells (Fish *et al* 2008). Although most cortical neurons in mammals are derived from basal progenitor cells (Haubensak *et al* 2004), most upper-layer cortical neurons in primates are generated from OSVZ cells (Lukaszewicz *et al* 2005), which indicates that the OSVZ played a significant evolutionary role in the extraordinary neocortical expansion observed in primates and mammals (Cheung *et al*. 2010). There is a strong correlation between an evolutionary increase of supragranular layer complexity in the cortex and increasing subventricular zone depth (Fig. 1).

Glia

In order to understand the functional significance of evolutionary changes in glia-neuron ratios, and identify the pressures selecting on those changes, I will review what glia do. In the broadest terms, glia are neural cells that are incapable of transmitting electrical signals in the form of action potentials (i.e., glia are not neurons). Instead of firing action potentials, glial cells guide the migration of neurons during embryonic development, regulate the ionic balance of extracellular fluids in the brain (Laming *et al* 2000; Hertz *et al* 2001), form an impermeable lining in the blood-brain barrier, lower the concentration of neurotransmitters near the synaptic cleft to terminate synaptic transmission (He & Sun 2007), synthesize myelin, and minimize neuronal damage and death (Allen & Barries 2005). The past decade has produced studies showing glia to be more than support cells; showing, in fact, that not only the structural architecture, but the communication pathways, activation thresholds, and plasticity of the brain rely on interactions of glia with vasculature (Doetsch 2003; Nedergaard *et al* 2003; Pellerin & Magistretti 2004; Allen & Barres 2005; Seifert *et al* 2006; He & Sun 2007). There are different types

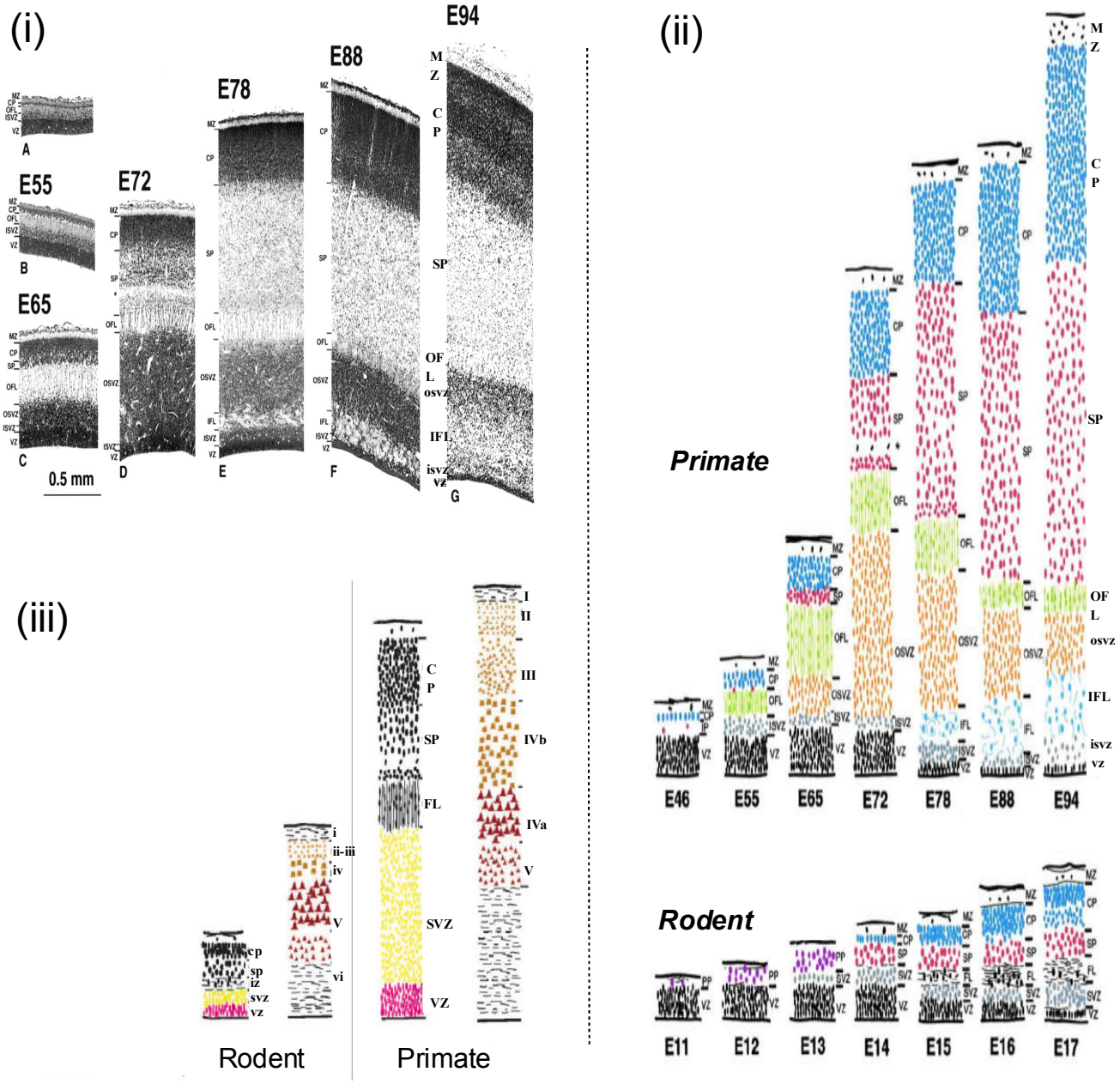

Figure 1. *(i) Transects of presumptive area 17 in a primate brain, (ii) an illustration of primate and rodent germinal zones in the dorsal cortex at equivalent developmental stages, and (iii) an illustration of the interspecific correlation between depth of subventricular zone and supragranular layer complexity. The depths of layers are to a common scale in (ii). The internal details of each layer in (b) and (c) are not to scale, but depict the orientation, shape, and relatively packing density of nuclei in each layer. In the primate, the ventricular zone (VZ) progressively decreases in size while the subventricular zone (SVZ) increases, until it is divided into an inner SVZ (ISVZ) and outer SVZ (OSVZ) by an intruding inner fiber layer (IFL). In contrast, no such division of the SVZ is observed in the rodent, where the VZ is the major germinal compartment throughout corticogenesis. Over 75% of cortical neurons destined for the upper layers of the primate visual cortex originate from SVZ precursors (Lukaszewicz et al, 2005). Abbreviations: CP, cortical plate; IZ, intermediate zone; MZ, marginal zone; OFL, outer fibre layer; SP, subplate proper. After Smart et al. (2002).*

of glia, distinguished by function and morphology and location, which take on different roles in the nervous system: astrocytes, oligodendrocytes, Schwann cells, and microglia. Schwann cells, which are located in the peripheral nervous system, and microglia, which are phagocytes and originate separately from other types of glia in the nervous system, were not included in the stereologic counts presented below and so will not be reviewed here. I will hereafter use glia to mean astrocytes and oligodendrocytes.

A subpopulation of precursor cells generated before embryonic neurogenesis, called radial glia, span the cortex with their long processes to provide substrates (so-called scaffolding) along which newly generated neurons will migrate (Hatten *et al* 1988; Malatesta *et al* 1999; Sauvageot & Stiles 2002; Sun *et al* 2003; Villegas *et al* 2003). During embryonic development, radial glia divide to form neural progenitor cells (NPC). These NPC line the ventricles to form a single layer (the ventricular zone, VZ), from which they proliferate and sequentially give rise to neurons (Sauvageot & Stiles 2002; Sun *et al* 2003). Once neuronal migration terminates, radial glia divide to form astrocytes.

Astrocytes are the most abundant type of glial cells and interact extensively with neurons. They are distributed isotropically in the cortical gray matter, separating the neuropil into astrocytic-delimited domains (Bushong *et al* 2003; Ogata & Kosaka 2003;Nedergaard *et al* 2003), and organized as networks that communicate through specialized communication channels (so-called gap junctions) (Kuffler & Nicholls 1977; Mugnaini 1986; Theis *et al* 2005; also see Giaume *et al* 2010). While neurons process information encoded as electrical signals, astrocytes support neurons and the neuronal environment by producing trophic agents (e.g., the soluble factors thrombospondins-1 and -2), which influence synaptogenesis (Hatten *et al* 1986; Muller *et al* 1993; Araque *et al* 1999; Barres & Smith 2001; Hidalgo *et al* 2001; Allen & Barres 2005). Neurons co-cultured with astrocytes have been shown to develop seven-times more synapses, with a seven-fold increase in synaptic efficiency, compared to neurons raised in the absence of astrocytes (Pfrieger & Barres 1997; Ullian *et al* 2001). Glia further support the proliferation, maturation, and survival of developing neurons, provide structural, trophic, and metabolic support (Nicholls *et al* 1992; Pixley 1992; Kandel *et al* 2000), and modulate neuronal activity by keeping the extracellular K^+ concentration approximately constant and lowering the neurotransmitter concentration to terminate synaptic transmission.(Laming *et al* 2000; Hertz *et al* 2001; also see Vesce *et al* 1999). Energetic metabolism in the brain and *de novo* synthesis of glutamate and γ-aminobutyric acid (GABA) transmitters are controlled by metabolic interactions between neurons and astrocytes. In addition to the pre- and post-synaptic neuronal elements of a synapse, many synapses are

enveloped by an astrocytic projection (forming a so-called tripartite synapse), a development that allows astrocytes to closely monitor and respond to neuronal activity (Mauch *et al* 2001; Ullian *et al* 2001; Allen & Barres 2005; He & Sun 2007). In response to increased neuronal activity, astrocytes signal to blood vessels, which are closely associated with the astrocytic processes, to increase blood flow (i.e., provide glucose and oxygen) to the region of increased neuronal activity. However, astrocytes do not just regulate the blood flow, but modulate – enhance (Fellin *et al* 2004; Fiaco & McCarthy 2004; Liu *et al* 2004; Perea & Araque 2005) and suppress (Newman 2003; Zhang *et al* 2003) – neuronal activity through three extracellular ion species: potassium $[K^+]_e$, calcium $[Ca^{2+}]_e$, and protons $[pH]_e$. The ability of astrocytes to regulate these ion concentrations – extracellular ion homeostasis – contributes to the maintenance of neuronal excitability (Barres 1991; Villegas *et al* 2003; for a review of the dynamics of ionic signaling and neuronal communication, see Laming *et al*. (2000) and Bezzi & Volterra (2001)). Glucose metabolism is coupled to glutamate-mediated neuronal activity by way of the Na^+/K^+-ATPase. Electrical activity involves the entry of Na+ to change the membrane potential or to provide the energy for uptake of neurotransmitters. This Na^+ needs to be pumped out of cells again, resulting in the Na^+/K^+-ATPase consuming ATP. It has been suggested that this promotes glycolysis, particularly in astrocytes that take up glutamate, which leads to enhanced lactate release from astrocytes, that is used to make ATP by oxidative phosphorylation in neurons to cope with the neuronal energy demands associated with synaptic transmission (Bittar *et al* 1996; Pellerin *et al* 1998; for reviews, see Magistretti 2003; Pellerin & Magistretti 2004; Magistretti 2006). Therefore, by secreting factors that regulate synapse formation and providing neurons with energy and substrates for neurotransmission, astrocytes induce synapse formation and actively control synaptogenesis, synapse number, synapse function, synaptic plasticity, and contribute to homeostasis in the brain (Meshul *et al* 1987; Mauch *et al* 2001; Ullian *et al* 2001; Barres 2003;Allen & Barres 2005; Haydon & Carmignoto 2006; Wang & Bordey 2008).

Neurogenesis in the mature brain is a feature of vertebrates (Altman & Das 1965; Altman 1969; Goldman & Nottebhom 1983; Burd & Nottenbohm 1985; Alvarez-Buylla & Lois 1995; Kornack & Rakic 1999; Barnea 2010). Astrocytes have been observed to regulate neurogenesis in the SVZ and the hippocampal dentate gyrus by promoting stem cell proliferation (Temple & Alvarez-Buylla 1999; Gage 2001; van Praag *et al* 2002; Rakic 2002; Song *et al* 2002). The proposed explanation for this phenomenon suggests that in the mature brain some glial cells are neural stem cells (Doetsch *et al* 1999; Johansson *et al* 1999; Alvarez-Buylla *et al* 2001). Why neurogenesis in the mature brain has

regional specificity is unknown. However, it has been hypothesized that the hippocampus contains newer astrocytes compared to other regions (e.g., the spinal cord) (Smith *et al* 1990) and that neurogenesis-inhibiting factors are absent in the hippocampus (Villegas *et al* 2003). Neither hypothesis has proved conclusive.

After neuronal migration has terminated and neurons have been surrounded by astrocytes and formed functional synapses, oligodendrocyte differentiation begins. Oligodendrocytes synthesize myelin, a lipid-rich membrane that ensheaths axons and increases the conduction velocity of electrical impulses. In the absence of myelin sheathing, conduction velocity of an action potential is directly proportional to the square root of axonal diameter (Fig. 2). As brain size increases, to maintain a fixed low conduction time between brain regions it is therefore necessary to increase axon size dramatically, which becomes prohibitively space-consuming in large brains. The ability to decrease axon membrane capacitance by wrapping it in myelin, and thus allow a given conduction speed to be achieved with a

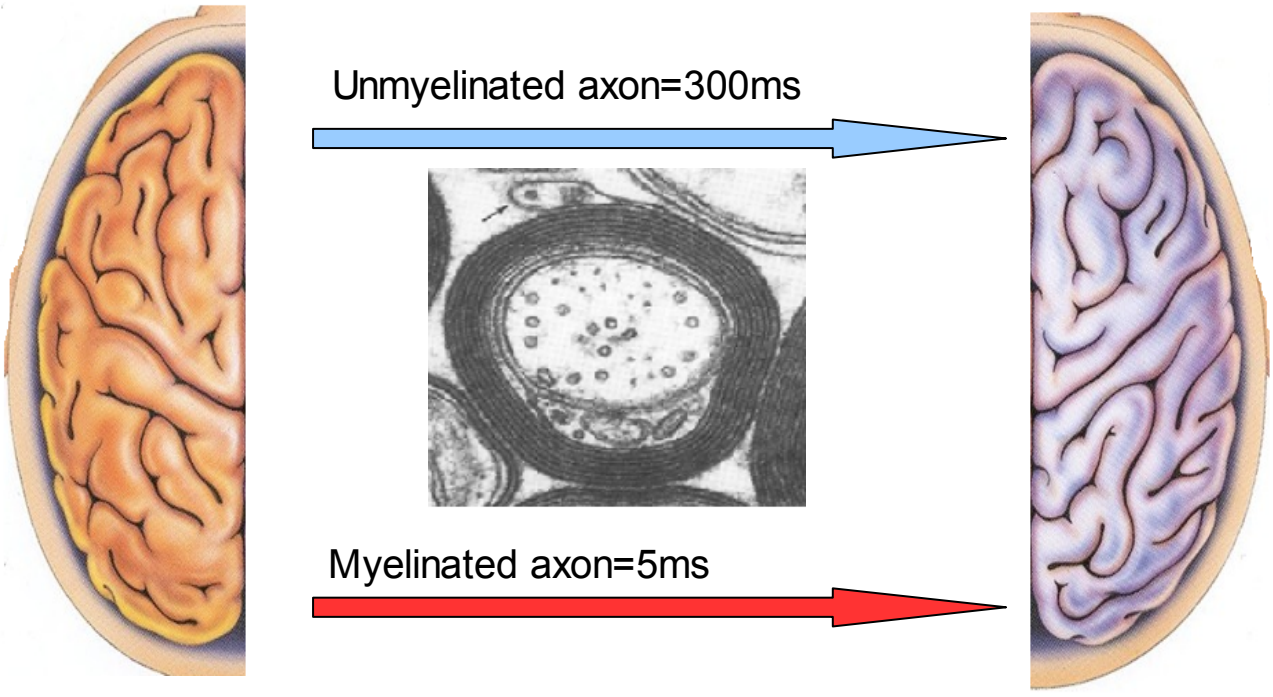

Figure 2. *The time it takes for a myelinated axon to pass a neuronal signal from one hemisphere to the other (1μm) is 60-times short than the time it takes for an unmyelinated axon. Pictured is a myelinated axon of a dog (Attwell, personal correspondence).*

smaller axon, has evolved separately in many phyla (Allman 1999). In addition, the conduction speed is proportional to axon diameter in myelinated axons, making it easier to increase conduction speed without a disproportionately smaller consumption of space. Furthermore, oligodendrocytes, like

astrocytes, induce synapse formation between neurons (Allen & Barres 2009).

The proliferation of glial cells in response to trophic cues associated with neuronal activity (Barres & Raff 1999; Sherwood *et al* 2006; Magistretti 2006; Karbowski 2007; Gomez-Pinilla 2008) suggests local glia-neuron ratios may be indirect measures of the metabolic support supplied to neurons. However, the relatively high glia-neuron ratio in the human brain (~1.4) compared to, for example, the mouse brain (~0.3) or the leech brain (~0.04) cannot simply be explained by differences in glial metabolic support, which are small across animals and inappreciable across higher vertebrates (Nedergaard *et al* 2003). The requirement of increasingly dense synaptic networks in larger, more complex brains for advanced degrees of local modulation and control may better explain the evolutionary march of the astrocyte. The implication that astrocytes may regulate the generation of new neurons (Song *et al* 2002; Horner & Palmer 2003; Nedergaard *et al* 2003), influence the development and synaptogenesis of those neurons (Pfrieger & Barres 1997; Kang *et al* 1998; Haydon 2001; Ullian *et al* 2001), and monitor neurometabolic interactions at the synaptic cleft (Laming *et al* 2000; Hertz *et al* 2001), as well as the need for oligodendrocytes to bypass axonal size constraints in increasingly larger brains, may suggest an evolutionary role for a relative increase in glial cells in larger-brained species. However, the rate of this relative increase is unknown and is likely to have regional specificity.

Brain metabolism

Neural tissue is energetically expensive, both while processing and at rest (Ames *et al* 1992; Attwell & Laughlin 2001; Lennie 2003; Niven *et al* 2003a; Nawroth *et al* 2007; Niven *et al* 2007; Scholvinck *et al* 2008). There is evidence that global blood flow to the brain, compared to the heart or liver, remains constant (and local blood flow may increase) during exercise in mammals (Raichle *et al* 1976; Orgogozo & Larsen 1979; Zapol 1979; Madsen *et al* 1993; Ide & Secher 2000). Even brief interruptions or minor reductions to the blood flow to the brain may result in long-term consequences or severe sensory and motor impairment, respectively (Hornbein 2001; also see Lipton 1999). The processes in the brain requiring continuous attention include the synthesis of neurotransmitter molecules, the synthesis of proteins and fatty acids, and, by far the major component (Attwell & Laughlin 2001), the maintenance of ionic concentration gradients (e.g., Na^+, K^+, and Ca^{2+}; see above). Maintenance of ionic gradients underlies the maintenance of membrane potentials at rest and the generation of synaptic and action potentials by sodium-permeable ion channels (Attwell & Laughlin

2001; Niven & Laughlin 2008). One of the reasons behind such high costs for neural tissue involves the noise and response speed of neural information processing (Laughlin 2001; Niven *et al* 2007), which are measured by the corruption and rate of transfer of the signal, respectively. By increasing the number of receptor molecules and ion channels for each neuron, the corruption of the signal is reduced (i.e., the signal-to-noise ratio improves) and the transfer rate of the signal improves (Weckstrom & Laughlin 1995; Laughlin 1996; Niven *et al* 2003b, 2007). Of course, each additional receptor and ion channel incurs a cost. There are other possible ways to improve the signal-to-noise ratio and transfer rate (see Niven & Laughlin 2008), but these are inevitably energy-consuming. Therefore, systems of information processing (for single neurons as well as neuronal populations) have been under strong selection to increase efficiency through, for example, distance-specific coding of information as graded or action potentials (Laughlin *et al* 1998, 2000; Sarpeshkar 1998), the activation/inactivation properties of ion channels (Niven *et al* 2003a,b), and by matching the filter properties of neuronal components to the signals they process (Vallet *et al* 1992; Laughlin & Weckstrom 1993; Laughlin 1994, 1996, 2001; Weckstrom & Laughlin 1995; Vahasoyrinki *et al* 2006; Niven *et al* 2007), placing brain regions with high interconnectivity adjacent to one another (Cherniak 1994, 1995; Chklovskii 2004), reducing the amount of redundant information in sensory systems (Atteneave 1954; Barlow 1961; Srinivisan *et al* 1982; Sillar & Skorupski 1986; Bell & Grant 1989; Gossard *et al* 1990, 1991; Wolf & Burrows 1995; Li *et al* 2002; Poulet & Hedwig 2006), and by sparse coding, in which only a small proportion of the neurons in a population represent information using a combinatorial code (Levy & Baxter 1996; Vinje & Gallant 2000; Balasubramanian *et al* 2001; Willmore & Tolhurst 2001; Perez-Orive *et al* 2002; Schreiber *et al* 2002; Olshausen & Field 2004; Hromadka *et al* 2008). It is not surprising, therefore, given the costs of maintaining neural tissue – and the complexity of cost-efficiency – that species living in environments without a high demand for a certain sensory system have reduced or lost that sensory system (e.g., blind mole rats have reduced their thalamocortical visual system) (David Gray *et al* 1998), or simply selected to reduce the size (i.e., cost) of one system at the expense of another (Aiello & Wheeler 1995; Hladik *et al* 1999; Fish & Lockwood 2003). Despite selective strategies for improving cost-efficiency, it seems that information processing in larger systems still incur relatively higher energetic costs (Niven *et al* 2007).

Evidence of the up-regulation of cortex-specific genes in human evolution (Caceres *et al* 2003; see Vallender *et al* 2008) suggests an influence of selection pressures on maintaining absolutely and relatively higher neuronal activity compared to our last common ancestor with chimpanzees.

Furthermore, cerebral glucose metabolism in humans is higher than in macaques (Bohnen *et al* 1999; Bentourka *et al* 2000; Cross *et al* 2000; Noda *et al* 2002), bucking the trend for larger brains to have lower metabolic rates (per unit of tissue) than smaller brains (Aiello & Wheeler 1995). The up-regulation of genes related to lipid metabolism and the importance of dietary docosahexaenoic acid with Na^+/K^+-ATPase activity (Bourre *et al* 1989; Djemli-Shipkolye *et al* 2003) may be indicative of the importance of dietary changes (e.g., the exploitation of lipid- and DHA-rich thalassic resources or the scavenging of organ tissue) in early human brain evolution (see Aiello & Wells 2002; Broadhurst *et al* 2002; Crawford 2006; Leonard *et al* 2007).

CHAPTER 2
THE COMPARATIVE METHOD IN NEUROSCIENCE

Brain scaling

The computational capacities of the brain are largely determined by cellular composition (Williams & Herrup 1988). In cats, for example, experimental doubling of the number of visual cortical neurons excited by one eye is associated with smaller receptive fields and improved discrimination abilities (Shook *et al* 1984). Thus, species with brains of similar size but different cognitive abilities should be expected to differ in cellular composition, and higher taxa with different cognitive specializations should be expected to achieve different cellular scaling rules.

The absence of significant correlations between relative cortical mass and relative neuronal number, found in studies of rodents (Nedergaard *et al* 2003; Herculano-Houzel *et al* 2006), Scandentia (Reichenbach 1989), cetaceans (Marino *et al* 2008), and primates (Sherwood *et al* 2006; Herculano-Houzel 2007), questions the validity of conclusions (e.g., Leiner *et al* 1991; Douglas & Martin 2004) drawn on relative brain mass, and argues against the use of brain volume as a proxy for neuronal number or computational capacity across animal orders. Lefebre *et al* (2004) argue for a correlative of volumetric encephalization in supernumerary neurons, in which "extra neurons" are available for associative, non-somatic functions, and thus account for increased cognitive flexibility observed in rodents with neuronal populations larger than predicted for their body size. Effectively, this means that a comparison of any two species with equal encephalization quotients will predict that the species with a larger absolute brain size will have superior cognitive abilities and a larger behavioral repertoire (Deaner *et al* 2007; see Krubitzer 2009). However, the phylogenetic level at which this is proposed to apply has not been tested (Rothe & Dicke 2005; Herculano-Houzel *et al* 2007). So far, brain mass has been observed to correlate hypermetrically with cortical (grey and white matter) glia-neuron ratios in rodents and *Eulipotyphla* (Herculano-Houzel *et al* 2006) and isometrically in anthropoids (Herculano-Houzel *et al* 2007). It is important to note, however, that neither of these studies corrected for statistical non-independence due to phylogenetic relatedness (but see Gabi *et al* 2010). Furthermore, it is problematic interpreting the whole brain in terms of cognitive ability.

The earliest studies of cellular scaling rules in mammalian brains (e.g., Blinkov & Gleezer 1968; Tower & Young 1973; Stolzenburg *et al* 1989) frequently claimed that glia-neuron ratios scale with brain size, citing, for example, perinatal glia proliferation as a response to inefficient clearance of K^+ ions due to thicker tissue in the brain as an explanation (Reichenbach 1989). While many of these

studies have since been judged as methodologically unsound (Shmitz & Hof 2005), it is still assumed that neuronal and glial cell populations increase concertedly with phylogeny and brain size (Kandel 2000; Doetsch 2003), although explanations now cite functional relationships between neurons and glia. One hypothesis suggests that increasingly dense and sophisticated synaptic networks (expansive dendritic arbors and long-range projecting axons) require greater degrees of local modulation and control – tasks for which glial cells are well suited (Laming *et al* 2000; Hertz *et al* 2001) – and, therefore, highly developed regions will have relatively high glia-neuron ratios only if those regions are enlarged (Nedergaard *et al* 2003; Sherwood *et al* 2006). This is complemented by the hypothesis that regions in which neuronal populations are established around birth will be enlarged by a tremendous post-natal increase in glial cells (Koenderink *et al* 1994; Sauvageot & Stiles 2002; Larsen *et al* 2006). Since oligodendrocytes add a volume proportionate to axonal length, higher glia-neuron ratios will in theory be concomitant with increased average axonal length and regional volumetric expansion (Friede 1963; Jehee & Murre 2008). Taken in full, encephalized regions will have significant evolutionary and developmental increases in glial cells with respect to a static number of neurons. These hypotheses remain speculative, as comparative investigations of glia-neuron ratios in specific brain regions are scarce and focus on few species.

The identification of phylogenetic diversity in features of cortical microstructure within homologous cortical regions (Glezer *et al* 1993; Semendeferi *et al* 1998 2001; Preuss & Coleman 2002; Sherwood *et al* 2003, 2004) suggests that architectural constraints do not govern variation in cortical complexity. Although there appear to be constraints on cellular scaling at the mammalian level (Prothero 1997; Changizi 2000), those constraints seem to be relaxed at the ordinal or even superordinal level. It is likely that, at the species level, variations in neuronal and glial cell density in certain brain regions may be explained by evolutionary adaptations within lineages.

Environment, behavior, and placentation

A cortical phenotype is the result of an interaction between the products of gene expression and environmental or behavioral factors. Alterations in the sensory environment of a species can change that species' cortical map (see Krubitzer & Kaas 2005). For example, the introduction of acoustic noise was observed to alter the cortical magnification of particular frequencies in the primary auditory cortex in ferrets (Chang & Merzenich 2003), mice selectively bred to have extra whiskers were observed to have additional barrels within the barrel field, a distinctive region of the somatosensory cortex that

receives contralateral thalamic inputs, of the primary somatosensory cortex (Catania & Kaas 1997), and, furthermore, it was shown that the size of the barrel field in mice could be regulated by modifying activity through environmental enrichment or whisker clipping during development (Machin *et al* 2004). Alternatively, small changes in non-coding regulatory elements could impact spatial and temporal expression patterns of key developmental genes, instituting profound phenotypic effects (King & Wilson 1975; Preuss *et al* 2004; Khaitovich *et al* 2006). Human-specific changes (perhaps only regulatory) to *MCPH* (Autosomal recessive primary microcephaly) and *HAR1* (human accelerated region) genes, for example, are suggested to have played major roles in evolving the human cortex (Prabhakar *et al* 2005; Woods *et al* 2005; Fish *et al* 2006; Pollard *et al* 2006; Vallender *et al* 2008; Pulvers *et al* 2010). These studies (and hypotheses) underlie a wide, although not universal, observation: species with enhanced behavior specializations have correlated cellular or molecular enhancements in the regions of the brain known to mediate those behaviors (Kandel 2006; Schoenemann 2006; Krubitzer 2007). The ability to undergo developmental or evolutionary cortical field map alterations in size, shape, location, and connectivity with fluctuations in the sensory environment may itself be a derived trait (Krubitzer & Kaas 2005; Lee & Erzurumlu 2005; Lee *et al* 2005). That is, the ability of a phenotype to respond optimally to its environment assumes selection on genes for plasticity rather than for particular phenotypes (Baldwin 1896; 1902; Downing 2004; see Kirschner & Gerhart 1998; Earl & Deem 2004).

Historically, the idea that explanatory variables may exist for evolutionary variations in brain size has been extrapolated to specific behaviors in hominins (e.g., Stout *et al* 2008) and to more abstract quantities in other mammals. Comparative analyses have assumed that complex behavior (e.g., innovation, deception, sociality) requires a relatively large brain. But, by defining the relatively large brain as uniquely capable of complex behavior, these analyses have been used to reinforce the original assumption that complex behavior drives encephalization (Healy & Rowe 2007). As correlations of brain size with activity period (Barton 1996), social group size (Joffe & Dunbar 1997), mating success (Pawlowski *et al* 1998), and tactical deception (Byrne & Corp 2004), to take a few examples, remain poorly justified, it may be helpful to ask, not what evolutionary variation in brain size affects, but what evolutionary variation in other biological systems affects brain size.

Although most evolutionary explanations for mammalian brain size variation are social or ecological, another class of explanations draws on the idea that the brain is not, in fact, a cloistered organ. Since neural tissue is metabolically expensive, encephalization must be constrained by the

energy available to a species to invest in additional neural tissue (Aiello & Wheeler 1995; Hladik *et al* 1999; Niven & Laughlin 2009). Across eutherian mammals, brain size can be log-log regressed against body size, metabolic rate, and gestational length with a slope of ~0.67 (Jerison 1973; Martin 1981). From these relationships, it has been suggested that brain size is the consequence of general energy throughput to the developing brain (Isler & van Schaik 2006). This theory would explain why fruit-eating species tend to have larger brains than leaf-eating species in many orders (Stephan & Frahm 1981).

But this theory fails against a number of its own predictions. Mammals with relatively high metabolic rates do not produce relatively large-brained young, as would be expected if infant brain size were determined by maternal metabolic rates (McNab 1989; Harvey & Krebs 1990). The slope and coefficient of determination for the best-fit line vary depending on which species data (or which measurements of species data) are used. A data set can be particularly affected by the inclusion or exclusion of baleen whales and small rodents (Smith 1994). And different taxonomic groups exhibit different scaling exponents (Martin 1981; Pagel & Harvey 1989; Cappellini 2010). Furthermore, since most species-typical body weights are estimated from dead captive animals, which tend to be either overweight or emaciated, body size estimates are often unreliable (Economos 1980). There is also some concern about the significance of basal metabolic rate (BMR) compared to field metabolic rate (Niven & Laughlin 2009).

Gestational length, however, remains a reliable predictor of brain size. Species with relatively long gestational lengths produce relatively large-brained neonates (Cunnane & Crawford 2003), suggesting that mode of placentation, if it is indeed related to gestation length, may influence neonatal growth (Martin 2008).

CHAPTER 3
HOW THE BRAIN EVOLVED

Homology

Homology refers to similarity arising from common ancestry. Since all comparative biological studies make explicit assumptions about homology, it is necessary that I explain my understanding of homology as it applies to this study.

Developmental, structural, positional, compositional, and functional features of the object under investigation (e.g., the amygdala, bipedality, laughter) can be useful in determining – or proposing – homology. Since only those features that can be traced to a common ancestor in a phylogenetic context are definitively homologous, congruence in the phylogenetic distribution of the object under investigation is the ultimate criterion (and, therefore, method of testing) for homology.

There have been two competing definitions of homology – phylogenetic and developmental – which have slowly been reconciled to incorporate the developmental definition into the phylogenetic one. Consequently, our broad definition of homologous traits as inherited from a common ancestor is ultimately incomplete.

The generation of different developmental precursors in different species convinced many developmental biologists that phylogenetic homology disappears when it is approached from a mechanistic perspective (Spemann 1915; de Beer 1971; Sattler 1984; Panchen 1999; Gilbert *et al* 1996; Webster & Goodwin 1996). A generative paradigm was therefore established, in which morphological homology can be strictly defined as the structural correspondence of traits. But this proved to be limited, and ultimately misleading, because it assumed that possible morphologies are limited by universal and constant rules of generative mechanisms and development, and thus evolutionary explanations of homology became merely explanatory. It may be that natural selection favors developmental processes that are canalized, modular, or constrained by stabilizing selection, so that conserved pathways persist, even when the phenotype is unexpressed (Wagner 2001). But this already presupposes that generative rules are subject to natural selection (Shubin 1994). Early on, Ernst Mayr (1960) suggested that the emergence of new structures reflects the intensification of existing selection on certain developmental processes rather than the evolution of new developmental regimes, an idea that resonates in “evolution by tinkering” (Jacob 1977), the “evolution of bricolage” (Doboule & Wilkins 1998), and the concept of deep homology (McShea 1996; Shubin *et al* 1997; Gerhart 2000; Hall 2002d). On this suggestion we can make two predictions: developmental mechanisms will be

conserved (i) when the trait is not generated (e.g., Hall 2003) and (ii) when the morphology of the trait is transformed. The first prediction is supported by the idea of deep homology, which is discussed below. The second prediction has empirical support and is quite relevant to recognizing homology in neurobiology (see Bock 1974; Patterson 1988; Streidter & Northcutt 1991; Bolker & Raff 1996; Arendt 2005). The premise of this second prediction is the observation that the position of a region (e.g., the primary visual cortex) relative to other cell groups tends to be highly conserved (Nieuwenhuys 1994; Puells & Medina 2002). Therefore, if structure A in species A has the same topological position as structure B in species B, but the histology of structure B differs radically from that in structure A, then the derived nature of structure B is considered to be novel by phylogenetic conversion (Streidter 2005), which is akin to the aforementioned morphological transformation. The mammalian neocortex, for example, is considered homologous to the dorsal pallium found in other vertebrate brains (see Aboitiz *et al* 2003), but it is novel by phylogenetic conversion. The lamination of the lateral geniculate nucleus (LGN) in primates, tree shrews, and carnivores, which is homogeneous in monotremes and most marsupials, is another example (Sanderson 1974; Kaas *et al* 1978; Kahn & Krubitzer 2002b).

A further criticism of the generative paradigm questions whether patently homologous traits can be derived from different developmental precursors (de Beer 1971; Hall 1995; Lieberman 1999; Butler & Saidel 2000; True & Haag 2001; Leigh 2007). For example, although mammals by default have darkly-pigmented irises, lemurs and humans are known to have blue eyes. In humans, this phenotype arises from a single nucleotide polymorphism, but by a different (unidentified) process in lemurs (Bradley *et al* 2009). In two congeneric species of tree frogs *(*genus *Rana*), which have homologous lenses, one uses the optic cup to induce the lens, while the other does not (Jacobson & Sater 1988; Hall 1999 2003), due to heterochronous eye development relative to body development (McNamara 1995; Zelditch 2001). Gastrulation, neural crest formation, and germ cell formation are other examples of structural homologues arising via different developmental processes in different taxa, which demonstrate that development may be modified early on in ontogeny without affecting the morphology of the adult phenotype (Bolker 1994; Hall 1995b, 1998 2003; Minsuk & Keller 1996). Fortunately, there is another term to take credit for many of these phenomena.

The term homoplasy was introduced by ER Lankester (1870) to describe phenotypic similarity resulting from independent evolution. Expounding on the interconnectedness of homology and homoplasy, David Wake (1996) explains that if homology is “the same thing”, then homoplasy is the appearance of “sameness”. Several types, or mechanisms, of homoplasy are recognized. Reversal is the

most straightforward, defined as the loss (hairlessness in cetaceans) or reduction (hairlessness in humans) of a phenotype in a lineage (Hall 2003). Parallelism explains homoplastic traits inherited by common genetic factors at a deeper phylogenetic level than the associated trait (Saether 1983, 1986). And convergence is the appearance of similar features in independent lineages. It is difficult (sometimes impossible) to distinguish the evolutionary patterns of parallelism and convergence from one another (Arendt & Reznick 2008). What underlies both is the importance of phylogenetic relations; neither can be interpreted without explicitly acknowledging the phylogenetic level of its application. The higher the phylogenetic level (i.e., the greater phyletic distance between the convergent traits), however, the more likely we are to find homologous developmental processes (Hall 2007). When we consider the convergent evolution of wings in insects and birds, for example, we are likely to find underlying developmental processes in the common ancestry of insects and birds to allow the evolution of wings (Shubin *et al* 1997). This discovery largely dismissed the ideal that historically defined homology and homoplasy as antithetical.

Brian Hall (2007) argues that homology and homoplasy are both types of descent. The presence of a trait may be discontinuous, but the underlying developmental mechanism for that trait can persist. Therefore, we may trace the evolutionary history of an assumed homoplastic trait in two species and find that a distant common ancestor of those species possessed the genetic or developmental mechanism for that trait. This is called deep homology (McShea 1996; Shubin *et al* 1997; Gerhart 2000; Hall 2002d; Hall & Hallgrimsson 2007) and is strictly defined as a shared genetic regulatory mechanism used to build morphologically and phylogenetically divergent traits (Shubin *et al* 2009). The idea of deep homology was originally applied to show that the pattern of analogous appendages and body outgrowths observed in vertebrates, insects, and other animals was contingent on the deployment of the *Distal-less* gene, which originated in a common ancestor in the coelomate phyla (Shubin *et al* 1997). The idea has since been extrapolated to explain relationships between homologs of morphological structures and genetic circuits. Charles Lockwood (1999) mapped postcranial characters onto alternative trees for the platyrrhine family *Atelidae* to analyze the evolution of certain character traits. Adaptations to climbing and suspension were observed to be such strong selective forces that homoplasy was identified as the dominant source of shared similarity in the data sets based on climbing anatomy (Lockwood 1999; Lockwood & Fleagle 1999). This emphasizes the role of homoplasy as evidence of shared ancestry, even if that ancestry is very distant.

The idea of homology now becomes directly related to our phylogenetic context: the more

phylogenetically distant the common ancestor, the more opportunity for modification and convergence (i.e., homoplasy); the more phylogenetically recent the common ancestor, the greater the likelihood of phenotypic similarity (i.e., homology). In this light, homology can be further defined as an epigenetic concept, in which development is viewed as a trajectory of a complex physical system with multiple stable states, so that homologs are traits (genetic or morphological) that appear reliably within that system as it perpetuates itself through stabilizing selection (Streidter 1998). The practical implication of this epigenetic concept is the definition of homology as a continuum that addresses the parallax of shared development (see Hall 2002d 2003 2007).

Mammalian brain

Mammals evolved in the early Mesozoic from cynodonts (Luo *et al* 2002). Broadly, fossil evidence and cladistic analyses suggest that centered hind limbs, oxidative metabolism, and endothermy evolved just prior to the origin of mammals (Bennett 1991; Blob 2001). It is possible to discern a number of derived traits of the ancestral mammalian brain.

Craniofacial morphology of early mammalian radiations and comparative molecular studies of extant mammalian species can be used to reconstruct early neural adaptations in the mammalian lineage. Comparative analyses of eyes in living tetrapods show that color vision in placental mammals was significantly reduced to red-green color-blindness (Jacobs 1993; Ahnelt & Kolb 2000). The enlarged nasal cavities of early mammalian fossil species, as well as evidence that mice have more than 1000 different olfactory receptor genes (compared to less than 100 in nonmammalian vertebrates), suggest early expansion of the olfactory system (Freitag *et al* 1998; Dryer 2000). Fossil endocasts (e.g., *Chulsanbaatar vulgaris*) further indicate that the olfactory bulb constituted about 10% of the total ancestral mammalian brain, which is comparable to what is found in hedgehogs and opossums (Stephan *et al* 1981; Kielan-Jaworowska 1983, 1984; Jerison 1990; Catania 2000). The appearance of ear drums, long coiled cochleas, and hair cells that amplify the intracochlear vibrations (Webster *et al* 1992; Dallos & Evans 1995) suggest increased sensitivity in the mammalian auditory system. Furthermore, fossil data (e.g., *Morganucodon*) reveal the presence of ossicles in early mammals, but not protomammals, which would have structurally and functionally uncoupled chewing and hearing and allowed the ear bones to become specialized for hearing (Kermack & Rigney 1981; Allin & Hopson 1992; Frost & Masterton 1994; Meng & Wyss 1995). The first evidence of a detached middle ear appears in the late protomammal *Hadrocodium*, which also appears to have had an endocranium

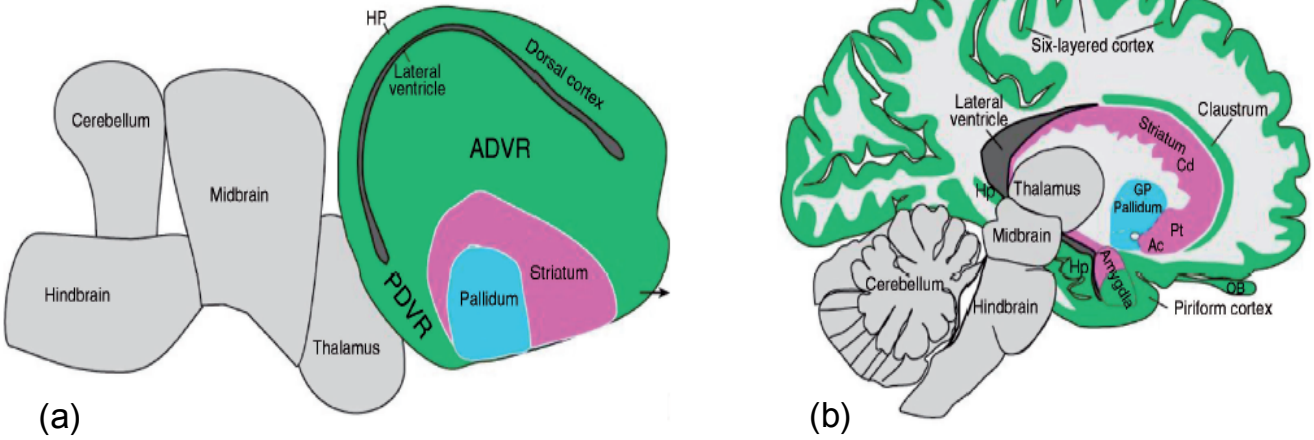

Figure 3. *The organization of the adult telencephalon in (a) reptiles and (b) mammals. Color-coding indicates pallial (green), striatal (blue), and pallidal (purple) domains. Abbreviations: ADVR, anterior dorsal ventricular ride; Cd, caudate; GP, globus pallidus; Hp, hippocampus; OB, olfactory bulb; PDVR, posterior dorsal ventricular ridge; Pt, putamen. Adapted from Jarvis (1991).*

significantly larger than expected for a protomammal of its body size (Kielan-Jaworowska 1986, 1997; Luo *et al* 2001). While there does not appear to be a causal relationship between detachment of the middle ear bones and encephalization (Rowe 1996b; Wang *et al* 2001; Luo *et al* 2002), it has been suggested that brain size increased as a response to the derived ability to hear higher frequencies (Streidter 2005). The absence of an homologous auditory cortex in non-mammals supports this hypothesis, although the available evidence ends there. The most conspicuous derived feature of the mammalian brain, compared to other non-mammalian vertebrates, is the neocortex.

It is debated whether the sauropsid dorsal ventricular ridge (DVR) or reptilian dorsal cortex can be considered homologous to the mammalian neocortex (see Aboitiz *et al* 2003). While it is outside the scope of this thesis to assess whether either of these structures is truly homologous to the neocortex, differences between the reptilian dorsal cortex and mammalian neocortex can be used to catalog some of the derived features of the mammalian brain (Fig. 3).

The primitive dorsal cortex of a turtle has four divisions, which receive major inputs from the dorsal thalamus. Most of the projection neurons, particularly from the LGN, are similar to mammalian pyramidal neurons (Connors & Kriegstein 1986; Desan 1988). Most strikingly, the reptilian dorsal cortex has only one prominent cell layer, sandwiched between two layers of dendrites and axons, compared to the six-layered neocortex (Butler & Hodos 2005). A seeming effect of this increased

lamination was the radial movement of dorsal thalamic axons, compared to the tangential movement in the dorsal cortex (Diamond & Ebnder 1990; Super & Uylings 2001), which allowed individual thalamic axons to project to fewer pyramidal neurons (Butler 1995). This, in turn, facilitated the emergence of neurons with small receptive fields and of radially and functionally organized cell columns (Raizada & Grossberg 2003). The wiring pattern in the neocortex, where most long connections run through underlying white matter, is more efficient than the wiring in the dorsal cortex, where axons are interspersed among neuronal cell bodies (Murre & Sturdy 1995; Wen & Chklovskii 2005; Chen *et al* 2006; Wang *et al* 2008), making scalability an adaptive consequence of the neocortex. This may explain why large neocortices are more common in mammals than large dorsal cortices are in reptiles.

Differences exist between mammals and non-mammalian vertebrates in sub-cortical structures as well, although these differences have not been as extensively documented. The hippocampal formation (HF) remained elusive in non-mammals until relatively recently. It was initially thought that the turtle's medial cortex was homologous to the mammalian HF (Holmgren 1922, 1925). However, subsequent studies showed this was not the case. Investigations using axon tracing were able to locate the homologous HF through projections to the highly conserved ipsilateral septum (Krayniak & Siegel 1978; Neary 1990). This structure was later shown to be implicated in spatial memory in the same way the HF is in rodents, although the pathway by which sensory information reaches the HF has changed dramatically in mammals (Colombo & Broadbent 2000; Salas *et al* 2003).

In mammals, the neocortex and olfactory cortex project to the entorhinal cortex (EC). Therefore, all sensory information passes through the EC on its way to the *cornu Ammonis* (CA) fields and the dentate gyrus (DG). In non-mammals, there is no such topographical distinction between input and processing (Neary 1990; Ulinksi 1990; Hoogland & Vermeulen-Vanderzee 1995). Although most subdivisions and connections found in the mammalian HF have also been reported in the avian HF (Montagnese *et al* 1996; Szekely 1999; Colombo & Broadbent 2000; Hough *et al* 2002; Kahn *et al* 2003), the absence of those subdivisions and connections in reptiles makes convergence the most parsimonious interpretation. If we assume that the reptilian medial cortex is homologous to the mammalian DG (Perez-Clausell 1988; Iglesia & Lopez-Garcia 1997), then it seems that evolution of the mammalian DG involved the loss of direct sensory inputs from the dorsal thalamus and direct projections out of the HF, transforming the DG from a major sensorimotor integration center into part of a processing zone that communicates mainly with the neocortex (Streidter 2005). There is also

evidence that the striatum, like the HF, has changed its major source of input from the thalamus to the neocortex (Parent & Hazrati 1995a,b), despite the highly conserved features of the mammalian striatum (Medina *et al* 1997; Jiao *et al* 2000).

Total brain size

The concept of relative brain size was introduced by Georges Cuvier (1837), who related brain size to body size by a straightforward isometric equation. This was amended by Brandt (1867), Snell (1891), and Dubois (1897), who interpreted the relationship as allometric, showing that a power function could best describe the dependence of brain size on body size. Encephalization quotient (EQ) was more recently adopted as a measure of predicted brain size for observed body size, which is thought to be a more accurate system of gauging relative brain size – and, therefore, intelligence – in different species (perhaps because humans exceed all other mammals by this system). Many authors have tried to discern the biological significance of EQ, most notably Harry Jerison, who argued that the brain scales with body surface as a reflection of the neural demands of somatic processes (Jerison 1973) . However, Jerison could not explain why brain regions unrelated to somatic processing also scale with body size (Fox & Wilczynski 1986). Further confounding this system is its sensitivity to the species sampled to drive the exponential parameters. The scaling relationship of primates, for example, is 12% steeper than that estimated for mammals (Martin 1981). In the face of different scaling relationships for different taxonomic groups, it is difficult to explain EQ as a reflection of body surface (Schoenemann 2006).

It is, nevertheless, difficult to discard brain size as a factor in interpreting selection pressures on functional evolution of the brain. Echolocating bats, for example, have subcortical auditory systems 63-times smaller than humans have, but in bats this system constitutes 1.6% of total brain size, compared to 0.015% in humans (Glendenning & Masterton 1998). If subcortical auditory system size is regressed against brain size, we see that echolocating bats have a subcortical auditory system larger than predicted for brain size, whereas humans have one smaller than predicted. Since bats are more dependent on hearing than humans (Dalland 1965), this system of measurement makes intuitive sense. Furthermore, the pattern of changes in brain size – and the apparent evolutionary costs involved in those changes (see Chapter 1, *Brain metabolism*)– strongly argue for an adaptive cognitive explanation of encephalization in humans. In primates, encephalization is correlated with longer gestational lengths, increased altriciality, and delayed reproduction (Harvey & Clutton-Brock 1985), in addition to a further

endothermic cost of maintaining an encephalized brain (Falk 1990). If these costs did not exist, then large-brained species would have a selective advantage. Reproductive benefits must have been at least marginally greater for large-brained species, a consideration that lends functional significance to relative and absolute brain size.

Before discussing the evolution of brain and body size, I would like to briefly review the developmental stages that may affect brain and body size (also see Chapter 1, *Neurogenesis and cortical expansion*).

Neuronal precursor tissue is signaled to partition from the embryo during gastrulation. The cells divide several times over before differentiating into neurons and glia. When the population of precursor cells is depleted, neurogenesis terminates (adult neurogenesis exists in certain brain structures, but this does not contribute to gross morphological increases in the brain). Following this, most brain growth is due to glial cell proliferation, axonal myelination, and enlarging neurons (Jessell *et al* 2000). In precocial species, this process is more or less completed at birth, so any postnatal increases in body size will consequently reduce the relative size of the brain. Relatively large-brained species, therefore, will produce infants that are large-brained at birth and/or infants that undergo a long postnatal development period that includes brain growth. In primates, compared to most other mammals, a greater proportion of the embryo is partitioned to become neuronal precursor tissue. And in humans, postnatal brain development, but not postnatal body development, is quite lengthy, even compared to chimpanzees (Streidter 2005). The mechanisms that underlie allometric brain and body growth across mammals are not fully understood (see Stern & Emlen 1999).

Relative brain size has increased and decreased repeatedly along different mammalian lineages (Streidter 2005; Montgomery *et al* 2010). The fossil record suggests that 50-150 million years ago mammalian relative brain size was similar to extant marsupial relative brain size (Jerison 1973), which is smaller than the average relative brain size found in extant monotremes and eutherians. The largest relative brain sizes in mammals belong to humans, dolphins, and elephants, which is a good argument for the convergence of independent increases in relative brain size along different lineages. Decreases in relative brain size have been observed in species of bats, shrews, tenrecs (Eisenberg 1981; Mace *et al* 1981) and even marmosets (Montgomery *et al* 2010), which, too, is a good argument for convergence. The observation that increases in relative brain size were often followed by major radiations may explain why the increases outnumber the decreases (Eldredge & Gould 1972; Sol *et al* 2002; Streidter 2005). Although some of the increases and decreases can be explained by dwarfism and

gigantism, respectively (e.g., Kamiya & Pirlot 1988), increases in relative brain size along most lineages have been associated with increases in absolute body size (Stanley 1973; Alroy 1998). This should not be surprising. While some small invertebrates may allow the cerebral ganglia to spill into the thorax (Beutel & Haas 1998), this is not an option for mammals. Large mammals will generally have less difficulty accommodating increases in brain size (perhaps with the exception of humans), while many small mammals would approach insurmountable difficulties trying to accommodate a larger brain (Northcutt & Streidter 2002).

Theories of evolutionary encephalization have claimed social, physiological, and ecological variables. Attempts to correlate behavior (or so-called social intelligence) with relative brain size often succumb to phylogenetic non-independence or overlook that our definition of intelligence is worded in human terms – those that fall into the latter camp ignore Nikolaas Tinbergen's (1951) warning that different species experience identical tasks differently. Social group size has been taken as an approximation for social intelligence, but correlations between relative brain size and social group size have been inconsistent (Dunbar 1998; Allman 1999; Kudo & Dunbar 2001). Diet has been a recurrent explanatory variable used for relative brain size, citing correlations between frugivory and relative brain size in bats (Eisenberg & Wilson 1978; Hutcheon *et al* 2002) and primates (Clutton-Brock & Harvey 1980). These theories are closely tied, although not necessarily explicitly, with proposed physiological constraints on encephalization. Robert Martin (1981) emphasizes the limiting role of metabolic resources in brain growth across species, an idea that is expicitly tested by the expensive-tissue hypothesis (Aiello & Wheeler 1995). However, a plot of the residuals of brain size and metabolic rate for mammals reveals that no correlation exists (although, this does not preclude the expensive-tissue hypothesis from applicability in hominin evolution (Leonard & Robertson 1997; Milton 2000; Aiello & Wells 2002; Cappellini 2010)). Foraging, tactical deception, grooming, and many other measures of intelligence have been forwarded with little concrete success as explanations for encephalization (see Healy & Rowe 2007; Park *et al* 2007). But it is yet possible that more than one of these factors contributed to evolutionary increases in brain size. While the expression of these measures in mammals is behaviorally distinct, they may not necessarily map onto distinct regions of the brain. In this case, it may be informative to look at evolutionary changes in the size of different brain regions.

Regional brain size

Mammalian brains are composed of structurally and functionally distinct cell groups, which

have been identified to configure a structural and functional topographical map (Kaas 1982; Passingham *et al* 2002). These maps seem to be largely conserved at a cursory level, but there are many examples of phylogenetic proliferation, addition, and segregation (Ramon-Moliner & Nauta 1966; Lende 1969; Kaas 1982, 1987; Butler 1994; Krubitzer 1995; Northcutt & Kaas 1995; Catania *et al* 1999a; Zeki 2003). It is clear that some species are behaviorally adapted to certain practices or faculties, and that certain brain regions are devoted to mediating quite specific behaviors, so it would seem likely – and in many taxa it is the case – that there should be some correlation between behavior and regional brain size. But the degree to which one region can evolve independently of functionally unrelated regions is unclear. In the previous section, I reviewed what insights the data available can give us about the functional significance of encephalization and concluded that there is no consensus on the explicit relationship between behavior and encephalization. So, in this section, I will largely ignore the behavioral implications of regional brain size and discuss the structural constraints on the evolution of regional brain size.

The topic of regional brain size evolution has been framed in terms of the concerted evolutionary hypothesis (CEH) and mosaic evolutionary hypothesis (MEH). The question asked is: to what extent is natural selection free to shape the form of the mammalian brain? One argument proposes that brain regions evolve in concert due to constraints of neural development (Finlay & Darlington 1995; Finlay *et al* 2001). The other argument says that this is not the case (Barton & Harvey 2000; de Winter & Oxnard 2001). An examination of the available evidence suggests that the mammalian brain is neither completely constrained by neural development nor completely free to evolve regions independently.

Beginning with the largest region, we see that the proportional size of the neocortex scales allometrically (power slope ~1.1) with absolute brain size (Passingham 1975; Deacon 1990). The implication of this relationship is that lineages that have evolved larger brains (e.g., primates) have evolved proportionally larger neocortices. If we move beyond the neocortex to the striatum, septum, diencephalon, midbrain, medulla, olfactory cortex, schizocortex, hippocampus, and cerebellum in primates, bats, and *Eulipotyphla*, a similar relationship holds: 96% of brain size variation is predicted by absolute brain size (Jerison 1989; Finlay & Darlington 1995). This effect has been explained in terms of epigenetic cascades: an increase or decrease in the size of one region leads to epigenetically correlated changes in the size of its targets or inputs (Finlay *et al* 1987). Since epigenetic cascades must occur relatively late in development, after axonal connections have formed and neurogenesis largely

ceased, they only influence cell death – although, this has been identified as a major determinant of overall cell number (see Chapter 1, *Neurogenesis and cortical expansion*).

It has been proposed that evolutionary changes in absolute brain size are controlled by expansions and contractions of a highly conserved schedule of neurogenesis (Finlay & Darlington 1995). Precursor cells are exhausted at different times during development, with posterior and ventral neurogenesis often beginning before anterior and dorsal neurogenesis (Finlay *et al* 2001). The scheduling of neurogenesis across mammalian brains seems to be highly conserved, with most changes affecting the lengths, rather than the order, of events. Moreover, brain regions that are observed to increase more rapidly with increasing brain size begin neurogenesis later than those observed to increase less rapidly with increasing brain size . That is, the later a region begins neurogenesis, the steeper its slope with brain size. This may be because regions developed earliest in brain ontogeny control essential functions (e.g., respiration) and are therefore safeguarded against disruptive changes. There is support for the CEH in preliminary studies of developmental scheduling in mammalian brains (Kornack & Rakic 1998; Clancy *et al* 2001), although even in the markedly small sample it is evident that neurogenetic schedules are not lengthened or contracted uniformly and that the rate of precursor cell division is not constant across species. However, neither of these departures necessarily falsifies the CEH.

The MEH does not reject the presence of developmental constraints on evolutionary changes in brain size, but claims that the constraints are not overpowering. The observation of grade-shifts in the scaling relationships of neocortex and rest-of-brain in different taxonomic groups (Barton & Harvey 2000) confounds the CEH, which only allows for minor differences between species. However, these grade-shifts are not statistically clean, and relatively few species exceed the minor differences predicted by concerted evolution. If we look at finer structures than the neocortex, the argument for mosaic evolution strengthens. The olfactory bulb, for example, plotted against medulla size shows that the olfactory bulb experienced a significant phylogenetic reduction in anthropoids (Stephan *et al* 1981), and that the olfactory cortex in anthropoids is larger than expected for a mammal with an anthropoid-size olfactory bulb. Since a tight correlation between olfactory bulb and olfactory cortex holds for *Eulipotyphla* and *Strepsirrhini*, it is suggested that the constraint controlling the scaling relationship between olfactory bulb and olfactory cortex size broke down in anthropoid evolution (Streidter 2005). If we add the hippocampus into the mix and plot it against medulla, olfactory bulb, and olfactory cortex size, it becomes apparent that the olfactory cortex and hippocampus evolved independently in size from

the non-olfactory brain (Darlington *et al* 1999). Additional evidence can be found for mosaic evolution when we consider the superior colliculus (the major visual region in the midbrain), which is exceptionally large in ground squirrels (10 times larger than predicted by allometry) and exceptionally small in blind mole rats (38 times smaller than predicted by allometry) for their respective brain sizes. The behavioral correlate of the mole rat seems obvious, since these animals are virtually blind. The developmental or functional uncoupling of these regions, however, seems rare. The inferior colliculus (the major auditory region in the midbrain), for example, is only three times larger in echolocating bats than in non-echolocating bats. In fact, differences at the ordinal level do not generally exceed three-fold differences (Streidter 2005). The evidence, overall, implies that constraints on the evolution of brain regions are conserved, but that major behavioral adaptations can manipulate the size of particular structures.

Comparative studies of connectivity and circuitry in the mammalian brain affirm many of the claims of concerted evolution. Neurons in developing brains often depend on trophic factors for survival. The trophic factors can originate in presynaptic cells or be target-derived (Linden 1994). The epigenetic population-matching (EPM) hypothesis proposes that neurons compete with one another for some trophic factor produced by their target region and, as a result of the competition, the number of projection neurons is matched to the number of available target cells (Katz & Lasek 1978). The sense of this hypothesis lies in the fact that genetic variation in the size of a certain region does not require matching mutations to adjust the size of the associated neuron pool. Several of the predictions made by the EPM hypothesis concerning the interconnectedness of brain structures have supporting evidence. For example, experimental removal of the retina during development leads to a dramatic size reduction of most retinal targets (Cullen & Kaiserman-Abramof 1976; Finlay *et al* 1986). More conspicuously, the retinal target regions in naturally blind species tend to be significantly smaller than in species with well-developed eyes (Cooper *et al* 1993a,b). The persistence of the suprachiasmatic nucleus (SCN) in blind mole rats is, in fact, consistent with EPM, since SCN neurons can survive without trophic support from the retina (Lehman *et al* 1995). While coordinated variations in the retinal system seem to have distinct epigenetic signatures (Cvekl & Mitton 2010), the mechanism of coordinated variation is not always clear. When a structural component in the trans-cerebellar loops (a series of parallel loops that pass through the cerebellar cortex and the inferior olive) becomes either hypo- or hypertrophied, for example, the other components follow suit (Voogd 2003). But without developmental data it is impossible to say that the population matching is epigenetically controlled. A further prediction of the

EPM hypothesis is the aforementioned epigenetic cascades (Wilczynski 1984), which propose that changes in the size of one structure will propagate throughout that structure's neural system. There is evidence in support of this prediction. The retina connects to the visual cortex indirectly via the LGN. Blind mole rats (and other naturally blind mammals) have abnormally small retinal targets, but they also have abnormally small visual cortices (Rakic *et al* 1991; Cooper *et al* 1993b; Dehay *et al* 1996b). Therefore, the reduction in the size of the visual cortex may be explained by an epigenetic cascade. However, this effect is not observed universally. Different species tend to elaborate pathways from a common source differently (Northcutt & Wulliman 1988). It seems most likely that epigenetic cascades operate successfully in linear circuits (e.g., the trans-cerebellar loops), but not in reticulate circuits, which is why mosaic evolution is possible.

But can we make any inferences about behavior? The principle of proper mass (Jerison 1973 2001) suggests that the importance of a function (e.g., spatial memory or olfaction) to a species is proportional to the amount of neural tissue the species devotes to the brain region controlling that function. This is difficult to test. The absolute size of the retina in mammals is directly related to the size of the visual receptive field of its neurons (since the neuronal population increases with the size of the retina), which is directly related to the ability of the retina to resolve small stimulus objects (Streidter 2005). But analogs of receptive fields are more elusive in most of the brain. If we simply consider that bigger is more important, then we must say that olfaction is more important to primates than it was to their earliest mammalian ancestors, since primates have larger olfactory cortices than the earliest mammals had (Laing *et al* 1991; Laska & Seibt 2002). But most would agree (e.g., Kielan-Jaworowska 1983, 1984; Jerison 1990; Catania 2007; Sarko 2009) that the earliest mammals had olfaction-centric sensory systems and that olfaction is not principally important to the sensory experiences of primates (Gilad *et al* 2003). Therefore, the importance of olfaction decreased as the olfactory bulb increased. This is an untenable conclusion. Furthermore, the high proportion of non-functional pseudogenes in the human olfactory receptor repertoire (Gilad *et al* 2000; Menashe *et al* 2006) or the specialization of certain species to detect particular odors (Buck & Axel 1991; Zou *et al* 2001; Leon & Johnson 2003) makes comparisons of the size of even specific structures across species problematic, as these comparisons assume that major molecular and cellular changes will necessarily be manifest in brain size variation.

Primate brain

Increased diurnality, reduced olfaction, improved color-vision, and increasingly complex social behavior are major, and probably interrelated, trends of haplorrhine evolution. The first primates likely emerged ~85 million years ago (Soligo *et al* 2007; Martin *et al* 2007). They are posited to have been arboreal, nocturnal, and somewhere between squirrel- and hare-sized, not unlike some living strepsirrhine species (Heesey & Ross 2001). The front-facing, enclosed eye orbits and abbreviated snouts of haplorrhines, which are suggested to be adaptations favoring sense of sight over smell, are indicative of a switch to diurnality in haplorrhine evolution (Ross 1996). Further increased specialization for diurnal living is evident in the reduced olfactory receptor repertoire (Rouquier *et al* 2000; Gilad *et al* 2003) and adaptation for trichromatic vision in catarrhines (Jacobs 1993; Dulai *et al* 1999). Body size and brain size are strikingly dissimilar in simians and prosimians, suggesting that increases in body and brain size have been positively selected for in simian evolution (Soligo 2006). While a comparison of tree shrews and prosimians shows a slight evolutionary jump in relative brain size in early primate evolution, perhaps due to a decrease in body size (Deacon 1997), brain size increases seem to have waited for body size increases in simian evolution. A cladistic analysis points to repeated selection for increased brain size in haplorrhines, catarrhines, hominoids, hominids, and hominins, although not without some evolutionary decreases in brain size along the way (e.g., marmosets) (Montgomery *et al* 2010).

An early derived trait of the encephalized primate brain is disproportionate neocorticalization. A small strepsirrhine (*Galago demidovii*) and a large insectivore (*Erinaceus europaeus*) have brains that weigh roughly 3.4g. However, the proportion of brain size devoted to neocortex in the strepsirrhine is 46% compared to 16% in the insectivore, and the neocortex-medulla ratio in the strepsirrhine is 9.3 compared to 1.6 in the insectivore (Stephan *et al* 1981). Even though the proportional volume of the neocortex is expected to increase with increasing brain volume, primates appear to have deviated from the mammalian values of this scaling relationship early on. The neocortex (grey and white matter) of the chimpanzee, for example, constitutes 76% of total brain size and is fifty times larger than the medulla (Stephan *et al* 1981).

Behavioral interpretations of primate neocorticalization have abounded, despite its elusive mechanistic provenance, the impossibility of assigning specific behaviors to the multifaceted region, and the implausibility of assuming that the entire neocortex was selected for a specific behavior. The primate brain and neocortex have been correlated with BMR, frugivory, longevity, and many

approximations for social intelligence (Clutton-Brock & Harvey 1980; Armstrong 1985; Dunbar 1998; Isler & van Schaik 2006 2009), none of which have been very useful in reconstructing the selection pressures behind primate brain evolution. However, by comparing brain structures and systems with specific empirical functions (and perhaps evidence of specific control over certain behaviors), our picture of primate brain evolution becomes clearer.

The visual system has been a center for considerable selection in primate brain evolution (Preuss 1999). The binocular-adapted front-facing eye orbits of early primates was likely associated with changes in how the retina projected to the superior colliculus. Primates, compared to most other mammals, have bilateral retinocollicular pathways, which improve depth perception by giving the superior colliculi and LGN access to information coming from both eyes (Kaas & Huerta 1988). The convergent evolution of bilateral retinocollicular pathways in primates and fruit-eating megabats (Pettigrew 1986; Rosa & Schmid 1994) suggests that this particular change in the visual system was selected for exploiting the fine-branch niche of an arboreal habitat.

There has also been positive selection on the primate cerebral motor system. Primates possess at least nine premotor areas, whereas most other mammals have, at most, four (Wu *et al* 2000). Several derived areas have been observed in the primate somatosensory cortex (Kaas 1983, 1988). The ventral premotor area, a derived feature of the primate motor system specialized for arm and mouth movements (Preuss *et al* 1996), has direct corticospinal projections, which are indicative of increased dexterity (Rizzolatti & Arbib 1998). Evolutionary changes in touch-sensitive fingertips and toes in primates likely had correlated changes in the somatosensory cortex (Manger *et al* 1996). The interconnectedness of the motor system, spinal cord, and somatosensory cortex together with the visual system form a hypothetical movement-control center, selection on which would have been advantageous to the reliance of early primates on hand-eye coordination in feeding (Soligo & Martin 2006) and exploiting the fine-branch niche (Kaas 2008; Shapiro & Young 2010) of an arboreal habitat.

Comparative analyses of the primate prefrontal cortex cannot make such robust claims. Pairing adaptive behavior (e.g., balancing on tree-branches) with cerebral adaptations for decision making, which is the generalized function of the prefrontal cortex (Krawczyk 2002), can be difficult. Perhaps for this reason, the prefrontal cortex has commanded the attention of comparative neurobiologists for decades. The primate prefrontal cortex is divided into three major regions. The anterior cingulate cortex, which mostly processes information about consciousness, affective state, and expression, and influences skeletomotor and autonomic activity (Devinsky *et al* 1995; Luu & Posner 2003; Botvinick

et al 2004), and the orbital prefrontal region, which is involved in sensory integration and valuation of rewarding external stimuli (Tremblay & Schultz 1999; Schoenbaum & Setlow 2001), constitute the emotional aspects of decision-making and are conserved in mammals (Damasio 1994; Dias *et al* 1996; Allman *et al* 2001; Streidter 2005). The lateral prefrontal cortex (LPC), however, whose neurons respond mostly to the physical attributes (e.g., spatial location) of external stimuli (Wallis & Miller 2003), is apomorphic in primates (Preuss 1995a; Elston *et al* 2005). Most interpretations of the LPC have implicated rational decision-making, such as allowing primates to consider alternative scenarios, which is often used as a proxy for intelligence (Owen *et al* 1999). The LPC is considered a definitive feature of primate brain evolution, and even a major component of what makes human intelligence unique (Tanji & Hoshi 2008). However, the usefulness of this added prefrontal region in early primates is difficult to categorize, making the identification of selection pressures on its inception, compared to adaptations described in the visual and motor systems, considerably speculative (see Sherwood *et al* (2008) for a review of hominoid cognition).

A general trend has been observed in primates to possess more cortical areas than other mammals (Felleman & Van Essen 1991; Preuss & Goldman-Rakic 1991) and to separate systems of long corticocortical connections into functional networks (Preuss 2001). Many higher-order association regions (e.g., posterior parietal and inferotemporal cortices, in addition to the LPC) may be unique to the primate brain (Allman 1977; Kaas 1987; Preuss 1995b; Preuss & Kaas 1999). Furthermore, primary sensory areas in primates are connected only to areas of the same sensory modality, which is not the case in rodents (Vogt & Miller 1983; Miller & Vogt 1984; Sukekawa 1988; Reep *et al* 1990; Paperna & Malach 1991; van Eden *et al* 1992; Conde *et al* 1995). It may be that larger-brained mammals generally possess more cortical areas than smaller-brained mammals (Kaas 1987) and that the functional segregation of networks is a reflection of constraints on connectivity (Krubitzer 2009). Nonetheless, the need for the proliferation of cortical areas in primates may itself be indicative of an increasing specialization of cerebral functions in primate evolution.

Considering humans, whose ratio of neocortical gray matter to medulla size is twice what it is in chimpanzees, we expect to find an arsenal of new cortical regions. This does not seem to be the case (perhaps due in part to the limited amount of research done on identifying homologous and non-homologous regions in humans and other primates). Intuitively, the primary contenders for derived human areas are Broca's and Wernicke's, which have been classified as two major language areas in the human brain. But, areas 44 and 45, which collectively comprise Broca's area in humans, have been

identified in other primates (Preuss & Golman-Rakic 1991c; Rizzolatti & Arbib 1998; Petrides & Pandya 1999; Wu *et al* 2000; Petrides & Pandya 2001; Schenker *et al* 2010). Area 45 has been described in macaques as having clusters of large, deeply stained pyramidal cells in the lower part of layer III and a well-developed layer IV (Petrides & Pandya 2001), which is qualitatively almost indistinguishable from what is observed in humans. A study of hominoids (including humans) and Old and New World monkeys showed that humans have not evolved differentially higher requirements of metabolic support in area 44 (Sherwood *et al* 2006). There is further evidence that Tpt, a component of Wernicke's area in humans, is homologous in non-human primates (Preuss & Goldman-Rakic 1991a; Pandya 1995) and even shows human-like asymmetry in association with area 45 in chimpanzees (Proctor *et al* 2010). In fact, population-level left hemisphere-dominant asymmetry of the planum temporale, a highly lateralized structure involved with language (Zheng 2009), can be traced to the catarrhine common ancestor (Gannon *et al* 1998, 2008; Hopkins *et al* 1998; Cantalupo & Hopkins 2001). While it is unlikely that all neocortical areas are conserved between humans and their closest relatives – e.g., parts of the LPC and the inferior parietal lobe are likely derived in humans (Karnath 2001) –, there is no evidence for an outburst of novelty (addition or segregation) in human evolution. It may be more informative to look at how homologous areas in humans differ, qualitatively and quantitatively, from their ape and monkey relatives.

The frontal lobe in primates increases proportionally with increasing brain size (Bush & Allman 2004). Humans have a predictably large frontal cortex that does not deviate from allometric predictions (Semendeferi 2002). However, if we look at the divisions of the frontal lobe separately, it seems that the LPC (especially area 10), compared to other regions of the frontal lobe, became disproportionately large in humans (Semendeferi *et al* 1998, 2001). There is further evidence that the LPC did not become independently encephalized; several other regions that form a circuit with the LPC also became selectively enlarged in human brains. Outside the neocortex, the LPC mainly interacts with the medial dorsal nucleus and the pulvinar, two cell groups in the dorsal thalamus that are disproportionately large in humans (Streidter 2005). Observed embryogenetic changes related to neurons in the pulvinar (Letinic & Raki 2001) suggest that pulvinar development was radically altered in human evolution (although, it is not known whether this alteration took place in hominin or in hominoid evolution). Pulvinar hypertrophy primarily implicates the dorsal pulvinar, which has strong reciprocal connections with the LPC (Romanski *et al* 1997; Gutierrez *et al* 2000). There are many hypotheses, some of which I have already described, for functional-behavioral correlates of an encephalized LPC in humans (e.g.,

Rizzolatti & Arbib 1998; Duncan & Owen 2000; Wise & Murray 2000; Miller & Cohen 2001; Wallis *et al* 2001; Gray *et al* 2002; Aron *et al* 2004; Streidter 2005; De Pisapia *et al* 2007; Lee *et al* 2007; Sakagami & Watanabe 2007; Jung *et al* 2008; Tanji & Hoshi 2008), not one of which is grounded in enough evidence to draw out a consensus.

Two other regions of notable encephalization in humans include the temporal lobe, which is larger than expected for a human-brain sized ape (Rilling & Seligman 2002), and the parietal lobe, which includes the potentially novel areas 39 and 40 (Preuss & Golman-Rakic 1991a). Expansion in the temporal lobe seems to have been mostly dorsal, in areas associated with processing speech (Farah *et al* 1999; Streidter 2005). Across primates, however, the temporal lobe is observed to proportionally decrease with increasing brain size (30% in squirrel monkeys compared to 16% in humans) and the scaling relationship of brain size and parietal lobe size is unknown.

There are at least three regions of the human brain which have decreased in size or complexity. The olfactory bulb in humans compared to non-human primates is smaller than expected and simpler in its structural details compared to other primates (Stephan & Andy 1970; Rouquier *et al* 2000; Streidter 2005). The dorsal cochlear nucleus (DCN) in humans is virtually un-laminated compared to the highly laminated DCN observed in strepsirrhines (Moore 1980). In fact, from strepsirrhines to hominoids the granule cell layers of the DCN become increasingly thin and superficial, until they are virtually absent in humans. This is possibly an effect of increasing brain size or less mobile pinnae in larger primates, but there is not enough evidence to support either of these claims. And perhaps the most notable reduction in the human brain is the relatively small primary visual cortex (V1), which occupies only 2% of the neocortex in humans compared to 5% in chimpanzees (Stephan *et al* 1981). Since V1 size scales predictably with neocortex size in primates, it is easy to see that the human V1 is smaller than expected for a human brain-sized primate. However, considering that human body size scales tightly with V1, as well as orbital size (Passingham 1973), it seems unlikely that V1 was reduced during human brain evolution, but that it did not grow at pace with other neocortical regions. Histological studies suggest that V1 in humans is distinguished from V1 in apes and monkeys in the way it segregates information arising from the magnocellular and parvocellular layers of the LGN (Preuss *et al* 1999). Imaging studies point to structural and functional differences between humans and other primates in higher-order visual cortical areas (Tootell & Taylor 1995; Tootell *et al* 1997; Preuss 2001). So, despite its volumetric stasis, the visual cortex has been a site of repeated selection in human brain evolution (see Chapter 5, *Evolution*).

Increasing brain size means increasing axonal length and decreasing proportional connectivity, which both have consequences for transmitting information and synchronizing neural activity in distant cortical regions. Encephalized primate brains have compensated for these consequences with at least two fundamental alterations in network design. Firstly, in haplorrhines, the somatosensory component of the dorsal thalamus projects uniquely to the primary somatosensory cortex, whereas in strepsirrhines and many non-primates it projects to multiple areas (Kaas & Preuss 2003). Likewise, the visual cortex in macaques is divisible into ventral and cortical streams and is (nearly) the exclusive projection center for the LGN, whereas a general pattern of diverging and converging visual cortical and LGN connections is observed in cats (Young 1992; Scannell & Young 1993). The functionality of such rewiring is cost-efficiency: serial thalamocortical and intracortical circuits, designed in a hierarchical system, minimize wiring costs by making each junction in the circuit responsible for processing the output from the prior junction (Wen & Chklovskii 2005; Chen *et al* 2006; Jehee & Murre 2008). Secondly, larger primate brains have evolved less densely connected and more functionally independent cerebral hemispheres, as evidenced by the disproportional shrinking of the corpus callosum as an effect of increasing neocortical size (Rilling & Insel 1999a; Olivares *et al* 2000; Hopkins *et al* 2008). Human brains are paragons of hemispheric asymmetry (Gannon *et al* 1998; Buxhoeveden & Casanova 2000; Gilissen 2001; Rogers & Andrews 2002). The effect of this disconnectedness, it seems most likely, has been to allow each hemisphere to specialize in certain tasks (Levy 1969; Doyle *et al* 1974; Davidson 1978; Rogers 2000; Sainburg 2005; Vallortigara & Rogers 2005).

An unfortunate effect of the human brain's solutions to the design problems of encephalization include unparalleled vulnerability to damage. Serial circuits, for example, compared to the parallel circuits observed in most mammals, tend to have information bottlenecks, the deletion or corruption of which is systemically deleterious (Rodman & Moore 1997; Preuss & Kaas 1999; Heitger *et al* 2004). Increased asymmetry in humans, too, has increased our vulnerability to focal brain damage compared to other primates (Heywood & Cowey 1992; Karnath 2001). Obviously, these costs of encephalization were not enough to overcome the selection pressures for encephalization in humans.

Carnivore brain

Carnivores show great diversity in ecology, sociality, life-history, and morphology (Wesley-Hunt 2005). They have a well-resolved phylogeny and an extensively sampled fossil record (Flynn *et*

al 2005; Wesley-Hunt & Flynn 2005; Finarelli 2008a). Comparative studies of the carnivore brain have been almost exclusively on brain volume. Reconstructions of ancestral caniform species suggest that all major caniform clades have experienced encephalization, and that encephalization occurred in parallel across caniform clades (Finarelli & Flynn 2006). However, neither ecology, sociality, life-history, nor morphology have been able to explain that encephalization. Whereas basal metabolic rate (BMR) appears to be highly and positively correlated with brain size in most eutherian mammals (Martin 1981; Isler & van Schaik 2006), BMR is not correlated with brain size in carnivores (Finarelli 2009). Whereas support for the maternal energy hypothesis (Martin 1981, 1996) exists in correlations between reproductive strategies (e.g., gestation length and weaning mass) and brain size in most eutherian mammals, reproductive strategies are not correlated with brain size in carnivores (Finarelli & Flynn 2009) – although more encephalized carnivore species tend to have fewer and larger offspring, two life-history traits that accompany longer gestation length, compared to less encephalized carnivore species (Finarellli 2009; Finarelli & Flynn 2009). While it appears at first that social group size impacts brain size in carnivores (Perez-Barberia *et al* 2007), closer inspection shows that the family *Canidae*, which is composed of mostly highly encephalized and social species, imposes a disproportionate bias on the dataset. Instead, carnivore species are a riot of encephalization and sociality: musteloids and ursids, which show comparable patterns of encephalization to canids, are non-social and solitary, respectively; and the families *hyaenidae* and *herpestidae* possess both social and non-social species with no associated affects on encephalization (Finarelli & Flynn 2009). Orbit orientation has been linked to food-gathering behavior and locomotion in mammals (e.g., Cartmill 1972, 1974; Ross 1995; Noble *et al* 2000; Heesy 2005). The orbital convergence angle, in particular, has been linked to stereoscopic vision and depth perception, as well as, in primates, arboreality and nocturnal visual predation (Cartmill 1970, 1972). No such pattern emerges in carnivores (Finarelli & Goswami 2009). This should be expected, however, since the carnivore skull has been shown to be characterized by multiple phenotypic modules, which show relatively high within-module and low among-module correlations (Goswami 2006a,b) that permit the independent evolution of certain modules without affecting the functional relationship among modules (Finarelli & Goswami 2009). This is much less the case in primates (Goswami & Polly 2010). If any conclusions can be drawn from this collection of studies, it is that patterns of encephalization in *Carnivora* are generally restricted to phylogenetic families.

CHAPTER 4
METHODOLOGY (BRAIN DATA)

In order to investigate the number of cells in a region of interest (ROI), it is necessary to slice the tissue of the ROI into sections and then inspect the sections. This method is complicated by the fact that slicing tissue into sections results in slicing individual cells, and counting cell fragments as complete cells introduces bias. Design-based stereology has developed a method to correct for such a bias.

Design-based stereology uses probes and sampling schemes defined *a priori* to ensure independence from assumptions about the shape, size, spatial orientation, and spatial distribution of the particles under investigation. The method can be used to analyze global characteristics that can be expressed as absolute values (e.g., the volume of the granule cell layer of the dentate gyrus) or relative values (e.g., the fraction of Betz cells in layer V of M1) and local characteristics (e.g., the volume of a Betz cell in M1). This study only analyzed global characteristics. For overviews of design-based stereology, see Cruz-Orive & Weibel (1990), (Gundersen 1992), Mayhew & Gundersen (1996), Howard & Reed (1998), and Schmitz & Hof (2005); for reviews of the applications of design-based stereology, see Gundersen *et al* (1988), Mayhew (1992), and West (1993, 1999 2002); for detailed overviews of the mathematical and statistical foundations of design-based stereology, see Jensen (1998) and Russ & Dehoff (2000).

Fractionator principle

In systematic sampling, the sampling interval is defined as the quotient of the population size and the sample size. Systematic random sampling (SRS) applies to this method the principle of simple random sampling, which gives every particle in a ROI equal probability of being sampled. Thus, particles of a region will be sampled at regular intervals from a random starting point. The fractionator principle, an application of SRS, can be written for the *i*th estimate of *n* sample as

$$X_i = \frac{x_i}{f} = \frac{x_i}{1/n} = n\, x_i \tag{1}$$

and for the mean of all estimates as

$$\hat{X} = \frac{1}{n} \sum_{i=1}^{n} n\, x_i = \sum_{i=1}^{n} x_i, \tag{2}$$

where x is the value measured from the sample (e.g., number of neurons counted), f is the fraction sampled, and X is the quantity of interest (e.g., population of neurons in V1). So long as x is unbiased, X is also unbiased. The value of f is determined by the worker based on a balance between the accuracy needed for the estimate and the amount of work that can be done. The value for f that best suits this balance is usually determined through a pilot study with the object and quantity of interest. Since design-based stereology is unbiased, the larger the value of f (i.e., the closer the worker is to exhaustively sampling the quantity of interest), the more X converges on the true quantity. This is clear from (2), which shows that the average of the estimates made with the fractionator is the true result.

Optical fractionator

The optical fractionator method estimates the total number of cells in a ROI from the number of cells sampled. The fractionator principle is used to select a series of SRS sections through the entire ROI. A randomly positioned, systematically spaced lattice is superimposed on each tissue section of the ROI. Unbiased virtual counting spaces are positioned at the cross-sections of the lattice that intersect with the ROI. A virtual cube (the disector), with three exclusion sides and three acceptance sides, is superimposed onto each counting space (Fig. 4a). The cube is represented to the worker in a 2-D counting frame on a computer screen (Fig. 4b), which is moved along the z-axis of the section tissue using a microcator, an electronic device that measures the vertical displacement of the microscope stage, and along the x,y-axis using a computer-controlled stepping motor, which directs the counting frame to each disector site. Particles are counted in the counting frame according to unbiased counting rules (Fig. 4a,b; also see West 1991; Keuker *et al* 2001). Since the size of the ROI is implicitly determined by the optical fractionator, the particle count is independent of shrinkage or swelling of the tissue.

The total particle count is determined using three sampling fractions. The section sampling fraction (*ssf*) is the proportion of sections of the entire, serially sectioned ROI that are sampled (Fig. 5a). The area sampling fraction (*asf*) is the proportion of the sectional area that is investigated within the sampled fractions, calculated as the ratio between the area of the counting frames and the x,y-distance between the counting frames (Fig. 5b). The thickness sampling fraction (*tsf*) is the cross-sectional area of the sampled sections, calculated as the ratio of the disector height and the total section thickness (Fig 5c). The total particle count (N) is then estimated as the product of the reciprocals of the fractions, such that

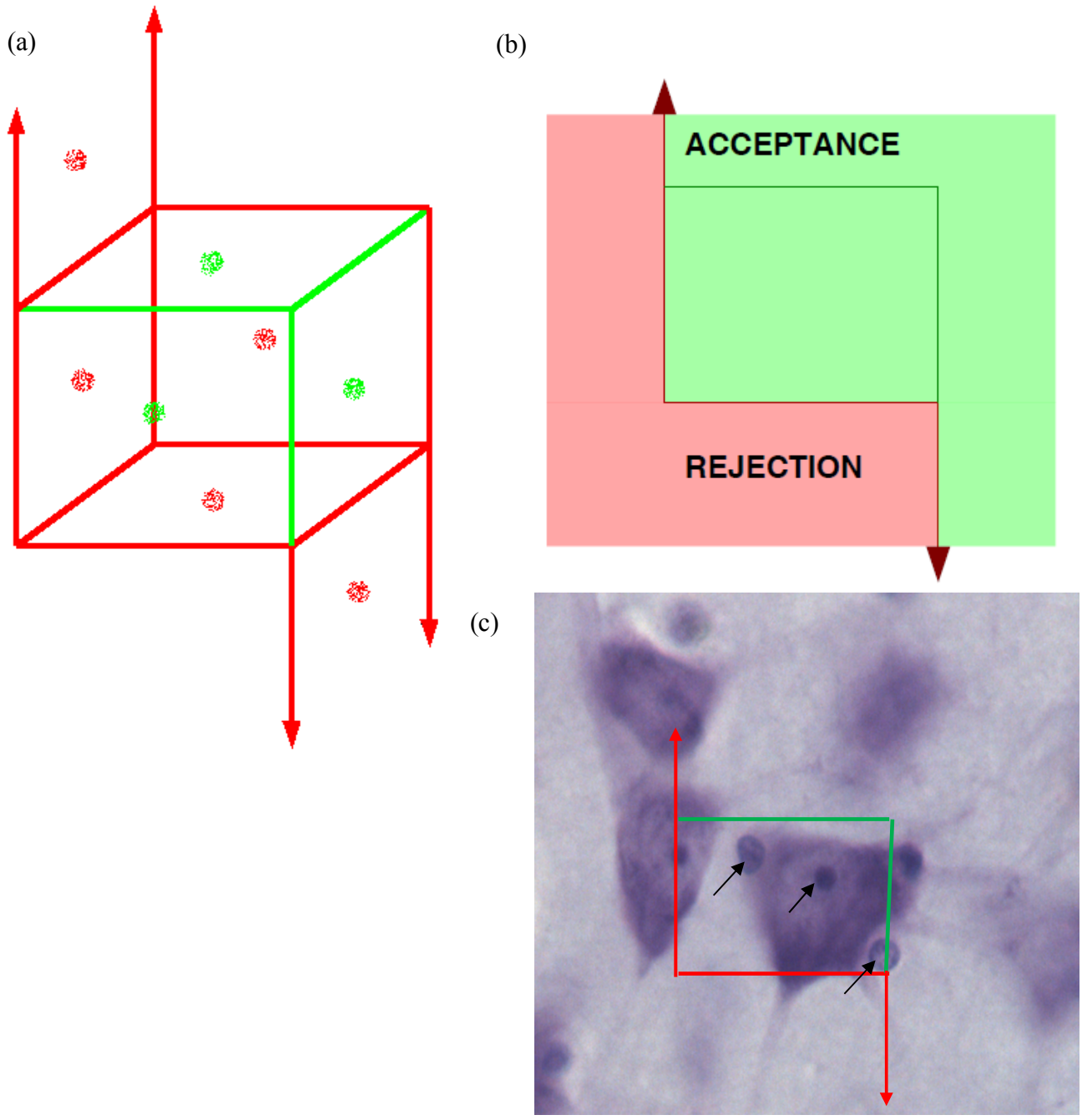

Figure 4. *(a) The 3D (x,y,z) disector has five rejection planes (defined by redlines) and three acceptance planes(defined by green lines). (b) The rejection (red) and acceptance (green) regions of the counting frame constitute a 2D (x,y) representation of the disector at each z-position of the tissue. The rejection and acceptance lines together span the entirety of the microscopic field. The space between the rejection and acceptance lines (i.e., the counting frame) is asymmetrical. A particle is counted if the user-defined characteristic point of the particle comes into focus (i) within the counting frame without touching a rejection line or (ii) touching an acceptance line but not a rejection line. Using the cell body and the nucleolus as the user-defined characteristic points for glia and neurons, respectively, the arrows (glia) and arrowheads (neurons) indicate which cells are counted in the specific z-position of the tissue.*

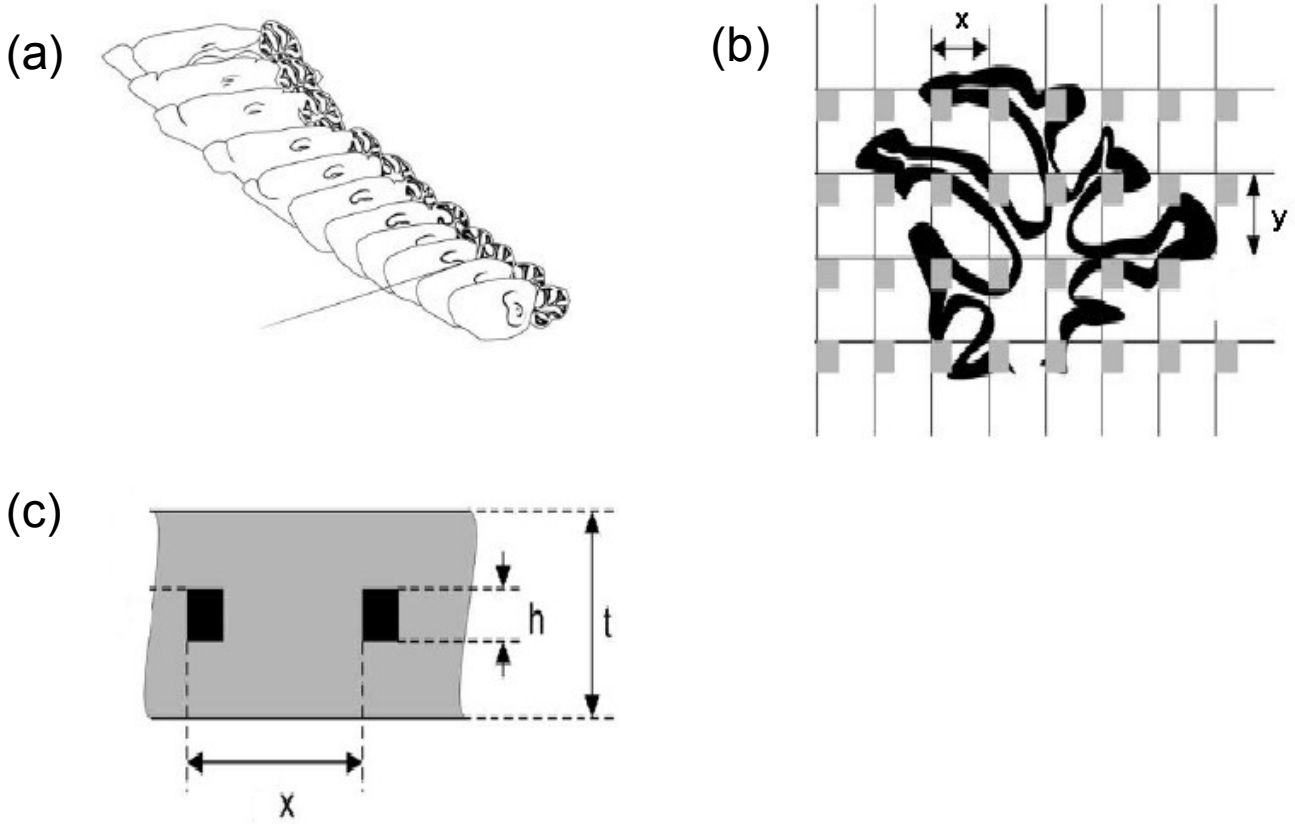

Figure 5. *The optical fractionator is applied in three stages. (a)The object is embedded and exhaustively sectioned; a known fraction, the section sampling fraction (ssf), of the sections is then sampled using systematic random sampling. (b)A lattice of known x and y is randomly positioned over the ROI; at each transect of the ROI and the lattice, a counting frame is placed; since the area of the counting frame and the x,y-distance between the counting frames are known, the x,y-space covered by each counting frame can be calculated as the area sampling fraction (asf). (c)The height (h) of the disector is user-defined and the thickness (t) of each section of tissue is estimated using the microcator at the first and final site of each tissue section; the ratio of these quantities is the thickness sampling fraction (tsf). The ssf, asf, and tsf are then used to estimate the total number of particles in a ROI. Adapted from Schmitz & Hof (2005).*

$$N = \Sigma Q \times \frac{1}{tsf} \times \frac{1}{asf} \times \frac{1}{ssf}\ , \tag{3}$$

where Q is the number of particles counted. The most suitable values for the sampling fractions can be determined in a pilot study with each individual. On average, a worker should sample 20 sections and expect to count 1-3 particles per disector (Gundersen *et al* 1987; Keuker *et al* 2001). In order to avoid potential bias from the partial loss of particles at the upper or lower surface of the sections (so-called

lost caps) or from uneven surfaces of the sections, it is necessary to introduce a guard zone at the upper and lower surfaces of the sections (Fig. 5c). That is, approximately 10% of the section thickness (and minimally 4μm) is not investigated at the top and bottom of each section (Andersen & Gundersen 1999; Schmitz & Hof 2005). It is also necessary (Dorph-Petersen *et al* 2001), in order to correct for potential non-uniform tissue deformation along the *z*-axis, to calculate the *tsf* using a *Q*-weighted mean section thickness (t_Q), such that

$$t_Q = \Sigma \frac{(t_i Q_i)}{\Sigma Q_i}, \tag{4}$$

where t_i is the section thickness for the *i*th counting frame with a disector count of Q_i.

Cavalieri volume estimtaor

The volume of a ROI can be estimated free of systematic error using the profile areas of the sliced sections of the ROI. The profile areas of the sections through the ROI are traced on a virtual image of the ROI represented on a computer screen (Fig 6). A systematically spaced and randomly positioned point-grid is superimposed on the virtual profile. The volume of the ROI can be estimated as

$$V = \frac{t}{ssf} \times a_p \sum_{i=1}^{n} P_i, \tag{5}$$

where *t* is the mean section thickness, P_i is the number of points landing within the object transect on the *i*th section, and a_p is the square of the distance between points on the grid. Therefore, the point-grid on a series of sections is a 3-D grid of points in space, where each point is assigned a volume element equal to $a_p t$.

The Cavalieri method is the most commonly used stereological method for estimating volume (Gundersen & Jensen 1987; Howard & Reed 1998). Fewer than ten sections per structure is an adequate sample for the Cavalieri estimator (Holm & West 1994), so long as the sampled sections are regularly spaced, the initial section is randomly selected, and the coefficient of error is not excessive (see below).

Coefficient of Error

The accuracy of an estimate obtained from design-based stereology is measured by the coefficient of error (CE), which is the quotient of the standard deviation and the mean (Gundersen &

Jensen 1987; Gundersen *et al* 1999; Slomianka & West 2005). Since the CE represents variation due to methodological uncertainty, it should contribute less than the biological coefficient of variation (BCV) to the total coefficient of variation (CV), where $CV^2 = CE^2 + BCV^2$ (West *et al* 1991). This ensures that the observed group variance is the result of biological variation rather than bias. The simplest estimate of CE is the Schmitz estimator, which calculates the CE as the reciprocal value of the square-root of the number of particles counted (Schmitz & Hof 2000).There are, in fact, a range of ways to calculate the CE (see Slomianka & West 2005), but the estimate that best fits the observed CE for the optical fractionator is the Gundersen-Jensen method (Gundersen *et al* 1999):

$$CE(Q)=\frac{\sqrt{[3(A-S^2)-4\mathrm{B}+C]/\alpha+S^2}}{(\Sigma Q_i)}, \tag{6}$$

where

$$A=\sum_{i=1}^{n}(Q_i)^2, \tag{7}$$

$$B=\sum_{i=1}^{n-1}Q_i\times Q_{i+1}, \tag{8}$$

$$C=\sum_{i=1}^{n-2}Q_i\times Q_{i+2}, \tag{9}$$

and S^2 is the variance introduced by local errors for either point counting or disector sampling, so that

$$S^2=0.0724\times shape\ factor\times\sqrt{n\times Q}, \tag{10}$$

where the shape factor is calculated as the average length of the boundaries of the structure divided by the square-root of its average area in the sections (Gundersen & Jensen 1987). The value of α, which can range from 1/12 to 1/240, is determined by the smoothness distribution, such that local variance becomes important as a function of the variance of its surroundings. The definition of smoothness here, however, is more precisely 'observed or perceived smoothness', as most biological structures will have smooth distributions. Therefore, general practice ascribes a smoothness factor of 0 (α=1/12) for section sampling intervals less than 8, and a smoothness factor of 1 (α=1/240) for section sampling intervals greater than 8 (Slomianka & West 2005).

Similarly, the CE for the Cavalieri method is proportional to the square-root of the variance and complexity (i.e., shape factor) of the of the total area under investigation. Using the following sums,

$$a = \sum_{i=1}^{n} (P_i)^2 , \tag{11}$$

$$b = \sum_{i=1}^{n-1} P_i \times P_{i+1} , \tag{12}$$

and

$$c = \sum_{i=1}^{n-2} P_i \times P_{i+2} , \tag{13}$$

then the CE is predicted to be

$$CE(\hat{V}) = \alpha(3(a - CE(\hat{P})) - 4\mathrm{b} + c) , \tag{14}$$

where the contribution of the point counting is

$$CE(\hat{P}) = 0.0724 \frac{B}{\sqrt{a_p}} \sqrt{n \sum_{i=1}^{n} P_i} , \tag{15}$$

and the overall CE is

$$CE = \frac{\sqrt{CE(\hat{V}) + CE(\hat{P})}}{\sum_{i=1}^{n} P_i} , \tag{16}$$

where α is the smoothness distribution as above and B is the mean boundary length (Cruz-Orive 1993)

The overall CE for both the optical fractionator method and Cavalieri method should not exceed 0.10 in order for the estimate to have statistical significance (Sahin *et al* 2003; Schmitz & Hof 2005).

Materials

The brain specimens used in this study were stained with Nissl, sliced coronally, horizontally, or sagitally, and with sections ranging in thickness from 25-80μm. The left hemispheres of adult male and female brains were sampled. When available, both the left and right hemispheres were sampled for cerebellar data.

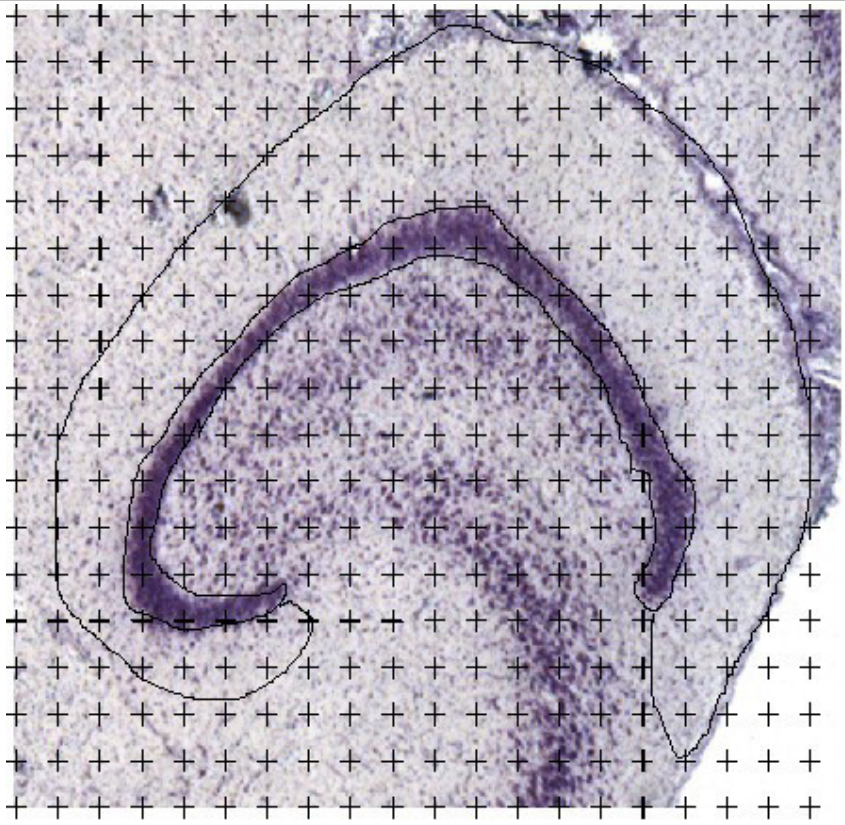

Figure 6. *A virtual profile of the ROI is projected onto a computer screen, where it is manually outlined. A point-grid of known spacing is randomly positioned over the ROI. Points falling within the outlined area are used to estimate the volume of the ROI according to Cavalieri's method.*

Research locations

All sections were investigated on-site at the National Museum of Health and Medicine (Washington, DC), the Laboratory of Neuromorphology at Mount Sinai Hospital (New York, NY), the Department of Evolutionary Neuroanatomy at George Washington University (Washington, DC), and the Pediatric Storage Disorders Lab at King's College London (London, UK). Brain specimens were donated for study after immersion fixation in 10% buffered formalin or 4% paraformaldehyde.

Slicing/Staining

Although most specimens were sliced and stained in the context of prior investigations, several brains or brain regions were sliced and stained personally. In those cases, the following procedure was used. Brains were frozen in 25% sucrose, then sliced at 40μm intervals using a freezing microtome. The sections were immediately mounted on Chrome Alum-coated slides and air-dried overnight (Fig 7). The sections were stained in Cresyl fast violet solution (0.5% aq) at 60^0C for 30 minutes, then rinsed in two changes of deionized water. The sections were processed in an ascending series of 8 graded alcohol and xylene solutions: 70% IMS (5 minutes), 80% IMS (2 minutes), 90% IMS (2 minutes), 95% IMS (2 minutes), 100% IMS (2 minutes), 100% IMS (2 minutes), 50% xylene in IMS (2 mintutes), and xylene (2 minutes). Sections were then passed through descending grades of alcohol and then again through ascending grades of alcohol until the background of the sections were sufficiently

clear. Each section was left in a xylene solution for an hour before being mounted with a glass cover-slip and a xylene-based mountant (DPX).

Stereology equipment

Zeiss (Oberkochen, Germany) Axioplan 2 photomicroscope equipped with a Ludl (Hawthorne, NY) XY motorized stage, Heidenhain (Plymouth, MN) *z*-axis encoder, an Optronics (East Muskogee, OK) Microfire color video camera, a Dell (Round Rock, TX) PC workstation, and *StereoInvestigator* software (MicroBrightfield, Wiliston, VT).

Specimens

One-hundred-and-two individuals were sampled from 74 species (Table 1, Fig. 8). When the taxonomic groups needed to constitute independent samples (e.g., ANOVAs), they were separated into Carnivora, Shrew-to-Whale, and Primates. Shrew-to-Whale included all non-carnivore/non-primate species sampled in this study. All species sampled were analyzed collectively for generalizing results to the class Mammalia. The species were separated into placental groups for certain analyses (Table 2).

Artifactual Error

As many of the specimens were collected in the context of other investigations, some of which are expected to have been opportunistic, it was impossible to control for idiosyncratic artifacts related to discrepancies in fixation length and postmortem delay. The recorded brain weights in my sample, nonetheless, do not show significant deviations from species-typical average fresh weights. Furthermore, comparable error from tissue shrinkage is assumed to be contained in both independent and dependent axes for each data point in bivariate plots, so error should only be expected to affect the elevation of regressions, but should not be expected to have a significant influence on scaling exponents and residuals. Analysis using the ratio of glial cells to neurons, as well, should be assumed to contain equal shrinkage-based error in the numerator and denominator, and thus error may be factored out (see Sherwood *et al* 2007).

The effect of phylogeny on scaling

The congruence of scaling relationship for species mean data and independent contrasts indicates that contemporary species values represent scaling rules that apply regardless of phylogenetic

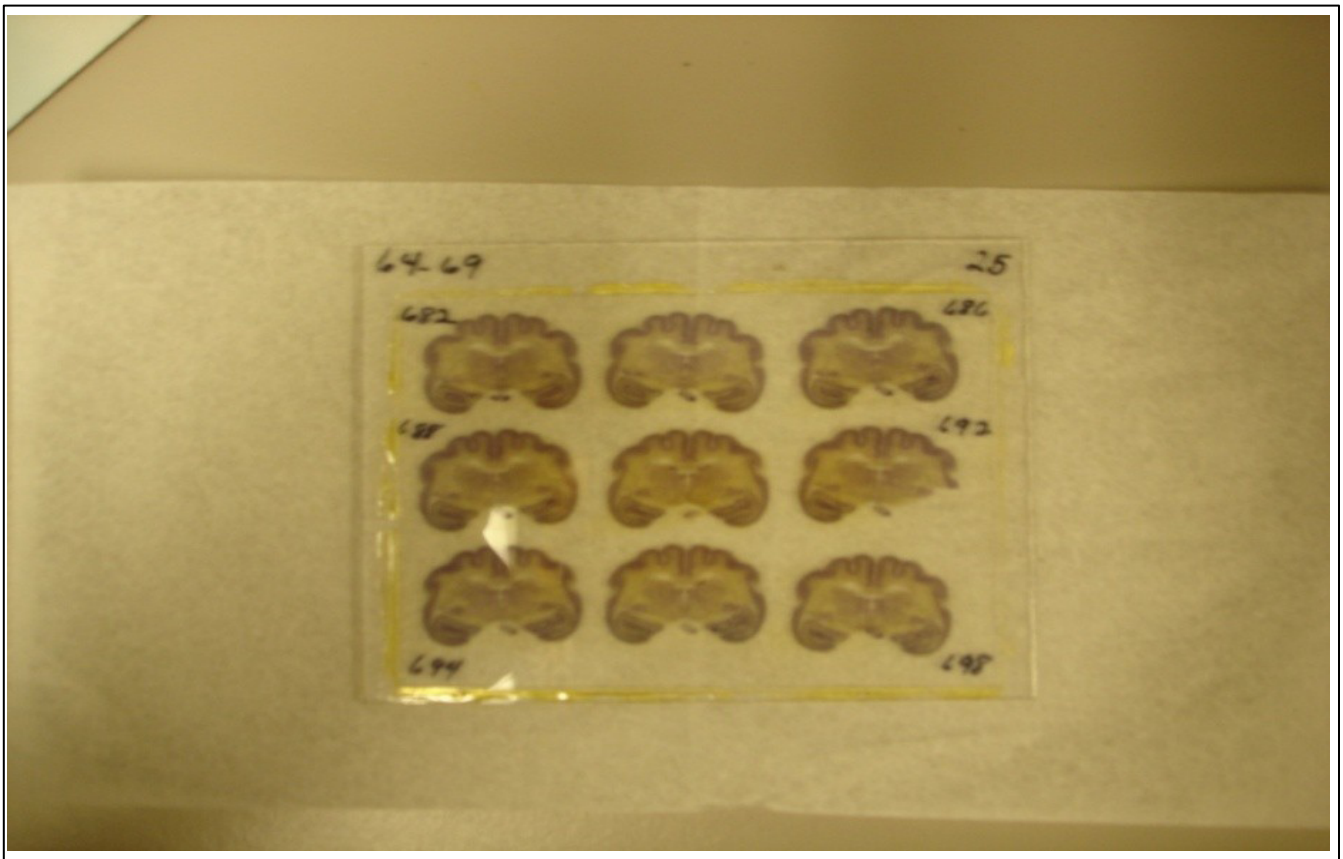

Figure 7. *After the tissue was sectioned and stained, it was mounted serially onto slides for inspection under the microscope.*

relatedness. Scaling relationships that show corresponding values for species mean data and independent contrasts, therefore, may be interpreted as being more strongly constrained or determined by scaling rules deep in the phylogeny rather than by effects of adaptation or inertia at terminal taxa. In this study, when independent contrast slopes were contained within the 95% confidence intervals of slopes calculated for species mean data I accepted it as indicative that the scaling relationship observed in contemporary species occurred repeatedly throughout multiple nodes in the phylogenetic tree and, therefore, represented functional constraints in the design of the region of interest.

Data analysis

Neuronal and glial cell densities, volumetric estimates of the granule cell and molecular layers of the dentate gyrus, and volumetric estimates of the granule cell layer of the cerebellum were plotted against brain mass, body mass, EQ, gestation length, and neocortical volume. When measurements of physiological variables were not available for the individuals studied, species mean data were taken

Table 1: List of species by taxonomic classification*

Taxonomic group	Subgroup	Species	Taxonomic group	Subgroup	Species
Primates	*Strepsirrhini*	*Galago senegalensis*+	*Carnivora*	*Caniformia*	*Mustela nigripes*+
		Nycticebus coucang			*Neovison neovison*
		Lemur catta+			*Mephitis mephitis*
		Eulemur mongoz			*Taxidea taxus*
		Microcebus murinus			*Procyon cancrivorus*
		Cheirogaleus medius			*Procyon lotor*+
	Tarsiidae	*Tarsius bancanus*			*Nasua nasua*
		Tarsius syrichta+			*Bassaricyon gabbii*+
	Haplorrhini	*Callithrix geoffroyi*			*Potos flavus*
		Leontopithecus rosalia			*Ailurus fulgens*
		Saguinus oedipus			*Zalophus californianus*
		Cebus capucinus			*Callorhinus ursinus*+
		Saimiri sciureus+			*Phoca vitulina*
		Aotus trivirgatus			*Ursus maritimus*+
		Callicebus moloch		*Feliformia*	*Canis lupus familiaris*
		Pithecia pithecia			*Canis latrans*+
		Alouatta caraya+			*Vulpes vulpes*
		Alouatta palliata			*Panthera pardus*+
		Ateles ater			*Felis catus*
		Macaca fascicularis (2)+			*Puma concolor*
		Macaca mulatta (2)			*Crocuta crocuta*+
		Macaca maura (5)			*Cynictis penicillata*
		Cercocebus torquatus	*Shrew-to-Whale (SW)*		*Dasyprocta leporina*+
		Mandrillus sphinx			*Lepus americanus*+
		Papio anubis (2)			*Cynocephalus volans*+
		Cercopithecus mitis			*Tupaia glis*+
		Cercopithecus nictitans			*Stenella coeruleoalba*+
		Erythrocebus patas (2)			*Tursiops truncatus*+
		Colobus angolensis+			*Megaptera novaeangliae*+
		Trachypithecus francoisi			*Sus scrofa*+
	Hominoidea	*Pongo pygmaeus (2)*+			*Rhinoceros unicornis*+
		Pan paniscus			*Manis gigantea*+
		Pan troglodytes (5)			*Scalopus aquaticus*+
		Homo sapiens (6)+			*Erinaceus europaeus*+
		Gorilla gorilla (2)			*Sorex araneus*+
		Hylobates muelleri+			*Trichechus manatus*+
		Symphalangus syndactylus			

*The number of individuals sampled for each species is listed. Where no number is listed, only one individual was sampled.

+Species included in All Species (AS) group

Table 2: List of species by placental characterization

Haemochorial	Endotheliochorial	Epitheliochorial
Callithrix geoffroyi	*Tupaia glis*	*Lemur catta*
Leontopithecus rosalia	*Felis catus*	*Eulemur mongoz*
Saguinus oedipus	*Panthera pardus*	*Microcebus murinus*
Cebus capucinus	*Puma concolor*	*Cheirogaleus medius*
Saimiri sciureus	*Cynictis penicillata*	*Galago senegalensis*
Aotus trivirgatus	*Crocuta crocuta*	*Nycticebus coucang*
Callicebus moloch	*Canis lupus familiaris*	*Manis gigantea*
Pithecia pithecia	*Canis latrans*	*Sus scrofa*
Alouatta caraya	*Vulpes vulpes*	*Rhinoceros unicornis*
Alouatta palliata	*Ailurus fulgens*	*Hexaprotodon liberiensis*
Ateles ater	*Ursus maritimus*	*Stenella coeruleoalba*
Macaca fascicularis	*Mephitis mephitis*	*Tursiops truncatus*
Macaca mulatta	*Bassaricyon gabbii*	*Megaptera novaeangliae*
Macaca maura	*Mustela nigripes*	
Cercocebus torquatus	*Taxidea taxus*	
Mandrillus sphinx	*Neovison neovison*	
Papio anubis	*Procyon cancrivorus*	
Cercopithecus mitis	*Procyon lotor*	
Cercopithecus nictitans	*Potos flavus*	
Erythrocebus patas	*Nasua nasua*	
Colobus angolensis	*Phoca vitulina*	
Trachypithecus francoisi	*Callorhinus ursinus*	
Pongo pygmaeus	*Zalophus californianus*	
Pan paniscus	*Trichechus manatus*	
Pan troglodytes	*Cynocephalus volans*	
Homo sapiens		
Gorilla gorilla		
Hylobates muelleri		
Symphalangus syndactylus		
Tarsius bancanus		
Tarsius syrichta		
Dasyprocta leporina		
Erinaceus europaeus		
Scalopus aquaticus		
Sorex araneus		
Lepus americanus		
Crocuta crocuta		

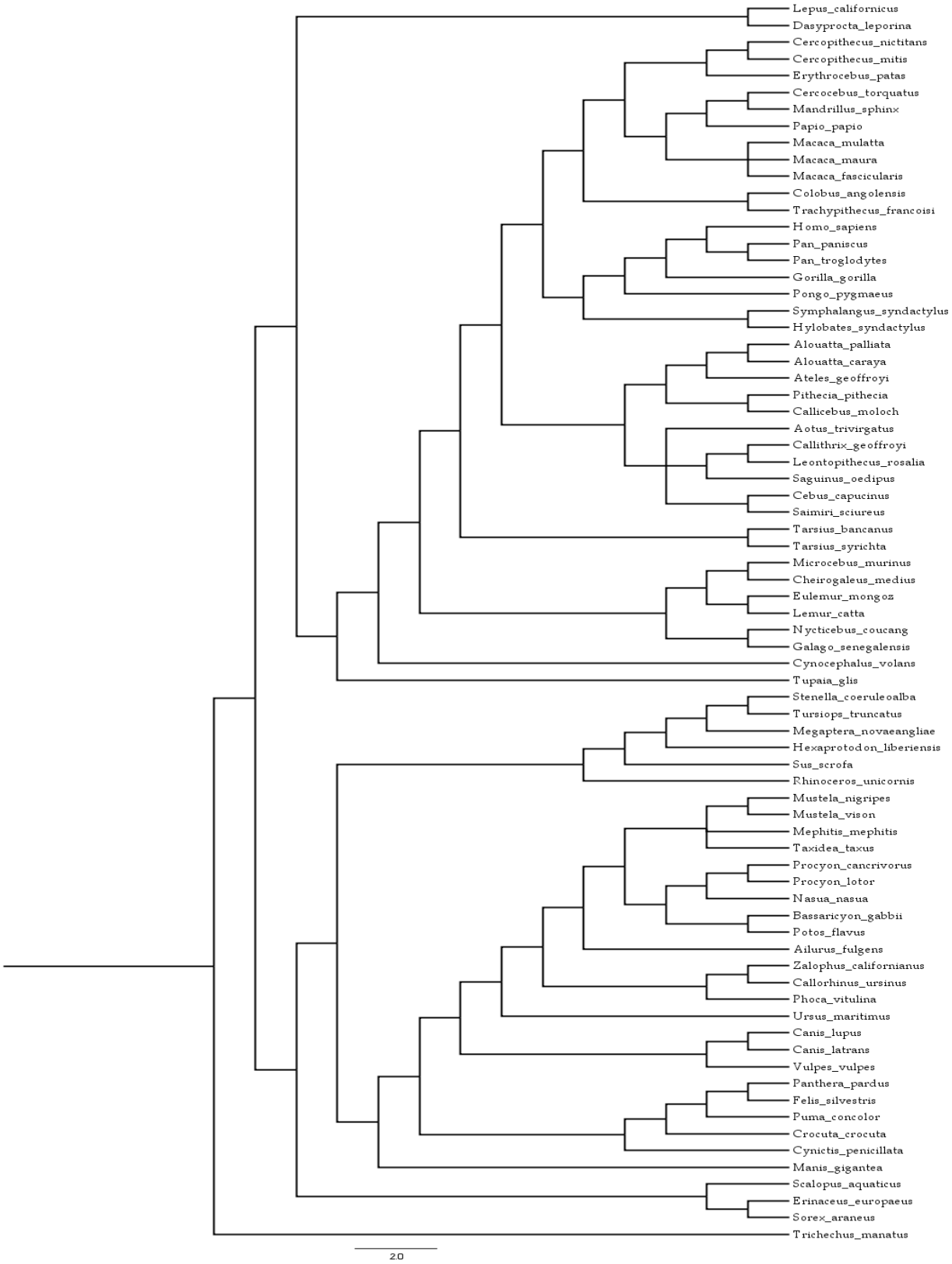

Figure 9. *Independent contrasts were calculated using this pruned phylogeny, adapted from Bininda-Emonds et al (2007).*

from the literature (Ross & Kirk 2007; de Sousa *et al* 2009 2010). Data on reproductive traits were taken from the literature (see Chapter 8, *Methodology B: Placental Data*). Scaling exponents were determined by reduced major axis (RMA) and least-squares (LS) line-fitting based on log-transformed data. To determine whether observed cellular densities and volumes in humans deviated significantly from allometric expectations based on non-human data, LS prediction equations and prediction intervals were generated using non-human species mean data and independent contrasts. The percentage differences between observed and predicted values were calculated as ((observed – predicted)/predicted) x 100).

Independent contrasts were calculated using the PDAP:PDTREE module of Mesquite (v2.72) from a pruned mammalian phylogeny from Bininda-Emonds *et al* (2007). Branch lengths were transformed according to Pagel (1992), as all the tips were contemporaneous. Prediction equations and intervals based on independent contrasts were generated by pruning humans from the tree, rerooting the tree at the last common ancestor of humans and mammals, and then computing LS regressions and prediction intervals for independent contrasts (Garland & Ives 2000). Human predictions were generated from non-human data based on LS regression, rather than RMA line-fitting, because the LS model was designed to generate predictions for y when x is known and produces residuals uncorrelated with the independent variables (Sokal & Rohlf 1995).

Recursive partitioning based on multiple regression analyses (see Breiman *et al* 1989; Clark & Pregibon 1992; see Hess *et al* 1999), stepwise AIC multiple regression (Yamashita 2007), and the relative importance metrics *lmg*, *pmvd*, *first*, and *last* (Chevan & Sutherland 1991; Johnson & Lebreton 2004; Feldman 2005; Gromping 2006, 2007) were used to isolate the best predictor variables for and determine the proportional contributions of regressors to cellular densities and volumes.

Recursive trees were built by first selecting the single variable which best split the data into two groups by administering an ANOVA. The same process was applied to split groups into subgroups and repeated recursively until no improvement could be made on the model. In regression trees using ANOVAs at each node, the splitting criterion that maximized the between-groups sum of squares (i.e., gave the best split) was equal to $SS_T - (SS_R + SS_L)$, where

$$SS_T = \Sigma (y_i - \bar{y})^2 \tag{17}$$

and SS_R and SS_L are the sums of squares for the left and right branches, respectively. Therefore, recursive partitioning identified which input variable best split the data for the output variable at each

node.

Each relative importance metric contributed something unique to understanding the allocation of variance in the quantity of interest among the variables (i.e., regressors). The metric *first* compared what each regressor alone was able to explain by comparing the coefficient of determination (R^2) values from *p* regression models with one regressor only. The metric l*ast* compared what each regressor was able to explain in addition to the other regressors, so that each regressor was ascribed the increase in R^2 when including the regressor being tested as the last of the regressors. Contributions were not made to sum to R^2 when the metrics *first* or *last* were used. The metrics *lmg* and *pmvd* used sequential sums of squares from the linear model (defined by the regressors x_k in order *r*) to obtain an overall assessment by averaging over the average contributions in models of exhaustive permutations of the available regressors. The metric *lmg* could thus be written as,

$$LMG(x_k) = \frac{1}{p!} \sum_{r\ permutation} seqR^2(x_k|r) , \tag{18}$$

where

$$seq\,R^2(M|S) = R^2(M \cup S) - R^2(S) , \tag{19}$$

for model *M* and set *S*. The metric *pmvd* was identical to *lmg*, except a data-dependent weight was added for each order, so the allocated contribution of a regressor asymptotically approached zero if the true coefficient was zero. Thus, *pmvd* became

$$LMG(x_k) = \frac{1}{p!} \sum_{r\ permutation} p(r)\, seqR^2(x_k|r) , \tag{20}$$

where *p(r)* denotes the data-dependent weights,

$$p(r) = \frac{L(r)}{\sum_{r\ permutation} L(r)} , \tag{21}$$

such that if all regressors had nonzero coefficients, the permutation *r* received a weight proportional to

$$L(r) = \prod_{i=1}^{p-1} seq\,R^2\left\{(x_{r_i+1}, \ldots, x_{r_p}) | (x_{r1}, \ldots, x_{r_i})\right\} . \tag{22}$$

It is important to note that the relative importance metrics and recursive tree models measure two distinct types of contributions. The relative importance metrics show the contributions of regressors, averaged over all individuals in the data set, in determining variance of the dependent variable in any individual. The recursive tree model, however, is designed to find the regressor that most effectively segregates – or splits – the data set, even if that regressor does not have the greatest explanatory power. It is also important to note that, when a regressor is determined as a splitter at a given node in a recursive tree, that regressor is ordered first in the ANOVA, which may positively bias the explanatory value (R^2, equal to the branch-length on the tree) of that regressor.

Data within taxonomic groups were tested for homogeneity of variance with Bartlett's test and for normality with the Shapiro-Wilk's *W* test. Differences in distributions between taxonomic groups were tested with a two-sample Kolmogorov-Smirnov goodness-of-fit test. Differences in neuron-glia ratios, cellular densities, and dentate gyrus and cerebellar volumes between different taxonomic groups were calculated using Kruskal-Wallis sum rank and comparison tests with a repeated-measures design. When the population of the variable was normally distributed, repeated-measures ANOVA were used to determine within- and between-group differences in glia-neuron ratio. Statistical significance for all analyses was set at 0.05 (two-tailed). All analysis was performed in *R* with my own code and the package *SMATR* (Warton *et al* 2006).

CHAPTER 5
PRIMARY VISUAL CORTEX

To understand the possible anatomical and functional implications of how glia and neurons in the primary visual cortex vary across species, we have to understand how anatomy and function in the visual cortex vary across species. In this chapter, I will provide the background material necessary to understand the results presented below.

Anatomy

The mammalian visual cortex is composed of striate and extrastriate cortices (Fig. 9a,b). The striate cortex (the primary visual cortex, V1) is the largest component and homologous in all mammals. The number and locations of extrastriate cortices vary considerably among species, but most common in primates are areas V2, V3, V4, and the medial temporal cortex (MT). Visual areas are distinguished by cytoarchitecture (cortical thickness, cell body size, and cell density), myeloarchitecture (distribution and density of myelinated axons), histochemistry, and immunocytochemistry. A combination of these cellular countenances is usually needed to distinguish extrastriate areas in tissue sections, whereas V1 is histologically distinct (although species-specific features of V1 have been discovered through histochemical and immunocytochemical techniques, which are discussed below). Generally, a distinct area is identified by its exclusive reception of axonal projections. For example, the MT was identified in macaques by its direct reception of connections from V1 (Gattass & Gross 1981). Likewise, an area can be distinguished by its projections. In platyrrhines, the temporal ventral posterior area was identified by its projections to V1 (Krubitzer & Kaas 1993; Beck & Kaas 1998; Rosa & Tweedale 2001). Neurons in each area provide a discrete representation of the visual field to allow different features of the visual image to be analyzed, although this analysis generally depends on multiple interconnected areas (see Rosa 2002).

Visual areas can be further divided into modules, in which neurons differ in their patterns of connection, physiological character, and/or neurochemical composition. It is suggested that modules develop when a new afferent pathway to an existing visual area emerges in a species (Krubitzer 2009). The benefit of modularization, compared to adding or segregating new areas, is that it allows circuits of neurons that analyze different aspects of an image to communicate more efficiently. For example, communication among three circuits that analyze color, texture, and luminance is more efficient for overall shape analysis if the circuits (or modules) are topographical neighbors (i.e., separated by

micrometers compared to millimeters). This is especially important for understanding how V1 functions.

Visual areas can be divided into functional groups (Fig. 9c). The pathways connecting V1 and V2 to lateral and dorsomedial areas, and eventually the posterior parietal cortex, analyze motion and spatial relationships and are collectively called the dorsal stream. The pathways connecting V1 and V2 to ventrolateral areas, and eventually the inferior temporal cortex, analyze shape, color, and texture and are collectively called the ventral stream. The dorsal and ventral streams have been defined as functional devices that tell us where and what things are, respectively. Both streams are conserved in mammals (Casagrande & Kaas 1994; Fitzpatrick 1996; Binzegger *et al* 2004; Casagrande *et al* 2007).

The primary visual cortex is the primary distributor of almost all corticocortical visual information. It is also the first cortical area to receive information from the retina (Schmid *et al* 2010). Most of the projections from the retina are channeled through the LGN, but a minority are projected to subcortical structures, including a pathway through the superior colliculus to the pulvinar. All extrastriate areas (V2, V3, V3A, V4, MT, parieto-occipital (PO), and posterior intraparietal (PIP)) receive, directly or indirectly, the majority of their inputs from V1. Posterior extrastriate areas V2, V3, V3A, V4, and MT have direct reciprocal connections with V1 (Rosa 2002; Felleman & Larry 2009). Most connections between visual areas possess both feed-forward and feedback connections reflecting a high degree of interactive processing, although V1 also receives feedback projections from areas to which it does not directly project (e.g., the inferotemporal cortex (IT), frontal eye fields, and auditory cortex) (Salin & Bullier 1995; Barone *et al* 2000; Falchier *et al* 2002).

Connections among cells in V1 suggest that its six cortical layers are arranged as sequential visual processing stages that interact horizonally (Fig. 10a), although layers interact vertically, too, using networks of intrinsic axons (Fig. 10b).

The cortical layers of V1 can be further divided into sublayers with distinct afferent and efferent connections (a unique quality of V1). In humans, for example, layer IV is subdivided into layers IVa, innervated by the magnocellular (M) layer of the LGN, and IVb, innervated by the parvocellular (P) layer of the LGN (Preuss 2000; Rosa 2002). The innervations of these sublayers are not conserved in primates, as I explain below, but the distinctiveness of layer IV, characterized by a conspicuous myelinated band, is conserved in primates (Preuss *et al* 1999). The functional multiplicity of the primate V1 is further characterized by its modular complexity. The response properties of cells in layer IVCb differ depending on whether or not they are associated with color-selective cells (so-called

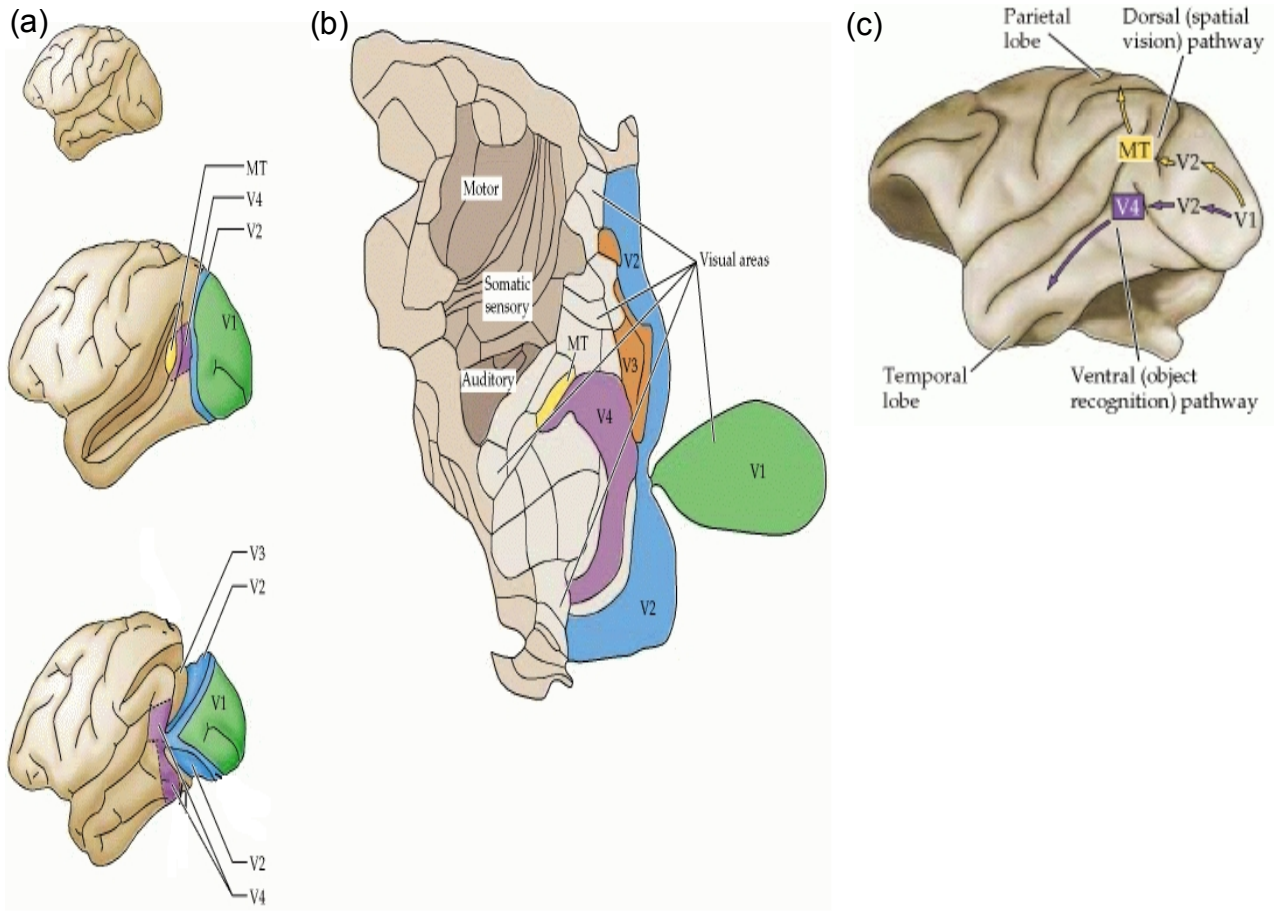

Figure 9. *Subdivisions of the extrastriate cortex in the macaque monkey. (a) Some of the more extensively studied extrastriate areas are specifically identified (V2, V3, V4, and MT, medial temporal cortex). (b) The arrangement of striate, extrastriate, and other neocortical areas in a flattened view. (c) A schematic of the broadly organized pathways of the visual areas: the ventral pathway leads to the temporal lobe and plays an important role in object recognition; the dorsal pathway leads to the parietal lobe and plays an important role in spatial vision. Adapted from Maunsell & Newsome, 1987; Felleman and Van Essen, 1991.)*

blobs), which receive inputs from the P layer of the LGN, or orientation-selective cells (interblobs) which receive inputs from both the P and M layers of the LGN (Wong-Riley 1993).

Since the visual cortex has been a site of repeated selection in mammalian evolution, it may be informative to consider V1 in an explicitly phylogenetic context.

Evolution

Only two visual areas (V1 and V2) have been identified in marsupials. Although some marsupial species (e.g., the woolly opossum and the quoll) have expanded their visual areas to occupy

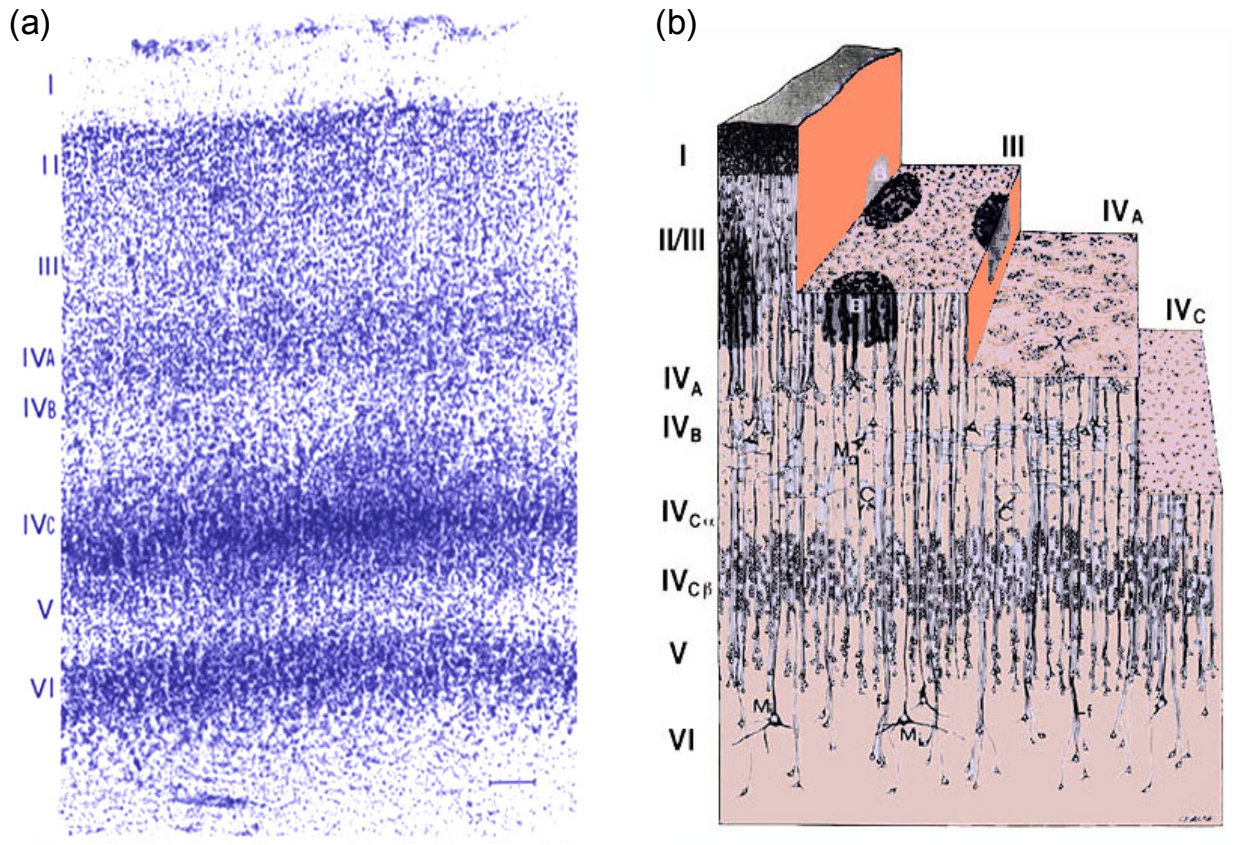

Fig 10: Nissl stain of the primary visual cortex clearly reveals the different layers (a). Layer IV is the principal cortical input layer; projections from the LGN terminate in this layer. Cells in layer IV then project neurons via vertical ascending axons to layers II and III, where extrinsic connections originate (i.e., projections to V2). Axons in layer III also project cells to layer V, the cells of which then project to layer VI. Layers V and VI constitute the main sources of extrinsic connections to subcortical nuclei (e.g. the LGN, superior colliculus, and claustrum). A schematic of the primary visual cortex shows neurons, networks of axons, columns and cytochrome oxidase blobs (b). Vertical interactions take place via networks of axons and form the dominant functional organization of the visual cortex: columns. Cortical columns are characterized by particular response properties shared by all the cells constituting that column. In many mammals, axons bring in information from the left and right eyes to non-overlapping ocular dominance stripes, the cells of which respond exclusively to stimulation from either the left or the right eye. These inputs are then communicated across other layers, forming ocular dominance columns that span all six cortical layers (Anderson et al, 1988; Erwin et al, 1995; Rosa, 2002). Images from http://webvision.med.utah.edu/authors.html

more than half their neocortices, these expansions were accomplished through enlargement of V1 and V2, not through the addition of new visual areas (Rosa 2002). This simple organization of the visual cortex is likely representative of the ancestral mammalian condition, from which nearly every mammalian lineage has evolved additional extrastriate areas (Kaas 2007; Felleman 2009). Comparative imaging research on the visual cortex, which has mostly involved carnivores (cats and ferrets) and primates (galagos and macaques), has identified several fundamental features of the mammalian visual

cortex (Payne 1993; Rosa 2002; Xu 2005; van Hooser 2007): each representation of the visual field maps onto a single cortical area; neurons characteristic of each cortical area respond to different features of visual stimuli (such as orientation, speed, colour); each cortical area forms unique functional connections with a set of other cortical areas and sub-cortical structures, which together contribute to the flow of information across the cortical surface; and the functions of cortical areas can be assessed behaviorally.

Mammals show considerable variation with respect to the wavelengths to which their receptors are maximally sensitive (Peichl 2005), types of sensory receptors present (Catania *et al* 1993; Krubitzer *et al* 1995), and in the size and number of visual cortical areas (Lyon 2006). While functional cell types (e.g., orientation-selective cells, such as simple and complex cells) are surprisingly conserved across mammals (Hubel & Weisel 1959, 1968; Girman *et al* 1999; Heimel *et al* 2005; Ibbotson *et al* 2005), the distributions and relative densities of functional cell types show a strong phylogenetic signal. In carnivores, two-thirds of visual cortical cells are directionally selective (i.e., they respond to stimulation in one direction compared to the opposite direction) (Gilbert 1977), whereas a minority of the cells in the primate visual cortex show direction selectivity (Orban *et al* 1986; Hawken *et al* 1988; O'Keefe *et al* 1998), and only one-fifth of the cells in the squirrel visual cortex show direction selectivity (Heimel *et al* 2005). Furthermore, direction-selective cells are present in all layers in the carnivore visual cortex, whereas they are only observed in layers IIIc, IVa, and VI in primates, and only in layer VI in squirrels. This may indicate that direction-selective cells are not homologous in mammals, but that the same receptive field property can be computed in different ways or at different lamina in different mammalian species (Van Hooser 2007).

The primary visual cortex is widely believed to be homologous across mammals: it receives major visual input from the LGN, possesses a highly granulated layer IV, and has a retinotopic space-map in all mammals (Rosa & Krubitzer 1999; van Hooser 2007). However, the underlying cortical mechanisms appear to be only analogous.

The mammalian dorsal LGN receives visual inputs from the retina and is reciprocally interconnected with the visual cortex. In lineages leading to carnivores, primates and tree shrews, and some marsupials, the LGN evolved a highly laminated structure (Sanderson 1974; Kaas *et al* 1978; Kahn & Krubitzer 2002b). Since different laminae in the LGN are assigned to receive visual inputs exclusively from the left or right eye, it has been suggested that lamination may have evolved in the LGN to prevent the convergence of visual information from both eyes at this level of the brain, as a

prelude to such interactions occurring in the cortex where they are essential for depth perception (Van Hooser 2007). There are three primary classes of retinal ganglion cells (i.e., retinal cells with different morphologies and different physiological response properties) that project to the LGN: parvocellular (P), magnocellular (M), and koniocellar (K) in haplorrhines; and X, Y, and W in all other mammals. It is unclear whether or not these cells can be considered homologous in haplorrhines and other mammals, but there are clear functional parallels. The P/X cells persistently respond to constant visual stimulation, whereas M/Y cells respond only transiently. Both cell types have center-surround receptive field organization (i.e., ganglion cells that transmit information about contrast) (Rodieck & Stone 1964; Cavanaugh *et al* 2002). K/W cells are a heterogeneous mix of several subtypes (Bullier *et al* 1984; Humphrey *et al* 1985; Martin *et al* 1997; Callaway 1998, 2005; Van Hooser 2007). Generally, P/X and M/Y cells project to cortical neurons in layer IV, but, specifically, P cells target the lowest tier of layer IV (IVCa) and M cells innervate the overlying sublamina (IVCb) (Humphrey *et al* 1985; Casagrande & Kaas 1994). The differences in cortical responses between P and M streams are much more pronounced than those between X and Y streams. Consequently, haplorrhines must use more than one strategy to resolve stimulus orientation (Ferster & Miller 2000; Sincich *et al* 2001), since their simple receptive fields are built by a core of linear components that are supplemented by nonlinear intracortical inputs (Rust *et al* 2005; Hirsch & Martinez 2006). In carnivores and tree shrews, however, individual cortical laminae receive highly overlapping inputs from X and Y cells (Leventhal 1979; Humphrey *et al* 1985; Casagrande & Norton 1991). All P/X and M/Y projections are restricted to V1 (although, there is some debate as to whether area 18, which is a recipient of Y cells in carnivores, is in V1 or V2). K/W cells make connections with superficial layers. Cytochrome oxidase (CO) is a protein complex that acts as the terminal enzyme of respiratory electron transport chains in mitochondria. It is used to identify interneurons functionally active in oxidative metabolism. In taxa with blobs of CO-rich color-sensitive cylinders in V1 (i.e., carnivores and haplorrhines), K/W cells target the blobs (Wong-Riley 1979; Horton & Hubel 1981). In taxa lacking blobs, projections of W cells to superficial layers are diffuse (Harting & Huerta 1983; Usrey *et al* 1992).

Most interspecific work on the visual cortex has been done on primates, and has revealed many structural and functional divergences from the ancestral condition. But before discussing primates, it is worth considering the tree shrew, which represents a sister taxa to primates. It is important to review the physiological and functional differences in V1 across taxonomic groups in order to interpret the results presented below and place them in the context of related discoveries.

The organization of V1 in primates and tree shrews is similar concerning topographic organization (Kaas *et al* 1972; Humphrey *et al* 1980a,b), callosal connections (Cusick *et al* 1985), intrinsic axon patches (Rockland & Lund 1982; Rockland *et al* 1982; Sesma *et al* 1984; Bosking *et al* 1997; Lyon *et al* 1998), and labeling for Cat-301 antigen, a monoclonal antibody that recognizes a surface-associated antigen on neurons (Jain *et al* 1994). Differences, however, abound, suggesting that the earliest primates underwent considerable changes in V1. Different from primates, the tree shrew V1 possesses a cleft in its granular layer, lacks blobs, and its modularity is organized according to ON/OFF domains (Humphrey *et al* 1980a, Lund *et al* 1985; Norton *et al* 1985; Kretz *et al* 1986; Wong-Riley & Norton 1988). Further differences are noted in the organization of and projections to the LGN, superior colliculus, and pulvinar (Lane *et al* 1971; Casagrande *et al* 1972; Sherman *et al* 1975; Norton *et al* 1977; Graham & Casagrande 1980; Casagrande & Norton 1991; Lyon *et al* 2003; Stepniewska 2003), as well as in the comparative paucity of extrastriate areas in the tree shrew (Lyon *et al* 1998; Rosa 1999; Preuss 2007). This does not mean that the tree shrew V1 is primitive; in fact, there is evidence that the tree shrew V1 has evolved an extraordinary overall functional capacity compared to primates (Poirazi & Mel 2000; Elston *et al* 2005).

Strepsirrhines represent an intermediary of visual cortical organization between ancestral primate features and haplorrhine features (Rosa *et al* 1997). The eyes of (nocturnal) strepsirrhines are said to retain hallmarks of the ancestral state, which anthropoids have lost. They lack a retinal fovea and have a tapetum lucidum (Preuss 2007). In addition to rods, strepsirrhines (and tarsiers) have both short-wavelength and medium-large-wavelength cones (Jacobs 1993; Hendrickson *et al* 2000), and greatest visual acuity in the central part of their visual field (Wikler & Rakic 1990). However, there are many features of strepsirrhine V1 organization that are conserved in anthropoids: the pattern of termination of geniculocortical P and M afferents relative to the cortical layers (Diamond *et al* 1985; Florence & Casagrande 1987; Kaas *et al* 1978; Lachica & Casagrande 1992; Kaas & Preuss 1993; Lachica *et al* 1993), the architectonic distribution of CO and calcium-binding proteins (Condo & Casagrande 1990; Johnson & Casagrande 1995), massive dorsolateral prefrontal cortical projections to the superior colliculus (Preuss 2006), neuronal response properties (DeBruyn *et al* 1993), and the pattern of projections to extrastriate cortex (Krubitzer & Kaas 1990, 1993). Therefore, these features of V1 organization were likely established early in primate evolution.

The organization of the visual cortex is largely conserved in haplorrhines. Similarities in the cortical mantle, retinotopic organization, stratification of layer IV into multiple sublayers, the shape of

V1, patterns of trans-cortical connections, the branching structure of pyramidal cells, and the presence of CO-rich and -poor compartments in V1 correspond strongly in the squirrel monkey, marmoset, owl monkey, and macaque (Allman *et al* 1979; Colby *et al* 1988; Gattass *et al* 1985; Weller & Kaas 1987; Allman & Mcguiness 1988; Krubitzer & Kaas 1990; Preuss & Goldman-Rakic 1991; Weller *et al* 1991;Rosa 2002; Elston & Garey 2004). A further derived feature of the haplorrhine visual cortex is the enlargement of Meynert cells in V1 (Le Gros Clark 1942; Zilles 1990; Kaas 2000). Meynert cells constitute a morphologically distinct neuronal subtype, which appear in small clusters between layers V and VI and are implicated in the detection of motion in the visual field (Meynert, 1867; Chan-Palay *et al* 1974; Palay 1977; Fries *et al* 1985; Movshon & Newsome 1996; Livingstone 1998; Hof *et al* 2000). The enlargement of Meynert cells is thought to represent the evolution of a cellular substrate for specialized sensorimotor capacities, related to the integration of somatosensory and visual signals that allowed fine motor control of the digits and control of eye convergence movements, which are functions that are poorly developed in carnivores (Sherwood *et al* 2003).

Of course, extensive similarities do not preclude interspecific differences. Most famously, catarrhines are distinctly characterized by routine trichromatic color vision (see Jacobs & Kaas 2007; Ross & Martin 2007; Solomon & Lennie 2007). But since this is mostly the prerogative of V4, not V1, I will not discuss it (but see Hurlbert (2003) for a potential role for V1 in color vision). Workers have documented phyletic variation in laminar, compartmental, and connectional organization of V1 among haplorrhines (e.g., Hassler 1967; Casagrande & Kaas 1994; Preuss 1995) and flagged neuronal morphologies and neurochemical phenotypes that distinguish hominoids from other primates (e.g., del Rio & DeFelipe 1997; Nimchinsky *et al* 1999; Hof *et al* 2000; Sherwood *et al* 2007; de Sousa *et al* 2009). Layer IVa of Old and New World monkeys (Fig. 11), for example, receive a direct geniculate projection arising from the P layers of the LGN (Lund 1973; Kaas *et al* 1976; Horton 1984; Chaudhuri *et al* 1995; Hof & Morrison 1995; Preuss *et al* 1999), whereas the reduction or loss of a P-geniculate projection to layer IVa is indicated in hominoids (Horton & Hedley-Whyte 1984; Hendry & carder 1993; Wong-Riley *et al* 1993; Clarke 1994; Yoshioka & Hendry 1995; Preuss *et al* 1999). Indeed, the human layer IVa further appears to be strongly related to the M pathway (Preuss *et al* 1999; Preuss *et al* 2002). Layer IVa in macaques is distinguished by a dense band of CO-staining that coincides with a terminal layer of P cells, reflecting a high level of metabolic activity in that sublayer (Sherwood & Hof 2007). The CO-rich band is actually a sheet of geniculate-recipient tissue punctuated by regular gaps, reflecting a high activity level of geniculostriate afferents and creating a so-called honeycomb

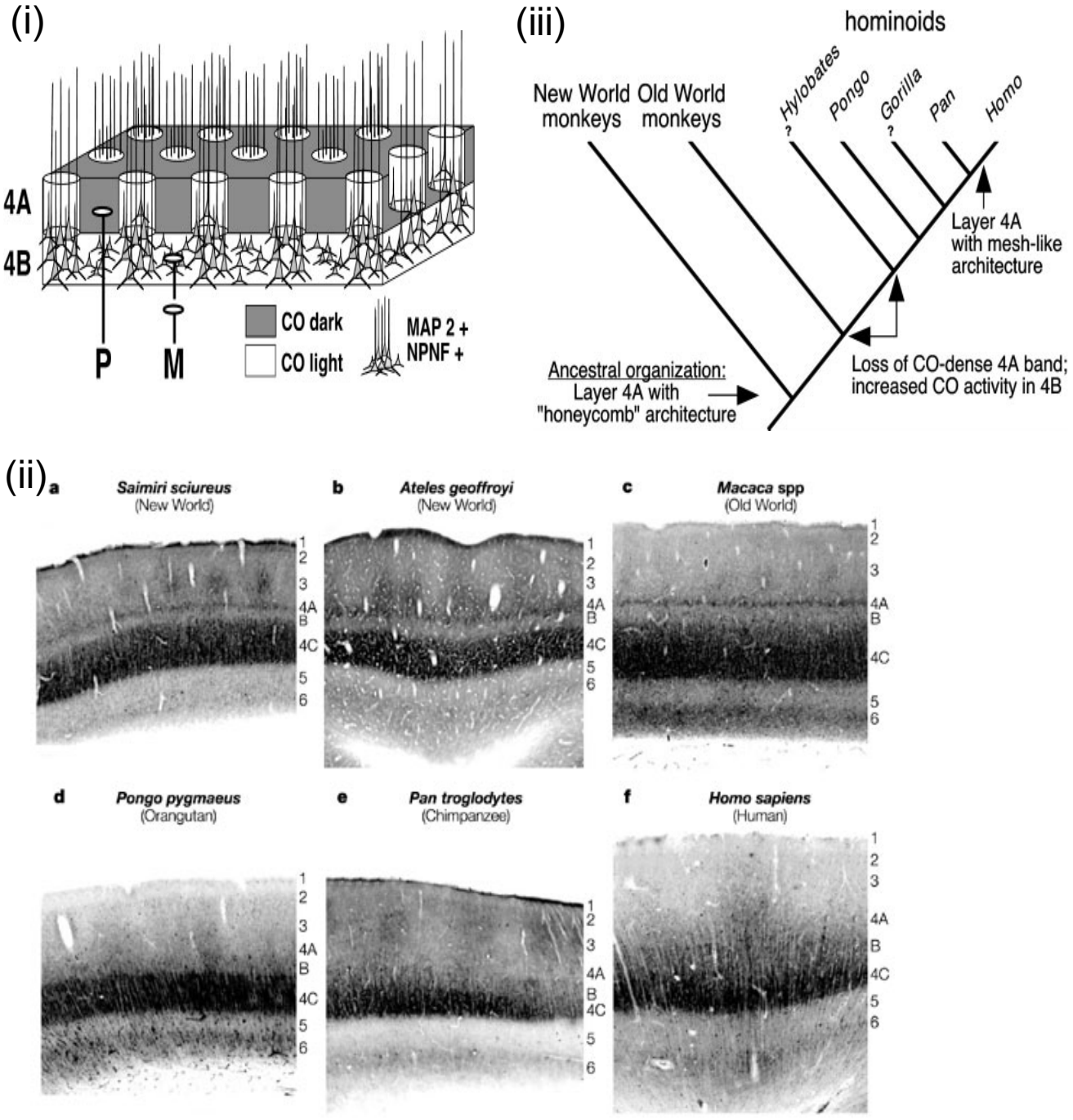

Fig. 11: (i) Schematic of the "honeycomb" model of layer 4A organization. Layer 4A in both Old and New World monkeys consits of a sheet of tissue that receives direct P-geniculate inputs that stain darkly for cytochrome oxidase (CO). The sheet is punctuated by clusters of apical dendrites and pyramidal cell somas extending upward from layer 4B, which receives indirect M-geniculate inputs and stain densely for MAP2 and NPNF. (ii) CO staining of area V1 in (a) Saimiri, (b) Ateles, (c) Macaca, (d) Pongo, (e) Pan, and (f) humans. A CO-dense band is observed in layer IVa in the monkeys (a-c), but is conspicuously absent in the hominoids (d-f). (iii) An interpretation of the cytochemical changes that took place to V1 during the evolutionary radiation of hominoids. From Preuss et al (1999).

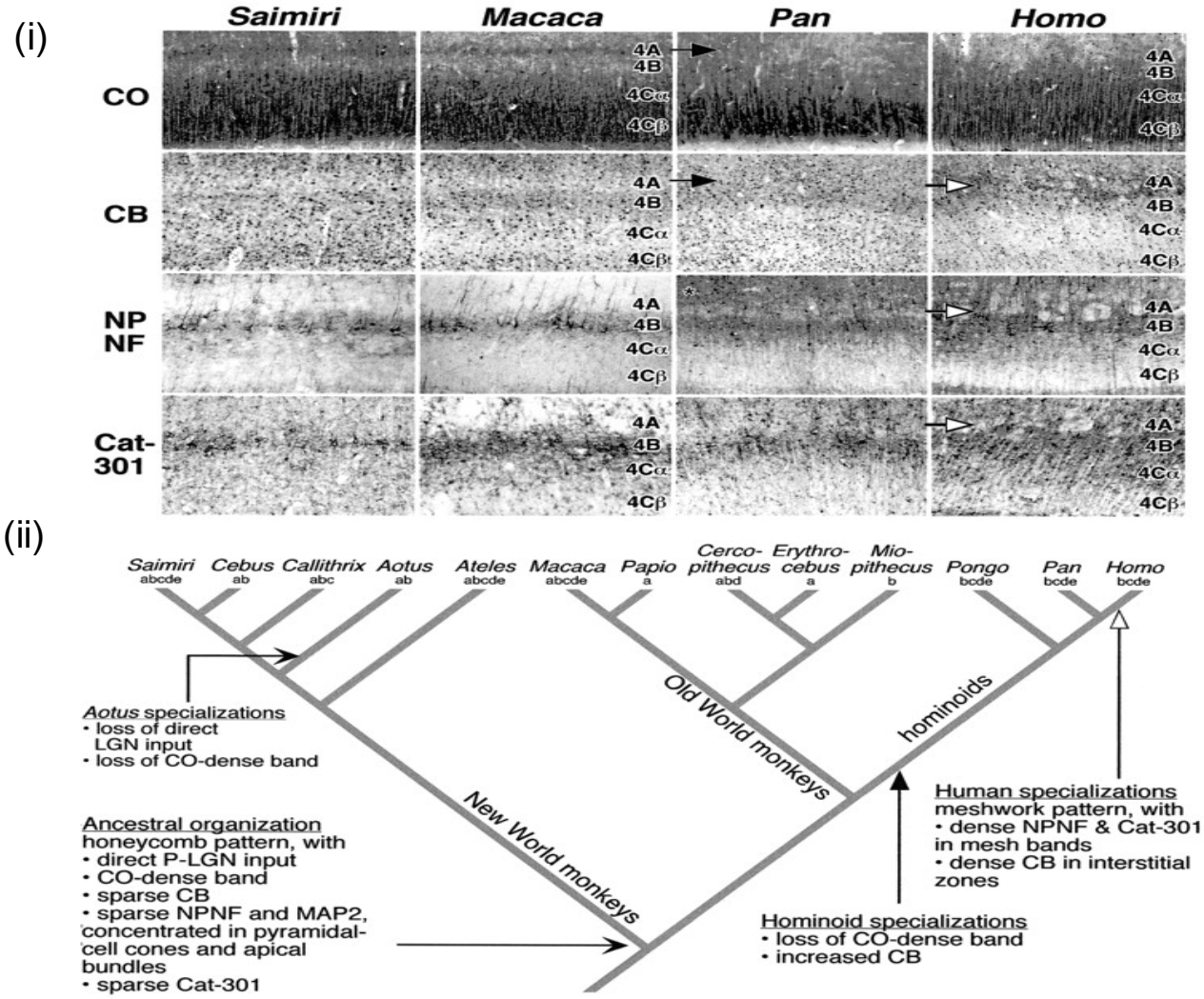

Fig. 12: A reconstruction of layer 4A evolution in anthropoid primates. (i) The condition of layer 4A and adjacent layers in sections stained for different histochemical markers in a New World monkey (Saimiri), an Old World monkey (Macaca), and two hominoids (Pan and Homo). (ii) The phylogenetic diagram the genetic relationships among anthropoid primates. The letter code beneath each genus name represents the kinds of data published for that genus: (a) the presence or absence of direct projections from LGN to 4A; (b) the presence or absence of a CO-dense band; (c) level of expression of calbindin in 4A; (d) pattern of expression of NPNF; and (e) the pattern of expression of Cat-301. Data are available for 13 anthropoid genera. A reconstruction from these data indicates that the last common ancestor of living anthropoid primates had a honeycomb-like layer 4A organization, similar to that present in most Old and New World monkeys (see Fig. 12). The ancestral condition was likely characterized by direct LGN inputs, a CO-dense band, low expression of calbindin, limited expression of NPNF, and low expression of the Cat-301 antigen. This condition, given the data so far available, was modified at least twice:after the divergence of the hominoid lineage from the catarrhines, and after the divergence of the Pan and Homo lineages. The first modification saw a loss of the CO-dense band and an increased expression of calbindin and NPNF. The reduction of CO in the evolution of the nocturnal owl monkey (Aotus trivirgatus), which was accompanied by a reduction of LGN afferents, may indicate that the CO reduction in hominoid evolution occurred in conjunction with the reduction of direct LGN afferents. The second modification was associated with an apomorphic a mesh-like pattern of NPNF and Cat-301 expression, as well as the dense expression of calbindin in the interstitial tissue zones. After Preuss & Coleman (2002).

appearance (Henrickson *et al* 1978; Horton 1984; Fitzpatrick *et al* 1985; Hevner & Wong-Riley 1990). Histochemical staining with microtubule-associated protein 2 (MAP2) and non-phosphorylated neurofilament (NPNF) antibodies has shown that pyramidal cell bodies and apical dendrites extend upward from layer IVb into IVa, effectively filling in the gaps of the honeycomb (Peters & Sethares 1991; Hendry & Bhandari 1992; Hof & Morrison 1995; Yoshioka & Hendry 1995; Chaudhuri *et al* 1996; Hof *et al* 1996; Preuss *et al* 1999). This is interpreted to mean that the macaque layer IVa receives both P cells (via the honeycomb wall) and M cells (via the gaps). Studies with thalamocortical connectivity (Wiesel *et al* 1974; Hendrickson *et al* 1978; DeBruyn & Casagrande 1981; Diamond *et al* 1985; Florence *et al* 1986; Spatz 1989), CO-staining (Carroll & Wong-Riley 1984; Horton & Hedley-Whyte 1984; Hess & Edwards 1987; Spatz *et al* 1994; Chaudhuri *et al* 1995; Preuss *et al* 1999), and NPNF immunohistochemistry (Hof & Morrison 1995; Chaudhuri *et al* 1996; Hof *et al* 1996; Preuss *et al* 1999) indicate that a honeycomb architecture is present in all Old and New World monkeys (except the nocturnal owl monkey). The dense CO band is conspicuously absent in hominoids. This may, as in the owl monkey, indicate a reduction or loss of P-geniculate projections to layer IVa (Horton & Hedley-Whyte 1984; Wong-Riley *et al* 1993; Preuss *et al* 1993). Alternatively, it may mean that P-geniculate projections are more dispersed in hominoids than in monkeys, however, evidence, including that presented below, does not support this (Tigges & Tigges 1979; Miklossy 1992). Greater functional or behavioral differences that might correlate with the reduction of P-geniculate afferents to the hominoid V1 are elusive.

Layer IVa in humans can be further distinguished from hominoids and monkeys (Fig. 12). Staining with Cat-301 antigen and NPNF reveals a meshwork of neuropil bands in the human layer IVa, which is not observed in any other primates (Preuss & Coleman 2002). Increased staining for Cat-301 and NPNF in humans compared with non-human haplorrhines suggests that the neural apparatus of human layer IVa became more strongly related to the M pathway, which finds functional support in comparisons between humans and macaques. For example, humans process global features of a compound stimulus faster than local features, whereas macaques show a local advantage (Fagot & Deruelle 1997); humans show greater temporal and spatial luminance contrast sensitivity than macaques at photopic luminances (De Valois *et al* 1974; Merigan 1980; Harwerth & Smith 1985); and attention-related modulation of activity in V1 has been observed to be greater in humans than macaques (Heeger 1999). These differences are not concrete and are reportedly confounded by the preference of workers for fMRI in humans compared to microelectrode recordings in macaques (Preuss & Coleman

2002). If accurate, however, they are consistent with an increase in M-related projections to the human V1. It may also be relevant that M-pathway pathology and dysfunction are common features of dyslexia (Livingstone *et al* 1991; Stein & Walsh 1997; Demb *et al* 1998; Vidyasagar 1999; Stein 2001).

The sizes of the human V1 and LGN are smaller than predicted for a primate of our brain size (Frahm *et al* 1984; Holloway 1996, 1997). It is unlikely that the human V1 was reduced during evolution, but rather that it did not keep pace with the expansion of the neocortex following divergence from the great apes. Furthermore, there is no evidence for relaxed visual acuity in humans compared to other primates (De Valois *et al* 1974).

ANALYSIS I

Aim

The aim of this analysis was to determine how glia and neurons scale in the primary visual cortex across taxa, while accounting for phylogeny, brain and body mass, EQ, and gestation length. Furthermore, I aimed to determine what, if any, influence mode of placentation, defined by the degree of invasion of trophoblast cells into the uterus, had on the above relationships.

Materials

Samples of the left hemisphere of non-pathological postmortem brains representing 73 mammalian species were used. All samples were from adult brains, except for *Trachypithecus francoisi* and *Pithecia pithecia*, which were from juveniles with brain sizes comparable to species-typical adult averages. Specimens from all collections were immersion-fixed with either 10% formalin or 4% paraformaldehyde, embedded in paraffin, serially sectioned, and stained with Nissl in the context of this research or unrelated experiments. The original research reported herein was performed under guidelines established by the Animals Scientific Procedures Act (ASPA).

Demarcation

The mammalian V1 is a readily identifiable architectonic area (Inouye 1909; Holmes 1917; Talbot and Marshall 1941; Daniel and Whitteridge 1961; Schwartz 1977, 1994; Tootell *et al*. 1988), which was identified on the basis of its topological location and distinct appearance in materials stained for Nissl (Allman & McGuinness 1988; Hof & Morrison 1995; DeFelipe *et al* 1999; Rosa & Krubitzer 1999; Rosa *et al* 2005). A thin band of heavily myelinated tissue in cortical layer IVCa (the so-called stria of Gennari in humans) provided a landmark for identifying the area and its boundaries (Boyd & Matsubara 2005). The delineation of V1 in cetaceans was achieved through the MRI studies of Marino *et al*, (2003 2004) and personal assistance from Patrick Hof. The region of V1 used was restricted to layers II-VI of the opercular portion of the calcarine cortex towards the occipital pole (Fig. 13).

Cell counting

Cell-counting was performed using *StereoInvestigator* software on the equipment outlined previously (see Chapter 4 for detailed methodology). For each individual, a random starting section was selected in V1. Serial sections spaced at 300-400μm were selected for analysis for each cell type.

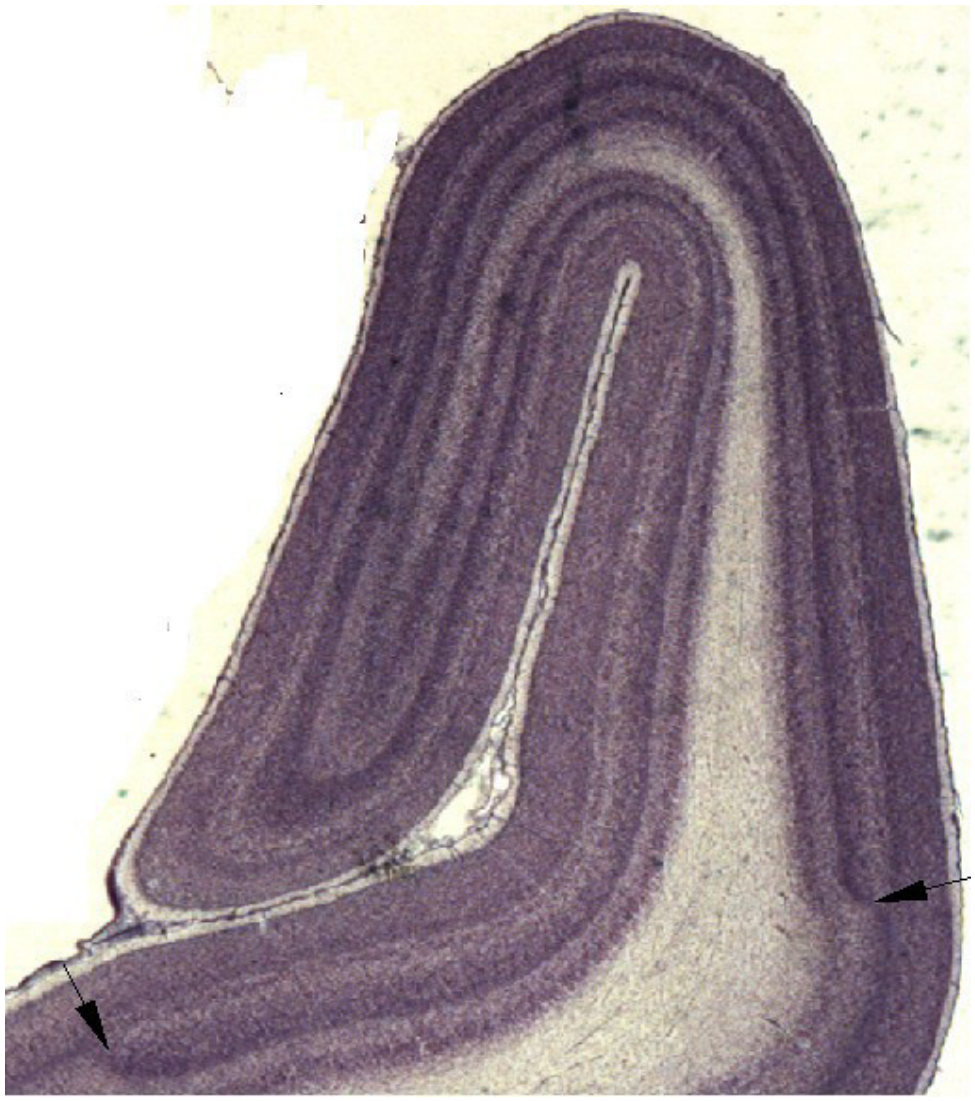

Fig. 13: The boundaries of V1 are demarcated by the termination (arrows) of the pronounced band of granule cells in layer IV. Photo of Callicebus moloch.

Boundaries of layers II-VI were outlined using a 10x objective, and a virtual 30 x 30µm lattice of counting frames was randomly positioned on each slide to cover the sampled area with approximately 30 frames per section. Counting was performed under Koehler illumination using a 63x (NA 1.4, dry) or 100x (NA 1.25, oil) objective – a 40x (NA 0.65, dry) was used with the cetacean species, one human individual, and one chimpanzee individual, as the slides were too thick for larger objectives. Section thickness ranged from 25µm – 100µm, so the disector thicknesses used also varied. A minimum 4µm guard zone, defined as the space between the boundary of the tissue section and the part of the section used for counting, was set on either side of each section. Pilot tests were performed for each individual to determine the optimal size of the counting frame (approximately 2 particles per counting frame). Section thickness was measured at the first and final counting site for each section using the microcator. The coefficient of error (CE) was held below 0.8 ± 0.1 for all analyses. Cellular density was calculated as the sum of neurons counted with the disectors, divided by the product of the sum of the disectors examined and the volume of the disector (Howard & Reed

1998).

Neurons were distinguished from non-neuronal cells by the presence of dark, coarsely stained Nissl substance in the cytoplasm, a large nucleus, a distinct nucleolus, ovoid shape, and lightly stained proximal segments of dendritic processes. Excitatory and inhibitory neurons were not differentiated. Glia were expected to lack a conspicuous nucleolus and contain less endoplasmic reticulum than neurons (Fig. 14). Astrocytes and oligodendrocytes were not differentiated and are classified simply as glia. Neither endothelial cells nor microglia were counted. The nucleolus of neurons and the body of glia were used for counting criteria.

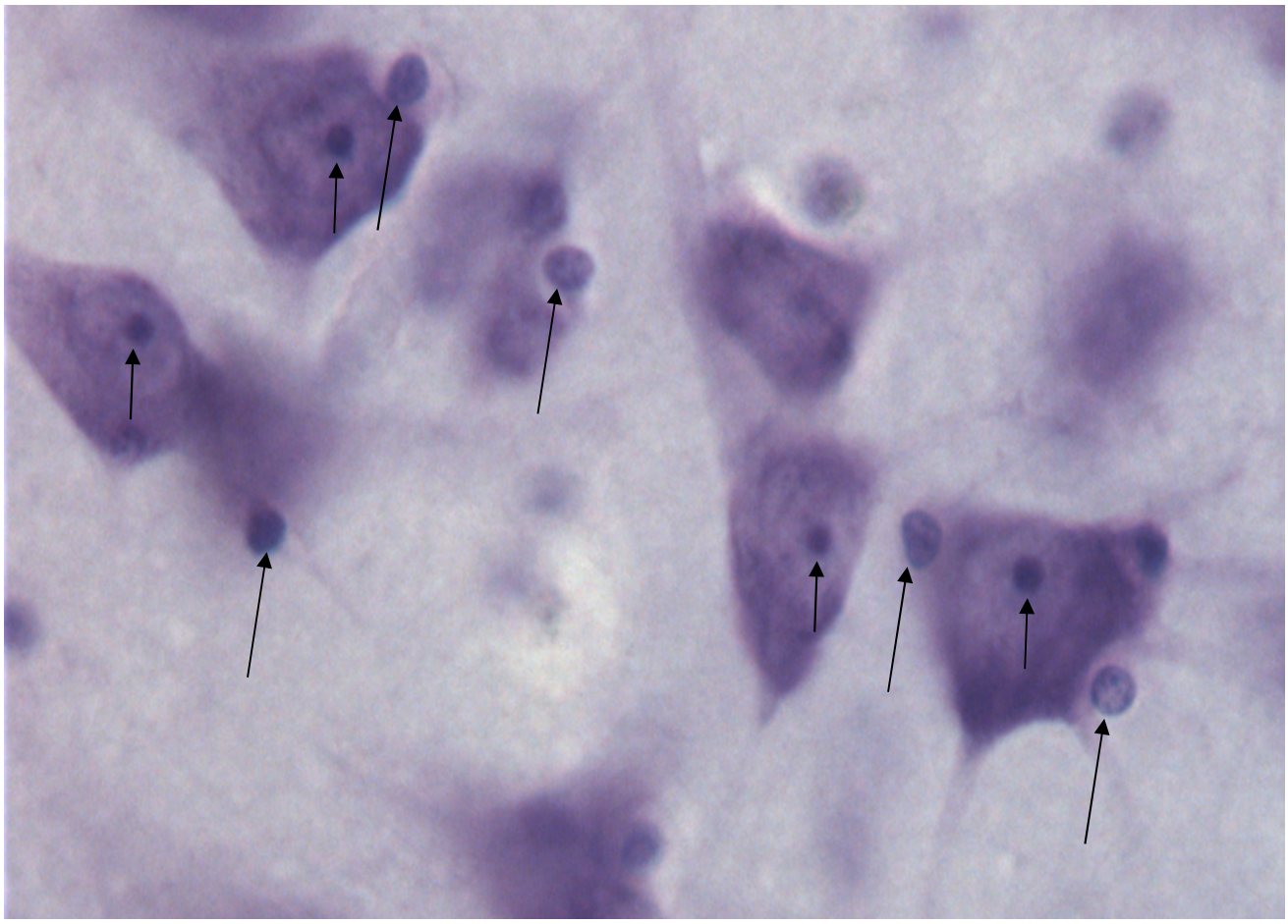

Fig. 14: Neurons (arrowheads) were identified by dark Nissl substance in the cytoplasm, lightly stained proximal segments of dendritic processes, and a prominent nucleolus, which was used as its characteristic point for counting. Glia (arrows) were identified by the absence of a conspicuous nucleolus and less endoplasmic reticulum than neurons. Astrocytes and oligodendrocytes were not differentiated.

RESULTS I

I first compared cellular densities among carnivores, primates, and all species (AS). The primate data were then divided into taxonomic subgroups to test whether cellular scaling relationships were conserved in primates. These subgroups were also used to determine if (1) humans and other apes deviated from predictions made on Old and New World monkeys and (2) tarsiers were better affiliated with *Strepsirrhini* or *Anthropoidea* in the context of glia and neuron scaling in V1. Finally, I compared cellular densities among placental groups to test whether mode of placentation, compared to behavior or phylogeny, had an influence on cellular densities in the primary visual cortex (V1).

Hypothesis and predictions

Comparative studies of the primary visual cortex have shown it to be a site of repeated selection both in mammalian and primate evolution. Differences in the cellular composition of V1 have been identified between primates and other mammals, strepsirrhines and haplorrhines, cercopithecoids and hominoids, and even between humans and other apes. These adaptations suggest that the constraints on the cellular organization of V1 are relaxed, and thus it is likely that the relationship of glia to neurons will not be uniform across mammalian or even primate taxa. Evidence that the human neocortex has been a site of repeated genetic selection, implicating a significant up-regulation in cortical metabolism in human evolution, suggests that the human V1 may carry a cellular signature of those molecular changes, differentiating its glia-neuron ratio from primate or even hominoid expectations.

Cellular scaling patterns among taxonomic groups

RMA exponents for species mean data and independent contrasts are presented in Table 3; and stereological results are presented in the appendix (Tables A1a-d). The All species (AS) group consists of 31 species, spanning 13 orders, and is considered representative of Eutheria: 14 species sampled that are neither primates nor carnivores, as well as a systematic random sampling of primate and carnivore species. For non-parametric tests the AS group was stripped of its primate and carnivore species, in order to avoid statistical non-independence when comparing the carnivores and primates with other species (Fig. 15). The stripped-down group is referred to as Shrew-to-Whale (SW).

Glial cell density was found to scale against neuronal density with a significant positive exponent for carnivores and AS, as revealed by analysis of both species mean data and independent contrasts. For carnivores, the 95% CI of the species mean data included isometry. In primates, glial cell

density scaled against neuronal density with a significant positive exponent only for independent contrasts, suggesting that the species mean data were obscuring grade shifts among major taxonomic groups within the primate data set (Garland *et al* 1993). Applying weighted least-squares for heteroscedasticity in neuronal density ($K^2 = 7.054$, p = 0.029), line-fitting through the origin of LS regression slopes for glial cell density on neuronal density for independent contrasts revealed statistically different slopes for carnivores (LS slope = 0.789, lower CI = 0.658, upper CI = 0.920, $R^2 = 0.365$, p = 0.037) and primates (LS slope = 0.536, lower CI = 0.420, upper CI = 0.652, $R^2 = 0.288$, p = 0.049), and a significant allometric slope for AS (LS slope = 0.541, lower CI = 0.390, upper CI = 0.692, $R^2 = 0.720$, p = 0.000). The RMA plots of glial cell density against neuronal density displayed significantly different *y*-intercepts for carnivores (*y*-intercept = -0.343, lower CI = -0.678, upper CI = -0.008; p = 0.049) and AS (*y*-intercept = 1.05, lower CI = 0.754, upper CI = 1.346; p = 0.000).

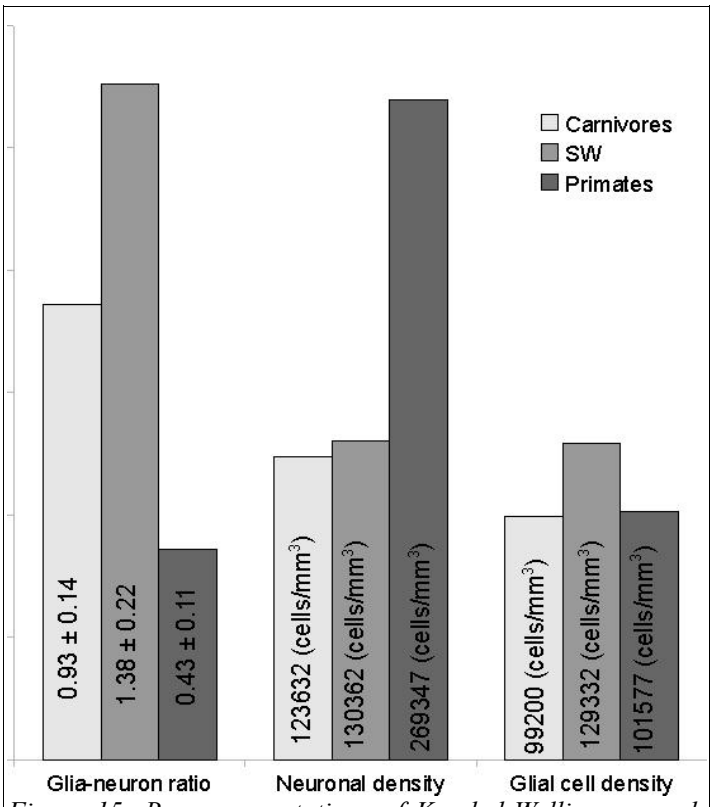

Figure 15: Bar representations of Kruskal-Wallis sum rank and multiple comparison tests showing significant differences among carnivores, SW, and primates for glia-neuron ratio (c2=28.71, p=0.000) and between SW and both carnivores and primates for neuronal density (c2=27.36, p=0.000). No significant differences are shown for glial cell density (c2=1.24, p=0.541). Two-sample Kolmogorov-Smirnov tests for normality of distribution (bootstrap=10000) showed significant differences between carnivores and primates for glia-neuron ratio (D=0.688, p=0.000) and neuronal density (D=0.675, p=0.000), and between SW and primates for glia-neuron ratio (D=0.765, p=0.000) and neuronal density (D=0.659, p=0.001). Raw values for glia-neuron ratio and neuronal and glial cell density are displayed within the bars. Bar representations are not shown to scale.

Cellular scaling patterns within Primates

Since the RMA exponent for glial cell density on neuronal density for *Haplorrhini* was only significant for independent contrasts, the extreme studentized deviate method and Cook's distance (set at 50%) were used to identify orangutans (*Z*=3.34) and gorillas (*Z*=3.20) as significant outliers. Thus, the ape lineage (*Hominoidea*) was removed from the *Haplorrhini* data set, as its constituents imposed too great an influence on the regression. Statistically different scaling exponents for glial cell density on neuronal density were then generated for

Table 3: Slope estimates and correlation coefficients for scaling relationships between cell densities in V1 and anatomical variables

Taxa	Dependent variable	Independent variable	*Species mean data*					*Independent contrasts*				
			RMA	R^2	Lower 95% CI	Upper 95% CI	p	RMA	R^2	Lower 95% CI	Upper 95% CI	p
AS (n=39)	Glia cell density	neuronal density	0.733	0.099	0.578	0.928	0.035	1.035	0.140	0.880	1.231	0.000
	Glia-neuron ratio	brain mass (g)	0.386	0.575	0.305	0.489	0.014	0.375	0.603	0.297	0.529	0.001
		body mass (kg)	0.311	0.726	0.249	0.387	0.000	0.319	0.691	0.239	0.440	0.003
		gestation length (d)	0.347	0.743	0.288	0.417	0.791	0.485	0.398			0.008
		EQ	-0.232	0.871	-0.191	-0.282	0.010	-0.452	0.444	-0.362	-0.588	0.633
Carnivores (n=21)	Glia cell density	neuronal density	1.051	0.003	0.691	1.599	0.049	1.221	0.102	0.928	1.392	0.028
	Glia-neuron ratio	brain mass (g)	0.419	0.583	0.284	0.619	0.009	0.568	0.321	0.449	0.802	0.013
		body mass (kg)	0.308	0.741	0.205	0.462	0.022	0.382	0.604	0.267	0.527	0.026
		gestation length (d)	0.999	0.000	0.679	1.472	0.008	1.702	0.281	1.395	2.178	0.087
		EQ	1.425	0.117	0.900	2.255	0.113	-1.385	0.099	-1.108	-1.800	0.531
Primates (n=37)	Glia cell density	neuronal density	1.073	0.005	0.759	1.518	0.101	1.256	0.082	1.118	1.494	0.000
	Glia-neuron ratio	brain mass (g)	0.333	0.660	0.236	0.469	0.113	0.525	0.333	0.415	0.741	0.208
		body mass (kg)	0.274	0.766	0.196	0.384	0.025	0.377	0.568	0.298	0.531	0.318
		gestation length (d)	1.635	0.210	1.145	2.334	0.42	2.006	0.367	1.505	2.769	0.435
		EQ	-0.981	0.000	-0.688	-1.399	0.150	0.858	0.024	0.686	1.116	0.606
		axial diameter (mm)	2.167	0.421	1.474	3.184	0.814	-2.138	0.412	-1.604	-2.951	0.763
		corneal diameter (mm)	2.380	0.493	1.623	3.489	0.620	-2.263	0.470	0.398	0.621	0.109
		V1 volume (cm^3)	0.417	0.502	0.274	0.637	0.330	0.457	0.443	0.388	0.544	0.526
		neocortex volume (cm^3)	0.426	0.554	0.291	0.624	0.010	0.499	0.380	0.424	0.594	0.392
		LGN volume (cm^3)	0.506	0.359	0.329	0.780	0.320	0.464	0.440	0.380	0.594	0.406

Strepsirrhini (RMA = 0.715, lower CI = 0.477, upper CI = 0.998, $R^2 = 0.335$, p = 0.011) and Old and New World monkeys (RMA = 1.544, lower CI = 1.22, upper CI = 1.97, $R^2 = 0.219$, p = 0.028) for species mean data, which also held for independent contrasts.

The species mean data and independent contrasts for Old and New World monkeys were used to generate log-log LS regression predictions of glial cell density on neuronal density, and glia-neuron ratio on brain mass. The values for apes for glia-neuron ratio as a function of brain mass, but not for glial cell density as a function of neuronal density (Table 4), fell within the 95% prediction intervals (PI) of the LS regression for independent contrasts (Fig. 16).

When the species mean data and independent contrasts from the non-human apes were used to generate log-log LS regression predictions of glial cell density on neuronal density, and glia-neuron ratio on brain mass, body mass, and gestation length, the observed human values for glial cell density against neuronal density were significantly greater than expected (paired-samples t-test: t=9.02, p=0.009) and the observed human values for glia-neuron ratio on brain mass were significantly less than expected (paired-samples t-test: t=10.07, p=0.012) for independent contrasts (Table 5). The observed values for glia-neuron ratio on body mass and gestation length fell within the 95% PI of the LS regression for non-human ape species mean data and independent contrasts.

Similarly, log-log regression predictions were generated for *Tarsius bancanus* and *Tarsius syrichta* from data based on Old and New World monkeys and *Strepsirrhini*. For both tarsier species, the observed glial cell density values fell within the 95% PI of the predicted values based on neuronal density scaling in Old and New World monkeys; but the observed glia-neuron ratio values fell within the 95% PI based on brain mass in *Strepsirrhini* (Fig. 16).

Table 4: Deviations of predicted from observed values for cell densities in V1 for apes based on OLS regressions generated from plots of Old and New World monkeys (p<0.05)

	Glial cell density on neuronal density					
			Species mean data		*Independent contrasts*	
Species	Observed value	Predicted value	% deviation	Within 95% PI	%deviation	Within 95% PI
Homo sapiens	169824	83884	51	no	42	no
Pan troglodytes	144544	79432	45	no	29	no
Pan paniscus	138038	79238	43	no	30	no
Gorilla gorilla	123027	63942	48	no	40	no
Pongo pygmaeus	134896	66024	51	no	43	no
Hylobates muelleri	93325	82593	12	yes	5	yes
Symphalangus syndactylus	101103	89839	11	yes	4	yes
Macaca fascicularis	100201	90002	10	yes	1	yes

Table 5: Deviations of predicted from observed values for cell densities in V1 for humans based on LS regressions of non-human apes ($p<0.05$)

				Species mean data		Independent contrasts	
Dependent variable	Independent variable	Observed value	Predicted value	% deviation	Within 95% CI	% deviation	Within 95% CI
Glia-neuron ratio	Brain mass	0.72	1.16	-60	no	-57	no
	Body mass		0.74	-3	yes	2	yes
	Gestation		0.67	8	yes	10	yes

Cellular scaling patterns among placental groups

Significantly different RMA exponents for glial cell density against neuronal density were found between the epitheliochorial (slope = -0.229, lower CI = -0.646, upper CI = 0.188, R^2=0.859, p = 0.000) and both the endotheliochorial (slope = 1.216, lower CI = 0.973, upper CI = 1.459, R^2 = 0.046, p=0.043), and haemochorial (slope = 1.240, lower CI = 1.004, upper CI = 1.476, R^2 = 0.056, p = 0.003) independent contrasts (Table A2). ANOVA revealed a significant main effect of placental group on glia-neuron ratio ($F_{2,80}$ = 14.25, p = 0.000). Bonferroni *post hoc* comparisons of mean glia-neuron ratio showed that the epitheliochorial (1.10 ± 0.35) and haemochorial (0.51 ± 0.21) groups differed significantly ($p < 0.05$).

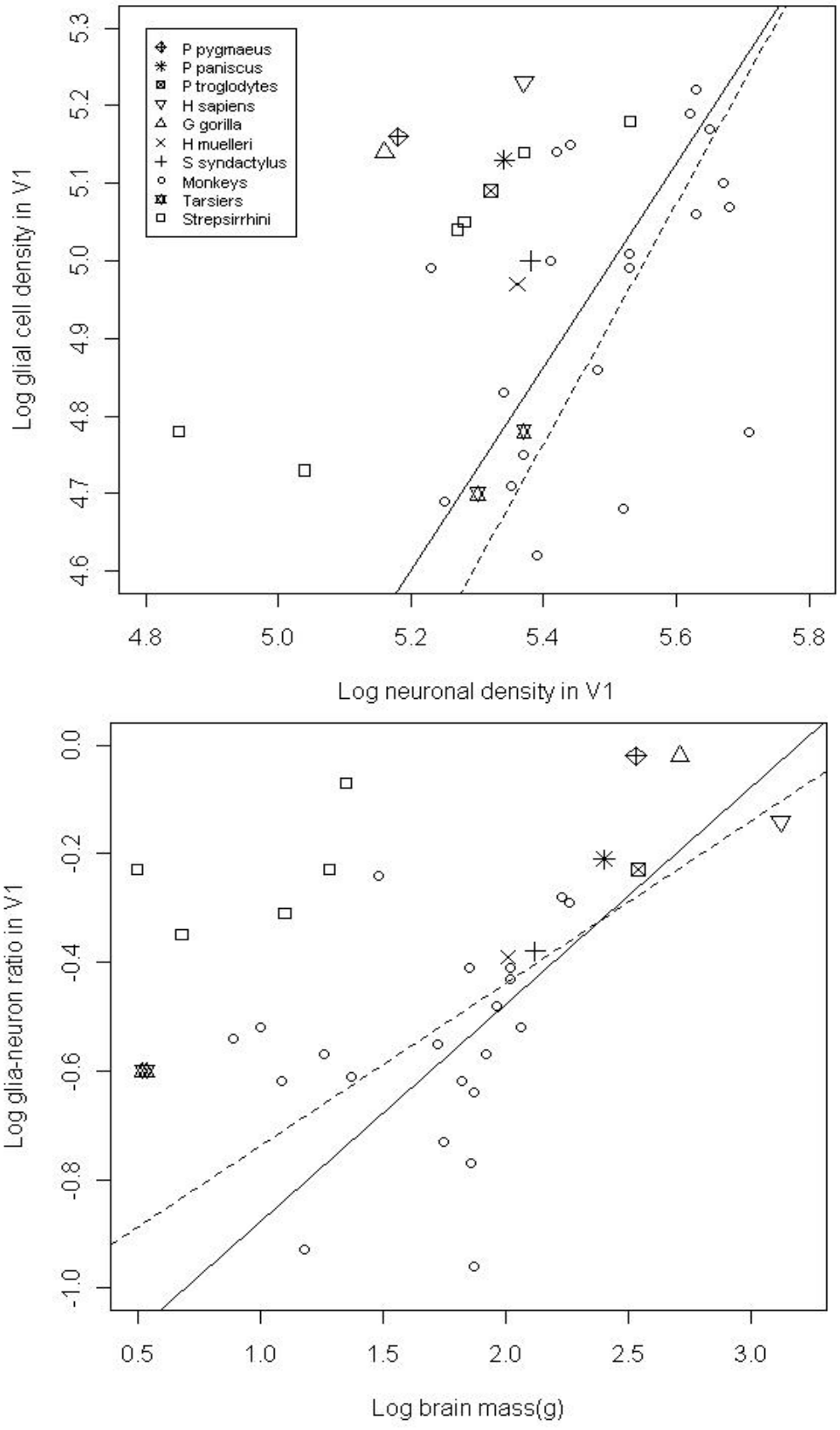

Figure 16: The allometric scaling of (top) glial cell density on neuronal density and (bottom) glia-neuron ratio on brain mass for species mean data in primates. (top) The dotted line represents LS regressions fitted to Old and New World Monkeys species mean data ($y = 1.54x – 3.55$, $R^2 = 0.531$, $p = 0.011$); the black line represents LS regressions fitted to independent contrasts mapped back into tip species space ($y = .31x – 2.21$, $p = 0.018$), calculated to predict hypothetical species points attached to the branch leading to apes by pruning apes from the tree and rerooting it at the last common ancestor of apes and other primates. (bottom) Significant scaling exponents are presented for Anthropoideafor species mean data ($y = 0.301x – 1.04$, $R^2 = 0.650$, $p = 0.000$) and independent contrasts ($y = 1.31x – 2.11$, $p = 0.002$).

DISCUSSION I

Across all species in our sample, the mammalian V1 displays a significant scaling relationship between glial cell density and neuronal density, with species mean data suggesting that increases in neuronal density in V1 outpace increases in glial cell density. For the same taxa, the ratio of glia to neurons in V1 are significantly explained by an isometric relationship with brain mass, although the explanatory value of this relationship is weak. In carnivores, glial cell density scales similarly with neuronal density, although the relationship here is isometric, and glia to neuron ratio is also significantly explained by brain mass. Primates, however, differ from this pattern in that there is no significant relationship between glial cell density and neuronal density, nor does glia to neuron ratio relate to brain mass across the order. This is likely due to substantial variation in scaling patterns between the taxonomic subgroups of primates. Furthermore, apes (including humans) display a higher ratio of glia to neurons than expected based on scaling expectations for Old and New World monkeys; and within the apes, humans display distinguished patterns of cellular densities. While relative increases in glia to neurons in larger cerebral cortices may often relate to the energetic costs of maintaining larger dendritic arbors and long-range projecting axons that are required, I propose that this relationship does not necessarily hold when considering a limited cortical region or restricted phylogenetic range. In primates, deviations in cellular densities observed in certain lineages may represent the evolution of specialized projection layers in V1 along those lineages. Accordingly, I suggest that the relative increase in glia to neurons in the human V1 may represent an evolutionary adaptation for increased metabolic activity among tightly packed populations of granule cells adapted for rapid, achromatic visual awareness.

Constraints on cellular densities in a limited cortical region

Previous studies have concluded that brain mass in mammals is an explanatory variable of the allometric relationship of glia to neurons in the neocortex (Hawkins & Olszewski 1957; Friede & Van Houten 1962; Tower & Young 1973; Herculano-Houzel *et al* 2007). These studies, however, were problematic for interpreting the evolution of cellular densities in the mammalian V1 because they represented few species and considered the neocortex as a single region. Furthermore, the scaling relationships in the above studies were calculated using only species mean data, so it remains unclear whether the observed relationships were real or artifacts of phylogenetic relatedness (but see Gabi *et al* 2010). My study was designed specifically to analyze cellular densities in the mammalian V1 with

respect to the effects of statistical non-independence due to phylogenetic relatedness. In cases where independent contrast slopes were contained within the 95% CI of slopes calculated for species mean data, I have concluded that the scaling relationships observed in contemporary taxa represent changes that have occurred repeatedly throughout multiple nodes in the phylogenetic tree and, therefore, represent functional constraints in the design of V1.

By examining allometric scaling relationships across taxa, it is possible to gain insight into the functional implications of changes in brain size, which is collectively determined by molecular, electrochemical, and physical design constraints. Other studies of species mean data sampled from a range of mammals have demonstrated that neuronal density in the neocortex scales with brain mass with an exponent of approximately -0.3 (Tower 1954; Prothero 1997; Sherwood *et al* 2007). My results produced similar scaling exponents for neuronal density on brain mass for AS (-0.376±0.61), suggesting that cortical neuronal density is limited by architectural constraints imposed by brain mass. In line with these results is a model predicting that a constant average percent of interconnectedness among neurons cannot be physically sustained with increasing gray matter volume, and therefore the reach of processing networks does not keep pace with brain size variation (Changizi 2001). However, the slightly steeper slopes observed in carnivores (-0.437 ± 0.50) and primates (-0.531 ± 0.23) demonstrate that neuronal density may become relatively disassociated from brain mass in certain taxa or when comparisons are made among close phylogenetic relatives (see Sherwood & Hof 2008). Factors underlying neuronal density, such as glial cell density, may reflect brain region-specific evolutionary adaptations within phylogenetic lineages that result in such deviations.

As brain size increases over evolutionary time, the distance that information must travel across an enlarged region or between regions also increases. This extra distance can cause substantial delays that may affect behavior (Swadlow 2000). Any mechanism capable of reducing the delay, therefore, will likely have a selective advantage. One of these mechanisms is myelination (Hartline & Colman 2007), which is able to reduce delays in information processing in larger brains by wrapping axons with myelin synthesized by oligodendrocytes (Wang *et al* 2008). Furthermore, the energy required per neuron is expected to increase with longer dendrites and axons, in order to sustain Na^+/K^+-pumps that restore ion gradients to propagate both actions potentials along the axon and excitatory potentials in the dendritic tree (Lennie 2003). Therefore, since neurons in large-brained mammals display larger dendritic arbors, more spines (Elston *et al* 2006), and have larger associated axonal diameter and length (Harrison *et al* 2002) than neurons in small-brained mammals, the role for glial cells in modulating

expansive arbors (Laming *et al* 2000; Hertz *et al* 2001) and long-range projecting axons predicts that larger-brained mammals will have increased glia-neuron ratios to pay for their increased costs of neuronal activity (see Nedergaard *et al* 2003; Sherwood *et al* 2006). My results only partially support this prediction. On the one hand, carnivores and AS demonstrated positive scaling exponents for glia-neuron ratio as a function of brain mass, showing that, indeed, large-brained species have higher glia-neuron ratios than small-brained species. But in contrast, glial cell density was not shown to outpace neuronal density in increasingly large brains in any taxonomic group; mean values of glial cell density were not significantly different across carnivores, SW, or primates; and glia-neuron ratio displayed pronounced diversity among taxonomic groups. Therefore, while brain size appears to contribute significantly to constraining neuronal density in a limited cortical region, and glial cell density is related to neuronal density, glial cell density in V1 does not appear to be directly constrained by brain size.

The phylogenetic diversity of glia-neuron ratio in my data highlight the difficulty of using brain mass as an indicator of cellular densities. I propose that such diversity is predicated on both cellular mechanisms acting on energy metabolism and behavioral adaptations affecting visual cortical processing, and that each adaptation promotes a quantifiable evolutionary signature in neuronal and glial cell proliferation.

Placentation and the neocortex in Eutheria

If increasing glia to neurons is metabolically expensive in the developing brain, then we should expect cellular densities to relate to the availability of maternal resources to the fetus in a species (Martin 1981; Elliot & Crespi 2009). My data support this prediction. The RMA scaling exponent for glial cell density on neuronal density in the epitheliochorial group, in which the fetus has only indirect access to the maternal blood supply (Mossman 1987), is negative for independent contrasts (RMA slope = -0.229, lower CI = -0.115, upper CI = -0.458, $R^2 = 0.86$, p = 0.000), whereas the slopes for independent contrasts in the endotheliochorial (RMA slope = 1.216, lower CI= 0.974, upper CI= 1.588, $R^2=0.046$, p=0.043) and haemochorial (RMA slope = 1.240, lower CI= 0.989, upper CI= 1.615, $R^2=0.056$, p=0.003) species, in which the fetus has more direct access to the maternal blood supply than species in the epitheliochorial group, scale with positive allometry. However, it is more than simply the invasiveness of the placenta, defined by the number of layers between fetal and maternal blood flow, that determine the efficiency of exchange or relative availability of resources in the

placenta (Enders & Carter 2004). Patterns of association between maternofetal interdigitation and interhemal barrier along eutherian lineages shown below (see Chapter 8, *Life-history Correlates of Placental Evolution*) have indicated that evolution of placental invasiveness was not principally driven by a need for more efficient oxygen exchange (also see Wildman *et al* 2006). The significant predictive power of gestation length for glia-neuron ratio in AS (t-value = 4.729, p = 0.000) and carnivores (t-value = 2.976, p = 0.008) and the significantly different scaling coefficients for cellular densities among the placental groups indicate that placentation affects the relationship of cortical glia to neurons in the evolving mammalian brain. While epitheliochorial species may benefit from long gestation periods, their placental antithesis, haemochorial species, benefit from the invasion of trophoblast cells into the uterus, allowing both invasive and non-invasive placental types to support increasing investment into the brain during the course of mammalian evolution.

Specializations in primate motion-processing pathways show glia-neuron signatures

My results suggest that evolutionary variation in the cortical microstructure (e.g., laminar, compartmental, connectional) of V1 displays phylogenetic diversity that is represented by quantitative changes in the cellular scaling of glia to neurons, which may themselves be considered evolutionary adaptations. Statistically significant differences in the scaling exponents of glia to neurons support three evolutionary events along the primate phylogenetic tree: the divergence of *Strepsirrhini* and *Haplorrhini*, the divergence of apes from Old and New World monkeys, and the divergence of humans from other apes. RMA scaling exponents for independent contrasts in *Haplorrhini*, but not in *Strepsirrhini*, deviate from the scaling exponent generated for AS. As such, it is more parsimonious to say that *Strepsirrhini* represents the ancestral primate condition, although it is also likely that both suborders have deviated from the ancestral condition with increased visual specialization.

In *Strepsirrhini*, glial cell density scales roughly isometrically with neuronal density. This is different from the pattern observed in Old and New World monkeys, but consistent with the relationships found in AS and SW (species mean: RMA slope=0.629, lower CI=0.376, upper CI=0.811, R^2=0.285, p=0.023; independent contrasts: RMA slope=0.677, lower CI=0.420, upper CI=0.845, R^2=0.212, p=0.029). Therefore, it appears there may have been little pressure along the strepsirrhine lineage to relax ancestral mammalian constraints on glia-neuron scaling in V1. The reliance of strepsirrhine visual acuity on rods, for example, as well as the reduced necessity of long-range, X-related thalamic inputs from the LGN in nocturnal species, may have displaced the need for changes in

glia-neuron metabolic coupling for adequate visual processing. The nocturnal owl monkey (*Aotus trivirgatus*), however, was not shown to deviate from expectations based on *Haplorrhini*.

The phylogenetic affinity for the family *Tarsiidae* has been debated for over a century (Hartwig 2002). To determine whether tarsiers are better affiliated with *Strepsirrhini* or *Anthropoidea* in the context of glial cell and neuronal densities in V1, I plotted the observed values for *Tarsius bancanus* and *Tarsius syrichta* against predictions for both species based on log-log LS regressions of *Strepsirrhini* and Old and New World monkeys. Although observed values for glia-neuron ratio fell closer to prediction values based on brain mass in *Strepsirrhini* than in Old and New World monkeys, glial cell density on neuronal density scaled with allometric expectations based on Old and New World monkeys, rather than *Strepsirrhini*. Therefore, while the tarsier V1 may have been impacted by certain life-history or anatomical adaptations associated with *Strepsirrhini* (e.g., nocturnality, short- and mid-wavelength cone distribution, and small body mass), the molecular mechanism constraining the relationship of glia to neurons observed in Old and New World monkeys seems most likely to have been established at the anthropoid stem lineage.

In *Haplorrhini*, glial cell density scaled significantly with neuronal density in V1 for species mean data and independent contrasts only when apes were not considered, suggesting an evolutionary shift in glia-neuron scaling in V1 at the divergence of apes and other haplorrhines. The novel honeycomb-like geometric arrangement of P- and M-related dendrites in layer IVa of Old and New World monkeys that is conspicuously absent in great apes (Preuss *et al* 1999) may have been concurrent with the observed shift in glia-neuron scaling. The loss of a P-geniculate projection to layer IVa in great apes also may have been accompanied by a concomitant shift in neuronal activity in V1.

While the observed human values for glial cell density on neuronal density fell outside the 95% PI based on a LS regression of Old and New World monkeys, the observed glia-neuron ratio in humans fitted well with predicted values based on brain mass, and much better, in fact, than with the predicted values based on a LS regression of non-human apes. Observed human values for glia-neuron ratio were lower than expected based on scaling exponents for brain mass and gestation length, but within 95% PI based on body mass, for non-human apes. A hypothetical species affixed to the hominoid phylogenetic tree with the observed human glia-neuron ratio I calculated to weigh 53 kg, gestate for 245 days, and have a brain weighing 318 g, showing that the human V1 deviates from the ancestral hominoid pattern of glia-neuron scaling. The presence of a strong M-geniculate projection to layer IVa in humans (Wong-Riley *et al* 1993), which is not found in any other great apes (Preuss & Coleman 2002), may be

the reason for the observed increase in neuronal activity. Furthermore, comparative studies of gene expression and cerebral blood flow indicate exceptionally high metabolic activity in the human neocortex that might generally explain increased neuronal activity in the human neocortex. High-density oligonucleotide arrays have identified many genes differentially expressed in the human brain (Caceres *et al* 2003; Uddin *et al* 2008), which predicts levels of neuronal activity to be exceptionally high in the human neocortex as a result of a considerable upregulation of total gene expression in human evolution (Dicicco-Bloom *et al* 1998; Suh *et al* 2001; Ferland *et al* 2004; Vallender *et al* 2008). The possibility that the human brain has a uniquely high metabolism is further defended by evidence that, despite trends for larger brains to have lower metabolic rates (per unit volume of tissue) than smaller brains (Aiello & Wheeler 1995), conscious-state cerebral glucose metabolic rates in the human brain (Bohnen *et al* 1999; Bentourkia *et al* 2000) are as high or higher than those in macaques (Cross *et al* 2000; Noda *et al* 2002). The upregulation of genes related to lipid metabolism and the importance of dietary docosahexaenoic acid to Na^+/K^+-ATPase activity (Bourre *et al* 1989; Djemli-Shipkolye *et al* 2003) may be indicative of the importance of dietary changes (e.g., the exploitation of lipid- and docosahexaenoic acid -rich thalassic resources or the scavenging of organ tissue) in early human brain evolution (see Aiello & Wells 2002; Broadhurst *et al* 2002; Crawford 2006; Leonard *et al* 2007).

Significant molecular changes in the brain may be reflected in corresponding compositional or connectional changes. There is evidence that biochemical mechanisms of generating energy have been under evolutionary selection as early as the anthropoid stem (Grossman *et al* 2001 2004), when brain size began increasing in primates above mammalian predictions. Considering together the consistency of human glia-neuron ratio with predictions based on overall brain mass and V1 volume (observed glia-neuron ratio=0.72; predicted=0.74, lower PI=0.66, upper PI=0.80) in Old and New World monkeys, the deviation of human glial cell density from predictions based on neuronal density in Old and New World monkeys, and recent evidence that the human V1 has a novel mesh-like arrangement of M-geniculate-related dendrites in layer IVa (Preuss *et al* 1999; Preuss & Coleman 2002) and considerable up-regulation of genes in the neocortex (Caceres *et al* 2003), it is possible that cortical specializations of the motion-processing pathway in humans occurred without dramatic changes in overall brain or even V1 size.

The diverse cellular scaling relationships among primate taxa, human divergence from glia-neuron ratios based on hominoid predictions, and decreased glial cell density based on neuronal density scaling in *Haplorrhini* emphasize phyletic variation in the evolution of V1, identify changes in glial

cell and neuronal densities as significant evolutionary adaptations, and support the claim that humans have evolved differentially higher requirements for metabolic support in the neocortex.

Body mass is a poor parameter for intelligence

The unparalleled enlargement of the human brain observed since *Homo erectus* against a backdrop of cultural and technological developments (Stout *et al* 2008; Stout & Chaminade 2009), and in the context of relatively static body size (see Robson & Wood 2008; Ruff 2010), has led many to speculate that the evolutionary enlargement of brain size as a function of body size may be taken as a proxy for intelligence (e.g., Jerison 1973; Kappelman 1996; Marino 1998). While this has certain obvious insights (e.g., metabolic investment in brain tissue is expensive), the use of body size as a parameter for intelligence must confront inconsistencies in the data. Simply because brain size scales with body size does not mean that intelligence is a function of deviations from brain-body scaling relationships. That is, the best physiological estimate of a behavioral capacity – a specific type of intelligence evolved to exploit a particular niche – cannot be determined *a priori*. If we assume that the model of intelligence based on brain-body scaling is accurate, then a tarsier (*Tarsius syrichta*) must employ more behavioral complexity than a bear (*Ursus maritimus*), since the former has a higher EQ than the latter (1.38 compared to 0.72). But then it is difficult to also assume that the extra 450g of brain weight in the bear has no behavioral implications. In other words (see Barlow 1985), why does an increase in EQ in a large-brained species require so much more brain tissue than an equal increase in a small-brained species, when the increases are expected to confer the same jump in intelligence? In hominin evolution, if evolutionary increases in brain size from *Australopithecus africanus* followed the primate brain-body scaling relationship, then we would expect Neanderthals to have displayed an increase in brain size of approximately 200cm^3 rather than the observed 1000cm^3, and humans to display an increase of approximately 100cm^3 rather than the observed 900cm^3 (Holloway 2008). If primate or mammalian brain-body scaling cannot explain brain evolution in hominins, should we expect it to explain brain evolution in other species?

Several recent studies have concluded that the cellular properties of different regions of the human brain scale well with predictions for other primate brains (Herculano-Houzel *et al* 2007; Sherwood *et al* 2007; Azevedo *et al* 2009). These studies conflict with the long-held view that the human brain is approximately four-times larger than expected for a primate of human body mass (Jerison 1973; Marino 1998). My data, too, show that the observed human glia-neuron ratio as a

function of brain mass can be explained by expectations based on haplorrhine species mean data. Furthermore, paired comparisons between individual observed human glia-neuron ratios and predictions based on a LS regression of Old and New World monkey independent contrasts did not reveal a significant difference (paired-samples t-test: $t = 1.17$, $p = 0.499$), suggesting that scaling constraints on the brain may be more conserved than those on the body. In this respect, perhaps it is worth considering (see Herculano-Houzel 2010) that body mass in great apes has deviated considerably from the primate trend, but with only minor affects on scaling of the brain. In most primate species, the brain represents approximately 2% of total body mass (Marino 1998), whereas the brains of gorillas and orangutans represent less than 1% of total body mass (Semendeferi & Damasio 2000). Rather than humans having a larger brain than expected for their body size, hominids (specifically gorillas and orangutans) may have evolved larger bodies than expected for their brain size. A recently discovered fossil of an ostensible stem catarrhine, with an indicated body mass of 15-20kg (Zalmout *et al* 2010), allows for the possibility that body mass has increased considerably in hominoid, but not Old or New World monkey, evolution (see Soligo 2006). The consistently poor correlations in my data between EQ and cellular densities, accompanied by recent evidence that absolute brain size is the parameter that best correlates with behavioral complexity in different species (Roth & Dick 2005; Deaner *et al* 2007), indicate that body size may not be a relevant parameter for measuring intelligence. If that is the case, then the intelligence of humans, or at least the constraints imposed on selection for processing the visual cortex, may be the consequence of a scaled-up monkey brain.

CHAPTER 6
HIPPOCAMPUS

To understand the possible anatomical and functional implications of how glia and neurons in the hippocampus vary across species, we must understand how hippocampal anatomy and function vary across species. In this chapter, I will provide the background material necessary to understand the results presented below.

Structure

The hippocampal formation (HF) occupies the medial wall of the temporal lobe (Fig. 17). It consists of the entorhinal cortex (EC) and subicular complex (SubC), in addition to the *cornu Ammonis* (CA) and dentate gyrus (DG, *fascia dentate*). The EC is the main input for cortical and subcortical projections (Butler & Hodos 2005). Flow of information in the HF is directional, with signals propagating from the DG to CA3 to CA1 to the SubC, and then out to the EC (Amaral & Insausti 1990; Joelving *et al* 2006). The amygdala is often considered as part of the HF, since it is the primary input structure of the hippocampus from the cortex (Russell & Gabrieli 1997). For comprehensive descriptions of the HF, see Ramon y Cajal (1911 1968), Lorente de No (1934), Vogt & Vogt (1937), Blackstad (1956 1958), Scoville & Milner (1957), Gastaut & Lammers (1961), Isaacson (1974), Angevine (1975), Chronister & White (1975), Tryhubczak (1975), O'Keefe & Nadel (1978), Carpenter & Sutin (1983), Schwerdtfeger (1984), Kahle (1986), Amaral & Insausti (1990), Williams (1995), Moser & Moser (1998), and Duvernoy (1998).

The hippocampus is located in the allocortex and consists of the CA and DG. The structure is bilaminar, with one lamina rolled up inside the other. In early development, the two laminae are continuous; the DG becomes concave and slips beneath the medial end of the CA until, finally, the DG and CA assume apposed C-shaped laminae separated by the hippocampal sulcus (Williams 1995), resembling a coupler on a train. In primates, compared to other mammals, the hippocampus is located inferiorly, as though the temporal lobe in which it resides has been rotated around the posterior pole of the corpus callosum. The hippocampus is structurally segmented into dorsal and ventral compartments (known as posterior and anterior in primates), which will be discussed below.

The CA is divided into six layers (Fig 18). In coronal sections, the CA is histologically heterogeneous and has been divided into four fields: CA1-4. Pyramidal neurons in CA1 are typically triangular and relatively scattered. Subfield CA2 is much denser and narrower than CA1, consisting of

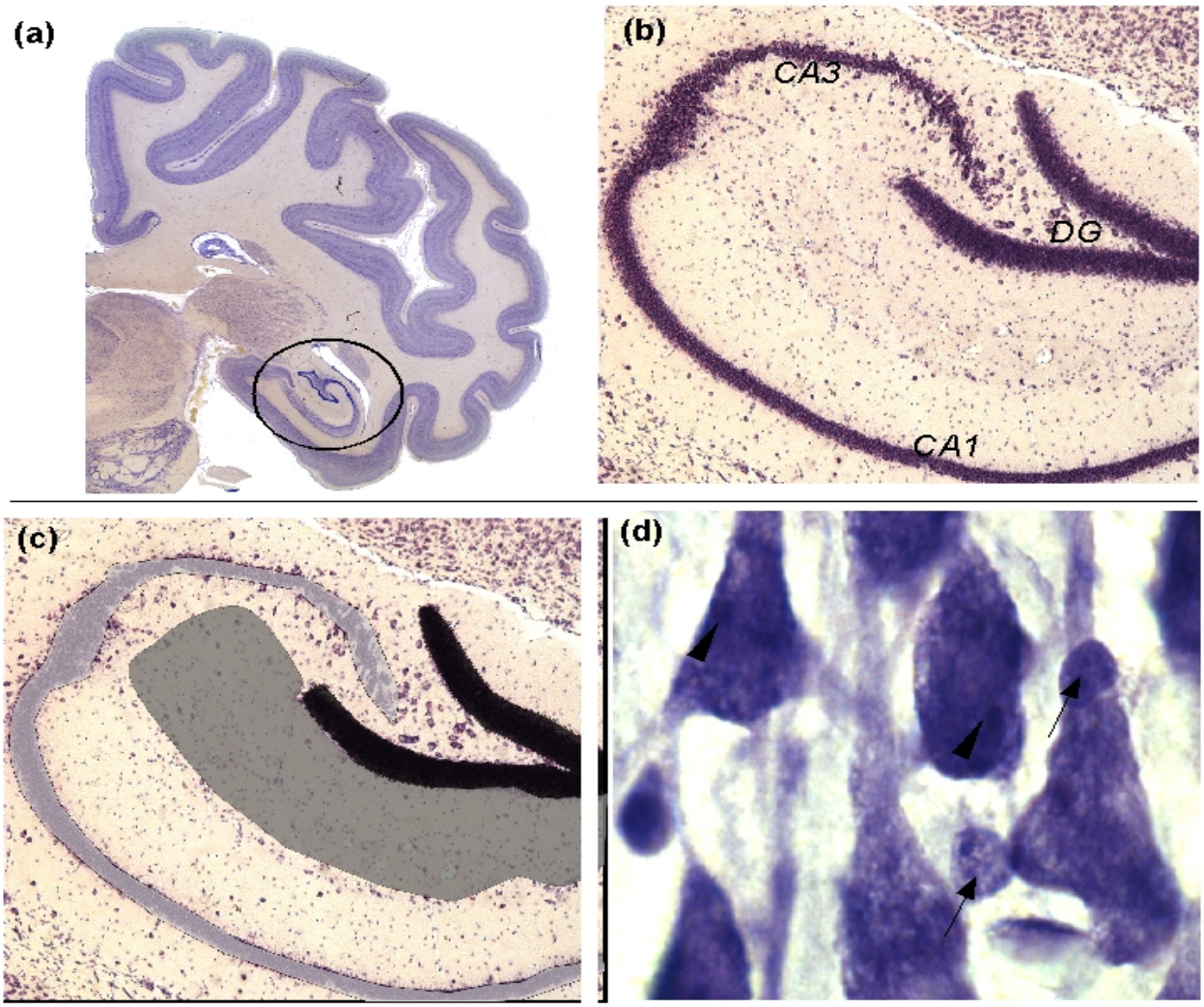

Figure 17. *(a) The hippocampal formation (HF) is located in the allocortex and consists of the cornua Ammonis (CA) and the dentate gyrus (DG). In early development, the CA and DG are continuous, until the latter becomes concave and slipes beneath the medial end of the former and the two lamina become apposed, separated by the hippocampal sulcus, resembling a coupler on a train (Williams, 1995). In primates, compared to other mammals, the hippocampus is located inferiorly, as though the temporal lobe in which it resides has been rotated around the posterior pole of the corpus callosum. The HF is a multilayered structure. The three layers highlighted here (b,c) were used in this study: (light grey) the stratum pyramidalecontains pyramidal neurons that constitute CA1-3 and whose dendrites arborize in deeper layers of the hippocampus; (dark grey) the stratum moleculareof the dentate gyrus receives fibres from the perforant pathway and possesses commissural and septal fibers; and (black) the stratum granulosum, or principal layer, of the dentate gyrus, contains somata of densely packed granular neurons that arborize superficially in the stratum moleculareand inputs to CA3 via mossy fibres. (d) Pyramidal neurons in CA1 are typically triangular and relatively scattered. Subfield CA2 is much denser and narrower than CA1, consisting of large, ovoid, densely packed somata. Pyramidal neurons in CA3 are also large and ovoid, but less densely packed than in CA2, and receive synaptic input from mossy fibres that arise from the dentate gyrus. Neurons (arrowheads) were identified by dark Nissl substance in the cytoplasm, lightly stained proximal segments of dendritic processes, and a prominent nucleolus, which was used as its characteristic point for counting. Glia (arrows) were identified by the absence of a conspicuous nucleolus, and their smaller size and less endoplasmic reticulum compared to pyramidal neurons. Astrocytes and oligodendrocytes were not differentiated. Photographs taken at the National Museum of Health and Medicine, Washington, D.C: (a)* Macaca nemestrina*, 1x objective; (b,c)* Sorex araneus*, 20x objective; (d)* Saguinus oedipus*, 100x objective.*

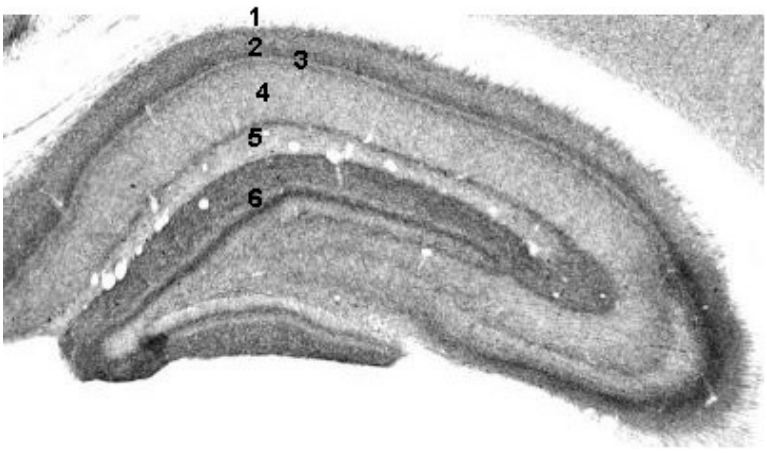

Figure 18. *The cornu Ammonis is divided into six layers: the alveus (1) contains axons of the hippocampal and subicular neurons; the stratum oriens (2) contains basket cells (GABAergic interneurons) and is crossed by axons of pyramidal neurons as they travel to the alveus; the stratum pyramidale (3) contains pyramidal neurons, whose dendrites arborize in the strata oriens and moleculare; the stratum radiatum (4) possesses mostly apical dendrites (traveling to the stratum moleculare) that connect with Schaffer collaterals, fibers from septal nuclei, and commissural fibers; the stratum lacunosum (5) is populated with axons formed of perforant fibers and Schaffer collaterals; and the stratum molecular (6), which contains a small population of interneurons only and blends with the dentate gyrus in later stages of development. Since the allocortex usually shows only three layers, the strata radiatum, lacunosum, and moleculare are grouped into one layer (i.e., the molecular zone). Image adapted from tissue immunostained with anti-ChAT antigen (www.brainmuseum.org).*

large, ovoid, densely packed somata; it is conspicuous in haplorrhines (Amaral *et al* 1984), but only arguably present in other mammals (Blackstad 1956; Schwerdtfeger 1984; Duvernoy 1998). Pyramidal neurons in CA3 are also large and ovoid, but less densely packed than in CA2, and receive synaptic input from mossy fibers that arise from the DG. The fourth division, CA4, more commonly known as the hilus, is situated within the concavity of the DG.

The DG is separated from CA1-3 by the hippocampal sulcus. The main layer of the DG is the stratum granulosum, which contains the somata of densely packed granular neurons that arborize superficially in the *stratum moleculare* and form synaptic contact with inputs from other brain regions (Bedi 2003; Keuker *et al* 2003). The outermost layers of the *stratum moleculare* receive fibers from the perforant pathway, while the innermost layer, which contacts the *stratum granulosum*, possesses commissural and septal fibers (Lynch & Cotman 1975; Cerbone *et al* 1993). The polymorphic layer of the DG is crossed by axons of granular neurons and conjoins the hilus to the *stratum granulosum*.

The DG is distinguished by postnatal and adult neurogenesis: the adult mammalian DG bears new functional neurons that are integrated into the hippocampal circuitry (Eriksson *et al* 1998; Van Praag *et al* 2002). The rat DG bears 80% of its granule cells after birth (Schlesinger *et al* 1975), and several studies have shown that these cells continue to be produced into adulthood (Bayer *et al* 1982; Kaplan & Bell 1983, 1984). The functional significance of new neurons in the adult hippocampus has not been

determined, although it is thought that the new neurons either replace dying neurons (Beibl *et al* 2000) or provide a greater degree of plasticity to the mature brain (Van Praag *et al* 2002).

Circuitry

Activity within the HF involves two circuits. Fibers originating in the posterior parietal cortex (Brodmann's area 7) project to the EC via the parahippocampal gyrus and eventually to the polysynaptic pathway described below. The association of the posterior parietal cortex with the superior colliculus indicates that its function involves perception of the spatial position of an object (Andersen *et al* 1990; Mountcastle 1995). The polysynaptic pathway is composed of a chain of glutamatergic neurons passing sequentially from the EC to the DG, CA3, CA1, and SubC (Amaral & Insausti 1990; Francis *et al* 1994). This outputs principally to the anterior thalamic nucleus, directly or by way of the mammilo-thalamic tract, and secondarily to the hypothalamus and intralaminar nucleus (O'Keefe & Nadel 1978; Teyler & DiScenna 1984; Bentivoglio *et al* 1993). Nervous implulses are projected from the thalamus to the cingulate cortex (area 23) and the retrospinal cortex (areas 29 and 30) (Duvernoy 1998). Fibers originating in the inferior temporal association cortex (areas 37 and 40) reach the entorhinal cortex by way of the perirhinal cortex and communicate information about the recognition and description of an object, which is then processed in the intra-hippocampal direct pathway. In the direct pathway, which bypasses the polysynaptic pathway, pyramidal neurons in CA1 project to the SubC, whose axons return to the deep layers of the EC (MacLean 1992), and then output to the inferior temporal association cortex, the temporal pole, and the prefrontal cortex (Squire *et al* 1994; Duvernoy 1998). These pathways thus segregate the processing of episodic and spatial memory (polysynaptic pathway) from semantic and non-spatial memory (direct pathway). Likewise, the EC, which is the sole input to the hippocampus, is segregated into functional zones, as is the SubC, which is the main output of the EC (Amaral *et al* 1987; Witter & Groenewegen 1992). Specific dorsal and ventral circuits are discussed in detail below.

Evolution

Most comparative studies of the HF have focused on identifying structural and functional homologs in vertebrates (Sherry & Schacter 1987; Squire 1992; Cohen & Eichenbaum 1993; Insausti 1993; Burwell *et al* 1995; Brown & Aggleton 2001; Aboitiz *et al* 2002; Bingham *et al* 2003; Day 2003; Jacobs 2003; Salas *et al* 2003). These studies have been extremely fruitful, because the cytoarchitecture

and connectivity of the hippocampus, and even features of the EC and SubC, are largely conserved in mammals, especially compared to the organizational diversity of the mammalian neocortex. This is somewhat surprising, since the many complex and highly organized patterns of interconnectivity of the HF would be ideal for evolutionary divergence. Furthermore, the HF serves the same basic mnemonic function across mammals: rapid learning, complex associative organization, and the recording of retrievable experiences (Poldrack & Gabrieli 1997; Schacter *et al* 1998; Eichenbaum & Cohen 2001; Manns & Squire 2002).

Similarities in topology, development, connectivity, neurochemistry, and neuroendocrinology have identified the dorsal and medial cortices in reptiles and the hippocampus and parahippocampus in birds as homologous regions of the mammalian hippocampus (Holmgren 1922, 1925; Northcutt 1974; Butler 1976, 1980; Ouimet *et al* 1985; Casini *et al* 1986; Berbel 1987; Martinez-Garcia & Olucha 1987; Bingman *et al* 1990; Bingman & Mench 1990; Martinez-Garcia & Lorente 1990; Northcutt & Ronan 1992; Davila *et al* 1993; Gahr *et al* 1993; Martinez-Garcia *et al* 1993; Luis del Iglesia *et al* 1994; Young *et al* 1994; Butler & Hodos 1996; Roth & Westhoff 1999; Lathe 2001; Gonzalez & Lopez 2002). Both homologous regions are three-layered, positioned medially, adjacent to the main ventricle, develop from the pallial telencephalon, receive strong projections from the olfactory and visual cortices (Hoogland & Vanderzee 1993; Lavenex & Amaral 2000; Atoji *et al* 2002), project strongly to the ipsilateral septum, which is also a highly conserved region in vertebrates (Krayniak & Siegel 1978; Neary 1990; Manns & Eichenbaum 2007), and have an ability to associate incoming information by virtue of synaptic plasticity (Bliss & Lomo 1973; Shapiro & Wieraszko 1996; Munoz *et al* 1998). Lesioning of the homologous hippocampus in reptiles, birds, and teleost fish (whose lateral pallium is widely considered to be homologous to the mammalian hippocampus (Rodriguez *et al* 2002)) has been documented to cause deficits in spatial memory similar to those observed in rodents (O'Keefe & Nadel 1978; Morris *et al* 1982; Powers 1990; Holtzmann 1999; Colombo & Broadbent 2000; Stone *et al* 2000; Day *et al* 2001; Lopez *et al* 2001; Rodriguez *et al* 2002; Bingman 2003; Salas *et al* 2003). It is most parsimonious, therefore, to assume that the fundamental organization of the hippocampus evolved early in vertebrate phylogeny and was retained in tetrapods. Certain features of the hippocampus have been selected on, however, in mammalian evolution. The route by which non-olfactory sensory information reaches the hippocampus, for example, has become increasingly ambagious over mammalian evolution (Neary 1990; Ulinksi 1990), so that the flow of ascending sensory information is re-routed through the neocortex. Furthermore, the losses of direct sensory inputs from the dorsal

thalamus to the DG and of direct projections out of the hippocampus in mammalian evolution mean that there are no homologs for the EC or SubC in reptiles (Perez-Clausell 1988; Iglesia & Lopez-Garcia 1997; Streidter 2005). There has been a general trend in mammalian evolution to connect the hippocampus to more cortical regions (Hoogland & Vermeulen-Vanderzee 1993; Dubbeldam 1998; Ten Donkelaar 1998; Atoji *et al* 2002). Some of these evolutionary changes, present in mammals and absent in reptiles, are confounded by their presence in birds. According to some (Montagnese *et al* 1996; Szekely 1999; Colombo & Broadbent 2000; Aboitiz *et al* 2002; Hough *et al* 2002; Kahn *et al* 2003), all major mammalian subdivisions of the HF, and even the wiring of the subdivisions, are present in birds. These similarities are most plausibly homoplastic. There is no evidence, however, that the homologous bird hippocampus is involved in non-spatial memory (Strasser *et al* 2004), although the homologous hippocampus in goldfish is reportedly important for spatial and non-spatial memory (Alvarez *et al* 2003; Broglio *et al* 2005). It is possible that the ancestral vertebrate hippocampus was involved in spatial and non-spatial memory, and that birds and reptiles selected for only the spatial aspect of the structure, while the increased adaptive value of the olfactory bulb in mammals (see Aboitiz *et al* 2002) advanced the evolution of the hippocampus to support non-topographic sensory information. In any case, the functional condition of the ancestral vertebrate hippocampus is difficult to tie down, but it is evident that, early in their evolution, vertebrates evolved a structure (or network of structures) to form stable associations among pieces of information that bear no shared topographic similarities. So advantageous was this structure, most mammalian adaptations have been focused on parahippocampal regions (e.g., the EC and SubC).

Variations observed in the HF of different mammalian species are rarely fundamental enough to be considered reorganizational and generally vary according to brain size. For example, the border demarcating CA1 to the SubC and the presence of CA2 are less clearly defined in smaller-brained mammals than in larger-brained mammals (Bakst & Amaral 1984; West *et al*, 984; Green & Mesulam 1988; Kunzle & Schuller 2001; Kunzle & Radtke-Schuller 2001). The overall size of the hippocampus increases in higher species (O'Keefe & Nadel 1978; Stephan 1983; West & Schwerdtfeger 1985), although cetaceans have an exceptionally small hippocampus (Jacobs *et al* 1979; Stephan & Manolescu 1980; Schwerdtfeger 1985). The EC follows a similar trend of increased differentiation in higher, larger-brained species (West *et al* 1984; Insausti 1993; Kunzle & Radtke-Schuller 2001; Manns & Eichenbaum 2007). Increased differentiation of the EC is not generally accompanied by changes in connectivity between the EC and the hippocampus (Witter & Groenewegen 1984; Buhl & Dann 1991;

Witter & Amaral 1991; Witter 1993; Van Groen *et al* 2002), although some differences have been observed in the laterality of projections (Amaral & Witter 1995). The only major variation in input to the HF documented in mammals concerns the olfactory bulb. In rats, a direct projection from the olfactory bulb to nearly the entire EC is observed (Price 1973), whereas the olfactory bulb projects to only 15% of the EC in macaques (Witter *et al* 1989) and 5% in humans (Insausti *et al* 1995). The strength of the olfactory bulb projection to the EC varies predictably, with strong projections found in macrosomatic mammals and weak projections found in microsomatic mammals (Insausti *et al* 2002). This reduction in primates is often interpreted as a reduction in the capacity for the EC to support odor-related memory, an interpretation supported by lesioning studies in rats (Dudchenko *et al* 2000) and humans (Levy *et al* 2003). Other differences in connectivity and structure (e.g., the apomorphic posterior parahippocampal cortex in primates (Preuss 2006) and the subdivision of retrosplenial area 29 in anthropoids (Zilles *et al* 1986)) are generally reflections of interspecific differences in neocortical, rather than hippocampal, organization. Species-specific variations in the distribution of neuropeptides (Sakamoto *et al* 1987) and the near absence of commissural fibers in humans compared to non-primates (Wilson *et al* 1987) suggest that functional differences of the hippocampus may also exist among mammals (see below).

Since the neural mechanisms underwriting quantifiable traits related to the hippocampus (e.g., episodic memory) are poorly understood, identifying selection pressures on those neural mechanisms across taxa is problematic. But it is important to understand what aspects of behavior, environment, and development may lead to altered numbers of glia and neurons in the hippocampus. On the assumption that the hippocampus is demonstrably important for spatial memory in mammals and birds (Sherry & Vaccarino 1989; Sherry *et al* 1989; Hampton & Shettleworth 1996), the adaptive specialization hypothesis (Krebs *et al* 1989) has been applied to the hippocampus, such that the volume of the hippocampus is proposed to be directly related to memory capability (Garamszegi & Eens 2004; Lucas *et al* 2004). This hypothesis recently found support in a study of chickadees, which observed hippocampal neuron numbers to correlate strongly with increasing climatic harshness (Roth & Pravosudov 2009). The authors explain that, in birds, the ability to retrieve caches during demanding times in harsh climates (defined as a function of latitude) may select for increased investment in the hippocampus. No experiment has yet been constructed to test morphology of the mammalian hippocampus as a function of a behavior analogous to food-storing or cache-retrieval. Studies in rats (Rapp & Gallagher 1996; Rasmussen *et al* 1996), mice (Calhoun *et al* 1998), tree shrews (Keuker *et al*

2004), and macaques (West *et al* 1993; Berman *et al* 1997; Keuker *et al* 2003a) have demonstrated that aging has no effect on neuron numbers in hippocampal subfields (CA1-4, DG, or SubC). Furthermore, tree shrews were shown to preserve neuron numbers despite measurements of impaired working memory, and some rats and macaques to preserve neuron numbers despite measurements of impaired reference memory (Keuker *et al* 2003a 2004). In a very different type of quantitative study in mammals, comparing polygamous meadow voles and monogamous field voles, hippocampal volume was recorded as absolutely and relatively larger in male than in female meadow voles, but of comparable absolute and relative size in male and female field voles (Jacobs *et al* 1990). It is unknown whether or not the hippocampus is a particularly vulnerable or favorable site for sexual dimorphism, nor is it clear why it would be. Further studies using mammalian species are needed to identify selection pressures that may have influenced interspecific variation in the mammalian hippocampus.

Shared and derived functions

This much is clear: removal of the hippocampus affects spatial learning, episodic memory, and contextual fear. The remarkable plasticity of hippocampal neurons, whose physiological states are modified by repetitive stimulation (i.e., long-term potentiation), are ideal for learning, conscious recollection of events and relations among events, and spatial recognition (Bliss & Lomo 1973; Alger & Teyler 1976; Trillet 1992; Kopelman 1993; Eichenbaum *et al* 1994; Kesner 1994; Markowitsch 1995a,b; for a review of neuronal and synaptic plasticity on memory processing, see Wang *et al*, (1997)). The hippocampus is further implicated in regulating emotional behavior and certain aspects of motor control. Projections from the polysynaptic pathway converge on the anterior cingulate cortex, where the spino-reticular-thalamo-cortical pathways involved in the perception of pain terminate (MacLean 1992; Vogt *et al* 1993; Graybiel *et al* 1994; Adolphs *et al* 1995; Ono *et al* 1995; Williams 1995). By virtue of its partial control of the limbic loop (ventral striatal loop), the hippocampus is suggested to be involved in motor behavior (Groenwegen *et al* 1991; Witter & Groenewegen 1992; MacLean 1992; Williams 1995). Most famously, however, the hippocampus is described functionally as a cognitive map, an integrator of environmental information. Effectively, the cognitive map of an environment becomes increasingly internalized (i.e., independent of external sources of information) as a function of an individual's familiarity with that environment (O'Keefe & Nadel 1978; Burgess *et al* 1999a,b; Jacobs 2003). Comparative studies may help demonstrate how limited these operational definitions of the hippocampus are, which features of the human hippocampus are derived, and whether

the cognitive map is generally an appropriate metaphor to describe how the hippocampus functions.

There is evidence that rats (and birds) are able to remember where and when unique events occurred (Morris 2001; Clayton *et al* 2003; Dere *et al* 2005; Eacott *et al* 2005), an ability that has been explicitly connected to hippocampal function (Ergorul & Eichenbaum 2004) and characterized as equivalent to episodic memory in humans (Tulving 1983; Clayton & Dickenson 1998). Studies using signal detection theory (Yonelinas 2001) further support this characterization (Yonelinas *et al* 2002; Fortin *et al* 2004; also see Donaldson 1996; Squire *et al* 2004). Further animal studies suggest that 'where' and 'when' information can be recorded in the absence of explicit motivation, and that the hippocampus supports purely cognitive memory (O'Keefe & Dostrovsky 1971; Barrientos *et al* 2002; Stote & Fanselow 2004).

Many studies have implicated hippocampal firing patterns in representing unique associations of stimuli, behavior, and place, and the context in which these associations are learned. In rats and humans, hippocampal cells fire in association with a particular odor and place, stimulus familiarity, and, sometimes, a particular goal (Wood *et al* 1999; Ekstrom *et al* 2003). Evidence from fMRI studies suggest that humans express highly abstracted representations of space in large, anisotropic neuronal ensembles in the hippocampus (Hassabis *et al* 2009). Additionally, humans and macaques are observed to have similar neuron firing patterns in the hippocampus in association with non-spatial stimuli (Kreiman *et al* 2000a; Hampson *et al* 2004), with further evidence that some hippocampal neurons represent abstract features (e.g., mental images) of non-spatial stimuli (Kreiman *et al* 2000b; Manns & Eichenbaum 2007). The hippocampus was initially proposed to be involved in emotional states based on its position in the Papez-MacLean limbic circuit (which involves the mammillary bodies, thalamic nucleus, cingulate cortex, prefrontal cortex, amygdala, and septum) (Papez 1937; MacLean 1952; Gray & Jeffrey 1971; Sokolov & Vinograda 1975) and evidence that removal of the medial temporal lobe resulted in profound emotional disturbances in macaques (Kluver & Bucy 1937). More recent studies showing the effects of the hippocampus on hormonal stress response (Jacobson & Sapolsky 1991; McEwen *et al* 1997; Herman *et al* 2005; Dedovic *et al* 2009) and associations of the hippocampus with post-traumatic stress disorder, depression, and bipolar disorder (Frey *et al* 2007; Bonne *et al* 2008) have strengthened initial proposals linking the hippocampus to emotion.

Thus, the hippocampus may be functionally segregated into two anatomical parts: the cognitive dorsal hippocampus (spatial memory) and the emotional ventral hippocampus (non-spatial memory) (Fanselow & Dong 2009), although the adjectival assignments may turn out to be somewhat superficial

with more research. Anatomical segregation of the hippocampus into dorsal and ventral parts (known as posterior and anterior parts in primates) was first proposed by Moser & Moser (1998), based on evidence that the dorsal hippocampus (DH) and ventral hippocampus (VH) have distinct inputs and outputs (Swanson & Cowan 1977), that spatial memory is uniquely dependent on the DH (Moser *et al* 1995), and that lesions on the VH, but not on the DH, alter hormonal stress responses and emotional behavior (Henke 1990). Division of the hippocampus into the DH and VH is further supported by gene expression divided along the rostral/caudal-dorsal/ventral extent of the hippocampus (Fanselow & Dong 2009), the significant discrepancy of place field density in the DH and VH (Jung *et al* 1994), and the preferential projection of visuo-spatial information from the caudolateral band of the EC and of visceral, gustatory, and olfactory information from the medial band of the EC to the DH and VH, respectively (Insausti *et al* 1997; Dolorfo & Amaral 1998; Burwell 2000). For these reasons, it is simplest to discuss the functional capacities of the hippocampus in terms of the unique capacities of the DH and VH.

Studies in rats and macaques have recorded the strongest cortical projections from the DH in the retrosplenial and anterior cingulate cortices (Vogt & Miller 1983; Risold *et al* 1997; Van Groen & Wyss 2003; Parvizi *et al* 2006; Cenquizca & Swanson 2007; Kobayashi & Amaral 2007; Roberts *et al* 2007), two areas that are principally involved in spatial navigation (Harker & Winshaw 2004; Maguire *et al* 2006; Spiers & Maguire 2006; Lavenex *et al* 2007), memory processing (Han *et al* 2003; Frankland *et al* 2004; Jones & Wilson 2005) and visuo-spatial information (Lavenex *et al* 2006), and the strongest subcortical projections in the mammillary nuclei and anterior thalamic complex (Swanson & Cowan, 2975; Kishi *et al* 2000; Ishizuka 2001), two areas favorably populated by orientation-selective neurons (Taube 2007). It is argued, therefore, that the dorsal circuit is an important interface for navigating, orienting, and executing behaviors in a familiar environment (Taube 1990; Muller *et al* 1996; Jeffrey 2007). Furthermore, connections with the ventral tegmental area, substantial nigra, and mammillary body (Mogenson *et al* 1983; Groenewegen & Russchen 1984; Groenewegen *et al* 1996) have been used to suggest a caudal behavior-control column that underlies expression of exploratory or foraging behavior (Swanson 2000) through control of locomotion, orientation, and spatial direction (Fanselow & Dong 2000). Lesioning and fMRI studies largely support these conclusions (Jarrard 1989; Moser *et al* 1993, 1995; Bannerman *et al* 1999 2002; McHugh *et al* 2004; also see Barkus *et al* 2010).

In rats and macaques, the VH is directly connected to the olfactory bulb, as well as the anterior olfactory nucleus, piriform cortex, and endopiriform nucleus (Cenquizca & Swanson 2007; Roberts *et*

al 2007). It has bidirectional connectivity with amygdalar nuclei receiving olfactory sensory inputs (Saunders *et al* 1988; Kishi *et al* 2000; Pitkanen *et al* 2000; Petrovich *et al* 2001; Witter & Amaral 2004; Cenquizca & Swanson 2007), as well as with the infralimbic, prelimbic, and agranular insular cortices (Chiba 2000; Thierry *et al* 2000; Jones & Wilson 2005; Hoover & Vertes 2007; Roberts *et al* 2007). These connections form a series of projections that innervate the paraventricular and medial zones of the hypothalamus, which control neuroendocrine, autonomic, and somatic motor activities associated with ingestion, reproduction, and defense (Kishi *et al* 2000; Dong *et al* 2001a; Petrovich *et al* 2001; Herman *et al* 2005; Dong & Swanson 2006). These connections, which form a VH network, are implicated in regulating response to psychological stress (Cullinan *et al* 1993; Choi *et al* 2007 2008) and anxiety (Walker *et al* 2009) through inhibiting hypophyseal secretion of adreno-corticotrophic hormones (Jacobs 1979; Teyler *et al* 1980; Herman *et al* 1989; Diamond *et al* 1996), as well as in mediating reward processing (Wassum *et al* 2009), taste aversion learning (Koh *et al* 2009), components of Pavlovian fear conditioning (McGaugh 2004; Fanselow & Poulos 2005; Rodrigues *et al* 2009), and possibly even sleep-wake circadian cycles (Saper *et al* 2005) through direct projections to amygdalar nuclei, the nucleus accumbens, and the suprachiasmatic nucleus (Watts *et al* 1987; Groenewegen *et al* 1996; Naber & Witter 1998; Pitkanen *et al* 2000; Petrovich *et al* 2001; Kishi *et al* 2006; Cenquizca & Swanson 2007).

ANALYSIS II

Aim

The aim of this analysis was to determine how glia and neurons scale in the CA fields across taxa, while accounting for phylogeny, brain and body mass, gestation length, and volumetric estimates of the dentate gyrus. Furthermore, I aimed to determine what, if any, influence mode of placentation, defined by the degree of invasion of trophoblast cells into the uterus, had on the above relationships.

Materials

Samples of non-pathological postmortem brains representing 62 mammalian species were used (Table 1). All samples were from adult brains, except for *Trachypithecus francoisi* and *Pithecia pithecia*, which were juveniles with brain sizes comparable with species-typical adult averages. Specimens from all collections were immersion-fixed with either 10% formalin or 4% paraformaldehyde, embedded in paraffin, serially sectioned, and stained with Nissl in the context of unrelated experiments. Specimens that were not previously serially sectioned and stained were processed as outlined above.

Demarcation of CA1-3

The pyramidal cell regions CA1-3 were not distinguished in this study. The end of the CA layer adjacent to the hilus was well defined in all species examined by the abrupt change in the organization of neuronal cell bodies (Rosene & Van Hoesen 1987; Amaral & Insausti 1990; Amaral & Witter 1995; Keuker *et al* 2003). The opposite end of the CA layer, which is adjacent to the SubC, was marked by progressively less dense cell populations. The border between the CA and the subiculum was defined as the point at which the superficial cells of the CA ceased to be contiguous (West *et al* 1991; Keuker *et al* 2003). The CA regions were delineated at 20x magnification (Fig. 17)

Demarcation of the dentate gyrus

The stratum granulosum of dentate gyrus (StrGr) is the most densely packed layer of the hippocampus and stains intensely for Nissl (Fig. 17). The layer is not in immediate contact with other densely packed layers of the hippocampus (e.g, CA1). Depending on the orientation of the sections, the DG appeared in the shape of a horseshoe or something similar to the outline of a steamer. The stratum

moleculare (StrMol) was delimited by the StrGr, CA1, hilus, and the strip of the stratum lacunosum, and was distinguished by a homogeneous opaqueness (Duvernoy 1998).

Cell counting in CA1-3

Cell-counting was performed using *StereoInvestigator* software on the equipment outlined previously (see Chapter 4*, Methodology A: Brain Data*). For each individual, a random starting section was selected in the CA. Serial sections spaced at 300-400μm were selected for analysis for each cell type. Boundaries were outlined using a 20x objective; a virtual 25 x 25μm lattice of counting frames were randomly positioned on each slide to cover the sampled area with approximately 30 frames per section. Counting was performed under Koehler illumination using a 100x (NA 1.25, oil) objective – a 63x (NA 1.40, dry) was used with one human and one chimpanzee individual, as the slides were too thick for larger objectives. Section thickness ranged from 25μm – 100μm, so the disector thicknesses used also varied. A minimum 4μm guard zone was set on either side of each section. Pilot tests were performed for each individual to determine the optimal size of the counting frame (approximately 2 particles per counting frame). Section thickness was measured at the first and final counting site for each section using the microcator. The average coefficient of error (CE) was 0.7 ± 0.1 for all analyses. Cellular densities were estimated using the sampling fractions derived from these stereologic estimates.

Neurons were distinguished from non-neuronal cells by the presence of dark, coarsely stained Nissl substance in the cytoplasm, a large nucleus, a distinct nucleolus, ovoid shape, and lightly stained proximal segments of dendritic processes. Excitatory and inhibitory neurons were not differentiated. Glia were expected to lack a conspicuous nucleolus and contain less endoplasmic reticulum than neurons (Fig. 17). Astrocytes and oligodendrocytes were not differentiated and are classified simply as glia. Neither endothelial cells, identified by their stellate outline and cytoplasm containing membrane-bound vesicles, nor microglia were counted (Sherwood *et al* 2006; Pelvig *et al* 2008).The nucleolus of neurons and the body of glia were used for counting criteria. The nuclei of basket cells, present in the CA, were of similar appearance to those of pyramidal neurons, so they were not distinguished from pyramidal cells and counted all the same. This is not assumed to have impacted significantly the estimated neuronal densities, as basket cells comprise less than 1% of the neurons in the CA (West *et al* 1991).

Volumetric estimates of the dentate gyrus

The volumes StrGr and StrMol of the DG were determined using Cavalieri's direct volume estimate (see Chapter 4*, Methodology A: Brain Data*). An average of 20 sections were sampled for each individual. The cross-sectional area for every 4-6th serial section was delineated at 40x magnification. Each delineated region was then projected onto a black screen at a known magnification, and a lattice of evenly spaced points was superimposed on it. The number of points falling on each layer were counted using a systematic 'paint' tool.

Section thickness ranged from 25μm – 100μm. The distance between points on the grid was 60μm. This distance was determined by pilot studies on mouse and human brains. Section thickness was measured at the first and final counting site for each section using the microcator at 63x magnification.

Estimates of the CEs were calculated with the Gundersen–Jensen estimator (Gundersen & Jensen 1987; Gundersen *et al* 1999) and held below 0.8 ± 0.1 for all analyses.

RESULTS II

I quantified glial cell and neuronal densities in CA1-3 and volumetric estimates of the *stratum granulosum* and *stratum moleculare* of the dentate gyrus in 66 mammalian species (spanning 11 orders). The purpose of the study was to test whether the developmental processes establishing adult glia and neuron densities in the hippocampus are conserved in mammals, whether cellular distributions of different subfields of the mammalian hippocampus evolve in concert, and, finally, how cellular properties of the different regions are influenced, over evolutionary time, by phylogeny, anatomy, and mode of placentation.

Hypothesis and predictions

Comparative studies of the hippocampal formation (HF) have indicated that, despite its complexity, it is a largely conserved system in the mammalian brain. It is likely, therefore, that the relationship of glia to neurons in CA1-3 will not vary significantly among the taxonomic groups. However, variation observed in CA2 between rodents and primates (Bakst & Amaral 1984; West *et al*, 984; Green & Mesulam 1988; Kunzle & Schuller 2001; Kunzle & Radtke-Schuller 2001) may lead to slightly different relationships between the scaling of cellular densities in CA1-3 and volumetric estimates of the dentate gyrus, since the geometric expansion of the HF may be expected to change according to the presence or absence of CA2. Furthermore, increasing connections between the HF and neocortical regions in larger mammalian brains (Hoogland & Vermeulen-Vanderzee 1993; Dubbeldam 1998; Donkelaar 1998; Atoji *et al* 2002) may suggest some increased degree of scaling between the HF and neocortex in higher primates. However, the early development of the HF during ontogeny suggests, according to the concerted evolution hypothesis (Finlay & Darling 1995), that the HF is highly constrained and unlikely to be a site of repeated or major selection. Cellular and volumetric properties of the HF are likely to show little variation across taxa with brain mass and body mass.

Scaling of the CA subfields in mammals

RMA exponents for species mean data and independent contrasts are presented in Table 6; and stereological results are presented in the appendix (Tables A1-d). For non-parametric tests the all species (AS) group was stripped of its primate and carnivore species in order to avoid statistical non-independence when comparing the carnivores and primates with other species. The stripped-down

Table 6: Slope estimates for scaling relationships among cell densities in CA1-3 (cells/mm³), volumetric estimates of the hippocampus, and anatomical variables

			Species mean data					*Independent contrasts*				
Taxa	Dependent variable	Independent variable	RMA	R^2	Lower 95% CI	Upper 95% CI	p	RMA	R^2	Lower 95% CI	Upper 95% CI	p
AS	Glial cell density	neuronal density	0.780	0.289	0.629	0.968	0.000	0.971	0.224	0.767	1.253	0.000
(n=39)		StrGc (µm³)	-0.739	0.070	-0.578	-0.946	0.037	-0.793	0.030	-0.651	-1.103	0.193
		StrMol (µm³)	-0.699	0.076	-0.547	-0.894	0.030	-0.773	0.044	-0.588	-1.090	0.116
	Neuronal density	StrGc (µm³)	-0.948	0.337	-0.769	-1.168	0.000	-0.819	0.245	-0.647	-1.056	0.000
		StrMol (µm³)	-0.896	0.319	-0.726	-1.108	0.000	-0.801	0.188	-0.609	-1.097	0.001
	Glia-neuron ratio	StrGc (µm³)	0.833	0.182	0.661	1.050	0.001	0.868	0.117	0.685	1.154	0.008
		StrMol (µm³)	0.788	0.159	0.623	0.996	0.001	0.837	0.059	0.653	1.147	0.065
		brain mass (g)	0.420	0.272	0.337	0.522	0.000	0.589	0.125	0.483	0.819	0.006
		body mass (kg)	0.323	0.228	0.258	0.405	0.000	0.391	0.156	0.309	0.505	0.002
		gestation length (d)	1.168	0.323	0.945	1.442	0.000	1.570	0.118	1.194	2.010	0.008
		EQ	1.307	0.062	1.022	1.671	0.050	-1.660	0.019	-1.261	-2.075	0.306
Carnivores	Glia cell density	neuronal density	0.872	0.095	0.553	1.375	0.032	1.009	0.192	0.777	1.258	0.046
(n=20)		StrGc (µm³)	-0.741	0.002	-0.460	-1.193	0.841	-0.836	0.005	-0.627	-1.171	0.791
		StrMol (µm³)	-0.670	0.003	-0.416	-1.079	0.818	-0.753	0.006	-0.558	-1.040	0.761
	Neuronal density	StrGc (µm³)	-0.850	0.424	-0.588	-1.227	0.002	-0.769	0.228	-0.630	-0.992	0.039
		StrMol (µm³)	-0.769	0.422	-0.532	-1.111	0.002	-0.706	0.186	-0.537	-0.975	0.066
	Glia-neuron ratio	StrGc (µm³)	0.939	0.311	0.630	1.402	0.011	0.908	0.142	0.681	1.271	0.111
		StrMol (µm³)	0.850	0.302	0.568	1.271	0.012	0.834	0.105	0.659	1.143	0.176
		brain mass (g)	0.471	0.301	0.315	0.705	0.012	0.610	0.133	0.500	0.860	0.125
		body mass (kg)	0.351	0.289	0.234	0.528	0.014	0.381	0.167	0.282	0.579	0.082
		gestation length (d)	1.096	0.445	0.764	1.572	0.001	1.510	0.253	1.133	1.948	0.028
		EQ	1.568	0.051	0.985	2.498	0.339	-1.626	0.034	-1.268	-2.228	0.450
Primates	Glia cell density	neuronal density	1.052	0.365	0.792	1.396	0.000	1.185	0.402	0.888	1.492	0.000
(n=34)		StrGc (µm³)	-0.900	0.103	-0.644	-1.257	0.065	-1.771	0.026	-1.346	-2.285	0.413
		StrMol (µm³)	-0.859	0.116	-0.616	-1.198	0.049	-1.151	0.153	-0.874	-1.484	0.040
	Neuronal density	StrGc (µm³)	-0.855	0.288	-0.634	-1.154	0.001	-1.592	0.022	-1.270	-2.180	0.447
		StrMol (µm³)	-0.817	0.275	-0.604	-1.104	0.001	-0.999	0.138	-0.739	-1.250	0.052
	Glia-neuron ratio	StrGc (µm³)	0.784	0.048	0.556	1.107	0.213	-1.425	0.004	-1.094	-1.852	0.750
		StrMol (µm³)	0.749	0.034	0.529	1.059	0.297	-1.054	0.011	-0.814	-1.359	0.601
		brain mass (g)	0.393	0.067	0.280	0.553	0.141	-0.763	0.008	-0.626	-1.083	0.648
		body mass (kg)	0.331	0.069	0.236	0.466	0.132	0.567	0.000	0.431	0.822	0.938
		gestation length (d)	-1.953	0.022	-1.378	-2.768	0.404	-2.718	0.219	-2.174	-3.724	0.014
		EQ	1.189	0.004	0.836	1.691	0.724	-1.562	0.048	-1.234	-2.080	0.261
		Neocortex volume (cm³)	0.529	0.072	0.350	0.799	0.240	0.962	0.001	0.735	1.386	0.906

group is referred to as Shrew-to-Whale (SW). Multivariate analyses for primates were calculated both including and omitting neocortical volume as a regressor. Unless explicitly stated, the calculations below refer to analyses that omitted neocortical volume.

Glial cell density was tested as a function of neuronal density for each taxonomic group and scaled with significant isometry in AS, carnivores, and primates for species mean data. The slopes were grade-shifted between primates (y-intercept = -0.686, lower CI = -0.912, upper CI = -0.499, $p < 0.05$) and both carnivores (y-intercept = 0.484, lower CI = 0.220, upper CI = 0.709, $p < 0.05$) and AS (y-intercept = 0.960, lower CI = 0.689, upper CI = 0.531, $p < 0.05$). Applying weighted least-squares for heteroscedasticity in neuronal density ($K^2 = 6.175$, $p = 0.046$), line-fitting through the origin of LS regression slopes for glial cell density on neuronal density revealed statistically similar slopes for AS (slope = 0.467, lower CI = 0.276, upper CI = 0.658 ; $R^2 = 0.650$, $p < 0.001$), carnivores (slope = 0.550, lower CI = 0.365, upper CI = 0.718 ; $R^2 = 0.190$, $p < 0.001$), and primate (slope = 0.733, lower CI =

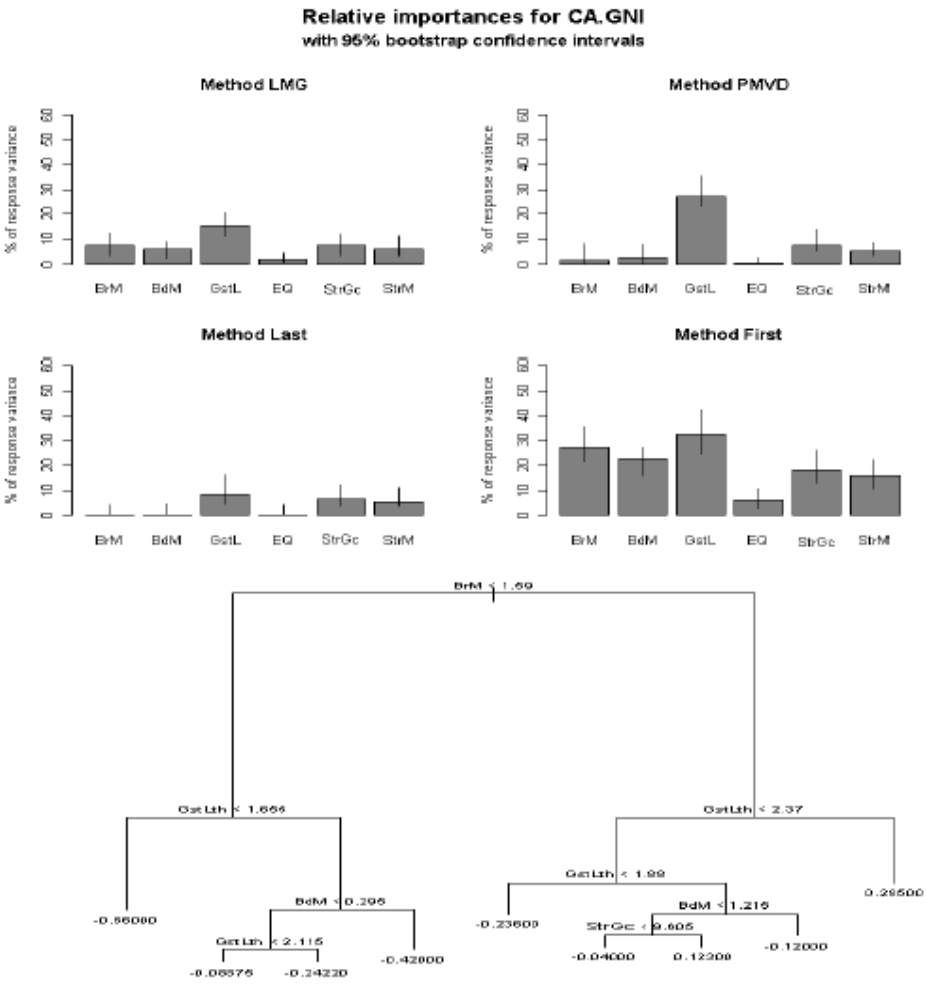

Figure 19a: Recursive trees and relative importance metrics for determining glia-neuron ratio in AS. The variables included (BrM, brain mass; BdM, body mass; GstL, gestation length; EQ, encephalization quotient; StrGr, volumetric estimate of the granule cell layer of the dentate gyrus; StrM, volumetric estimate of the molecular layer of the dentate gyrus) collectively explain 43.34% of the variance observed in glia-neuron ratio in AS. The relative importance metrics lmg and pmvd show the differential contribution of gestation length to be significantly greater than the contributions of each of the other variables (i.e., the 95% CI for the differences do not include zero). The metric last shows comparable (i.e., the 95% CI for the differences include zero) contributions from gestation length, StrGr, and StrM, and the metric first shows all variables, except EQ, to give comparable significant contributions to variance in glia-neuron ratio. The recursive tree model for glia-neuron ratio shows brain mass to be the foremost and greatest (branch lengths are representative of the deviance explained by each variable) contributor to variance in glia-neuron ratio, with gestation length becoming the principal determinant in both small-brained (<39 g) and large-brained (>39 g) species, revealing complexity in the model. The variable StrGr only becomes significant at a terminal node in large-brained, small-bodied (<16 kg) species, reflecting its relative importance in the metric last. All values in (i) and (ii) are log-transformed.

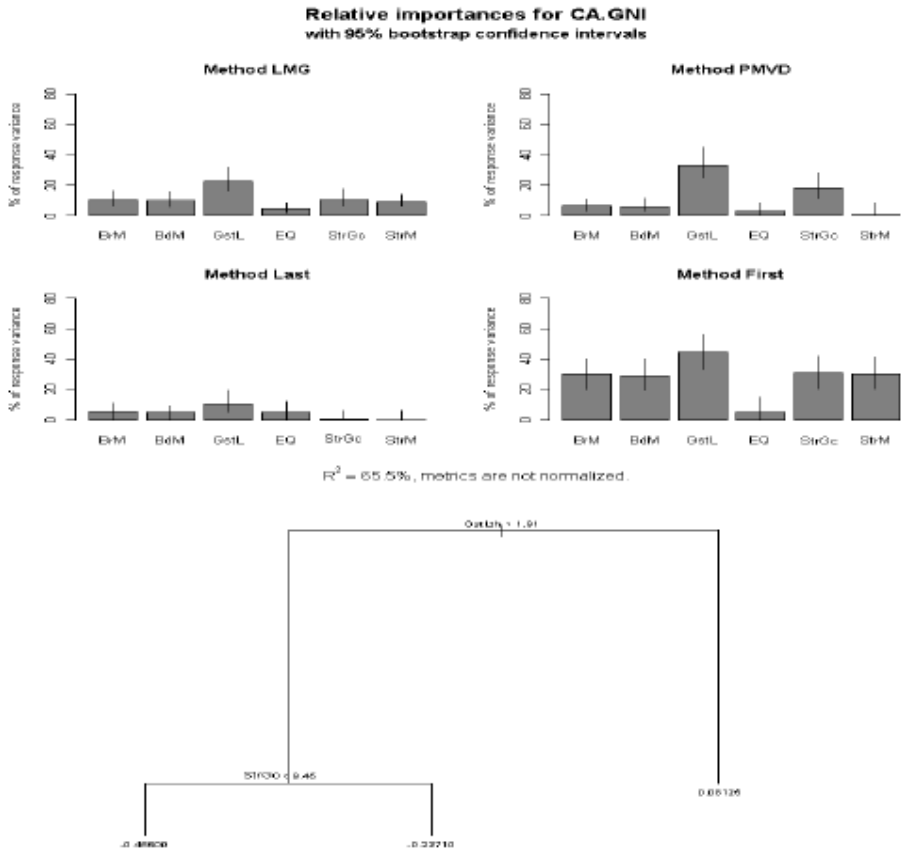

Figure 19b: Recursive trees and relative importance metrics for determining glia-neuron ratio in Carnivores. The variables included (BrM, brain mass; BdM, body mass; GstL, gestation length; EQ, encephalization quotient; StrGr, volumetric estimate of the granule cell layer of the dentate gyrus; StrM, volumetric estimate of the molecular layer of the dentate gyrus) collectively explain 65.5% of the variance observed in glia-neuron ratio. The relative importance metrics lmg and pmvd show the differential contribution of gestation length to be significantly greater than the contributions of each of the other variables (i.e., the 95% CI for the differences do not include zero). The metric last shows comparable (i.e., the 95% CI for the differences include zero) significant contributions from all variables, and the metric first shows all variables, except EQ, to give comparable significant contributions to variance in glia-neuron ratio. The metric pmvd further shows the contribution of StrGr to be significantly greater than the contributions of each of the other variables, except gestation length. The recursive tree model supports the pmvd metric, with gestation length explaining the majority of variance in glia-neuron ratio, and StrGr becoming the principal determinant in species with a short gestation length (<81 d). All values in (i) and (ii) are log-transformed.

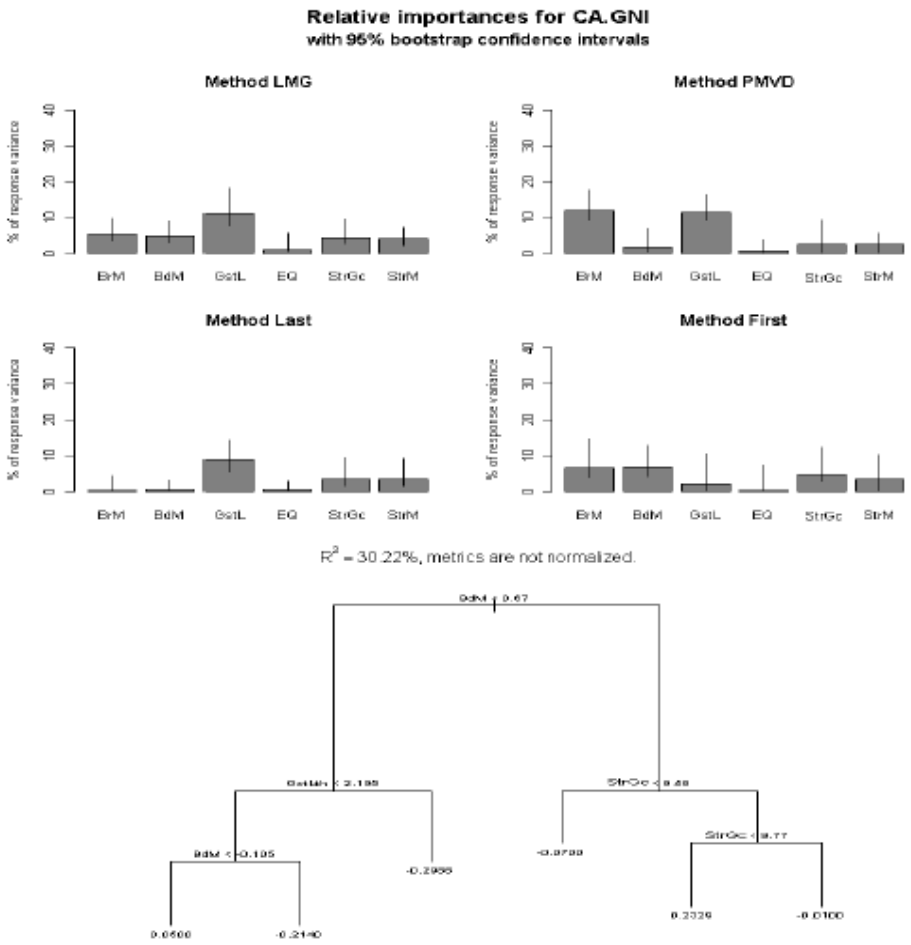

Figure 19c: Recursive trees and relative importance metrics for determining glia-neuron ratio in Primates. The variables included (BrM, brain mass; BdM, body mass; GstL, gestation length; EQ, encephalization quotient; StrGr, volumetric estimate of the granule cell layer of the dentate gyrus; StrM, volumetric estimate of the molecular layer of the dentate gyrus) collectively explain 30.22% of the variance observed in glia-neuron ratio. The relative importance metric lmg shows the differential contribution of gestation length to be significantly greater than the contributions of each of the other variables (i.e., the 95% CI for the differences do not include zero). The metric pmvd shows brain mass and gestation length to make comparable contributions (i.e., the 95% CI for the differences include zero), but greater contributions than any of the other variables. The metric last shows comparable contributions from gestation length, StrGr, and StrM, and the metric first shows comparable contributions from all variables, except EQ. Perhaps surprisingly, the recursive tree displays body mass as the foremost contributor to variance in glia-neuron ratio, separating large-bodied catarrhines from small-bodied platyrrhines, tarsiers, and strepsirrhines. In species with a large body mass (>4.7 kg), StrGr is the principal determinant of glia-neuron ratio, whereas in species with a small body mass (<4.7 kg), gestation length is the principal determinant. All values in (i) and (ii) are log-transformed.

0.539, upper CI = 0.927; R^2= 0.381, $p < 0.001$) independent contrasts. In AS, body mass, brain mass, and gestation length scaled with significant positive exponents with glia-neuron ratio.

Glia-neuron ratio scaled significantly against gestation length in carnivores for species mean data and independent contrasts, although in primates the relationship was only significant for independent contrasts, suggesting that the species mean data obscured grade shifts among major taxonomic groups within the primate dataset (Garland *et al* 1993).

Stepwise AIC (Akaike's Information Criterion) multiple regressions showed (Table A3) glial cell density to be a significant predictor of neuronal density in AS ($t = 5.160$, $p < 0.001$), carnivores ($t = 2.607$, $p < 0.05$), and primates ($t = 4.470$, $p < 0.001$), and neuronal density to be a significant predictor of glial cell density in AS ($t = 5.514$, $p < 0.001$), carnivores ($t = 2.272$, $p < 0.05$), and primates ($t = 4.385$, $p < 0.001$). Pearson product-moment correlations between glial cell density and neuronal density supported results from the relative importance metrics for AS ($r = 0.568$, $p < 0.001$) and primates ($r = 0.604$, $p < 0.001$).

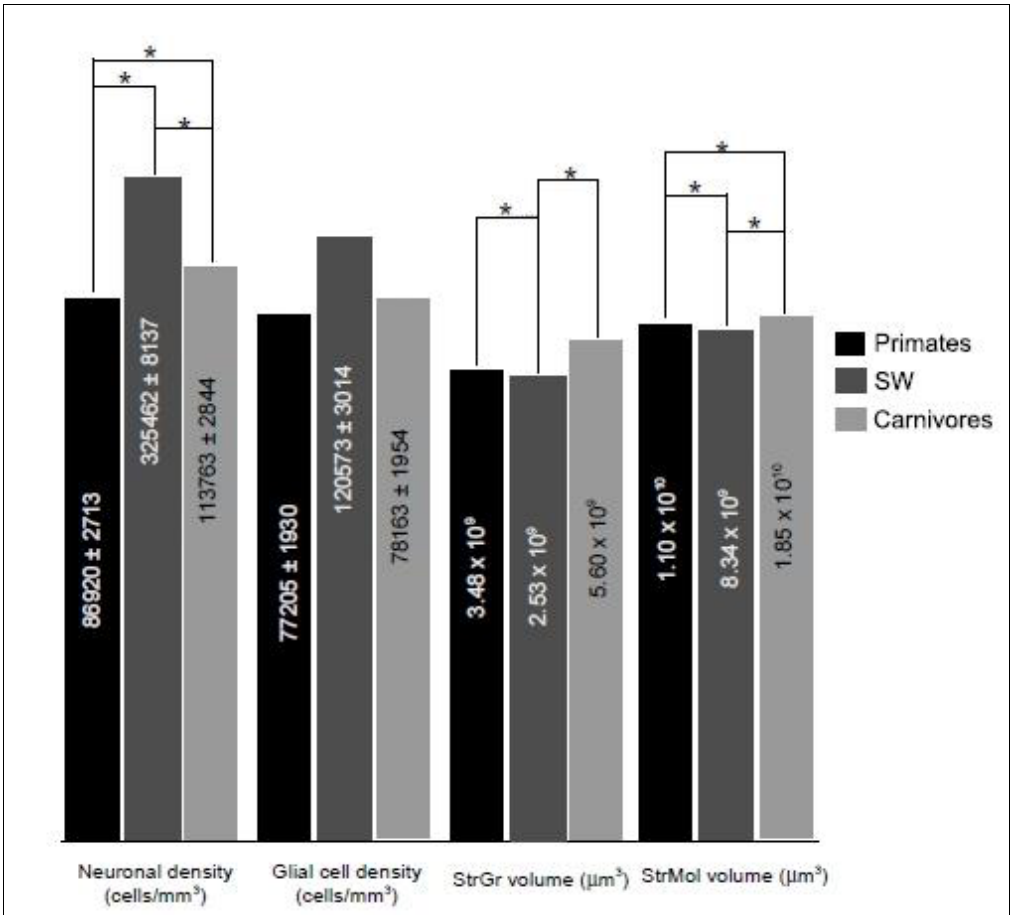

Figure 20: Significant differences in unplanned multiple comparisons following from Kruskal-Wallis tests are shown with asterisks, when the observed difference between two groups exceeded the critical difference, for mean values for neuronal density (c2=10.33, p=0.01) and glial cell density (c2=2.20, p=0.33) in CA1-3, and volumetric estimates of StrGr (c2=15.14, p=0.00) and StrMol (c2=28.72, p=0.00) of the dentate gyrus in three taxonomic groups. Bars (but not values) of neuronal density and glial cell density are presented as log(base 4)-transformed and bars of StrGr and StrMol are presented as log(base 10)-transformed. Abbreviations: StrGr, stratum granulosum; StrMol, stratum moleculare; SW, Shrew-to-Whale.

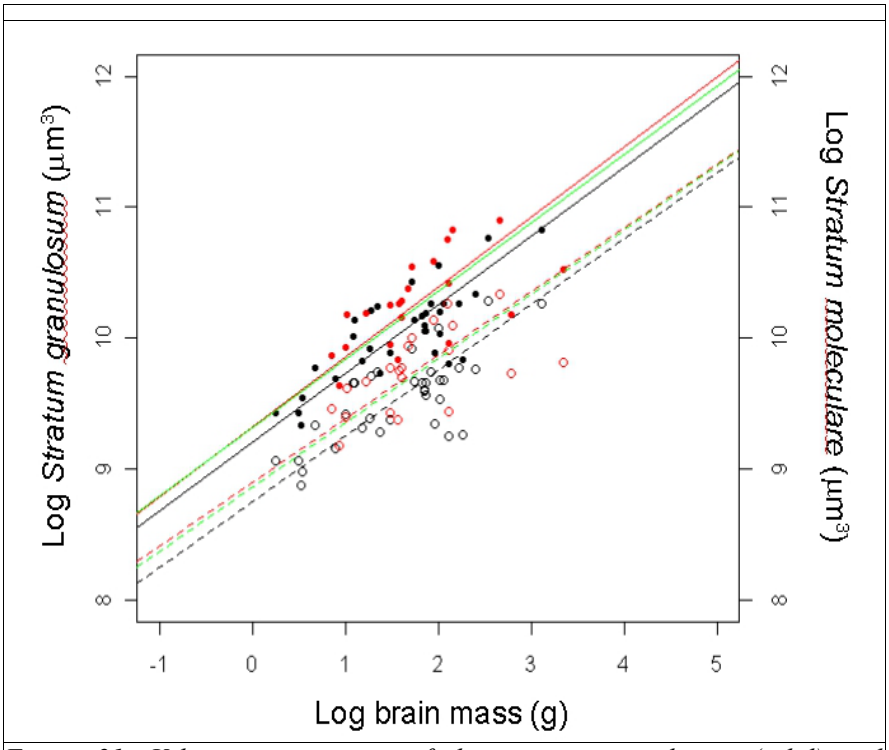

Figure 21: Volumetric estimates of the stratum granulosum (solid) and stratum moleculare (hollow) are presented in log-log regression plots as functions of brain mass for AS (green), carnivores (red), and primates (black). The slopes and y-intercepts for stratum granulosum with brain mass are statistically similar in AS (y = 0.490x + 8.86, R2 = 0.712, p < 0.05), carnivores (y = 0.485x + 8.90, R2 = 0.478, p < 0.05), and primates (y = 0.502x + 8.75, R2 = 0.546, p < 0.05); the slopes and y-intercepts for stratum moleculare with brain are also statistically similar in AS (y = 0.522x + 9.31, R2 = 0.655, p < 0.05), carnivores (y = 0.522x + 9.33, R2 = 0.421, p < 0.05), and primates (y = 0.525x + 9.21, R2 = 0.564, p < 0.05), demonstrating the conserved organization of the dentate gyrus with brain size across eutherian phylogeny.

Stepwise AIC multiple regressions showed gestation length to be a significant predictor of glia-neuron ratio in AS (t-value = 4.63, p < 0.001), carnivores (t-value = 2.07, p < 0.05), and primates (t-value = -2.84; p<0.01). Recursive tree models supported these results for AS and carnivores (Figs. 19a-c). Relative importance metrics showed gestation length to be the principal contributor to variance in glia-neuron ratio in AS (30%) and carnivores (40%), and also in primates (15%) when neocortical volume was included as a regressor .

Pearson product-moment correlations showed glia-neuron ratio to be strongly positively correlated ($r > 0.476$, $p < 0.05$) with brain mass, body mass, and gestation length in AS and carnivores. In primates, brain mass was also shown to be a significant predictor of glia-neuron ratio ($t = 3.04$, $p < 0.01$).

The CA subfields and the dentate gyrus

Two-sample Kolmogorov-Smirnov tests showed significant differences between carnivores and primates in their distributions of StrGr volume ($D = 0.460$, p=0.007) and StrMol volume ($D = 0.837$, p = 0.000), and Kruskal-Wallis sum rank and comparison tests showed significant differences between SW and both carnivores and primates in StrGr, StrMol, and glia-neuron ratio (Fig. 20).

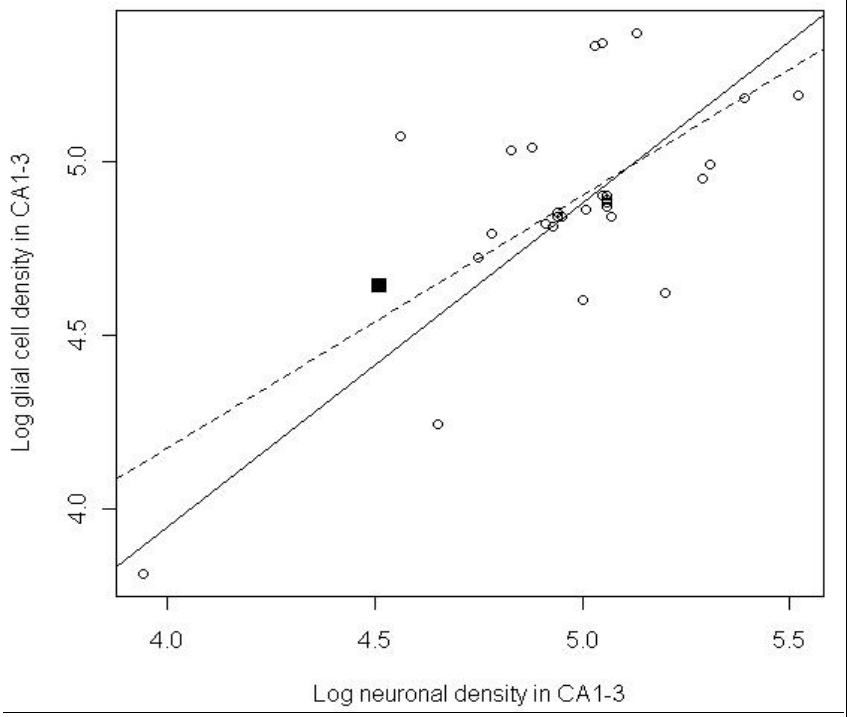

Figure 22: The scaling in CA1-3 of glial cell density as a function of neuronal density for species mean data in primates. The dotted line represents the LS regression lines fitted to non-human primates for glial cell density against neuronal density (y = 0.0.727x + 1.226, R2 = 0.261, p < 0.05); the solid line is fitted to independent contrasts mapped back into tip species space (y = 0.930x + 0.227, R2 = 0.185, p < 0.05), calculated to predict hypothetical species points attached to the branch leading to humans by pruning humans from the tree and rerooting it at the last common ancestor of humans and non-human primates.

Both StrGr and StrMol scaled with significant exponents against brain mass and body mass for species mean data and independent contrasts in AS, carnivores, and primates (Fig. 21). These exponents were not shown to be statistically different ($p < 0.05$).

Stepwise AIC multiple regressions (Table A3) found StrGr to be a significant predictor of glia-neuron ratio in AS (t-value = 2.302, p = 0.025) and carnivores (t-value = 2.148, p = 0.050), but these results were not supported by relative importance metrics (S Figs. 1b,h).

Human predictions for the cellular hippocampus based on primates and other mammals

Old World and New World monkey species mean data and independent contrasts were used to generate log-log LS regression predictions of glial cell density on neuronal density (Fig. 22). The mean observed human value for glial cell density was not significantly different from the predicted value based on the non-human primate species mean LS regression of glial cell density against neuronal density (t = 6.034, p = 0.455). This prediction held within 95% PI for independent contrasts.

Non-human species mean data and independent contrasts were used to generate log-log LS regression predictions for glial cell density on neuronal density, and glia-neuron ratio on brain mass (Fig. 23). The mean observed human value for glial cell density fell within the 95% PI based on neuronal density (4%), but observed glia-neuron ratio fell outside the 95% PI based on brain mass (-12%). These predictions held for independent contrasts.

Mode of placentation and the hippocampus

The glia-neuron ratio was tested as functions of brain mass, body mass, EQ, gestation length, StrGr, and StrMol in placental groups (Table 7). Glia-neuron ratio was found to scale as a function of gestation length with significant RMA exponents in both haemochorial and endotheliochorial species for species mean data and independent contrasts. Epitheliochorial species showed significantly different RMA scaling exponents and y-intercepts for StrGr as a function of brain mass compared to both haemochorial and endotheliochorial species (Fig. 24).

Table 7: Slope estimates for scaling relationships among cell densities in CA1-3 (cells/mm³), volumetric estimates of the dentate gyrus, and anatomical variables

Group	Dependent variable	Independent variable	*Species mean data*					*Independent contrasts*		
			RMA	R^2	Lower 95% CI	Upper 95% CI	p	RMA	R^2	p
Epitheliochorial (n=8)	Glia cell density	neuronal density	1.868	0.000	0.699	4.992	0.965	0.994	0.259	0.303
		StrGc (μm³)	-0.789	0.658	-0.420	-1.482	0.027	-0.772	0.668	0.091
		StrMol (μm³)	-0.630	0.611	-0.323	-1.226	0.038	-0.673	0.658	0.096
	Neuronal density	StrGc (μm³)	-0.422	0.019	-0.159	-1.121	0.771	-0.825	0.646	0.054
		StrMol (μm³)	-0.337	0.015	-0.127	-0.896	0.790	-0.722	0.601	0.070
	Glia-neuron ratio	StrGc (μm³)	-0.883	0.443	-0.406	-1.922	0.103	0.799	0.003	0.924
		StrMol (μm³)	-0.705	0.417	-0.319	-1.557	0.117	0.700	0.001	0.958
		brain mass (g)	-0.495	0.228	-0.204	-1.205	0.278	0.403	0.049	0.634
		body mass (kg)	-0.308	0.255	-0.128	-0.739	0.247	0.255	0.098	0.495
		gestation length (d)	-1.637	0.935	-1.226	-2.186	0.000	1.131	0.024	0.739
		EQ	1.464	0.184	0.587	3.650	0.337	-1.099	0.323	0.183
Endotheliochorial (n=22)	Glia cell density	neuronal density	1.010	0.079	0.654	1.559	0.206	1.080	0.063	0.271
		StrGc (μm³)	0.690	0.012	0.440	1.080	0.629	0.663	0.057	0.299
		StrMol (μm³)	0.669	0.010	0.427	1.049	0.655	0.634	0.049	0.333
	Neuronal density	StrGc (μm³)	-0.683	0.261	-0.462	-1.010	0.015	-0.614	0.238	0.025
		StrMol (μm³)	-0.663	0.268	-0.449	-0.978	0.014	-0.587	0.220	0.032
	Glia-neuron ratio	StrGc (μm³)	0.823	0.271	0.558	1.213	0.013	0.777	0.346	0.005
		StrMol (μm³)	0.798	0.269	0.541	1.178	0.013	0.743	0.313	0.008
		brain mass (g)	0.432	0.333	0.297	0.626	0.005	0.555	0.292	0.011
		body mass (kg)	0.317	0.360	0.220	0.457	0.003	0.360	0.349	0.005
		gestation length (d)	1.039	0.514	0.754	1.430	0.000	1.232	0.291	0.012
		EQ	1.435	0.027	0.916	2.247	0.468	-1.747	0.023	0.516
Haemochorial (n=34)	Glia cell density	neuronal density	0.676	0.444	0.516	0.885	0.000	-0.034	0.086	0.116
		StrGc (μm³)	-0.774	0.152	-0.556	-1.078	0.025	-0.824	0.122	0.054
		StrMol (μm³)	-0.740	0.144	-0.531	-1.033	0.029	-0.791	0.156	0.028
	Neuronal density	StrGc (μm³)	-1.147	0.484	-0.884	-1.488	0.000	-1.419	0.214	0.009
		StrMol (μm³)	-1.096	0.455	-0.839	-1.432	0.000	-1.514	0.170	0.021
	Glia-neuron ratio	StrGc (μm³)	0.859	0.335	0.640	1.152	0.000	0.829	0.079	0.133
		StrMol (μm³)	0.821	0.314	0.609	1.107	0.001	0.773	0.016	0.505
		brain mass (g)	0.427	0.478	0.329	0.555	0.000	-0.041	0.108	0.076
		body mass (kg)	0.349	0.413	0.264	0.460	0.000	0.374	0.112	0.070
		gestation length (d)	1.342	0.508	1.040	1.731	0.000	1.962	0.158	0.033
		EQ	1.535	0.143	1.110	2.122	0.030	-1.787	0.001	0.851

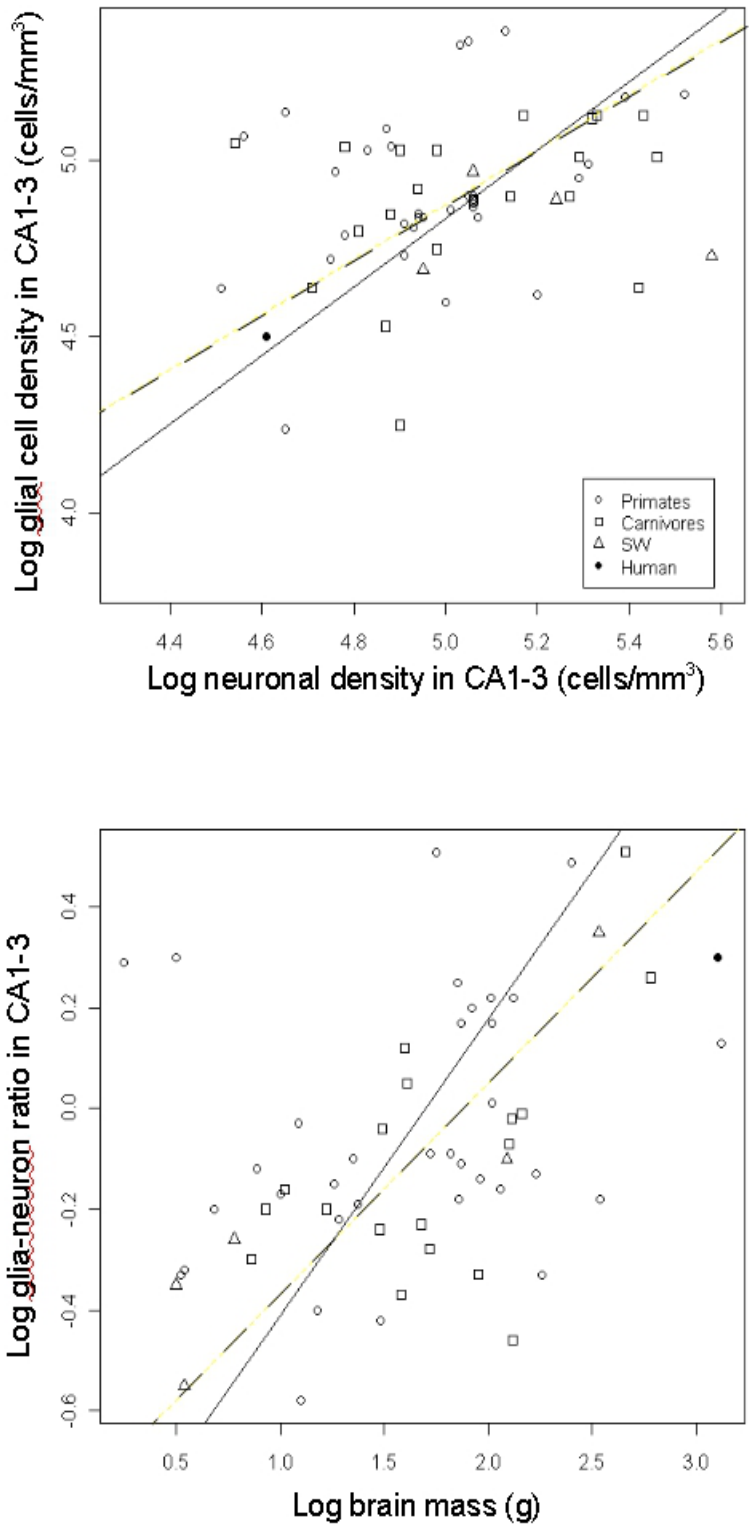

Figure 23: (top) The scaling in CA1-3 of glial cell density as a function of neuronal density and (bottom) glia-neuron ratio as a function of brain mass for species mean data. The dotted lines represent the LS regressions fitted to non-human species for glial cell density against neuronal density (y=0.814x + 0.975, r=0.664, p=0.000) and glia-neuron ratio against brain mass (y=0.469x – 0.789, r=0.610, p=0.000). The solid lines represent the LS regressions fitted to independent contrasts mapped back into tip species space, calculated to predict a hypothetical species point attached to the branch leading to humans by pruning humans from the tree and rerooting it at the last common ancestor of humans and non-human mammals.

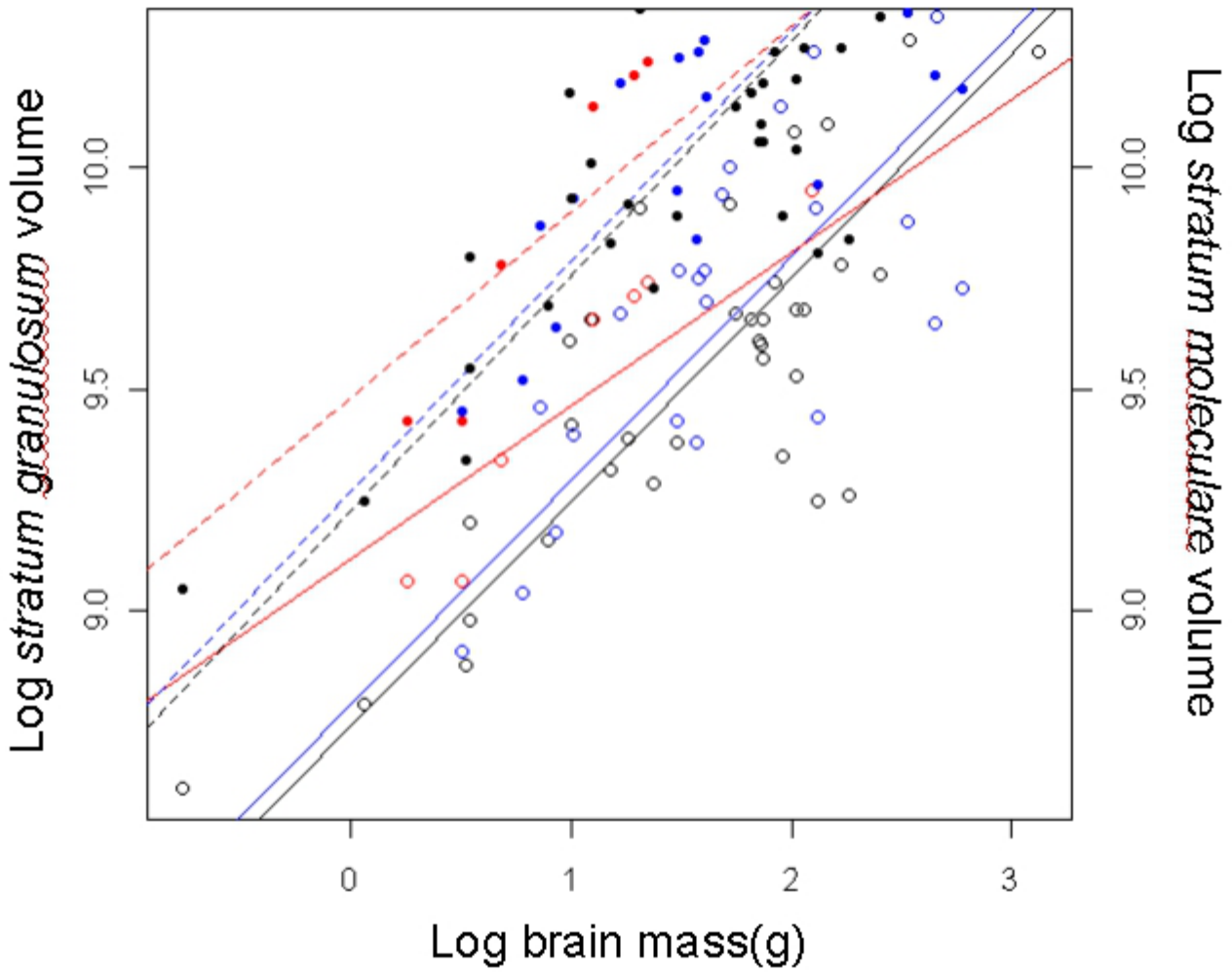

Figure 24: A log-log regression plot of stratum granulosum (solid lines) as a function of brain mass shows similar RMA exponents for (black) haemochorial (slope = 0.504, lower CI = 0.407, upper CI = 0.616, R2 = 0.593, p < 0.05) and (blue) endotheliochorial (slope = 0.505, lower CI = 0.410, upper CI = 0.620, R2 = 0.489, p < 0.05) species, but significantly different exponents for (red) epitheliochorial (slope = 0.315, lower CI = 0.222, upper CI = 0.401, R2 = 0.887, p < 0.05) species. RMA exponents for stratum moleculare (dotted lines) as a function of brain mass, however, show similar exponents for haemochorial (slope = 0.525, lower CI = 0.427, upper CI = 0.645, R2 = 0.589, p < 0.05), endotheliochorial (slope = 0.520, lower CI = 0.379, upper CI = 0.713, R2 = 0.497, p < 0.05), and epitheliochorial (slope = 0.419, lower CI = 0.263, upper CI = 670, R2 = 0.803, p < 0.05) species. The regressions also revealed significantly different y-intercepts between epitheliochorial species and both haemochorial (p = 0.018) and endotheliochorial (p = 0.031) for StrGr, but not for StrMol, as a function of brain mass.

DISCUSSION II

I have demonstrated that the scaling of glia to neurons in the hippocampal subfields is conserved in mammals. Likewise, the scaling of glial cell and neuronal density, glia-neuron ratio, and volumetric estimates of the dentate gyrus against brain mass, body mass, and gestation length are also conserved. Humans did not display significant deviations from mammalian predictions. Considering the largely conserved circuitry, cytoarchitecture, and function of the hippocampal formation in mammalian evolution, this is not surprising. Minor grade-shifts in the scaling of glial cell density with neuronal density between primates and other mammals (Fig. 25), as well as significant differences in mean values of neuronal density between carnivores and primates, show that conserved organization and functionality in the hippocampus has not proscribed quantitative modification. However, the central importance of the hippocampus (e.g., to respiration) it seems has resulted in its safeguarding against disruptive evolutionary changes. More interestingly, gestation length was consistently shown to be a stronger predictor than brain or body mass of cellular and volumetric properties of the hippocampus; and mode of placentation clearly figures in the regulation of these properties. In agreement with evidence demonstrating an effect of prenatal nutrition on hippocampal development (Guesry 1998; Bedi 2003; Niculescu & Lupu 2009), I propose that the conserved composition of the hippocampus observed in my data is a consequence of differentially evolved maternal investment strategies in different mammalian taxa, rather than positive selection on safeguarding the hippocampus specifically. Since the hippocampus develops early in ontogeny, and despite its major role in behavior, it appears largely resistant to evolutionary modification and therefore its closely regulated quantitative cellular distributions may be a minimum production of maternal investment. As such, my data demonstrate a critical evolutionary role for prenatal development in the maintenance and evolution of neurogenetic scheduling.

Fetal development regulates evolution of the hippocampus

The mean values of glia-neuron ratios in carnivores and primates were not shown to be significantly different across taxonomic groups. Predictions for glia density in humans as a function of neuron density based on a LS regression of AS showed that humans do not deviate from the mammalian pattern. Volumetric estimates of the dentate gyrus were shown to scale isometrically with glia-neuron ratio in AS and contribute significantly more to variance in glia-neuron ratio than either

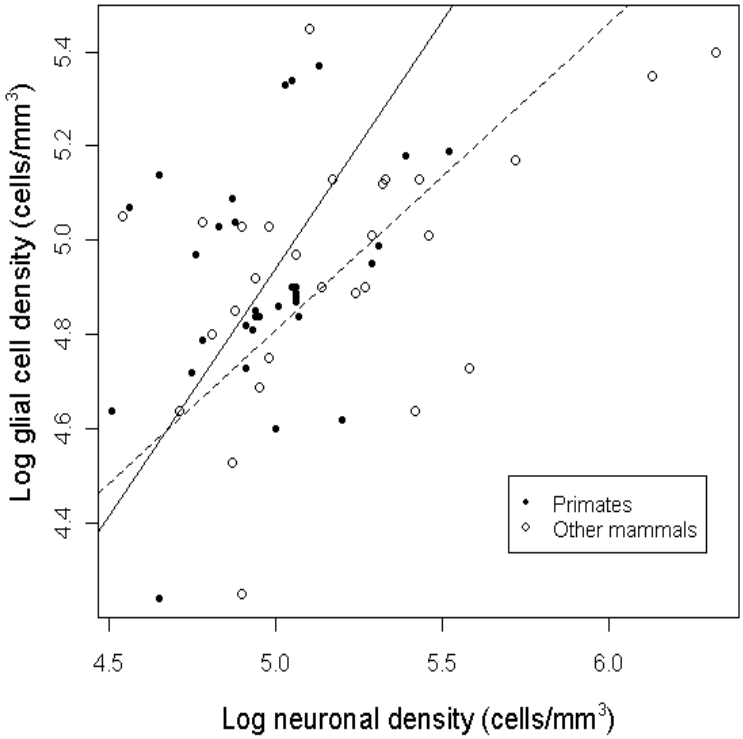

Figure 25: Log-log regression of neuronal density with glial cell density for species mean data in primates (solid line) and other mammals (dashed line). Although there is no significant difference in the RMA slopes for primates (slope = 1.052, lower CI = 0.792, upper CI = 1.396, R2=0.365, $p < 0.05$) and other mammals (slope = 0.654, lower CI = 0.465, upper CI = 0.921, R2 = 0.204, $p < 0.05$), there is a significant grade-shift between the primates (y-intercept= -0.307, lower CI=-1.030, upper CI=0.350) and other mammals (y-intercept = 1.555, lower CI = 0.784, upper CI = 2.191, $p < 0.05$).

brain or body mass. These data indicate that the cytoarchitecture and structure of the hippocampus are conserved in mammals. However, gestation length was the greatest contributor to variance in glia-neuron ratio in AS, and neuronal density scaled as a function of StrGr volume and brain mass with a considerably (2-3 times) steeper slope in haemochorial than epitheliochorial species. Furthermore, StrGr was shown to scale as a function of brain with a significantly different slope in epitheliochorial compared to haemochorial or endotheliochorial species.

Prenatal development, as effected by gestation length and mode of placentation, may alter evolution of the hippocampus. Studies of maternal nutrition during gestation have demonstrated that malnutrition may have a specific affect on development of the hippocampus (Gordon 1997; Guesry 1998; Mattson 2003; Mattson & Shea 2003; Cserjesi *et al* 2007), manifested in a decreased proliferation of neural precursors, depressed adult population of granule cells, and retarded neuronal differentiation in the dentate gyrus (Bedi 2003; Tozuka *et al* 2009). There is further evidence that prenatal nutrition affects the population of apoptotic cells in the CA subfields of the hippocampus (Niculescu & Lupu 2009). It is possible, therefore, that the resulting deficit in cells may be due to changes in neurogenetic scheduling (i.e., the timing of cell-cycles). Similar studies of the cerebellum, testing whether maternal malnutrition during gestation affects adult neuronal populations, have only produced ambiguous results (Persson & Sima 1975; Conradi & Muntzing 1985; Bedi 2003), indicating that the hippocampus may be especially

vulnerable to changes in prenatal nutrient transfer. One explanation, which would help resolve a specific role for placentation in hippocampal development, is the differential production of leptin in different taxa. Leptin is a protein hormone produced by adipose tissue and placenta that contributes to the regulation of maternal energy balance (Zhang *et al* 1994; Pelleymounter *et al* 1995; Trayhurn *et al* 1998), affects fetal growth and development (Ashworth *et al* 2000), and is essential, at least in early stages of gestation (Mounzih *et al* 1998), to successful parturition in mammals. Leptin has also been shown to be expressed in the hippocampus (Louis & Myers 2007) and even affect long-term potentiation in CA1 (Oomura *et al* 2006). As placental leptin expression and secretion are species-specific traits that may have been adapted for different levels of adiposity during gestation in different species (Zhao *et al* 2003), I suggest that the diversity of fat storage necessary for different modes of placentation has influenced selection for increased (or decreased) expression of leptin. If, as the above evidence suggests, leptin plays an important role in development of the hippocampus, then mode of placentation, which determines the fat storage required for gestation (Enders & Carter 2004) and thus the necessary level of leptin expression required for parturitional success in a species (e.g., Kind *et al* 2005), may directly influence the evolutionary development of the hippocampal formation. These results more generally suggests that selection for a biological process in the placenta during evolution (e.g., longer gestation length or decreased placental invasiveness) affects brain development, perhaps through an influence on the timing of early cell-cycles.

CHAPTER 7
DEVELOPMENTAL CONSTRAINTS

The mammalian brain is composed of structurally distinct cell groups, which are configured into topographical maps underlying sensorimotor and cognitive functions (Kaas 1982; Passingham *et al* 2002; Krubitzer 2009). While it is clear that some species are behaviorally adapted and display remarkable specializations, and that certain brain areas are devoted to mediating quite specific behaviors, the degree to which one region can evolve independently of functionally unrelated regions is poorly understood. On one hand, it has been suggested that the size of different brain regions evolves in concert due to constraints of neural developmental timing (Finlay & Darlington 1995). In contrast, it has been proposed that developmental constraints are not sufficient to overpower the ability of regions to evolve independently (Barton & Harvey 2000; de Winter & Oxnard 2001).

Comparative studies of connectivity and circuitry in the mammalian brain confirm many of the claims of concerted evolution. Structural components in the trans-cerebellar loops, for example, have been observed to covary in size across species (Voogd 2003). Similarly, reduction in the amount of retinal afferents has been shown to cause corresponding reductions in the lateral geniculate nucleus and visual cortex (e.g., Rakic *et al* 1991; Cooper *et al* 1993b; Dehay *et al* 1996b). Epigenetic population-matching, wherein competition for some trophic factor produced by a target region generates an equal number of available target cells to projection neurons (Katz & Lasek 1978; Linden 1994; Yeo & Gautier 2004), may, in part, explain these phenomena. However, patterns predicted by epigenetic population-matching are not observed universally – different species tend to elaborate pathways from a common source differently (Northcutt & Wulliman 1988) – and, without developmental data, it is impossible to say that the population-matching is epigenetically controlled (see Bunker & Nishi 2002). It may be that epigenetic cascades operate successfully in linear circuits, but not in reticulate circuits, which is why an examination of the available evidence suggests that the structure of region sizes in the mammalian brain is neither completely constrained by developmental timing nor completely free to evolve independently.

Volumetric size, however, is a poor estimate of the cellular composition of brain tissue (Azevedo *et al* 2009). Increasing evidence for phyletic variation in the cellular organization of homologous regions of mammalian brains (e.g., Preuss & Coleman 2002; Hammock & Young 2005; Hutsler *et al* 2005; Sherwood & Hof 2007) has demonstrated that interspecific variation in factors underlying brain size variation (e.g., cellular density, degree of dendritic arborization, and cell soma

size) may also reflect evolutionary adaptations within lineages in conjunction with morphological or volumetric changes. Comparing cellular properties in disparate brain regions across taxa provides a new perspective to explore the extent to which developmental constraints act on the evolving mammalian brain.

My aim here was to test, using the materials and methods outlined in chapters 5 and 6, in addition to granular cell volume estimates in the cerebellum, whether the density of neurons and glia co-varies across different regions of the brain among mammalian species. The regions examined here – the primary visual cortex and subfields of the hippocampal formation – are not directly interconnected with one another and therefore may be free to evolve independently. From evidence that the mammalian brain is loosely modularized (see Krubitzer 2007), such that one region is rarely isolated for specialization at the expense of others, but that the design of modularization itself can be selected, it is likely that the degree to which certain brain regions must evolve in concert and can evolve independently will carry a deep phylogenetic signal. In the current study, I compared neuronal and glial cell densities in the primary visual cortex (V1) and subfields of the hippocampus proper (CA1-3) in 37 primate species, 21 carnivore species, and 14 other mammalian species (spanning 11 orders). I provide evidence for developmental constraints controlling the concerted evolution of neuronal and glial cell densities in disparate regions of the mammalian brain, but also find evidence of specialization in the proportions of these different cells along the primate lineage.

Cerebellar function and evolution

In order to understand the implication of findings based on scaling relationship between the cerebellum and cortical structures, it is necessary to briefly review what the cerebellum has been observed to do, and how it has adapted in mammalian evolution.

At the gross anatomy level (Fig. 26), the cerebellum consists of a median vermis and two lateral hemispheres (Braitenberg *et al* 1997; Dom & Strick 2003; Kelly & Strick 2003; Rilling 2007). The main divisions of the cerebellum are the corpus cerebelli and cerebellar auricle, which are formed by the cerebellar cortex and, sometimes, a distinct layer of white matter. The cerebellar cortex has three layers: outer molecular layer, middle Purkinje layer, and inner granular layer (Fig. 27). The main function of the cerebellum appears to be motor-related (Ghez & Thach 2000; Sultan & Glickstein 2007), and it has been shown to be involved in reflex modulation (Robinson 1976; De Zeeuw *et al* 1998; Kishimoto & Kano 2006; Timmann & Daum 2007) and accurate prediction of goal-oriented

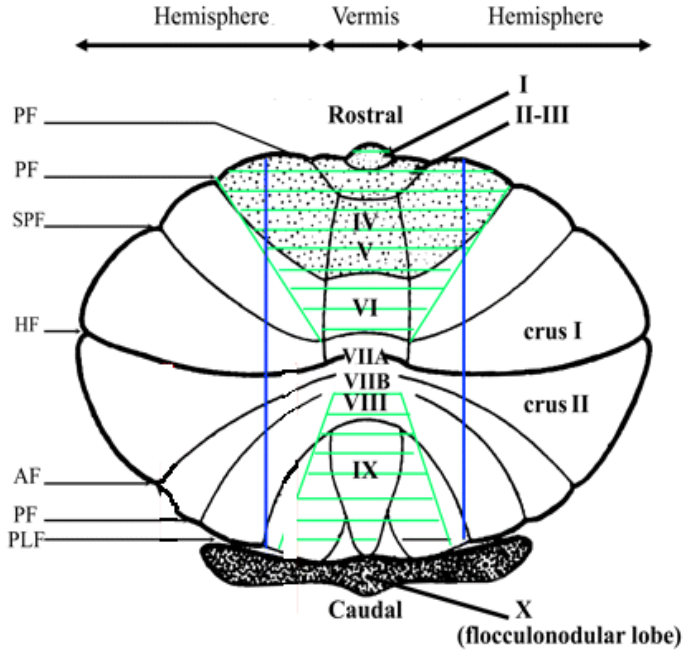

Figure 26. *Diagram of the flattened cerebellar surface. It is is divided into lobes and lobules (I-X) by five deep fissures (the primary fissure (PrF), the posterior superior fissure (SPF), the horizontal fissure (HF), the pre-pyramidal fissure (PpF), and the posterolateral fissure (PLF)): the flocculonodular lobe on the ventral surface, which receives input from the primary vestibular afferents and governs eye movements and body equilibrium during stance and gait; the vermis, which occupies the midline of the cerebellum, has its primary inputs from spinocerebellar tracts carrying somatosensory information from proximal and axial body parts; the intermediate portions of the hemispheres lateral to the vermis, which relay information to interposed cerebellar nuclei to affect both ascending and descending efferents to nuclei involved in the coordination of distal limbs and muscles; and the lateral hemispheres, whose main source of afferents is the cerebral cortex and whose main output is directed to the dentate nucleus, which projects to the parvicellular portion of the red nucleus and ventrolateral thalamus. Adapted from Habas et al (2009).*

tasks via control of saccadic movements (Masao 1984; Takagi *et al* 1998). The parallel encephalization of the dentate nucleus of the cerebellum and the frontal cortex of the cerebrum observed in phylogenetic and ontogenetic development in primates (Leiner *et al* 1986 1989) has lead to suppositions that the cerebellum may have a role beyond motor function. While clinical signs of impairment to cortico-cerebellar networks in patients with cerebellar lesions have only been minor compared to patients with damage to cortical areas (Timmann & Daum 2007), suggesting that the role of the cerebellum is primarily related to motor function, non-motor functional hypotheses for the cerebellum now include spatial cognition, visuo-spatial problem solving, verbal fluency, procedural learning, syntax, timing, semantic phonological word retrieval, sensory discrimination, and abstract reasoning (Dow 1988; Bower 1997; Leiner *et al* 1997; Desmond & Fiez 1998; Schmahmann 1998; Ghez & Thach 2000; Rapoport *et al* 2000; Marien *et al* 2001; Ivry & Spencer 2004; Ito 2005; Thach 2007). Based on these motor and non-motor hypotheses of cerebellar function, what assumptions can we make when comparing cerebral and cerebellar structures across phylogenies?

Work on cellular scaling in the cerebellum and cerebral cortex have, it appears, revealed some general rules. The relative size of the cerebellum fails to keep pace with the relative size of the cerebral cortex as the brain gets larger with phylogeny (Clark *et al* 2001; Sultan 2002). In *Eulipotyphla*, primates, and rodents, the cerebellum and cerebral cortex increase in absolute size as the brain encephalizes; but, juxtaposed to the cerebral cortex, the relative size of the cerebellum remains static

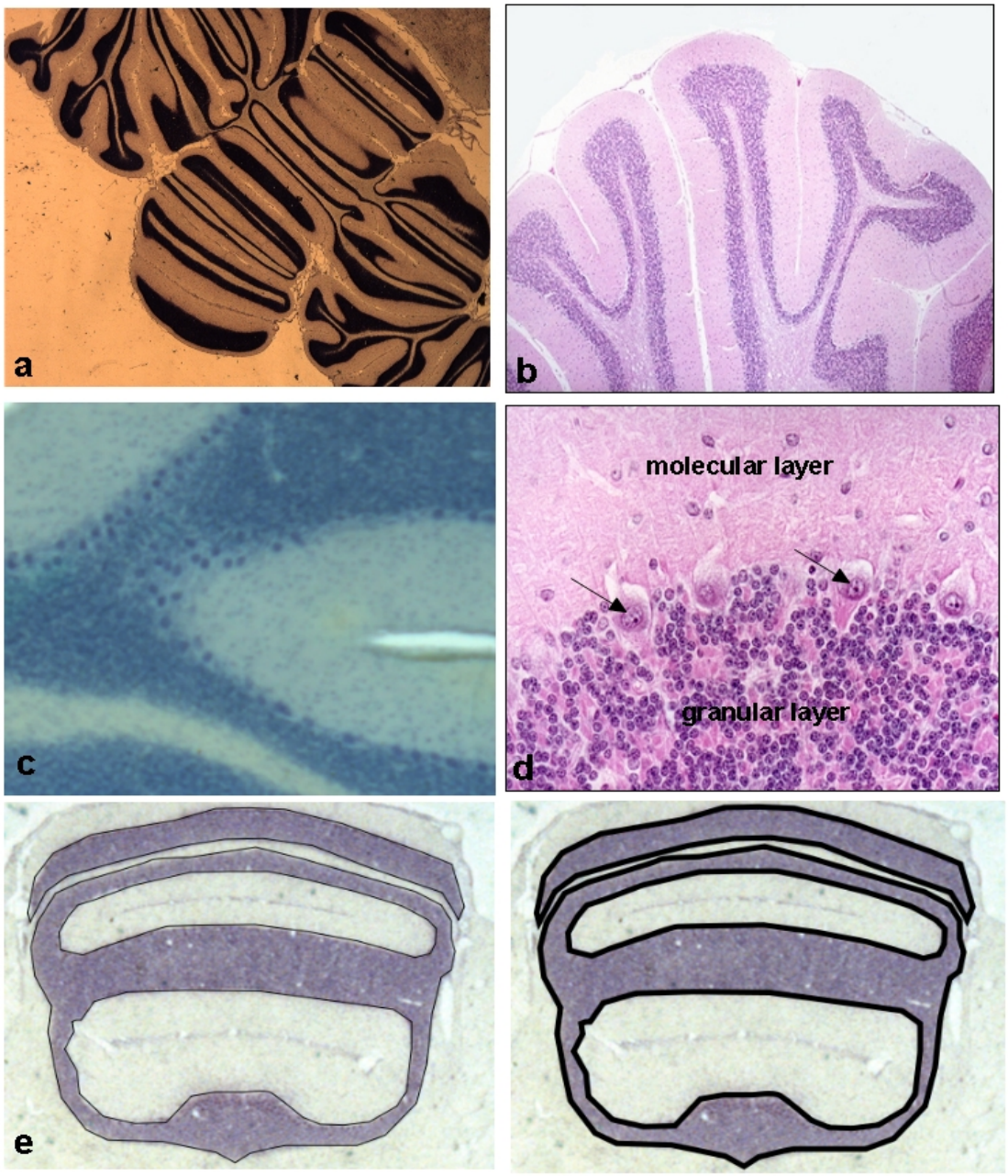

Figure 27: The outer molecular layer and inner granular layer of the cresyl violet-stained cerebellum are easily distinguished in (a) and (b). The Purkinje cells (arrows), which constitute a middle layer, become distinct from the granule cells in (c) and (d). (e) granule cell layer of the cerebellum was distinguished from the white matter by dramatic changes in cell type and density. The volume of the granule cell layer of the cerebellum was estimated using Cavalieri's method. taken at the National Museum of Health and Medicine, Washington, D.C (a, Potos flavus, 1x objective; c, Macaca mulatta*, 10x objective) and Institute of Psychiatry, King's College London (b,* Mus musculus*, 4x objective; d, Mus musculus, 40x objective).*

(Stephan *et al* 1981; Clark *et al* 2001; Sultan 2002). Nonetheless, the vast majority of neurons in the mammalian brain are in the cerebellum – 60% of all neurons in the mouse, small shrew, and marmoset; 70% in the rat, guinea pig, and macaque; and 80% in the common agouti, galago, and human (Andersen *et al* 1992; Herculano-Houzel *et al* 2006, 2007; Azevedo *et al* 2009; Sarko *et al* 2009). So, contrary to the volumetric preponderance of the cerebral cortex in encephalized brains – and despite the different cerebral neuronal scaling rules observed in different mammalian orders (Herculano-Houzel *et al* 2006, 2007) – the number of neurons in the cerebellum covaries with the number of neurons in the cerebral cortex at a rate of about four to one, regardless of brain size (Herculano-Houzel 2010). One explanation of this relationship points to the functional importance of long-range connectivity through subcortical (neuron-bare) white matter for the operation of associative networks in the cerebral cortex (Wen & Chklovskii 2005) compared to the mostly short-range connections in the cerebellar (neuron-full) gray matter (Bush & Allman 2003), which causes neocortical white matter to increase faster than cerebellar white matter in larger brains (Herculano-Houzel *et al* 2006; Sarko *et al* 2009). This has not been quantitatively tested.

Although these scaling relationships are observed in primates (Herculano-Houzel 2010), hominoids appear to have altered the relationship (MacLeod *et al* 2003; Rilling 2006; Balters *et al* 2009). In anthropoids, cerebellar size is largely explained by body size, and cerebellar contrasts are significantly correlated with neocortical contrasts (Winter & Oxnard 2001). However, there is a clear grade shift between hominoids and other anthropoids. That is, hominoid evolution involved larger increases in cerebellar size (mostly in the hemispheres) than predicted by increases in cerebral cortical size in anthropoids (MacLeod *et al* 2003). Furthermore, in hominoids, the dentate nucleus consists of a plesiomorphic dorsomedial part and an apomorphic ventrolateral part (Leiner *et al* 1991). It is suggested that the ventrolateral part of the hominoid dentate nucleus plays a role in cognition. Although the ventrolateral dentate nucleus appears to project to non-motor regions (e.g, the frontal lobe), adaptive non-motor hypotheses remain as robust as our markedly tenuous (see above) understanding of the role of the cerebellum in cognition.

So, why have hominoids evolved larger-than-expected cerebella? Some authors point to the complexity of movement of hominoids (Povinelli & Cant 1995; MacLeod *et al* 2003). Compared to anthropoids, hominoids exhibit more complex pre-shaping of their hands when reaching for objects (Christel 1993; Christel *et al* 1998), exercise pre-syntactical motor planning (Ott *et al* 1994), and use corrective guidance during the execution of foraging tasks (Byrne 2004). These movements are not

only complex in themselves, but require planning. Quantitative differences have been observed among hominoids, too. After adjusting for body weight, the human cerebellum (and particularly dentate nucleus) is larger than expected for a hominoid of our body size (Matano & Hirasaki 1997; Rilling & Insel 1998; Semendeferi & Damasio 2000). Most of this size increase in the dentate nucleus has occurred in the ventrolateral region (Matano 2001). However, adjusted for cerebral cortical size, the human cerebellum is smaller than expected for a hominoid of our cerebral cortical volume. That is, humans fall below the hominoid regression line for cerebral cortical-cerebellar volume. Since humans do not have a disproportionately small cerebellum in absolute terms or when regressed on other brain regions (Deacon 1998; Rilling & Insel 1999), it is likely that the cerebral cortex enlarged at a faster rate than the cerebellum in human evolution (and unlikely that the cerebellum shrunk). Rilling & Seligman (2002) suggest that the extra-allometric expansion of the temporal lobe, a region that is not intimately connected with the cerebellum, may explain how the cerebral cortex was structurally able to enlarge at a faster rate than the cerebellum. Cognitive explanations of the human deviation from the hominoid pattern are plentiful (e.g., Gallup 1970; Tomasello & Call 1997; Tomasello *et al* 2003; Walter & Joanette 2007), but the evidence remains unconvincing (see Glickstein 2006).

ANALYSIS III

Volumetric estimates of the cerebellum

Methods used to quantify neuron and glia densities in the primary visual cortex and hippocampus proper and volumes of the dentate gyrus are outlined in chapters 5 and 6. Methods for processing brain tissue are also outlined in chapters 5 and 6.

Volumetric estimates of the granule cell layer of the cerebellum (CrbGc) were determined using Cavalieri's direct volume estimate (Fig. 27). An average of twenty sections were sampled for each individual. The cross-sectional area of the tissue was delineated with 10x objective (NA 0.25, air) in every 20th serial section. Each delineated region was then projected onto a computer screen at a known magnification, and a virtual point-grid of evenly spaced points was superimposed onto the region. The number of points falling on the region were counted using a systematic 'paint' tool. The distance between points on the grid was determined by pilot studies on mouse and human brains and set at 60 μm for the CrbGc. The thickness of sections cut from the microtome ranged from 25 - 100 μm, and mounted section thickness was measured in the *z*-plane of four randomly selected mounted sections using a 63x objective (NA 1.4, dry). Analysis of tissue samples was performed under brightfield microscopy with StereoInvestigator (MBF Bioscience, Willington, VT, USA).

Estimates of the coefficient of error were calculated with the Gundersen–Jensen estimator (Gundersen & Jensen 1987; Gundersen *et al* 1999) and held below 0.8 ± 0.1 for all analyses. For applications of Cavalieri's direct volume estimate, see Roberts *et al* (1994), Garcia-Fiñana *et al* (2003), and Sonmez *et al* (2010).

Statistical analyses are outlined in Chapter 5 (*Analysis I*) and 6 (*Analysis II*).

RESULTS III

The stereological results for all species are listed in Table A1a,b. In each taxonomic group (Table 1), I investigated allometric scaling relationships among cellular densities in the primary visual cortex (V1) and CA subfields of the hippocampus (CA1-3), volumetric estimates of the granule cell layer (StrGr) and molecular layer (StrMol) of the dentate gyrus, volumetric estimates of the granule cell layer of the cerebellum (CrbGc), brain mass, body mass, encephalization quotient (EQ), and gestation length. I additionally investigated scaling relationships with cerebellar and neocortical volume in primates. Scaling exponents generated by RMA line-fitting for species mean data and independent contrasts are presented in Table 8 along with 95% confidence intervals (CI). Recursive partitioning based on ANOVAs, stepwise AIC multiple regression, and the relative importance metrics *lmg*, *pmvd*, *first*, and *last* were used to isolate the best predictor variables for and determine the proportional contributions of regressors to cellular densities in V1 and CA1-3 and volumetric estimates of StrGr, StrMol, and CrbGc.

The All species (AS) group consists of 31 species, spanning 13 orders, and is considered representative of Eutheria (Table 1). The AS group includes the 14 species sampled that are neither primates nor carnivores, as well as a systematic random sampling of primate and carnivore species that was limited to 3 species in any taxonomic family to avoid bias towards any taxa.

Hypotheses and predictions

Recent studies have shown that the relationship of neuronal density in the cerebrum to the cerebellum does not at all reflect the relationship of the gross morphology of the two regions (Azevedo *et al* 2009; Sarko *et al* 2009; Herculano-Houzel 2010). As investigations into the evolution of multiple brain regions have focused almost exclusively on gross morphology, it is not known whether the relationship of glia to neurons or the evolutionary proliferation of neurons in one area of the brain is constrained or influenced by the dynamics in another area. I have specifically designed this project to test just that. The regions tested here – the primary visual cortex and hippocampal proper – are not intimately connected and therefore should, by merit of their loose correspondence, be free to evolve independently of one another. However, even if a tight correlation is not expected, the degree to which the cytoarchitecture of any brain region can evolve independently is unknown. I predict that the co-evolution of the these regions will conform to allometric scaling expectations, but that those

expectations will vary across taxonomic groups. Since taxa are rarely observe to isolate one region for selection at the expense of others, and that modules of the mammalian brain are regulated by developmental programs which can themselves be adapted, I expect quantitative differences in the co-evolution of different brain regions to be found between, but not within, orders.

Regressors of the cerebellum

CrbGc volume was tested as an independent variable against glia-neuron ratio in V1 and CA1-3 and both volumetric estimates of the dentate gyrus (Table 8). In carnivores, all scaling relationships held for species mean data and independent contrasts, whereas in AS only glia-neuron ratio in CA1-3 and StrGr volume scaled significantly with CrbGc for species mean data and independent contrasts. In primates, both volumetric estimates of the dentate gyrus, but glia-neuron ratio in neither region, scaled significantly with CrbGc volume for species mean data and independent contrasts. Significant slopes were not shown to be statistically different or grade-shifted between groups (Fig. 28).

Table 8: Slope estimates for scaling relationships between the granule cell layer of the cerebellum (μm^3) and cerebral properties

			Species mean data					*Independent contrasts*				
Taxa	Independent variable	Dependent variable	RMA	R^2	Lower 95% CI	Upper 95% CI	p	RMA	R^2	Lower 95% CI	Upper 95% CI	p
AS	CrbGc	Glia-neuron ratio in V1	0.307	0.707	0.204	0.461	0.000	0.497	0.428	0.395	0.626	0.000
(n=31)		Glia-neuron ratio in CA1-3	0.455	0.653	0.337	0.614	0.000	0.617	0.227	0.481	0.792	0.685
		StrGr (μm^3)	0.521	0.614	0.406	0.668	0.000	0.810	0.151	0.657	0.998	0.012
		StrMol (μm^3)	0.537	0.594	0.420	0.687	0.000	0.821	0.161	0.666	1.011	0.199
Carnivores	CrbGc	Glia-neuron ratio in V1	0.478	0.537	0.377	0.606	0.000	0.650	0.220	0.423	0.999	0.006
(n=20)		Glia-neuron ratio in CA1-3	0.518	0.492	0.412	0.650	0.000	0.754	0.459	0.489	1.163	0.002
		StrGr (μm^3)	0.554	0.417	0.438	0.700	0.000	0.823	0.056	0.551	1.228	0.037
		StrMol (μm^3)	0.611	0.352	0.490	0.761	0.000	0.865	0.036	0.592	1.262	0.011
Primates	CrbGc	Glia-neuron ratio in V1	0.395	0.584	0.290	0.538	0.000	0.579	0.261	0.399	0.841	0.785
(n=34)		Glia-neuron ratio in CA1-3	0.472	0.422	0.336	0.663	0.000	-0.846	0.027	-0.571	-1.254	0.354
		StrGr (μm^3)	0.602	0.363	0.472	0.769	0.000	0.582	0.336	0.424	0.798	0.003
		StrMol (μm^3)	0.631	0.372	0.506	0.787	0.000	0.910	0.014	0.664	1.247	0.000

Table 9: Slope estimates for scaling relationships based on cell densities (cells/mm^3) in CA1-3 and V1

			Species mean data					*Independent contrasts*				
Taxa	Dependent variable	Independent variable	RMA	R^2	Lower 95% CI	Upper 95% CI	p	RMA	R^2	Lower 95% CI	Upper 95% CI	p
AS	Glia-neuron ratio in V1	Glia-neuron ratio in CA1-3	0.923	0.127	0.733	1.215	0.006	0.728	0.134	0.604	0.925	0.005
(n = 31)	Neuron density in V1	Neuron density in CA1-3	0.929	0.135	0.754	1.145	0.003	0.706	0.227	0.572	0.932	0.000
	Glia density in V1	Glia density in CA1-3	1.120	0.127	0.953	1.316	0.004	0.955	0.142	0.754	1.270	0.019
Carnivores	Glia-neuron ratio in V1	Glia-neuron ratio in CA1-3	0.923	0.663	0.695	1.226	0.000	0.919	0.422	0.781	1.121	0.003
(n = 20)	Neuron density in V1	Neuron density in CA1-3	0.922	0.572	0.671	1.268	0.000	0.997	0.292	0.808	1.246	0.025
	Glia density in V1	Glia density in CA1-3	1.11	0.759	0.871	1.410	0.000	1.183	0.685	0.994	1.467	0.000
Primates	Glia-neuron ratio in V1	Glia-neuron ratio in CA1-3	0.829	0.017	0.584	1.176	0.457	-0.677	0.000	-0.528	-0.840	0.933
(n = 34)	Neuron density in V1	Neuron density in CA1-3	0.640	0.000	0.450	0.911	0.955	0.624	0.078	0.499	0.805	0.142
	Glia density in V1	Glia density in CA1-3	-0.705	0.002	-0.496	-1.003	0.815	0.697	0.009	0.537	0.906	0.616

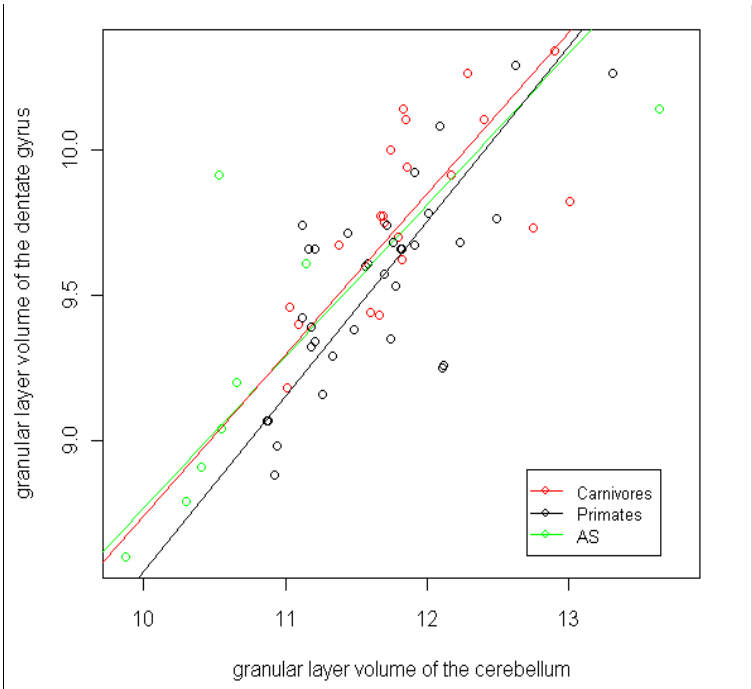

Figure 28: Log-log regression plots of StrGr volume as a function of CrbGc volume shows the y-intercept to be grade-shifted slightly, but not significantly, downwards in primates (y = 2.534, lower CI = 0.804, upper CI = 4.264, p = 0.005) compared to carnivores (y = 3.196, lower CI = 1.645, upper CI = 4.747, p = 0.000) and AS (y = 3.560, lower CI = 2.043, upper CI = 5.077, p = 0.000). The slopes, too, are statistically similar (Table 8).

V1 and the hippocampal formation

In AS and carnivores, glia-neuron ratio, neuronal density, and glial cell density in V1 were shown to scale isometrically with glia-neuron ratio, neuronal density, and glial cell density in CA1-3, respectively, for species mean data and independent contrasts (Fig. 29). In primates, none of the variables in V1 scaled significantly with any of the variables in the hippocampus for species mean data or independent contrasts (Table 9).

Pearson product-moment correlations (PMCC) showed glial cell density ($R^2 = 0.537$, $p = 0.007$) in V1 and CA1-3 and neuronal density ($R^2 = 0.498$, $p = 0.013$) in V1 and CA1-3 to be significantly correlated in AS. In carnivores, glia-neuron ratio ($R^2 = 0.814$, $p = 0.000$), neuronal density ($R^2 = 0.751$, $p = 0.000$), and glial cell density ($R^2 = 0.862$, $p = 0.000$) in V1 and CA1-3 showed strong linear dependence. PMCC showed no significant correlations between V1 and CA1-3 in primates.

In AS, stepwise AIC multiple regression (Table A4) showed only glial cell density in CA1-3 ($t = 2.979$, $p = 0.004$) and neuronal density in V1 ($t = 2.906$, $p = 0.005$) to be significant predictors of glial cell density in V1. Likewise, relative importance metrics and the recursive tree model revealed that neuronal density in V1 was the principal contributor and glial cell density in CA1-3 the secondary contributor to variance in glial cell density in V1 (see Supplemental Figs. 1a-r). In carnivores, hippocampal variables were shown to be strong predictors of V1 variables. Stepwise AIC multiple regressions showed glia-neuron ratio in CA1-3 to be the greatest predictor of glia-neuron ratio in V1 ($t = 4.477$, $p = 0.001$) and glial cell density in CA1-3 to be the greatest predictor of glial cell density in V1 ($t = 7.429$, $p = 0.000$). Relative importance metrics and recursive tree models strongly supported these results (see Supplemental Figs. 1a-r). In primates, no metric showed variables in V1 and CA1-3

to significantly predict or contribute to variance in one another.

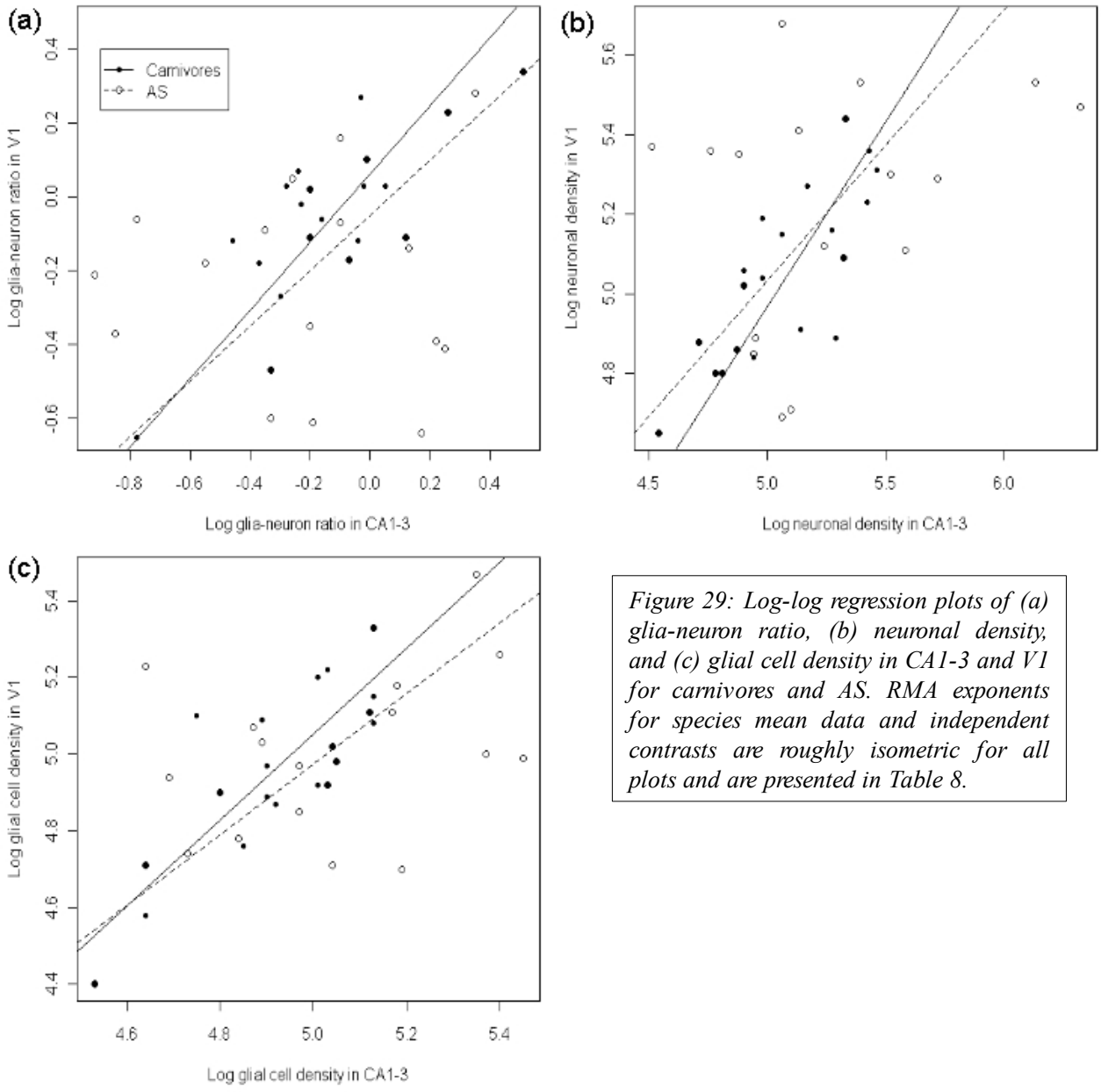

Figure 29: Log-log regression plots of (a) glia-neuron ratio, (b) neuronal density, and (c) glial cell density in CA1-3 and V1 for carnivores and AS. RMA exponents for species mean data and independent contrasts are roughly isometric for all plots and are presented in Table 8.

DISCUSSION III

Most comparative studies have focused on the evolutionary relationships among different brain-region volumes (Jerison 1973; Gould 1975; Stephan *et al* 1981; Finlay & Darlington 1995; Barton & Harvey 2000; Clark *et al* 2001; Lefebvre *et al* 2004; Yopak *et al* 2010), however, no studies have yet considered the coordinated evolution of cellular distributions in disparate brain regions. As recent evidence has confirmed that the volume and neuronal population in a given brain region show phylogenetically variable relationships to one another (Herculano-Houzel *et al*. 2006, 2007), investigating species diversity at the cellular level can help identify evolutionary physiological constraints acting on the mammalian brain. My data revealed significant relationships between neurons and glia in the primary visual cortex (V1) and hippocampal subfields (CA1-3) in mammals, that appear evolutionarily derived in primates (Fig. 30). Specifically, primates showed no significant scaling relationship between neurons and glia in V1 and CA1-3. I propose that the pattern observed in non-primates is indicative of constraints acting on evolutionary processes affecting mammalian brain development, and that the alteration of that pattern observed in primates represents a removal or relaxation of certain constraints. It is possible, for example, that evolutionary adaptations in one brain region in primates have influenced certain neurogenetic mechanisms, such as apoptosis (see Lietzau *et al* 2009), and thus affected late-stage cell proliferation in other regions. As an induction of evolutionary change, the removal or relaxation of constraints may be a condition for adaptation.

Divorcing the cerebrum and the cerebellum

My data showed the granule cell layers of the cerebellum and dentate gyrus to scale with significantly similar slopes in all taxonomic groups, indicating a conserved relationship between these regions across the eutherian phylogeny. However, while both AS and carnivores showed significant and similar allometric relationships between the cerebellum and neocortex for species mean data and independent contrasts, no such relationship existed for primates (Table 8). This difference may indicate a developmental dissociation along the primate lineage between expansion of the cerebellum and neocortex.

In human evolution, a hyperallometric expansion of the temporal and frontal lobes contributes to the disproportionate enlargement of the neocortex relative to the cerebellum (Rilling & Seligman 2002). Adapted independence of the these cortical areas from the rest of the cerebrum early in primate

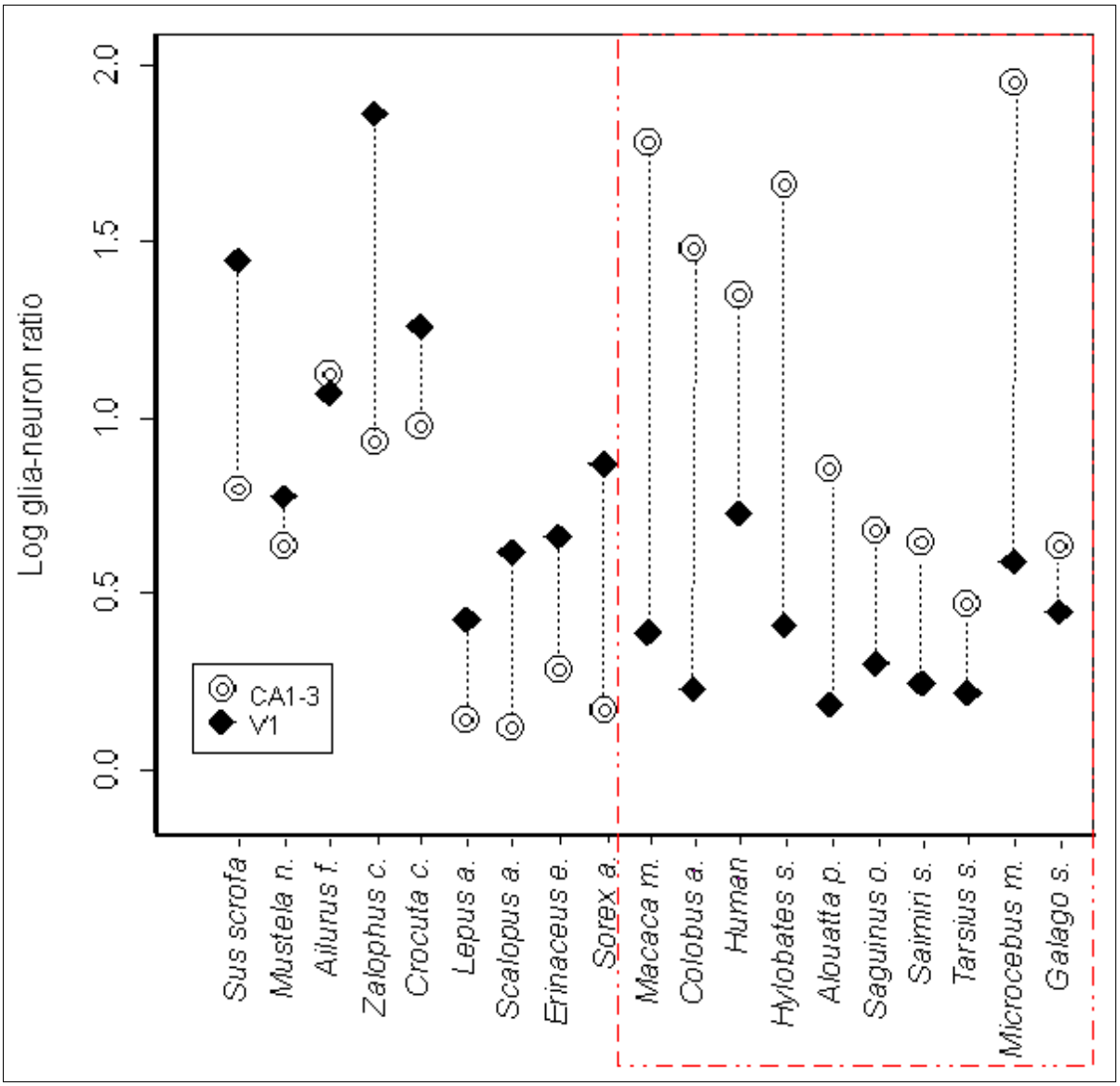

Figure 30: Glia-neuron ratios in V1 and CA1-3 for non-primate and primate (red-dashed box) species show consistently higher values in V1 (mean = 1.05 ± 0.36) than in CA1-3 (mean = 0.78 ± 0.22) in non-primates, but consistently lower values in V1 (mean = 0.41 ± 0.17) than in CA1-3 (mean = 1.07 ± 0.24) in primates. Mean values are significantly different in non-primates and primates for both V1 (t = 6.733, p = 0.000) and CA1-3 (t = -2.377, p = 0.021) when all species are sampled.

evolution may explain the derived relationship observed here between the cerebellum and neocortex. But inferring evolutionary patterns from correlations between traits absent of identifying selective pressures may lead to erroneous conclusions. While relationships may indicate mechanistic constraints limiting evolutionary divergence (Blows & Hoffman 2005), the covariation of traits should not presumptively be considered the result of parallel evolution or even of one trait evolving as a correlated

response to changes in the other (Riska & Atchley 1985; Price & Langen 1992). There may be no functional explanation for the divorce of the cerebellum from the neocortex in primate evolution, but, instead, the divorce itself may be the result of an adaptation unrelated to communication between the two structures. Since recent evidence has shown neuronal populations in the cerebellum and neocortex to scale linearly, with four cerebellar neurons for every neocortical neuron, across primates (Herculano-Houzel 2010), the findings in my data may more specifically represent the increased specialization of the primary visual cortex along the primate lineage, rather than deviations from a mammalian cerebellar-neocortical relationship. Nonetheless, according to my data, the limit imposed by the granule cell layer of the cerebellum on the development of the primary visual cortex, or *vice versa*, has deviated from the mammalian trend in primate evolution.

Constraints on cellular reorganization in diverse regions of the brain

In carnivores, glia-neuron ratio and glial cell density in V1 were the strongest predictors of glia-neuron ratio and glial cell density in CA1-3, respectively. And in AS, glial cell density in CA1-3 contributed to variance in glial cell density in V1 with significantly more explanatory power than brain or body mass, EQ, or gestation length. The cellular densities of V1 and CA1-3 in primates, however, were shown to be largely disassociated from one another. It is likely, therefore, that primate evolution experienced the removal or relaxation of a constraint binding the concerted development of glia to neurons in the allocortex and neocortex. Others have shown that the most enlarged regions of the brain in a species have been able to break constraints imposed by energetics by adapting highly nonsynaptic-based functions (Gibbons 1998; Laughlin *et al* 1998), such that, for complex functions, synaptic neurotransmission may be largely replaced by nonsynaptic diffusion neurotransmission (Bach-y-Rita 1994, 2001; Aiello & Bach-y-Rita 2000). Neuronal representation by nonsynaptic-based functions may have evolved differently in the primate neocortex and allocortex. However, nonsynaptic diffusion neurotransmission is highly debated (see Fuxe *et al* 2007) and intra- and extracellular microelectrode studies across taxa and brain regions would be needed to supply evidence for its presence. Nonetheless, my data show that variation in the cellular organization of two diverse brain regions is constrained in mammals, but may be relaxed or specialized along certain lineages.

In addition to interspecific differences in the number of cortical areas, with a proliferation of cortical areas generally following an increase in brain size (Krubitzer & Huffman 2000), interspecific differences in cortical cytoarchitecture have been shown to exist (Hof *et al* 2000). Adaptations in

cellular organization, which often represent isolated functional or behavioral variations and may be more easily interpreted than differences in cortical size across taxa (Sherwood *et al* 2003, 2009; Hof & Sherwood 2005; Raghanti *et al* 2008), suggest that cellular reorganization may be one pathway to the independent specialization of brain regions. However, this conclusion may be making the same unsettled assumptions previously made in comparative neuroanatomy about cortical size (see Wilczynski 2001; Healy & Rowe 2007). Since the adult forms of cortical areas are a result of developmental processes that associate diverse cortical regions, there is a fundamental difficulty in selecting on one region without affecting all other developmentally associated regions. This appears to be the case morphologically (Finlay *et al* 2001), but it is still unclear whether the same principle applies to neurotransmitters, receptors, the expression of neuromodulators, and cell structure and organization. Is an increase in glia to neurons in V1 likely to be accompanied *a priori* by a similar increase in the hippocampus? Is the principle of concerted evolution relevant at the cellular level? The observation that glia-neuron ratios in the neocortex and allocortex – or even brain size and body size – show tight statistical correlations across non-primate mammals may simply mean that the only selection pressure acting to stabilize the relationship is a constraint on a developmental process. The proliferation of glia subsequent to the proliferation of neurons in the mammalian brain makes it difficult to draw a clear analogy between conserved developmental timing in the evolution of different cell types and the concerted evolution hypothesis.

I have provided evidence that diverse regions of the mammalian brain are not *de facto* capable of evolving independently at the cellular level, with the implication that regions may only evolve independently following deep phylogenetic adaptations to conserved developmental processes.

CHAPTER 8
LIFE-HISTORY CORRELATES OF PLACENTAL EVOLUTION

Materials and methods

Data on placentation and life history variables in 132 therian mammals were obtained from the literature (see Tables A6-9 for data matrices). Placentation variables and discrete life-history variables were categorized according to definitions in the literature (Table 10). Continuous life-history variables were log-transformed after controlling for body size (Table A9), then discretized into groups either using natural distribution breaks calculated with fixed point clusters or k-means clustering. The strongest method for each variable was selected using cluster validation statistics. Cluster optimization is a within-group variance minimization approach equivalent to unconstrained clustering originally formulated in Fisher (1958). The point of cluster optimization is to find natural breaks that maximize homogeneity of the clusters. Homogeneity is the point at which a cluster can be adequately described by some homogeneous parametrical distribution, from which there must be no outliers. By definition, all data points not contained within the distribution are outliers. If the linear regression cluster of a dataset is represented by

$$Z=(X,y) \tag{23}$$

$$X=(x_1,\ldots,x_n)\in(IR^p)^n \tag{24}$$

$$y=(y_1,\ldots,y_n)\in(IR^p)\,, \tag{25}$$

which is a subset of data points that can be characterized by approximately the same linear relationship between a *p*-dimensional independent variable *x* and a dependent variable *y*, then the dataset can be described by a cluster reference distribution of the form

$$L(y|x)=F_{(x,\beta,\sigma^2)}\,, \tag{26}$$

where

$$y=x'\beta+\beta_{p+1}+u\,, \tag{27}$$

$$L(u)=N_{(0,\sigma^2)}\,, \tag{28}$$

$$(\beta,\sigma^2)\in IR^{p+1}\times IR_0\,. \tag{29}$$

The alternative algorithm used for clustering N data points into K subsets S_j containing N_j data points minimizes the sum-of-squares criterion

$$J = \sum_{j=1}^{K} \sum_{n \in S_j} \left| x_n - \mu_j^2 \right| , \tag{30}$$

where x_n is a vector representing the nth data point and μ_j is the geometric centroid of the data points in S_j. Cluster validation statistics are then used to determine the prediction strength, *ps*, of each clustering, where

$$ps(k) = \min_{1 \le j \le k} \frac{1}{n_{kj}(n_{kj}-1)} \sum_{i \ne i' \in A_{kj}} I\left(D\left[C(X_g, k), X_h\right]_{ii'} = 1\right) , \tag{31}$$

with observations $n_{k1...kk}$ and indices $A_{k1...kk}$ for the observations in cluster 1,2,...k, sets X_g and X_h, and clustering operator $C(X,k)$, such that if X has n observations, then $D[C(...),X)]$ is an n x n matrix with ii'th element $D[C(...),X]_{ii'}$=1 if observations i and i' happen to be in the same cluster. For examples, see (Jenks & Caspall (1971), Hartigan & Wong (1979), Hennig (1997, 1998a), Dudiot *et al* (2002) Armstrong *et al* (2003), Tibshirani & Walther (2005), or Beese *et al* (2008).

Table 10: Placental and life-history characters and states

Placental character states		*Life-history characters*
Uterus	bicornuate	Activity cycle
	simplex	Dietary breadth
	duplex	Interbirth interval
	bipartite	Litters per year
	unfused horns	Teat number
Shape	diffuse	Terrestriality
	cotyledonary	Trophic level
	discoid	Adult body mass
	zonary	Age at first birth
Interdigitation	villous to trabecular	Basal metabolic rate
	labyrinthine	Basal metabolic rate per mass
Interhemal barrier	epitheliochorial	Gestation length
	endotheliochorial	Litter size
	haemochorial	Maximum longevity
Yolk sac	free	Neonate mass
	inverted	Age at maturity
	trilaminar	Social group size
		Age at weaning
		Mass at weaning
		Development at birth

(Left) List of placental characters and their character states used for ancestral reconstructions, correlation analyses, and mutational mappings. (Right) Life-history

The phylogeny used in this analysis (Fig. 31) was derived from a species-level supertree (Bininda-Emonds *et al* 2007), with amendments and branch length improvements

provided by Bininda-Emonds (personal communication). As the rooting of the mammalian supertree remains ambiguous (see Murphy *et al* 2001; Lin *et al* 2002; Hallstrom *et al* 2007; Murphy *et al* 2007; Waters *et al* 2007; Wildman *et al* 2007; Prasad *et al* 2008; Nishihara *et al* 2009), three alternative rootings of the Eutherian phylogeny were used in this analysis (Fig. 32).

Ancestral state reconstructions for placental character states were approached with parsimony, maximum-likelihood, and Bayesian methods. Previous studies have reconstructed the ancestral states of several of the placental characteristics tested here, using similar phylogenetic analyses and producing comparable results (e.g., Carter & Enders 2004; Vogel 2005; Mess & Carter 2006; Wildman *et al* 2006; Elliot & Crespi 2009). It was necessary, however, to repeat these reconstructions to

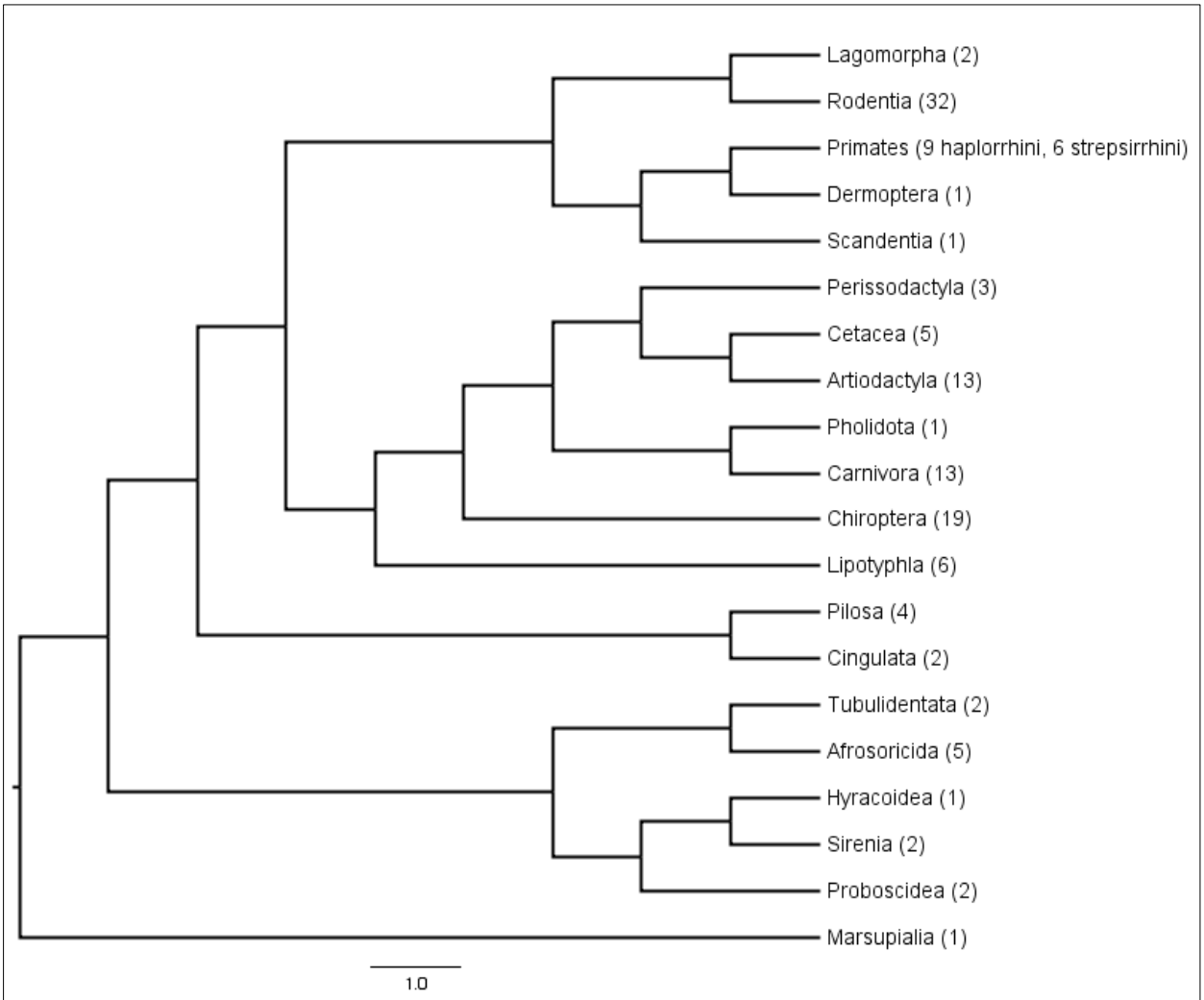

Figure 31. Phylogeny of orders and number of species within orders sampled in this study. Adapted from Bininda-Emonds et al (2007).

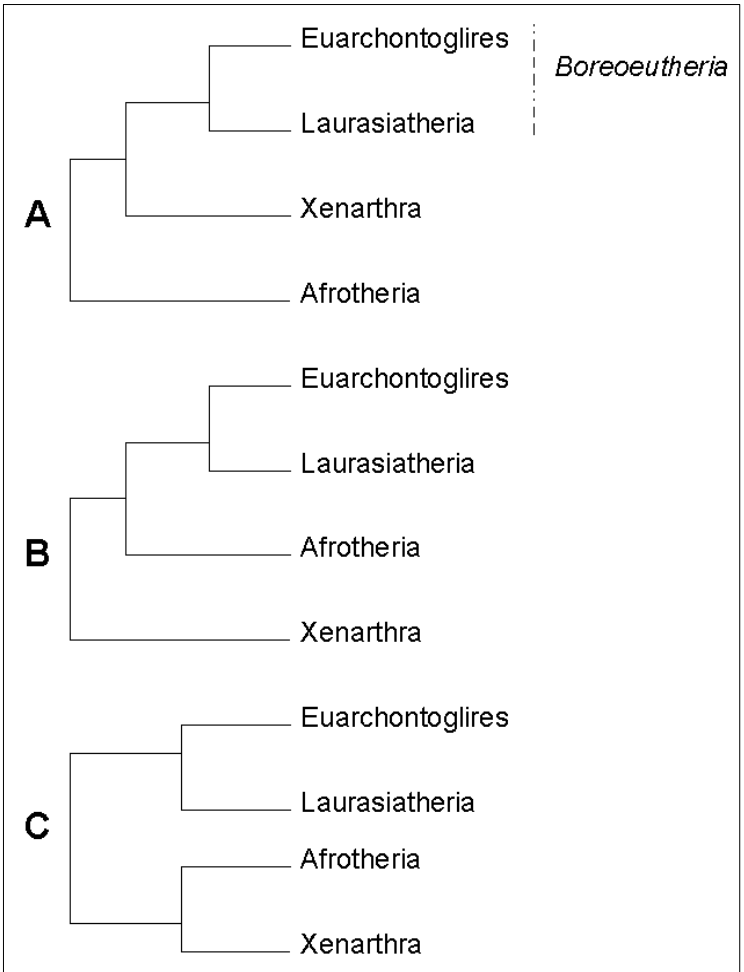

Figure 32. Three possible rootings for placental mammals: (A) between Xenarthra and Boreoeutheria + Afrotheria; (B) between Afrotheria and Boreoeutheria + Xenarthra; and (C) between Boreoeutheria and Afrotheria + Xenarthra. Adapted from Prasad et al (2008).

completely control for all variables in the subsequent analyses of correlated states.

Parsimony reconstructions were done in Mesquite v2.7 (Maddison & Maddison 2009) with permutations of topological variables (i.e., ordered and unordered) designed with respect to the nature of each character state. Maximum-likelihood reconstructions were also done in Mesquite to take advantage of the branch-length data incorporated in the tree (see Schluter *et al* 1997; Pagel 1999; Lewis 2001).

The parsimony method of mapping character states on a single phylogenetic tree assumes that the tree truly represents the hierarchical relationships and relative degrees of divergence among the species mapped (Felsenstein 1985; Harvey & Pagel 1991). In order to avoid the potentially confounding effect of this assumption, I applied hierarchical Bayesian methods (Cunningham 1999; Schultz & Churchill 1999; Huelsenbeck & Renquist 2001; Lewis 2001; Nielsen 2002; Ronquist *et al* 2005) in SIMMAP v1.5 (Bollback 2006), which summarizes character histories across the phylogeny using posterior probabilities, reporting the expected number of changes, the direction of changes if the tree is rooted, and the association between character states (Huelsenbeck *et al* 2003; Bollback 2006). Samples (10), prior draws (10), and predictive samples (10) were taken from the posterior distribution of the overall rate. In order to accommodate uncertainty in the overall rate of evolution of the character state, I employed a discrete gamma prior (Schultz & Churchill 1999; Huelsenbeck *et al* 2003), with

gamma distribution (expected value = 5.0, standard deviation = 5.0) parameters $\alpha = 0.1$ and $\beta = 0.2$ and distribution categories $k = 60$. The same gamma prior was used to simulate the history of each placental character state. Different sets of the gamma prior were tested for character histories and ancestral reconstruction, although these yielded more or less uniform results.

Mutational maps of placental characters were plotted in SIMMAPv1.5 to determine the histories of the characters. In addition to the ancestral states, the aggregate of sums, rates, and types of changes for each placental character along the tree is important to understanding what is effectively the narrative (or the average of many possible narratives) of the evolution of a character (Cunningham 1999; Huelsenbeck *et al* 2003).

Associations along phylogenetic histories between the individual states of each character (*d*) and the overall association (*D*) between characters were calculated in SIMMAP v1.5 using flat priors ($\alpha = 1.0$, $\beta = 0.2$, $\kappa = 60$). Association analyses examined the difference between the observed and expected values for each combination of states (Nielsen 2002; Huelsenbeck *et al* 2003; Bollback 2005). If the observed association of two characters (*i* and *j*) was less than expected under independence, then the value of *d* was negative; the overall association was the agreement between the observed (*o*) and expected (*e*) associations of the states (*a*) for the two characters. Thus,

$$d_{ij} = a_{ij}^{(o)} - a_{ij}^{(e)}$$

and

$$D = \Sigma_{i=1}^{n} \Sigma_{j=1}^{m} \left| d_{ij} \right| ,$$

where *n* and *m* are the number of states for characters *i* and *j*, respectively. The posterior predictive value was calculated by simulating many character histories under the assumption that the two characters were independent. The association between one state and another, therefore, was the frequency of occurrence of states on the phylogeny (Huelsenbeck *et al* 2003; Bollback 2006). Observed values were considered significantly different from expected values if they fell outside 95% of the probability density of the simulated distribution.

A second statistic, comparable in form to the mutational information content (MIC) statistic, was implemented in SIMMAP v1.5, such that

$$M = \Sigma_{i=1}^{x} \Sigma_{j=1}^{y} \left| m_{ij} \right|$$

and

$$m_{ij} = f_{ij} \log_2 \frac{f_{ij}}{f_i f_j} .$$

This evaluated the association between character histories along the phylogeny for two characters (*M*) and their states (*m*) based on the fraction of time (*f*) one state is associated with another in a character history (Bollback 2006).

Both ordered and unordered models were used for mutational mapping and association analysis. For some characters (e.g., interhemal barrier), evolution of distant states should clearly be more expensive than evolution of adjacent states (Martin 2007, 2008). However, as this quality is not clearly absent or present for all characters in this study, both ordered and unordered models were tested in each analysis and interpreted appropriately. Furthermore, despite recent advances in analysis of placental tissue (e.g., electron microscopy), which have refined and proliferated definitions of placental character states, the terminology used in this study remains useful for understanding and quantifying the evolution of placentation (Enders 1965; Mossman 1987; Benirschke & Kaufmann 2000; Wildman *et al* 2006; Mess & Carter 2006).

Definitions

Uterus: The uterine lumen (Fig. 33) can be arranged in several ways (Mossman 1987; Shoshani & McKenna 1998): bicornuate, simplex, duplex, bipartite, and unfused. In a bicornuate uterus (e.g., dogs), the uterine horns join internally to form a heart-shaped corpus (Mess & Carter 2007). A simplex uterus (e.g., humans) has a single unpaired corpus and immature horns (Martin 2003). In a duplex uterus (e.g., rabbits), the uterine tubes open independently into the vagina (Mossman 1987; Mess & Carter 2007). In the bipartite uterus (e.g., cats) the uterine tubes are mostly independent, but share a single cervix. The uterine tubes are unfused in marsupials, so each uterus communicates with the urogenital sinus through a separate vagina (Mess & Carter 2007). Parsimony reconstruction indicates that the bicornuate uterus, which is found in all superorders except Xenarthra, is the plesiomorphic condition for Eutheria (Mess & Carter 2007).

Placental shape: According to the design of the maternofetal contact acrea (Fig. 34), gross placental morphology in Eutherian mammals can be categorized as diffuse, cotyledonary, discoid, and

zonary (Steven & Morriss 1975; Mossman 1987). A diffuse shape (e.g., pigs) requires the entire surface of the allantochorion to be involved in formation of the placenta; the placenta forms a sac covered with small villi, which interdigitate and extend over the entire surface of the chorionic sac (Wildman *et al* 2006; Mess & Carter 2007). In a cotyledonary placenta (e.g., sheep), cotyledons and caruncles, concentrated villi on the fetal and maternal contact sites, respectively, form small disks. In a zonary placenta (e.g., bears), the trophoblast forms a complete or incomplete equatorial band of tissue surrounding the fetus. A single placenta, discoid in shape, constitutes a discoid placenta (e.g., humans), although some species have a secondary disk (e.g., tree shrews). The discoid morphology has been identified in all Eutherian superorders, except Xenarthra, and is thus regarded as the plesiomorphic condition (Mess & Carter 2007).

Interdigitation: Maternofetal interdigitation (Fig. 35) defines the form taken by the contact area between maternal and fetal tissue (Wildman *et al* 2006). Since the contact area of the chorion and endometrium is insufficient to meet fetal demands, maternofetal interdigitation is used to increase the placental exchange (Benirschke & Kaufmann 2000). Maternofetal interdigitation may take as many as five definitive forms, however, several of these forms can be functionally grouped (see Mess & Carter 2007). A villous placenta has tree-like branching of the chorion, where the fetal surface is either dedicated to maternal villi (e.g., humans) or invested by the epithelial walls of maternal crypts (e.g., cows). Intermediate forms of villous interdigitation occur, in which finger-like villi divaricate from branching folds (e.g., dolphins). In labyrinthine interdigitation, web-like channels of maternal blood of the exchange area are completely closed in by a tissue block of trophoblast (e.g., elephants). The labyrinthine pattern is regarded as the plesiomorphic condition, appearing in all Eutherian superorders, except Xenarthra (Vogel 2005; Wildman *et al* 2006; Mess & Carter 2007).

Interhemal barrier: According to whether or not the trophoblast is apposed to the uterine epithelium, the endothelium of maternal vessels, or directly to the maternal blood (Fig. 36), the placenta is classified as epitheliochorial (e.g., pigs), endotheliochorial (e.g., cats), or haemochorial (e.g., humans), respectively (Mossman 1987). All three classifications have areas of comparable proximity of the maternal and fetal blood streams reducing the diffusion distance (Wooding & Flint 1994). It is important to note that the number of maternal tissue layers penetrated by the fetal tissue bears no relationship to the ability of the placenta to transfer oxygen to the fetus (Enders & Carter

2004; Wildman *et al* 2006), although nutrient transfer is affected by the number of layers separating the fetal and maternal blood. For example, haemochorial placentas are more permeable to lactate and exhibit less effective transfer of non-esterified fatty acids than epitheliochorial placentas (Kastendieck & Moll 1977; Wooding & Burton 2008). While much is known about how interhemal distance is physiologically increased or decreased (see Enders *et al* 1998; Abd-Elnaiem *et al* 1999; Mess *et al* 2003; Enders & Carter 2004), the evolutionary process remains elusive, despite transformations along every major Eutherian clade. It is debated whether the plesiomorphic Eutherian condition is endotheliochorial (Luckett 1976, 1993; Mossman 1991; Haig 1993; Pijnenborg 2004; Enders & Carter 2006; Carter & Mess 2007) or haemochorial (Lillegraven 1987; Vogel 2005; Elliot & Crespi 2008, 2009).

Yolk sac: Fetal organ systems differentiate during an embryonic period administered by a functional yolk sac (Figs. 37-8) (see Amoroso 1959; Wooding & Burton 2008; Freyer & Renfree 2009). Interactions between the allantois and yolk sac vary considerably, however. In some Eutherian mammals (e.g., tree shrews), a trilaminar omphalopleure is retained until term in close association with the maternal epithelium. In others, the yolk sac is used as an exchange region during the early anaerobic stage before internal circulation begins (King & Enders 1993; Burton *et al* 2002; Jauniaux *et al* 2004; Wildman *et al* 2006; Mess & Carter 2007). Reduction of the yolk sac cavity produces different degrees of so-called inversion of the tissue sequence at the maternofetal interface, which is due to the loss of the non-vascularized bilaminar yolk sac layers adjacent to the endometrium (Wooding & Burton 2008). In some cases (e.g., moles), the inverted yolk sac may persist, partially or completely inverted, until term (Miglino *et al* 2008). In many species (e.g., macaques), however, the yolk sac is never truly formed or is displaced and floats freely in the exocelom (Jauniaux *et al* 2004). Thus, the yolk sac at term can be categorized by its duration and inversion in the placenta as: free, inverted, or trilaminar. Absence of the yolk is regarded as the plesiomorphic condition in Eutheria, while partial or complete inversion is regarded as apomorphic (Mess & Carter 2007).

For definitions of behavioral and life history variables, see Table A9.

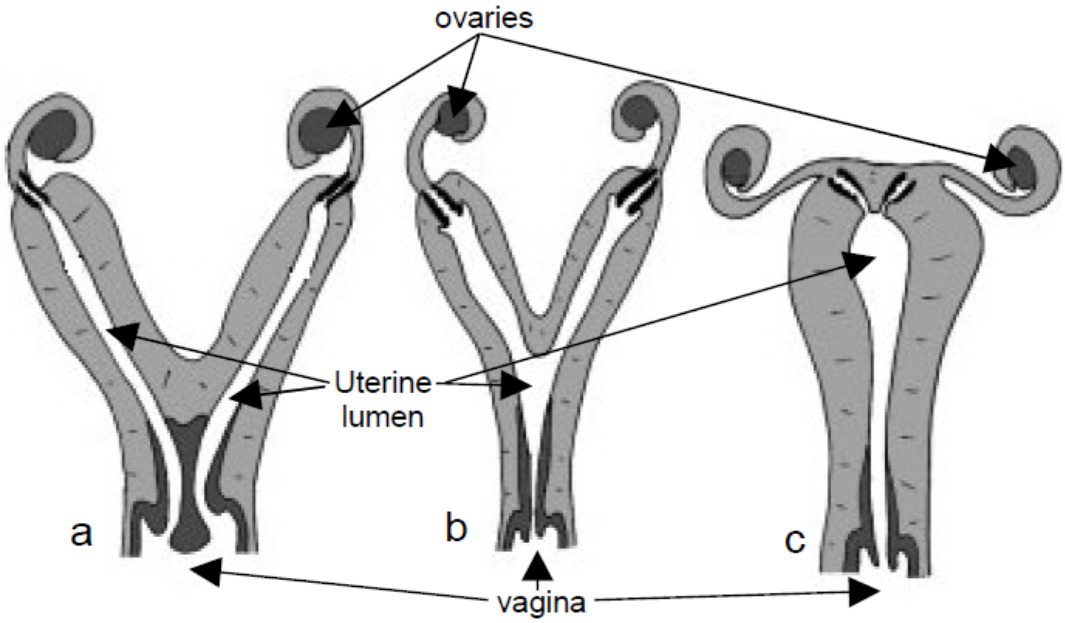

Figure 33: Illustration of a duplex (a), bicornuate (b), and simplex (c) uterus.

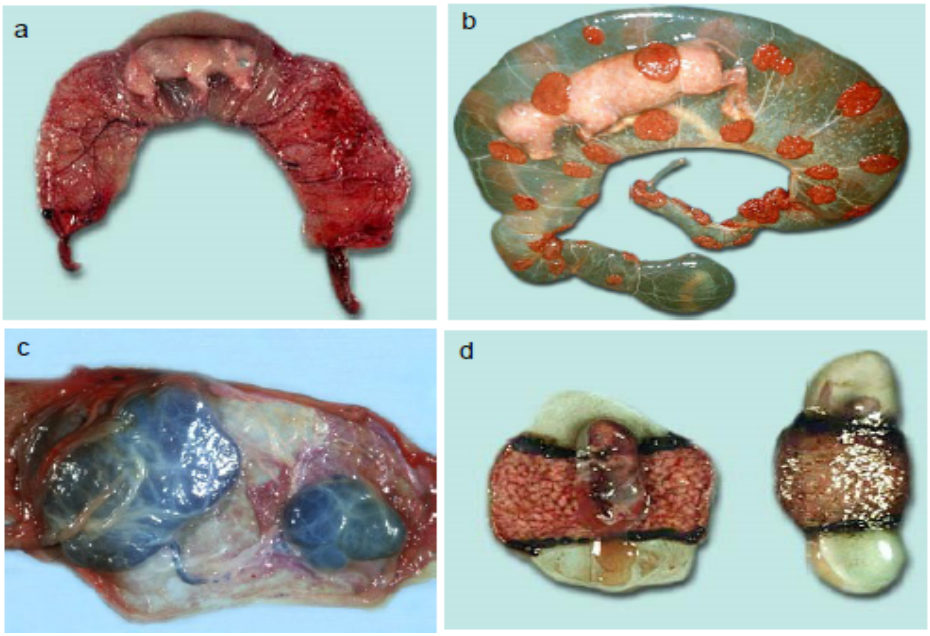

Figure 34: Different species show considerable differences in the shape and contact area manifest between fetal and maternal tissues. These differences can, however, be classified into four types. In the diffuse placenta (a), nearly the entire surface of the allantochorion is involved in forming the placenta. In the cotyledonary placenta (b), multiple discrete patches (i.e., cotyledons) are formed through interactions of allantochorion with endometrium. In the discoid placenta (c), a single placenta is formed. In the zonary placenta (d), the placenta takes the form of a (complete or incomplete) band of tissue surrounding the fetus. Photographs from http://www.embryology.ch.

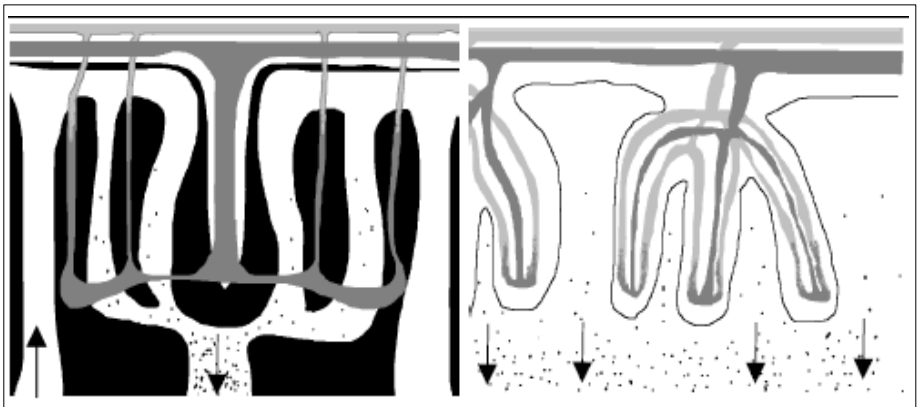

Figure 35: Illustration of a lobule of a labyrinthine haemochorial placenta (left) and of a villous haemochorial placenta (right). The general direction of bloodflow in each placenta is indicated by the arrows. Depleted arterial fetal blood (dark grey) and oxygenated venous fetal blood (light gray) vessels, trophoblast (black), oxygenated arterial maternal blood (white), and depleted venous maternal blood (stippled) are presented. Adapted from Mossman (1987).

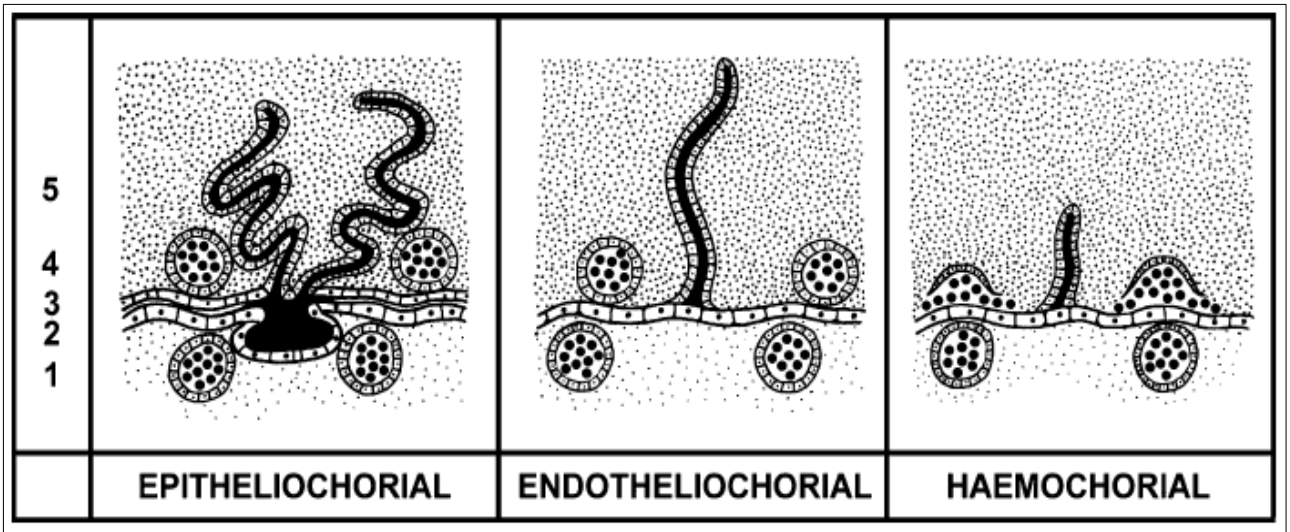

Figure 36: Illustration of different classifications of the interhemal barrier in Eutherian mammals. The chorion (2) constitutes a barrier to diffusion between blood vessels on the maternal (4) and embryonic/fetal (1) sides. Uterine glands (5) are best developed in an epitheliochorial placenta, where the uterine epithelium (3) remains intact and special areas of the chorion (areolae) lie opposite clusters of gland outlets. From Martin (2008).

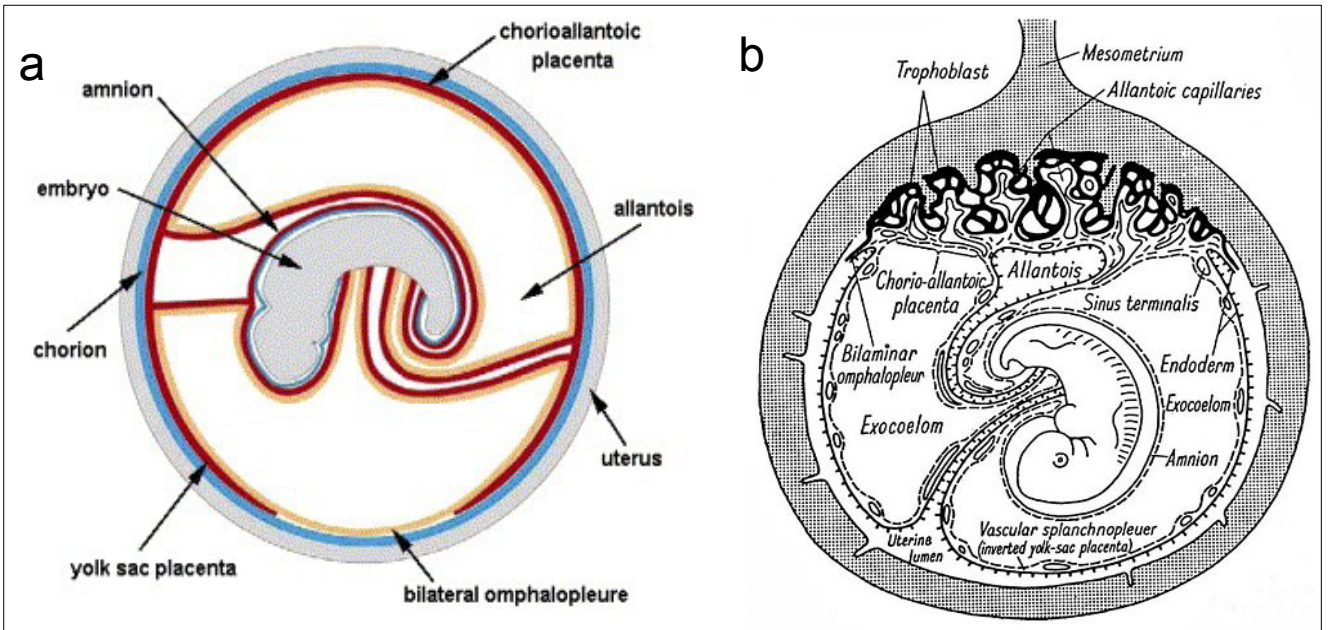

Figure 37: (a) Schematic of the fetal membranes of placental mammals. The embryo is enclosed in the amnion. Trophoblast (blue) and mesoderm (red) form the chorion. Trophoblast and yolk sac endoderm (yellow) together constitute a bilaminar omphalopleure. A choriovitelline or yolk sac placenta is formed by interposition of mesoderm containing fetal blood vessels. Later the allantois (i.e., mesoderm and endoderm) expands into the exocoelom and the allantoic and chorionic mesoderm fuse to form a chorioallantoic placenta. The allantois will continue to expand into the exocoelom and eventually displace the yolk sac. (b) Illustration of the complete inversion of the yolk sac. From http://placentation.ucsd.edu.

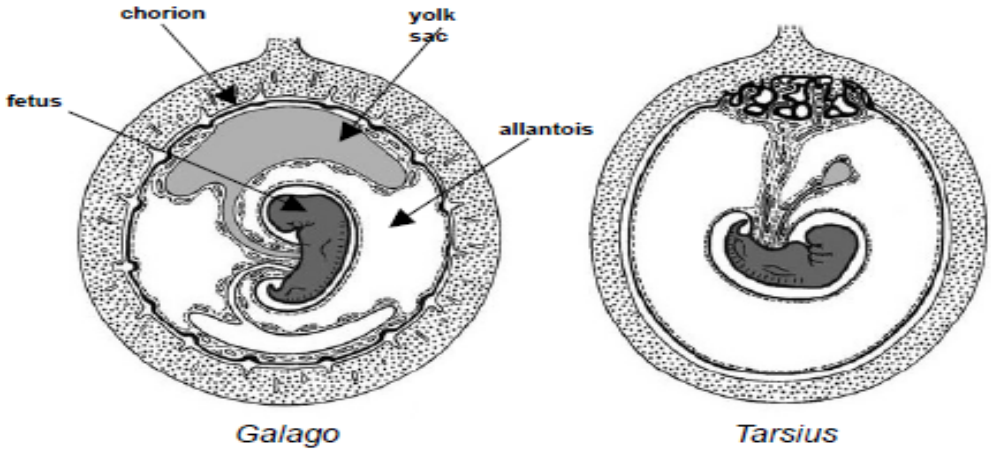

Figure 38: Illustration of the interspecific physiological diversity of the fetal membrane interaction with the placenta. The diffuse, epitheliochorial placenta of the Galago is associated with pronounced development of uterine glands and the presence of chorionic vessels (shown as identations in the chorion). Its yolk sac and blood vessels are prominent early in pregnancy, but are progressively replaced by the allantois. Almost antithetically, the discoidal, haemochorial placenta of the Tarsius has only weakly developed uterine glands, its yolk sac is poorly developed, and its yolk sac vessels are not involved in placentation at all. From Martin (2008).

RESULTS IV

Ancestral reconstructions

Ancestral eutherian and primate states for five placental characters were reconstructed under parsimony, maximum likelihood, and stochastic models (Table 11). These gave compatible results, although the parsimony reconstructions were occasionally equivocal and the Bayesian analysis was uninformative for reconstructing the ancestral primate states. Alternative tree rootings did not result in differences in ancestral reconstruction for any of the characters.

While there was general agreement between the ordered and unordered parsimony models in reconstructed ancestral states, only the ordered model produced an unambiguous reconstruction of the eutherian state as haemochorial. The maximum likelihood reconstructions closely corroborated the results of the parsimony reconstructions, resolving a bicornuate uterus and labyrinthine interdigitation for the ancestral condition. There was, however, some conflict between the unordered parsimony and likelihood reconstructions of placental shape, which reconstruct the ancestral state as zonary and discoid, respectively (although the unordered parsimony model ambivalently reconstructs this ambivalently as zonary/discoid). In this respect, I can only emphasize the resolution of the likelihood result (0.99), which is supported by the Bayesian analysis as well as previous studies (Wildman *et al* 2006; Elliot & Crespi 2009). These results imply that anthropoids (including humans) retain the ancestral condition for placental shape and barrier, but derived uterus type and interdigitation.

The ordered and unordered parsimony reconstructions were generally in agreement with the likelihood reconstructions of primates. Although the parsimony models gave equivocal reconstructions of interhemal barrier, neither the ordered nor unordered model proposed endotheliochorial as a possible

Table 11: Ancestral state reconstructions for definitive placental characters

Taxa	*Character*	*Parsimony (ordered)*	*Parsimony (unordered)*	*Maximum Likelihood (mk1)*	*Stochastic*
Eutheria	Uterus	bicornuate/simplex	bicornuate	bicornuate (0.99)	bicornuate (0.99)
	Placental shape	zonary	discoid/zonary	discoid (0.99)	discoid (0.99)
	Maternal interdigitation	labyrinthine	labyrinthine	labyrinthine (0.99)	labyrinthine (0.99)
	Interhemal barrier	haemochorial	uninformative	haemochorial (0.89)	haemochorial (0.89)
	Yolk sac	free	free	free (0.99)	free (0.9)
Primata	Uterus	bicornuate	bicornuate	bicornuate (0.99)	
	Placental shape	discoid	discoid/diffuse	discoid (0.86), diffuse (0.13)	
	Maternal interdigitation	villous	villous	villous (0.83), labyrinthine (0.17)	
	Interhemal barrier	uninformative	epitheliochorial/haemochorial	haemochorial (0.9)	
	Yolk sac	free	free	Free (0.99)	

Parsimony (ordered and unordered), maximum likelihood (ML), and Bayesian (BI) ancestral state reconstructions for placental character states.
All ML and BI results are statistically significant ($p<0.01$).

Table 12: Mutational maps for placental characters

Model	Site	*E[Subs]*	*E[1->2]*	*E[2->1]*	*E[2->3]*	*E[3->2]*	*E[3->4]*	*E[4->3]*	*E[4->5]*	*E[5->4]*	*E[Time(1)]*	*E[Time(2)]*	*E[Time(3)]*	*E[Time(4)]*	*E[Time(5)]*	*E[Rate]*
Ordered	Uterus	192	60.44	42.92	39.86	15.56	16.19	9.19	4.82	4.02	0.35	0.16	0.09	0.04	0.01	0.3
	Placental shape	275	30.88	48.41	71.64	36.88	33.47	29.79	11.42	12.56	0.17	0.29	0.31	0.12	0.04	0.24
	linterdigitation	145.36	54.98	41.04	23.65	25.7	-	-	-	-	0.41	0.41	0.07	-	-	0.09
	Interhemal barrier	147.81	17.26	27.01	43.06	29.08	15.66	15.75	-	-	0.18	0.38	0.38	0.05	-	0.09
	Yolk sac	84.62	40.93	24.85	9.82	6.64	1.63	0.76	-	-	0.54	0.26	0.03	0.01	-	0.09
		E[Subs]	*E[1->2]*	*E[1->3]*	*E[1->4]*	*E[1->5]*	*E[2->1]*	*E[2->3]*	*E[2->4]*	*E[2->5]*	*E[3->1]*	*E[3->2]*	*E[3->4]*	*E[3->5]*	*E[4->1]*	*E[4->2]*
Unordered	Uterus	56.29	5.95	8.48	6.52	3.42	3	1.95	1.01	0.75	6.61	1.9	2.04	1.57	2.83	1
	Placental shape	58.59	1.62	3.9	1.63	1.04	1.76	4.48	1.18	0.67	9.97	4.73	8.47	3.87	2.33	1.87
	linterdigitation	85.35	19.02	6.57	-	-	25.53	13.3	-	-	8.73	12.21	-	-	-	-
	Interhemal barrier	83.4	6.6	8.13	2.19	-	4.93	9.02	2.23	-	13.1	19.12	6.59	-	2.93	3.56
	Yolk sac	66.59	16.13	6.97	6.31	-	9.39	4.2	3.51	-	4.83	3.84	1.16	-	4.92	4.04

	E[4->3]	*E[4->5]*	*E[5->1]*	*E[5->2]*	*E[5->3]*	*E[5->4]*	*E[Time(1)]*	*E[Time(2)]*	*E[Time(3)]*	*E[Time(4)]*	*E[Time(5)]*	*E[Rate]*
Uterus	2.64	0.71	2.49	1.06	1.56	0.81	0.47	0.07	0.19	0.06	0.03	0.09
Placental shape	4.59	0.91	1.34	0.58	2.63	1.01	0.15	0.05	0.58	0.12	0.02	0.09
linterdigitation	-	-	-	-	-	-	0.28	0.54	0.07	-	-	0.09
Interhemal barrier	4.99	-	-	-	-	-	0.2	0.2	0.53	0.04	-	0.09
Yolk sac	1.31	-	-	-	-	-	0.52	0.29	0.04	0.04	-	0.09

Transformation rates between character states, as well as overall transformation rates and dwell times for placental characters.

Table 13: Association *d* statistics among placental character states

		UTERUS				*PLACENTAL SHAPE*				*INTERDIGITATION*		*INTERHEMAL BARRIER*		
		Bicornuate	Simplex	Duplex	Bipartite	Diffuse	Cotyledonary	Discoid	Zonary	Villous to trabecular	Labyrinthine	Epitheliochorial	Endotheliochorial	Haemochorial
UTERUS	Bicornuate													
	Simplex													
	Duplex													
	Bipartite													
PLACENTAL SHAPE	Diffuse									0.033	-0.033	0.019	-0.019	-0.020
	Cotyledonary											-0.010		
	Discoid									-0.025	0.025	-0.036		0.031
	Zonary									-0.018	0.018	-0.014	0.013	
INTERDIGITATION	Villous to trabecular					0.033						0.044	-0.021	-0.026
	Labyrinthine					-0.033						-0.044	0.021	0.026
INTERHEMAL BARRIER	Epitheliochorial					0.030		-0.035						
	Endotheliochorial					-0.018								
	Haemochorial					-0.020		0.020						
YOLK SAC	Free			-0.012		0.012						0.032	0.029	-0.040
	Inverted			0.016		-0.016				-0.034	0.034	-0.032	-0.029	0.040
	Trilaminar													

Associations among placental character states for both an ordered (white) and unordered (grey) model. All associations are significant to $p<0.001$.

plesiomorphic condition for primates. There was also ambiguity in two of the likelihood reconstructions: the likelihood model finds significant alternative reconstructions for both placental shape (discoid: 0.86; diffuse: 0.13) and maternofetal interdigitation (villous: 0.83; labyrinthine: 0.17). There appears to be an outside possibility, then, that *Strepsirrhini* and *Tarsiidae*, not *Anthropoidea*, retain the ancestral placental shape, and that the labyrinthine interdigitation of *Saimiri sciureus* is a plesiomorphic, rather than convergent, condition. The disparities in likelihood values between the alternative reconstructions, in both placental shape and maternofetal interdigitation, however, are quite large.

Mutational mapping

Mutational maps for placental characters are shown for ordered and unordered models (Table 12). There was clear evidence of directionality in type of uterus (bicornuate to bipartite), interhemal barrier (haemochorial to endotheliochorial), and yolk sac (free to trilaminar), whereas directionality seemed more relaxed in placental shape and maternofetal interdigitation. Dwell times showed similar patterns in both the ordered and unordered models. However, the ordered model showed maternofetal interdigitation dividing its time more evenly between villous to trabecular and labyrinthine states than in the unordered model, which favored labyrinthine interdigitation; the unordered model showed placental shape and interhemal barrier spending more time as discoid and haemochorial, respectively. The overall rate changes in both models were uniform (0.09), with the exception of uterus type and placental shape, which were recorded to change at three-fold the rate (0.3 and 0.24, respectively) of the other characters.

Transformations to haemochorial and epitheliochorial states occured in all major clades.

Character associations

The character states of twenty life-history and five placental variables (Table 10) were analyzed for associations among placental characters and between placental and life-history characters (Table A10a-e). The overall measurement of the disagreement between the observed and expected associations of the states, represented by the test statistic *D*, was analyzed first: no associations were found among the placental characters; positive associations between placental character states and life-history states ranged from 0.017 to 0.107. The test statistic *D* accounts for association in all of the pairwise comparisons of states, however, and likely masks significant associations between individual characters

(see Huelsenbeck *et al* 2003). Examination of the test statistic *d* was much more informative, providing information on the nature of the co-variations. All significant associations between individual states, as measured by the test statistic *d*, identified complementary negative and positive results.
The test statistic *M* produced no significant results; test statistic *m* identified positive and negative associations comparable to those identified by *d*.

Associations among placental characters showed small but significant associations between character states, without any contradictions of associations (Table 13; Fig. 39). The duplex uterus, for example, was positively associated with a free yolk sac (0.016) and negatively associated with an inverted yolk sac (-0.012). The diffuse placental shape was positively associated with villous to trabecular interdigitation (0.033), an epitheliochorial interhemal barrier (0.030) and an inverted yolk sac (0.012), whereas the discoid placental shape was associated with labyrinthine interdigitation (0.025) and a haemochorial interhemal barrier (0.020). The haemochorial state was associated with labyrinthine interdigitation (0.026) and an inverted yolk sac (0.040), whereas the epitheliochorial state was associated with villous to trabecular interdigitation (0.044) and a free yolk sac (0.032). These associations reveal distinct bands of co-varying placental character states.

Associations between placental character states and life-history variables produced non-contradictory positive and negative results. It cannot be said that any one placental character state monopolized any one life-history character state. However, by segregating the life-history variable associations according to the associations found among placental states, two rather distinct eutherian constellations appeared (Table 14). Indirectly tested co-variation of life-history variables (e.g., development at birth and age at weaning, social group size and gestation length), which appear to be frequently partnered in associations with placental character states, may give further insights into the selective pressures behind those life-history variables. These tests support previous studies linking placental invasiveness with adult body mass (Martin 2008; Elliot & Crespi 2009).

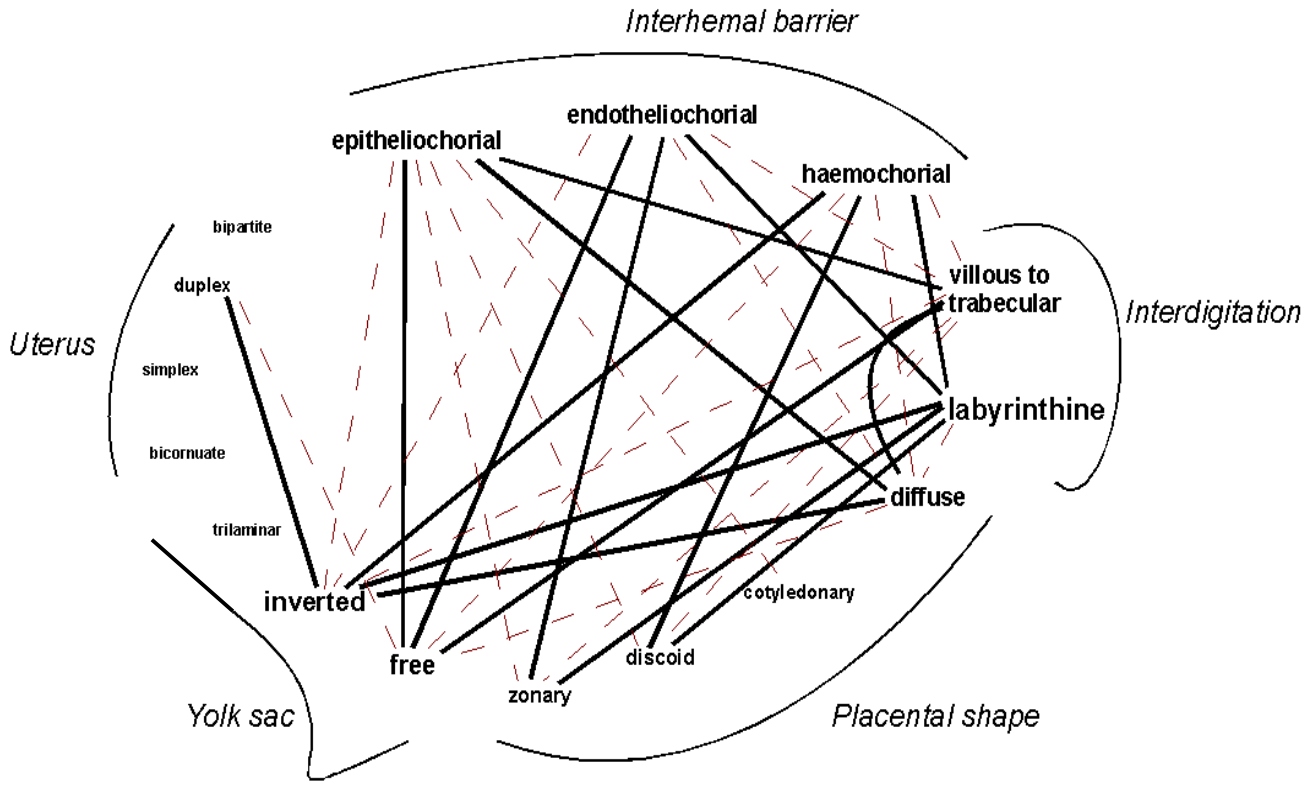

Figure 39: Schematic of positive (continuous lines) and negative (dashed lines) associations between placental character states. The type-font of each character state is weighted according to its volume of associations.

Table 14: Eutherian constellations

	Type I	Type II
Placenta	epitheliochorial	haemochorial
	villous to trabecular	labyrinthine
	diffuse	discoid
	free yolk sac	inverted yolk sac
Life-history	long lifespan	short lifespan
	precocial	altricial
	small litter	large litter
	large neonates	small neonates
	late weaning and maturity	early weaning and maturity
	small social group size	large social group size
	long gestation period	short gestation period
	high interbirth intervals	low interbirth intervals
		herbivorous
Examples	*Otolemur crassicaudatus*	*Spilogale putorius*
	Equus caballus	*Oryctolagus cuniculus*

Summary of placental and life-history character states as they are generally segregated in the analysis.

DISCUSSION IV

Phylogenetic reconstructions resolve the ancestral eutherian condition as labyrinthine haemochorial, discoidal in shape, with a free yolk sac and a bicornuate uterus, suggesting that, contrary to early views that the human condition is synapomorphic (Hill 1932; Le Gros Clark 1959; Luckett 1974, 1977), the haplorrhine placenta is primitive with regards to invasiveness and shape. This is in agreement with previous work done on ancestral reconstruction in placental mammals (Wildman *et al* 2006; Elliot & Crespi 2009). Martin (1990 2008) has argued that the ancestral condition was somewhat more likely to have been endotheliochorial than haemochorial, and this study cannot definitely resolve that debate. But despite the incorrect coding for certain species in Wildman *et al* (2006) (see Carter *et al* 2007), my findings, with the correct codings for those species, still gives stronger support for a haemochorial ancestral eutherian condition. There is now, in any case, broad agreement that the ancestral interhaemal barrier was invasive to at least some degree. Furthermore, the analyses here, showing an inclination for certain placental character states to co-evolve along all lineages, do not preclude either endotheliochorial or haemochorial placental barriers from co-evolving with a discoidal placental shape, which is generally agreed to be primitive (Martin 2008).

Many placental characters lack a strong phylogenetic signal, implying that they are not strongly conserved over evolutionary time and suggesting, instead, a substantial degree of evolutionary plasticity. Despite this, much progress remains to be made before the functional consequences of variation in placental morphology are understood (Vogel 2005; Martin 2008). Phylogenetic associations between such characters and other placental morphologies or life-history variables can identify constraints on placental evolution and improve our understanding of the selection pressures that drive their phyletic diversity. I have identified two constellations, or syndromes, of combined placentation and life-history character states, characterized by multiple associations between each other (Fig. 40). These are not exclusive associations, but they provide a useful framework from which to explore the functional basis of character associations. The associations of life-history characteristics in Type I (long gestation periods, smaller litter of larger, precocial neonates, which are weaned late, mature late and live for longer) and Type II (short gestation periods, larger litter of small, altricial neonates, which are weaned early, mature early and have shorter lifespans) species are indicative of slow and fast life histories, respectively (Promislow & Harvey 1990; Dobson & Oli 2007). The extent to which these empirically derived constellations, based on evolutionary associations between placental morphologies

and between placental morphologies and life-history characters, coincide with this dichotomy in life-history strategies, strongly suggests that life-history strategies have exerted a key influence on the evolution and diversification of placental structures in *Eutheria*. Ultimately, the success of pregnancy requires a balance between fetal and maternal demands, and my results suggest that selection pressures on placentation stem significantly from variation in reproductive strategies. In terms of placental morphology, the two extremes on the scale of life-history strategies are characterized by differences in placental shape (diffuse for Type I; discoid for Type II), yolk sac morphology (free for Type I; inverted for Type II), and the form and nature of the contact area between maternal and fetal tissues (villous to trabecular and epitheliochorial, i.e., non-invasive, for Type I; labyrinthine and haemochorial, i.e., invasive, for Type II).

Yolk sac and placental shape

Mossman (1987) attempted to group eutherian taxa by yolk sac morphology and inferred a group consisting of vespertilionid bats, tree shrews, and golden moles. The phylogenetic signal of the yolk sac is not only weak, but its association with other placental characters is ambiguous. A free yolk sac is considered ancestral for eutherian mammals as a whole (Mess & Carter 2007; Table 11). The inverted yolk sac is the only placental character state in this study to be negatively correlated with both an invasive (endotheliochorial) and non-invasive (epitheliochorial) placentation (Table 13; Fig 39). This may be explained by the degree of functional differences found among inverted yolk sacs (e.g., the yolk sac of the armadillo, particularly towards the end of gestation, subserves different functions than the highly vascularized inverted yolk sac of rodents) (Carter 2001). It may also be explained by a strong selective pressure for yolk sac displacement in placentation. The separation of the yolk sac endoderm from direct association with the trophoblast frees a valuable region for histotrophic exchange (Wildman *et al* 2006). Many mammals, predominantly endotheliochorial or epitheliochorial (Carter *et al* 2005; Enders & Carter 2006), respond to this by developing specialized regions that augment histotrophic transfer (e.g., haemophagous regions). Certain genes influencing metabolism (e.g., insulin-like growth factor II) are imprinted on the human yolk sac, suggesting that retention of the primitive free yolk sac is driven by its importance in embryo development (Freyer & Renfree 2009). Two categories of placental shape indicate a relationship with reproductive strategies. The diffuse placenta is associated with the production of precocial infants that are weaned relatively late, indicating high investment in individual offspring, whereas the discoid placenta is associated with the frequent

production of small, altricial infants, indicating low investment per individual infant. Interestingly, the discoid placenta is also associated with medium and medium-large social group sizes (see below). Similarly, the free yolk sac is associated with the relatively late weaning of precocial offspring, whereas the inverted yolk sac is associated with the frequent production of large litters of altricial infants. It is, thus, unexpected that a free yolk sac was reconstructed as being ancestral for eutherians since the life-history characteristics associated with an inverted yolk sac are more in line with what is expected to have been the ancestral eutherian pattern of life-history strategies. The diffuse placenta and free yolk sac of placental constellation Type I combine to maximise the amount of chorionic surface involved in maternofetal interchange through the placenta, whereas the discoid placenta and inverted yolk sac of Type II have the effect of limiting the amount of chorionic surface involved in forming the placenta.

Diffusion and exchange

Maternofetal interdigitation encourages fetal exchange. This study and others have resolved the ancestral state for Eutheria to be labyrinthine, which is a condition retained in all superorders and only partnered with endotheliochorial and haemochorial placentae (Mess & Carter 2005). There is a strong dichotomy of associated reproductive strategies between the different types of interdigitation, with villous to trabecular interdigitation clearly linked to characters that suggest extensive investment into individual offspring (long interbirth intervals and small litters of precocial infants that are born after long gestation periods and weaned late), whereas labyrinthine interdigitation is associated with maximizing quantity of offspring (medium to large litters of altricial infants that are born after short to medium gestation periods and weaned early). In addition, the same association with social group size occurs here as in relation to placental shape. The association of labyrinthine interdigitation with short to medium gestation lengths and with altricialitiy is consistent with differences in concentrations of placental lactogens, a measure that is directly proportional to fetal utilization of maternal resources (Braunstein *et al* 1980; Handwerger & Brar 1992; Haig 1996 2008; Homko *et al* 1999; Carter 2009; Papper *et al* 2009). In most rodents, the majority of which have labyrinthine placentae, placental lactogens are secreted throughout pregnancy (Voogt *et al* 1982; Flietstra & Voogt 1996), whereas in primates and ruminants, the majority of which have villous placentae, placental lactogens are mainly secreted during the second-half of pregnancy (Belanger *et al* 1971; Chard 1982). Thus, the short gestational period of the labyrinthine placenta corresponds to a more intense provision of maternal resources to the fetus than the longer gestational period associated with villous interdigitation (see Baur

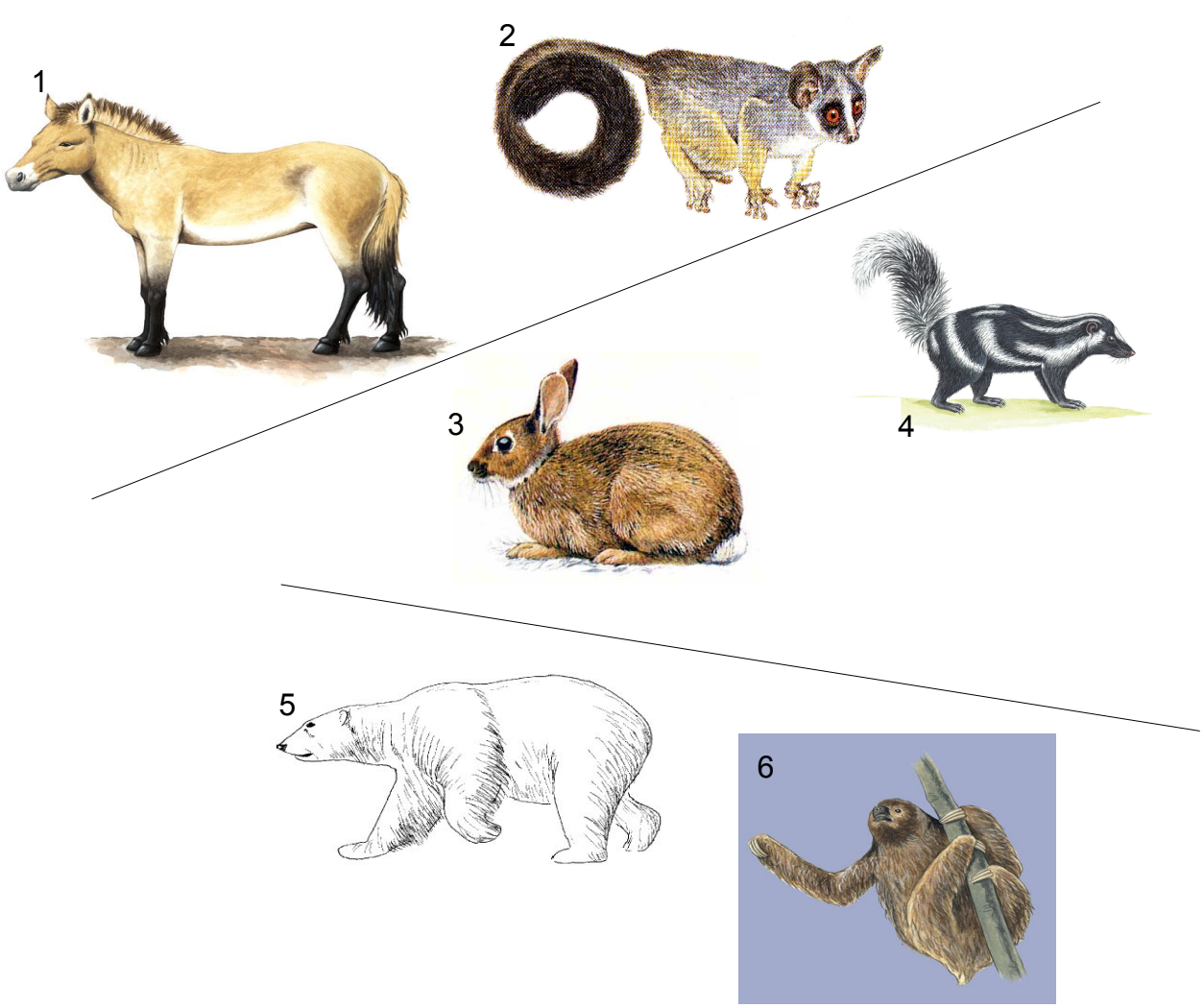

Figure 40: Sketches of species representative of three Eutherian constellations of placental morphology and life-history variables. Species in the first constellation (1, Equus caballus; 2, Otolemur crassicaudatus) are characterized by a diffuse, epitheliochorial placenta, villous interdigitation, and a free yolk sac, as well as large body mass, precociality, and a long gestation period. Species in the second constellation (3, Oryctolagus cuniculus; 4, Spilogale putorius) are characterized by a discoid, haemochorial placenta, labyrinthine interdigitation, and an inverted yolk sac, as well as small adult body mass, altriciality, gregariousness, and a short gestation length. The third constellation (5, Ursus maritimus; 6, Bradypus variegatus) is less distinct that the first two and more closely represents a variation, albeit qualitatively significant, on the second constellation. Species in this constellation are characterized by a zonary, endotheliochorial placenta and labyrinthine interdigitation; they tend to have medium-to-large body, altricial young, and socialize with large groups. Pictures from http://animaldiversity.ummz.umich.edu.

1977, 1981). The directional evolution of villous interdigitation in primates – from the labyrinthine dermoptera and tree shrews (the two potential sister groups of primates) to the more labyrinthine-than-villous tarsier (Hill 1932) to the trabecular network of platyrrhines (Wislocki 1929; Hill 1932) that exhibit only late-stage branched villi and relatively continuous intervillous space to the ubiquitous branched villi in catarrhines (Carter 2009) – suggests that villous interdigitation evolved to help sustain longer gestational periods without excessively depleting maternal resources, which is represented in my data by a positive association between villous to trabecular interdigitation and a long gestation period.

As with placental shape, yolk sac morphology, and maternofetal interdigitation, my data associate different types of interhemal barriers with different strategies of investment into offspring, with the most invasive (haemochorial) type characterized by life-history traits that maximize speed of reproduction and number of offspring (relatively low interbirth intervals and large litters of altricial infants that are born after short gestation periods and weaned early) and the least invasive (epitheliochorial) type associated with traits that maximize investment in individual offspring (longer interbirth intervals and small litters of precocial infants that are born after long gestation periods and weaned late). The main differences between the dichotomies associated with interdigitation and those associated with interhemal barrier are that interhemal barriers also appear to be linked to neonatal size (a less invasive placenta is associated with larger neonates than a more invasive one) and overall lifespan (a less invasive placenta is associated with longer individual lifespans than a more invasive one), two effects not seen with respect to differences in maternofetal interdigitation. My data also confirm earlier observations of an association between type of interhemal barrier and adult body mass, where haemochorial placentae are associated with lower adult body mass than endotheliochorial or epitheliochorial placentae (Martin 1990, 2008).

Of all the characters associated with variation in placental morphology, the interhemal barrier has received by far the most attention to date. Early suggestions, based on comparisons between epitheliochorial strepsirrhine primates and haemochorial haplorrhine primates, of a progression from generally less efficient epitheliochorial to more efficient haemochorial placentation (Leutenegger 1973) were later dismissed based on more comprehensive analyses (Martin 1990, 2008; Vogel 2005). More recently, Elliot & Crespi (2008) have described differences in patterns of brain-body allometry between mammals with different types of interhemal barriers. They have suggested the existence of trade-offs over the allocation of resources to brain growth vs. other life-history traits such as litter size or the overall energetic cost of litter production, citing differences in the average size of litters between the

three main types of interhemal barriers as tentative evidence. These suggestions are clearly confirmed by my analyses for litter size, where I report a positive association between haemochorial placentation and medium to large litters. Otherwise, however, more expensive strategies tend to associate with less invasive placentae, including gestation length (longer in epitheliochorial species, shorter in haemochorial species), neonate mass (higher in epitheliochorial species, lower in heamochorial species), development at birth (precocial in epitheliochorial species, altricial in endotheliochorial and haemochorial species) and age at weaning (higher in epitheliochorial species, lower in endotheliochorial and haemochorial species).

Clearly the association between placental morphologies and the dichotomy between opposite strategies of offspring investment is not absolute, as many species combine elements of placental morphologies that are associated with both types of strategies. For example, the convergence of villous placentation between haemochorial haplorrhines and mostly epitheliochorial ferungulates, as well as the retention of villous interdigitation in epitheliochorial strepsirrhines, suggests either different physiological roles for interhemal barrier and interdigitation, or the possibility of achieving largely equivalent maternofetal interchange through different routes. The observed association between interdigitation and interhemal barrier along the mammalian phylogeny may point to a selective advantage of villous interdigitation in epitheliochorial species. The number and nature of layers between fetal and maternal blood flow bear no relationship to the ability of placentae to provide oxygen to the fetus (Enders & Carter 2004), although this does not preclude differences in how oxygen is exchanged. The advantage to the embryo of haemochorial placentation, compared to epitheliochorial placentation, is direct access to the maternal blood: by placing the surface of the trophoblast in contact with maternal blood, the transport of glucose, amino acids, and inorganic ions are facilitated (Jelkmann & Bauer 1977; Petschow *et al* 1978; Franzke & Jelkmann 1982; Martin 2003; Vogel 2005; Kriegs *et al* 2006). In epitheliochorial placentae, transfer of nutrients such as iron and lipids is enhanced by the conspicuous development of the uterine glands, which typically occur in clusters adjacent to specially developed absorptive areas of the chorion (Martin 1980). Oxygen exchange, however, depends on more than placental invasiveness; oxygen capacity and affinity of maternal and fetal blood, direction and rate of maternal and fetal blood flow, oxygen diffusing capacity of the placenta, and placental oxygen consumption are all principal phenomena affecting oxygen exchange (Metcalfe *et al* 1967; Ashwal *et al* 1984; Carter 1989, 1999; Wilkening & Meschia 1992; Carter 2009; Mess & Carter 2009). The efficiency of exchange can be predicted by interdigitation and the placental shape. In labyrinthine

placentae, counter-current flow with cross-current components is the most common arrangement (Carter *et al* 2004; Miglino *et al* 2004), with counter-current flow considered the most effective for maternofetal exchange (Faber *et al*. 1992); whereas the predominant cross-current flow in villous placentae are buttressed by the ratio of maternofetal blood flow (Schröder & Power 1997; also see Moll 1972; Benirschke & Kaufmann 2000, pp35-38). The diffusion capacity of a placenta is proportional to surface area and inversely proportional to mean diffusion distance (Longo & Ching 1977), so the small surface of an epitheliochorial placenta is compensated by the more efficient transportation implicated in a greater diffusion distance. However, in a review of the physiology of placental transfer in mammals, Faber *et al*. (1992) considered the labyrinthine haemochorial placentae of rabbits, rats and guinea pigs to be more efficient than either villous epitheliochorial placentation in artiodactyls or villous haemochorial placentation in rhesus monkeys and humans. Since my analyses infer the labyrinthine haemochorial condition to be ancestral for eutherians, later diversification of, and the observed association between, maternofetal interdigitation and interhemal barrier along most lineages suggests that the evolution of these two characters was not principally driven by a need for more efficient oxygen or nutrient transfer.

Viviparity-driven and maternal-fetal conflicts

While most of the associations of life-history characters with placental morphologies I have described may be explained as reflections of different strategies of resource allocation to individual offspring, the association between the labyrinthine, haemochorial placenta and large social group size cannot be explained in those terms.

Placentation is a complex sequence of two-way interactions between fetal and maternal tissues. Embryonic development in eutherian mammals creates an arena for genomic conflict (Zeh & Zeh 1996, 1997) between mothers and developing embryos, between sibling embryos, and between maternal and paternal genomes (Haig 1996; Spencer *et al* 1999; Crespi & Semeniuk 2004), in which the evolutionary interest of the embryo to maximize its access to maternal resources is promoted, against the interest of the mother, through uniquely Y-chromosome genes and paternally imprinted alleles (Moore & Haig 1991; Haig 1993; McVean & Hurst 1997; Haig 2004; Bressan *et al* 2009). Since maternal and paternal genomes will likely vary in their genetic compatibility (Reik & Walter 1998), normal offspring production will only be the consequence of pairing compatible genomes (Zeh & Zeh 2000; Graves 2010), which in this case might be a paternal genotype of aggressive resource transfer activity and a

maternal genotype of similarly aggressive resource transfer suppression activity. Otherwise, the resulting embryo is likely to be either too demanding on the mother or unable to expropriate sufficient maternal resources. Immunologically, intolerance of the embryo is a barrier to reproduction. Recent evidence suggests that immune tolerance is established between the mother and fetus through innate immunological interactions between maternal uterine natural killer (uNK) cells and trophoblast cells (Croy *et al* 2006; Carter *et al* 2007) and that maternal immunological reactions are mostly directed against paternal antigens expressed by paternally imprinted genes in the placenta (Zeh & Zeh 2000; Bressan *et al* 2009; Graves 2010). This enlists maternal-fetal conflicts as a response to viviparity-driven conflicts. Decreasing the risk of immunological compromise during pregnancy becomes increasingly important for precocial species with long gestation lengths (Haig 1996). In this study, epitheliochorial placentation was positively associated with precociality and long gestation length, whereas haemochorial placentation was positively associated with altriciality and both short and medium gestation lengths, suggesting a relationship between both development at birth and gestation length and immunological risk during pregnancy. In fact, haemochorial placentation has been implicated in bleeding at parturition, microchimerism, and erythroblastosis fetalis in species with relatively long gestation periods (Benirschke & Kaufmann 2000; Bianchi & Lo 2001; Nelson 2003; Moffett & Loke 2006). The susceptibility of epitheliochorial placentation to immunological risk is diminished due to the minimal invasion of trophoblast cells into the uterus (Moffett & Loke 2006); this, however, has the attending effect of decreasing the susceptibility to viviparity-driven conflict of epitheliochorial species, leaving the fetus with only limited control over the maternal system. Although, it is argued that evolution of the cotyledonary placental shape (and, especially, giant trophoblast cells) in cetartiodactyls may have permitted viviparity-driven conflict to persist in epitheliochorial species (Klisch & Mess 2007).

The viviparity-driven conflict hypothesis for speciation suggests that intense mother-embryo conflict, resulting from intimate physiological interaction between mother and embryo during embryonic development, in viviparous species promotes reproductive isolation and that it is intensified by multiple paternity (Zeh & Zeh 2000). Multiple paternity is predicted to promote the evolution of more aggressive paternal genomes (Zeh & Zeh 2000), and since viviparity-driven conflict is predicted to be most intense where genomic-imprinting is most effective (Zeh & Zeh 2008), we may expect a more rapid evolution of postzygotic reproductive barriers in species with more invasive interhemal barriers and particularly high rates of speciation in lineages combining invasive placentation with

social systems that allow for multiple paternity. While social organization was not directly tested in this study, the positive association between haemochorial placentation and large group size in my data may be indicative of the effect of social behavior, and polyandry in particular, on the importance of genomic-imprinting in a species. A resulting increase in rates of speciation in haemochorial polyandrous species may then explain the preponderance of evolutionary associations between large social group size and haemochorial interhaemal barriers. My results therefore suggest that regulation of maternal investment by both maternal and paternal genomic-imprinting, driven at least in part by the social structure of a species, rather than efficiency of maternal expenditure per ounce of fetal weight gain *per se*, is an important element of selective pressure behind the evolution of the placental barrier. The reconstruction of an invasive haemochorial placenta as ancestral for eutherians could therefore suggest an important role for viviparity-driven conflict in the early diversification of crown group Eutheria. It should be noted, however, that Elliot & Crespi (2006) have argued that the maternal immune response is more strongly suppressed in species with highly invasive placentae than in species with less invasive placentae and that, as a result, hybrids remain viable at higher genetic distances in haemochorial species than in species with less invasive types of interhaemal barrier. A consequence would be that mammals with less invasive placentation should evolve reproductive isolation through hybrid inviability more rapidly than mammals with more invasive placentae, presumably resulting in higher rates of speciation in the former and directly contradicting the predictions made by the viviparity-driven conflict hypothesis. Clearly, a formal comparison of evolutionary rates of speciation in lineages with different types of interhemal barriers, and taking social organisation into consideration, would be highly informative. Informally, it may be noted that the two orders of extant mammals with the highest numbers of species, Chiroptera and Rodentia (Wilson & Reeder 2005), both have predominantly invasive interhemal barriers.

CONCLUSIONS

Interpreting allometric relationships can be problematic. It is impossible to predict the behavioral differences between two species falling contiguously on an allometric slope, no matter what the plotted variables are. The failure of allometry to provide evidence for anything more than a developmental constraint across taxa limits the descriptive power of this study to address brain structural variation and behavioral differences without referencing existing data. But, in reconstructing the evolutionary history of placentation and deriving patterns of placental morphology across extant taxa, I have tried to put a very specific face on one element contributing to constraining brain structural variation. And in targeting the cellular organization, rather than the gross morphology, of brain regions, I have further tried to provide a more realistic picture of the physiological constraints at work within taxonomic groups and throughout mammalian brain evolution than studies predicated on size alone. The recent orientation of comparative neurobiology – which I think this study is aligned with – has stolen away from using gross morphology as an accepted proxy for function, with the aim of discovering complex mechanisms of selection on the mammalian brain. By contextualizing cellular brain development in mode of placentation, I have provided evidence for an evolutionary relationship between adaptive processes in the placenta and brain.

My data show that two biological constellations of placental morphology have evolved in *Eutheria*. If variability in placental morphology is adaptive in the sense that different morphologies support different life-history strategies – or that variation in placental morphology adapted independently of ecology encourages certain life-history strategies over others - , we should expect placental morphologies to correlate with life-history strategies, especially those that directly relate to reproduction. Indeed, it seems that each constellation has placed constraints on life-history strategies. A species with an epitheliochorial placenta will typically gestate longer, produce precocial offspring, weigh more, and be less gregarious (i.e., be monogamous) compared to a species with a haemochorial or endotheliochorial placenta. The observed association in my data between social group size and placental invasiveness, placental shape, and maternofetal interdigitation may epitomize a selective pressure that has acted on the transformation and retention of definitive placental morphologies. Since viviparity-driven conflict is most intense where genomic-imprinting is most effective (Zeh & Zeh 2008), and genomic-imprinting is most effective in non-monogamous species, due to multi-male competition, I have suggested that a major selection pressure on the evolution of these constellations is

social: the regulation of paternal investment by both maternal and paternal genomic-imprinting, guided by the social behavior of a species, has contributed majorly to the evolution of discrete syndromes of placental morphology in mammals. How then, if at all, have these placental morphologies affected cellular organization of the brain in different taxa? Is there an evolutionary relationship between variation in the placenta and the cellular brain?

Shifts in ecological or genetic pressures and constraints can both influence the evolution of and change the associations among characters over evolutionary time. Such associations can arise if the characters are under correlated selection (Felsenstein 1988; Martins *et al* 2000; Jones *et al* 2003; Arnold & Futuyma 2009), if they are functionally integrated (Walker 2007; Collar *et al* 2008; Calsbeek & Irschick 2009), or if the characters themselves are genetically correlated (Lande & Arnold 1983; Estes & Arnold 2007; Revell & Harmon 2008). Comparisons of annotated mammalian genes show that, while some genes for sensory perception and immune defense show evidence of positive selection, genes with maximal expression in the brain shown no evidence of positive selection. Rather, genes involved in spermatogenesis in primates (Nielsen *et al* 2005) and placentation in mammals (Rawm & Cross 2008) show an excess of positive selection. Perhaps this underlies a directionality in the evolutionary relationship between placentation and brain organization, suggesting, in agreement with recent evidence (Drake 2007; Gonzalez-Voyer *et al* 2009), that biological and behavioral reproductive strategies are under stronger selection than cognitive processes during adaptive radiations. Recent advances in quantitative genetics have allowed workers to map gene loci that underlie genetic variances and covariances for quantitative traits, which may pertain to both the mechanisms and selective pressures acting on the proliferation of glia and neurons in different brain regions. The acquisition of data on the quantitative genetic architecture of brain systems may be able to identify deep conservation in developmental brain structures. Alternatively, variation in cognitive processes may be exceedingly vulnerable, at least compared to processes implicating reproductive strategies, to developmental changes in regulatory RNA. The evolutionary plasticity of phenotypic traits absent changes in protein coding sequences, late-stage cell-fate decisions, and the differential expression of conserved developmental regimes in the brain across taxa suggest a major role for non-coding RNA, protein mediators, and transgenerational epigenetic inheritance in brain evolution. The coordination of data at the cellular and molecular level on phyletic diversity in brain organization will help us understand how variation in the brain is represented in behavior and how behavior is targeted in the evolving brain.

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APPENDIX

Table A1a: Results of stereologic estimates of cellular densities (cells per mm³) and volumetric estimates (μm³) in all brain regions

	PRIMARY VISUAL CORTEX			CORNU AMMONIS					
Species	Glia-neuron ratio	Neuronal density	Glial cell density	Glia-neuron ratio	Neuronal density	Glial cell density	StrGr	Str Mol	CrbGc
Dasyprocta leporina	1.12	77625	87096	--	--	--	8090270000	22691400000	33884415614
Lepus americanus	0.43	128825	54954	0.14	380189	53703	4073802778	14791083882	141253754462
Cynocephalus volans	1.12	77625	87096	0.55	89125	48978	1096478196	3311311215	35481338923
Tupaia glis	0.81	131826	107152	0.45	173780	77625	812830516	2818382931	25703957828
Stenella coeruleoalba	2.95	46774	138038	--	--	--	--	--	14791083881682
Tursiops truncatus	1.55	147911	229087	--	--	--	--	--	58884365535559
Megaptera novaeangliae	--	--	--	--	--	--	13803842646	48977881937	43651583224017
Sus scrofa	1.45	48978	70795	0.79	114815	93325	8912509381	37153522910	--
Rhinoceros unicornis	--	--	--	--	--	--	--	--	5248074602498
Mustela nigripes	0.78	275423	213796	0.63	213796	134896	1513561248	4365158322	102329299228
Neovison neovison	0.54	229087	120226	0.5	269153	134896	2884031503	7413102413	107151930524
Mephitis mephitis	0.22	169824	38019	0.17	263027	43652	2511886432	8511380382	123026877081
Taxidea taxus	1.07	77625	83176	0.52	194984	102329	1010310570	35481338923	549540873858
Procyon cancrivorus	0.66	144544	93325	0.43	186209	79433	5623413252	18197008586	501187233627
Procyon lotor	0.78	104713	83176	1.32	79433	107152	5888436554	19498445998	489778819368
Nasua nasua	1.17	109648	125893	0.58	95499	56234	2691534804	8912509381	457088189615
Bassaricyon gabbii	1.05	123027	128825	0.63	208930	131826	4677351413	15488166189	239883291902
Potos flavus	0.76	186209	141254	0.91	147911	134896	5888436554	17782794100	467735141287
Ailurus fulgens	1.07	154882	165959	1.12	95499	107152	5011872336	14454397707	630957344480
Zalophus californianus	1.86	30903	57544	0.93	75858	70795	6606934480	33884415614	10232929922808
Callorhinus ursinus	1.7	63096	104713	1.82	60256	109648	5370317964	15135612484	5623413251903
Phoca vitulina	--	--	--	--	--	--	4466835922	16218100974	3090295432514
Ursus maritimus	2.19	44668	95499	3.24	34674	112202	21877616239	79432823472	7943282347243
Canis lupus familiaris	0.76	204174	158489	0.35	288403	102329	2754228703	9120108394	398107170553
Canis latrans	0.34	72444	25119	0.47	74131	33884	13803842646	38904514499	676082975392
Vulpes vulpes	0.95	81283	77625	0.59	138038	79433	8709635900	23988329190	724435960075
Panthera pardus	0.68	75858	51286	0.85	51286	43652	18197008586	56234132519	1949844599758
Felis catus	0.2	114815	22909	0.22	79433	17783	2398832919	6918309709	301995172040
Puma concolor	1.07	69183	74131	0.95	87096	83176	8128305162	26302679919	1479108388168
Crocuta crocuta	1.26	63096	79433	0.98	64565	63096	12589254118	67608297539	2511886431510
Cynictis penicillata	0.87	141254	123027	0.69	114815	77625	4168693835	15135612484	660693448008
Manis gigantea	--	--	--	--	--	--	--	--	1071519305238
Scalopus aquaticus	0.62	295121	181970	0.12	2089296	251189	616595002	1778279410	19952623150
Erinaceus europaeus	0.66	194984	128825	0.28	524807	147911	1584893192	6309573445	45708818961
Sorex araneus	0.87	338844	295121	0.17	1348963	223872	398107171	1122018454	7413102413
Trichechus manatus	1.91	51286	97724	2.24	125893	281838	7585775750	22387211386	--

Abbreviations: CrbGc, granule cell layer of the cerebellum; StrGr, *stratum granulosum*; StrMol, *stratum moleculare*

Table A1b: Physiological variables for non-primate species*

Species	Brain mass (g)	Body mass (kg)	Gestation length (d)
Dasyprocta leporina	20.42	3.02	104
Lepus americanus	9.77	1.51	37
Cynocephalus volans	6.03	1.41	105
Tupaia glis	3.16	0.15	46
Stenella coeruleoalba	812.83	56	350
Tursiops truncatus	1819.7	209	363
Megaptera novaeangliae	6456.54	38905	324
Sus scrofa	123.03	112	115
Rhinoceros unicornis	501.19	1698	479
Mustela nigripes	8.51	0.58	43
Neovison neovison	7.24	0.76	62
Mephitis mephitis	10.23	2.34	63
Taxidea taxus	52.48	6.03	42
Procyon cancrivorus	38.02	5.01	60
Procyon lotor	39.81	6.17	65
Nasua nasua	30.2	5.01	74
Bassaricyon gabbii	16.6	0.83	52
Potos flavus	30.9	1.95	107
Ailurus fulgens	40.74	3.72	135
Zalophus californianus	2187.76	347	331
Callorhinus ursinus	602.56	148	339
Phoca vitulina	446.68	107	302
Ursus maritimus	457.09	363	251
Canis lupus familiaris	131.83	33	63
Canis latrans	89.13	10.47	62
Vulpes vulpes	47.86	6.03	55
Panthera pardus	125.89	51	100
Felis catus	37.15	4.68	66
Puma concolor	128.82	42	89
Crocuta crocuta	144.54	66	110
Cynictis penicillata	10.47	0.59	56
Manis gigantea	NA	33	--
Scalopus aquaticus	1.15	0.04	45
Erinaceus europaeus	3.47	0.93	40
Sorex araneus	0.17	0.01	20
Trichechus manatus	338.84	427	339

*Data from Jones et al (2009).

Table A1c: Results of stereologic estimates of cellular densities (cells per mm³) and volumetric estimates (μm³) in all brain regions

	PRIMARY VISUAL CORTEX			CORNU AMMONIS					
Species	Glia-neuron ratio	Neuronal density	Glial cell density	Glia-neuron ratio	Neuronal density	Glial cell density	StrGr	Str Mol	CrbGc
Callithrix geoffroyi	0.29	338844	97724	0.76	85114	64565	1445439771	4897788194	181970085861
Leontopithecus rosalia	0.24	301995	72444	0.93	56234	52481	4570881896	10232929923	144543977075
Saguinus oedipus	0.3	338844	102329	0.69	112766	77625	2630267992	8511380382	131825673856
Cebus capucinus	0.17	245471	41687	0.66	114900	75858	3981071706	12589254118	363078054770
Saimiri sciureus	0.25	478630	117490	0.65	114815	74131	1949844600	5370317964	213796208950
Aotus trivirgatus	0.15	410950	59930	0.4	100009	39811	2089296131	6760829754	151356124844
Callicebus moloch	0.27	467735	125893	0.71	102329	72444	2454708916	8317637711	151356124844
Pithecia pithecia	0.58	169824	97724	0.38	44668	17378	2398832919	7762471166	301995172040
Alouatta caraya	0.22	194984	42658	3.24	36308	117490	4677351413	13803842646	812830516164
Alouatta palliata	0.28	176349	49168	0.81	81283	66069	8317637711	26915348039	812830516164
Ateles ater	0.3	218776	67608	0.7	112851	79433	4786300923	18620871367	1698243652462
Macaca fascicularis	0.14	331131	47863	1.78	134896	234423	4073802778	11481536215	380189396321
Macaca mulatta	0.27	422149	113783	1.58	67608	107152	5495408739	18197008586	131825673856
Macaca maura	0.18	361470	64343	--	--	--	--	--	--
Cercocebus torquatus	0.39	426580	165959	1.02	60256	61660	3388441561	10964781961	602559586074
Mandrillus sphinx	0.52	263027	138038	0.74	87092	64563	6025595861	18620871367	1023292992281
Papio anubis	0.51	275423	141254	0.47	194984	89125	1819700859	6918309709	1318256738556
Cercopithecus mitis	0.16	245471	39811	0.8	97146	78177	3715352291	11481536215	501187233627
Cercopithecus nictitans	0.26	302604	78168	0.78	89125	69183	4475932206	14791083882	645654229035
Erythrocebus patas	0.37	416869	154882	1.4	74189	104056	4786300923	15848931925	575439937337
Colobus angolensis	0.23	223872	51286	1.48	75858	109648	4570881896	15488166189	660693448008
Trachypithecus francoisi	0.33	446684	147911	0.72	112202	79433	2238721139	7762471166	549540873858
Pongo pygmaeus	0.96	151356	144544	--	--	--	--	--	3981071705535
Pan paniscus	0.62	218776	134896	3.09	44668	138038	5754399373	21877616239	3090295432514
Pan troglodytes	0.59	208930	123027	0.66	81283	53703	19498445998	58884365536	4168693834703
Homo sapiens	0.72	234423	169824	1.35	32359	43652	18197008586	67608297539	20417379446695
Gorilla gorilla	0.95	144544	138038	--	--	--	--	--	6309573444802
Hylobates muelleri	0.41	229087	93325	1.66	57544	93325	12022644346	36307805477	1230268770812
Symphalangus syndactylus	0.42	239883	101103	1.66	74131	123027	1778279410	6456542290	1288249551693
Tarsius bancanus	0.26	234510	60256	0.48	204174	97724	954992586	3548133892	87096358996
Tarsius syrichta	0.25	200103	50425	0.47	331131	154882	758577575	2187761624	83176377110
Lemur catta	0.85	70795	60256	0.79	87096	69183	5495408739	17378008287	524807460250
Eulemur mongoz	0.59	234423	138038	0.63	117490	73926	5128613840	16218100974	275422870334
Microcebus murinus	0.59	190546	112202	1.95	112202	218776	1174897555	2452316441	75857757503
Cheirogaleus medius	0.59	186209	109648	2	107152	213796	1210144403	2691534804	74131024130
Galago senegalensis	0.45	338844	151356	0.63	245471	151356	2187761624	6025595861	162181009736
Nycticebus coucang	0.49	109648	53703	0.26	158489	41687	4570881896	13803842646	162181009736

Abbreviations: CrbGc, granule cell layer of the cerebellum; StrGr, *stratum granulosum*; StrMol, *stratum moleculare*

Table A1d: Physiological variables for primate species

Species	Brain mass (g)	Body mass (kg)*	Gestation length (d)*	Cerebellar volume (cc^3)	Axial diameter(mm)[a]	Corneal diameter (mm)[a]	Neocortex volume (cm^3)[b]	V1 volume (cm^3)[b]	LGN volume (cm^3)[b]
Callithrix geoffroyi	7.76	0.23	145	0.76	11.5	5.6	4.37	0.6	0.03
Leontopithecus rosalia	12.3	0.65	132	--	11.2	6.6	--	--	--
Saguinus oedipus	10	0.32	178	0.95	11.7	6.5	5.89	0.79	0.03
Cebus capucinus	72.44	3.39	162	--	15.8	10.0	46.77	3.8	0.14
Saimiri sciureus	22.91	0.78	145	2	15.5	7.8	15.49	1.91	0.06
Aotus trivirgatus	13.18	0.81	132	1.66	19.1	12.9	10	1	0.03
Callicebus moloch	18.2	0.79	129	1.29	13.2	7.1	11.22	1.2	0.05
Pithecia pithecia	30.2	1.45	170	--	14.1	7.8	20.89	1.7	0.08
Alouatta caraya	56.23	7.24	138	--	16.2	9.8	31.62	1.91	0.09
Alouatta palliata	52.7	6.9	139	--	--	--	--	--	--
Ateles ater	102.33	8.51	141	12.3	20.4	11.0	70.79	3.8	0.15
Macaca fascicularis	91.2	11.22	170	8.51	18.2	9.5	63.1	5.25	0.16
Macaca mulatta	70.8	5.06	162	7.94	18.4	9.6	--	--	--
Macaca maura	83.82	7.53	165	--	20.0	10.8	--	--	--
Cercocebus torquatus	104.71	8.71	166	9.12	19.5	11.2	--	--	--
Mandrillus sphinx	158.49	3.02	129	--	22.9	12.9	--	--	--
Papio anubis	154.88	23.99	182	19.05	20.9	11.0	141.25	10	0.4
Cercopithecus mitis	70.79	5.25	186	6.92	19.5	11.0	50.12	4.17	0.15
Cercopithecus nictitans	66.7	4.32	180	--	17.6	10.4	--	--	--
Erythrocebus patas	102.33	7.94	166	--	22.4	11.2	--	--	--
Colobus angolensis	74.13	8.91	162	8.71	19.1	10.2	--	--	--
Trachypithecus francoisi	91.2	7.59	200	--	18.6	11.0	--	--	--
Pongo pygmaeus	338.84	66.07	249	38.9	21.4	11.2	269.15	8.13	0.26
Pan paniscus	316.23	43.65	240	--	--	--	245.47	11.48	
Pan troglodytes	346.74	47.86	229	45.71	20.9	10.5	263.03	8.32	0.25
Homo sapiens	1230.27	64.57	269	134.9	--	--	1003	15.14	0.34
Gorilla gorilla	512.86	151.36	257	70.79	22.9	12.3	281.84	9.12	0.31
Hylobates muelleri	102.33	6.03	209	12.02	20.0	10.7	67.61	4.07	0.17
Symphalangus syndactylus	131.83	11.22	209	--	--	--	--	5.5	--
Tarsius bancanus	3.47	0.11	178	--	16.2	12.9	--	--	--
Tarsius syrichta	3.31	0.09	179	0.43	17.0	13.8	22.91	0.3	0.02
Lemur catta	22.39	2.88	138	--	15.5	12.0	--	--	--
Eulemur mongoz	19.05	3.02	129	--	--	--	--	--	--
Microcebus murinus	1.78	0.07	60	0.22	9.1	7.9	16.98	0.1	0.01
Cheirogaleus medius	3.16	0.27	62	0.4	10.2	8.7	12.59	0.2	0.01
Galago senegalensis	4.79	1.86	135	0.68	12.9	10.0	21.38	0.3	0.02
Nycticebus coucang	12.59	2	191	1.32	15.8	12.0	23.44	0.69	0.04

*Jones et al (2009)

[a] Ross & Kirk (2007)

[b] de Sousa et al (2009, 2010)

Table A2: Slope estimates and correlation coefficients for scaling relationships from species means for placental groups for cell densities in V1 and anatomical variables

Taxa	Dependent variable	Independent variable	*Species mean data*					*Independent contrasts*		
			RMA	R^2	Lower 95% CI	Upper 95% CI	p	RMA	R^2	p
Epitheliochorial (n=10)	Glia cell density	neuronal density	0.553	0.368	0.307	0.994	0.068	-0.229	0.859	0.000
	Glia-neuron ratio	brain mass (g)	0.184	0.954	0.117	0.291	0.001	0.172	0.899	0.175
		body mass (kg)	0.273	0.856	0.165	0.451	0.003	0.195	0.873	0.241
		gestation length (d)	0.238	0.881	0.141	0.402	0.046	0.149	0.919	0.317
		EQ	-0.183	0.925	-0.106	-0.314	0.714	-0.139	0.934	0.289
Endotheliochorial (n=24)	Glia cell density	neuronal density	1.023	0.001	0.684	1.532	0.053	1.216	0.046	0.043
	Glia-neuron ratio	brain mass (g)	0.375	0.632	0.254	0.552	0.020	0.504	0.436	0.012
		body mass (kg)	0.273	0.788	0.185	0.403	0.023	0.329	0.712	0.022
		gestation length (d)	0.912	0.013	0.639	1.301	0.002	1.187	0.230	0.128
		EQ	-1.223	0.040	-0.789	-1.898	0.239	-1.280	0.060	0.566
Haemochorial (n=32)	Glia cell density	neuronal density	1.053	0.065	0.742	1.495	0.209	1.240	0.056	0.003
	Glia-neuron ratio	brain mass (g)	0.304	0.745	0.221	0.416	0.319	0.345	0.640	0.111
		body mass (kg)	-0.235	0.803	-0.164	-0.336	0.078	0.306	0.690	0.132
		gestation length (d)	0.452	0.533	0.335	0.609	0.352	0.641	0.211	0.158
		EQ	-0.248	0.824	-0.181	-0.340	0.031	-0.483	0.402	0.969

Appendix 3: Predictors of CA1-3 cellular densities based on stepwise AIC multiple regression models

Taxa	Variable	Predictor	Estimate	St dev	AIC	t-value	Pr(>|t|)
AS	Glia-neuron ratio	StrGc (µm³)	1.193	0.518	-166.702	2.302	0.025
	R^2=0.386	StrMol (µm³)	-0.948	0.493	-165.115	-1.924	0.059
	p=0.000	Brain mass	--	--	--	--	--
		Body mass	--	--	--	--	--
		EQ	--	--	--	--	--
		Gestation length	0.587	0.127	-151.039	4.630	0.000
	Neuronal density	StrGc (µm³)	-1.240	0.444	-182.517	-2.793	0.007
	R^2=0.667	StrMol (µm³)	1.059	0.452	-184.808	2.342	0.023
	p=0.000	Brain mass	-0.127	0.078	-187.780	-1.614	0.112
		Body mass	--	--	--	--	--
		EQ	--	--	--	--	--
		Gestation length	-0.465	0.137	-179.02	-3.391	0.001
		Glial cell density	0.510	0.099	-166.485	5.160	0.000
	Glial cell density	StrGc (µm³)	0.793	0.496	-176.094	1.599	0.115
	R^2=0.328	StrMol (µm³)	-0.708	0.463	-176.324	-1.528	0.132
	p=0.000	Brain mass	--	--	--	--	--
		Body mass	--	--	--	--	--
		EQ	--	--	--	--	--
		Gestation length	0.343	0.140	-172.584	2.455	0.017
		Neuronal density	0.616	0.120	-155.096	5.154	0.000
Carnivora	Glia-neuron ratio	StrGc (µm³)	0.416	0.194	-55.304	2.148	0.050
	R^2=0.532	StrMol (µm³)	--	--	--	--	--
	p=0.006	Brain mass	-21.843	14.426	-57.968	-1.514	0.152
		Body mass	14.568	9.706	-58.018	1.501	0.156
		EQ	21.915	14.509	-57.982	1.510	0.153
		Gestation length	0.669	0.323	-55.659	2.070	0.048
	Neuronal density	StrGc (µm³)	-0.378	0.115	-61.592	-3.280	0.005
	R^2=0.698	StrMol (µm³)	--	--	--	--	--
	p=0.000	Brain mass	--	--	--	--	--
		Body mass	--	--	--	--	--
		EQ	--	--	--	--	--
		Gestation length	-0.529	0.135	-64.806	-3.927	0.001
		Glial cell density	0.380	0.146	-68.012	2.607	0.019
	Glial cell density	StrGc (µm³)	--	--	--	--	--
	R^2=0.242	StrMol (µm³)	0.275	0.208	-57.809	1.321	0.209
	p=0.137	Brain mass	-25.277	14.349	-56.047	-1.762	0.102
		Body mass	16.850	9.651	-56.115	1.746	0.104
		EQ	25.41	14.43	-56.05	1.76	0.1
		Gestation length	0.492	0.353	-57.539	1.395	0.187
		Neuronal density	0.655	0.288	-53.638	2.272	0.041
Primates	Glia-neuron ratio	StrGc (µm³)	--	--	--	--	--
	R^2=0.194	StrMol (µm³)	--	--	--	--	--
	p=0.024	Brain mass	--	--	--	--	--
		Body mass	0.201	0.066	-88.297	3.041	0.005
		EQ	0.3	0.21	-95.195	1.43	0.16
		Gestation length	-1.213	0.427	-89.336	-2.840	0.008
	Neuronal density	StrGc (µm³)	--	--	--	--	--
	R^2=0.556	StrMol (µm³)	--	--	--	--	--
	p=0.000	Brain mass	-0.222	0.053	-95.718	-4.170	0.000
		Body mass	--	--	--	--	--
		EQ	-0.355	0.168	-106.813	-2.115	0.043
		Gestation length	0.992	0.346	-103.214	2.866	0.008
		Glial cell density	0.517	0.116	-93.868	4.470	0.000
	Glial cell density	StrGc (µm³)	--	--	--	--	--
	R^2=0.386	StrMol (µm³)	--	--	--	--	--
	p=0.000	Brain mass	0.122	0.074	-95.159	1.646	0.110
		Body mass	--	--	--	--	--
		EQ	--	--	--	--	--
		Gestation length	-0.834	0.384	-93.138	-2.171	0.038
		Neuronal density	0.732	0.167	-81.260	4.385	0.000

Table A4a: Predictors based on stepwise AIC multiple regression models for AS

Taxa	Region	Variable	Predictor	Estimate	St dev	AIC	t-value	Pr(>|t|)
AS	V1	Glia-neuron ratio	CA glia-neuron ratio	--	--	--	--	--
		R^2=0.236	CrbGc	0.331	0.131	-159.775	2.529	0.014
		P=0.001	StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	-0.391	0.197	-162.238	-1.981	0.052
			Body mass	0.250	0.122	-161.974	2.046	0.045
			EQ	--	--	--	--	--
			Gestation length	-0.356	0.177	-162.125	-2.009	0.049
		Neuronal density	V1 glial cell density	0.283	0.117	-189.246	2.408	0.019
		R^2=0.418	CA neuronal density	--	--	--	--	--
		P=0.000	CrbGc	-0.291	0.107	-187.617	-2.724	0.009
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	1.250	0.447	-187.199	2.800	0.007
			Body mass	-0.898	0.301	-186.130	-2.989	0.004
			EQ	-0.961	0.467	-190.855	-2.059	0.044
			Gestation length	0.284	0.141	-191.024	2.020	0.048
		Glial cell density	V1 neuronal density	0.263	0.090	-188.385	2.906	0.005
		R^2=0.211	CA glial cell density	0.275	0.092	-187.994	2.979	0.004
		P=0.000	CrbGc	--	--	--	--	--
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
	CA1-3	Glia-neuron ratio	V1 glia-neuron ratio	--	--	--	--	--
		R^2=0.409	CrbGc	0.236	0.112	-158.437	2.115	0.039
		P=0.000	StrGr	1.653	0.581	-154.896	2.845	0.006
			StrMol	-1.689	0.602	-155.094	-2.808	0.007
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	0.397	0.161	-156.831	2.467	0.017
		Neuronal density	CA glial cell density	0.514	0.104	-159.240	4.932	0.000
		R^2=0.682	V1 neuronal density	--	--	--	--	--
		P=0.000	CrbGc	-0.186	0.095	-177.455	-1.945	0.057
			StrGr	-1.532	0.494	-171.680	-3.102	0.003
			StrMol	1.421	0.514	-173.570	2.766	0.008
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	-0.487	0.138	-169.113	-3.522	0.001
		Glial cell density	CA neuronal density	0.521	0.110	-153.753	4.750	0.000
		R^2=0.379	V1 glial cell density	0.270	0.130	-170.027	2.084	0.042
		P=0.000	CrbGc	0.205	0.092	-169.362	2.235	0.030
			StrGr	0.977	0.544	-171.191	1.796	0.078
			StrMol	-1.118	0.560	-170.392	-1.998	0.051
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		StrGr	CrbGc	--	--	--	--	--
		R^2=0.974	StrMol	0.934	0.019	-172.550	48.995	0.000
		P=0.000	Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		StrMol	CrbGc	--	--	--	--	--
		R^2=0.974	StrGr	1.042	0.021	-120.080	48.995	0.000
		P=0.000	Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
	OTHER	CrbGc	CA glia-neuron ratio	0.219	0.098	-180.200	2.231	0.030
		R^2=0.904	V1 glia-neuron ratio	--	--	--	--	--
		P=0.000	CA neuronal density	--	--	--	--	--
			V1 neuronal density	-0.266	0.104	-178.688	-2.556	0.013
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	0.748	0.043	-75.039	17.364	0.000
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		Brain mass	CA glia-neuron ratio	--	--	--	--	--
		R^2=0.904	V1 glia-neuron ratio	--	--	--	--	--
		P=0.000	CA neuronal density	--	--	--	--	--
			V1 neuronal density	0.112	0.031	-349.060	3.638	0.001
			CrbGc	0.122	0.026	-341.850	4.675	0.000
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Body mass	0.665	0.019	-163.500	35.398	0.000
			EQ	0.963	0.044	-219.840	22.024	0.000
			Gestation length	--	--	--	--	--

Table A4b: Predictors based on stepwise AIC multiple regression models for carnivores

Taxa	Region	Variable	Predictor	Estimate	St dev	AIC	t-value	Pr(>|t|)
Carnivores	V1	Glia-neuron ratio	CA glia-neuron ratio	0.783	0.175	-53.225	4.477	0.001
		R^2=0.710	CrbGc	0.467	0.182	-62.807	2.561	0.023
		P=0.000	StrGr	-0.478	0.200	-63.603	-2.390	0.031
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	-0.641	0.320	-65.316	-2.003	0.065
		Neuronal density	V1 glial cell density	0.249	0.076	-83.016	3.251	0.005
		R^2=0.889	CA neuronal density	--	--	--	--	--
		P=0.000	CrbGc	-0.489	0.067	-64.215	-7.334	0.000
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	0.312	0.138	-87.605	2.255	0.040
		Glial cell density	V1 neuronal density	0.754	0.266	-75.897	2.834	0.014
		R^2=0.861	CA glial cell density	0.833	0.112	-53.552	7.429	0.000
		P=0.000	CrbGc	0.484	0.180	-76.673	2.682	0.019
			StrGr	-0.284	0.127	-78.809	-2.246	0.043
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	-0.393	0.221	-80.906	-1.778	0.099
	CA1-3	Glia-neuron ratio	V1 glia-neuron ratio	0.704	0.150	-58.950	4.678	0.000
		R^2=0.782	CrbGc	--	--	--	--	--
		P=0.000	StrGr	1.253	0.472	-69.256	2.652	0.018
			StrMol	-0.988	0.443	-71.218	-2.230	0.041
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	0.319	0.147	-71.479	2.171	0.046
		Neuronal density	CA glial cell density	0.405	0.139	-65.482	2.910	0.011
		R^2=0.755	V1 neuronal density	--	--	--	--	--
		P=0.000	CrbGc	-0.863	0.192	-57.527	-4.488	0.001
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	0.317	0.124	-67.227	2.548	0.023
			EQ	0.497	0.210	-68.093	2.362	0.033
			Gestation length	--	--	--	--	--
		Glial cell density	CA neuronal density	--	--	--	--	--
		R^2=0.746	V1 glial cell density	0.786	0.104	-57.203	7.532	0.000
		P=0.000	CrbGc	--	--	--	--	--
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		StrGr	CrbGc	--	--	--	--	--
		R^2=0.947	StrMol	0.886	0.046	-51.701	19.327	0.000
		P=0.000	Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		StrMol	CrbGc	--	--	--	--	--
		R^2=0.947	StrGr	1.072	0.055	-47.501	19.327	0.000
		P=0.000	Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
	OTHER	CrbGc	CA glia-neuron ratio	-0.332	0.155	-93.691	-2.141	0.056
		R^2=0.989	V1 glia-neuron ratio	0.538	0.138	-83.890	3.886	0.003
		P=0.000	CA neuronal density	-0.454	0.121	-84.643	-3.754	0.003
			V1 neuronal density	--	--	--	--	--
			StrGr	0.388	0.078	-78.045	4.950	0.000
			StrMol	--	--	--	--	--
			Brain mass	0.349	0.099	-85.901	3.533	0.005
			Body mass	0.278	0.043	-70.646	6.435	0.000
			EQ	--	--	--	--	--
			Gestation length	0.517	0.125	-82.432	4.146	0.002
		Brain mass	CA glia-neuron ratio	--	--	--	--	--
		R^2=0.999	V1 glia-neuron ratio	--	--	--	--	--
		P=0.000	CA neuronal density	--	--	--	--	--
			V1 neuronal density	--	--	--	--	--
			CrbGc	--	--	--	--	--
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Body mass	0.670	0.001	-21.510	731.000	0.000
			EQ	1.003	0.004	-72.488	229.400	0.000
			Gestation length	--	--	--	--	--

Table A4c: Predictors based on stepwise AIC multiple regression models for primates

Taxa	Region	Variable	Predictor	Estimate	St dev	AIC	t-value	Pr(>|t|)
Primates	V1	Glia-neuron ratio	CA glia-neuron ratio	--	--	--	--	--
		R^2=0.167	CrbGc	0.172	0.061	-104.123	2.816	0.008
		P=0.022	StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		Neuronal density	V1 glial cell density	0.351	0.116	-130.980	3.038	0.005
		R^2=0.444	CA neuronal density	--	--	--	--	--
		P=0.000	CrbGc	-0.397	0.102	-126.075	-3.886	0.001
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	0.516	0.124	-124.268	4.180	0.000
			Body mass	-0.207	0.091	-134.847	-2.265	0.031
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		Glial cell density	V1 neuronal density	0.452	0.181	-112.295	2.504	0.017
		R^2=0.170	CA glial cell density	--	--	--	--	--
		P=0.018	CrbGc	0.129	0.057	-113.319	2.273	0.030
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
	CA1-3	Glia-neuron ratio	V1 glia-neuron ratio	--	--	--	--	--
		R^2=0.167	CrbGc	--	--	--	--	--
		P=0.022	StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	0.184	0.066	-89.611	2.783	0.009
			EQ	--	--	--	--	--
			Gestation length	-0.942	0.389	-91.305	-2.421	0.022
		Neuronal density	CA glial cell density	0.517	0.116	-93.868	4.470	0.000
		R^2=0.566	V1 neuronal density	--	--	--	--	--
		P=0.000	CrbGc	--	--	--	--	--
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	-0.222	0.053	-95.718	-4.170	0.000
			EQ	-0.355	0.168	-106.813	-2.115	0.043
			Gestation length	0.992	0.346	-103.214	2.866	0.008
		Glial cell density	CA neuronal density	0.745	0.163	-81.080	4.565	0.000
		R^2=0.415	V1 glial cell density	--	--	--	--	--
		P=0.000	CrbGc	0.200	0.105	-95.159	1.897	0.068
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	-0.906	0.385	-93.266	-2.350	0.026
		StrGr	CrbGc	--	--	--	--	--
		R^2=0.981	StrMol	1.005	0.028	-80.735	35.926	0.000
		P=0.000	Brain mass	--	--	--	--	--
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	-0.298	0.073	-193.681	-4.085	0.000
		StrMol	CrbGc	--	--	--	--	--
		R^2=0.985	StrGr	0.919	0.034	-103.509	26.778	0.000
		P=0.000	Brain mass	--	--	--	--	--
			Body mass	0.036	0.016	-207.472	2.260	0.031
			EQ	--	--	--	--	--
			Gestation length	0.255	0.070	-200.386	3.639	0.001
	OTHER	CrbGc	CA glia-neuron ratio	--	--	--	--	--
		R^2=0.883	V1 glia-neuron ratio	--	--	--	--	--
		P=0.000	CA neuronal density	--	--	--	--	--
			V1 neuronal density	-0.688	0.185	-102.048	-3.726	0.001
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Brain mass	0.783	0.050	-37.596	15.745	0.000
			Body mass	--	--	--	--	--
			EQ	--	--	--	--	--
			Gestation length	--	--	--	--	--
		Brain mass	CA glia-neuron ratio	--	--	--	--	--
		R^2=0.999	V1 glia-neuron ratio	--	--	--	--	--
		P=0.000	CA neuronal density	--	--	--	--	--
			V1 neuronal density	--	--	--	--	--
			CrbGc	--	--	--	--	--
			StrGr	--	--	--	--	--
			StrMol	--	--	--	--	--
			Body mass	0.757	0.001	-29.760	530.400	0.000
			EQ	0.999	0.006	-108.440	177.800	0.000
			Gestation length	--	--	--	--	--

Table A6a: Placenta data matrix

Species	A	B	C	D	E	Reference*
Anomalurus derbianus	3	3	1	3	2	10
Pedetes capensis	3	3	2	2	2	9, 79-81
Jaculus jaculus	1	3	2	3	2	40
Zapus princeps	1	3	2	3	2	40
Hydromys chrysogaster	0	0	0	0	0	127
Mus musculus	3	3	2	3	2	9
Peromyscus maniculatus	3	3	2	3	2	36
Tachyoryctes splendens	1	1	1	1	1	98
Castor canadensis	3	3	2	3	2	9, 25-7
Perognathus parvus	0	0	0	3	0	1
Chaetodipus fallax	3	0	2	2	2	7
Dipodomys ordii	0	0	0	2	0	55
Microdipodops pallidus	0	0	0	2	0	1
Thomomys bottae	1	3	2	3	1	53
Octodon degus	0	0	0	3	2	7, 9, 133-7
Ctenodactylus gundi	1	3	2	3	2	37
Hydrochoerus hydrochaeris	0	0	0	2	2	9, 28-9
Dinomys branickii	0	0	0	3	2	9, 28-9
Petromus typicus	0	3	2	3	0	178-9
Cavia porcellus	3	3	2	3	2	1, 9, 28, 30, 32
Dasyprocta leporina	3	3	2	3	2	28-9
Myocastor coypus	1	0	2	2	1	9, 31, 70
Proechimys setosus	1	4	2	2	0	1
Capromys pilorides	3	3	2	3	2	132
Cuniculus paca	0	1	2	3	2	28-30, 163-5
Hystrix cristata	1	3	2	3	2	18
Thryonomys swinderianus	3	0	2	3	2	112-3
Bathyergus janetta	0	3	2	3	2	18
Erethizon dorsatum	3	3	2	3	3	9, 50
Chinchilla lanigera	3	3	2	3	2	9, 31, 34-5
Aplodontia rufa	3	3	2	3	2	14
Xerus inauris	3	3	2	3	2	1
Oryctolagus cuniculus	3	3	2	3	2	9, 65
Ochotona princeps	3	3	2	3	2	1, 180
Macaca mulatta	2	3	1	3	1	1
Gorilla gorilla	2	3	1	3	1	9
Homo sapiens	2	3	1	3	1	1
Pan troglodytes	2	3	1	3	1	9
Pongo pygmaeus	2	3	1	3	1	9
Hylobates moloch	0	0	0	3	0	1
Ateles geoffroyi	0	0	0	3	1	9, 15-6
Pithecia pithecia	0	0	1	3	1	9
Saimiri sciureus	3	3	2	3	1	9
Tarsius syrichta	1	1	1	1	0	106
Microcebus murinus	0	1	1	1	0	174-5
Indri indri	0	1	1	1	1	64
Daubentonia madagascariensis	1	1	1	1	1	9, 38
Lemur catta	1	1	1	1	1	9
Nycticebus pygmaeus	1	1	1	1	1	9
Otolemur crassicaudatus	1	1	1	1	1	52
Galeopterus variegates	0	3	2	3	0	1
Tupaia glis	1	3	2	2	3	118-20
Naemorhedus goral	0	3	2	2	0	9
Gazella gazella	4	2	1	1	1	9
Cephalophus silvicultor	4	2	1	1	1	9
Redunca arundinum	4	2	1	1	1	128-9
Bos taurus	4	2	1	1	1	9
Pudu puda	3	3	2	3	1	9
Moschus moschiferus	4	2	1	1	1	9
Antilocapra americana	4	2	1	1	1	9, 11-13
Giraffa camelopardalis	4	2	1	1	1	54
Tragulus javanicus	1	3	2	3	3	9, 115-6
Phocoena phocoena	1	1	1	1	0	82
Tursiops truncatus	1	1	1	1	1	9, 39
Delphinapterus leucas	0	1	1	1	0	9
Platanista gangetica	1	1	1	1	0	85
Megaptera novaeangliae	0	1	1	1	0	17
Hippopotamus amphibius	1	1	1	1	1	9, 56-7
Sus scrofa	1	3	2	3	2	9, 99-101
Catagonus wagneri	1	1	1	1	1	9, 107
Lama glama	4	1	1	1	1	9, 20-23
Rhinoceros unicornis	4	2	1	1	1	9, 89-91
Tapirus terrestris	3	3	2	2	1	105
Equus caballus	1	1	1	1	1	9, 47-9
Neovison vison	1	3	2	3	2	69
Spilogale putorius	1	3	2	3	2	68
Procyon lotor	1	4	2	2	1	159-62
Ailurus fulgens	1	3	1	2	1	9
Odobenus rosmarus	1	4	2	2	1	9
Callorhinus ursinus	1	4	2	2	1	9
Lobodon carcinophaga	1	4	2	2	1	156-8
Ursus maritimus	1	4	2	2	1	121
Canis lupus	1	4	2	2	1	9, 24
Panthera tigris	1	4	2	2	1	9
Crocuta crocuta	1	4	2	3	1	9, 59-63
Viverra civettina	1	4	2	2	1	1
Nandinia binotata	4	2	1	1	1	1
Manis tricuspis	3	1	1	1	1	9
Pteropus giganteus	0	3	2	3	1	88
Taphozous melanopogon	2	3	1	3	1	46, 147
Rhinopoma hardwickii	1	3	2	2	1	92
Megaderma lyra	1	3	2	2	2	67
Rhinolophus rouxii	0	1	1	1	0	141-2
Rhinonicteris aurantia	1	3	2	2	1	46
Hipposideros bicolor	0	0	0	3	0	58
Myzopoda aurita	0	3	1	3	1	75
Thyroptera tricolor	0	0	0	3	2	114
Furipterus horrens	1	3	2	3	2	1
Natalus tumidirostris	0	0	0	2	1	1
Noctilio albiventris	1	3	2	2	2	169-71
Pteronotus davyi	0	0	0	3	0	1
Desmodus rotundus	1	3	2	3	2	9, 83-4
Macrotus californicus	2	3	2	3	2	153-5
Carollia perspicillata	0	0	0	0	0	143-146
Tadarida brasiliensis	0	0	0	3	0	166-8
Molossus rufus	1	3	2	3	1	148-50
Myotis lucifugus	0	3	2	3	2	138-40
Talpa europaea	1	3	2	3	1	102
Scalopus aquaticus	2	3	1	3	1	103-4
Erinaceus europaeus	3	3	2	3	2	51
Suncus etruscus	0	0	0	2	1	94-7
Sorex araneus	1	3	2	2	1	181
Solenodon paradoxus	1	3	2	3	1	93
Choloepus didactylus	0	0	0	2	0	8,9
Bradypus variegatus	2	3	2	2	1	8, 9, 19
Tamandua tetradactyla	3	3	2	2	2	8, 71-3
Myrmecophaga tridactyla	1	3	2	3	1	8-9, 74
Chaetophractus villosus	2	3	1	3	2	172-3
Dasypus novemcinctus	2	3	1	3	2	11, 172-3, 176-7
Potamogale velox	1	3	2	3	1	109
Micropotamogale lamottei	1	3	2	2	1	110
Hemicentetes semispinosus	1	3	2	3	1	151-2
Tenrec ecaudatus	1	3	1	3	1	1
Setifer setosus	1	4	1	1	2	108
Rhynchocyon petersi	1	3	2	2	1	66
Orycteropus afer	3	4	2	2	2	9, 76-8
Dugong dugon	1	4	1	2	0	130-1
Trichechus inunguis	4	1	1	2	1	117
Procavia capensis	1	4	2	3	1	9, 86-7
Elephas maximus	1	4	2	2	1	9, 45
Loxodonta africana	1	4	2	2	1	9, 41-4
Didelphis virginiana	5	5	3	4	4	124-6

A, uterus; B, placental shape; C, maternofetal interdigitation; D, interhemal barrier; E, yolk sac

*See appendix bibliography

Table A6b: Categories for variables in placenta data matrix

#	Uterus	Placental shape	Maternofetal interdigitation	Interhemal barrier	Yolk sac
1	bicornuate	diffuse	villous to trabecular	epitheliochorial	free
2	simplex	cotyledonary	labyrinthine	endotheliochorial	inverted
3	duplex	discoid	marsupial	haemochorial	trilaminar
4	bipartite	zonary	--	marsupial	marsupial
5	unfused horns	marsupial	--	--	--
6	marsupial	--	--	--	--
0	NA	NA	NA	NA	NA

Table A7: Categories and ranges for discrete variables in the life-history data matrix*

#	A	B	C	D	E	F	G	H	I	J	K
1	Nocturnal	See definition	[-0.51,-0.14]	[-0.52,-0.29]	[0]	Fossorial	Herbivore	[0.799,4.09]	[-0.51,-0.31]	[-0.19,-0.04]	[1.68,4.46]
2	Crepuscular	--	[-0.13,0.06]	[-0.28,-0.05]	[2]	Above-ground	Omnivore	[4.10,7.37]	[-0.30,-0.12]	[-0.03,0.08]	[4.47,7.25]
3	Diurnal	--	[0.07,0.23]	[-0.04,0.16]	[4]	--	Carnivore	[7.38,10.7]	[-0.11,0.01]	[0.09,0.19]	[7.26,10]
4	--	--	--	--	[6]	--	--	[10.8,13.9]	[0.02,0.18]	[0.20,0.30]	[10.01,12.8]
5	--	--	--	--	[8,∞]	--	--	[14,17.2]	[0.19,0.37]	--	--
6	--	--	--	--	--	--	--	--	--	--	--
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

#	L	M	N	O	P	Q	R	S
1	[-1.22,-0.55]	[-0.54,-0.23]	[-1.20,-1.03]	[-0.28,-0.14]	[-0.57,-0.38]	[-0.005,1.15]	[-1.11,-0.94]	[-0.09,-0.01]
2	[-0.54,-0.01]	[-0.22,-0.02]	[-1.02,-0.85]	[-0.13,-0.02]	[-0.38,-0.05]	[1.16,2.3]	[-0.93,-0.41]	[0,0.08]
3	[0,0.44]	[-0.01,0.10]	[-0.84,-0.50]	[-0.01,0.12]	[-0.04,0.24]	[2.31,3.46]	[-0.41,-0.10]	--
4	--	[0.11,0.23]	[-0.49,0.01]	[0.13,0.29]	--	[3.47,4.61]	[-0.09,0.31]	--
5	--	--	[0.02,0.42]	[0.30,0.55]	--	--	--	--
6	--	--	--	[0.56,0.85]	--	--	--	--
0	NA	NA	NA	NA	NA	NA	NA	NA

*Values in variables H-S are log-transformed

Table A8: Life-history data matrix

Species	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Ailurus fulgens	2	3	2	1	2	1	1	3	3	3	3	2	1	3	3	2	0	2	0
Anomalurus derbianus	1	1	0	2	0	2	1	2	0	0	0	0	0	0	0	0	1	0	0
Antilocapra americana	0	2	2	1	0	1	1	4	2	4	4	3	2	2	5	2	3	2	2
Aplodontia rufa	0	2	0	1	0	1	1	2	3	2	2	1	2	2	3	2	0	2	1
Ateles geoffroyi	3	2	3	0	0	2	1	3	4	0	0	3	1	4	4	3	4	4	2
Bathyergus janetta	0	4	0	2	0	1	1	2	0	2	2	0	2	0	3	0	1	1	0
Bos taurus	0	0	0	1	0	0	0	5	0	0	0	3	0	3	0	2	0	0	0
Bradypus variegatus	2	1	2	0	0	2	1	3	0	3	3	2	0	0	4	0	1	1	0
Callorhinus ursinus	2	6	2	1	0	1	2	4	0	0	0	3	1	4	5	3	0	2	2
Canis lupus	2	1	2	2	4	1	3	4	3	4	4	2	3	4	4	2	0	1	0
Capromys pilorides	0	3	0	0	2	2	2	3	0	2	3	2	2	2	4	2	0	1	0
Carollia perspicillata	1	3	1	2	0	2	2	1	2	1	1	2	0	2	2	2	0	1	1
Castor canadensis	2	3	0	1	2	1	1	3	0	0	0	2	2	3	4	2	2	1	0
Catagonus wagneri	3	6	0	0	3	1	2	4	3	0	0	2	2	2	4	2	2	2	0
Cavia porcellus	0	0	0	5	1	1	0	2	0	0	0	2	2	3	3	1	0	1	1
Cephalophus silvicultor	2	5	2	0	2	1	2	4	0	0	0	3	0	3	5	0	1	1	0
Chaetodipus fallax	0	3	0	1	0	1	1	1	0	1	1	1	2	2	0	1	1	0	0
Chaetophractus villosus	0	0	0	0	0	1	0	3	0	3	3	2	1	3	3	2	0	2	0
Chinchilla chinchilla	2	6	0	3	3	1	1	2	0	0	0	2	2	2	0	2	0	2	0
Choloepus didactylus	2	3	3	0	1	2	2	3	0	0	0	3	0	4	4	3	1	2	0
Crocuta crocuta	1	1	3	0	2	1	3	4	0	0	0	2	2	4	4	2	0	3	2
Ctenodactylus gundi	0	0	1	0	0	0	0	2	0	0	0	2	2	0	3	1	0	0	0
Cuniculus paca	1	5	1	2	4	1	1	3	0	3	3	2	1	3	4	2	1	2	0
Dasyprocta leporina	3	3	0	0	0	1	1	3	0	3	3	2	1	3	0	0	0	2	0
Dasypus novemcinctus	2	5	0	0	2	1	2	3	0	3	3	2	3	3	3	2	1	2	0
Daubentonia madagascariensis	1	6	3	1	1	2	2	3	4	0	0	2	1	3	3	2	1	3	2
DelphiOpterus leucas	0	2	3	1	0	0	3	5	0	0	0	3	1	4	6	3	2	4	0
Desmodus rotundus	0	1	2	2	0	2	3	1	0	1	1	3	0	3	2	0	0	3	0
Didelphis virginiana	1	4	1	2	4	2	2	3	1	3	3	1	4	1	1	1	1	2	1
Dinomys branickii	1	4	0	0	4	1	1	3	0	0	0	3	2	2	4	0	0	0	0
Dipodomys ordii	1	5	1	2	0	0	2	1	0	1	1	1	2	2	2	1	0	0	0
Dugong dugon	2	4	3	0	0	0	2	4	0	0	0	3	0	5	6	3	2	4	0
Elephas maximus	2	3	3	0	1	1	1	5	5	0	0	3	1	5	6	3	2	3	0
Equus caballus	2	1	3	1	1	1	1	4	3	0	0	3	0	5	6	2	0	3	0
Erethizon dorsatum	1	6	0	0	2	2	1	3	0	0	0	3	0	3	4	2	1	1	0
Erinaceus europaeus	2	8	0	2	4	1	2	2	2	2	2	1	3	3	3	2	0	1	1
Furipterus horrens	0	1	0	0	0	2	3	1	0	0	0	0	0	0	0	0	0	0	0
Galeopterus variegates	1	3	0	0	1	2	1	2	0	0	0	2	0	1	0	0	0	0	0
Gazella gazella	2	3	2	0	0	1	1	3	3	0	0	3	1	3	5	2	2	2	0
Giraffa camelopardalis	2	5	3	1	2	1	1	5	4	0	0	3	1	4	6	3	4	3	0
Gorilla gorilla	3	3	3	0	0	1	2	4	5	0	0	3	1	4	5	3	2	4	2
Hemicentetes semispinosus	2	1	0	2	0	1	3	2	0	1	2	2	3	1	2	1	0	1	0
Hippopotamus amphibius	2	2	3	1	0	1	2	5	4	0	0	3	0	4	6	3	0	3	2
Perognathus parvus	2	3	0	2	0	1	2	1	0	0	0	1	3	1	2	2	1	1	0

Species	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Hipposideros bicolor	0	1	0	0	0	2	3	1	0	0	0	1	1	0	1	2	0	0	0
Homo sapiens	3	0	3	0	0	0	0	4	5	0	0	3	0	5	5	3	0	4	2
Hydrochoerus hydrochaeris	2	5	0	1	4	2	1	4	0	4	4	2	2	2	5	2	2	2	0
Hydromys chrysogaster	2	2	1	3	2	1	3	2	1	2	2	1	2	2	3	1	0	1	1
Hylobates moloch	3	4	3	1	0	0	2	3	0	0	0	3	0	0	0	0	1	0	0
Hystrix cristata	1	6	0	2	3	1	2	3	0	0	0	2	1	0	0	0	0	0	0
Indri indri	3	4	3	1	1	2	1	3	0	0	0	2	1	0	0	3	1	3	0
Jaculus jaculus	0	0	3	2	0	0	0	1	2	2	1	1	2	2	2	2	0	2	0
Lama glama	0	2	0	1	0	1	1	4	0	0	0	3	0	4	5	2	0	2	2
Lemur catta	2	4	3	1	0	2	2	3	3	0	0	2	1	4	3	2	3	2	0
Lobodon carcinophaga	2	1	3	0	0	1	3	4	4	0	0	3	1	4	6	3	0	1	2
Loxodonta africana	3	4	3	0	1	1	1	5	5	0	0	3	1	5	6	3	3	4	2
Macaca mulatta	3	1	2	1	0	0	1	3	4	3	3	2	1	4	4	2	4	3	2
Macrotus californicus	0	2	0	0	0	2	2	1	2	1	1	3	0	2	2	1	0	1	0
Manis tricuspis	0	0	2	1	0	0	0	2	0	3	3	2	0	0	3	2	0	3	1
Megaderma lyra	0	2	0	1	0	2	3	1	3	0	0	2	0	3	2	2	0	1	0
Megaptera novaeangliae	0	2	3	1	0	0	3	5	0	0	0	3	0	5	6	3	1	3	0
Microcebus murinus	1	5	2	0	0	2	2	2	2	2	2	2	2	3	2	2	1	1	0
Microdipodops pallidus	1	2	0	0	0	1	2	1	0	1	1	0	3	0	0	0	0	0	0
Micropotamogale lamottei	1	2	0	0	4	2	3	2	0	0	0	0	3	0	0	0	0	0	0
Molossus rufus	2	3	0	1	0	0	1	3	0	0	0	2	1	0	4	2	1	1	0
Moschus moschiferus	2	3	0	1	0	0	1	3	0	0	0	2	1	0	4	2	1	1	0
Mus musculus	0	1	0	3	4	2	3	1	1	1	1	1	3	2	1	1	0	1	1
Myocastor coypus	2	6	1	3	4	1	2	3	2	0	0	2	3	2	4	1	2	2	2
Myotis lucifugus	0	1	0	1	0	2	3	1	3	1	1	2	0	4	2	2	0	1	1
Myrmecophaga tridactyla	2	1	0	1	0	1	3	4	0	3	4	3	0	3	5	3	1	2	2
Myzopoda aurita	0	1	0	0	0	2	3	1	0	0	0	0	0	0	0	0	0	0	0
Naemorhedus goral	2	2	2	0	2	1	1	4	0	0	0	3	0	3	5	2	0	2	0
Nandinia binotata	1	2	1	0	2	2	1	3	0	3	3	2	2	3	3	2	0	2	0
Natalus tumidirostris	0	1	0	0	0	2	3	1	0	1	1	0	0	0	0	0	0	0	0
Nectogale elegans	0	2	0	0	0	1	3	1	0	0	0	0	0	0	0	0	0	0	0
Neovison vison	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Noctilio albiventris	2	3	0	0	0	2	2	1	0	1	1	0	1	0	2	0	0	2	1
Nycticebus pygmaeus	0	0	0	0	0	0	0	2	0	0	0	3	1	0	3	0	1	0	0
Ochotona princeps	3	2	1	2	0	1	1	2	0	2	2	1	2	2	2	2	0	1	1
Octodon degus	2	7	0	2	4	2	2	2	0	2	2	2	3	2	2	1	0	1	1
Odobenus rosmarus	2	6	3	0	0	1	2	5	4	0	0	3	1	4	6	3	0	4	2
Orycteropus afer	1	1	0	1	2	1	3	4	4	4	4	3	1	3	5	2	1	1	2
Oryctolagus cuniculus	2	2	1	3	0	0	1	2	1	0	0	1	3	3	3	1	0	1	1
Otolemur crassicaudatus	1	5	2	0	0	0	2	2	3	2	2	2	1	3	3	2	2	2	1
Pan troglodytes	3	6	3	0	1	2	2	4	5	4	4	3	1	5	5	3	4	4	2
Panthera tigris	1	1	3	1	0	1	3	4	4	4	4	2	2	3	4	3	0	2	2
Pedetes capensis	1	3	1	0	0	1	1	3	0	3	3	2	1	3	4	2	0	1	2
Peromyscus maniculatus	1	4	1	3	0	2	2	1	1	1	1	1	3	0	2	1	0	1	1

Species	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
Petromus typicus	3	3	0	1	0	1	1	2	0	0	0	0	1	0	0	0	1	0
Phocoena phocoena	0	2	2	1	0	0	3	4	4	0	0	3	1	3	5	3	4	3
Pithecia pithecia	3	2	3	0	0	2	1	3	3	0	0	2	1	3	0	2	1	2
Platanista gangetica	0	2	0	0	0	0	3	4	0	0	0	3	1	4	0	0	0	3
Pongo pygmaeus	3	5	3	0	0	2	2	4	5	0	0	3	1	5	5	3	1	4
Potamogale velox	1	2	0	2	0	1	3	2	0	0	0	0	2	0	0	0	0	0
Procavia capensis	3	5	2	1	3	2	1	3	4	3	3	3	2	3	4	2	3	2
Procyon lotor	2	6	2	1	3	2	2	3	0	3	3	2	2	3	3	2	0	2
Pteronotus davyi	0	1	0	1	0	2	3	1	0	1	1	0	1	0	1	0	0	0
Pteropus giganteus	0	1	0	1	0	2	1	2	0	2	2	2	1	4	3	2	0	3
Pudu puda	2	4	0	0	0	1	1	3	0	0	0	3	1	3	4	1	0	2
Redunca arundinum	2	2	2	0	2	1	1	4	0	0	0	3	1	3	5	0	1	0
Rhinoceros unicornis	2	3	3	0	0	1	1	5	5	0	0	3	1	4	6	3	1	3
Rhinolophus rouxii	0	1	0	1	0	2	3	1	3	0	0	2	1	1	2	2	0	2
Rhinonicteris aurantia	1	1	0	1	0	2	3	1	2	0	0	2	0	0	2	2	0	2
Rhinopoma hardwickii	0	1	0	1	0	2	3	1	2	0	0	2	1	0	2	2	0	2
Rhynchocyon petersi	0	0	0	0	0	0	0	2	0	0	0	0	2	0	0	0	0	0
Saimiri sciureus	3	3	2	0	0	2	2	2	4	3	2	2	0	4	3	3	3	3
Scalopus aquaticus	2	4	0	1	3	1	2	2	0	0	0	1	3	2	2	2	0	1
Setifer setosus	1	2	0	2	4	1	2	2	0	2	2	2	2	2	3	1	0	1
Solenodon paradoxus	2	2	0	2	1	2	3	2	0	0	0	2	1	2	3	2	1	2
Spilogale putorius	1	6	2	0	4	1	2	2	0	2	2	1	3	2	2	1	0	2
Suncus etruscus	0	0	0	3	0	0	0	1	0	0	0	1	3	1	1	0	1	1
Sus scrofa	2	5	2	2	4	0	2	4	2	0	0	2	3	3	4	2	3	2
Tachyoryctes splendens	0	0	1	2	0	0	0	2	0	2	2	1	1	0	3	1	1	1
Tadarida brasiliensis	0	1	0	1	0	2	3	1	0	1	1	2	1	3	2	2	0	2
Talpa europaea	2	1	0	1	4	1	3	2	2	0	0	1	3	2	2	2	0	1
Tamandua tetradactyla	2	1	0	1	0	2	3	3	0	3	3	2	0	2	0	0	1	0
Taphozous melanopogon	1	0	0	1	0	2	0	1	3	0	0	2	1	0	2	2	0	1
Tapirus terrestris	2	5	0	0	1	1	2	4	0	0	0	3	0	4	5	2	1	3
Tarsius syrichta	1	3	2	0	0	0	2	2	3	2	2	3	0	2	3	2	2	2
Tenrec ecaudatus	2	3	0	1	4	1	2	2	0	2	2	2	4	2	3	1	0	1
Thomomys bottae	2	4	0	2	0	1	1	2	1	2	2	1	3	1	2	1	1	1
Thryonomys swinderianus	1	2	0	2	0	1	1	3	3	0	0	2	3	1	3	1	1	1
Thyroptera tricolor	0	1	0	2	0	2	3	1	0	0	0	2	1	0	1	0	0	0
Tragulus javanicus	1	3	0	0	2	0	1	3	0	3	3	2	1	2	0	1	1	1
Trichechus inunguis	2	3	0	0	0	0	1	4	0	4	4	3	0	4	0	3	1	4
Trinomys setosus	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Tupaia glis	3	4	1	3	2	2	2	2	2	2	2	1	2	2	2	1	0	1
Tursiops truncatus	0	2	3	0	0	0	3	4	4	0	0	3	1	4	6	3	2	4
Ursus maritimus	3	3	3	0	2	1	2	4	4	4	4	2	1	4	4	3	0	3
Viverra civettina	1	6	0	0	0	1	2	3	0	0	0	0	0	0	0	0	0	0
Xerus inauris	3	4	0	1	0	1	1	2	0	2	2	1	2	3	3	2	3	2
Zapus princeps	0	3	0	1	0	0	2	1	0	0	0	1	3	0	0	0	0	1

Table A9 : Life-history variable definitions*

	Definition	Unit
A	Activity cycle of each species measured for non-captive populations; adult or age unspecified individuals, male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities. Species were defined as (1) nocturnal only, (2) nocturnal/crepuscular, cathemeral, crepuscular or diurnal/crepuscular and (3) diurnal only.	NA
B	Number of dietary categories eaten by each species measured using any qualitative or quantitative dietary measure, over any period of time, using any assessment method, for non-captive or non-provisioned populations; adult or age unspecified individuals, male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities. Categories were defined as vertebrate, invertebrate, fruit, flowers/nectar/pollen, leaves/branches/bark, seeds, grass and roots/tubers.	No. of dietary categories
C**	The length of time between successive births of the same female(s) after a successful or unspecified litter using non-captive, wild, provisioned, or unspecified populations; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	days
D	Number of litters per female per year using non-captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	No. of litters
E	Total number of teats present, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	No. of teats
F	Degree of terrestriality of each species measured using any qualitative or quantitative time measure, for non-captive populations; adult or age unspecified individuals, male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities. Species were defined as (1) fossorial and/or ground dwelling only and (2) above ground dwelling.	NA
G	Trophic level of each species measured using any qualitative or quantitative dietary measure, over any period of time, using any assessment method, for non-captive or non-provisioned populations; adult or age unspecified individuals, male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities. Species were defined as (1) herbivore (not vertebrate and/or invertebrate), (2) omnivore (vertebrate and/or invertebrate plus any of the other categories) and (3) carnivore (vertebrate and/or invertebrate only).	NA
H	Mass of adult (or age unspecified) live or freshly-killed specimens (excluding pregnant females) using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	grams
I**	Age at which females give birth to their first litter (eutherians), or their young attach to teats (metatherians) or hatch out (monotremes), using non-captive, wild, provisioned, or unspecified populations; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	days
J**	Basal metabolic rate of adult (or age unspecified) individual(s) using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities. Metabolic rate was measured when individual(s) were experiencing neither heat nor cold stress (i.e., are in their thermoneutral zone); are resting and calm; and are post–absorptive (are not digesting or absorbing a meal) and data were only accepted where there was also a measure of body mass for the same individual(s).	mL.O2/hr
K	Mass of individual(s) from which the basal metabolic rate was taken.	grams
L**	Length of time of non-inactive fetal growth, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities. Gestation was measured between specified start and end points as follows: Start points – conception, fertilization, first observed copulation, fertilization, implantation, laying, palpably pregnant, removal of pouch young, capture (except marsupials) or unspecified. End points – birth, hatching or unspecified.	days
M**	Number of offspring born per litter per female, either counted before birth, at birth or after birth, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	No. of offspring
N**	Maximum adult age measured either through direct observation, capture-recapture estimates, projected from physical wear or unspecified, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; in all localities.	months
O**	Mass of live or freshly-killed specimens of infants at either a near term embryonic stage, birth, immediately after birth or up to an age of seven days after birth, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	grams
P**	Age when individuals are first physically capable of reproducing, defined as either physically sexually mature, age at first mating or unspecified (males and females), age at first estrus or age at first pregnancy (females only), age at spermatogenesis or age at testes descent (males only), using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals, primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	days
Q	Number of individuals, adults or definition unspecified in a group that spends the majority of their time in a 24 hour cycle together, measured over any duration of time, using non-captive populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	No. of individuals
R**	Age when primary nutritional dependency on the mother ends and independent foraging begins to make a major contribution to the offspring's energy requirements, measured as either weaning/lactation length, nutritionally independent, first solid food, last observed nursing, age at first flight (bats only), age at pouch exit or length of teat Attachment (marsupials only) or unspecified definition, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	days
S**	Mass of live or freshly-killed specimens of weanlings, using captive, wild, provisioned, or unspecified populations; male, female, or sex unspecified individuals; primary, secondary, or extrapolated sources; all measures of central tendency; in all localities.	grams

*See Jones et al, 2008

Table A9: Residuals of life-history variables after phylogenetic size-correction

Species	interbirth interval	litters per year	age at first weaning	bmr	gestation length	litter size	maximum longevity	neonate mass	age at maturity	age at weaning	weaning body mass
Anomalurus derbianus	0.07	0.01	0.13	-0.02	-0.15	0.06	0.11	-0.28	0.09	0.03	0.08
Pedetes capensis	0.05	-0.03	0.1	-0.19	0.05	0.04	0	0	-0.03	-0.03	-0.02
Jaculus jaculus	-0.02	-0.01	--	-0.18	-0.07	-0.03	-0.09	0.04	-0.08	-0.1	-0.03
Zapus princeps	0.23	0.07	0.37	-0.04	0.44	0.07	0.42	-0.16	0.23	0.31	0.01
Hydromys chrysogaster	0.12	-0.05	0.1	0.02	0.1	-0.12	-0.03	0.08	0.05	0.1	0.06
Mus musculus	-0.15	0.05	-0.1	-0.04	0.07	0.01	0.03	-0.02	0.03	0.07	0.01
Peromyscus maniculatus	--	-0.06	0.03	-0.02	-0.08	-0.05	0.04	0	0	-0.02	0.03
Tachyoryctes splendens	-0.08	0.02	-0.01	-0.04	0.06	-0.04	-0.04	0.08	-0.1	-0.06	-0.01
Castor canadensis	-0.15	-0.02	-0.16	0.03	0.04	0.06	0.05	-0.05	0.11	-0.02	--
Perognathus parvus	-0.07	0	--	-0.09	0.03	-0.15	-0.02	0.12	-0.05	-0.07	0.07
Chaetodipus fallax	--	--	--	--	--	0.02	--	--	--	--	--
Dipodomys ordii	-0.07	0.13	0.04	-0.02	0.03	-0.02	0.03	0.06	-0.11	-0.08	--
Microdipodops pallidus	--	0.08	--	--	0.04	-0.11	--	--	--	0.04	--
Thomomys bottae	0.08	-0.1	--	-0.13	-0.06	-0.22	--	0.12	-0.08	-0.08	--
Octodon degus	--	-0.18	-0.32	-0.07	-0.08	-0.2	-0.29	0.19	-0.23	-0.17	0.01
Ctenodactylus gundi	--	0.02	--	--	0.08	-0.04	-0.02	0.03	-0.11	-0.01	--
Hydrochoerus hydrochaeris	--	0.04	--	0.03	-0.15	-0.05	-0.29	-0.02	-0.28	-0.08	--
Dinomys branickii	--	0.07	--	-0.02	-0.08	-0.05	-0.08	0.05	-0.47	--	--
Petromus typicus	--	0.16	--	--	-0.03	0.06	-0.2	--	0.12	--	--
Cavia porcellus	--	--	--	0.09	--	-0.16	--	0.26	--	--	--
Dasyprocta leporina	0.03	0.02	--	-0.07	0.08	-0.04	0.06	-0.08	0	0.02	0
Myocastor coypus	--	--	--	--	-0.04	-0.1	--	0.04	-0.02	--	--
Trinomys setosus	--	--	--	--	0.02	0.12	0.02	-0.02	-0.05	0.02	--
Capromys pilorides	--	--	--	--	--	--	--	--	--	--	--
Cuniculus paca	--	0.01	--	0.01	-0.03	0.02	-0.02	-0.01	0.06	0.01	--
Hystrix cristata	-0.02	0.06	--	--	0	0.04	0.04	-0.05	-0.11	-0.02	-0.07
Thryonomys swinderianus	0.13	-0.06	0.09	0.09	0.08	-0.03	-0.04	-0.03	0.11	0.09	-0.02
Bathyergus janetta	--	--	--	--	0.09	0.01	0.32	--	--	--	--
Erethizon dorsatum	0	0.01	0.04	0.02	0.05	-0.02	0.01	0.05	0.05	0.04	-0.02
Chinchilla lanigera	-0.03	--	0.04	0.06	-0.02	0.05	0.05	-0.07	-0.01	0.07	--
Aplodontia rufa	0	--	0.09	-0.1	0.05	0.04	0.09	-0.08	0.02	0.06	-0.04
Xerus inauris	0.09	0.06	0.13	0	0.08	0.03	0.1	-0.1	0.11	0.1	0.02
Oryctolagus cuniculus	0.07	--	--	--	0.1	0.07	--	--	--	--	--
Ochotona princeps	-0.03	--	0.04	--	0.01	0	0.03	0	0.03	0	-0.01
Macaca mulatta	0.01	--	0.02	--	0.06	0.03	0.01	-0.13	-0.01	0.02	0.02
Gorilla gorilla	-0.06	--	0.02	--	0.03	0.01	0.1	0.02	0.06	-0.06	-0.01
Homo sapiens	0.01	--	0.01	--	0.03	0.04	-0.01	-0.13	-0.04	0.03	0.01
Pan troglodytes	0.05	--	0.12	--	0.05	0.04	0.05	--	0.05	0.18	--
Pongo pygmaeus	0.06	--	-0.03	-0.13	-0.01	0.01	-0.05	-0.01	0.05	0.01	0.02
Hylobates moloch	-0.21	--	-0.05	--	0.02	-0.02	-0.08	0	-0.12	0.05	--
Ateles geoffroyi	0.04	-0.05	0.02	--	0.02	0	-0.01	0.03	0.03	0.06	--
Pithecia pithecia	-0.01	0.03	--	--	0	0.02	--	--	0.04	0.03	--
Saimiri sciureus	--	--	--	--	-0.05	-0.03	--	-0.03	--	--	--
Tarsius tarsier	--	-0.2	0.33	0	-0.12	-0.33	-0.22	0.39	0.22	-0.24	0.01
Microcebus murinus	-0.51	0.15	-0.51	0.16	-0.4	0.23	-0.26	-0.17	-0.57	-0.22	-0.03
Indri indri	0.07	0.06	0.04	-0.01	0.17	0.03	0.08	-0.02	0.06	0.07	0.01
Daubentonia madagascariensis	0.03	0.01	0.1	--	0.06	0.01	0.07	-0.02	0.04	0.07	--
Lemur catta	--	0.03	--	--	0.01	0.03	0.02	-0.09	0.04	0.02	-0.04
Nycticebus pygmaeus	0.08	0	0.1	--	0.1	-0.04	0.11	0.03	0.08	0.08	0.05
Otolemur crassicaudatus	0.1	0.03	0.1	--	0.18	0.08	0.22	-0.11	0.24	0.25	0.01
Galeopterus variegates	--	--	--	0.01	0.11	0.07	0.13	--	0.15	0.15	--
Tupaia glis	0.1	0.03	0.16	--	0.16	0.1	0.12	-0.1	0.15	0.21	-0.01
Naemorhedus goral	--	0.09	--	--	0.14	0	0.14	0	0.17	0.05	--
Gazella gazella	--	--	--	--	0.17	--	0.17	--	0.13	--	--
Cephalophus silvicultor	0	--	--	--	0.03	0.01	0.02	-0.02	--	--	--
Redunca arundinum	--	--	--	--	-0.01	0.04	--	-0.07	0.07	0	--
Bos taurus	0.11	0.07	0.28	--	0.18	0.04	0.23	-0.11	0.19	0.16	--
Pudu pudu	0.01	-0.02	0.09	--	0	0.01	0.04	0.04	0.01	0	--
Moschus moschiferus	0.11	0.06	--	--	0.22	0.09	0.27	-0.14	0.13	0.13	--
Antilocapra americana	--	--	--	--	0.05	0.02	0.04	--	--	0.04	--
Giraffa camelopardalis	0.1	0.03	--	--	0.12	0.06	0.15	-0.15	0.09	0.11	--
Tragulus javanicus	0.07	--	0.08	--	0.07	0.03	0.13	-0.09	0.1	0.08	--
Phocoena phocoena	--	--	-0.01	--	0.02	0.04	0.08	-0.04	-0.02	0.05	--
Tursiops truncatus	0.04	--	0.1	--	0.03	0.01	0	-0.06	0.03	0.01	--
Delphinapterus leucas	--	--	--	--	0.08	0.05	0.09	-0.04	0.1	0.06	--
Platanista gangetica	0.03	0.05	--	-0.02	0.05	0.08	--	-0.11	0.03	0	-0.03
Megaptera novaeangliae	0.02	0.03	0.02	-0.01	0.02	0.02	0.01	-0.01	-0.01	-0.01	0
Hippopotamus amphibius	0.03	0.07	0.11	0.19	0.06	-0.04	0.01	0	0.04	0.07	--
Sus scrofa	0.06	--	0.07	0.15	0.07	0.03	0.12	-0.18	0.1	0.1	-0.09
Catagonus wagneri	0.06	0.01	0.2	--	0.26	-0.01	0.21	0.04	0.18	0.1	0.06
Lama glama	-0.01	0	--	-0.17	0.1	-0.07	0.01	0.02	0.05	0.05	--
Rhinoceros unicornis	-0.02	--	--	0.11	0.11	-0.04	0.08	-0.03	0.08	0.06	--
Tapirus terrestris	0	--	0.07	--	0.03	0.01	0.01	-0.01	0.03	0.12	-0.05
Equus caballus	0.11	--	--	--	0.13	0.07	0.15	-0.13	0.12	0.19	0.03
Neovison vison	0.1	--	--	0.13	0.16	0.07	0.14	-0.07	0.04	0.15	--
Spilogale putorius	0.04	--	--	--	0.03	0.03	0.01	-0.07	0.06	-0.04	-0.05
Procyon lotor	--	--	--	--	--	--	--	--	--	--	--
Ailurus fulgens	--	0.03	--	0.07	-0.42	0.07	-0.33	0.02	-0.56	-0.22	--
Odobenus rosmarus	-0.26	-0.09	-0.24	--	-0.35	0.01	-0.36	0.06	-0.06	-0.03	0.01
Callorhinus ursinus	--	0.01	-0.12	--	-0.13	0.01	--	0.05	-0.25	-0.14	0
Lobodon carcinophaga	--	0	0.04	--	0.01	0	--	0.03	0.09	-0.03	-0.04
Ursus maritimus	--	0.02	-0.36	--	-0.25	0.02	-0.05	0.12	-0.45	-0.31	--
Canis lupus	--	0.01	-0.01	--	-0.04	0.01	--	0.09	-0.25	-0.11	--
Panthera tigris	--	--	--	--	0.3	0	--	0.19	-0.12	--	--
Crocuta crocuta	--	0.16	-0.45	0.05	0.36	0.02	-0.41	-0.1	-0.26	-0.1	-0.05
Viverra civettina	--	--	--	--	--	0	--	--	--	--	--
Nandinia binotata	--	--	--	--	--	--	--	--	--	--	--
Manis tricuspis	--	--	--	-0.05	--	0.01	--	0.09	--	-0.07	0.02
Pteropus giganteus	--	0.11	--	-0.03	--	0.01	--	0.25	--	--	--
Taphozous melanopogon	-0.03	-0.09	--	-0.11	-0.24	0.02	-0.14	0.04	--	0.24	--
Rhinopoma hardwickii	--	--	-0.2	0.13	-0.4	0.01	-0.14	0.1	-0.14	-0.13	--
Megaderma lyra	--	0.01	--	0.01	-0.08	0.03	-0.41	0.03	-0.17	0.01	0.02
Rhinolophus rouxii	--	-0.13	--	--	-0.39	-0.26	-0.43	0.4	0.01	-0.35	--
Rhinonicteris aurantia	--	-0.37	-0.07	--	-0.71	-0.32	-0.73	0.52	-0.11	-0.63	0.01
Hipposideros bicolor	--	0	--	--	-0.05	0	0.02	-0.07	0	0.01	--
Myzopoda aurita	--	-0.52	--	--	-1.22	-0.54	-1.2	0.85	--	-1.11	-0.02
Thyroptera tricolor	--	--	--	--	--	--	--	--	--	--	--
Funipterus horrens	0.06	--	--	-0.04	0.06	-0.05	0.02	0.04	0.08	-0.02	--
Natalus tumidirostris	--	--	--	--	0.04	0.01	--	-0.02	--	0.03	--
Noctilio albiventris	--	0.05	--	-0.08	0.08	0.05	0.18	--	--	--	--
Pteronotus davyi	--	--	0.09	-0.04	-0.05	-0.07	0.02	0.02	-0.05	-0.04	--
Desmodus rotundus	--	0.02	--	-0.06	0.17	0.02	0.17	-0.03	0.16	0.19	0.03
Macrotus californicus	--	0.03	--	0.05	0.11	-0.02	0.12	-0.04	0.1	0.07	0
Carollia perspicillata	--	--	--	--	--	-0.07	--	--	--	--	--
Tadarida brasiliensis	--	0.05	--	--	--	0.06	--	--	--	--	--
Molossus rufus	--	--	--	--	--	-0.09	--	--	--	--	--
Myotis lucifugus	0.08	-0.02	0.19	0.06	0	0.16	-0.15	-0.14	-0.13	-0.02	--
Talpa europaea	0.07	--	--	--	0.15	0.04	0.18	-0.12	0.14	0.11	0.03
Scalopus aquaticus	--	--	--	-0.15	0.11	0.01	0.15	-0.06	0.13	0.13	0.04
Erinaceus europaeus	0.03	--	0	--	0.01	0.01	-0.03	--	-0.03	0	--
Suncus etruscus	-0.12	--	-0.03	--	0.01	-0.02	0.01	-0.02	0.02	0.09	--
Nectogale elegans	--	0.03	--	0.09	-0.09	-0.05	--	-0.01	-0.03	-0.07	0.03
Solenodon paradoxus	--	--	--	--	0.01	0.05	0.05	-0.05	--	--	--
Choloepus didactylus	--	0.09	--	--	--	0.11	--	--	--	--	--
Bradypus variegatus	--	-0.12	--	--	0.15	-0.03	0.03	-0.11	0.19	0.18	--
Tamandua tetradactyla	--	--	--	-0.12	0.05	0.05	0.01	--	--	-0.09	--
Myrmecophaga tridactyla	0.02	0.04	--	0.3	0.01	0.04	0.03	0.04	-0.01	-0.03	0.03
Chaetophractus villosus	--	0	--	-0.14	-0.01	-0.06	0.01	0.04	0.04	0.03	--
Dasypus novemcinctus	--	0.02	-0.01	--	-0.02	0	--	--	--	--	--
Potamogale velox	--	0	--	--	0.01	-0.05	0.12	0.04	0.03	0.09	-0.06
Micropotamogale lamottei	--	0.05	--	0.01	--	-0.03	--	0.03	--	0.08	--
Hemicentetes semispinosus	0.04	--	--	--	0.05	-0.06	0.03	0.03	0.1	-0.09	--
Tenrec ecaudatus	0.03	--	--	--	0.02	-0.01	0.01	-0.04	0.06	-0.02	--
Setifer setosus	--	--	--	--	0.05	0.02	0.04	-0.04	--	-0.03	--
Rhynchocyon petersi	--	--	--	--	--	--	--	--	--	--	--
Orycteropus afer	--	-0.17	--	0.05	-0.72	0.03	--	0.14	--	--	--
Dugong dugon	--	--	--	0.01	0	0.01	-0.02	-0.03	0.01	0.05	--
Trichechus inunguis	0	-0.02	0	0.06	-0.02	0.11	0.1	-0.04	0.14	-0.03	--
Procavia capensis	--	0.01	--	0.01	-0.03	0.01	-0.02	-0.01	0.06	0.01	--
Elephas maximus	0.06	0.01	-0.13	0.16	-0.13	0.01	0.12	0.06	-0.26	-0.15	0
Loxodonta africana	0.06	0.01	-0.13	0.15	-0.13	0.01	0.12	0.05	-0.26	-0.14	0
Didelphis virginiana	--	0.09	-0.01	-0.05	-0.02	0.01	--	0.09	--	-0.07	0.02

Table A10a: Uterus association *d* statistics

Character	State	Bicornuate	Simplex	Duplex	Bipartite
GROUP SIZE	Small	-0.014[U]			
	Medium-large	0.014[U]			
	Large	0.016[U]			
TROPHIC LEVEL	Herbivore	-0.013, -0.013[U]			
	Omnivore	0.010, 0.015[U]		0.014[U]	
	Carnivore	0.017[U]		-0.012, -0.013[U]	
DEVELOPMENT	Altricial				-0.013, -0.013[U]
	Precocial				0.013, 0.013[U]
ADULT BODY MASS	Small		-0.012	-0.010[U]	
	Large		0.012	0.010[U]	

All associations are significant to $p<0.001$.

U association derived from unordered model.

Table A10b: Placental shape association *d* statistics

Character	State	Diffuse	Cotyledonary	Discoid	Zonary
ADULT BODY MASS	Medium-large	0.014[U]		-0.015[U]	
AGE AT WEANING	Low	-0.010[U]			
	Medium	-0.012[U]			
	Medium-high	0.014[U]			
	High	0.013[U]			
DEVELOPMENT AT BIRTH	Altricial	-0.018[U]		0.016, 0.015[U]	
	Precocial	0.018[U]		-0.016, -0.015[U]	
GESTATION LENGTH	Short			0.020[U]	
	Long	0.010[U]		-0.022[U]	
INTERBIRTH INTERVAL	Short			0.014	
	Medium			-0.015, -0.010[U]	
LITTER SIZE	Small	-0.024, -0.024[U]			
	Large			0.016	
MASS AT WEANING	Large		-0.013		
NEONATE MASS	Small	-0.010		0.010[U]	
	Medium	0.010		-0.012[U]	
	Large			-0.017, -0.014[U]	
SOCIAL GROUP SIZE	Small	0.011		-0.012	
	Medium			0.011	
	Medium-large			0.012	

All associations are significant to $p<0.001$.
U association derived from unordered model.

Table A10c: Maternofetal interdigitation association *d* statistics

Character	State	Villous to trabecular	Labyrinthine
ADULT BODY MASS	Small	0.013, 0.014^{U}	-0.013,-0.014^{U}
	Medium-small	-0.015	0.015
	Medium	-0.013^{U}	0.013^{U}
	Medium-large	0.011^{U}	-0.011^{U}
AGE AT WEANING	Low	-0.013, -0.014^{U}	0.013, 0.014^{U}
	Medium-low	-0.018, -0.018^{U}	0.018, 0.018^{U}
	Medium-high	0.017	-0.017
DEVELOPMENT AT BIRTH	Altricial	-0.033	0.033
	Precocial	0.033	-0.033
GESTATION LENGTH	Short	-0.016, -0.014^{U}	0.016, 0.014^{U}
	Medium	-0.011^{U}	0.011^{U}
	Long	0.034, 0.034^{U}	-0.034, -0.034^{U}
INTERBIRTH INTERVAL	Medium-low	-0.014	0.014
	High	0.012^{U}	-0.012^{U}
LITTER SIZE	Small	0.019^{U}	-0.019^{U}
	Medium-small	-0.032	0.032
	Medium	-0.032^{U}	0.032^{U}
	Medium-large	-0.013	0.013
	Large	-0.012^{U}	0.012^{U}
SOCIAL GROUP	Small	0.021, 0.019^{U}	-0.021, -0.019^{U}
	Medium-small	0.013^{U}	-0.013^{U}
TEAT NUMBER	Two	0.013	-0.013

All associations are significant to $p<0.001$.

U association derived from unordered model.

Table A10d: Interhemal barrier association *d* statistics

Character	State	epitheliochorial	endotheliochorial	haemochorial
ACTIVITY CYCLE	Diurnal	0.014	-0.017	
	Nocturnal	-0.012		
ADULT BODY MASS	Small	-0.023, -0.022[U]	-0.014	0.018, 0.037[U]
	Medium-small		-0.012	0.011, 0.036[U]
	Medium-large	0.023, 0.029[U]	0.015	-0.012, -0.040[U]
	Large	0.022		-0.015
AGE AT FIRST BIRTH	Low	0.010[U]		
	Medium-high		-0.017	
AGE AT MATURITY	Low	-0.033, -0.033[U]		0.022, 0.023[U]
	High	0.034, 0.032[U]		-0.020, -0.020[U]
AGE AT WEANING	Low	-0.021, -0.025[U]	0.023, 0.023[U]	0.010
	Medium	0.015[U]	-0.016	
	High	0.022, 0.025[U]		-0.014, -0.014[U]
GESTATION LENGTH	Short	-0.028, -0.028[U]	-0.016	0.024
	Medium	-0.020[U]	0.019	0.038
	Long	0.030, 0.031[U]		-0.038, -0.040[U]
DEVELOPMENT AT BIRTH	Altricial	-0.044, -0.042[U]	0.018, 0.015[U]	0.021[U]
	Precocial	0.044, 0.042[U]	-0.018, -0.015[U]	-0.021[U]
TROPHIC LEVEL	Herbivore		-0.023[U]	0.017, 0.011[U]
	Omnivore	-0.025		-0.019[U]
	Carnivore		0.020[U]	
LITTERS PER YEAR	One		-0.010	
	Two		-0.010	
LITTER SIZE	Small	0.010, 0.010[U]		-0.032, -0.032[U]
	Medium	-0.011, -0.010[U]		0.024, 0.024[U]
	Large	-0.035, -0.034[U]		0.022, 0.020[U]
TERRESTRIALITY	Fossorial	0.015[U]	-0.018	
	Above ground	-0.015[U]	0.018	
INTERBIRTH INTERVAL	Short	-0.010, -0.011[U]		
	Medium			-0.021[U]
	Long	0.011, 0.011[U]		-0.022
NEONATE MASS	Small	-0.016, -0.016[U]	0.010, 0.010[U]	0.033, 0.033[U]
	Medium	0.029[U]	0.010, 0.010[U]	-0.010, -0.011[U]
	Large	0.032, 0.033[U]		-0.028, -0.026[U]
SOCIAL GROUP SIZE	Small		-0.013	-0.020, -0.020[U]
	Medium-large			0.018, 0.019[U]
	Large			0.018
MAXIMUM LONGEVITY	Low	-0.022, -0.022[U]		0.011[U]
	Medium	0.018, 0.018[U]	0.011, 0.011[U]	0.010, 0.010[U]
	High	0.020[U]		-0.010, -0.011[U]
LITTERS PER YEAR	One		-0.010	
	Two		-0.010	
LITTER SIZE	Small	0.010, 0.010[U]		-0.032, -0.032[U]
	Medium	-0.011, -0.010[U]		0.024, 0.024[U]
	Large	-0.035, -0.034[U]		0.022, 0.020[U]
TERRESTRIALITY	Fossorial	0.015[U]	-0.018	
	Above ground	-0.015[U]	0.018	
INTERBIRTH INTERVAL	Short	-0.010, -0.011[U]		
	Medium			-0.021[U]
	Long	0.011, 0.011[U]		-0.022
NEONATE MASS	Small	-0.016, -0.016[U]	0.010, 0.010[U]	0.033, 0.033[U]
	Medium	0.029[U]	0.010, 0.010[U]	-0.010, -0.011[U]
	Large	0.032, 0.033[U]		-0.028, -0.026[U]
SOCIAL GROUP SIZE	Small	0.015	-0.013	-0.020, -0.020[U]
	Medium-large			0.018, 0.019[U]
	Large			0.018
MAXIMUM LONGEVITY	Low	-0.022, -0.022[U]		0.011[U]
	Medium	0.018, 0.018[U]	0.011, 0.011[U]	0.010, 0.010[U]
	High	0.020[U]		-0.010, -0.011[U]

All associations are significant to $p<0.001$.
U association derived from unordered model.

Table A10e: Yolk sac association *d* statistics

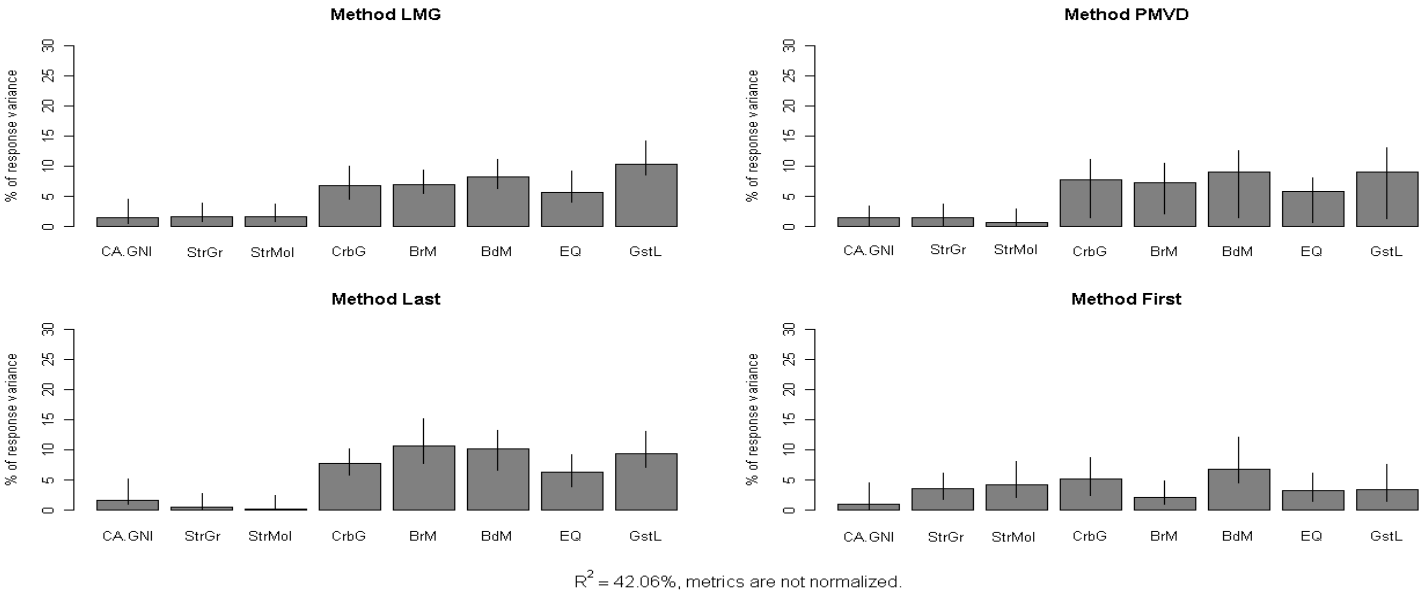
Character	State	Free	Inverted	Trilaminar
ADULT BODY SIZE	Small	0.010[U]		
	Medium-small		0.021[U]	
	Medium-large	0.025[U]	-0.026[U]	
AGE AT MATURITY	Low	-0.014[U]	0.027[U]	
	High	0.014[U]	-0.027[U]	
AGE AT WEANING	Medium	0.010[U]	0.010	
	High	0.015[U]	-0.012	
LITTER SIZE	Small	-0.033[U]		
	Medium		0.029	
	Large		0.033, 0.033[U]	
LITTERS PER YEAR	Two	-0.019[U]		
GESTATION LENGTH	Short	-0.018[U]		
	Medium		0.013	-0.029
	Long	0.016[U]	0.010, 0.010[U]	
DEVELOPMENT AT BIRTH	Altricial	-0.018[U]	0.027	
	Precocial	0.017[U]	-0.027[U]	
NEONATE MASS	Small	-0.013, -0.013[U]	0.011	
	Large	0.015, 0.015[U]	-0.010	
TROPHIC LEVEL	Herbivore	-0.019[U]		
	Omnivore	0.025[U]	-0.021	
	Carnivore	0.022[U]	-0.023	
SOCIAL GROUP SIZE	Small		-0.019	
	Medium-large	-0.017[U]	0.023	
MAXIMUM LONGEVITY	Short	-0.012, -0.012[U]	0.018	
	Medium	0.014, 0.015[U]	0.010	
	Long	0.012[U]	-0.011	
TEAT NUMBER	Two		-0.011	
INTERBIRTH INTERVAL	Short	-0.012, -0.012[U]		
	Medium		-0.016	-0.029
	Long	0.010, 0.010[U]	-0.019	

All associations are significant to $p<0.001$.
U association derived from unordered model.

Character	State	Free	Inverted	Trilaminar
NEONATE MASS	Small	-0.013, -0.013[U]	0.011	
	Large	0.015, 0.015[U]	-0.010	
TROPHIC LEVEL	Herbivore	-0.019[U]		
	Omnivore	0.025[U]	-0.021	
	Carnivore	0.022[U]	-0.023	
SOCIAL GROUP SIZE	Small		-0.019	
	Medium-large	-0.017[U]	0.023	
MAXIMUM LONGEVITY	Short	-0.012, -0.012[U]	0.018	
	Medium	0.014, 0.015[U]	0.010	
	Long	0.012[U]	-0.011	
TEAT NUMBER	Two		-0.011	
INTERBIRTH INTERVAL	Short	-0.012, -0.012[U]		
	Medium		-0.016	-0.029
	Long	0.010, 0.010[U]	-0.019	

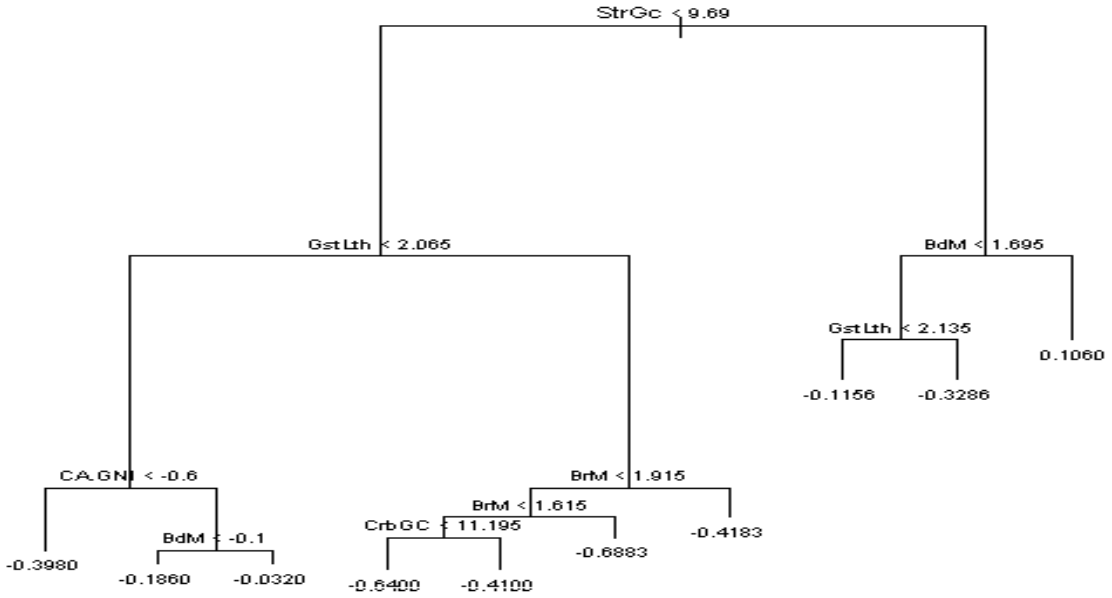
All associations are significant to $p<0.001$.
U association derived from unordered model.

Relative importances for glia-neuron ratio in V1 in AS
(with 95% bootstrap confidence intervals)



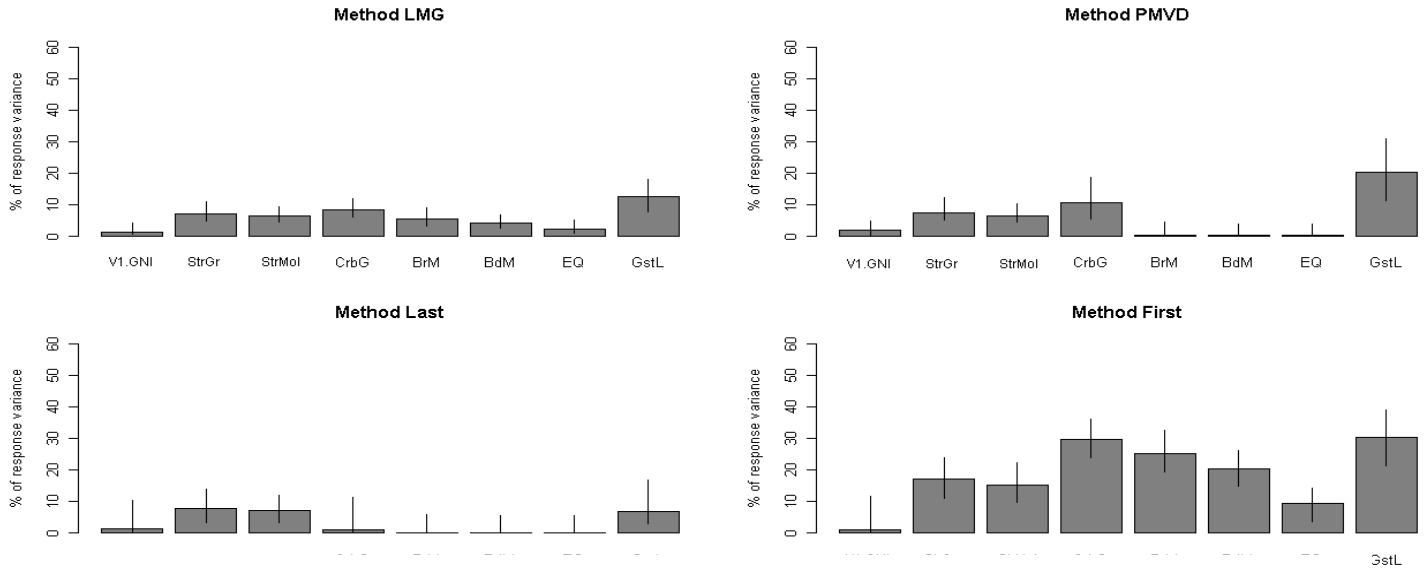
R^2 = 42.06%, metrics are not normalized.

Recursive tree for glia-neuron ratio in V1 in AS

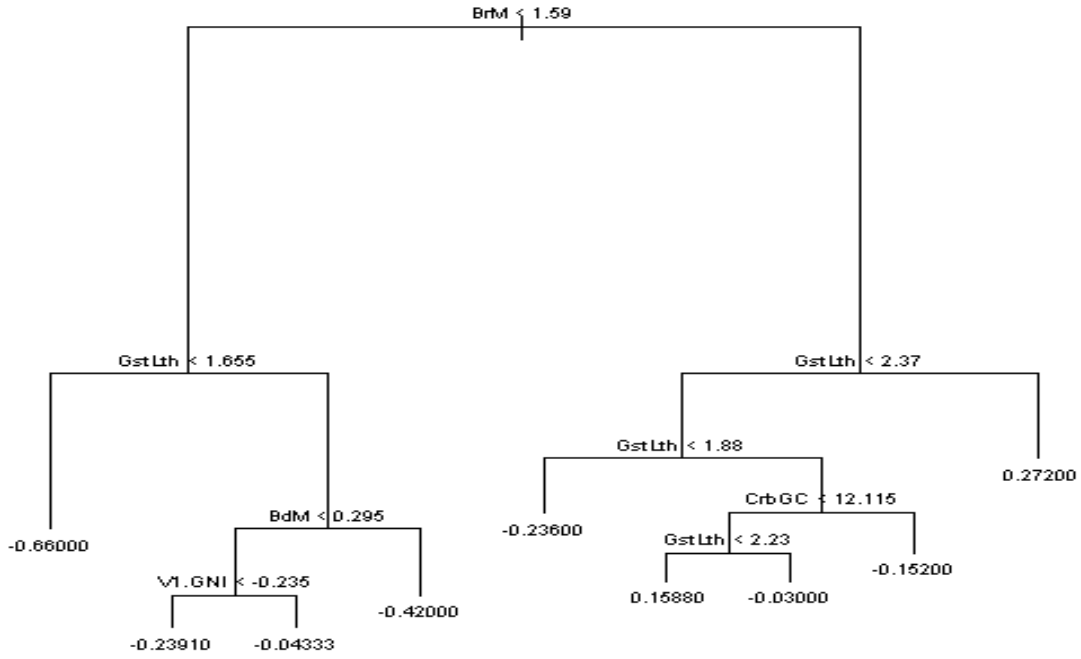


Supplemental Figure1a: Recursive trees and relative importance metrics for determining glia-neuron ratio in V1 in AS. The branch lengths in the recursive trees are representative of the deviance explained by each variable. The variables collectively explained 42.06% of the observed variance. The differential contributions of CrbGC, brain mass (BrM), body mass (BdM), encephalization quotient (EQ), and gestation (GstLth) are shown to be significantly greater than those of glia-neuron ratio in CA1-3 (CA.G), and both volumetric measurements of the dentate gyrus (StrGr, StrMol) according to the metrics lmg, pmvd, and last. The differential contributions of all variables are not shown to be significantly different (i.e., the 95% CI for the differences included zero) according to the metric first. The recursive tree shows StrGr to be the foremost contributor to variance in glia-neuron ratio in V1, although gestation length appears to make the greatest contribution. Body mass is shown to contribute in species with a large StrGr (>4.9x10^9μm^3), but also in species with a high glia-neuron ratio in CA1-3 (>0.25), low gestation length (<116d), and a small StrGr (<4.9x10^9μm^3). Gestation, too, contributes to variance in species with a large (>4.9x10^9μm^3) and small (<4.9x109 μm^3) DG, although only in species with a small body mass (<49.5kg). This suggests that the model may be complex. All variables in the recursive tree models are presented as log-transformed. Abbreviations: BdM, body mass (kg); BrM, brain mass (g); CA.g, glial cell density in CA1-3 (cells/mm3); CA.GNI, glia-neuron ratio in CA1-3; CA.n, neuronal density in CA1-3 (cells/mm^3); CrbGc, volumetric estimate of the granule cell layer of the cerebellum (μm^3); EQ, encephalization quotient; GstLth, gestation length (days); StrGr, volumetric estimate of the stratum granulosum (μm^3); StrMol, volumetric estimate of the stratum moleculare (μm^3); V1.g, glial cell density in V1 (cells/mm^3); V1.GNI, glia-neuron ratio in V1; V1.n, neuronal density in V1 (cells/mm^3).

Relative importances for glia-neuron ratio in CA1-3 in AS
(with 95% bootstrap confidence intervals)

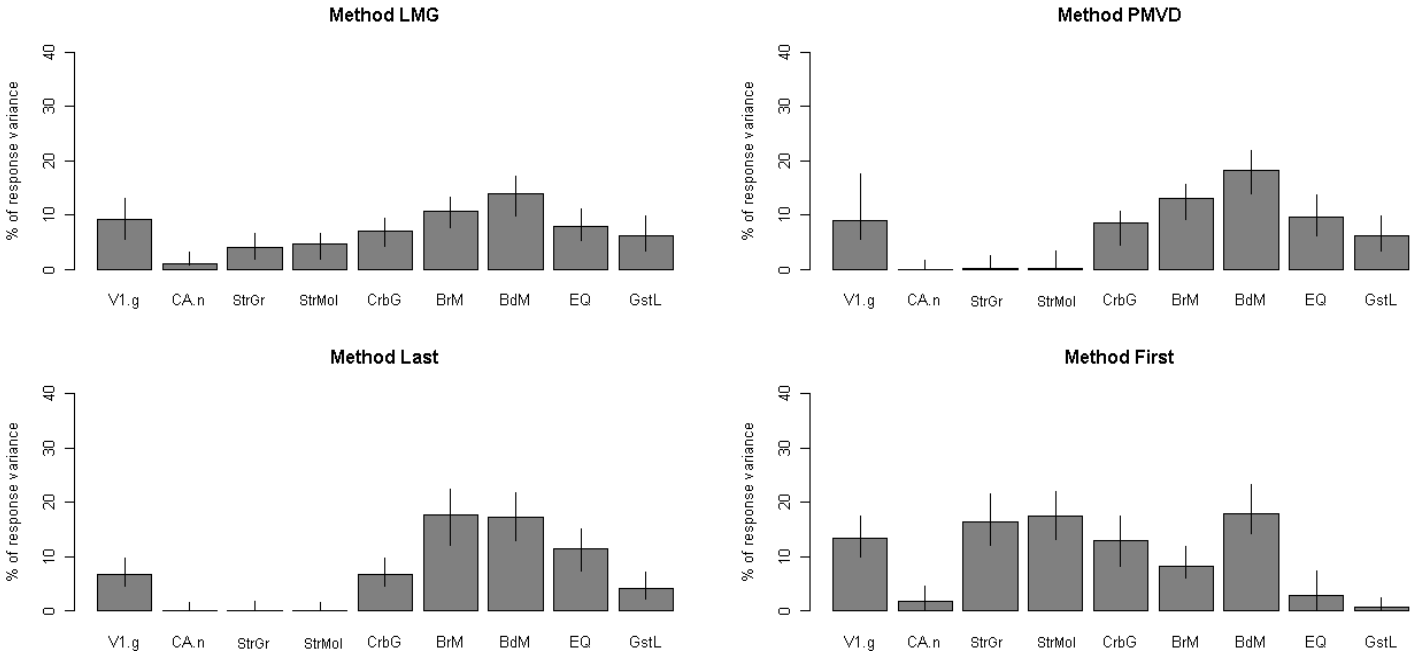


Recursive tree for glia-neuron ratio in CA1-3 in AS

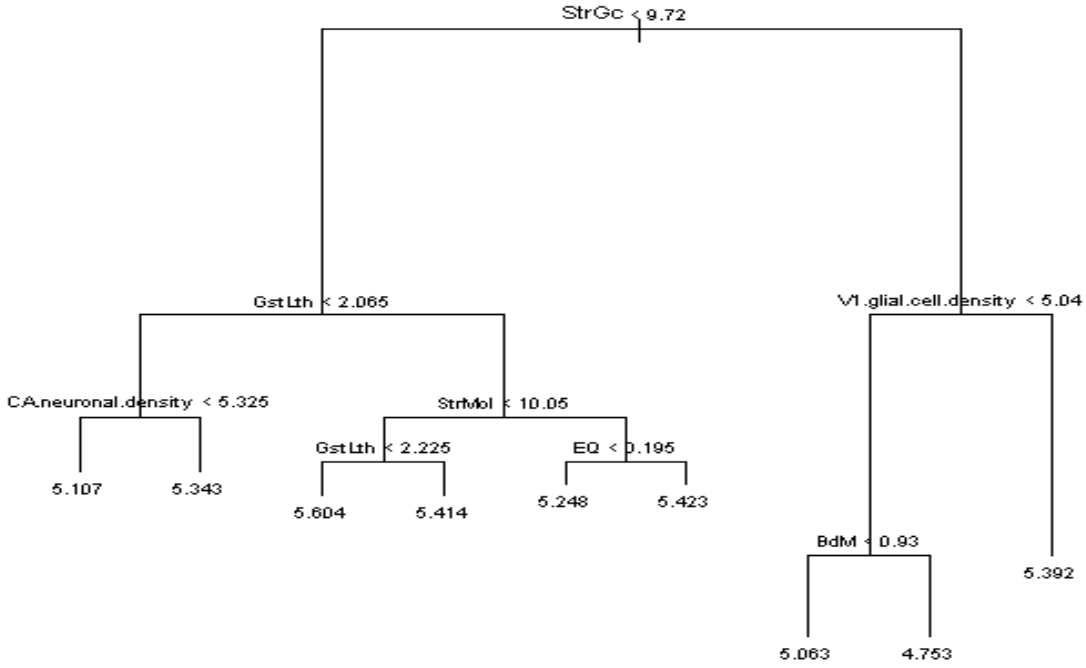


Supplemental Figure 1b: Recursive trees and relative importance metrics for determining glia-neuron ratio in CA1-3 in AS. The variables collectively explained 46.64% of the observed variance. The differential contributions of StrGr, StrMol, CrbGC and gestation length (GstLth) are shown to be significantly greater than those of glia-neuron ratio in V1 (V1.GNI), brain mass (BrM), body mass (BdM), and EQ, according to the metric pmvd. StrGr, StrMol, and gestation length are also shown to make differentially greater contributions than the other variables according to the metric first. The recursive tree model shows brain mass to be the foremost and greatest contributor to variance in glia-neuron ratio in CA1-3. Gestation length is shown to be important in species with both small (<39g) and large (>39g) brain mass, indicating that the model may be complex.

Relative importances for neuronal density in V1 in AS
(with 95% bootstrap confidence intervals)

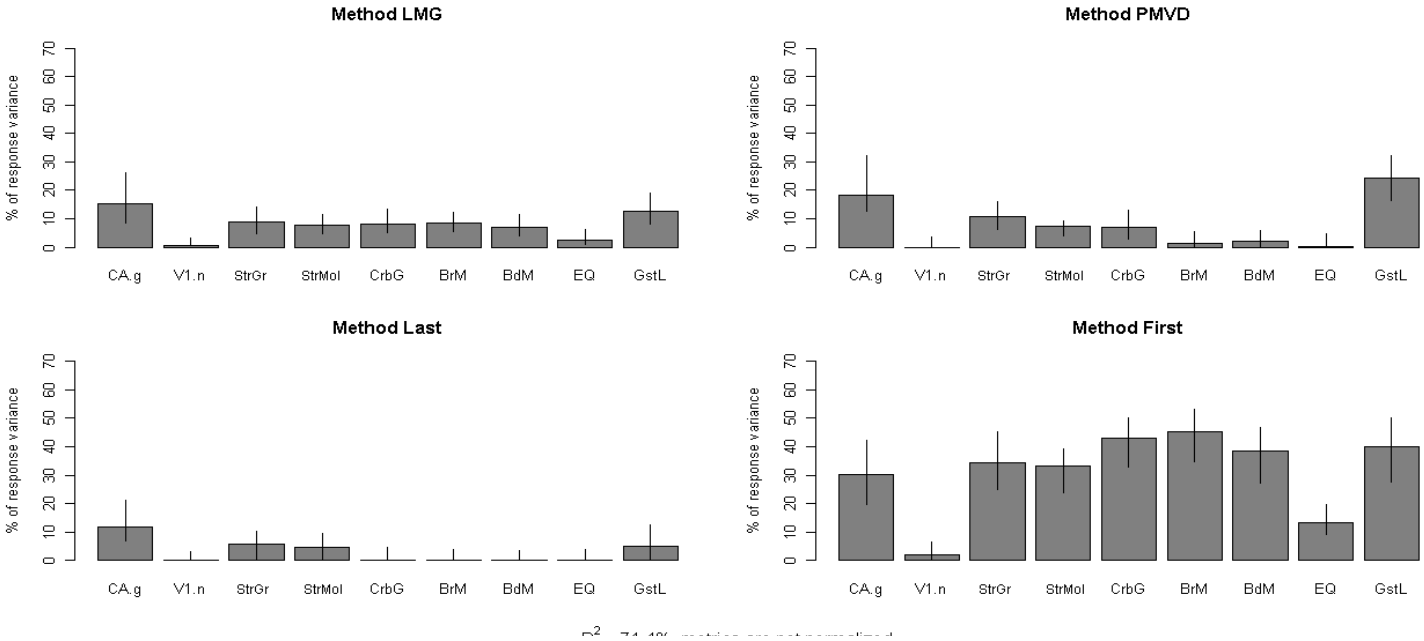


Recursive tree for neuronal density in V1 in AS

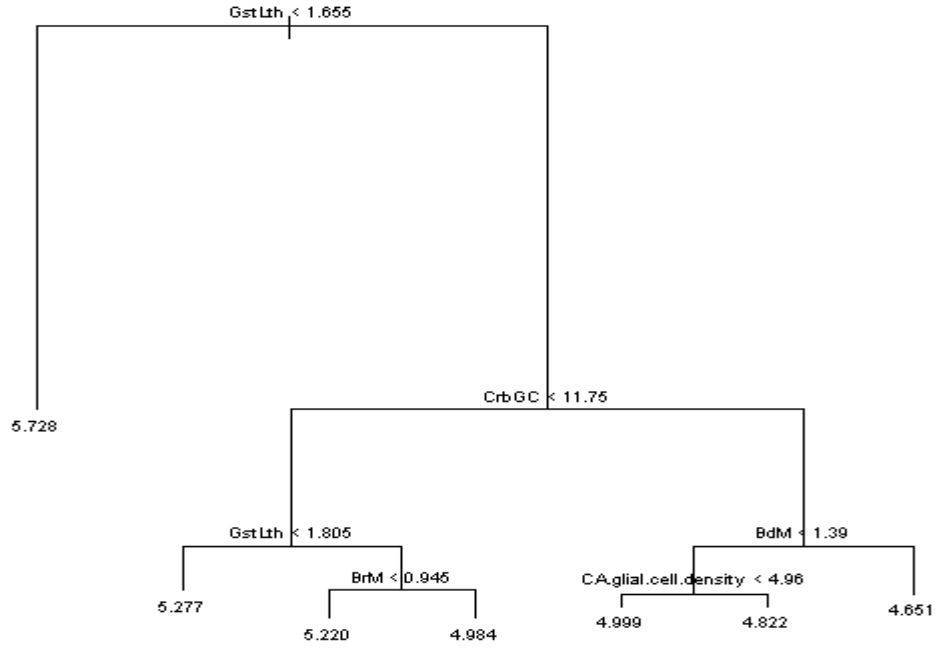


Supplemental Figure 1c: Recursive tree and relative importance metrics for determining neuronal density in V1 in AS. The variables collectively explained 64.57% of the observed variance. The differential contributions of glial cell density in V1 (V1.g), CrbGc, brain mass (BrM), body mass (BdM), encephalization quotient (EQ), and gestation length (GstLth) are shown to be significantly greater than those of neuronal density in CA1-3 (CA.n), and both volumetric measurements of the dentate gyrus (StrGr, StrMol), according to the metrics pmvd and first. The 95% CI of the differential contribution of neuronal density in CA1-3 are shown to include zero for all metrics. StrGr is shown to be the foremost contributor to variance in neuronal density in V1, with glial cell density in V1 making an equally great contribution in species with a large StrGr (>5.25x10^9μm^3). Neuronal density in CA1-3 is shown to an important contributor at a terminal node, in species with a small StrGr (<5.25x10^9μm^3) and a short gestation length (<116d). The model is not shown to be complex.

Relative importances for neuronal density in CA1-3 in AS
(with 95% bootstrap confidence intervals)

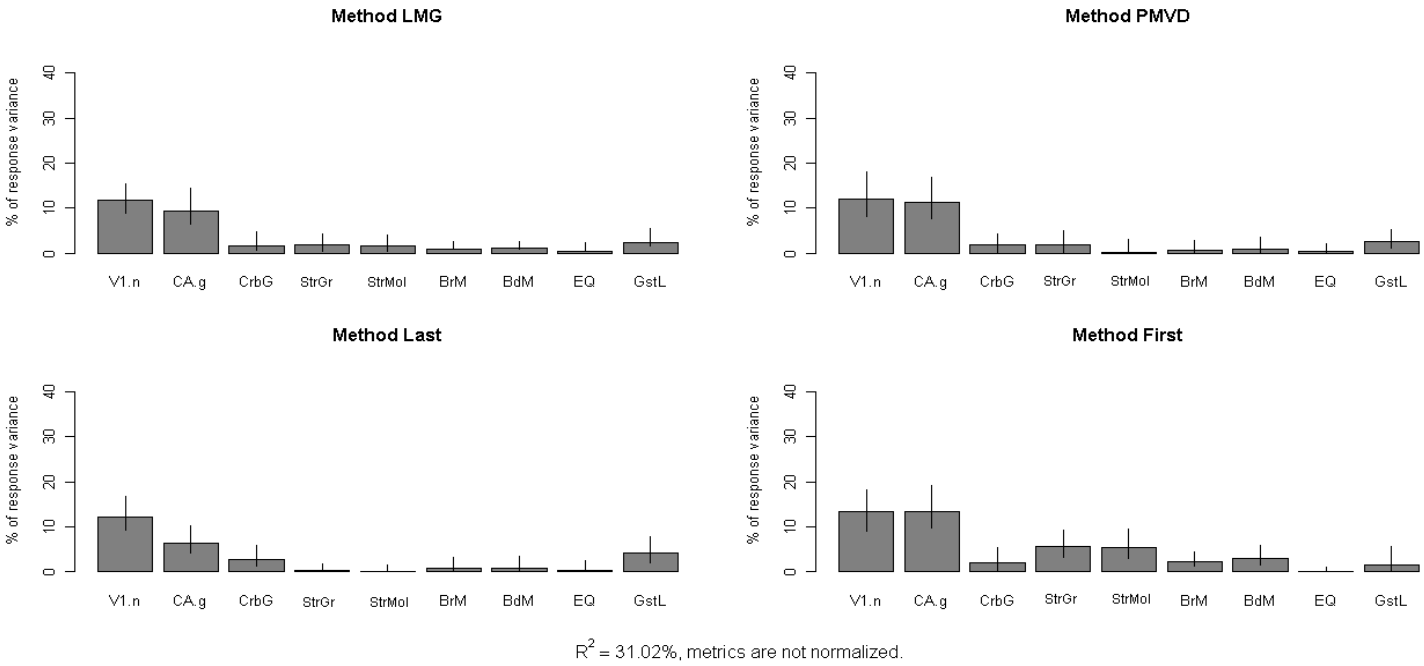


Recursive tree for neuronal density in CA1-3 in AS



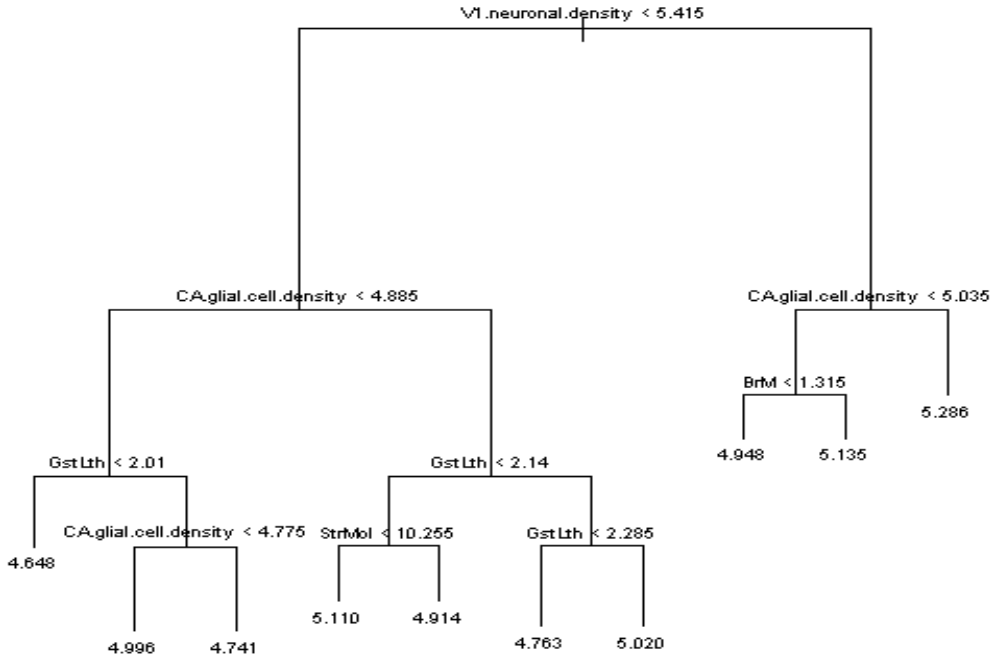
Supplemental Figure 1d: Recursive tree and relative importance metrics for determining neuronal density in CA1-3 in AS. The variables collectively explained 71.4% of the observed variance. The differential contributions of glial cell density in CA1-3 (CA.g), StrGr, StrMol, and gestation length (GstLth) are shown to be significantly greater than the other variables according to the metrics pmvd and last, and CrbGC is shown to make a significantly greater contribution than neuronal density in V1 (V1.n), brain mass, body mass, and EQ according to the metric pmvd. The 95% CI of the differential contribution of neuronal density in V1 included for all metrics. The recursive tree shows gestation length to be the foremost and greatest contributor to variance in neuronal density in CA1-3. Glial cell density in CA1-3 is shown to become important at a terminal node, in species with a long gestation length (>45d), large CrbGC (>5.62x10^{11}μm^3), and small body mass (<25kg).

Relative importances for glial cell density in V1 in AS
(with 95% bootstrap confidence intervals)



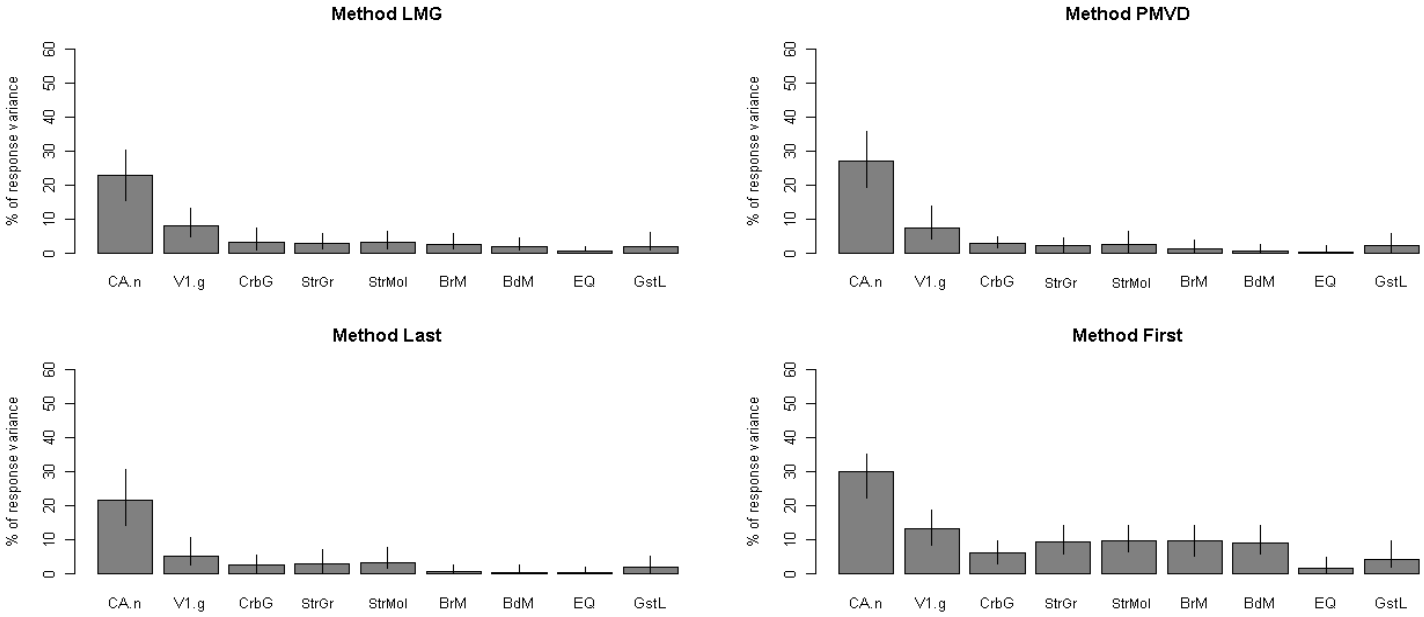
R^2 = 31.02%, metrics are not normalized.

Recursive tree for glial cell density in V1 in AS



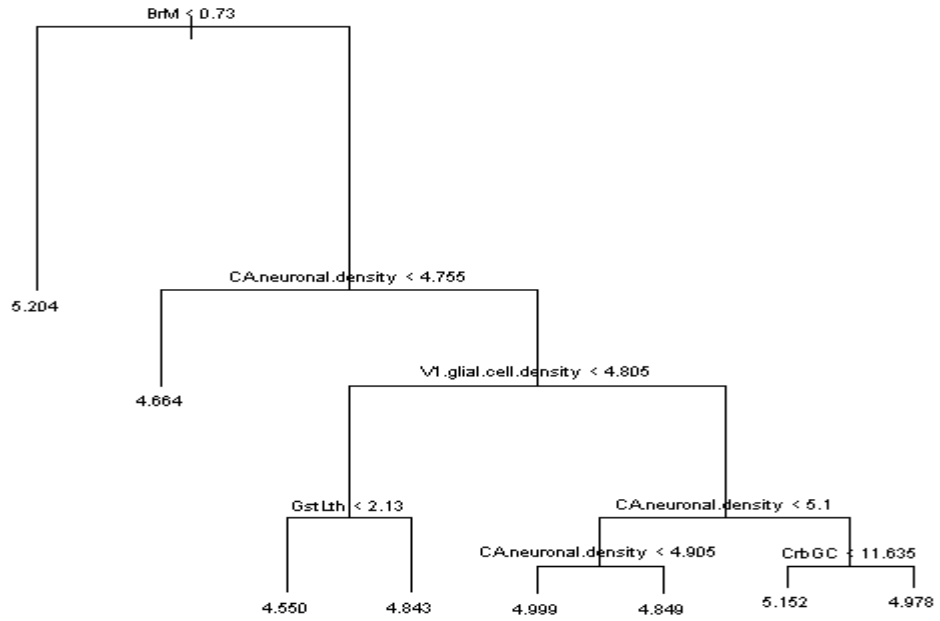
Supplemental Figure 1e: Recursive tree and relative importance metrics for determining glial cell density in V1 in AS. The variables collectively explained 31.02% of the observed variance. The differential contributions of neuronal density in V1 (V1.n) and glial cell density in CA1-3 (CA.g) are shown to be significantly greater than those from all other variables according to all metrics. The contribution of gestation length is shown to be significantly greater than that of all other variables, except V1.n and CA.g, for the metric last. The 95% CI of the contribution of EQ are shown to include zero for all metrics. The recursive tree shows neuronal density in V1 to be the foremost and greatest contributor to variance. The penultimate contribution is shown to be from glial cell density in CA1-3, in species with both a small (<260015 cells/mm^3) and large (>260015 cells/mm^3) neuronal density. Gestation length is shown to contribute in species with both a small (76736 cells/mm^3) and large (76736 cells/mm^3) glial cell density in CA1-3. These nodes suggest the model may be complex.

Relative importances for glial cell density in CA1-3 in AS
(with 95% bootstrap confidence intervals)



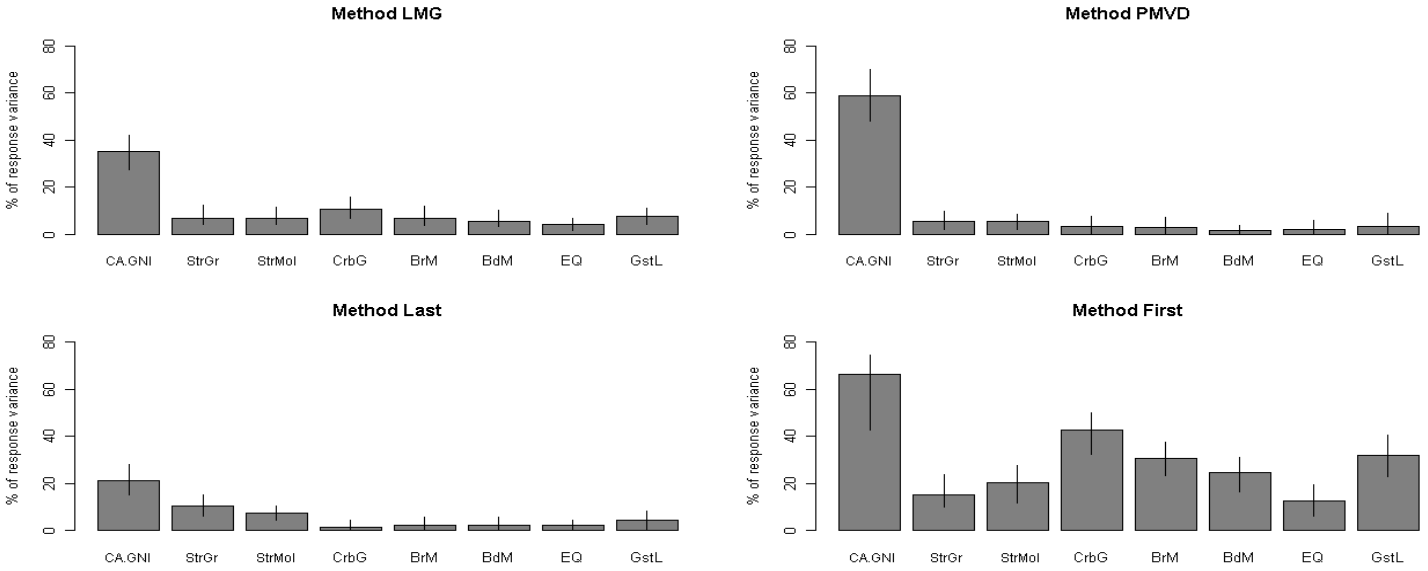
R^2 = 45.83%, metrics are not normalized.

Recursive tree for glial cell density in CA1-3 in AS



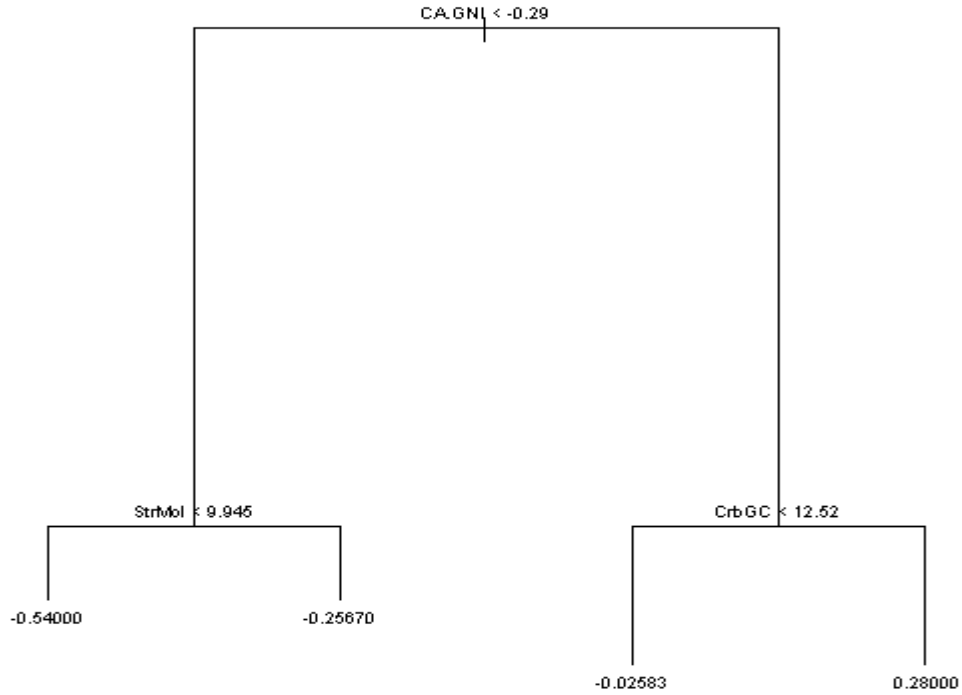
Supplemental Figure 1f: Recursive tree and relative importance metrics for determining glial cell density in CA1-3 in AS. The variables collectively explained 45.83% of the observed variance. The differential contributions of neuronal density in CA1-3 (CA.n) and glial cell density in V1 (V1.g) are shown to be significantly greater than those from all other variables according to the metrics lmg and last. The recursive tree shows brain mass to be the foremost and greatest contributor to variance in glial cell density in CA1-3. Neuronal density in CA1-3 is shown to become an important contributor in species with a small brain mass (>5.37g), and glial cell density in V1 is shown to become important in species with a small brain mass and large neuronal density (>56885 cells/mm^3). The recursive tree model is not complex.

Relative importances for glia-neuron ratio in V1 in Carnivores (with 95% bootstrap confidence intervals)



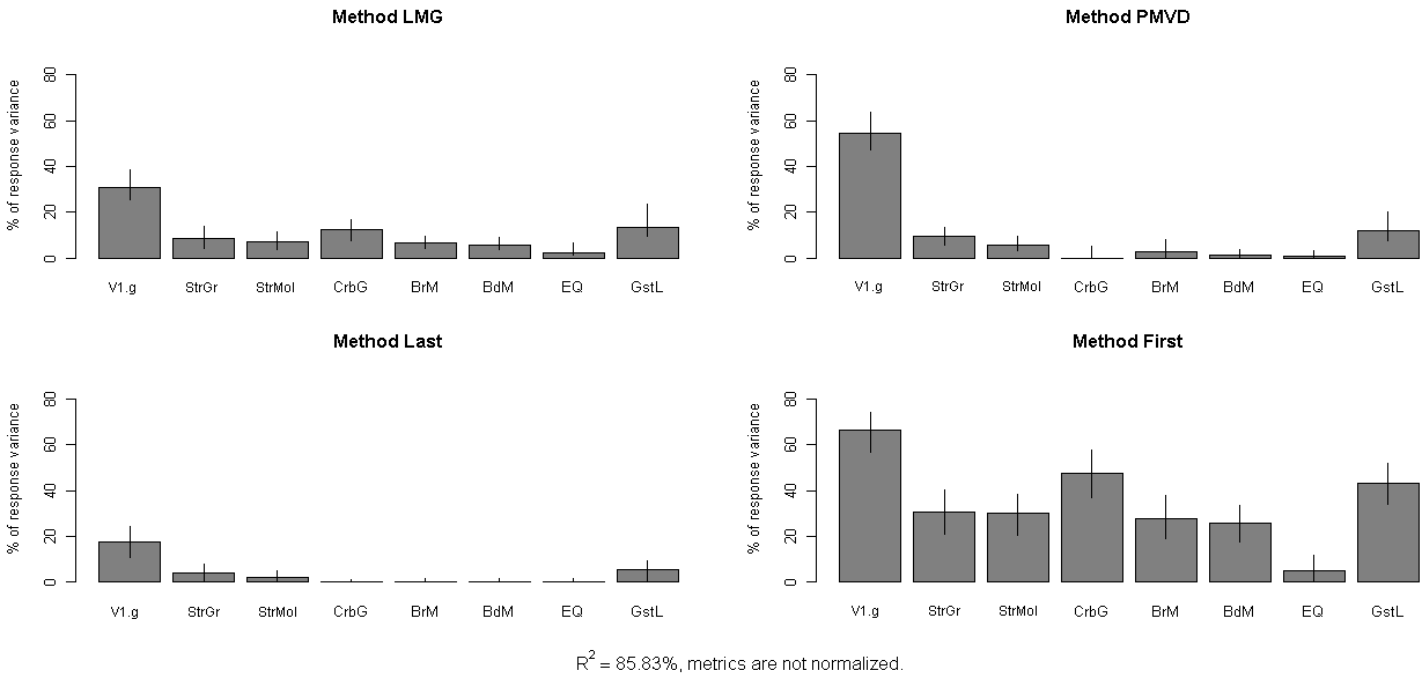
R^2 = 82.91%, metrics are not normalized.

Recursive tree for glia-neuron ratio in CA1-3 in Carnivores



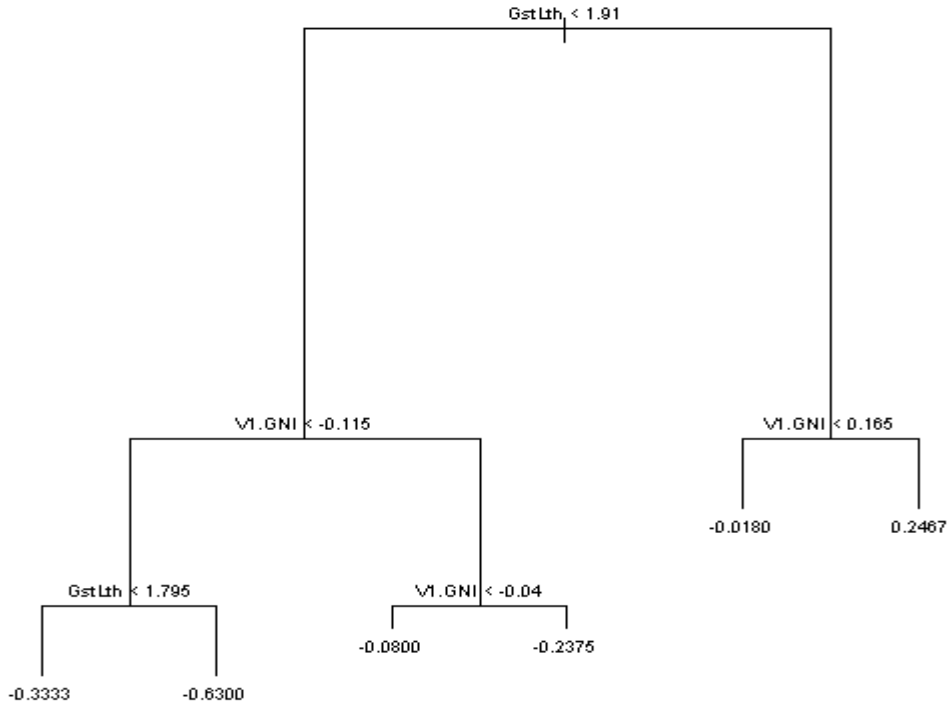
Supplemental Figure 1g: Recursive tree and relative importance metrics for determining glia-neuron ratio in V1 in Carnivora. The branch lengths in the recursive tree are representative of the deviance explained by each variable. The variables collectively explained 82.91% of the observed variance. The contribution of glia-neuron ratio in CA1-3 (CA.GNI) is shown to be significantly greater than that of any of the other variables for the metrics lmg, pmvd, and last. The recursive tree shows CA.GNI to be the foremost and greatest contributor to variance in glia-neuron ratio in V1, with StrMol becoming a significant contributor in species with a low CA.GNI (<0.51) and CrbGc becoming a significant contributor in species with a large CA.GNI (>0.51). All variables in the recursive tree models are presented as log-transformed. Abbreviations: BdM, body mass (kg); BrM, brain mass (g); CA.g, glial cell density in CA1-3 (cells/mm3); CA.GNI, glia-neuron ratio in CA1-3; CA.n, neuronal density in CA1-3 (cells/mm^3); CrbGc, volumetric estimate of the granule cell layer of the cerebellum (μm^3); EQ, encephalization quotient; GstLth, gestation length (days); StrGr, volumetric estimate of the stratum granulosum (μm^3); StrMol, volumetric estimate of the stratum moleculare (μm^3); V1.g, glial cell density in V1 (cells/mm^3); V1.GNI, glia-neuron ratio in V1; V1.n, neuronal density in V1 (cells/mm^3).

Relative importances for glia-neuron ratio in CA1-3 in Carnivores (with 95% bootstrap confidence intervals)

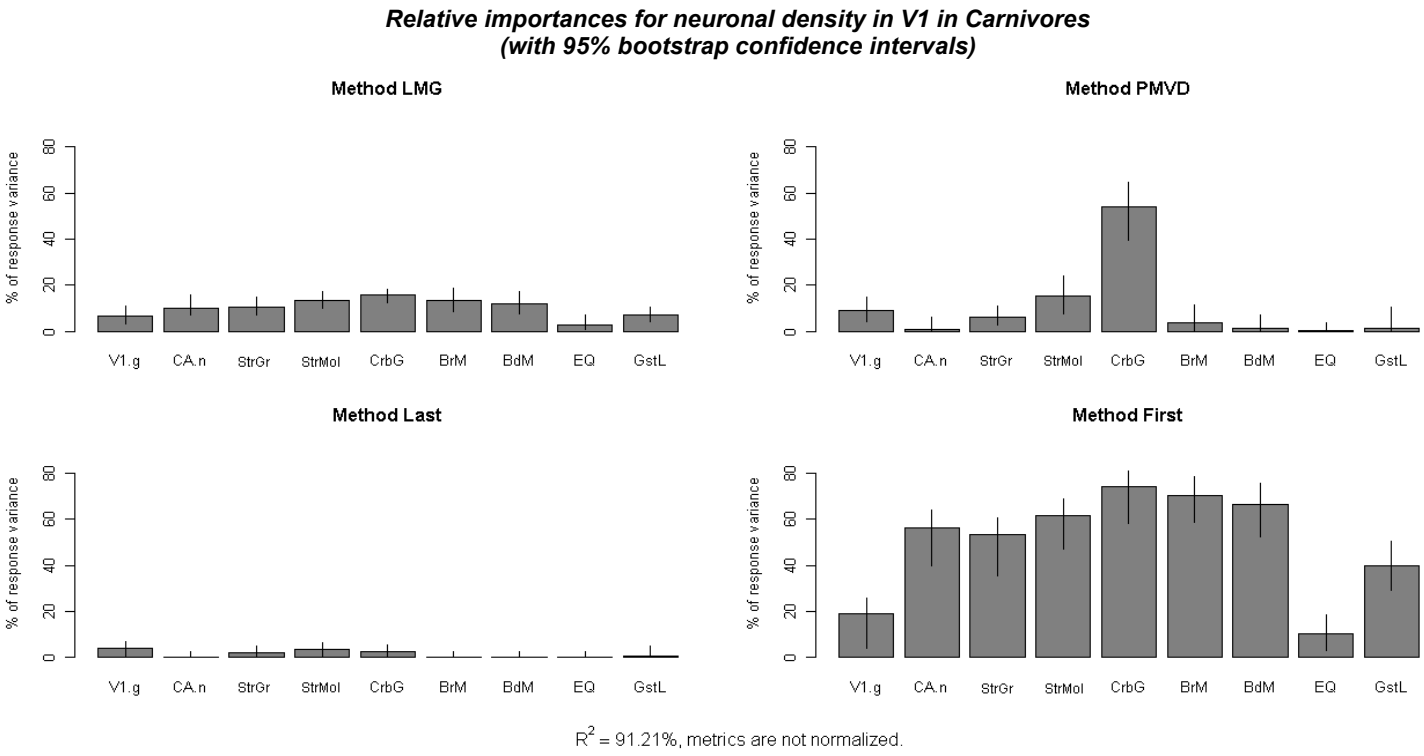


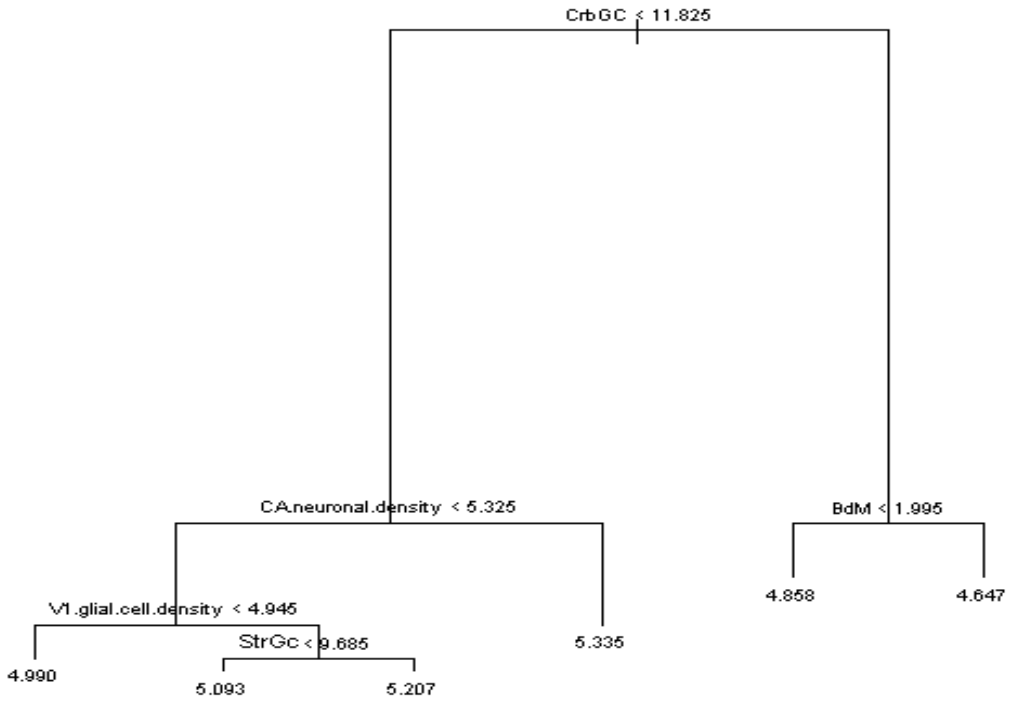
R^2 = 85.83%, metrics are not normalized.

Recursive tree for glia-neuron ratio in CA1-3 in Carnivores



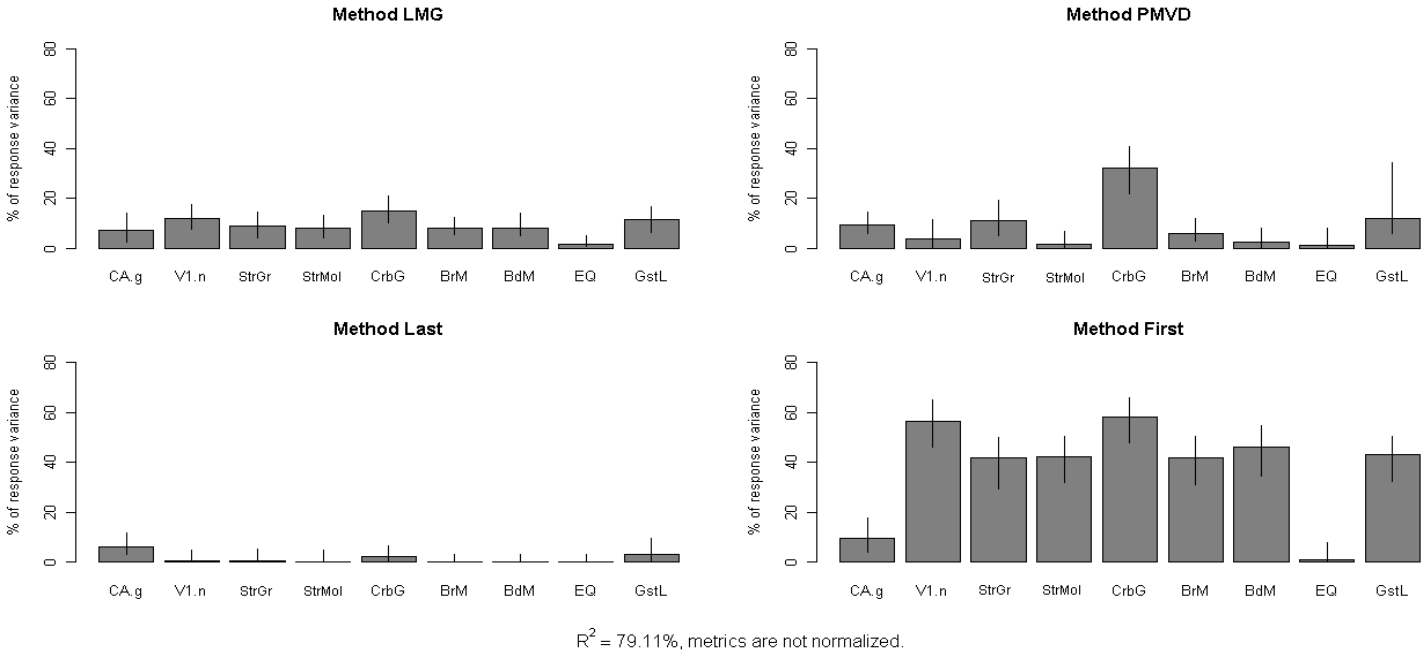
Supplemental Figure 1h: Recursive tree and relative importance metrics for determining glia-neuron ratio in CA1-3 in Carnivora. The variables collectively explained 85.83% of the observed variance. The contribution of glia-neuron ratio in V1 (V1.GNI) is shown to be significantly greater than that of any other variable for the metrics lmg, pmvd, and last. Gestation length (GstLth) is shown to contribute significantly more to the observed variance in than brain mass (BrM), body mass (BdM), and EQ, and CrbGc for the metrics pmvd and last. The recursive tree model shows gestation length to be the foremost and greatest contributor to variance in glia-neuron ratio in V1. However, V1.GNI is shown to be an important contributor in species with both a short (<81d) and long (>81d) gestation length, indicating that the model may be complex.



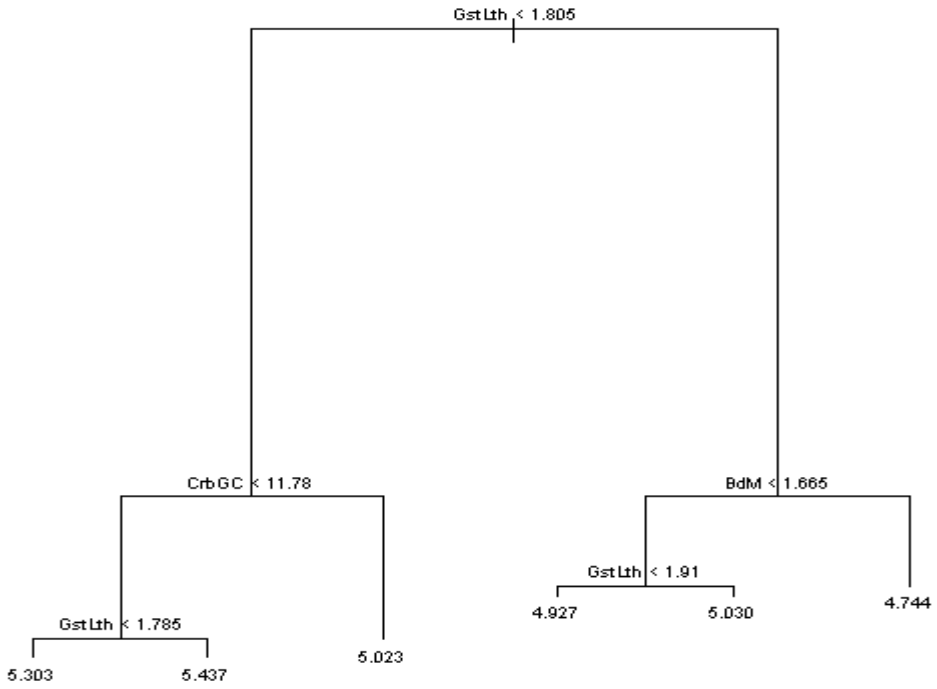


Supplemental Figure 1i: Recursive tree and relative importance metrics for determining neuronal density in V1 in Carnivora. The variables collectively explained 91.21% of the observed variance. The contribution to variance in neuronal density in CA1-3 of CrbGC was significantly greater than that of the other variables for the metric pmvd. The differential contributions of all the variables, except EQ, are not shown to be significantly different (i.e., the 95% CI of the differences between their contributions included zero) for the metrics lmg and first. The recursive tree shows CrbGC to be the foremost and greatest contributor to variance in neuronal density in V1. Neuronal density in CA1-3 (CA.n) is shown to become an important contributor in species with a small CrbGc (<6.68x10^{11}μm^3), and body mass is shown to become an important contributor in species with a large CrbGc (>6.68x10^{11}μm^3). Glial cell density in V1 (V1.g) is shown to become an important contributor in species with a small CrbGc (<6.68x10^{11}μm^3) and a small CA.n (211349 cells/mm^3).

Relative importances for neuronal density in CA1-3 in Carnivores (with 95% bootstrap confidence intervals)

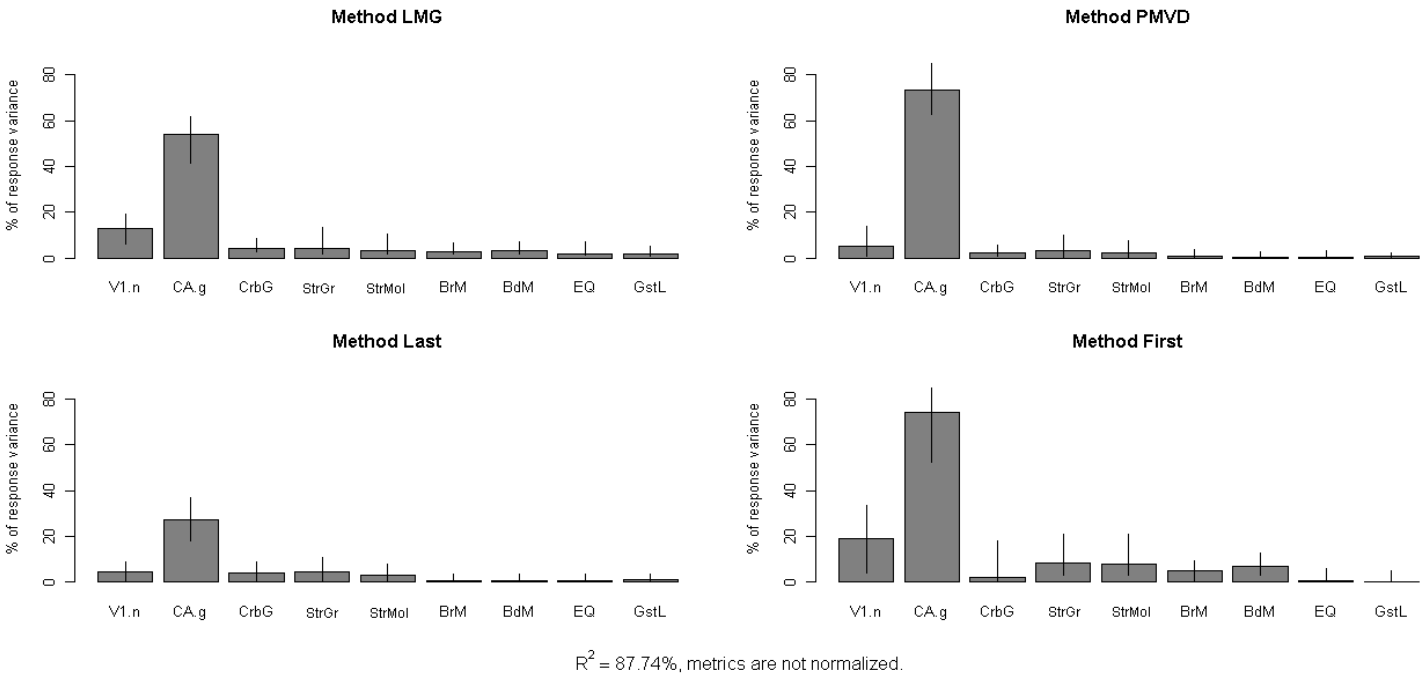


Recursive tree for neuronal density in CA1-3 in Carnivores



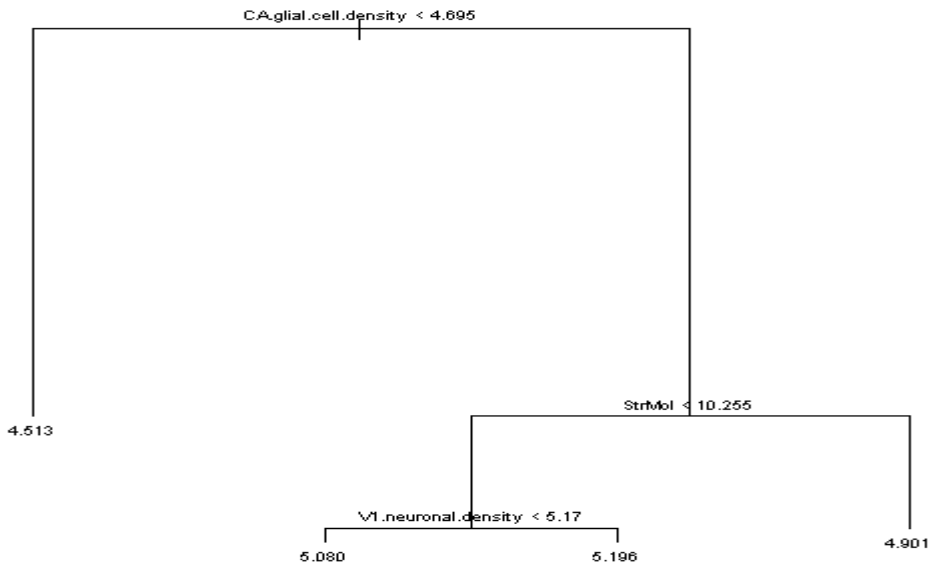
Supplemental Figure 1j: Recursive tree and relative importance metrics for determining neuronal density in CA1-3 in Carnivora. The variables collectively explained 79.1% of the observed variance. The contribution of CrbGC to variance in neuronal density in CA1-3 is shown to be significantly greater than that from the other variables and the differential contributions of glial cell density in CA1-3 (CA.g), StrGr, and gestation length (GstLth) are shown to be significantly greater than those from the other variables, except CA.g, for the metric first. The differential contributions of CA.g, CrbGC, and gestation length are shown to be significantly greater than the contributions from the other variables for the metric last. The recursive tree shows gestation length to be the foremost and greatest contributor to variance in neuronal density in CA1-3, with CrbGC becoming an important contributor in species with a short gestation length (<64d) and body mass (BdM) becoming an important contributor in species with a long gestation length (>64d).

Relative importances for glial cell density in V1 in Carnivores (with 95% bootstrap confidence intervals)



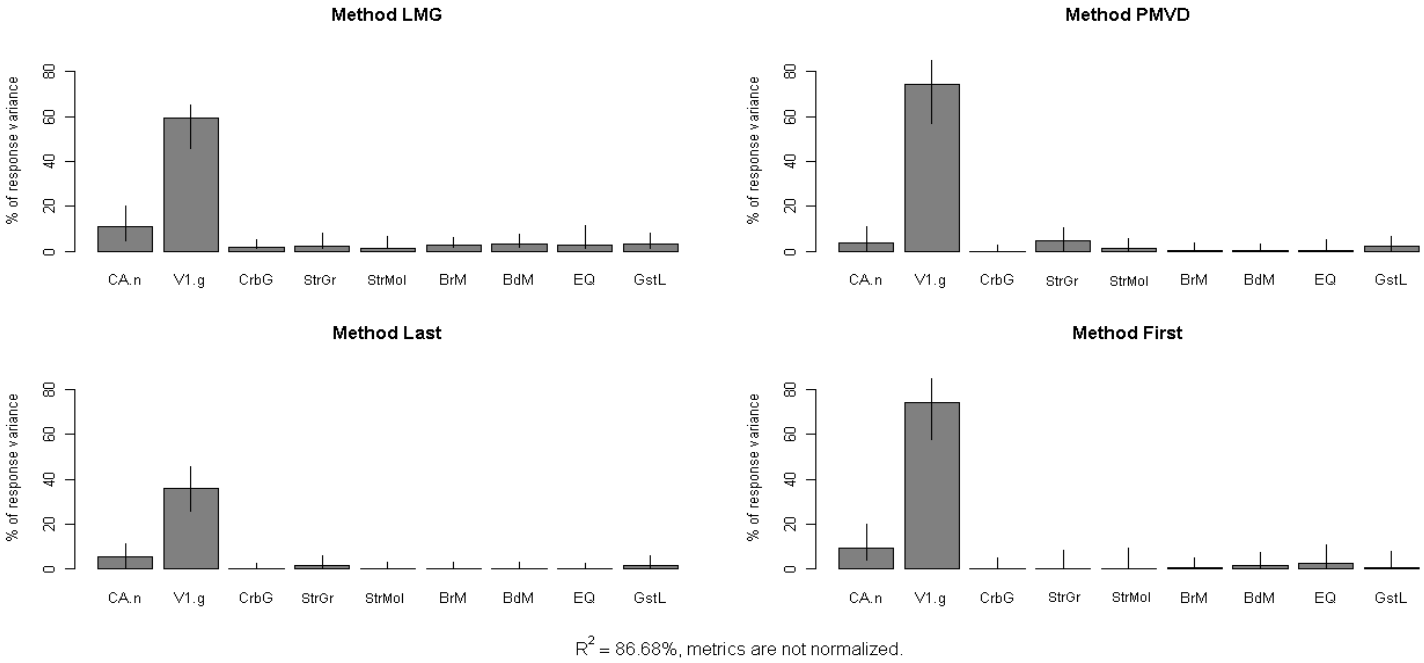
R^2 = 87.74%, metrics are not normalized.

Recursive tree for glial cell density in V1 in Carnivores



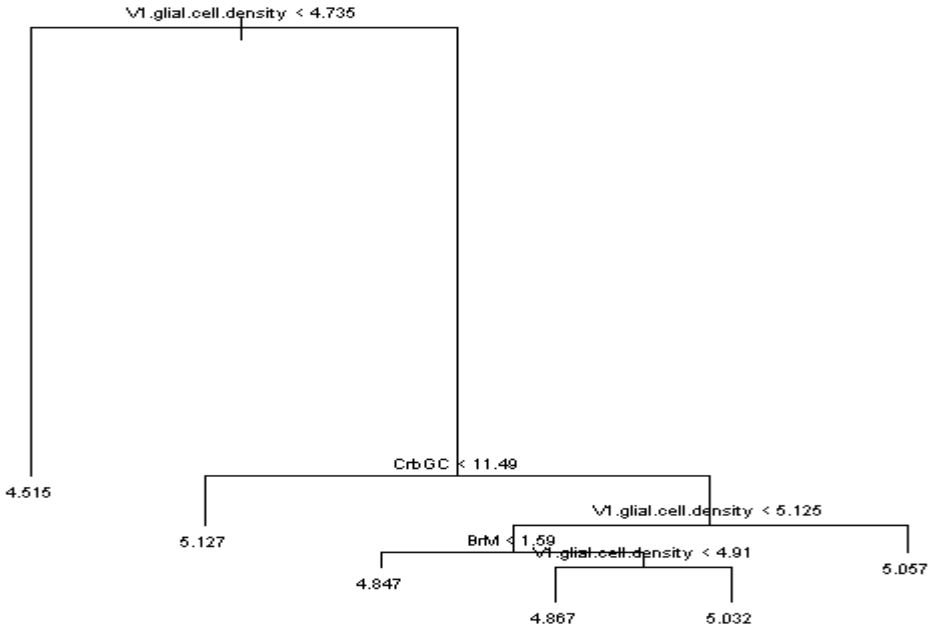
Supplemental Figure 1k: Recursive tree and relative importance metrics for determining glial cell density in V1 in Carnivora. The variables collectively explained 87.74% of the observed variance. The contribution to variance of glial cell density in CA1-3 (CA.g) is significantly greater than the differential contributions of the other variables for all metrics. The contribution of neuronal density in V1 (V1.n) is significantly greater than that of the other variables, except CA.g, for the metrics lmg and first. The recursive tree shows CA.g to be the foremost and greatest contributor to variance in glial cell density in V1. StrMol becomes an important contributor in species with a large CA.g (>49545 cells/mm^3), and V1.n then becomes important in species with a small StrMol (<1.8x10^{10}µm^3).

Relative importances for glial cell density in CA1-3 in Carnivores (with 95% bootstrap confidence intervals)



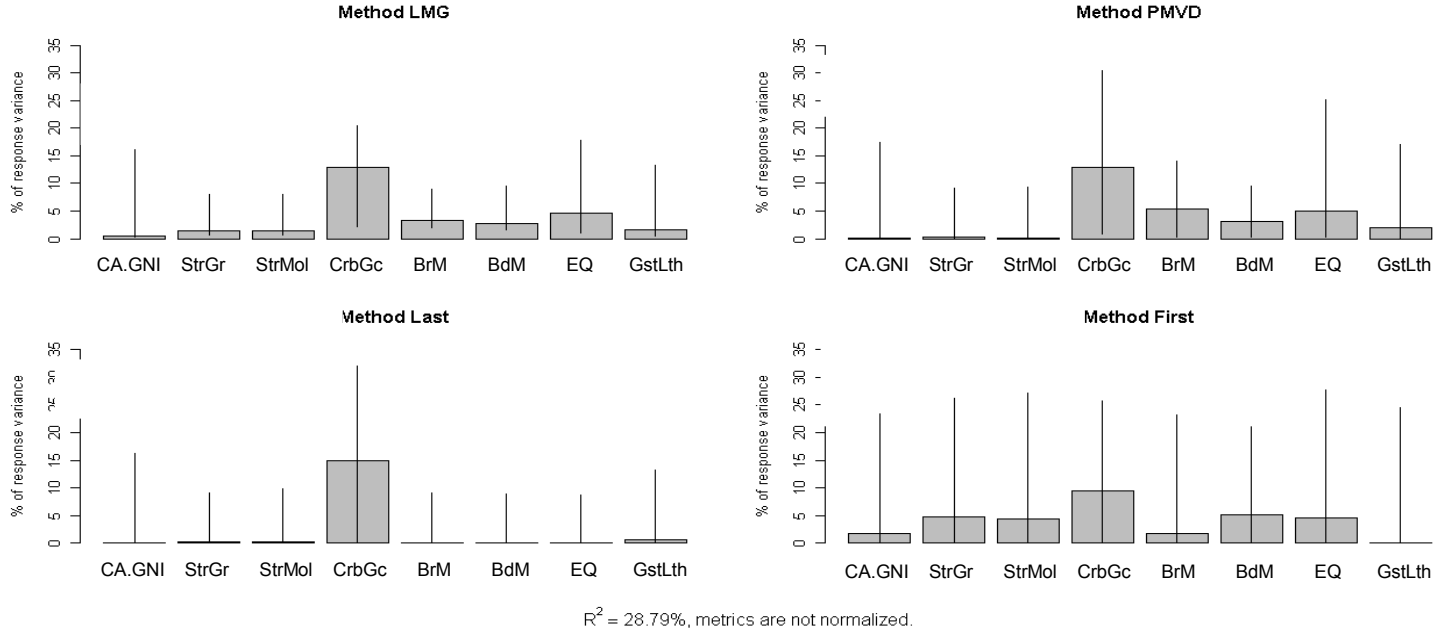
R^2 = 86.68%, metrics are not normalized.

Recursive tree for glial cell density in CA1-3 in Carnivores

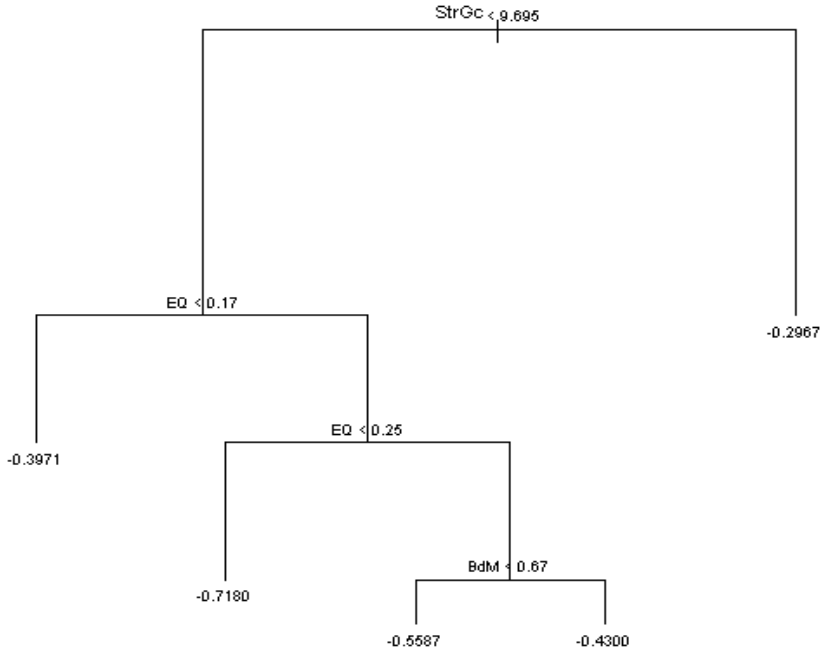


Supplemental Figure 1l: Recursive tree and relative importance metrics for determining glial cell density in CA1-3 in Carnivora. The variables collectively explained 88.68% of the observed variance. The contribution of glial cell density in V1 (V1.g) is shown to be significantly greater than that of other variables for all relative importance metrics. The contribution of neuronal density in CA1-3 (CA.n) is shown to be significantly greater than that of other variables, except CA.g, for the metrics lmg, last, and first. The recursive tree shows V1.g to be the foremost and greatest contributor to variance in glial cell density in CA1-3, with CrbGC and brain mass (BrM) becoming important contributors in species with a large V1.g (54325 cells/mm^3).

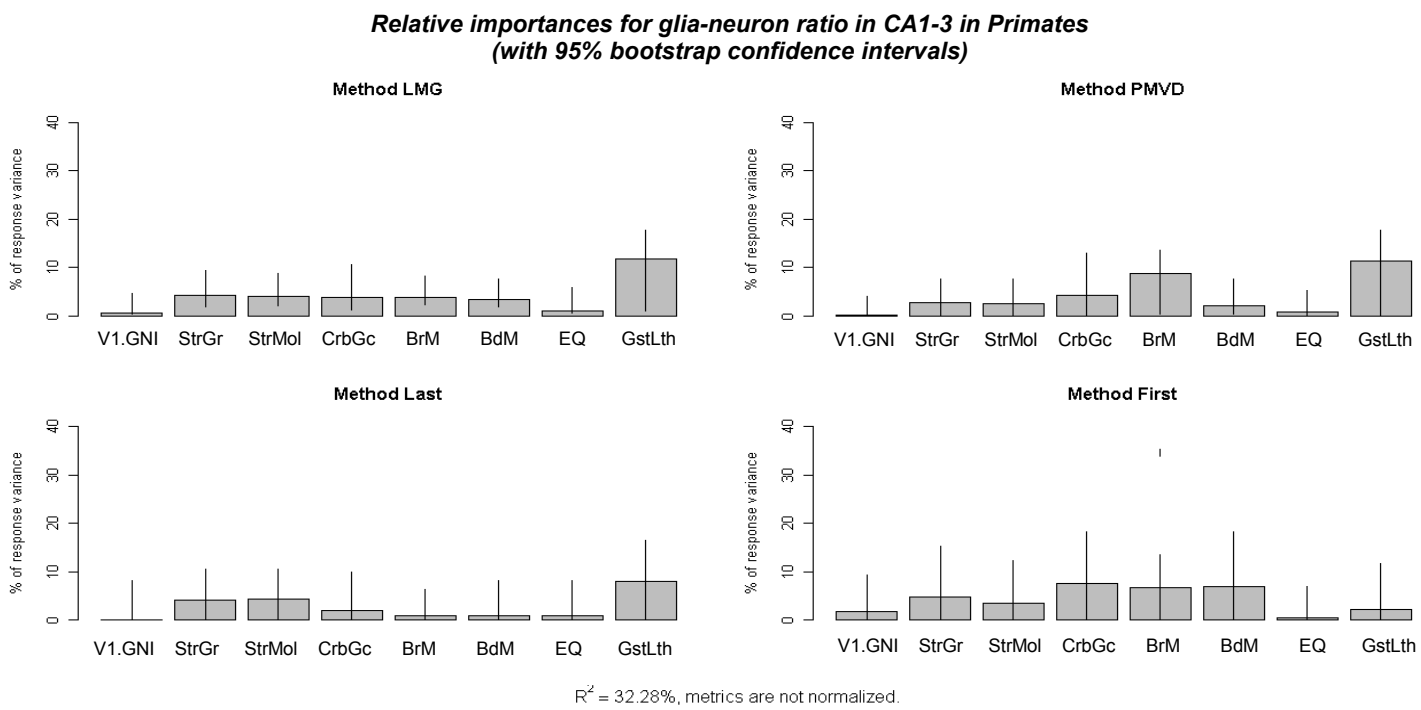
Relative importances for glia-neuron ratio in V1 in Primates (with 95% bootstrap confidence intervals)

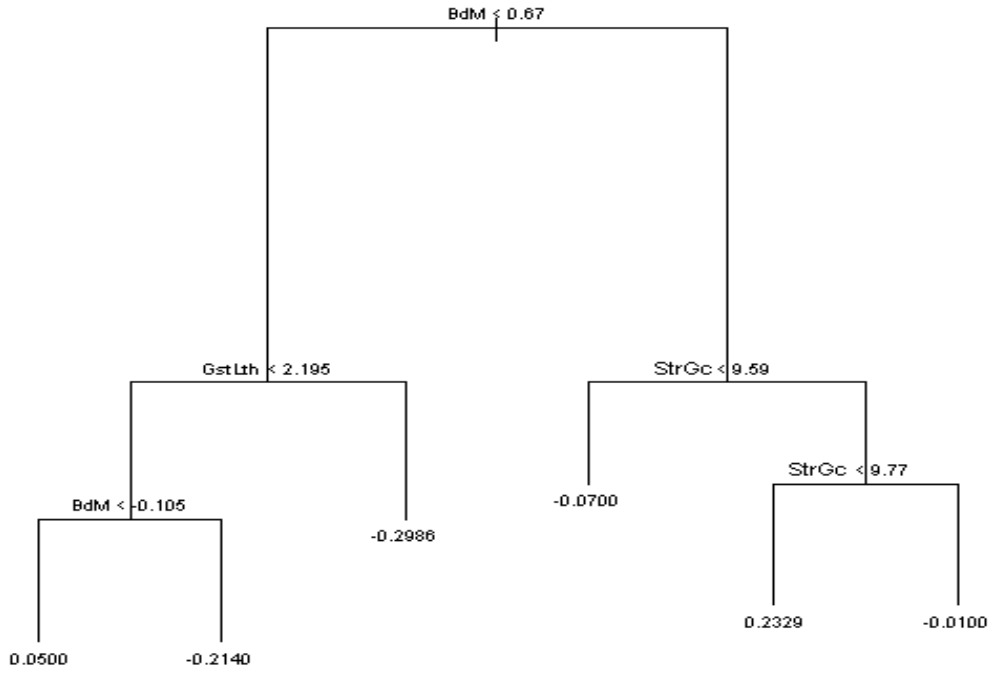


Recursive tree for glia-neuron ratio in V1 in Primates

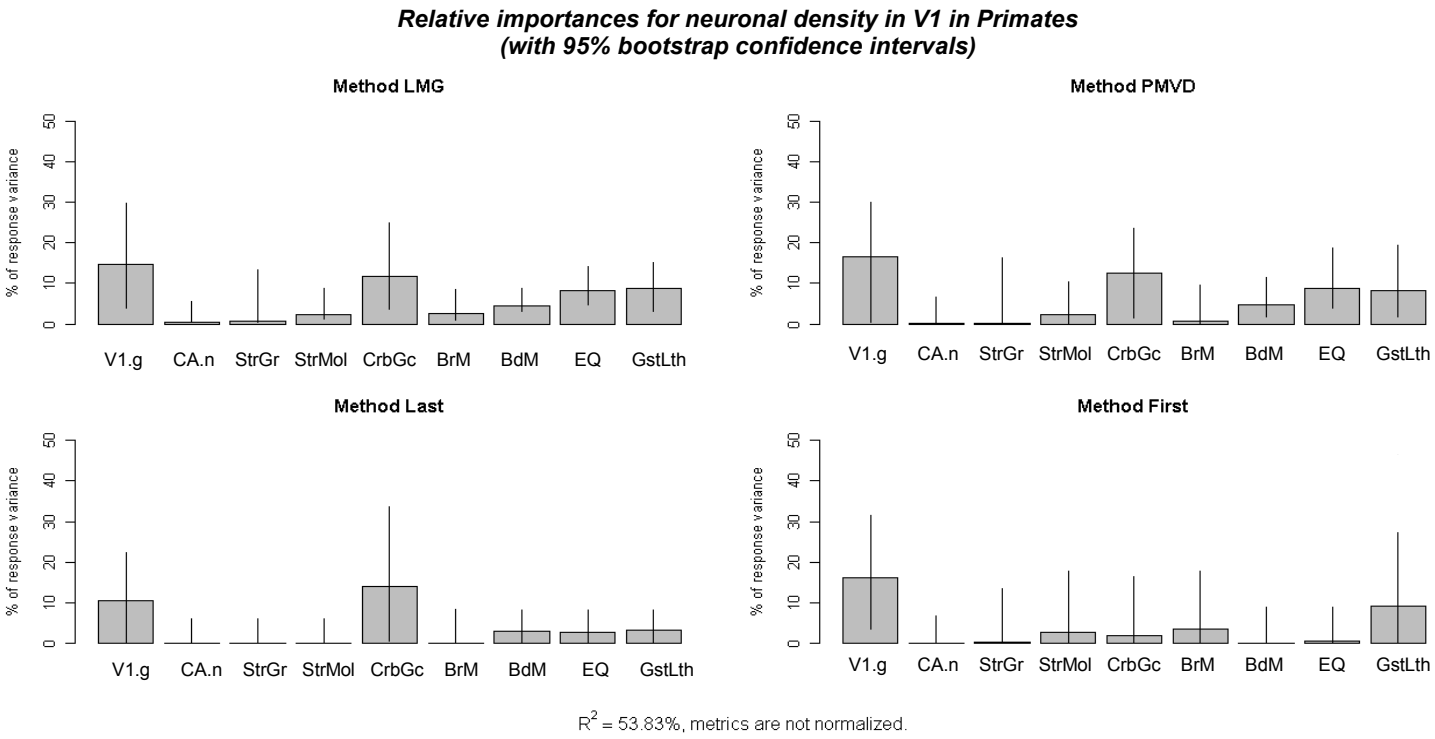


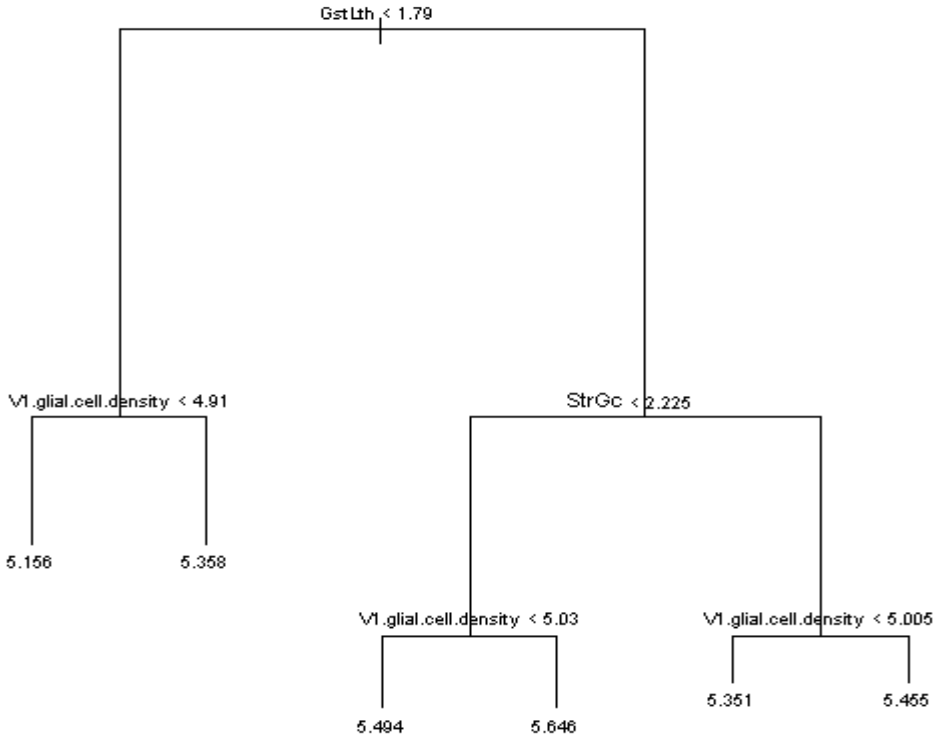
Supplemental Figure 1m: Recursive tree and relative importance metrics for determining glia-neuron ratio in V1 in Primates. The branch lengths in the recursive tree are representative of the deviance explained by each variable. The variables collectively explained 28.79% of the observed variance. The contribution of CrbGc is shown to be significantly greater than that of any of the other variables for the metrics lmg, pmvd, and last. The recursive tree shows StrGr to be the foremost contributor to variance in glia-neuron ratio in V1, with EQ becoming an important contributor in species with a small StrGr (<4.96x10^{9}μm^3) All variables in the recursive tree models are presented as log-transformed. Abbreviations: BdM, body mass (kg); BrM, brain mass (g); CA.g, glial cell density in CA1-3 (cells/mm3); CA.GNI, glia-neuron ratio in CA1-3; CA.n, neuronal density in CA1-3 (cells/mm^3); CrbGc, volumetric estimate of the granule cell layer of the cerebellum (μm^3); EQ, encephalization quotient; GstLth, gestation length (days); StrGr, volumetric estimate of the stratum granulosum (μm^3); StrMol, volumetric estimate of the stratum moleculare (μm^3); V1.g, glial cell density in V1 (cells/mm^3); V1.GNI, glia-neuron ratio in V1; V1.n, neuronal density in V1 (cells/mm^3).



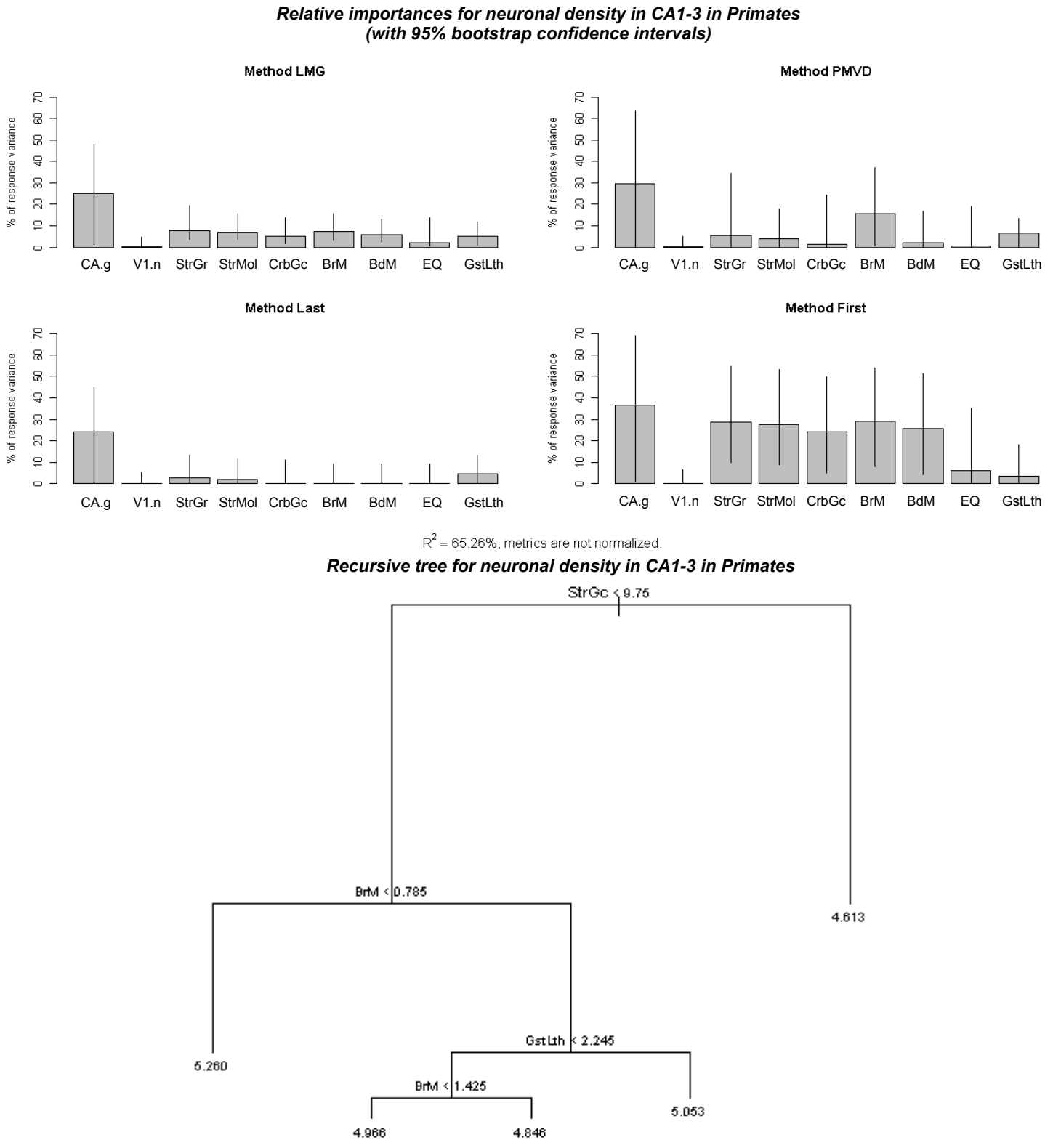


Supplemental Figure 1n: Recursive tree and relative importance metrics for determining glia-neuron ratio in CA1-3 in Primates. The variables collectively explained 32.28% of the observed variance. The contribution of gestation length (GstLth) is shown to be significantly greater than that of any other variable for the metrics lmg, pmvd, and last. The recursive tree model shows body mass (BdM) to be the foremost and greatest contributor to variance, with gestation length and StrGr becoming important contributors in species with small (<4.68kg) and large (>4.68kg) body masses, respectively.

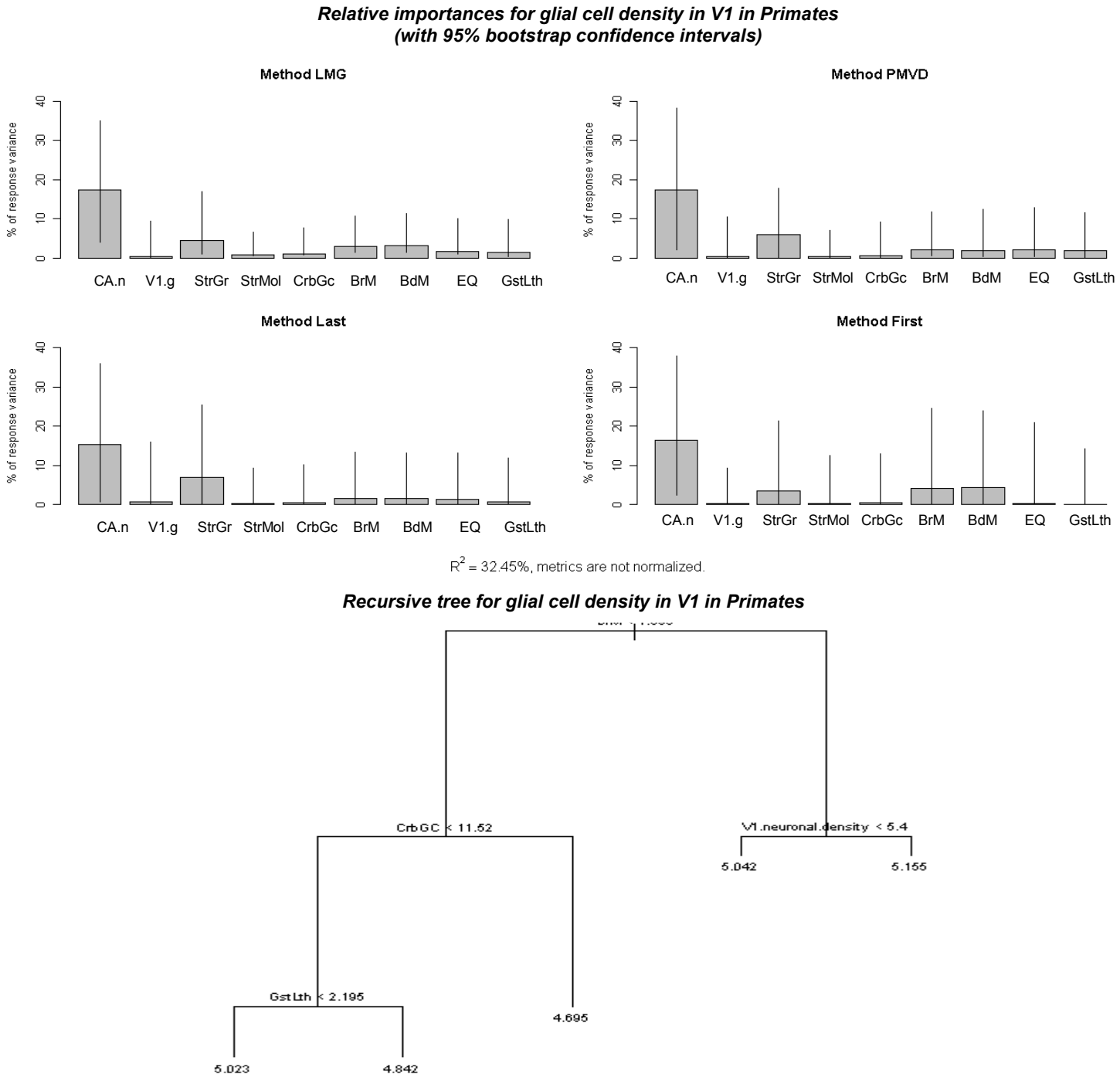




Supplemental Figure 1o: Recursive tree and relative importance metrics for determining neuronal density in V1 in Primates. The variables collectively explained 53.83% of the observed variance. The differential contributions of glial cell density in V1 (V1.g) and CrbGc are shown to be significantly greater than those of other variables for the metric last, while the differential contributions of V1.g and gestation length (GstLth) are shown to be significantly greater than those of other variables for the metric first. The 95% CI of the contributions of both volumetric estimates of the dentate gyrus include zero for the metrics pmvd, first, and last. The recursive tree shows gestation length to be the foremost and greatest contributor to variance, with V1.g and StrGr becoming important contributor in species with short (<62d) and long (>62d) gestation lengths, respectively. However, the appearance at nodes on either side of gestation length and on either side of StrGr indicates that the model may be complex.

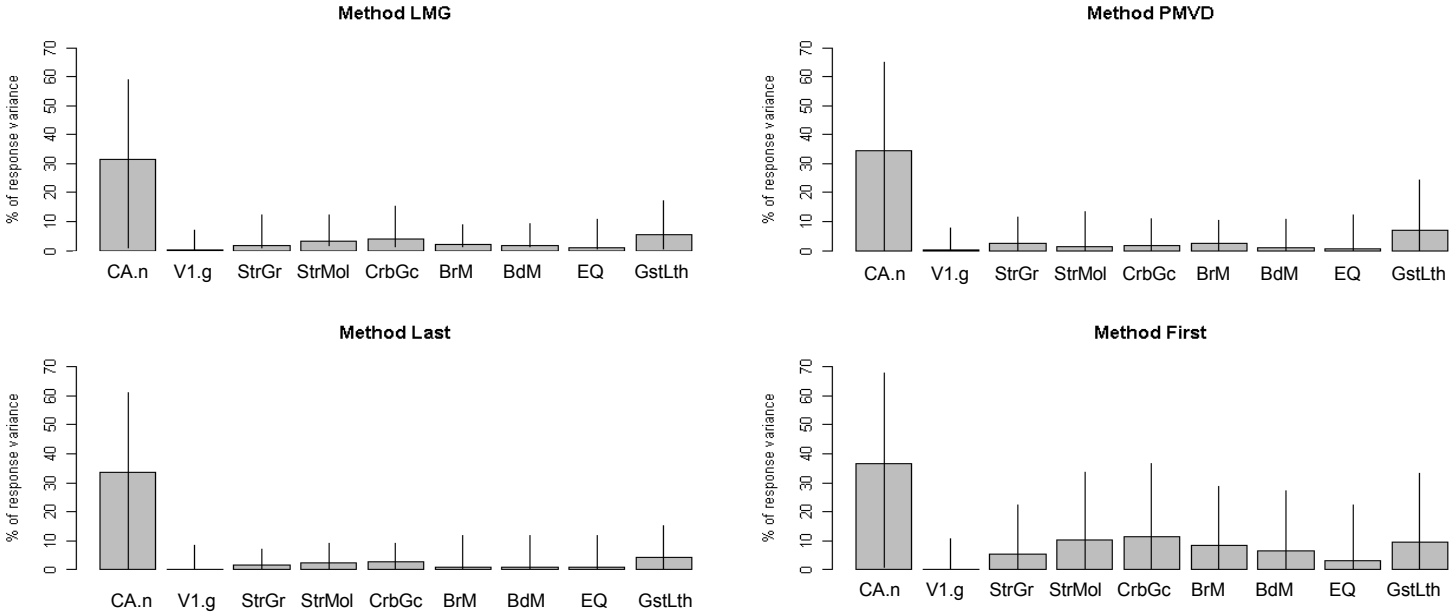


Supplemental Figure 1p: Recursive tree and relative importance metrics for determining neuronal density in CA1-3 in Primates. The variables collectively explained 65.26% of the observed variance. The contribution to variance in neuronal density in CA-13 of glial cell density in CA1-3 (CA.g) is shown to be significantly greater than that of the other variables for the metrics lmg, pmvd, and last. The contribution of neuronal density in V1 (V1.n) is shown to be insignificant for all metrics. The recursive tree shows StrGr to be the foremost contributor to variance in neuronal density in CA1-3, with brain mass becoming an important contributor in species with a small StrGr (<5.62x10^9μm^3), and then gestation length (GstLth) becoming an important contributor in species with a large brain mass (>6.1g).



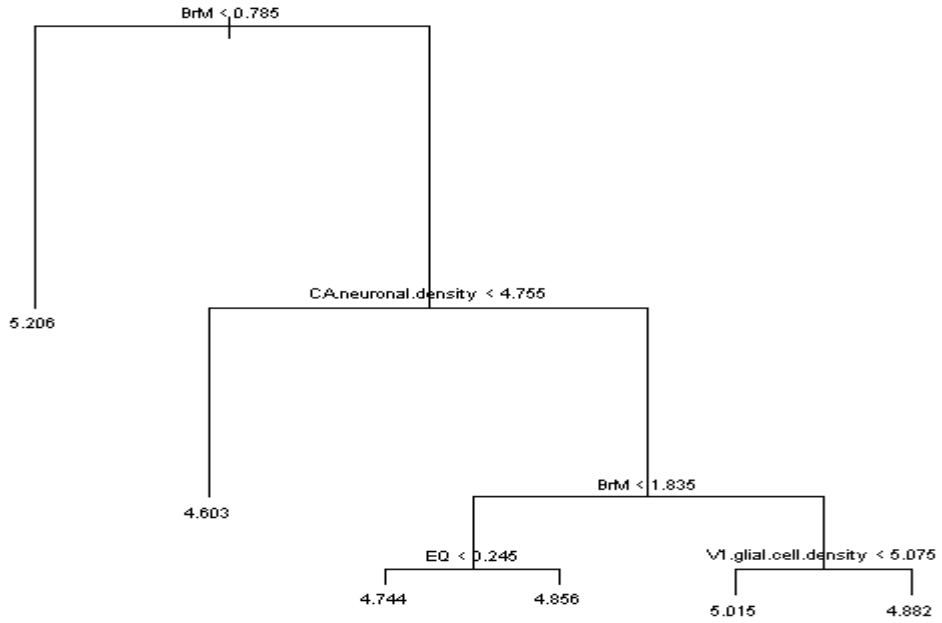
Supplemental Figure 1q: Recursive tree and relative importance metrics for determining glial cell density in V1 in Primates. The variables collectively explained 32.45% of the observed variance. The contribution of neuronal density in V1 (V1.n) is shown to be significantly greater than that of other variables for all metrics. The contribution of CrbGC is slightly, but still significantly, greater than that of other variables, except V1.n, for the metrics lmg, pmvd, and last. The 95% CI of the differential contributions of glial cell density in CA1-3 (CA.g) and both volumetric estimates of the dentate gyrus include zero for all metrics. The recursive tree shows brain mass (BrM) to be the foremost contributor to variance. In species with a large brain mass (>79g), V1.n becomes an important contributor. In species with a small brain mass (<79g), CrbGC becomes an important contributor, followed by gestation length in species with a small CrbGC (<3.31x10^{11} μm^3).

Relative importances for glial cell density in CA1-3 in Primates
(with 95% bootstrap confidence intervals)



R^2 = 51.14%, metrics are not normalized.

Recursive tree for glial cell density in CA1-3 in Primates



Supplemental Figure 1r: Recursive tree and relative importance metrics for determining glial cell density in CA1-3 in Primates. The variables collectively explained 51.14% of the observed variance. The contribution of neuronal density in CA1-3 (CA.n) is shown to be significantly greater than that of other variables for all metrics. The contribution of gestation length (GstLth) is shown to be significantly greater than that of other variables, except CA.n, for metrics pmvd and last. The recursive tree shows brain mass to be the foremost contributor to variance in glial cell density in CA1-3, followed by CA.n in species with large brains (>6.1g). Glial cell density in V1 becomes an important contributor at a terminal node in species with high neuronal density (>46885cells/mm^3) small brains (>68g).