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Taking the Measure of Diversity: Comparative Alternatives to the Model-Animal Paradigm in Cortical Neuroscience

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Mammals · Primates · Evolution · Animal model · Cerebral cortex · Visual cortex

Abstract

Cortical neuroscience is founded on studies of a very few model organisms, mainly rats, cats, and macaque monkeys. The concentration of effort on such a few species would be defensible if cortical organization were basically uniform across mammals, as is commonly believed. Although there is little reason to doubt that some features of cortical organization are indeed widespread among mammals, phyletic variation in cortical organization is far more extensive than has generally been appreciated or acknowledged. Rats, for example, differ from other mammals in the genetics and chemistry of their cortical neurons, in connectivity and areal organization, and in the functions of specific cortical regions. Likewise, macaque monkeys, although widely used as models of the human visual system, lack a number of features found in human visual cortex. Given the variability of cortical organization, how should neuroscientists approach the study of nonhuman species, and what can we reasonably expect to learn from them? First, by examining a wider range of species than are currently employed, and by using modern techniques of phyletic analysis, neuroscientists can more rigorously identify those features of cortical organization that are, in fact, widely shared among mammals or among particular mammalian subgroups. Second, by taking account of variations, neuroscientists can abstract more reliable and general principles of structure-function relationships in the nervous system. Finally, freed from the doctrine of basic uniformity, neuroscientists can pursue the study of human cortical specializations, and so advance our understanding of what distinguishes humans as a biological species.

Introduction

It is a striking feature of the biological sciences that they embrace two very different ways of looking at organisms. Many scientists follow a research tradition that emphasizes features of organisms thought to be widely shared among species. This tradition is particularly strong in the biomedical sciences, in some branches of psychology (notably behavioristic animal psychology), and in the neurosciences. Workers who emphasize general features of biological organization typically focus on a few 'model' organisms, and are interested in these organisms particularly to the extent they seem useful for representing the biological systems of other organisms, especially the human organism. Different biological disciplines have adopted different model organisms: In genetics, for example, the animals of choice have included fruit flies and mice. Pigeons and rats have played central roles in the history of experimental psychology. In cortical neuroscience, rats, cats, and macaque monkeys have long been the favored model animals.

By contrast to the model-organism (or model-animal) tradition, which emphasizes evolutionarily conserved characteristics, scientists working in the tradition of comparative

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biology give center stage to the diversity of living forms. To understand how evolution produced the diversity of existing life forms, it is necessary to compare a wide array of species, and therefore comparative biologists are disinclined to limit their research to the established stable of laboratory animal species. Indeed, to scientists working in the model-animal tradition, comparative biologists must often appear too obsessed with Nature's oddities to be taken entirely seriously, focusing on precisely those species and systems that seem most unusual from a human point of view – such as the nearly blind star-nose mole, which explores the world with finger-like appendages extending from its nose [Catania, 2000], and the platypus, a toothless, web-footed, semi-aquatic mammal that tracks its prey with electrical sensors housed in its duck-like beak [Krubitzer and Huffman, 2000].

One might regard the model-animal and comparative paradigms as simply two alternative and complementary approaches to the study of biological systems. I do not take this view. Rather, I contend that the model-animal paradigm, as an approach to the study of cortical neuroscience, is fundamentally flawed because it is founded on the false assumption that cortical organization is basically uniform across mammals. Comparative biology, by contrast, is not hampered by this assumption. Furthermore, it provides the methodological tools required to determine empirically which features of organization are, in fact, widely shared among organisms, as well as the means to rigorously identify specializations of cortical organization that distinguish particular mammalian groups. I suggest that the comparative biology provides a better framework for conducting research on cortical neuroscience than the model-animal approach, even if one is more interested in what we can learn about humans by studying other animals than in understanding the evolutionary diversification of cortical organization.

Animal Models and Model Animals

To begin, I need to draw a distinction between different senses of the term 'model.' One sense is used when scientists refer to an animal model of a particular disease. The strategy employed in such cases is to identify a system in a nonhuman species that is similar in structure and function to that of humans (so far as we know), to manipulate the system in a way that might illuminate what happens when its human counterpart breaks down, and to explore possible treatment strategies. So, for example, a biological condition approximating that of Parkinson's disease in humans can be produced in nonhuman primates by administering 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), which destroys the dopamine-containing neurons of the brainstem that project to the striatum and cortex [Burns et al., 1983]. This animal model can be used to explore the biochemical mechanisms of Parkinsonism and the pathological consequences of destruction of dopaminergic pathways in ways that are not possible in Parkinsonian patients, as well as to provide a means of testing treatment strategies.

I have no problem with animal models of this sort. The MPTP model of Parkinsonism, for instance, is reasonable because humans do, in fact, share with Old World and New World monkeys many features of the anatomy and biochemistry of dopaminergic systems. Moreover, the model can provide useful information about humans even if the model system is not identical to that of humans in every respect; if humans don't react like monkeys in some ways, they might yet react like monkeys in others. The model is understood to be heuristic, and researchers appreciate that specific predictions derived from the animal model need to be tested in humans.

Neuroscientists use 'model' in a somewhat different sense when we apply the term to a single species that is used to uncover general principles of structure and function, principles thought to apply to much larger groups of animals. This is the sense employed when neuroscientists treat rats as model (or representative) mammals or macaque monkeys as model primates or surrogate humans. In these cases, scientists often refer to the species in question as an 'animal model,' but the term 'model animal' (or 'model organism') probably better conveys the intended meaning. It is the model-animal paradigm, rather than animal models, that I want to critique in this paper.

The Model-Animal Paradigm

What justifies the traditional concentration of research effort in cortical neuroscience on just a few model species? One very important consideration is practicality: neuroscientific research is laboratory centered and it is difficult to maintain a wide range of species in captivity. We know a great deal about how to maintain rats and rhesus monkeys in captivity, what kinds of reinforcers they will work for, what drug doses are appropriate for them, and so forth. Many of the benefits of one-hundred years of laboratory experience would be lost were we suddenly to decide to concentrate on other species. Another important consideration is that by focusing on a few well-known species, one is in a better position to bring a variety of investigative techniques to

bear on a single neuroscientific problem than one would be if research effort were dispersed across an array of species.

These practical considerations are decisive, however, only if there are good reasons for supposing that we can learn what we want to know about cortical organization by studying only a few species. In the model-animal tradition, it is taken for granted that animals share basic or essential features of biological and psychological organization, with the result that the choice of species to be studied becomes largely a matter of convenience. This assumption of cross-species commonality or continuity has been made explicit in cortical neuroscience in the claim that there is a 'basic uniformity' of cortical organization among mammals [Rockel et al., 1980], and in related doctrines.

This emphasis on commonality should not be understood as a denial that animals differ. It does, however, suggest that variable characteristics are less important than widely or universally shared characteristics. (It is interesting how frequently neuroscientists use the terms 'basic' and 'essential' as synonyms for 'shared.') Moreover, certain kinds of variations have been regarded as reflections of an underlying unity. For example, it has been suggested that there is a regular relationship between brain size and the degree of areal or architectonic differentiation within the cortex [Le Gros Clark, 1959; Sanides, 1970]. A variety of additional cortical neuroanatomical parameters – from synaptic space to degree of gyrification – are proposed to scale in a regular, law-like way with brain size [Bok, 1959; Jerison, 1973; Finlay and Darlington, 1995]. From this perspective, differences among species become predictable consequences of brain-size variation, of less importance than the common design and transformation principles animals are thought to share. Bigger brains can be regarded as more *differentiated* than smaller brains, from this perspective, without acknowledging that they are *different* in fundamental ways.

The combination of practical and theoretical considerations encouraging emphasis on a few model species is reinforced by the tendency for model species to become nuclei for research traditions. People who work on rats, for example, tend to follow the rat literature particularly closely, and their research reports tend to emphasize the significance of results with respect to previous work on rats. Likewise, people who study monkeys focus on the monkey literature. (Indeed, as the co-author of several papers on the cortex of owl monkeys, I have been surprised to discover how common it is for people who study *macaque* monkeys to ignore the literature on other primate species.)

Research traditions are social institutions, and social institutions are notorious for zealously defending their parochial interests. Evidence of variation is threatening, as it raises the specter that results found in the favored model species do not apply to animals more generally. It's not surprising, then, that there is a sturdy tradition of debunking claims of phyletic differences in cortical organization [e.g. Huxley, 1863; Elliot Smith, 1924; Rose and Woolsey, 1948; Akert, 1964]. Even when reports do acknowledge differences, they tend to downplay their significance [e.g. Blümcke et al., 1990; Payne, 1993; Yoshioka and Hendry, 1995].

Just how strong is the sentiment that differences are deficiencies was brought home to me several years ago at a meeting hosted by a foundation that supports neuroscientific research. In my presentation, I suggested that it might be misleading to refer to macaque monkeys as 'the primate,' in view of the fact that there are at least 200 living primate species (fig. 1), and furthermore, given the diversity of anatomy and behavior among primates, that we should not be surprised to find that humans and macaques differ in some respects [Preuss, 1995a]. For this I was called to task by several colleagues who study macaques on the grounds that my comments amounted to an attack on animal research. Later, in private, it was represented to me that altough there presumably were differences between humans and monkeys, we shouldn't discuss this possibility publicly, and certainly not in front of representatives of funding organizations. Now, I suspect that most members of the public (not to mention representatives of funding organizations) are comfortable with the idea that humans differ from monkeys. The fact that neuroscientific professionals find this idea troubling is reason enough to take a close look at model-animal paradigm.

Practical and political considerations aside, the validity of the model-animal paradigm ultimately rests on questions of fact: if mammalian cortical organization is highly conserved across species, and if the differences that occur can be understood as predictable effects of size, then it is reasonable to use one or a few mammals as stand-ins for mammals generally. If these conditions are not met, we need to consider alternatives to the model-animal paradigm. In the following sections, I evaluate the merits of the paradigm by scrutinizing two of the most commonly used models in cortical neuroscience, rats and macaque monkeys.

The Rat Model

As a glance at any recent issue of one of the major neuroscience journals will reveal, rats are the mammals of choice in the neurosciences. Is the extreme concentration of effort on rats justified by a high degree of similarity between the cortical organization of rats and that of other mammals?

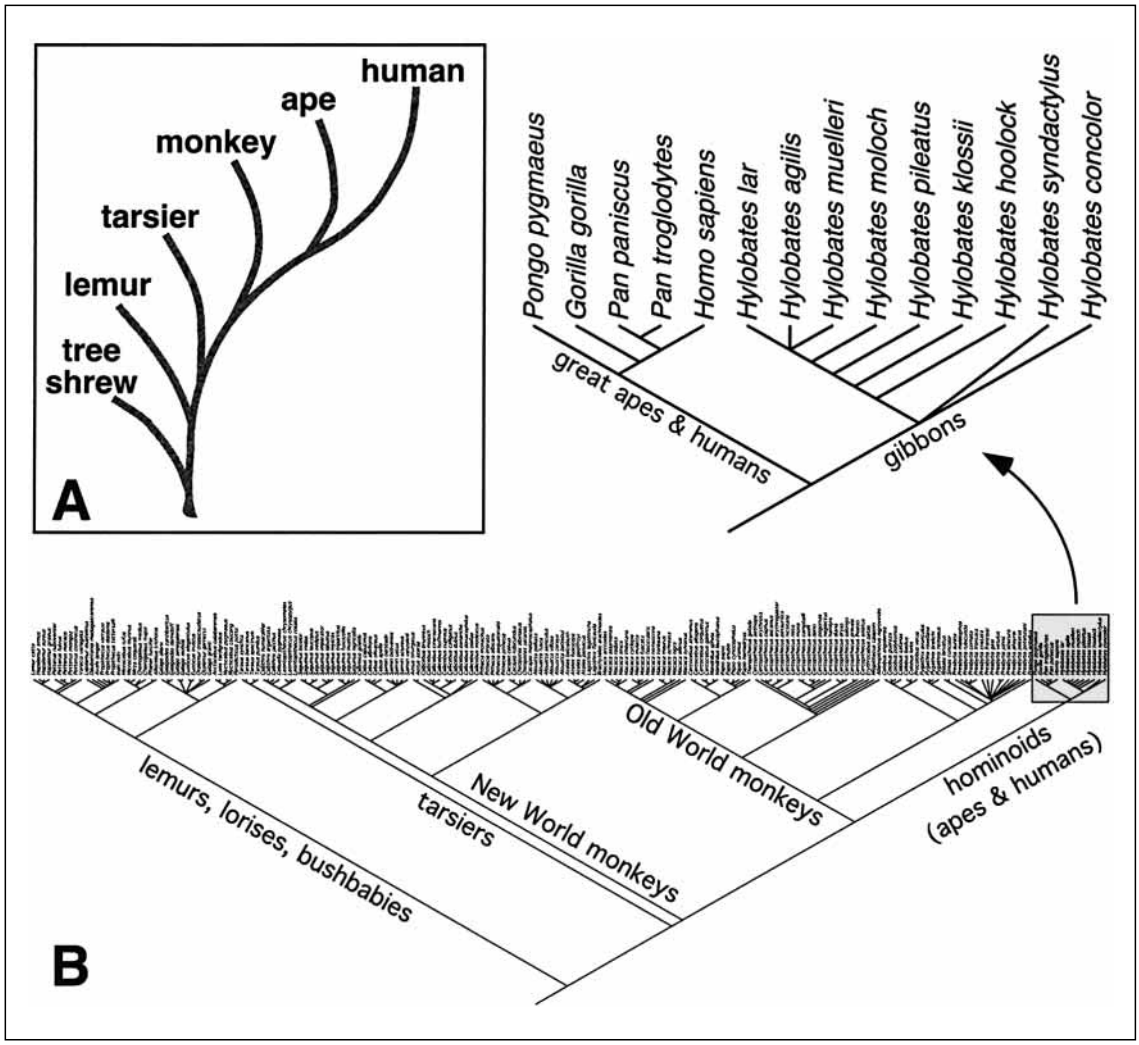


Fig. 1. Two views of primate phylogeny. The tree shown in **A** is adapted from the classic work of Le Gros Clark [1959] and illustrates the idea that the living primates can be grouped into a small number of grades arranged in an ascending series, from the most primitive (the tree shrew grade) to the most progressive (the human grade). (Note that tree shrews are no longer consider to be primates, although they are probably close relatives.) Primatologists today have largely abandoned the concept of grades, focussing instead on the diversity of primate species, on the relationships among different lineages, and on the evolved specializations that distinguish one primate group from another. Modern phylogenies of the primates, such as the tree shown in **B** [adapted from Purvis, 1995] includes 200 primate species currently recognized and offers an interpretation of how these species are related to one another. In this approach, humans are presented as one primate species among many, rather than as the pinnacle of primate evolution.

There are to be sure many similarities in cortical organization between rats and other mammals. Rats have the standard set of primary sensory and motor areas, positioned within the cortical mantle in a manner similar to that of many other placental mammals [Northcutt and Kaas, 1995], although perhaps not all [Glezer et al., 1988]. Thalamo-cortical projections are almost entirely uncrossed in rats, as in most other mammals, although not all [Regidor and Divac, 1992]. The majority of projection neurons in rat cortex are recognizably pyramidal in morphology, and rats possess a morphologically diverse array of GABAergic interneurons [White, 1988]. Nevertheless, rat cortex also differs from that of other mammals in numerous and non-trivial ways. For example, many rat cortical interneurons contain the calcium-binding protein parvalbumin, and this protein is apparently expressed only in interneurons in the adult cortex of

rats [Celio, 1990; Brückner et al., 1994]. By contrast, some other groups of mammals have prominent populations of parvalbumin-immunoreactive layer V pyramidal cells: these include the Betz cells of primates [Preuss and Kaas, 1996a] and much of the layer-V pyramidal cell population of the rodent *Meriones unguiculatus* [Mongolian gerbil; Brückner et al., 1994]. Thus, parvalbumin is associated with different types of neurons in different species. The same is true of the calcium-binding protein calbindin [see Hof et al., 1999, 2000].

In rats, as in other mammals, certain populations of cortical neurons are invested with specializations of the extracellular matrix known as perineuronal nets (PNNs). PNNs and their proteoglycan constituents are currently the focus of much research, as they are thought to be involved in regulating the development of neuronal morphology and perhaps in stabilizing synaptic connections [Celio and Blümcke, 1994]. In rats, PNNs are reported to be exclusively associated with interneurons [Brückner et al., 1994]. Rats are evidently exceptional in this regard, however, as PNNs have been reported to invest certain groups of pyramidal neurons in other taxa that have been examined, including other rodents such as gerbils [Brückner et al., 1994] and guinea pigs [Ohyama and Ojima, 1997], in the marsupial *Monodelphis* [Brückner et al., 1998], the tree shrew *Tupaia* [Jain et al., 1994], cats [Hendry et al., 1988], and several primate species [Hendry et al., 1988; McGuire et al., 1989], including humans [Hausen et al., 1996].

The distinctiveness of rat cortex is evident in its connectivity as well as its cell biology. Rats, like primates and many other placental mammals, possess an easily recognized primary motor area (M1). Rat area M1, however, receives virtually no input from midbrain dopamine neurons [Berger and Gaspar, 1995], whereas M1 in humans and in nonhuman primates is the target of some of the densest dopaminergic projections to reach any part of the cortical mantle [Gaspar et al., 1989, 1992; Williams and Goldman-Rakic, 1993; Berger and Gaspar, 1995]. Furthermore, rat area M1 has a substantial projection to orbitofrontal cortex [van Eden et al., 1992], a projection that has not been observed in the numerous modern studies of M1 connectivity in primates. There are additional examples of rat areas having different cortico-cortical connections than the homologous areas of primates or carnivores [Preuss, 2001].

It is generally accepted that one can distinguish fewer cortical areas in rodents than in primates. Despite this, rats have been said to possess homologues of some of the higher-order association areas of primates, although perhaps in relatively undifferentiated form. For instance, it has been argued that the medial frontal cortex (MFC) of rats is homologous to the dorsolateral prefrontal cortex (DLPFC) of primates [e.g. Divac et al., 1978; Kolb, 1984; van Eden et al., 1992; Berger and Gaspar, 1995]. Although markedly different in histological appearance from the granular DLPFC of primates, certain connectional and functional similarities between rat MFC and primate DLPFC have been cited in support of homology – specifically, strong inputs from the mediodorsal thalamic nucleus and dopaminergic brainstem nuclei, and involvement in spatial delayed-reaction tasks [Divac et al., 1978]. However, current evidence indicates that these are all attributes of the medial frontal cortex of primates (i.e. the anterior cingulate and prelimbic regions), as well as of primate DLPFC [Condé et al., 1995; Preuss, 1995b; Williams and Goldman-Rakic, 1998]. Taking into consideration the entire range of known anatomical and functional characteristics, the medial frontal cortex of primates makes a very good match for the medial frontal cortex of rodents, and there is no evidence that the rat medial frontal region possesses additional cortex homologous to dorsolateral prefrontal cortex, even in cryptic or undifferentiated form [Preuss, 1995b]. Rat cortex is perhaps simpler than that of primates in the sense of having fewer areas, but rat cortex is not primate cortex in an undifferentiated state: it's simply different.

In view of the variations described above, it should be plain that any generalization about mammalian cortex based solely on studies of rats stands a good chance of being false. Indeed, it is by no means clear that one is safe in generalizing from rats to other rodents, even to other muroid rodents. This point is made dramatically in a recent paper by McNamara et al. [1996]. This research group uses the rat hippocampus as a model system for studying the molecular biology of learning and memory. Having identified changes in rat hippocampi in the expression of a growth-associated protein (GAP 43) that occur in response to long-term potentiation or kainate injection, they turned to the geneticist's favorite model mammal – the mouse – to explore the genomic control of GAP 43 expression. To their surprise, McNamara et al. found that constituent levels of GAP 43 expression in mouse hippocampus were different than in rats, and that kainate injections did not induce increased GAP 43 expression in mice. Even in transgenic mice into which the rat GAP 43 gene and its promoter had been inserted, the expression of GAP 43 did not follow a completely rat-like pattern. They concluded that hippocampal gene transcription is probably regulated differently in rats and mice. Suspecting that mouse-rat differences in hippocampal organization could have behavioral correlates, McNamara et al. then investigated whether mice and rats behave similarly in situations classically thought to involve

the hippocampus, including the 8-arm radial maze, which is widely used in tests of spatial memory. They found that mice did very poorly on the 8-arm maze, although they performed as well as rats (and in some cases better) on other types of learning tasks. McNamara et al. suggest that different evolutionary pressures may have resulted in 'differences in wiring and cellular chemistry' in rats and mice, and question the generality of results obtained in rodents for understanding memory mechanisms in primates.

The Monkey Model

Many neuroscientists have never accepted the rat as an adequate general model for understanding human cerebral cortex, and the microphthalmic rat seems a particularly poor choice as a surrogate for studying the well-developed human visual system. Therefore, many neuroscientists have employed nonhuman primate models. A variety of species have been used, but by far the most commonly used primates are macaque monkeys *(Macaca)*, a genus of about 16 species belonging to the Old World monkey group of primates. Although there are at least 200 species of primates living today [Purvis, 1995; Fleagle, 1999], including nearly 90 species of Old World monkeys, in the common parlance of neuroscientists, rhesus macaques and other macaque species are known simply as 'the monkey' or even 'the primate.'

There is a strong temptation to view macaques as model humans, a temptation reinforced by the way primate evolution has traditionally been portrayed (fig. 1A). T.H. Huxley [1863], and later the great anatomists G. Elliot Smith [1924] and W.E. Le Gros Clark [1959], portrayed primate evolution as approximating a natural phyletic scale: a nearly linear progression from insectivores to prosimians, New World and Old World monkeys, apes, and – at the top – humans. This makes it easy to conceive of macaques as simplified or undifferentiated models of human beings. Although the views of Elliot Smith and Le Gros Clark informed several generations of neuroscientists, modern primatology has entirely abandoned them (fig. 1B), emphasizing instead that each branch of the primate tree has its own distinctive suite of anatomical and behavioral specializations [for reviews, see Martin, 1990; Fleagle, 1999]. Moreover, the aforementioned reviews make it clear that the last common ancestor of the Old World monkey-ape-human group did not bear a particularly close resemblance to macaque monkeys.

It is important, therefore, to address the question of whether macaques are typical primates and whether they provide a general model for understanding human cortical organization. I will limit my discussion to features of the visual system, and specifically to the primary visual cortex (area V1). In part, this is because area V1, unlike most other brain regions, has been examined in many primate groups, which makes it possible to evaluate the representativeness of macaques in some detail. It bears remembering, however, that much of what we think we know about human visual cortex comes from studies of macaques.

One conspicuous feature of V1 organization is the well-known pattern of cytochrome oxidase (CO) 'blobs' or 'puffs' (fig. 2). Blobs are punctate zones of high metabolic activity (and thus dense CO staining) localized mainly within cortical layers 2 and 3 [Wong-Riley, 1994], that correspond to the termination sites of a particular class of afferents arising from the lateral geniculate nucleus (LGN). These are the K (koniocellular) afferents, which originate from very small cells situated between the main magnocellular (M) and parvocellular (P) layers of the LGN [Casagrande and Kaas, 1994]. Macaques possess blobs, as do all other primates that have been examined with appropriately preserved material [for reviews, see Horton, 1984; Preuss and Kaas, 1996b]. Given that blobs appear to be absent in the animals most closely related to primates (bats and tree shrews), they are likely to represent an evolutionary specialization of primate cortex [Preuss and Kaas, 1996b]. With respect to blobs, then, macaques are indeed typical primates.

Another conspicuous feature of area V1 in primates is the remarkable stratification of layer 4. In all primates, layer 4 consists of a densely packed band of very small cells (granule cells) that receives projections from the M and P layers of the LGN. Some primates, however, possess an additional band of very small cells, superficial to and separate from the main band, which is usually denoted as layer 4A. In macaques, layer 4A receives parvocellular LGN afferents [Brodmann, 1909]. Layer 4A seems to be a common, and perhaps universal, feature of New World and Old World anthropoid primates, including apes and humans [Brodmann, 1909]. It is not universal to primates as a whole, however, because layer 4A is absent in at least some of the strepsirhine (prosimian) primates [Preuss and Kaas, 1996b].

So far, so good – macaque V1 shares a number of characteristics with humans and with many (although not all) other primates. We would expect this, given the close relationship of the Old World monkey and ape-human (hominoid) groups (fig. 1B). The existence of numerous macaque-human similarities does not, however, preclude the possibility of important differences. One well-documented difference pertains to the laminar distribution of CO staining. Most Old World and New World monkeys have a dis-

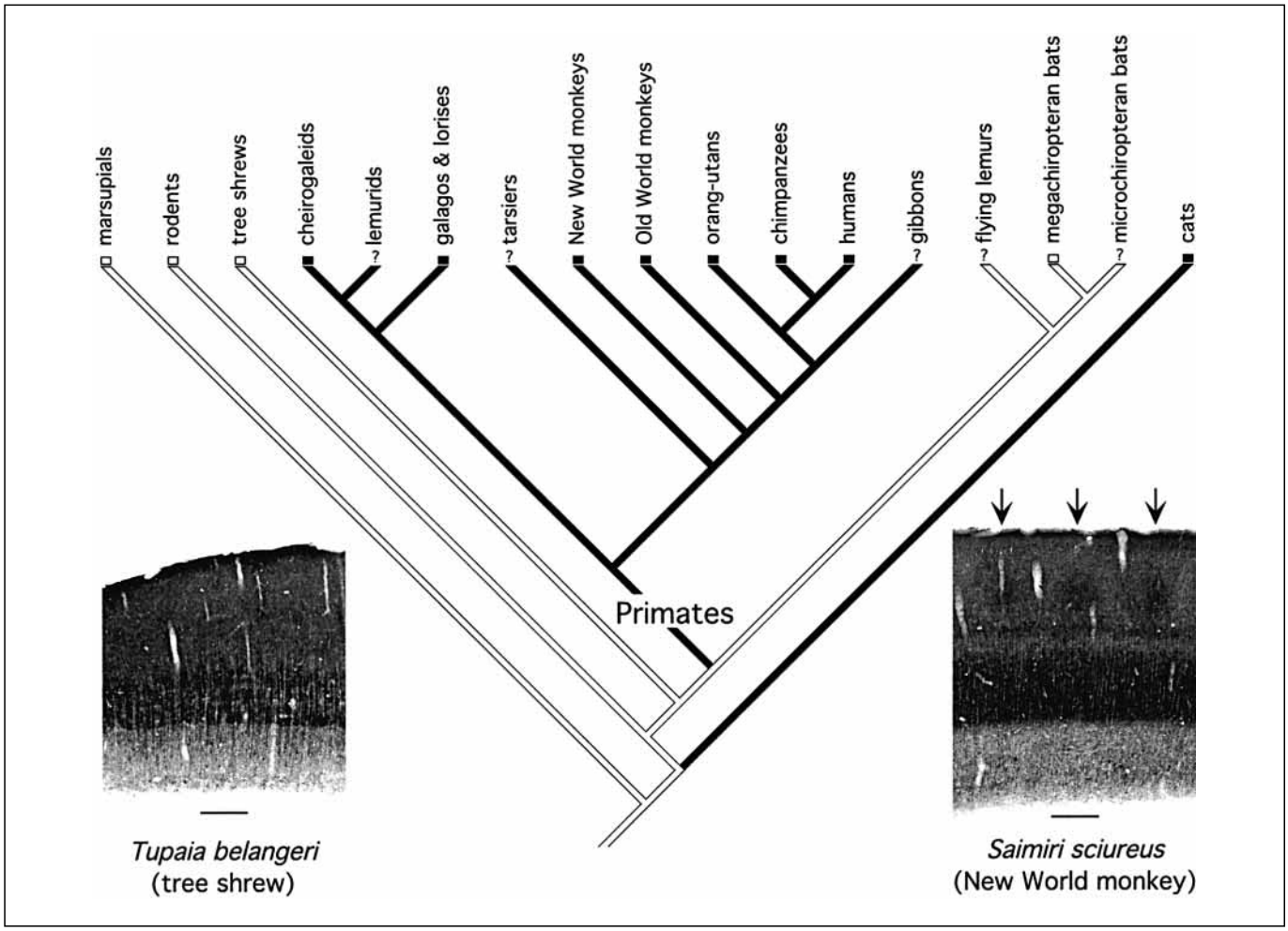
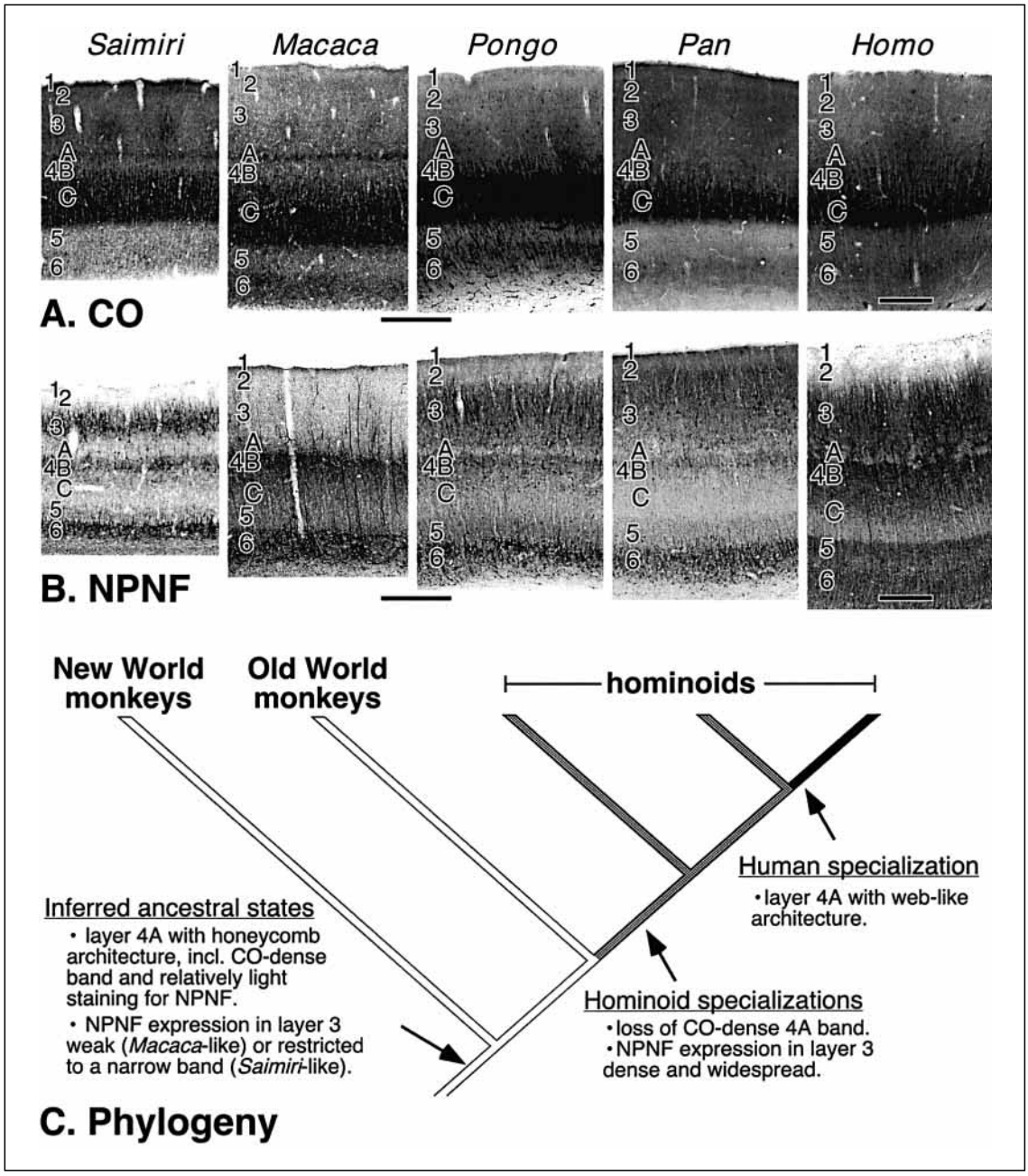


Fig. 2. A cladogram representing the phyletic distribution of cytochrome-oxidase-rich 'blobs' in primary visual cortex. Taxa that possess blobs are denoted with filled squares; taxa that lack blobs are denoted with open squares; taxa that have not been examined are denoted with questions marks. All primate species that have been examined with suitable techniques have been shown to possess blobs. Blobs are evidently absent, however, among the animals most closely related to primates. These include tree shrews and megachiropteran bats; the status of blobs in other relevant taxa, notably flying lemurs and microchiropteran bats, has not been assessed. Most other mammalian groups that have been examined appear to lack blobs. Cats, however, have been reported to exhibit cytochrome-oxidase-rich compartments in V1 that resemble the blobs of primates, although the distribution of blobs among living taxa suggests that the blobs of primates and cats have separate evolutionary origins and therefore are not homologous. This account is based primarily on Preuss and Kaas [1996b] and data cited therein. The interpretation of blob evolution is a maximum-parsimony analysis generated with MacClade software [Maddison and Maddison, 1992]. The phylogenetic tree combines information on primate relationships from Purvis [1995] with information on the relationships of mammalian orders from Shoshani and McKenna [1998]. Scale bars are 250 µm.

tinct, thin band of CO staining in layer 4A, coincident with the thin band of parvocellular LGN terminations discussed above; the high level of CO activity is thought to reflect the normally high activity levels of LGN afferents [Horton, 1984]. Among monkeys that have been examined, only owl monkeys *(Aotus)* lack a dense band of CO staining in layer 4A and the corresponding band of LGN afferents [Horton, 1984]. Given the prevalence of these features of V1 organization in New World and Old World monkeys, it would seem a safe bet that they also exist in apes and humans. But they do not: layer 4A in apes and humans stains only weakly for cytochrome oxidase (fig. 3A) [Horton and Hedley-



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Whyte, 1984; Wong-Riley et al., 1993; Preuss et al., 1999]. Thus, layer 4A was modified during the early evolution of the ape-human group (i.e. the hominoid primates), and modified in a way suggesting that apes and humans underwent reduction or loss of the parvocellular LGN projection found in most monkeys [Horton and Hedley-Whyte, 1984; Preuss et al., 1999].

In addition to this ape-human specialization of layer 4A, humans possess a feature of layer 4A found in no other primate that has been examined. In macaques, layer 4A is organized in a honeycomb-like manner: afferents from the parvocellular LGN terminate in a thin sheet that is interrupted by bundles of dendrites (and the odd cell body) extending upward from layer 4B, a layer that is related to the magnocellular LGN. Thus layer 4A is a mosaic of territories related to the P and M geniculate layers, with cores of M-like tissue surrounded by walls of P-like tissue [for review, see Preuss et al., 1999]. This organization can be

visualized in macaques using immunocytochemistry to stain proteins that are concentrated in the M pathway, specifically microtubule-associated protein 2 (MAP 2) and nonphosphorylated neurofilament protein (NPNF). Similar results have been obtained in New World monkeys and in apes, suggesting that the honeycomb is a common feature of organization in New World and Old World monkeys, and in great apes [Preuss et al., 1999]. Human layer 4A is markedly different, however. In humans, the staining for neurofilaments and MAP 2 reveals prominent, tightly packed bands of cell bodies and dendrites that weave through layer 4A in an irregular, net-like pattern [Preuss et al., 1999] (fig. 3B). Recently, a similar pattern has been noted in human V1 tissue stained with the Cat-301 antibody [Preuss and Coleman, 2000], a relatively selective marker for the M pathway. The distinctive pattern of human staining for NPNF, MAP 2, and Cat-301 suggests that a significant modification of the M-related elements took place in human evolution subsequent to the divergence of the human lineage from the African ape lineage.

Human V1 therefore differs from macaque V1 in at least two respects. Humans (and also apes) lack the band of dense CO staining in layer 4A that is so characteristic of monkeys, a difference that may reflect changes in the P-related elements of area V1, and humans have modified the (presumably) M-related elements in layer 4A to yield a distinctive, net-like architecture different from the architecture of apes and monkeys. As noted above, these differences probably constitute specializations of the human (or ape-human) lineages, with most Old World and New World monkeys preserving the ancestral anthropoid condition (fig. 3C).

Fig. 3. Evolution of area V1 organization in monkeys, apes, and humans, based on data presented by Preuss et al. [1999]. The panel of photomicrographs in **A** show sections stained for cytochrome oxidase (CO); those in **B** show sections stained for nonphosphorylated neurofilaments (NPNF) with the SMI-32 antibody. **C** presents an interpretation of the evolutionary history of V1 based on maximum parsimony. Taxa illustrated here are a New World monkey, the squirrel monkey *(Saimiri sciureus)*; an Old World macaque monkey *(Macaca assamensis)*; and three members of the ape-human (hominoid) clade, the orangutan *(Pongo pygmaeus)*, common chimpanzee *(Pan troglodytes)*, and human *(Homo sapiens)*. Additional New World and Old World monkey species examined in this study are not shown. As illustrated in **A**, New World and Old World monkeys typically have a thin, distinct band of CO staining in layer 4A that is absent in apes and humans. This may represent the reduction or loss of the projection of the parvocellular (P) layers of the lateral geniculate nucleus to layer 4A that corresponds to the CO-dense band in New World and Old World monkeys. Further modification of area V1 took place following the separation of the chimpanzee and human lineages. This change was marked by the appearance of an irregular network of dense NPNF staining in human layer 4A, a layer that is relatively lightly stained in other species. Similar patterns are observed in tissue stained for microtubule-associated protein 2 (MAP 2). Since NPNF and MAP 2 are believed to preferentially mark tissue compartments associated with magnocellular (M) layers of the lateral geniculate, the characteristic pattern of staining for these proteins in human layer 4A suggests that the organization of M-related elements in area V1 was modified during human evolution. Scale bars are 500 μm.

From Model Animals to Comparative Neuroscience

Phyletic variation in cortical structure is extensive and involves many dimensions of organization. Rats are not typical mammals, nor are macaque monkeys generalized primates or simplified humans. Furthermore, the differences between rats, macaques, and humans, are not readily accounted for in terms of some general process of differentiation: rats, macaques, and humans are irreducibly different in many respects.

The ubiquity of variation seems to pose a challenge to animal research, for if every species is unique, how can we hope to learn anything about humans by studying other animals? I suggest that this dilemma is more apparent than real. The fact that variation is extensive does not mean that there are no important cross-species commonalities. After all, rats do possess many features of cortical organization found widely among mammals. The problem is that we cannot be sure that any *particular* feature of rats is a widespread feature of mammalian organization by studying rats alone. To identify the characteristics rats share with other mammals, it is necessary to compare rats to a variety of other mammals. Similarly, macaques possess many features in common with other primates and with humans, but it is necessary to consider results from a variety of primate species in order to correctly identify those features. In short, rats and macaques can provide information that pertains rather directly to humans, but only if we study rats and macaques in a broader comparative context. Thus, cortical neuroscientists need to pursue an explicitly comparative research program.

How would adopting a comparative agenda affect the practice of cortical neuroscience? Certainly, many research goals would remain unchanged, although the means employed to achieve them would be modified. Consider the following example. The modern history of neuroscience is replete with attempts to distill a ‘basic circuit’ of cortical organization, a set of cells and local connections that constitutes the core information-processing architecture of the cor-

tex [e.g. Creutzfeldt, 1977; Szentágothai, 1978; Shepherd, 1988; White, 1988; Somogyi et al., 1998]. To date, these attempts have rested on extremely narrow foundations, relying on studies of but a few taxa (mainly macaques and cats, with some rodent work) and a very few cortical areas (mainly the primary visual and somatosensory areas). If we are serious about identifying widely shared features of cortical organization, then we need to study members of all the major mammalian lineages (eutherians, marsupials, and monotromes), not just a few eutherians, and we need to use appropriate phylogenetic methods for reconstructing the ancestral pattern of cortical histology and intracortical circuitry.

Reconstructing the ancestral characteristics of an organ that doesn't fossilize might seem a fanciful enterprise. Yet evolutionary biologists have developed rigorous formal techniques for reconstructing ancestors through comparisons of living forms [see, for example, Maddison and Maddison, 1992], methods that are widely used in other branches of biology that do not benefit from a significant fossil record, such as molecular biology. Although these techniques have not yet been extensively employed in the neurosciences, they are beginning to make their mark (fig. 2 illustrates one such application). Evolutionary biologists continue to refine methods for reconstructing evolutionary history and are currently developing quantitative techniques for evaluating alternative reconstructions of ancestral organization [Cunningham et al., 1998].

Reconstructing ancestors is the central task of phylogenetic analysis, providing the baselines against which evolutionary changes in descendent lineages are assessed. We might wish, for example, to investigate the changes in cortical organization that accompanied the divergence of the eutherian and marsupial lineages, which would require reconstructing the ancestral organization of the eutherians and of the marsupials. In similar fashion, we might want to reconstruct the ancestral organization of selected mammalian orders, such as primates, carnivores, and rodents, so as to understand which features of cortical organization distinguish each of these groups from other mammals – the distinctive specializations (or derived characteristics) of each of these groups.

The evolutionary specializations of particular mammalian subgroups are by definition features that have a restricted phyletic distribution. As such, they are not 'basic' or 'essential' or 'general' features of cortical organization. Although the model-animal paradigm encourages neuroscientists to downplay specializations (sometimes dismissively referred to as 'species differences'), there are good reasons to take them seriously.

Understanding phyletic variation and specialization is essential for establishing appropriate animal models for investigating normal cortical functions and dysfunctions in humans. If one is interested in developing an animal model for exploring the contribution of dorsolateral prefrontal cortex to human behavior, for example, or for understanding how particular drugs impinge on the functioning of human DLPFC, one will want to choose an animal that does, in fact, possess DLPFC – which is to say a primate. On the other hand, if one wants an animal model to explore the functions of the human medial prefrontal region, one has more choices, because homologues of at least some portions of the human medial prefrontal region (specifically, anterior cingulate and prelimbic cortex) appear to be present in a wide variety of mammalian groups, including rodents [Preuss, 1995b]. Of course, no animal model will have exactly the characteristics of human DLPFC or medial frontal cortex, but an exact match is not required for a model to have heuristic value.

In addition to providing a rational guide for developing animal models, the study of phyletic variation can provide critical insights into structure-function relationships. Simply put, we can obtain a richer understanding of the functions of nervous system elements by studying those elements over a broad phyletic range. For example, if one's goal is to understand the physiology or developmental role of perineuronal nets, an interpretation based only on the study of rats (in which only interneurons are surrounded by nets), is unlikely to be as useful as one based on studies that include primates, gerbils, and marsupials (in which nets ensheath pyramidal cells as well as interneurons). Similarly, we can expect to obtain sounder conclusions about the functions of the M and P visual pathways by comparing these pathways across a variety of species than by focusing on a single species.

In general, by correlating the evolution of neural specializations of particular groups with their behavioral specializations, we can expect to obtain new insights into how nervous systems can instantiate particular functions. The systematic study of variation is particularly valuable for exposing spurious structure-function correlations and suggesting new relationships. Consider blobs, for example. Although blobs have been implicated in color processing [Livingstone and Hubel, 1988], it is unlikely that blobs per se are structural specializations for color vision, as nocturnal primates lacking acute color vision (such as owl monkeys and many prosimians) possess blobs [Horton, 1984; Preuss and Kaas, 1996b]. Either blobs possess characteristics that preadapted them for use in color vision when it evolved [Allman and Zucker, 1990], or the reported association between blobs and color processing is incorrect. The

likelihood that blobs evolved convergently (independently) in cats and primates [Preuss and Kaas, 1996b] suggests that blobs might be related to the demands of vision under low-light conditions [Allman and Zucker, 1990], as the ancestors of both these groups were probably nocturnal predators that used vision to seize small prey [Cartmill, 1992]. The anatomical evidence is consistent with this interpretation. In primates, blobs have comparatively weak connections with the P pathway, the pathway principally involved in fine form and color discrimination under high-luminance conditions, but instead receive their major inputs from the K and M pathways [Casagrande and Kaas, 1994; Callaway, 1998]. The connections of cat blobs appear to be similar [Boyd and Matsubara, 1996].

The foregoing discussion illustrates why the mere fact that cortical organization is phyletically variable does not compromise the importance of animal research for understanding humans. Furthermore, the fact that variation is widespread does not mean that we should abandon the study of rats, cats, and monkeys. It does, however, suggest that we would benefit from expanding the range of mammals we study and adopting modern methods of evolutionary analysis. There will always be practical limits to the number of species we can study, of course, and there is no denying that many benefits accrue from applying a wide range of techniques to a single species. Nevertheless, pursuing the study of 'exotic' species does not necessarily pose insuperable difficulties for investigators: scientists who have thought it important to study moles, bats, possums, platypuses, galagos, or whales have generally found ways to do so. As a discipline, we should encourage the study of these and other non-standard species, for they have much to teach us about their natures and about ours.

Postscript

Acknowledging the diversity of cortical organization has additional, and perhaps surprising, consequences for the neuroscientific profession. Presumably, many people who become neuroscientists rather than taking up some other line of work, do so because they think there's something special about the human brain and its functions. How ironic, then, that our science has so consistently diminished the importance of phyletic differences! The result is that neuroscientists have little to offer beyond speculation when asked what is specifically human about the human brain [Preuss, 2000]. Only if we accept the importance of phyletic diversity, and begin to systematically pursue the study of human brain specializations, can we begin to develop a neuroscientific account of why humans think and act differently than monkeys and rats.

The historical emphasis on cross-species similarity in the neurosciences, and in the biomedical sciences more generally, is the source of at least one additional irony that bears on the very enterprise of animal research. Neuroscientists are inclined to regard opponents of animal research as opponents of science. Yet consider that opponents and proponents of animal research alike have been united by their commitment to a common principle, namely, that the similarities between humans and other animals are of far greater importance than the differences. Scientists should ask themselves whether the evidence really justifies this belief, for unless advocates of animal research can articulate a coherent and empirically well-founded view of how humans differ from other animals – and not just how we resemble them – conscientious people will have reason to lose sleep over the propriety of animal research.

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