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Trends in Neurosciences

CellPress REVIEWS

Special Issue: Time in the Brain

Review

The Combinatorial Creature: Cortical Phenotypes within and across Lifetimes

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The neocortex is one of the most distinctive structures of the mammalian brain, yet also one of the most varied in terms of both size and organization. Multiple processes have contributed to this variability, including evolutionary mechanisms (i.e., alterations in gene sequence) that alter the size, organization, and connections of neocortex, and activity dependent mechanisms that can also modify these same features. Thus, changes to the neocortex can occur over different time-scales, including within a single generation. This combination of genetic and activity dependent mechanisms that create a given cortical phenotype allows the mammalian neocortex to rapidly and flexibly adjust to different body and environmental contexts, and in humans permits culture to impact brain construction.

Brain, Body, and Environment Interactions

In this review we discuss the evolution and development of mammalian neocortex. We examine the combinatorial nature of cortical phenotypes, explore the different time-scales over which the neocortex can change, and consider how relationships between the brain, the body, and the environment have shaped different phenotypes, including our own. Our review is based on three propositions.

The first is that all behavior is generated by the embodied brain which ties sensation to action in a loop through the world [1,2]. Thus, any change in behavior can be linked to alterations in the brain, the body, or the environment. The brain is not directly exposed to the environment and the only information about the external world that is delivered to the brain during development, and throughout a lifetime, is derived from a restricted set of sensory inputs from the eyes, ears, skin, muscles and joints, nose, and tongue. The body and its sensory receptor arrays make behavior possible, but they also constrain what kinds of behaviors can be generated. Moreover, the form of the body itself simplifies the problem of motor control for the brain by making certain kinds of behavior easier (walking, running, grasping), and other types of behavior (flying in humans) difficult or impossible [3]. For example, legs have dynamical properties suited for walking, where they operate like inverted pendulums, creating an intrinsically stable gait that needs only limited active control [4]; the configuration of the hand enables certain synergetic grasp positions that reduces the degrees of freedom of movement, making control of grasping easier [5]. The environment creates affordances for behavior [6,7]; a pool affords drinking or swimming, a tree – climbing, and this keyboard – typing. The relationship between brains, bodies and the environment are thus reciprocal and each shapes the others on a moment-by-moment basis and over longer periods of time.

The second proposition is that there are multiple time scales that are relevant for understanding how any extant brain phenotype emerges. Brains can change across large, evolutionary time scales of thousands to millions of years; across shorter time scales such as generations; and

Highlights

There are multiple time-scales that are relevant for understanding how a given phenotype emerges. Brains change across large, evolutionary time-scales, shorter time-scales such as generations, and within the life of an individual.

Any given phenotype is a combination of genes involved in brain and body development, behavior, and the environment in which an individual develops. A similar phenotype in different species may be due to homology, but can also be the result of a different combination of factors.

There are several constraints that restrict the avenues along which evolution of the brain and body can proceed. One of these constraints is the contingent nature in which genes are deployed during development. Another constraint is genetic pleiotropy; a single gene can be expressed in different portions of the nervous system at different times in development and can be involved in different aspects of brain and body organization. Finally, the laws of physics constrain brain evolution.

The human neocortex has an extraordinary capacity to adapt based on context, allowing for rapid phenotypic change even within a single generation. Our species has also evolved a remarkably fluid brain/body interface with the environment, such that tools and machines can be incorporated into our body schema, which extends our embodiment and peripersonal space.

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across the life of an individual: day-by-day, within hours, minutes, and even on a time scale of a second. Thus, your brain is different now than when you first began reading this review.

A final proposition is that any extant phenotype is a unique 'combinatorial creation' of the genetic cascades involved in brain construction and the wider embryological, bodily, and environmental context in which development happens [8,9,95]. Genes are the heritable components of evolution and essential agents in the developmental processes that build brains. Although genes are instrumental in shaping the brain, they co-vary with these more proximal targets of selection (Figure 1) [10], and how genes contribute to complex behavior is nuanced.

While these propositions can apply to any consideration of brain evolution, the specific focus of our review is on the mammalian neocortex because of its important contribution to perception, cognition, and volitional motor control. It is one of the portions of the brain that has changed most dramatically over the course of mammalian evolution, including, in some mammals, expansions in relative size compared to other parts of the brain such as the spinal cord, hindbrain and midbrain [11]. In this review we first provide a brief background on the basic pattern of organization and connectivity of the neocortex that all mammals possess and the types of changes that have occurred to this pattern over the course of evolution. We then consider factors that constrain the evolution of the brain and the body, the mechanisms by which phenotypic transformations occur, and the time courses over which change is possible. Finally, we discuss how understanding these factors can provide insight into how cultural evolution impacts cortical organization and behavior. This is especially relevant given the rapidly changing social milieu in which contemporary human brains develop and behave.

A Basic Plan and Alterations to This Plan

The neocortex is particularly large in non-human and human primates. We have known since the early studies of Brodmann (1909) and colleagues (e.g., [12,13]; see [14] for review) that it is not simply the expansion of the cortical sheet that accounts for some of our remarkable abilities, but the increase in the number of cortical fields that compose the neocortex and their patterns of connections. The fossil record indicates that the first mammals had a relatively small neocortex in terms of proportional volume [15], and comparative studies indicate that the earliest mammalian brains were simply organized and likely contained 15–20 cortical fields, similar to the neocortex of a short-tailed opossum (Figure 2). However, the number of cortical fields in modern living mammals ranges from 15 to over 200 (in humans, at least according to some definitions) [16]. How did the neocortex evolve from a simple structure with a few cortical fields, present in our common ancestor 200 million years ago, to the much more complex structure with multiple interconnected areas that are observed in the larger-brained, modern-day mammals? This question is difficult to address because brains do not fossilize, and modern-day brains are the result of an accumulation of changes that have occurred over millions of years.

Fortunately, we can circumvent problems associated with understanding brain evolution in two important ways: comparative studies and developmental studies. In comparative studies we examine the products of the evolutionary process (e.g., brains and bodies of different modern-day mammals) to understand 'what' evolution has produced. This type of analysis allows us to uncover common features of brain organization that are present in all mammals due to inheritance from a common ancestor (**homology**; see Glossary), as well as unique specializations that different mammals possess. While comparative studies of the neocortex are useful and have increased our understanding of the types of changes that have been made to brains,

Glossary

Apoptosis: naturally occurring cell death during development.
Cell cycle kinetics: the cycle of processes through which cells duplicate themselves. For neurogenesis of the mammalian neocortex, this occurs in the ventricular and subventricular zone.
Cortical arealization: the process by which cortical fields emerge during development.
DNA methylation: an epigenetic mechanism that can change gene expression without altering the underlying DNA sequence.
Epigenetic: the study of heritable changes in the phenotype that do not involve direct changes in DNA sequences.
Histone acetylation: an epigenetic mechanism that regulates gene expression, primarily by suppressing gene transcription.
Homology: phenotypic characteristics that are inherited from a common ancestor.
Self-organization: the capacity of complex dynamic systems, including bodies and nervous systems, to spontaneously create intrinsic order.
Subventricular zone: a layered structure in the vertebrate central nervous system containing progenitor cells that give rise to new cortical neurons during brain development. In mammals both an outer and an inner ventricular zone have been identified.

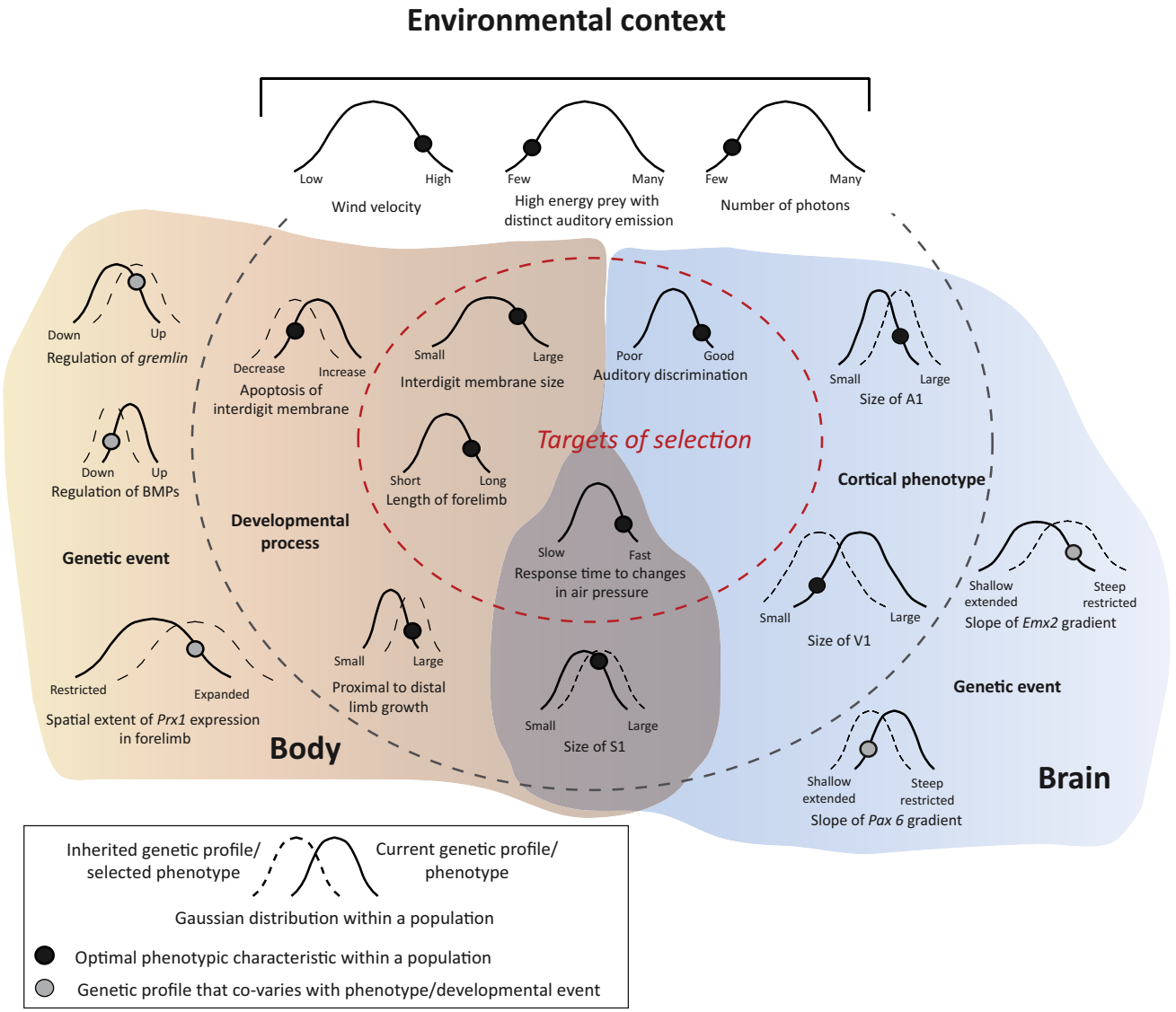

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Figure 1. Schematic Illustration Demonstrating the Co-variation between the Targets of Selection and Genes. Genetic events that construct the brain and the body could lead to inheritance of genes that generate a population of future individuals with a unique combination of adaptive phenotypic characteristics. Orange shading corresponds to factors associated with the development of the body (forelimb morphology), and blue shading corresponds to factors associated with the development of the cortex. The development of the brain and body are not strictly separate but interact to some extent (gray). The Gaussian curves represent the range of naturally occurring variability in a particular characteristic; narrower curves represent robust characteristics and wider curves represent stochastic characteristics. The black and gray circles represent the location of the optimal characteristic for a particular environmental context along the current distribution (unbroken curve). Selection pressures will eventually push the population to a new distribution, centered around the optimal/adaptive characteristic (broken curve) for a given environment. In this example, the species is an echolocating bat, and the environmental context is illustrated at the top. Some of the targets of selection (Gaussian curves inside the red, broken oval) would be characteristics of the forelimb that allow for flight, as well as behaviors such as fast response time and good auditory discrimination. Features of the cortical phenotypic located between the dark gray and red broken lines underlie auditory and tactile discriminatory ability (e.g., increase in the size of A1 and S1 and an increase in the wing representation within S1). Underlying developmental processes associated with wing formation include a decrease in apoptosis in the interdigit membranes and a lengthening of the forelimb. At the far perimeter (far left and far right) of this schematic are the genetic events that co-vary with features of the body and brain phenotypes (adapted from [10]).

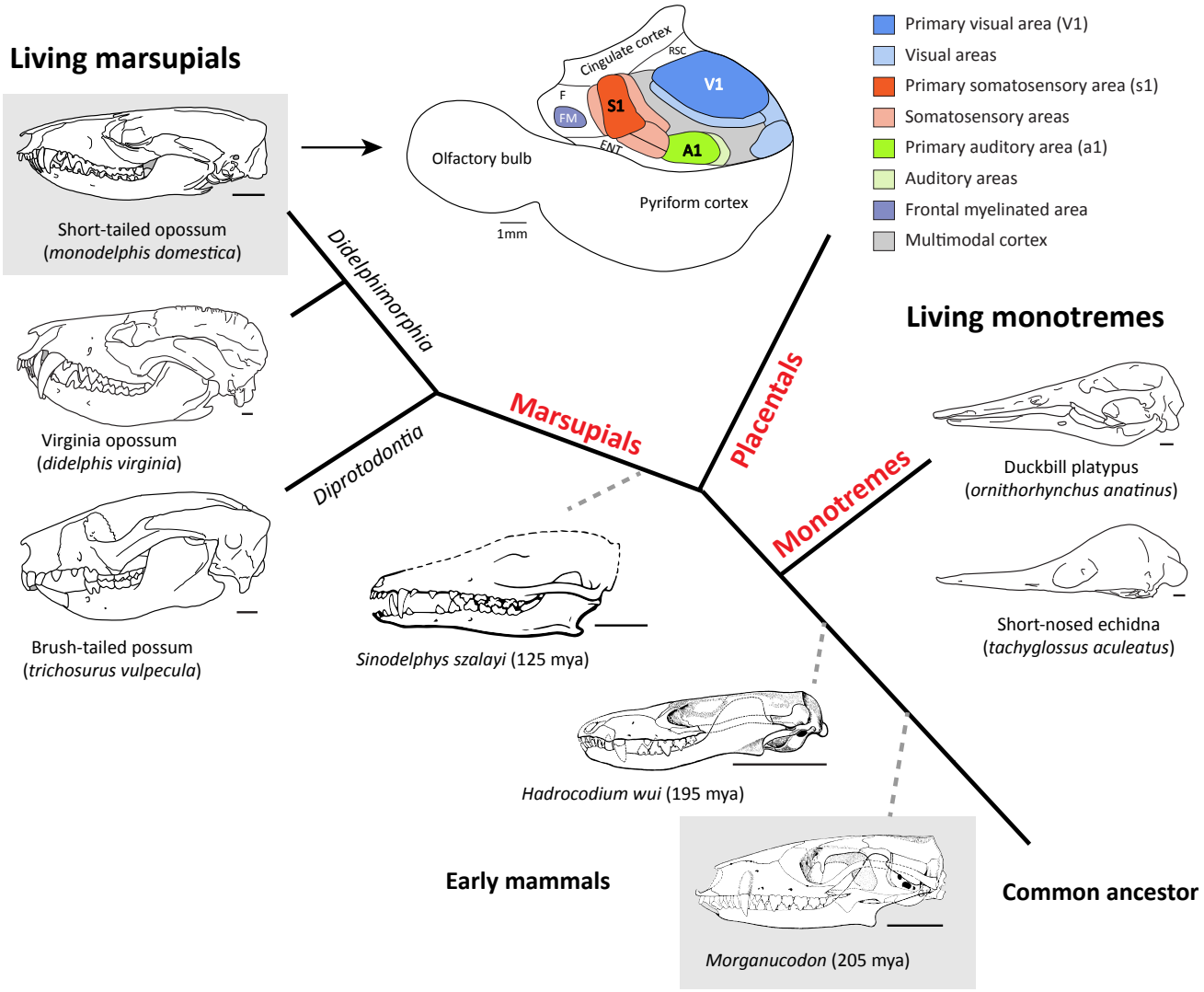

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Figure 2. Stylized Cladogram Summarizing the Phylogenetic Relationships of the Three Major Mammalian Radiations and the Skull Morphology of both Living and Extinct Mammals. Monotremes diverged earlier than marsupials and eutherians, but have highly derived oral facial specializations, skulls, brains, and lifestyles. Fossils of early extinct mammals (*Morganucodon, Hadrocodium wui*, bottom) and early marsupials (*Sinodelphis szalayi*, center) share many characteristics with the skulls of some extant marsupials (left), particularly didelphids, while differing sharply from extant monotremes (right). The orofacial configuration, body size, and brain size of *Monodelphis domestica* (top left) indicate that it may be the best extant model for early marsupials and early mammals. The brain organization and connectivity of didelphids and especially *M. domestica* may reflect that of the common ancestor of all marsupials and all mammals. Studies of the functional organization, architecture and connections of Monodelphis *M. domestica* neocortex indicate that there are a number of well-defined sensory and multisensory cortical areas (see key at right), as well as frontal area (F), retrosplenial areas (RSC), entorhinal areas (ENT) and cingulate cortex. Thus, this comparison suggests that early mammals likely had at least 17 cortical areas or more. Scale bars of skulls = 5 mm; mya = million years ago. Gray broken lines indicate extinct mammals. Skull drawings adapted from the following sources: *M. domestica* [82]; *Tachyglossus aculeatus* [83]; *Didelphis virginiana* [84]; *Ornithorhynchus anatinus* [85]; *Trichosurus vulpecula* [86], *H. wui* [87], *S. szalavi* [88], *Morganucodon* [89].

they are limited since they do not tell us 'how' these phenotypic transformations occur. To understand how these transformations happened, one can study neural development, since the evolution of the neocortex is, in part, the evolution of the developmental mechanisms that give rise to the cortical phenotype [17].

Comparative studies in a variety of mammals allow us to appreciate that, notwithstanding the wide variety of patterns of neocortical organization across mammalian brains, there is a fundamental plan that all mammals share with our common ancestor (see [18] for review; Figure 3). This constellation of homologous cortical areas includes primary sensory areas (S1, V1, A1; see Table 1), second sensory areas (S2/PV, V2, rostral auditory area), and, at least in eutherians (placental mammals), separate motor areas (e.g., M1, PM, SMA). These cortical areas have thalamocortical and corticocortical connections which have been maintained across species (e.g., geniculocortical pathways); but these networks have also been elaborated in different lineages with the addition of new fields. Interestingly, even when a sensory receptor array goes into disuse, such as the eyes in the blind mole rat, aspects of this

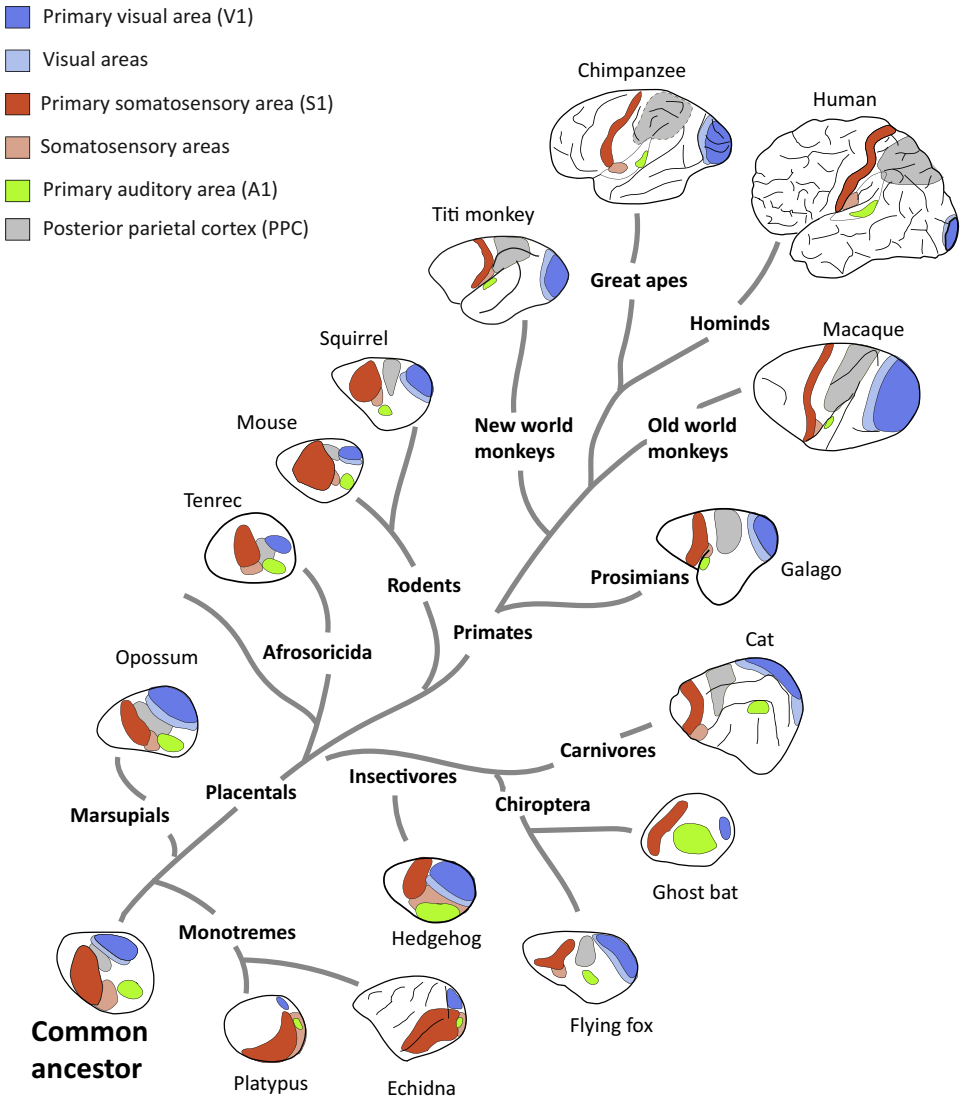

Figure 3. Cladogram of Phylogenetic Relationships for the Major Subclasses of Mammals. All species examined have a constellation of cortical fields that includes multiple visual, somatosensory, and auditory areas as well as a posterior parietal cortex (see color codes). However, the size of the neocortex varies greatly across species as does the relative size and location of cortical fields. Brains are not drawn to scale. Adapted from [90].

Table 1. List of Abbreviations

A1	Primary auditory area
AAF	Anterior auditory field
AC	Auditory cortex
AD	Anterodorsal nucleus
AV	Anteroventral nucleus
CT	Caudotemporal area
ENT	Entorhinal cortex
F	Frontal cortex
FM	Frontal myelinated area
LD	Lateral dorsal nucleus
LGd	Dorsal lateral geniculate nucleus
LP	Lateral posterior nucleus
M1	Primary motor area
MM	Multimodal area
OT	Optic tract
PM	Premotor area
PPC	Posterior parietal cortex
PV	Parietal ventral area
RSC	Retrosplenial area
S1	Primary somatosensory area
S2	Second somatosensory area
SMA	Supplementary motor area
V1	Primary visual area
rV1	Reorganized primary visual area
V2	Second visual area
VL	Ventrolateral thalamic nucleus
VP	Ventral posterior nucleus

homologous network, including the presence of a V1 and the geniculocortical pathway, can still be observed ([19,20], [21] Figure 4). Rather than processing visual information, the 'visual' structures of the blind mole rat have been co-opted by the auditory system, suggesting that the cortex is not constrained by the modality of sensory input, and that it is the input, rather than intrinsic factors, that determines ultimate function (see below).

Comparative studies have also uncovered a number of systems level changes that have been made to this common plan of neocortical organization in mammals, and alterations to this plan often take a similar form ([22], Figure 5). The most obvious alteration is a change in the size of the cortical sheet that can scale with the size of the body or become enlarged relative to the rest of the brain or body. Mammalian brains vary in size (and accordingly weight) by five orders of magnitude, ranging from a fraction of a gram in some shrews to nearly 10 kg in sperm whales (see [23] for review).

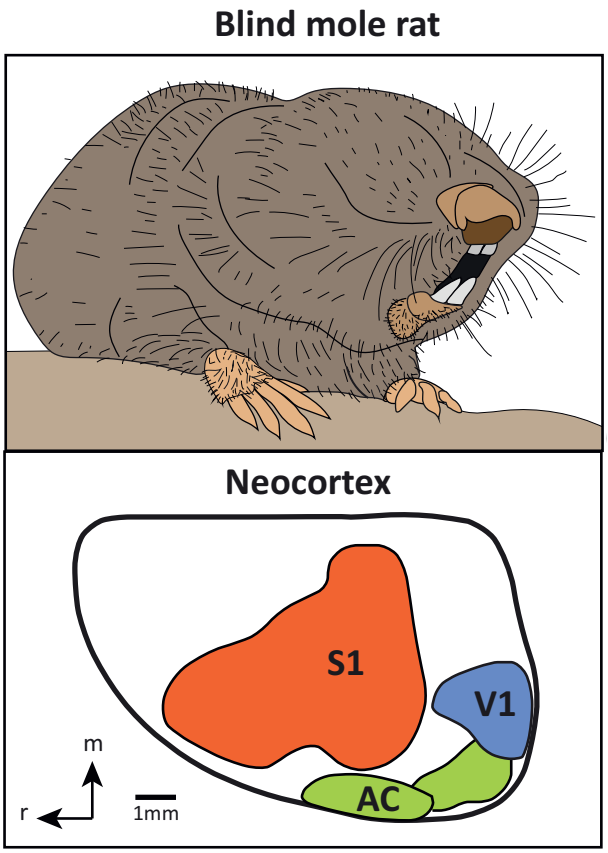

Figure 4. The Brain and Body of a Blind Mole Rat. An illustration of the burrowing blind mole rat (*Spalax ehrenbergi*, top) and the organization of its neocortex (bottom). Although skin has grown over the eyes and the visual system is used primarily for circadian functions, these animals still have a V1 and a retino-geniculo-cortical pathway. However, visual cortex has been co-opted by the auditory system. Abbreviations: AC, auditory cortex; S1, primary somatosensory area; V1, primary visual area. Cortical organization is adapted from [19].

There is also wide variability in the amount of the neocortex devoted to processing inputs from a particular sensory system (sensory domain allocation). For example, in echolocating, microchiropteran bats' auditory cortex is greatly enlarged, whereas in rodents with a similar sized neocortex, somatosensory cortex dominates the cortical sheet ([24,25] Figure 8C). Another alteration is the magnification of behaviorally relevant sensory receptor arrays. For example, in the somatosensory system this could include an increased size in the representation of the bill of a platypus, the hand of a primate, and the vibrissae of a mouse. There have also been changes in the relative size of cortical fields, in cortical field numbers, and in the connections of cortical fields, all of which can contribute to differences in behavior.

The Combinatorial Creature: Diversity in the Face of Constraint

Two important questions that arise from these observations are: What factors contribute to these systems level modifications to the neocortex? And, what is the time course over which these alterations emerge? It is tempting to hunt for 'the' way by which some aspect of the phenotype is modified: What is 'the way' in which the cortical sheet can increase in size? What

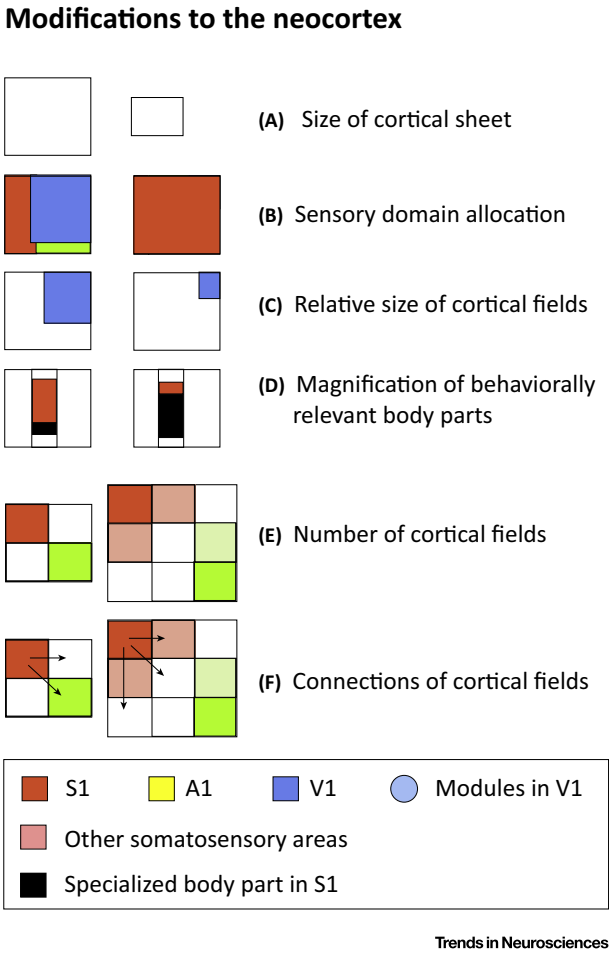

Figure 5. Systems-Level Modifications that Have Been Observed in the Neocortex across Different Species. Each box represents the entire cortical sheet, and smaller boxes within represent either sensory domains (B), cortical fields (C, E, and F), or representations within cortical fields (D). Many of these changes (e.g., B, C, D, and F) have been observed over short time-scales, including within the life of an individual. Adapted from [22].

is 'the way' in which the size of a cortical field is determined? And what is 'the way' in which connections of a cortical field are altered? However, there is no single process by which any given aspect of the cortical phenotype can be modified. There are multiple mechanisms through which a given characteristic could be assembled, including those that directly alter the neocortex itself, those that alter the body, those that impact both (e.g., through global changes in developmental timing [26]), and those that alter cellular mechanisms that allow the environment in which the brain develops to impact nervous system construction. However, the ways in which the brain can be altered are, nevertheless, limited.

One of the most significant constraints that restricts the avenues along which evolution of the brain and body can proceed is the contingent nature in which genes are deployed during development. For example, there are transcription factors (e.g., Pax6) expressed during development in the neocortical epithelial progenitor cells that play a number of roles in cortical development, such as establishing patterning and regulating neurogenesis. They also either promote or repress the transcription of a number of downstream targets including other

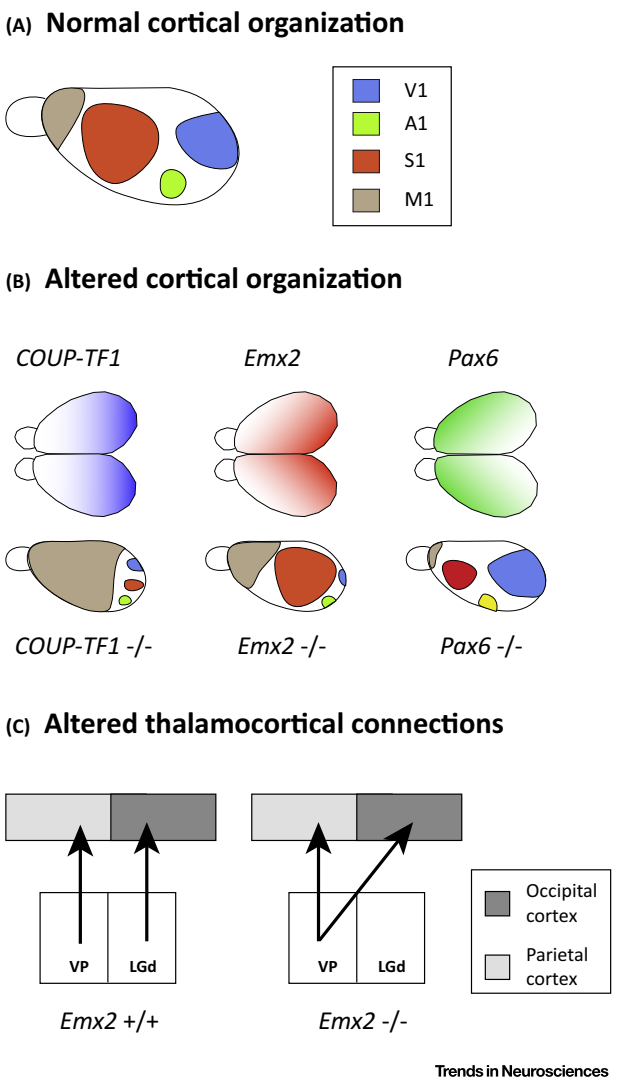

Figure 6. Genetic Manipulation of Early Transcription Factors. The cortical organization in a mouse brain (A), alterations in the relative size and locations of cortical fields (B), and thalamocortical connections of cortical fields (C) resulting from genetic manipulation of early transcription factors. The top row in (B) illustrates the normal expression patterns of transcription factors involved in the development of cortical fields. When *COUP-TF1* is knocked out there is a contraction of sensory areas and an enlargement of motor cortex; when *Emx 2* is knocked out there is an enlargement of S1 and a contraction of V1; and lastly when *Pax 6* is knocked out, there is a contraction of motor cortex and an enlargement of V1. This latter manipulation also leads to alterations in thalamocortical connections such that the projection zone of the ventral posterior nucleus (VP), normally associated with somatosensory processing in parietal cortex has expanded and projects to occipital cortex. These studies demonstrate that both the size and connections of cortical fields can be altered by changing the relative expression patterns of genes intrinsic to the developing neocortex. Data for these illustrations is for *Mus musculus* from [46,91]. Abbreviation: LGd, dorsal lateral geniculate nucleus.

transcription factors, cell adhesion molecules, and axon guidance molecules, which continue the process of constructing the nervous system (see [27] for review). Experimental manipulation of the expression of early patterning genes (e.g., Pax6, COUP-TF1) alters the relative size and the connections of cortical fields as well as the relative locations of cortical fields (see [28] and Figure 6). This type of contingent deployment serves as a major constraint for future evolution since altering early events affects subsequent events, which may result in a non-viable offspring. Thus, some aspects of cortical organization persist even in the absence of apparent use (e.g., the presence of a V1 even in the absence of vision; Figure 4). This reflects a general rule that the molecular regulators and the resulting anatomical structures that are generated very early in development are generally not sensitive to sensory input and other potential selective evolutionary pressures.

The same holds true for genes that are involved in the construction of the body. Homeobox genes (*Hox*) are a large family of genes that guide the construction of the hindbrain, spinal cord,

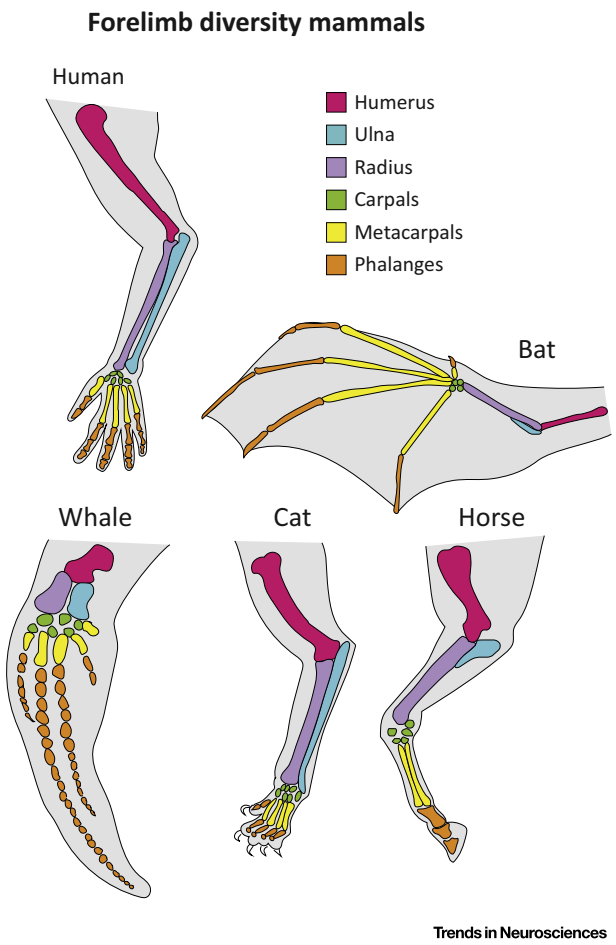

Figure 7. Examples of Forelimb Diversity in Mammals. These drawing indicate similar bones of the forelimb (see color code) that have been modified in their size and relative location in different mammals. The evolutionary modifications are due to alterations in the expression of homeobox genes that are involved in constructing the limb during development (see Figure 8). Such alterations can generate hands (human), wings (bat), flippers (whale), legs (cat), and hooves (horse).

neck, body and limbs during early embryonic development. They are highly conserved from flies to mammals, direct the deployment of downstream genes involved in limb construction, and constrain the types of alterations that can be made to the body. While evolution has transformed basic limb structure into hands, wings, hooves and flippers (Figure 7), every mammal is constrained by a basic body plan controlled by these *Hox* genes. As with transcription factors in the neocortex, alterations in the temporal and spatial pattern of *Hox* genes can alter forelimb development in rather radical ways, as demonstrated in comparative studies of limb development in bats and mice ([29–31]; see [32] for review; Figure 8). The morphological structure of the forelimb in each of these species is remarkably different, which seems to imply that there must be major differences in genes involved in the construction of the limbs. In fact, this is not the case; there are alterations in spatiotemporal patterns of expression of a handful of genes, or in the suppression of some genes, that can account for these morphological difference (e.g., [31,33,34]). Thus, notwithstanding the apparent variability in forelimb morphology and use, mammals remain tetrapods with a basic body plan, and have not evolved extra limbs, or even digits.

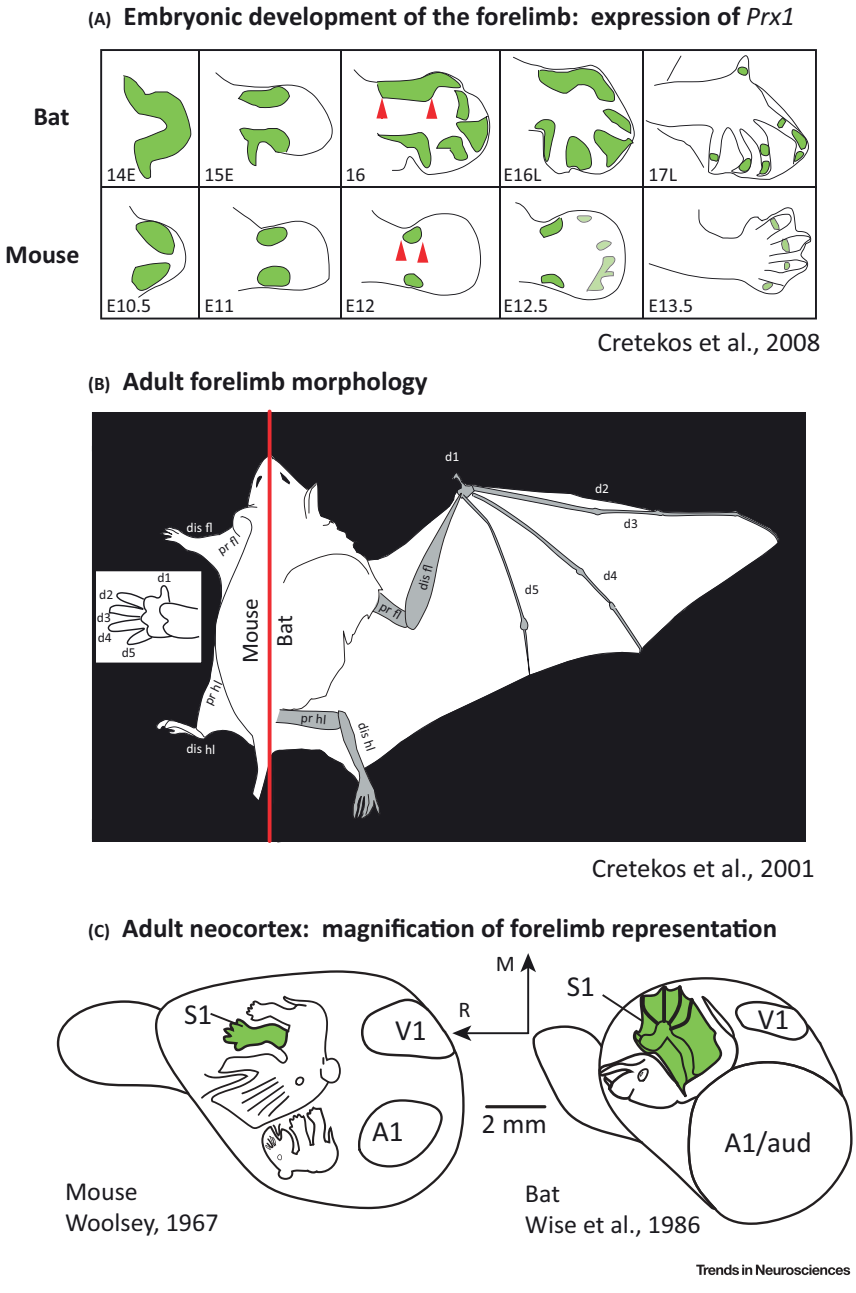

Figure 8. Brain and Body in Mice and Bats. Embryonic development (A), morphology (B), and cortical representation (C) of the forelimb in mice and bats. Differences in the patterns of expression of genes involved in forelimb development can account for a wide variety of forelimb structures such as mouse paws and bat wings. At middle stages of development, the spatial pattern of expression of *Prx1* (green) in the distal forelimb is expanded in bats (red arrows) compared to mice. This alteration, amongst a number of other molecular changes, accounts for the radical differences in the mouse forepaw compared to the bat wing. These morphological differences in the distal forelimb along with differential use of the paw versus the wing have likely contributed to the differences in size and internal organization of the forelimb representation in the primary somatosensory cortical area (C). Species shown are mouse (*Mus musculus*) and the short-tailed fruit bat (*Carollia perspicillata*) in (A and B), and the Australian ghost bat (*Macroderma gigas*) in (C). Figures adapted from [29,33,92,93].

The laws of physics also constrain the evolution of sensory systems. For example, while photons are distributed differently in aquatic and terrestrial environments, they have immutable characteristics; specifically, they are discrete quanta of electromagnetic energy that are always in motion and travel at the speed of light in a vacuum. Likewise, regardless of the medium (solid, liquid, or gas), sound waves travel through each of these media by vibrating molecules within them. While the density of the medium in which an animal lives can change the speed at which sound travels, the auditory system must adapt to optimally capture this source of energy. This constrains the evolution of sensory organs and their receptors that must transduce this energy, which the nervous system will ultimately translate and act upon.

Despite these rather large constraints imposed on brain and body construction, there are multiple ways in which any given aspect of the cortical phenotype can be altered; here we provide three distinct examples. First, alterations in the overall size of the cortical sheet might be achieved through a number of mechanisms that alter **cell cycle kinetics**, or progenitor pools from which neurons arise. Previous studies have shown that during cortical neurogenesis, macaque monkeys, which have a large cortical sheet, have an extended period of cortical neurogenesis with an increased rate of cell division compared to mice [35,36]. These dissimilarities can account for some of the differences in cortical sheet size exhibited by these mammals. Another possible way in which the size of the neocortex can be altered is by the addition of extra neurogenic cells (intermediate progenitors) within the **subventricular zone** of the developing brain [37–39]. In addition to intermediate progenitors, there are also increases in the number of outer radial glial progenitors that undergo self-renewing, symmetric divisions (e.g., [40]). Finally, subpopulations of GABAergic cells can be generated in a variety of different locations, including the ganglionic eminence, the dorsal telencephalon [41] and the embryonic preoptic area [42].

A second example is that of cortical field size. It has been demonstrated that genes intrinsic to the developing neocortex can alter the relative size of cortical fields (Figure 6; see [28] for review). In addition, cortical field size can be regulated by altering the overall size of the cortical sheet [43], by changes in the size of thalamic nuclei, and by differences in spontaneous and sensory driven activity present during early development [28,44]. A final example is that of corticocortical and thalamocortical connections, which can be changed by altering the expression of genes intrinsic to the neocortex (Figure 6; [28,45–47]), by altering the size of the cortical sheet [43], by changes in the developing thalamus (see [28] for review), by early exposure to toxins such as ethanol [48], or by altering the ratio of incoming sensory driven activity early in development. Importantly, these modifications can be linked to alterations in sensory mediated behavior as explored later.

Timescales of Evolution and Development

In the previous section, we discussed the different factors that contribute to the cortical phenotype; but how and why do these changes come about? Evolutionary theory tells us that phenotypic change results from natural selection across variation within a population. Variation can take the form of genetic change, for instance, alterations in DNA sequence due to substitution, insertion or deletion, or through genetic (allelic) drift. Contemporary evolutionary biology has highlighted the complementary role of experience in shaping development and producing phenotypic differences for selection to act upon (see [8] for review). Indeed, it has become increasingly clear that the success of the mammalian brain architecture, in adapting to a wide range of habitats, has occurred by avoiding over-specification of the nervous system in the genome, and by invoking developmental mechanisms that respond adaptively to both genetic and environmental change in order to configure a brain that is appropriately tuned to the

animal's environmental niche [9,17]. Computer simulation of these mechanisms (e.g., [9,49]) is essential to our understanding of how the brain self-assembles and to identifying how a balance between genetic specification, **self-organization** of network structure, and sensitivity to internal and external feedback has given rise to the diversity of neocortical forms that we observe in extant mammals.

While changes in the genome that induce phenotypic variation in brain organization accumulate and spread through the population over many generations, phenotypic transformations in brain organization and connectivity can also occur within the lifetime of an individual. The mechanisms by which the latter occur are varied. For example, environmentally induced changes in **histone acetylation** and **DNA methylation** can alter where and when genes are expressed [50], which in turn can alter connectivity of a brain area. Likewise, alterations in intracellular and synaptic mechanisms involved learning, memory, and plasticity (e.g., pre- and postsynaptic NMDA receptors [51,52]) can generate large changes in how information is processed in the brain and the behavior that the brain ultimately generates.

We have known since the studies of Waddington that a given genotype is capable of creating a range of phenotypes [53]; however what we do not know is how far we can experimentally push a genotype. Can we induce massive changes in cortical organization and connectivity within individual lifetimes, like those produced throughout the course of evolution, or is the final phenotypic outcome more constrained? To address how early sensory context impacts cortical organization and connectivity, and ultimately the behavior that the brain produces, we describe a series of experiments in which either the sensory receptor array, the environmental context, or the exposure to sensory input has been modified very early in development.

To completely lose a source of afferent sensory input is one of the most devastating things that can happen to a developing brain. While rare in nature, the manner in which the neocortex responds to such a trauma provides a good indication of its adaptive capability, which may be harder to see with more subtle interventions that better reflect changes in the body that happen more frequently in natural conditions. As an example, to determine the effect of a complete sensory loss on cortical organization, the Krubitzer laboratory made bilateral enucleations in the South American short-tailed opossum before retinal and thalamic projections had reached their targets and prior to the onset of spontaneous activity [54]. This drastically changed the ratio of incoming sensory inputs to the developing neocortex and resulted in alterations in the size, connectivity, and the functional organization of V1 (the targeted sensory system) and S1 (the spared sensory system). V1 was reduced to half of its normal size, neurons in the reorganized V1 (rV1) responded to somatosensory and auditory stimulation, and rV1 received inputs from somatosensory and auditory regions of the dorsal thalamus and neocortex ([55,56] see Figure 9). Similar effects were found following different types of experimentally induced sensory loss including congenital deafness [57,58], decreased sensory-driven activity [59,60], and peripheral lesions [54,61,62]. Importantly, these experiments suggest that the cortical phenotype is capable of remarkable change when inputs from different sensory systems are altered, underscoring the importance of spontaneous and sensory driven activity for normal development at all levels of the nervous system. Interestingly, not only are the connections of the re-organized visual cortex altered, but the neural response properties, receptive field characteristics, and cortical and subcortical connections of the primary somatosensory cortex also undergo changes [63]. Recent work in the Krubitzer laboratory also indicates that these functional and neuroanatomical alterations in the neocortex are accompanied by an enhancement in vibrissal mediated behaviors [64], confirming that cortical re-organization is adaptive.

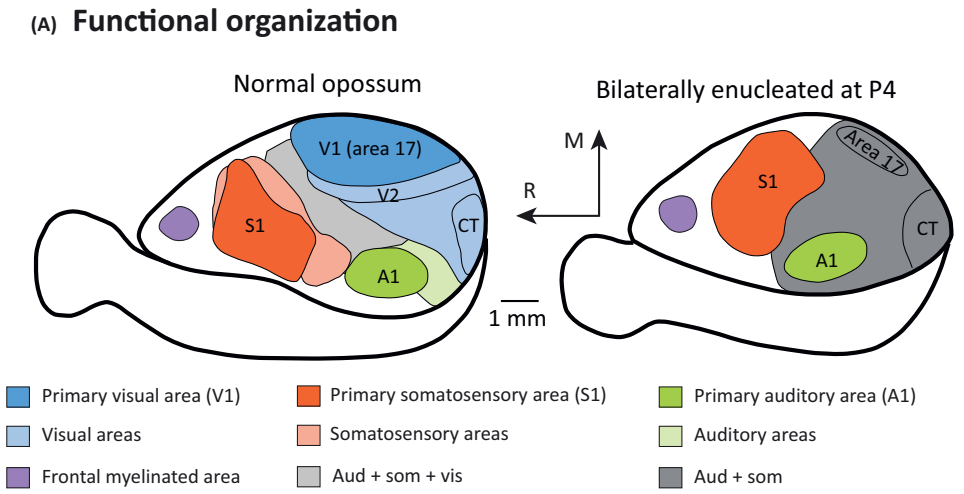

Figure 9. Alterations in Cortical Organization and Connections in Early Blind Mammals. Changes in the functional organization (A) and corticocortical and thalamocortical connections (B) following early loss of vision via bilateral enucleation in the short-tailed opossum (*Monodelphis domestica*). Changing the ratio of sensory inputs very early in development, prior to the onset of spontaneous activity in the retina or the formation of thalamocortical connections, radically alters the functional organization of the neocortex as determined using electrophysiological recording techniques. All of what would be visual cortex is taken over by the somatosensory and auditory systems. Also, what would normally be V1 receives input from nuclei in the thalamus and cortical fields normally associated with somatosensory and auditory processing. See Table 1 for abbreviations. Data from [54,56].

A second series of studies compared the size of cortical fields in nocturnal rodents (rats) to diurnal rodents (tree squirrels, ground squirrels and Nile grass rats), and also compared laboratory rats to wild caught rats [65]. This study addresses the question of how a change in lifestyle or habitat impacts the developing brain. These studies demonstrated that diurnal rodents had significantly larger visual areas (V1, V2 and OT) whereas nocturnal rodents had significantly larger somatosensory (S1, S2) and auditory areas (A1 + AAF). Similar expansions of visual cortex have also been observed in diurnal versus nocturnal primates [66,67]. Especially interesting was the observation that the same species of rat (*Rattus norvegicus*) reared in different environments (wild versus laboratory) had significant differences in the size of primary auditory and somatosensory cortex, although the magnitude of the difference in the size of somatosensory and auditory cortex was much smaller than that described above for early blind animals (10% and 27%, respectively). In addition, there were significant differences in brain to body ratios (wild caught rats had a relatively bigger brain) and in the percentage of the brain

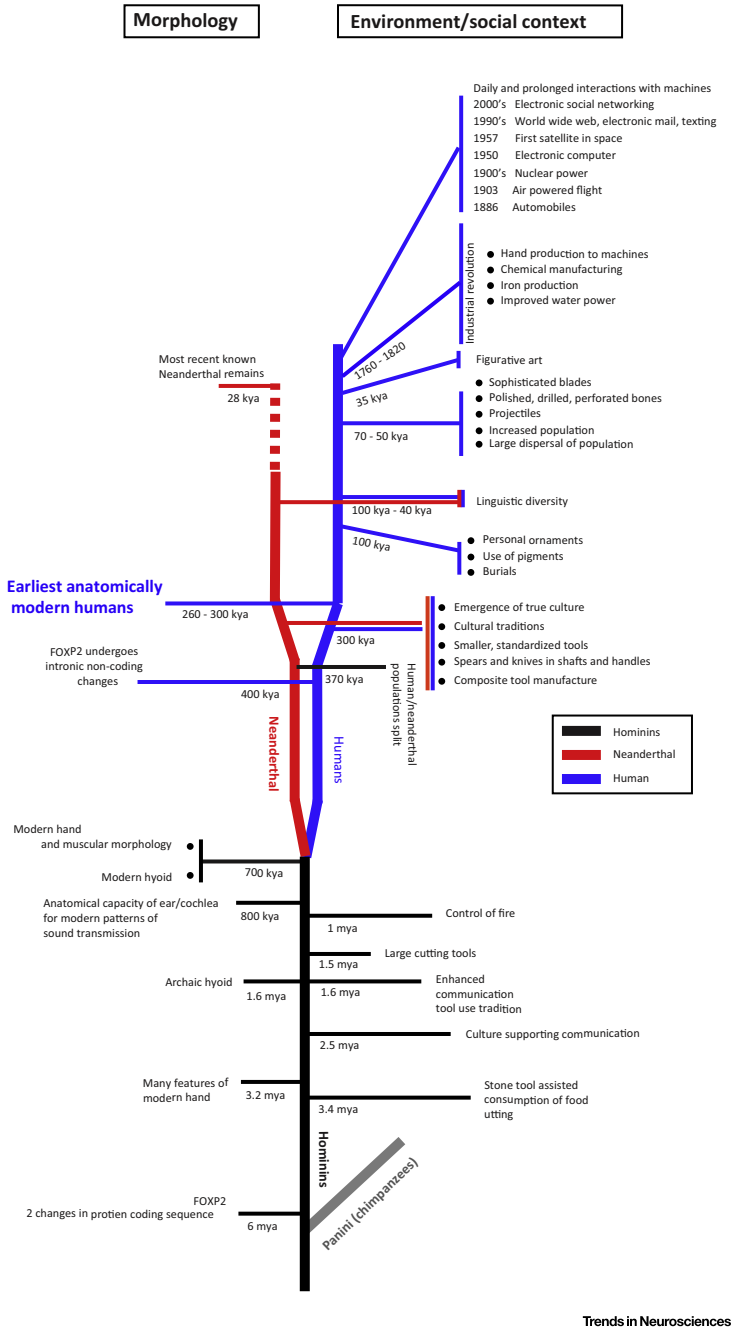

Figure 10. The Relationship between Chimpanzees, Humans, and Neanderthals. Some of the morphological (left) and environmental/social contextual changes (right side) that occurred during human evolution. While morphological changes to the body were relatively few, the social and technological behavior of humans (and Neanderthals) changed relatively rapidly. Although the anatomically modern human emerged about 260–350 kya, the explosion of culture, art, and technology occurred within the past 50,000 years. This suggests that activity-dependent mechanisms must play a significant role in shaping the portions of the brain (particularly the neocortex) most associated with modern human behavior. Abbreviations: mya, million years ago; kya, thousand years ago. Adapted from [94].

occupied by the neocortex (wild rats had relatively large cortices). Subsequent studies of cellular composition revealed that wild rats had a larger percentage of neurons and a greater density of neurons in V1 compared to laboratory-reared animals [68]. Perhaps these findings are not too surprising, since laboratory reared animals are highly deprived in terms of both sensory input and movement options. They also demonstrate the need to investigate the brains of animals in more enriched environments to get a deeper understanding of natural brain development and function [69].

A final series of studies in the monogamous prairie vole underscores the importance of early sensory experience in constructing a cortical phenotype. Prairie voles are biparental and both parents contribute to infant care, which is relatively rare among mammals. Importantly, voles naturally engage in different rearing styles in which the amount of tactile contact (high, HC versus low, LC) delivered to the infants by the parents is normally distributed [70]; and infants adopt the rearing style of their parents. The Krubitzer lab took advantage of this natural variability and examined both the size of cortical fields and the connections of somatosensory cortex in high versus low contact infants and found that high contact animals (females) had a relatively large motor cortex [71], and that the cortical and callosal connections of somatosensory cortex differed between the two contact groups in both the density of connections and the location of its inputs from different cortical fields [72]. These studies demonstrate that, within a single lifetime, aspects of lifestyle or 'culture' can impact cortical field size and connectivity.

These three series of studies indicate that sensory input and environmental context play a critical role in phenotypic outcome. We believe that these aspects of the phenotype generated by sensory input and the environment will persist across generations if the context is maintained, and that the phenotype can undergo rapid change, from generation to generation, if the environment is highly variable. Thus, from our perspective, what needs to be better studied and explained is the evolution of the developmental mechanisms that allow such striking sensitivity to context over short time-scales.

Concluding Remarks and Future Perspectives

In this review, we discussed multiple mechanisms by which the same phenotypic characteristic (e.g., size of a cortical field; connections of a cortical field) can be altered. These include traditional evolutionary mechanisms that operate directly on the neocortex and body, and activity dependent mechanisms that can alter the functional organization and connections of the brain, and the behavior that the brain generates in the course of a lifetime. Thus, radical changes to the phenotype occur over both long and short time scales. Changes occurring over shorter time scales are likely driven by the long-term evolution of synaptic, cellular, and/or **epigenetic** mechanisms that allow the developing organism to construct a cortical phenotype that is adapted to its environmental context.

With respect to our own species, we believe that we should consider social learning, culture, and language as complex patterns of multisensory activity impinging on the developing nervous system. These social constructs can fundamentally alter a number of aspects of organization, including size of cortical fields, cortical and subcortical connections, and neural response properties, which in turn alters behavior. Support for this supposition comes from studies of human evolution. Anatomically modern humans have existed for 260–350 thousand years [73] and features of the modern hand that could support tool use [74], and of a supralaryngal tract that could support speech [75,76] evolved much earlier. Yet, our most complex behaviors, such as the ability to craft complex artifacts, and our capacity for spoken language as evidenced by traces of symbolic activity, have emerged more recently [77]. We hypothesize

Outstanding Questions

What are the underlying mechanisms that allow the developing brain to be shaped by the environment?

How do alterations in the brain co-evolve with alterations in the body?

How flexible is the genome in producing a wide range of phenotypes?

To what extent are our brains, and our success, tied to the technologies that humans create?

that although the first modern humans had brains and bodies that were capable of complex physical and social interactions with the world, the emergence of human culture, beginning some 200 thousand years ago [77], likely played an important role in shaping the modern human brain. In recent millennia, cultural evolution has seen accelerating growth (Figure 10). For example, the industrial revolution occurred less than 300 years ago; air powered flight, nuclear technologies and electronic computers are all less than a century old; and our social and technical interactions with machine-generated virtual worlds began less than three decades ago. The implication is that if our behavior and the environments that we inhabit have radically altered over relatively short time scales (centuries to decades), then features of the human cortical phenotype must also have undergone rapid and possibly dramatic changes within recent history. In fact, we would argue that humans have an extraordinary capacity to construct our neocortex based on context, over the course of a prolonged infancy and childhood, allowing for rapid phenotypic change within even a single generation. Our species has also evolved a remarkably fluid brain/body interface with the environment, such that tools and machines can be incorporated into our body schema [78,79], extending our embodiment and peripersonal space, and expanding the loop between our brains, our bodies, and the world. This eventuality has made us into uniquely biohybrid creatures [80,81] whose brains adapt and bootstrap themselves with the technologies they have given rise to, and with whom our futures are increasingly entwined.

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