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Arealization of the Neocortex in Mammals: Genetic and Epigenetic Contributions to the Phenotype

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Evolution · Cerebral cortex · Development · Plasticity

Abstract
The neocortex is composed of areas that are functionally, anatomically and histochemically distinct. In comparison to most other mammals, humans have an expanded neocortex, with a pronounced increase in the number of cortical areas. This expansion underlies many complex behaviors associated with human capabilities including perception, cognition, language and volitional motor responses. In the following review we consider data from comparative studies as well as from developmental studies to gain insight into the mechanisms involved in arealization, and discuss how these mechanisms may have been modified in different lineages over time to produce the remarkable degree of organizational variability observed in the neocortex of mammals. Because any phenotype is a result of the complex interactions between genotypic influences and environmental factors, we also consider environmental, or epigenetic, contributions to the organization of the neocortex.

Introduction

The neocortex is divided into a number of functionally distinct divisions or areas, and the number and types of areas vary widely across species. The underlying assumption is that phenotypic variability in the size, number and interconnectedness of cortical areas is the substrate for phenotypic variability in the complexity of perceptual, motor, language and cognitive abilities. Despite these widespread assumptions about cortical areas, there is little understanding of how areas evolve, and how complex abilities, or behaviors are generated over time in different lineages.

Our questions revolve around determining how cortical areas are added in different mammalian lineages, and the selection pressures that operate to generate the wide range of phenotypic variability observed in extant species. Originally, we approached this issue from a strictly comparative perspective. Because it is difficult to study evolution directly, we proposed that one could make inferences about the evolutionary process by examining the products of the process. Thus, by examining a variety of species that represent a number of different lineages, we could determine common features of organization likely to be present in the common ancestor, as well as independently evolved features of organization specific to individual species. We further reasoned that if the modifications to the common plan of organization (independently evolved features) take the same form in different lines of descent, then perhaps the ways in which brains could be modified is constrained [Krubitzer,

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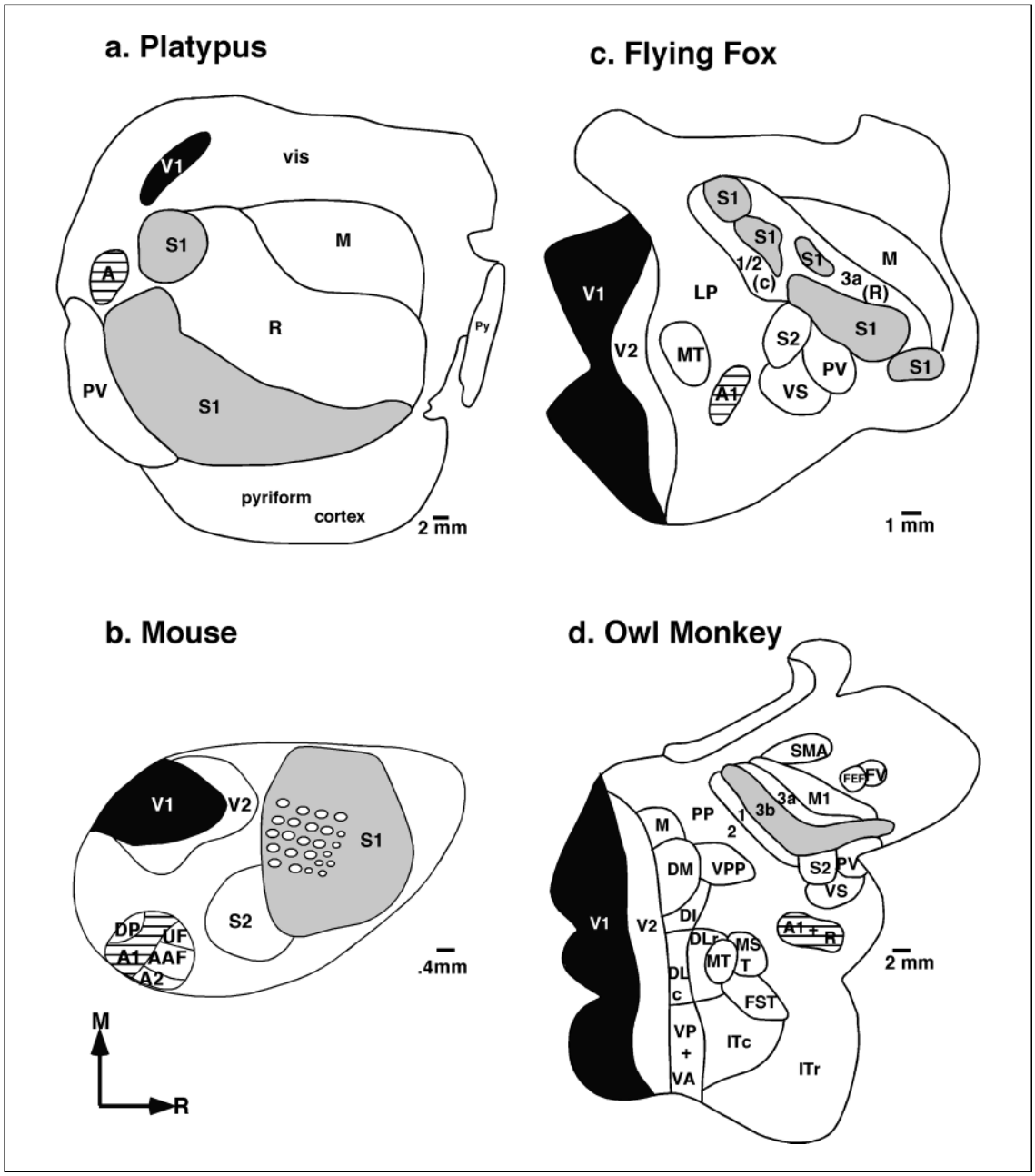

Fig. 1. The organization of the neocortex in four different mammals. Despite the difference in brain size, and cortical area number, several homologous areas can be identified in these mammals including the primary somatosensory area (S1; gray), the primary auditory area (A or A1; stripes), and the primary visual area (V1; black). The relative location of these cortical areas to each other, and to other cortical areas has shifted, often dramatically, in different lineages. However, V1 is always located caudally or caudomedially, A1 is always lateral to V1, and S1 is always rostral to both. This indicates that the evolution of the neocortex is in some ways constrained, and the mechanisms that determine gross rostrocaudal and mediolateral coordinates may be intrinsic to the neocortex. [Platypus, Krubitzer et al., 1995a; Mouse, Woolsey, 1967, Woolsey and Van der Loos, 1970; Wagor et al., 1980; Carvell and Simmons, 1986 and Stiebler et al., 1997; Flying fox, Krubitzer and Calford, 1992; Owl monkey, Cusick et al., 1989; Kaas, 1997.]

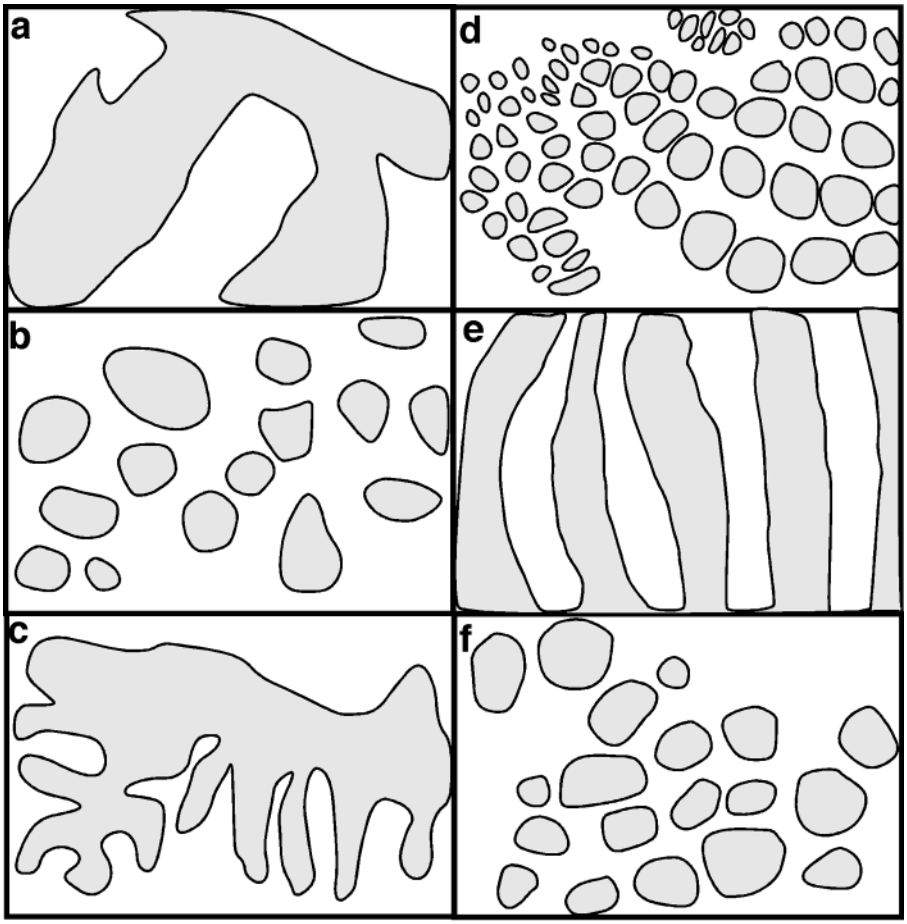

Fig. 2. A graphic depiction of modules in the neocortex in different mammals in different sensory systems; squirrel monkey myelin dark (gray) and light bands in the second visual area (**a**), entorhinal cytochrome oxidase blobs (gray) in macaque monkeys (**b**), electrosensory/mechanosensory bands (gray) in S1 of the platypus (**c**), Nissl-stained barrels (gray) in the primary somatosensory cortex of the rat (**d**), ocular dominance columns in talopoin monkeys (**e**), and insular blobs (gray) in the dolphin neocortex. All of these illustrations of modules demonstrate that the neocortex segregates inputs in a similar fashion, regardless of the sensory system or mammal. This again suggests that even though modifications to the neocortex arise independently in different lineages, the ways in which the neocortex can be modified is restricted. [Modified from Manger et al., 1998.]

1995; 2000]. Our comparative approach allowed us to observe common features of organization in a number of distantly related species with different sized neocorticies (fig. 1). As predicted, we observed a restricted repertoire of modifications in the neocortex of these species (table 1; fig. 2).

Although the very important tie between the evolution and the development of the nervous system has been appreciated for some time [e.g. Deacon, 1989; Killackey, 1990], we have only recently turned our attention to studies of the development of the neocortex and the mechanisms associated with the formation of cortical areas [e.g. Krubitzer and Calford, 1992; Krubitzer 1995; Huffman et al., 1999]. The evolution of the neocortex is linked to the evolution and elaboration of developmental mechanisms that contribute to arealization, or the formation of cortical areas. Ideally, theories of cortical development will explain how the neocortex develops within the life of an individual, and account for developmental changes of the neocortex across generations in different lineages. Likewise, theories of evolution must invoke developmental mechanisms to explain evolutionary change. We presume some critical change, which is genetically mediated, occurs during development and generates some alteration in the organization of the neocortex. This alteration is either selected for, or against. Thus, we examine the types of modifications to the neocortex that have

Table 1. Modifications to the neocortex

Changes in the size of the cortical sheet
Changes in the amount of neocortex that sensory systems occupy (sensory domains)
Changes in the geographic location of cortical areas
Changes in the functional organization of homologous areas
Changes in connections
Addition of modules to existing fields
Addition of cortical areas to the neocortex

occurred in different lineages, and look to studies of neocortical development in an effort to deduce possible mechanisms responsible for these changes. Several of the most salient features of modification in different lineages include the expansion of the cortical sheet, a change in the amount of neocortex occupied by different sensory systems (sensory domains), and an increase in the number of cortical areas.

At the time we began to appreciate these types of pervasive modifications, Rakic [1995; Kornack and Rakic, 1998] postulated that a simple change in the timing of horizontal proliferation in the ventricular zone during development could induce exponential changes in the size of the cortical sheet. This change in timing, or heterochrony, would be under genetic control. Recently a different explanation has been generated to account for changes in the size of the cortical sheet. Kuida et al. [1998], examined mutant Caspace 9 *(Casp9–/–)* deficient mice in which apoptosis of developing neuroepithelial cells was significantly decreased. The *Casp9–/–* mice exhibited an enlargement of the proliferative zone in the forebrain, among other regions, and an increase in the size of the neocortex. Genetically mediated heterochrony in dividing ventricular cells or decreased cell death might account for changes in the size of the cortical sheet; however, they do not explain major shifts in sensory domains captured on the cortical sheet or changes in the number of cortical areas.

Our ideas regarding changes in sensory domain shifts and increases in cortical area number were generated from comparative studies that demonstrated the remarkable correspondence between peripheral morphology and cortical organization [Krubitzer, 1995, 2000; Kaas, 2000b]. We believed, as did many other evolutionary and developmental neurobiologists [Chang et al., 1986; O'Leary, 1989; Killackey, 1990; Roe et al., 1990; Molnár and Blakemore, 1991; Schlaggar and O'Leary, 1991; Krubitzer and Calford, 1992; Krubitzer, 1995], that in early development the neocortex is unspecified, and that thalamocortical afferents must play a very large role in the formation of cortical fields (cortical arealization). We originally took a hard line on this stance, and sought to test it experimentally by making manipulations to the developing neocortex that we believed were under genetic control in the normal developing animal. We hypothesized that if the areas of the neocortex were not pre-specified, and if we reduced the size of the cortical sheet prior to the arrival of thalamocortical afferents, then we would not lose any cortical fields. Rather, we predicted a compression of cortical fields on the reduced sheet [Huffman et al., 1999]. In other words, we expected the organization of the neocortex to appear normal, only smaller. To a large extent, this hypothesis was supported. In animals in which approximately the caudal 2/3 of the neuroepithelial sheet was removed before thalamocortical afferents had reached the cortex, all sensory modalities were represented on the remaining sheet, and the relative distribution of thalamocortical afferents was maintained. Regions of the neocortex that normally would not be occupied by visual inputs contained neurons that responded to visual stimulation, and received inputs from the lateral geniculate nucleus (LGN; fig. 3). An equally interesting observation was that although no lesions were made to the dorsal thalamus or superior colliculus, these structures became proportionately smaller on the side ipsilateral to the lesioned cortex. Thalamic sensory nuclei ipsilateral to the lesion appeared smaller, but were

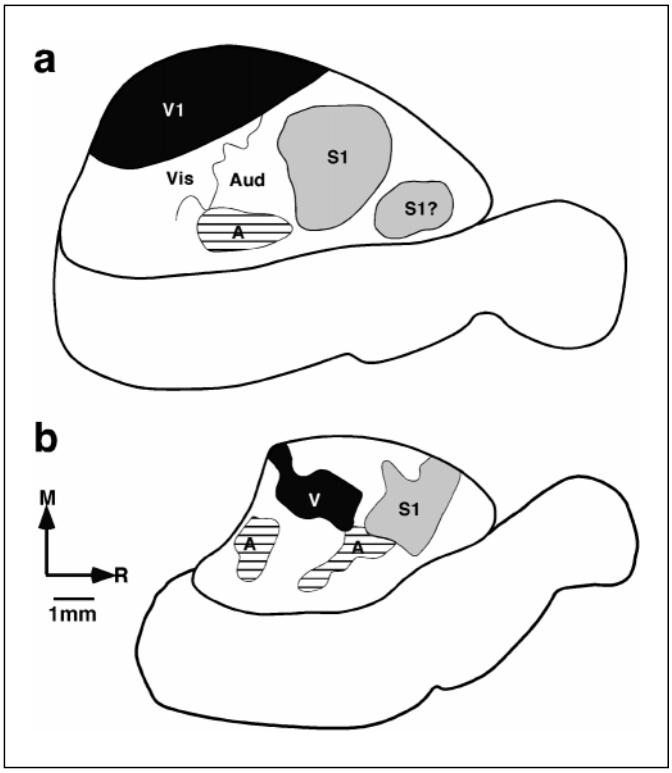

Fig. 3. The organization of neocortex in the normal *Monodelphis domestica* (**a**), and in a *Monodelphis* in which approximately 1/2 of the caudal neocortex was removed prior to the arrival of thalamocortical afferents at P4 (**b**). Cortical areas that compose part of the common network of mammals are shown in gray, black and stripes (see figure 1). Despite the removal of all of what would become visual cortex and most of auditory cortex, a visual cortex, which receives input from the LGN still forms on the remaining cortical sheet. Auditory cortex is present as well. These results indicate that thalamocortical afferents are capable of re-distributing on a reduced neocortical sheet, and play a large role in the arealization of the neocortex. [Modified from Huffman et al., 1999.]

still present. Therefore, a reduction in the size of the neuroepithelial sheet early in development also reduced the size of subcortical structures. From these observations we concluded that cortical sheet size can regulate the size of structures along the neuroaxis, but the internal organization or arealization of the cortex was driven by activity patterns in thalamocortical afferents, which in turn were driven by activity in the periphery.

However, recent studies demonstrating a heterogeneity in gene expression in the cortical plate in the absence of thalamocortical input in developing mutant mice [Miyashita-Lin et al., 1999; Nakagawa et al., 1999], suggest that arealization is, in part, guided by mechanisms intrinsic to the cortex. Further, mutant mice in which the distribution of regulatory genes such as *Emx2* had been altered [Bishop et al., 2000; see below for more details], have shifts in thalamocortical connections.

In the following review, we consider observations from studies of both the developing neocortex and comparative studies in extant mammals in an effort to provide a unified theory to account for phenotypic variability in cortical organization across mammals. Further, we incorporate results from studies of cortical plasticity in adult mammals to extend current theories to include activity dependent influences on cortical arealization within the life of an individual, among individuals within a species, and across species.

Developmental Studies

Until recently, there were two opposing theories regarding the process of arealization of the cerebral cortex. One view, the protomap hypothesis [Rakic, 1988], is that cortical areas develop very early, some time before cortical cells are actually generated or any connections are made [e.g. DeHay et al., 1993; Polleux et al., 1997a, b]. Several observations support this view. The first comes from studies by Levitt and colleagues in which pyriform cortex was transplanted into somatosensory cortex in immature rats [Barbe and Levitt, 1995]. If transplanted after E13, somatosensory cortex subsequently assumed the connections of pyriform cortex. However, these studies are difficult to interpret because the transplants were not made between two different sensory regions of neocortex. Rather, they occurred between two fundamentally and phylogenetically different pieces of cortex that may be inherently different. Another observation that supports the protomap hypothesis is that cell division in the ventricular zone does not appear to be homogeneous [Polleux et al., 1997a, b]. Rather, some regions appear to contain cells that subdivide at a higher rate than other regions [DeHay et al., 1993]. Third, studies in which E14–16 parietal and occipital explants were transplanted into P0–P1 occipital and parietal cortex respectively, demonstrate that transplanted cells maintained their early 'fate' [Cohen-Tannoudji et al., 1994].

A second view regarding the process of arealization is that cortical areas are initially unspecified, and the formation of cortical areas depends on inputs from the thalamus as well as inputs from other sources [Chang et al., 1986; O'Leary, 1989; Killackey, 1990; Roe et al., 1990; Molnár and Blakemore, 1991; Schlaggar and O'Leary, 1991; O'Leary et al., 1994]. This view is supported by studies in which the developing visual cortex in rats was transplanted into the developing somatosensory cortex. The transplanted cortex took on properties of the cortex normally located in the host region, in this case somatosensory cortex [Schlaggar and O'Leary, 1991; also see Stanfield and O'Leary, 1985; O'Leary and Stanfield, 1989]. Also, explants from the developing LGN of the thalamus that were co-cultured with frontal, hippocampal and cerebellar cortex grew towards any region of the cortex, but not to the cerebellum [Molnár and Blakemore, 1991]. This suggests that although thalamic neurons have an affinity to grow towards the cortex (and not other structures like the cerebellum), they do not appear to prefer a specific region of the cortex. With new data constantly emerging, particularly from studies in transgenic mice, these two seemingly opposing schools of thought are moving closer together. Investigators from both camps would agree that the process of arealization requires both area specific markers intrinsic to the neocortex and the presence of thalamocortical afferents, as well as cortico-cortical and interhemispheric connections.

Some of the newer breakthroughs that address the issue of arealization include studies in *Gbx2* [Miyashita-Lin et al., 1999] and *Mash1* [Nakagawa et al., 1999] deficient mutant mice that fail to develop thalamocortical afferents. In the former study, there were clear graded and abrupt patterns of gene expression such as *Cad6, EphA7, Id2* and *RZR-beta*. The conclusion drawn by these investigators was that these expression patterns marked functional boundaries of cortical fields, or corresponded to the boundaries of sensory systems. Because these boundaries developed independently of thalamic input, expression boundaries are likely to be intrinsic to the developing neocortex. Unfortunately, there is no evidence that these graded and areal expression patterns of molecular markers are actually related to functional areas of the neocortex.

In the *Mash1* mutants, the distribution patterns of transcription factors *Lhx, SCIP, Emx1,* and type 2 cadherins such as *Cad6, 8* and *11* were similar to those in wild type

mice [Nakagawa et al., 1999]. Some of these molecules, such as the cadherins, are involved in both homophilic and heterophilic adhesion, and are candidates for selective axon fasciculation, and adhesion of axons to pathways and target cells [Goodman and Tessier-Levigne, 1997]. Others, such as *Lhx*, are involved in neuronal differentiation [Xu et al., 1993]. These authors did not rule out an important role of thalamocortical afferents in arealization, but they concluded that differential gene expression was established in the neocortex by intrinsic mechanisms.

Some proposed mechanisms for the targeting of thalamocortical axons are based on chemoaffinity between the target and growing axons [Sperry, 1963; also see Lotto and Price, 1994, 1995]. Target-derived signals, such as growth factors and neuronal activity, serve as cues for the guidance of developing axons [Catalano and Shatz, 1998; see Katz and Shatz, 1996 and McAllister et al., 1999 for review]. Growth factors such as nerve growth factor, brain derived nerve growth factor, neurotrophin 3 and neurotrophin 4/5 serve not only a permissive role for survival, but also mediate synaptic plasticity (i.e. their expression and secretion is activity dependent). The latter is an important caveat, as the efficacy of these neurotrophins is often activity dependent.

Bishop et al. [2000] provide compelling data that suggest the presence of signals intrinsic to the neocortex that provide positional cues for incoming thalamocortical afferents. In this study, the regulatory genes *Emx2* and *Pax6* were examined in mutant mice. Both *Emx2* and *Pax6* are expressed in opposite gradients (fig. 4), and promote the expression of some classes of cadherins such as *Cad6, 8* and *11*. Although these investigators demonstrate rostral and caudal shifts of molecular markers such as *Cad6* and *Cad8* in the absence of *Emx2* or *Pax6*, the most persuasive evidence that these regulatory genes provide positional cues for incoming thalamic afferents was the alteration in thalamocortical connections observed in *Emx2 –/–* mice. Bishop et al. [2000] clearly demonstrate that when *Emx2* is absent in the developing cortex, the caudal portion of cortex (which would normally receive inputs from the LGN) receives inputs from the ventral posterior nucleus, suggesting that somatosensory cortex shifted caudally. LGN inputs were present, but occupied only the extreme caudal pole of the neocortex.

Although these experiments demonstrate that gross thalamocortical relationships are under genetic control and are independent of activity in the thalamus or periphery, several important questions regarding the evolution of developmental mechanisms that generate these relationships still need to be addressed. Do changes in molecular gradients account for the sensory domain shifts observed across mammals?

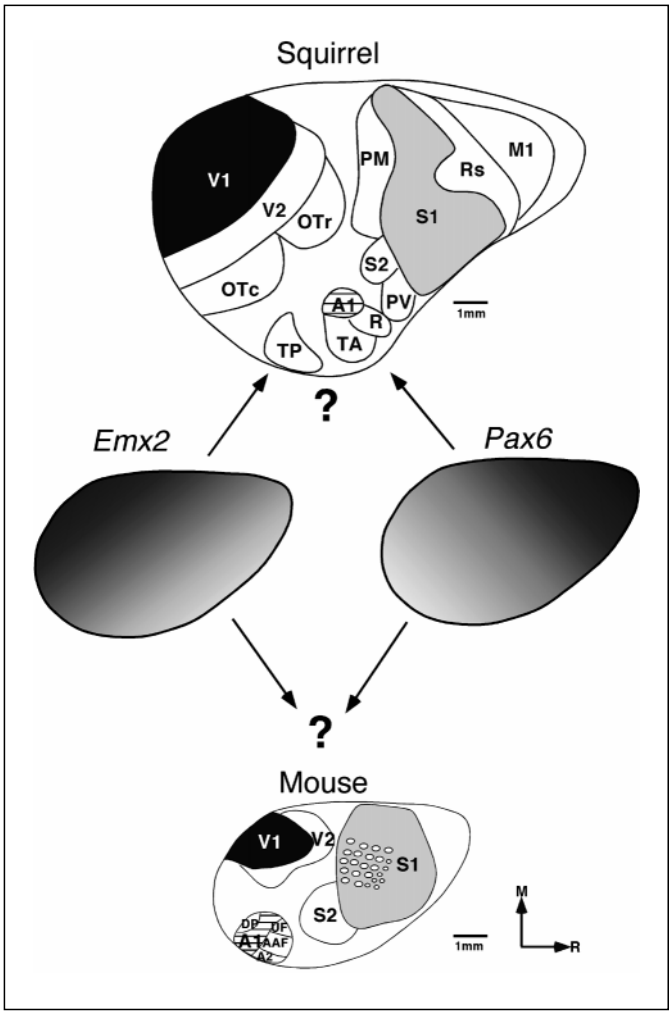

Fig. 4. The graded distribution of regulatory genes *Emx2* and *Pax6* in the mouse neocortex (middle figures), and the adult organization of the mouse (bottom) and squirrel (top) neocortex. While it seems plausible that graded expression patterns can assign a general rostral and caudal organization to incoming thalamic afferents, it is difficult to imagine how such a pattern can generate the precise organization observed in the adult mouse neocortex, and mediate major sensory domain shifts that are tied to the periphery. Further, if the common ancestor of rodents had graded expression patterns like those depicted in the middle illustrations, how are new areas added in some lineages of rodents such as visual areas in the squirrel and auditory areas in the mouse? [Middle figures are modified from Bishop et al., 2000. Subdivisions of the squirrel are from Kaas et al., 1972, 1989; Merzenich et al., 1976; Sur et al., 1978; Nelson et al., 1979; Krubitzer et al., 1986; Luethke et al., 1988; and Slutsky et al., 2000. Subdivisions from the mouse are from Woolsey, 1967; Woolsey and Van der Loos, 1970; Wagor et al., 1980; Carvell and Simmons, 1986 and Stiebler et al., 1997.]

Do changes in gradients and related changes in expression of molecules such as *Cad6, Cad8,* and *Id2* cause changes in cortical area number within a species over generations, or across different, although related species (fig. 4)? It seems unlikely that these gradients, or changes therein, are responsible for shifts in the amount of cortical territory devoted to a given sensory domain, although they may change as a result of peripheral morphological changes. Rather, sensory domain shifts are likely to occur as a result of changes in the periphery, and hence the thalamus, since the amount of cortex any given sensory system occupies is related to peripheral specialization (see below). It also seems unlikely that these regulatory genes are responsible for the arealization or the addition of new areas as new cortical areas appear to be interspersed between phylogenetically older fields and are not necessarily added hierarchically (see below; fig. 5). This would require some sort of break or rupture in the existing expression pattern. Finally, the patterns demonstrated with *Cad6* and *Cad8* appear to correspond to large sensory territories, and clearly encompass more than a single cortical area. Most evidence indicates that these initial patterns of thalamocortical connections can be dramatically altered by genetically mediated changes in peripheral morphology, but we would also argue that these initial thalamocortical relationships can be altered by epigenetic events (see below).

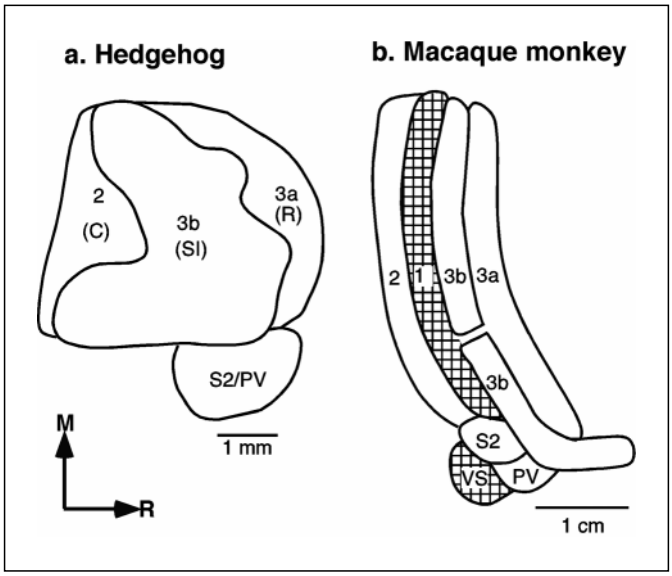

Fig. 5. The organization of anterior parietal cortex in the hedgehog (**a**) and macaque monkey (**b**). Comparative studies indicate that anterior parietal cortex in most mammals is composed of three separate areas including a primary somatosensory area (3b or S1), a rostral deep area (3a or R), and a caudal deep area (2 or C). In primates, an additional field, area 1, has evolved between areas 3b and 2. Also, a ventral somatosensory area, VS, is found in primates, but not in most other mammals. VS is interspersed between phylogenetically old areas, such as S2 and PV and between auditory cortex. This figure demonstrates that cortical fields are not only added to the ends of processing hierarchies, but can evolve between existing fields. This observation must be reconciled with current theories of the mechanisms involved in the development of cortical areas. [Modified from Nelson et al, 1980; Porbirsky et al., 1998; and Krubitzer and Calford, 1992; Krubitzer et al., 1995b. See Slutsky et al., 2000 for further discussion.]

Comparative Studies

Observations in a variety of mammals indicate that there is a common plan of neocortical organization. This plan is composed of a constellation of cortical fields and a network of thalamocortical and corticocortical connectivities [fig. 1; Krubitzer, 1995, 2000]. Features of the neocortex have a continuity across species, such that the rostrocaudal and mediolateral global organization of sensory domains is maintained and the gross thalamocortical topography is respected, regardless of the specialization of a species. Thus, it would appear that basic topographic interactions between the thalamus and the cortex are highly constrained due to the conservation of developmental mechanisms that generate them. Further support has come from highly derived species that have lost or significantly reduced the peripheral components of a particular sensory system. For instance, blind mole rats are micropthalmic; their eyes are vestigial and covered completely with hairy skin [Cooper et al., 1993]. These animals do not use the visual system to see, yet still possess geniculocortical connections, and have an architectonically and connectionally defined primary visual cortex, V1. In anopthalmic mice, V1 can be identified architectonically and by its connections with the LGN [Bronchti et al., 1999]. However, neurons in 'V1' respond to auditory stimulation and ultimately receive their inputs from the inferior colliculus via the LGN. Additionally, the duckbilled platypus closes its eyes, ears and nose during the pursuit of prey, an activity that assumes a major part of its active cycle. Thus, the platypus does not use the visual system for many behaviors that are critical for survival such as prey capture. As a result, the entire visual system is poorly developed. Yet, the platypus still retains a geniculocortical pathway and a small V1 [Krubitzer, 1998].

These observations demonstrate that even when a particular sensory system is not used, the constellation of cortical areas, the geographic relationships among these areas, and thalamocortical relationships are maintained. The major change seems to be a diminution of the thalamocortical network associated with that sensory system. Thus, there may

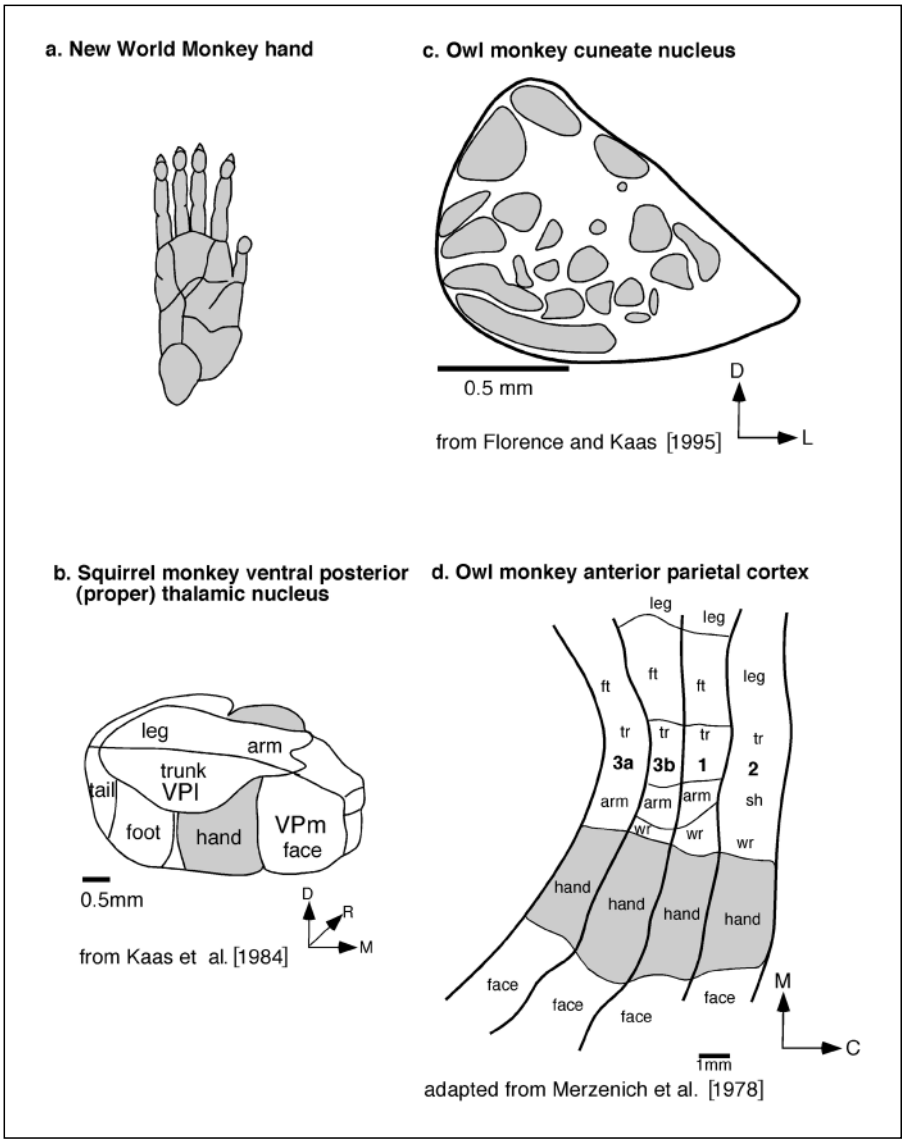

Fig. 6. The topographic organization of the representation of the hand (shaded region) of New World monkeys in the cuneate nucleus (**a**), ventral posterior nucleus of the thalamus (**b**) and the neocortex (**c**). The glabrous hand of primates is specialized for tactile discrimination and object recognition, and this specialization is reflected at multiple levels of the nervous system. At the level of the sensory receptor, cutaneous receptors such as Merkel's discs and Miessner's corpuscles are concentrated on the glabrous surface of the hand, particularly at the digit tips (**a**). In the brainstem cuneate nucleus, a large portion of the representation therein is devoted to representing the glabrous hand (**b**). This is also true for the ventral posterior lateral nucleus (VPl) of the thalamus (**c**). The magnification of the representation of the hand is most pronounced at the level of the cerebral cortex in anterior parietal fields 3a, 3b, 1 and 2 (**d**). The match between peripheral specialization and the functional organization of the hand representation along the entire neuroaxis is proposed to be due to genetic changes at the level of the periphery, and activity dependent mechanisms related to specialized use. An alternative, although less probable, explanation is that compatible genetic changes (mutations) are occurring simultaneously at all levels of the nervous system.

indeed be mechanisms that are involved in the assignation of general thalamocortical relationships that exist independent of the periphery. In this respect, comparative observations are highly compatible with recent observations in developing mutant mice *(Emx2 –/–)*, which provide strong evidence that the general pattern of thalamocortical relationships may be established via mechanisms intrinsic to the neocortex. These mechanisms, in turn, constrain the evolution of the neocortex. Although studies in these mutant mice may begin to explain how basic topographic thalamocortical relationships are established in development, they do not explain how different sensory systems come to occupy different amounts of cortical territory, or how cortical areas are added to existing networks in different lineages.

Major Domain Shifts and Peripheral Specialization

In different lines of descent, the neocortex has undergone dramatic shifts in the amount of cortical territory assumed by different sensory systems, and these shifts are intimately tied to the organization of the periphery [Krubitzer, 1995; Kaas, 2000b]. Alterations in the peripheral receptor sheet are reflected at many levels of the central nervous system, and are very pronounced at the level of the cerebral cortex (fig. 6). Changes in the size of the animal or size of a particular body part, changes in the distribution of existing receptors, or the evolution of a new receptor type are some of the genetically mediated peripheral changes observed across species. Some examples include the evolution of electroreceptors in the duck-billed platypus [Scheich et al., 1986],

touch domes in the wings of megachiropteran bats [Crowley and Hall, 1994], and the expansion or modification to portions of the cochlea devoted to processing behaviorally relevant frequencies in echolocating bats [Kössel and Vater, 1985; Vater et al., 1985; Henson and Henson, 1991; Vater and Siefer, 1995]. In primates, the evolution of three cone color vision, and changes in receptor distribution on behaviorally relevant body parts, such as the glabrous hand, lips and tongue, have a significant impact on the organization of all levels of the nervous system, particularly the neocortex (fig. 6). Such alterations in peripheral morphology are accompanied by relative changes in activity patterns between sensory systems as well as specialized behaviors associated with the specialized receptor surface (see below).

How Are New Cortical Areas Added?

Although we are gaining some insight into genetically mediated changes in the periphery and cortex that contribute to the arealization of the neocortex, it is still not clear how new cortical areas are added. Comparative studies indicate that as the neocortex increases in size, cortical areas often increase in size. However, the increase in the size of areas is proportionately less than the increase in the size of the entire neocortex, and the additional cortical space is occupied by more cortical fields. Our proposition for how cortical areas are added is drawn from three main observations.

The first observation is that cortical areas are not always added hierarchically but often are interspersed between existing cortical areas (fig. 5). Although we think of sensory processing streams as being hierarchical, there is no evidence that areas were added to the ends of hierarchies in evolution. Indeed, there is no direct evidence that 'primary' areas are evolutionarily older than other cortical areas [see Slutsky et al., 2000 for review]. For example, in anterior parietal somatosensory cortex, comparative data indicate that area 1 is a more recently evolved area in primates that emerged between two phylogenetically old areas of an existing network, areas 3b (S1) and 2 (C) (fig. 5) [Krubitzer and Calford, 1992; Pobirsky et al., 1998].

The second observation is that although the gross rostrocaudal and mediolateral thalamocortical relationships across mammals appear to be invariant, shifts in the spatial relationships of areas with each other can be observed. For instance, auditory cortex in the platypus is immediately caudal to S1, medial to the parietal ventral area, PV, and lateral to V1. V1 in the platypus resides just medial to the foot representation in S1. This organization is dramatically different from the relationship of these areas in other species (fig. 1).

The third observation is that cortical areas do not appear to be homogeneous, but are often interspersed with discrete groups of neurons that are architectonically, electrophysiologically and neuroanatomically distinct. These criteria are usually used to distinguish cortical areas. These smaller units within a cortical area are termed modules and are observed across sensory systems and across mammals. Examples include barrels in S1 of some rodents, thick and thin bands in V2 of some primates, and electrosensory/mechanosensory bands in S1 of platypus (see fig. 2).

These observations indicate to us that specific types of thalamocortical afferents are capable of shifting targets across the cortical sheet and that the cortical sheet must be incompletely specified early in development. They also suggest that new areas arise via alterations in existing patterns of thalamocortical activation. We propose that a cortical area is a pattern of interconnections upon the cortical sheet, and the large shifts in the location of homologous areas relative to other areas in different lineages results from a redistribution of thalamocortical afferents across the sheet [Krubitzer, 1995, 2000]. Although recent studies demonstrate that there are intrinsic (cortical) mechanisms operating to establish global thalamocortical relationships, this finding is not at odds with our current theory, as such relationships are maintained in different lineages.

We have several ideas regarding the emergence of new cortical fields. We believe that cortical modules arise with either the evolution of a new receptor in the periphery (e.g. electrosensory receptors and electrosensory bands in S1 of the platypus), by a specialized peripheral arrangement of existing receptors (e.g. vibrissae barrels in S1 of some rodents), or with the advent of new circuitry within a system (e.g. bands in V2 of monkeys). In some lineages, there are selective pressures for these modules to aggregate, possibly to decrease the length of connections and increase the speed of transmission between similar inputs [Ringo et al., 1994; Cherniak, 1994; Krubitzer et al., 1998; Manger et al., 1998]. In some instances, we believe that these modules 'pull out' of an existing area to form a new cortical field [Krubitzer, 1995, 2000; Krubitzer et al., 1995a]. Thus, modules potentially represent a stage in the evolution of a cortical area. This does not imply that at any stage modules are not functionally significant to neocortical processing [see Kaas, 1997]. Indeed, this aggregation of modules need not occur if the present arrangement is adaptive. In this scenario, the addition of a new cortical area is commonly dependent on peripheral receptor changes or other changes in inputs to the cortex.

An alternate, but not mutually exclusive, proposition is that even in the absence of peripheral changes, some sort of discorrelation could occur in thalamocortical afferents that allows for new combinations of inputs from existing tha-

lamic nuclei to terminate on the cortical sheet. Because comparative data suggest that thalamocortical afferents shift on the sheet across lineages, this proposition seems plausible and can account for the interspersion of new cortical fields between phylogenetically older fields.

A final possibility is that a simple change in the size of the cortical sheet allows for new types of thalamocortical and corticocortical interactions. Thus, the creation of a new cortical area may not depend on new inputs from the periphery. New classes of neurons can be created in the early forming cortical areas. These neurons and/or their connections to other cortical areas may produce modules and areas, and therefore may be sufficient to explain the emergence of new cortical fields. However, this latter 'intrinsic' hypothesis would require some disruption in the normal pattern of molecular gradients, or some changes to proliferative cells in the ventricular zone.

Studies of Cortical Plasticity

Thus far, we have limited this review to possible intrinsic, genetically driven contributions to phenotypic variability in cortical organization across species. However, we believe a major factor that contributes to the differences observed across mammals, both within and among species, is related to the ability of the neocortex to change or be plastic within the life of an individual. We know from studies of adult plasticity that changes in activity patterns of the sensory epithelium due to denervations, amputations, or specialized or repeated use result in cortical map reorganization [see Kaas, 1991, 2000a; Donoghue, 1995; Gilbert, 1998; Recanzone, 2000 for review]. If deprivations occur, the portion of the cortical map that normally represents the deprived sensory receptor surface decreases, and adjacent representations expand into that cortical space. This type of plasticity has been demonstrated for several sensory systems [e.g. somatosensory, Merzenich et al., 1983; 1984; Wall et al., 1986; Calford and Tweedale, 1990; visual, Kaas et al., 1990; Darian-Smith and Gilbert, 1995; auditory, Rajan et al., 1993]. On the other hand, under conditions in which a portion of the sensory epithelium is over-stimulated as in a training condition, the representation devoted to that body part expands [Recanzone et al., 1992a–c]. This is true for the motor system as well [Donoghue et al., 1990; Nudo et al., 1996; Sanes and Donoghue, 1997]. These types of expansions with use have also been observed in humans who play stringed instruments [Elbert et al., 1995], and in Braille readers [Pascual-Leone and Torres, 1993]. Further, large sensory domain shifts from visual to somatosensory have been observed in individuals blinded early in life. Visual cortex, which would normally not be activated during sophisticated tactile discriminations, comes to be activated during the reading of Braille [Sadato et al., 1996; Cohen et al., 1997].

The type of sensory domain shifts observed in blind individuals is compatible with observations in mammals in which the visual system has been greatly reduced, such as echolocating bats, platypus and blind mole rats. Presumably genetic changes to the sensory receptor sheet would have the greatest effect during the development of the nervous system. The types of contractions and expansions observed within cortical fields with expansions or contractions in the sensory epithelium are qualitatively similar to those observed within a cortical field in different phylogenies. These contractions and expansions that occur throughout the life of an individual cannot be passed on, and therefore do not represent true evolution. However, the ability of the neocortex to be plastic which is due in part to both ligand-gated and voltage gated membrane receptors could serve as the evolutionary vehicle for this phenomena.

The Relationship Between Cortical Plasticity and Phenotypic Variability Across Species

Without exception, any specialized body part or sensory surface associated with altered use results in an expansion of that sensory system and/or an increase in the amount of cortex devoted to the representation of the specialized sensory epithelium [Kaas, 2000b]. For example, the platypus uses its bill in underwater navigation, prey location and capture and has evolved a unique oscillatory movement of the bill while hunting, which allows the bill to serve as an antenna to obtain the direction and distance of prey [Fjällbrant et al., 1998]. Approximately 70–75 % of the entire neocortex is devoted to processing inputs from the bill. Another example is the glabrous hand of primates. Genetically mediated changes in the structure, receptor type and distribution are clearly associated with specialized behaviors such as tactile exploration and object manipulation. All anterior parietal areas in somatosensory cortex have very large representations of the hand [Merzenich et al., 1978; Nelson et al., 1980; fig. 6]. Likewise, large portions of motor cortex are devoted to the representation of the hand [e.g. Gould et al., 1986]. Finally, there is a region in posterior parietal cortex that contains neurons with bilateral receptive fields on the hand. This region is involved in the generation of functionally relevant behaviors associated

with the hand [active touch and exploration; Iwamura et al., 1994; Iwamura and Tanaka, 1996; Taoka et al., 1998]. Human primates engage in complex behaviors including sculpting, painting, Braille reading and the playing of musical instruments. Recent imaging studies of the human brain in individuals who excel in these specialized behaviors have indicated that the representation of the hand in anterior parietal somatosensory areas was larger than in normal individuals [Pascual-Leone and Torres, 1993; Elbert et al., 1995].

Examples of these types of specializations exist for the auditory and visual systems as well. Most echolocating bats are micropthalmic and have an increased cochlear surface related to behaviorally relevant frequencies [Suga, 1982; Kössel and Vater, 1985; Vater et al., 1985; Henson and Henson, 1991; Vater and Siefer, 1995]. The relative increase in the ratio of activity of hair cells to ganglion cells is likely to be pronounced in this animal. It is not surprising then that large scale changes in the amount of cortical territory occupied by auditory inputs, and the addition of specialized fields related to echolocation, have been observed [Suga, 1982]. Such large-scale changes in activity across different receptor surfaces could account for the sensory domain shifts observed in different lineages. In addition, more subtle changes within a given cortical area, such as enlargement of the cortical representation of a specialized portion of the receptor surface, or highly trained receptor surface, is likely to be due to similar forces, although the magnitude of the change is less dramatic.

Conclusions

Studies in developing animals indicate that the size of the cortical sheet is likely to be largely under genetic control. Further, recent studies in transgenic mice suggest that the graded expression of regulatory genes may instruct thalamocortical afferents (as yet unassigned) into the appropriate mediolateral and rostrocaudal locations. Genetically induced changes in peripheral morphology clearly contribute to differences in the organization of the neocortex. Changes in the size of the animal or size of a particular body part, an altered distribution of sensory receptors, and the evolution of a new receptor type are common modifications, and manifest in alterations in the functional organization of multiple levels of the nervous system (fig. 6). The map alterations observed in species over time are correlated with use-dependent changes and modifications of peripheral morphology, and are remarkably similar to changes observed in the cortex in normal adults with altered peripheral inputs.

Although many believe that activity refines the initial cortical organization set up by intrinsic, genetically mediated mechanisms in the cortex, we would argue that 'refinement' is too subtle a word. Rather, the amount of cortical territory captured by a specialized sensory system, and the changes in internal organization of cortical fields with respect to changes in peripheral morphology, must be highly dependent on activity. The match between the periphery and the cortex is precise, and is unlikely to be due to simultaneous mutations along the entire neuroaxis. We believe that small genetic changes that affect either the central or peripheral nervous system or both can have far reaching effects. For example, genetically induced changes in the size of the cortical sheet can have a top-down effect on the entire neuroaxis. We know that a simple reduction in the size of the immature cortical sheet before thalamocortical afferents have arrived results in proportionate reductions in other structures of the central nervous system such as the dorsal thalamus and superior colliculus [Huffman et al., 1999].

Additionally, changes in the sensory receptor sheet can have a bottom-up effect. For instance, animals enucleated bilaterally early in development have a reduced LGN and inferior pulvinar in the thalamus, and a reduced striate cortex, V1 [DeHay et al., 1991, 1996]. In mice selectively bred for supernumerary whiskers, the primary somatosensory area, S1, becomes larger than in normal mice [Welker and Van der Loos, 1986]. Of course in these animals, it is difficult to separate the effects of genetically mediated receptor differences from the role of alterations in activity patterns. Regardless, changes in either the size of the cortical sheet or the sensory epithelium may be sufficient to explain changes in the size of structures along the entire neuroaxis.

The role neural activity plays in phenotypic alterations of mammalian brains is clearly important. These phenotypes are normally distributed within a species, and any given genotype is capable of developing into a wide range of phenotypes within this distribution. The width of the distribution (the variability) is likely to be dependent on the feature in question and its impact on survival. Thus, the regions of the brain that control basic homeostatic functions, such as cardiovascular integrity, are likely to be highly conserved across species, under strict genetic control, and the phenotypic organization of these centers probably can be described by a relatively narrow distribution (i.e. not highly variable across species). Indeed, the organization and neuropharmacology of the brain stem, medulla and spinal cord nuclei responsible for this function appear to be relatively static across species [Ross et al., 1984; Somogyi et al., 1989; Morrison et al., 1991; Aicher et al., 1995]. On the other hand, comparative studies demonstrate that the orga-

nization of the neocortex is highly variable across species, due to both genetic and epigenetic influences. Although only genetic changes can account for evolutionary change, the larger issue of phenotypic variability requires examination of epigentic influences as well.

We believe that there are both passive and active environmental influences. Passive environmental influences include changes in temperature, pH, levels of pathogens in the environment, and nutrition, for example. When one of these influences is extreme, as in the case of fetal alcohol syndrome, a viable phenotype may be produced, but it may lie in the tail of the distribution of phenotypes. Active environmental influences include the increased use of a specialized receptor surface, such as a glabrous hand, the bill of a platypus or the cochlea of an echolocating bat. In humans there are more complex active influences such as language and social and cultural learning. These types of interactions within a group influence the development of any individual brain within the group, and contribute to the phenotype that will ultimately be expressed.

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