23 Captured in the Net of Space and Time: Understanding Cortical Field Evolution

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Glossary

analogous	Having the same function.
Baldwin effect	The ability of an animal to respond optimally to a given environment.
cortical domain	The portion of cortex devoted to a given sensory system.
cortical field	The fundamental organizational feature of the cortex.
cortical field magnification	The amount of cortex within a cortical field devoted to processing inputs from a behaviorally relevant body part is enlarged.
evolvability	The ability of an organism to generate heritable, selectable phenotypic variation.
genetic assimilation	How an environmentally induced phenotypic characteristic becomes genetically coded in a population.
homologous	A characteristic inherited from a common ancestor.
homoplaseous	An independently evolved characteristic that looks the same across species.
module	Smaller units of organization within a defined cortical field.
pleiotropy	A single gene controls numerous activities during development resulting in various phenotypic effects in the adult organism.

23.1 Introduction

Examination of a number of different mammalian brains demonstrates that brain organization, particularly the neocortex, varies dramatically across species. This variation in neocortical organization is accompanied by a considerable degree of behavioral diversity. Specifically, differences in cortical sheet size, organization, number of cortical fields, and connections are associated with differences in sensory, perceptual, cognitive, and motor abilities. How these differences in neocortical organization in mammals arise in evolution and how these alterations generate variable behavioral repertoires are difficult questions to investigate directly because the evolutionary process is highly dynamic, and alterations to the brain occur over hundreds of thousands to millions of years. Despite the fact that evolution cannot be studied 'head on', we can circumvent the problems associated with studying evolution in two ways. First, we can examine the products of evolution, namely extant mammals, and compare their brain organization, to make inferences about the evolutionary process. Alternatively, we can study the developmental processes that generate different aspects of brain organization, since the evolution of the neocortex is the evolution of the developmental mechanisms that give rise to adult phenotypes. We can then postulate how developmental mechanisms may have been altered to produce different phenotypes (see The Origin of Neocortex: Lessons from Comparative Embryology).

The use of the comparative approach has led to number of important insights regarding brain evolution. Likewise, studies of development, particularly recent molecular studies, have provided much needed information on the genes that are involved

in various aspects of cortical development and organization. However, utilizing the comparative or the developmental approach in isolation in an attempt to uncover principles of brain evolution is problematic. In terms of the comparative approach, examining any extant mammal allows us to observe only a static moment in the evolutionary process. In essence, we have captured, in our net of space and time, a number of individual phenotypes, or individual snapshots, in a process that is constantly in a state of flux. We take these snapshots out of our net, use a number of different tools to dissect and examine them, and then put them together to make an evolutionary moving picture. The problem is that each extant mammalian brain that we observe is a frozen frame or moment in its own moving picture; it has its own evolutionary history and will move in a unique future trajectory. Further, this approach tells us little about the transition between frames and how phenotypic transformations may occur. This is where studies of cortical development merge with comparative analyses.

Studies of the development of the nervous system can strengthen our inferences regarding how phenotypic transitions occur by providing a number of possible mechanisms for this process. However, like the use of the comparative approach, using a developmental approach in isolation to understand brain evolution is problematic. While a number of recent studies provide insight into potential mechanisms that could be involved in some aspect of cortical organization, such as regulating cortical sheet size, they do not demonstrate that such a mechanism is actually being employed in a naturally evolving system. Thus, only by combining both the comparative approach and developmental approach can we appreciate the types of changes that have occurred in different lineages, predict how these transitions may have happened, and validate these predictions by manipulating some aspect of development and determining if the resulting phenotype is consistent with a type of neocortical organization that would naturally occur, as validated through comparative studies.

In this article, we begin by exploring what constitutes a cortical field and discuss homologous features of cortical organization across mammals. Next, we discuss the importance of distinguishing homology from instances of homoplasy when making comparisons across species. Because the concepts regarding what constitutes a cortical field are changing in light of new studies on molecular development, in the second section of this article we discuss some of the molecular aspects of cortical field development, and describe both intrinsic and extrinsic contributions to cortical development, and the role of peripheral morphology and behavior in shaping the cortical field throughout the life of an individual. Then, we discuss the evolution of the neocortex and outline the types of systems level modifications that have been made to evolving brains. Finally, we speculate on the idea that the neocortex evolves to be flexible, and that genetically based adaptations of the brain and body may initially have been activity-dependent features of organization that were present only under unique and consistent environmental conditions.

23.2 What is a Cortical Field? Homology, Homoplasy, and Analogy

A cortical field is considered to be the principal organizational feature of the cortex, and most neuroscientists would contend that the addition of cortical fields to the neocortex is what endows greater degrees of neural and behavioral complexity to mammals. Indeed, most would agree that the neocortex, in general, and cortical fields, in particular, are the essence of the mammalian brain; the feature that distinguishes mammals from other vertebrates. We raise the question of what is a cortical field because this issue is particularly important for the study of cortical evolution. If one is interested in the evolution of the neocortex and the addition of cortical fields, then defining homologous cortical fields across mammals is critical. Specifically, it is important to determine which features of the cortical field are most usefully compared across species, and ultimately to appreciate how these features change during evolution.

Although concepts regarding what constitutes a cortical field are changing in light of new studies on the molecular development of the neocortex, in adult mammals, a cortical field is determined by a number of well-defined anatomical, histochemical, and electrophysiological criteria. These criteria were previously outlined by Kaas (1982), and although not exhaustive, have enabled investigators to subdivide the neocortex in a variety of mammals with a high degree of success. Some of these criteria include a complete representation of the contralateral sensory surface (or visual field for visual cortical areas), a unique architectonic appearance, and a distinctive pattern of connectivity. Other criteria include utilization of some subset of neurotransmitters, or the presence of particular behavioral deficits when the area is lesioned. Because errors can be made in subdividing the neocortex when any single criteria is used in isolation, using a combination of criteria to subdivide the

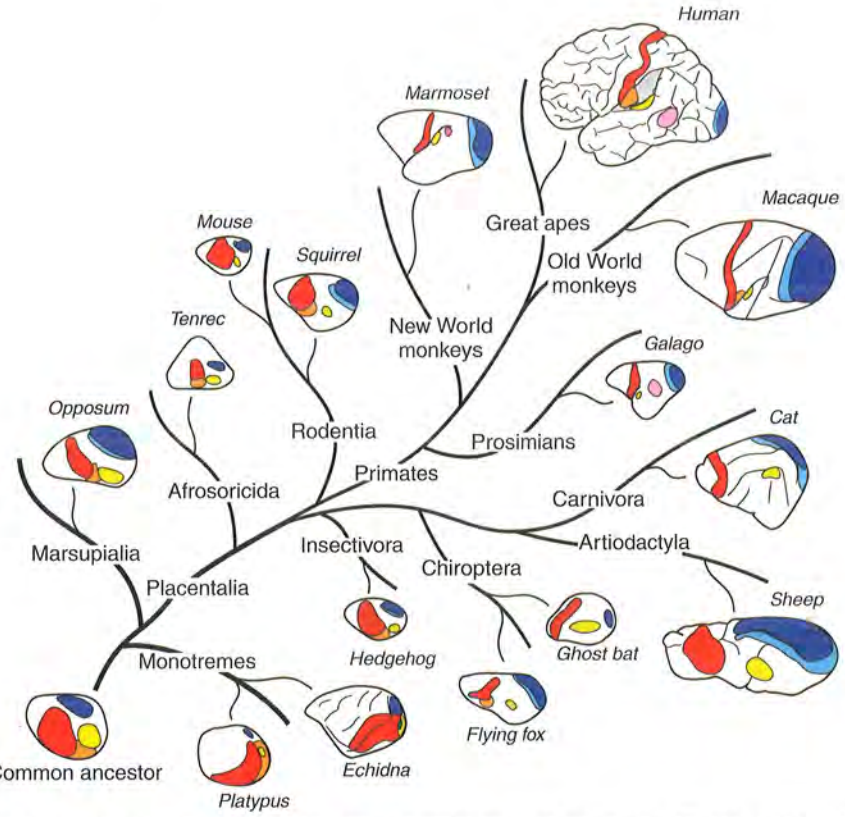

Figure 1 A phylogenetic tree depicting the relationships between major mammalian lineages. The cortex of each mammal contains a constellation of cortical fields that have been identified in all mammals examined. These cortical areas were likely inherited from a common ancestor, and therefore are homologous. Although the organization of the neocortex of the common ancestor is not known, a cladistic analysis allows one to infer the organization of unknown forms, such as the common ancestor. Dark blue = primary visual area; light blue = second visual area; red = primary somatosensory area; orange = second somatosensory area; yellow = primary auditory area; pink = middle temporal visual area. Redrawn from Krubitzer, L. and Kahn, D. 2003. Nature vs. nurture: An old idea with a new twist. *Prog. Neurobiol.* 70, 33–52.

neocortex allows for more accurate comparisons of cortical organization across mammals.

Using these criteria, it has been determined that in some mammals, such as mice, the number of areas that compose the neocortex is relatively small, on the order of 7–12 cortical fields. In other mammals, such as macaque monkeys, the number of cortical fields is larger, on the order of 30–50 cortical areas (see Kaas, 1988, 1993, for review). This increase in the number of cortical fields in some lineages, at least in part, is the neural basis of complex behaviors such as sophisticated communication (language in humans), learning, and cognition. While the number of cortical fields is highly variable in mammals, several cortical fields are common to all species (see Krubitzer, 1995; Krubitzer and Kahn, 2003; Krubitzer and Kaas, 2005). These fields include the primary sensory areas (primary visual area, V1; primary somatosensory area, S1; and primary auditory area, A1), second sensory areas (secondary visual area, V2; secondary somatosensory area, S2; secondary auditory area, A2, and rostral auditory area, R), as well as motor areas such as primary motor area, M1 (Figure 1). These fields are homologous because they have been identified in all mammals examined, and it is likely that these cortical areas arose early in mammalian evolution and were inherited from a common ancestor in all lineages, rather than having evolved independently in each group. As such, a number of features of organization are similar across groups of mammals including similarities in topographic organization, aspects of cortical architecture, and thalamocortical and corticocortical connections. Later in this article we will discuss the types of modifications made to this homologous plan of organization and how these modifications might have arisen in evolution.

A broad comparative analysis also indicates that some features of cortical organization look strikingly similar in different mammals, but this similarity is not due to inheritance from a common ancestor. Rather, these features are homoplaseous, and have independently evolved in each mammal.

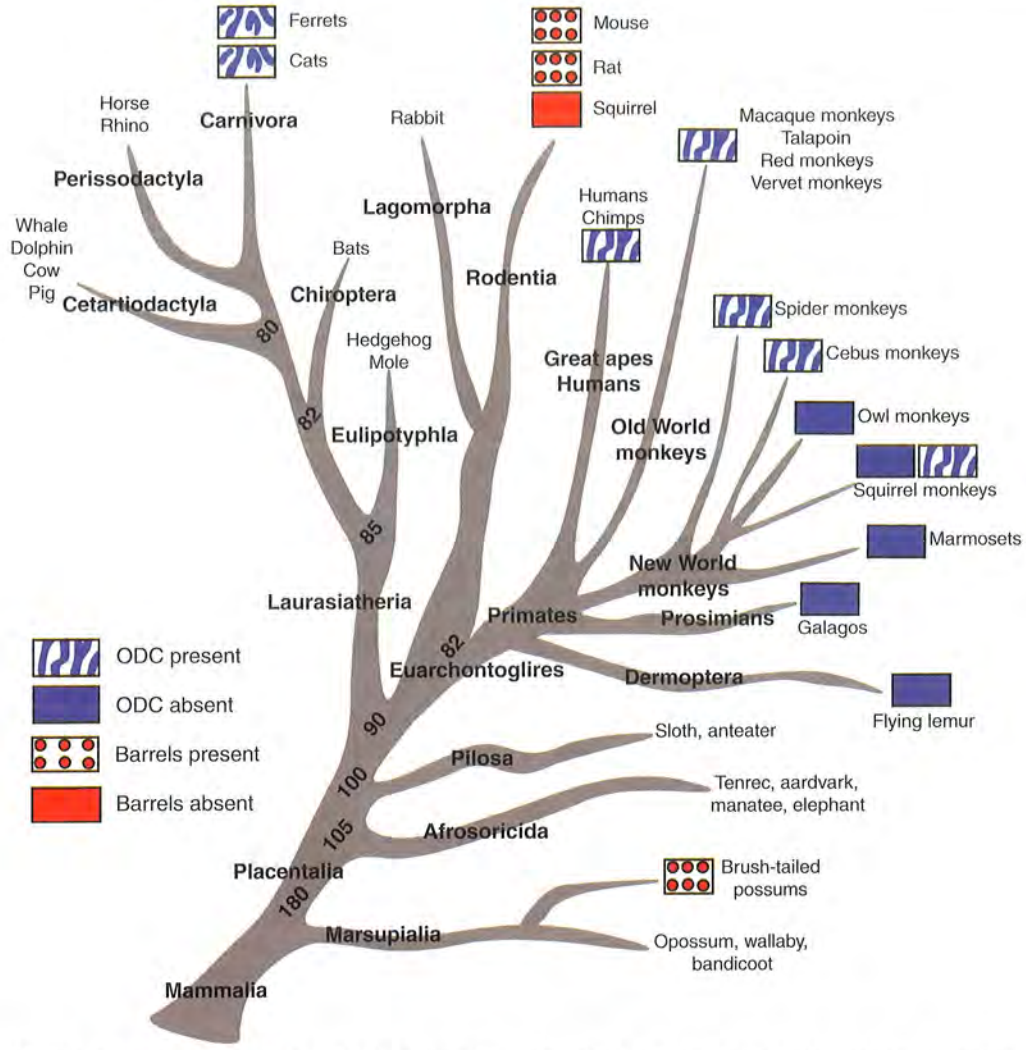

Figure 2 Homoplasy-independent evolution: a phylogenetic tree depicting the relationships between major mammalian lineages and the emergence of independently evolved features of cortical organization. Because the emergence of barrels in mice and rats arose independently from those in brush-tailed possums, they are considered as homoplaseous rather than homologous. Likewise, the presence of ODCs in ferrets and cats arose independently from those in some primate lineages. The fact that such similarities in organization emerge in different lineages despite over 90 million years of independent evolution indicates that the evolution of the neocortex is highly constrained. It also indicates that although the features themselves are homoplaseous, their presence could reflect the presence of homologous developmental mechanisms. Phylogenetic relationships based on Murphy, W. J., Pevzner, P. A., and O'Brien, S. J. 2005. Mammalian phylogenetics comes of age. *Trends Genet.* 20, 631–639.

An excellent example of a homoplaseous feature of the neocortex is the barrel field in the rat and mouse, and the brush-tailed possum (Figure 2; Weller and Haight, 1973; Weller, 1993). An out group comparison indicates that no intervening group of mammals has barrel cortex. Thus, the most parsimonious explanation for their presence in each group is that they have evolved independently in rodents and brush-tailed possums. Another example of homoplasy is the presence of ocular dominance columns (ODCs) in carnivores and some primates. ODCs are present in great apes and humans (Tigges and Tigges, 1979; Horton and Hedley-Whyte, 1984), Old World monkeys (e.g., LeVay *et al.*, 1975; Florence and Kaas, 1992), and a few species of New World monkeys (e.g., Florence *et al.*, 1986; Rosa *et al.*, 1992). They are absent in other New World monkeys, prosimians, and dermopotera (Figure 2), and in all other clades except carnivores (e.g., Löwel and Singer, 1987; Law *et al.*, 1988). This out-group comparison indicates that ODCs arose in primates after the divergence of New and Old World monkeys from prosimians (approximately 70 Mya), and that ODCs were lost in some New World species. The presence of ODCs in only two species of carnivores suggests that ODCs arose

independently in carnivores and primates, since the lineage that leads to carnivores diverged from that leading to primates over 90 Mya, and no intervening groups possess ODCs. What is remarkable about ODCs and the barrel cortex is that despite 90–180 million years of independent evolution, the arrangement of these modules looks very similar in carnivores and primates, and in rodents and brush-tailed possum respectively.

When making cross-species comparisons, there is often an assumption that homologous fields perform the same function or are analogous. However, this may not be the case. For example, over the years, a solid case for the presence of V1 in a variety of species has been established. All data indicate that V1 resides on the caudal pole of occipital cortex, contains a complete, first-order representation of the visual hemifield, receives connections from the dorsal division of the lateral geniculate nucleus (LGNd) of the thalamus, and has a striated appearance in tissue that has been sectioned perpendicular to the cortical layers and stained for Nissl substance. In cortex that has been sectioned tangentially and stained for myelin, V1 appears as a densely myelinated wedge at the caudal pole of the neocortex. Given these identifying features, V1 is proposed to be homologous across all mammals, and to form a basic component of a visual processing network in the mammalian neocortex. But what of analogy? Does it naturally follow that V1 as a homologous cortical area has a similar function or set of functions across groups of mammals?

The answer is 'no'. If we examine V1 in the mouse and compare it to V1 in the macaque monkey, several differences emerge. Most notable are the addition of modules to V1, such as orientation and ODCs, the addition of visual cortical fields, and the concomitant change in cortical connections in monkeys. Thus, V1 in monkeys and mice varies substantially in organization, and intrinsic and extrinsic connectivity. To illustrate this concept we have drawn a simple circuit containing three separate nodes (cortical fields A, B, and C in Figure 3). These nodes have a homologous pattern of interconnection across mammals (connections 1, 2, and 3 in Figure 3). In some groups of mammals, the nodes have been further subdivided to mimic the generation of modules (Figure 3). In addition, new nodes, representing new cortical areas, have been added to the network (D, Figure 3), which result in the addition of new connections and a potential re-weighting of existing connections between homologous nodes. This example shows that because of the emergence of new organizational features

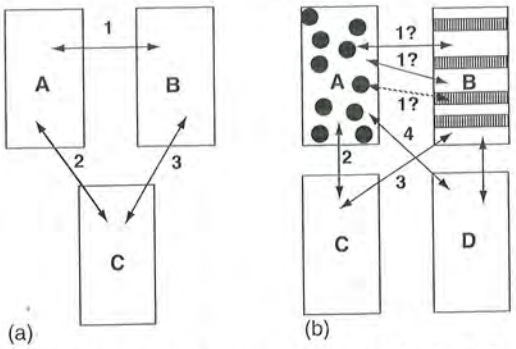

Figure 3 A hypothetical processing network (a) originally consisting of three cortical fields (A, B, and C) with a set of interconnections (1, 2, and 3). The evolution of this network (b) includes the addition of a new cortical field (D), the emergence of modules within existing cortical fields (circles in A and stripes in B), the emergence of new connections (4), and the re-weighting of existing connections (compare thick vs. thin line of connection 2 in (a) and (b)). These types of changes that naturally occur in evolution, indicate that homologous cortical fields may not be analogous since the interconnection relationships change and intrinsic processing modules emerge.

(modules), new inputs, and a re-weighting of retained connections, homologous cortical fields may not have the same function.

In answer to the question posed at the beginning of this section 'what is a cortical field?', we believe that it may be fruitful to consider cortical fields, at least in part, as homologous patterns of interconnection upon the cortical sheet. These patterns appear to be quite robust across species, and are associated with the emergence of specific architecture and neural properties in the developing nervous system. While maintaining their global relationships, these patterns shift, or 'float' upon the cortical sheet within the life of an individual (particularly during development), and to a greater extent, within and across species over time.

23.3 The Development of Cortical Fields

It has been appreciated for some time that both genes and the environment, as broadly defined, contribute to the development and the organization of the neocortex. How each of these factors contributes to development is couched in the long-standing 'nature vs. nurture' debate (see Krubitzer and Kahn, 2003 for review). Fortunately, the issue of the inherent, genetic contribution to the cortical phenotype has recently crystallized into hypotheses which are amenable to vigorous experimentation regarding the temporal and spatial distribution of genes and proteins that occur in development, and give rise to aspects of cortical organization including

cortical field location, size, and connectivity. The 'nurture' side of the debate has also become more experimentally tractable, and questions regarding the activity-dependent cellular mechanisms that alter aspects of development including the expression of genes, regulation of synaptic morphology and function, and dendritic and axon growth are now being examined. The problem is that in some instances it is difficult to draw a distinct line between genetic and epigenetic contributions to the phenotype, and the two become intricately intertwined.

23.3.1 Nature: The Contribution of Genes to Cortical Field Development

Understanding how genes control cortical field development can be broken into three broad categories. First, there are several genes that are intrinsic to the neocortex which control specific aspects of cortical development. The expression of these genes occurs in the normal developing system, and their action is independent of neural activity. Second, the expression of some genes in the central nervous system is induced by activity and requires feedback from the developing system to become activated. Finally, there are genes that regulate aspects of the body plan and peripheral morphology that contribute substantially to aspects of cortical organization.

23.3.1.1 Activity-independent genes intrinsic to the neocortex Recent work indicates that genes intrinsic to the neocortex, or the developing ventricular zone, control a number of aspects of cortical development, all of which have a large impact on the organization and function of the neocortex in the adult phenotype. Some examples include the regulation of the size of the cortical sheet, cortical field coordinates in the rostrocaudal and mediolateral axis, and thalamocortical connectivity.

In terms of the overall size of the cortical sheet, studies on cell cycle kinetics of neocortical progenitor cells in the ventricular zone indicate that the size of the cortical sheet is intrinsically regulated and that there are a number of plausible ways in which this regulation can occur. In general terms, the number of cells in the developing ventricular zone can be increased by extending the length of time that cells undergo symmetric divisions, and/or the rate at which cell divisions occur. A comparative analysis of small-brained mammals, such as mice, and large-brained mammals, such as macaque monkeys, indicates that cortical neurogenesis is both prolonged and accelerated in macaque monkeys compared to mice (Kornack and Rakic, 1998; Kornack, 2000). Several hypotheses regarding the specific genes and proteins involved in this process and the types of alterations to the kinetics of division have recently been proposed. For example, 'beta-catenin' is an intracellular protein that is expressed in neuroepithelial precursor cells during neurogenesis (Chenn and Walsh, 2002). In transgenic mice that over express a form of this protein, the size of the neocortex increases dramatically. This massive increase in the size of the cortical sheet is due to an increase in the proportion of progenitor cells that re-enter the cell cycle and continue mitotic division. Another gene proposed to alter cell cycle kinetics is *Brain Factor-1* (*BF-1* or *Foxg1*). This gene is expressed in telencephalic progenitor cells (Tao and Lai, 1992), and regulates cell proliferation and differentiation in the developing neocortex (Hanashima *et al.*, 2002). *BF-1* is regulated by *FGF2*, which is also involved in regulating cortical sheet size by determining the number of cycles of division that progenitor cells undergo during cortical neurogenesis. For example, injections of FGF2 into the ventricle of embryonic rats results in a substantial increase in cortical volume (Vaccarino *et al.*, 1999), and FGF2 knockouts have smaller neocorticies (Raballo *et al.*, 2000). These studies indicate that the disproportionate size of the neocortex in different lineages could be regulated in several ways by different genes that affect the kinetics and timing of cell division in the ventricular zone.

Related studies of cell cycle kinetics in monkeys indicate that primary areas, such as V1, may be specified very early in development, during neurogenesis. For example, in primates, V1 is characterized by an increase in cell density and laminar complexity compared to other cortical areas, and compared to other mammals. In development, the rate of production cells in the ventricular zone is higher in the region where V1 will ultimately reside than in other regions (DeHay *et al.*, 1993). Differences in laminar histogenesis for different regions of the ventricular zone have also been observed in mice (Polleux *et al.*, 1997). These studies indicate that areal differences arise very early in neocortical development, well before thalamic innervation of the neocortex occurs.

In addition to intrinsic mechanisms that operate during cortical neurogenesis to specify cortical fields, recent work indicates that somewhat later in cortical development, the transcription factors *Emx2* and *Pax6* are involved in the expression and

patterning of downstream genes in the rostrocaudal axis of the neocortex, and potentially even cortical field size. For example, experiments in which these genes are deleted result in shifts of downstream genes such as *Cad8* and *Cad6* either rostrally (for *Emx2* deletion) or caudally (for *Pax6* deletion; Bishop *et al.*, 2000). In addition to the observed changes in gene expression, *Emx2* and *Pax6* mutants also exhibit alterations in thalamocortical connectivity. In experiments in which *Emx2* is deleted and the neocortex is rostralized (e.g., rostral cortical fields are shifted caudally), cortex at the caudal pole that would normally receive thalamic input from the LGN receives inputs from the ventral posterior nucleus (VP) (which normally projects to somatosensory cortex rostral to this region; Bishop *et al.*, 2000). Furthermore, mice in which *Emx2* is overexpressed have a significantly larger V1 than in normal animals (i.e., cortex has been caudalized; Hamasaki *et al.*, 2004).

In terms of connectivity, some of the cadherins appear to regulate thalamocortical connectivity. For example, *Cad6*, *8*, and *11* are expressed in unique subsets of thalamic afferents (Suzuki *et al.*, 1997; Korematsu and Redies, 1997). Further, *Cad6* is co-localized with the synaptic marker, synaptotagmin, and is correlated with the formation of synaptic connectivity between a source and its target in the developing nervous system (Inoue *et al.*, 1998). The ephrins have also been proposed to play a role in thalamocortical development. While their presence in locations extrinsic to the neocortex, such as the ventral telencephalon, serves a role in gross topographic guidance, they appear to intrinsically mediate the refinement of thalamocortical connectivity within a cortical field (see Vanderhaeghen and Polleux, 2004 for review). For the development of cortical connections, recent work has demonstrated that FGF2, which may be regulated by *Emx2*, is involved in guiding (modulating) corticocortical connections (Huffman *et al.*, 2004). Thus, the transcription factor *Emx2* controls a genetic cascade involved in structure formation, location, and connections.

It is important to note that evolutionarily, this type of regulation of events imposes formidable constraints on the developing and evolving nervous system. Given the constraints imposed by such a contingent system, it seems inevitable that very small changes in the timing and spatial distribution via base substitutions, recombination, and transposition, for example, of any one of the genes involved in these aspects of cortical field development can have a very large effect on the phenotype.

As mentioned earlier, a recent perspective on how cortical fields should be defined is to consider the subdivisions or areas of the neocortex from a spatiotemporal perspective. In this view, cortex is examined over time as a series of coordinated patterns of gene expression which are thought to be involved in generating features of the neocortex that will ultimately be realized in the adult, such as cortical layering, architecture, transmitter utilization, and connectivity. While this perspective is certainly important from both a developmental and evolutionary perspective, it may not be appropriate to define a cortical field in terms of the patterns of gene expression exhibited early in development for two reasons. First, the direct relationship between a functionally defined cortical field and some pattern or patterns of gene expression has yet to be established. Second, in the neocortex, early patterns of gene expression often represent potential, while the adult form directly generates the behavior that is the target of selection.

23.3.1.2 Activity-dependent regulation of genes that control aspects of cellular morphology, connection, and function In addition to the genes we described above, a number of studies describe intracellular, molecular mechanisms that are driven and regulated by neural activity, and generate changes in the temporal expression of genes within a cell employing these mechanisms. Altering the expression of genes can change aspects of synaptic morphology. For example, recent work demonstrates that increases in intracellular calcium, due to changes in neuronal activity, trigger a cascade of events, including the activation of the cAMP pathway and phosphorelation of CREB, which binds to the regulatory region of a gene and induces transcription of genes (see Finkbeiner and Greenberg, 1998; West *et al.*, 2001 for review). There are several different types of molecules which are regulated by activity, and which in turn are involved in synaptic modeling during development. One of these is a class of proteins called neurotrophins. These proteins are relevant to the discussion above because their levels and secretion are regulated by activity, they are expressed in synapses, and they regulate morphological changes in both the pre- and postsynaptic elements (McAllister *et al.*, 1995, 1999; Lein *et al.*, 2000; McAllister, 2001 for review). Neurotrophins such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophic factor 4/5 (NT4/5) play a number of important roles in nervous system development

including mediation of rates of neuronal survival (see Levi-Montalcini, 1987; Miller and Kaplan, 2001 for review), induction of cell migration out of the ventricular zone (Borghesani *et al.*, 2002), regulation of the extent of axon outgrowth (Segal *et al.*, 1995), enhancement of dendritic outgrowth, and stimulation of protein synthesis in dendrites (Aakalu *et al.*, 2001).

Another group of molecules recently identified by Shatz and colleagues (Corriveau *et al.*, 1998; Huh *et al.*, 2000) are the class I major histocompatibility complex (class I MHC) antigens. The expression of class I MHC is reduced in the developing cat LGN with the application of tetrotótoxin (TTX) via intraocular injections given *in utero* (Corriveau *et al.*, 1998). TTX blocks neural activity by deactivating sodium channels. In cats that are monocularly deprived during the critical period, class I MHC expression is reduced in the eye-specific layers of the LGN that were deprived. Further, in mice lacking class I MHC, refinement of retinogeniculate connections is incomplete (Huh *et al.*, 2000). Thus, as in the above example for BDNF, activity controls the expression of these molecules, which in turn alters aspects of synaptic development.

While the above descriptions are brief and the intracellular processes that are modified by activity are not completely known, there are a number of potential intracellular mechanisms and molecules involved in nervous system construction whose action is modulated by activity. In the beginning of this section on development, we suggested that the boundary between genetic and activity-dependent contributions is somewhat blurred. This is the case for the scenario described above in which activity regulates gene expression, which in turn regulates aspects of nervous system construction and function. This type of activity-dependent regulation depends on calcium sensitive intracellular mechanisms that may be genetically determined and intrinsic to the composition of the cell. If this is the case, then the ability of the developing organism to respond to environmental fluctuations may be genetically specified and selected for in evolution, but the resulting phenotype would only be expressed in a particular environment (Krubitzer and Kahn, 2003; Krubitzer and Kaas, 2005). If the environment is stable, the specific phenotypic characteristic generated would be stable, and in essence would masquerade as an evolutionary (heritable) phenomenon.

23.3.1.3 Genes extrinsic to the neocortex but intrinsic to the organism contribute to aspects of cortical development and organization All mammals have a conserved body plan that includes forelimbs with distal appendages, hind limbs with distal appendages, a trunk, neck, head, face, snout, two eyes, two ears, one nose, and one mouth. Interestingly, this basic plan has been conserved in all vertebrates, due to genetic constraints, and like the neocortex, has been modified in a very limited fashion. Homeodomain genes, such as T-box genes and Hox genes, are involved in specification of the body plan; they arose early in the evolution of living organisms, and are highly conserved across taxa from arthropods to vertebrates (e.g., Patel, 2003; Boncinelli *et al.*, 1994; Schilling and Knight, 2001; Banerjee-Basu and Baxevanis, 2001; Showell *et al.*, 2004).

Despite the restrictions these genes place on the evolving body, morphological diversity of the limbs, head, and face abound. For example, limbs have been modified into wings (bats), flippers (dolphins), hoofs (ungulates), claws (cats), and hands (primates). For the head and face, alterations have been made to the location of the eyes on the head, the size, location, and mobility of the pinna, and the presence of vibrissae, follicles on a nose, or specialized oral structures. At a finer level of organization, the receptor arrays associated with a specialized morphology and behavior also undergoes modifications. However, like those of the body and brain, they are generally limited in number and include:

1. alterations in the location of receptors,
2. alterations in the density of receptors,
3. alterations in the number of receptors,
4. addition of new receptors, and
5. sensitivity of receptors.

Specific examples of some of these modifications would include the disproportionate amount and density of cutaneous receptors on the glabrous digit tips of the hands of primates, the concentration of cones at the fovea of primates and visual streak in rabbits (Hughes, 1977), the differential expansion of particular portions of the basilar membrane devoted to ultrasonic frequencies in echolocating bats (Ramprashad *et al.*, 1979), and the addition of electrosensory receptors in the bill of a platypus (Scheich *et al.*, 1986; Manger and Pettigrew, 1996), to name a few.

Not only does the actual structure of the body part contribute to features of cortical organization, but also how these body parts are utilized and modified for exploration is equally important. For example, for the somatosensory system, primates tactually explore objects with their glabrous hands, elephants with their distal trunk, muriad rodents with their vibrissae, the star nosed mole with the

many follicles of the nose, and the naked mole rat with their teeth (see Catania, 2005). Thus, body parts and associated receptor arrays that are used repeatedly and uniquely have large amounts of cortical space devoted to their representation in both sensory and motor cortex. Indeed, without exception, behaviorally relevant, specialized sensory receptor surfaces occupy a greater amount of cortical space than less relevant surfaces. This is observed at the sensory systems level in cortical domain allocation, and at the level of the individual cortical field (cortical magnification). A cortical domain is the amount of space allotted to a particular sensory system, and this differs for different mammals, even those with approximately the same size cortical sheet. For example the amount of cortical territory devoted to processing visual inputs is greater in the highly visual squirrel than in the mouse (Figure 4; Rosa and Krubitzer, 1999). In terms of cortical field magnification, the amount of cortex devoted to processing inputs from the fovea is greatly enlarged in V1 of primates compared to the amount of cortex devoted to processing inputs from the rest of the eye. For the somatosensory cortex, in S1 and other

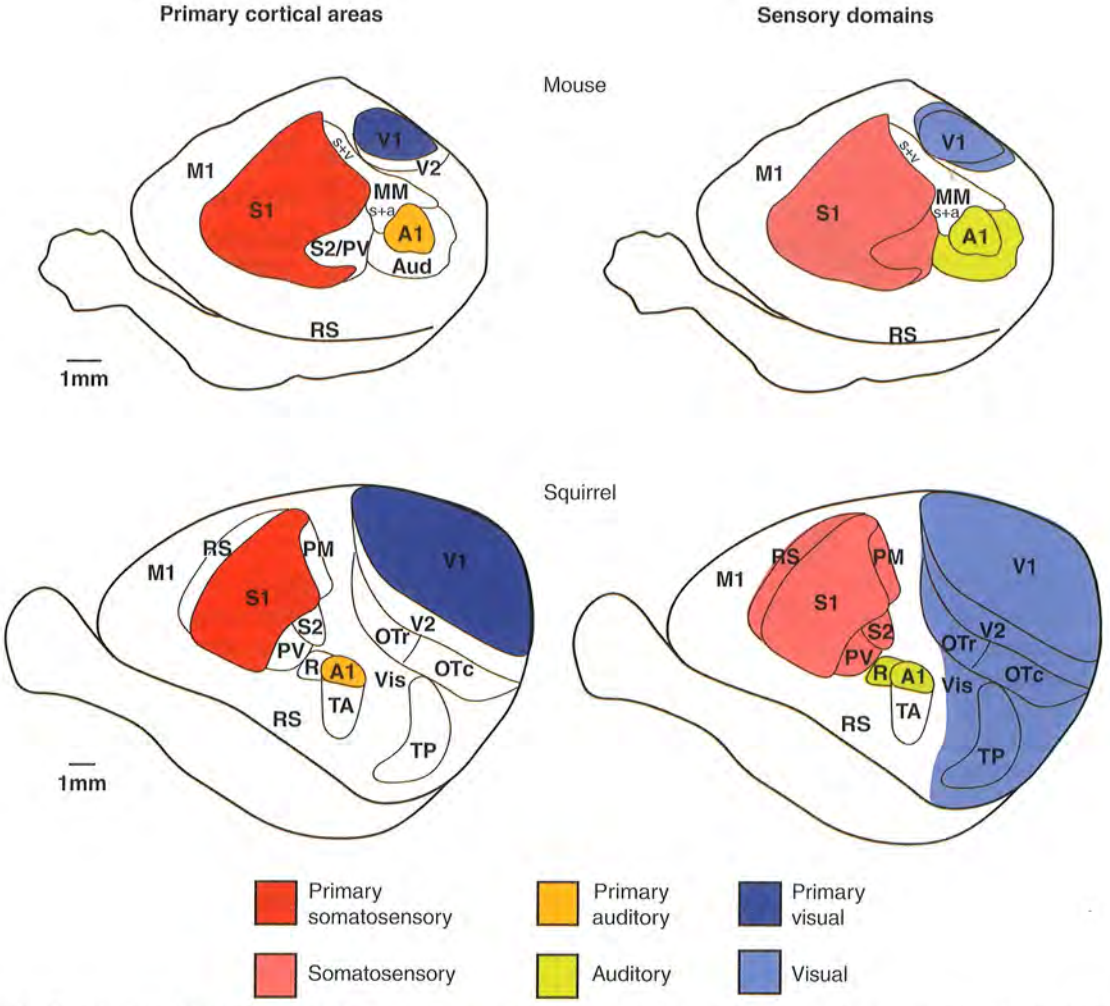

Figure 4 The organization of primary cortical areas and sensory domain allocation in the mouse (top) and squirrel (bottom). Each of these rodents occupies a particular niche and relies on different sensory systems for survival. The mouse is a terrestrial rodent that explores and navigates with its vibrissae, while the squirrel is an arboreal rodent that relies heavily on vision. Differences in cortical organization are observed at both the level of the cortical field and cortical domain. In the mouse, the primary somatosensory area is relatively large and occupies a good deal of cortex, while in the squirrel the primary visual area is relatively large compared to other primary sensory fields. Sensory domains, or the amount of cortex devoted to processing inputs from a particular sensory system, are also distributed differently in each species. In mice, the somatosensory domain is relatively large, while in the squirrel, the visual domain is extremely large and occupies at least one third of the entire cortical sheet. a, auditory; A1, primary auditory area; Aud, auditory; M1, primary motor area; MM, multimodal; OTc, caudal occipital-temporal cortex; OTr, rostral occipital-temporal cortex; PM, parietal medial area; PV, parietal ventral area; RS, rhinal sulcus; s, somatosensory; S1, primary somatosensory area; S2, secondary somatosensory area; v, visual; V1, primary visual area; V2, secondary visual area; Vis, visual.

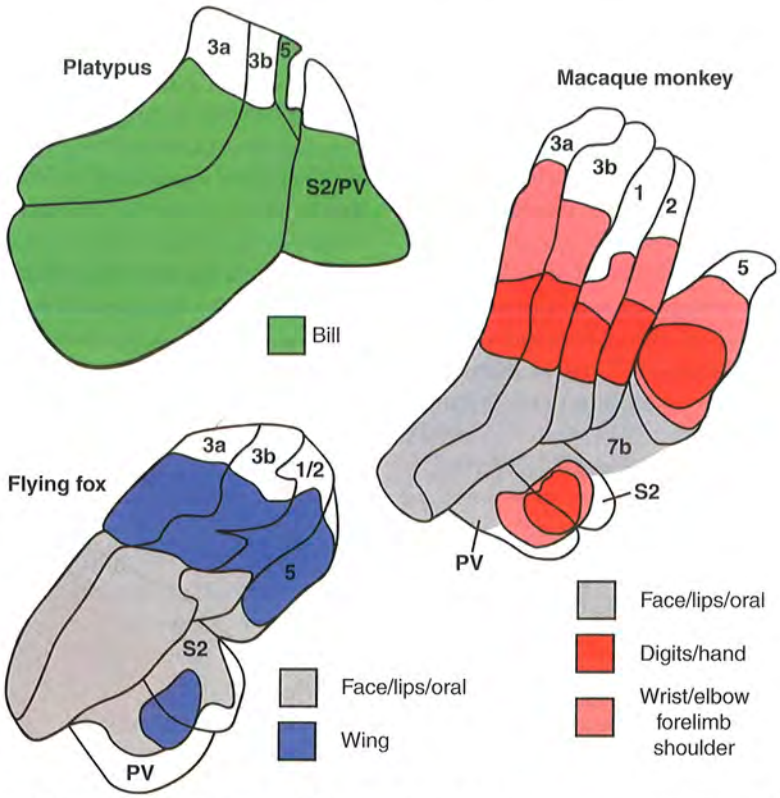

Figure 5 Cortical magnification of behaviorally relevant body parts within the somatosensory cortex of different mammals. In the duck-billed platypus, the bill representation (green) dominates all three somatosensory fields identified (R or area 3a, 3b, or S1, and S2/PV). In the highly dexterous macaque monkey, the representation of the glabrous digits (dark red), forelimb (light red), and oral structures (gray) dominate all somatosensory fields identified. In some fields, such as area 5, the magnification of the hand and forelimb dominates almost the entire field. Finally, in the flying fox, the wing (blue) and oral structures (gray) dominate all somatosensory areas identified.

cortical fields, the hand and mouth representations are magnified in primates, the wing and mouth representations are magnified in the flying fox, and the bill representation is magnified in the platypus (Figure 5; see Krubitzer and Disbrow, 2005 for review). As noted earlier, these specialized receptor surfaces are interfaced with the stimulus to be explored via specialized motor sequences. Thus, the motor system and the behaviors that allow for this interface are an integral part of sensory reception and cortical organization.

Since there is clearly an important relationship between cortical organization, peripheral morphology, and use, it is important to understand how body morphology evolves and how variability in body morphology is achieved in different lineages. Interestingly, the questions regarding diversification of the body plan in mammals are the same as those that arise when considering diversity in neocortical organization. Given the rather large constraints imposed on a basic plan of organization by these homeodomain genes, how can morphological diversity arise? It has been suggested that while the protein coding sequence of these homeodomain genes is relatively static across lineages, divergence in the regulatory portion of the gene can account for much of the morphological diversity observed in mammal body plans (Cretekos *et al.*, 2001). Thus, slight differences in the temporal and spatial patterning of genes generates large modifications in body plan organization. For example, the expression of a gene involved in the specification of the body plan (Hoxd9–13) was compared in two mammals with strikingly different forelimb morphology, the short-tailed fruit bat and the mouse (Figure 6; Chen *et al.*, 2005). Comparison of the distribution of Hoxd9–13 in bats and mice revealed that there were significant differences in the expression of this gene in the distal forelimb (dfl), but not the hindlimb, in later stages of limb development. Specifically, the anterior expression boundary of Hoxd9–13 in the bat is shifted posteriorly in the mouse (Figure 6). Thus, phenotypic diversity, or the transition from one phenotype to another that occurs in evolution, could be accomplished by subtle shifts in the expression of genes involved in

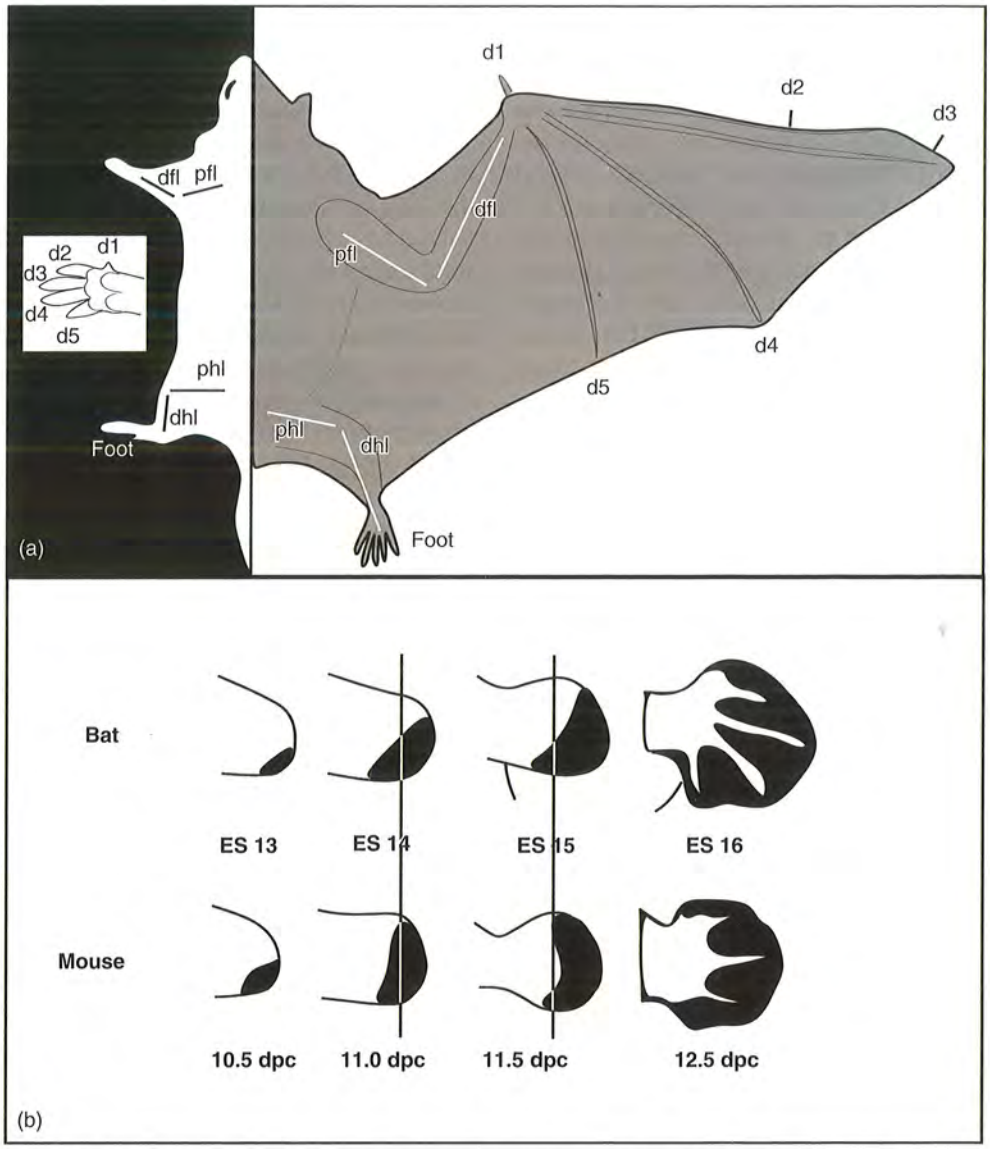

Figure 6 a, The body plan in mice and bats has a similar structural organization. Major body axis such as proximal and distal forelimbs and hind limbs (pfl, dfl, phl, and dhl), as well as individual digits (d1–d5), can be identified in both animals. However, modifications have evolved in each lineage in the form of the forepaw of a mouse and the wing of a bat. b, The expression pattern of Hoxd13 in the developing forelimb of the bat and mouse. The extent of the expression differences in bats and mice is evident during particular phases of limb development (bat ES 14, ES 15; mouse 11 dpc, 11.5 dpc), and such differences in homeodomain gene expression patterns could, at least in part, account for variations in forelimb morphology observed in each species. Such differences in expression are not noted for the hindlimb. dfl, distal forelimb; dhl, distal hindlimb; dpc, days post coitus; ES, embryonic stage; pfl, proximal forelimb; phl, proximal hindlimb. a, Modified from Cretekos, C. J., Rasweiler, J. J., and Behringer, R. R. 2001. Comparative studies on limb morphogenesis in mice and bats: A functional genetic approach towards a molecular understanding of diversity in organ formation. *Reprod. Fertil. Dev.* 13, 691–695. b, Modified from Chen, C. H., Cretekos, C. J., Rasweiler, J. J. T., and Behringer, R. R. 2005. Hoxd13 expression in the developing limbs of the short-tailed fruit bat, *Carollia perspicillata*. *Evol. Dev.* 7, 130–141.

major aspects of body and brain development. It should be noted that alterations in the temporal and spatial dynamics of gene expression have been known to account for variation of body segmentation in insects for some time (see Davis and Patel, 2002). It is only relatively recently that these well-established ideas from work on insects have been used to understand the evolution of the mammalian nervous system.

The case of body plan organization is another example where the boundary between intrinsic genetic contributions to the phenotype and activity dependent or environmental contributions are often difficult to draw. As Figures 4 and 5 illustrate,

specialized body morphology and use affect cortical domain allocation and sensory field magnification. The genes, which are involved in setting up the body plan organization, do not exclusively determine the final morphology of a particular body part, nor the resultant cortical organization. Indeed, several extrinsic factors related to the development of a body part contribute to the organization of the neocortex. For example, use directly affects the skeletal morphology, which in turn affects cortical organization. Several studies have shown that alterations in mastication behavior in development, often brought about by changes in diet, have a direct effect on craniofacial morphology (He, 2004), skull dimensions (Katsaros *et al.*, 2002), mandibular morphology (Bresin, 2001), and bone density (Davies *et al.*, 2005). The types of diet that produce such alterations during development are associated with hard versus soft food sources and the presence or absence of particular nutrients. Other extrinsic factors, which directly contribute to the development of body morphology and indirectly to cortical organization, are factors such as temperature, humidity, salinity, diet (see Johnston and Gottlieb, 1990 for review) and even gravity (e.g., Singh *et al.*, 2005). The observation that body plan morphology can be altered by epigenetic factors is analogous to the observations made for the neocortex. That is, despite the very large constraints imposed by regulatory genes on fundamental aspects of body morphology or cortical organization, a large degree of phenotypic variability is still possible, and alterations to the body plan can indirectly alter cortical organization.

23.3.2 Nurture: How Activity Contributes to the System Level Aspects of Cortical Development and Organization

The relationship between the cortical domain, cortical field magnification, peripheral morphology, and use in the adult mammalian neocortex has important implications for developmental and adult plasticity, and evolution. In terms of development, it seems clear that peripheral morphology, sensory receptor organization, and the specialized motor programs that are part of efficient sensory reception, play a very large role in determining a number of aspects of cortical organization that are observed in adult mammals. Several series of recent experiments in our laboratory in which peripheral sensory receptor arrays have been physically excised or activity has been modified throughout development underscore this point. For example, in a recent study *Monodelphis domestica* were bilaterally enucleated well before the retinal ganglion cells reached the diencephalon and before the thalamocortical afferents reached the neocortex (Kahn and Krubitzer, 2002). Using electrophysiological, anatomical, and architectonic analyses in these animals after they reached adulthood, we found large shifts in sensory domain allocation, in that all of cortex that would normally be occupied by the visual system was occupied by the auditory and somatosensory system (Figures 7a and 7b). Interestingly, architectonically defined area 17 was still present, although reduced in size, and major thalamic projections from the LGN were preserved. However, there were also alterations in thalamic projections in that area 17 or 'V1' received additional input from the VP nucleus, the medial geniculate (MG) nucleus, and nuclei in the anterior group (Kahn *et al.*, 2006). Further, corticocortical connections were altered in that area 17 received inputs from S1, A1, and frontal cortex. These patterns of thalamocortical and corticocortical connections are not observed in normal *Monodelphis* (Kahn *et al.*, 2000).

Related experiments in congenitally deaf mice revealed much the same results (Hunt *et al.*, 2005, 2006). These experiments were somewhat more subtle in that the sensory receptor array was not removed, but the ability to transduce auditory stimuli was eliminated in these animals throughout development. As with the blinded animals, congenitally deaf mice had large alterations in sensory domain allocation and alterations in cortical and thalamocortical connections (Figures 7c and 7d). All of cortex that would normally process auditory inputs contained neurons responsive to visual and somatic stimulation (Hunt *et al.* 2006). A surprising observation was that this lack of sensory driven activity resulted in alterations in connectivity at very early stages of sensory processing. In addition to its normal targets, the retina also projected to the MG nucleus and middle layers of the superior colliculus, structures generally associated with auditory processing (Hunt *et al.*, 2005).

In adult mammals, plasticity within cortical fields has been observed, but the magnitude of the reorganization is much less pronounced than that observed in developing animals. The studies that examined the relationship between sensory experience and cortical map reorganization detailed the precise conditions under which plasticity will occur and described the map changes that were generated under those conditions. For example, studies in which monkeys were trained on digit discrimination tasks demonstrated a direct relationship between increased discrimination performance and an increase in the cortical space in

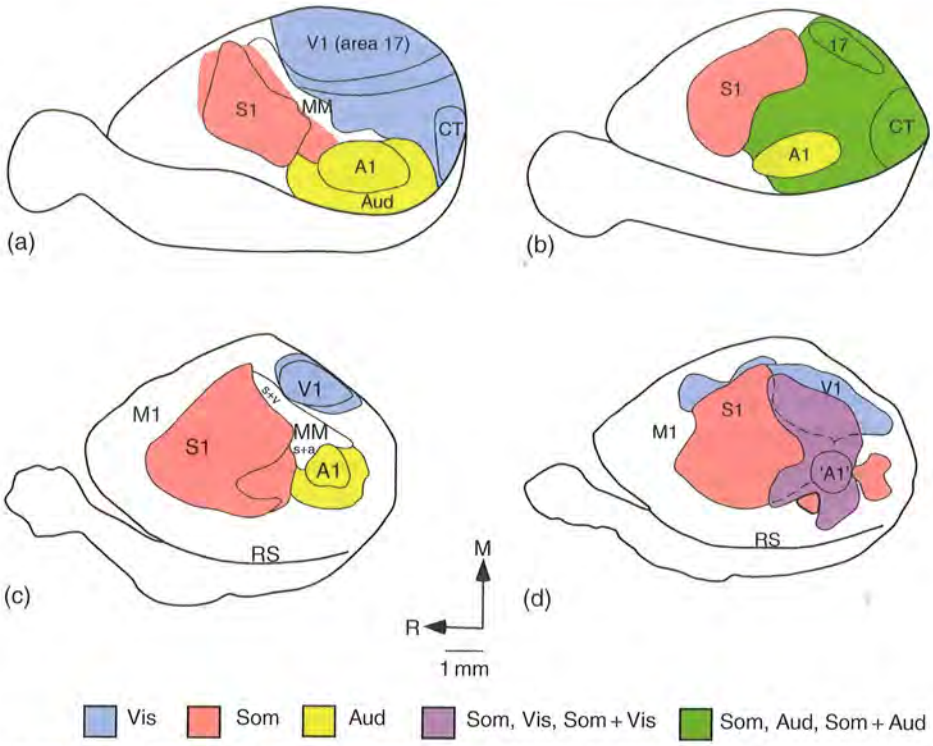

Figure 7 The organization of neocortex in normal opossums (a), opossums bilaterally enucleated very early in development (b), normal mice (c), and congenitally deaf mice (d). In the normal animals, both cortical fields and cortical domains are illustrated. In the bilaterally enucleated opossum, all of cortex that would normally be involved in visual processing, contains neurons responsive to somatic, auditory, or both somatic and auditory stimulation (green). In the congenitally deaf mouse, the cochlea is still present and a reduced eighth nerve exists, but no auditory driven activity is present. In this mouse all of cortex that would normally be devoted to processing auditory inputs contains neurons responsive to somatic, visual, or both somatic + visual stimulation. In both of these animals, the cross modal plasticity is extremely large such that all of cortex that is deprived of normal inputs is responsive to new types of sensory stimulation. In both mice and opossums, the cortical areas deprived of their normal inputs can still be identified architectonically, but at least in the opossum, the fields are smaller than in normal animals. a, auditory; A1, primary auditory area; Aud, auditory; M1, primary motor area; MM, multimodal; RS, rhinal sulcus; s, somatosensory; S1, primary somatosensory area; Som, somatosensory; v, visual; V1, primary visual area; Vis, visual. b, Modified from Kahn, D. M. and Krubitzer, L. 2002. Massive cross-modal cortical plasticity and the emergence of a new cortical area in developmentally blind mammals. *Proc. Natl. Acad. Sci. USA* 99, 11429–11434. d, Data from Hunt, D. L., Yamoah, E. N., and Krubitzer, L. 2006. Multisensory plasticity in congenitally deaf mice: How are cortical areas specified? *Neuroscience* 139, 1507–1524.

S1 (area 3b) devoted to the trained digit, while no expansion of adjacent nontrained digits was observed (Figure 8a; Recanzone *et al.*, 1992a, 1992b). Further, a requisite of the expansion was that the animal must attend to the task; repeated passive stimulation of the digit alone did not result in an expansion. Similar results have been observed for the auditory and motor cortex. In the auditory system, discrimination training of particular frequencies leads to an expansion of the cortical space devoted to that frequency (Figure 8b; Recanzone *et al.*, 1993). Likewise, training in a motor control task that involves particular hand movements, results in an expansion of those movement representations in motor cortex (Nudo *et al.*, 1996). These studies are important because they are the first to demonstrate a direct relationship between alterations in the neocortex with learning, and thus, the neural substrate for behavioral fluidity within the life of the individual.

The studies of developmental and adult plasticity demonstrate that peripheral morphology, sensory driven activity, and in normal circumstances, the behaviors associated with sensory reception play a large role in generating aspects of cortical organization including sensory domain assignment, cortical field size, the amount of space devoted to representing a particular body part or sensory receptor surface, and cortical and subcortical connectivity. These alterations are independent of the genes intrinsically expressed in the neocortex, which restricts the avenues along which evolution can travel. Thus, despite these restrictions, a fair amount of functional and anatomical fluidity is possible both within the life of an individual and in species over the course of evolution.

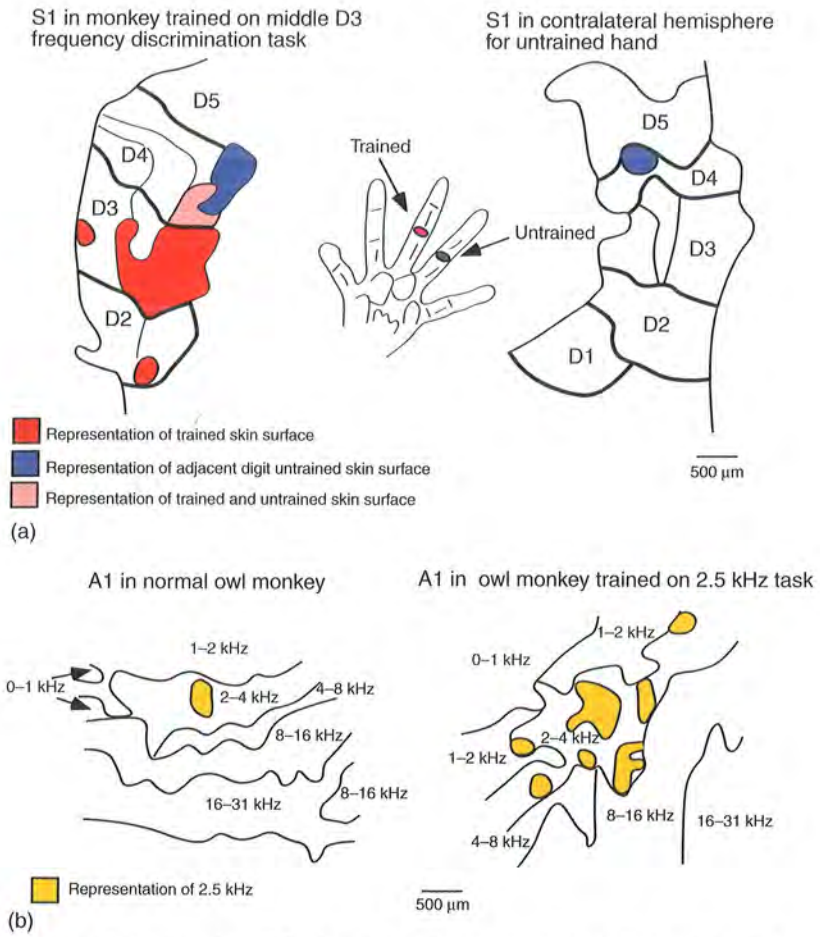

Figure 8 Cortical plasticity in adult owl monkeys following: a, somatosensory and b, auditory training. In the somatosensory cortex, training on somatosensory discrimination tasks increases the animal's ability to detect differences between two different stimuli, and this improvement in discriminatory ability is associated with an increase in the amount of neocortex devoted to representing the skin of the trained digit (red). In this case, the middle glabrous D3 was trained, and the contralateral S1 representing that portion of D3 (red) had an expanded representation compared to nontrained digits (blue). This plasticity was not observed in the hemisphere ipsilateral to the trained hand. Indeed, the portion of the cortex that represents the same location on the skin of the hand opposite to that trained was so small it was not found. A similar result was observed for the primary auditory cortex (A1). In owl monkeys trained on a 2.5 kHz discrimination task, the amount of cortex devoted to representing this frequency was expanded (b, yellow in left panel). A1, primary auditory area; S1, primary somatosensory area. a, Modified from Recanzone *et al.* (1992a, 1992b). b, Modified from Recanzone, G. H., Schreiner, C. E., and Merzenich, M. M. 1993. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J. Neurosci.* 13, 87–103.

23.4 The Evolution of Cortical Fields

Earlier in this article we described the basic plan of cortical organization that all mammals possess, likely due to inheritance from a common ancestor (homology). Despite the large alterations that can occur in peripheral morphology, use, and lifestyle, the basic aspects of organization and connectivity of these fields are highly stable across lineages. However, there are modifications to this plan of organization, and a comparative analysis reveals that, at least at the systems level, these modifications take a similar form. In this section, we will describe some of the alterations that have been made to the cortical sheet in general, and to cortical fields in particular. We then postulate how some of these changes may have arisen in evolution, based in part on the information we have gained regarding the developmental mechanisms that construct cortical fields and their connectivities.

23.4.1 Changes in the Size of the Cortical Sheet

In addition to considering the cortical field in isolation, it is also necessary to consider general features of the brain as a whole that vary in predictable ways across species, which in turn have a large impact on the internal organization of the neocortex and the cortical field. The most

obvious feature is a change in the size of the brain and the size of the cortical sheet. Observations in a variety of mammalian brains indicate that there are two distinct types of changes in cortical sheet size, one in which the entire brain and its parts, including the neocortex, increase in size proportionately, and one in which there is a disproportionate expansion of the neocortex relative to the size of the rest of the brain.

Proportional changes in the overall size of the brain can result in an absolute increase in the size of the cortical sheet and the size of cortical fields. For instance, marsupials range in size from 4g to 67kg. Like the body, the range in brain size in marsupials is extreme. The marsupials we have examined in our laboratory include the dunnart (marsupial mouse, *Sminthopsis crassicaudata*), striped possum (*Dactylopsila trivirgata*), quoll (*Dasyurus hallucatus*), and short-tailed opossum (*Monodelphis domestica*; see Huffman *et al.*, 1999). In all but the striped possum, the most remarkable difference in the brains of these animals is that of absolute size. For example, the quoll and dunnart are both Polyprotononts from the family *Dasyuridae*. They differ substantially in body size with the dunnart weighing an average of 10g, and the quoll weighing an average of 750g. However, both are terrestrial hunters, occupy a similar niche, and have similar sensory specializations related to their predatory lifestyles (i.e., well-developed visual system). Examination of the neocortex of each animal demonstrates a clear difference in absolute size. However, much of the organization in terms of relative location and size of primary cortical fields are remarkably similar. This is best illustrated when the quoll brain is scaled to that of the dunnart. This scaling of brain size to body size and neocortex size relative to the rest of the brain is observed in other orders of mammals as well. For example, in a wonderful comparative analysis by Campos and Welker (1976), the neocortex of the capybara and guinea pig were compared. These investigators demonstrated that the size and relative location of primary cortical fields in the very large capybara compared to the much smaller guinea pig scales with the size of the body and the size of the brain as a whole (Figure 9).

The idea that the size of a cortical field scales linearly with brain size must be qualified. Comparative analysis has also shown that with dramatic specializations in the sensory epithelium, concomitant changes occur in the amount of neocortex devoted to that specialized sensory system, and the sizes of primary areas associated with that sensory system increase. Thus, if cortical sheet size is held constant and the internal organization of two highly derived species is compared, then differences in the allotment of neocortex and cortical field size can be readily observed.

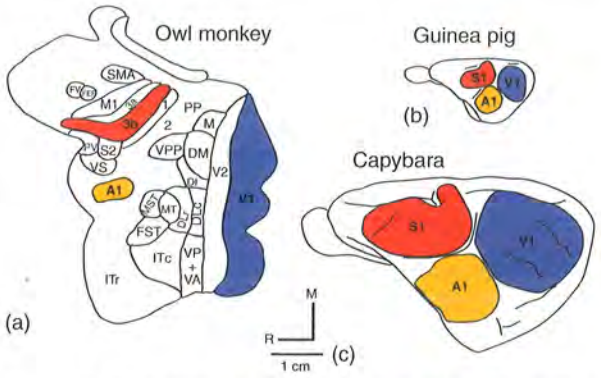

Figure 9 The organization of primary cortical fields in the: a, owl monkey; b, guinea pig; and c, capybara drawn to scale. In some species, the size of the brain has increased with body size, and the neocortex has increased in size proportionately with the rest of the brain (capybara). In this case, cortical field size has scaled linearly and the organization of the neocortex is much like that of other smaller rodents such as the guinea pig. In mammals, such as the owl monkey, whose body size is about ten times smaller than that of the capybara, the neocortex has enlarged disproportionately to the rest of the brain, although its absolute size approximates that of the guinea pig. With this disproportionate increase, the size of primary fields is reduced and more cortical fields are present. A1, primary auditory area; DLc, caudal division of dorsolateral visual complex; DLr, rostral division of dorsolateral visual complex; DM, dorsomedial visual area; FEF, frontal eye field; FST, fundal superior temporal area; FV, frontal ventral eye movement field; ITc, caudal division of inferotemporal cortex; ITr, rostral division of inferotemporal cortex; M, medial visual area; M1, primary motor area; MST, medial superior temporal area; MT, middle temporal visual area; PP, posterior parietal cortex; PV, parietal ventral area; S1, primary somatosensory area; SMA, supplementary motor area; V1, primary visual area; V2, secondary visual area; VA, ventral anterior area; VP, ventral posterior nucleus; VPP, ventral posterior parietal area; VS, ventral somatosensory area. a, Adapted from Krubitzer, L. and Kaas, J. H. 1993. The dorsomedial visual area of owl monkeys: Connections, myeloarchitecture, and homologies in other primates. *J. Comp. Neurol.* 334, 497–528. b and c, Modified from Campos, G. B. and Welker, W. I. 1976. Comparisons between brains of a large and a small hystricomorph rodent: Capybara, Hydrochoerus and guinea pig, Cavia; neocortical projection regions and measurements of brain subdivisions. *Brain Behav. Evol.* 13, 243–266.

The second type of size change that can occur is a disproportionate increase in the size of the neocortex compared to the rest of the brain. This results in a change in the pattern of neocortical organization. As in proportional increases in brain size, a disproportionate increase results in an absolute increase in the size of homologous cortical fields; however, the increase is less extreme than in the former type of size change. Furthermore, with a disproportionate

increase an additional organizational change to the neocortex is observed in that the number of cortical fields increases (Figure 9). This is nicely illustrated by comparing species that have different sized bodies, a similar absolute neocortical size, but a different neocortical size relative to brain and body size. For instance, although the capybara is well over 50 times the size of the owl monkey (50–70 kg vs. 1 kg), the neocortex of the owl monkey is disproportionately expanded, and its absolute size approximates that of the capybara. Examination of the neocortex of both species reveals very different types of organization. In the capybara, V1, A1, and S1 are large and compose much of the neocortex. In the owl monkey, V1, A1, and S1 are smaller than in the capybara, but many more cortical fields are present (Figure 9).

The question of how a disproportionate increase in neocortical size results in an increase in cortical field number is difficult to answer. It is possible that an increase in cortical field number, with an increase in the size of the neocortex relative to the rest of the brain, is due to a physical mismatch in the target (cortical sheet) and the projection zone (dorsal thalamus), or to a mismatch in the molecular coordinates between the thalamus and the cortex. This mismatch may result in new combinations of thalamocortical connections projecting to the expanded cortical sheet, in addition to the retained, highly restricted thalmocortical patterns of the primary and second sensory fields.

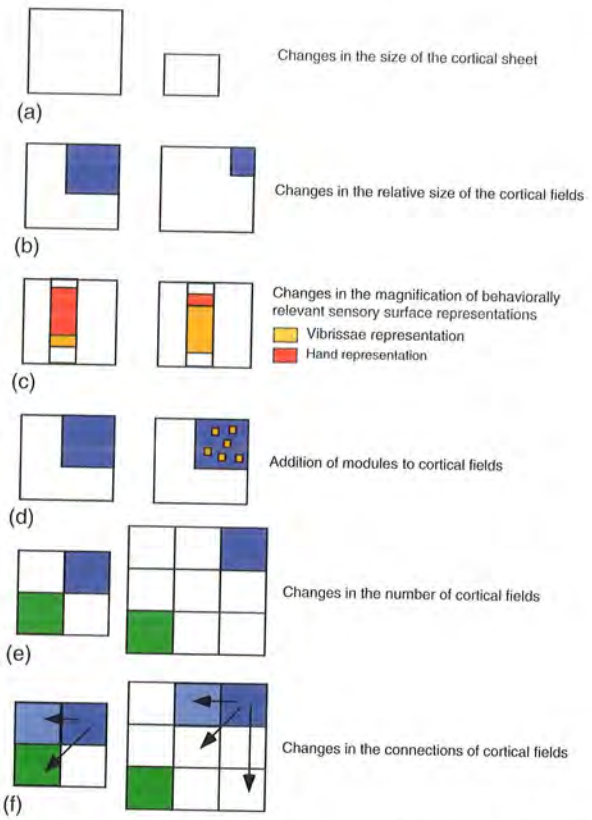

Figure 10 Modifications to the neocortex: a schematic representing the types of systems level changes that have evolved in different mammals. These changes, although few in number, presumably account for the wide range of behavioral differences observed in different lineages. Modified from Krubitzer, L. and Kaas, J. 2005. The evolution of the neocortex in mammals: How is phenotypic diversity generated? *Curr. Opin. Neurobiol.* 15, 444–453.

23.4.2 What Features of the Cortical Field Have Changed during Evolution?

In addition to changes in the size of the cortical sheet, several types of modifications have been made to the evolving neocortex (Figure 10). These modifications have been well documented (Krubitzer, 1995; Krubitzer and Kahn, 2003; Krubitzer and Kaas, 2005) and include:

1. changes in the relative size and internal organization of cortical fields,
2. changes in lamination of cortical fields,
3. changes in cell types,
4. changes in cortical thickness,
5. changes in the connections of cortical fields,
6. changes in the number of cortical fields,
7. the addition of modules to cortical fields, and
8. changes in the size of the cortical sheet (see above).

Interestingly, the brevity of this list of possible systems level modifications that brains have undergone or potentially could undergo suggests that it must be extremely difficult to modify the neocortex in evolution. Indeed, while we cannot predict the exact changes that may occur in future brains, we could predict with a fair amount of certainty what would not happen, and the types of changes that one would likely see. The observation that the types of modifications that have been made to the brain are limited indicates that these systems level modifications can generate a tremendous amount of phenotypic variability in terms of behavior.

23.4.3 The Module and Cortical Field Evolution

The module has been described in sensory cortex for a variety of different mammals (Figure 11). Modules are smaller units of organization that reside within a classically defined cortical field, and they have a long and dynamic history. Mountcastle (1957) described the first module, termed the cortical

column, almost 50 years ago (also see Mountcastle, 1978). He described the cortical column as a fundamental unit of cortical organization composed of a vertical group of cells extending through all of the cortical layers. This unit should not be considered as a fixed structure, but as a continuum with set dimensions, and no absolute boundaries. The modern concept of the module is different than its original conception in that it refers to different configurations of horizontal or tangential cell groups that do have fixed boundaries, and do not necessarily traverse all cortical layers. We have defined modules as "small architectonic, neuroanatomical, and physiological territories that can be distinguished from other tissue within the classically defined cortical field" (Manger *et al.*, 1998).

Modules have been observed in a number of different cortical fields in different mammals and examples include barrels in rodent S1, blobs in V1 of primates, stripes in S1 of the star-nosed mole, ocular dominance bands in V1 of primates, and cytochrome oxidase (CO) bands in V2 of primates, to name a few (Figure 11). Although modules are a common feature of cortical organization that most mammals share, in most instances they are homoplaseous. The similarity of size and structure of modules across mammals argues that large constraints must be placed on evolving nervous systems. While evolution has been likened to a 'tinkerer', the bag of tools used to generate new phenotypes and the genetic material available for construction is highly limited. Thus, while the particular module itself may be homoplaseous, its presence may be due to homologous developmental programs (coordinated patterns of genetic interactions) that unravel in a particular molecular, neural, and sensory environment.

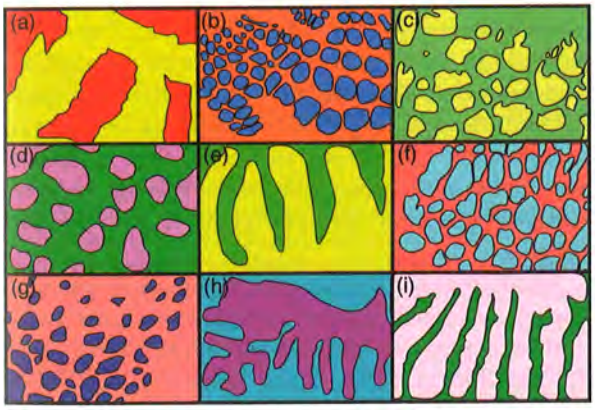

Figure 11 A schematic representing the many types of modules that have been identified in different sensory cortical areas in different mammals. While independently evolved or homoplaseous, the similarity in structure, shape, and size indicates that there are similar constraints imposed on the evolving and developing nervous system. a, Myelin bands in V2 of squirrel monkeys; b, barrel cortex in S1 of rats; c, modules in insular cortex of dolphins; d, clusters in entorhinal cortex in macaque monkeys; e, ODCs in V1 of talapoin monkeys; f, clusters in entorhinal cortex of humans; g, barrel cortex in S1 of brush-tailed possums; h, electrosensory/mechanosensory bands in S1 of platypus; i, rhinarium bands in S1 of the star-nosed moles. Modified from Manger, P., Sum, M., Szymanski, M., Ridgway, S., and Krubitzer, L. 1998. Modular subdivisions of dolphin insular cortex: Does evolutionary history repeat itself. *J. Cog. Neurosci.* 10, 153–156.

The identification of modules within cortical fields has implications for how a cortical field is defined. The traditional, and still dominant, view of cortical organization holds that the neocortex is compartmentalized into highly discrete cortical areas. However, the evidence for modular organization in cortical fields calls into question the traditional view of neocortical compartmentalization. Modules meet most of the criteria that generally are used to define a cortical field in that they are architectonically or histochemically distinct, have a unique set of connections, and contain neurons that are functionally distinct. When considered together, they form a complete representation of the sensory epithelium. An apt comparison between traditional and modern views of cortical fields is illustrated well for V1 and V2 of squirrel monkey neocortex (Figure 12). Until relatively recently, V1 and V2 were described as discrete, homogeneous representations of the visual hemifield with a distinct architectonic appearance and pattern of connectivity. The use of new histochemical staining techniques, optical imaging techniques, and fine-grained electrophysiological exploration of these fields has provided a very different view compared to traditional views. Rather than appearing as homogenous regions of cortex, both V1 and V2 have been further divided into modules. V1 is composed of blobs, interblobs, orientation columns, and ODCs. V2 is composed of thick and thin CO dense bands as well as interbands, and contains multiple representations of the visual hemifield.

Electrophysiological recording experiments of V2 in cebus monkeys and optical imaging experiments in macaque monkeys indicate that there is a re-representation of the same portions of the visual hemifield in these different bands (Rosa *et al.*, 1988; Roe and Ts'o, 1995). Therefore, there is more than one map of the visual field in V2, and the separate maps are architectonically, histochemically, and connectionally distinct. These results suggest that 'chunking' V2 into one large, coherent field may

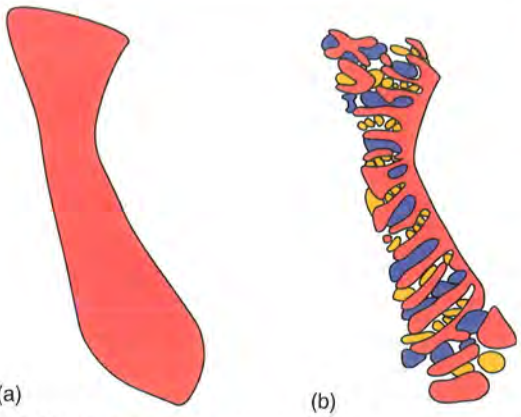

Figure 12 A schematic representing the: a, traditional and b, modern view of the organization of V2 in monkeys. Traditionally, V2 was considered to be a single, homogenous field adjacent to the rostral border of V1. Anatomical and functional studies (Rosa *et al.*, 1988; Roe and Ts'o, 1995) of the organization of V2 have since determined that it is modularly organized, and that there appear to be three independent representations of the visual field within this traditional area, associated with different histochemically identified stripes. These different strips, or bands in V2, have different patterns of connectivity. Thus, a new interpretation of this region of cortex is that three separate, completely interdigitated fields exist within the traditional V2. Adapted from Krubitzer, L. and Kaas, J. H. 1990. Convergence of processing channels in the extrastriate cortex of monkeys. *Vis. Neurosci.* 5, 609–613.

not be appropriate. Rather, V2 in primates could be considered as three separate, interdigitated fields (Figure 12).

In terms of modular organization and the evolution of cortical fields, we have proposed previously (Krubitzer, 1995; Krubitzer and Kahn, 2003) that modules reflect a stage in cortical field evolution within a lineage; that 'snapshot' alluded to in the introduction of this article. As noted earlier, we believe that a cortical field represents, at least in part, some patterns of connectivity on the cortical sheet. Within the life of an individual (particularly during development), and across species over time, this pattern of connectivity can shift such that the position of homologous fields is geographically displaced (Figure 13). Further, there are discontinuities within a cortical field (modules) that may represent an invasion of new inputs, discorrelated with existing inputs. This could represent fields completely embedded within other fields, as we believe is the case for V2. Over time, if selected for, these inputs coalesce and form partially invaginated regions, which may ultimately completely coalesce to form a new cortical field (Figure 13; see Krubitzer, 1995; Krubitzer and Kahn, 2003 for full explanation). Thus, the different modular and nonmodular organization of cortical fields within different sensory systems in different mammals represents different stages of this process in each lineage.

23.4.4 What Constrains Cortical Evolution?

There are three observations from comparative studies which indicate that neocortical evolution must be highly constrained. The first is the very presence of a common constellation of cortical fields, which was outlined in Section 23.2. That these fields and aspects of their connectivity and function can be modified substantially is without question. However, what is notable is that they have never been completely lost, even in highly derived mammals, such as the blind mole rat, which has micro-ophthalmic eyes covered by skin and a highly degraded retinofugal pathway (Klauer *et al.*, 1997; David-Gray *et al.*, 1998). The reduced visual system in blind mole rats is only involved in the circadian system. Yet, despite the lack of use of this system for visual functions, the geniculo-cortical pathway is still intact, and area 17 or V1, as architectonically defined, is still present and resides in the far rostral pole of the neocortex. The second observation is the very limited types of systems level changes that have been made to the brain, as outlined above. This suggests that the neocortex is not altered in a random fashion. The final, related observation is the instance of homoplasy. The fact that remarkably similar modules have formed, despite hundreds of millions of years of independent evolution, indicates that considerable constraints are placed on evolving nervous systems and that modularity is a part of this process.

What imposes constraints of the evolving neocortex? Primarily, genes constrain evolution and limit the types of phenotypic modifications that are possible, and these constraints are due to both pleitropy and contingency. Genetic pleitropy, or the fact that a single gene controls a number of activities in development, leads to functional integration, and as a result, it exerts a restriction on the number of possible changes that could be effected by any particular gene. Genetic contingencies restrict neural development and evolution in that any genetically mediated event is most often dependent on one or more prior genetic events and in turn may instruct some combination of downstream genetic events. Thus, it is rather difficult to substantially modify an organism by extreme genetic manipulations. This suggests that small genetic alterations can generate large phenotypic

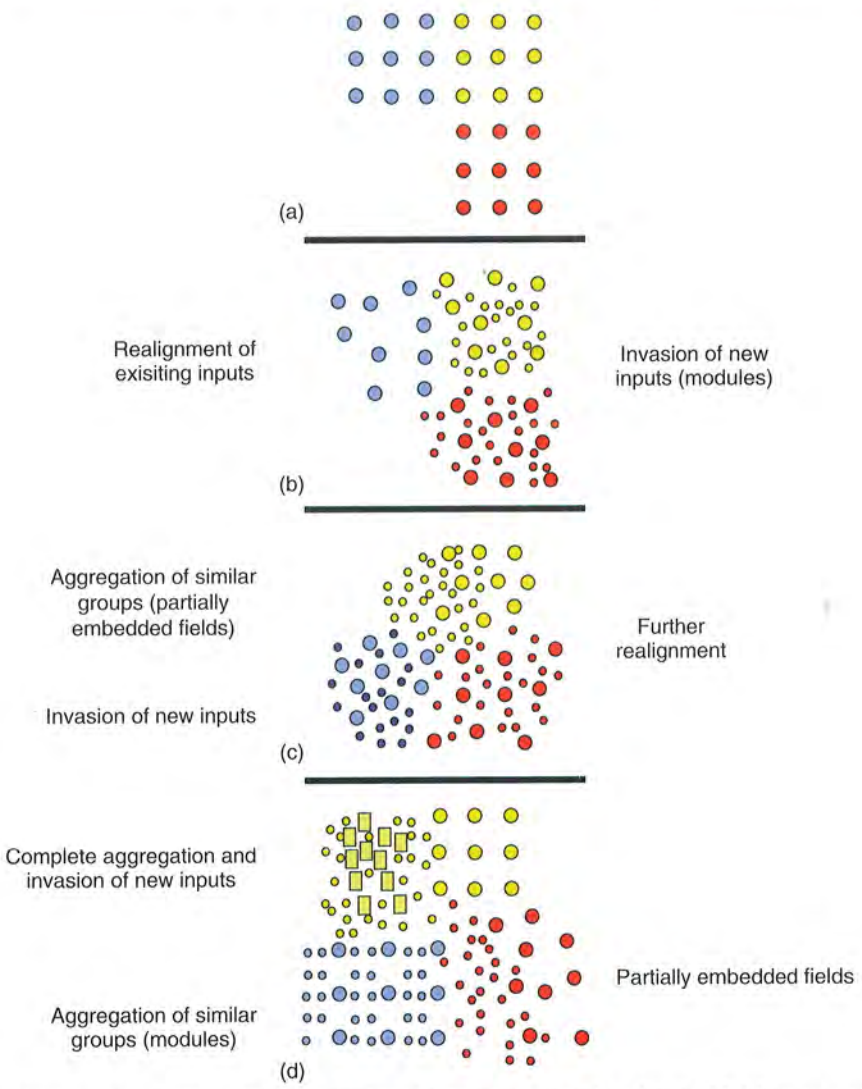

Figure 13 A theory representing the relationship between modules and the evolution of cortical fields. a, represents a hypothetical state of the neocortex with different colored circles representing a cortical field, or some pattern of thalmocortical interconnections within a field. An invasion of new inputs to existing fields (b, small red and yellow dots) results in a modular organization within these fields and a realignment of existing inputs. Modularly organized inputs may aggregate to form a partially embedded field (small yellow dots in (c)), causing a further realignment of fields, and new inputs may invade existing fields (small blue dots). Inputs that initiated within a cortical field and formed a modular arrangement (yellow dots), may completely aggregate to form a new field, and new inputs may invade this field (yellow squares). We propose that this is how cortical fields evolve and that each figure (a–d) illustrates snapshots or frozen frames that we observe in extant mammals. Modified from Krubitzer, L. 1995. The organization of neocortex in mammals: Are species differences really so different? *Trends Neurosci.* 18, 408–417.

modifications and that phenotypic change can be accomplished in the absence of nonactivity-dependent genetic change.

In addition to genetic forces, there are also substantial constraints imposed on evolving nervous systems by the environment in which an animal operates. When we discuss the nervous system, we rarely talk about physics, but the physical parameters of any environment are set and quantifiable. For example, nervous systems must contend with gravity, self-movement, and the movement of objects and other animals in time and in the three dimensions of our universe. The physical parameters of a stimulus are also important, and include the presence or absence of photons, the rate at which a stimulus travels and bends through space, the diffusion of molecules through different media, and the perturbations of molecules in different media, such as changes in air pressure. Although the amount and patterns of a physical stimulus that impinge on any given mammalian sensory receptor array may be distributed

differently in different terrestrial and aquatic environments, and in diurnal versus nocturnal mammals, the actual physical unit that is transduced, such as a photon, is invariant and therefore serves to anchor the evolutionary boat. While it seems clear that genes and their highly coordinated activities constrain a system, it is important to keep in mind that within a population of individuals, both the spatial and temporal expression of genes involved in the processes described above are normally distributed. This natural variability allows for some degree of flexibility within a relatively fixed genetic environment. Energy, while absolute, is variably distributed within any environment such that the amount and pattern of photons falling on a retina, for example, is different in different ecospheres. While we have noted above that both genes and the physical parameters of the environment constrain the development and evolution of mammalian neocortex, and ultimately behavior, it should be noted that the combinatorial possibilities of these two fixed parameters can generate a high number of degrees of freedom for potential phenotypic outcomes despite these constraints.

Despite these constraints, it is clear that sensory driven activity and the animal's own movement within an environment can generate a large amount of phenotypic variability. We have discussed the types of systems level changes that can occur with variable use and under particular environmental conditions in the developing and adult nervous system. But, how do such alterations become genetically encoded within a population and ultimately evolve?

At first reading, the idea that acquired traits can somehow evolve seems to smack of Lamarkianism. However, the notion that a living organism's ability to respond to environmental fluctuations has a genetic basis is relatively well established and compatible with Darwinian selection. This idea was formulated over a century ago by Baldwin (1886, 1902), and termed the Baldwin effect. The Baldwin effect is the ability of an animal to respond optimally to a particular environment. This effect could hold true for behaviors as well as anatomical features or aspects of functional organization of the neocortex. Thus, the Baldwin effect is the idea that genes for plasticity evolve, and that the phenotype that is optimal for a given environment could become genetically encoded and evolve if the genes that encode for plasticity and those for the actual phenotypic feature in question covary (Figure 14). This characteristic would then be selected for and be displayed even in the absence of the original environmental stimulus that induced it. This phenomenon was experimentally tested by Waddington and termed genetic assimilation (Waddington, 1959, 1961).

A related process has recently been described as 'evolvability'. Evolvability is the ability of an organism to generate heritable, selectable phenotypic variation (Kirschner and Gerhart, 1998). These authors propose that selection for evolvability has occurred and has three components. At the level of the individual, the ability to be flexible would contribute directly to physiological fitness. At a group level, individuals within the group would be buffered against the lethal effects of mutation. Finally, at the level of the clade, such an ability would allow the clade to radiate into new (emptied) environments. Recently, experimental support for the notion that evolvability is a selected trait has been put forward by Earl and Deems (2004). They find evidence that the rate at which genetic change in the form of recombination, substitutions, and transpositions occurs is variable in different lineages and is genetically encoded.

Taken together, it appears that activity can regulate gene expression which, in turn, can regulate anatomical and functional characteristics of the developing nervous system within an individual lifetime. This process, or the ability to respond to some external stimulus, is optimal in some individuals and can be selected for (the Baldwin effect). In a particular environment, an optimal trait can become genetically encoded in a population and evolve if there is a strong correlation between phenotypic and genotypic space (genetic assimilation). Finally, the ability to respond optimally and to assimilate, while maintaining a fundamental plan of organization, is a variable trait itself, and is the target of selection (evolvability).

23.5 Conclusions

How should we view the evolution of the cortical field? While a cortical field has been previously proposed to be a fixed, genetically determined structure that occupies some area on the cortical sheet, a comparative analysis highlights the dynamic nature of a cortical field within the life of an individual and over generations within and across lineages. We believe that the cortical field is an event or a process, not an entity that is easily captured. While genes and the physical environment impose severe constraints on this process, neural activity within the developing organism generated by the highly constrained physical

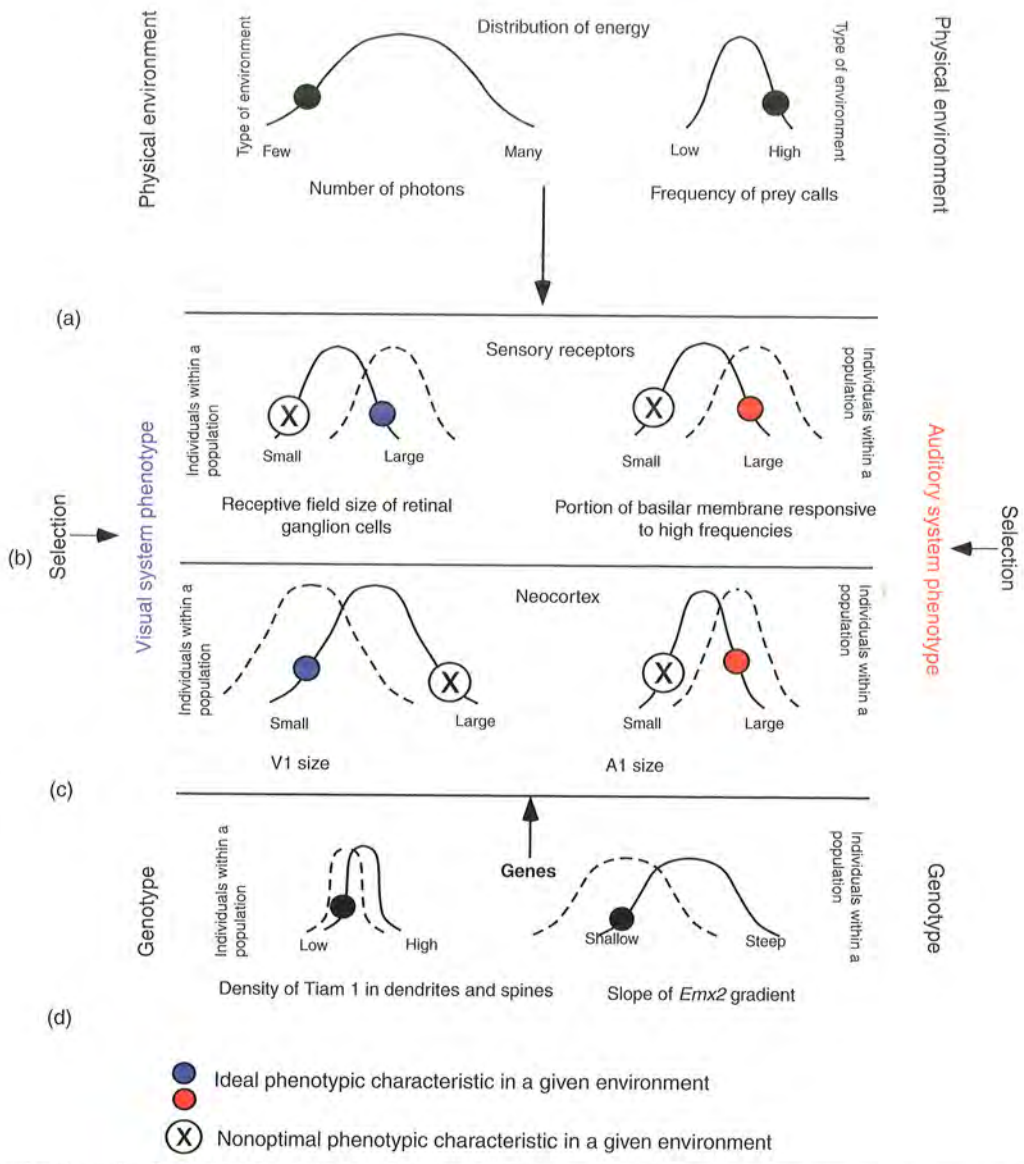

Figure 14 A schematic illustrating the Baldwin effect and genetic assimilation, and how features of cortical organization that are initially activity dependent, become encoded by genes and evolve. Within a particular environment (a), light levels may be low, and prey call frequency may be high (black dots on the distributions in a). The optimal sensory receptor phenotype (b), receptive fields size of ganglion cells distribution of frequency on the basilar membrane (blue and red dots respectively) are normally distributed within a population. For the neocortex (c), the optimal phenotype for this environment would be a small V1 and a large A1 (blue and red dots respectively). These size differences of cortical fields are normally distributed within a population. Finally, particular genes which are normally distributed in a population (d) control aspects of cortical field organization either directly via *Emx2*, or indirectly through activity-dependent mechanism (e.g., Tiam 1). Although natural selection acts on the phenotype, the genes that control for the particular phenotype in question as well as plasticity may co-vary, and thus allow activity-dependent contributions to the phenotype to become genetically encoded and evolve. This type of selection could shift the distribution (dashed lines) of genes that both enable plasticity (activity dependent), as well as those directly determine the characteristic (e.g., *Emx2* and size of cortical fields). A1, primary auditory area; V1, primary visual area. Modified from Krubitzer, L. and Kaas, J. 2005. The evolution of the neocortex in mammals: How is phenotypic diversity generated? *Curr. Opin. Neurobiol.* 15, 444–453.

parameters of the environment, and the movement of the organism itself in time and space, serves to loosen these constraints. An extant mammal represents only a snapshot in this process. This snapshot may give the impression that a cortical field is static, when, in reality, we have simply caught a frozen moment in the continually moving picture of life.

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