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The evolution of the neocortex in mammals: how is phenotypic diversity generated?

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Evolution of the mammalian neocortex is difficult to examine directly. For this reason, comparative studies and developmental studies are the best way of gaining insight into the evolutionary process. Comparative studies indicate that neocortical evolution is constrained, and that the types of systems-level modifications made to the neocortex are limited. Developmental studies of gene expression suggest that genetic contingencies set up aspects of cortical organization and connectivity, and that the complex spatial and temporal interactions of genes constrain development and evolution. Although genes obviously contribute to phenotypic variability, variability can also be achieved through alterations in the sensory receptor arrays, or changes in sensory driven activity. The intracellular mechanisms that enable phenotypic variability might evolve, but often the phenotypic characteristic in question is context-dependent.

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Introduction

The study of nervous system evolution, especially that of the neocortex, is inherently interesting because it relates to the issue of how complex behaviors arose in different lineages, particularly that of humans. How did a neocortex with a large number of cortical areas evolve, and how do features of neocortical organization and modification endow individuals with a remarkable number of perceptual and cognitive abilities? Unfortunately, understanding brain evolution and, for our purposes here, neocortical evolution, is hindered by two major obstacles. First, because the products of evolution accumulate slowly over many generations, the direct study of mammalian brain evolution is difficult. As a result, the evolutionary process is not very amenable to laboratory experimentation. Second, unlike portions of the skeleton, soft tissue such as the brain is not preserved in the fossil record; therefore information is limited to endocasts of fossil skulls, and regards only the size and shape of the brain [1,2]. Because of the problems associated with studying evolution directly, it is necessary to make inferences about evolutionary processes by examining the end products of evolution, namely the brains of living species [3], and to study the developmental mechanisms that recreate brain phenotypes in each generation [4,5].

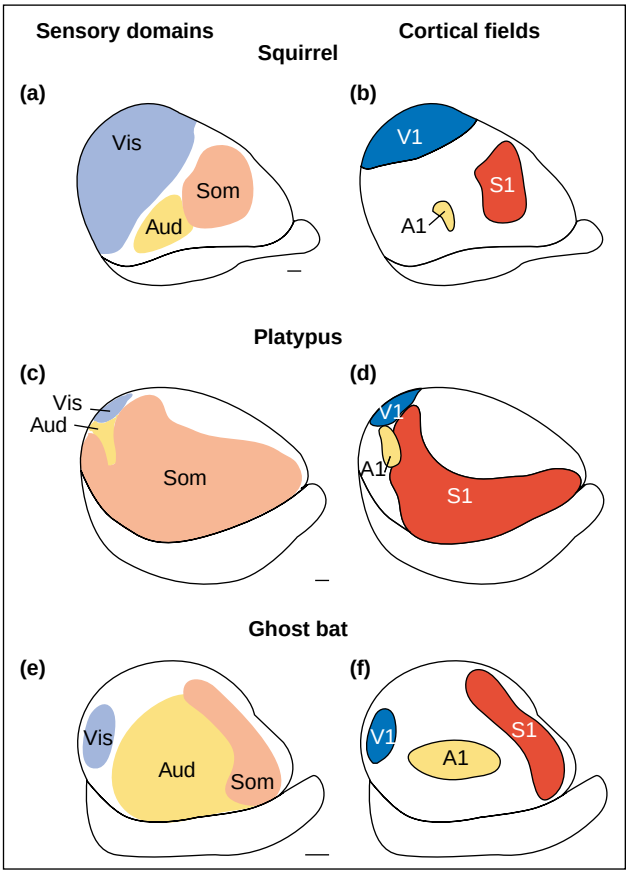
A cortical phenotype is the result of the interaction between the products of gene expression (heritable traits) and the factors that, broadly speaking, come from the environment. Environmental factors include passive influences, such as temperature and pH, and active influences, such as sensory experience. Although evolution reflects changes in the heritable components of traits, namely genes, natural and sexual selection are based on the phenotype. Thus, phenotypic alterations over long time scales are due to changes in genetic makeup, and the environmental factors that affect gene expression. Although environmental factors contribute to features of the phenotype that are not heritable, relatively stable environmental effects on the phenotype can present themselves as products of evolution.

Although cortical organization certainly reflects the state of subcortical sensory structures, and sensory receptor arrays, this review is restricted to the discussion of the evolution of sensory neocortex, particularly the primary sensory areas. First, we describe the similarities and differences in neocortical organization among species, and then discuss the role of genes and sensory experience in generating features of cortical organization. Finally, we discuss how variability within a species forms the substrate for phenotypic change over the longer time scales of evolution.

All mammals have a common plan of cortical organization that has been modified in a restricted fashion

Using a variety of different methods, several cortical areas, including the primary somatosensory area (S1) [6,7], the primary visual area (V1) [8], and the primary auditory area (A1) [9], have been identified in all, or nearly all, mammals examined ([10,11]; Figure 1). These fields are defined by a topographic representation of the sensory surface co-extensive with a distinct architectonic and/or histochemical appearance [12]. Despite the extreme morphological and behavioral specializations of many

Figure 1



The sensory domain allocation and location and size of primary sensory fields in the neocortex of three different mammals with different sensory specializations. The arboreal squirrel is a highly visual rodent, **(a)** and much of its neocortex is devoted to the visual system. **(b)** Furthermore, the relative size of V1 compared with other primary sensory areas is large. The duck-billed platypus has an extremely well developed bill that is composed of densely packed mechanosensory and electrosensory receptors. The platypus uses its bill for most activities including navigating in water, prey capture, predator avoidance and mating. **(c)** Most of the neocortex in this mammal is devoted to the somatosensory system, **(d)** and the relative size of S1 compared with other primary fields is quite large. The ghost bat is an echolocating mammal that relies on its auditory system for most vital behaviors. **(e)** It is not surprising that a large proportion of its neocortex is devoted to the auditory system, **(f)** and that the relative size of A1 is large compared with other primary fields. In the left column, sensory domains, or the amount of cortex devoted to processing inputs from a particular sensory system, are denoted in different colors. Light blue indicates the amount of the neocortex devoted to processing visual inputs, light yellow indicates the amount of cortex devoted to processing auditory inputs, and light red indicates the amount of cortex devoted to processing somatic inputs. In the right column, primary cortical areas are denoted in blue (V1), yellow (A1), and red (S1). Note that even in the absence of extensive use (such as the visual system of the platypus), the primary cortical fields are readily identified, and their geographic location relative to each other is maintained, although their relative size is altered. Scale bar = 1 mm.

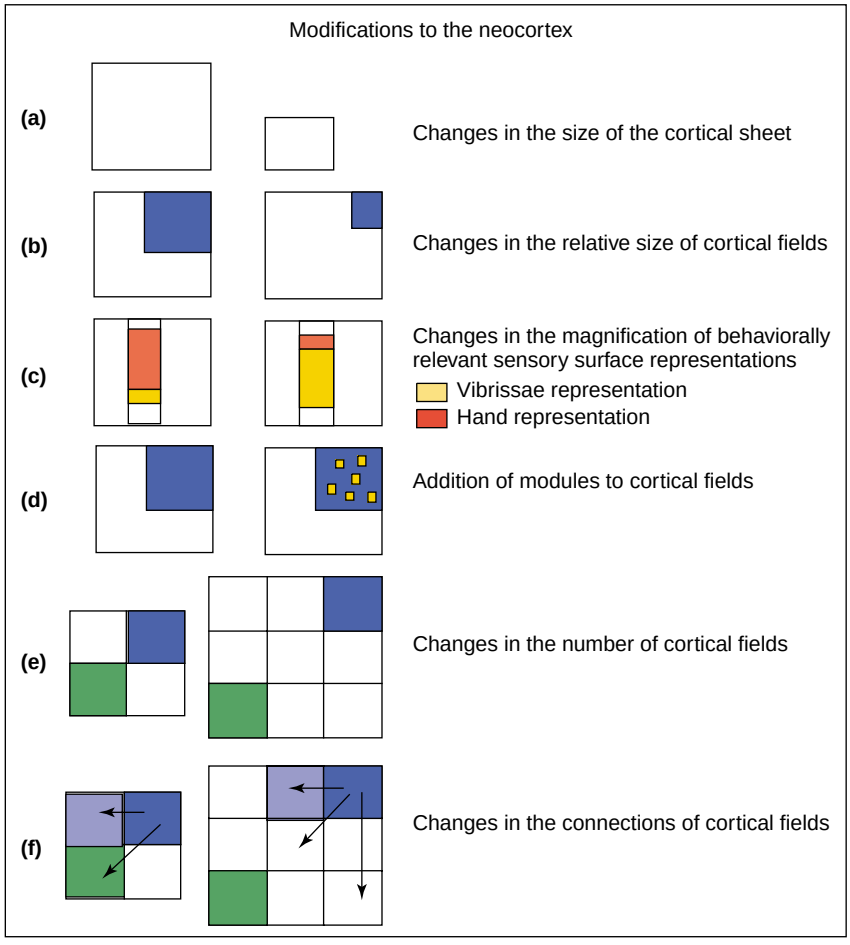
mammals (e.g. [10,13,14]), this constellation of fields is always present, even in the absence of apparent use [15–17]. The ubiquity of these fields, aspects of their corticocortical and thalamocortical connectivity, and their general geographic arrangement across species indicate that they were present in the last common ancestor, and that they cannot be eliminated under most circumstances. These fields reflect the constraints imposed on the evolution of the neocortex. This arrangement of primitive areas is probably genetically regulated, as recent molecular studies of the developing cortex suggest (see below).

Although always present and constrained in relative location, these fields have been significantly modified in different lineages (Figures 1 and 2). Basic modifications have taken similar forms in various lines of descent. These modifications include changes in absolute and relative cortical field size, changes in cortical field size relative to areas of other modalities, cortical magnification of the representation of behaviorally relevant sensory surfaces, modular subdivisions associated with disruptions in the receptor sheet or mode of sensory activation, changes in cortical domain (the amount of neocortex devoted to processing inputs from a particular sensory system), and changes in cortical connections ([11]; Figures 1 and 2). The basic cortical areas are targets of a series of relays from the receptor surface to the cortex, and modifications of the sensory system at early levels of processing, from sensory receptor arrays through the brainstem, midbrain and thalamic relays, alter the organization of the cortical area. Similar to the presence of the fields themselves, the invariant nature of systems-level modifications indicates that the developmental mechanisms that give rise to these modifications take the form of contingencies, or cascades of effects, that are initially instigated by individual genes or a combination of genes (see [18,19]). Below we describe recent developmental work that demonstrates the role of genes in determining several aspects of primary sensory field organization.

Genes are the stuff of evolution

Given that there is a common plan of cortical organization that all mammals possess, and that there is a restriction on the types of modifications to the neocortex, it seems reasonable to conclude that the presence of the primary cortical areas, their connections, their modular organization and their size are, in large part, genetically determined. There is evidence for this from studies of cortical development. For example, transcription factors such as *Emx 2* and *Pax6* appear to have an important role in assigning the geographic relationships between primary fields in the rostrocaudal axis and, ultimately, the patterning of thalamocortical connections (see [18,20,21]). Both *Emx2* and *Pax6* regulate the expression pattern of proteins, such as some of the cadherins (Cad 6, Cad 8 and Cad 11), which are restricted to particular portions of the neocortex [20]. Cadherins have been proposed to regulate

Figure 2

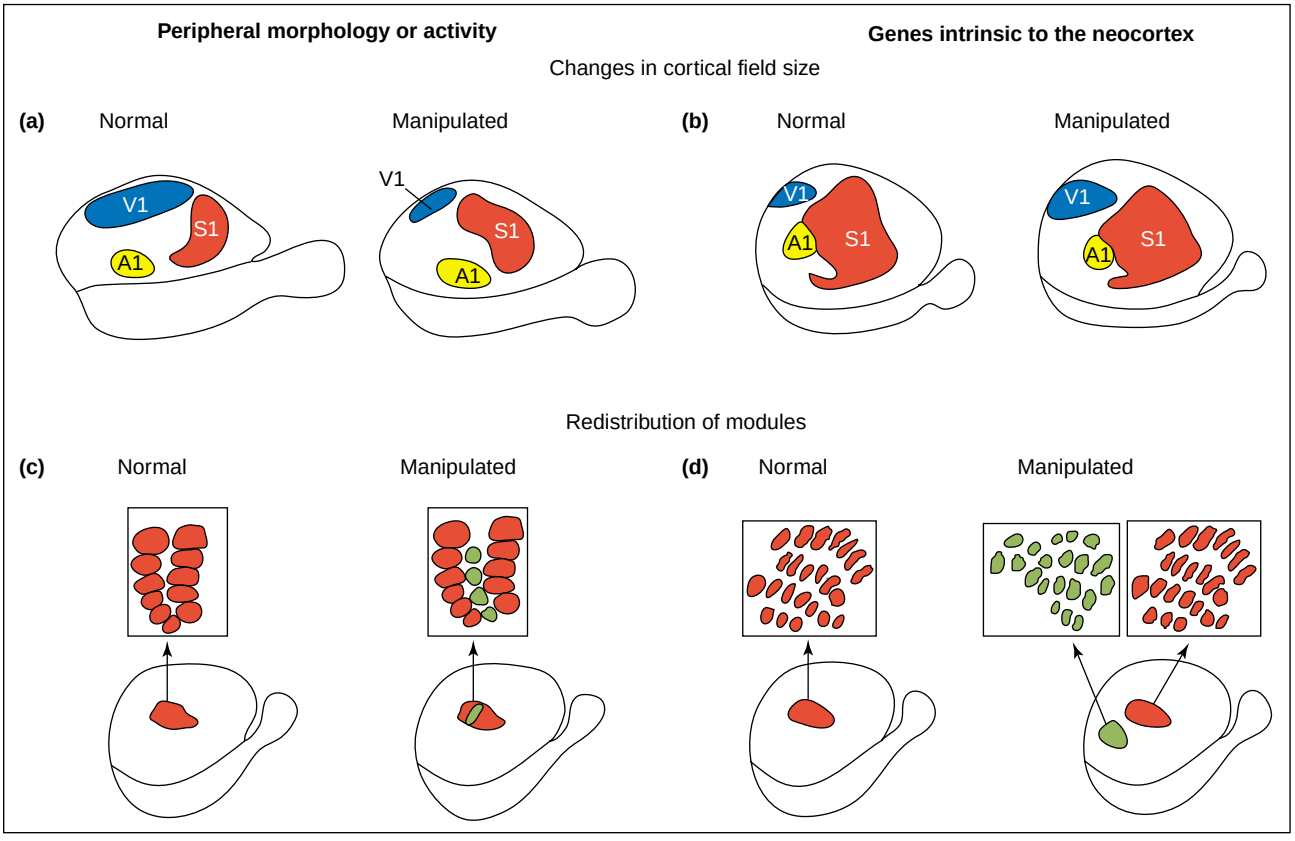


A schematic drawing that illustrates the types of consistent systems-level modifications made to the mammalian cortex in evolution. These include; **(a)** changes in the size of the cortical sheet; **(b)** changes in the relative size of cortical fields (blue box); and **(c)** changes in the magnification of behaviorally relevant sensory surface representations. For this latter modification, we denote changes in the somatosensory cortex. The red boxes indicate the hand representation and the yellow box indicates the vibrissae representation as examples of cortical magnification in S1 in different species. Other types of modifications that can be made to the neocortex include; **(d)** the addition of modules (small yellow boxes) to a cortical field; **(e)** changes in the number of cortical fields (indicated by an increase in the number of boxes); **(f)** and changes in the connections of homologous fields. Homologous fields are indicated by a similar color such as blue and green. With the increase in cortical field number, some connections of fields are lost, and new connections are established.

aspects of thalamocortical patterning [20,22]. In mice lacking *Emx2*, thalamic afferents from the ventral posterior nucleus, which normally innervates S1, are shifted far caudally into cortex that would normally develop into visual cortex. This demonstrates that *Emx2* has an important role in patterning of thalamocortical connections, possibly via regulation of some of the cadherins. Although our understanding of which genes are involved in regulating corticocortical connections is limited, recent work indicates that connections are, at least in part, genetically determined. For example, FGF8 (fibroblast growth factor 8), which is involved in setting up anterior–posterior patterning via the regulation of expression of *Emx2* [19], also regulates patterning of developing corticocortical connections [23]. Furthermore, this intrinsic regulation of normal corticocortical connections can occur even in the absence of thalamocortical afferents [23].

In addition to determining the relative locations of primary cortical areas, and controlling the formation of their basic connections, genes also influence cortical field size and modular organization (Figure 3). For example, mice genetically engineered to overproduce nestin-*Emx2* have a larger V1 than normal animals, and other primary fields, such as S1, have shifted rostrally ([24]; Figure 3b). In terms of modular organization, when the signaling protein FGF8, normally located in the rostral pole of the neocortex, is electroporated into an ectopic location caudal to S1, a duplicate cortical barrel field (defined histochemically) is observed just caudal to S1 ([25]; Figure 3d).

Figure 3



Experimental manipulations that have induced similar types of systems-level modifications to those that have been made to the neocortex in naturally evolving systems. One of the consistent modifications made to the neocortex is a change in the size of a cortical field. This has been accomplished experimentally using two distinct manipulations. **(a)** The first is to alter peripheral morphology by bilaterally enucleating the eyes early in development of opossums [28], **(b)** and the other way is to overexpress genes, such as *Emx2*, that are intrinsic to the neocortex [24]. In both studies, the size of V1 was altered. In the former study (a), V1 decreased in size and in the latter study (b), V1 increased in size. Electrophysiological recordings in bilaterally enucleated opossums demonstrate that although a small architectonically defined V1 is still present, it contains neurons that respond to somatosensory and auditory stimulation. Another type of modification made to the neocortex is the addition of modules. **(c)** This has been accomplished experimentally by selectively breeding mice to grow extra whiskers [34], **(d)** or by electroporating the signaling molecule (FGF8) into an ectopic location in cortex caudal to the normal location of the barrel fields [25]. In both experiments, additional barrels (green) were generated. These studies indicate that similar types of modifications in naturally evolving neocortices can be induced by entirely different mechanisms.

Taken together, these molecular studies in developing animals indicate that several of the ubiquitous features of cortical organization, such as primary sensory field location, thalamocortical and corticocortical connectivity, size, and modular organization, can be regulated genetically.

Because the types of naturally occurring modifications that occur in the neocortex are limited, neocortical evolution is constrained. This could be because of genetic pleiotropy, in which a single gene regulates several traits and/or functions of both neural and non-neural tissue development [26,27], and because of genetic contingencies. For example, the regulation of thalamocortical afferents appears to be the result of a series of molecular events starting with the spatial regulation of *Emx2* by FGF8, the requirement for both *Pax6* and *Emx2* to define the geographic location of fields in the rostrocaudal axis, and the downstream regulation by *Emx2* of particular molecules such as the cadherins. The cadherins, in turn, regulate thalamocortical connections. This series of genetically mediated events would considerably constrain potential alterations in thalamocortical connectivity in evolution. If one considers these contingencies as an 'if-then' proposition, then altering any step in this temporally sequenced combination of events would inevitably change the trajectory of the entire developing neocortex and organism. Because major changes often result in non-viable offspring, as evidenced by the early postnatal death of many genetically altered mice, this type of process would enable only subtle changes in the timing, distribution and gradients of expression of reg-

ulatory genes and downstream signaling proteins, or changes at the very late stages of cortical development, as has been suggested previously by Finlay and Darlington [4].

Phenotypic variability is only partially explained by gene expression in the neocortex

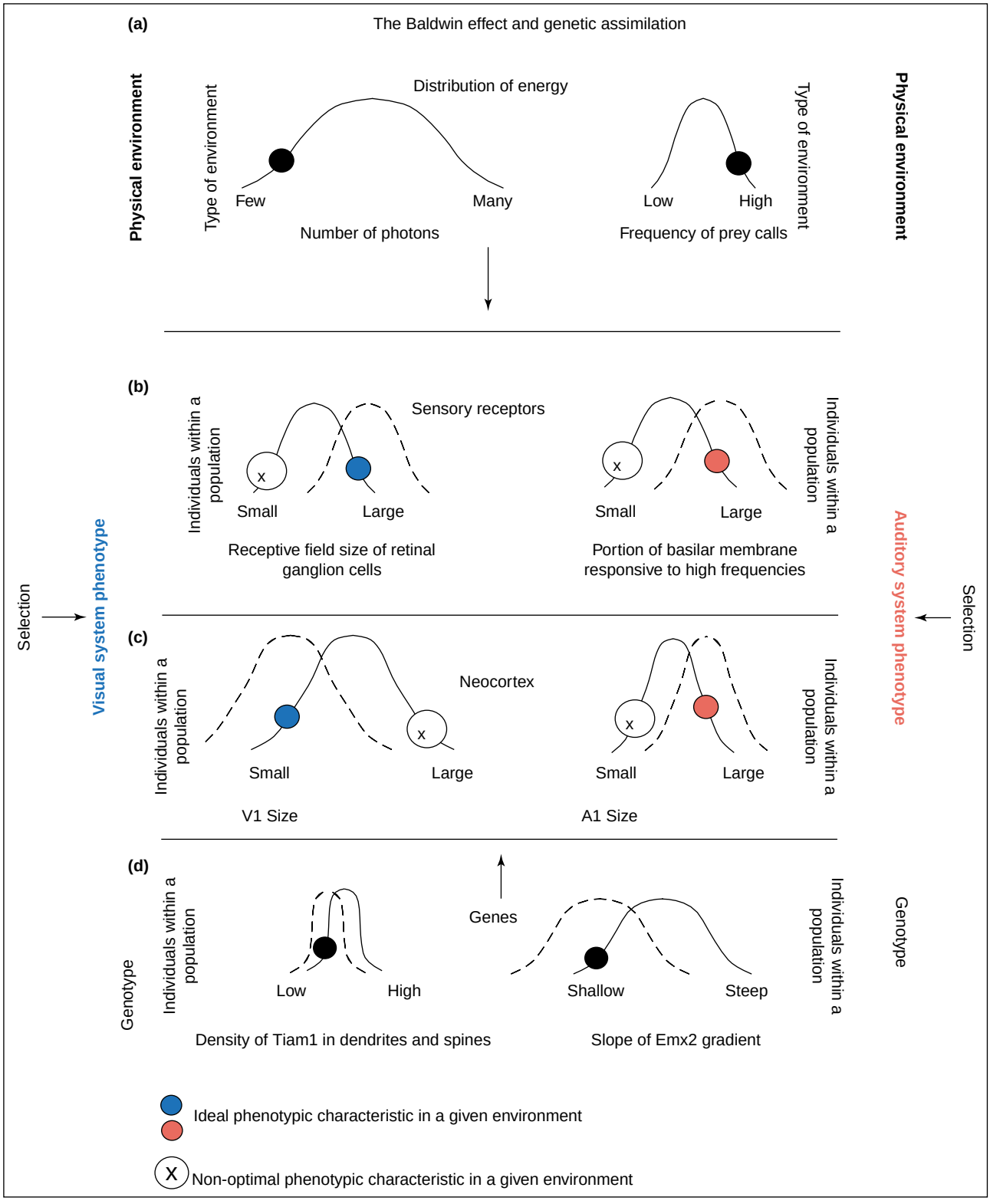
If we are interested strictly in evolution, then we must limit our discussion to events in development that are heritable. However, if we are interested in mechanisms that contribute to phenotypic variability, which is at the heart of natural selection, then we must delve into studies of how sensory driven activity alters cortical maps, and the cellular mechanisms that enable plasticity during development. There is a wealth of data in developing mammals that indicate that peripheral sensory receptor arrays play an enormous part in assigning cortical domains, determining the functionality of cortical fields, and influencing the internal organization of cortical fields, the sizes of cortical fields, and the connectivities of cortical fields. For example, recent work in opossums [28] indicates that removing a sensory receptor array early in development leads to massive reorganization of the neocortex. In these animals, cortex that would normally be devoted to the lost sensory system is taken over by remaining sensory systems. In terms of cortical field size, loss of sensory apparatus [28,29] or loss of sensory-driven activity [30] leads to a large reduction in the size of the primary cortical area associated with the impaired sensory system (Figure 3a).

At a finer level of organization, alterations in the sensory environment, such as the introduction of acoustic noise, can alter the cortical magnification of particular frequencies in A1 [31]. Furthermore, the spatial tuning characteristics of primary auditory cortex neurons in ferrets are altered by the growth of the head and ears [32], and in rats the temporal characteristics of neurons in the primary auditory cortex can be altered with auditory training [33]. Likewise, modular organization within a field can also be modified by manipulating sensory receptor arrays. Early work by Van der Loos and coworkers [34] in which mice were selectively bred to have extra whiskers, demonstrates that these animals have additional barrels within the barrel field of S1 that reflect these peripheral modifications ([35]; Figure 3c). Recently, it has also been demonstrated that the size of the barrel field can be regulated by modifying activity through environmental enrichment or through whisker clipping during development [36]. Finally, alterations in thalamocortical and corticocortical connections can be achieved by mechanisms extrinsic to the neocortex. For example, lesions of the lateral geniculate nucleus in postnatal day one hamsters result in alterations in corticocortical connections such that V1 receives inputs from regions of somatosensory and temporal cortex [37]. In bilaterally enucleated opossums, thalamocortical afferents have been demonstrated to undergo significant modifications, in that the architectonically defined V1 receives inputs from the LGN, MGN and VPN [38]. Thus, one particular type of modification to primary cortical areas can be accomplished by two entirely different mechanisms, by either altering gene expression in the neocortex or altering the peripheral sensory sheet and/or sensory driven activity.

The alterations in sensory driven activity, to a large extent, are non-evolutionary because they are dependent upon the sensory environment in which an individual genetic cascade unravels. However, the cellular mechanisms that enable such phenotypic variability in the neocortex via alterations in sensory driven activity might be heritable. Several types of synaptic plasticity have been described in developing and adult nervous systems including N-methyl-D-aspartate receptor (NMDAR)-mediated plasticity [39,40], homeostatic plasticity [41], and brain derived neurotrophic factor (BDNF)-regulated plasticity [42,43]. Although the mechanisms for each form of plasticity might differ, the presence and location of molecules necessary for cellular activities that generate plasticity appear to be genetically regulated (e.g. [39,44]). Furthermore, all of these types of plasticity require neural (or sensory) activity to generate changes in the structure and strength of synapses, synaptic receptor density, dendritic spine size, and spine density. Recent work indicates that these cellular and subcellular mechanisms generate the systems-level changes described above [45]. For example, in mice in which NMDAR function has been genetically altered, particularly in the trigeminal system, the face representation in S1 is significantly reduced in size [45]. A related study by these same investigators [46] indicates that in the absence of NMDAR function in cortical neurons, thalamocortical afferents have an arborization that is twice the size of that in normal mice, and these afferents fail to respect the boundaries of barrels in S1. Thus, the ability to undergo cortical field map alterations in size, shape, territory and connectivity with fluctuations in the sensory environment might indeed be an evolved trait, but the alterations in these features themselves depend on the environment.

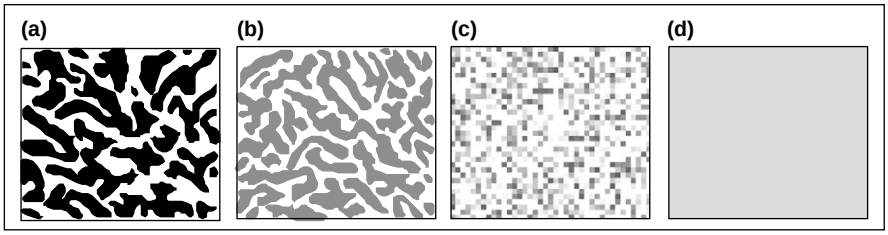
Although the phenotype generated is context-dependent, the ability to respond to the context has a genetic basis. This phenomenon is known as the Baldwin effect [47,48]. In essence, the Baldwin effect is the evolution of the ability to respond optimally to a particular environment ([49]; Figure 4). Thus, genes for plasticity evolve, rather than genes for a particular phenotypic characteristic, although selection acts upon the phenotype. A recent rendition of these concepts has been put forward by Kirschner and Gerhart [50] and Earl and Deems [51], who state, ''Not only has life evolved, but

Figure 4



A schematic depicting how sensory receptors might co-evolve with cortical maps. In any population, aspects of cortical organization and peripheral sensory morphology are normally distributed with the size of cortical fields varying from small to large, for example, and features of sensory receptors, such as receptive field size, also varying. **(a)** In a given environment in which light levels are low for example, and the frequency of prey calls is high, **(b)** the ideal phenotype of sensory receptors (red and blue dots) might be ganglion cells that have large receptive

Figure 5



Variability in ocular dominance columns in V1 of squirrel monkeys (from Adams and Horton [62]). This study demonstrates that within-species variability for ocular dominance columns ranges from **(a)** highly distinct with sharp boundaries, **(b)** to moderately distinct, **(c)** to barely visible, **(d)** to absent. These findings demonstrate that variability in features of neocortical organization can be extreme. They also underscore the idea that aspects of organization might be epiphenomenal, rather than fundamental units of processing necessary for certain functions, such as binocularity.

life has evolved to evolve''. These investigators contend that the rate at which base substitutions, recombination, transposition and horizontal gene transfer occur is variable and actually selected for in different lineages, and this evolvability is particularly prevalent in rapidly changing environments.

A particular phenotypic characteristic that is optimal for a given environment can become incorporated into the genome over successive generations by endowing a selective advantage to those individuals who display these optimal characteristics, and who have a strong correlation between genotypic and phenotypic space (Figure 4). This characteristic is then displayed even in the absence of the environmental condition that first produced it. This process, known as genetic assimilation [52–55], accounts for how activity-dependent modifications to the phenotype come under genetic control and become part of the evolutionary process.

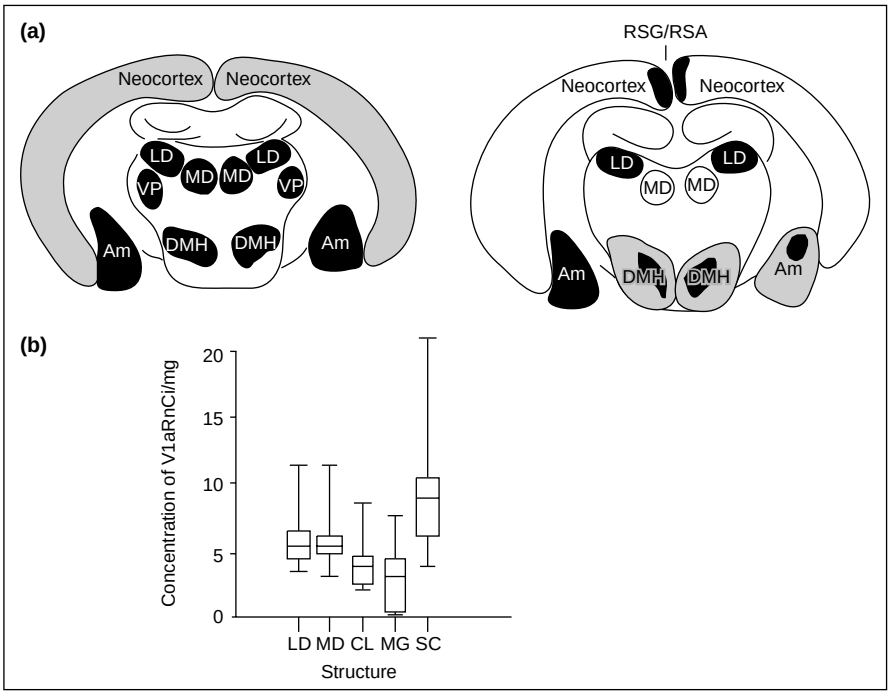
Individual variability is the heart of natural selection

As noted above, genes appear to regulate several aspects of cortical field organization that have been modified in different lineages throughout evolution. Although there is a lot of information on how aspects of cortical organization vary across lineages (see above), there is little information on how particular genes involved in aspects of primary sensory field development vary across species, and thereby account for some of the systems-level differences observed. However, there are a few recent studies that enable us to begin to address this issue. The first study examined protein evolution in several different mammals and found that there was an accelerated rate of protein evolution for nervous system related genes versus housekeeping genes in primates [56]. This acceleration is particularly prominent in humans. The second study examined the ASPM gene, which is believed to control cortical sheet size in anthropoid primates [57], and showed that this gene had accelerated evolution in hominids. In a third study, investigators examined the size of V1, of the barrel field in S1, and the overall size of neocortex in two inbred strains of mice, C57BL/6J and DBA2J. Ultimately, they aimed to relate distinctions in cortical field organization to differences in expression patterns of genes believed to be involved in cortical arealization [58]. These investigators found that the overall sizes of V1 and S1 barrel field differed between strains, suggesting that these inbred strains harbor enough genetic differences to result in differing cortical phenotypes.

The information regarding within-species variability at both the systems and the genetic levels is much more limited than that for cross species variations. At a gross morphological level, we know that sulcal patterns, particularly for mammals with a large neocortex, can be highly variable within a species (e.g. [59]). In addition, we know that representations of a particular sensory surface, such as the glabrous hand representation in S1, can also be variable within a species [60], although the architectonically identified cortical isomorphs, which represent each finger, are much less variable [61]. Within a cortical field, modular organization also shows a large degree of variability. Most notably, recent work by Adams and Horton [62] demonstrates that ocular

(Figure 4 Legend continued) fields and a basilar membrane with large portions devoted to high frequencies. **(c)** The ideal phenotype of cortical field size (red and blue dots) in this same environment might be a relatively small V1 and a large A1. **(d)** Although natural selection acts on the phenotype, genes, such as *Emx2* for example, control several features of organization such as size of V1. Activity-dependent intracellular mechanisms, which are normally distributed in a population, enable variability in features of cortical organization, such as cortical field size and aspects of connectivity. This type of selection might slowly shift the distribution of the genes that enable cortical plasticity, cortical field size and location such that the distribution of phenotypes shifts and the optimal phenotypic characteristic is now at the center of the distribution. In this way, the evolution of genes involved in aspects of cortical arealization proceeds, and activity-dependent features of organization can ultimately become incorporated into the genome.

Figure 6



Variability in the expression patterns of vasopressin 1a receptors (V1aR) in cortical and subcortical structures of the prairie vole, one of a small percentage of monogamous mammals (adapted from Hammock *et al*. [63]). The concentration of V1aR in dorsal thalamus, hypothalamus, and portions of the midbrain such as the superior colliculus is highly variable. These investigators demonstrate that the variability in expression of V1aR is correlated with variations in social and anxiety-related behaviors. **(a)** In coronal sections through the cortex and dorsal thalamus, dark regions represent sites of high expression, gray regions indicate sites of moderate expression, and white regions indicate no expression of V1aR. **(b)** A box and whisker plot indicating the concentration of V1aR on the *y-axis* and the structure labeled on the *x-axis*. The horizontal line within the box indicates the mean concentration, the upper and lower box lines indicate the standard deviation, and the bars indicate the upper and lower quartiles. Abbreviations: Am, amygdala; CL, centrolateral nucleus; DMH, dorsomedial hypothalamus; LD, lateral dorsal nucleus; MD, medial dorsal nucleus; MG, medial geniculate nucleus; RSG/RSA, retrosplenial cortex; SC, superior colliculus.

dominance columns in V1 of individual squirrel monkeys differ, and range in expression from highly discreet to completely absent (Figure 5). To our knowledge, there are no studies that describe the natural variability in patterns of gene expression in sensory neocortex of mammals. However, a recent study in prairie voles demonstrates that there is a high degree of variability in the expression patterns of vasopressin 1a receptors (V1aR) in cortical and subcortical structures, and that this variability in expression of V1aR is correlated with variations in social and anxiety-related behaviors ([63]; Figure 6).

Conclusions

The few reports of within-species variability indicate that the phenotypic distribution of an individual trait or characteristic can be extremely broad. However, it is not known if such variability is genetically mediated, activity dependent, or some combination of both (however, see Airey *et al*. [58]). Presumably, there are selection pressures within a variable population of individuals to modify peripheral morphology, expand or contract cortical fields, and modify connections, all of which can alter function (Figure 4). Unfortunately, there are only a few studies of cortical organization and development that describe the natural variability encountered for any cortical feature. Although collecting such information, as opposed to averaging across individuals to remove individual variability, would be labor intensive in most research studies, such information is invaluable for understanding the nature of phenotypic variability that exists for selection and evolution. Once we appreciate the degree to which certain gene expression patterns vary, for example, we could then determine how this variation is related to variation in aspects of cortical organization, connections and functionality. We could also associate this cortical variability with variability in peripheral morphology, such as receptor density and location, and better appreciate how the neocortex and sensory receptor surfaces co-evolve. Furthermore, there is no information on how genetically mediated cellular mechanisms that give rise to synaptic plasticity during development are distributed within a population. These normally distributed, genetically regulated cellular, cortical and morphological

systems must co-evolve and give rise to highly dynamic organisms that are, paradoxically, constrained by genes and the parameters of the physical environment in which they operate.

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