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The discovery of cerebral diversity: an unwelcome scientific revolution

Studies of mammalian and primate brain evolution have traditionally focused on changes in encephalization, that is, changes in brain size statistically adjusted to compensate for changes in body size, rather than on changes in the internal organization of the brain. There are some very sound reasons for stressing size. Mammals do indeed vary dramatically in absolute and relative brain size: at a given body weight, brain weight can vary more than five-fold across species (Stephan *et al.*, 1988). Moreover, brain size changes can have profound consequences for the developmental biology and ecology of mammalian taxa, because larger-brained taxa grow more slowly and live longer than do smaller-brained taxa of comparable body size (Sacher, 1982; Finlay & Darlington, 1995) and because brain tissue is energetically very demanding (Aiello & Wheeler, 1995). Conveniently, brain size is relatively tractable empirically, which is to say that one can measure it with reasonable precision in all sorts of living and extinct taxa, whereas the internal features of brain organization can be examined only with difficulty in extant taxa and not at all in extinct forms. Finally, there can be little doubt that variations in brain size are in some way related to variations in cognitive and behavioral abilities.

But in precisely *what* ways are brain size, cognition, and behavior related? Harry Jerison has ably articulated the view that encephalization serves as an index of general animal intelligence (see especially Jerison, 1961, 1973), and in doing so has provided the underpinning for modern brain allometry studies. His approach has not been universally embraced, however, Ralph Holloway (see especially Holloway, 1966a,b) being notable among those who have questioned whether there is a straightforward relationship between brain size and cognitive capacity, emphasiz-

ing instead that evolutionary changes in cognitive and behavioral capacities reflect reorganization of systems internal to the brain.

How one reckons the relative importance of size and reorganization in brain evolution depends on one's conception of mammalian brain structure and how that structure varies between mammalian groups. If the internal organization of the brain remains constant as brain size varies, or if brain organization changes in regular and predictable ways as brain size varies, then knowing a species' level of encephalization tells us something significant about the status of that species' brain relative to the brains of other species, because all species are regular variants of a common plan of brain organization. Under this view, it is reasonable to regard more encephalized animals as having more of some general information-processing substrate than less encephalized animals. If brains vary significantly in their internal organization, however, encephalization indices can not reasonably be considered as proxies for general cognitive ability across a wide variety of mammalian species. The task of understanding the brain organization of any one species becomes much more difficult, as does the business of relating brain to behavior and cognition.

The controversy over quantitative versus qualitative change did not begin with Jerison and Holloway: it goes back to the very beginnings of evolutionary biology and of the neurosciences (Preuss, 1993, 1995a). The proponents of quantity have generally held the upper hand. Darwin and Huxley strongly defended the idea that the human mind and brain are extensions of the minds and brains of our close relatives – that the difference between us and them are matters of degree rather than of kind (Huxley, 1863; Darwin, 1871). The consensus view among neuroscientists in the late 1800s and early 1900s seems to have been that brain evolution was mainly a matter of progressive encephalization and differentiation within the bounds of a common brain plan (Preuss, 1995a). The concept of differentiation was invoked because workers believed that in larger brains, one could distinguish more cell types, the cellular laminae of the cerebral cortex appeared to be more sharply defined, and one could distinguish more subdivisions (areas) of the cortex. It is important to appreciate that these neuroscientists did not necessarily regard the appearance of additional cell types, cellular strata, and areas, as tantamount to the evolution of new structural elements within the brain. Rather, these were regarded as the products of differentiation, by which was meant an unfolding of structural tendencies or potentialities latent in the basic

mammalian brain plan (see, for example, Elliot Smith, 1924, and Le Gros Clark, 1959). That is, as brains got bigger, existing components become more refined and better sorted out, but nothing new was added. This view of brain evolution accorded well with the popular view that the course of evolution was linear and progressive. Thus, the early neuroscientific literature is filled with references to the 'phylogenetic scale' and to 'higher' and 'lower' mammals, concepts that modern evolutionists regard as problematic. One gets little sense that there is a diversity of mammalian brain organization – that different groups of mammals (primates, rodents, cetaceans, and so forth) evolved their own distinctive specializations of brain organization (for a conspicuous exception, see Brodmann, 1909).

The view that the internal histological and connectional organization of mammalian brains are fundamentally conservative crystallized at an early point in the history of neuroscience, when knowledge of brain structure was quite rudimentary by modern standards. In the early 1970s there began a revolution in neuroscientific methodology that continues to this day. The fruits of this revolution include new techniques for studying the physiology and molecular biology of neurons, and – for the first time – reliable and sensitive methods for studying the connections between neurons. Our understanding of the structure of cerebral cortex, in particular, has been profoundly affected by these developments. Once regarded by some as a relatively homogenous neural net, today cerebral cortex is recognized as perhaps the most complex entity known to science. Moreover, since the cortex is the largest component of mammalian brains (Stephan *et al.*, 1981), undergoes enormous evolutionary changes in absolute and relative size, and provides much of the neural substrate for cognitive processing, cortical organization and its phyletic variations are matters of vital importance to students of brain evolution. How does our new and detailed understanding of the organization of cerebral cortex bear on the question of encephalization versus reorganization? The answer to this depends on what you read. If you read the neuroscience textbooks and review papers, you get the impression that there is very little variation in the internal organization of cerebral cortex, and that brain evolution must be mainly about size. A careful perusal of the primary literature, however, suggests that the cortex is a veritable hotbed of evolutionary reorganization.

Cortical organization and evolution: the doctrine of basic uniformity

In this section, I give a synopsis of mammalian cortical anatomy as it is presented in modern textbooks and review papers (for example, Eccles, 1984; White, 1988; Churchland & Sejnowski, 1992; Shepherd, 1994; Hendry, 1996), and then consider some contemporary ideas about cortical evolution. Cerebral cortex is a bilateral structure that caps the brainstem. It consists of a thin, outer shell of cells (the gray matter) overlying a mass of axons (the white matter) passing to and from the cortex. Cortex is divided into two broad regions, the neocortex (or isocortex) and the allocortex. Allocortex includes the hippocampus, olfactory cortex, and related regions situated along the margins of the cortical sheet. Neocortex, which makes up the largest part of the cerebral mantle in most mammals, includes regions devoted to vision, somatosensation, audition, equilibrium, motor cortex, and higher-order cognitive functions. The main subdivisions of the cortex are called *areas*. Cortical areas are distinguished from one another by their appearance in tissue stained for cell bodies ('cytoarchitecture') and for myelinated fibers ('myeloarchitecture'), as well as by their connections and functional properties. Neuroscientists do not yet have a complete accounting of cortical areas for any mammalian species, although there is reason to think that the number of cortical areas is phyletically variable. Cortical areas receive inputs from subcortical structures, the most numerous inputs arising from the thalamus. Groups of functionally related areas tend to be located close to one another and to form strongly interconnected networks. Cortex exerts its influence on behavior by means of projections to deep brain structures and to the spinal cord.

Cerebral cortex consists of a variety of neurons, which can be grouped broadly into pyramidal and non-pyramidal classes (Fig. 7.1). Pyramidal cells are generally large cells with a distinctive, elongated apical dendrite that extends towards the cortical surface, several basal dendrites, and a long axon that may branch repeatedly and which makes synaptic contacts that release an excitatory transmitter (glutamate or aspartate). Pyramidal cells are the main extrinsic cells of the cortex, giving rise to projections to distant cortical areas as well as to subcortical structures. Non-pyramidal cells are mainly intrinsic neurons (also known as interneurons or local-circuit neurons), with axons that synapse on cells close to the parent cell body. Non-pyramidal cells consist of both excitatory and inhibitory

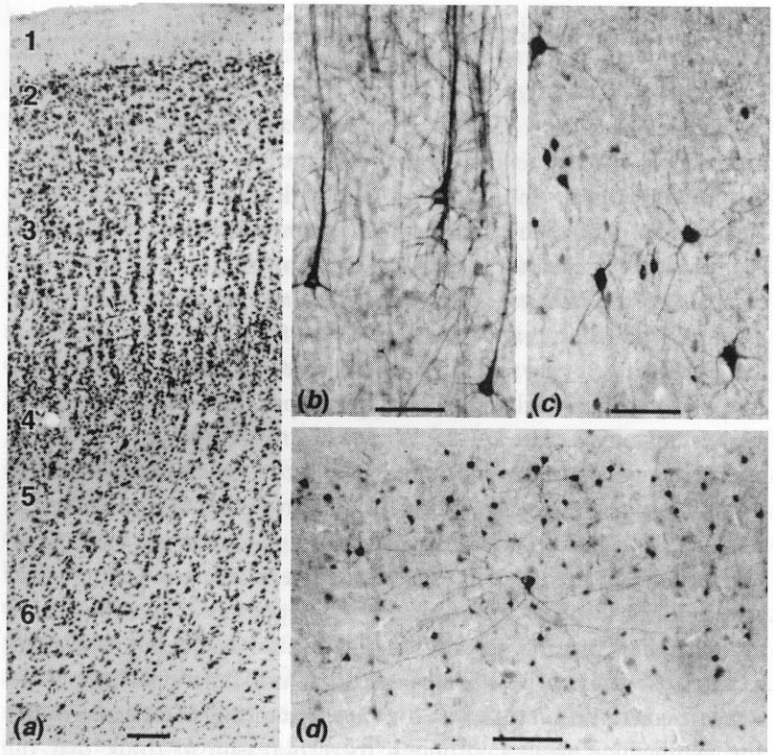

Fig. 7.1. At low magnification (*a*), the stratification of cortex into layers can be discerned, as in this Nissl-stained section from the extrastriate cortex of a chimpanzee. In this section, the clustering of cells into vertical aggregates or columns can also be seen (especially in layers 3, 4, and 5), although other cortical regions are not so obviously columnar. The Nissl stain only shows cell bodies; immunocytochemical techniques can often reveal more of the distinctive morphologies of cortical cell types. Pyramidal cells stained for neurofilament protein are shown in (*b*); the tall, broad apical dendrites and the finer basal dendrites of these cells are clearly visible in this preparation. Presumed inhibitory interneurons immunoreactive for parvalbumin and calbindin are shown in (*c*) and (*d*), respectively. Figs. 7.1 (*b*), (*c*), and (*d*), were taken from the motor cortex of a chimpanzee. Scale bars = 100 μm.

classes. The main excitatory cells are the so-called spiny stellate cells, upon which thalamic fibers synapse. Inhibitory interneurons, which express the transmitter γ-amino butyric acid (GABA), display a remarkable variety of morphological, connectional, and biochemical phenotypes (Figs. 7.1*c*,*d*). Interneurons are subdivided into classes based on differences in morphology and biochemistry. Much current interest focuses on identifying the morphological and connectional properties of neurons that

express specific calcium-binding proteins (CBPs; especially parvalbumin, calbindin, or calretinin), cells that are readily stained with immunocytochemical techniques (Andressen *et al.*, 1993). Calcium-binding proteins regulate intracellular calcium concentrations, and thereby influence cellular excitability; thus, cells that express different calcium-binding proteins may have different physiological properties (Baimbridge *et al.*, 1992).

Cortical neurons are arrayed through the thickness of the gray matter in several more-or-less distinct layers (laminae), which are distinguished on the basis of cell size and packing density. In the neocortex, most workers enumerate six layers (following Brodmann, 1909), although subdivisions of these layers can be recognized in some cortical areas. Inputs to the cortex tend to be layer specific. For example, in many mammals, a major afferent projection from the thalamus terminates in layer 4 and deep layer 3 of neocortex (Fig. 7.2). Afferents from other sources terminate in other layers. Similarly, projections from the cortex to sites in other parts of the brain tend to arise from layer-specific populations of pyramidal cells. For example, the projections to the spinal cord arise from large pyramidal cells, the cell bodies of which reside in layer 5. Projections to other neocortical areas can arise from any combination of the layers that contain pyramidal cells, namely layers 2, 3, 5, and 6.

Within a neocortical area, the flow of information has a strong vertical component. There are strong connections between neurons and the cells located immediately above and below them, and indeed in some cortical regions, examination of sections stained to show cell bodies suggest that cells are grouped into vertical clusters that span the thickness of the cortex (Fig. 7.1*a*). These vertical aggregations are called *columns*. As a result of the vertical organization of connections, information conveyed by thalamic fibers terminating in layer 4 is transformed and conveyed to deeper and more superficial layers, where further transformations are effected and from which output projections arise. In addition to vertical connections, the cells of a given column may have horizontally directed connections with nearby columns of the same area.

Students of evolution will naturally want to know what happens to the structure of the neocortex over the course of evolutionary history. Not much, would seem to be the answer implied by textbook and review-paper accounts of cortical organization. I say 'implied' because textbook accounts rarely have much to say about evolution, presenting their subject matter in a nearly species-free fashion. When results are related to particular species, the point is usually to illustrate allegedly *general* princi-

ples of organization rather than species- or taxon-specific characteristics. This is not merely a matter of convenience or simplification. Hand in hand with recent progress in the study of cortical organization has come a new interpretation – or more accurately, a family of kindred interpretations – of cortical evolution. These interpretations share the view that there is a 'basic uniformity of structure' of the neocortex across species, as Rockel *et al.*, (1980) expressed it.

The doctrine of basic uniformity is founded on the concept that neocortex is comprised of cell columns, which are viewed as the basic structural-functional units of cortical organization (see especially Szentágothai, 1975, 1978; Creutzfeldt, 1977, 1978; Goldman & Nauta, 1977; Hubel & Wiesel, 1977; Mountcastle, 1978; Rockel *et al.*, 1980; Eccles, 1984). One of the key tenets of this doctrine is the idea that columns preserve a nearly invariant cellular composition. In their seminal paper, Rockel *et al.* (1980) reported the number of neurons in columns of specific neocortical areas in different species. They took as their working unit of tissue a volume measuring 25 × 30 μm across the surface of the cortex (reflecting their estimate of typical column width) and extending through the thickness of the cortex (which varies between areas and species). Rockel *et al.* reported that columns have nearly the same number of cells, approximately 110, in whatever area of the cortex they are located, and they reported this number to be nearly constant across species. They found only one major exception to this rule – the primary visual cortex of primates, in which cell number was found to be much higher, approximately 270 cells per column.

Basic uniformity extends also to the cellular and connectional organization of the neocortex. There is thought to be a basic complement of cell types, distributed in a particular laminar pattern, and with a stereotyped set of interconnections so as to constitute a 'basic cortical circuit' (see especially Shepherd, 1988, and White, 1988, and also Creutzfeldt, 1977, 1978). Also, the laminar organization of extrinsic inputs and outputs conforms to a common plan. In one version of this theory (Creutzfeldt, 1977, 1978), each cortical column performs the same transformation on incoming information. As a result, differences in the functions of particular cortical areas arise from differences in their input sources and output targets, rather than from differences in the information-processing functions of the columns that comprise the areas. Differences in input and output parameters are also invoked to explain variations in the histological appearance (i.e. cyto- and myeloarchitecture) of areas (Creutzfeldt, 1977,

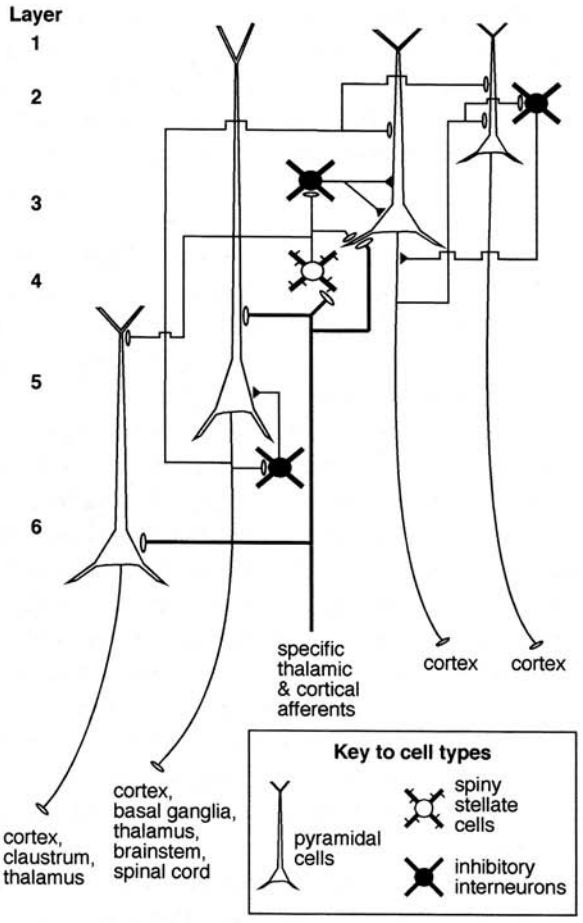

Fig. 7.2. A highly simplified schematic representation of the laminar organization and local circuitry of cerebral cortex, abstracted from diagrams presented in modern textbooks and review papers (see especially, Shepherd, 1988, White, 1988, and Douglas & Martin, 1998). The major excitatory inputs to the cortex arise from the thalamus and cortex and terminate at middle levels of the cortex (layer 4 and deep 3), synapsing on spiny stellate cells and on portions of pyramidal cells that lie within these layers. Excitation is then passed to more superficial layers and to deeper layers by means of the excitatory outputs of the spiny stellate cells and by local collaterals of pyramidal cell axons. Excitation of pyramidal cells is constrained by strong projections from inhibitory interneurons, which are themselves activated by collateral fibers arising from excitatory neurons. Pyramidal cells are the major output neurons of the cortex and the most numerous cell type, comprising about 70% of the neuronal population of the cortex. In addition to inputs to the middle layers from the thalamus and cortex, other layers receive afferents from a variety of cortical and subcortical sources.

1978; Rockel, *et al.*, 1980; Eccles, 1984). Neocortex is thus held to be constructed in a *modular* fashion, comprised of myriad, nearly identical columns arrayed across the cerebral mantle that serve as the basic information-processing units of the cortex. They may also be fundamental developmental units, as it has been proposed that each column represents a clonal cell line originating from a single progenitor cell, or small group of progenitors (Rakic, 1988).

The concepts of basic uniformity and columnar organization have been enormously influential. As Skoglund *et al.* (1996a) note, the number of cells in a cortical column – 110 – as reckoned by Rockel *et al.* (1980) 'has more or less become a neuroanatomical constant.' Faith in the uniformity of columnar organization across species is very strong, as evidenced by the preponderance of species-free treatments of cortical anatomy. It should not be surprising, then, that to the extent that contemporary neuroscientists talk about evolution, they tend to emphasize the enlargement of the cortical mantle, an enlargement attributed to the replication or proliferation of cortical columns (e.g. Mountcastle, 1978; Bugbee & Goldman-Rakic, 1983; Rakic, 1988; Allman, 1990; Killackey, 1995). By contrast, relatively little attention has been paid to possible evolutionary changes in other aspects of cortical structure. It is true that some neuroscientists such as John Allman (1977, 1990) and Jon Kaas (1987, 1995) have emphasized that new neocortical subdivisions (i.e. areas) emerged during the evolution of the various mammalian groups, and that this may be an important mechanism of brain enlargement. Opinion differs about the significance of this phenomenon, however. Kaas and Allman take the view that the advent of new areas provides the opportunity for the evolutionary of novel functional capacities, and thus represent important evolutionary innovations. Other workers, however, are inclined to view the advent of new areas in terms of differentiation, in the sense of an elaboration, refinement, or segregation of preexisting structural characteristics and functional capacities (as discussed in Preuss, 1995a).

The remarkable diversity of mammalian cortical organization

The modern, canonical view of cortical organization, with its emphasis on the microanatomical similarities among mammalian species, would seem to provide strong justification for the view that brain evolution is mainly or exclusively a matter of size, and that one can downplay changes

in the internal organization of the brain. If one goes beyond the textbooks and review papers to the primary literature, however, one quickly discovers that mammalian cortical organization is remarkably diverse: neuroscientists have documented differences at virtually every level of cortical organization that has been examined. What follows is merely a sampler.

Variations in columnar and cellular organization

It is increasingly clear that the strong claims made by Rockel *et al.* (1980) concerning the constancy of cell number in a column, or alternatively, under a unit area of neocortical surface, cannot be sustained. Beaulieu (1993) and Skoglund *et al.* (1996b) have reported large differences in column cell number between different areas of rat cortex (as high as 45% in the Skoglund study). Although comprehensive comparisons of different species have yet to be carried out using modern quantitative techniques, there is also evidence for major phyletic differences in column cell number. In cetaceans, it has been reported that there are only 20% as many cortical neurons below a unit area of cortical surface as indicated by Rockel *et al.* (Garey & Leuba, 1986; see also Haug, 1987). Among primates, Zilles and colleagues (1986) found that layer 4 of the posterior cingulate cortex was less densely packed with small cells in prosimians than in anthropoids. The observations of Preuss & Goldman-Rakic (1991) suggest that the differences in layer 4 cell density between prosimians and anthropoids extend throughout much of the parietal and temporal cortex.

Rockel *et al.* (1980) evidently assumed that column width was essentially invariant (~30 μm) across species and did not actually identify discrete columns before counting cells. Peters & Yilmaz (1993) attempted to do just this. They noted that the apical dendrites of pyramidal cells form bundles, and thus defined a column as the set of cells associated with a single dendritic bundle. They used this approach to compare the columnar organization of the primary visual area (V1) of cats with that of macaque monkeys (Peters & Sethares, 1991), and reported that cat V1 columns are wider than those of macaques (56 μm vs. 31 μm) and contained more neurons (203 vs. 142). In addition, they reported lamina-specific differences in neuron number between cats and macaques, cats having for example a very cell-rich layer 6.

There are many additional phyletic differences in the laminar organization of isocortex that can be observed with Nissl-stained material. For example, as shown in Fig. 7.3, cetaceans have an extremely thick layer 1

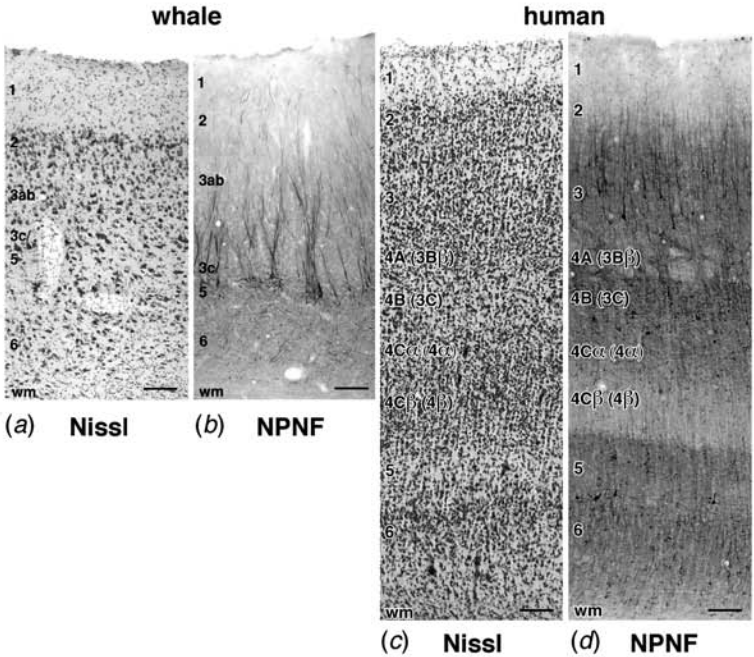

Fig. 7.3. Comparative histology of the primary visual area (V1) of a pygmy sperm whale (*Kogia breviceps*) and a human (*Homo sapiens*). Sections were cut frozen at 50 μm thickness and stained for Nissl or for nonphosphorylated neurofilament protein (NPNF) using the SMI-32 antibody. All sections are shown at the same magnification. In humans, and most other mammals, there is a preponderance of very small cells in cortical layer 4; in primates, layer 4 is very well developed in area V1, and subdivisions have been distinguished (there are alternative numbering schemes). By contrast, cetaceans have virtually no small-celled layer 4 in visual cortex or in any other part of the cortex. Layer 1 is relatively very broad in cetaceans, although the cortex is very narrow overall. Note also that in cetaceans, nonphosphorylated neurofilament is expressed only in a restricted set of pyramidal cells, forming a narrow band in the middle of the cortex, whereas in humans, this protein is expressed by a variety of pyramidal cell populations in both the superficial and deep cortical layers. Photographs of the whale material were kindly supplied by Dr Patrick Hof. Scale bars = 150 μm.

and a prominent layer 2, and lack a well-developed, small-celled layer 3 (Morgane *et al.*, 1985; Glezer *et al.*, 1988). Only in the primary visual cortex of cetaceans has an incipient layer 4 been described (Garey *et al.*, 1985; Morgane *et al.*, 1988). The cortex of some bats and insectivores bears at least a superficial resemblance to that of cetaceans in these and other features. It has been suggested that the prominence of layers 1 and 2 in ceta-

ceans, bats, and insectivores, and the poor development of layer 4, represent the primitive, reptile-like condition of mammalian cortex (Sanides, 1970; Morgane *et al.*, 1985; Glezer *et al.*, 1988). The peculiar traits of cetaceans, bats, and insectivores are lacking, however, in the outgroups of the main eutherian radiation (specifically edentates, marsupials, and monotremes), and therefore it is more likely that they represent independently evolved specializations rather than primitive retentions. There is some evidence that the unusual features of cortical lamination in these mammals reflect unusual patterns of connectivity. Specifically, it has been argued (on the basis of indirect histochemical evidence) that thalamic projections terminate primarily in layers 1 and 3 in cetaceans (Glezer *et al.*, 1988; Revishchin & Garey, 1996), rather than layer 4 and the deep part of layer 3, as they do in animals such as primates.

Few studies have attempted to compare the intrinsic connectivity of homologous cortical areas in different species or to compare the local connections of different areas within a taxon. There is, nonetheless, evidence of variation in these aspects of organization. LaChica *et al.* (1993) noted differences in the interlaminar connections of the primary visual cortex of the primates *Galago* and *Saimiri*. Kritzer and colleagues have reported differences in the intrinsic connectivity of prefrontal cortex and primary visual cortex in macaque monkeys (Kritzer *et al.*, 1995) as well as differences between the primary visual area and higher-order visual areas (Kritzer *et al.*, 1992).

By contrast to the paucity of dedicated comparative studies of local circuitry, there are numerous studies comparing the neuronal phenotypes of different cortical regions and different taxa. These studies are pertinent to the claim of a basic cortical circuit, because the functions of local cortical circuits must depend on the morphology and physiology of the pyramidal and non-pyramidal cells that comprise them. All mammalian groups that have been examined possess cells that can be classified with confidence as pyramidal cells on morphological groups. This said, some mammals have morphologically distinctive subsets of pyramidal cells. In cetaceans, and in at least some bat and insectivore species, layer 2 contains numerous large, dark cells with distinctive, bifurcating apical dendrites that ramify within layer 1, as well as poorly developed basal dendrites; these cells are believed to be modified pyramidal cells (Sanides & Sanides, 1972; Valverde, 1983, 1986). Cetecean also exhibit a variety of other unusual morphologies among pyramidal cells located in deeper layers (Garey *et al.*, 1985). Whereas most mammalian taxa have pyramidal cells

with a single main apical dendrite trunk, in one marsupial species, the quokka (*Setonix brachyurus*), most pyramidal cells in the primary visual cortex have paired apical dendrites (Tyler *et al.*, 1998). In rats, layer 4 of primary visual cortex contains small 'star pyramidal' cells, which have an apical dendrite; these cells are probably homologous to the spiny stellate cells found in layer 4 of macaques and cats, which lack an apical dendrite (Peters & Yilmaz, 1993).

Cortical neurons are biochemically variable across taxa. For example, there is abundant evidence that the pyramidal cells of rats do not express parvalbumin (Celio, 1990), while many of the layer 5 pyramidal cells of Mongolian gerbils do (Brückner *et al.*, 1994). The primates *Galago* and *Macaca* also possess parvalbumin-positive pyramidal cells, although possibly only in somatic sensorimotor areas (Preuss & Kaas, 1996). As illustrated in Fig. 7.3, there are also phyletic differences in the expression of a cytoskeletal protein (neurofilament) by pyramidal cells (Campbell & Morrison, 1989; Hof *et al.*, 1992; Preuss *et al.*, 1999). Among inhibitory interneurons, there appear to be important phyletic distributions of cells expressing particular calcium-binding proteins. In a broad comparative study that included cetaceans (whales and dolphins), primates, rodents, bats, and insectivores, Glezer and colleagues (Glezer *et al.*, 1993) noted layer-specific differences in the numbers of cells expressing a particular CBP as well as differences in the morphologies of interneurons expressing a particular CBP (see also Glezer *et al.*, 1992). There are also reports indicating that primate species vary in the laminar organization of interneurons and neuropil expressing parvalbumin or calbindin in homologous cortical areas (Blümcke *et al.*, 1990; Hendry & Carder, 1993; Preuss & Kaas, 1996; del Río & DeFelipe, 1997).

Variations in long connections and large-scale organization

Mammalian groups display a number of differences in the connections of the cortex with subcortical structures and in the connections among cortical areas. In all mammals that have been examined, the primary visual area (V1) receives a strong projection from the lateral geniculate nucleus (LGN), which in turn receives projections arising from the retina. The precise sources and laminar distribution of these inputs vary across taxa, however (Casagrande & Kaas, 1994). In all prosimian and anthropoid primates that have been examined, LGN afferents terminate in a broad band in the middle of the cortical thickness corresponding to Brodmann's layer

4C. In most Old World and New World monkeys that have been examined, there is an additional, more superficial tier of projections that terminate in layer 4A of Brodmann. However, this projection is reported to be absent in *Aotus* (Horton, 1984), the only nocturnal anthropoid, and there is indirect evidence from histochemical studies suggesting that this projection may be reduced or absent in apes (Preuss *et al.*, 1998, 1999) and in humans (Horton & Hedley-Whyte, 1984; Wong-Riley *et al.*, 1993). Tree shrews exhibit a different, and evidently unique, distribution of geniculate terminations within V1 (Hubel, 1975). Whereas the LGN projects exclusively (almost) to area V1 in primates and tree shrews, this nucleus sends strong projections to the second visual area (V2) as well as to V1 in at least some carnivores (Dreher, 1986) and probably also in bats (Funk & Rosa, 1998).

Some of the most remarkable connectional variants found in mammals involve the somatic sensorimotor cortex. In most mammals that have been examined (including a variety of eutherians, marsupials, and monotremes), the projections from the thalamus to the cortex are almost entirely uncrossed or ipsilateral; that is, the right thalamus projects to the right cortex and the left thalamus to the left cortex. However, in hedgehogs (*Erinaceus europaeus*), the thalamus of each hemisphere sends a major projection to the somatic sensorimotor cortex of *both* hemispheres (Regidor & Divac, 1992; Dinopoulos, 1994). Moreover, the cortical projections to the spinal cord are largely uncrossed in hedgehogs, whereas in most other mammals the largest contingent of corticospinal fibers are crossed (Nudo & Masterton, 1990). These specializations are not found in all insectivores: tenrecs (*Echinops telfairi*) are reported to have mainly uncrossed thalamocortical projections (Künzle, 1995) and least shrews (*Cryptotis parva*) display predominantly crossed corticospinal projections (Nudo & Masterton, 1990), similar to most other mammals. Clearly, the somatic cortex of hedgehogs is remarkably specialized – a point worth bearing in mind given that hedgehogs have often been cast in the role of *ur*-mammals.

Inputs to the cortex arise from nuclei in the brainstem that contain the monoaminergic transmitters dopamine, norepinephrine, and serotonin. These substances are thought to modulate the responsiveness of cortical neurons to other kinds of inputs, rendering some classes of inputs more effective than others (e.g. Arnsten, 1997). An important series of comparative studies has revealed remarkable differences between rats and anthropoid primates (specifically macaques and humans) in the laminar

organization of projections to the frontal lobe arising from the dopamine-containing nuclei of the brainstem (Berger *et al.*, 1991; Berger & Gaspar, 1995). In rats, for example, the dopaminergic projections to the medial frontal cortex are distributed mainly to the deep cortical layers (5 and 6), while in primates these projections are preferentially distributed to the superficial layers (1–3). There are important regional differences in dopamine innervation as well: the primary motor area (M1) of rats is nearly devoid of dopaminergic fibers, while M1 is among the areas most densely innervated by dopaminergic fibers in macaques and humans (Gaspar *et al.*, 1989; Williams & Goldman-Rakic, 1998). In view of these differences, it is not surprising that laminar and regional distribution of receptor molecules specific for dopamine (D1 and D2 receptors) varies widely across taxa (Richfield *et al.*, 1989; Berger *et al.*, 1990). There is much additional evidence of phyletic variation in the distribution of neurotransmitters and receptors between the different orders of mammals (Berger *et al.*, 1988; Zilles *et al.*, 1993; Hof *et al.*, 1995) as well as within orders (Kosofsky *et al.*, 1984; Gebhard *et al.*, 1995; Dupouy *et al.*, 1996; Wang *et al.*, 1997).

The systems of long corticocortical connections that link cortical areas into functional networks have been studied in only a few taxa (mainly primates, carnivores, and rodents, with some limited investigations of bats and tree shrews), yet some intriguing differences stand out. In all primates and carnivores that have been examined (and in bats and tree shrews also, as far as is known), the primary sensory areas are connected only to areas of the same sensory modality. For example, the first (V1) and second visual areas (V2) are connected with other visual areas, but not with the primary somatosensory (S1) or auditory cortex (A1); there are no connections between V1 and the frontal lobe. Rats are different. In rats, V1 and V2 are both interconnected with a variety of frontal areas, and furthermore, there are direct connections between V2 and the primary somatosensory and primary auditory areas (Vogt & Miller, 1983; Miller & Vogt, 1984; Sukekawa, 1988; Reep *et al.*, 1990; Paperna & Malach, 1991; van Eden *et al.*, 1992; Condé *et al.*, 1995).

It is now widely accepted that mammals vary in the number of cortical areas they possess. It seems likely that larger-brained mammals generally possess more cortical areas than do smaller-brained taxa (Kaas, 1987). For example, primates evidently possess on the order of 50–100 cortical areas (Felleman & Van Essen, 1991; Preuss & Goldman-Rakic, 1991), while there

is good reason to believe that rats possess only a small fraction of that number (Zilles & Wree, 1985). Once we account for the areas that primates and rodents both possess (which are mainly lower-order sensory and motor areas, such as V1, and certain limbic areas such as orbital, insular, and cingulate cortex), we have accounted for most of rodent cortex but for only a small part of anthropoid cortex. Primates therefore have many areas that have no obvious counterparts in rodents or in other relatively small-brained mammals, including animals such as bats and tree shrews, which are thought to be close relatives of primates (Preuss & Kaas, 1999). It is very likely that primates possess many unique cortical areas, including a number of higher-order sensory areas (Allman, 1977; Kaas, 1987) as well as the classical higher-order association regions – the dorsolateral prefrontal, posterior parietal, and inferotemporal cortex (Preuss, 1995b; Preuss & Kaas, 1999). It is interesting that the higher-order association regions of primates are strongly connected with each other and these regions are all connected with a prominent thalamic structure, the medial pulvinar, which has no obvious counterpart in other mammals (Preuss, 1993). Thus, not only do primates possess primate-specific higher-order cortical territories, but these territories form a distinctive connectional system.

The evidence presented in this section belies the claim that there is a basic uniformity of cortical organization among mammals. The existence of extensive variation in cortical organization does not, of course, preclude the possibility that there are some features of cortical biology that are widely or even universally shared among mammals (see, e.g., Tyler *et al.*, 1998). For example, all mammalian groups that have been examined possess a cortical mantle, and this structure receives inputs from the thalamus, gives rise to descending projections, and is comprised of neurons with recognizably pyramidal morphologies as well as non-pyramidal, GABA-containing neurons. Furthermore, even if columns are not the immutable modules depicted in some theories, many cortical areas from a diverse range of taxa do display some sort of columnar organization. To focus exclusively on the ancestral features of cortical organization that mammals share, however, is to ignore those features of cortical organization that distinguish one group of mammals from another and provide the basis for their particular behavioral and cognitive abilities. Among other things, such a focus leaves one with little to say about the distinctively human characteristics of the human brain (Preuss, 2000).

New approaches to human brain evolution

The discovery of cortical diversity could not be more inconvenient. For neuroscientists, the fact of diversity means that broad generalizations about cortical organization based on studies of a few 'model' species, such as rats and rhesus macaques, are built on weak foundations. To obtain better-founded generalizations about widely shared characteristics, and to better understand the remarkable modifications of cortical organization produced by evolution, neuroscience needs to adopt a genuinely comparative methodology based on modern phylogenetic principles (Nishikawa, 1997).

The fact of cortical diversity is perhaps even more inconvenient for those anthropologists and paleontologists wanting to investigate brain evolution. To acknowledge the diversity of cerebral organization is to acknowledge that the issue of reorganization versus encephalization has been settled in favor of reorganization. There is no longer a good reason to consider encephalization as an index of some general functional capacity (intelligence) that is common to all mammals. We must face up to the fact that encephalization is largely uninterpretable in terms of cognitive or behavioral processes. Having said this, I want to emphasize that I am not proposing that we ignore brain size. After all, mammals do vary enormously in brain size, and the peculiarly large size of the human brain demands explanation. I suggest, rather, that we treat evolutionary changes in brain size as symptoms of changes in internal organization. Thus, among the questions we must consider about human brain evolution are, what kinds of changes in internal organization could result in massive increases in brain size?

One plausible account of human brain evolution involves the differential enlargement of particular brain subdivisions. Given the enormous enlargement of the brain that occurred during human phylogeny, we might expect that certain regions of the human brain are differentially enlarged compared to their ape homologues. Classically, human brain enlargement has been linked to the expansion of the higher-order association regions of the frontal, temporal, and parietal lobes (Brodmann, 1909, 1912; Blinkov & Glezer, 1968). Recently, the idea that the frontal lobe expanded during human evolution has been challenged (Semendeferi *et al.*, 1997). In my view, however, there are sound empirical grounds (reviewed in Preuss, 2000) for supposing that the *prefrontal* portion of the frontal lobe was enlarged during human evolution in comparison to

primary sensorimotor structures, as were portions of posterior association cortex. Nevertheless, it would be very useful to have additional information about the absolute and relative sizes of homologous brain structures in humans, apes, and other primates, and advancements in this area are being made (Matano & Hirasaki, 1997; Rilling & Insel, 1998; Semendeferi *et al.*, 1998).

As noted above, it appears that larger-brained mammals tend to have more cortical areas than smaller-brained taxa. For this reason, it is very tempting to suppose that the expansion of human cortex was accompanied by the addition of new areas, and the classical language-related territories (Broca's and Wernicke's areas) have been cited as likely neomorphic structures (Brodmann, 1909; Crick & Jones, 1993; Killackey, 1995). At the present time, however, there is no good evidence that humans possess species-specific cortical areas, and furthermore, there are well-founded claims that homologues of Broca's and Wernicke's areas are present in nonhuman primates (Preuss, 2000). Once again, however, we must also confess that the data currently available for addressing the possibility of human-specific cortical areas are very deficient: we simply do not possess maps of human and ape cortical areal organization that are of sufficient detail and reliability to determine which cortical fields are shared by apes and humans and which are unique to one group or another. Developing such maps should be a major priority for research in the near future, as much progress could be made on this front using histochemical and immunocytochemical techniques currently available.

Although the enormous size of the human brain constitutes its most conspicuous characteristic, there are good reasons to think that human brain evolution was not exclusively a matter of enlargement. If it is the case, as has been suggested, that homologues of at least some of the human cortical language areas are present in apes and monkeys, then we must suppose that the evolution of language entailed changes in the internal organization of the language areas and perhaps also changes in the interconnections of human cortical areas. While there is as yet no direct evidence regarding the nature of changes in the classical language-related areas, there is evidence bearing on other cortical regions. We have recently found histological evidence suggesting that the human primary visual area differs from that of both apes and monkeys in the way it segregates information arising from the magnocellular (M) and parvocellular (P) layers of the lateral geniculate nucleus (Preuss *et al.*, 1999). Humans also possess structural and functional characteristics of higher-order

visual cortical areas that distinguish them from monkeys (Tootell & Taylor, 1995; Tootell *et al.*, 1997), although as yet the higher-order visual areas of apes have not been examined with comparable techniques. The functional significance of these changes are unclear, but their character suggests that humans have enhanced capacities for analyzing moving stimuli (Preuss *et al.*, 1999). It is tempting (if very premature) to speculate that these changes occurred in response to the challenge of visually decoding the rapid mouth movements of speech, stimuli that can exert a strong influence on the interpretation of speech in face-to-face interactions (McGurk & MacDonald, 1976), and in addition the task of monitoring the manual gestures that normally accompany speech (McNeill, 1992).

The evidence that the visual system was modified in human evolution comes as quite a surprise (to me, at least), as it is axiomatic among neuroscientists and psychologists that the visual abilities of humans and monkeys (macaque monkeys, anyway) are virtually identical. One wonders whether this is just the tip of the iceberg: if the human visual system shows such specializations, what surprises await us when we explore the microanatomy of brain regions more commonly identified with human-specific psychological abilities, such as the classical language areas and the prefrontal cortex?

In advocating evolutionary studies of cortical microanatomy, I want to emphasize that I am not proposing that we ignore brain size. Indeed, there are reasons to suspect that the evolutionary enlargement of the human brain may have been related to modifications of cortical microanatomy. Consider the changes in the structure of cortical areas that would likely have accompanied the evolution of new functional capacities. Functional imaging studies in humans indicate that higher-order cognitive tasks engage multiple cortical areas dispersed across the cortical mantle (Roland, 1993; Frackowiack *et al.*, 1997), areas that are probably linked by direct corticocortical connections. The evolution of new cognitive abilities might involve the enhancement of existing links between areas, or even the establishment of links between previously unconnected areas. In either case, the proliferation of connections would produce a cascade of effects. In the areas giving rise to new projections, existing pyramidal cells would have to be enlarged to support new axon collaterals or new pyramidal cells would need to be generated. On the receiving end of the projections, the dendrites of cells upon which the new axons terminate would enlarge to accommodate the additional synapses. These

increases in gray matter would be accompanied by increases in white matter as new fibers are generated. Furthermore, the size-increasing effects of all these kinds of changes would be multiplied because cortical areas tend to be reciprocally connected. Finally, in addition to size changes resulting from the generation of new connections, the intrinsic information-processing demands imposed on cortical areas by the evolution of new functions could also promote their enlargement. If the processing demands of a new cognitive function were incompatible with older (but still important) functions carried out by cortical areas, the cell populations mediating the new function might become spatially segregated from populations supporting the old function. This would result in the formation of separate compartments within the original area, each specialized for different tasks. Cortical areas commonly display internal compartmentation, the best known example being the ocular dominance columns of area V1 of primates, in which projections from the left and right eyes terminate in alternating compartments within area V1 (for a description, see Casagrande & Kaas, 1994). It is reasonable to think that the evolutionary addition of functionally specialized territories within existing areas would result in the enlargement of those areas.

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