Reconstructing the Organization of the Forebrain of the First Mammals


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

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Glossary

biallelic: Having the same function.

biological: Having the same function.

baldwin effect: The ability of an animal to respond optimally to a given environment.

cortical domain: The partition 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.

homoplasmous: An independently evolved characteristic that looks the same across species.

module: Smaller units of organization within a defined cortical field.

physiotype: 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, the study 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 lenses 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 and developmental approach can we appreciate the types of changes that have occurred during different lineages, and these changes 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 homologs 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, Homoplasmy, and Analogy

A cortical field is considered to be the principal organizational feature of the cortex, and most neuroscientists would agree 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 constitutes 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 useful 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 molecular development, in adult mammals, a cortical field is determined by a number of well-defined anatomical, biochemical, and electrophysiological criteria. These criteria were originally outlined by Kaas (1982), and although not exhaustive, have enabled investigators to subdivide the neocortex in a variety of mammals with 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 clear orientation to and topographic 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 criteria can be made in subdividing the neocortex when any single criteria is used in isolation, using a combination of criteria to subdivide the 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, 1982, 1995, 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 Knaus, 2003). These fields include the primary sensory areas (primary sensory area, V1; primary somatosensory area, S1; and primary auditory area, A1), secondary sensory areas (secondary visual area, V2; secondary somatosensory area, S2; secondary auditory area, A2, and rostral auditory area, R1), 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 homoplasous, and have independently evolved in each mammal.
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Although 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.

Figure 1 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 are 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 Kaas, J. H. 2003. Nature ver. n. brain: An old idea with a new twist. Prog. Neurobiol. 70, 33-52.

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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 (e.g., A and stripes in B), the emergence of new connections (4), and the reweighting of existing connections (compare thick vs. thin line of connection 2 in a and b). These changes of networks can naturally occur in evolution. Indicate that homologous cortical fields may not have the same function.

An example of a homoplasious feature of the neocortex is the barrel field in the rat and mouse, and the brush-tailed possum. 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 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., Flores et al., 1986; Rosa et al., 1992). They are absent in other New World monkeys, prosimians, and dromeopeters (Figure 2), and in all other clades except humans (e.g., 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 the 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 stratiﬁed 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 necessarily 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 V1 to the brain in V4, such as orientation and color, and to the adduction of visual cortical features in V4, 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 modules representing new cortical areas, have been added to the network (D, Figure 3), which result in the addition of new connections and a potential reweighting of existing connections between homologous nodes. This example shows that because of the emergence of new functional features (modules), new inputs, and a reweighting of existing connections, homologous cortical fields may not have the same function.

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 use of the inherited, genetic contribution to the cortical phenotype has recently crystallized into hypotheses which are amenable to rigorous experimentation regarding the temporal and spatial distribution of genes and proteins that occur in development, and give rise to aspects of cortical organization including...
An excellent example of a homoplasy-free feature of the neocortex is the barrel field in the rat and mouse, and the brush-tailed possum. However, 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; Flores and Kaas, 1992), and 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 dromopithecines (Figure 2), and in all other clades except Cebidae (e.g., Lowel 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.

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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 areal boundaries and 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.

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cortical field location, size, and connectivity. The hypothesis of the deficit becoming the superficially tractable, and questions regarding the regarding the activity-dependent cellular mechanisms that 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 layers, it is difficult to distinguish a distance 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 actions are 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 numbers of aspects of cortical development, all of which have a large impact on the organization and function of the neocortex. Some examples include the regulation of the size of the cortical sheet, cortical field coordinates in the rostrorstral and mediolateral axis, and thalamocortical connections.

In terms of the overall size of the cortical sheet, studies on cell kinetics of neocortical progenitor cells in the ventricular zone indicate that the size of the cortical sheet is more regulated than that of the subventricular zone, in which there are a number of plausible ways in which this regulation can occur. In general, the number of cells in the developing ventricular zone can be increased by extending the period of time that cells attain symmetric divisions, and/or the rate at which cell divisions occur. A comparative analysis of growth control in different kinds of brain tissue, such as macaque monkeys, indicates that cortical neogenesis is both prolonged and accelerated in macaque monkeys compared to mice or rat brain, and potentially even cortical field size. 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 (Hatten and Walsh, 1992). In transgenic mice that overexpress 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 (BF1 or Fgf2). This gene is expressed in telencephalic progenitor cells (Tao and Lai, 1992), and regulates cell proliferation and differentiation in the developing neocortex (Matsushita et al., 1994). BF1 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 cor neogenesis (Koga et al., 1994, Kurokawa and Redies, 1997). Furthermore, mice in which FGF2 is overexpressed have a significantly larger V1 than normal animals (i.e., cortex is less organized; Hatten and Sun, 1992). In terms of connectivity, some of the calbindins appear to regulate thalamocortical connectivity. For example, Calb2, 8, and 11 are expressed in unique subsets of thalamocortical neurons (Sakurai et al., 1997, 1998, 1999). These studies indicate that the disproportionate size of the neocortex in different lineages could be regulated in similar ways by different genes that affect the kinetics and timing of cell division in the ventricular zone.

Related studies of cell cycle kinetics in mon ky 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 (pial) surface also have been noted (Niida et al., 1997). These studies indicate that areal differences arise very early in neocortical development, well before thalamic innervation of the neocortex begins. In addition to intrinsic mechanisms that operate during cortical neogenesis to specify cortical field location, size, and connectivity, the aspects of cortical field development, the transcription factors Em2 and Pax6 are involved in the expression and patterning of downstream genes in the rostral caudal axis, GABAergic and glutamatergic neuronal subtypes, and potentially even cortical field size. For example, experiments in which these genes are deleted result in shifts of downstream genes such as Gad1 and Gad2 either rostrally (for Em2) or caudally (for Em2 knock-out, Bishop et al., 2000). In addition to the observed changes in gene expression, Em2 and Pax6 mutants also showed altered regionalization in thalamocortical connections. In experiments in which Em2 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 Em2 is overexpressed have a significantly larger V1 than in normal animals (i.e., cortex is less organized; Hatten and Sun, 1992). In terms of connectivity, some of the calbindins appear to regulate thalamocortical connectivity. For example, Calb2, 8, and 11 are expressed in unique subsets of thalamocortical neurons (Sakurai et al., 1997, 1998, 1999). These studies indicate that the disproportionate size of the neocortex in different lineages could be regulated in similar ways by different genes that affect the kinetics and timing of cell division in the ventricular zone.

As mentioned earlier, a recent perspective on how genes control cortical field development suggests that 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 that either coalesce or become involved in generating features of the neocortex that will ultimately be realized in the adult, such as cortical field location, size, 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 pattern of gene expression has yet to be established. Second, in the neocortex, early patterns of gene expression may represent developmental 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 other genes that are activated by neural activity and gene expression changes in the temporal expression of genes within a cell explaining these mechanisms. Altering the expression of genes can change aspects of synaptic morphology. For example, recent work demonstrates that increases in intra cellular calcium, due to changes in neuronal activity, trigger a cascade of events, including the activation of the CAM pathway and phosphorylation of CREB, which binds to the regulatory region of a gene and is a transcription factor for a number 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 involved in the survival of developing neurons and post synaptic elements (McCaffrey et al., 1995, 1999; Lein et al., 2000; McAllister, 2001 for review). Neurotrophins such as brain-derived neurotrophic factor and neurotrophic factor 4/5 (NTF4/5) play a number of important roles in nervous system development.
cortical field location, size, and connectivity. The development of the dendrites become remarkably experimentally tractable, and questions regarding the activity-dependent cellular mechanisms that underlie 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 laboratories, it is difficult to establish a distinction between genetic and epigenetic contributions to the phenotype, and the two become intrinsically intertwined.

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Another gene proposed to alter cell cycle kinetics is Brain Factor-1 (BF-1 or Fsg1). This gene is expressed in telencephalic progenitor cells (Tao and Lai, 1992), and regulates cell proliferation and differentiation in the developing neocortex (Hamashima et al., 2000). BF-1 is regulated by FGZ2, which is also involved in regulating the size of the cortical sheet by determining the number of cycles of division that progenitor cells undergo during neurogenesis (Suzuki et al., 1997). Injection of FGZ2 into the ventricle of embryonic rats results in a substantial increase in cortical volume (Vaccarino et al., 1999; and FGZ2 knockouts show an increase in the number of cortical territories (Kornmatus and Reclis, 1997). Further, CaR6 is co-localized with the synaptic marker, synaptotagmin, and is correlated with the formation of synaptic contacts between neocortical neurons and their target in the developing nervous system (Isocir et al., 1998). These data and others indicate that the disproportionate size of the neocortex in different lineages could be regulated in two ways by different genes that affect the kinetics and timing of cell division in the ventricular zone.

Related studies of cell cycle kinetics in mononucleate 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 reported (Friedema et al., 1997). These studies indicate that areal differences arise very early in neocortical development, well before thalamic innervation of the neocortex.

In addition to intrinsic mechanisms that operate during cortical neurogenesis to specify cortical fields, the expression of some aspects of cortical field development can have a very large effect on the phenotype. As mentioned earlier, a recent perspective on how genes have evolved to cause the development of 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 cell shape and activity. This pattern is likely to be involved in generating features of the neocortex that will ultimately be realized in the adult, such as cortical associations and thalamocortical connectivity, 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 pattern 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 have described, a number of studies have describe intracellular and extracellular mechanisms that are driven and regulated by neural activity, and generate changes in the temporal expression of genes within a cell encoding these mechanisms. Altering the expression of genes can change aspects of synaptic morphology. For example, recent work demonstrates is that non-linear changes in intracellular calcium, due to changes in neuronal activity, trigger a cascade of events, including the activation of the CAM pathway and phosphorylation of CREB, which binds to the regulatory region of a gene and regulates the 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 modulating during development. One of these is a class of proteins called neurotrophins. These proteins are secreted by the postsynaptic region of a synapse and post-synaptic elements (McAlistier et al., 1995, 1999; Leit et al., 2000; McAlistier, 2001 for review). Neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor have important roles in the development of the nervous system and can have a very large effect on the phenotype.
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 (Borgues et al., 2002), regulation of the extracellular matrix organization (Ethington et al., 1995), enhancement of dendritic outgrowth, and stimulation of protein synthesis in dendrites (Aldalou et al., 2001).

Another group of molecules recently identified by Shatz and colleagues (Corvea et al., 1999; Hub et al., 2000) are the class I MHC antigens. The expression of class I MHC is reduced in the developing rat LGN with the application of tetrotoxin (TTX) via intracellular injections given in stnO (Corvea et al., 1998). TTX blocks neural activity by deactivating sodium channels. In cats that are monocarly 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 (Hub et al., 2000). Thus, as in the above model 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 actions are 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 phenotypes would only be expressed in a particular environment (Krubitzer and Kast, 2003; Kast and Kast, 2003). If the environment is stable, the specific phenotypic characteristic generated would be stable, and it is possible that such a process can transpire as an evolutionary (heritable) phenomenon.

23.5.1.3. 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, nose, two eyes, two ears, one nose, and one mouth. Interestingly, this basic plan has been conserved in all vertebrates, due to genetic constraints, and the neocortex has been modified in a very limited fashion. Homeodomain genes, such as homebox genes, are involved in specification of the body plan that arise 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 Raxevans, 2001; Shawell 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), hooves (ungulates), claws (cats), and hands (humans). 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 the nose, or specialized oral structures. At a finer level of organization, the receptor arrays associated with a specialized morphology and behavior also undergo modifications. However, like those of the body and brain, they are generally limited in number and include:

1. alternations in the location of receptors,
2. alternations in the density of receptors,
3. alternations in the number of receptors,
4. addition of new receptors,
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 (Baranski et al., 1979), and the addition of electroreceptive receptors on a plesiosaur (Scheib, 1986; Man and Pettigrew, 1996), to name a few.

Not only does the actual structure of the body manifest change, but also how these new 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, murid 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 VI 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...
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 (Borguesi et al., 2002), regulation of the extracellular matrix outgrowth (Kolodkin et al., 1995), enhancement of dendritic outgrowth, and stimulation of protein synthesis in dendrites (Aldalu et al., 2001).

Another group of molecules recently identified by Slatz and colleagues (Corvera et al., 1998; Hub 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 rat LGN with the application of tetrodotoxin (TTX) via intraventricular injections given in utero (Corvera et al., 1998). TTX blocks neural activity by deactivating sodium channels. In cats that are monoclonally 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 reinnervating connections is incomplete (Hub et al., 2000). Thus, as in the case of activity for BDNF, activity controls the expression of these molecules, which in turn alters aspects of synaptic development.

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23.5.1.3 Genes extrinsic to the neocortex but intrinsic to the organism contribute to aspects of cortical development and organization. All mammalian CNS development body plans that include 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 even to the newborn, 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 by the embryo 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 Ravevian, 2002; 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), hooves (ungulates), claws (cats), and hands (hominids). 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 undergo modifications. However, like those of the body and brain, they are generally limited in number and include:

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Not only does the actual structure of the body contribute to the organization of the CNS, but also how these body parts are utilized and modified for exploration is equally important. For example, for the somatosensory system, primates have developed tactilely specific receptors with their glabrous hands, elephants with their distal trunk, mired 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 system 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
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 Dale, 2003 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 noncortical organization. Given the rather large constraints imposed on a basic plan of organization by these homedomain genes, how can morphological diversity arise? It has been suggested that while the protein coding sequence of these homedomain genes is relatively static across lineages, divergence in the regulatory portion of the gene can account for much of the morphological diversity observed in mammalian body plans (Cretu 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 (Hox9–13) 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 Hox9–13 in bats and mice revealed that there were significant differences in the expression of this gene in the distal forelimb (dfl), but not in the hindlimb, in later stages of limb development. Specifically, the anterior expression boundary of Hox9–13 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 a. The body plan in mice and bats has a similar structural organization. Major body axes such as proximal and distal forelimbs and hindlimbs (pfl, df, ph, and dfh), as well as individual digits (d0–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 Hox13 in the developing forelimbs 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, 13.5 dpc), and such differences in homedomain 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; dfh, distal hindlimb; dp, days post coitus; ES, embryonic stage; pfl, proximal forelimb; ph, proximal hindlimb. a, Modified from Cretu et al., 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, 691–696. b, Modified from Chen, C. H., Cretu, C. J., Rassweiler, J. J., and Behringer, R. R. 2001. 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 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,
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 Dabilow, 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 homoeodomain genes, how can morphological diversity arise? It has been suggested that while the protein coding sequence of these homoeodomain genes is relatively static across lineages, divergence in the regulatory portion of the gene can account for much of the morphological diversity observed in mammalian body plans (Cerebros, et al., 2001). Thus, slight differences in the temporal and spatial patterning of genes generate large modifications in body plan organization. For example, the expression of a gene involved in the specification of the body plan (Hox9-13) 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 Hox9-13 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 Hox9-13 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 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, can subsequently determine the final morphology of a particular body part, not the resultant cortical organization. Indeed, several extrinsic factors relate to the development of a body part contribute to the organization of the neocortex. For example, direct effects the skeletal morphology, which in turn affects cortical organization. Several studies have shown that alterations in mastication behavior, often brought about by changes in diet, have a direct effect on the neocortex morphology (Ha, 2004), skull dimensions (Kasnakos et al., 2002), mandibular morphology (Barin, 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., 2003). 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 changes 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.

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

The relationship between the cortical domain, cortical field magnification, cortical morphogenesis, 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 the neocortex, the sensory receptor organization, and the specialized motor programs that are part of efficient sensory reception play a very large role in determining the number of aspects of the cortical organization that are observed in adult mammals. Several studies have found evidence in our laboratory in which peripheral sensory receptor arrays have been physically excited or activity has been modified throughout development, we note that for example, in a recent study, Mammal neocortical cells were biolistically excited well before the retinal ganglion cells reached the diencephalon and before the thalamocortical afferentreached the neocortex (Kahn and Krubitzer, 2001). Using electrophysiological, anatomical, and morphometric analyses in these animals before they reached adulthood, we found that the sensory domain in all that cortex that was normally occupied by the visual system was occupied by the auditory and somatosensory systems (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 VIP 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 Monomethyl (Kahn et al., 2000).

Related experimental changes in genetically 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 through outgrowth of the cochlea. As with the blind animals, genetically 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 somatosensory stimuli (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 the normal targets, the retinas were projects to the MG nucleus and multiple 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 neuropsychological reorganization is much less pronounced than that observed in developing animals. As with the blind animals, the relationship between sensory experience and cortical map reorganization detailed the precise conditions under which plasticity will occur and describe the techniques used in an expansion of these experiments. 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 5a (area 3B) devoted to the trained digit, while no expansion of adjacent untrained 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.
specialized body morphology and use affect cortical domain allocation and sensory field magnification. The genes, which are involved in setting up the body plan at an early stage, may 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, often brought about by dietary changes, have a direct effect on craniofacial morphology (Ha, 2004), skull dimensions (Katsanis et al., 2002), mandibular morphology (Breslin, 2001), and bone density (Davies et al., 2006). 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., 2003).

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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 thalamicocortical 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 through genetic manipulation. 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 was also projected to the thalamic nucleus and cell 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. It has been argued that the relationship between sensory experience and cortical map reorganization detailed the precise conditions under which plasticity will occur and described the mechanisms that underlie changes in those representations. 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 SI (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 development 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 7](image_url) The organization of neocortex in normal (open square), open square bilaterally enucleated very early in development (b), normal (open circle), and congenitally deaf mice (square). In the normal animals, both cortical fields and cortical domains are illustrated. In the bilaterally enucleated opusmus, 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 mice, the cortex 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 a visual stimulation. In both of these animals, the cross modal plasticity is extremely large such that all of cortex is devoted to the normal inputs in response to new types of sensory stimulators. In both mice and opusmus, the cortical areas deprived of normal inputs can still be identified architectonically, but at least in the opusmus, the fields are smaller than in normal animals, a, auditory; A1, primary auditory area; Aud, auditory, M1, primary motor area; VM, multimodal neural, Visual, auditory, 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. Multimodal cortical plasticity and the emergence of new cortical areas in developmentally blind mammals. Proc. Natl. Acad. Sci. USA 99, 11425-11434. d, Data from Hunt, D. L., Yamosh, E. N., and Krubitzer, L. 2006. Multimodal plasticity in congenitally deaf mice. How are cortical areas specified? Neuroncience 139, 1500-1524.)
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 proportionally, and the other in which there is a disproportionate expansion of the neocortex relative to 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 hypnorum*), striped possum (*Dasyula tristigmata*), quoll (*Dasyurus hallucatus*), and short-tailed opossum (*Monodelphis domestica*; see Huffman et al., 1991). 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 relatively small marsupials of 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 caybaya and guinea pig were compared. These investigators demonstrated that the size and relative location of primary cortical fields in the very large caybaya 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 understood.

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 nonneocortical organizations. As in proportional increases in brain size, a disproportionate increase results in an absolute increase in the size of homonymous cortical fields, but the increase is less extreme than in the former type of size change. Furthermore, with a disproportionate increase...
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 with 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 proportionally, and one in which there is a disproportionate expansion of the neocortex relative to 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 67lg. 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, Smarothrax eximicandatus), striped possum (Dasyula tridactyla), 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 polyprotoments 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 caybarya and guinea pig were compared. These investigators demonstrated that the size and relative location of primary cortical fields in the very large caybarya 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).

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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 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 thalamocortical patterns of the primary and second sensory fields.

23.4.2 What Features of the Cortical Field Have Evolved 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, 2001; 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 the number of cortical fields,
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 reject 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 30 years ago (also see Bouret, 1999). It is 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 from 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 arboritecnic, neurometaplastic, and physiological territories that can be distinguished from other tissue within the classically defined cortical field." (Manger et al., 1999).

Modules have been observed in a number of different cortical fields in different mammals and examples include barrels in somatosensory cortex (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 homoplasmous. The similarity of size and structure of modules across species suggests that constraints must be placed on evolving nervous systems. While evolution has been likened to a "inkeret", 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 homoplasmous, its presence may be due to homologous programs (sets of coordinated patterns of genetic interactions) that unravel in a particular molecular, neural, and sensory environment.

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 organization. Modules meet most of the criteria that generally are used to define a cortical field in that they are architectonically or histochromically 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 homogeneous 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 interband, 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 portion of the visual hemifield in these different bands (Kosa et al., 1988; Roe and Te'o, 1995). Therefore, there is more than one map of the visual field in V2, and the separate maps are architectonically, and connectionally distinct. These results suggest that 'chunking' V2 into one large, coherent field may
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 80 times the size of the owl monkey (50-70kg vs. 1kg), 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 between the retinotopic coordinates of the thalamus and cortex. This mismatch may result in new combinations of thalamocortical connections projecting to the expanded cortical sheet, in addition to the retained, highly restricted thalamocortical patterns of the primary and second sensory fields.

23.4.2 What Features of the Cortical Field Have Implications for Evolutionary Change?

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, 1993; Krubitzer and Kahn, 2001; Krubitzer and Kaas, 2005) and include:

1. changes in the relative size and internal organization of cortical fields,
2. changes in laminar architecture of cortical fields,
3. changes in the number of cortical fields,
4. changes in cytoarchitecture of the cortex,
5. changes in the connections of cortical fields,
6. changes in the size of cortical fields,
7. the addition of modules across cortical fields, and
8. changes in the size of the cortical sheet (see above).

Interestingly, the brevity of this list of possible levels of 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 would be likely to occur. 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.

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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 (Ross et al., 1988; Roe and Tey, 1995). Therefore, there is more than one map of the visual field in V2, and the separate maps are architectonically, and functionally, and connectivity distinct. These results suggest that 'chunking' V2 into one large, coherent field may
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 23.3. 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-ophtalmic eyes covered by skin and a highly degraded retinocortical 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 homoplasys. 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 on the evolving neocortex? Primarily, genes constrain evolution and limit the types of phenotypic modifications that are possible, and these constraints are due to both pleiotropy and contingency. Genetic pleiotropy, 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, which 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 genes, also restrict 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 modifications and that phenotypic change can be accomplished in the absence of non-activity-dependent genetic changes.

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 inspires on any given mammalian sensory receptor array may be distributed
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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 retinotopic pathway (Klauser et al., 1997; David-Gray et al., 1998). The reduced visual system in blind mole rats is not 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 that the very different 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 homology. 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.

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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...
phenomenon was experimentally tested by Waddington and termed genetic assimilation (Waddington, 1959, 1966). A related process has recently been described as ‘evolvability’. Evolvability is the ability of an organism to generateheritable, 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 could contribute directly to physiological fitness. At a group level, individuals within the group would be buffered against the lethal effects of mutations. 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 Deem (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 stimuli, 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 optically 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 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.

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 sizes of ganglion cell distributions 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 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 Emu2 or indirectly through activity-dependent mechanism (e.g., Tim1). 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 (closed line of gray) that both encode plasticity (activity dependent), as well as those directly determine the plasticity (e.g., Emu2 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 plasticity diversely generated? Curr. Opin. Neurobiol. 15, 444–452.
different 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 absoluted, is variously distributed within any environment such that the amount and pattern of photons falling on a retina, for example, is different in different ecologies. While we have noted above that both genes and the physical parameters of the environment constrain the development and evolution of mammalian neurocircuits, and ultimately behavior, it should be noted that the corresponding 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 Lamarckism. 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. If the 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 that are causally linked change. Figure 14: A schematic illustration of the Baldwin effect and genetic assimilation, and how features of cortical organization that are likely activity dependent, become encoded by genes and evolve. Within a particular environment (e.g., light levels may be low, and prey call frequency may be high) the distribution of frequency on the basilar membrane (blue and red dots respectively) are normally distributed within a population. For the neurons, the optimal phenotype for this environment would be small V1 and a large A1 (blue and red dots respectively). These two differences of cortical fields are normally distributed within a population. Finally, particular genes which are normally distributed in a population (e.g., motor cortex, A1, primary auditory area, V1, primary visual area, and several others. Modified from Krubitzer, L. and Kaas, J. 2005. The evolution of the neocortex in mammals. Is phenotypic diversity generated? Curr. Opin. Neurobiol. 15, 444–453.

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24 The Evolution of the Dorsal Thalamus in Mammals

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24 Introduction
24.2 The Lateral Geniculate Nucleus
24.3 The Visual Pulvinar
24.4 The Somatosensory Thalamus: The Ventroposterior Complex and the Adjoining Posterior Complex
24.5 The Auditory Thalamus: The Medial Geniculate Complex
24.6 The Motor Thalamus: The Ventral Lateral Complex and the Ventral Anterior Complex
24.7 The Anterior and Lateral Dorsal Nuclei
24.8 The Mediodorsal and Intralaminar Thalamic Nuclei
24.9 Conclusions

Glossary

layers and subnuclei
nuclear complex
nucleus
thalamus

Parts of nuclei sometimes differ somewhat in histological characteristics, connections, and neuron response characteristics to the extent that they are recognized as subnuclei or layers, while having enough features in common to include them in a nucleus. Sometimes subnuclei are called nuclei.

Adjoining nuclei of related functions are sometimes grouped into a complex such as the pulvinar complex. In some instances, the nuclei of the complex may have differentiated from a single ancestral nucleus.

A collection of neurons and other cells in the thalamus that are united by a common function. Nuclei have been historically identified in brain sections as groups of neurons that differ from surrounding thalamus in the packing of neurons, cell types, and other histological characteristics. Neuronal differences also occur in connection and, of course, the properties of their afferents.

A part of the forebrain between the cerebral cortex and midbrain. This region contains the dorsal thalamus, the division that is largest in mammals, and projects to neocortex.

While the region of the diencephalon called the thalamus includes the ventral thalamus, the hypothalamus, and the epithalamus, authors commonly use the term to refer to the dorsal thalamus only, the topic of this review. The dorsal thalamus of mammals is a collection of nuclei in the diencephalon with neurons that project to neocortex. If the neocortex is removed, the projection neurons die, leaving the nuclei of the dorsal thalamus severely degenerated, while the nuclei of the ventral thalamus, hypothalamus, and epithalamus remain intact or slowly respond to changes of the dorsal thalamus (Rose and Woolsey, 1943). In this way, the dorsal thalamus can be experimentally distinguished from other parts of the thalamus. This is not to say that all of the neurons of the dorsal thalamus project to neocortex, as there are many intrinsic neurons as well, and a number of neurons project to the striatum (Jones, 1985), a major target of some of the nuclei of the dorsal thalamus of the eutherian ancesors of mammals. The major steps in the evolution of the thalamus in vertebrates, and the transition from the thalamus of reptiles to that of mammals, have been discussed in this series and elsewhere (Butler, 1994; Pauli, 2001; see Evolution of the Nervous System in Reptiles). Therefore, this review focuses on the specializations of nuclei of the mammalian thalamus as the various branches of the mammalian radiation lead to the over 4500 extant species (Wilson and Reeder, 1993). Of course, there have been few or no observations on the thalamus of most of these species, so the concentration is necessarily on the thalamic nuclei of the few well-studied taxa. Jones (1985) defined a thalamic nucleus as "a circumscribed region of cytoarchitecture receiving a particular set of afferent connections and projecting within the borders of a particular field or fields." To elaborate on this definition, a nucleus is a collection of...