4.21 The Evolution of Neuron Types and Cortical Histology in Apes and Humans

C C Sherwood, Kent State University, Kent, OH, USA
P R Hof, Mount Sinai School of Medicine, New York, NY, USA
© 2007 Elsevier Inc. All rights reserved.

4.21.1 Introduction
4.21.1.1 Evolutionary History of the Hominoids 2
4.21.1.2 History of Studies Concerning Hominoid Cortical Histology 3

4.21.2 Comparative Anatomy of the Cerebral Cortex
4.21.2.1 Topology of Cortical Maps 4
4.21.2.2 Architecture of the Cortex 4
4.21.2.3 Primary Visual Cortex 5
4.21.2.4 Auditory Cortex 8
4.21.2.5 Primary Motor Cortex 10
4.21.2.6 Inferior Frontal Cortex 12
4.21.2.7 Prefrontal Cortex 13
4.21.2.8 Anterior Cingulate Cortex 14

4.21.3 Patterns of Cortical Organization in Hominoids
4.21.3.1 The Emergence of Cell Types and their Distribution 15
4.21.3.2 The Evolution of Cortical Asymmetries 15
4.21.3.3 How much Variation in Cortical Architecture can be Attributed to Scaling versus Specialization? 17
4.21.3.4 Genomic Data Provide Insights into Cortical Specializations 18
4.21.3.5 On the Horizon 19

Glossary

Allometry
Many biological traits scale with overall size in a nonlinear fashion. Such allometric scaling relationships can be expressed by the power function: \( Y = bX^a \). The logarithmic transformation of the allometric scaling equation yields: \( \log Y = \log b + a \log X \). The exponent of the power function becomes the slope of the log-transformed function. The slope of this line can then be interpreted in terms of a biological scaling relationship between the independent and dependent variable. Positive allometry refers to a scaling relationship with an exponent that is greater than 1, which means that the structure in question grows disproportionately larger or more numerous with increases in the size of the reference variable. Negative allometry refers to a scaling relationship with an exponent that is less than 1, which means that the structure in question becomes proportionally smaller or less numerous with increases in the size of the reference variable.

Chemoarchitecture
The microanatomical organization of the cerebral cortex revealed by staining for biochemical substances using techniques such as immunohistochemistry and enzyme or lectin histochemistry.

Dysgranular Cortex
A type of cortex that has a weakly defined layer IV because it is variable in thickness. At points, layer IV seems to disappear because neurons from layers IIIc and Va intermingle.

Encephalization
A relative measure of a species’s brain size that represents the degree to which it is larger or smaller than expected for a typical animal of its body size.

Granular Cortex
A type of cortex that has a clearly identifiable layer IV.

Grey Level Index (GLI)
The proportion of an area of reference that is occupied by the projected profiles of all Nissl-stained elements. This value...
provides an estimate of the fraction of tissue that contains neuronal somata, glial cell nuclei, and endothelial nuclei versus neuropil. GLI values are highly correlated with the volume density occupied by neurons since glial and endothelial cell nuclei contribute only a very small proportion of the total volume.

A phylogenetic clade that includes lesser apes (gibbons and siamangs), great apes (orang-utans, gorillas, chimpanzees, and bonobos), and humans.

Cortical layers that are deep to granular layer IV, i.e., layers V and VI.

Morphologically, minicolumns appear as a single vertical row of neurons with strong vertical interconnections among layers, forming a fundamental structural and functional unit. The core region of the column contains the majority of the neurons, their apical dendrites, and both myelinated and unmyelinated fibers. A cell-poor region, containing dendritic arbors, unmyelinated axons, and synapses, surrounds each column.

The unstained portion of Nissl-stained tissue, which is comprised of dendrites, axons, and synapses.

Cortical layers that are superficial to granular layer IV, i.e., layers I, II, and III.

4.21.1 Introduction
4.21.1.1 Evolutionary History of the Hominoids

Apes and humans are members of the primate superfamily Hominoida (Figure 1). Molecular evidence indicates that the hominoid lineage split from the Old World monkeys about 25 Ma (Wildman et al., 2003). The extant representatives of this phylogenetic group include two families. The Hylobatidae comprises gibbons and siamangs, and the Hominidae includes great apes (i.e., orang-utans, gorillas, chimpanzees, and bonobos) and humans (Groves, 2001). Living hominoids are distinguished by a suite of shared derived traits that point to the key adaptations of this clade. These characters include lack of an external tail, modifications of the shoulder girdle and wrist for greater mobility, and stabilization of the lower back (Begun, 2003). These adaptations allow hominoids to exploit resources in small branches of trees by developing suspensory postures to distribute their body weight. This form of locomotion may have been particularly important in allowing certain species to increase body size. In addition, compared to other primates, hominoids have extended periods of growth and development (Schultz, 1969), an increased complexity of social interactions (Potts, 2004), and larger brains than would be expected for a monkey of the same body size (Rilling and Insel, 1999). The increased encephalization and associated life history elongation of these species suggest that cognitive flexibility and learning were important aspects of the hominoid adaptive complex, which allowed them to deal with locating ephemeral resources from fruiting trees and to negotiate more complicated relationships in fission–fusion societies (Potts, 2004).

Figure 1 Cladogram showing the phylogenetic relationships of living hominoids and other primates. Estimated divergence dates are taken from Goodman et al. (2005).
Although only a small number of hominoid species persist today, the fossil record reveals a diverse array of successive adaptive radiations of hominoids in the past. During the Miocene epoch, global climates were warm and humid, supporting dense forests and lush woodlands extending throughout the tropics and into northern latitudes. These environmental conditions were favorable for the diversification of arboreal specialists, such as the hominoids. In fact, hominoids were the most abundant type of anthropoid primate throughout the Miocene in Africa and Eurasia, occupying a range of different ecological niches (Begun, 2003). The earliest apes in the fossil record are characterized by hominoid-like dental morphology, but monkey-like postcranial anatomy. The best known of these early dental apes is the genus Proconsul from the Early Miocene (20–18 Ma) of East Africa. Proconsul africanus endocasts show a frontal lobe morphology that is similar to modern hominoids in being gyrified and lacking the simple V-shaped arcuate sulcus that is characteristic of most Old World monkeys (Radinsky, 1974). Furthermore, Proconsul africanus had a relatively larger brain than extant monkeys of comparable body size (Walker et al., 1983). Thus, increased encephalization and perhaps a greater degree of frontal lobe gyration were present early in the evolution of the hominoids.

With the emergence of arid climates in the transition to the Pliocene and the replacement of forests by mosaic habitats, the arboreal specializations of hominoids were less successful. The relatively slow reproductive rates of these taxa, moreover, made it difficult for many to endure habitat loss resulting from climate change and human encroachment in recent times (Jablonski et al., 2000). In the context of these dramatic environmental changes, one lineage adopted a new form of locomotion, upright bipedal walking, which would give rise to modern humans. Other hominoids, however, fared less well and today apes are restricted to a small number of endangered tropical forest species.

4.21.1.2 History of Studies Concerning Hominoid Cortical Histology

At the beginning of the twentieth century, neuroanatomists applied new histological staining techniques to reveal the architecture of the cerebral cortex in numerous species, including apes and humans (Campbell, 1905; Mauss, 1908; Brodman, 1909; Mauss, 1911; Beck, 1929; Filimonoff, 1933; Strasburger, 1937a, 1937b). In addition, with the advent of various techniques for tracing neuronal connectivity based on intracellular pathological changes subsequent to ablation, some studies also examined cortical projection systems in apes (Walker, 1938; Lassè and Wheatley, 1945; Kuypers, 1958; Jackson et al., 1969). After the 1950s, however, the amount of research directed toward understanding variation in the hominoid brain declined. There are three main reasons for this. First, the development of molecular biological techniques caused neuroscientists to focus on a small number of model species under the implicit assumption that many aspects of cortical structure are evolutionarily conserved. These ideas were further bolstered by claims of uniformity in the basic columnar architecture of the cerebral cortex (Rockel et al., 1980). Second, findings from the first systematic studies of great ape behavior from the field and laboratory were beginning to be appreciated (e.g., Kortlandt, 1962; Schaller, 1963; e.g., Yerkes and Learned, 1925; Yerkes and Yerkes, 1929). These studies contributed to a more sophisticated understanding of cognitive and emotional complexity in great apes and suggested that they deserve special protected status with respect to the ethics of invasive neurobiological experimentation. Third, the book Evolution of the Brain and Intelligence (Jerison, 1973) had an enormous influence on the direction of later research in comparative neuroanatomy. This book argued for the predictability of neuroanatomical structure from brain size and encephalization, suggesting that these metrics form the most significant contribution to species diversity in brain organization. Combined with the ready availability of comparative brain region volumetric data in primates and other mammals from the publications of Heinz Stephan, Heiko Frahm, George Baron, and colleagues (e.g., Stephan et al., 1981), a great deal of research effort has been expended in studies of allometric scaling and covariance of large regions of the brain (Finlay and Darlington, 1995; Barton and Harvey, 2000; de Winter and Oxnard, 2001). In contrast, much less attention has been paid to the possibility of phylogenetic variation in cortical histology (Preuss, 2000). Fortunately, advances in quantitative neuroanatomy and immunohistochemical staining techniques have opened new avenues of research to reveal interspecific diversity in the microstructure of hominoid cerebral cortex.

The history of studies of hominoid cortical histology, therefore, has resulted in two eras of research. The early era comprises several qualitative comparative mapping studies of the cerebral cortex based on cyto- and myeloarchitecture, with the occasional comment regarding species differences in the microstructure of homologous cortical areas.
While the neuroanatomical structure of one hominoid species in particular has been studied most extensively, it is well beyond the scope of this article to provide a comprehensive review of human cortical architecture. Here we focus explicitly on comparative studies of the histology of hominoid cerebral cortex, highlighting evidence concerning shared derived traits of hominoids in comparison to other primates, as well as indicating possible species-specific specializations. Hence, the studies reviewed in this chapter provide the most direct evidence currently available to delimit which aspects of cortical histology are uniquely human, which are derived for all hominoids, and which reflect the specializations of each species.

4.21.2 Comparative Anatomy of the Cerebral Cortex

4.21.2.1 Topology of Cortical Maps

Total brain weight in hominoids ranges from approximately 90g in Kloss’s gibbons (Hylobates klossii) to 1,400g in humans (Homo sapiens) (Table 1). While there is a large range of variation among hominoids in total brain size, mapping studies of the cortex (Figure 2) generally agree that the location of the primary sensory and motor areas are similar across species (Grünbaum and Sherrington, 1903; Campbell, 1905; Mauss, 1908; Brodmann, 1909; Mauss, 1911; Leyton and Sherrington, 1917; Beck, 1929; Bailey et al., 1950; Freuss et al., 1999; Hackett et al., 2001; Bush and Allman, 2004a, 2004b; Sherwood et al., 2004b). In particular, the primary visual cortex lies within the banks of the calcarine sulcus. Primary auditory cortex is located on the posterior superior plane of the superior temporal gyrus, usually comprising the transverse gyrus of Heschl in great apes and humans. Primary somatosensory cortex is found within the posterior bank of the central sulcus and extends on to the postcentral gyrus. Primary motor cortex is located mostly on the anterior bank of the central sulcus. One notable difference is the fact that primary visual cortex extends to only a very small portion of the lateral convexity of the occipital lobe in humans, whereas a much larger part of the lateral occipital lobe is comprised of striate cortex in apes (Zilles and Rehkämper, 1988; Holloway et al., 2003). This is because the primary visual cortex in humans is 121% smaller than expected for a primate of the same brain size (Holloway, 1996). Other higher-order areas, particularly within the frontal cortex, have also been shown to occupy similar locations across these species (Strasburger, 1937a, 1937b; Semendeferi et al., 1998; Semendeferi et al., 2001; Sherwood et al., 2003a).

4.21.2.2 Architecture of the Cortex

The general histological architecture of the neocortex in hominoids shares many features in common...
with other primates and mammals in general, such as a fundamental six-layered and columnar organization (Mountcastle, 1998). Compared to other mammals of similar brain size, however, the cerebral cortex of hominoids is reported to have a relatively low density of glial cells and a greater variety of neuron soma sizes (Haug, 1987).

Astroglia of the cerebral cortex in great apes, as revealed by immunohistochemistry for glial fibrillary acidic protein (GFAP), resemble other primates in forming long, radially oriented interlaminar processes spanning supragranular cortical layers (Colombo et al., 2004). This configuration may be unique to primates, as GFAP staining in the cortex of other mammals appears distinctly different, comprising a network of stellate astroglial somata with short, branching processes (Colombo, 1996; Colombo et al., 2000; Colombo and Reisin, 2004).

Comparison of mammalian brains indicates that the surface area of the cerebral sheet can vary by more than five orders of magnitude, while the thickness of the cortex varies by less than one order of magnitude (Allman, 1990). Accordingly, evolutionary changes in the size of the cerebral cortex have occurred primarily in the tangential dimension, while the vertical dimension of the cortex may be more constrained by the development of columnar units (Rakic, 1988, 1995). Nonetheless, the cortical sheet does tend to display increased thickness in mammals with larger brains (Hofman, 1988). Due to these scaling trends, hominoids have thicker cortices than other smaller-brained primates and homologous cortical areas in humans tend to be thicker than in apes (Figure 3).

With the relative ease of establishing homology among the primary sensory and motor cortical areas on the basis of cytoarchitecture and topology, several studies have compared the microstructure of these areas among different hominoid species (reviewed below). On the whole, the cytoarchitecture of homologous cortical areas shows only subtle differences across hominoid species. Indeed, an early quantitative comparative analysis of the cytoarchitecture of primary cortical areas (areas 3, 4, 17, and 41/42), found marked similarities among species (orang-utans, gorillas, chimpanzees, and humans) in terms of the relative thickness of different layers and the proportion of neuropil in each layer (Zilles and Rehkmper, 1988). Only minor differences were noted, such as greater relative thickness of layer III in primary somatosensory cortex (area 3) in humans and gorillas, an increase in the proportion of neuropil in layers V and VI of area 3 in orang-utans, and a relatively thicker layer IV of primary auditory cortex (area 41/42) in orang-utans. These results were interpreted to corroborate the qualitative observations of Campbell (1905) and Brodmann (1909), indicating that there are not any substantial differences between humans and apes in the cytoarchitecture of these primary cortical areas. The study by Zilles and Rehkmper (1988), however, was based on small samples, which did not permit statistical evaluation of species differences. More recent studies using larger samples, different staining techniques, and more refined quantitative methods have revealed interesting phylogenetic differences among hominoids in cortical histological structure.

### 4.21.2.3 Primary Visual Cortex

Important modifications of primary visual cortex (Brodmann’s area 17) histology, particularly of the...
thalamic recipient layer IV, have taken place at several points in the evolution of hominoids. Distinct parallel ascending fiber systems arising from retinal ganglion cells project to the lateral geniculate nucleus (LGN) of the thalamus. The M-type retinal ganglion cells give rise to the magnocellular channel, which is involved in the analysis of motion and gross spatial properties of stimuli. The P-type ganglion cells process visual information with high acuity and color sensitivity, and project to parvocellular layers of the LGN. In the geniculostriate component of these parallel pathways, different systems derive from distinct portions of the

Figure 2 Parcellation maps of the cerebral cortex of apes. Chimpanzee (Pan troglodytes) cortical maps reproduced from (a) Campbell (1905) and (b) Bailey et al. (1950). Orang-utan (Pongo pygmaeus) cortical maps reproduced from (c) Campbell (1905) and (d) Mauss (1908, 1911) compiled in Zilles and Rekämper (1988).
LGN and synapse within separate sublayers of layer IV in primary visual cortex. The complexity of segregated geniculostriate projects is reflected in the development of at least three subdivisions of layer IV in primates as demarcated by Brodmann (1909). Two cell-rich layers, IVA and IVC, are separated by a cell-poor layer IVB, which contains a dense plexus of myelinated axons known as the stria of Gennari. Neurons in the magnocellular layers of the LGN project to the upper half of layer IVC. Neurons in the parvocellular layers of the LGN project to layer IVA.

The chemoarchitecture of layer IVA is markedly different in hominoids compared to other primates (Figure 4). In most monkeys, except the nocturnal owl monkey, there is a dense band of cytochrome oxidase (CO)-rich staining in layer IVA (reviewed in Preuss et al., 1999), reflecting high levels of metabolic activity within this sublayer. However, in the hominoid species examined to date (orangutans, chimpanzees, and humans), intense CO staining in layer IVA is absent, suggesting that the direct parvocellular-geniculate projection to layer IVA was either reduced or more dispersed to include both layers IVA and IVB in the last common ancestor of this phylogenetic group (Preuss et al., 1999; Preuss and Coleman, 2002). Primary visual cortex of great apes and humans is further distinguished from monkeys in having increased staining of CB-immunoreactive (-ir) interneurons and neuropil in layer IVA (Preuss and Coleman, 2002).

Layer IVA of primary visual cortex in humans exhibits additional modifications to the basic hominoid plan described above. In humans, a meshwork pattern is observed in which compartments of neuropil that stain intensively for Cat-301 and nonpyramidal NPNFP-ir cells, and neurites alternate with bands of high densities of CB-ir interneurons (Preuss and Coleman, 2002). These changes in human primary visual cortex have been interpreted to reflect a closer association of this layer to M-pathway inputs than observed in any other primates. The functional implications of these histological changes are unclear; however, it has been suggested that these alterations are related to specializations in humans for the visual perception of rapid orofacial gestures in speech (Preuss and Coleman, 2002).

Another distinctive feature of primary visual cortex organization in many primates is ocular dominance columns, which correspond to the horizontal segregation of inputs from the two retinas to
different compartments in layer IV of primary visual cortex. Ocular dominance columns have been anatomically demonstrated in Old World monkeys, humans, and some other primates, such as the New World spider monkey and the strepsirrhine galago (reviewed in Allman and McGuinness, 1988). A similar pattern of alternating patches of ocular representation within primary visual cortex has been described in a chimpanzee after monocular injection of a transneuronal tritiated tracer substance (Tigges and Tigges, 1979). It is worth noting, however, that this study revealed geniculate projections to layer IVC, but not to layer IVA, as is observed in monkeys.

Large pyramidal neurons, which are found at the boundary between layers V and VI, called Meynert cells, are prominent in the primary visual cortex of primates, and their soma size displays interspecific variation (Figure 5) (Sherwood et al., 2003c). These cells can be distinguished as a unique subtype on the basis of their morphology and connectivity. Their thick axon collaterals project to both area MT/V5 and the superior colliculus, suggesting that these cells are involved in processing visual motion (Fries et al., 1985; Movshon and Newsome, 1996; Livingstone, 1998). In a comparative study, Meynert cell somata were found to be on average 2.8 times larger than other layer V pyramidal neurons across a range of primates (Sherwood et al., 2003c). Because the basal dendrites and axon collaterals of Meynert cells extend horizontally in layers V and VI to integrate information and facilitate responses across widespread areas of visual space, interspecific variation in Meynert cell size appears to be largely constrained by their function in the repetitive stereotyped local circuits that represent the retinal sheet in primary visual cortex. In the context of the general scaling patterns of Meynert cells, it is interesting that soma volumes of these neurons fit closely with predictions among humans (2.84 times larger than neighboring pyramidal cells) and gorillas (2.98 times), whereas they are relatively large in chimpanzees (3.78 times) and relatively small in orang-utans (1.94 times). These differences in neural organization for the processing of visual motion may relate to socioecological differences among these apes. Because wild chimpanzees engage in aggressive incursions into the territory of neighboring groups (Watts and Mitani, 2001) and hunt highly mobile prey such as red colobus monkeys (Watts and Mitani, 2002), we speculate that relatively large Meynert cells evolved in this species to enhance detection of visual motion during boundary patrolling and hunting. In contrast, relatively small Meynert cells in orang-utans may relate to the fact that these apes are solitary, large-bodied, committed frugivores (van Schaik and van Hooff, 1996), which allows them to maintain low levels of vigilance for motions of predators, competitors, and food items.

4.21.2.4 Auditory Cortex

There are two parallel thalamocortical projections from the medial geniculate nucleus (MGN) to the superior temporal cortex of primates. Neurons in the ventral division of the MGN supply a tonotopic projection to the core region of auditory cortex (Brodmann’s areas 41 and 42). Neurons in the dorsal and medial divisions of the MGN project to areas surrounding the core. The core region of auditory cortex has been identified in macaques, chimpanzees, and humans as a discrete architectural zone as compared to the surrounding belt cortex (Hackett et al., 2001). The core can be recognized by a broad layer IV that receives a dense thalamic projection, heavy myelination, and intense expression of acetylcholinesterase (AChE), CO, and PV in the neuropil of layer IV. In macaques, the relatively high density of cells and fibers makes the auditory cortex core appear structurally homogeneous as compared to the hominoids. In contrast, the medial and lateral domains of the core region of auditory cortex are more clearly differentiated in humans and chimpanzees because of the lower packing density of structural elements. Additionally, the network of small horizontal and tangential myelinated fibers in layer III appears most complex in humans, intermediate in chimpanzees, and least elaborate in macaques.

The auditory core region is enveloped by several higher-order belt and parabelt fields (Figure 6). The

Figure 5 The location and morphology of Meynert cells in an orang-utan (Pongo pygmaeus). Meynert cells are located at the boundary between layers V and VI, as indicated by the arrow in the Nissl-stained section (a). The morphology of Meynert cells as revealed by immunostaining for NPNFP with Nissl counterstain is shown (b). Scale bar (a) = 250 μm. Scale bar (b) = 50 μm.
The comparative anatomy of one particular region of auditory association cortex has been studied most extensively. In humans, Wernicke’s area, a region important for the comprehension of language and speech, is located in the posterior superior temporal cortex. Gross anatomic observations indicate that asymmetries similar to humans are present in the superior temporal lobe of non-human primates, such as leftward dominance of the planum temporale in great apes (Gannon et al., 1998; Hopkins et al., 1998) and a longer left sylvian fissure in many anthropoid species (LeMay and Geschwind, 1975; Yeni-Kmschian and Benson, 1976; Heilbroner and Holloway, 1988; Hopkins et al., 2000).

Several investigations have examined the microstructure of the cortical area most closely associated with Wernicke’s area. Area Tpt (Galaburda et al., 1978) or area TA1 (von Economo and Koskinas, 1925) comprises a portion of posterior Brodmann’s area 22 located on the upper bank of the superior temporal gyrus and sometimes extending to part of the parietal operculum and the convexities of the temporal and parietal lobes (Galaburda et al., 1978). This area represents a transition between auditory association cortex and cortex of the inferior parietal lobule (Shapleske et al., 1999). Cortex with the cytoarchitectural characteristics of area Tpt has been described in galagos, macaques, chimpanzees, and humans (Galaburda and Pandya, 1982; Preuss and Goldman-Rakic, 1991; Buxhoeveden et al., 2001a, 2001b). The microstructure of area Tpt in these primates is distinguished by a eulaminate appearance, with a poorly defined border of layer IV due to the encroachment of pyramidal cells in adjacent layers IIIc and Va, and an indistinct border between layers IV and V due to curvilinear columns of neurons that bridge the two layers (Galaburda and Sanides, 1980).

There are differences among rhesus monkeys, chimpanzees, and humans in the details of minicolumn structure in area Tpt. In the left hemisphere, area Tpt of humans has wider minicolumns as compared to macaques or chimpanzees, whereas the width of minicolumns is similar in the non-human species (Buxhoeveden et al., 2001b). These findings suggest that wider minicolumns in human area Tpt...
may be a species-specific specialization that allows for more extensive neuropil space containing interconnections among neurons.

The microstructure of area Tpt has also been shown to be asymmetric in humans, possibly as a neural substrate of hemispheric dominance in the cerebral representation of language. Long-range intrinsic connections within area Tpt labeled in postmortem brains with lipophilic dyes have revealed greater spacing between interconnected patches in the left hemisphere compared to the right (Galuske et al., 2000). Furthermore, left area Tpt has a greater number of the largest pyramidal cells in layer III, known as magnopyramidal cells, that give rise to long corticocortical association projections (Hutsler, 2003). In addition, AChE-rich pyramidal cells display greater cell soma volumes in the left hemisphere despite lacking asymmetry in number (Hutsler and Gazzaniga, 1996). In humans, left area Tpt has also been shown to contain a greater amount of neuropil and axons with thicker myelin sheaths (Anderson et al., 1999). Of particular significance, a comparative analysis of area Tpt found that only humans, but not rhesus macaques or chimpanzees, exhibit left dominant asymmetry in area Tpt, with wider minicolumns and a greater proportion of neuropil (Buxhoeveden et al., 2001a).

4.21.2.5 Primary Motor Cortex

The primary motor cortex (Brodman's area 4) has a distinctive cytoarchitectural appearance in primates (Geyer et al., 2000; Sherwood et al., 2004b), containing giant Betz cells in the lower portion of layer V, low cell density, large cellular sizes, an indistinct layer IV, and a diffuse border between layer VI and the subjacent white matter (Figure 7a). In humans, the region of primary motor cortex that corresponds to the representation of the hand exhibits interhemispheric asymmetry in its cytoarchitectural organization. Concomitant with strong population-wide right handedness in humans, most postmortem brains display a greater proportion of neuropil volume in the left hemisphere of this part of primary motor cortex (Amunts et al., 1996). Interestingly, brains of captive chimpanzees (Hopkins and Cantalupo, 2004) and capuchin monkeys (Phillips and Sherwood, 2005) show humanlike asymmetries of the hand region of the central sulcus that are correlated with the direction of individual hand preference. However, the histology of primary motor cortex in non-human primates has not yet been examined for asymmetry (see 00021).

While the cytoarchitectural organization of primary motor cortex is generally similar across species, interspecific differences have been described. The cytoarchitecture of the region corresponding to orofacial representation of primary motor cortex in several catarrhine species (long-tailed macaques, anubis baboon, orang-utans, gorillas, chimpanzees, and humans) was analyzed using the Grey Level Index (GLI) method (Sherwood et al., 2004b). Compared to Old World monkeys, great apes and humans displayed an increased relative thickness of layer III and a greater proportion of neuropil space. A stereologic investigation of NPNFP and calcium-binding protein-ir neurons was also conducted in this same comparative sample (Sherwood et al., 2004a). Primary motor cortex in great apes and humans was characterized by a greater percentage of neurons enriched in NPNFP and PV compared to the Old World monkeys (Figure 8). Conversely, the percentage of CB- and CR-ir neuron subtypes did not significantly differ among these species. These modifications of particular subsets of neuron types might contribute to the voluntary dexterous control of orofacial muscles exhibited in the vocal and gestural communication of great apes and humans. Enhancement of PV-ir interneuron-mediated lateral inhibition of cell columns may enhance specificity in the recruitment of
The giant Betz cells are found in the lower half of Figure 8 (Figure 7b) (soma at several locations around its surface) number of primary dendritic shafts that leave the layer V of primary motor cortex and possess a large size (relatively enlarged with increases in brain and body volumes in the region of hand representation of primates revealed that these cell subtypes become larger with increasing brain size. Due to these scaling trends, among hominoids Betz cells are relatively largest in humans (10.96 times larger than neighboring pyramidal cell), then gorillas (8.37 times), chimpanzees (7.02 times), and orang-utans (6.51 times).

Specializations of biochemical phenotypes are known for certain regionally restricted subsets of pyramidal neurons. Although calcium-binding proteins are expressed transiently during prenatal and early postnatal development (Moon et al., 2002; Ulfig, 2002), their expression in pyramidal neurons of adult mammals is more limited. Neurons expressing the calcium-binding proteins – CB, CR, and PV – are thought to have relatively high metabolic rates associated with fast repolarization for multiple action potentials (Baimbridge et al., 1992). While such calcium buffering mechanisms are most commonly associated with GABAergic interneurons, the presence of calcium-binding proteins in pyramidal cells might reflect a neurochemical specialization for higher rates of activity. In this context, it is interesting that faint CR immunoreactivity is observed in isolated medium- and large-size layer V pyramidal neurons in primary motor cortex of great apes and humans, but not in macaques or baboons (Hof et al., 1999; Sherwood et al., 2004a). PV-ir pyramidal neurons are also very rarely observed in the neocortex of mammals (see 00055). However, large layer V pyramidal neurons, including Betz cells, have been reported to express PV immunoreactivity in primary motor cortex of humans (Nimchinsky et al., 1997; Sherwood et al., 2004a). Evidence concerning the existence of PV-ir pyramidal neurons in other non-human primates is somewhat contradictory. In one study, PV-ir pyramidal neurons were observed in primary motor and somatosensory cortices of galagos and macaques (Preuss and Kaas, 1996). Another study, however, failed to label PV-ir pyramidal cells in macaques (DeFelipe et al., 1989), probably due to methodological discrepancies among experiments. A comparative study of primary motor cortex using the same different muscle groups for dynamic modulation of fine orofacial movements (Scheiber, 2001). Increased proportions of NPNFP-ir pyramidal cells, on the other hand, may be a correlate of greater descending cortical innervation of brainstem cranial motor nuclei by heavily myelinated axons to allow for more voluntary control (Kuypers, 1958).

The giant Betz cells are found in the lower half of layer V of primary motor cortex and possess a large number of primary dendritic shafts that leave the soma at several locations around its surface (Figure 7b) (Braak and Braak, 1976; Scheibel and Scheibel, 1978; Meyer, 1987). They are largest and most numerous in the cortical representation of the leg, where axons project farther along the corticospinal tract to reach large masses of muscles (Laszek, 1948; Rivara et al., 2003). Betz cells are strongly immunoreactive for NPNFP among humans, great apes, and Old World monkeys (Sherwood et al., 2004a). An analysis of scaling of Betz cell somata volumes in the region of hand representation of primates revealed that these cell subtypes become relatively enlarged with increases in brain and body size (Sherwood et al., 2003c). At larger sizes, there is an increase in the distance to the spinal representation of target muscles and a greater number of less densely distributed corticospinal neurons (Nudo et al., 1995). In larger brains and bodies, Betz cell axons need to become thicker to maintain conduction speed to reach more distant targets in the spinal cord. Accordingly, Betz cells are scaled to global connectivity constraints and therefore increase in somatic volume in a manner that is correlated with brain size. Due to these scaling trends, among hominoids Betz cells are relatively largest in humans (10.96 times larger than neighboring pyramidal cell), then gorillas (8.37 times), chimpanzees (7.02 times), and orang-utans (6.51 times).
Considering the preponderance of left hemisphere dominance control of language in humans, several studies have examined the cortex of the inferior frontal gyrus in humans for microstructural asymmetries. Using GLI profile analysis methods to quantify regional variation in cytoarchitecture, area 44 has been shown to display left dominance in terms of volume and an increased proportion of neuropil space, whereas area 45 does not show a consistent direction of asymmetry (Amunts et al., 1999). In addition, the total length of pyramidal cell dendrites is longer in the left opercular region of the inferior frontal gyrus due to a selective increase in the length of higher-order segments (Scheibel et al., 1985). Using different methods, another study examined asymmetries in only magnopyramidal cells in layer III of area 45 and found total dendritic length, dendritic complexity (numbers of branches and maximal branch order), and spine densities to be greater in the right (Hayes and Lewis, 1996). In area 45, AChE-positive layer III magnopyramidal cells have larger somata in the left hemisphere, despite lacking asymmetry in their density (Hayes and Lewis, 1995; Garcia et al., 2004).

While asymmetries of the inferior frontal cortex are well established in humans, the condition of non-human primates is less clear. Although population-level leftward asymmetry of the fronto-orbital sulcus, a portion of the inferior frontal gyrus, has been reported in great apes (Cantalupo and Hopkins, 2001), it remains to be known whether humanlike microstructural asymmetries are present...
in the inferior frontal cortex of these species. In humans and chimpanzees, the borders of areas 44 and 45 have been shown to correspond poorly with external sulcal landmarks (Amunts et al., 1999; Sherwood et al., 2003a). Thus, determination of whether asymmetries are evident in regional volumes and intrinsic circuitry of areas 44 and 45 of great apes will require histological studies.

4.21.2.7 Prefrontal Cortex

While it has been a popular notion that human cognitive abilities are associated with disproportionate enlargement of the frontal or prefrontal cortex, recent data show that the human frontal cortex is no larger than expected for a hominoid of the same brain size (Semendeferi et al., 1997; 2002). Furthermore, progressive increase in the relative size of the frontal cortex accompanies enlarging brain size for primates in general, with hominoids simply continuing this scaling trend (Bush and Allman, 2004a) (see 00061, 00066, 00081). At present, the comparative quantitative data available concerning the volume of specific prefrontal cortical areas in hominoids are scanty, representing only areas 10 and 13 in one individual per species (Semendeferi et al., 1998, 2001). Taken together, however, it does not seem that these prefrontal areas are disproportionately enlarged in human beyond what is expected for a hominoid of the same brain size (Holloway, 2002). Nonetheless, quantitative cytoarchitectural analyses have shown that some prefrontal cortical areas differ in their histological organization among hominoid species.

Area 13 is a dysgranular field located in the posterior orbitofrontal cortex (Figure 10). This cortical area is remarkably integrative, receiving inputs from olfactory, gustatory, and visceral centers, as well as premotor, somatosensory, auditory, visual, and parahippocampal cortices (Carmichael and Price, 1995; Cavada et al., 2000). Damage to this region disrupts performance on tasks that require behavioral inhibition and causes impairments in emotional control (Fuster, 1998; Roberts and Wallis, 2000). In a study of the cytoarchitecture of area 13 across macaques and hominoids, several similarities were observed that suggest homology among these species (Semendeferi et al., 1998).

This cortical area is distinguished by a poorly defined layer IV, horizontal striations of cells in layers V and VI, large pyramidal cells in layer V, relatively thick infragranular layers as compared with supragranular layers, and greater neuropil space in supragranular layers as compared with deeper layers. Among hominoids, area 13 is located in the posterior portion of the medial orbital and posterior orbital gyri. This concords with the earlier description of an area labeled FF in the posterior orbitofrontal cortex of chimpanzees that seems to correspond to these cytoarchitectural features (Bailey et al., 1950).

While general similarities are found in the cytoarchitecture of area 13 of hominoids, quantitative analyses have identified some interspecific differences. For example, layer IV in orang-utans is relatively wide, making this cortex appear more similar to granular prefrontal cortex. Compared to other hominoids, area 13 in humans and bonobos occupies a small proportion of total brain volume.
volume and more cytoarchitectonic subdivisions occupy the orbitofrontal cortex adjacent to area 13. In contrast, area 13 of orang-utans is relatively large and thus occupies the majority of the orbitofrontal region.

Area 10 is a granular cortex that forms a part of the frontal pole in most hominoid species, including humans, chimpanzees, bonobos, orang-utans, and gibbons (Figure 11) (Semendeferi et al., 2001). This cortical area is involved in planning and decision-making (Fuster, 1998). Area 10 receives highly processed sensory afferents from corticocortical connections in addition to inputs from the mediodorsal nucleus of the thalamus, striatum, and many limbic structures (Öngür and Price, 2000). In hominoids, the cytoarchitecture of area 10 is characterized by a distinct layer II, a wide layer III with large pyramidal cells in its deep portion, a clearly differentiated granular layer IV, large pyramidal cells in layer Va, and a sharp boundary between layer VI and the white matter. Quantitative analyses reveal a similar pattern of relative laminar widths among humans, chimpanzees, and bonobos, such that the supragranular layers are relatively thick compared to the infragranular layers (Semendeferi et al., 2001). In contrast, the infragranular layers comprise a greater proportion of cortical thickness in the other hominoids. When GLI profile curves describing laminar variation in neuron volume densities are compared among taxa, apes and macaques follow a similar pattern with roughly equal GLI throughout the cortical depth. The proportion of neuropil space in layers II and III relative to infragranular layers, however, is greater in humans. Notably, Semendeferi et al. (2001) raise uncertainty regarding whether a homolog of area 10 is present in gorillas. In particular, the cortex of the frontal pole in gorillas has a prominent layer II and Va, features that are not found in macaques or other hominoids.

4.21.2.8 Anterior Cingulate Cortex

In layer Vb of anterior cingulate cortex (subareas 24a, 24b, and 24c), large spindle-shaped cells are found only in great apes and humans, to the exclusion of hylobatids and other primates (Nimchinsky et al., 1999). These neurons have a very elongate, gradually tapering, large soma that is symmetrical about its vertical and horizontal axes (Figure 12). This distinctive somatic morphology arises from the presence of a large apical dendrite that extends toward the pial surface, as well as a single large basal dendrite that extends toward the underlying white matter, without any other dendrites branching from the basal aspect of the cell. These unique neurons are also substantially larger in size than other neighboring pyramidal cells. Interestingly, spindle neurons increase in soma size, density, and clustering from orang-utans to gorillas, chimpanzees, bonobos, and humans. Furthermore, spindle-shaped neurons have been observed in layer Vb of area 24b in a fetal chimpanzee (E 224), indicating that this specialized projection cell type differentiates early in development (Hayashi et al., 2001). Notably, neurons with a spindle phenotype also have a phylogenetically restricted distribution within another region, the frontoinsular cortex. Spindle cells are found in layer V in the frontoinsular cortex only in humans and African great apes (i.e., gorillas, chimpanzees, and bonobos), being far

Figure 11 The cytoarchitecture of area 10 in hominoids. Scale bar = 500 μm. Modified from Semendeferi et al. (2001).
The restricted phylogenetic distribution of spindle-shaped cells and CR-ir pyramidal neurons in layer V of anterior cingulate cortex may reflect specializations of projection neurons in this region for a role in the control of vocation, facial expression, attention, the expression and interpretation of emotions, and autonomic functions (Nimchinsky et al., 1999; Allman et al., 2001; Hof et al., 2001). Of particular interest, in humans, CR-immunoreactive layer V pyramidal neurons are also present in the anterior paracingulate cortex (area 32) (Hof et al., 2001). The presence of this distinctive projection cell type in area 32 of humans is intriguing, considering that this cortical area has been found to be recruited in tasks that require theory of mind (Gallagher et al., 2000), which is the capacity to attribute mental states such as attention, intention, and beliefs to others and may be a cognitive capacity that is exclusive to humans (Tomasello et al., 2003).

4.21.3 Patterns of Cortical Organization in Hominoids

4.21.3.1 The Emergence of Cell Types and their Distribution

Particular cellular subtypes appear to have phylogenetically restricted distributions. It is interesting that among hominoids, the presence of these unique neuron phenotypes accords with the hierarchical nested structure of monophyletic taxa, suggesting that they are indicators of phylogenetic relationships (Table 2). For example, in all great apes and humans, spindle-shaped neurons are found in layer V of anterior cingulate cortex. Also in these taxa, CR-ir pyramidal cells are found in layer V of anterior cingulate cortex and primary motor cortex. In just African great apes and humans, layer V spindle-shaped neurons are found in frontoinsular cortex.

It is tempting to speculate that the evolution of each unique neuron type marks specializations of the cortical areas involved. In particular, the morphomolecular characteristics of these novel neuron types suggest that there have been modifications of specific efferent projections to facilitate high levels of activity or higher conduction velocity for outputs. The possibility that the great ape and human clade is distinguished by such specializations of projection cells is especially intriguing in light of recent hypotheses that intelligence among mammals is correlated with the rate of information processing capacity as represented by axonal conduction speed (Roth and Dicke, 2005). The presence of unique neuron classes in great apes and humans extends this hypothesis to suggest that specific cortical efferents located within behaviorally relevant circuits may be selectively modified. It is also significant that a common feature of these novel projection cells is their localization in layer V. This laminar distribution indicates that evolutionary modifications have been focused upon descending cortical control over targets in the brainstem and spinal cord.

4.21.3.2 The Evolution of Cortical Asymmetries

A substantial body of evidence shows that the human cerebral cortex expresses lateralization in the control of language and fine motor actions of the hand (Toga and Thompson, 2003). Asymmetries in histological structure have been demonstrated across cortical areas implicated in these processes in humans, including Broca’s area (areas 44 and 45),
Wernicke’s area (area Tpt), and the hand representation of primary motor cortex (area 4). Some authors have hypothesized that these anatomical asymmetries are exclusive adaptations of the human brain that are encoded genetically and comprise the chief evolutionary novelty in the speciation of modern humans (Crow, 2000; Annett, 2002).

An alternative view is that functional and anatomical lateralization may be a byproduct of increases in overall brain size (Ringo et al., 1994; Hopkins and Rilling, 2000). One cost of increasing brain size is that axons must propagate action potentials over a greater distance to communicate between the hemispheres (Harrison et al., 2002). While these delays in conduction can be overcome to some extent by increasing axon cross-sectional area and myelination (Changizi, 2001), the design problems associated with large brains ultimately may necessitate increased modularity of processing and more of an emphasis on local network connectivity (Kaas, 2000). In particular, as brains grow in size, the efficiency of interhemispheric transfer of information by long connections diminishes because costs, in terms of wiring space, dictate that axons cannot increase cross-sectional area sufficiently to keep pace with demands for processing speed (Abotiz and Montiel, 2003). Hence, it is expected that cortical processes in large brains, especially those that

Table 2  Phylogenetic distribution of some cortical histological traits

<table>
<thead>
<tr>
<th>Cortical area</th>
<th>Layer</th>
<th>Trait</th>
<th>Homo sapiens</th>
<th>Pan paniscus</th>
<th>Pan troglodytes</th>
<th>Gorilla gorilla</th>
<th>Pongo pygmaeus</th>
<th>Hylobates sp.</th>
<th>Macaca sp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary motor cortex</td>
<td>V</td>
<td>CR-ir pyramidal neurons</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>Primary motor cortex</td>
<td>V</td>
<td>PV-ir pyramidal neurons</td>
<td>++</td>
<td>?</td>
<td>++</td>
<td>?</td>
<td>++</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Primary motor cortex</td>
<td>III and V</td>
<td>NPNFP-ir pyramidal neurons</td>
<td>++</td>
<td>?</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Primary visual cortex</td>
<td>IVA</td>
<td>Dense CB-ir neurons and neuropil</td>
<td>+</td>
<td>?</td>
<td>++</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Auditory belt cortex</td>
<td>Layers III and V</td>
<td>AchE-stained pyramidal cells</td>
<td>++</td>
<td>?</td>
<td>++</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Vb</td>
<td>Spindle-shaped neurons</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Vb</td>
<td>CR-ir pyramidal neurons</td>
<td>+</td>
<td>?</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>Anterior paracingulate cortex</td>
<td>Vb</td>
<td>CR-ir pyramidal neurons</td>
<td>+</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>Frontoinsular cortex</td>
<td>Vb</td>
<td>Spindle-shaped neurons</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) Sherwood et al., 2004a
\(^b\) Preuss and Coleman, 2002
\(^c\) Hackett et al., 2001
\(^d\) Nimchinsky et al., 1999
\(^e\) Hof et al., 2001
\(^f\) Hakeem et al., 2004

+ = present; ++ = present and abundant in comparison to other species; – = absent
depend on rapid computations, will come to rely on specialized processing that is dominant in one hemisphere. Indeed, it has been shown that increasing brain size is accompanied by reduced hemispheric interconnectivity via the corpus callosum (Ringo et al., 1994; Olivares et al., 2001) and the development of more pronounced gross cerebral asymmetries among anthropoid primates (Hopkins and Rilling, 2000).

One consequence of lateralized hemispheric specialization of function may be divergence in the histological organization of homotopic cortical areas. Unfortunately, there is a surprising absence of data from non-humans concerning microstructural asymmetries in the homologues of Broca’s area, Wernicke’s area, and primary motor cortex. At present, the sole study of such histological asymmetry indicates that lateralization is not present in area Tpt of chimpanzees or macaques, while asymmetry of neuropil space and minicolumn widths are observed in humans (Buxhoeveden et al., 2001a).

Although this is an important finding, it should be kept in mind that there are many other aspects of microstructural organization that have been demonstrated to be asymmetric in the human cortex, such as distributions of cell volumes and dendritic geometry, which have yet to be investigated in other species. Thus, at the present time, there are still insufficient data to adequately resolve whether many of the observed microstructural asymmetries of the human cerebral cortex are unique species-specific adaptations that are related to language and handedness.

How much Variation in Cortical Architecture can be Attributed to Scaling versus Specialization?

Interpretation of interspecific differences in the histological structure of the cortex in hominoids requires parsing the source of this variation. Certainly a portion of it can be attributed to specific alterations of circuitry that generate behavioral differences among species. Another cause, however, may be the effects of allometric scaling. That is, as overall brain size changes, predictable changes occur in cell sizes, cell packing density, dendritic geometries, and other aspects of microstructure (Jerison, 1973; Striedter, 2005). Thus, with variation in brain size among hominoids, some of the observed interspecific differences may simply be the result of scaling to maintain functional equivalence and may not indicate any significant differences in computational capacities. For example, how can we know whether greater densities of AChE-stained neurons in the auditory belt of hominoids (Hackett et al., 2001) is of functional importance until we have developed a clearer understanding of the scaling principles that govern the distribution of AChE-enriched neurons in general? Hence, whenever possible it is best to evaluate phylogenetic variation in cortical histology from the perspective of allometric scaling. Accordingly, the case for declaring that a trait is a phylogenetic specialization is strengthened when it can be demonstrated that individual species depart from allometric expectations or that an entire clade scales along a different trajectory (e.g., grade shift).

It is well established that cortical neuron density varies among mammalian species. Across a large sample of mammals ranging from mouse to elephant, there is a negative correlation between cortical neuron density and brain size (Tower, 1954; Cragg, 1967; Haug, 1987; Prothero, 1997). Despite this broad trend, however, some evidence suggests that neuron densities may be higher in hominoids (gorilla, chimpanzee, and human) than expected for their brain size (Haug, 1987). It has also been shown that the fraction of the cortex that is comprised by neuropil space versus cell somata increases in a negative allometric fashion with greater brain size (Shariff, 1953; Tower, 1954; Bok, 1959; Tower and Young, 1973; Zilles et al., 1982; Armstrong et al., 1986; Haug, 1987). These empirical findings fit with a model predicting that a constant average percent interconnectedness among neurons cannot feasibly be maintained in the face of increasing gray matter volume, so the reach of processing networks cannot keep pace with brain size variation (Changizi, 2001).

Many of these theories concerning the scaling of network connectedness across brain size, however, were developed to explain variation in mouse to elephant comparisons. Are these predicted allometric relationships between neuron density, neuropil space, and brain size maintained when comparisons are restricted to the hominoids? Table 3 shows the results of stereologic estimates of neuron density and GLI from recent comparative studies of areas 4, 10, and 13 in hominoids. In each of these cortical areas, there is not a correlation between neuron densities or GLI and brain size. Therefore, the mammal-wide relationship between these parameters and brain size may not explain interspecific variance in interconnectedness within cortical areas of hominoids. This raises the interesting possibility that differences among hominoid species in these variables might instead correspond to functionally significant modifications in the organization of cortical interconnections.
Other aspects of network scaling in the cerebral cortex are less well understood. For example, there does not appear to be a correlation between brain size and the density of glial cells (Tower and Young, 1973; Haug, 1987). However, phylogenetic differences in glial cell densities have not yet been systematically examined using modern immunohistochemical markers to identify astrocytes and oligodendrocytes separately. Furthermore, questions regarding the scaling of subpopulations of interneurons and pyramidal cells have only begun to be addressed. Evidence suggests that the proportion of pyramidal neurons that are enriched in NPNFP may increase with brain size. In the orofacial representation of primary motor cortex, there is a striking increase in the percentage of neurons stained for NPNFP in larger-brained great apes and humans in comparison to smaller-brained Old World monkeys (Sherwood et al., 2004a).

Tsang and colleagues (2000) also found increasing NPNFP labeling in primary motor cortex across a sample including rats, marmosets, rhesus macaques, and humans. In addition, Campbell and Morrison (1989) found a larger proportion of NPNFP-ir pyramidal neurons, particularly in supragranular layers, in humans compared to macaque monkeys across several different cortical areas.

Interneuron subtypes, as revealed by labeling for calcium-binding proteins, appear to adhere to different scaling trends in anthropoid primates depending on the cortical area. For example, when regressed on total neuron density, the density of PV-ir neurons scales with negative allometry in the primary motor cortex and thus a greater proportion of PV-ir neurons is observed in hominoids compared to Old World monkeys (Sherwood et al., 2004a). In contrast, CB-ir neurons scale against total neuron density with positive allometry in areas V1 and V2, resulting in a smaller percentage of CB-ir interneurons in apes compared to monkeys in these areas (Sherwood et al., 2005). Further studies using allometric approaches to examine the scaling of different neuron subtypes will be necessary to elucidate phylogenetic specializations of cortical circuitry.

### 4.21.3.4 Genomic Data Provide Insights into Cortical Specializations

Recent studies of phylogenetic variation in gene sequences and expression provide additional insights into cortical specializations among hominoids. While most of these studies have been directed at determining the genetic basis for human neural uniqueness (Enard et al., 2002a; 2002b; Caceres et al., 2003; Dorus et al., 2004; Üdïn et al., 2004), some molecular data point to changes that occurred at earlier times in the hominoid radiation. For instance, all hominoids have evolved a novel biochemical mechanism to support high levels of glutamate flux in neurotransmission through the retroposition of the gene \textit{GLUD1} (Burki and Kaessmann, 2004). This duplicated gene, \textit{GLUD2}, which is unique to hominoids, encodes an isotype of the enzyme glutamate dehydrogenase that is expressed in astrocytes. All hominoid \textit{GLUD2} sequences contain two key amino acid substitutions that allow the GLUD2 enzyme to be activated in astrocytes during conditions of high glutamatergic neurotransmitter flux. Concordant with this evidence for alterations in the molecular machinery necessary for enhanced neuronal activity in apes, it has been shown that the gene encoding the

<table>
<thead>
<tr>
<th>Species</th>
<th>Area 4a GLI</th>
<th>Neuron density</th>
<th>Area 10b GLI</th>
<th>Neuron density</th>
<th>Area 13c GLI</th>
<th>Neuron density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homo sapiens</td>
<td>11.65</td>
<td>18,048</td>
<td>15.17</td>
<td>34,014</td>
<td>14.18</td>
<td>30,351</td>
</tr>
<tr>
<td>Pan troglodytes</td>
<td>13.19</td>
<td>22,177</td>
<td>17.52</td>
<td>60,468</td>
<td>18.63</td>
<td>50,686</td>
</tr>
<tr>
<td>Pan paniscus</td>
<td>–</td>
<td>–</td>
<td>15.87</td>
<td>47,300</td>
<td>14.62</td>
<td>54,783</td>
</tr>
<tr>
<td>Gorilla gorilla</td>
<td>8.76</td>
<td>24,733</td>
<td>20.10</td>
<td>78,182</td>
<td>18.55</td>
<td>42,400</td>
</tr>
<tr>
<td>Pongo pygmaeus</td>
<td>10.61</td>
<td>18,825</td>
<td>18.90</td>
<td>86,190</td>
<td>13.33</td>
<td>53,830</td>
</tr>
<tr>
<td>Hylabates lar</td>
<td>–</td>
<td>–</td>
<td>20.34</td>
<td>–</td>
<td>18.36</td>
<td>–</td>
</tr>
<tr>
<td>Macaca sp.</td>
<td>15.58</td>
<td>50,798</td>
<td>20.34</td>
<td>–</td>
<td>18.36</td>
<td>–</td>
</tr>
<tr>
<td>Papio anubis</td>
<td>14.85</td>
<td>33,661</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

In all studies, neuron densities were estimated by the optical dissector method.

\( ^a \) (Sherwood et al., 2003b; Sherwood et al., 2004b)

\( ^b \) (Semendeferi et al., 2001)

\( ^c \) (Semendeferi et al., 1998)
cytochrome c oxidase subunit 4-1 underwent rapid nonsynonymous evolution in the hominoid stem, followed by purifying selection in descendent lineages (Wildman et al., 2002). Because these nucleotide substitutions have functional consequences for the manner and rate at which electrons are transferred from cytochrome c to oxygen, it is likely that these modifications were selected to serve the needs of cells with high aerobic energy demands, such as neurons.

Also of significance, an alternative splice variant of neuropsin (type II) has originated in recent hominoid evolution (Li et al., 2004). Neuropsin is expressed in hippocampal pyramidal neurons and is involved in neuronal plasticity. The high incidence of polymorphisms in the coding region of this protein in gibbons and orang-utans, however, suggests that it may not be functional in these species. In contrast, the coding region of the type II splice form of neuropsin shows relatively little variation in gorillas, chimpanzees, and humans, signifying that it is maintained by functional constraint and that it might be involved in a molecular pathway important for learning and memory in these hominoids.

With respect to brain size, several genes that are involved in controlling the development of cerebral cortex size have undergone accelerated rates of sequence evolution in the hominoid lineage. The microcephalin gene shows an upsurge of nonsynonymous amino acid substitutions in a protein-coding domain of the last common ancestor of great apes and humans (Wang and Su, 2004). Additionally, the ASPM gene shows evidence of adaptive sequence evolution in all African hominoids (i.e., gorillas, chimpanzees, bonobos, and humans) (Kouprina et al., 2004).

These data put into phylogenetic context evidence that, in the lineage leading to humans, several genes important in the development, physiology, and function of the cerebral cortex show positive selection (Enard et al., 2002b; Dorus et al., 2004; Evans et al., 2004). Furthermore, findings from studies that have compared human and chimpanzee transcriptomes indicate that the human cerebral cortex is distinguished by elevated expression levels of many genes associated with energy metabolism (Caceres et al., 2003; Uddin et al., 2004), suggesting that levels of neuronal activity might be higher in humans compared to chimpanzees (Preuss et al., 2004). While the phenotypic correlates of many of these genetic changes await characterization by in situ hybridization and immunohistochemical studies, it is clear that intensified efforts at analyzing variation in the histological organization of the hominoid cerebral cortex will be necessary if there is any hope of understanding how such molecular differences translate into modifications of the computational capacities of cortical circuits.

### 4.21.3.5 On the Horizon

There remains an extraordinary amount to learn regarding the microstructure of the cerebral cortex of hominoids. Even the basic cytoarchitecture of many cortical areas, such as the posterior parietal cortex, inferior temporal cortex, posterior cingulate cortex, and premotor cortex, has not yet been explored using the methods of modern quantitative neuroanatomy. Moreover, there is not a single recent study of parcellation for any part of the cerebral cortex using chemoarchitectural staining techniques in apes. It will also be important to examine the scaling patterns that govern the distribution of neurochemically identified subsets of pyramidal neurons, interneurons, and glia across different cortical areas from a broad phylogenetic perspective in order to clearly distinguish network allometric scaling from phylogenetic specialization. Finally, determination of whether humanlike histological asymmetries of cortical areas important in language and control of the hand are present in other apes still requires systematic study. By taking seriously the task of understanding such species-specific neural adaptations, we stand to learn an extraordinary amount about the underlying substrates of the cognitive abilities of humans and our closest relatives.

### Acknowledgements

This work was supported by the National Science Foundation (BCS-0515484 and BCS-0549117), the Wenner-Gren Foundation for Anthropological Research, and the James S. McDonnell Foundation (22002078). The great ape brain materials were available from the Great Ape Aging Project, Cleveland Metroparks Zoo, and the Foundation for Comparative and Conservation Biology.

### Further Reading


References


b0435 Kaas, J. H. 2000. Why is brain size so important: design problems and solutions as neocortex gets bigger or smaller. *Brain Mind* 1, 7–23.


The Evolution of Neuron Types and Cortical Histology in Apes and Humans

Evolution of specialized pyramidal neurons in primate visual and motor cortex. *Brain Behav. Evol.* 61, 28–44.


